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Supervisory Concurrence	
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Dosage Form(s) and Route(s) of Administration	< No Dosage Forms >
Dosing Regimen	< No Dosing Regimen >
Indication(s) and Intended Population(s)	< No Indication >

Table of Contents

1. Executive Summary	5
2. Clinical and Regulatory Background.....	9
2.1 Disease or Health-Related Condition(s) Studied	9
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s).....	10
2.3 Safety and Efficacy of Pharmacologically Related Products.....	10
2.4 Previous Human Experience with the Product (Including Foreign Experience)	10
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission.....	11
3. Submission Quality and Good Clinical Practices	12
3.1 Submission Quality and Completeness.....	12
3.2 Compliance With Good Clinical Practices And Submission Integrity	12
3.3 Financial Disclosures	13
4. Significant Efficacy/Safety Issues Related to Other Review Disciplines.....	13
4.1 Chemistry, Manufacturing, and Controls.....	13
4.2 Assay Validation.....	13
4.3 Nonclinical Pharmacology/Toxicology	13
4.4 Clinical Pharmacology.....	16
4.4.1 Mechanism of Action.....	17
4.4.2 Human Pharmacodynamics (PD).....	17
4.5 Statistical	18
4.6 Pharmacovigilance.....	19
5. Sources of Clinical Data and Other Information Considered in the Review	19
5.1 Review Strategy.....	19
5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review	20
5.3 Table of Studies/Clinical Trials	21
5.4 Consultations	23
5.4.1 Advisory Committee Meeting (if applicable)	23
5.4.2 External Consults/Collaborations.....	23
5.5 Literature Reviewed (if applicable)	23
6. Discussion of Individual Studies/Clinical Trials	27
6.1 Trial #1	27
6.1.1 Objectives (Primary, Secondary, etc).....	28
6.1.2 Design Overview	28
6.1.3 Population	28
6.1.4 Study Treatments or Agents Mandated by the Protocol.....	29
6.1.6 Sites and Centers.....	30
6.1.7 Surveillance/Monitoring	30
6.1.8 Endpoints and Criteria for Study Success	31
6.1.9 Statistical Considerations & Statistical Analysis Plan	31
6.1.10 Study Population and Disposition.....	32
6.1.11 Efficacy Analyses	37
6.1.12 Safety Analyses.....	43
6.2 Trial #2	62
6.2.1 Objectives (Primary, Secondary, etc).....	62
6.2.2 Design Overview	62
6.2.3 Population	63
6.2.4 Study Treatments or Agents Mandated by the Protocol.....	64

6.2.6 Sites and Centers	65
6.2.7 Surveillance/Monitoring	65
6.2.8 Endpoints and Criteria for Study Success	66
6.2.9 Statistical Considerations & Statistical Analysis Plan	66
6.2.10 Study Population and Disposition	69
6.2.11 Efficacy Analyses	76
6.2.12 Safety Analyses	86
7. Integrated Overview of Efficacy	111
7.1.8 Persistence of Efficacy	112
7.1.10 Additional Efficacy Issues/Analyses	112
7.1.11 Efficacy Conclusions	116
8. Integrated Overview of Safety	118
8.1 Safety Assessment Methods	118
8.2 Safety Database	120
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	120
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	121
8.2.3 Categorization of Adverse Events	123
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	124
8.4 Safety Results	124
8.4.1 Deaths	124
8.4.2 Nonfatal Serious Adverse Events	124
8.4.4 Common Adverse Events	132
8.4.5 Clinical Test Results	132
8.4.6 Systemic Adverse Events	138
8.4.7 Local Reactogenicity	141
8.4.8 Adverse Events of Special Interest	142
8.5 Additional Safety Evaluations	148
8.5.1 Dose Dependency for Adverse Events	148
8.5.2 Time Dependency for Adverse Events	148
8.5.3 Product-Demographic Interactions	148
8.5.4 Product-Disease Interactions	149
8.5.8 Immunogenicity (Safety)	150
8.6 Safety Conclusions	150
9. Additional Clinical Issues	151
9.1 Special Populations	151
9.1.1 Human Reproduction and Pregnancy Data	151
9.1.2 Use During Lactation	152
9.1.3 Pediatric Use and PREA Considerations	152
9.1.4 Immunocompromised Patients	152
9.1.5 Geriatric Use	153
10. Conclusions	153
11. Risk-Benefit Considerations and Recommendations	153
11.2 Risk-Benefit Summary and Assessment	153
11.3 Discussion of Regulatory Options	155
11.4 Recommendations on Regulatory Actions	155
11.6 Recommendations on Postmarketing Actions	157

1. EXECUTIVE SUMMARY

HEPLISAV was evaluated in two pivotal phase 3 immunogenicity and safety studies (DV2-HBV-10 and -16; N=3777 HEPLISAV recipients (safety population)), three supportive immunogenicity studies (N=110 HEPLISAV recipients (safety population)) and seven supportive safety studies (N=648 HEPLISAV recipients (safety population)) in adults 18 years of age and older. Immunogenicity of HEPLISAV was assessed by determining the seroprotection rate (SPR): the proportion of subjects with an anti-HBsAg level ≥ 10 mIU/mL, an antibody concentration recognized as conferring protection against hepatitis B virus infection (1, 2).

The primary immunogenicity endpoint in Study DV2-HBV-10 was defined as the difference in SPR between the Engerix-B group at Week 28 (4 weeks after the last active dose at 24 weeks) and HEPLISAV group at Week 12 (8 weeks after the last active dose at 4 weeks). The two-sided 95% CI on the difference (Engerix-B minus HEPLISAV) in SPR was evaluated. Success criteria were defined as follows: the HEPLISAV SPR was considered non-inferior to Engerix-B if the upper limit of the 2-sided 95% CI on the difference in SPRs (Engerix-B minus HEPLISAV) was < 0.10 . The primary immunogenicity differed slightly for Study DV2-HBV-16 in that the primary immunogenicity endpoint in Study DV2-HBV-10 was defined as the difference in SPR between the Engerix-B group at Week 32 (8 weeks after the last active dose at 24 weeks) and HEPLISAV group at Week 12 (8 weeks after the last active dose at 4 weeks).

Additional immunologic endpoints that were evaluated in both phase 3 studies included the SPR and geometric mean concentration (GMC) evaluated at each study visit.

Study DV2-HBV-10 enrolled adolescents and adults 11-55 years of age; Study DV2-HBV-16 enrolled adults 40-70 years of age. In both pivotal studies, the SPR following two doses of HEPLISAV was non-inferior to the SPR induced by three doses of the licensed hepatitis B vaccine Engerix-B (GlaxoSmithKline; GSK). The peak SPR and GMC occurred at Week 28 in HEPLISAV vaccinated subjects in both phase 3 studies. At least 90% of healthy adult subjects maintained seroprotective antibody levels against hepatitis B at 48 weeks after two doses of HEPLISAV in Study DV2-HBV-16. Findings for the modified intent-to-treat (mITT) population paralleled that of the per protocol (PP) population. Subgroup analyses did not reveal clinically significant differences between antibody responses in younger and older subjects, or between males and females. Conclusions could not be drawn regarding differences among ethnic and racial subgroups, though the SPRs were similar among all ethnic groups examined. Study DV2-HBV-16 was also designed to evaluate lot consistency between three consecutively manufactured lots of HEPLISAV (lots TDG008, TDG009, and TDG010) and to evaluate consistency between the newer (lots TDG008, TDG009, and TDG010) and an older lot (lot TDG006) of HEPLISAV. Lot consistency was demonstrated for the three consecutive lots and between the newer and older lots of HEPLISAV.

In summary, HEPLISAV demonstrated a rapid, robust and sustained SPR against hepatitis B for all study populations evaluated.

Safety was evaluated in 5845 subjects (HEPLISAV: n=4425, Engerix-B: n=1420) 18 years of age and older enrolled in nine clinical trials: 2 pivotal studies, DV2-HBV-10 and DV2-HBV-16 and 7 supportive studies. The phase 3 studies were conducted in 4,864 subjects (HEPLISAV: n=3777, Engerix-B: n=1087) followed for adverse events for 28 weeks and for serious adverse events for 28 weeks in Study DV2-HBV-10 and 52 weeks in Study DV2-HBV-16. The other 7 supportive studies were conducted in a total of 981 subjects (HEPLISAV: n=648; Engerix-B: n=333), followed for safety events for various time periods. The safety evaluation comprised an assessment of local and systemic reactogenicity monitored for days 0-6 after vaccination in both pivotal studies, unsolicited adverse events (AEs) and serious adverse events (SAEs) monitored through week 28 in Study DV2-HBV-10. In Study DV2-HBV-16, unsolicited AEs were monitored through week 28 and SAEs and autoimmune events were monitored through week 52. Anti-dsDNA and anti-nuclear antibody (ANA) levels were measured in both pivotal studies. Anti-neutrophil cytoplasmic antibody (ANCA) levels were evaluated retrospectively on banked serum from subjects enrolled in Study DV2-HBV-10 and in one uncontrolled supportive study.

The overall incidence of non-serious unsolicited adverse events was similar between treatment groups (HEPLISAV: 58.1%, Engerix-B: 61.2%), and most were mild to moderate in severity. Most AEs were related to local reactogenicity, were described as mild in intensity, and did not differ significantly from the licensed comparator, Engerix-B. More subjects receiving HEPLISAV reported redness at the injection site (3.5% vs. 1.0%) than did subjects receiving Engerix-B. The overall incidence of swelling and pain at the injection was similar between groups. Solicited systemic reactions of fever, malaise, headache and fatigue occurred with similar incidence among treatment groups.

Non-fatal serious adverse events (SAEs) were reported by 2.7% of HEPLISAV and 3.7% of Engerix-B recipients, respectively. There was a numerical imbalance between the incidence of pulmonary embolus in HEPLISAV and Engerix-B recipients at 5 (0.1%) and 0 subjects, respectively. Four of the five events occurred in individuals with underlying predisposition to thrombosis. Non-serious thrombotic events occurred with similar incidence between groups. Two deaths occurred in Study DV2-HBV-16. One, 46-year old previously healthy male subject who was vaccinated with HEPLISAV died of a pulmonary embolus (b) (6) days after the second study injection. One, 64-year old male subject vaccinated with Engerix-B with multiple comorbidities died of cardiac arrest after having a myocardial infarction (b) (6) days after the second study injection.

Because HEPLISAV includes CpG, a novel adjuvant that mediates its effect through the TLR-9 receptor, efforts were made to identify clinical cases of autoimmunity and evaluate biomarkers of autoimmunity, such as ANA, anti-dsDNA and erythrocyte sedimentation rate (ESR) in individuals enrolled in studies of HEPLISAV.

No significant differences in ESR, c-reactive protein (CRP), ANA titers, or anti-dsDNA levels were detected between recipients of HEPLISAV or Engerix-B. ESR was evaluated in three early studies. There were both HEPLISAV and active control recipients who experienced post-vaccination elevations in ESR, but no consistent trend was observed.

The applicant did not provide a pooled analysis of these data. CRP levels were evaluated in subjects in Study DV2-HBV-10 and in an uncontrolled supportive study (DV2-HBV-14). In Study DV2-HBV-14, CRP levels were evaluated in 191 of the 207 enrolled subjects; 86.9% were negative at baseline. Seven subjects had CRP concentrations < 0.8 mg/dL at baseline and became positive at Month 3. Seven subjects had CRP concentrations < 0.8 mg/dL at baseline and became positive at Month 7. As raw CRP data were not provided by the applicant, the review of these data is limited to the analyses performed by the applicant.

While prospective laboratory evaluations of autoimmunity did not raise any clinical concerns, one case each of vasculitis in the HEPLISAV treatment arm (cytoplasmic-ANCA [c-ANCA] positive Wegener's granulomatosis (WG)) and Engerix-B treatment arm (perinuclear-ANCA [p-ANCA] positive vasculitis) and one case of Guillain-Barre syndrome in the HEPLISAV arm, were identified in pivotal study DV2-HBV-10 which prompted a closer examination for autoimmune adverse events in Study DV2-HBV-16. The case of WG was new-onset during the clinical study follow-up period while the case of p-ANCA positive vasculitis occurred in a subject with a history of mixed connective tissue disease (MCTD).

Based on the occurrence of these two events, serum specimens from subjects in study DV2-HBV-10 and a supportive uncontrolled trial, DV2-HBV-14, were retrospectively tested for ANCA (anti-neutrophil cytoplasmic antibody). Serum with positive screen, (b) (4) assays for anti-MPO and anti-PR3, were then confirmed using (b) (4)

In addition to the two subjects from study DV-2-HBV-10 with ANCA associated vasculitides, serum screening studies were performed on 2376 additional subjects (1780 in the HEPLISAV arm and 596 in the Engerix-B arm) in that study. No individual was found to have a confirmed assay result.

The applicant attempted prospectively to assess possible cases of autoimmune adverse events (AIAEs) in study HBV-16 with adjudication of potential autoimmune events (AIAEs). All potential events were adjudicated by a Safety Evaluation and Adjudication Committee (SEAC). The SEAC determined that three cases of new-onset autoimmune disease occurred, two cases of hypothyroidism and one of vitiligo. All three cases were determined by the SEAC to be unrelated to the vaccine. One case of erythema nodosum was determined by the SEAC to be related to vaccination but not autoimmune in nature.

CBER-generated post-hoc analyses of potential autoimmune adverse events from all studies were also performed and included analyses of thyroid associated events and events requiring immunosuppressive therapy. This independent CBER analysis revealed that thyroid-related AEs were reported by HEPLISAV recipients with a frequency similar to that of Engerix-B recipients and a frequency similar to the background incidence rate across all studies.

The CBER-generated analysis of adverse events that required immunosuppressive therapy (excluding asthma exacerbations) revealed that 0.2% of subjects in each treatment arm required immunosuppressive therapy while on study. On further detailed review of these cases it was found that one subject in the HEPLISAV arm was diagnosed with possible Tolosa-Hunt syndrome—a granulomatous disorder of the cavernous sinus (3-6). The subject's diagnosis was subsequently changed to cavernous sinus syndrome after further discussion between the applicant and the neurologist of record. This case is notable because of its potential vasculitic or other autoimmune etiology and reports in the literature suggesting this condition could be a limited form or initial presentation of Wegener's granulomatosis in which ANCA testing is often negative (7-9).

Although the incidence of adverse events of special interest was low, all potential autoimmune AEs evaluated prospectively in study HBV-16 occurred in HEPLISAV recipients. Given the randomization ratio employed in this study and the low background incidence of many autoimmune diseases, the clinical significance of the 0.5% difference in the incidence of potential autoimmune disease between groups is in this study unclear. An integrated retrospective analysis of adverse events occurring in all studies revealed a similar overall incidence of thyroid-associated disorders and events requiring immunosuppressive therapy between treatment arms. However, the occurrence of rare autoimmune events in these studies, and limitations involved in the size of the database, the overall randomization ratio, the safety follow-up periods and the low background incidence of many autoimmune diseases, it is difficult to determine the clinical significance of the incidence of potential autoimmune events in these studies. The safety database for HEPLISAV may not have sufficient power to detect rare adverse events such as these autoimmune AEs.

These safety data were presented to the Vaccines and Related Biologic Products Advisory Committee (VRBPAC) on November 15, 2012. Although the committee voted 13:1 committee members in support of a sufficient demonstration of vaccine immunogenicity, the committee also voted 8:5 members (with 1 abstention) that inadequate safety data were available to recommend licensure of HEPLISAV at this time. An additional concern was voiced that the studies did not evaluate the vaccine in a representative population of subjects who were most likely to benefit from this vaccine (e.g. African-Americans, Asians), that the studies performed were not adequately balanced in terms of the racial and ethnic groups studied, and that concomitant administration studies were not done.

Regarding the safety evaluation, the clinical reviewers' conclude that no significant signals were seen for local or systemic reactogenicity, but the potential for autoimmunity with HEPLISAV immunization, given the case of Wegener's granulomatosis and the possible case of Tolosa-Hunt syndrome, in HEPLISAV-vaccinated subjects, requires further evaluation in a larger population database and specifically, a closer review of the case of Tolosa-Hunt syndrome by a group of clinical experts. Pending consultations for external expert review of this case are essential to the completion of the safety review, and therefore licensure of this product cannot be considered until these consultations are complete..

Additionally, the reviewers have concerns regarding the size of the safety database, the randomization ratios and the length of safety follow-up. The relatively short time for which patients were followed in some of the studies is particularly problematic when evaluating adverse events of potentially insidious nature such as autoimmune events. The reviewers believe the current safety data are insufficient to determine the safety of this vaccine. At this time, approval of HEPLISAV for healthy subjects, 18-70 years of age for the prevention of hepatitis B infection is not recommended by the clinical reviewers given these safety concerns and pending additional safety evaluation. Prior to consideration for licensure of this product for use in adults 18-70 years of age, further clinical evaluation of safety will be necessary.

2. CLINICAL AND REGULATORY BACKGROUND

Product: HEPLISAV (rHBsAg-1018 ISS)

- Recombinant Hepatitis B surface antigen (rHBsAg), subtype *adw*, produced in yeast cells (*Hansenula polymorpha*).
- Combined with a novel cytosine phosphoguanine (CpG) enriched oligodeoxynucleotide (ODN) phosphorothioate immunostimulatory adjuvant.
- 1018 ISS used in HEPLISAV is a 22-mer oligonucleotide with the sequence:

5' TGA CTG TGA ACG TTC GAG ATG A 3'

Proposed Indication: Active immunization against all subtypes of hepatitis B virus infection in adults 18-70 years of age.

Dosage and Administration: Each 0.5mL dose contains 20 mcg rHBsAg and 3000 mcg 1018 ISS adjuvant. The dosing regimen is two 0.5 mL doses administered 4 weeks apart.

2.1 Disease or Health-Related Condition(s) Studied

Hepatitis B infects more than 2 billion persons worldwide, and 350-400 million persons are chronic carriers. Each year chronic HBV causes 0.5 to 1.0 million deaths from end-stage liver disease and hepatocellular carcinoma. In the U.S., universal childhood vaccination has been recommended since 1992. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.6 per 100,000 (2006). Prevalence remains high at 800,000 to 1.4 million, and chronic HBV infection causes 2,000-4,000 deaths annually. CDC estimated that there were 38,000 new HBV infections in 2009 with 43% occurring in adults over 40 years of age. Forty-seven to 70% of U.S. residents with chronic HBV infection were born in other countries.

Transmission of HBV is by percutaneous and mucosal exposure to infectious blood or body fluids. In the U.S. transmission is primarily sexual. Injection drug use (IDU) accounts for 16% of new HBV infections. Nosocomial transmission between patients and from patients to health care workers (HCW), including hemodialysis (HD) and oncology units, has become rare, declining 95% since implementation of routine vaccination and standard precautions for blood-borne pathogens. The incidence of HBV infection among hemodialysis patients was 1.2% in 2002.

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds are currently available for the prevention of HBV in adults in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in adults and adolescents as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Additionally an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12.

These vaccines are highly effective, as shown in controlled clinical trials of efficacy against acute hepatitis B infection (1) and prospective observational studies (2,10), and elicit a SPR in approximately 95% of healthy adults. Long-term studies of immunocompetent adults and children indicate that immune memory remains intact for up to two decades and protects against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time (10).

Breakthrough infections (detected by presence of anti-HBc antibodies or HBV DNA) have occurred in immunized people, but these infections typically are transient and asymptomatic. Chronic HBV infection in immunized people has been documented in dialysis patients whose anti-HBsAg antibody concentrations fell below 10 mIU/mL. For adults on dialysis, formulations of Engerix-B and Recombivax HB containing 40 mcg per dose administered in a 3 or 4 dose series are approved. In dialysis patients, the need for booster doses is assessed by annual antibody testing, and revaccination is indicated when anti-HBsAg levels decline below 10 mIU/mL.

2.3 Safety and Efficacy of Pharmacologically Related Products

Currently, there are no approved products containing this 1018 ISS novel adjuvant.

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Limited prior human experience exists for the adjuvant 1018 ISS. More clinical experience is available with CpG 7909 (ProMune, Coley Pharmaceuticals), another immunostimulatory synthetic cytosine phosphoguanine oligonucleotide (ODN) agonist of TLR9, in the context of use in the cancer patient population. Although there have been more than 25 human studies which included use of this adjuvant, they have been difficult to interpret due to the heterogeneous population of cancer patients (n ~ 2000) receiving various vaccines and antigenic tumor peptides, some with chemotherapy and other immunomodulators. A summary of autoimmune events for CpG 7909 from reports in the literature did not reveal autoimmune signals. Seroconversions occurred for anti-dsDNA

(25%), ANA (10%), rheumatoid factor (RF, 7%), and anti-thyroid antibody (3.5%), but without clinical evidence of autoimmune disease.

CpG 7909 has been administered with Engerix-B in a double-blind phase 1/2 study in healthy subjects 18-35 years of age (11). The most frequently reported adverse events were injection site reactions, flu-like symptoms and headache. Autoimmune adverse events were not reported. A second, similar study performed in thirty-eight HIV-infected individuals 18-55 years of age (12) failed to reveal any autoimmune adverse events, although transient elevations above normal range for anti-dsDNA were noted in two subjects who received Engerix-B plus CpG 7909 and in two subjects who received CpG 7909 alone. These subjects were ANA negative.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The HEPLISAV regulatory background is summarized as follows:

- 30 Sep 2005, IND 12692 filed for evaluation of rHBsAg-1018 ISS in end stage renal failure patients.
- 27 March 2007, IND 13332 filed for evaluation of rHBsAg-1018 ISS in healthy adult subjects.
- 5 March 2008, initial serious adverse event report (SAE) of c-ANCA positive Wegener's Granulomatosis reported in a 55 year otherwise healthy German woman (ID # 24-057/ECE) enrolled in the phase 3 study DV2-HBV-10 under IND 12692, Amendment 6. The event was deemed possibly associated with HEPLISAV and biologically plausible.
- 14 April 2008, INDs 12692 and 13332 were placed on clinical hold.
- 18 Sept 2008, Dynavax submitted a complete response to clinical hold. Review of the response indicated remaining safety concerns regarding risk of autoimmune disease, revised inclusion/exclusion criteria, and requirement for closer safety monitoring for autoimmune adverse events of interest. A continued clinical hold was issued on 17 October 2008 for both INDs.
- 08 Jan 2009, CBER Clinical Hold Oversight Meeting to discuss the SAE of Wegener's granulomatosis.
- 24 March 2009, complete response to clinical hold submitted by Dynavax.
- 24 April 2009, continued clinical hold recommended by the clinical reviewer.
- 09 Aug 2009, Dynavax submitted a complete response to clinical hold and provided a comprehensive prospective safety monitoring plan and algorithm to evaluate autoimmune adverse events.
- 26 August 2009, clinical hold was lifted for IND 12692. The clinical hold for IND 13332 remains, to date, in effect.
- 25 Jan 2012 Pre-BLA Meeting with FDA to discuss filing of HEPLISAV for use in healthy adults.
- 26 April 2012 BLA filed for HEPLISAV with the FDA.
- 03 October 2012, PeRC Meeting to Discuss the Full Waiver for HEPLISAV. Full Waiver granted. The PeRC recommended labeling the vaccine vial for "adult use only".

- 15 November 2012, VRBPAC to discuss effectiveness and safety of HEPLISAV. The VRBPAC vote was as follows: 13:1 in favor of a finding that adequate immunogenicity was demonstrated; 8:5 (with 1 abstention) voting in favor of a determination that safety presented within the BLA was not adequate to support licensure at this time.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Overall, the clinical portions of the submission were fairly well organized into the various modules. However, there were items that were difficult to find within the substance of the modules making the ability to locate and review data challenging at times. The applicant accommodated the reviewers' requests for additional information pertaining to datasets, hyperlinks and other information alleviating some of these challenges. However, substantive discrepancies pertaining to the categorization, organization and completeness of some adverse event data required additional safety information to be requested throughout the entire review cycle. Clinical information requests are outlined here. Outstanding requests are noted in section 11.4 of this review.

- September 12, 2012: Various clinical safety data requests and clarifications sent to applicant regarding both Phase 3 trials and the integrated summary of safety
- September 28, 2012: Dynavax responded via amendment 125428/0.7
- October 15, 2012: Clinical safety data requests regarding product lots used in study DV2-HBV-10 and the datasets for study DV2-HBV-16
- October 31, 2012: Dynavax responded via amendment 125428/0.11
- November 1, 2012: Various case report forms requested
- November 5, 2012: Dynavax responded via amendment 125428/0.13
- November 5, 2012: Treatment arm clarification request for a subset of subjects experiencing adverse events
- November 6, 2012: Dynavax responded via amendment 125428/0.14
- November 6, 2012: Various case report forms requested
- November 9, 2012: Case report form requested for individual subject
- November 13, 2012: Dynavax responded via amendment 125428/0.17
- November 21, 2012: Source documents requested for individual subject
- November 30, 2012: Dynavax responded via amendment 125428/0.23

3.2 Compliance With Good Clinical Practices And Submission Integrity

Bioresearch monitoring inspections were issued for 2 investigators conducting investigations at sites 22, 23, 24, 25, 26 and 38. At site 38, the inspection revealed the presence of three protocol deviations. Twelve subjects were prematurely unblinded at site 24 for study DV2-HBV-16. The results of the inspections at these two sites (24 and 38) generated a Complete Response from the bioresearch monitoring review. Please see the full bioresearch monitoring review for further details regarding these findings.

From the clinical safety standpoint, at least one serious and unexpected adverse event was not submitted as an expedited safety report as outlined in section 5.17.1 of the FDA Guidance for Industry: E6 Good Clinical Practice: Consolidated Guidance and in 21 CFR 312.32(c)(B). Other aspects of Good Clinical Practice such as submission to and compliance with Institutional Review Boards, provision of an Investigator's Brochure and Informed Consent documents, clinical protocol compliance and medical care of trial subjects, appear to be satisfactory. Please also see the Chemistry Manufacturing and Controls review regarding section 5.13 of the aforementioned Guidance regarding the manufacturing, packaging, labeling and coding of investigational products.

3.3 Financial Disclosures

One clinical investigator, who participated at Study Site 21 (Dr. Norman Lunde), in the pivotal efficacy study DV2-HBV-16, disclosed a financial interest. This investigator is a former Principal Investigator to Dynavax and provided study protocol oversight in accordance with FDA form 1572 commitments from November 2009 to September 2010 for HEPLISAV. The investigator purchased (b) (6) shares of Dynavax stock in December 2010 which exceeded a value of (b) (6) in February 2011, however the investigator's involvement with the study officially ended in September 2010. Study DV2-HBV-10 continued under the oversight of a new Principal Investigator, effective September 2010.

The original investigator enrolled 84 subjects in Study DV2-HBV-16. A total of 47 subjects were eligible for the primary immunogenicity analysis. The number of subjects randomized at Site 21 comprised 3.5% of the subjects randomized into the study. The investigator did not have access to study records after September 2010 as he was no longer an active Investigator. During his tenure as PI, he did not have access to unblinded data prior to database lock and completion of data analysis according to the signed statistical analysis plan (SAP).

No other investigators for any of the pivotal or supportive studies conducted reported a financial conflict of interest.

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

Clinical Hold was recommended. See section 11.4 of this review for details.

4.2 Assay Validation

Clinical Hold was recommended. See section 11.4 of this review for details.

4.3 Nonclinical Pharmacology/Toxicology

Non-clinical toxicology studies were conducted with HEPLISAV or 1018 ISS alone in a mice and non-human primates (NHPs).

Findings in key toxicology studies are summarized below. For a full discussion, please see Dr. Claudia Wrzesinski's and Dr. Steven Kunder's full toxicology reviews.

Toxicology studies with the adjuvant alone (1018 ISS):

The 1018 ISS adjuvant alone was evaluated in 3 genotoxicity studies, 2 safety escalation studies (rabbit and baboons) and 3 repeated toxicology studies (mice, rats and cynomolgus monkeys).

The panel for genotoxicity studies for the 1018 ISS adjuvant included a bacterial mutation test, a chromosome aberration assay in human PBMCs, and a mouse erythrocyte micronucleus test. There was no mutagenic effect attributed to 1018 ISS adjuvant.

A rising-dose tolerability study was conducted with 1018 ISS Adjuvant alone in rabbits (doses up to □0.8 mg/kg, IV) and in baboons (doses up to 2.5 mg/kg, SC or IV). These studies included evaluation of changes in blood pressure, heart rate, body temperature, and respiration rate. Escalating doses of 1018 ISS adjuvant alone were well tolerated and there were no effects on any of these parameters in either species.

A repeat-dose toxicity study with 1018 ISS adjuvant alone was conducted in mice (very similar to the toxicology study in mice with the HEPLISAV vaccine, see below). Mice received a total of 3 IM doses (2 mg/kg/dose, clinical dose is 0.05mg/kg) of the 1018 ISS adjuvant alone separated by 2 weeks. No mortality or clinical signs of toxicity was observed. The main findings included splenomegaly, lymphoid hyperplasia, mononuclear cell infiltrates in multiple tissues as well as extramedullary hematopoiesis (EMH) in the spleen and liver accompanied by a mild anemia. After the recovery phase reversibility was observed. These findings are consistent with the adjuvant class effect; phosphorothioate oligonucleotides are described to inhibit the intrinsic coagulation pathway and activate the alternative complement system.

Repeat-dose toxicity studies with the 1018 ISS adjuvant alone (SC injections from 0.5 to 12.5 mg/kg/week for 8-weeks) were conducted in rats and cynomolgus monkeys. Animals received 10 to 250 times the human dose based on mg/kg (0.5, 2.5 or 12.5 mg/kg) weekly for 8 weeks. The effects of 1018 ISS adjuvant in rats were more pronounced than in monkeys, reflecting the higher sensitivity to TLR9 agonists typically observed in rodents. The main treatment-related findings were inflammatory changes at the injection-sites and in key target organs, including the liver, kidney, lymph nodes and spleen. These changes were consistent with manifestations of the immunostimulatory activity of 1018 ISS adjuvant and its adjuvant class effects. In general, most of the changes observed in the target organs were not degenerative in nature and reversible, except for at the highest dose levels in rats where proximal tubular degeneration in the kidneys occurred. Even with this finding, no effect on renal function, and no specific findings of glomerulonephritis or vasculitis were detected.

In the cynomolgus monkey (NHP=non-human primate) study adjuvant-related observations included a modest increase in activated partial thromboplastin time, splenomegaly and hyperplasia of the Kupffer cells with blue granular pigment inclusions at the highest dose group level; and minimal to mild injection site inflammation and minimal mononuclear cell infiltration in the liver at the lowest dose level. No evidence of renal toxicity was seen in the NHP study.

Toxicology studies with HEPLISAV (Recombinant HBsAg vaccine plus 1018 ISS adjuvant):

A repeat dose toxicology study of HEPLISAV in mice was conducted. Mice received a total of 3 doses (0.5 mcg HBV antigen and a maximum dose of the adjuvant ISS 1018 50 mcg, or 2.5 mg/kg) separated by 2 weeks. The target organs were the hematopoietic system, spleen, liver and injection site. The main findings included splenomegaly, lymphoid hyperplasia, mononuclear cell infiltrates in multiple tissues and extramedullary hematopoiesis in the spleen and liver.

The immune stimulation is a typical finding associated with repeated administration of phosphorothioate oligonucleotides in rodents. The increased splenic weight and the extramedullary hematopoiesis observed in spleens and livers of the vaccine treated mice were consistent with the adjuvant class effect. The immunostimulatory response was reversed following recovery. Inflammation at the site of administration is also a class effect, and was partially reversed following recovery. Mild anemia was observed in this study and was previously observed in rodents receiving phosphorothioate oligonucleotides.

HEPLISAV was also studied in rats in a reproductive, and developmental toxicity study which assessed the potential effects on mating behavior, fertility, gestation, embryo-fetal development, parturition, lactation and maternal behavior (from implantation through lactation and weaning) and on the development of the offspring of the treated female rats, including an extended postnatal behavioral/functional and immunological evaluation. HEPLISAV was administered as 4 IM injections before and during gestation. The highest dose level resulted in maternal toxicity (mortality/humane sacrifice in 5 of 97 pregnant female rats). There were no adverse effects on maternal reproductive performance, fetal development, or the growth and development of the offspring. The intended clinical application will use 2 injections on days 0 and 28 with a dose of 3000 ug 1018 ISS in combination with 20 ug rHBsAg.

Toxicology studies were performed at many fold higher doses of 1018 ISS on a mass basis compared to that intended for clinical use and exceeded the number of doses administered. On a mg/kg dose, the clinical dose of 0.05 mg/kg is approximately 250-fold lower than that used in the toxicity studies which demonstrated acceptable toxicity. No dose limiting toxicities were observed in the GLP studies. A number generally known class effects were observed characteristic of immune stimulators and phosphorothioate oligonucleotides. Additionally, a number of clinical studies have

already been performed using similar or higher dosing schemes as the one currently proposed.

4.4 Clinical Pharmacology

HEPLISAV is a mixture of HBsAg and 1018 ISS adjuvant. These two components are not adsorbed or linked together, and therefore are expected to exhibit pharmacokinetic (PK) properties of the individual components. Dynavax did not formally evaluate the PK properties of HBsAg alone or in HEPLISAV. It is traditionally held that protein antigens administered by intramuscular (IM) injection distribute from the site of injection via lymphatic channels to the draining lymph node, where the antigens are processed into peptides, presented by antigen-presenting cells, and ultimately digested into shorter peptides or individual amino acids. It is expected that the HBsAg in HEPLISAV would exhibit PK properties typical of protein antigens in general.

The 1018 ISS adjuvant in HEPLISAV is a phosphorothioate oligodeoxynucleotide (PS ODN). PS ODNs exhibit a distinct and consistent set of properties. Following intravenous or subcutaneous administration, PS ODNs are rapidly absorbed and detected in the plasma. They bind nonspecifically and reversibly to plasma proteins. Distribution from the plasma into tissues is rapid. PS ODNs primarily distribute into kidney, liver, lymph nodes, spleen, adipose tissue and bone marrow. Tissue distribution studies in mice revealed highest concentrations in kidney, liver, lymph node, and spleen. The primary mode of clearance is by degradation (exonuclease activity) in tissues and is slow because the phosphorothioate backbone resists degradation. Renal clearance is low and elimination from tissues is slow. PS ODNs have minimal distribution to heart, lung, and skeletal muscle and do not cross the blood-brain barrier.

The half-life of PS ODNs in plasma is measured in hours, whereas the half-life in tissues is days to weeks. PS ODNs are metabolized by nucleases into shorter oligonucleotides, which ultimately lose biological activity and protein-binding capacity. The shorter oligonucleotides are primarily filtered through the glomeruli and excreted in the urine. PS ODNs have not been reported to have any interaction with the cytochrome P450 system.

Dynavax evaluated the PK properties of 1018 ISS, alone and as a component of HEPLISAV in preclinical studies. 1018 ISS has PK properties similar to those of other PS ODNs. Following IM injection of HEPLISAV, the 1018 ISS adjuvant enters the plasma and is rapidly absorbed and cleared.

Dynavax also evaluated the PK properties of the 1018 ISS as a component of HEPLISAV in subjects with chronic kidney disease (CKD) in study HBV-09, and as a single agent in subjects with colorectal cancer in DV2-ONC-01. In these studies, 1018 ISS exhibited rapid distribution into, and clearance from, plasma. The maximum observed plasma concentrations in ONC-01 were approximately dose-linear. The calculated single-compartment volume of distribution was consistent with that of a small hydrophilic molecule and was similar to the volume of distribution reported for other PS ODNs in humans.

4.4.1 Mechanism of Action

HEPLISAV consists of rHBsAg and a synthetic cytosine phosphoguanine oligodeoxynucleotide (CpG ODN) adjuvant, 1018 ISS, which is comprised of cytosine and guanine enriched unmethylated single strand DNA sequences. There is currently no other licensed vaccine in the U.S. that contains this adjuvant. The mode of action of CpG ODNs is based on the concept that, whereas vertebral (self) DNA is usually methylated when a cytosine is followed by a guanine, bacterial and viral DNA contain unmethylated CpG sequences which are recognized as foreign by the innate immune system through interaction with toll-like receptor 9 (TLR9).

TLR9 receptors are located within the cytoplasm of plasmacytoid dendritic cells (pDCs) and B cells, on the surface of the endoplasmic reticulum (ER). They are present to a lesser degree in NK cells. Activation of antigen-presenting pDCs and B-cells occurs when intracellular viral and bacterial pathogens containing unmethylated CpG sequences are recognized by TLR9 receptors. Activated pDCs become antigen presenting cells (APCs) and secrete interferon-alpha (IFN- α), which in turn stimulates a T helper 1 (Th1) immune response, and the secretion of other proinflammatory cytokines that activate macrophages, monocytes, and NK cells. Activated B-cells are stimulated to secrete antibodies, nonspecifically autoantibodies, and contribute to the overall biased Th1 cellular immune response by facilitating opsonization and antibody-dependent cytotoxic T cell responses.

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

In summary, HEPLISAV is proposed to act by using an adjuvant that activates TLR9 in pDCs which, combined with HBsAg, leads to production of HBsAg-specific antibodies.

4.4.2 Human Pharmacodynamics (PD)

The rationale for dose selection of 1018 ISS for further clinical development and for the candidate vaccine formulation was based on results from the pilot Study DV2-HBV0001. This was a phase 1, observer-blind, randomized, dose-escalation study performed in healthy, seronegative adults 18-55 years of age, which evaluated the safety, tolerability and immune response to rHBsAg, 20 micrograms (mcg), co-administered IM with differing doses of 1018 ISS. Doses of 1018 ISS administered were 300, 650, 1000, or 3000 mcg.

Two IM doses of rHBsAg, 20 mcg, combined with the highest dose of 1018 ISS evaluated in this study (3000 mcg) yielded the highest seroprotection rate, based on the limited seroprotective response data presented.

4.5 Statistical

Statistical review of the effectiveness and safety of HEPLISAV was performed by Dr. Mridul Chowdhury (Final Statistical Review and Evaluation, HEPLISAV, Dynavax Technologies, BLA 125428, 01/29/13, Mridul K. Chowdhury, Ph.D.). The BLA demonstrated that in both pivotal studies, the primary immunogenicity endpoint of seroprotection with HEPLISAV vaccine met the non-inferiority criterion when compared with Engerix-B vaccine. In Study DV2-HBV-10, the observed SPRs in the HEPLISAV and Engerix-B arms were, respectively, 95.1% and 81.1%, the 95% CI lower limit of difference (HEPLISAV-Engerix-B) was +10.7. In Study DV2-HBV-16, the observed lower limit was +14.6%. Both of these lower limits exceeded the pre-specified margin of -10%, supporting HEPLISAV's non-inferiority in both phase 3 studies.

Study DV2-HBV-16 also sought to demonstrate clinical lot consistency in the three manufacturing lots, using the pair-wise 95% CIs for the ratios of GMCs, which would exclude both a 2/3-fold decrease and a 3/2-fold increase per specification. The assessment of this consistency was pre-planned at Week 8 but was changed post-hoc to Week 12. The applicant's data unblinding revealed that the measurements at the pre-planned Week 8 did not satisfy the lot consistency criterion, but did so at Week 12. The applicant's calculations for the post-hoc endpoint conformed with the statistical reviewer's results, but the statistical reviewer expressed concern for using a post-hoc change in the endpoint's measurement. Dr. Chowdhury deferred to the clinical team for the final decision on acceptance of these data (see Clinical Review for Study DV2-HBV-10). The clinical review team's conclusion regarding the lot consistency studies and change in the pre-specified time point from Week 8 to Week 12 was that the Week 12 time point represented a more clinically relevant time point for measurement of lot consistency, as supported by choice of the Week 12 time point as the primary immunogenicity time point. Lot consistency at Week 12 was demonstrated.

Immunogenicity bridging was a secondary objective of Study DV2-HBV-16. The study showed comparable immunogenicity between the old lot TDG006 and the combine three new consistency lots of HEPLISAV, in terms of GMCs. In the per-protocol population, the GMC ratios (new vs. old lot) excluded both a 2/3-fold decrease and a 3/2-fold increase, supporting the bridging of immunogenicity results at both time points of Week 8 and Week 12. In the modified intent-to-treat (mITT) population at these same time points, the respective GMC ratios and confidence bounds were 1.21 (95% CI: 0.95, 1.55) and 1.20 (95% CI: 0.98, 1.47), showing the observed upper bound of 1.55 exceeded the 3/2-fold increase at Week 8.

For both phase 3 studies, a higher rate of seroprotection and GMCs, and a faster rise in these respective parameters, occurred in the HEPLISAV arm compared to Engerix-B, regardless of subjects' demographic characteristics. The higher SPR and GMCs in the HEPLISAV-immunized subjects persisted throughout the study duration.

Statistical review of safety focused on review of reported post-injection local and systemic reactions and general AEs reported in the integrated summary of safety. A safety signal for HEPLISAV was not identified based on this analysis. In the two phase

3 trials, post-injection site reaction, such as redness, seemed to occur with a higher rate (3.7%, 95% CI: 3.1%-4.4%) in the HEPLISAV arm compared to Engerix-B (1.1%, 95%: 0.6%-1.9%). The incidence of redness, however, was infrequent. The rates of post-injection systemic reactions were comparable between treatment arms. Two cases of death were reported but were considered by the study investigator as unrelated to the treatment groups. The applicant performed a retrospective analysis of selected neuroinflammatory, musculoskeletal, gastrointestinal, metabolic, skin & autoimmune disorders considered adverse events of special interest (AESIs) in attempts to identify potential autoimmune adverse events. Overall, there were 10 (0.2%) adverse events of special interest in the HEPLISAV group and 5 (0.4%) in the Engerix-B group.

4.6 Pharmacovigilance

In this submission, the applicant proposed an open-label prospective observational phase 4 study of 5000 HEPLISAV recipients and 15,000 Engerix-B recipients to assess the incidence of medically significant AEs including autoimmune disease for 12 months after the 1st injection. Data collection is proposed to begin 1 year after approval. They projected the last subject will be enrolled 2 years after study initiation and anticipate data will be available 4 years after the start of data collection (5 years after approval). At the VRBPAC, the applicant presented an alternate plan in which enrollment would ultimately be expanded beyond the initial 5,000 HEPLISAV recipients enrolled. Please see the review from the Office of Biostatistics and Epidemiology for further details and comments regarding the discussions surrounding pharmacovigilance for this product.

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The immunogenicity review was conducted by Dr. Alexandra Worobec. Studies chosen for immunogenicity review were those that utilized the *adw* strain of hepatitis B surface antigen (Phase 3 Studies DV2-HBV-10 and DV2-HBV-16, along with the supportive studies HBV0001, HBV-02 and HBV-03). Because the supportive studies were phase 1 and 2 studies performed in a small number of subjects who received a different dosing schedule than the 'to-be-marketed' schedule, these studies were not deemed as critical for licensure as the two phase 3 studies. For both of the phase 3 immunogenicity studies, immunogenicity analysis focused on the pre-specified primary and secondary endpoints, as delineated in the sponsor's statistical analysis plan (SAP). Exploratory immunogenicity analyses of non-inferiority between the HEPLISAV arm and active comparator arm was evaluated at the pre-specified study visits, for the purpose of showing that the immune response to HEPLISAV was sustained over the study duration and robust. For both phase 3 studies, sub-group analysis of immunogenicity by age, gender, ethnic and racial subgroups, and body mass index (BMI) was performed in order to detect any clinically significant differences between antibody responses in the different subgroups that could impact dosing recommendations. Additional sub-group analysis for type 2 diabetic status was performed in Study DV2-HBV-16. No other post-hoc analyses were performed.

An integrated summary of efficacy was not performed for HEPLISAV since the two phase 3 studies evaluated the primary immunogenicity endpoint at different time points in each respective study, which made integration of immunogenicity data not possible. Because the results of both of these phase 3 studies demonstrated that HEPLISAV was strongly immunogenic, the conclusions derived from the phase 1 and 2 studies regarding immunogenicity of HEPLISAV were consistent with those of the phase 3 studies and did not change the conclusion regarding immunogenicity of the vaccine. The proposed target population of HEPLISAV is the broad age range of 18-70 years and was based on the immunogenicity findings of the two phase 3 studies, which studied subjects aged 18-55 years and 40-70 years, and which showed a high seroprotective rate against hepatitis B for all subjects in these age groups.

The safety review was conducted by Dr. Lorie Smith. This review consisted of the evaluation of safety data from each of the individual studies (HBV-10, HBV-16, HBV-14, HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, and HBV-08). The products used in these studies included all vaccine formulations used during development to capture a broader safety database. Solicited local and systemic AEs, unsolicited non-serious AEs, SAEs, laboratory evaluations and AIAEs (Study HBV-16 only) were included in the evaluation for each study. In addition, the integrated safety data from all studies, including solicited local and systemic AEs, unsolicited non-serious AEs, laboratory evaluations, and AESIs were reviewed. Additional retrospective CBER-generated safety analyses of AIAEs, AESIs and SAEs requiring immunosuppressive therapy and of thyroid associated events were conducted. As outlined in Table 47, section 8.1 of this review, these trials varied in respect to the safety data collected and the safety follow-up periods. These differences limit data pooling, and were taken into consideration in a qualitative manner during the review. Where deemed necessary, individual case report forms were carefully reviewed, with additional clinical information requested for clarification. Literature review took place as outlined in section 5.5. Details of the review are provided in subsequent sections of this document.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

- STN 125428/0.0 sections 1.3.4, 1.6.3, 1.7.1, 1.9, 1.14.1, 1.16, 2.2, 2.3, 2.4, 2.5, 2.6, 2.7, 3.2,S.1, 3.2 P.1, 5.2, 5.3.3, 5.3.5, 5.4 (see also section 5.5 of this review)
- STN 125428/0.1 section 5.3.5
- STN 125428/0.7 section 1.2, 5.3.5
- STN 125429/0.9 section 1.14.1
- STN 125429/0.11 sections 1.2, 5.3.5
- STN 125429/0.12 section 1.2
- STN 125429/0.13 sections 1.2, 5.3.5
- STN 125429/0.14 section 1.2
- STN 125429/0.15 sections 1.2, 5.3.5
- STN 125429/0.17 sections 1.2, 5.3.5
- STN 125429/0.23 sections 1.2, 5.3.5

5.3 Table of Studies/Clinical Trials

The following studies in Table 1 comprised the immunogenicity and safety analysis:

Table 1: Summary of the Completed Studies of HEPLISAV using the ‘To-be-Marketed’ Formulation of HEPLISAV for the Immunogenicity and Safety Analysis

Phase of Study	Study Design	HEPLISAV Dose/Schedule/ ^a N	Active Comparator Dose/Schedule/ ^a N	Key Immunogenicity Endpoint(s)
Pivotal Studies				
HBV-10 NCT00435812	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy subjects 11-55 years of age conducted in Canada and Germany	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1809	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks N=606	Primary Endpoint: SPR at Week 12 for HEPLISAV and Week 28 for Engerix-B
HBV-16 NCT01005407	Phase 3, observer-blind, randomized, active-controlled, parallel group, multi-center study in healthy adult subjects 40-70 years of age conducted in Canada and Germany	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM (placebo at 24 weeks) N=1969	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks N=483	Primary Endpoint: SPR at Week 12 for HEPLISAV and Week 32 for Engerix-B Lot consistency of HEPLISAV measured by GMC at Week 8
Supportive Studies				
HBV0001	Phase 1 Observer-blind, randomized, dose-escalation study of the 1018 ISS Adjuvant component of vaccine in healthy, seronegative adults 18-55 years of age conducted in Canada.	1018 ISS Adjuvant: 300 mcg, ± 20 mcg HBsAg 650 mcg, ± 20 mcg HBsAg 1000 mcg, ± 20 mcg HBsAg 3000 mcg, ± 20 mcg HBsAg Schedule: 0, 8 weeks IM N=32	HBsAg: 20 mcg N=8 1018 ISS Adjuvant Alone: 300, 650, 1000, 3000 mcg N=8	Anti-HBsAg GMC measured after vaccination
HBV-02	Phase 2 Observer-blind, randomized, parallel group study of hypo- and non-responders to licensed hepatitis vaccine in adults 18-65 years of age conducted in Canada	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: Single injection IM N=30	Engerix-B: 20 mcg HBsAg Schedule: Single injection IM N=29	SPR at Week 4

Phase of Study	Study Design	HEPLISAV Dose/Schedule/ ^a N	Active Comparator Dose/Schedule/ ^a N	Key Immunogenicity Endpoint(s)
HBV-03	Phase 2 Observer-blind, randomized, parallel-group study in adults 18-28 years of age conducted in Canada.	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 8 weeks IM (placebo/meningococcal vaccine at 24 weeks) N=48	Engerix-B: 20 mcg HBsAg Schedule: 0, 8, 24 weeks IM N=51	SPR at Week 28

SPR: Seroprotective Rate: anti-HbsAg level \geq 10 mIU/mL; ^aN= Randomized number of subjects
Source: BLA STN 125428, Summary of Clinical Efficacy, Table 2.7.3-2, page 14 of 77

The following additional clinical studies were also included in the safety analysis (Table 2):

Table 2: Summary of Additional Completed Studies of HEPLISAV for the Safety Analysis

Phase of Study	Study Design	HEPLISAV Dose/Schedule/N	Active Comparator Dose/Schedule/N
HBV-14 NCT00511095	Phase 2, multicenter, open-label, single-arm study in healthy subjects 11-55 years of age conducted in the U.S.	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 4 weeks IM N=207	None
HBV-04	Phase 3, multicenter, double-blind, randomized, parallel group, active control study in healthy adult subjects 40-70 years of age conducted South Korea, Philippines, and Singapore.	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 8, 24 weeks IM (placebo at 4 weeks) N=207	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM (placebo at 8 weeks) N=213
HBV-05	Phase 2 multicenter, double-blind, randomized, parallel-group, active control study in healthy subjects 40-70 years of age conducted in Singapore.	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: 0, 8, 24 weeks IM (placebo at 4 weeks) N=48	Engerix-B: 20 mcg HBsAg Schedule: 0, 4, 24 weeks IM (placebo at 8 weeks) N=48
HBV-08	Phase 1 single-center, double-blind, randomized, parallel group study in healthy subjects 18-39 years of age conducted in Canada	HEPLISAV: 20 mcg HBsAg/3000 mcg 1018 ISS adjuvant Schedule: -0, 4 weeks (placebo at 8 weeks), N=18 -0, 8 weeks (placebo at 4 weeks), N=23 HEPLISAV: 10 mcg HBsAg/1500 mcg 1018 ISS adjuvant Schedule: -0, 4 weeks (placebo at 8 weeks), N=20	None

Source: BLA STN 125428, Section 5.2 Tabular Listing of All Clinical Studies, Table 5.2-1, pages 1-7

5.4 Consultations

5.4.1 Advisory Committee Meeting (if applicable)

The immunogenicity and safety data were presented to the VRBPAC on November 15, 2012. At the conclusion of this meeting, the committee raised concerns that the safety database was insufficient to recommend approval of HEPLISAV. Although VRBPAC members voted 13:1 that the data submitted in the BLA adequately demonstrated HEPLISAV immunogenicity, the Committee voted 8:5, with one abstention, that inadequate safety data were available to recommend approval of HEPLISAV. The VRBPAC also noted that the studies did not evaluate the vaccine in a representative population of subjects who were most likely to benefit from this vaccine (e.g. African-Americans and Asians), that the studies performed were not adequately balanced in terms of the racial and ethnic groups studied, and that concomitant administration studies were not done. Further details can be found at:

<http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm288695.htm>.

5.4.2 External Consults/Collaborations

Experts outside of CBER were consulted regarding the potential case of Tolosa-Hunt syndrome reported in study DV2-HBV-16. This event is discussed in detail in section 6.2.12.4. Reports of those consultations are pending at this time. The potential occurrence of a second granulomatous disease is of particular concern given that a case of Wegener's granulomatosis, believed to be vaccine-related, was reported in study DV2-HBV-10. These outstanding expert consultations are essential to the completion of the safety review of this product.

5.5 Literature Reviewed (if applicable)

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

A Phase 3 Safety and Efficacy Study to Compare Immune Responses following Injection with Either Two Doses of HEPLISAV or Three Doses of Engerix-B (Protocol DV2-HBV-10; NCT00435812)

6.1.1 Objectives (Primary, Secondary, etc)

The primary immunogenicity objective of this study was to compare the proportion of subjects who exhibit a seroprotective immune response (SPR, defined as: anti-HBsAg antibody levels greater than or equal to 10 mIU/mL) when measured at Week 12 following vaccination with HEPLISAV at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 28 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with HEPLISAV when administered to adolescent and adult subjects.

6.1.2 Design Overview

This phase 3 study was a subject- and observer-blind, randomized, controlled study of approximately 2400 subjects, 11-55 years of age (ages 18-55 in Germany) conducted at 21 sites in Canada and Germany. Subjects were randomized 3:1 to receive vaccination with either HEPLISAV (3000 mcg 1018 ISS adjuvant plus 20 mcg recombinant HBsAg) or 20 mcg Engerix-B vaccine. Subjects were stratified by age (11 to 39 years of age versus 40 to 55 years of age) prior to randomization. Subjects randomized to Engerix-B received three injections of Engerix-B, at Weeks 0, 4 and 24. Subjects randomized to HEPLISAV received HEPLISAV vaccinations at Weeks 0 and 4 and saline placebo at Week 24. Thus, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4 (1 month), and Week 24 (6 month). The duration of the study was 28 weeks.

Because of the different volume and appearance of study vaccines administered, the pharmacist or nurse that prepared the injection, as well as the physician or nurse who administered the injection, may have been aware of the vaccine assignment of each subject. In an effort to decrease bias in evaluating reactions to the vaccines, the investigator and study staff working with the subjects and the subjects themselves were to remain unaware of the treatment assignment, hence the observer-blind approach in this Phase 3 study.

Reviewer Comment: Given the caveats of a difference in the volume delivered per vaccination and solution appearance between the HEPLISAV and Engerix-B vaccines, an observer-blinded study was appropriate.

6.1.3 Population

The study population comprised HBV seronegative male and female subjects who met the following inclusion and exclusion criteria:

Inclusion Criteria:

- At least 11-55 years of age (at least 18 and up to 55 years of age for Germany).
- Serum negative for HBsAg, anti-HBsAg antibody and anti-HBcAg antibody.
- Childbearing age females: appropriate practice of birth control for the duration of the study.

Exclusion Criteria:

- Any history of HBV infection.
- Prior immunization with any HBV vaccine (one or more doses).
- History of or laboratory evidence of diseases of autoimmune origin.
- At high risk for recent exposure to HBV, HCV or HIV, e.g. current intravenous (IV) drug use, unprotected sex with known HBV, HCV or HIV positive partner.
- Receipt of blood products or immunoglobulin within 3 months prior to study entry, or likely to require infusion of blood products during the study period.
- Receipt of a DNA plasmid or oligonucleotide injection.
- Use of G/GM-CSF within 4 weeks prior to study entry.
- Use of systemic corticosteroids (more than three consecutive days), other immunomodulators or immunosuppressive medications 4 weeks prior to study entry, with the exception of inhaled steroids (check on this in final clinical report).
- Receipt of any vaccines 4 weeks prior to study entry or plans for elective vaccination that will occur during the one week before or 2 weeks after each study injection.
- History of sensitivity to any component of the study vaccines (1018 ISS synthetic cytosine phosphoguanine oligodeoxynucleotide adjuvant, rHBsAg, Alum).
- Receipt of any other investigational medicinal agent in the 4 weeks prior to the study.
- Clinically debilitating acute or chronic disease (including fever greater than or equal to 38° C within 72 hours prior to study injection) and current substance or alcohol abuse.
- Female subjects who are pregnant or nursing.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to the HEPLISAV group received a total of two injections of HEPLISAV, (3000 mcg of 1018 ISS-HBsAg plus 20 mcg of rHBsAg), manufactured by Rentschler BioTechnologie GmbH, Laupheim, Germany. The rHBsAg component of HEPLISAV was derived from yeast cells transformed with an expression vector containing HBsAg (b) (4), subtype *adw*. The 1018 ISS adjuvant is a 22-mer cytosine phosphoguanine (CpG) enriched oligonucleotide with the sequence: 5' TGA CTG TGA ACG TTC GAG ATG A 3' and which is a toll-like receptor 9 agonist and immunostimulant. Injections were administered at Week 0 and 4. Each injection was given intramuscularly (IM) into the deltoid muscle of either arm using a 1 to 1.5 inch, 25-gauge needle. The arm used for injection was alternated with each injection. Total injection volume was 0.5 mL to deliver 3000 mcg of 1018 ISS and 20 mcg of HBsAg. For the third injection at Week 24, HEPLISAV group subjects received placebo (0.9% sterile saline for injection), administered in 0.5 mL in the same manner as the 1018 ISS-HBsAg. The only lot number used in this study was TDG003.

Engerix-B (20 mcg HBsAg combined with 50 mcg alum adjuvant, GlaxoSmithKline Biologicals) was used as the active comparator in this study and dosed according to the manufacturer's instructions. Subjects in the Engerix-B group received three injections, given as a 1.0 mL injection using a 25-gauge needle, at Week 0, 4, and 24. The lot numbers used for this study were: AHBVB247AE, AHBVB294AA, AHBVB247AF,

AHBVB306AB, AHBVB357DH, AHBVB306AC, AHBVB306AD, AHBVB247AG, AHBVB277AI, AHBVB233BA, AHBVB356AE, and AHBVB305AB.

6.1.6 Sites and Centers

This phase 3 study was conducted at 14 sites in Canada and 7 sites in Germany. The principal investigator was Scott Halperin, M.D., at Dalhousie University, Nova Scotia, Canada.

6.1.7 Surveillance/Monitoring

Following their first injection of vaccine (either HEPLISAV or Engerix-B), subjects were observed for 30 minutes for AEs. Local and systemic reactogenicity were evaluated at this time point and subjects were given a diary card on which to record the following reactogenicity symptoms for the following 7 days: redness, pain, and swelling at or near the injection site, malaise, headache, and fatigue. Study staff measured and recorded the redness and swelling at the injection site of the 30 minute post-injection assessment. All other symptoms were rated according to a 0 = none, 1 = mild (no interference with activity), 2 = moderate (some interference with activity), and 3 = severe (significant, prevents daily activity) scale. A summary table of study assessments is provided in Table 3 below:

Table 3: Study Schedule

Visit	1 (Screen)	2	TC ^a	3	TC ^a	4	5	6	TC ^a	7
Day	-28 to -3	0	3	28	31	56	84	168	171	196 Term
Week				4		8	12	24		
Visit Window from day ^b	-28 to -3	0	+3	-2 to+4	+3	± 7	± 7	± 7	+3	± 7
Study Injection		X		X				X		
Local and Systemic Reactogenicity ^c		X		X				X		
Informed Consent	X									
Medical History (+ medications)	X									
Physical Exam	X									
Vital signs	X	X		X		X	X	X		X
Interim history (+ medications)		X		X		X	X	X		
Serum pregnancy test	X									
Urine pregnancy test		X		X				X		
Anti-HBSAg ^d	X			X		X	X	X		
Hepatitis Screen ^e	X									X
ANA, anti-ds DNA	X									X
Diary review ^f		X		X		X	X	X		X
Concomitant medications ^g		X				X	X	X		X
SAEs ^h		X	X	X	X	X	X	X	X	X
AEs ^h		X		X		X	X	X		X

AEs = adverse events, ANA = antinuclear ant body; anti-ds DNA = ant body to double-stranded deoxyribonucleic acid, Anti-HBsAg = ant body to hepatitis B surface antigen; SAEs = serious adverse events; TC = telephone contact; term = termination visit.

^a Telephone contacts to remind subjects to maintain their diaries.

^b There was a minimum of 21 days between any study injection and subsequent anti-HBsAg sample collection.

^c Evaluated during a 30 minute observation period post-injection.

^d Blood was taken prior to injection, and the serum from HBsAg samples was aliquoted and then frozen at -20°C or below.

^e Hepatitis screen included hepatitis B surface antigen, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen.

^f A diary card was issued at each visit to record solicited local and systemic reactions for Days 0-6 following each injection, adverse events, and changes to concomitant medication usage.

^g Concomitant medications were all medications taken by the subject from the first injection (Visit 2) through approximately 28 days after the last injection (Visit 7).

^h All AEs and SAEs were reported from immediately after the first injection through study termination.

Source: BLA 125428, DV2-HBV-10, Clinical Study Report, Table 9-2, Page 29 of 204

At Study Week 0, and subsequently at Weeks 4, 8, 12, 24, and 28 subjects returned to the study site to have blood drawn for quantitative measurement of anti-HBsAg concentrations and for evaluation of safety and tolerability. The immune response (anti-HBsAg) was measured using the (b) (4). The accepted criterion for immunity to HBV is anti-HBsAg greater than or equal to 10 mIU/mL (13,14).

6.1.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoint was the SPR after the final active injection. The SPR was defined as the proportion of subjects who exhibit a seroprotective immune response, defined as an anti-hepatitis B surface antigen antibody level greater than or equal to 10 mIU/mL. The primary SPR for HEPLISAV was measured at Week 12, and the primary SPR for Engerix-B was measured at Week 28.

The secondary immunogenicity endpoint was the SPR at Week 4, which was measured 4 weeks after the first injection (onset of response) for both treatment groups.

An exploratory analysis evaluated the SPR for HEPLISAV vs. Engerix-B at all other serology time points (Weeks 8, 12, 24, and 28).

6.1.9 Statistical Considerations & Statistical Analysis Plan

For a full assessment of the Statistical Analysis Plan (SAP), please see the statistical review by Dr. Mridul Chowdhury.

The statistical analysis was based on the Statistical Analysis Plan (SAP) dated June 17, 2008. The study was powered to demonstrate non-inferiority of HEPLISAV compared to Engerix-B with respect to the SPR rate with a non-inferiority margin of 10%. This comparison of the two groups was to be based on HEPLISAV data obtained at Week 12 and Engerix-B data obtained at Week 28. The calculation assumed a 3:1 (HEPLISAV vs. Engerix-B) randomization ratio and an SPR of greater than 90% for Engerix-B. The treatment group ratio (3:1) was stratified by age, 11 to 39 years and 40 to 55 years. The sample size required to achieve at least 90% power with $\alpha = 0.025$ (one-sided test) was 1176 for the HEPLISAV group and 392 for the Engerix-B group, for a total of 1568 subjects. The study met these criteria by enrolling 2400 subjects in the trial, including 1800 in the HEPLISAV group and 600 in the Engerix-B group.

The primary immunogenicity analysis determined the difference in SPR between Engerix-B at Week 28 and HEPLISAV at Week 12 with a 2-sided 95% confidence interval (CI) with significance level of 0.05 on the difference (Engerix-B minus HEPLISAV) in SPR. This was the equivalent of testing the null hypothesis using a one-sided type 1 error rate of 0.025. If the upper limit of the CI was below the pre-specified

non-inferiority criterion of +10%, HEPLISAV would be determined to be non-inferior to Engerix-B. Since there was only one primary immunogenicity endpoint, multiplicity was not an issue in this study.

The secondary immunogenicity analysis tested the SPR for non-inferiority between HEPLISAV and Engerix-B at Week 4.

An exploratory analysis tested SPR for non-inferiority between HEPLISAV and Engerix-B at all other serology time points (Weeks 8, 12, 24, and 28) and described the serum geometric mean titers (GMTs) observed for HEPLISAV and Engerix-B when calculated at Weeks 4, 8, 12, 24, and 28. Several additional exploratory analyses were performed in the study and comprised: a test of the SPR for non-inferiority between HEPLISAV at Week 8 and Engerix-B at Week 28, and a descriptive summary of geometric mean titer (GMT) for both treatment groups at each study time point.

Secondary and exploratory endpoints were summarized by time (Weeks 4, 8, 12, 24, and 28).

All data analyses were performed using Statistical Analysis Systems (SAS®) for Windows 95/NT (SAS Institute, Cary, North Carolina). There were no significant changes in the planned statistical analyses.

A summary table of immunogenicity testing and description of primary, secondary, and exploratory endpoints is presented in Table 4.

Table 4: Immunogenicity Testing

Hypothesis	HEPLISAV Time points	Engerix-B Time points	Study Parameter	Test
Primary	12	28	SPR	Non-inferiority
Secondary	4	4	SPR	Non-inferiority
Exploratory	8, 12, 24, 28	8, 12, 24, 28	SPR	Non-inferiority
Exploratory	8	28	SPR	Non-inferiority
Exploratory	4, 8, 12, 24, 28	4, 8, 12, 24, 28	GMT	Descriptive

Source: BLA 125428, DV2-HBV-10, Statistical Analysis Plan, Table 1, Page 12 of 30

6.1.10 Study Population and Disposition

This phase 3 study was originally designed to evaluate safety and immunogenicity in subjects aged 11 to 55 years. Because only 13 of the 2428 subjects (0.5%) enrolled in the study were younger than 18 years, the results of this study focused on adult subjects only (18 through 55 years).

A total of 2910 subjects were screened for this study and 2428 enrolled. Thirteen subjects were adolescents (< 18 years) and included 11 subjects randomly assigned to the HEPLISAV group and 2 subjects assigned to Engerix-B. The remaining 2415 subjects were adults, including 1809 subjects assigned to HEPLISAV and 606 subjects assigned to Engerix-B.

Safety and tolerability was evaluated on the basis of the following parameters: solicited post-injection local and systemic adverse events (AEs), unsolicited AEs, serious adverse events (SAEs), clinical laboratory results, including anti-nuclear antibody (ANA) and anti-double stranded DNA (anti-ds DNA), vital signs (blood pressure, heart rate, respiratory rate and oral temperature), and concomitant medications or vaccines. Descriptive statistical analyses (count and percentage) were provided for all clinical parameters. ANA and anti-ds DNA were measured at baseline and at Week 28. Clinical laboratory results were evaluated using descriptive statistical analyses.

6.1.10.1 Populations Enrolled/Analyzed

Two populations were considered for the immunogenicity analysis in Study DV2-HBV-10:

1. The Per-Protocol Population: defined as subjects who met the eligibility criteria, did not violate the protocol in a substantial manner, received all protocol-specified study injections, had anti-HBsAg measurements and all injections within the specified day ranges, and had an anti-HBsAg measurement at their primary endpoint.
2. The modified intent-to-treat (ITT) Population: defined as subjects who received at least one study injection and had at least one post-baseline anti-HBsAg level.

The immunogenicity analysis using the per-protocol population was considered primary. The baseline value was defined as the last non-missing measurement prior to the first vaccination. In computing the SPR rates for the mITT population, a subject who had missing anti-HBsAg titers at a given time point was considered as having a missing SPR and was excluded at that time point. There was no imputation of missing anti-HBsAg data at any visit. If a subject had a missing anti-HBsAg result at a primary endpoint, that subject was excluded from the per protocol population. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL, as per the SAP.

Reviewer Comment: The clinical reviewer agrees with the applicant's approach to handling of missing data for the purpose of immunogenicity evaluation.

Safety was evaluated using the safety population, defined as enrolled subjects who received at least one study injection and had any post-baseline safety data. Subjects were included in the treatment group corresponding to the study treatment they actually received for the analysis of safety data. All 2415 enrolled subjects were included in the safety analysis population (n=1809 in HEPLISAV and n=609 in the Engerix-B groups).

6.1.10.1.1 Demographics

Subject demographics are summarized in Table 5:

Table 5: Summary of Demographic and Baseline Characteristics: Safety Analysis Population: Adults Only (Subjects 18 – 55years of age)

Characteristic	HEPLISAV (n=1809)	Engerix-B (n=606)	Total (n=2415)
Age, years, n (%)			
18-39	818 (45.2%)	275 (45.4%)	1093 (45.3%)
40-55	991 (54.8%)	331 (54.6%)	1322 (54.7%)
N	1809	606	2415
Mean (SD)	39.9 (9.4%)	39.8 (9.0%)	39.9 (9.3%)
Range	18-55	18-55	18-55
Gender, n (%)			
Male	852 (47.1%)	262 (43.2%)	1114 (46.1%)
Female	957 (52.9%)	344 (56.8%)	1301 (53.9%)
Race, n (%)			
White	1690 (93.4%)	556 (91.7%)	2246 (93.0%)
Black or African American	39 (2.2%)	20 (3.3%)	59 (2.4%)
Asian	43 (2.4%)	22 (3.6%)	65 (2.7%)
American Indian or Alaska Native	16 (0.9%)	3 (0.5%)	19 (0.8%)
Native Hawaiian or Other Pacific Islander	1 (0.1%)	0	1 (0.0%)
Other	20 (1.1%)	5 (0.8%)	25 (1.0%)
Ethnicity, n (%)			
Hispanic or Latino	46 (2.5%)	24 (4.0%)	70 (2.9%)
Non-Hispanic or Non-Latino	1763 (97.5%)	582 (96.0%)	2345 (97.1%)
Baseline Serostatus, n (%)			
Negative	1797 (99.3%)	605 (99.8%)	
Positive	6 (0.3%)	0	
Unknown	3 (0.2%)	1 (0.2%)	nc

n= number of subjects reporting the specific characteristic, nc= not calculated, nd = not done, SD = standard deviation
Seronegative to hepatitis B corresponds to antibody level < 5 mIU/mL.
Seropositive to hepatitis B corresponds to antibody level ≥ 5 mIU/mL.
Source: BLA 125428, DV2-HBV-10, Clinical Study Report, Table 10-4, Pages 56-57 of 204

Demographic and baseline characteristics were similar between the two treatment groups. Within each group, almost all subjects were white or non-Hispanic/Latino, the mean age was approximately 40 years, and the percentage of females was slightly higher than that of males. The breakdown by age stratum was similar between the two treatment groups, with slightly more subjects in the 40 through 55 year subgroup (991 and 331 subjects, respectively for HEPLISAV vs. Engerix-B) than the 18 through 39 year subgroup (818 and 275, respectively, HEPLISAV vs. Engerix-B). More than 99% of subjects in each treatment group had an anti-HBsAg level below 5 mIU/mL at baseline. Subjects were also categorized by weight, height, body mass index, and smoking status as exploratory variables. No significant differences between the two treatment groups were seen for these characteristics. The majority of enrolled study subjects (63-64% for both treatment groups) were non-smokers, non-diabetic (97%), and non-obese (defined as a BMI ≥ 30 kg/m² for both treatment groups; 72-75% non-obese by this definition).

Reviewer Comment: *With the exception of ethnicity and race (where the majority of subjects were Caucasian), the study was well-balanced in terms of age strata and gender. The two treatment groups were comparably similar in terms of demographic*

characteristics. Greater than 99% of subjects enrolled in the study were seronegative for hepatitis B.

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

No significant difference in prevalent medical conditions was noted between the two treatment groups that would impact evaluation of efficacy or safety in this study. The percentage of subjects reporting any medical or surgical history was similar between HEPLISAV and Engerix-B vaccinated subjects. The most frequently reported medical conditions comprised headache (15.5% (HEPLISAV) vs. 14.2% (Engerix-B)) and back pain ((11.7% (HEPLISAV) vs. 12.4% (Engerix-B)). Likewise, similar percentages of medication use prior to study initiation were reported by both treatment groups (10.4% HEPLISAV) vs. 12.9% (Engerix-B)). The types of medications used by both groups were also similar, with ibuprofen (2.9% vs. 2.1%) and paracetamol (1.1% vs. 1.5%) being most commonly used prior to study initiation. Eight subjects in the HEPLISAV group and one subject in the Engerix-B group reported receiving prior vaccinations, administered more than 4 weeks prior to the first study injection. This likely did not impact immunogenicity or safety as these were administered within the allowed time frame prior to study initiation. Similar percentages of subjects in both treatment groups reported using concomitant medications during the study (78.3% vs. 77.2%). A small percentage of subjects in both groups received concomitant vaccinations during the study (n=143 for HEPLISAV (7.9%) vs. n = 46 for Engerix-B (7.6%)), with the most frequently reported class of concomitant vaccination being influenza vaccine (n= 96 for HEPLISAV (5.3%) vs. n = 31 for Engerix-B (5.1%)).

Reviewer Comment: No significant issues were identified in terms of medication use prior to or during study enrollment for Study DV2-HBV-10 that would impact interpretation of immunogenicity findings.

6.1.10.1.3 Subject Disposition

A total of 2910 subjects were screened for this study, including 482 subjects who were subsequently deemed “screen failures.” Frequent reasons for exclusions as a result of screening included antibody positivity to hepatitis B and withdrawal of consent or being lost to follow-up. The remaining 2428 subjects were enrolled at 21 study sites.

Thirteen subjects were adolescents (< 18 years) and included 11 subjects randomly assigned to the HEPLISAV group and 2 subjects assigned to Engerix-B. The remaining 2415 subjects were ≥18 years old, including 1809 subjects assigned to HEPLISAV and 606 subjects assigned to Engerix-B. Approximately 97% of all adult subjects completed the study. The most common reason for subject discontinuation was ‘lost to follow-up’, reported by 1.7% of subjects in each group. Additional reported reasons for discontinuation were AEs, subject noncompliance, and subject withdrawal of consent. Subject compliance in the study was defined as subject receipt of intended vaccinations following the protocol-specified schedule. Administration was documented in the CRF by study site personnel and a table displayed the count and percentage of subjects receiving each vaccination and all vaccinations by treatment group.

Reviewer Comment: Subject compliance for Study DV2-HBV-10 was reasonable, with approximately 97% of subjects in both groups completing the study.

Documented reasons why subjects withdrew consent were related to family, work, relocation or development of an SAE (e.g. breast cancer, vasculitis, pregnancy). Two subjects in the HEPLISAV group and no subjects in the Engerix-B group discontinued due to protocol violations. In the HEPLISAV group, subjects 13091 and 13159 were discontinued from the study after receiving the first injection because they had anti-HBsAg levels greater than 5.0 mIU/mL at screening.

A summary of subject disposition is provided in Table 6:

Table 6: Subject Disposition: Adults (18-55 years of age)

Disposition	HEPLISAV (n, %)	Engerix- B (n, %)	Total (n, %)
Enrolled ^a	1809	606	2415
Completed	1746 (96.5%)	588 (97.0%)	2334 (96.6%)
Discontinued			
Adverse Event	2 (0.1%)	2 (0.3%)	4 (0.2%)
Subject noncompliance	3 (0.2%)	2 (0.3%)	5 (0.2%)
Subject withdrew consent	18 (1.0%)	2 (0.3%)	20 (0.8%) ^b
Subject lost to follow-up	30 (1.7%)	10 (1.7%)	40 (1.7%)
Death	0	0	0
Protocol violation	2 (0.1%) ^c	0	2 (0.1%)
Other	8 (0.4%) ^d	2 (0.3%) ^e	10 (0.4%)
Per-protocol analysis population	1557 (86.1%) ^f	533 (88.0%)	2090 (86.5%)
Intent-to-treat analysis population	1789 (98.9%)	603 (99.5%)	2392 (99.0%)
Safety analysis population	1809 (100.0%)	606 (100.0%)	2415 (100.0%)

^a Enrolled refers to screened subjects received the first study injection.

^b Reasons subjects withdrew consent, when given, were related to work, family, relocation, and adverse events of ongoing/recurrent breast cancer and scleroderma.

^c Subjects 13091 and 13159 had anti-HBsAg > 5.0 mIU/mL at screening and were discontinued after receiving the first injection.

^d Subjects 06337, 08027, 08075, 11171, 12084, 12115 (pregnancy), Subject 06313 (withdrawn by applicant because subject would be out of country too long, and Subject 13112 (pre-existing seizure disorder).

^e Subject 06049 (withdrawn by PI because subject didn't disclose information about an SAE (delirium tremens) that occurred on-study and medical history (alcoholism) and Subject 12155 (pregnancy).

^f 1556 subjects were used in the primary immunogenicity analysis of subjects aged 18 through 55 years; following database lock, 1 additional subject (Subject 14042) was determined to be aged 18 years or older at the time of enrollment.

Source: BLA STN 125428, HBV-DV2-10, Clinical Study Report, Section 10.1 Disposition of Subjects, page 47 of 204

Overall, 2090 subjects were included in the 'per protocol' analysis population; 1557 subjects in the HEPLISAV group and 533 subjects in the Engerix-B group. The percentage of subjects excluded from this population was similar between the two groups (13.9% vs. 12.0%, respectively). The most common reason why subjects were discontinued from the per protocol population were: having primary serology samples outside the visit windows (n=168 (9.3%) HEPLISAV vs. n= 48 (7.9%) Engerix-B), having received study injection outside the visit windows (n=126 (7%) HEPLISAV vs. n= 36 (5.9%) Engerix-B), having had missing anti-HBsAg at Week 12 or 28 (n=79 (4.4%) HEPLISAV vs. n= 19 (3.1%) Engerix-B), and not receiving all three study

injections (n= 54 (3.0%) HEPLISAV group, vs. n= 16 (2.6%) Engerix-B group). Eleven subjects in the HEPLISAV group and six subjects in the Engerix-B group were excluded from the per protocol analysis due to a history of, or lab evidence of disease of autoimmune origin.

The ITT analysis population comprised subjects who had at least one injection following the baseline anti-HBsAg level and at least one post-baseline anti-HBsAg level. The ITT population comprised 2392 subjects total, including 1789 subjects in the HEPLISAV arm and 603 subjects in the Engerix-B arm. The percentage of subjects excluded from the ITT was similar between treatment groups (1.1% vs. 0.5%, respectively).

For the Safety population (at least 1 study injection and any post-baseline safety data), 2415 subjects were included, comprised of 1809 subjects in the HEPLISAV arm and 606 subjects in the Engerix-B arm.

A complete listing of all reasons for exclusion from the analysis populations (per protocol, ITT, safety) was presented by the applicant in Table 10-2 of the final clinical study report for BLA STN 14892/0000 (data not presented here).

Reviewer Comment: While rare, premature unblinding was noted during review of DV2-HBV-10. Three subjects, two in the HEPLISAV group and one in the Engerix-B group, had treatment assignments prematurely unblinded. The first subject (No. 11168; HEPLISAV group) was a 36 year old woman who developed Guillain-Barre Syndrome five days after receiving influenza vaccine and 110 days after receiving the second study injection of HEPLISAV. The subject was admitted to the hospital due to Guillain-Barre Syndrome. Though the investigator assessed the development of Guillain-Barre Syndrome as not related to study treatment, the subject was discontinued from the study. The second subject (No. 24057, HEPLISAV group) was a 55 year old woman who developed a pericardial effusion and glomerulonephritis while hospitalized for treatment of relapsed sinusitis. Subsequent evaluation, including c-ANCA testing showed that the subject had Wegener's granulomatosis. This SAE was deemed possibly related to study treatment and the subject's treatment assignment was unblinded. The third subject (No. 06083, Engerix-B group) was a 45 year old woman who developed a pneumonia-like illness that was subsequently classified as a p-ANCA-associated vasculitis following laboratory diagnosis. This SAE was deemed not related to study treatment but the subject's treatment assignment was unblinded.

Due to the small number of subjects (3) that were prematurely unblinded, it is not likely that this impacted the final immunogenicity result findings given the number of subjects who were blinded and did complete the study (n=2090).

6.1.11 Efficacy Analyses

6.1.11.1 Analyses of Primary Endpoint(s)

The primary immunogenicity endpoint for Study DV2-HBV-10 was defined as the SPR at Week 12 following two injections of HEPLISAV compared with the SPR at Week 28 following three injections of Engerix-B, using the per protocol population for adult

subjects 18-55 years of age,. The SPR was 95.0% in the HEPLISAV group at Week 12 and 81.1% in the Engerix-B group at Week 28. The estimated difference between the Engerix-B and HEPLISAV groups and associated 95% CI was -13.9% (CI: -17.6, -10.6). Because the upper limit of the CI was -10.61%, which was below the pre-specified non-inferiority criterion of +10%, the immune response at this respective time point for HEPLISAV (Week 12) was non-inferior to that of Engerix-B at Week 28. These data are presented in tabular form in Table 7. Evaluation of the primary immunogenicity endpoint for the HEPLISAV group by study site indicated no significant differences in the SPR at week 12 for HEPLISAV between the different study sites (see reviewer comment below).

Table 7: Primary Immunogenicity Endpoint Analysis (Study DV2-HBV-10): SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 28): Per-Protocol Analysis Population, Adults 18-55 years of age

Visit	HEPLISAV ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (Engerix-B – HEPLISAV (95%) CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 12/ Week 28	95.0 % (1479/1556)	81.1 % (432/533)	-13.9 (-17.6, -10.6)	Yes

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 levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.

^d Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).

Source: BLA STN 125428, Clinical Study Report, HBV-DV2-10, Section 11.1.1, Table 11-1, page 63 of 204

Reviewer Comment: The SPR for HEPLISAV was found to be statistically non-inferior to the active comparator. Accordingly, the pre-specified primary immunogenicity endpoint for HEPLISAV in this study was achieved. The similarity of the SPR for HEPLISAV across study sites supports the consistency of the immunogenicity findings for HEPLISAV throughout Study DV2-HBV-10. An immunogenicity analysis of the primary immunogenicity endpoint was also performed for the ITT population and was found to be consistent with that of the per protocol population (data not shown).

6.1.11.2 Analyses of Secondary Endpoints

One secondary immunogenicity endpoint was pre-defined for Study DV2-HBV-10—the SPR at Week 4, for both the HEPLISAV and Engerix-B ‘per protocol’ adult population (age 18-55 years). The SPRs at this time point were 23.6% for HEPLISAV and 4.0% for Engerix-B, respectively. The estimated difference between the Engerix-B and HEPLISAV groups and associated 95% CI was -19.7% (CI: -22.4, -16.8). Because the upper limit of the CI was -10.6%, which was below the pre-specified non-inferiority criterion of +10%, the immune response at the Week 4 time point for HEPLISAV was found to be non-inferior to that of Engerix-B. Results of the secondary endpoint analysis are presented in Table 8:

Table 8: Secondary Immunogenicity Endpoint Analysis (Study DV2-HBV-10): SPR at Week 4 for HEPLISAV compared with Engerix-B: Per-Protocol Analysis Population, Adults 18-55 years of age

Visit	HEPLISAV ^a SPR (%) n, N	Engerix-B ^b SPR (%) n, N	Estimated Difference in SPR ^c (Engerix-B – HEPLISAV (95%) CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 4	23.6 % 366, 1547	4.0 % 21, 531	-19.7 (-22.4, -16.8)	Yes

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 levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.

^d Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).

Source: BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-2, page 64 of 204

Reviewer Comment: Similar to results of the primary immunogenicity endpoint, the SPR for HEPLISAV was found to be non-inferior to that of the active comparator, Engerix-B, for the secondary immunogenicity endpoint, the SPR at 4 weeks.

6.1.11.3 Subpopulation Analyses

Subpopulation analyses of the SPRs for the per protocol population was evaluated for the primary immunogenicity time point (Week 12 for HEPLISAV and Week 28 for Engerix-B) and at each respective time point (Week 4, 8, 12, 24, 28) for subjects aged 18-39 years and 40-55 years. These data are presented in Table 9:

Table 9: SPR by Visit and Age Strata (Study DV2-HBV-10): Per-Protocol Analysis Population (Adults 18-55 years of Age)

Visit Age Stratum	HEPLISAV ^a		Engerix-B ^b	
	SPR (95% CI)	n/N	SPR (95% CI)	n/N
Week 12 ^c /Week28 ^d				
18-39 years	98.7 (97.8, 99.5)	667/676	89.4 (85.4, 93.4)	202/226
40-55 years	92.3 (90.5, 94.0)	813/881	74.9 (70.1, 79.8)	230/307
Week 4				
18-39 years	30.5 (27.0, 33.9)	204/670	5.8 (2.7, 8.9)	13/224
40-55 years	18.5 (15.9, 21.0)	162/878	2.6 (0.8, 4.4)	8/307
Week 8				
18-39 years	94.8 (93.1, 96.5)	639/674	33.0 (26.9, 39.2)	74/224
40-55 years	83.7 (81.2, 86.1)	733/874	21.5 (16.9, 26.1)	66/307
Week 12				
18-39 years	98.7 (97.8, 99.5)	667/676	30.1 (24.1, 36.1)	68/226
40-55 years	92.3 (90.5, 94.0)	813/881	16.9 (12.7, 21.1)	52/307
Week 24				
18-39 years	99.6 (99.1, 100.0)	671/674	39.7 (33.3, 46.1)	89/224
40-55 years	97.3 (96.2, 98.3)	851/875	27.0 (22.1, 32.0)	83/307

	HEPLISAV ^a		Engerix-B ^b	
Week 28				
18-39 years	99.3 (98.6, 99.9)	671/676	89.4 (85.4, 93.4)	202/226
40-55 years	96.9 (95.8, 98.1)	854/881	74.9 (70.1, 79.8)	230/307
Week 8 ^c /Week28 ^d				
18-39 years	94.8 (93.1, 96.5)	639/674	89.4 (85.4, 93.4)	202/226
40-55 years	83.7 (81.2, 86.1)	733/874	74.9 (70.1, 79.8)	230/307

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 levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c HEPLISAV treatment group

^d Engerix-B treatment group

Source: BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-6, page 71 of 204

SPRs were consistently found to be higher in younger aged individuals for both the HEPLISAV and Engerix-B treatment groups and were somewhat more pronounced during earlier time points in the study (Week 4, 8) than later time points, where a greater percentage of all subjects (young and older) had seroconverted. By Week 28 of the study, GMCs for both age groups, 18-39 years and 40-55 years, were comparable for the HEPLISAV treatment arm. In contrast, for the Engerix-B treatment arm, younger individuals continued to have slightly higher GMCs than the older group at Week 28.

Reviewer Comment: While generally faster and higher immune responses are well documented across vaccines for younger individuals, the finding that this effect leveled out over time for HEPLISAV was not expected, given that the pattern of a more robust immune responses associated with younger age is one that tends not to improve with the duration of the immunization series. Based on Study DV2-HBV-10, older individuals (40-55 years) vaccinated with HEPLISAV were eventually (i.e. by Week 24) able to mount a seroprotective response that was almost as good as that of younger individuals (18-39 years).

Study DV2-HBV-10 did not present subgroup data for gender, ethnicity or race for the HEPLISAV and Engerix-B groups, although both study groups predominantly comprised Caucasian subjects. The applicant presented subgroup analysis data for these demographic groups as part of a combined analysis for this study and DV2-HBV-16 under the 'Integrated Summary of Efficacy' (ISE).

6.1.11.4 Dropouts and/or Discontinuations

Immunogenicity analysis was performed using the per-protocol population and was considered the primary analysis. In computing the SPR rates for the mITT population, a subject who had missing anti-HBsAg titers at a given time point was considered as having a missing SPR and was excluded at that time point. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL. There was no imputation of missing anti-HBsAg data at any visit.

A total of 97% of subjects completed the study for both treatment arms (HEPLISAV and Engerix-B). A very low rate of subject discontinuation was reported. As previously discussed, the most common reasons subjects were discontinued from the study were as follows: having primary serology samples outside the visit windows; having received

study injection outside the visit windows; having had missing anti-HBs Ag at Week 12 or 28; and not receiving all three study injections. Subject compliance was documented to be very high across both groups for the duration of the study.

Reviewer Comment: Criteria for discontinuation for subjects and for inclusion in the per protocol population were appropriate and were handled appropriately by the applicant. The high completion rate in the study adds credibility to the immunogenicity data and non-inferiority analyses in the final study report.

6.1.11.5 Exploratory and Post Hoc Analyses

Study DV2-HBV-10 evaluated a number of exploratory endpoints, which comprised the SPR at Weeks 8, 12, 24, and 28 and the GMC at Weeks 4, 8, 12, 24, and 28 for both treatment groups. An additional exploratory endpoint evaluated was the SPR at 4 weeks after the final active injection (Week 8 for HEPLISAV and Week 28 for Engerix-B). A summary table of the exploratory endpoints with their respective assessment of non-inferiority and superiority is provided in Table 10:

Table 10: Exploratory Endpoints (Study DV2-HBV-10): Non-Inferiority Comparison of the SPR at Weeks 8, 12, 24, and 28 for HEPLISAV and Engerix-B: Per-Protocol Analysis Population, Adults 18-55 years of age

Visit	HEPLISAV ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (Engerix-B – HEPLISAV (95% CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 8	88.5 % (1372/1549)	26.5 % (140/531)	-62.1 (-66.0, -57.9)	Yes
Week 12	95.0% (1479/1556)	22.6% (120/533)	-72.5 (-76.0, -68.6)	Yes
Week 24	98.3% (1521/1548)	32.5% (172/531)	-65.8 (-69.7, -61.60)	Yes
Week 28	97.9% (1524/1556)	81.1% (432/533)	-16.8 (-20.4, -13.6)	Yes
Week 8 ^e / Week 28 ^f	88.6% (1372/1549)	81.1% (432/533)	-7.4 (-11.2, -3.9)	Yes

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 levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Estimated response (proportion), their difference, and associated confidence intervals are based on a statistical analysis model adjusting for age groups (18-39 years vs. 40-55 years). The Miettinen and Nurminen method was used to calculate the 95% confidence intervals.

^d Non-inferiority is supported if the upper bound of the 2-sided 95% CI is < 0.10 (+10%).

^e HEPLISAV treatment group

^f Engerix-B treatment group

Source: BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-3, page 66 of 204

Reviewer Comment: Based on data in this table, earlier on in the immunization series and even later in the immunization series (e.g. Weeks 8, 12, and 24), the HEPLISAV treatment group showed a greater increase in SPR over the Engerix-B treatment arm and statistical analysis showed that these were non-inferior. It is important to note however, that the full immunization series for Engerix-B was only completed by Week 24, hence the expected lower SPR for Engerix-B immunized subjects at the earlier time points in the study (e.g. Week 8, 12).

Evaluation of the SPR at 4 weeks after the final active injection (Week 8 for HEPLISAV and Week 28 for Engerix-B) also indicates that the SPR was non-inferior between HEPLISAV and Engerix-B and was greater for HEPLISAV at this early time point (Table 10).

Anti-HBs Ag GMCs are presented in Table 11. These data confirm that a more rapid increase in GMC against hepatitis B surface antigen is seen with the first dose of HEPLISAV administration, and a greater increase in GMC is seen during the early weeks of immunization, when compared with Engerix-B. At Week 28, the Engerix-B GMC levels were shown to be slightly higher (348.2 mIU/mL) than that of HEPLISAV (320.0 mIU/mL) but non-inferior statistically. The standard deviation in the Engerix-B group, however, was larger than that in the HEPLISAV group due to the larger percentages of non-responders (anti-HBs Ag < 10 mIU/mL) and hyper-responders (defined as anti-HBs Ag > 100,000 mIU/mL) among Engerix-B recipients. Accordingly, this finding may have been influenced by the greater effect of hyper-responders in the Engerix-B group on the mean GMC.

Table 11: Serum Anti-HBsAg Antibody Geometric Mean Concentration by Visit: Per-Protocol Analysis Population (Adults 18-55 Years of Age)

Visit	HEPLISAV (N=1557)*	Engerix-B (N=533)
	GMC (mIU/mL), 95%CI	GMC (mIU/mL), 95%CI
Week 4	5.5 (5.1, 5.9)	2.9 (2.8, 3.1)
Week 8	81.5 (75.1, 88.5)	6.4 (5.6, 7.4)
Week 12	136.9 (127.5, 146.8)	5.5 (4.6, 6.2)
Week 24	342.5 (320.2, 366.5)	7.2 (6.3, 8.2)
Week 28	320.0 (298.2, 343.3)	348.8 (265.9, 455.9)

* N= Number of subjects in the analysis population in the treatment group.
Non-missing anti-HBsAg results reported as < 5 mIU/mL were considered as 2.5 mIU/mL.
Source: BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-4, page 67 of 204

Reviewer Comment: Review of the GMCs and the SPR at the Week 4, 8, 12, 24, and 28 time points all confirmed a rapid and robust immune response in HEPLISAV treated subjects. High levels of seroprotection (88.5%) were seen at 1 month after the first dose of HEPLISAV and elevated levels of seroprotection were sustained beyond the

one month time point (SPRs elevated at the last time point—Week 28—evaluated in the study). Comparison with Engerix-B indicated that this seroprotective response was at least as good than that of the active comparator.

Immunogenicity Conclusion: *Based on the primary and secondary immunogenicity endpoint data presented in Study DV2-HBV-10, HEPLISAV was shown to generate a rapid and robust immune response against HBsAg. This immune response remained sustained for the 28 week period during which it was evaluated.*

6.1.12 Safety Analyses

6.1.12.1 Methods

The safety population consisted of all subjects who received at least one study injection and had any post-baseline safety data. Diary cards solicited information about the presence and severity of post-injection local (injection-site) reactions (redness, swelling, pain) and systemic reactions (fatigue, headache, malaise). Oral temperature was also recorded. Diary entries were completed by the subject on Days 0-6.

The intensity of solicited post-injection reactions and all other AEs were reported by the subject as grades 0 through 3 using the following definitions:

- Grade 0 = none
- Grade 1 = mild (no interference with activity)
- Grade 2 = moderate (some interference with activity)
- Grade 3 = severe (significant interference, prevents daily activity)

The intensity of redness at the injection site and swelling at the injection site were defined using the following quantitative ranges:

- None:* diameter less than 2.5 cm
- Mild:* diameter 2.5 to 5.0 cm
- Moderate:* diameter 5.1 to 10.0 cm
- Severe:* diameter greater than 10.0 cm

AEs were recorded by the subjects on diary cards from Week 0 through Week 28. (A solicited post-injection reaction was not considered an AE unless it lasted beyond Day 6). Laboratory tests included HBV screening, measurement of antinuclear antibody (ANA) and antibody to double-stranded deoxyribonucleic acid (anti-dsDNA) levels, and serum and urine pregnancy tests.

Table 3 in section 6.1.7 outlines the safety evaluation procedures. Section 6.1.9 describes how the safety data was analyzed.

Post-hoc laboratory evaluations performed on banked serum are discussed in sections 6.1.12.6 and 8.4.5.

6.1.12.2 Overview of Adverse Events

An overall summary of adverse events for subjects ≥ 18 years old is provided in Table 12.

Table 12: Summary of Adverse Events for Subjects age 18-55 by Treatment Group

Adverse Event Category, n (%)	HEPLISAV N=1809	Engerix-B N=606
≥1 Adverse Event (AE)	1094 (60.5)	376 (62.0)
Injection Site AE	17 (0.9)	4 (0.7)
Systemic AE	1091 (60.3)	375 (61.7)
Treatment-Related AE	92 (5.1)	36 (5.9)
Treatment Related Injection Site AE	11 (0.6)	4 (0.7)
Treatment Related Systemic AE	82 (4.5)	32 (5.3)
Serious Adverse Event (SAE)	28 (1.5)	13 (2.1)
Treatment related SAE	1 (0.1)	0
AE leading to death	0	0
AE leading to discontinuation from study	2 (0.1)	2 (0.3)
Treatment related AE leading to discontinuation from study	0	1 (0.2)
SAE leading to discontinuation from study	2 (0.1)	0
Treatment related SAE leading to discontinuation from study	0	0

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report Table 12-8, p. 87

Most subjects experienced at least one adverse event (HEPLISAV 1094 [60.5%], Engerix-B 376 [62.0%]). A minority of events were considered to be treatment related by the investigator (HEPLISAV 92 [5.1%], Engerix-B 36 [5.9%]). Twenty-eight subjects (1.5%) in the HEPLISAV arm reported SAEs compared to 13 subjects (2.1%) in the Engerix-B arm. One of these events in the HEPLISAV arm was considered to be treatment-related by the investigator.

Reviewer Comment: Solicited events were only categorized as adverse events if they persisted or worsened beyond Day 6. There does not appear to be a significant difference in the incidence of local AEs, systemic AEs, SAEs, treatment related events, or events leading to discontinuation from study between treatment arms. One SAE, Wegener’s granulomatosis, was considered possibly related to the study vaccine. This event will be discussed in section 6.1.12.5.

Solicited Reactions

Solicited adverse events included local pain, redness and swelling, fatigue, headache malaise and oral temperature.

Solicited injection site reactions reported by subjects 18 years of age or older are summarized by injection, severity and treatment group in Table 13. The HEPLISAV group received placebo for the third injection at Week 24.

Table 13: Summary of Solicited Local Reactions (Days 0-6) Following Each Injection for Subjects ≥ 18 Years Old

	Week 0 (Dose 1)	Week 0 (Dose 1)	Week 4 (Dose 2)	Week 4 (Dose 2)	Week 24 (Dose 3)	Week 24 (Dose 3)
Reaction	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	Placebo N=1809 n (%)	Engerix-B N=606 n (%)
Subjects with follow-up	1809 (100)	606 (100)	1797 (99.3)	604 (99.7)	1768 (97.7)	598 (98.7)
≥1 Local AE	728 (40.2)	206 (34.0)	640 (35.6)	152 (25.2)	116 (6.6)	123 (20.6)
Pain	697 (38.5)	203 (33.5)	624 (34.7)	150 (24.8)	109 (6.2)	121 (20.2)
Mild Pain	618 (34.2)	178 (29.4)	504 (28.0)	125 (20.7)	97 (5.5)	102 (17.1)
Moderate Pain	75 (4.1)	25 (4.1)	115 (6.4)	22 (3.6)	9 (0.5)	17 (2.8)
Severe Pain	4 (0.2)	0	5 (0.3)	5 (0.8)	3 (0.2)	2 (0.3)
Redness ¹	75 (4.1)	3 (0.5)	53 (2.9)	6 (1.0)	5 (0.3)	4 (0.7)
Mild Redness	72 (4.0)	3 (0.5)	47 (2.6)	4 (0.7)	5 (0.3)	3 (0.5)
Moderate Redness	3 (0.2)	0	4 (0.2)	0	0	0
Severe Redness	0	0	2 (0.1)	2 (0.3)	0	1 (0.2)
Swelling ¹	41 (2.3)	4 (0.7)	27 (1.5)	3 (0.5)	3 (0.2)	3 (0.5)
Mild Swelling	39 (2.2)	4 (0.7)	21 (1.2)	1 (0.2)	2 (0.1)	2 (0.3)
Moderate Swelling	2 (0.1)	0	4 (0.2)	0	1 (0.1)	0
Severe Swelling	0	0	2 (0.1)	2 (0.3)	0	1 (0.2)

¹Redness and swelling events < 2.5cm are not included in the table.

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report Table 12-4, p. 81

Overall, more subjects receiving HEPLISAV reported local pain, redness and swelling after the first or second dose than subjects receiving Engerix-B. The majority of events were reported as mild in intensity.

Reviewer Comment: Solicited local adverse events after active injections were more common in the HEPLISAV group. Since the majority of these events were categorized as mild, this does not raise significant clinical concerns.

Solicited systemic adverse events are summarized by severity, injection and treatment group in Table 14 for subjects 18 years of age and older.

Table 14: Summary of Solicited Systemic Adverse Events (Days 0-6) Following Each Injection for Subjects ≥ 18 Years Old

	Week 0 (Dose 1)	Week 0 (Dose 1)	Week 4 (Dose 2)	Week 4 (Dose 2)	Week 24 (Dose 3)	Week 24 (Dose 3)
Reaction	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	Placebo N=1809 n (%)	Engerix-B N=606 n (%)
Subjects with follow-up	1809 (100.0)	606 (100.0)	1797 (99.3)	604 (99.7)	1768 (97.7)	598 (98.7)
Any systemic reaction	487 (26.9)	177 (29.2)	382 (21.3)	112 (18.5)	227 (12.8)	87 (14.5)
Fatigue	315 (17.4)	101 (16.7)	248 (13.8)	73 (12.1)	139 (7.9)	60 (10.0)
Mild Fatigue	215 (11.9)	63 (10.4)	169 (9.4)	42 (7.0)	83 (4.7)	30 (5.0)
Moderate Fatigue	79 (4.4)	34 (5.6)	66 (3.7)	25 (4.1)	46 (2.6)	26 (4.3)
Severe Fatigue	21 (1.2)	4 (0.7)	13 (0.7)	6 (1.0)	10 (0.6)	4 (0.7)
Headache	304 (16.8)	117 (19.3)	229 (12.7)	75 (12.1)	159 (9.0)	57 (9.6)
Mild Headache	192 (10.6)	70 (11.6)	145 (8.1)	47 (7.8)	92 (5.2)	32 (5.4)
Moderate Headache	94 (5.2)	39 (6.4)	67 (3.7)	24 (4.0)	53 (3.0)	21 (3.5)
Severe Headache	18 (1.0)	8 (1.3)	17 (0.9)	4 (0.7)	14 (0.8)	4 (0.7)
Malaise	166 (9.2)	54 (8.9)	137 (7.6)	39 (6.5)	76 (4.3)	38 (6.4)
Mild Malaise	100 (5.5)	32 (5.3)	89 (5.0)	26 (4.3)	41 (2.3)	19 (3.2)
Moderate Malaise	56 (3.1)	17 (2.8)	36 (2.0)	10 (1.7)	25 (1.4)	16 (2.7)
Severe Malaise	10 (0.6)	5 (0.8)	12 (0.7)	3 (0.5)	10 (0.6)	3 (0.5)

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report Table 12-5, p. 83

Overall, the incidence and severity of fatigue, headache and malaise were similar between treatment groups.

Reviewer Comment: A similar percentage of subjects in each treatment group reported fatigue, headache or malaise. The majority of these events were categorized as mild in intensity. These data do not raise clinical safety concerns.

Oral temperature recordings are summarized in Table 15 by injection, treatment arm and the severity grading used in The FDA Guidance For Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials .

Table 15: Maximum Oral Temperature Recordings and Fever Grades Reported on Days 0-6 after Vaccination by Subjects ≥ 18 Years Old by Treatment Group

	Week 0 (Dose 1)	Week 0 (Dose 1)	Week 4 (Dose 2)	Week 4 (Dose 2)	Week 24 (Dose 3)	Week 24 (Dose 3)
	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)	Placebo N=1809 n (%)	Engerix-B N=606 n (%)
Subjects with follow-up	1783 (98.6)	597 (98.5)	1763 (97.5)	591 (97.5)	1675 (92.6)	561 (92.6)
< 100.4°F (38.0°C)	1764 (98.9)	586 (98.2)	1738 (98.6)	580 (98.1)	1653 (98.7)	551 (98.2)
Grade 1 Fever: ≥ 100.4°F (38.0°C) to <101.3°F (38.5°C)	10 (0.6)	6 (1.0)	9 (0.5)	7 (1.2)	13 (0.8)	5 (0.9)
Grade 2 Fever: ≥101.3°F (38.5°C) to <102.2°F (39.0°C)	6 (0.3)	1 (0.20)	12 (0.7)	2 (0.3)	8 (0.5)	3 (0.5)
Grade 3 Fever: ≥102.2°F (39.0°C) to <104.0°F (40.0°C)	3 (0.2)	4 (0.7)	4 (0.2)	1 (0.2)	1 (0.1)	2 (0.4)
Grade 4 Fever: ≥104.0°F (40.0°C)	0	0	0	1 (0.2)	0	0

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report, Table 12-7, p. 85

The vast majority of subjects were afebrile. Grade 3 fevers were rare occurring in 0.2% of subjects in the HEPLISAV arm and 0.7% of subjects in the Engerix-B arm after the first injection, and 0.2% in each arm after the second injection. One Grade 4 fever occurred after the second injection in a subject in the Engerix-B arm.

Reviewer Comment: The vast majority of subjects in each treatment arm did not report fever on days 0-6 after each vaccination, and there were no important differences noted between recipients of HEPLISAV and Engerix B. The review of this maximum oral temperature data did not reveal safety concerns.

There is no evidence that repeated vaccination invokes greater severity of local or systemic solicited reactions.

Solicited Reactions in Subjects < 18 Years Old

Nine of 11 subjects < 18 years of age in the HEPLISAV arm and 2 of 2 subjects < 18 years of age in the Engerix-B arm reported at least 1 solicited post-injection reaction. The most common reaction was injection site pain. All of the solicited post-injection reactions were rated as mild or moderate with the exception of 1 episode of severe pain in the HEPLISAV group. No injection site erythema or swelling was reported by subjects < 18 years of age in either treatment group. One pediatric subject in the HEPLISAV arm reported a temperature of 38.1 °C one day after receiving the first injection. In the HEPLISAV arm, 3 subjects in this age group experienced 4 episodes of malaise (2 mild, 2 moderate), 3 subjects reported 5 episodes of mild headache, and 2 subjects reported mild fatigue. In the Engerix-B arm, no temperature elevations were reported, 1 of the 2 subjects in this age group experienced 5 episodes of fatigue (3 mild, 2 moderate), 4 episodes of headache (3 mild, 1 moderate) and 5 episodes of fatigue (3 mild, 1 moderate).

Reviewer Comment: The majority of solicited post-injection reactions occurring in subjects <18 year old were mild to moderate in intensity. The review of the solicited adverse events occurring in this study population did not raise concerns for safety in the proposed population.

Unsolicited adverse events reported by subjects ≥18 years old are summarized by system organ class (SOC), toxicity grade and treatment group in Table 16.

Table 16: Unsolicited Adverse Experiences by Maximum Intensity, System Organ Class and Treatment Group for Subjects ≥ 18 Years Old

System Organ Class	HEPLISAV Mild n (%)	HEPLISAV Moderate n (%)	HEPLISAV Severe n (%)	HEPLISAV Total n (%)	Engerix-B Mild n (%)	Engerix-B Moderate n (%)	Engerix-B Severe n (%)	Engerix-B Total n (%)
≥1 AE	408 (22.6)	494 (27.3)	192 (10.6)	1094 (60.5)	124 (20.5)	165 (27.2)	87 (14.4)	376 (62.0)
Blood and Lymphatic System Disorders	4 (0.2)	2 (0.1)	1 (0.1)	7 (0.4)	3 (0.5)	1 (0.2)	0	4 (0.7)
Cardiac Disorders	6 (0.3)	4 (0.2)	1 (0.1)	11 (0.6)	3 (0.5)	3 (0.5)	0	6 (1.0)
Congenital, Familial and Genetic Disorders	0	0	1 (0.1)	1 (0.1)	0	0	0	0
Ear and Labyrinth Disorders	27 (1.5)	12 (0.7)	1 (0.1)	40 (2.2)	8 (1.3)	5 (0.8)	1 (0.2)	14 (2.3)
Endocrine Disorders	6 (0.3)	2 (0.1)	1 (0.1)	9 (0.5)	1 (0.2)	1 (0.2)	0	2 (0.3)
Eye Disorders	18 (1.0)	8 (0.4)	1 (0.1)	27 (1.5)	12 (2.0)	3 (0.5)	1 (0.2)	16 (2.6)
Gastrointestinal Disorders	99 (5.5)	74 (4.1)	28 (1.5)	201 (11.1)	29 (4.8)	40 (6.6)	17 (2.8)	86 (14.2)
General and Administration Site Conditions	54 (3.0)	41 (2.3)	4 (0.2)	99 (5.5)	21 (3.5)	14 (2.3)	4 (0.7)	39 (6.4)

System Organ Class	HEPLISAV Mild n (%)	HEPLISAV Moderate n (%)	HEPLISAV Severe n (%)	HEPLISAV Total n (%)	Engerix-B Mild n (%)	Engerix-B Moderate n (%)	Engerix-B Severe n (%)	Engerix-B Total n (%)
Hepatobiliary Disorders	0	2 (0.1)	2 (0.1)	4 (0.2)	0	2 (0.3)	0	2 (0.3)
Immune System Disorders	7 (0.4)	7 (0.4)	2 (0.1)	16 (0.9)	3 (0.5)	2 (0.3)	2 (0.3)	7 (1.2)
Infections and Infestations	273 (15.1)	257 (14.2)	58 (3.2)	588 (32.5)	91 (15.0)	63 (10.4)	32 (5.3)	186 (30.7)
Injury, Poisoning and Procedural Complications	50 (2.8)	58 (3.2)	16 (0.9)	124 (6.9)	17 (2.8)	31 (5.1)	9 (1.5)	57 (9.4)
Investigations (Laboratory)	3 (0.2)	2 (0.1)	0	5 (0.3)	1 (0.2)	1 (0.2)	0	2 (0.3)
Metabolism and Nutrition Disorders	13 (0.7)	6 (0.3)	0	19 (1.1)	6 (1.0)	4 (0.7)	0	10 (1.7)
Musculoskeletal and Connective Tissue Disorders	108 (6.0)	112 (6.2)	47 (2.6)	267 (14.8)	30 (5.0)	37 (6.1)	18 (3.0)	85 (14.0)
Neoplasms Benign, Malignant and Unspecified	17 (0.9)	2 (0.1)	2 (0.1)	21 (1.2)	5 (0.8)	1 (0.2)	1 (0.2)	7 (1.2)
Nervous System Disorders	98 (5.4)	110 (6.1)	46 (2.5)	254 (14.0)	27 (4.5)	43 (7.1)	14 (2.3)	84 (13.9)
Psychiatric Disorders	30 (1.7)	24 (1.3)	5 (0.3)	59 (3.3)	9 (1.5)	10 (1.7)	4 (0.7)	23 (3.8)
Renal and Urinary Disorders	4 (0.2)	9 (0.5)	4 (0.2)	17 (0.9)	4 (0.7)	10 (1.7)	1 (0.2)	15 (2.5)
Reproductive System and Breast Disorders	25 (1.4)	26 (1.4)	6 (0.3)	57 (3.2)	11 (1.8)	8 (1.3)	3 (0.5)	22 (3.6)
Respiratory, Thoracic, and Mediastinal Disorders	94 (5.2)	75 (4.1)	16 (0.9)	185 (10.2)	35 (5.8)	14 (2.3)	6 (1.0)	55 (9.1)
Skin and Subcutaneous Tissue Disorders	58 (3.2)	27 (1.5)	5 (0.3)	90 (5.0)	12 (2.0)	6 (1.0)	0	18 (3.0)
Surgical and Medical Procedures	2 (0.1)	1 (0.1)	1 (0.1)	4 (0.2)	0	0	0	0
Vascular Disorders	27 (1.5)	16 (0.9)	2 (0.1)	45 (2.5)	14 (2.3)	8 (1.3)	2 (0.3)	24 (4.0)

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report, Table 15.2.1B, p. 1062

Overall, unsolicited AEs occurred with similar incidence and severity among subjects in each treatment group. A larger proportion of subjects in the Engerix-B arm experienced a severe unsolicited AE (87 [14.4%]) compared to the HEPLISAV arm (192 [10.6%]).

All endocrine disorders reported were thyroid disorders and included the following conditions: hyperthyroidism (HEPLISAV 3 [0.2%], Engerix-B 0), hypothyroidism (HEPLISAV 3 [0.2%], Engerix-B 1 [0.2%]), Basedow's disease (HEPLISAV 1 [0.1%], Engerix-B 1 [0.2%]), Thyroid disorder (HEPLISAV 1 [0.1%], Engerix-B 0) and Thyroiditis (HEPLISAV 1 [0.1%], Engerix-B 0). One case of Basedow's disease in the HEPLISAV arm was graded as severe, all other thyroid disorders were graded as mild or moderate.

Immune system disorders occurred with similar incidence among subjects in each treatment group (HEPLISAV 16 [0.9%], Engerix-B 7 [1.2%]). Musculoskeletal and connective tissue disorders occurred with similar incidence and severity in both groups (HEPLISAV total 267 [14.8%], Engerix-B total 85 [14.0%]). One case each of rheumatoid arthritis (HEPLISAV), systemic lupus erythematosus (HEPLISAV), fibromyalgia (Engerix-B) and mixed connective tissue disease (Engerix-B) were diagnosed during the study.

Reviewer Comment: The incidence and severity of unsolicited adverse events, including those categorized as immune system disorders and musculoskeletal and connective tissue disorders, was similar between groups. No safety signals were identified in the review of these data.

Unsolicited Adverse Events in Subjects < 18 Years Old

Thirteen pediatric subjects were enrolled in this study: 11 HEPLISAV recipients and 2 Engerix-B recipients. Neither of the 2 Engerix-B recipients reported an unsolicited AE. Four HEPLISAV recipients under the age of 18 experienced 12 unsolicited AEs including fever (n=2), ear pain, otitis media, head injury, black eye/periorbital hematoma, headache, rhinorrhea, nasal congestion, generalized rash, Group A streptococcal pharyngitis and viral upper respiratory infection. All events resolved prior to study end and were deemed "not related" or "probably not related" to the investigational vaccine by the investigator. The generalized rash was rated as "severe" in intensity, the remainder of the events were categorized as moderate in intensity. One 12 year old female experienced moderate fever, headache, rhinorrhea, nasal congestion and Group A pharyngitis along with a severe generalized rash 19 days after the second study injection. The rash lasted 11 days and was deemed probably not related to the study vaccination.

Reviewer Comment: While HEPLISAV is proposed for adult use, all recipients of any formulation of the vaccine were included in the safety review. All 12 unsolicited AEs reported in children 11-18 years of age occurred in HEPLISAV recipients. However, there were only 13 children enrolled and after randomization, the ratio of children in the HEPLISAV group to those enrolled in the Engerix-B group was > 5:1. Additionally, 2 individuals experienced multiple AEs which were likely secondary to

the primary AE (e.g., otitis media with ear pain and fever). Given these limitations, an accurate determination of any difference in the incidence of unsolicited AEs between treatment groups among pediatric subjects is difficult. As discussed in section 6.1.12.4, no SAEs occurred in this population and none of the unsolicited AEs discussed were adverse events of special interest (AESIs). The evaluation of adverse events in this small subgroup did not reveal any identifiable safety risks to the indicated population.

6.1.12.3 Deaths

No deaths were reported.

6.1.12.4 Nonfatal Serious Adverse Events

All SAEs occurred in subjects 18 years of age and older. Table 17 summarizes SAEs by SOC, preferred term and treatment group.

Table 17: Summary of All Serious Adverse Events Reported by Subjects in Study HBV-10 by System Organ Class/Preferred Term and Treatment Group

System Organ Class Preferred Term	HEPLISAV N=1809	Engerix-B N=606
≥1 Serious Adverse Event	28 (1.5)	13 (2.1)
Cardiac disorders	1 (0.1)	2 (0.3)
Angina pectoris	1 (0.1)	0
Arrhythmia	0	1 (0.2)
Supraventricular tachycardia	0	1 (0.2)
Gastrointestinal Disorders	1 (0.1)	1 (0.2)
Gastritis	1 (0.1)	0
Pancreatitis	0	1 (0.2)
Hepatobiliary disorders	1 (0.1)	0
Cholecystitis acute	1 (0.1)	0
Immune system disorders	0	1 (0.2)
p-ANCA positive vasculitis	0	1 (0.2)
Infections and Infestations	1 (0.1)	2 (0.3)
Tonsillitis	1 (0.1)	0
Adnexitis	0	1 (0.2)
Liver abscess	0	1 (0.2)
Septic Shock	0	1 (0.2)
Injury, poisoning and procedural complications	8 (0.4)	2 (0.3)
Jaw fracture	2 (0.1)	0
Ankle fracture	1 (0.1)	0
Dislocation of joint prosthesis	1 (0.1)	0
Meniscus lesion	1 (0.1)	0
Patella fracture	1 (0.1)	0
Sternal fracture	1 (0.1)	0
Tendon rupture	1 (0.1)	0
Ulna fracture	1 (0.1)	0
Femur fracture	0	1 (0.2)
Joint injury	0	1 (0.2)
Musculoskeletal and connective tissue disorders	2 (0.1)	1 (0.2)
Bursitis	1 (0.1)	0
Gouty arthritis	1 (0.1)	0
Intervertebral disc protrusion	0	1 (0.2)

System Organ Class Preferred Term	HEPLISAV N=1809	Engerix-B N=606
Neoplasms benign, malignant and unspecified	5 (0.3)	0
Breast cancer	2 (0.1)	0
Breast cancer recurrent	1 (0.1)	0
Meningioma	1 (0.1)	0
Papillary thyroid cancer	1 (0.1)	0
Nervous system disorders	2 (0.1)	0
Cerebral ischemia	1 (0.1)	0
Guillain-Barre Syndrome	1 (0.1)	0
Psychiatric disorders	2 (0.1)	1 (0.2)
Depression	2 (0.1)	0
Delirium tremens	0	1 (0.2)
Renal and urinary disorders	1 (0.1)	0
Renal failure	1 (0.1)	0
Reproductive system and breast disorders	1 (0.1)	2 (0.3)
Prostatitis	1 (0.1)	0
Menorrhagia	0	1 (0.2)
Ovarian cyst	0	1 (0.2)
Respiratory, thoracic and mediastinal disorders	6 (0.3)	1 (0.2)
Pulmonary embolism	3 (0.2)	0
Pneumothorax	2 (0.1)	0
c-ANCA positive vasculitis (Wegener's granulomatosis)	1 (0.1)	0
Asthma	0	1 (0.2)
Surgical and medical procedures	1 (0.1)	0
Meningioma surgery	1 (0.1)	0

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report, Table 12-13, p. 96

Twenty-eight (1.5%) of subjects in the HEPLISAV arm and 13 (2.1%) of subjects in the Engerix-B arm experienced at least one SAE.

Reviewer Comment: Overall, the incidence of SAEs was low and comparable between treatment groups. There were slightly more injuries and neoplasms in the HEPLISAV group compared to the Engerix-B group. As the incidence of these events was very low and their association with vaccination doubtful, they were unlikely to represent a safety concern with this vaccine. Of note, a case of Wegener's granulomatosis was categorized as a pulmonary disorder. If it had been categorized as a connective tissue disorder or as an immune system disorder, the percentage of subjects in each corresponding SOC would change only minimally. The overall incidence of SAEs in study DV2-HBV-10 did not generate safety concerns. However, the case of Wegener's granulomatosis is believed to be related to vaccine administration and will be discussed further in section 6.1.12.5 and in the context of the integrated safety review.

6.1.12.5 Adverse Events of Special Interest (AESI)

In attempts to identify adverse events of autoimmune origin, adverse events of special interest (AESIs) were evaluated retrospectively by the applicant for all trials. An AESI was defined as follows:

- **Neuroinflammatory disorders**
 - Optic neuritis, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain Barre syndrome, myasthenia gravis, encephalitis, neuritis, Bell's palsy
- **Musculoskeletal disorders**
 - Systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, juvenile rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, spondylarthropathy
- **Gastrointestinal disorders**
 - Crohn's disease, ulcerative colitis, celiac disease
- **Metabolic disease**
 - Autoimmune thyroiditis, Grave's/Basedow's disease, Hashimoto's thyroiditis, Type 1 diabetes mellitus, Addison's disease
- **Skin disorders**
 - Psoriasis, vitiligo, Raynaud's phenomenon, erythema nodosum, autoimmune bullous skin diseases
- **Others**
 - ANCA positive vasculitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, antiphospholipid antibody syndrome, temporal arteritis, Behcet's syndrome, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune cardiomyopathy, renal vasculitis, sarcoidosis, Stevens-Johnson syndrome, Wegener's granulomatosis

AESIs will be discussed in the context of the integrated safety summary in section 8.4.8.

Autoimmune Adverse Events

While ANA and anti-dsDNA were evaluated at baseline and Week 28, active surveillance for autoimmune adverse events (AIAEs) was not performed prospectively for this study. However, based on the occurrence of three AIAEs in this study, the applicant analyzed ANCA levels retrospectively on banked serum. The applicant also implemented active surveillance and independent review of AIAEs prospectively in the subsequent pivotal trial, study HBV-16. Please also refer to section 2.5.

In the HEPLISAV group, two AIAEs occurred: C-ANCA positive vasculitis (Wegener's Granulomatosis) and Guillain-Barre Syndrome. In the Engerix-B group, one subject was diagnosed with p-ANCA positive vasculitis

c-ANCA positive vasculitis (Wegener's granulomatosis) (Subject 24057, 1018 ISS-HBsAg Group)

Subject 24057 was a 55-year-old white woman with a medical history of menopause. Eighteen days after the first study injection, she experienced severe widespread

urticaria which was attributed to the consumption of herring. No action regarding further injections was taken at that time, and subsequent injections were administered. Eleven days after the second study injection, the subject presented with vocal hoarseness which was treated with topical medication (Locabiosol – locally acting ‘fusafungin,’ pressurized aerosol). Approximately 8 weeks later, the subject reported symptoms of sinusitis. She reported never having had similar episodes before.

Approximately 5 weeks after reporting these symptoms, the subject was hospitalized for septal plastic surgery with drainage of the left paranasal sinus. The sinusitis was considered resolved on follow-up 3 weeks later.

Approximately 8 weeks later, she was re-hospitalized for recurrent sinusitis. During this hospitalization the subject developed a pericardial effusion and was admitted to an intensive care unit for a pericardiocentesis, which showed an exudate. In addition, the subject had pulmonary infiltrates and bilateral pleural effusions. She was also found to have proteinuria, and the possibility of glomerulonephritis was considered. An (b) (4) test was positive for c-ANCA (titer of 1:128, positive for proteinase-3). The c-ANCA test was repeated at 2 outside reference laboratories with comparable results. A diagnosis of Wegener’s granulomatosis was made and she was started on corticosteroids and cyclophosphamide. The subject had both anti-ds DNA and ANA levels within the normal range throughout the study.

Approximately 6 weeks after the second hospitalization, the subject underwent renal biopsy. The biopsy was performed approximately 2 months after the initiation of corticosteroid and cyclophosphamide therapy. The number of glomeruli obtained was suboptimal, but the evaluation revealed a multifocal, chronic tubulo-interstitial damage affecting 25% of the cortex. It was focal, potentially reversible, with no evidence of necrotizing glomerulitis or immune complex glomerulonephritis. However, a necrotizing glomerulonephritis or degeneration could not be ruled out.

Additionally, a retrospective evaluation of banked serum showed the following ANCA results:

- Screening visit: Negative
- 4 weeks after Dose 1: ANCA to PR-3 weakly positive
- 8 weeks after Dose 1 (4 weeks after Dose 2): ANCA to PR-3 weakly positive
- 12 weeks after Dose 1 (8 weeks after Dose 2): ANCA to PR-3 positive
- 23 weeks after Dose 1 (19 weeks after Dose 2): ANCA to PR-3 strongly positive
- 28 weeks after Dose 1 (24 weeks after Dose 2): ANCA to PR-3 strongly positive

There was no action taken regarding the investigational product. The subject’s Wegener’s granulomatosis was determined by the investigator to be clinically stable 4 months after diagnosis. The investigator considered the initial diagnosis of sinusitis as the initial symptoms of Wegener’s granulomatosis. The investigator assessed the event as serious, severe, and possibly related to study treatment.

Reviewer Comment: Wegener's granulomatosis occurred in temporal association with the receipt of HEPLISAV. The individual developed sinusitis 2.5 months after her second active injection. Additionally, urticaria is not uncommonly a presenting non-specific symptom of autoimmune disease. Additionally, there appears to be a dose-response relationship between vaccination and ANCA positivity. Given the mechanism of action of the immunostimulatory adjuvant via TLR9 activation and induction of T helper cell 1 (Th1) cytokines, biologic plausibility for a potential role of HEPLISAV in the development of Wegener's granulomatosis in this patient cannot be ruled out, given that this is a Th1-driven disorder, as are many autoimmune diseases (15-18). Therefore, the reviewer has assessed that the case of Wegener's granulomatosis likely was related to receipt of the study vaccine. This case prompted a clinical hold of the developmental program. After intense review and expert consultation, the hold was removed. Clinical laboratory monitoring for autoimmunity and prospective protocols for evaluation of autoimmune events was implemented in future trials. Please see further discussion of this case in the context of potential autoimmune event analyses and comments regarding the potential clinical concerns surrounding granulomatous disease in the integrated safety review.

Guillain-Barré Syndrome (Subject 11168, 1018 ISS-HBsAg Group)

Subject 11168 was a 36-year-old woman with a medical history of splenectomy in 1985 for unknown reasons. She received two study injections and an influenza injection 105 days after her second study injection. No complaints or reactogenicity events were noted during this period.

Five days after receiving an influenza injection, the subject was hospitalized complaining of progressive weakness that progressed to respiratory failure. A diagnosis of Guillain-Barré Syndrome was made. The subject's hospitalization was prolonged by the diagnosis of a follicular variant of papillary carcinoma (thyroid) and bilateral pulmonary embolism. She also experienced multiple urinary tract infections (reported as AEs). While hospitalized, she was treated with anticoagulants, antibiotics, immunoglobulins, and plasmapheresis, resulting in noticeable improvement.

The subject's Guillain-Barré Syndrome was assessed by the investigator as being severe and probably not related to study treatment but, instead, related to the influenza vaccine the subject received 5 days prior to symptom onset. The subject was discontinued from the study due to the Guillain-Barré Syndrome.

Reviewer Comment: The reviewer agrees with the investigator's assessment of this event as likely unrelated to receipt of HEPLISAV.

p-ANCA Positive Vasculitis (Subject 06083, Engerix-B Group)

Subject 06083 was a 44-year-old white woman with a medical history of mixed connective tissue disease, osteoarthritis (hand and shoulders), neck pain, food allergy, myopia, presbyopia, constipation, headache, and tension headache. She received two study injections. Approximately 3 months after the 2nd study injection, while on a trip to Brazil, the subject had fever and malaise. Upon returning home, her general practitioner

prescribed antibiotics for presumed pneumonia. After about 10 days there was no improvement and she developed pleuritic pain. As a result, she visited the emergency room. Results of a chest x-ray were normal, and the subject was sent home with medication for pain.

127 days following her second study injection, she returned to the hospital with severe dyspnea, hemoptysis, and pleuritic pain. She required intubation and mechanical ventilation. Frank blood was aspirated from the endotracheal tube and a bronchoscopy showed pulmonary hemorrhage. A chest CT scan disclosed bilateral diffuse air space consolidation, consistent with pulmonary hemorrhage. Upon discharge, there was extreme proximal weakness attributed to steroid myopathy.

During the hospitalization a blood test revealed positive myeloperoxidase-p-ANCA (no titer reported). The subject was then given a provisional diagnosis of p-ANCA associated vasculitis and started on pulse methylprednisolone and cyclophosphamide.

On a further review of the subject's history it was determined that she demonstrated some features of scleroderma but was considered to have a possible crossover syndrome. Further investigation later disclosed a medical history (approximately 10 years prior) of mixed connective tissue disease (MCTD) that was diagnosed and treated with prednisone and chloroquine for over 2 years in Brazil. This medical history of MCTD was not disclosed by the subject at the time of study enrollment. From specimens collected at screening, the subject was later determined to have anti-ds DNA levels within normal range, while her ANA levels were elevated (> 1:5120).

The subject was discharged from the hospital on one month after admission, when the event of p-ANCA associated vasculitis was considered to be resolved. She left the hospital on cyclophosphamide and with recommended pulmonary rehabilitation and a prescription for prednisone.

The subject's study injections were interrupted as a result of the SAE, and she did not receive her third injection prior to withdrawing consent and being discontinued from the study. The investigator assessed the p-ANCA associated vasculitis as severe and not related to study treatment.

Reviewer Comment: The narrative for subject 06083 states that the vasculitis was considered to be resolved upon hospital discharge. Autoimmune vasculitides are chronic in nature and as such generally do not resolve, but patients may achieve remission with treatment. This reviewer, therefore disagrees with the assessment that the p-ANCA vasculitis had resolved.

The two cases of vasculitis in this study may not be comparable given that the subject in the Engerix-B arm had a history of autoimmune disease. However, the 3:1 randomization ratio, the single occurrence of this disease, the 28 week follow-up period of this study, and the non-specific nature in which many autoimmune diseases present

illustrate the difficulties inherent in making a causal assessment of receipt of a vaccine and development of a rare SAE such as a vasculitis.

Other Adverse Events of Interest

Cerebral ischemia

Subject 06174, a 55 year old man with a past medical history that included a myocardial infarction, depression, bipolar disorder, headaches, obesity and facial paresis reported worsening headache 3 months after his second injection of HEPLISAV. Twelve days later, he experienced numbness in his hands. The subject was admitted to the hospital with right facial numbness and dysphasia. A CT scan of the brain was normal, an ECG showed an old inferior myocardial infarct of undetermined age. During hospitalization, he was diagnosed with amnesia, dysphasia, dyslipidemia, carpal tunnel syndrome and hypertension. At screening and all study prior study visits, his blood pressure was normal. An MRI of the brain, carotid ultrasound and echocardiogram were normal other than the suggestion of decreased ventricular flow compliance. The patient began treatment with aspirin, ramipril and atorvastatin calcium and was discharged home with prescriptions for valproate sodium and venlafaxine hydrochloride 3 days after admission. The amnesia, dysphasia, dyslipidemia, hypertension and carpal tunnel syndrome were ongoing. Approximately 2.5 months after discharge, he was seen in a neurology clinic where he had no symptoms suggestive of recurrent cerebral ischemia. The investigator assessed the event as moderate in intensity and not related to the study treatment.

Reviewer Comment: While it is likely that this event is not related to study treatment, the reviewer is requesting additional information due to the nature and unclear etiology of these deficits.

6.1.12.6 Clinical Test Results

ANA, anti-dsDNA and urine pregnancy tests were performed in this trial. ANA and anti-dsDNA were evaluated at Week 0 and Week 28. Urine pregnancy tests were performed prior to each injection.

Antinuclear Antibody Assessment

Table 18 outlines the baseline and Week 28 ANA titers for subjects by treatment group and antibody dilution. ANA titers < 1:160 were considered normal.

Table 18: Antinuclear Antibody Titers by Treatment Group

Result	HEPLISAV Baseline N=1809 n (%)	HEPLISAV Week 28 N=1809 n (%)	Engerix-B Baseline N=606 n (%)	Engerix-B Week 28 N=606 n (%)
Number of subjects with titers available	1804	1741	605	583
<1:160	1616 (89.3)	1662 (91.9)	541 (89.3)	554 (91.4)

Result	HEPLISAV Baseline N=1809 n (%)	HEPLISAV Week 28 N=1809 n (%)	Engerix-B Baseline N=606 n (%)	Engerix-B Week 28 N=606 n (%)
≥1:160	188 (10.4)	79 (4.4)	64 (10.6)	29 (4.8)
1:160	115 (6.4)	41 (2.3)	39 (6.4)	13 (2.1)
1:320	50 (2.8)	19 (1.1)	17 (2.8)	13 (2.1)
1:640	14 (0.8)	11 (0.6)	2 (0.3)	1 (0.2)
1:1280	5 (0.3)	5 (0.3)	4 (0.7)	1 (0.2)
1:2560	2 (0.1)	2 (0.1)	1 (0.2)	0
1:5120	0	0	0	1 (0.2)
>1:5120	2 (0.1)	1 (0.1)	1 (0.2)	0

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report, Table 12-16, p. 108

The majority of subjects in both treatment arms had normal titers at baseline and at Week 28.

Reviewer Comment: *Most subjects had ANA titers < 1:160 in both treatment groups. The percentage of subjects with results within each serial dilution was comparable between treatment groups. No trend towards increasing percentages of individuals with ANA titers ≥1:160 in the weeks subsequent to vaccination was noted among subjects receiving either HEPLISAV or Engerix B.*

Table 19 summarizes the changes in ANA titer from Week 0 to Week 28 by treatment group and antibody dilution.

Table 19: Summary of Change in Antinuclear Antibody (ANA) Titers from Baseline to Week 28 by Treatment Group

Change from Baseline at Week 28	HEPLISAV N=1809 n (%)	Engerix-B N=606 n (%)
1-dilution increase	31 (1.7)	8 (1.3)
2-dilution increase	10 (0.6)	6 (1.0)
3-dilution increase	1 (0.1)	0
4-dilution increase	0	0
>4-dilution increase	0	0
≥ 2-dilution increase	11 (0.6)	6 (1.0)
Any increase	53 (2.9)	20 (3.3)

Source: Adapted from STN 125428, DV2-HBV-10, Clinical Study Report, Table 12-16, p. 108

All subjects with titers that increased from baseline were ≥ 18 years old. The percentage of subjects experiencing an increase in ANA titer from baseline was similar between treatment groups.

Reviewer Comment: Only a small percentage of individuals were found to manifest an increase in ANA titers from baseline at 28 weeks following vaccination. No difference in the proportion of subjects developing increases in ANA titers was noted between HEPLISAV and Engerix-B recipients. Most subjects experiencing an increase in ANA titer had only a 1-dilution increase. Eleven HEPLISAV recipients (0.6%) and six Engerix-B recipients (1.0%) had an increase in ANA titer of ≥ 2 -dilutions.

Laboratory findings considered “clinically important” by the site investigator were reported as AEs regardless of any other associated AE reported by the subject. Two subjects (0.1%) in the HEPLISAV group and 1 subject (0.2%) in the Engerix-B group had increases in ANA at Week 28 reported as AEs. Table 20 summarizes the baseline and Week 28 titers for these subjects.

Table 20: Changes in ANA Titers Reported as Adverse Events

Arm/Subject Number	Baseline Result	Week 28 Result	Dilution Increase	Other AEs	Onset of Other AEs
HEPLISAV/03074	<1:160	1:160	1	None	N/A
HEPLISAV/14046	1:640	1:1280	1	Urticaria	28 days after 1 st injection
Engerix-B/03096	<1:160	1:160	1	Back Pain; Pain in Extremities	6 days after 2 nd injection; 24-28 days after 1 st injection and 5-37 days after 3 rd injection

Source: STN 125428, Study DV2-HBV-10, CSR, text from page 109

Reviewer Comment: The incidence of “clinically important” elevations in ANA requiring reporting as AEs was similar between treatment groups. However, it appears that there are no standard criteria for the “clinically important” designation. Therefore, the interpretation of these data is limited by the variations in the clinical opinions of the individual site investigators. The associated AE of urticaria in subject 14046 raised concern due to the fact that urticaria can be a presenting symptom of autoimmune disease. Since these were not SAEs, no narratives exist for these subjects. However, upon further review of the data, it appears that the urticaria was an exacerbation of pre-existing urticaria and lasted only 1 day and therefore was likely of little clinical significance. Finally, the result for subjects 03074 and 03096 should be reported as “ ≥ 1 -dilution increase” in the opinion of this reviewer since the original value could have been < 1:40, 1:40, or 1:80.

Anti-double stranded DNA Assessment:

Anti-dsDNA was measured at Week 0 and Week 28. Table 21 summarizes the results by week and treatment group. In the HEPLISAV arm, more subjects had a positive result at Week 28 than at baseline (0.6% versus 0.3%). There was no change in the percentage of subjects with a positive result at Week 28 compared to baseline in the Engerix-B arm (0.5% at both time points). Table 20 summarizes changes in result from baseline to Week 28. All subjects with changes in anti-dsDNA from baseline to Week 28 were ≥ 18 years old. There was no difference between groups in the percentage of subjects who had a negative result at baseline and a positive result at Week 28.

Table 21: Summary of Anti-Double Stranded DNA by Visit and Treatment Group for Subjects ≥ 18 Years Old

Result	HEPLISAV Baseline N=1809	HEPLISAV Week 28 N=1809	Engerix-B Baseline N=606	Engerix-B Week 28 N=606
Number of Subjects with Anti-dsDNA data	1799	1740	602	583
Positive	6 (0.3)	10 (0.6)	3 (0.5)	3 (0.5)
Negative	1793 (99.1)	1730 (95.6)	599 (98.8)	580 (95.7)

Source: STN 125428; Study DV2-HBV-10, CSR, Table 12-18, p. 110

Table 22: Summary of Change in Anti-Double Stranded DNA from Baseline to Week 28 by Treatment Group for Subjects ≥ 18 Years Old

Result	HEPLISAV N=1809	Engerix-B N=606
Negative to Negative	1716 (94.9)	573 (94.6)
Negative to Positive	9 (0.5)	3 (0.5)
Positive to Negative	5 (0.3)	3 (0.5)
Positive to Positive	0	0

Source: STN 125428, Study DV2-HBV-10, CSR, Table 12-18, p. 110

Reviewer Comment: *The review of the anti-dsDNA data did not raise clinical safety concerns.*

C-reactive protein

Baseline samples were available for 2362 subjects in study DV2-HBV-10. Of these, 2153 had a negative result at baseline: 91.6% (1620/1769) of HEPLISAV recipients and 89.9% (533/593) Engerix-B recipients. Table 23 shows the percentage of subjects with normal and elevated CRP concentrations by visit.

Table 23: Proportion of Subjects with Normal and Elevated CRP Concentrations by Visit and Treatment Group for study DV2-HBV-10

Visit	CRP (mg/dL)	HEPLISAV	Engerix-B
Baseline	<0.8	1620 (91.6%)	533 (89.9%)
Baseline	≥ 0.8	149 (8.4%)	60 (10.1%)
Visit 5*	<0.8	1518 (92.7%)	469 (89.3%)

Visit	CRP (mg/dL)	HEPLISAV	Engerix-B
Visit 5*	≥0.8	120 (7.3%)	56 (10.7%)
Visit 7**	<0.8	1557 (91.2%)	516 (90.5%)
Visit 7**	≥0.8	150 (8.8%)	54 (9.5%)

*Visit 5 = 8 weeks post-last injection for HEPLISAV recipients and 8 weeks post second injection for Engerix-B recipients

**Visit 7= 6 months post-last injection for HEPLISAV recipients and 1 month post-last injection for Engerix-B recipients

Source: Adapted from STN 125428, Common Technical Report, Table 6, page 13

Seventy-nine subjects in study DV2-HBV-10 (HEPLISAV: 53 (3.3%), Engerix-B: 26 (5.0%)) had CRP concentrations <0.8 mg/dL at baseline and became positive at Visit 5, which was 8 weeks after the last injection for HEPLISAV recipients and 8 weeks after the second injection for Engerix-B recipients. The applicant reports that reported AEs temporally associated with increases in CRP concentrations showed that the most commonly reported AE was nasopharyngitis (HEPLISAV: n=13, Engerix-B: n=4), followed by headache (HEPLISAV: n=3, Engerix-B: n=1) and tooth disorder (HEPLISAV: n=1, Engerix-B: n=2).

Reviewer Comment: Based on the data provided, a similar proportion of subjects in each arm reported elevated CRP concentrations. CRP evaluations were performed retrospectively and raw CRP data were not provided by the applicant, therefore the review of this data is limited to the applicant's analyses. It is therefore difficult for the reviewer to comment on the clinical safety implications of the CRP evaluations.

6.1.12.7 Dropouts and/or Discontinuations

The applicant reports that 2 (0.1%) HEPLISAV recipients (0.1%) and 2 Engerix-B recipients (0.3%) discontinued due to adverse events. A 26 year old HEPLISAV recipient developed a pulmonary embolus after rupturing her anterior cruciate ligament approximately one month after her 2nd dose. Another HEPLISAV recipient developed Guillain-Barre syndrome 5 days after an inactivated influenza vaccine as discussed in detail in section 6.1.12.5. In the Engerix-B group, one subject discontinued due to blurred vision and increased intraocular pressure, and another subject discontinued due to an exacerbation of an unspecified arthritis of the hands. Only the arthritis exacerbation was considered by the investigator as possibly related to study treatment.

In addition to these withdrawals, 2 additional subjects experienced AEs leading to discontinuation, but these were captured as "subject withdrew consent." In the HEPLISAV group, a 37 year old female with a history of breast cancer had a breast lump discovered on routine mammogram 16 days after her first vaccination that was later confirmed cancerous. The event was not considered treatment related by the investigator. An Engerix-B recipient withdrew from the study after developing p-ANCA positive vasculitis. This event is discussed in detail in section 6.1.12.5.

6.2 Trial #2

An observer-blinded, randomized, parallel-group, multi-center phase 3 study comparing the safety and immunogenicity of HEPLISAV to Licensed Vaccine (Engerix-B) among Healthy Adults 40 to 70 years of Age (Protocol DV2-HBV-16; NCT01005407)

6.2.1 Objectives (Primary, Secondary, etc)

The primary immunogenicity objective of this phase 3 study was to compare the proportion of subjects who exhibit a seroprotective immune response (SPR, defined as anti-HBsAg antibody levels greater than or equal to 10 mIU/mL) when measured at Week 12 following vaccination with HEPLISAV at 0 and 1 month to the proportion of subjects who exhibit SPRs when measured at Week 32 following vaccination with the active comparator, Engerix-B, at 0, 1, and 6 months. An additional primary objective of this study was to demonstrate lot consistency for immune response as measured by the geometric mean concentration (GMC) at 4 weeks after the last active dose (Week 8) among three consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification. The primary safety objective of this study was to demonstrate safety and tolerability of vaccination with HEPLISAV when administered to subjects 40 to 70 years of age and to compare the safety profile to that of Engerix-B for this age group.

The time point for comparing the SPR between HEPLISAV and Engerix-B in Study DV2-HBV-16 (Week 12 vs. Week 32) for the primary immunogenicity endpoint was different from that in the pivotal phase 3 study DV2-HBV-10 (Week 12 for HEPLISAV vs. Week 28 for Engerix-B) and represents a more equitable comparison of immunogenicity between the two study groups than was done in Study DV2-HBV-10; as SPR was assessed 8 weeks after the last dose of vaccine for both study arms in Study DV2-HBV-16, rather than at 8 weeks for HEPLISAV and 4 weeks for Engerix-B, respectively, as was done in Study DV2-HBV-10. The choice of the Week 28 endpoint in Study DV2-HBV-10 was based on initial immunogenicity data, but further immunogenicity testing from Study DV2-HBV-10 indicated that the peak immunogenicity response for Engerix-B was better evaluated at 8 weeks and not 4 weeks after the last dose of Engerix-B and this time point for primary immunogenicity comparison was adopted by the applicant for this second, phase 3 study.

6.2.2 Design Overview

The study was a subject- and observer-blinded, randomized, controlled study of approximately 2000 adult subjects, 40 to 70 years of age. The study was conducted by 25 investigators at 29 sites in the U.S.A. and by 3 investigators at 3 sites in Canada. Initially, 400 subjects were randomized to receive HEPLISAV lot TDG006 (the lot prior to minor manufacturing process modifications), one of the three consistency lots of HEPLISAV (TDG008, TDG009, and TDG010), or Engerix-B at a 3:1:1:1:1 allocation ratio. After reaching the subject enrollment target of 400 subjects for lot TDG006, 1200 subjects were randomized to receive one of the three consistency lots or Engerix-B at a 1:1:1:1:1 allocation ratio until enrollment was completed.

The overall allocation ratio of HEPLISAV to Engerix-B was 4:1. For the primary objective of noninferiority, the allocation ratio of the three consistency lots to Engerix-B was 3:1. For the primary objective of lot consistency, the allocation ratio was 1:1:1. Randomization was stratified by age (40 to 49 years, 50 to 59 years, and 60 to 70 years), and by study site. Study eligible, consented subjects were vaccinated IM with either HEPLISAV (3000 mcg 1018 ISS plus 20 mcg recombinant HBsAg) or 20 mcg Engerix-B vaccine.

The dosing regimen and schedule was identical to that of the pivotal phase 3 study, DV2-HBV-10. Subjects randomized to Engerix-B received injections of this vaccine at Week 0, Week 4 (1 month) and Week 24 (6 months). Subjects randomized to HEPLISAV received two injections of HEPLISAV vaccine at Weeks 0 and 4 and saline placebo at Week 24. Accordingly, all subjects received a total of three injections (active vaccine or matching placebo), given on Day 0, Week 4, and Week 24. Upon completion of Week 0, subjects returned to the clinical site at Weeks 4, 8, 12, 18, 24, 28, 32, 36, 44, and 52 to undergo clinical safety evaluations and to have blood drawn for safety laboratory studies and anti-HBsAg serum concentrations. The duration of the study was 56 weeks.

Efforts to blind Study DV2-HBV-16 encountered the same problem as DV2-HBV-10—namely a different volume and appearance of study vaccines when administered. The pharmacist or nurse that prepared the injection, as well as the physician or nurse who administered the injection, may have been aware of the vaccine assignment of each subject. In an effort to decrease bias in evaluating reactions to the vaccines, the investigator and study staff working with the subjects and the subjects themselves were to remain unaware of the treatment assignment (an observer-blind approach) in this Phase 3 study. Study injections for all groups were administered in the alternate arm from the previous injection.

Reviewer Comment: Given the caveats of a difference in the volume delivered per vaccination and solution appearance between the HEPLISAV and Engerix-B vaccines, an observer-blinded study is appropriate.

6.2.3 Population

The study population comprised HBV seronegative male and female subjects who met the following inclusion and exclusion criteria:

Inclusion Criteria:

- 40 to 70 years of age.
- Serum negative for HBsAg, anti-HBsAg antibody and anti-HBcAg antibody, and human immunodeficiency virus (HIV).
- Childbearing age females: appropriate practice of birth control for the duration of the study (defined as 28 days after the last injection with test article).

Exclusion Criteria:

- Any history of HBV or HIV infection or considered by the PI to be at high risk for recent exposure to HBV or HIV, e.g. current intravenous (IV) drug use, unprotected sex with known HBV or HIV positive partner.
- Prior immunization with any HBV vaccine (one or more doses).
- Known history of autoimmune disease.
- Receipt of blood products or immunoglobulin within 3 months prior to study entry, or likely to require infusion of blood products during the study period.
- Receipt of any inactivated vaccine 21 days prior to the first injection.
- Receipt of any live virus vaccine, systemic corticosteroids, G/GM-CSF, or any other investigational medicinal agent 4 weeks prior to the first injection.
- History of sensitivity to any component of the study vaccines.
- Undergoing chemotherapy or expected to receive chemotherapy during the study period; a diagnosis of cancer within the last 5 years other than squamous or basal cell carcinoma.
- Clinical condition that in the opinion of the PI would interfere with compliance or interpretation of the study results (e.g. substance or alcohol abuse).
- Pregnant, breastfeeding, or planning a pregnancy during the study.

Reviewer Comment: The inclusion and exclusion criteria for DV2-HBV-16 were appropriate.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Subjects randomized to the HEPLISAV group received a total of two injections of HEPLISAV. Injections were administered at Week 0 and 4. Each injection was given intramuscularly (IM) into the deltoid muscle of either arm using a 1 to 1.5 inch, 25-gauge needle. The arm used for injection was alternated with each injection. Total injection volume was 0.5 mL to deliver 3000 mcg of 1018 ISS and 20 mcg of HBsAg. For the third injection at Week 24, HEPLISAV group subjects received placebo (0.9% sterile saline for injection), administered in 0.5 mL in the same manner as the 1018 ISS-HBsAg. The test product was 20 mcg recombinant HBsAg subtype *adw* with 3000 mcg 1018 ISS adjuvant, manufactured by Rentschler BioTechnologie GmbH, Laupheim, Germany. The lot numbers used in this study were TDG006, TDG008, TDG009, and TDG010.

Engerix-B (20 mcg HBsAg combined with 50 mcg alum adjuvant, GlaxoSmithKline Biologicals) was used as the active comparator in this study and dosed according to the manufacturer's instructions. Subjects in the Engerix-B group received three IM injections, given as a 1.0 mL injection using a 25-gauge needle, at Week 0, 4, and 24.

Placebo was 0.9% sterile saline for injection manufactured by Hospira, Inc. and was used as the third dose in the HEPLISAV arm.

6.2.6 Sites and Centers

This phase 3 study was conducted at 29 sites in the U.S. (25 investigators) and 3 sites in Canada (3 investigators). The principal investigator was Scott Halperin, M.D., Dalhousie University, Nova Scotia, Canada.

6.2.7 Surveillance/Monitoring

Subjects were given their first injection of vaccine (either HEPLISAV or Engerix-B) and observed for 30 minutes for AEs. Local and systemic reactogenicity were evaluated at this time point and subjects were given a diary card on which to record the following reactogenicity symptoms for the following 7 days: redness, pain, and swelling at or near the injection site, malaise, headache, and fatigue. Study staff measured and recorded the redness and swelling at the injection site of the 30 minute post-injection assessment. All other symptoms were rated according to a 0 = none, 1 = mild (no interference with activity), 2 = moderate (some interference with activity), and 3 = severe (significant, prevents daily activity) scale. Study assessments are summarized in Table 24:

Table 24: Study Schedule: DV2-HBV-16

Visit	Screen	1	2	3	4	5	6	7	8	9	10	11	ED
Day	-28 to -1 (±7)	1 (±3)	29 (±7)	57 (±7)	85 (±7)	127 (±7)	169 (±7)	197 (±7)	225 (±7)	252 (±7)	309 (±7)	365 (±7)	
Week	-4	0	4	8	12	18	24	28	32	36	44	52	
Informed consent	X												
Inclusion/exclusion criteria	X												
Medical/Medication History	X	X											
Complete Physical Exam		X											
Limited Physical Exam ^a	X		X	X	X	X	X	X	X	X	X	X	X
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X	X
Autoimmune Questionnaire	X	X	X	X	X	X	X	X	X	X	X	X	X
Anti-HBsAg ^b		X	X	X	X	X	X	X	X	X	X	X	X
Reserve Serum Aliquot	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry/hematology testing	X	X	X				X	X					X
HIV/Hepatitis screen ^c	X												
ANA and anti-ds DNA		X										X	X
Serum Pregnancy Test	X												
Urine Pregnancy Test		X	X	X	X	X	X	X	X	X	X	X	X
Randomization		X											
Study Injection		X	X				X						
30'-Observation post-injection		X	X				X						
AE Assessment		X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Meds		X	X ^d	X	X	X	X	X ^e	X				
Diary Card Collection			X	X				X					

Abbreviations: AEs = adverse events, ANA = antinuclear antibody; anti-ds DNA = antibody to double-stranded deoxyribonucleic acid, Anti-HBsAg = ant body to hepatitis B surface antigen; SAEs = serious adverse events; ED: early discontinuation.

^aLimited physical exams were performed as needed if a subjects had a change in medical history or had an adverse event or autoimmune reaction.

^bThere was a minimum of 21 days between any study injection and subsequent anti-HBsAg sample collection.

^cHepatitis screen included hepatitis B surface antigen, antibody to hepatitis B surface antigen, and antibody to hepatitis B core antigen.

^dConcomitant medications taken up to 4 weeks prior to the first injection were to be reported.

^eConcomitant medications were all medications taken by the subject through Week 28 or Early Discontinuation. Concomitant medications were only to be reported after Week 28 if they were ongoing or if the subject received new medications to treat an SAE (Weeks 32 through 52).

Source: BLA 125428, DV2-HBV-16, Clinical Study Report, Table 9-3., Pages 36-37 of 215

At Study Week 0, and subsequently at Weeks 4, 8, 12, 24, 28, 32, 36, 44, and 52 (or early termination) subjects returned to the study site to have blood drawn for quantitative measurement of anti-HBsAg concentrations and for evaluation of safety and tolerability. The immune response (anti-HBsAg) was measured using the (b) (4). The accepted criterion for immunity to HBV is anti-HBsAg greater than or equal to 10 mIU/mL (6).

All study injections were administered by designated study personnel who also recorded all subject injection information on the appropriate CRF, and completed drug accountability logs following pre-specified study guideline procedures to monitor subject compliance with treatment.

Reviewer Comment: The study design demonstrated an appropriate plan for measuring anti-HBsAg antibody levels, for safety monitoring, and for insuring subject compliance with the vaccination schedule.

6.2.8 Endpoints and Criteria for Study Success

The primary immunogenicity endpoints of the study were the following:

1. The seroprotective rate (SPR) after the final active injection. The SPR was defined as the proportion of subjects who exhibit a seroprotective immune response, defined as: an anti-hepatitis B surface antigen antibody level greater than or equal to 10 mIU/mL. The primary SPR for HEPLISAV was measured at Week 12, and the primary SPR for Engerix-B was measured at Week 32.
2. Lot consistency in three consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification, measured by GMC at 4 weeks after the last active dose of HEPLISAV (Week 8).

The secondary immunogenicity endpoint was:

1. The determination of lot consistency between lot TDG006 (the initial lot studied) and the HEPLISAV consistency lots measured by GMC at 4 weeks after the last active dose of HEPLISAV (Week 8).

6.2.9 Statistical Considerations & Statistical Analysis Plan

The statistical analysis was based on Dynavax's Statistical Analysis Plan (SAP) dated March 17, 2011.

All statistical tests based on demographic, immunogenicity and safety data in study DV2-HBV-16 were performed at the two-sided 5% significance level. No adjustments for multiple testing performed for immunogenicity. All tests of noninferiority based on seroprotection rates (SPR) assumed a noninferiority margin of 10%.

No imputations were made for missing immunogenicity data. In computing the SPR rates, a subject who had missing anti-HBsAg titers at a given time point was considered as having a missing SPR and was excluded at that time point. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL.

Sample size estimates took into account a dropout rate of approximately 10%. Subject dropouts were not replaced. A sample size of 360 for each of the five randomization arms of the study was used in the power calculation.

The sample size of this study was driven not only by the need to establish noninferiority of HEPLISAV to Engerix-B but also the need to establish (a) the lot consistency and (b) the bridging between lot TDG006 and the three combined consistency lots of HEPLISAV (TDG008, TDG009 and TDG010). Most of the assumptions made for the sample size and power calculation were based on results from study DV2-HBV-10, conducted in healthy subjects 18-55 years of age and randomized within two strata (18-39 years and 40-55 years).

For the lot-to-lot consistency study based on GMC, an evaluable sample size of 360 per arm would generate a greater than 99% power if the similar common standard deviation of 0.52 from Study DV2-HBV-10 were to be observed in this study. Lot consistency analysis was adjusted for study site. GMC ratios between each pair of the three consistency lots were computed by ANOVA with the \log_{10} of the anti-HBsAg concentrations at each visit as the dependent variable and with factors for vaccine lot, study center and age category. GMC ratios and 95% CIs for the ratios of GMCs were constructed by exponentiating the difference of the least square means of the log-transformed concentrations and the lower and upper limits of the 95% CIs.

For the bridging study, which compared the immune response of subjects who were vaccinated with the 'old' HEPLISAV (lot 6) to the immune response of subjects vaccinated with the 'new' HEPLISAV (lots 8, 9, and 10), the power calculation was the same as that of the lot-to-lot consistency, using the same consistency criteria. Assuming 360 subjects in each group were evaluable, the power calculation was the same as that for the lot-to-lot consistency, using the same consistency criteria.

A summary table of immunogenicity testing and description of primary and secondary endpoints is presented in Table 25.

Table 25: Immunogenicity Testing (Study DV2-HBV-16)

Hypothesis	Study Parameter	Test
Primary	Non-inferiority of SPR, measured at 8 weeks after the last active dose of HEPLISAV (combined lots) vs. Engerix-B	Non-inferiority
Primary	Lot-to-lot consistency measured by GMC at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010).	Non-inferiority
Secondary	Lot-to-lot consistency measured by SPR at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010).	Non-inferiority
Secondary	Bridging lot-to-lot consistency: measured by SPR and GMC at 4 weeks after last active dose among 3 consecutively manufactured HEPLISAV lots (008, 009, 010) and an older lot of HEPLISAV (006).	Non-inferiority
Secondary	Noninferiority of SPR, measured at 8 weeks after the last active dose of HEPLISAV (combined lots) vs. Engerix-B in Type 2 Diabetics	Non-inferiority

Source: BLA 125428, DV2-HBV-16, Statistical Analysis Plan, 2. Study Objectives Page 8 of 38, Section 4.5. Immunogenicity Evaluation, pages 13-18 of 38

Reviewer Comment: A detailed description of the statistical methodology utilized to assess the primary and secondary endpoints can be found in Dr. Chowdhury's statistical review (Statistical Review and Evaluation. BLA STN 125438, Dr. Mridul K. Chowdhury, 01/29/2013).

Primary Immunogenicity Endpoints:

1. For the primary immunogenicity endpoint of 'comparison of the SPR between HEPLISAV and Engerix-B after the last dose of vaccine', HEPLISAV was declared non-inferior to Engerix-B with respect to SPR if the lower limit of the 95% CIs of the difference in seroprotection rates (HEPLISAV seroprotection rate at Week 12 minus the Engerix-B seroprotection rate at Week 32) was greater than -10%.
2. For the second, primary immunogenicity endpoint of 'lot-to-lot consistency for the immune response as measured by the GMC at 4 weeks after the last active dose among three consecutively manufactured lots of HEPLISAV after minor modification in the manufacturing process', lot-to-lot consistency was established if all three CIs for the pairwise ratios of GMCs were embedded in the interval between 2/3 (0.667) and 1.5.

Secondary Immunogenicity Endpoints:

1. Lot-to-lot consistency for the immune response, as measured by the SPR at 4 weeks after the last active dose among three consecutively manufactured lots of HEPLISAV from the manufacturing process after minor modification, was established if all 3 confidence intervals were embedded in the interval between -10% and +10%.
2. For the bridging study, the secondary immunogenicity objective was to demonstrate consistency of immune response at 4 weeks after the last active dose between HEPLISAV lots (008, 009, 010) prior to and after minor modifications to the manufacturing process (Lot 6). Consistency in the GMCs was shown if the entire

confidence interval of the consistency lots and Lot 6 of HEPLISAV was embedded in the interval between 0.667 and 1.5 and in SPRs, if the entire confidence interval was embedded in the interval between -10% and +10%.

All safety data were analyzed descriptively and based on the safety population. The most important safety parameters were presented for all sites combined. Summary statistics were used to describe autoimmune AEs, solicited post-injection reactions, AEs, and vital signs. A study sample size of 2000 subjects would result in approximately 1600 subjects on HEPLISAV (1200 on the 3 new lots and 400 on the previous lot). For this sample size, an event with an underlying rate of 0.20% (2 events in 1000) has a 96% chance of being detected, whereas an event with an underlying rate of 0.10% (1 event in 1000) has an 80% chance of being observed.

Reviewer Comment: An inconsistency was noted throughout study DV2-HBV-16 regarding testing of noninferiority of HEPLISAV against Engerix-B in type 2 diabetics in the SAP, clinical protocol, and final clinical report. The clinical reviewer relied on the SAP for the definitive determination of this secondary immunogenicity endpoint, as listed in Table 25.

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Three per protocol populations were used for the immunogenicity analysis in Study DV2-HBV-16, one for the noninferiority immunogenicity analysis, one for the lot consistency immunogenicity analysis, and one for the bridging study analysis (consistency of immune responses between lot TDG006 and the three combined consistency lots). These per protocol populations were defined as follows:

- **Noninferiority Per Protocol Population:** randomized subjects who received one of the three consistency lots of HEPLISAV or Engerix-B, received all three study injections as randomized and within the study visit windows, had no major protocol deviations, and had anti-HBsAg measurements and all injections within the specified day ranges.
- **Lot Consistency Per Protocol Population:** all subjects randomized to one of three consistency lots of HEPLISAV (TDG008, TDG009, and TDG010) who received the first two study injections within the study visit windows, had no major protocol deviations, and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.
- **Bridging Study Per Protocol:** all subjects randomized to lot TDG006 or to one of three consistency lots of HEPLISAV (TDG008, TDG009, and TDG010) concurrently with lot TDG006 who received the first two study injections within the study visit windows, had no major protocol deviations and had anti-HBsAg levels obtained within study visit windows at baseline and Week 8.

The other study analysis populations evaluated in this study comprised the following:

- The modified intent-to-treat (mITT) Population: defined as subjects who received at least one study injection and had at least one post-injection immunogenicity evaluation.
- The screened population: all subjects who consented to participate in the study and who were screened for eligibility assessment.
- The randomized population: all subjects who were randomized into the study.
- The safety population: all subjects who received at least one study injection, excluding subjects who had no on-study safety data.

In determining which subjects met criteria for inclusion into the per protocol populations, major protocol deviations were defined as any of the following:

- Subject did not meet one or more enrollment criteria,
- Subject did not receive correct vaccine as randomized,
- Vaccine was given outside protocol-specified visit windows at the following visits: Noninferiority population--Weeks 4 or 24; lot consistency population--Week 4,
- Serum sample collection was obtained outside protocol-specified windows at the following visits: Noninferiority population--Weeks 12 or 32; lot consistency population--Week 8,
- Subject received prohibited concomitant medication(s) through the following visits: Noninferiority population--Week 32; lot consistency population--Week 8.

The immunogenicity analysis using the per-protocol population was considered primary.

Safety was evaluated using the safety population, defined as enrolled subjects who received at least 1 study injection and had any post-baseline safety data.

Reviewer Comment: Protocol deviations for all treatment groups in the Lot Consistency Per Protocol Immunogenicity Analysis (n=1745 for HEPLISAV consistency lots total and Lot TDG006) fell within acceptable limits of approximately 9%-14% (86.2%-90.7% of subjects were included in this population), but were significantly higher for subjects randomized to the Noninferiority Per Protocol Immunogenicity Analysis (n=1513 for HEPLISAV consistency lots total and Lot TDG006; BLA 125428/0000, Study DV2—HBV-16, Clinical Study Report, Table 10-1., pages 58-59 of 215; data not shown).

The percentage of subjects excluded from this per protocol population for the noninferiority analysis ranged from 19.9% to 26.1%. The most common reasons for exclusion included (in order of frequency): vaccination given outside the allowed window, serum sample collection outside the allowed window, use of prohibited medication, no immunogenicity evaluations at 8 weeks after the last dose, and for a small number of subjects (range 1-15), not receiving the correct vaccine as randomized.

Accidental unblinding of treatment assignments occurred among 12 HEPLISAV subjects at Site 24 (Subjects 24-313, 24-305, 24-602, 24-312, 240303, 24-310, 24-304, 24-306, 24-307, 24-308, 24-301, 24-601). The unblinded study coordinator documented a protocol deviation for these 12 subjects which contained details of treatment assignment. The incident was discovered by Dynavax on May 27, 2011 after the study was completed; therefore no corrective action was taken.

Reviewer Comment: *This incident had no effect on the primary immunogenicity analysis because it occurred after Week 32 for all subjects involved. This incident also had a minimal effect on safety analysis of HEPLISAV, because all of these subjects had completed Week 36 or Week 44 and thus had already undergone blinded evaluation for reactogenicity and non-serious AEs prior to the incident. No site personnel involved in safety assessments for SAEs received the unblinded information. Three unrelated AEs were reported after the third study injection in Subject 24-305 (moderate insomnia), Subject 24-308 (mild finger infection), and Subject 24-602 (moderate left hip flexor sprain). Three reactogenicity events (mild myalgia, malaise and fatigue) were reported in Subject 24-305 after the third study injection. No SAEs were reported in these 12 subjects.*

6.2.10.1.1 Demographics

Demographic and baseline characteristics were similar between the two treatment groups, with no statistically significant differences found. Subject demographics are summarized in Table 26.

Table 26: Summary of Demographic and Baseline Characteristics (Study DV2-HBV-16): Randomized Population: Adults Only (Subjects 40 – 70 years of age)

Characteristic	Lot TDG008 (N=481)	Lot TDG009 (N=483)	Lot TDG010 (N=477)	HEPLISAV consistency Lots Total ^a (N=1441)	Lot TDG006 (N=528)	Engerix-B (n=483)	Total (n=2452)
Age, years, n (%)							
40-49	152 (31.6%)	153 (31.7%)	157 (32.9%)	462 (32.1%)	175 (33.1%)	160 (33.1%)	797 (32.5%)
50-59	193 (40.1%)	194 (40.2%)	189 (39.6%)	576 (40.0%)	208 (39.4%)	191 (39.5%)	975 (39.8%)
60-70	136 (28.3%)	136 (28.2%)	131 (27.5%)	403 (28.0%)	145 (27.5%)	132 (27.3%)	680 (27.7%)
N	481	483	477	1441	528	483	2452
Mean (SD)	54.1 (7.8)	54.1 (7.8)	53.9 (7.8)	54.0 (7.8)	54.1 (8.1)	53.8 (7.8)	54.0 (7.9)
Range	40-70	40-70	40-70	40-70	40-70	40-70	40-70
Gender, n (%)							
Male	241 (50.1%)	229 (47.4%)	218 (45.7%)	688 (47.7%)	255 (48.3%)	237 (49.1%)	1180 (48.1%)
Female	240 (49.9%)	254 (52.6%)	259 (54.3%)	753 (52.3%)	273 (51.7%)	246 (50.9%)	1272 (51.9%)
Race, n (%)							
White	400 (83.2%)	403 (83.4%)	389 (81.6%)	1192 (82.7%)	427 (80.9%)	402 (83.2%)	2021 (82.4%)
Black or African American	66 (13.7%)	72 (14.9%)	79 (16.6%)	217 (15.1%)	81 (15.3%)	68 (14.1%)	366 (14.9%)

Characteristic	Lot TDG008 (N=481)	Lot TDG009 (N=483)	Lot TDG010 (N=477)	HEPLISAV consistency Lots Total ^a (N=1441)	Lot TDG006 (N=528)	Engerix-B (n=483)	Total (n=2452)
Asian	4 (0.8%)	4 (0.8%)	6 (1.3%)	14 (1.0%)	12 (2.3%)	4 (0.8%)	30 (1.2%)
American Indian or Alaska Native	6 (1.2%)	1 (0.2%)	0	7 (0.5%)	4 (0.8%)	1 (0.2%)	12 (0.5%)
Native Hawaiian or Other Pacific Islander	0	0	1 (0.2%)	1 (0.1%)	0	0	1 (0.0%)
Other	5 (1.0%)	3 (0.6%)	2 (0.4%)	10 (0.7%)	4 (0.8%)	8 (1.7%)	22 (0.9%)
Ethnicity, n (%)							
Hispanic	32 (6.7%)	28 (5.8%)	28 (5.9%)	88 (6.1%)	29 (5.5%)	33 (6.8%)	150 (6.1%)
Non-Hispanic	447 (93.3%)	455 (94.2%)	449 (94.1%)	1351 (93.9%)	499 (94.5%)	450 (93.2%)	2300 (93.9%)
Baseline Anti-HBs Antibody, n (%)							
Positive ^b	9 (1.9%)	11 (2.3%)	10 (2.1%)	30 (2.1%)	19 (3.6%)	8 (1.7%)	57 (2.3%)

N= number of subjects randomized to the treatment group; SD = standard deviation

^a Lots TDG008, TDG009, and TDG010.

^b Seropositive to hepatitis B corresponds to antibody level ≥ 5 mIU/mL.

Source: BLA 125428, Clinical Study Report, DV2-HBV-16, Table 10-3, Pages 69-70 of 215

Subjects were also categorized by weight, height, body mass index, and smoking status as exploratory variables (data not presented). No significant differences between the two treatment groups were seen for these characteristics. The majority of enrolled study subjects (79% for both treatment groups) were non-smokers, non-diabetic (91-92%), and non-obese ($BMI \leq 30 \text{ kg/m}^2$ 56-57% for both treatment groups).

Reviewer Comment: Aside from an older age group enrolled in Study DV2-HBV-16, subject demographics for Study DV2-HBV-16 were similar across treatment groups to those noted in Study DV2-HBV-10: most subjects were hepatitis B seronegative Caucasians. An equal distribution of males and females were seen and a reasonably equal distribution of subjects across the three age strata were noted (somewhat higher in the age 50-59 year subgroup).

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

In the randomized population, the large majority of subjects (95.2%) reported a previous medical condition. No consistent medical condition(s) were noted between the two treatment groups that would significantly impact evaluation of efficacy or safety in this study. The percentage of subjects reporting any medical or surgical history was similar between HEPLISAV and Engerix-B vaccinated subjects. The most frequently reported medical conditions for all treatment groups combined were hypertension (29.5%), osteoarthritis (19.2%), and seasonal allergy (16.1%). Thirty-eight subjects were identified as having a diagnosis of hepatitis C virus infection at baseline (HEPLISAV consistency lots: n=24; lot TDG006: n=10, and Engerix-B: n=4).

As a secondary endpoint, this study sought to characterize the seroprotective rate of subjects with type 2 diabetes mellitus. A total of 219 subjects (8.9% of the randomized population) with confirmed type 2 diabetes were evaluated and similar across treatment groups (9.0% in the HEPLISAV consistency lot group, 9.7% in the TDG006 group, and 8.1% in the Engerix-B group). All 219 subjects with type 2 diabetes mellitus were included in the safety population.

Because prior history of autoimmune disease was of special interest in assessing safety for HEPLISAV, Dynavax sought to carefully characterize subjects with a history of, or active autoimmune disease before enrollment and throughout the study duration. A total of 30 subjects were identified as having pre-existing autoimmune disorders prior to vaccination. In these cases, the subject either reported an initial history of a general condition that was later confirmed as autoimmune, or while on study, volunteered additional history that was not initially provided. The common pre-existing autoimmune disorder of interest was hypothyroidism (n=10/30; 33%), followed by Bell's palsy (n=6/30; 20%). Ulcerative colitis, psoriasis, and pernicious anemia were reported in 2/30 subjects (7%). Of the 30 subjects identified, 23 subjects received HEPLISAV consistency lots and 7 subjects received Engerix-B. Nineteen of the 23 subjects completed the full three-dose regimen (HEPLISAV consistency lots: n=9; lot TDG006: n=5; Engerix-B: n=5). The other 11 subjects had treatment withdrawn after one injection.

A total of 80.5% of subjects reported taking at least one medication prior to study initiation. The most common classes of medications reported by more than 10% of subjects were multivitamins (20.1%), acetylsalicylic acid as a thrombolytic agent (15.2%), and ibuprofen (10.4%). The percentage of subjects using prior medications was similar among treatment groups for each therapeutic class.

Concomitant medication use during the study was reported by 86.3% of randomized subjects and was similar in frequency overall across treatment groups. The most common medications (used by 10% or more subjects) were: anti-inflammatory and antirheumatic agents (33.3%), lipid modifying agents (30.4%), vitamins (29.0%), analgesics (27.5%), agents acting on the rennin-angiotensin system (20.5%), antithrombotic agents (18.2%), antibacterials for systemic use (17.2%), psychoanaleptics (16.8%), drugs for acid-related disorders (14.3%), mineral supplements (13.3%), and antihistamines (13.0%). These represent medication classes commonly used in the general population for a myriad of common medical conditions.

Reviewer Comment: Review of medication use prior to, and for the study duration did not reveal any imbalance in medication use across the different treatment groups. The types of medications used in abundance were those used for common chronic medical conditions such as hypertension, hypercholesterolemia, etc. These would not be expected to impact immunogenicity responses, based on their mechanism of action.

The applicant did not provide summary data of vaccine use for each treatment group for the study duration, but review of individual subject data by line listings indicated

that concomitant vaccination during the study was rare. When reported, the most common vaccines administered were influenza vaccine and diphtheria pertussis and tetanus (DPT) vaccine (inactivated vaccines).

6.2.10.1.3 Subject Disposition

A total of 3793 subjects were initially screened for this study but 164 subjects went through the screening process twice because they were outside the window between screening and enrollment for the first screening. Of the subjects who were rescreened, 149 subjects were enrolled and 15 subjects failed rescreening. A total of 2452 (67.5%) randomized into the study. Screen failures comprised 1178 (32.5%) subjects. The most common reasons for screen failure were seropositivity for anti-HBs Ag (24.6%), a PI's assessment of poor general health (13.0%), seropositivity for anti-HBc Ag (10.7%), a known history of autoimmune disease (6.6%), and withdrawal of consent (6.3%).

Subjects were enrolled at 32 study sites: 29 sites in the U.S. and three in Canada. A total of 1441 subjects were randomized to one of the three consistency lots of HEPLISAV and 1969 subjects were randomized to any HEPLISAV treatment group. The actual randomization ratio by lot was similar to the planned ratio of 1:1:1:1. The actual randomization ratio of HEPLISAV to Engerix-B was similar to the planned ratio of 4:1. The actual randomization ratio of lot TDG006 concurrently to each of the 3 consistency lots and to Engerix-B was similar to the planned ratio of 3:1:1:1:1.

The noninferiority per protocol population comprised 1872 subjects (lot TDG008: n=366; lot TDG009: n=375; lot TDG010: n=382; lot TDG006: n=390; Engerix-B: n=359); representing 76.3% of the randomized population. The noninferiority per protocol population for the HEPLISAV lot consistency lot group included 1123 subjects (77.9% of those randomized). A similar percentage of subjects were excluded from the noninferiority per protocol population across treatment groups.

Reviewer Comment: The lower overall inclusion rate for the noninferiority per protocol population over that of the lot consistency per protocol population primarily resulted from the requirement that subjects receive all three study injections and all three anti-HBsAg collections within the appropriate visit window regardless of their treatment group.

In contrast to the lot consistency analysis, the noninferiority analysis involved comparisons between HEPLISAV and Engerix-B. These strict criteria for the noninferiority per protocol population were implemented in order to minimize bias against the immunogenicity of Engerix-B due to non-compliance with the third study injection. The most common reasons for exclusion from the noninferiority per protocol population were the following: receiving vaccination outside the visit window (n=104, 7.2%), applicant-designated exclusions relating to enrollment criteria or the temperature excursions in IMP storage (6.2%), serum sample collection outside the visit window (n=82, 5.7%), and receipt of a prohibited medication (n=54, 3.7%). The most common prohibited medications resulting in exclusion were systemic

corticosteroids and live and inactivated viral vaccines. Reasons for exclusion from the noninferiority per protocol population were similar across treatment groups.

Three randomized subjects (lot TDG009: n=2; Engerix-B: n=1) did not receive any study treatment and were therefore excluded from the safety population. The safety population included 2449 subjects (lot TDG008: n=481; lot TDG009: n=481; lot TDG010: n=477; lot TDG006: n=529; Engerix-B: n=481). Lot TDG006 had one subject more in the safety population than in the randomized population because one subject (Subject 47-007) randomized to Engerix-B was misdosed with a second injection of TDG006 and therefore reassigned to the TDG006 safety population. In addition, two subjects randomized to TDG009 and one subject randomized to Engerix-B withdrew consent. Therefore, because of the minimal difference between the randomized population and safety population, the demographics and baseline characteristics of the randomized population were similar to those of the safety population.

A total of 2269 subjects (92.5% of the randomized population) completed the study and 183 subjects (7.5%) discontinued the study early (before Week 52). The percentage of subjects completing the study was similar across all treatment groups. The most common reasons for early study discontinuation were loss to follow-up (3.8%), consent withdrawn (2.3%), and 'other' reasons (0.7%). Discontinuations due to adverse events occurred in one subject in the lot TDG008 group due to worsening hyponatremia in a subject with underlying hyponatremia (Subject 41-654). Two deaths occurred in the study (pulmonary embolism in Subject 22-003 in the TDG006 group and heart failure in Subject 92-638 in the Engerix-B group). Neither of these events were deemed related to study treatment by the Principal Investigator.

A summary of subject disposition for Study DV2-HBV-16 is provided in Table 27 below:

Table 27: Subject Disposition (Study DV2-HBV-16): Adults (40-70 years of age)

Disposition	Lot TDG008 (N=481)	Lot TDG009 (N=483)	Lot TDG010 (N=477)	HEPLISAV consistency Lots Total ^a (N=1441)	Lot TDG006 (N=528)	Engerix-B (n=483)	Total (n=2452)
Screened							3793
Randomized	481	483	477	1441	528	483	2452
--Subjects enrolled in parallel with Lot TDG006	187 (38.9%)	183 (37.9%)	181 (37.9%)	551 (38.2%)	528 (100.0%)	185 (38.3%)	1264 (51.5%)
Safety Population	481	481	477	1439	529^b	481	2449
--Subjects enrolled in parallel with Lot TDG006	187 (38.9%)	182 (37.7%)	181 (37.9%)	550 (38.2%)	529 (100.0%)	185 (38.2%)	1264 (51.5%)
mITT Population	476	478	472	1426	521	476	2423
--Subjects enrolled in parallel with Lot TDG006	186 (38.7%)	182 (37.7%)	178 (37.3%)	546 (37.9%)	521 (98.7%)	476 (98.6%)	2423 (98.8%)
Lot Consistency Per Protocol Population	428	438	424	1290	455	420	2165
--Subjects enrolled in parallel with Lot TDG006	170 (35.3%)	168 (34.8%)	164 (34.4%)	502 (34.8%)	455 (86.2%)	160 (33.1%)	1117 (45.6%)
Noninferiority Per Protocol Population	366	375	382	1123	390	359	1872
--Subjects enrolled in parallel with Lot TDG006	170 (35.3%)	168 (34.8%)	164 (34.4%)	502 (34.8%)	455 (86.2%)	160 (33.1%)	1117 (45.6%)
Completed Study	445	444	446	1335	483	451	2269
--Subjects enrolled in parallel with Lot TDG006	170 (35.3%)	168 (34.8%)	164 (34.4%)	502 (34.8%)	455 (86.2%)	160 (33.1%)	1117 (45.6%)
Discontinued	36 (7.5%)	39 (8.1%)	31 (6.5%)	106 (7.4%)	45 (8.5%)	32 (6.6%)	183 (7.5%)

Disposition	Lot TDG008 (N=481)	Lot TDG009 (N=483)	Lot TDG010 (N=477)	HEPLISAV consistency Lots Total ^a (N=1441)	Lot TDG006 (N=528)	Enerix-B (n=483)	Total (n=2452)
--Adverse Event	1 (0.2%)	0	0	1 (0.1%)	0	0	1 (0.0%)
--Subject Non-Compliance	2 (0.4%)	2 (0.4%)	1 (0.2%)	5 (0.3%)	1 (0.2%)	3 (0.6%)	9 (0.4%)
--Consent Withdrawn	9 (1.9%)	13 (2.7%)	8 (1.7%)	30 (2.1%)	15 (2.8%)	12 (2.5%)	57 (2.3%)
--Lost to Follow-up	17 (3.5%)	21 (4.3%)	15 (3.1%)	53 (3.7%)	28 (5.3%)	13 (2.7%)	94 (3.8%)
--Death	0	0	0	0	1 (0.2%)	1 (0.2%)	2 (0.1%)
--Protocol Violation	1 (0.2%)	0	2 (0.4%)	3 (0.2%)	0	1 (0.2%)	4 (0.2%)
--Other	6 (1.2%)	3 (0.6%)	5 (1.0%)	14 (1.0%)	0	2 (0.4%)	16 (0.7%)

N= number of subjects randomized to the treatment group; mITT: Modified intent-to-treat.

^a Lots TDG008, TDG009, and TDG010.

^b In the safety population, subjects were grouped based on actual treatment received. Subject 47-707 was randomized to Enerix-B but received HEPLISAV lot TDF006 for injection 2 and was analyzed under HEPLISAV lot TDG006.

Source: BLA STN 125428, Clinical Study Report, DV2-HBV-16, Section 10.2 Disposition of Subjects, Pages 65-66 of 215

Reviewer Comment: The rate of loss to follow-up was acceptable, was balanced between the treatment arms, and accordingly was unlikely to bias the findings of this study.

Treatment compliance of the randomized population with the three-dose regimen remained high throughout the study. Compliance was similar across all treatment groups, with 94.3% of HEPLISAV consistency lot groups, 92.0% of the TDG006 group, and 94.4% of Enerix-B group subjects receiving all three doses of vaccine.

Reviewer Comment: In all HEPLISAV dose groups, 1922 subjects (97.6%) received at least two doses, representing the complete regimen of active injections of HEPLISAV. Because the third dose of the three-dose regimen in the HEPLISAV treatment groups was placebo, the extent of exposure to HEPLISAV did not completely correspond with treatment compliance.

6.2.11 Efficacy Analyses

6.2.11.1 Analyses of Primary Endpoint(s)

Two primary immunogenicity endpoints were defined in Study DV2-HBV-16. The first primary immunogenicity analysis was a comparison of the SPR at 8 weeks after the last active dose of study treatment between HEPLISAV (Week 12) and Enerix-B (Week 32), using the noninferiority per protocol population that combined the three HEPLISAV consistency lots (TDG008, TDG009, and TDG010; also referred to as the HEPLISAV group).

The lot consistency per protocol population was used for the co-primary immunogenicity endpoint of lot consistency of the immune response in subjects who received one of three HEPLISAV consistency lots.

Table 28 presents the non-inferiority comparison of SPRs at 8 weeks after the last active dose of study treatment between HEPLISAV (Week 12) and Enerix-B (Week 32) for the per protocol population.

**Table 28: Primary Immunogenicity Endpoint Analysis:
SPR for HEPLISAV (Week 12) compared with Engerix-B (Week 32):
Per-Protocol Analysis Population, Adults 40-70 years of age (Study DV2-HBV-16)**

Visit	HEPLISAV ^a SPR (%) (n/N)	Engerix-B ^b SPR (%) (n/N)	Estimated Difference in SPR ^c (HEPLISAV-Engerix-B (95%) CI)	Non-inferiority Criteria Met? ^d (Yes/No)
Week 12/ Week 32	90.0 % (1011/1123)	70.5 % (253/359)	19.6% (14.7%, 24.7%)	Yes

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 levels \geq 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Two-sided 95% CIs of the difference in seroprotection rates between the HEPLISAV group at 12 weeks and the Engerix-B group at 32 weeks was supported using the Newcombe score method with continuity correction.

^d Non-inferiority was supported if the lower bound of the 2-sided 95% CI was $>$ -10%.

Source: BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-1, Page 83 of 215

The SPR in the HEPLISAV group was 90.0% and that of the Engerix-B group was 70.5%; the estimated difference between these rates was 19.6% (HEPLISAV- Engerix-B; 95% CI 14.7%, 24.7%).

Reviewer Comment: Because the lower limit of the 95% CI (14.7%) was greater than -10%, the SPR for the HEPLISAV group at Week 12 was noninferior to the SPR for the Engerix-B group at Week 32.

When the mITT population was evaluated, the difference in SPRs between the HEPLISAV group (87.7%) and the Engerix-B group (66.8%), 8 weeks after the last active dose of study treatment, was slightly higher than that observed in the noninferiority per protocol population (difference in SPRs=20.9% (95% CI, 16.4%, 25.5%).

For the co-primary endpoint of lot consistency of the immune response to consecutively manufactured lots of HEPLISAV, subjects were randomized to receive one of three 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 for primary analysis because data from Study DV2-HBV-10 suggested that the standard deviation (SD) induced by HEPLISAV at that time point was smaller than at later time points and would provide greater statistical power. However, after DV2-HBV-16 was unblinded and the data were analyzed, the SD of the GMC at Week 8 was found to be larger than at later weeks. The applicant reanalyzed the data from DV2-HBV-10 and found similar results to this study and different from the initial analysis of the SD in study DV2-HBV-10. This discrepancy was deemed an error in analysis used for planning DV2-HBV-16.

Reviewer Comment: *The applicant chose to evaluate lot consistency at a time point that had the least variability surrounding the GMC point estimate. As stated in Dr. Lorie Smith’s review of these data (Memorandum, Lorie Smith, M.D., M.H.S., 06/24/2011), submitted under IND 12692, Amendment 89, it is unclear why the time point with the most clinical relevance was not chosen. A review of these data by CBER concluded that although lot consistency criteria were not met at the pre-specified time point, lot consistency was met at 8 weeks after the last vaccination, the time point with the most clinical relevance (the primary immunogenicity endpoint), as well as several other time points [Memorandum, Lorie Smith, M.D., M.H.S., 06/24/2011, IND 12692, Amendment 89]. Accordingly, CBER agreed that clinical consistency of the three consecutively manufactured lots of HEPLISAV were demonstrated.*

The applicant’s GMC data from both Week 8 and Week 12, which corresponds to the primary immunogenicity endpoint for the noninferiority per protocol analysis, were analyzed and are presented in Table 29 below, which presents comparisons of GMCs at 4 weeks (Week 8) and 8 weeks (Week 12) after the last active dose in subjects who received one of three HEPLISAV consistency lots.

Table 29: Primary Immunogenicity Endpoint Analysis (Study DV2-HBV-16): Anti-HBsAg Geometric Mean Concentrations (mIU/mL) Among HEPLISAV Consistency Lots at Week 8 and Week 12 (Consistency Per Protocol Population); Adults 40-70 years of age

Visit	Lot TDG008 GMC (mIU/mL); 95% CI	Lot TDG009 GMC (mIU/mL); 95% CI	Lot TDG010 GMC (mIU/mL); 95% CI
Week 8 ^a	35.3 (27.5, 45.1) N=428	34.1 (26.5, 43.8) N=438	41.9 (32.5, 54.0) N=424
Week 12 ^b	77.6 (63.4, 95.1); N=426	82.9 (67.4, 101.9); N=434	90.5 (73.4, 111.6); N=422
	Adjusted GMC Ratio ^a (95% CI) Lot TDG008/Lot TDG009	Adjusted GMC Ratio ^a (95% CI) Lot TDG010/Lot TDG008	Adjusted GMC Ratio ^a (95% CI) Lot TDG010/Lot TDG009
Week 8 ^a	1.0 (0.8, 1.4)	1.2 (0.9, 1.6)	1.2 (0.9, 1.7)
Week 12 ^b	0.9 (0.7, 1.2)	1.2 (0.9, 1.5)	1.1 (0.9, 1.4)

CI = Confidence interval, GMC= geometric mean concentration, N = number of subjects with non-missing results in the analysis population in the treatment group. GMCs were adjusted for lot, center and age category.

^a 4 weeks after the last dose of HEPLISAV.

^b 8 weeks after the last dose of HEPLISAV.

Source: BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-2, Page 85 of 215

The 95% CI of the ratio of the GMCs of lots TDG008, TDG009 (ratio 1.04, 95% CI, 0.76, 1.41) was embedded in the interval between 0.667 and 1.5 and met the prespecified lot consistency criterion. However, the 95% CI of the ratio of the GMCs of lots TDG 010 and TDG008 (ratio 1.19; 95% CI, 0.87, 1.62) and of lots TDG 010 and TDG009 (ratio 1.23; 95% CI, 0.90, 1.67) were not embedded in the interval between 0.667 and 1.5 and did not meet the prespecified criterion because the GMC of lot TDG010 was higher than that of the other two lots.

At eight weeks after the last active dose of study treatment (Week 12), the 95% CIs of the pairwise ratios of the GMCs between the lots were entirely embedded within the interval between 0.667 and 1.5. Clinical consistency of the three consecutively manufactured lots

of HEPLISAV as manufactured by GMC was established by Week 12. The lot consistency results as measured by GMC in the mITT population were similar to those observed in the lot consistency per protocol population (data not shown, Table 14.1.3-17).

The 95% CIs of the three pair-wise ratios of the GMCs were within 0.667 and 1.5, inclusive at Weeks 18, 24, and 28 (data not shown). Lot consistency was also analyzed in the mITT population and was established by SPR at 4 weeks after the last active dose of HEPLISAV (Week 8).

Reviewer Comment: Review of the two primary immunogenicity endpoints demonstrated that HEPLISAV has a robust immune response and was noninferior in its immune response to the chosen active comparator, Engerix-B. Lot-to-lot consistency was demonstrated for the three consecutively manufactured lots, when compared at the most clinically relevant time point, which corresponded to that of the primary immunogenicity endpoint, i.e. measurement at 8 weeks after administration of the last dose of vaccine. The applicant fulfilled the criteria for success for the two co-primary endpoints.

6.2.11.2 Analyses of Secondary Endpoints

In addition to evaluation of the GMCs of the consecutively manufactured lots, the SPRs were also measured as part of the determination of lot consistency and as a secondary immunogenicity endpoint. Table 30 presents a comparison of SPRs in the HEPLISAV consistency lots at 4 weeks (Week 8) and 8 weeks (Week 12) after the last active dose.

Table 30: Secondary Immunogenicity Endpoint Analysis (Study DV2-HBV-16): Comparison of the SPR Among HEPLISAV Consistency Lots at Week 8 and 12 (Lot Consistency Per Protocol Population); Adults 40-70 years of age

Visit	Lot TDG000 SPR (95% CI) ^a	Lot TDG009 SPR (95% CI) ^a	Lot TDG010 SPR (95% CI) ^a
Week 8 ^c	327 (76.4%) (72.1%, 80.3%) N=428	320 (73.1%) (68.6%, 77.2%) N=438	329 (77.6%) (73.3%, 81.5%) N=424
Week 12 ^d	381 (89.4%); (86.1%, 92.2%) N=426	385 (88.7%) (85.3%, 91.5%) N=434	380 (90.0%) (86.6%, 92.7%) N=422
	% Difference (95% CI)^b Lot TDG008-Lot TDG009	% Difference (95% CI)^b Lot TDG010-Lot TDG008	% Difference (95% CI)^b Lot TDG010-Lot TDG009
Week 8 ^c	3.3% (-2.5, 9.1)	1.2% (-4.5, 6.8)	4.5% (-1.2, 10.2)
Week 12 ^d	0.7% (-3.5%, 4.9%)	0.6% (-3.5%, 4.7%)	1.3% (-2.8%, 5.5%)

CI = Confidence interval, N = number of subjects in the analysis population in the treatment group.

^a Calculated using the Clopper Pearson method.

^b Two-sided 95% CI of the % differences in seroprotection rates were calculated using the Newcombe score method with continuity correction.

^c Four weeks after the last active dose of HEPLISAV.

^d Eight weeks after the last active dose of HEPLISAV.

Source: BLA STN 125428, Clinical Study Report, DV2-HBV-16, Table 11-3, Page 87 of 215

At the prespecified time point of 4 weeks after the last active dose of HEPLISAV (Week 8), the 95% CI for the pair-wise comparisons of the differences of SPRs between lot TDG008 and TDG009 (95% CI, -2.5%, 9.1%) and between TDG010 and TDG008 (95% CI, -4.5%, 6.8%) were embedded in the interval between -10% and 10% and therefore met the prespecified lot consistency criterion. However, the upper 95% CI limit of the difference of TDG010-TDG009 (95% CI, -1.2%, 10.2%) was >10%. Lot consistency of the immune response was not established by SPR at 4 weeks after the second dose of HEPLISAV (Week 8) because of the higher immunogenicity of lot TDG010. At Week 12 (8 weeks after the last active dose of HEPLISAV, also the time point for the primary immunogenicity endpoint), the 95% CIs of the pair-wise differences of the SPRs between the lots were entirely embedded in the interval between -10% and 10%. Clinical consistency of the three consecutively manufactured lots of HEPLISAV, as measured by SPR, was established at Week 12. At all subsequent study visits (Weeks 18, 24, 28, 32, 36, 44, and 52), the 95% CIs of all of the three pair-wise comparisons of the differences of SPRs were embedded in the interval between -10.0% and 10.0% (data not shown).

Reviewer comment: These data support a determination of lot consistency.

Bridging of the immune response between HEPLISAV lots produced using the final manufacturing process (combined lots TDG008, TDG009, and TDG010) to a previously manufactured lot (TDG006) comprised an additional secondary immunogenicity endpoint. This analysis 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. GMC and SPR data for this bridging study are presented in Table 31.

Table 31: Secondary Immunogenicity Endpoint Analysis: GMCs and SPRs of Combined Consistency Lots (TDG008, TDG009, TDG010) compared to Lot 006

Study Parameter	Combined Consistency Lots (008, 009, 010), N	Lot TDG006, N	
			Ratio of GMCs (HEPLISAV/ Engerix-B); 95% CI
GMC at Week 8, 95%CI	38.7 (31.6, 47.4) N=502	35.4 (28.4, 44.0) N=455	1.1 (0.8, 1.5)
GMC at Week 12 95%CI	91.7 (77.7, 108.2) N=499	77.0 (64.6, 91.8) N=450	1.2 (0.9, 1.5)
			Difference in GMCs (HEPLISAV - Engerix-B)
SPR at Week 8	76.3% (72.3, 80.0) N=502	74.5% (70.2%, 78.4%) N=455	1.8% (-3.7, 7.3)
SPR at Week 12	90.4% (87.4%, 92.8%) N=499	88.4% (85.1%, 91.2%) N=450	1.9% (-2.0%, 5.9%)

Source: BLA STN 125428, Clinical Study Report, DV2-HBV-16, Section 11.2.2, Bridging of the Immune Response Between HEPLISAV Lots Produced Using the Final Manufacturing Process and a Previously Manufactured Lot, Page 88-89 of 215, Table 14.1.3-9, pages 24-26 of 180

The immunogenicity of consistency lots TDG008, TDG009, and TDG010 was similar to the immunogenicity of a previously manufactured lot (TDG006) measured by the GMC at 4 weeks after the last active dose of HEPLISAV (Week 8). The ratio of the GMC in subjects who received one of the combined consistency lots (38.7 mIU/mL; 95% CI, 31.6, 47.4) to the GMC in subjects who received lot TDG006 (35.4 mIU/mL; 95% CI, 28.4, 44.0) was 1.09 (95% CI, 0.81, 1.47).

At the primary immunogenicity endpoint of 8 weeks after the last active dose of HEPLISAV (Week 12), the GMCs in subjects who received one of the consistency lots was 91.7 mIU/mL and in subjects who received lot TDG006 was 77.0 mIU/mL. The ratio of the GMCs of those who received one of the consistency lots to those who received lot TDG006 was 1.19 (95% CI, 0.94, 1.51).

Reviewer comment: The combined consistency lots produced using the final manufacturing process were slightly more immunogenic than the previously manufactured lot. The immunogenicity of the consistency lots was similar to the immunogenicity of the previously manufactured lot (TDG006), measured by the SPR 4 weeks after the last active dose of HEPLISAV (Week 8).

At the primary immunogenicity time point of 8 weeks after the last active dose of HEPLISAV (Week 12), the SPR in subjects who received one of the consistency lots was 90.4% and in subjects who received lot TDG006 was 88.4%. The difference in SPRs between those who received one of the consistency lots and those who received lot TDG006 was 1.9% (95% CI, -2.0%, 5.9%)—a minor difference between the two lot comparisons.

Reviewer Comment: Lot consistency was demonstrated between the combined consistency lots using the final manufacturing process and an earlier lot (TDG006) when measured 4 weeks after the final vaccination (Week 8) but the combined lots were slightly more immunogenic when measured 8 weeks after the last vaccination (Week 12). This result was driven by slightly higher GMCs in the combined consistency lots, in particular, lot TDG010, though the SPR between the two groups at this time point did not differ significantly.

6.2.11.3 Subpopulation Analyses

Subpopulation analysis of the immune response to HEPLISAV vs. Engerix-B was conducted by age, as stratified by subjects 40-49 years of age, 50-59 years, and those 60-70 years, and by gender. Because the majority of subjects were Caucasian, the study was not adequately powered to detect significant changes in SPR based on racial and ethnic profiles and these analyses were not conducted by the applicant nor provided in the final clinical study report.

Table 32 presents a comparison of SPRs by age strata, for the ‘per protocol’ combined HEPLISAV and Engerix-B vaccinated subjects.

**Table 32: Seroprotection Rates by Visit and Age Strata (Study DV2-HBV-16):
Per-Protocol Analysis Population (Adults 40-70 years of Age)**

Visit	n/N	HEPLISAV ^a SPR (95 %CI)	n/N	Enerix-B ^b SPR (95% CI) ^c	% Difference in SPR ^d (HEPLISAV-Enerix-B (95% CI)
Week 4					
40-49 years	87/367	23.7% (19.4%, 28.4%)	4/116	3.4% (0.9%, 8.6%)	20.3% (13.6%, 25.3%)
50-59 years	100/455	22.0% (18.3%, 26.1%)	8/138	5.8% (2.5%, 11.1%)	16.2% (9.8%, 21.0%)
60-70 years	36/301	12.0% (8.5%, 16.2%)	4/105	3.8% (1.0%, 9.5%)	8.2% (1.6%, 12.8%)
Week 8					
40-49 years	309/367	84.2% (80.1%, 87.8%)	27/116	23.3% (15.9%, 32.0%)	60.9% (51.5%, 68.4%)
50-59 years	348/454	76.7% (72.5%, 80.5%)	30/138	21.7% (15.2%, 29.6%)	54.9% (46.2%, 61.9%)
60-70 years	202/301	67.1% (61.5%, 72.4%)	16/105	15.2% (9.0%, 23.6%)	51.9% (42.0%, 59.4%)
Week 12					
40-49 years	346/367	94.3% (91.4%, 96.4%)	24/116	20.7% (13.7%, 29.2%)	73.6% (64.8%, 80.2%)
50-59 years	417/455	91.6% (88.7%, 94.0%)	22/138	15.9% (10.3%, 23.1%)	75.7% (68.1%, 81.3%)
60-70 years	248/301	82.4% (77.6%, 86.5%)	15/105	14.3% (8.2%, 22.5%)	68.1% (58.8%, 74.7%)
Week 18					
40-49 years	358/367	97.5% (95.4%, 98.9%)	28/116	24.1% (16.7%, 33.0%)	73.4% (64.6%, 80.3%)
50-59 years	438/455	96.3% (94.1%, 97.8%)	27/138	19.6% (13.3%, 27.2%)	76.7% (68.9%, 82.6%)
60-70 years	266/301	88.4% (84.2%, 91.8%)	15/105	14.3% (8.2%, 22.5%)	74.1% (65.1%, 80.3%)
Week 24					
40-49 years	359/367	97.8% (95.8%, 99.1%)	26/116	22.4% (15.2%, 31.1%)	75.4% (66.7%, 82.1%)
50-59 years	437/455	96.0% (93.8%, 97.6%)	30/138	21.7% (15.2%, 29.6%)	74.3% (66.4%, 80.5%)
60-70 years	272/301	90.4% (86.5%, 93.5%)	21/105	20.0% (12.8%, 28.9%)	70.4% (60.8%, 77.4%)
Week 28					
40-49 years	357/366	97.5% (95.4%, 98.9%)	89/116	76.7% (68.0%, 84.1%)	20.8% (13.8%, 29.4%)
50-59 years	437/455	96.0% (93.8%, 97.6%)	99/137	72.3% (64.0%, 79.6%)	23.8% (16.7%, 31.9%)
60-70 years	270/301	89.7% (85.7%, 92.9%)	72/104	69.2% (59.4%, 77.9%)	20.5% (11.5%, 30.4%)
Week 32					
40-49 years	360/367	98.1% (96.1%, 99.2%)	90/116	77.6% (68.9%, 84.8%)	20.5% (13.6%, 29.0%)
50-59 years	436/455	95.8% (93.6%, 97.5%)	96/138	69.6% (61.2%, 77.1%)	26.3% (18.9%, 34.5%)
60-70 years	269/301	89.4% (85.3%, 92.6%)	67/105	63.8% (53.9%, 73.0%)	25.6% (16.1%, 35.5%)
Week 36					
40-49 years	352/361	97.5% (95.3%, 98.9%)	85/113	75.2% (66.2%, 82.9%)	22.3% (15.0%, 31.1%)
50-59 years	429/451	95.1% (92.7%, 96.9%)	89/138	64.5% (55.9%, 72.4%)	30.6% (22.8%, 39.1%)
60-70 years	267/299	89.3% (85.2%, 92.6%)	59/104	56.7% (46.7%, 66.4%)	32.6% (22.6%, 42.6%)
Week 44					
40-49 years	347/359	96.7% (94.2%, 98.3%)	74/111	66.7% (57.1%, 75.3%)	30.0% (21.6%, 39.3%)
50-59 years	421/450	93.6% (90.0%, 95.6%)	83/138	60.1% (51.5%, 68.4%)	33.4% (25.2%, 42.0%)
60-70 years	262/294	89.1% (85.0%, 92.4%)	54/104	51.9% (41.9%, 61.8%)	37.2% (27.0%, 47.2%)
Week 52					
40-49 years	344/359	95.8% (93.2%, 97.6%)	72/112	64.3% (54.7%, 73.1%)	31.5% (22.9%, 40.9%)
50-59 years	413/447	92.4% (89.5%, 94.7%)	82/138	59.4% (50.7%, 67.7%)	33.0% (24.7%, 41.6%)
60-70 years	255/295	86.4% (82.0%, 90.1%)	55/104	52.9% (42.8%, 62.8%)	33.6% (23.3%, 43.7%)

CI = Confidence interval, N = number of subjects in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Calculated using the Clopper Pearson method.

^d Two-sided 95% CI of the % difference in seroprotection rates between the HEPLISAV and Enerix-B were calculated using the Newcombe score method with continuity correction.

Source: BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-11, pages 101-102 of 215

After Week 4, the SPR for both treatment groups were consistently highest in the age 40-49 year subgroup, followed by the 50-59 year subgroup. The SPR in the HEPLISAV group was higher than the Enerix-B group at all visits and for all age strata, and also appeared to increase more rapidly in the younger age group than in the oldest age group.

Reviewer Comment: *The SPR in the oldest age group who received HEPLISAV was higher than the SPR in the youngest age group who received Engerix-B at each visit. In the oldest age group, the SPR in the HEPLISAV group (90.4%) peaked 20 weeks after the last active dose of HEPLISAV and decreased only 4.4% to 86.4% at Week 52. The peak SPR in the oldest group who received Engerix-B (69.2%) was at Week 28, 4 weeks after the last dose of active vaccine, and decreased 23.6% to 52.9% at Week 52. The robust immune response to HEPLISAV appeared to be sustained somewhat longer than did Engerix-B, in older subjects.*

A comparison of anti-HBsAg GMCs by age strata and by study visit between the HEPLISAV and Engerix-B groups were generally consistent with the findings reported for the SPR (data not shown, BLA STN 125428, DV2-HBV-10, Clinical Study Report, Table 11-12, pages 104-105 of 215). Higher GMCs were reported in the HEPLISAV group than in the Engerix-B group for each age subgroup at all visits. At Week 28, when the GMC for Engerix-B peaked, the GMC in the HEPLISAV age groups ranged from 2-fold higher than Engerix-B, in the 40-49 year old group to 3-fold higher in the 50-59 year old group. At Week 52, the GMC in the HEPLISAV age groups ranged from 7-fold higher than Engerix-B in the 40- to 49-year old group to 8-fold higher in the 60-70 year old group.

Gender sub-group analyses are presented in Table 33.

Table 33: Seroprotection Rates in Females and Males by Visit (Study DV2-HBV-16): Per-Protocol Analysis Population (Adults 40-70 years of Age)

Visit	n/N	HEPLISAV ^a SPR (95 %CI)	n/N	Engerix-B ^b SPR (95% CI) ^c	% Difference in SPR ^d (HEPLISAV-Engerix-B (95% CI)
Week 4					
Females	113/586	19.3% (16.2%, 22.7%)	11/181	6.1% (3.1%, 10.6%)	13.2% (7.8%, 17.5%)
Males	110/537	20.5% (17.1%, 24.1%)	5/178	2.8% (0.9%, 6.4%)	17.7% (12.8%, 21.6%)
Week 8					
Females	469/586	80.0% (76.6%, 83.2%)	48/181	26.5% (20.2%, 33.6%)	53.5% (45.8%, 60.1%)
Males	390/536	72.8% (68.8%, 76.5%)	25/178	14.0% (9.3%, 20.0%)	58.7% (51.6%, 64.3%)
Week 12					
Females	539/586	92.0% (89.5%, 94.0%)	38/181	21.0% (15.3%, 27.7%)	71.0% (64.0%, 76.6%)
Males	390/536	87.9% (84.8%, 90.5%)	23/178	12.9% (8.4%, 18.8%)	75.0% (68.5%, 79.8%)
Week 18					
Females	557/586	95.1% (93.0%, 96.7%)	47/181	26.0% (19.7%, 33.0%)	69.1% (61.9%, 875.1%)
Males	505/537	96.3% (91.7%, 95.9%)	23/178	12.9% (8.4%, 18.8%)	81.1% (74.9%, 85.6%)
Week 24					
Females	560/586	95.6% (93.6%, 97.1%)	51/181	28.2% (21.8%, 35.3%)	67.4% (60.1%, 73.6%)
Males	508/537	94.6% (92.3%, 96.4%)	26/178	14.6% (9.8%, 20.7%)	80.0% (73.6%, 84.7%)
Week 28					
Females	558/586	95.2% (93.2%, 96.8%)	140/180	77.8% (71.0%, 83.6%)	17.4% (11.6%, 24.2%)
Males	506/536	94.4% (92.1%, 96.2%)	120/177	67.8% (60.4%, 74.6%)	26.6% (19.8%, 34.0%)
Week 32					
Females	560/586	95.6% (93.6%, 97.1%)	139/181	76.8% (70.0%, 82.7%)	18.8% (12.9%, 25.6%)
Males	505/537	94.0% (91.7%, 95.9%)	114/178	64.0% (56.5%, 71.1%)	30.0% (22.9%, 37.5%)
Week 36					
Females	550/580	94.8% (92.7%, 96.5%)	135/180	75.0% (68.0%, 81.1%)	19.8% (13.7%, 26.8%)
Males	498/531	93.8% (91.4%, 95.7%)	98/175	56.0% (48.3%, 63.5%)	37.8% (30.3%, 45.4%)

Visit	n/N	HEPLISAV ^a SPR (95 %CI)	n/N	Engerix-B ^b SPR (95% CI) ^c	% Difference in SPR ^d (HEPLISAV-Engerix-B (95% CI)
Week 44					
Females	542/576	94.1% (91.8%, 95.9%)	125/178	70.2% (62.9%, 76.8%)	23.9% (17.3%, 31.2%)
Males	488/527	92.6% (90.0%, 94.7%)	86/175	49.1% (41.5%, 56.8%)	43.5% (35.7%, 51.0%)
Week 52					
Females	534/575	92.9% (90.5%, 94.8%)	126/178	70.8% (63.5%, 77.3%)	22.1% (15.5%, 29.4%)
Males	478/526	90.9% (88.1%, 93.2%)	83/176	47.2% (39.6%, 54.8%)	43.7% (35.9%, 51.3%)

CI = Confidence interval, N = number of subjects in the analysis population in the treatment group, n = number of subjects with post-injection anti-HBsAg levels ≥ 10 mIU/mL.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Calculated using the Clopper Pearson method.

^d Two-sided 95% CI of the % difference in proportions between the HEPLISAV and Engerix-B group were computed using the Newcombe score method with continuity correction.

Source: BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-14, pages 110-111 of 215

Reviewer Comment: Gender subgroup analysis revealed that both men and women responded robustly to HEPLISAV vaccination, though the SPR was generally slightly higher in women than men. Based on the numerical differences seen, it is unlikely that these differences would be statistically or clinically significant.

In summary, subgroup analysis of HEPLISAV response based on age and gender did not reveal differences that were likely to have any clinical significance.

6.2.11.4 Dropouts and/or Discontinuations

Dropouts and missing data were assumed to be missing completely at random. No imputations were made for missing data. In the computation for GMC, anti-HBsAg levels below the lower limit of detection and reported as < 5 mIU/mL were considered as 2.5 mIU/mL.

Reviewer Comment: Although the data for the mITT population were not presented in this review, the primary and secondary immunogenicity endpoint findings for this population and conclusions reached regarding seroprotection and antibody responses, did not differ significantly from the per protocol population.

6.2.11.5 Exploratory and Post Hoc Analyses

Exploratory analyses comprised a comparison of SPR and GMCs, for HEPLISAV and Engerix-B vaccinated subjects, at each study visit. Table 34 summarizes the comparisons of the estimated SPRs for each time point. Throughout the study duration, SPRs in HEPLISAV vaccinated subjects surpassed those of Engerix-B vaccinated subjects.

Table 34: Comparison of the SPR Between HEPLISAV and Engerix-B by Visit (Study DV2-HBV-16): Per-Protocol Analysis Population (Adults 40-70 years of Age)

Visit	n/N	HEPLISAV ^a SPR (95 %CI)	n/N	Engerix-B ^b SPR (95% CI) ^c	% Difference in SPR ^d (HEPLISAV-Engerix-B (95% CI)
Week 4	223/1123	19.9% (17.6%, 22.3%)	16/359	4.5% (2.6%, 7.1%)	15.4% (11.9%, 18.4%)

Visit	n/N	HEPLISAV ^a SPR (95 %CI)	n/N	Engerix-B ^b SPR (95% CI) ^c	% Difference in SPR ^d (HEPLISAV-Engerix-B (95% CI)
Week 8	859/1122	76.6% (74.0%, 79.0%)	73/359	20.3% (16.3%, 24.9%)	56.2% (51.1%, 60.7%)
Week 12	1011/1123	90.0% (88.1%, 91.7%)	61/359	17.0% (13.3%, 21.3%)	73.0% (68.4%, 76.9%)
Week 18	1062/1123	94.6% (93.1%, 95.8%)	70/359	19.5% (15.5%, 24.0%)	75.1% (70.4%, 79.0%)
Week 24	1068/1123	95.1% (93.7%, 96.3%)	77/359	21.4% (17.3%, 26.1%)	73.7% (68.9%, 77.7%)
Week 28	1064/1122	94.8% (93.4%, 96.1%)	260/357	72.8% (67.9%, 77.4%)	22.0% (17.4%, 27.0%)
Week 32	1065/1123	94.8% (93.4%, 96.1%)	253/359	70.5% (65.5%, 75.1%)	24.4% (19.7%, 29.4%)
Week 36	1048/1111	94.3% (92.8%, 95.6%)	233/355	65.5% (60.4%, 70.6%)	28.7% (23.7%, 33.9%)
Week 44	1030/1103	93.4% (91.8%, 94.8%)	211/353	59.8% (54.5%, 64.9%)	33.6% (28.4%, 39.0%)
Week 52	1012/1101	91.9% (90.1%, 93.5%)	209/354	59.0% (53.7%, 64.2%)	32.9% (27.6%, 38.3%)

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

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

^c Calculated using the Clopper Pearson method.

^d Two-sided 95% CI of the % difference in proportions between the HEPLISAV and Engerix-B group at each visit were computed using the Newcombe score method with continuity correction.

Source: BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-7, page 93 of 215

Reviewer Comment: HEPLISAV vaccinated subjects demonstrated a rapid and sustained increase in SPR. Starting with Week 12, which corresponded to the time point used for assessing the primary immunogenicity endpoint, the SPR in HEPLISAV vaccinated subjects exceeded 90% and remained above 90% at the final study time point—Week 52. The SPRs in Engerix-B vaccinated subjects peaked at 76.6% (Week 28) and declined thereafter. Based on the SPR data, the majority of subjects given HEPLISAV appeared to be protected against hepatitis B by Week 8 (SPR=76.6%), whereas the majority of Engerix-B vaccinated subjects were protected by Week 28 (SPR=72.8%).

A similar trend in immune response was seen with analysis of the GMCs by study visit for HEPLISAV vs. Engerix-B, as depicted in Table 35 below.

Table 35: Comparison of Anti-HBsAg Geometric Mean Concentration (mIU/mL) Between HEPLISAV and Engerix-B by Study Visit (Study DV2-HBV-16): Per-Protocol Analysis Population (Adults 40-70 years of Age)

Visit	N	HEPLISAV ^a GMC (95 %CI)	N	Engerix-B ^b GMC (95% CI)	Ratio HEPLISAV/Engerix-B (95% CI)
Week 4	1123	1.3 (1.1, 1.6)	359	0.2 (0.2, 0.3)	5.75 (4.2, 7.7)
Week 8	1122	41.5 (36.1, 47.6)	359	0.9 (0.7, 1.2)	44.23 (33.0, 59.2)
Week 12	1123	93.0 (82.9, 104.2)	359	0.8 (0.6, 1.1)	113.35 (88.4, 145.4)
Week 18	1123	192.2 (173.8, 212.6)	359	0.9 (0.7, 1.1)	220.44 (175.4, 277.1)
Week 24	1123	232.7 (210.2, 257.5)	359	1.0 (0.8, 1.3)	137.67 (188.8, 299.2)
Week 28	1122	232.0 (209.2, 257.2)	356	88.5 (59.4, 131.9)	2.62 (2.0, 3.5)
Week 32	1123	222.3 (200.3, 246.7)	359	61.4 (41.7, 90.5)	3.62 (2.7, 4.8)
Week 36	1111	208.6 (187.6, 231.9)	355	46.8 (31.8, 68.8)	4.46 (3.4, 5.9)
Week 44	1103	180.1 (161.9, 200.5)	353	27.2 (18.7, 39.6)	6.62 (5.0, 8.8)
Week 52	1101	150.7 (134.8, 168.5)	354	19.5 (13.5, 28.1)	7.74 (5.8, 10.3)

GMC= geometric mean concentration, N = number of subjects in the analysis population in the treatment group.

^a Study injections were given at Weeks 0, 4, 24 (placebo).

^b Study injections were given at Weeks 0, 4, 24.

Source: BLA STN 125428, DV2-HBV-16, Clinical Study Report, Table 11-9, page 98 of 215

Reviewer Comment: The GMCs were higher, peaked more quickly and remained elevated longer in HEPLISAV vaccinated subjects. Based on the GMC data, subjects appeared to be protected against hepatitis B by the Week 8 time point for HEPLISAV and Week 28 time point for Engerix-B. These findings were consistent with those seen for the SPR analyzed at each respective time point.

SUMMARY of the Immunogenicity Analysis: Review of primary, secondary, and exploratory immunogenicity endpoints confirmed that HEPLISAV demonstrated a robust immune response against hepatitis B surface antigen, as shown by GMCs and the seroprotective rate, defined as a GMC greater than or equal to 10 mIU/mL. GMCs and SPR were non-inferior to the chosen active comparator, Engerix-B. The immune response after vaccination with HEPLISAV to HBsAg was rapid and sustained. Subgroup analysis for age and gender did not reveal any clinically relevant discrepancies amongst the age groups evaluated, nor for men vs. women. Because the majority of subjects evaluated in this study were Caucasian, as subgroup analysis for race and ethnicity would not yield informative data and thus was not performed.

6.2.12 Safety Analyses

6.2.12.1 Methods

The safety population consisted of all subjects who received at least 1 study injection, excluding subjects who had no on-study safety data. Three randomized subjects (lot TDG009: n=2; Engerix-B: n=1) did not receive any study treatment and were therefore excluded from the safety population. The safety population included 2449 subjects (lot TDG008: n=481; lot TDG009: n=481; lot TDG010: n=477; lot TDG006: n=529; Engerix-B: n=481). One subject randomized to Engerix-B was misdosed with a second injection of TDG006 and was therefore reassigned to the TDG 006 safety population. Two subjects randomized to TDG009 and 1 subject randomized to Engerix-B withdrew before dosing.

Diary cards solicited information about the presence and severity of post-injection local (injection-site) reactions (redness, swelling, pain) and systemic reactions (fatigue, headache, malaise). Oral temperature was also recorded. Diary entries were completed by the subject on Days 0-6.

The intensity of solicited post-injection reactions were reported by the subject as grades 0 through 3 using the following definitions:

- Grade 0 = none
- Grade 1 = mild (no interference with activity)
- Grade 2 = moderate (some interference with activity)
- Grade 3 = severe (significant interference, prevents daily activity)

The intensity of redness at the injection site and swelling at the injection site were defined using the following quantitative ranges:

- Diameter less than < 25mm
- Mild*: diameter >25mm to ≤50 mm
- Moderate*: diameter >50mm to ≤100mm
- Severe*: diameter greater than >100 mm

AEs were recorded by the subjects on diary cards from Week 0 through Week 28. The severity of AEs was graded based on the toxicity grading scale known as the Common Terminology Criteria for Adverse Events provided by the Cancer Therapy Evaluation Program (CTEP). Events not listed in this toxicity grading scale were graded as follows:

- Grade 1 = mild (no interference with activity)
- Grade 2 = moderate (some interference with activity, requiring medical intervention)
- Grade 3 = severe (prevents daily activity and requires medical intervention)
- Grade 4 = potentially life threatening (emergency room visit or hospitalization)
- Grade 5 = Death

Table 24 in section 6.2.7 outlines the safety evaluation procedures. Section 6.2.9 describes how the safety data was analyzed.

6.2.12.2 Overview of Adverse Events

The reporting period for non-serious AEs was the time period from the first injection (Week 0) until 4 weeks after the third injection (Week 28). Table 36 provides an overall summary of adverse events by treatment group.

Table 36: Overall Summary of Adverse Events by Treatment Group for Subjects Enrolled in Study HBV-16

Event, n (%)	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Any AE	230 (47.8)	243 (50.5)	254 (53.2)	727 (50.5)	268 (50.7)	255 (53.0)
Any Related AE	32 (6.7)	32 (6.7)	39 (8.2)	103 (7.2)	39 (7.4)	29 (6.0)
Any AE Grade 3 or above	21 (4.4)	24 (5.0)	20 (4.2)	65 (4.5)	30 (5.7)	26 (5.4)
Any AE within 28 Days after Active Injection	150 (31.2)	148 (30.8)	147 (30.8)	445 (30.9)	156 (29.5)	250 (52.0)
Any Investigator-Reported AIAE	3 (0.6)	2 (0.4)	2 (0.4)	7 (0.5)	0	0

Event, n (%)	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Any Related Investigator-Reported AIAE	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.3)	0	0
Any SAE	18 (3.7)	12 (2.5)	19 (4.0)	49 (3.4)	27 (5.1)	23 (4.8)
Any Related SAE	0	0	0	0	0	1 (0.2)
Any AE Leading to Discontinuation of Study Vaccine	4 (0.8)	4 (0.8)	5 (1.0)	13 (0.9)	4 (0.8)	2 (0.4)
Death	0	0	0	0	1 (0.2)	1 (0.2)

Source: Adapted from STN 125428/0. DV2-HBV-16 Clinical Study Report, Table 12-10, page 148.

Overall, the proportion of subjects experiencing any AE was similar among treatment groups. There were more active injections in the Engerix-B group and therefore more AEs reported after active injections in this treatment arm than in other arms. Based on the information provided in this table, there were 7 (0.5%) investigator-reported AIAEs among the HEPLISAV consistency lots, but none in Lot TDG006 or Engerix-B arms. Four (0.3%) of those AIAEs were considered related to the investigational product. Nine total events among HEPLISAV recipients were considered potential AIAEs and were sent to the SEAC for adjudication. Five of those events were considered by the investigator as related to the study vaccine. Section 6.2.12.5 provides further detail on the applicant's AIAE analysis. SAEs occurred with similar frequency among treatment groups, with the lowest frequency occurring in the HEPLISAV consistency lots (total 3.4%). More AEs lead to discontinuation of treatment in the HEPLISAV lots (consistency lots total: 0.9%, Lot TDG006: 0.8%) than in the Engerix-B arm (0.4%).

Reviewer Comment: The overall incidence of AEs, Grade 3 or greater AEs and SAEs was similar between groups. While there were more AIAEs in the HEPLISAV lots than in the Engerix-B arm, the overall incidence of AIAEs was low in the prospective AIAE analysis. See further comments in sections 6.2.12.3-6 and the CBER-generated analyses of potential autoimmune events in the integrated safety review.

Solicited Adverse Events

Solicited adverse events included local pain, redness and swelling, fatigue, headache malaise, myalgia and oral temperature. Solicited local adverse events are summarized by injection, severity and treatment group in Table 37.

Table 37: Summary of Solicited Local Adverse Reactions (Days 0-6) by Active Injection, Severity and Treatment Group

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix- B N=481
Dose 1						
Redness						
n	475	479	473	1427	525	477
Subjects with Redness, n (%)	77 (16.2)	79 (16.5)	88 (18.6)	244 (17.1)	103 (19.6)	72 (15.1)
1mm- ≤10mm	69 (14.5)	76 (15.9)	79 (16.7)	224 (15.7)	90 (17.1)	65 (13.6)
>10mm- <25mm	5 (1.1)	2 (0.4)	4 (0.8)	11 (0.8)	4 (0.8)	4 (0.8)
≥25mm- ≤50mm	3 (0.6)	1 (0.2)	5 (1.1)	9 (0.6)	8 (1.5)	3 (0.6)
>50mm- ≤100mm	0	0	0	0	1 (0.2)	
>100mm	0	0	0	0	0	0
Swelling						
n	475	479	473	1427	525	477
Subjects with Swelling, n (%)	40 (8.4)	37 (7.7)	46 (9.7)	123 (8.6)	49 (9.3)	38 (8.0)
1mm- ≤10mm	32 (6.7)	33 (6.9)	33 (7.0)	98 (6.9)	41 (7.8)	33 (6.9)
>10mm- <25mm	5 (1.1)	1 (0.2)	5 (1.1)	11 (0.8)	4 (0.8)	2 (0.4)
≥25mm- ≤50mm	3 (0.6)	2 (0.4)	7 (1.5)	12 (0.8)	4 (0.8)	3 (0.6)
>50mm- ≤100mm	0	1 (0.2)	1 (0.2)	2 (0.1)	0	0
>100mm	0	0	0	0	0	0
Pain						
n	475	479	473	1427	525	477
Subjects with Pain, n (%)	96 (20.2)	102 (21.3)	121 (25.6)	319 (22.4)	143 (27.2)	88 (18.4)
Mild	84 (17.7)	88 (18.4)	107 (22.6)	279 (19.6)	124 (23.6)	76 (15.9)
Moderate	10 (2.1)	13 (2.7)	12 (2.5)	35 (2.5)	15 (2.9)	11 (2.3)
Severe	2 (0.4)	1 (0.2)	2 (0.4)	5 (0.4)	4 (0.8)	1 (0.2)
Dose 2						
Redness						
n	467	469	462	1398	507	464
Subjects with Redness, n (%)	49 (10.5)	53 (11.3)	48 (10.4)	150 (10.7)	84 (16.6)	45 (9.7)

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix- B N=481
1mm- ≤10mm	42 (9.0)	48 (10.2)	39 (8.4)	129 (9.2)	78 (15.4)	42 (9.1)
>10mm- <25mm	4 (0.9)	4 (0.9)	6 (1.3)	14 (1.0)	0	2 (0.4)
≥25mm- ≤50mm	2 (0.4)	1 (0.2)	3 (0.6)	6 (0.4)	6 (1.2)	1 (0.2)
>50mm- ≤100mm	1 (0.2)	0	0	1 (0.1)	0	0
>100mm	0	0	0	0	0	0
Swelling						
n	467	469	462	1398	507	464
Subjects with Swelling, n (%)	27 (5.8)	30 (6.4)	30 (6.5)	87 (6.2)	37 (7.3)	26 (5.6)
1mm- ≤10mm	20 (4.3)	26 (5.5)	27 (5.8)	73 (5.2)	31 (6.1)	23 (5.0)
>10mm- <25mm	3 (0.6)	1 (0.2)	1 (0.2)	5 (0.4)	3 (0.6)	0
≥25mm- ≤50mm	3 (0.6)	3 (0.6)	2 (0.4)	8 (0.6)	2 (0.4)	3 (0.6)
>50mm- ≤100mm	1 (0.2)	0	0	1 (0.1)	1 (0.2)	0
>100mm	0	0	0	0	0	0
Pain						
n	467	469	462	1398	507	464
Subjects with Pain, n (%)	103 (22.1)	102 (21.7)	109 (23.6)	314 (22.5)	120 (23.7)	74 (15.9)
Mild	91 (19.5)	92 (19.6)	94 (20.3)	277 (19.8)	103 (20.3)	64 (13.8)
Moderate	11 (2.4)	10 (2.1)	14 (3.0)	35 (2.5)	17 (3.4)	9 (1.9)
Severe	1 (0.2)	0	1 (0.2)	2 (0.1)	0	1 (0.2)

Source: Adapted from STN 125428, DV2-HBV-16, Main Study Report Table 14.1.4-4, pp. 8-16

The majority of reactions were mild in intensity. Overall, the proportion of subjects experiencing solicited local AEs were similar among treatment groups. After both active doses, a slightly larger proportion of subjects receiving Lot TDG006 experienced redness (Dose 1: 19.6%, Dose 2: 16.6%) than subjects receiving one of the consistency lots (Dose 1: 17.1%, Dose 2: 10.7%) or Engerix-B (Dose 1: 15.1%, Dose 2: 9.7%). Similarly, more subjects receiving Lot TDG006 reported pain (Dose 1: 27.2%, Dose 2: 23.7%) than did subjects receiving one of the consistency lots (Dose 1: 22.4%, Dose 2: 22.5%) or Engerix-B (Dose 1: 18.4%, Dose 2: 15.9%). After both doses, more subjects in the HEPLISAV groups experienced pain than did subjects in the Engerix-B group.

Reviewer Comment: *The older HEPLISAV lot, Lot TDG006, was associated with more local reactogenicity than the Consistency Lots or Engerix-B. Additionally, more subjects receiving HEPLISAV reported injection site redness and pain than did subjects receiving Engerix-B. This difference is not surprising given the presence of the 1018 ISS adjuvant in the HEPLISAV vaccine product. However, the majority of solicited local adverse events were graded as mild in intensity and do not raise clinical safety concerns.*

Subjects in the HEPLISAV groups received placebo for dose 3, while subjects in the Engerix-B group received active injection. After dose 3, the incidence and severity of injection site redness and swelling were similar between groups. However, more subjects in the Engerix-B arm experienced pain (13.8% versus 6.5% in the consistency lots and 7.7% in Lot TDG006). The majority of injection site reactions reported after the third dose were rated as mild in intensity.

Solicited systemic adverse reactions are summarized by dose, severity and treatment group in Table 38.

Table 38: Summary of Solicited Systemic Adverse Events (Days 0-6) by Injection, Severity and Treatment Group

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix- B N=481
Dose 1						
Malaise						
n	475	479	473	1427	525	477
Subjects with Malaise, n (%)	36 (7.6)	32 (6.7)	40 (8.5)	108 (7.6)	43 (8.2)	41 (8.6)
Mild	22 (4.6)	22 (4.6)	26 (5.5)	70 (4.9)	25 (4.8)	24 (5.0)
Moderate	11 (2.3)	8 (1.7)	10 (2.1)	29 (2.0)	12 (2.3)	9 (1.9)
Severe	3 (0.6)	2 (0.4)	4 (0.8)	9 (0.6)	6 (1.1)	8 (1.7)
Headache						
n	475	479	473	1427	525	477
Subjects with Headache, n (%)	58 (12.2)	47 (9.8)	64 (13.5)	169 (11.8)	61 (11.6)	57 (11.9)
Mild	29 (6.1)	37 (7.7)	47 (9.9)	113 (7.9)	46 (8.8)	41 (8.6)
Moderate	23 (4.8)	8 (1.7)	13 (2.7)	44 (3.1)	11 (2.1)	11 (2.3)
Severe	6 (1.3)	2 (0.4)	4 (0.8)	12 (0.8)	4 (0.8)	5 (1.0)

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix- B N=481
Myalgia						
n	475	479	473	1427	525	477
Subjects with Myalgia, n (%)	40 (8.4)	36 (7.5)	40 (8.5)	116 (8.1)	50 (9.5)	46 (9.6)
Mild	28 (5.9)	26 (5.4)	30 (6.3)	84 (5.9)	34 (6.50)	30 (6.3)
Moderate	11 (2.3)	9 (1.9)	8 (1.7)	28 (2.0)	11 (2.1)	12 (2.5)
Severe	1 (0.2)	1 (0.2)	2 (0.4)	4 (0.3)	5 (1.0)	4 (0.8)
Fatigue						
n	475	479	473	1427	525	477
Subjects with Fatigue, n (%)	63 (13.3)	53 (11.1)	62 (13.1)	178 (12.5)	68 (13.0)	61 (12.8)
Mild	42 (8.8)	36 (7.5)	41 (8.7)	119 (8.3)	38 (7.2)	36 (7.5)
Moderate	18 (3.8)	14 (2.9)	17 (3.6)	49 (3.4)	22 (4.2)	16 (3.4)
Severe	3 (0.6)	3 (0.6)	4 (0.8)	10 (0.7)	8 (1.5)	9 (1.9)
Dose 2						
Malaise						
n	467	469	462	1398	507	464
Subjects with Malaise, n (%)	33 (7.1)	30 (6.4)	29 (6.3)	92 (6.6)	42 (8.3)	33 (7.1)
Mild	23 (4.9)	20 (4.3)	19 (4.1)	62 (4.4)	24 (4.7)	22 (4.7)
Moderate	9 (1.9)	10 (2.1)	9 (1.9)	28 (2.0)	17 (3.4)	8 (1.7)
Severe	1 (0.2)	0	1 (0.2)	2 (0.1)	1 (0.2)	3 (0.6)
Headache						
n	467	469	462	1398	507	464
Subjects with Headache, n (%)	35 (7.5)	38 (8.1)	41 (8.9)	114 (8.2)	41 (8.1)	44 (9.5)
Mild	22 (4.7)	22 (4.7)	27 (5.8)	71 (5.1)	32 (6.3)	33 (7.1)
Moderate	11 (2.4)	14 (3.0)	12 (2.6)	37 (2.6)	7 (1.4)	9 (1.9)
Severe	2 (0.4)	2 (0.4)	2 (0.4)	6 (0.4)	2 (0.4)	2 (0.4)

	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix- B N=481
Myalgia						
n	467	469	462	1398	507	464
Subjects with Myalgia, n (%)	23 (4.9)	27 (5.8)	30 (6.5)	80 (5.7)	42 (8.3)	37 (8.0)
Mild	16 (3.4)	15 (3.2)	17 (3.7)	48 (3.4)	24 (4.7)	25 (5.4)
Moderate	5 (1.1)	11 (2.3)	12 (2.6)	28 (2.0)	16 (3.2)	9 (1.9)
Severe	2 (0.4)	1 (0.2)	1 (0.2)	4 (0.3)	2 (0.4)	3 (0.6)
Fatigue						
n	467	469	462	1398	507	464
Subjects with Fatigue, n (%) (9.4)	44 (9.4)	50 (10.7)	53 (11.5)	147 (10.5)	58 (11.4)	56 (12.1)
Mild	30 (6.4)	33 (7.0)	30 (6.5)	93 (6.7)	34 (6.7)	43 (9.3)
Moderate	13 (2.8)	15 (3.2)	21 (4.5)	49 (3.5)	20 (3.9)	11 (2.4)
Severe	1 (0.2)	2 (0.4)	2 (0.4)	5 (0.4)	4 (0.8)	2 (0.4)

Source: Adapted from STN 125428, DV2-HBV-16, Main Study Report Table 14.1.4-4, pp. 8-16

Overall, the incidence and severity of malaise, headache, myalgia and fatigue were similar among treatment groups for both active doses. A lower percentage of subjects in the Consistency lot arms (5.7%) reported myalgia after injection 2 than did subjects in the Lot TDG006 arm (8.3%) or the Engerix-B arm (8.0%). The majority of solicited systemic adverse events were graded as mild or moderate in intensity.

Reviewer Comment: Overall, the incidence and severity of solicited systemic adverse events after active dose of vaccine was similar between groups. The majority of these events were categorized as mild or moderate in intensity. In addition, there were no clinically significant differences in the incidence or severity of solicited systemic adverse events after dose 3 which contained placebo for the HEPLISAV groups and active injection for the Engerix-B group. These data raise no clinical safety concerns.

Oral temperature recordings are summarized in Table 39 by active injection, treatment arm and the severity grading used in The FDA Guidance For Industry Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventative Vaccine Clinical Trials. The vast majority of subjects were afebrile and fever intensity was similar between treatment groups.

Table 39: Oral Temperature Recordings (Days 0-6) by Active Injection, Treatment Arm and Severity for Subjects Enrolled in Study HBV-16

Body Temperature	HEPLISAV Consistency Lot TDG008 N=481	HEPLISAV Consistency Lot TDG009 N=481	HEPLISAV Consistency Lot TDG010 N=477	All HEPLISAV Consistency Lots N=1439	HEPLISAV Lot TDG006 N=529	Engerix-B N=481
Dose 1						
n	467	474	467	1408	515	472
<38.0 °C	466 (99.8)	472 (99.6)	463 (99.1)	1401 (99.5)	510 (99.0)	469 (99.4)
≥38.0 °C	1 (0.2)	2 (0.4)	4 (0.9)	7 (0.5)	5 (1.0)	3 (0.6)
Grade 1 Fever: 38.0 °C to 38.4 °C	1 (0.2)	2 (0.4)	3 (0.6)	6 (0.4)	4 (0.8)	2 (0.4)
Grade 2 Fever: 38.5 °C to 38.9 °C	0	0	0	0	0	0
Grade 3 Fever: 39.0 °C to 40.0 °C	0	0	1 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)
Grade 4 Fever: >40.0 °C	0	0	0	0	0	0
Dose 2						
n	462	464	459	1385	502	459
<38.0 °C	462 (100.0)	458 (98.7)	456 (99.3)	1376 (99.4)	499 (99.4)	455 (99.1)
≥38.0 °C	0	6 (1.3)	3 (0.7)	9 (0.6)	3 (0.6)	4 (0.9)
Grade 1 Fever: 38.0 °C to 38.4 °C	0	3 (0.6)	1 (0.2)	4 (0.3)	3 (0.6)	0
Grade 2 Fever: 38.5 °C to 38.9 °C	0	2 (0.4)	2 (0.4)	4 (0.3)	0	3 (0.7)
Grade 3 Fever: 39.0 °C to 40.0 °C	0	0	0	0	0	1 (0.2)
Grade 4 Fever: >40.0 °C	0	1 (0.2)	0	1 (0.1)	0	0

Source: Adapted from STN 125428, DV2-HBV-16, Main Study Report, Table 14.1.4-4, pp. 8-16

Reviewer Comment: The vast majority of subjects did not report fever on Days 0-6 after any dose. Grade 3 or 4 fevers were very rare. The solicited oral temperature data does not raise any clinical safety concerns.

Unsolicited Adverse Events

Unsolicited adverse events are summarized by toxicity grade and treatment group in Table 40. Most events were mild or moderate in intensity.

Table 40: Summary of Adverse Events by CTC Toxicity Grade, System Organ Class, and Treatment Group

Adverse Event, n (%)	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Any Mild AE (Grade 1)	113 (23.5)	121 (25.2)	128 (26.8)	362 (25.2)	133 (25.1)	119 (24.7)
Any Moderate AE (Grade 2)	96 (20.0)	98 (20.4)	106 (22.2)	300 (20.8)	104 (19.7)	108 (22.5)
Any Severe AE (≥ Grade 3)	21 (4.4)	24 (5.0)	20 (4.2)	65 (4.5)	31 (5.9)	28 (5.8)
Severe Musculoskeletal Disorders	4 (0.8)	7 (1.5)	8 (1.7)	19 (1.3)	4 (0.8)	9 (1.9)
Severe Injuries	3 (0.6)	5 (1.0)	2 (0.4)	10 (0.7)	4 (0.8)	4 (0.8)
Severe Infections	2 (0.4)	4 (0.8)	3 (0.6)	9 (0.6)	6 (1.1)	3 (0.6)
Severe Neoplasms	3 (0.6)	1 (0.2)	4 (0.8)	8 (0.6)	1 (0.2)	2 (0.4)
Severe Respiratory Disorders	2 (0.4)	1 (0.2)	2 (0.4)	5 (0.3)	2 (0.4)	3 (0.6)
Severe Gastrointestinal Disorders	1 (0.2)	0	0	1 (0.1)	5 (0.9)	1 (0.2)
Severe General Disorders	1 (0.2)	0	3 (0.6)	4 (0.3)	3 (0.6)	3 (0.6)
Severe Hepatobiliary Disorders	0	0	1 (0.2)	1 (0.1)	1 (0.2)	0
Severe Cardiac Disorders	3 (0.6)	0	0	3 (0.2)	2 (0.4)	4 (0.8)
Severe Ear & Labyrinth Disorders	0	1 (0.2)	0	1 (0.1)	0	2 (0.4)
Severe Nervous System Disorders	2 (0.4)	1 (0.2)	0	3 (0.2)	2 (0.4)	3 (0.6)
Severe Vascular Disorders	1 (0.2)	0	2 (0.4)	3 (0.2)	1 (0.2)	1 (0.2)
Severe Investigations	2 (0.4)	0	0	2 (0.1)	1 (0.2)	0

Adverse Event, n (%)	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Severe Metabolic Disorders	2 (0.4)	0	0	2 (0.1)	0	1 (0.2)
Severe Psychiatric Disorders	0	2 (0.4)	0	2 (0.1)	0	1 (0.2)
Severe Renal Disorders	0	1 (0.2)	0	1 (0.1)	0	1 (0.2)
Severe Reproductive Disorders	0	1 (0.2)	0	1 (0.1)	0	0
Severe Skin Disorders	0	1 (0.2)	0	1 (0.1)	0	0

Note: CTC = Common Terminology Criteria for Adverse Events provided by the Cancer Therapy Evaluation Program (CTEP).

Adapted from STN 125428, *Clinical Study Report, DV2-HBV-16, Table 12-13, page 159*

The majority of unsolicited adverse were deemed unrelated to the study vaccine by the investigator. Events rated as grade 3 or higher occurred with a slightly lower incidence in the HEPLISAV consistency lots (4.5%) than in Lot TDG006 (5.9%) or the Engerix-B arm (5.8%). Cardiac disorders were slightly more common in the Engerix-B arm (0.8%) compared to the HEPLISAV consistency lots (0.2%) or Lot EDG006 (0.4%). Metabolic disorders were slightly more common in Lot TDG006 (0.8%) compared to the HEPLISAV consistency lots (0.1%) or Engerix-B (0.2%).

One HEPLISAV recipient, subject 32-018, was a 43 year old female diagnosed with narcolepsy 13 days following her second study injection. She was treated with armodafinil and sodium oxybate. The adverse event was graded as mild in intensity and was deemed unrelated to study vaccine by the investigator. No action was taken with regard to further study treatments. The subject also had an asthma exacerbation, deemed an SAE while on study.

Reviewer Comment: Most events were mild or moderate in intensity. Overall, the incidence and severity of adverse events was similar between treatment groups. The event of narcolepsy is notable due to the autoimmune nature of some types of narcolepsy. Source documents pertaining to this event will be requested from the applicant.

6.2.12.3 Deaths

There were two deaths in study HBV-16, one in a HEPLISAV recipient and one in a recipient of Engerix B:

1. Subject 22-003 was a 46 year old active white male with no relevant past medical history including no history of a coagulation disorder, preceding trauma, or other pre-

disposing cause for hypercoagulability. He received study injections with HEPLISAV Lot TDG006 on 12 March 2010 and 9 April 2010. (b) (6) days after the second study injection, he experienced swelling and leg pain, pressure in the right chest and shortness of breath. He had been playing softball and collapsed. He was resuscitated on the field by emergency medical technicians but died en route to the hospital. The applicant reports that an emergency medical technician report was not available; and that requests for the autopsy report were not successful. A record of a telephone conversation between study site personnel and the subject's friend was the only source document available indicating the pulmonary embolism had occurred. The subject's laboratory results at Visit 3 on 8 May 2010 ((b) (6) days prior to the event) were within normal limits. The investigator assessed the event as not related to study treatment.

2. Subject 92-638 was a 64 year old black or African American male with a history of gout, hypertension, gastroesophageal reflux and bilateral knee osteoarthritis received Engerix-B injections on 12 May 2010 and 10 June 2010. (b) (6) days after the second study injection, he was hospitalized in critical condition following a heart attack. On the second day of hospitalization, he experienced pulmonary arrest and ventricular fibrillation. Despite emergency cardiac support including medications and cardioversion, the event was fatal. Screening laboratory results were normal except for serum creatinine of 110.5 µmols/L (<103.0 µmols/L), neutrophil percentage of 77.0% (43.0-73.0%) and platelet count of 108 x 10⁹/L (145-390 x 10⁹/L). The investigator assessed the event of "heart failure" as not related to the study treatment.

Reviewer Comment: The death of Subject 22-003, a previously healthy active individual, secondary to a pulmonary embolism does not appear to be temporally related to vaccination with HEPLISAV. Based on the available information, the investigator's assessment of a lack of relatedness to receipt of the vaccine is reasonable. A numerical imbalance in the overall incidence of pulmonary emboli across all studies was noted, with all five reports of pulmonary emboli occurring in HEPLISAV recipients. As noted in the integrated safety review, however, Subject 22-003 was the only individual for whom an underlying predisposition to pulmonary embolus was not described.

Based on the narrative, it appears that subject 92-638 had cardiac arrest. The reviewer agrees with the investigator's assessment that this event was likely not related to the receipt of Engerix-B.

6.2.12.4 Nonfatal Serious Adverse Events

The reporting period for SAEs was the time period from the first injection (Week 0) until the last study visit (Week 52). Table 41 summarizes SAEs by SOC, preferred term and treatment group.

Table 41: Summary of Serious Adverse Events by System Organ Class and Preferred Term for Subjects Enrolled in Study DV2-HBV-16

SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
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SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Subjects with any SAE	18 (3.7)	12 (2.5)	19 (4.0)	49 (3.4)	27 (5.1)	23 (4.8)
Blood & Lymphatic System Disorders	0	0	0	0	0	1 (0.2)
Anemia	0	0	0	0	0	1 (0.2)
Cardiac Disorders	3 (0.6)	0	0	3 (0.2)	4 (0.8)	4 (0.8)
Acute Myocardial Infarction	1 (0.2)	0	0	1 (0.1)	1 (0.2)	1 (0.2)
Angina Pectoris	1 (0.2)	0	0	1 (0.1)	0	0
Angina Unstable	0	0	0	0	0	1 (0.2)
Atrial Fibrillation	1 (0.2)	0	0	1 (0.1)	0	0
Cardiac Failure	0	0	0	0	0	1 (0.2)
Cardiomyopathy	0	0	0	0	1 (0.2)	0
Coronary Artery Disease	0	0	0	0	2 (0.4)	1 (0.2)
Coronary Artery Stenosis	0	0	0	0	0	1 (0.2)
Ear & Labyrinth Disorders	0	1 (0.2)	0	1 (0.1)	0	0
Vertigo	0	1 (0.2)	0	1 (0.1)	0	0
Gastrointestinal Disorders	1 (0.2)	0	1 (0.2)	2 (0.1)	5 (0.9)	2 (0.4)
Abdominal Hernia	1 (0.2)	0	0	1 (0.1)	0	0
Barrett's Esophagus	0	0	0	0	0	1 (0.2)
Erosive Esophagitis	0	0	0	0	1 (0.2)	0
Gastric Hemorrhage	0	0	0	0	0	1 (0.2)
Gastric Ulcer	0	0	0	0	1 (0.2)	0
Gastroesophageal Reflux Disease	0	0	0	0	1 (0.2)	0
Hematemesis	0	0	1 (0.2)	1 (0.1)	0	0
Inguinal Hernia	0	0	0	0	1 (0.2)	0
Small Intestinal Obstruction	0	0	0	0	1 (0.2)	0

SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
General Disorders & Administrative Site Conditions	0	0	1 (0.2)	1 (0.1)	2 (0.4)	2 (0.4)
Chest Pain	0	0	0	0	0	1 (0.2)
Non-Cardiac Chest Pain	0	0	1 (0.2)	1 (0.1)	2 (0.4)	1 (0.2)
Hepatobiliary Disorders	0	0	0	0	1 (0.2)	0
Cholecystitis	0	0	0	0	1 (0.2)	0
Infections & Infestations	0	2 (0.4)	1 (0.2)	3 (0.2)	4 (0.8)	1 (0.2)
Cavernous Sinus Syndrome versus Tolosa-Hunt Syndrome	0	1 (0.2)	0	1 (0.1)	0	0
Diverticulitis	0	0	0	0	1 (0.2)	0
Gastroenteritis Salmonella	0	0	0	0	0	1 (0.2)
Localized Infection	0	0	0	0	1 (0.2)	0
Perirectal Abscess	0	0	0	0	1 (0.2)	0
Pneumonia	0	0	1 (0.2)	1 (0.1)	0	0
Post Procedural Infection	0	1 (0.2)	0	1 (0.1)	0	0
Staphylococcal Infection	0	0	0	0	1 (0.2)	0
Injury, Poisoning & Procedural Complications	4 (0.8)	4 (0.8)	3 (0.6)	11 (0.8)	2 (0.4)	3 (0.6)
Alcohol Poisoning	2 (0.4)	0	0	2 (0.1)	0	0
Ankle Fracture	1 (0.2)	0	0	1 (0.1)	1 (0.2)	0
Contusion	0	0	0	0	1 (0.2)	0
Delayed Recovery From Anesthesia	0	0	0	0	0	1 (0.2)
Fall	0	1 (0.2)	0	1 (0.1)	0	0
Fibula Fracture	0	0	1 (0.2)	1 (0.1)	0	0
Foot Fracture	0	0	1 (0.2)	1 (0.1)	0	0
Gun Shot Wound	0	1 (0.2)	0	1 (0.1)	0	0

SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Joint Injury	0	1 (0.2)	0	1 (0.1)	0	1 (0.2)
Meniscus Lesion	0	0	1 (0.2)	1 (0.1)	0	1 (0.2)
Muscle Strain	1 (0.2)	0	0	1 (0.1)	0	0
Thermal Burn	0	1 (0.2)	0	1 (0.1)	0	0
Tibia Fracture	0	0	1 (0.2)	1 (0.1)	0	0
Metabolism & Nutrition Disorders	3 (0.6)	1 (0.2)	1 (0.2)	5 (0.3)	1 (0.2)	1 (0.2)
Dehydration	0	0	0	0	0	1 (0.2)
Diabetic Ketoacidosis	0	0	0	0	1 (0.2)	0
Hyperglycemia	1 (0.2)	0	0	1 (0.1)	0	0
Hypokalemia	1 (0.2)	0	0	1 (0.1)	0	0
Hyponatremia	1 (0.2)	1 (0.2)	0	2 (0.1)	0	0
Water Intoxication	0	0	1 (0.2)	1 (0.1)	0	0
Musculoskeletal & Connective Tissue Disorders	4 (0.8)	4 (0.8)	8 (1.7)	16 (1.1)	3 (0.6)	5 (1.0)
Bursitis	0	0	0	0	0	1 (0.2)
Intervertebral Disc Degeneration	1 (0.2)	0	0	1 (0.1)	0	1 (0.2)
Intervertebral Disc Protrusion	1 (0.2)	0	1 (0.2)	2 (0.1)	2 (0.4)	0
Loose Body in Joint	0	0	1 (0.2)	1 (0.1)	0	0
Lumbar Spinal Stenosis	0	0	1 (0.2)	1 (0.1)	0	1 (0.2)
Musculoskeletal Chest Pain	0	0	1 (0.2)	1 (0.1)	0	0
Neck Pain	0	0	0	0	1 (0.2)	0
Osteoarthritis	1 (0.2)	3 (0.6)	4 (0.8)	8 (0.6)	1 (0.2)	2 (0.4)
Spinal Column Stenosis	1 (0.2)	1 (0.2)	0	2 (0.1)	0	0
Spondylolisthesis	0	0	1 (0.2)	1 (0.1)	0	0
Neoplasms	3 (0.6)	0	5 (1.0)	8 (0.6)	1 (0.2)	5 (1.0)

SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Brain Neoplasm	1 (0.2)	0	0	1 (0.1)	0	0
Breast Cancer	0	0	1 (0.2)	1 (0.1)	0	2 (0.4)
Colon Adenoma	1 (0.2)	0	1 (0.2)	2 (0.1)	0	0
Colon Cancer Stage IV	0	0	1 (0.2)	1 (0.1)	0	0
Inflammatory Carcinoma of the Breast	1 (0.2)	0	0	1 (0.1)	0	0
Non-Small Cell Lung Cancer Metastasis	0	0	0	0	1 (0.2)	0
Prostate Cancer	0	0	1 (0.2)	1 (0.1)	0	3 (0.6)
Uterine Leiomyoma	0	0	1 (0.2)	1 (0.1)	0	0
Nervous System Disorders	0	0	1 (0.2)	1 (0.1)	1 (0.2)	1 (0.2)
Benign Intracranial Hypertension	0	0	0	0	0	1 (0.2)
Spondylitic Myelopathy	0	0	1 (0.2)	1 (0.1)	0	0
Subarachnoid Hemorrhage	0	0	0	0	1 (0.2)	0
Psychiatric Disorders	0	1 (0.2)	0	1 (0.1)	0	0
Major Depression	0	1 (0.2)	0	1 (0.1)	0	0
Reproductive System & Breast Disorders	1 (0.2)	1 (0.2)	0	2 (0.1)	0	1 (0.2)
Endometriosis	1 (0.2)	0	0	1 (0.1)	0	0
Hemorrhagic Ovarian Cyst	0	0	0	0	0	1 (0.2)
Menstruation Irregular	0	1 (0.2)	0	1 (0.1)	0	0
Respiratory Disorders	1 (0.2)	0	2 (0.4)	3 (0.2)	2 (0.4)	2 (0.4)
Asthma	1 (0.2)	0	0	1 (0.1)	2 (0.2)	0
Bronchial Hyperreactivity	0	0	0	0	0	1 (0.2)
Chronic Obstructive Pulmonary Disease	0	0	1 (0.2)	1 (0.1)	0	1 (0.2)

SOC and Preferred Term	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots Total N=1439	Lot TDG006 N=529	Engerix-B N=481
Hypoxia	0	0	1 (0.2)	1 (0.1)	0	0
Pulmonary Embolism	0	0	1 (0.2)	1 (0.1)	1 (0.2)	0
Vascular Disorders	1 (0.2)	0	1 (0.2)	2 (0.1)	1 (0.2)	1 (0.2)
Deep Vein Thrombosis	1 (0.2)	0	1 (0.2)	2 (0.1)	0	1 (0.2)
Hypertension	0	0	0	0	1 (0.2)	0

Source: STN 125428, DV2-HBV-16, CSR, Table 12-14, p. 168 and source table 14.1.4-18

Overall, 120 SAEs occurred in 99 subjects. Forty-nine-(3.4%) of subjects in the HEPLISAV consistency lots experienced 62 SAEs, 27 (5.1%) subjects in the lot TDG006 group experienced 28 SAEs, and 23 (4.8%) subjects receiving Engerix-B experienced 30 SAEs. Overall, the most common SOCs represented by SAEs were musculoskeletal and connective tissue disorders (HEPLISAV consistency lots: 1.1%, TDG006 0.6%, Engerix-B 0.1%), injury, poisoning and procedural disorders (HEPLISAV consistency lots: 0.8%, TDG006: 0.4%, Engerix-B 0.6%), neoplasms (HEPLISAV consistency lots: 0.6%, TDG006: 0.2%, Engerix-B 1.0%) and cardiac disorders (HEPLISAV consistency lots: 0.2%, TDG006 0.8%, Engerix-B 0.8%).

Reviewer Comment: Overall, SAEs occurred with similar incidence among HEPLISAV and Engerix-B recipients.

During the course of the study, one subject received an initial clinical diagnosis of Tolosa-Hunt syndrome, a painful ophthalmoplegia resulting from granulomatous inflammation of the cavernous sinus. This diagnosis subsequently was changed to cavernous sinus syndrome. A case narrative is provided for this subject here:

Subject 40-616 was a 69-year-old white man with a medical history that included presbyopia, hypertension, osteoarthritis, 2 ruptured discs, trauma to the back, cervical ruptured discs, recurrent rashes, and allergy to penicillin and ibuprofen. Concomitant medications included diovan, diclofenac, fluticasone nasal, hytrin, lotrisone, loratadine, famotidine, omeprazole, aspirin, B-6 vitamins, B complex vitamins, vitamin C, multivitamins with minerals, vitamin E, simethicone, iron, melatonin, psyllium, saw palmetto, fish oil, gabapentin, hydrocodone, and pneumococcal and influenza vaccines on October 26, 2010.

The subject received active study injections on March 22, 2010, and April 19, 2010, as well as saline placebo on September 8, 2010. Adverse events and serious adverse events occurring in this subject will be briefly summarized here.

- Early October 2010: 1 month after the last study injection, the subject developed amblyopia; failed to improve with changes in corrective lenses.

- November 22, 2010: developed sensitivity to light with excessive lacrimation
- Early December 2010: onset of severe headaches
- (b) (6) : Subject went to the emergency room (ER) for evaluation of a 3-week history of daily left frontal headaches. A computed tomography (CT) scan of the head showed no acute intracranial pathology .A maxillofacial CT scan showed minimal mucosal thickening involving the ethmoid air cells bilaterally. He was discharged from the ER with the diagnosis of sinusitis. Discharge medications were azithromycin, hydrocodone for pain, and loratadine with pseudoephedrine and asked to follow up in 3 days.
- (b) (6) : returned to the ER with left-sided headache, now with pain around the left eye and shooting pain and numbness of the left forehead and sensitivity to light. Physical exam was notable for photophobia and numbness in the left cranial nerve V1 distribution. A CT scan showed no acute intracranial pathology. The subject was given methylprednisolone and his pain resolved while in the ER.
- Early January 2011: seen by an ophthalmologist for intermittent diplopia associated with headaches. He received courses of oral steroids during the first and third weeks of January with significant improvement the day after starting, but the headache returned after steroids were discontinued. Initial magnetic resonance imaging (MRI) and magnetic resonance angiography (MRA) studies were performed on January 15, 2011 and were negative for focal abnormalities or aneurysms.

On (b) (6) , approximately 5 months after the last study injection, the subject presented to the ER complaining of persistent double vision of 5 days duration, a severe left upper headache, numbness on the left side of the face, worsening of left eye droop, increased sensitivity to light in the left eye, and worsening of vision.

- On physical examination, he was afebrile, noted to have a left ptosis, slight adduction deficit, deviation to the left on primary position, pupils equally reactive to light, cranial nerve V was intact except for the left V1 distribution. Fundoscopic exam was normal.
- A CT scan of the head showed no acute intracranial process. A brain MRI showed scattered white matter T2/FLAIR hyperintensities, suggestive of chronic microvascular ischemic disease; it was otherwise unremarkable. A CT angiography (CTA) scan of the head showed fetal origin of the left PCA, which demonstrates tortuosity and a questionable 3 mm medially projected outpouching. Calcified plaques within the bilateral cavernous portions of the carotid arteries were also seen. No acute intracranial abnormality was observed. It is noted that the CTA was a nondiagnostic study due to the lack of contrast opacification of the vasculature and that a vascular abnormality could not be excluded. MRI of the orbits were normal. An MRA of the circle of Willis was within normal range. A

lumbar puncture and cerebrospinal fluid analysis showed the following: pink, hazy CSF with 750 RBC/mm³, <5 WBC/mm³, glucose 59 mg/dL (40-75 mg/dL), protein 46 mg/dL (15-45 mg/dL), IgG 3.8 mg/dL (0.0-6.0 mg/dL), VDRL non-reactive and bacterial culture negative at 72 hours. A serologic workup showed a TSH of 0.843 mIU/mL (0.350-5.500 mIU/mL), angiotensin converting enzyme levels of 15 and 35 U/L (9-67 U/L), nonreactive RPR, serum IgG of 833 mg/dL (600-1550 mg/dL), ESR of 16 mm/hr (0-20 mm/hr), CRP of 11.28 mg/L (0.00-10.00 mg/dL), and an ANA < 1:40. Antibodies to myeloperoxidase, serine protease 3, Smith antigen, SSA, SSB and RNP were not detected. Hemoglobin A1C was 5.9 % (0.1-6.4%) and blood glucose ranged from 85 mg/dL-173 mg/dL (60-100 mg/dL). Platelet count was 266 K/ μ L (150-450 K/ μ L), INR 1.1 (0.8-1.2).

- The patient had significant clinical improvement in his headache and eye symptoms on steroid therapy. He initially noted slow improvement on February 5, 2011. By February 7, 2011, his headache, numbness of the face and left eye pain had resolved and the left eye ptosis had vastly improved. Diplopia and adductor deficit continued. He was discharged on February 7, 2011 with the diagnoses of cranial nerve III palsy and Tolosa-Hunt syndrome with instructions to continue oral prednisone and taper as instructed. He was instructed to follow-up with the ophthalmologist within 1 week and the neurologist.
- The event of Tolosa-Hunt syndrome was considered resolved on March 27, 2011. Subsequent discussions between the applicant and attending neurologist took place on April 1, 2011 and the neurologist changed the diagnosis from Tolosa-Hunt syndrome to cavernous sinus syndrome. The investigator assessed the event of cavernous sinus syndrome as severe in intensity and not related to study treatment.

Reviewer Comment: Subject 40-616 initially was diagnosed with Tolosa-Hunt syndrome, a granulomatous inflammatory disease of the cavernous sinus, while on study. The diagnosis was subsequently changed to cavernous sinus syndrome. However, it appears that the International Classification of Headache Disorders (ICHD) II diagnostic criteria for Tolosa-Hunt syndrome were met in this case (19). Tolosa-Hunt syndrome is notable because of its granulomatous nature and potential vasculitic/autoimmune etiology. There are reports in the literature suggesting this condition could be a limited form or initial presentation of Wegener's granulomatosis in which ANCA testing is often negative (3, 20, 21). In light of the case of Wegener's granulomatosis developing in a subject subsequent to receipt of HEPLISAV and assessed as likely associated with receipt of this vaccine (Study HBV-10, Subject 24057; see section 6.1.12.5 of this review) the possibility that a second recipient of HEPLISAV may have developed manifestations of a rare immunopathological process that may be related to the immunopathology manifest in Wegener's granulomatosis raised concerns and triggered CBER's request for outside expert consultation regarding this case. The reports from these consultations are pending at this time.

6.2.12.5 Adverse Events of Special Interest (AESI)

The reporting period for AESIs was the time period from the first injection (Week 0) until the last study visit (Week 52).

Subjects with Pre-Existing Autoimmune Disorders

Due to concern for potential exacerbation of pre-existing autoimmune disorders (PEAI), subanalyses of certain safety parameters were performed on the subset of 30 subjects with a PEA. Within this subset, 15 subjects were randomized to HEPLISAV consistency lots, 8 to Lot TDG006 and 7 to Engerix-B. Eighteen subjects (60.0%) in the PEA population reported at least 1 AE, compared with 51.5% of subjects reporting any AE in the overall safety population. Within the PEA population, 60.0% of subjects in the HEPLISAV consistency lots group, 62.5% of subjects in the Lot TDG006 group and 57.1% of subjects in the Engerix-B group reported any AE. No individual AE occurred in more than one subject with PEA in any treatment group. Nine subjects experienced 12 events in the HEPLISAV consistency lots arm, 5 subjects experienced 14 events in the Lot TDG008 arm, and 4 subjects experienced 9 events in the Engerix-B arm.

Three of 30 subjects in the PEA population (10.0%) experienced SAEs compared with 99/2449 (4.0%) in the overall study population. These were noncardiac chest pain in 2 subjects who received HEPLISAV (lot TDG006: n=1, lot TDG010: n=1) and joint injury in 1 subject in the Engerix-B group. One subject in the PEA population (3.3%) experienced a confirmed AIAE compared with 3/2449 (0.1%) in the overall study population.

Reviewer Comment: It appears that AEs and SAEs occur with higher frequency in individuals with PEA than in the general study population. However, the frequency of AEs and SAEs among the relatively small number of subjects with PEA was similar between treatment groups. Given the small number of subjects with PEA inadvertently enrolled in this study and the duration of safety follow-up, the clinical significance of an increased frequency of AEs and SAEs in this subpopulation compared to the remainder of the study population remains unclear at this time.

Autoimmune Adverse Events

Nine potential autoimmune adverse events were reported: hypothyroidism (n=5), Bell's palsy (n=1), erythema nodosum (n=1), vitiligo (n=1) and microscopic colitis (n=1). Seven of these events were confirmed by expert evaluation to be potentially autoimmune in nature: hypothyroidism (n=4), Bell's palsy (n=1), erythema nodosum (n=1), and vitiligo (n=1). All of these events occurred in subjects in the HEPLISAV consistency lot group (7/1439, 0.5%), were mild to moderate in severity, and were considered nonserious.

Per protocol, these potential new-onset AIAEs were referred to the Safety Evaluation and Adjudication Committee (SEAC) for adjudication. Five of these 7 events were initially confirmed by the SEAC as new-onset autoimmune events: hypothyroidism (n=4) and

vitiligo (n=1). Of the 4 initially confirmed events of hypothyroidism, post-study testing of banked baseline serum from two of these subjects revealed a high thyroid stimulating hormone (TSH) level and low free T4 level, providing laboratory evidence of pre-existing hypothyroidism, and they were therefore not new onset events. Upon revision of adjudications, three cases of SEAC-confirmed new-onset AIAEs were determined to have occurred: hypothyroidism (n=2) and vitiligo (n=1).

Reviewer Comment: In addition to the 2 diagnoses of hypothyroidism that were determined to be new-onset AIAEs, another case of new-onset hypothyroidism was referred to the SEAC and was determined to be of non-autoimmune origin. That subject had a baseline ANA titer of <1:40 and a Week 52 ANA titer of 1:40, speckled pattern.

While the incidence of autoimmune events was low, all autoimmune AEs occurred in HEPLISAV recipients. Given the randomization ratio employed in this study, the safety follow-up period and the low background incidence of many autoimmune diseases, it is not possible to determine the clinical significance of the 0.5% difference in the incidence of potential autoimmune disease between groups in this study. Independent CBER analyses of potential autoimmune events occurring in all studies were performed as well and are discussed in the integrated summary of safety.

An individual with a history of Grave's disease developed recurrence of hyperthyroid symptoms while on study and was diagnosed with hyperthyroidism due to Grave's disease and treatment was resumed on study. Another subject developed a rash of unknown etiology that prompted discontinuation of injections. A third subject developed hand pain and swelling along with generalized body aches while on study. She was referred for medical evaluation of a potential autoimmune event. These events are described in detail below.

Additional Adverse Events of Interest

Subject 20-606, a 63 year old female HEPLISAV recipient with a medical history that included Grave's disease, obesity and a recorded history of acute congestive heart failure, was admitted with complaints of atypical chest pain and shortness of breath 51 days after the second study injection. She also complained of excessive sweating, poor sleep, worsening anxiety and increased appetite since 50 days after her second injection. A cardiac workup ensued and positive findings included a stress test with single-photon emission computed tomography that revealed an atypical area of reversible ischemia and an ejection fraction of 62%. Laboratory evaluation showed that free thyroxine levels were elevated at 2.4ng/dL and TSH levels were 0.005mIU/L. She was diagnosed with hyperthyroidism likely due to Grave's disease with associated high output heart failure and was treated with methimazole, lorazepam and heparin. A subsequent cardiac catheterization was normal and the event was considered non-cardiac atypical chest pain that resolved. The investigator assessed the event as severe in intensity and not related to study treatment.

Subject 42-320, a 57 year old female HEPLISAV recipient with a medical history that included osteoarthritis, pain in legs and feet and allergic rhinitis developed a rash on her stomach of unknown cause on the day of the first study injection. One month later she began tramadol, amitriptyline and naproxen for bilateral hand and foot pain. Six weeks after her first injection, she developed swelling of the face of unknown cause for which she received diphenhydramine and an 8 day course of oral prednisone. Nine days after the facial swelling, she developed a “skin rash” of unknown cause. She received her second vaccination as scheduled, but further vaccinations were not administered due to the unknown nature of the rash. The investigator assessed the event as mild in intensity and possibly related to the study treatment.

Subject 21-640, a 68 year old female HEPLISAV recipient with a past medical history that included cervical stenosis, laminoplasty and hypertension developed moderate left hand swelling and aching 3 days following her first and only study injection. One week later, she developed severe general body aches. She was treated with celecoxib and ibuprofen. At her next study visit, the investigator noted an abnormal musculoskeletal exam and a suspected autoimmune adverse event for which the subject was referred for medical evaluation and care. One month later she developed left foot swelling and bruising that resolved in 12 days and was deemed unrelated to the study treatment. Approximately 1 month later she developed mild pain in her right upper shin that resolved approximately 2.5 months later. Her left hand swelling and left hand aching were ongoing at the end of the study. The hand aching, swelling and general aches were assessed by the investigator as possibly related to the study treatment. Injections were discontinued due to these events.

Reviewer Comment: The reviewer agrees with the investigator’s assessment that these events were possibly related to the study treatment. Additional records will be requested for this subject to obtain more information.

6.2.12.6 Clinical Test Results

Hematology and serum chemistry testing was performed at Weeks 0, 4, 24, and 28 or at the point of early discontinuation. Laboratory parameters were evaluated using mean values, changes from baseline, and shift tables of changes from baseline. All mean hematology and serum chemistry values at all visits were within the normal range, were similar across treatment groups, and did not change significantly from baseline.

Antinuclear Antibody Evaluation

ANA and anti-dsDNA were performed at Weeks 0 and 52 or at the point of early discontinuation. Table 42 compares the baseline ANA status and change from baseline ANA status among treatment groups.

Table 42: Antinuclear Antibody Titers by Treatment Group and Visit

Result	HEPLISAV Consistency Lots Baseline N=1439 n (%)	HEPLISAV Consistency Lots Week 52 N=1439 n (%)	Lot TDG006 Baseline N=529	Lot TDG006 Week 52 N=529	Engerix-B Baseline N=481 n (%)	Engerix-B Week 52 N=481 n (%)
Number of subjects with titers available	1439	1356	529	486	480	455
<1:160	1375 (95.6)	1208 (89.1)	499 (94.3)	404 (83.1)	447 (93.1)	390 (85.7)
≥1:160	64 (4.4)	148 (10.9)	30 (5.7)	82 (16.9)	33 (6.9)	65 (14.3)
1:160	29 (2.0)	96 (7.1)	14 (2.6)	49 (10.1)	22 (4.6)	37 (8.1)
1:320	22 (1.5)	35 (2.6)	11 (2.1)	18 (3.7)	8 (1.7)	16 (3.5)
1:640	8 (0.6)	12 (0.9)	3 (0.6)	7 (1.4)	2 (0.4)	7 (1.5)
1:1280	5 (0.3)	4 (0.3)	2 (0.4)	6 (1.2)	1 (0.2)	5 (1.1)
1:2560	0	1 (0.1)	0	2 (0.4)	0	0
>1:2560	0	0	0	0	0	0

Source: Adapted from STN 125428, DV2-HBV-16, Main Study Report; Table 12-19, p. 185

The majority of subjects had a negative ANA, defined as <1:160. Positive ANA values were stratified by serial dilution. The distribution of titers within each serial dilution was similar between treatment groups. The change in the percentage of subjects with positive ANA values from baseline to Week 52 was 6.5% in the HEPLISAV Consistency Lots Total group, 11.2% in the Lot TDG006 group and 7.4% in the Engerix-B group.

Reviewer Comment: *The 1:160 dilution was chosen to optimize specificity. The majority of subjects had ANA titers <1:160. The distribution of serial dilutions was similar between groups. More subjects receiving Lot TDG006, an older lot used in early studies, converted to positive ANA status than in the other groups. The percentage of subjects with positive titers increased by a similar amount in the HEPLISAV consistency lots and the Engerix-B group at Week 52. An additional analysis showed that the distribution of ANA titers below the 1:160 dilution (<1:40, 1:40, and 1:80) were similar between HEPLISAV and Engerix-B recipients. Review of the ANA evaluation does not raise clinical concerns.*

Table 43 summarizes the change in ANA titer from baseline to Week 52 by treatment group. Most subjects had a negative ANA titer at baseline.

Table 43: Change in ANA titer from Baseline to Week 52 by Treatment Group

Change from Week 0 to Week 52	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Negative at Week 0	373	356	368	1097	401	367

Change from Week 0 to Week 52	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Negative at Week 0, Positive at Week 52 n, (%)	89 (23.9)	95 (26.7)	89 (24.2)	273 (24.9)	114 (28.4)	106 (28.9)
Positive at Week 0	82	94	83	259	85	87
Positive at Week 0, Higher titer at Week 52 n, (%)	38 (46.3)	42 (44.7)	31 (37.3)	111 (42.9)	44 (51.8)	38 (43.7)
Positive at Week 0, Negative at Week 52 n, (%)	13 (15.9)	12 (12.8)	14 (16.9)	39 (15.1)	10 (11.8)	13 (14.9)

Source: STN 125428, Study DV2-HBV-16, Table 14.1.4-46, p. 568

Among subjects with negative titers at baseline, 24.9% of those receiving HEPLISAV consistency lots, 28.4% of those receiving Lot TDG006 and 28.9% of those receiving Engerix-B had a positive result at Week 52. Among subjects with positive ANA titers at baseline, more subjects in the TDG006 arm had a higher titer at Week 52 (51.8%) than in the HEPLISAV consistency lots (42.9%) or the Engerix-B arm (43.7%).

Reviewer Comment: The majority of subjects in each arm had negative ANA titers at baseline. A comparable proportion of subjects in each arm converted from a negative baseline titer to a positive titer at Week 52. While more subjects in the Lot TDG006 arm had an increase in positive titer from baseline to Week 52 than any other arm, the percentage of subjects experiencing an increase was similar between the HEPLISAV consistency lots and the Engerix-B arm. Change in ANA status was similar between the study vaccine and the active comparator and therefore raises no clinical concerns.

Anti-dsDNA Evaluation

Table 44 summarizes the results of the anti-dsDNA evaluation by treatment group.

Table 44: Anti-dsDNA Antibody Results at Baseline and Week 52 by Treatment Group

Result	Lot TDG008 N=481	Lot TDG009 N=481	Lot TDG010 N=477	HEPLISAV Consistency Lots N=1439	Lot TDG006 N=529	Engerix-B N=481
Negative anti-dsDNA Week 0	476/481 (99.0%)	471/481 (97.9%)	470/477 (98.5%)	1417/1439 (98.5%)	519/529 (98.1%)	467/480 (97.3%)
Negative anti-dsDNA Week 52	445/455 (97.8%)	441/450 (98.0%)	439/451 (97.3%)	1325/1356 (97.7%)	469/485 (96.7%)	439/455 (96.5%)
Negative at Week 0, Positive at Week 52	10/450 (2.2%)	4/442 (0.9%)	10/446 (2.2%)	24/1338 (1.8%)	12/465 (2.5%)	7/434 (1.6%)
Positive at Week 0, Negative at Week 52	0/5 (0.0%)	5/8 (62.5%)	2/5 (40.0%)	7/18 (39.9%)	4/8 (50.0%)	9/13 (69.2%)

Source: STN 125428, Study DV2-HBV-16, Clinical Study Report, Table 12-20, p. 186

The majority of subjects had negative results at baseline and Week 52. A similar proportion of subjects converted from a negative to a positive result by Week 52, with the exception of Lot TDG009 which had the least amount of subjects convert to positive.

Reviewer Comment: The vast majority of subjects had negative anti-dsDNA results at baseline and Week 52 for all treatment groups. The proportion of subjects converting from a negative to a positive result by Week 52 was comparable between recipients of HEPLISAV and Engerix-B. A small number of subjects with positive results at baseline had negative results at Week 52. The clinical significance of this change is unclear. No safety signals were found upon review of the anti-dsDNA data.

The incidence of adverse events was analyzed by ANA and anti-dsDNA status. The percentage of subjects with a positive ANA titer at Week 0 experiencing any AE was higher than the overall percentage of subjects experiencing an AE in all treatment groups (HEPLISAV consistency lots: 54.7% vs 50.5%, Lot TDG006: 70.0% vs 50.7%, Engerix-B: 54.5% vs 53.0%). The percentage of subjects with a positive ANA titer at Week 52 was lower than the overall percentage of subjects experiencing an AE (HEPLISAV consistency lots: 46.6% vs 50.5%, Lot TDG006: 58.5% vs 50.7%, Engerix-B: 58.5% vs 53.0%). The incidence of AEs was similar among those with positive anti-dsDNA at Weeks 0 and 52 when compared to the overall incidence of AEs for both the HEPLISAV consistency lots group and the Engerix-B group and lower in the Lot TDG006 group. However, the number of subjects with a positive anti-dsDNA titer was low both at Week 0 and at Week 52 for all treatment groups, and therefore the interpretation of AE frequencies in these subjects is limited.

Reviewer Comment: Overall, there did not appear to be a significant increase in the occurrence of AEs among subjects with a positive ANA or anti-dsDNA at Week 52 based on the data presented.

Other Events

A 42 year old subject had a positive urine pregnancy test approximately 7.5 months after her last injection of TDG006. The subject did not respond to contact attempts and was declared lost to follow-up. There was no available information on pregnancy outcome.
6.2.12.7 Dropouts and/or Discontinuations

Nineteen subjects had treatment withdrawn due to an AE: 13 subjects (0.9%) in the HEPLISAV lot consistency group, 4 subjects (0.8%) in the TDG006 group, and 2 subjects (0.4%) in the Engerix-B group.

In the HEPLISAV lot consistency group, subjects had study treatment withdrawn for: pain in the injection arm (2 subjects), hyperglycemia (1 subject), upper respiratory tract infection (1 subject), thermal burn (1 subject), gun shot wound (1 subject), worsening of hypertension (1 subject), rash (1 subject), breast cancer (1 subject), and potential AIAEs of hypothyroidism (1 subject), erythema nodosum (1 subject), and microscopic colitis (1 subject). One additional subject was withdrawn from study treatment and discontinued from the study due to the AEs of hyponatremia, nausea, vomiting, weight loss and headache.

In the TDG006 group, 1 subject had study treatment withdrawn for a small bowel obstruction, 1 subject had treatment withdrawn for a vesicular rash, 1 subject had treatment withdrawn for neutropenia, and 1 subject had treatment withdrawn for 8 AEs (peripheral edema, allergy to vaccine, rhinitis, upper respiratory tract infection, back pain, sneezing, macular rash, and skin exfoliation).

In the Engerix-B group, 1 subject had treatment withdrawn for prostate cancer, and 1 subject had treatment withdrawn for coronary artery disease.

Reviewer comment: In addition, study injections were discontinued for two subjects receiving lot TDG010 (subjects 42-320 and 21-640 discussed in the previous section). There were more discontinuations due to adverse events in the HEPLISAV group than the Engerix-B group, but overall the incidence of discontinuations due to adverse events was small.

7. INTEGRATED OVERVIEW OF EFFICACY

The ISE submitted by the applicant consists solely of data from the 2 studies previously reviewed. Pooled data from these studies did not change the immunogenicity conclusions reached after assessment of each study individually.

7.1.8 Persistence of Efficacy

Persistence of effectiveness was evaluated in the phase 3 study DV2-HBV-16 and the supportive study HBV-03, using SPRs and GMCs as the measure of the immune response. Study DV2-HBV-16 evaluated SPRs and GMCs up to 52 weeks (48 weeks after the final dose of HEPLISAV and 24 weeks after the final dose of Engerix-B). These data were previously presented in Table 23 (Study DV2-HBV-16) of this clinical review.

At Week 52, SPRs and GMCs induced by HEPLISAV were higher (91.9%) than those induced by Engerix-B (59.0%); the difference in SPRs was 32.9% (95% CI, 27.6%, 38.3%). The difference in SPRs increased from 22.0% at Week 28 to 32.9% at Week 52. In addition, at Week 52 the GMC in the HEPLISAV group (150.7 mIU/mL; 95% CI, 134.8, 168.5 mIU/mL) was higher than in the Engerix-B group (19.5 mIU/mL; 95% CI, 13.5 mIU/mL, 28.1 mIU/mL), with a ratio of GMCs of 7.7 (95% CI, 5.8, 10.3) and was higher than the peak GMC in the Engerix-B group at Week 28 (88.5 mIU/mL).

Reviewer Comment: Although higher GMCs per se, do not support a longer duration of immunity, since the threshold of protection for hepatitis B (10 mIU/mL) was exceeded for both HEPLISAV and Engerix-B at 52 weeks, the implication of higher GMCs in Engerix-B subjects at 1 year is that as a group, these subjects may be protected longer than those immunized with Engerix-B, assuming a similar decay of the immune response over time as Engerix-B and as supported by published data (70). Data from study DV2-HBV-16 indicate that the rate of decrease in antibody levels over time in HEPLISAV is likely slower than that for Engerix-B, as the difference in SPRs between HEPLISAV and Engerix-B increased at later time points in the study. These data suggest that immunologic memory induced by HEPLISAV is, at a minimum, at least as good as that induced by Engerix-B, and more likely the case, significantly better than that induced by Engerix-B.

The supportive study, HBV-03 evaluated subjects for a year after their second injection of HEPLISAV. At Week 60, the SPR in subjects who received HEPLISAV was higher (100%) than in those who received Engerix-B (89.6%). The peak GMC in the Engerix-B group at Week 28 (5239 mIU/mL) was higher than the peak GMC in the HEPLISAV group at Week 24 (2074 mIU/mL). By Week 60, however, the GMC in the HEPLISAV was higher than the GMC in the Engerix-B group (617 mIU/mL).

7.1.10 Additional Efficacy Issues/Analyses

Supportive Clinical Efficacy Studies (DV2-HBV0001, HBV-02, and HBV-03)

Study DV2-HBV0001

This was a phase 1, observer-blind, randomized, dose-escalation study performed in healthy, seronegative adults 18-55 years of age, that evaluated the safety, tolerability and immune response to fixed dose of recombinant hepatitis B virus surface antigen (rHBsAg) vaccine, 20 mcg, co-administered by intramuscular injection (IM) with

differing doses of Dynavax Immunostimulatory Phosphorothioage Oligonucleotide (1018 ISS). This was a dose-escalation study of the 1018 component of the vaccine. Doses of 1018 ISS administered were 300, 650, 1000, or 3000 mcg.

Hepatitis B seronegative subjects who met all inclusion and no exclusion criteria were randomized to receive: (1) rHBsAg alone, (2) 1018 ISS alone, or (3) rHBsAg co-administered with 1018 ISS. Subjects received two doses of test article, at Day 0 and Day 56. Escalation of 1018 ISS to the next higher dose occurred only after safety data accrued for 7 days after each immunization were reviewed and deemed acceptable by the principal investigator, medical monitor and an independent physician. Twelve subjects were randomized into each dose cohort (n=48 total).

Summary of the immunogenicity data showed that co-injection of rHBsAg with 1018 ISS provided a statistically significant increase in the protective antibody response to HBV, compared to rHBsAg alone or to 1018 ISS alone. A summary of seroprotective data is presented in Table 45 below:

Table 45: Subjects per Cohort with Anti-HBs Titers ≥ 10 mIU/mL following Injection

Vaccine, Dose	SPR (Month 1 post- injection #1) (N=8)	SPR (Month 2 post- injection #1) (N=8)	SPR (Month 1 post- injection #2) (N=8)	SPR (Month 4 post- injection #2) (N=8)	SPR (Month 12 post- injection #2) (N=8)
rHBsAg, 20 mcg alone	0	0	0	0	N/A
1018 ISS alone (all doses)	0	0	0	0	N/A
1018 ISS, 300 mcg	0	0	5	7	5 (N=5)
1018 ISS, 650 mcg	2	3	8	8	7 (N=7)
1018 ISS, 1000 mcg	6	7 (N=7)	7 (N=7)	7 (N=7)	7 (N=7)
1018 ISS, 3000 mcg	7	7	8	8	7 (N=7)
Total # subjects with titer ≥ 10 mIU/mL	15/32	17/31	28/31	30/31	26/26

Source: BLA STN 125428, DV2-HBV-0001, Clinical Study Report, Table 4, page 26 of 551

Of the eight recipients immunized with rHBsAg alone or 1018 ISS alone, none developed a serologic response after the first study injection. Of the 15 subjects who received rHBsAg co-administered with 1018 ISS at doses of 1000 mcg or 3000 mcg, 14 were seroprotected two months after the first injection, and were slightly better for the 3000 mcg 1018 ISS dose group. Seroprotection two months after the first dose for individuals who received combination rHBsAg and 1018 ISS was significantly lower at the 300 mcg or 650 mcg doses of 1018 ISS (n=3/8 subjects). A protective titer of serum anti-HbsAg antibody was seen in 28/31 subjects one month after receiving the second injection with

the combination of rHBsAg and 1018 ISS vaccine. Serum samples obtained four months after the second study injection demonstrated protective levels of antibody for 30/31 subjects who received a second immunization with this combination. Serum samples obtained 12 months after the second study injection indicated protective levels of antibody for 26/26 subjects who received two doses of rHBsAg and 1018 ISS.

Geometric mean titers (GMT) for anti-HBsAg titers were measured 1 month after the first and second immunization and 12 to 15 months after the second immunization for subjects in the 300, 650, 1000, and 3000 mcg 1018 ISS plus rHBsAg groups. One month after the first dose of vaccine, GMTs were 1.22 mIU/mL, 5.78 mIU/mL, 24.75 mIU/mL, and 206.5 mIU/mL, respectively. None of the recipients of either rHBsAg alone (N=8) or 1018 ISS alone (N=8) had a positive serologic response after the first vaccine dose.

GMTs at 1 month after the second immunization for subjects in the 300, 650, 1000, and 3000 mcg 1018 ISS plus rHBsAg groups were 65 mIU/mL, 878 mIU/mL, 1545 mIU/mL, and 3045 mIU/mL, respectively.

Twelve to 15 months after the second immunization, blood was drawn for measurement of serum anti-HBs antibody titers in 30/32 subjects, 26 of whom had antibody titers ≥ 100 mIU/mL at Visit 9 and had not received a booster of Engerix-B. The GMTs for the 26 subjects who received 1018 ISS plus rHBsAg and who had not received an Engerix-B booster were 59 mIU/mL, 288 mIU/mL, 356 mIU/mL and 423 mIU/mL in the 300, 650, 1000, and 3000 mcg 1018 ISS plus rHBsAg groups, respectively. A single subject (005) in the 300 mcg group had a GMT of 1 mIU/mL at Visit 10 and after a booster of Engerix-B. All other subjects tested were both seropositive (titer ≥ 2 mIU/mL) and seroprotected (titer ≥ 10 mIU/mL).

No safety concerns or signals were identified in this phase 1 study. The conclusion obtained from this study was the following: two IM doses of a combination of rHBsAg vaccine, 20 mcg, combined with the highest dose of 1018 ISS evaluated in this study (3000 mcg) yielded the optimal seroprotective response, based on the limited seroprotective response data presented.

Reviewer Comment: Based on the SPR data, with the exception of the immune response evaluated after the first dose of vaccine—where the 3000 mcg dose of 1018 ISS demonstrated the highest SPR, all subjects in the 1000 mcg 1018 ISS group also developed a protective antibody level (SPR) against HBsAg. A dose response in GMTs was seen with increasing doses of the 1018 ISS adjuvant, with highest GMTs measured one month after the first and second doses, and 12-15 months after the second dose of the 3000 mcg 1018 ISS plus rHBsAg dose group. Nonetheless, 12-15 months after the second dose of vaccine, all doses of 1018 ISS (plus rHBsAg) generated seroprotective levels of anti-HBs antibody, despite the numerically higher GMTs seen at higher doses of 1018 ISS. On a purely numerical basis, the 3000 mcg 1018 ISS dose resulted in the highest GMT levels, but lower doses of 1018 ISS demonstrated adequate seroprotection, using the criterion of antibody levels against hepatitis B surface antigen ≥ 10 mIU/mL.

DV2-HBV-02

Study DV2-HBV-02 was a phase 2, observer-blinded, randomized, parallel-group study of hypo- and non-responders aged 18-65 years, to licensed hepatitis B vaccine to compare safety, tolerability, and immune response following an additional immunization with either Engerix-B HBV Vaccine or Recombinant Hepatitis B Virus Surface Antigen (rHBs Ag) co-administered with Dynavax Technologies Immunostimulatory Phosphorothioate Oligodeoxyribonucleotide (1018 ISS). The study was conducted at 3 sites in Canada. Up to 100 subjects who had previously failed to generate seroprotection and had anti-HBsAg levels < 10 mIU/mL within 6 months following the completion of the standard three dose immunization series (0, 1, and 6 months) with licensed HBV vaccine were randomized 1:1 to receive either HBsAg (*adw* subtype) co-administered with 3000 mcg 1018 ISS or Engerix-B. 1018 ISS and HBsAg were supplied in separate vials that were drawn into the same syringe and coadministered. HBsAg lot number PWF001 and 1018 ISS lot number LOF002 were used in this study. All subjects received a single injection and returned at Week 4, 26, and 52 after injection to measure anti-HBsAg antibody levels and for safety and tolerability follow-up.

A total of 35 subjects (n=19 for HBsAg plus 1018 ISS adjuvant and n=16 for Engerix-B) were enrolled in the immunogenicity and safety populations. The primary immunogenicity endpoint for this study was the seroprotection rate (proportion of subjects achieving anti-HBsAg \geq 10 mIU/mL 4 weeks after injection). Results for the primary and secondary immunogenicity endpoint determinations are presented in Table 46.

Table 46: Summary Table of Primary and Secondary Immunogenicity Endpoints: Subjects Achieving the Seroprotective Rate (Anti-HBsAg \geq 10 mIU/mL)

Visit (weeks post-immunization)	HBsAg + 1018 ISS		Engerix-B		P=Value ^a
	SPR	n/N	SPR	n/N	
Visit 2 ^{b,c} (Week 4)	52.6%	10/19	37.5%	6/16	Not significant
Visit 3 ^c (Week 26)	88.9%	8/9	66.7%	4/6	Not significant
Visit 4 ^c (Week 52)	50.0%	5/10	16.7%	1/6	Not significant

^a Calculated using the Mantel-Haenszel test of unit relative risk.

^b Primary immunogenicity endpoint: seroprotective rate at Week 4 (Visit 2)

^c Secondary immunogenicity endpoint at Week 26 (Visit 3), and Week 52 (Visit 4)

Source: BLA STN 125428, DV2-HBV-02, Clinical Study Report, Table 11-1, page 45 of 104

For the primary endpoint, subjects in the HBsAg-1018 ISS group had higher immune responses than subjects in the Engerix-B group, although the differences were not statistically significant due to the small sample size. A higher proportion of subjects in the combination group had anti-HBsAg levels \geq 10 mIU/mL compared with the Engerix-B group at the Week 4 endpoint (52.6% (10/19) vs. 37.5% (6/16)), at the Week 26 endpoint (88.9% (8/9) vs. 66.7% (4/6)), and at the Week 52 endpoint (50% (5/10) vs.

16.7% (1/6)). GMCs were higher in the combination group compared to Engerix-B at Weeks 4, 26, and 52, though the differences were not statistically significant.

The conclusion of this study was that the combination of HBsAg vaccine with 1018 ISS adjuvant given as a single dose enhanced seroprotection in hepatitis B vaccine hyporesponders. Findings from this study were used to support administration of a second dose of vaccine following the prime dose in subsequent studies, in an effort to further enhance the immune response.

7.1.11 Efficacy Conclusions

Efficacy of HEPLISAV was evaluated using the seroprotective rate (SPR), defined as the proportion of subjects with anti-HBsAg antibody levels greater than or equal to 10 mIU/mL, after completion of vaccination along with geometric mean concentration (GMC) levels of antibody. Because the SPR represents a threshold of protection, subjects who developed GMCs greater than or equal to 10 mIU/mL are considered protected against hepatitis B.

Two pivotal studies, DV2-HBV-10 and DV2-HBV-16, and three supportive studies, DV2-HBV0001, DV2-HBV-02, and DV2-HBV-03 evaluated the SPR and/or GMC.

Although data from all studies were reviewed, only studies DV2-HBV-10, DV2-HBV-16, DV2-HBV0001 and DV2-HBV-02 are discussed in this review, as Study DV2-03 was a supportive study that utilized different doses of the adjuvant 1018 ISS, different dosing schedules than that ultimately selected, and an earlier formulation of the to-be-marketed product. With the exception of a dose-ranging study (DV2-HBV0001), where the dose of 1018 ISS adjuvant was varied and whose objective it was to determine the most immunogenic dose of hepatitis B vaccine and adjuvant combination, all of the immunogenicity studies performed included an active comparator arm (Engerix-B). An additional open-label study DV2-HBV-014 was performed that evaluated a fixed dose of the vaccine and adjuvant but did not have a comparator and thus was not included in this efficacy analysis.

The proposed to-be-marketed dose of HEPLISAV was a 20 mcg dose of recombinant HBsAg plus 3000 mcg of 1018 ISS adjuvant, given IM at Month 0 and 1 (two doses). Engerix-B, the comparator, was administered IM at Month 0, 1, and 6 (three doses).

Results of the two pivotal studies showed that SPRs induced by HEPLISAV at the pre-specified primary immunogenicity endpoint (Week 12 for HEPLISAV and Week 28 or 32 for Engerix-B) were greater and noninferior to that of Engerix-B for all age groups studied (18-70 years). These data were also replicated at each study visit, up to Week 52 (in Study DV2-HBV-52) and indicated that HEPLISAV had a faster, more robust and more sustained immune response than did Engerix-B. Subgroup analysis by age, gender, and race failed to indicate any significant differences amongst the subgroups studied, but for these analyses as well, the HEPLISAV response was stronger than that of Engerix-B. Type 2 diabetic subjects were studied as a secondary immunogenicity endpoint in the pivotal phase 3 study DV2-HBV-16 as a representative of what the applicant defined as a

“hypo-responsive” population, given that many diabetics do not respond as well to vaccination in general, as do healthy individuals. In this subset of subjects, HEPLISAV induced a stronger immune response than did Engerix-B and cross-analysis comparison of the SPR seen in diabetic subjects in comparison to all study subjects combined for study DV2-HBV-16 indicated that the diabetic immune response was slightly lower than that of all study subjects. The difference in response in diabetics, however, paralleled that of all subjects combined.

One of the supportive studies, DV2-HBV-02, was performed in subjects with documented hypo-responsiveness to a course of vaccination against hepatitis B vaccine. This phase 2, observer-blinded, randomized, parallel-group study of hypo- and non-responders aged 18-65 years, evaluated subjects who did not develop adequate seroprotective levels against hepatitis B after completion of a vaccination series. Up to 100 subjects who had previously failed to generate seroprotection and had anti-HBsAg levels < 10 mIU/mL within 6 months following the completion of the standard three dose immunization series (0, 1, and 6 months) with licensed HBV vaccine were randomized 1:1 to receive either HBsAg (*adw* subtype) co-administered with 3000 mcg 1018 ISS or Engerix-B. For the primary endpoint, subjects in the HBsAg-1018 ISS group had higher immune responses than subjects in the Engerix-B group, though the differences were not statistically significant due to the small sample size. A higher proportion of subjects in the combination group had anti-HBsAg levels \geq 10 mIU/mL compared with the Engerix-B group at the Week 4 endpoint (52.6% (10/19) vs. 37.5% (6/16)), at the Week 26 endpoint (88.9% (8/9) vs. 66.7% (4/6)), and at the Week 52 endpoint (50% (5/10) vs. 16.7% (1/6)). GMCs were higher in the combination group compared to Engerix-B at Weeks 4, 26, and 52, although the differences were not statistically significant. The conclusion of this study was that the combination of HBsAg vaccine with 1018 ISS adjuvant given as a single dose did enhance seroprotection in hepatitis B vaccine hypo-responders, even though the increase was not statistically significant when compared to an additional dose of an active comparator (Engerix-B). An adequately powered prospective study would be necessary to confirm this finding, though these preliminary data are very encouraging in the hepatitis B vaccine hypo-responder population.

Finally, an evaluation of persistence of the immune response in Study DV2-HBV-16 indicated that at 1 year and beyond (up to 60 weeks studied), the SPRs and GMCs in HEPLISAV vaccinated remained significantly elevated (SPR > 90%), suggestive that this vaccine was able to induce immunologic memory.

In summary, HEPLISAV demonstrated an adequate immune response against hepatitis B and showed that it was able to induce a high SPR rapidly (by Week 8). This high seroprotection level was sustained for at least 48 to 52 weeks after the last dose of vaccine given.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Table 47 summarizes the trial design and safety assessments conducted for each trial included in the integrated summary of safety.

Table 47: Safety Assessment Schedule by Trial

Phase/Trial Number	Trial Design	Formulation/ Schedule/N	Comparator/ Schedule/N	Safety Assessments (time following 1 st dose)
Tier 1				
Phase 3/ HBV-10	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy subjects 11 to 55 years of age in Canada and Germany	HEPLISAV: 0,4 weeks (placebo at 24 weeks) N= 1820 ^a	Engerix-B: 0,4,24 weeks N=608 ^a	AEs: 28 weeks SAEs: 28 weeks Solicited AEs: 7 days post injection(s) ANA, anti-ds DNA: S ^b , 28 weeks
Phase 3/ HBV-16	Observer-blind, randomized, active-controlled, parallel-group, multicenter trial in healthy adults 40 to 70 years of age in the US and Canada	HEPLISAV: 0,4 weeks (placebo at 24 weeks) N=1968	Engerix-B: 0,4,24 weeks N=481	AEs: 28 weeks SAEs and potential AIAEs: 52 weeks Solicited AEs: 7 days post injection(s) Serum chemistry, hematology: S,4,8,24,28 weeks ANA, anti-dsDNA: S,52 weeks
Tier 2				
Phase 2/ HBV-14	Open-label trial in healthy subjects 11-55 years of age in the US	HEPLISAV: 0,4 weeks N=207 ^a	None	AEs: 28 weeks SAEs: 28 weeks Solicited AEs: 7 days post-injection(s) Serum chemistry, hematology: S,2 (subgroup only), 8 weeks ANA, anti-dsDNA: S, 28 weeks
Tier 3				

Phase/Trial Number	Trial Design	Formulation/ Schedule/N	Comparator/ Schedule/N	Safety Assessments (time following 1 st dose)
Phase 1/ HBV0001	Observer-blind, randomized, dose-escalation trial of the 1018 ISS component of vaccine in healthy, seronegative adults 18-55 years of age in Canada	HEPLISAV (F1): 0, 8 weeks HBsAg/1018 ISS doses: 20/300mcg: n=8 20mcg/650mcg: n=8 20mcg/1000mcg: n=8 20mcg/3000mcg: n=8 HBsAg alone (20mcg): n=8 1018 ISS Adjuvant alone: 300 mcg: n=2 650 mcg: n=2 1000mcg: n=2 3000mcg: n=2	None	AEs: 62 weeks SAEs: 62 weeks Solicited AEs: 7 days post injection(s) Serum chemistry, hematology, urinalysis: S, 1, 8, 9, 13 weeks ANA, anti-dsDNA, anti-ssDNA: S, 4, 8, 13, 24 weeks ESR, C3, C4: 1, 4, 8, 9, 13, 24 weeks
Phase 2/ HBV-02	Observer-blind, randomized, parallel-group trial of hypo- and nonresponders to licensed hepatitis B vaccine in adults 18 to 65 years of age in Canada	HEPLISAV (F1): Single injection Primary: N=19 Substudy: N=11 Total N=30	Engerix-B: Single injection Primary: N=16 Substudy: N=13 Total: N=29	AEs: 4 weeks SAEs: 52 weeks Solicited AEs: 7 days post injection(s) Serum chemistry: S, 4 (subset) weeks Hematology, ESR: S, 4 weeks ANA, anti-dsDNA, anti-ssDNA: S, 4, 26, 52 weeks
Phase 2/ HBV-03	Observer-blind, randomized, parallel-group trial in adults 18-28 years of age in Canada	HEPLISAV (F1): 0, 8 weeks, (placebo/meningococcal vaccine at week 24) N=48	Engerix-B: 0, 8, 24 weeks N=51	AEs: 28 weeks SAEs: 60 weeks Solicited AEs: 7 days post injection(s) Serum chemistry, hematology, ESR: S, 4, 12 weeks Urinalysis: S, 1, 4, 8, 9, 12 weeks ANA, anti-dsDNA, anti-ssDNA: S, 8, 12, 28, 60 weeks Complements (C3, C4): S, 8, 9 weeks

Phase/Trial Number	Trial Design	Formulation/ Schedule/N	Comparator/ Schedule/N	Safety Assessments (time following 1 st dose)
Phase 2/ HBV-05	Double-blind, randomized, parallel- group trial in adults 40 to 70 years of age in Singapore	HEPLISAV (F2): 0,8,24 weeks N=48	Engerix-B: 0,4,24 weeks N=47	AEs: 25 weeks SAEs: 50 weeks Solicited AEs: 7 days post injection(s) Serum chemistry, hematology: S, 12 weeks ANA, anti-dsDNA: S, 28 weeks
Phase 3/ HBV-04	Double-blind, randomized, parallel- group trial in adults 40 to 70 years of age in South Korea, Philippines, and Singapore	HEPLISAV (F2): 0,8,24 weeks (placebo at 4 weeks) N=206	Engerix-B: 0,4,24 weeks (placebo at 8 weeks) N=206	AEs: 28 weeks SAEs: 50 weeks Solicited AEs: 7 days post injection(s) Serum chemistry, CK, LDH, hematology: S, 12 weeks
Phase 2/ HBV-08	Double-blind, randomized, parallel- group trial in adults 18 to 39 years of age in Canada	HEPLIIV (F2): 0,4 weeks and 0,8 weeks HEPLISAV (F2) Half Dose (10mcg/1500mcg): 0,4 weeks N=61	None	AEs: 12 weeks SAEs: 32 weeks Solicited AEs: 7 days post-injection(s) Serum chemistry, hematology, ANA, urinalysis: S, 32 weeks

^a All enrolled subjects of all ages included in N; ^b Screening
AEs = adverse events; SAEs = serious adverse events; AIAEs = autoimmune adverse events; ANA = antinuclear antibody; anti-dsDNA = antibody to double-stranded DNA; anti-ssDNA = antibody to single-stranded DNA; C3/C4 = complement components 3 and 4; ESR = erythrocyte sedimentation rate; F1 = formulation 1; F2= formulation 2
Source: Adapted from STN 125428 Summary of Clinical Safety. Table 2.7.4-1, pp 18-22

Reviewer Comment: The tiered assessment of safety data is described in Section 8.2.1, Table 48.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

During the clinical development of HEPLISAV, three formulations of vaccine were administered:

- **HEPLISAV Formulation 3 (F3)**, the proposed commercial formulation, was used in the pivotal phase 3 trials HBV-10 and HBV-16 as well as HBV-14. F3 consists of 20 mcg of HBsAg subtype *adw* + 3000 mcg of 1018 ISS in a single vial presentation.
- **HEPLISAV (F2)** was used in trials HBV-04, HBV-05 AND HBV-08. F2 consisted of 20 mcg of HBsAg subtype *adr* + 3000 mcg of 1018 ISS in either a single or 2 vial presentation.

- **HEPLISAV (F1)** was used in trials HBV0001, HBV-02 AND HBV-03. F1 consisted of 20 mcg of HBsAg subtype *adw* + variable concentrations of 1018 ISS in a 2 vial presentation.

In the Integrated Summary of Safety, safety data is presented using a tiered approach outlined in Table 48. This approach distinguishes the Phase 3 trials from supportive trials and allows evaluation of potential differences between the safety profiles of the three formulations used throughout the development program. The safety population includes subjects who received at least 1 dose of study vaccine and had any post-baseline safety assessment.

Table 48: Description of Safety Tiers used in the Integrated Safety Analyses

Tier	Studies Included	HEPLISAV Formulation(s) Used	Number of subjects receiving HEPLISAV	Population Description
Tier 1 (T1SP)	HBV-10 ¹ , HBV-16	F3	3788	Subjects in the pivotal phase 3 trials
Tier 2 (T2SP)	Tier 1 plus HBV-14	F3	3995	All recipients of the proposed commercial formulation of HEPLISAV
Tier 3 (T3SP)	Tier 2 plus HBV0001, HBV-02, HBV-03, HBV-04, HBV-05 and HBV-08	All	4436	All recipients of all formulations of HEPLISAV

¹Study HBV-10 included thirteen subjects age 11-17 years old. Eleven were randomized to the HEPLISAV group and 2 were randomized to the Engerix-B group.

Source: STN125248, *Integrated Summary of Clinical Safety*, pp 9-16

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Tables 49 through 51 summarize the subject characteristics by treatment group for each safety tier.

Table 49: Subject Characteristics by Treatment Group for Tier 1 (T1SP)

Characteristic	HEPLISAV N=3788	Engerix-B N=1089
Female, n (%)	1984 (52.4)	591 (54.3)
11-17 years, n (%)	11 (0.3)	2 (0.2)
18-39 years, n (%)	818 (21.6)	275 (25.3)

Characteristic	HEPLISAV N=3788	Engerix-B N=1089
40-55 years, n (%)	2116 (55.9)	614 (56.4)
≥ 56 years, n (%)	843 (22.3)	198 (18.2)
Mean age in years (SD)	47.2 (11.29)	46.0 (11.05)
Median age in years	48	46
Min-Max age in years	11-70	13-70
White, n (%)	3318 (87.6)	957 (87.9)
Black or African American, n (%)	337 (8.9)	89 (8.2)
Asian, n (%)	69 (1.8)	26 (2.4)
Other ¹ , n (%)	64 (1.7)	17 (1.6)
Hispanic, n (%)	164 (4.3)	58 (5.3)
Non-Hispanic, n (%)	3622 (95.6)	1031 (94.7)
Missing, n (%)	2 (0.1)	

¹Other = combined American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander and Other
Source: Adapted from STN 125428, Table ISS 2.1.5, pp 40-41

In Tier 1, there were more females that received both HEPLISAV and Engerix-B than males. Most subjects in both treatment groups were age 40-55, of White race, and non-Hispanic ethnicity.

Reviewer Comment: *The demographic characteristics of subjects receiving HEPLISAV and Engerix-B in Tier 1 do not suggest that selection bias based on age, sex, race or Hispanic ethnicity was introduced. Additionally, weight, height, BMI and smoking status were also similar between groups.*

Table 50: Subject Characteristics by Treatment Group for Tier 2 (T2SP)

Characteristic	HEPLISAV N=3995	Engerix-B N=1089
Female, n (%)	2117 (53.0)	591 (54.3)
11-17 years, n (%)	11 (0.3)	2 (0.2)
18-39 years, n (%)	880 (22.0)	275 (25.3)
40-55 years, n (%)	2260 (56.6)	614 (56.4)
≥ 56 years, n (%)	844 (21.1)	198 (18.2)
Mean age in years (SD)	46.9 (11.19)	46.0 (11.05)
Median age in years	48	46
Min-Max age in years	11-70	13-70
White, n (%)	3503 (87.7)	957 (87.9)
Black or African American, n (%)	351 (8.8)	89 (8.2)
Asian, n (%)	75 (1.9)	26 (2.4)
Other ¹ , n (%)	66 (1.7)	17 (1.6)
Hispanic, n (%)	170 (4.3)	58 (5.3)
Non-Hispanic, n (%)	3823 (95.7)	1031 (94.7)

¹Other = combined American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander and Other

Source: Adapted from STN 125428, Table ISS 2.2.3, pp 50-51

In Tier 2, more females than males were enrolled in each treatment arm. Most subjects were 40-55 years old, of white race, and non-Hispanic ethnicity.

Reviewer Comment: The demographic characteristics of subjects receiving HEPLISAV and Engerix-B in Tier 2 do not suggest that selection bias based on age, sex, race or Hispanic ethnicity was introduced. Additionally, weight, height, BMI and smoking status were also similar between groups.

Table 51: Subject Characteristics by Treatment Group for Tier 3 (T3SP)

Characteristic	HEPLISAV N=4436	Engerix-B N=1422
Female, n (%)	2390 (53.9)	807 (56.8)
11-17 years, n (%)	11 (0.2)	2 (0.1)
18-39 years, n (%)	1039 (23.4)	336 (23.6)
40-55 years, n (%)	2483 (56.0)	830 (58.4)
≥ 56 years, n (%)	903 (20.4)	254 (17.9)
Mean age in years (SD)	46.4 (11.47)	45.7 (11.22)
Median age in years	47	46
Min-Max age in years	11-70	13-70
White, n (%)	3682 (83.0)	1032 (72.6)
Black or African American, n (%)	356 (8.0)	90 (6.3)
Asian, n (%)	329 (7.4)	280 (19.7)
Other ¹ , n (%)	68 (1.5)	19 (1.3)
Missing, n (%)	1 (0.0)	1 (0.1)
Hispanic, n (%)	170 (3.8)	58 (4.1)
Non-Hispanic, n (%)	4263 (96.1)	1363 (95.9)
Missing, n (%)	3 (0.1)	1 (0.1)

¹Other = combined American Indian or Alaskan Native, Native Hawaiian or Other Pacific Islander and Other

Source: Adapted from STN 125428, ISS, Table 2.2.9, pp 86-87

In Tier 3, more females than males were enrolled in each treatment arm. Most subjects were 40-55 years old, of white race, and non-Hispanic ethnicity. There were more Asian subjects in the Engerix-B arm than in the HEPLISAV arm (19.7% versus 7.4%).

Reviewer Comment: A higher proportion of Asian subjects received Engerix-B than HEPLISAV in Tier 3 due to the selection of some of the initial study sites in southeast Asia, an area with relatively high prevalence of hepatitis B. Overall, the demographic characteristics of subjects receiving HEPLISAV and Engerix-B in Tier 3 do not suggest that selection bias based on age, sex, race or Hispanic ethnicity was introduced. Additionally, weight, height, BMI and smoking status were also similar between groups in this tier.

8.2.3 Categorization of Adverse Events

As noted in the appropriate sections of this review, incidences of miscategorization of events were present in this submission. Examples include a case of Wegener's granulomatosis that was categorized as a pulmonary event in one clinical study report and as a vascular event in the integrated study report and a case of potential Tolosa-Hunt syndrome versus cavernous sinus syndrome that was miscoded as a cavernous sinus thrombosis. The data were carefully reviewed and events were recategorized/reanalyzed when necessary. See section 3.1 as well.

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

General limitations of pooling data across trials in this submission include but are not limited to variations in vaccination schedule, safety follow-up periods, laboratory evaluation periods relative to injection times, randomization ratios, and subject selection criteria. Some evaluations (e.g. AESI analysis) took place retrospectively among subjects enrolled in trials using various selection criteria with respect to autoimmune history.

8.4 Safety Results

8.4.1 Deaths

There were two deaths in study HBV-16 which are described in section 6.2.12.3. There were no deaths in studies HBV0001, HBV-02, HBV-03, HBV-04, HBV-05, HBV-08, HBV-14 or HBV-10.

8.4.2 Nonfatal Serious Adverse Events

Table 52 compares treatment emergent serious adverse events (SAEs) by treatment group and safety tier using MedRA system organ class and preferred term.

Table 52: Summary of Treatment Emergent SAEs by System Organ Class and Preferred Term by Treatment Group and Safety Tier for Subjects 18-70 Years Old

System Organ Class Preferred Term	T1SP HEPLISAV N=3777	T1SP Engerix-B N=1087	T2SP HEPLISAV N=3984	T2SP Engerix-B¹ N=1087	T3SP HEPLISAV N=4425	T3SP Engerix-B N=1420
Subjects with Any SAE	104 (2.7%)	36 (3.3%)	106 (2.7%)	36 (3.3%)	121 (2.7%)	52 (3.7%)
Blood and Lymphatic System Disorders	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Anemia	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Cardiac Disorders	8 (0.2%)	6 (0.6%)	8 (0.2%)	6 (0.6%)	9 (0.2%)	7 (0.5%)
Acute Myocardial Infarction	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Angina Pectoris	2 (0.1%)	0	2 (0.1%)	0	2 (0.1%)	0
Angina Unstable	0	1 (0.1%)	0	1 (0.1%)	0	2 (0.1%)
Atrial Fibrillation	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Cardiac Failure	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Cardiomyopathy	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Coronary Artery Disease	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	2 (0.0%)	1 (0.1%)
Coronary Artery Stenosis	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Supraventricular Tachycardia	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Ear and Labyrinth Disorders	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Vertigo	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0

System Organ Class Preferred Term	T1SP HEPLISAV N=3777	T1SP Engerix- B N=1087	T2SP HEPLISAV N=3984	T2SP Engerix- B ¹ N=1087	T3SP HEPLISAV N=4425	T3SP Engerix- B N=1420
Gastrointestinal Disorders	8 (0.2%)	3 (0.3%)	8 (0.2%)	3 (0.3%)	10 (0.2%)	4 (0.3%)
Abdominal Hernia	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Barrett's Esophagus	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Enteritis	0	0	0	0	0	1 (0.1%)
Erosive Esophagitis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Gastric Hemorrhage	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Gastric Ulcer	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Gastritis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Gastroenteritis	0	0	0	0	1 (0.0%)	0
Gastroesophageal Reflux Disease	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hematemesis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Inguinal Hernia	1 (0.0%)	0	1 (0.0%)	0	2 (0.0%)	0
Pancreatitis	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Small Intestinal Obstruction	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
General Disorders & Administration Site Conditions	4 (0.1%)	2 (0.2%)	5 (0.1%)	2 (0.2%)	5 (0.1%)	2(0.1%)
Chest Pain	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Device Dislocation	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hernia Obstructive	0	0	1 (0.0%)	0	1 (0.0%)	0
Non-Cardiac Chest Pain	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Hepatobiliary Disorders	2 (0.1%)	0	3 (0.1%)	0	4 (0.1%)	0
Cholecystitis	1 (0.0%)	0	1 (0.0%)	0	2 (0.0%)	0
Cholecystitis Acute	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Cholelithiasis	0	0	1 (0.0%)	0	1 (0.0%)	0
Immune System Disorders	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
ANCA Positive Vasculitis	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Infections & Infestations	8 (0.2%)	3 (0.3%)	9 (0.2%)	3 (0.3%)	12 (0.3%)	7 (0.5%)
Abscess Neck	0	0	0	0	1 (0.0%)	0
Cavernous Sinus syndrome versus Tolosa-Hunt syndrome	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Dengue Fever	0	0	0	0	1 (0.0%)	0
Diverticulitis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Gastroenteritis	0	0	0	0	1 (0.0%)	0
Gastroenteritis Salmonella	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Latent Tuberculosis	0	0	0	0	0	1 (0.1%)
Liver Abscess	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Localized Infection	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Perirectal Abscess	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0

System Organ Class Preferred Term	T1SP HEPLISAV N=3777	T1SP Engerix- B N=1087	T2SP HEPLISAV N=3984	T2SP Engerix- B ¹ N=1087	T3SP HEPLISAV N=4425	T3SP Engerix- B N=1420
Pneumonia	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	1 (0.1%)
Post-Procedural Infection	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Acute Pyelonephritis	0	0	0	0	0	1 (0.1%)
Salpingo-Oophoritis	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Septic Shock	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Staphylococcal Infection	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	1 (0.1%)
Tonsillitis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Urinary Tract Infection	0	0	1 (0.0%)	0	1 (0.0%)	0
Injury, Poisoning & Procedural Complications	21 (0.6%)	5 (0.5%)	22 (0.6%)	5 (0.5%)	25 (0.6%)	8 (0.6%)
Alcohol Poisoning	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Ankle Fracture	3 (0.1%)	0	3 (0.1%)	0	3 (0.1%)	0
Concussion	0	0	0	0	0	1 (0.1%)
Contusion	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Delayed Recovery from Anesthesia	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Fall	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Femur Fracture	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Fibula Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Foot Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Fracture	0	0	0	0	0	1 (0.1%)
Fracture Sacrum	0	0	0	0	1 (0.0%)	0
Gun Shot Wound	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hip Fracture	0	0	0	0	1 (0.0%)	1 (0.1%)
Jaw Fracture	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Joint Dislocation	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Joint Injury	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Ligament Rupture	0	0	0	0	0	1 (0.1%)
Meniscus Lesion	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	2 (0.0%)	1 (0.1%)
Muscle Strain	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Patella Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Post Procedural Complication	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Postoperative Ileus	0	0	1 (0.0%)	0	1 (0.0%)	0
Spinal Column Injury	0	0	0	0	1 (0.0%)	0
Sternal Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Tendon Rupture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Thermal Burn	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Tibia Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Ulna Fracture	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Metabolism & Nutrition Disorders	6 (0.2%)	1 (0.1%)	7 (0.2%)	1 (0.1%)	8 (0.2%)	1 (0.1%)
Dehydration	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Diabetic Ketoacidosis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hyperglycemia	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hypokalemia	1 (0.0%)	0	2 (0.1%)	0	2 (0.0%)	0

System Organ Class Preferred Term	T1SP HEPLISAV N=3777	T1SP Engerix- B N=1087	T2SP HEPLISAV N=3984	T2SP Engerix- B ¹ N=1087	T3SP HEPLISAV N=4425	T3SP Engerix- B N=1420
Hyponatremia	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Type II Diabetes Mellitus	0	0	0	0	1 (0.0%)	0
Water Intoxication	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Musculoskeletal & Connective Tissue Disorders	21 (0.6%)	6 (0.6%)	21 (0.6%)	6 (0.6%)	23 (0.5%)	7 (0.5%)
Bursitis	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	2 (0.1%)
Gouty Arthritis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Intervertebral Disc Degeneration	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	2 (0.0%)	1 (0.1%)
Intervertebral Disc Protrusion	4 (0.1%)	1 (0.1%)	4 (0.1%)	1 (0.1%)	5 (0.1%)	1(0.1%)
Loose Body in Joint	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Lumbar Spinal Stenosis	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Musculoskeletal Chest Pain	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Neck Pain	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Osteoarthritis	9 (0.2%)	2 (0.2%)	9 (0.2%)	2 (0.2%)	10 (0.2%)	2 (0.1%)
Spinal Column Stenosis	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Spondylolisthesis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Neoplasms Benign, Malignant & Unspecified	14 (0.4%)	5 (0.5%)	14 (0.4%)	5 (0.5%)	14 (0.3%)	7 (0.5%)
Brain Neoplasm	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Breast Cancer	3 (0.1%)	2 (0.2%)	3 (0.1%)	2 (0.2%)	3 (0.1%)	2 (0.1%)
Breast Cancer Recurrent	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Colon Adenoma	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Colon Cancer Stage IV	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Inflammatory Carcinoma of the Breast	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Marrow Hyperplasia	0	0	0	0	0	1 (0.1%)
Meningioma	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Non-Small Cell Lung Cancer Metastatic	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Prostate Cancer	1 (0.0%)	3 (0.3%)	1 (0.0%)	3 (0.3%)	1 (0.0%)	3 (0.2%)
Thyroid Cancer	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Uterine Leiomyoma	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	1 (0.1%)
Nervous System Disorders	4 (0.1%)	1 (0.1%)	5 (0.1%)	1 (0.1%)	6 (0.1%)	3 (0.2%)
Benign Intracranial Hypertension	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Cerebral Ischemia	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Cerebrovascular Accident	0	0	0	0	0	1 (0.1%)
Grand Mal Convulsion	0	0	0	0	0	1 (0.1%)

System Organ Class Preferred Term	T1SP HEPLISAV N=3777	T1SP Engerix-B N=1087	T2SP HEPLISAV N=3984	T2SP Engerix-B ¹ N=1087	T3SP HEPLISAV N=4425	T3SP Engerix-B N=1420
Guillain-Barre Syndrome	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Spondylitic Myelopathy	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Subarachnoid Hemorrhage	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Syncope	0	0	1 (0.0%)	0	1 (0.0%)	0
Seventh Nerve Paralysis	0	0	0	0	1 (0.0%)	0
Psychiatric Disorders	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Delirium Tremens	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Depression	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Major Depression	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Renal & Urinary Disorders	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	1 (0.1%)
Renal Failure	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Urinary Incontinence	0	0	0	0	0	1 (0.1%)
Reproductive System & Breast Disorders	3 (0.1%)	3 (0.3%)	3 (0.1%)	3 (0.3%)	4 (0.1%)	3 (0.2%)
Endometriosis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Hemorrhagic Ovarian Cyst	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Menorrhagia	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Menstruation Irregular	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Ovarian Cyst	0	1 (0.1%)	0	1 (0.1%)	1 (0.0%)	1 (0.1%)
Prostatitis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0
Respiratory, Thoracic & Mediastinal Disorders	10 (0.3%)	3 (0.3%)	11 (0.3%)	3 (0.3%)	12 (0.3%)	4 (0.3%)
Asthma	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	3 (0.1%)	1 (0.1%)
Bronchial Hyperreactivity	0	1 (0.1%)	0	1 (0.1%)	0	1 (0.1%)
Chronic Obstructive Pulmonary Disease	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)	1 (0.0%)	1 (0.1%)
Hypoxia	1 (0.0%)	0	2 (0.1%)	0	2 (0.0%)	0
Nasal Septum Deviation	0	0	0	0	0	1 (0.1%)
Pneumothorax	2 (0.1%)	0	2 (0.1%)	0	2 (0.0%)	0
Pulmonary Embolism	5 (0.1%)	0	5 (0.1%)	0	5 (0.1%)	0
Surgical & Medical Procedures	0	0	0	0	0	2 (0.1%)
Abortion Induced Complete	0	0	0	0	0	1 (0.1%)
Hip Arthroplasty	0	0	0	0	0	1 (0.1%)
Vascular Disorders	4 (0.1%)	1 (0.1%)	4 (0.1%)	1 (0.1%)	4 (0.1%)	2 (0.1%)
Deep Vein Thrombosis	2 (0.1%)	1 (0.1%)	2 (0.1%)	1 (0.1%)	2 (0.0%)	1 (0.1%)
Hypertension	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	1 (0.1%)
Wegener's Granulomatosis	1 (0.0%)	0	1 (0.0%)	0	1 (0.0%)	0

¹The T2SP safety population includes subjects from trials in which the proposed commercial formulation of HEPLISAV was used. These include studies DV2-HBV-10, DV2-HBV-16 (T1SP), and DV2-HBV-14, an uncontrolled study. Therefore, the percentage of events occurring in the Engerix-B group is the same for T1SP and T2SP.

Source: STN 125428/0. Integrated Summary of Safety, Tables 11.1.4.3, 11.2.4 and 11.2.5, pages 1185, 1209 and 1215.

SAEs are presented for all subjects 18-70 years of age. None of the 13 subjects age 11-17 years reported SAEs. The proportion of subjects with any SAE was similar between treatment groups for all tiers. Overall, the incidence of SAEs was similar between treatment groups.

Five cases of pulmonary embolus were reported among HEPLISAV recipients and none were reported among Engerix-B recipients. One case was fatal as described in section 6.1.12.3. Brief narratives of the remaining four cases will be described here.

Subject 22-601, a 62 year old male with a past medical history that included hyperlipidemia, hypertension, sleep apnea treated with continuous positive airway pressure and hand tendonitis presented to the emergency department 8 months after the last active study injection complaining of right sided chest pain, left calf pain and shortness of breath with ambulation. Pertinent findings included a d-dimer of 23,978 ng/mL (0.0-499.ng/mL) and a computed tomography angiogram (CTA) of the chest that confirmed extensive bilateral pulmonary emboli with a clot at the bifurcation of both main pulmonary arteries and an extensive clot extending into the upper and lower lobes of both lungs. Enoxaparin and IV heparin therapy were initiated. Ultrasound evaluation showed extensive deep venous thrombosis on the left leg in the main femoral vein, popliteal, posterior tibial and peroneal veins. He was discharged from the hospital four days after admission on at least 6 months of warfarin therapy. An evaluation for an underlying clotting disorder was planned and results pending. He had a history of frequent traveling and had recently taken an interstate road trip. The investigator assessed the events as severe and not related to study treatment.

Subject 11168, a 36 year old female with a medical history that included splenectomy for unknown reason, back pain, depression and anxiety was hospitalized 111 days following her second study injection and 5 days after an influenza vaccination for Guillain-Barre Syndrome. During her hospitalization, approximately one month after admission, she developed extensive bilateral pulmonary emboli with extended her hospital stay. She was treated with heparin followed by oral warfarin. The investigator assessed the pulmonary embolism as severe and probably not related to study injection.

Subject 21047, a 32 year old female with a medical history that included obesity, smoking and use of an etonogestrel ethinyl vaginal ring reported pain in her right arm 38 days after her second study injection. The pain worsened and she was admitted and was diagnosed with pulmonary embolism, pleuritis, pneumonia and cystitis 44 days following her second study injection. A chest CTA showed a pulmonary arterial embolism with thrombotic material in segmental inferior lobe arteries in addition to a small right lower lobe infiltrate and pleural effusion. A thrombophilia diagnostic study was negative, but antiphospholipid antibodies were elevated. An ultrasound examination of the legs was

limited due to the subject's obesity but no sign of deep vein thrombosis was found on this limited exam. It is unclear how the embolus was treated. She was discharged from the hospital two weeks after admission. The investigator assessed the event as severe and probably not related to study treatment. She was subsequently readmitted for intravenous antibiotic therapy for lingual tonsillitis.

Subject 22070, a 26 year old male with a medical history of asthma, had a traumatic rupture of the anterior cruciate ligament (ACL) of the right knee one month after his second study injection. He was treated with prophylactic dalteparin. Nine days after ACL rupture, he was diagnosed with phlebothrombosis of the complete right leg and treated with phenprocoumon. The following day he was hospitalized with suspicion of pulmonary embolism which was confirmed by chest CT. He was treated with fondaparinux sodium and the event was considered resolved 9 days later. He was discontinued from the study due to this SAE. The investigator assessed the event as severe in intensity and not related to study treatment. At the time of discontinuation, a follow-up concerning hereditary causes of thrombosis was pending.

Reviewer Comment: Although there was a numerical imbalance in the number of subjects for whom pulmonary emboli were reported (HEPLISAV: n=5 with one fatality; Engerix-B: n=0), four of these cases occurred in individuals with some degree of underlying predisposition to thrombosis. Given the other clinical factors potentially contributing to the occurrence of these thrombotic and embolic events, it is difficult to discern the clinical significance, if any of the numerical imbalance in the incidence of these events observed in this study. Follow-up information regarding the thrombotic workup for subject s reporting pulmonary emboli will be requested.

A case of Wegener's granulomatosis is categorized as a vascular disorder here and as a respiratory disorder in the individual clinical study report. While this disease is a vasculitis that does involve the respiratory system, it is of autoimmune origin. Furthermore, it is an ANCA positive vasculitis and should be categorized under that heading in this table in the opinion of this reviewer. Recategorization in this manner would not impact the incidence of ANCA positive vasculitides across these studies. Additionally, one subject was diagnosed with possible Tolosa-Hunt syndrome, a granulomatous inflammation of the cavernous sinus. The diagnosis was subsequently changed to cavernous sinus syndrome, but remains in question. Given the vaccine-related case of Wegener's granulomatosis that occurred in study DV2-HBV-10, the possible occurrence of a case of a second granulomatous disease, Tolosa-Hunt syndrome, in study DV2-HBV-16 presents a potentially serious safety concern. This case is the subject of expert consultation which is pending at present.

8.4.3 Study Dropouts/Discontinuations

Subject disposition was not provided in an integrated manner. Please see sections 6.1.10.1.3 and 6.2.10.1.3 for the dropout/discontinuation information for studies DV2-HBV-10 and DV2-HBV-16 respectively.

In study HBV0001, 47 of 48 subjects received the two scheduled study injections. Subject 053 withdrew consent following the first study injection due to injection-site

swelling and erythema, moderate disorientation and dizziness, moderate myalgia and fatigue and mild shortness of breath on the day of the first injection with 1000mcg of 1018 ISS + rHBsAg. These complaints caused the subject to leave work early that day, but he was able to return to work the following day at which time the dizziness, disorientation and fatigue had resolved. The myalgia resolved by the third day after injection. Forty-five of the subjects had a safety follow-up visit at Visit 10, the final study visit (month 12-15). Subject 053 reported no adverse events at Visit 10.

In study DV2-HBV-02, one subject in the Engerix-B arm discontinued due to a protocol violation.

In study DV2-HBV-03, 5/51 subjects in the Engerix-B group and 1/48 subjects in the HEPLISAV group did not complete the study. Of the 5 subjects in the Engerix-B group who did not complete the study, 4 (Subjects 1058, 1087, 1093, 3005) discontinued due to noncompliance and 1 (Subject 3006) was lost to follow-up. Subjects 1058, 1087 and 3005 had all 3 immunizations. Subject 1093 had 2 immunizations and Subject 3006 had one immunization. In the HEPLISAV group, Subject 3008 discontinued due to noncompliance. This subject had one immunization.

In study DV2-HBV-05, 96 subjects were randomized (48 to the HEPLISAV arm and 48 to the Engerix-B arm). Four subjects discontinued prematurely (3 from the HEPLISAV group and 1 from the Engerix-B group). One subject in each group withdrew consent. Subjects 1020 and 1090 in the HEPLISAV arm emigrated. Two additional subjects in the Engerix-B group (1013 and 1108) had completion status that was missing.

In study DV2-HBV-08, one HEPLISAV recipient discontinued due to a protocol violation. The subject received one injection, but was later found to have an elevated baseline ANA level and was therefore discontinued. No post-injection evaluation of ANA or antiHBsAg was performed.

In study DV2-HBV-04, a total of 420 subjects were randomized: 207 to receive HEPLISAV and 213 to receive Engerix-B. Thirty-two subjects were prematurely discontinued including 10 (4.8%) of subjects in the HEPLISAV group and 22 (10.3%) in the Engerix-B group. Three subjects in the HEPLISAV arm and four subjects in the Engerix-B arm were lost to follow-up. One subject in the Engerix-B arm was withdrawn due to a protocol violation. One subject in the HEPLISAV arm discontinued to pursue a job opportunity abroad. Subject 14047 an Engerix-B recipient discontinued subsequent to 2 SAEs that were not considered by the investigator to be treatment related. She was a 45 year old woman diagnosed with marrow hyperplasia and pneumonia while on study.

In study DV2-HBV-14, an uncontrolled study, 207 subjects were enrolled. Eleven subjects discontinued prematurely. Reasons for discontinuation were lost to follow-up (6 [2.9%] subject), subject noncompliance (1 [0.5%] subject), consent withdrawn (1 [0.5%] subject), and protocol violation (1 [0.5%] subject). In addition, 2 (1.0%) subjects were discontinued due to pregnancy. Subject 01009 had a negative urine pregnancy test on the day of enrollment. She reported using appropriate birth control methods as specified in

the protocol. She notified the site of her pregnancy approximately 12 days after receiving the first study injection. She was discontinued from the study and reported a full-term healthy female baby. Subject 03048 was a 29 year old woman with a history of hypertension who withdrew from the study due to pregnancy approximately 1.5 months after her first and only study injection. Approximately one month later she was diagnosed with cholecystitis and underwent a laparoscopic cholecystectomy. Approximately 2 months later she reported no fetal movement for 2 days. After monitoring, normal fetal movements were evaluated. Approximately 5 days later, an ultrasound indicated intrauterine fetal demise with no fetal heart tones. The subject was admitted, labor induced and a 13 ounce stillborn female was delivered at the gestational age of 23 weeks, 2 days. The fetal death certificate noted the condition that most likely began the sequence of events resulting in the death of the fetus was maternal chronic hypertension. The investigator assessed the event as severe and not related to study treatment.

Reviewer Comment: Overall, a similar proportion of subjects discontinued from each treatment arm. Specific events discussed in this section are further discussed as appropriate in the sections of this review pertaining to their respective studies.

8.4.4 Common Adverse Events

Adverse events were collected in all trials. An AE was defined as any untoward medical occurrence in a clinical investigation subject, whether or not there was a causal relationship with the investigational treatment. Predefined post-injection reactions with a duration of more than 7 days were considered AEs. Table 47 in section 8.1 outlines the collection period for AEs for each study. Briefly, AEs were followed for 28 weeks (4 weeks after the last injection or 24 weeks after the last HEPLISAV injection) in the Tier 1 trials. The follow-up period for AEs in study HBV-14, the only additional trial in Tier 2, was 28 weeks (24 weeks after the last injection). In the additional supportive trials comprising Tier 3, AEs were evaluated from 12 to 68 weeks on study (1 week to 54 weeks following the last injection). Overall, unsolicited adverse events occurred with similar frequency between treatment groups in all tiers (T1SP: HEPLISAV 55.3% Engerix-B 58.0%; T2SP: HEPLISAV 55.9%, Engerix-B 58.0%; T3SP: HEPLISAV 58.1%, Engerix-B 61.2%). Most were mild to moderate in intensity.

Reviewer Comment: No safety concerns were raised in the review of the unsolicited non-serious adverse events reported for all studies in all tiers.

8.4.5 Clinical Test Results

Table 47 in section 8.1 outlines the laboratory investigation schedule for each study.

Serum Chemistry

The applicant did not provide an integrated analysis of the results of serum chemistry investigations.

The mean chemistry values, standard deviations, medians, minimum and maximum values as well as change from baseline were provided by treatment group and study visit

for Study DV2-HBV-16. All values were similar between treatment groups. All mean chemistry values were within the normal range.

Reviewer Comment: The applicant reports that pooling of laboratory data would be inappropriate due to variations over time in reference laboratories, laboratory kits and methods, and reference ranges. However, all serum chemistry data (from all studies in which serum chemistry investigations were performed) were reviewed and no safety concerns were identified.

Urinalyses

Urinalyses were performed at multiple timepoints in studies HBV0001, HBV-03 and HBV-08. An integrated analysis of urinalysis results was not provided.

Reviewer Comment: Urinalysis results were reviewed for the individual studies. In study HBV0001, one individual in the HBsAg + 300 mcg ISS group had trace blood that progressed to large blood post vaccination. There were other individuals with intermittent trace blood on urine dipstick, which can occur normally. All subjects' urine dipsticks were negative for protein. No patterns of abnormal urine indices were observed. Study HBV0001 was a dose-escalation trial with no comparator arm.

In study HBV-08, there were 2 individuals with >5rbc/hpf post vaccination. Menstrual records were provided and these individuals were not menstruating at the time. All urine dipsticks were negative for protein. No patterns of abnormal urine indices were observed. Study HBV-08 had no comparator arm.

In study HBV-03, a similar percentage of individuals without hematuria at screening had some degree of hematuria on semi-quantitative analysis (22.6% HEPLISAV recipients and 23.5% of Engerix-B recipients with post-baseline urinalysis results available). However on quantitative analysis, 2 HEPLISAV recipients (6.5%) and 5 Engerix-B recipients (14.7%) had >5rbc/hpf post vaccination. A similar proportion of subjects from each group had some degree of proteinuria (16.1% HEPLISAV, 12.1% Engerix-B). There were no subjects with persistent proteinuria. Two HEPLISAV recipients and 3 Engerix-B recipients had 1000 mg/dl of protein recorded. It appears these events were not captured as AEs likely because laboratory values were recorded as AEs only if they were thought to be "clinically significant" by the investigator and these events appear to be transient. Other urinalysis results were reviewed and did not appear to differ between treatment groups.

As outlined in section 4.3, repeat-dose toxicity studies with the 1018 ISS adjuvant alone were conducted in rats and cynomolgus monkeys. Animals received 10 to 250 times the human dose based on mg/kg (0.5, 2.5 or 12.5 mg/kg) weekly via SC administration for 8 weeks. The effects of 1018 ISS adjuvant in rats were more pronounced than in monkeys, reflecting the higher sensitivity to TLR9 agonists typically observed in rodents. At the highest dose levels in rats, diffuse proximal tubular degeneration occurred in the kidneys, but there was no effect on renal function.

As outlined in Table 47 in section 8.1, urinalyses were performed in three clinical trials (HBV0001, DV2-HBV-03, DV2-HBV-08) which included a total of 157 HEPLISAV recipients and 52 Engerix-B recipients. Serum chemistries were performed at baseline and at various post-vaccination time points in all studies except study DV2-HBV-10. Based on these studies, there were no patterns consistent with findings of acute diffuse proximal tubular damage such as Fanconi's syndrome or acute renal failure. Renal insults causing permanent injury, however, have the potential to cause chronic kidney disease and a progressive decline in kidney function and the study follow-up periods limit the ability to evaluate such findings. Longer follow-up periods would permit a better assessment of this risk. The reviewer recommends that urinalyses, urinary microalbumin studies and serum chemistries be considered for inclusion in the safety follow-up evaluations to occur during the additional pre-marketing safety assessment that will be recommended at the conclusion of this review.

Hematology

With the exception of labs pertaining to autoimmunity, the applicant did not provide an integrated analysis of the results of laboratory investigations. The applicant reports that pooling of laboratory data would be inappropriate due to variations over time in reference laboratories, laboratory kits and methods, and reference ranges.

The mean hematology values, standard deviations, medians, minimum and maximum values as well as change from baseline were provided by treatment group and study visit for Study DV2-HBV-16. All values were similar between treatment groups. All mean hematology values were within the normal range.

Reviewer Comment: In studies of rodents exposed to HEPLISAV, mild reversible anemia was observed. This was a finding consistent with previous studies of rodents receiving oligonucleotides such as 1018 ISS. After review of all clinical hematology laboratory data for all studies in which a hematology investigation was performed, no clinical safety concerns were raised.

Complement Components 3 (C3) and 4 (C4)

As outlined in Table 47, C3 and C4 were measured prior to each vaccination, 1 and 4 weeks after each vaccination, and at the end of the study in Study HBV0001. In study HBV-03 C3 and C4 were measured pre-vaccination, immediately before the second vaccination and 1 week after the second vaccination.

Reviewer Comment: The applicant reports that since the findings in both of these trials were "negative," results were not pooled. The "class effects" seen in animals exposed to oligonucleotides such as 1018 ISS can include activation of the complement, specifically the alternative complement pathway. Review of the results submitted for the individual clinical studies did not reveal a trend toward a post-vaccination decrease in C3 or C4 concentrations.

Erythrocyte Sedimentation Rate (ESR)

In study HBV0001, ESR was measured prior to each vaccination, 1 week after each vaccination, 1 month after each vaccination and at study end. In study HBV-02, ESR was measured prior to vaccination and 4 weeks after the first injection. In study HBV-03, EAR was measured prior to vaccination and 4 weeks after each of two vaccinations.

Reviewer Comment: The applicant did not provide an integrated analysis of ESR evaluations. Dynavax reports that pooling results from study HBV-02 with results from other studies would be inappropriate as study HBV-02 was conducted in individuals previously vaccinated with a licensed hepatitis B vaccine.

The results of ESR investigations were reviewed for HBV0001, a Phase 1 dose escalation trial, as well as the Phase 2 trials with active control, studies HBV-02 and HBV-03. In study HBV0001, there were individuals from each dosing group with mild elevations in ESR. There was no consistent trend or dose-depending increase post-vaccination. In studies HBV-02 and HBV-03, post-vaccination elevations in ESR were seen in some HEPLISAV recipients and active control recipients, but no consistent trend was seen.

C-reactive protein

C-reactive protein (CRP) concentrations were evaluated in a portion of subjects enrolled in studies HBV-10 and HBV-14. The results of the applicant's analysis of CRP data for study HBV-10 are presented in section 6.1.12.6. In study HBV-14, 191 of the 207 of subject enrolled in this uncontrolled supportive study had a sample available for testing at baseline. One-hundred-sixty-six (86.9%) were negative. Seven subjects were CRP negative at baseline and became positive at Visit 5, which was 8 weeks after the last injection of HEPLISAV. Two of these subjects' CRP concentrations remained positive (≥ 0.8 mg/dL) throughout the study. Another seven subjects who were negative at baseline became positive at Visit 6, which was 6 months after the last active injection of HEPLISAV. Three of these subjects had AEs that were temporally associated with this increase.

Reviewer Comment: Raw CRP data was not submitted with this application and CRP was not designated as a laboratory evaluation in the schedules of events or protocols for these studies. The review of the CRP data is limited to those retrospective analyses provided by the applicant. The reviewer can only conclude that most subjects in studies HBV-10 and HBV-14 had CRP concentrations below 0.8 mg/dL at baseline and at the post-vaccination time points provided, and that a similar proportion of subjects in each treatment arm in study HBV-10 had elevated CRP concentrations at baseline, and the provided post-baseline time points. Quantitative assessment of elevated CRP concentrations is not possible based on the data provided.

Autoantibody Assessment

ANA testing was performed as a protocol-specified assessment in all trials except HBV-04. ANA results from HBV0001 were excluded from analysis because they were not reported as titers. Anti-dsDNA testing was performed as a protocol-specified assessment in all trials except HBV-04 and HBV-08. ANCA testing was performed retrospectively on banked specimens from HBV-10 and HBV-14.

Results of the ANA assessments are presented in by tier and vaccine arm in Table 53. ANA results of 1:160 or higher were considered positive.

Table 53: Antinuclear Antibody (ANA) Results by Tier and Treatment Group

ANA Result	Tier 1 HEPLISAV	Tier 1 Engerix-B	Tier 2 HEPLISAV	Tier 2 Engerix-B	Tier 3 HEPLISAV	Tier 3 Engerix-B
Pre-Treatment Negative n, (%)	3490/3772 (92.5)	988/1085 (91.1)	3681/3979 (92.5)	988/1085 (91.1)	3854/4164 (92.6)	1101/1209 (91.1)
Pre-Treatment Positive n, (%)	282/3772 (7.5)	97/1085 (8.9)	298/3979 (7.5)	97/1085 (8.9)	310/4164 (7.4)	108/1209 (8.9)
Post-Treatment Negative n, (%)	3274/3583 (91.4)	944/1038 (90.9)	3457/3779 (91.5)	944/1038 (90.9)	3623/3960 (91.5)	1050/1156 (90.8)
Post-Treatment Positive n, (%)	309/3583 (8.6)	94/1038 (9.1)	322/3779 (8.5)	94/1038 (9.1)	337/3960 (8.5)	106/1156 (9.2)
Change from Negative to Positive ¹ n, (%)	189/3333 (5.7)	50/950 (5.3)	193/3514 (5.5)	50/950 (5.3)	201/3684 (5.5)	54/1057 (5.1)
Increase from positive baseline titer to higher titer n, (%)	42/272 (15.4)	16/95 (16.8)	42/287 (14.6)	16/95 (16.8)	44/299 (14.7)	18/106 (17.0)

Note: ANA results of 1:160 or higher were considered positive. Denominators include subjects with ANA-data available at that time point (e.g., pre-treatment, post-treatment or both pre- and post-treatment for status change assessment)

Source: Adapted from STN 125428, ISS, Table 2.7.4-42, p 119

The majority of subjects had negative ANA results both at baseline and post-treatment in all treatment groups and tiers. Approximately 5% of subjects in each treatment group had ANA titers that changed from a negative to a positive after treatment, regardless of tier.

Overall, slightly more subjects receiving Engerix-B had titers that increased from a positive baseline titer to a higher titer post-treatment.

Reviewer Comment: *The ANA evaluations took place at various time points from day 28 to Week 32 on study. The largest study in which ANA titers were evaluated was study HBV-DV2-16 in which 1968 HEPLISAV and 481 Engerix-B recipients had ANA levels drawn at baseline and Week 52. Based on these data, there does not appear to be an increased risk of converting from an ANA titer of <1:160 to a higher titer for HEPLISAV recipients over that of Engerix-B recipients.*

Anti-dsDNA Assessment

Studies HBV-10, HBV-14, HBV0001, HBV-03 and HBV-05 employed a qualitative (b) (4) assay (b) (4) reporting negative and positive results, which were used as reported. HBV-16 employed a quantitative assay and reported qualitative results (negative, borderline, or positive). The applicant reports that borderline results from HBV-16 (30-75 mIU/mL) were counted as positive for this analysis because they would typically be positive by (b) (4). Results from HBV-02 were excluded, because according to the applicant, this study used a quantitative assay with a very low cutoff of 10mIU/mL for positive (which would not typically be positive by (b) (4)), and reported qualitative (negative or positive) results that could not be re-graded.

The results of the anti-dsDNA assessment are presented by tier and treatment group in Table 54.

Table 54: Anti-double stranded DNA Results by Tier and Treatment Group

Anti-dsDNA	Tier 1 HEPLISAV	Tier 1 Engerix-B	Tier 2 HEPLISAV	Tier 2 Engerix-B	Tier 3 HEPLISAV	Tier 3 Engerix-B
Pre-treatment Positive n, (%)	38/3767 (1.0)	16/1082 (1.5)	40/3974 (1.0)	16/1082 (1.5)	43/4117 (1.0)	17/1177 (1.4)
Post-Treatment Positive n, (%)	57/3581 (1.6)	19/1038 (1.8)	57/3780 (1.5)	19/1038 (1.8)	61/3922 (1.6)	20/1133 (1.8)
Change from Negative to Positive n, (%)	45/3540 (1.3)	10/1017 (1.0)	45/3737 (1.2)	10/1017 (1.0)	46/3876 (1.2)	11/1111 (1.0)

Note: Denominators include subjects with anti-dsDNA data available at that time point (e.g., pre-treatment, post-treatment or both pre- and post-treatment for status change assessment).

Source: Adapted from STN 125428, ISS, Table 2.7.4-42, p 120

The majority of subjects maintained a negative anti-dsDNA test throughout the study. A similar proportion of subjects in each treatment group had negative anti-dsDNA results at baseline and a positive result post-treatment.

Reviewer Comment: Review of the data from the anti-dsDNA evaluations does not raise clinical safety concerns.

Anti-neutrophil Cytoplasmic Antibodies (ANCA) Assessment

As described in section 8.4.8, two subjects in study HBV-10 developed ANCA-associated vasculitides. A 55 year old woman in the HEPLISAV arm developed Wegener's granulomatosis, a C-ANCA associated vasculitis. A 44 year old woman in the Engerix-B arm with an undisclosed history of mixed connective tissue disease developed a p-ANCA associated vasculitis and features of scleroderma. Based on the occurrence of these two events, serum specimens from subjects in trial HBV-10 and HBV-14 were retrospectively tested for ANCA. Serum with positive screening (b) (4) assays for anti-MPO and anti-PR3, was then confirmed using (b) (4). In addition to the two subjects from study HBV-10 with ANCA associated vasculitides, serum screening studies performed on 2376 additional subjects (1780 in the HEPLISAV arm and 596 in the Engerix-B arm). A total of 3/1780 subjects (0.17%) in the HEPLISAV group and 2/596 subjects (0.34%) in the Engerix-B group had a positive screening (b) (4) for either anti-MPO or anti-PR3. Confirmatory (b) (4) testing for all five of these subjects was negative. Of note, subject 07-004 from study HBV-10 had a positive anti-PR3 screening (b) (4) pre- and post-vaccination. Confirmatory (b) (4) was negative for c-ANCA and p-ANCA but stained cells in an atypical pattern at both time points. The subject is a 45 year old female who received Engerix-B and experienced 1 mild AE of nasopharyngitis deemed unrelated to treatment.

From study HBV-14, a total of 192 HEPLISAV recipients were analyzed, of which 1/192 (0.52%) had a positive screening (b) (4) for anti-MPO. The confirmatory (b) (4) test was negative.

Reviewer Comment: With the exception of the two subjects in study DV2-10 that developed ANCA-positive vasculitides, tested subjects in studies DV2-10 and DV2-14 did not have ANCA antibodies present during the trials. ANCA testing was not performed in study DV2-HBV-16. Based on the limited data from study HBV-10, there does not appear to be an increased risk of developing anti-neutrophil cytoplasmic antibodies among HEPLISAV recipients as compared to recipients of the active control. The utility of ANCA as a screening mechanism in asymptomatic individuals is limited.

8.4.6 Systemic Adverse Events

In all trials, reactogenicity was evaluated by solicitation of specific local and systemic post-injection reactions, which were predefined as related to treatment. Solicitation of reactions was broadest in early trials and narrowed to commonly reported reactions in subsequent trials. Solicited reactions from the day of injection (Day 0) to Day 6 were

assessed by subjects using diary cards. Table 55 outlines the solicited local and adverse events captured for each study.

Table 55 summarizes the local and systemic adverse events that were solicited for 7 days after each injection for each study included in the integrated summary of safety.

Table 55: Local and Systemic Solicited Adverse Events (Days 0-6) Collected for Each Study Included in the Integrated Summary of Safety

Study	Solicited Local Adverse Events	Solicited Systemic Adverse Events
HBV-16	Redness, Swelling, Pain	Malaise, Headache, Fatigue, Oral Temperature, Myalgia
HBV-10	Redness, Swelling, Pain	Malaise, Headache, Fatigue, Oral Temperature
HBV-14	Redness, Swelling, Pain	Malaise, Headache, Fatigue, Myalgia, Vomiting, Diarrhea, Oral Temperature
HBV0001	Redness, Swelling, Temperature, Tenderness, Pain to Arm Movement	General Muscle Aches, Nausea, Vomiting, Diarrhea, Headache, Fatigue, Chills, General Joint Pain, Oral Temperature
HBV-02	Redness, Swelling, Temperature, Tenderness, Pain to Arm Movement	General Muscle Aches, Nausea, Vomiting, Diarrhea, Headache, Fatigue, Chills, Joint Pain, Oral Temperature
HBV-03	Redness, Swelling, Temperature, Tenderness, Pain to Arm Movement	General Muscle Aches, Nausea, Vomiting, Diarrhea, Headache, Fatigue, Chills, Joint Pain, Oral Temperature
HBV-04	Redness, Swelling, Pain	Malaise, Headache, Fatigue, Oral Temperature
HBV-05	Myalgia, Soreness, Tenderness, Pruritis, Erythema, Ecchymosis, Swelling, Warmth, Nodule Formation	None
HBV-08	Redness, Swelling, Pain	Malaise, Headache, Fatigue, Oral Temperature

Source: CBER generated table derived from individual clinical study reports and legacy reports submitted to STN 125428

Table 56 compares solicited systemic reactions by treatment group and safety tier. In the integrated analysis of post-injection systemic reactions in the T3SP, data from studies HBV-02 and HBV-05 were excluded. Data from study HBV-02 were not pooled with that of other studies as the study population was comprised of Hepatitis B vaccine-experienced individuals. Data from study HBV-05 were excluded due to differences in the number of active injections in this trial compared to other trials, the shorter time period over which solicited events were actively collected (30 minutes), and that these reactions were recorded in the trial database as AEs.

Table 56: Summary of Solicited Systemic Reactions Occurring Within 7 Days Post Injection across All Active Injections by Treatment Group and Tier

Systemic Reaction n, (%)	T1SP HEPLISAV N=3788	T1SP Engerix-B N=1089	T2SP HEPLISAV N=3995	T2SP Engerix-B N=1089	T3SP HEPLISAV N=4358	T3SP Engerix-B N=1346
Fever	3744	1078	3949	1078	4312	1333
Fever (≥38°C) present	65 (1.7)	37 (3.4)	67 (1.7)	37 (3.4)	77 (1.8)	47 (3.5)
Mild Fever (38°C – 38.4°C)	34 (0.9)	16 (1.5)	36 (0.9)	16 (1.5)	42 (1.0)	21 (1.6)

Systemic Reaction n, (%)	T1SP HEPLISAV N=3788	T1SP Engerix-B N=1089	T2SP HEPLISAV N=3995	T2SP Engerix-B N=1089	T3SP HEPLISAV N=4358	T3SP Engerix-B N=1346
Moderate Fever (38.5°C - 38.9°C)	21 (0.6)	11 (1.0)	21 (0.5)	11 (1.0)	24 (0.6)	14 (1.1)
Severe Fever (39°C - 40°C)	9 (0.2)	10 (0.9)	9 (0.2)	10 (0.9)	10 (0.2)	12 (0.9)
Potentially Life Threatening Fever (>40°C)	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Malaise	3773	1086	3980	1086	4247	1290
Malaise present	524 (13.9)	174 (16.0)	558 (14.0)	174 (16.0)	620 (14.6)	225 (17.4)
Mild	317 (8.4)	96 (8.8)	337 (8.5)	96 (8.8)	384 (9.0)	134 (10.4)
Moderate	167 (4.4)	55 (5.1)	181 (4.5)	55 (5.1)	192 (4.5)	65 (5.0)
Severe	40 (1.1)	23 (2.1)	40 (1.0)	23 (2.1)	44 (1.0)	26 (2.0)
Headache	3773	1086	3980	1086	4343	1341
Headache present	758 (20.1)	275 (25.3)	817 (20.5)	275 (25.3)	931 (21.4)	358 (26.7)
Mild	472 (12.5)	158 (14.5)	512 (12.9)	158 (14.5)	587 (13.5)	224 (16.7)
Moderate	231 (6.1)	95 (8.7)	247 (6.2)	95 (8.7)	281 (6.5)	109 (8.1)
Severe	55 (1.5)	22 (2.0)	58 (1.5)	22 (2.0)	63 (1.5)	25 (1.9)
Fatigue	3773	1086	3980	1086	4343	1341
Fatigue present	807 (21.4)	273 (25.1)	858 (21.6)	273 (25.1)	955 (22.0)	349 (26.0)
Mild	498 (13.2)	155 (14.3)	533 (13.4)	155 (14.3)	605 (13.9)	214 (16.0)
Moderate	250 (6.6)	92 (8.5)	264 (6.6)	92 (8.5)	284 (6.5)	105 (7.8)
Severe	59 (1.6)	26 (2.4)	61 (1.5)	26 (2.4)	66 (1.5)	30 (2.2)

Source: Adapted from STN 125428, Summary of Clinical Safety, Table 5.2.4.1 on pp 126-129, Table 5.2.3 on pp122-125, and Table 5.3.3 on pp 154-157

Reviewer Comment: *The data presented in Table 56 show that fever, malaise, headache and fatigue occurred with a similar frequency and intensity among subjects in each treatment group for all tiers.*

Myalgia was an additional solicited event in Study HBV-16. The incidence of myalgia was lower in the HEPLISAV consistency lots (11.6%) than in the older lot, Lot TDG006 (15.2%) or the Engerix-B group (15.9%). Most myalgia was categorized as mild in intensity. Additional systemic events were solicited in earlier studies. In study HBV0001, muscle aches, nausea, vomiting, diarrhea, chills and joint pain were also solicited. The review of these data did not raise safety concerns. In study HBV-02, muscle aches, nausea, vomiting, diarrhea, chills and joint pain were also evaluated and occurred in each group with similar incidence. In study HBV-03, muscle aches, chills, nausea, vomiting, diarrhea and joint pain were also assessed. The review of these data raised no safety concerns. Upon review of study HBV-14, an uncontrolled Phase 2 trial in which myalgia, vomiting and diarrhea were among solicited systemic events, 16.9% and 17.7% of subjects reported joint pain after the 1st and 2nd injections, respectively. However, joint pain was evaluated in two controlled trials and the incidence of joint

pain was similar between treatment groups. Overall, the review of solicited adverse events did not raise safety concerns.

8.4.7 Local Reactogenicity

Table 57 compares solicited local (injection site) reactions by treatment group and safety tier. In the integrated analysis of post-injection reactions in the T3SP, partial data from HBV-04 were included. Redness and swelling data from HBV-04 were excluded because the measured diameter was graded differently for this trial than for others. Data from study HBV-02 were not considered appropriate for pooling with that of the other trials because this trial was performed in vaccine-experienced subjects with up to 6 prior doses. Additionally, the integrated analysis did not include data from study HBV-05 because this study employed a 3 dose regimen while a 2 dose regimen was evaluated in other studies. Additionally, post-injection reactions occurring more than 30 minutes after injection were collected by spontaneous reporting rather than active solicitation in study HBV-05.

Table 57: Summary of Solicited Injection Site Reactions Occurring Within 7 Days Post Injection across All Active Injections by Treatment Group and Tier

Injection Site Reaction, n (%)	T1SP HEPLISAV N=3788	T1SP Engerix-B N=1089	T2SP HEPLISAV N=3995	T2SP Engerix-B N=1089	T3SP HEPLISAV N=4358	T3SP Engerix-B N=1346
Redness	3773	1086	3980	1086	4343	1343
Redness	3773	1086	3980	1086	4343	1343
Redness present	141 (3.7)	12 (1.1)	146 (3.7)	12 (1.1)	153 (3.5)	14 (1.0)
≥25mm - ≤50mm (mild)	131 (3.5)	12 (1.1)	135 (3.4)	12 (1.1)	142 (3.3)	13 (1.0)
>50mm - ≤100mm (moderate)	9 (0.2)	0	10 (0.3)	0	10 (0.2)	1 (0.1)
>100mm (severe)	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Swelling	3773	1086	3980	1086	4343	1343
Swelling present	90 (2.4)	14 (1.3)	94 (2.4)	14 (1.3)	98 (2.3)	14 (1.0)
≥25mm - ≤50mm (mild)	79 (2.1)	14 (1.3)	82 (2.1)	14 (1.3)	86 (2.0)	14 (1.0)
>50mm - ≤100mm (moderate)	10 (0.3)	0	11 (0.3)	0	11 (0.3)	0
>100mm (severe)	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Pain	3773	1086	3980	1086	4282	1341
Pain present	1576 (41.8)	440 (40.5)	1680 (42.2)	440 (40.5)	1821 (42.5)	544 (40.6)
Mild	1293 (34.3)	358 (33.0)	1387 (34.8)	358 (33.0)	1506 (35.2)	450 (33.6)

Injection Site Reaction, n (%)	T1SP HEPLISAV N=3788	T1SP Engerix-B N=1089	T2SP HEPLISAV N=3995	T2SP Engerix-B N=1089	T3SP HEPLISAV N=4358	T3SP Engerix-B N=1346
Moderate	262 (6.9)	78 (7.2)	272 (6.8)	78 (7.2)	294 (6.9)	87 (6.5)
Severe	21 (0.6)	4 (0.4)	21 (0.5)	4 (0.4)	21 (0.5)	7 (0.5)

Source: Adapted from STN 125428, Summary of Clinical Safety, Tables 5.2.4.1 on pp 126-129, Table 5.2.3 on pp122-125, and Table 5.3.3 on pp 154-157

Reviewer Comment: *The local reactogenicity profile of HEPLISAV was similar to that of Engerix-B and did not appear to differ significantly between tiers. Similar findings were obtained when local reactogenicity was compared between treatment groups for each active injection.*

Local reactogenicity data from the three studies excluded from this analysis, Studies HBV-04, -02, and -05 were reviewed individually. In study HBV-04, the number of subjects with any local reaction was similar between groups. After the second vaccination, there were more HEPLISAV recipients reporting pain than Engerix-B recipients (23.4% versus 13%), but most were mild in intensity. For study HBV-02, more subjects in the HEPLISAV groups experienced any local reaction than did those in the Engerix-B groups primarily after the first injection (primary study 68.4% versus 37.5%; substudy 81.8% versus 46.2%). This was largely driven by pain/tenderness. For study HBV-05, more subjects in the Engerix-B arm experienced any local reaction after the first and second vaccinations (1st vaccination: HEPLISAV 6.3%, Engerix-B 10.6%, 2nd vaccination: HEPLISAV 8.3%, Engerix-B 13.0%). This difference was primarily due to pain/tenderness.

Overall, no clinical safety concerns were raised regarding local reactogenicity.

8.4.8 Adverse Events of Special Interest

Adverse events of special interest and autoimmune adverse events will be presented in this section.

Adverse events of special interest (AESIs) were evaluated retrospectively for all trials. The applicant defined an AESI as follows:

- **Neuroinflammatory disorders**
 - Optic neuritis, multiple sclerosis, demyelinating disease, transverse myelitis, Guillain-Barre syndrome, myasthenia gravis, encephalitis, neuritis, Bell's palsy
- **Musculoskeletal disorders**
 - Systemic lupus erythematosus, cutaneous lupus, Sjogren's syndrome, scleroderma, dermatomyositis, polymyositis, rheumatoid arthritis, juvenile rheumatoid arthritis, polymyalgia rheumatica, reactive arthritis, psoriatic arthropathy, ankylosing spondylitis, spondylarthropathy
- **Gastrointestinal disorders**
 - Crohn's disease, ulcerative colitis, celiac disease

- **Metabolic disease**
 - Autoimmune thyroiditis, Grave’s/Basedow’s disease, Hashimoto’s thyroiditis, Type 1 diabetes mellitus, Addison’s disease
- **Skin disorders**
 - Psoriasis, vitiligo, Raynaud’s phenomenon, erythema nodosum, autoimmune bullous skin diseases
- **Others**
 - ANCA positive vasculitis, autoimmune hemolytic anemia, idiopathic thrombocytopenic purpura, antiphospholipid antibody syndrome, temporal arteritis, Behcet’s syndrome, pernicious anemia, autoimmune hepatitis, primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune glomerulonephritis, autoimmune uveitis, autoimmune cardiomyopathy, renal vasculitis, sarcoidosis, Stevens-Johnson syndrome, Wegener’s granulomatosis

Table 58 summarizes AESIs by category, preferred term, tier and treatment group.

Table 58: Adverse Events of Special Interest by Category, Preferred Term, Tier and Treatment Group

Category/ Preferred Term, n (%)	Tier 1 HEPLISAV N=3777	Tier 1 Engerix B N=1087	Tier 2 HEPLISAV N=3984	Tier 2 Engerix- B N=1087	Tier 3 HEPLISAV N=4425	Tier 3 Engerix- B N=1420
Subjects with any AESI	8 (0.2)	4 (0.4)	8 (0.2)	4 (0.4)	10 (0.2)	5 (0.4)
Neuroinflammatory Disorders	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)	3 (0.1)	1 (0.1)
Guillain-Barre Syndrome	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Vllth Nerve Palsy	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)	2 (0.0)	1 (0.1)
Musculoskeletal Disorders	2 (0.1)	1 (0.1)	2 (0.1)	2 (0.2)	3 (0.1)	2 (0.1)
Mixed Connective Tissue Disease	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Rheumatoid Arthritis	1 (0.0)	0	1 (0.0)	0	2 (0.0)	1 (0.1)
Scleroderma	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Systemic Lupus Erythematosus	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Gastrointestinal Disorders	0	0	0	0	0	0
Metabolic Disorders	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Basedow’s Disease	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)
Skin Disorders	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)	2 (0.1)	1 (0.1)
Erythema Nodosum	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Vitiligo	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0
Raynaud’s Phenomenon	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Other Disorders	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)	1 (0.0)	1 (0.1)

Category/ Preferred Term, n (%)	Tier 1 HEPLISAV N=3777	Tier 1 Engerix B N=1087	Tier 2 HEPLISAV N=3984	Tier 2 Engerix- B N=1087	Tier 3 HEPLISAV N=4425	Tier 3 Engerix- B N=1420
p-ANCA Positive Vasculitis	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)
Wegener's Granulomatosis (c-ANCA positive)	1 (0.0)	0	1 (0.0)	0	1 (0.0)	0

Source: STN 125428, ISS, Table 2.7.4-32, p. 100

Overall, the proportion of subjects experiencing an AESI was low and comparable among treatment groups for all tiers. No AESIs occurred in subjects < 18 years of age. In Tier 1, 0.2% of HEPLISAV recipients and 0.4% of Engerix-B recipients experienced an AESI. There were no additional AESIs in the T2SP. In Tier 3, 2 AESIs occurred in more than one subject in the HEPLISAV arm (VIIth nerve palsy (n=2) and rheumatoid arthritis (n=2)). No other AESIs were reported by more than one subject in any arm or any tier, including Tier 1 which includes subjects who received the proposed formulation of HEPLISAV.

Three subjects in the T1SP experienced serious AESIs: 2/2377 (0.05%) in the HEPLISAV group and 1/1087 (0.09%) in the Engerix-B group. In the HEPLISAV group, a 36 year old female developed Guillain-Barre Syndrome 110 days after the last active dose. This grade 3 event resolved by the end of the study and was deemed probably not related. A 54 year old female in the HEPLISAV group (T1SP) developed Wegener's Granulomatosis 72 days after the last active injection. This grade 3 event was ongoing at the end of the study and was deemed possibly related. Also in the HEPLISAV group (T3SP) a 53 year old female developed VIIth nerve paralysis 15 days after the last active dose. This grade 2 event had not yet recovered at the end of the study and was deemed probably not related. A 44 year old female in the Engerix-B group with a history of mixed connective tissue disease developed an ANCA-positive vasculitis and scleroderma 126 days after the last active injection. The vasculitis was a grade 3 event, was considered resolved. by the end of the study and was deemed not related to study vaccine.

Reviewer Comment: The incidence of AESIs as analyzed by the applicant, was low and similar between treatment groups. It is the opinion of this reviewer that the relatively brief safety follow-up periods may have limited the identification of such adverse events given their often indolent nature and because they can present with non-specific initial findings. Independent, retrospective CBER-generated analyses of potential autoimmune thyroid events and events requiring immunosuppression are discussed below. However, this limitation will apply to those analyses as well.

Autoimmune Adverse Events (Study HBV-16 only)

As described in section 6.2.12.5, the evaluation of potential autoimmune adverse events (AIAEs) was outlined prospectively in protocol HBV-16. This adjudication process was not used in any other trial. Nine potential autoimmune adverse events were reported:

hypothyroidism (n=5), Bell’s palsy (n=1), erythema nodosum (n=1), vitiligo (n=1) and microscopic colitis (n=1). Seven of these events were confirmed by expert evaluation to be potentially autoimmune in nature: hypothyroidism (n=4), Bell’s palsy (n=1), erythema nodosum (n=1), and vitiligo (n=1). All of these events occurred in subjects in the HEPLISAV consistency lot group (7/1439, 0.5%), were mild to moderate in severity, and were considered nonserious.

Per protocol, these potential new-onset AIAEs were referred to the Safety Evaluation and Adjudication Committee (SEAC) for adjudication. Five of these 7 events were initially confirmed by the SEAC as new-onset autoimmune events: hypothyroidism (n=4) and vitiligo (n=1). Of the 4 initially confirmed events of hypothyroidism, post-study testing of banked baseline serum from two of these subjects revealed a high thyroid stimulating hormone (TSH) level and low free T4 level, providing laboratory evidence of pre-existing hypothyroidism, and they were therefore not new onset events. Upon revision of adjudications, three cases of SEAC-confirmed new-onset AIAEs were determined to have occurred: hypothyroidism (n=2) and vitiligo (n=1).

Reviewer Comment: Upon review of the AIAE data from study HBV-16 in which autoimmune events were evaluated prospectively, all potential AIAEs occurred in the HEPLISAV consistency lot group. It appears that three additional HEPLISAV recipients had potential AIAEs: an exacerbation of Grave’s disease, the events of hand pain and body aches, and a case of narcolepsy, a disorder that is potentially autoimmune in nature. The overall incidence of AIAEs, however, was low. Limitations of sample size and safety follow-up periods, the relatively low background incidence of autoimmune events and the indolent nature of many of these diseases make an accurate assessment of risk of autoimmune disease in this study difficult.

Events requiring immunosuppressive therapy

Individuals were excluded from enrollment in clinical trials involving HEPLISAV if they used systemic corticosteroids for more than 3 consecutive days or other immunomodulators or immunosuppressive medications within 4 weeks of enrollment (with the exception of inhaled steroids). To further evaluate potential autoimmune events in an integrated fashion, CBER analyzed SAEs, AESIs and AIAEs treated with immunosuppressive medication (excluding asthma exacerbations). In each treatment arm, 0.2% of subjects had events treated with immunosuppressive therapy. Table 59 displays these events by treatment arm for the safety population.

Table 59: CBER Analysis of Events Categorized by the Applicant as Serious Adverse Events, Adverse Events of Special Interest and Autoimmune Adverse Events for which Immunosuppressive Therapy was Prescribed

AE	Arm	Days after Last Active Injection	Past Medical History of the AE?	Treatment	Background Incidence per Year

AE	Arm	Days after Last Active Injection	Past Medical History of the AE?	Treatment	Background Incidence per Year
Tolosa-Hunt Syndrome?	HEPLISAV	165	No	Steroids	1/1,000,000
Wegener's granulomatosis	HEPLISAV	72	No	Steroids, Cyclophosphamide	7.4-12.2/1,000,000
Erythema nodosum	HEPLISAV	19	No	Steroids	1-5/100,000
Bell's Palsy	HEPLISAV	15	No	Steroids	13-34/100,000
Bell's Palsy	HEPLIAV	270	No	Steroids	13-34/100,000
Uveitis	HEPLISAV	30	No	Steroids	20-52/100,000
Vitiligo	HEPLSIAV	1	No*	Topical steroids, Elidel	0.14-8.8/100
Lupus profundus	HEPLISAV	84	Yes	Hydroxychloroquine	Exacerbation
Rheumatoid arthritis	HEPLISAV	5	Yes	Etoricoxib, Diclofenac	Exacerbation
Rheumatoid arthritis	HEPLISAV	22	Yes	Rofecoxib, Ibuprofen	Exacerbation
Microscopic colitis	HEPLISAV	3	Yes	Budesonide	Exacerbation
p-ANCA vasculitis	Engerix-B	126	No*	Steroids, Cyclophosphamide	7.7-12.6/1,000,000
Bell's palsy	Engerix-B	121	No	Steroids	13-34/100,000
Rheumatoid arthritis	Engerix-B	20	No**	Steroids, Meloxicam	41/100,000
Reactive airway disease***	Engerix-B	56	No	Steroids	N/A

*Past medical history of another autoimmune disease

** History of symptoms consistent with the disease

*** An SAE of bronchial hyperreactivity for which a Churg-Strauss workup was performed that was negative. Not included in the percentage counts for the Engerix-B group

Source: CBER generated analysis from data submitted in STN 125428/0

In addition, at least two HEPLISAV recipients in study DV2-HBV-16 had treatment discontinued due to adverse events: facial swelling and skin rash of unknown etiology (subject 42-320) and hand swelling and body aches referred for autoimmune evaluation (subject 21-640), were treated with anti-inflammatory agents (naproxen, celecoxib) as detailed in section 6.2.12.5.

Reviewer Comment: To evaluate the potential for induction or exacerbation of autoimmune disease in individuals receiving the TLR-9 agonist contained in HEPLISAV, CBER conducted this retrospective analysis of potential autoimmune events. SAEs, AESIs and AIAEs requiring immunosuppressive therapy occurred with similar incidence in each treatment group. Given the randomization ratio, the non-specific and indolent nature of many autoimmune diseases, the sample size, duration of follow-up and the relatively low background incidence of many of these diseases, it is difficult to determine the clinical significance of these events. However, the potential occurrence of two extremely rare granulomatous diseases in HEPLISAV recipients is

concerning. The diagnosis of Tolosa-Hunt is in question and this case is the subject of pending external expert consultations. The reviewer, therefore cannot make a determination regarding this potential safety signal at this time.

Thyroid events

Thyroid-associated events were included in the CBER analysis of adverse events of potential autoimmune origin because the most common cause of hypothyroidism in iodine sufficient countries is autoimmune thyroiditis (Hashimoto’s thyroiditis), the most common cause of hyperthyroidism is Grave’s disease/Basedow’s disease. Both clinical states can present as goiter, hypothyroidism or hyperthyroidism. Therefore, a CBER analysis of all thyroid AEs is presented in Tables 60-61.

Table 60: Thyroid Adverse Events Occurring in the Phase 3 Trials DV2-HBV-10 and DV2-HBV-16 by Treatment Group

AE	Treatment Arm	Days After Dose 1	Days After Dose 2	Days After Dose 3	Past Medical History of the AE?
Low TSH	HEPLISAV	44	17	N/A	No*
Hyperthyroidism	HEPLISAV	30-60	1-31	N/A	Yes
Hypothyroidism	HEPLISAV	173	145	0	Yes, required increased medication dose
Hypothyroidism	HEPLISAV	218	187	N/A	Yes**
Hypothyroidism	HEPLISAV	52	33	N/A	Yes**
Hyperthyroidism	HEPLISAV	36	8	N/A	No
Hypothyroidism	HEPLISAV	69	42	N/A	No
Hyperthyroidism		154	127	N/A	
Thyroiditis	HEPLISAV	73	45	N/A	No
Goiter	HEPLISAV	32	7	N/A	No
Hypothyroidism	HEPLISAV	48	34	N/A	No
Graves/Basedows Disease	HEPLISAV	72	43	N/A	No
Hypothyroidism	HEPLISAV	26-30	-2-+2	N/A	No
Hypothyroidism	HEPLISAV	58	29	N/A	No
Hypothyroidism	HEPLISAV	196	168	N/A	No
Graves/Basedows Disease	HEPLISAV	28	51	N/A	Yes
Graves/Basedows Disease	Engerix-B	85	57	N/A	Yes
Decreased T4	Engerix-B	22	N/A	N/A	No
Hypothyroidism	Engerix-B	~150	~120	N/A	No

* History of symptoms consistent with disease

** Laboratory evidence of disease when banked baseline serum evaluated

Source: CBER generated analysis from data submitted in STN 125428/0

Table 61: Thyroid Adverse Events Occurring in the Supportive Trials by Treatment Group

AE	Treatment Arm	Days After Dose 1	Days After Dose 2	Days After Dose 3	Days After Dose 4	Past Medical History of the AE?
Thyroid Disorder Hyperthyroidism Hypothyroidism	HEPLISAV	109	45	N/A	N/A	Yes
Enlarged Thyroid	HEPLISAV	462	436	238	N/A	No
Multinodular Goiter	HEPLISAV	3	N/A	N/A	N/A	Unclear
Diffuse Nontoxic Goiter*	HEPLISAV	7	N/A	N/A	N/A	Yes
Thyroid Mass*	HEPLISAV	211	191	166	113	No

* Not considered autoimmune in nature

Source: CBER generated analysis from data submitted in STN 125428/0.

Twenty-one thyroid diseases/laboratory results were reported as adverse events by 18 subjects (0.4%) receiving HEPLISAV in these studies. Three thyroid diseases/laboratory results were reported as adverse events in 3 subjects (0.2%) receiving Engerix-B. The relative risk (HEPLISAV/Engerix-B) of a thyroid associated event was 1.9, 95% confidence interval (0.6, 6.1).

Reviewer Comment: Thyroid events occurred in a slightly higher proportion of subjects receiving HEPLISAV than those receiving Engerix-B. However, the 95% confidence interval surrounding the relative risk of a thyroid associated event included 1, and therefore the difference is not statistically significant. The incidence rate in each group also approximated that of the background incidence rate in the general population. Therefore, the review of thyroid associated events in these studies did not generate safety concerns.

8.5 Additional Safety Evaluations

8.5.1 Dose Dependency for Adverse Events

An overall assessment of dose-dependency for adverse events is often difficult in Phase 3 vaccine trials. However, in the case of Wegener's granulomatosis, a retrospective evaluation of banked serum showed an apparent dose-response relationship between injection and ANCA positivity. In trial HBV0001, a small phase 1 study (N=48), there were no distinct clinical safety patterns based on adjuvant dosing.

8.5.2 Time Dependency for Adverse Events

Please see discussions of individual events.

8.5.3 Product-Demographic Interactions

The majority of subjects enrolled in the HEPLISAV trials were > 40 years of age, of white race and non-Hispanic ethnicity. Based on the demographics of the safety population, there was no selection bias based on age, race, sex or ethnicity. Subgroup analyses of immunogenicity were performed for age, sex and race. The SPRs were

similar for individuals receiving HEPLISAV regardless of age (18-39 versus 40-70). Females had slightly higher SPRs at early time points, but this difference dissipated by Week 24. The racial subgroup analysis was limited due to the Caucasian predominance in the safety population, but the SPRs were similar across the racial groups studied.

Reviewer Comment: Several members of the VRBPAC voiced concern regarding what was viewed as a lack of racial and ethnic diversity in the safety database for a product containing a novel adjuvant.

8.5.4 Product-Disease Interactions

Due to concern for potential exacerbation of pre-existing autoimmune disorders (PEAI), subanalyses of certain safety parameters were performed on the subset of 30 subjects with a PEA I inadvertently enrolled in study DV2-HBV-16. Within this subset, 15 subjects were randomized to HEPLISAV consistency lots, 8 to Lot TDG006 and 7 to Enderix-B. Eighteen subjects (60.0%) in the PEA I population reported at least 1 AE, compared with 51.5% of subjects reporting any AE in the overall safety population. Within the PEA I population, 60.0% of subjects in the HEPLISAV consistency lots group, 62.5% of subjects in the Lot TDG006 group and 57.1% of subjects in the Enderix-B group reported any AE. No individual AE occurred in more than one subject with PEA I in any treatment group. Nine subjects experienced 12 events in the HEPLISAV consistency lots arm, 5 subjects experienced 14 events in the Lot TDG008 arm, and 4 subjects experienced 9 events in the Enderix-B arm.

Three of 30 subjects in the PEA I population (10.0%) experienced SAEs compared with 99/2449 (4.0%) in the overall study population. These were noncardiac chest pain in 2 subjects who received HEPLISAV (lot TDG006: n=1, lot TDG010: n=1) and joint injury in 1 subject in the Enderix-B group. One subject in the PEA I population (3.3%) experienced a confirmed AIAE compared with 3/2449 (0.1%) in the overall study population.

Reviewer Comment: It appears that AEs and SAEs may occur with higher frequency in individuals with PEA I than in the general study population. However, the frequency of AEs and SAEs among the relatively small number of subjects with PEA I was similar between treatment groups. Given the small number of subjects with PEA I inadvertently enrolled in this study and the duration of safety follow-up, the clinical significance of an increased frequency of AEs and SAEs in this subpopulation compared to the remainder of the study population remains unclear at this time.

To evaluate the potential for induction or exacerbation of autoimmune disease in individuals receiving the TLR-9 agonist contained in HEPLISAV, CBER conducted retrospective analyses of potential autoimmune events occurring in all studies. Individuals were excluded from enrollment in clinical trials involving HEPLISAV if they used systemic corticosteroids for more than 3 consecutive days or other immunomodulators or immunosuppressive medications within 4 weeks of enrollment (with the exception of inhaled steroids). To further evaluate potential autoimmune events in an integrated fashion, CBER analyzed SAEs, AESIs and AIAEs treated with

immunosuppressive medication (excluding asthma exacerbations). In each treatment arm, 0.2% of subjects had events treated with immunosuppressive therapy. Four (0.1%) subjects receiving HEPLISAV and no subjects receiving Engerix-B experienced exacerbation of an underlying autoimmune disease (rheumatoid arthritis: n=2, microscopic colitis: n=1, lupus profundus: n=1). One additional HEPLISAV recipient with a past medical history of psoriasis and a family history of vitiligo developed vitiligo on study. One Engerix-B recipient with a past medical history of mixed connective tissue disease developed p-ANCA positive vasculitis and one Engerix-B recipient with a history of hand pain developed rheumatoid arthritis while on study. Seven HEPLISAV recipients (0.2%) and one (0.1%) Engerix-B recipient with a history of thyroid disease experienced exacerbations or new thyroid diagnoses on study.

Reviewer Comment: Individuals with a known history of autoimmune disease or a history of immunosuppressive therapy were excluded from these trials. In study 16, a more rigorous autoimmune questionnaire was used to screen subjects for enrollment. The number of individuals with autoimmune disease that were inadvertently enrolled in these studies was therefore small making an assessment of disease-product interactions in individuals with underlying autoimmune disease difficult. Additionally, given the non-specific and indolent nature of many autoimmune diseases and the sample sizes and duration of follow-up employed in many of these studies, a reliable assessment of disease-product interactions cannot be performed at this time.

8.5.8 Immunogenicity (Safety)

See overall safety conclusions.

8.5.9 Person-to-Person Transmission, Shedding

Not applicable.

8.6 Safety Conclusions

There were no concerning patterns evaluated in the review of the clinical test result data. Limitations to the review include the safety follow-up periods of some trials, only one of which (HBV-16) followed subjects for the full year generally sought by CBER for individuals receiving vaccines containing novel adjuvants. Additionally, as noted by the VRBPAC during the meeting of November 15, 2012, the overall safety database is small for a product containing a novel adjuvant, particularly given the safety uncertainties raised by the development of the case of Wegener's granulomatosis and the possible identification of a subject with Tolosa-Hunt syndrome.

More subjects receiving HEPLISAV reported injection site redness and swelling than did subjects receiving Engerix-B. Most redness and swelling was reported as mild or moderate in intensity. The review of solicited local reactions and solicited systemic reactions did not raise clinical safety concerns.

In study DV2-HBV-16, the applicant conducted a prospective analysis of potential AIAEs. Nine such events were identified by the investigator, all in HEPLISAV recipients. Three of these events were considered to be new onset autoimmune events by the SEAC. The applicant conducted a retrospective analysis of AESIs for all studies and found 0.2% of HEPLISAV recipients and 0.4% of Engerix-B recipients had AESIs. To further evaluate potential autoimmune events, FDA independently conducted a retrospective analysis of SAEs, AIAEs and AESIs for which immunosuppressive therapy was initiated. In that analysis, 0.2% of subjects in each treatment group required immunosuppressive therapy while on study. Thyroid events of potential autoimmune nature were also analyzed and no statistically significant difference in the incidence of such events occurred between treatment groups.

Rare autoimmune events were observed in the safety population. A case of Wegener's granulomatosis occurred in a HEPLISAV recipient. Due to an apparent temporal association with vaccine administration, dose-response relationship between ANCA positivity and vaccine administration and biologic plausibility, this case is believed to be related to the study vaccine. Additionally, a HEPLISAV recipient was diagnosed with possible Tolosa-Hunt syndrome, another granulomatous inflammatory condition of the cavernous sinus. The diagnosis is currently in question and the case is the subject of outside expert consultation. CBER has concerns regarding the *possibility* that two subjects developed rare granulomatous diseases while on study and has sought outside expert consultation. Consultation reports are pending at this time.

There are uncertainties that remain about the autoimmune potential of this novel adjuvant. Determining the clinical significance of the occurrence of individual autoimmune adverse events is limited by the size of the safety database and duration of safety follow-up, the insidious onset of and relatively low background incidence of many autoimmune diseases. For these reasons, the reviewer does not recommend approval of HEPLISAV at this time. As outlined in 21 CFR 601.3(a)(2), the available data are insufficient to adequately determine the safety of the product.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancy was an exclusion criterion for all clinical trials of HEPLISAV. No trials were conducted specifically to assess the safety of HEPLISAV in pregnancy. Limited data are available from subjects who became pregnant after receiving HEPLISAV. Nineteen total pregnancies occurred on study. Twelve pregnancies resulted in healthy term infants. One healthy infant was born "prematurely" at 37 weeks gestation. Four pregnancies were ended by elective termination. One subject was lost to follow-up. One pregnancy resulted in intrauterine fetal demise and subsequent stillbirth at 23 weeks gestation. The narrative for that pregnancy is provided here.

Subject 03048 was a 29 year old woman with a history of hypertension who withdrew from the study due to pregnancy approximately 1.5 months after her first and only study injection. Approximately one month later she was diagnosed with cholecystitis and underwent a laparoscopic cholecystectomy. Approximately 2 months later she reported no fetal movement for 2 days. After monitoring, normal fetal movements were evaluated. Approximately 5 days later, an ultrasound indicated intrauterine fetal demise with no fetal heart tones. The subject was admitted, labor induced and a 13 ounce stillborn female was delivered at the gestational age of 23 weeks, 2 days. The fetal death certificate noted the condition that most likely began the sequence of events resulting in the death of the fetus was maternal chronic hypertension. The investigator assessed the event as severe and not related to study treatment.

Reviewer Comment: The reviewer concurs that this event likely was not related to the receipt of HEPLISAV. Data are inadequate, however, to determine the safety of HEPLISAV in pregnancy.

9.1.2 Use During Lactation

No clinical data are available to address the use of HEPLISAV during lactation.

9.1.3 Pediatric Use and PREA Considerations

The Pediatric Research Committee (PeRC) convened on October 3, 2012 to consider the proposal for a full waiver of pediatric studies in the HEPLISAV developmental program. The PeRC ultimately agreed to a full pediatric waiver for all pediatric subgroups due to no meaningful therapeutic benefit. Some of the discussion points included:

- There are 4 vaccines currently licensed for vaccination against hepatitis B in children. Two of these are combination vaccines (Comvax, Pediarix). Combination vaccines are the preferred method of vaccine administration in children per the ACIP. The current hepatitis B vaccines are very effective in this population with efficacy rates of 96-100% (22).
- The developmental program of HEPLISAV has been directed at hyporesponders, those needing accelerated protection and at improving compliance. OVRP outlined how these issues do not apply to the pediatric population as they do adults.
- The PeRC expressed concerns regarding the possibility that providers caring for adults and children may try to substitute this adult vaccine for one of the ACIP recommended vaccines in the pediatric vaccination schedule. It was determined that the vial should clearly indicate that this vaccine is for vaccination of adults only.

9.1.4 Immunocompromised Patients

No data have been submitted regarding the safety and immunogenicity of this product in immunocompromised patients.

9.1.5 Geriatric Use

As discussed in section 6.2, individuals age 18-70 were enrolled in study DV2-HBV-16. In the per protocol population, 2004 (74.8%) HEPLISAV recipients and 666 (74.7%) Engerix-B recipients were between the ages of 40-70. The mean age of HEPLISAV recipients and Engerix-B recipients in this population was 45.9 and 46, respectively. Subgroup analyses were performed for 18-39 year olds and 40-70 year olds. No specific subgroup analyses were performed in the geriatric population.

10. CONCLUSIONS

HEPLISAV demonstrated an adequate immune response against hepatitis B and showed that it was able to induce a high SPR rapidly (by Week 8). This high seroprotection level was sustained for at least 48 to 52 weeks after the last dose of vaccine given. A majority of the VRBPAC, however, expressed an opinion that the safety data submitted were insufficient to adequately ascertain the safety of the product. The clinical reviewer concurs with this assessment. Furthermore, the development of a rare autoimmune-mediated disease, Wegener's granulomatosis, apparently associated with receipt of HEPLISAV, and the possible development of another rare and potentially related autoimmune disease, Tolosa-Hunt syndrome, in another HEPLISAV recipient, has prompted CBER to seek additional expert consultations which are pending at this time.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.2 Risk-Benefit Summary and Assessment

Hepatitis B infects more than 2 billion persons worldwide, and 350-400 million persons are chronic carriers. Each year chronic HBV causes 0.5 to 1.0 million deaths from end-stage liver disease and hepatocellular carcinoma. In the U.S., universal childhood vaccination has been recommended since 1992. Subsequently, the incidence of HBV infection has substantially decreased from 8.5 per 100,000 (1990) to 1.6 per 100,000 (2006). Prevalence remains high at 800,000 to 1.4 million, and chronic HBV infection causes 2,000-4,000 deaths annually. CDC estimated that there were 38,000 new HBV infections in 2009 with 43% occurring in adults over 40 years of age. Forty-seven percent to 70% of U.S. residents with chronic HBV infection were born in other countries.

Two licensed vaccines, both made from yeast-derived recombinant antigen adsorbed to aluminum compounds, are currently available for the prevention of HBV in adults in the U.S., Engerix-B (GSK) and Recombivax HB (Merck). There is also one combination vaccine for adults, Twinrix (GSK), which includes a hepatitis A vaccine component. Engerix-B and Recombivax HB are both approved for use in adults and adolescents as a three-dose series to be administered at months 0, 1 to 2, and 6 to 12. A two-dose Recombivax HB series, administered at 0, and 4 to 6 months, is also approved for adolescents 11 to 15 years of age. Additionally an accelerated schedule is licensed for Twinrix—a series of four doses (1 mL each), given on Days 0, 7 and Days 21 to 30, followed by a booster dose at Month 12.

These vaccines are highly effective, as shown in controlled clinical trials of efficacy against acute hepatitis B infection (1) and prospective observational studies (2, 10), and elicit seroprotection in approximately 95% of healthy adults. Long-term studies of immunocompetent adults and children indicate that immune memory remains intact for up to two decades and protects against symptomatic acute and chronic HBV infection, even though anti-HBs antibody concentrations may become low or undetectable over time (10).

The applicant reports that among individuals 40 years of age and older, the proportion of individuals who achieve seroprotection after a 3-dose regimen of the currently licensed hepatitis B vaccines declines below 90%, and by age 60, seroprotection develops in only 75% of those vaccinated. The applicant also reports that the third dose of the currently licensed vaccines, which is administered 6 months following the initial dose, is critical for most individuals to achieve seroprotection and long-lasting immunity. Not all individuals receive the complete vaccine regimen, however, leaving them susceptible to HBV infection. In a large retrospective Vaccine Safety Datalink (VSD) Study of more than 88,000 adult, hepatitis B vaccine recipients 18 years of age and older, only 63.7% of those vaccinated received all 3 doses of vaccine during an 8-year study period, and 80.5% of recipients received only 2 doses. The clinical development of HEPLISAV has been directed toward those who are hypo- or non-responders to currently licensed vaccines and to those who seek rapid protection.

HEPLISAV has the potential to provide a clinical benefit due to the immunogenic properties of the vaccine. Results of the two pivotal studies showed that SPRs induced by HEPLISAV at the pre-specified primary immunogenicity endpoint (Week 12 for HEPLISAV and Week 28 or 32 for Engerix-B) were noninferior to those of Engerix-B for all age groups studied (18-70 years). These data were also replicated at each study visit, up to Week 52 (in Study DV2-HBV-52) and indicated that HEPLISAV had a faster, more robust and more sustained immune response than did Engerix-B. Therefore, this vaccine has the potential to address what may be considered an unmet medical need in hypo-responders to currently licensed vaccines, or in those seeking/needing more rapid protection.

The question of potential clinical risk, however, cannot be adequately answered at this time. CBER and the VRBPAC have expressed concerns surrounding the limited size of the safety database in this product that contains a novel immunostimulatory adjuvant. The review of unsolicited nonserious AEs, solicited local and systemic events, and laboratory evaluations did not reveal safety concerns. Retrospective analyses of potential autoimmune events did not reveal a numerical imbalance in the incidence of autoimmune events between groups. However, at least one, and possibly two rare autoimmune events were identified among HEPLISAV recipients in these studies: a case of Wegener's granulomatosis, believed to be related to vaccination, occurred in a HEPLISAV recipient while another HEPLISAV recipient received a possible diagnosis of Tolosa-Hunt syndrome, another granulomatous inflammatory condition of the cavernous sinus. The diagnosis is currently in question and the case is the subject of outside expert consultation. There are uncertainties that remain about the potential clinical safety risks

associated with this vaccine. Therefore, it is the opinion of the reviewer that at this time the potential risks of this vaccine outweigh the potential benefits and therefore approval is not recommended.

11.3 Discussion of Regulatory Options

At this juncture, the findings of the outside clinical consultants will direct the pathway forward. If it is determined that the two clinical cases do not indicate a safety signal or if the results are inconclusive, then the potential regulatory options include conducting additional studies to expand the size of the safety database and the length of safety follow-up, and potentially limiting the indication to populations with different risk-benefit considerations.

11.4 Recommendations on Regulatory Actions

The reviewer does not recommend approval of HEPLISAV. As outlined in 21 CFR 601.3(a)(2), the available data are insufficient to adequately determine the safety of the product.

Complete Response Clinical Comments:

1. We consider the size of the safety database in your license application to be insufficient to support the proposed indication and use of your Hepatitis B Vaccine (Recombinant), Adjuvanted, i.e., for prevention of Hepatitis B infection in adults 18-70 years of age. In addition, we are concerned that two subjects may have developed rare granulomatous diseases after receipt of your vaccine. One was a documented case of granulomatous polyangiitis (Wegener's granulomatosis). Another subject may have developed Tolosa-Hunt Syndrome, a serious medical condition of multiple possible etiologies that, in some cases, may be a manifestation of granulomatous polyangiitis. As each of these diagnoses is rare, it would be highly unlikely for both to be observed among the 4,425 recipients of Hepatitis B Vaccine (Recombinant), Adjuvanted, in the clinical trials on the basis of random occurrence. We also note the absence of post-marketing safety experience for any licensed product containing the adjuvant component of your vaccine that could supplement the evaluation of safety. Additionally, we refer you to the discussion of the safety of your vaccine before the Vaccines and Related Biologic Products Advisory Committee on November 15, 2012, and the negative vote by the committee on the question regarding adequacy of the safety information to support the proposed indication and use. Therefore, prior to consideration of licensure of your Hepatitis B Vaccine (Recombinant), Adjuvanted, for use in adults 18-70 years of age, further clinical evaluation of safety will be necessary, whereby the design and size of the additional safety study or studies will require discussion with CBER.

However, as we indicated in the telephone conversation dated February 12, 2013, between Dynavax and CBER, the safety data required to support licensure of your Hepatitis B Vaccine (Recombinant) Adjuvanted, will depend on the indication and use and a favorable benefit/risk determination associated with that indication and use. We are willing to discuss with you information that would be needed to support a more restricted use of your vaccine, including the size of a safety database and any additional immunogenicity data that may be required.

2. Incomplete information was provided regarding several subjects who experienced adverse events. Please provide the following additional information:
 - a. For subject 32-018, please provide any medical records related to the diagnosis and treatment of narcolepsy.
 - b. Subject 42-320 was discontinued from study due to facial swelling and a rash of unknown etiology. If referral for medical evaluation took place, please provide those documents.
 - c. Subject 21-640 was referred for medical evaluation of a potential autoimmune event. Please provide the records pertaining to that evaluation.
 - d. Please provide the hospital records and neurological outpatient follow-up records for subject 06174.
 - e. Clotting disorder evaluations were performed for three subjects reporting pulmonary emboli (22-601, 21047 and 22070). Please provide the results of those evaluations including any serologic markers of autoimmune disease.

3. Three disks containing radiographic, computed tomography and magnetic resonance images pertaining to the potential case of Tolosa-Hunt syndrome together with a cover letter were submitted to CBER for review. These files could not be accepted for review in the form submitted; therefore, please make the following changes and resubmit the files containing these images.
 - a. To comply with 21 CFR 20.63(b), please remove all patient identifiers from the images and files before they are submitted to the FDA.
 - b. Please resubmit these images to CBER on a disk. The viewing software must be on a separate disk from the images (see item 3 c. below). Please name each image file with the date and radiological test (e.g., MRI, CT) and the subject number (i.e., the number assigned when the subject was entered into the study). Place the patient's image files together in a folder on the disk.
 - c. For archiving purposes, please submit a copy of the software required to view these images along with a site license allowing the FDA to use the software on a separate disk. After installing and opening the software, inserting the subject number should take the reviewer to the image files on the disk containing the image files. The software should then allow those files to be opened and viewed.
 - d. Please provide detailed instructions on how to install the viewer software and to view the images, with each set of disks.
 - e. Please submit five copies of each disk as soon as possible. To expedite review of these images it is acceptable to respond to this comment and submit these five copies as soon as possible and before you respond to the other items in this Complete Response Letter.

- f. Please amend your eCTD submission through the Electronic Submission Gateway (ESG). The cover letter for the submission which responds to this item should state the contents of each disk. Please notify the review team when the disks have been mailed and when the eCTD amendment has been sent through the ESG. Please provide at that time, the CoreId, which is the number conveyed to you when the ESG received your submission.

11.5 Labeling Review and Recommendations

Not applicable at this time.

11.6 Recommendations on Postmarketing Actions

Not applicable at this time.

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