Supplementary Table 1: Definition of Outcomes

Hepatic decompensation*: occurrence of ascites, hepatic hydrothorax, variceal or portal hypertensive bleeding, hepatic encephalopathy or Child-Turcotte-Pugh (CTP) score ≥7 (based on presence or absence of ascites and encephalopathy, and albumin, bilirubin and INR values)

Hepatocellular carcinoma*: based on histology or imaging per American Association for Study of Liver Diseases guidelines

Liver Transplant*: occurrence of liver transplantation; occurring >24 weeks after enrollment

HBV-related death*: deaths deemed to be related to HBV-related liver disease; occurring >24 weeks after enrollment

Incident cirrhosis*: histology, hepatic decompensation or CTP score ≥7; and in the absence of the above criteria by 2 of the following: splenomegaly or nodular liver on radiological imaging, or platelet count <120,000/mm^3; occurring >24 weeks after enrollment

Major clinical outcome: first occurrence of hepatic decompensation, HCC, liver transplant or HBV-related death

Non HBV-related death*: deaths not deemed to be related to HBV-related liver disease; occurring >24 weeks after enrollment

Incident ALT flare*: first occurrence of ALT ≥10x upper limit of normal (30 U/L for men and 20 U/L for women) after enrollment, and prior to initiation of antiviral therapy

Ever become HBeAg-: first negative result on HBeAg test in participants HBeAg-positive at baseline, based on central lab testing, supplemented by local lab result if central lab result not available

Ever become HBsAg-: first negative result on HBsAg test, based on central lab testing, supplemented by local lab result if central lab result not available

HBV treatment initiation: first occurrence of HBV antiviral treatment initiation per standard of care, >24 weeks after enrollment that lasted ≥24 weeks. (Data of participants who started treatment in HBRN clinical trials were excluded at or after entry into the trials.)

*Outcomes adjudicated by HBRN committee based on established definitions and after review of source documents.

Supplementary Table 2: Incidence Rates of HBV Treatment Initiation among 1418 Participants

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
Age (Years)	<30	250	50	775	6.45 (4.89, 8.52)
	30 - 50	761	135	2751	4.91 (4.15, 5.81)
	>50	407	89	1502	5.93 (4.81, 7.30)
Sex	Male	688	141	2351	6.00 (5.09, 7.08)
	Female	730	133	2676	4.97 (4.19, 5.89)
Race	White	142	23	572	4.02 (2.67, 6.06)
	Black	179	17	645	2.63 (1.64, 4.24)
	Asian	1055	225	3668	6.13 (5.38, 6.99)
	Other/Mixed	39	9	134	6.72 (3.50, 12.91)
HBeAg Status	Negative	1048	169	4001	4.22 (3.63, 4.91)
	Positive	331	98	886	11.07 (9.08, 13.49)
HBV DNA (log_{10} IU/mL)	<3	497	32	2026	1.58 (1.12, 2.23)
	3 - 5	489	100	1897	5.27 (4.33, 6.41)
	>5	431	141	1103	12.79 (10.84, 15.08)
qHBsAg (log_{10} IU/mL)	<3	466	60	1825	3.29 (2.55, 4.23)
	3 - 4	503	117	1812	6.46 (5.39, 7.74)
	>4	385	84	1173	7.16 (5.78, 8.87)
HBV Genotype	A	219	29	776	3.74 (2.60, 5.38)
	B	523	110	1839	5.98 (4.96, 7.21)
	C	434	108	1463	7.38 (6.11, 8.91)
	D	87	12	362	3.32 (1.88, 5.84)
	E	33	2	118	1.70 (0.43, 6.80)
	Mixed/Other	5	1	22	4.62 (0.65, 32.82)
APRI	≤0.5	943	154	3679	4.19 (3.57, 4.90)
	>0.5 - 2	244	61	651	9.37 (7.29, 12.05)
	>2	22	12	31	38.76 (22.01, 68.26)
FIB-4	<1.45	966	161	3611	4.46 (3.82, 5.20)
	1.45 - 3.25	222	59	711	8.30 (6.43, 10.71)
	>3.25	21	7	39	18.17 (8.66, 38.10)
Platelets ($x10^3/mm^3$)	<150	105	32	245	13.07 (9.25, 18.49)
	≥150	1114	197	4154	4.74 (4.12, 5.45)

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
AST x ULN	≤1 x ULN	1103	196	4175	4.69 (4.08, 5.40)
	>1 - 2 x ULN	211	48	580	8.27 (6.23, 10.98)
	>2 x ULN	65	21	154	13.67 (8.91, 20.97)
ALT x ULN	≤1 x ULN	466	38	1881	2.02 (1.47, 2.78)
	>1 - 2 x ULN	622	133	2320	5.73 (4.84, 6.79)
	>2 x ULN	313	101	772	13.08 (10.76, 15.89)
Baseline Cirrhosis	No	1397	261	5002	5.22 (4.62, 5.89)
	Yes	21	13	25	51.67 (30.00, 88.99)

[a] *Confidence interval (CI) based on Wald*

PY = person-years; APRI = AST-platelet ratio index; FIB-4 = Fibrosis 4 marker; ULN = upper limit of normal
Only treatment lasting ≥24 weeks and initiated >24 weeks after enrollment were considered.

Supplementary Table 3: Incidence Rates of ALT Flare

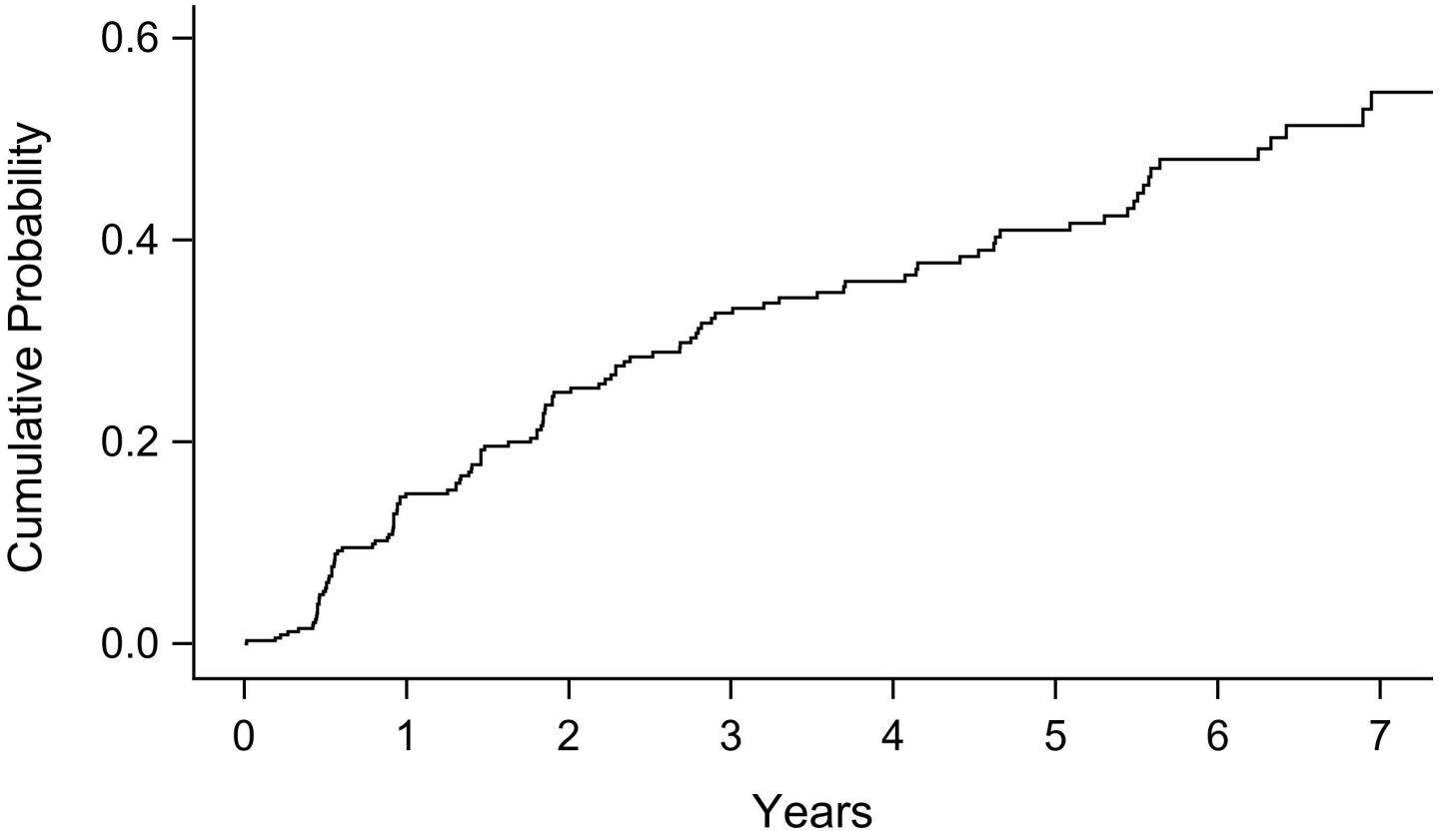
Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
Age (Years)	<30	248	25	837	2.99 (2.02, 4.42)
	30 - 50	759	46	2998	1.53 (1.15, 2.05)
	>50	398	12	1644	0.73 (0.41, 1.29)
Sex	Male	680	45	2563	1.76 (1.31, 2.35)
	Female	725	38	2916	1.30 (0.95, 1.79)
Race	White	142	8	615	1.30 (0.65, 2.60)
	Black	177	8	709	1.13 (0.56, 2.26)
	Asian	1045	64	4002	1.60 (1.25, 2.04)
	Other/Mixed	38	3	145	2.08 (0.67, 6.44)
HBeAg Status	Negative	1037	34	4371	0.78 (0.56, 1.09)
	Positive	329	48	958	5.01 (3.78, 6.65)
HBV DNA (log_{10} IU/mL)	<3	489	5	2202	0.23 (0.09, 0.55)
	3 - 5	486	18	2080	0.87 (0.55, 1.37)
	>5	429	60	1195	5.02 (3.90, 6.47)
qHBsAg (log_{10} IU/mL)	<3	460	11	1994	0.55 (0.31, 1.00)
	3 - 4	499	24	1976	1.21 (0.81, 1.81)
	>4	382	46	1270	3.62 (2.71, 4.83)
HBV Genotype	A	218	9	852	1.06 (0.55, 2.03)
	B	516	33	2008	1.64 (1.17, 2.31)
	C	431	34	1585	2.14 (1.53, 3.00)
	D	87	1	397	0.25 (0.04, 1.79)
	E	33	3	132	2.28 (0.73, 7.06)
	Mixed/Other	5	1	21	4.81 (0.68, 34.17)
APRI	≤0.5	935	35	4010	0.87 (0.63, 1.22)
	>0.5 - 2	243	33	692	4.77 (3.39, 6.71)
	>2	22	4	38	10.45 (3.92, 27.84)
FIB-4	<1.45	959	55	3906	1.41 (1.08, 1.83)
	1.45 - 3.25	220	16	788	2.03 (1.24, 3.31)
	>3.25	21	1	47	2.15 (0.30, 15.25)
Platelets ($x10^3/mm^3$)	<150	105	10	280	3.57 (1.92, 6.64)
	≥150	1105	63	4503	1.40 (1.09, 1.79)
AST x ULN	≤1 x ULN	1094	39	4575	0.85 (0.62, 1.17)
	>1 - 2 x ULN	210	25	615	4.06 (2.74, 6.01)

Baseline Characteristic		No. of Participants	No. with Outcome	Total PY	Incidence/100 PY (95% CI) [a]
	>2 x ULN	65	15	158	9.52 (5.74, 15.79)
ALT x ULN	≤1 x ULN	462	11	2045	0.54 (0.30, 0.97)
	>1 - 2 x ULN	617	29	2545	1.14 (0.79, 1.64)
	>2 x ULN	312	42	830	5.06 (3.74, 6.85)
Baseline Cirrhosis	No	1384	79	5451	1.45 (1.16, 1.81)
	Yes	21	4	28	14.42 (5.41, 38.41)

[a] *Confidence interval (CI) based on Wald*

PY = person-years; APRI = AST-platelet ratio index; FIB-4 = Fibrosis 4 markers; ULN = upper limit of normal
Only ALT flares after enrollment and prior to Initiating HBV treatment were considered among the 1405 with follow-up ALT

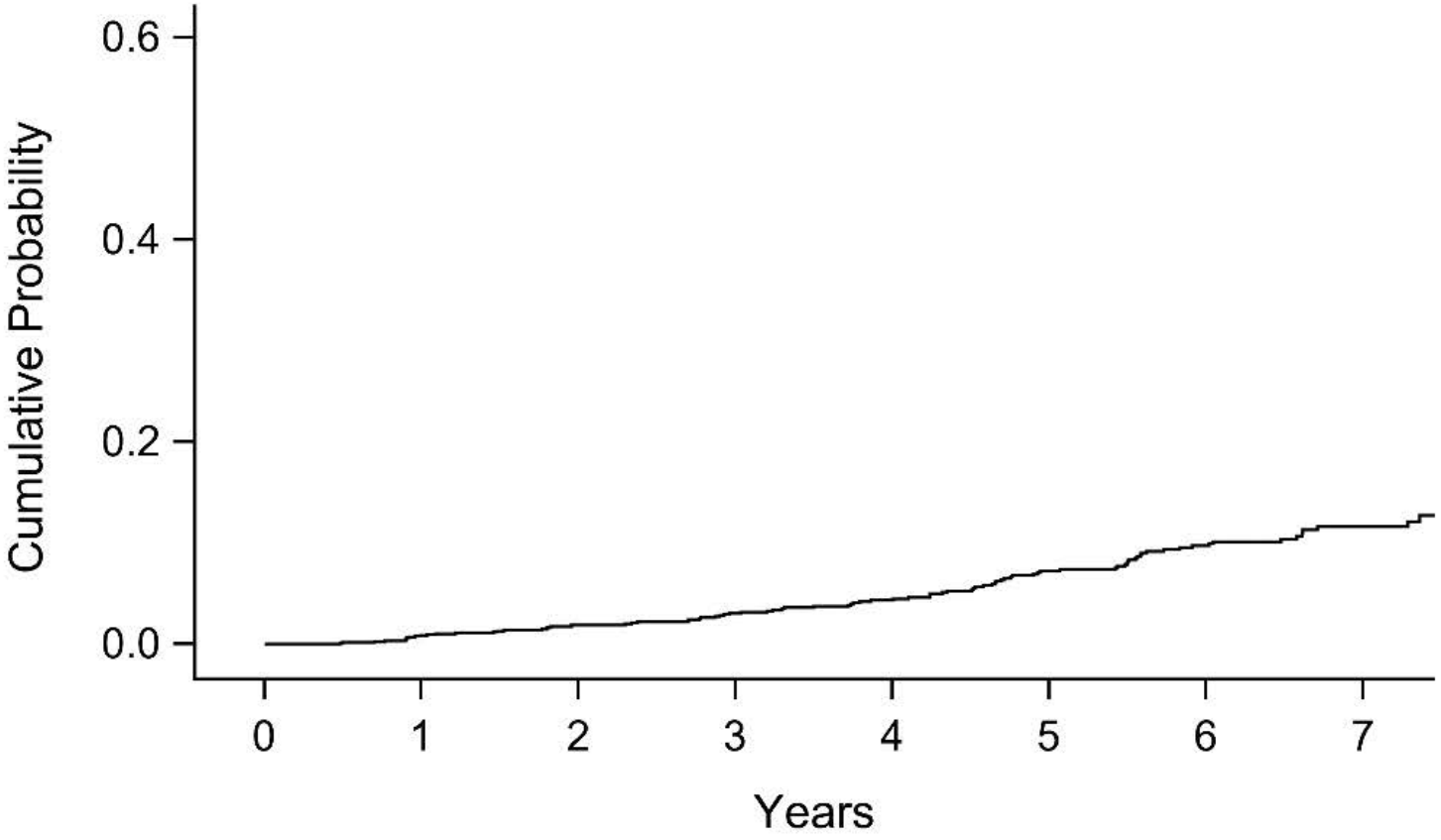
Supplementary Figure 1A: Cumulative Probability of Ever Becoming HBeAg− among Participants HBeAg+ at Baseline (118 events)



At Risk							
331	248	177	133	111	86	54	24

Cumulative Probability of HBeAg−						
0.15	0.25	0.33	0.36	0.41	0.48	0.55

Supplementary Figure 1B: Cumulative Probability of Ever Becoming HBsAg− (90 events)



At Risk							
1418	1193	1030	880	742	628	475	229
Cumulative Probability of HBsAg−							
	0.01	0.02	0.03	0.04	0.07	0.10	0.12