Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eMethods 1. Exclusion Criteria

Participants with any of the following criteria were excluded:

1. Previous vaccination with any HBV vaccine (licensed or experimental)
2. Treatment by immunosuppressant within 30 days of enrollment including but not limited to corticosteroids at a dose that was higher than an oral or injected physiological dose, or > 20 mg/day prednisolone equivalent (inhaled and topical steroids are allowed)
3. History of immunological function impairment, including but not limited to:
    a) Autoimmune diseases (eg, multiple sclerosis; type 1 diabetes; myasthenia gravis; Crohn's disease and other inflammatory bowel diseases; celiac disease; systemic lupus erythematosus, scleroderma, including diffuse systemic form and CREST syndrome; systemic sclerosis; dermatomyositis polymyositis; rheumatoid arthritis; juvenile idiopathic arthritis; autoimmune thyroiditis, including Hashimoto's thyroiditis, Grave's or Basedow's disease; immune thrombocytopenic purpura; autoimmune hemolytic anemia; autoimmune hepatitis; psoriasis; vitiligo; vasculitis; Guillain-Barré syndrome; Addison's disease; Bell's palsy; and alopecia areata)
    b) Secondary immunodeficiency disorders (eg, AIDS caused by HIV infection, solid organ transplant, splenectomy
    c) Primary immunodeficiency disorders (eg, common variable immune deficiency, defective phagocytic cell function and neutropenia syndromes, complement deficiency
4. Pregnancy or breastfeeding
5. Immunization with attenuated vaccines (eg, MMR) within 4 weeks before enrollment

6. Immunization with inactivated vaccines (eg, influenza) within 2 weeks before enrolment
7. Received blood products or immunoglobulin within 90 days before study entry or likely to require blood products during the study period.
8. Subject in another clinical trial with an investigational drug or a biologic within 30 days of enrollment
9. Received granulocyte-macrophage stimulating factor (G/GM-CSF) or erythropoietin (EPO) within 30 days of enrollment or likely to require GM-CSF erythropoietin during the study period.
10. Any history of cancer requiring chemotherapy or radiation within 5 years of randomization or current disease. Participants with a history of low-risk basal cell carcinoma were accepted (low risk was defined as: 1) location on the trunk of the body, arms, legs, cheeks, forehead, temples, scalp, neck, or chin; 2) less than 2 cm; 3) nodular or superficial; 4) primary cancer that had not recurred after treatment; 5) edge of the cancerous area was clear and smooth and 6) not located in or around nerves)
11. Any skin abnormality or tattoo that would limit post-vaccination injection site assessment.
12. History of allergic or anaphylactic reaction(s) to any vaccine component
13. Unwilling, or unable, in the opinion of the investigator, to comply with study requirements, including the use of an adequate birth control method.
14. An immediate family member of study center staff (eg, parent, sibling, child)
15. Current or past hepatitis B infection or prior vaccination, as evidenced by HBV infection markers (anti-HBc, anti-HBs, HBsAg) at screening

16. Known hepatitis C infection or positive hepatitis C serology at screening, unless treated and cured (defined as documented sustained virologic response [SVR] or negative viral load ≥ 12 weeks after cessation of antiviral therapy)
17. Known HIV infection or positive HIV serology at screening.
18. Renal impairment with glomerular filtration rate (GFR) of <60 mL/min/1.73m^2
19. Body mass index (BMI) ≥35 kg/m^2
20. Uncontrolled hypertension (defined as an average systolic blood pressure ≥ 150 mm Hg on the last 3 measurements in those diagnosed and treated for hypertension, or an average diastolic blood pressure ≥ 95 mm Hg on the last 3 measurements in those without a diagnosis of hypertension)
21. Diagnosis of Type 1 or 2 diabetes or a hemoglobin A1c ≥ 6.5% at screening
22. Any laboratory test abnormality that would be considered of Grade 1 severity or above as per FDA guidelines for grading clinical laboratory abnormalities and was considered as clinically significant by the Investigator. Grade 3 severity or above was exclusionary, regardless of clinical assessment.

eMethods 2. Exploratory End Points Assessed

i) Geometric Mean Concentration (GMC) of anti-HBs in serum after two vaccinations, just prior to receiving the third vaccination, and 24 weeks after the third vaccination with 3A-HBV or 1A-HBV, on Study Days 168 and 336, respectively; ii) SPR after two vaccinations, just prior to receiving the third vaccination, and 24 weeks after the third vaccination with 3A-HBV or 1A-HBV, on Study Days 168 and 336, respectively; iii) proportion of participants achieving anti-HBs concentrations ≥ 100mIU/mL in serum, as a measure of an especially robust immune response, on Study Days 168 and 196, just prior to and four weeks after the third vaccination with 3A-HBV or 1A-HBV, and on Study Day 336; iv) rate of non-response on Study Day 196, four weeks after the third vaccination with 3A-HBV or 1A-HBV; v) SPR, GMC and rate of non-response in sub-groups of interest (e.g. BMI > 30), four weeks after receiving the third vaccination with 3A-HBV or 1A-HBV . Each of the above exploratory objectives were assessed for each 3A-HBV lot separately, as well as for the difference between each 3A-HBV lot, pooled 3A-HBV lots, for the 1A-HBV group and for the difference between all three pooled lots of 3A-HBV and 1A-HBV.

eMethods 3. Immunogenicity and Safety Assessments

Immunogenicity

Immunogenicity was assessed by measurement of anti-HBs levels on Study Days 0, 168 (just before the third injection), 196 (four weeks after the third injection), and 336 (24 weeks after the third injection). Serum anti-HBs concentrations were measured by a validated VITROS anti-HBs quantitative assay using the VITROS anti-HBs reagent pack and the VITROS anti-HBs calibrators on the VITROS 5600 Immunodiagnostic System using Intellicheck™ Technology. The measuring range for the assay is 4.23 to 1000 mIU/mL. Values below 4.23 mIU/mL were set to half that limit and above 1000 mIU/mL were automatically diluted on the system up to 400-fold and tested. A cut-off of 20,000 mIU/mL was the upper limit in the analysis reporting anti-HBs concentrations. Vaccine-induced seroprotection, considered a surrogate of protection against infection, was defined as anti-HBs concentrations ≥10 mIU/mL. SPR was defined as the percentage of participants achieving seroprotection.

Safety and reactogenicity

All participants came for a total of 5 visits (denoted V1, V2, V3, V4, and end of study visit, V5) on Study Days 0, 28, 168, 196 and 336, respectively. Participants were followed a minimum of 48 weeks after receiving the first vaccination on Study Day 0, with at least a 24-week follow-up after receiving the third injection. Participants were provided with 28-day diary cards at each vaccination visit, at baseline (Study Day 0) and on Study Days 28 and 168, which were collected at the next study visit. On the diary card, the participant recorded solicited events capturing body temperature (oral), local reactions at the injection site (redness/erythema, pain, tenderness, swelling/edema, pruritus) and systemic reactions (nausea/vomiting, diarrhea, headache, fatigue, myalgia) daily, from the day of vaccination and during the next six days. In addition, the

participant also recorded any unsolicited adverse events (AEs) on the day of vaccination and during the next 27 days on the 28-day diary card and any changes in concomitant medication. AEs were classified by Medical Dictionary for Regulatory Activities (MedDRA) system organ class (SOC) and preferred term. The FDA grading scale (21) was used to assess severity of reported AEs. At each study visit (through Study Day 336), participants were followed up for serious AEs (SAE), medically-attended AEs (MAAE), and any new onset of chronic illness (NOCI) which were evaluated by the medical monitor against the Center for Disease Control definition of chronic diseases at the time of the analysis. Any changes in concomitant medication were also recorded at each study visit.

Finally, the number (%) of participants with abnormal vital sign measurements and physical examination findings compared with baseline and number (%) of participants with abnormal clinical laboratory parameters from baseline assessments on Study Days 7, 35, and 175, one week after each vaccination (in participants in the clinical laboratory sub-study, conducted at select sites) also was recorded.

eMethods 4. Statistical Analysis

Adjusted estimates of GMCs and their associated 95% CIs were each determined using an analysis of covariance (ANCOVA) model with a factor for vaccine lot and a covariate for the log transformed pre-vaccination (baseline) titer. The ratio of GMCs between each vaccine lot group, including and their associated 2-sided 95% CIs were presented. If the upper and lower bound of the 2-sided 95% CI of the GMC of anti-HBs ratios 4 weeks after the third vaccination for all 3 pairwise comparisons were within [0.67, 1.5], lot-to-lot consistency (manufacturing equivalence) was demonstrated. Statistical analyses were performed on the logarithmically (base 10) transformed values. The analysis conducted on per protocol set 1 (PPS1; defined as all participants who received all 3 vaccinations, had evaluable serum immunogenicity samples at baseline and at the timepoint of interest, were seronegative at baseline, and had no major protocol deviations leading to exclusion as identified prior to unblinding) was considered primary. As immunogenicity for 3A-HBV has previously shown to be insensitive to out of window assessments, participants were not excluded if their immunogenicity assessments were out of the permitted windows for visit 3 (Study Day 168) and visit 4 (Study Day 196).

The non-inferiority of 3A-HBV to 1A-HBV four weeks after the third vaccination (Study Day 196) was based on the difference in SPR and the 2-sided 95% CI. If the lower bound of the 2-sided CI was > -5%, non-inferiority of 3A-HBV to 1A-HBV was demonstrated. The primary non-inferiority analysis data set was the same as the primary immunogenicity endpoint, however participants with out-of-window immunogenicity assessments were excluded from the analysis dataset, designated as PPS2, in the event that 1A-HBV was more sensitive to immunogenicity assessments that were out of the permitted windows, so as not to bias the comparative analysis.

All statistical analyses were performed using SAS® version 9.3 or later. All statistical tests were 2-sided and were performed at the 5% level of significance, unless otherwise stated. The primary immunogenicity variable of this study was GMC of anti-HBs titre at Study Day 196. The All-Enrolled Set consisted of all screened participants who provided informed consent and provided demographic and/or baseline screening assessments, regardless of the subject's randomization and vaccination status in the study. The primary analysis to determine the lot-to-lot equivalence of three independent consecutive 3A-HBV lots was conducted on per-protocol set-1 (PPS1) (all participants in the Full Analysis Set, comprising all participants in the All Enrolled Set, who received at least 1 injection and provided at least one evaluable serum immunogenicity sample both at baseline and after baseline, who received all three injections, had evaluable serum immunogenicity samples at baseline and at the time point of interest, were seronegative at baseline, and had no major protocol deviations leading to exclusion as identified prior to unblinding) and per-protocol set-2 (PPS2) (all participants in per-protocol set-1, but excluding those who attended study visits outside of the following windows: V3/Study Day 168 (+/- 28 days) and V4/ Study Day 196 (-7/+14 days).

To assess the primary objective (lot-to-lot consistency) in terms of GMC, 95% CIs of the GMC ratios of anti-HBs concentrations four weeks after the third injection with 3A-HBV were computed for each pair of vaccine lots (A *vs* B, A *vs* C, B *vs* C), using an analysis of covariance (ANCOVA) model on the $\log_{10}$ transformation of the anti-HBs concentrations. The ANCOVA model included a fixed factor for vaccine lot group, and a covariate for the log transformed baseline titer. The primary objective was met if the upper and lower bound of the two-sided 95% confidence interval (CI) of the GMCs for all three pairwise comparisons (GMC of anti-HBs in Lot A/GMC of anti-HBs in Lot B, GMC of anti-HBs in Lot A/ GMC of anti-HBs in Lot C, GMC

of anti-HBs in Lot B/ GMC of anti-HBs in Lot C), were within 0.67 and 1.5. If lot-lot-consistency was demonstrated, then data from the three lots were combined to compute the 95% CIs for the difference in proportions [SPR(3A-HBV)–SPR(1A-HBV)] to address the secondary objective. To demonstrate that the SPR of 3A-HBV (pooled data for Lots A, B and C) is non-inferior to 1A-HBV, the lower bound of the 95% two-sided CI of the difference between the SPR for 3A-HBV and 1A-HBV [SPR(3A-HBV)–SPR(1A-HBV)] needed to be > -5%. To assess the safety and reactogenicity of 3A-HBV compared to 1A-HBV, safety and reactogenicity were analysed in all participants who received at least one vaccine dose. Demographic characteristics were summarized by group using descriptive statistics.

eTable 1: Geometric Mean Concentration (GMC) of Anti-HBs and GMC Ratio at Study Days 168, 196, and 336 by Vaccine Group

	1A-HBV (N=603)			Pooled 3A-HBV (N=1778)		
Day	**168**	**196**	**336**	**168**	**196**	**336**
n	603	592	580	1775	1753	1718
Mean (SD)	15.0 (7.1)	1526.3 (11. 8)	473.0 (11.8)	119.0 (6.6)	5443.1 (5.8)	2093.8 (6.8)
Median	11.5	2900.0	581.5	128.0	11700.0	3135.0
Mean Adjusted GMC (SE)	15.1 (1.1)	1567.2 (1.1)	473.1 (1.1)	118.8 (1.0)	5442.4 (1.0)	2093.7 (1.1)
95% CI	13.0, 17.5	1338.7, 1834.8	399.6, 560.2	108.8, 129.7	4967.2, 5963.0	1897.9, 2309.6
Ratio (3A-HBV /1A-HBV)				7.9	3.5	4.4
95% CI of the difference				6.6, 9.4	2.9, 4.2	3.6, 5.4

Abbreviations: ANCOVA= analysis of covariance; anti-HBs=hepatitis B surface antibody; CI=confidence interval; GMC=geometric mean concentration; Q=quartile; SD=standard deviation; SE=standard error

Note: The mean and SD are based on $\log_{10}$-transformed data, then transformed back to anti-HBs concentration. Adjusted GMC, GMC ratio, and corresponding 95% CI were analyzed using ANCOVA with a factor for vaccine lot group, and a covariate for the log transformed pre-vaccination (baseline) titer.

Note: Difference presents the ratio of GMCs (Pooled 3A-HBV /1A-HBV)

eTable 2: Solicited Local Adverse Events by Vaccine Group and Severity—Interval of Onset: Day 1 to Day 7 of Any Vaccination (Safety Set)

Solicited Local Adverse Event Severity (Grade)	1A-HBV (N=712) n (%)	3A-HBV			
		Pooled (N=2124) n (%)	Lot A (N=711) n (%)	Lot B (N=708) n (%)	Lot C (N=705) n (%)
Any Solicited Local Adverse Event					
None (0)	243 (34.1)	319 (15.0)	122 (17.2)	106 (15.0)	91 (12.9)
Mild (1)	358 (50.3)	1063 (50.0)	345 (48.5)	357 (50.4)	361 (51.2)
Moderate (2)	101 (14.2)	670 (31.5)	219 (30.8)	223 (31.5)	228 (32.3)
Severe (3)	8 (1.1)	61 (2.9)	21 (3.0)	20 (2.8)	20 (2.8)
Potentially life-threatening (4)	2 (0.3)	11 (0.5)	4 (0.6)	2 (0.3)	5 (0.7)
Redness/erythema					
None (0)	700 (98.3)	2063 (97.1)	684 (96.2)	688 (97.2)	691 (98.0)
Mild (1)	7 (1.0)	45 (2.1)	20 (2.8)	16 (2.3)	9 (1.3)
Moderate (2)	2 (0.3)	6 (0.3)	2 (0.3)	3 (0.4)	1 (0.1)
Severe (3)	1 (0.1)	1 (0.0)	1 (0.1)	0	0
Potentially life-threatening (4)	2 (0.3)	9 (0.4)	4 (0.6)	1 (0.1)	4 (0.6)
Pain					
None (0)	328 (46.1)	519 (24.4)	184 (25.9)	172 (24.3)	163 (23.1)
Mild (1)	354 (49.7)	1367 (64.4)	450 (63.3)	460 (65.0)	457 (64.8)
Moderate (2)	27 (3.8)	218 (10.3)	69 (9.7)	68 (9.6)	81 (11.5)
Severe (3)	3 (0.4)	20 (0.9)	8 (1.1)	8 (1.1)	4 (0.6)
Potentially life-threatening (4)	0	0	0	0	0
Swelling/edema					
None (0)	706 (99.2)	2069 (97.4)	693 (97.5)	693 (97.9)	683 (96.9)
Mild (1)	3 (0.4)	36 (1.7)	14 (2.0)	10 (1.4)	12 (1.7)
Moderate (2)	3 (0.4)	15 (0.7)	3 (0.4)	4 (0.6)	8 (1.1)
Severe (3)	0	2 (0.1)	1 (0.1)	0	1 (0.1)
Potentially life-threatening (4)	0	2 (0.1)	0	1 (0.1)	1 (0.1)
Tenderness					
None (0)	321 (45.1)	529 (24.9)	192 (27.0)	173 (24.4)	164 (23.3)
Mild (1)	302 (42.4)	944 (44.4)	307 (43.2)	321 (45.3)	316 (44.8)
Moderate (2)	84 (11.8)	606 (28.5)	198 (27.8)	199 (28.1)	209 (29.6)
Severe (3)	5 (0.7)	45 (2.1)	14 (2.0)	15 (2.1)	16 (2.3)
Potentially life-threatening (4)	0	0	0	0	0

Solicited Local Adverse Event Severity (Grade)	1A-HBV (N=712) n (%)	3A-HBV			
		Pooled (N=2124) n (%)	Lot A (N=711) n (%)	Lot B (N=708) n (%)	Lot C (N=705) n (%)
Pruritus/itching					
None (0)	624 (87.6)	1843 (86.8)	627 (88.2)	603 (85.2)	613 (87.0)
Mild (1)	79 (11.1)	250 (11.8)	76 (10.7)	92 (13.0)	82 (11.6)
Moderate (2)	7 (1.0)	27 (1.3)	8 (1.1)	11 (1.6)	8 (1.1)
Severe (3)	2 (0.3)	4 (0.2)	0	2 (0.3)	2 (0.3)
Potentially life-threatening (4)	0	0	0	0	0

Note: Implausible measurements, Erythema: ≥900 mm or <0 mm and swelling: ≥500 mm or <0 mm, were removed from the analysis but included in listings.
Note: Maximal severity is reported.
Grade: 1=Mild, 2=Moderate, 3=Severe, 4=Potentially life threatening. Grade 0 includes subjects who reported redness or swelling measured < 2.5 cm.
Note: Reports of Grade 4 / potentially-life-threatening erythema and swelling were based on the subject-reported presence of skin necrosis or exfoliative dermatitis at injection site while the actual measurement of erythema and edema would correspond to severity of none to Grade 1.

eTable 3: Solicited Systemic Adverse Events by Vaccine Group and Severity—Interval of Onset: Day 1 to Day 7 of Any Vaccination (Safety Set)

Solicited Systemic Adverse Event Severity (Grade)	1A-HBV (N=712) n (%)	3A-HBV			
		Pooled (N=2124) n (%)	Lot A (N=711) n (%)	Lot B (N=708) n (%)	Lot C (N=705) n (%)
Any Systemic					
Mild (1)	249 (35.0)	893 (42.0)	275 (38.7)	301 (42.5)	317 (45.0)
Moderate (2)	158 (22.2)	482 (22.7)	149 (21.0)	170 (24.0)	163 (23.1)
Severe (3)	21 (2.9)	68 (3.2)	26 (3.7)	26 (3.7)	16 (2.3)
Potentially life-threatening (4)	0	2 (0.1)	1 (0.1)	1 (0.1)	0
Nausea/vomiting					
Mild (1)	67 (9.4)	198 (9.3)	73 (10.3)	65 (9.2)	60 (8.5)
Moderate (2)	18 (2.5)	50 (2.4)	11 (1.5)	20 (2.8)	19 (2.7)
Severe (3)	1 (0.1)	2 (0.1)	1 (0.1)	1 (0.1)	0
Potentially life-threatening (4)	0	1 (0.0)	0	1 (0.1)	0
Diarrhea					
Mild (1)	90 (12.6)	231 (10.9)	81 (11.4)	71 (10.0)	79 (11.2)
Moderate (2)	15 (2.1)	38 (1.8)	12 (1.7)	12 (1.7)	14 (2.0)
Severe (3)	0	8 (0.4)	1 (0.1)	4 (0.6)	3 (0.4)
Potentially life-threatening (4)	0	0	0	0	0
Headache					
Mild (1)	182 (25.6)	586 (27.6)	178 (25.0)	198 (28.0)	210 (29.8)
Moderate (2)	78 (11.0)	208 (9.8)	67 (9.4)	73 (10.3)	68 (9.6)
Severe (3)	8 (1.1)	16 (0.8)	9 (1.3)	4 (0.6)	3 (0.4)
Potentially life-threatening (4)	0	1 (0.0)	1 (0.1)	0	0
Fatigue					
Mild (1)	178 (25.0)	567 (26.7)	175 (24.6)	198 (28.0)	194 (27.5)
Moderate (2)	95 (13.3)	250 (11.8)	75 (10.5)	84 (11.9)	91 (12.9)
Severe (3)	11 (1.5)	35 (1.6)	16 (2.3)	14 (2.0)	5 (0.7)
Potentially life-threatening (4)	0	0	0	0	0
Myalgia					
Mild (1)	175 (24.6)	719 (33.9)	214 (30.1)	226 (31.9)	279 (39.6)
Moderate (2)	49 (6.9)	197 (9.3)	68 (9.6)	78 (11.0)	51 (7.2)
Severe (3)	7 (1.0)	26 (1.2)	7 (1.0)	12 (1.7)	7 (1.0)
Potentially life-threatening (4)	0	0	0	0	0

Note: Maximal severity is reported.

eTable 4: Summary of Unsolicited TEAEs Reported in at Least 1% of Participants in Either 1A-HBV or Pooled 3A-HBV Group by Standard of Care and Preferred Term—Interval of Onset: Day 1 to Day 28 of Any Injection (Safety Set)

System Organ Class Preferred Term	1A-HBV (N=712)	3A-HBV				Total (N=2836)
		Pooled (N=2124)	Lot A (N=711)	Lot B (N=708)	Lot C (N=705)	
Participants with at least one TEAE	348 (48.9)	1042 (49.1)	329 (46.3)	358 (50.6)	355 (50.4)	1390 (49.0)
Infections and infestations	**168 (23.6)**	**466 (21.9)**	**152 (21.4)**	**163 (23.0)**	**151 (21.4)**	**634 (22.4)**
Upper respiratory tract infection	63 (8.8)	196 (9.2)	61 (8.6)	69 (9.7)	66 (9.4)	259 (9.1)
Nasopharyngitis	45 (6.3)	104 (4.9)	30 (4.2)	36 (5.1)	38 (5.4)	149 (5.3)
Influenza	16 (2.2)	34 (1.6)	12 (1.7)	13 (1.8)	9 (1.3)	50 (1.8)
Sinusitis	7 (1.0)	24 (1.1)	11 (1.5)	7 (1.0)	6 (0.9)	31 (1.1)
Gastroenteritis	8 (1.1)	22 (1.0)	6 (0.8)	7 (1.0)	9 (1.3)	30 (1.1)
Urinary tract infection	10 (1.4)	20 (0.9)	7 (1.0)	5 (0.7)	8 (1.1)	30 (1.1)
Nervous system disorders	**103 (14.5)**	**307 (14.5)**	**94 (13.2)**	**115 (16.2)**	**98 (13.9)**	**410 (14.5)**
Headache	87 (12.2)	252 (11.9)	78 (11.0)	96 (13.6)	78 (11.1)	339 (12.0)
Dizziness	6 (0.8)	31 (1.5)	8 (1.1)	8 (1.1)	15 (2.1)	37 (1.3)
Migraine	7 (1.0)	14 (0.7)	7 (1.0)	3 (0.4)	4 (0.6)	21 (0.7)
Musculoskeletal and connective tissue disorders	**84 (11.8)**	**217 (10.2)**	**74 (10.4)**	**67 (9.5)**	**76 (10.8)**	**301 (10.6)**
Back pain	18 (2.5)	59 (2.8)	18 (2.5)	19 (2.7)	22 (3.1)	77 (2.7)
Myalgia	20 (2.8)	57 (2.7)	18 (2.5)	19 (2.7)	20 (2.8)	77 (2.7)
Neck pain	9 (1.3)	28 (1.3)	7 (1.0)	13 (1.8)	8 (1.1)	37 (1.3)
Pain in extremity	10 (1.4)	22 (1.0)	8 (1.1)	5 (0.7)	9 (1.3)	32 (1.1)
Arthralgia	7 (1.0)	21 (1.0)	5 (0.7)	9 (1.3)	7 (1.0)	28 (1.0)
Muscle tightness	10 (1.4)	17 (0.8)	7 (1.0)	4 (0.6)	6 (0.9)	27 (1.0)
Musculoskeletal pain	8 (1.1)	13 (0.6)	5 (0.7)	3 (0.4)	5 (0.7)	21 (0.7)
General disorders and administration site conditions	**46 (6.5)**	**207 (9.7)**	**67 (9.4)**	**62 (8.8)**	**78 (11.1)**	**253 (8.9)**
Fatigue	17 (2.4)	80 (3.8)	23 (3.2)	20 (2.8)	37 (5.2)	97 (3.4)
Injection site pain	12 (1.7)	46 (2.2)	17 (2.4)	18 (2.5)	11 (1.6)	58 (2.0)
Injection site bruising	7 (1.0)	21 (1.0)	7 (1.0)	8 (1.1)	6 (0.9)	28 (1.0)
Pyrexia	7 (1.0)	14 (0.7)	6 (0.8)	6 (0.8)	2 (0.3)	21 (0.7)
Gastrointestinal disorders	**37 (5.2)**	**132 (6.2)**	**41 (5.8)**	**51 (7.2)**	**40 (5.7)**	**169 (6.0)**
Abdominal pain upper	8 (1.1)	31 (1.5)	10 (1.4)	10 (1.4)	11 (1.6)	39 (1.4)

System Organ Class Preferred Term	1A-HBV (N=712)	3A-HBV				Total (N=2836)
		Pooled (N=2124)	Lot A (N=711)	Lot B (N=708)	Lot C (N=705)	
Diarrhoea	7 (1.0)	30 (1.4)	10 (1.4)	11 (1.6)	9 (1.3)	37 (1.3)
Toothache	7 (1.0)	17 (0.8)	8 (1.1)	5 (0.7)	4 (0.6)	24 (0.8)
Respiratory, thoracic, and mediastinal disorders	**37 (5.2)**	**120 (5.6)**	**38 (5.3)**	**38 (5.4)**	**44 (6.2)**	**157 (5.5)**
Oropharyngeal pain	21 (2.9)	65 (3.1)	22 (3.1)	20 (2.8)	23 (3.3)	86 (3.0)
Cough	9 (1.3)	28 (1.3)	11 (1.5)	9 (1.3)	8 (1.1)	37 (1.3)
Reproductive system and breast disorders	**32 (4.5)**	**104 (4.9)**	**30 (4.2)**	**27 (3.8)**	**47 (6.7)**	**136 (4.8)**
Dysmenorrhoea	31 (4.4)	91 (4.3)	28 (3.9)	23 (3.2)	40 (5.7)	122 (4.3)

eTable 5: Summary of All Serious Unsolicited Adverse Events Reported During the Entire Study Period—Interval of Onset: Day 1 to Day 336 (Safety Set)

Preferred Term	1A-HBV (N=712) n (%)	3A-HBV				Total (N=2836) n (%)
		Pooled (N=2124) n (%)	Lot A (N=711) n (%)	Lot B (N=708) n (%)	Lot C (N=705) n (%)	
Participants with at least 1 SAE	3 (0.4)	42 (2.0)	12 (1.7)	18 (2.5)	12 (1.7)	45 (1.6)
Number of SAEs	4	47	15	20	12	51
Appendicitis	0	3 (0.1)	1 (0.1)	1 (0.1)	1 (0.1)	3 (0.1)
Intervertebral disc protrusion	0	3 (0.1)	1 (0.1)	2 (0.3)	0	3 (0.1)
Erysipelas	0	2 (0.1)	1 (0.1)	0	1 (0.1)	2 (0.1)
Chlamydial infection	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Infectious mononucleosis	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Laryngitis	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Pneumonia	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Pyelonephritis	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Pyelonephritis acute	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Tonsillitis	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Vestibular neuronitis	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Ankle fracture	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Concussion	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Head injury	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Humerus fracture	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Joint dislocation	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Lower limb fracture	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Post procedural haemorrhage	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Spinal compression fracture	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Tendon rupture	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Tibia fracture	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Upper limb fracture	1 (0.1)	0	0	0	0	1 (0.0)
Back pain	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Pain in extremity	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Rheumatoid arthritis	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Spinal osteoarthritis	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Migraine	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)

Preferred Term	1A-HBV (N=712) n (%)	3A-HBV				Total (N=2836) n (%)
		Pooled (N=2124) n (%)	Lot A (N=711) n (%)	Lot B (N=708) n (%)	Lot C (N=705) n (%)	
Seizure	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Syncope	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Vertigo	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Vertigo positional	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Alcoholic liver disease	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Cholecystitis chronic	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Stress cardiomyopathy	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Gastrointestinal arteriovenous malformation	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Haemorrhoidal haemorrhage	1 (0.1)	0	0	0	0	1 (0.0)
Sudden cardiac death	0	1 (0.0)	1 (0.1)	0	0	1 (0.0)
Abortion spontaneous	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Depression	0	1 (0.0)	0	0	1 (0.1)	1 (0.0)
Acute kidney injury	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Tonsillar hypertrophy	0	1 (0.0)	0	1 (0.1)	0	1 (0.0)
Skin necrosis	1 (0.1)	0	0	0	0	1 (0.0)
Deep vein thrombosis	1 (0.1)	0	0	0	0	1 (0.0)