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Hepatitis B — The Pursuit of Functional Cures — Bepirovirsen Comes to the Forefront

Debjit Chattopadhyay, Ph.D.
debjit.chattopadhyay@guggenheimpartners.com
212 823 6584

Seamus Fernandez
seamus.fernandez@guggenheimpartners.com
617 859 4637

Robert Finke, Pharm.D.
robert.finke@guggenheimpartners.com
212 901 9343

Evan Wang
evan.wang@guggenheimpartners.com
212 651 9756

Zach Dunn, Ph.D.
zach.dunn@guggenheimpartners.com
617 859 4603

Ry Forseth, Ph.D.
ry.forseth@guggenheimpartners.com
212 518 9226

Key Message: Chronic Hepatitis B impacts ~300M individuals WW, and is broadly incurable leading to liver fibrosis, cirrhosis, and deaths in many. Next-gen therapies, led by bepirovirsen (GSK / IONS) has the potential to be practice changing, in a setting where SoC functional cure rates are ≤4%. In the attached Deep Dive, we highlight the potential of HBV suppression and immune-mediated medicines to achieve clinically meaningful cure rates, that could unlock multi-billion dollar annual sales. In conjunction, we conducted a prescriber survey—which indicate broad interest in bepirovirsen, and hosted an HBV expert call—with takeaways (Here).

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Addressing the Unmet Need in Chronic Hepatitis B — The Quest for a Functional Cure

Standard of care, particularly nucleos(t)ide analogues (NA), have made HBV a treatable and controllable disease. However, despite treatment advances, HBV infection remains broadly incurable, with approximately 300M (per CDC) people infected worldwide, and ~10% diagnosis rate WW. We estimate the U.S. chronic Hep B population at 1-2 million individuals and addressable market of ~250,000. Infected individuals face an elevated risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, with more than 800,000 deaths attributed to HBV-related complications annually. Treatment of HBV with nucleos(t)ide analogues (NAs) decrease HCC risk by effectively decreasing viral load and inflammation. Even so, HCC rates vary between 0.6% and 9.2% on NA therapy depending on ethnicity and underlying cirrhosis status. U.S. and EU guidelines view functional cure as achievable and defined as sustained HBsAg loss (based on assays with lower limit of detection [LLOD] ~0.05 IU/mL) in addition to undetectable HBV DNA 6 months post treatment. In the ongoing Ph 3 trials of bepirovirsen (GSK / IONS), HBsAg loss in ≥15% of patients is deemed clinically significant. This is highly congruent with the results of our Hepatitis B prescriber survey (below) which indicate a functional cure rate of >20% would support broad adoption.

Bepirovirsen's Poised to be a $2B+ product

Oral NA treatment results in a functional cure rate of 1-2%. Bepirovirsen Ph 2, stratified by baseline HBsAg titers ≤3,000 IU/mL, demonstrated functional cure rates of 16% to 25%, which represents the first program to provide meaningful functional cures in the absence of external immunomodulators. Research into bepirovirsen's mechanism of action suggests efficacy may be driven by a combination of ASO-based RNA interference and intrinsic immunomodulator activity. We note, in the SONIC-B database (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9159342/pdf/jiaa192.pdf), approximately 40% of HBeAg-negative patients had HBsAg titers ≤3,000 IU/mL, suggesting a large addressable population based on the HBsAg inclusion criteria. In the bepirovirsen Ph 3 B-Well clinical trials, recapitulation of the Ph 2b data including strength of signal, durability of response, and confirmation of the subgroup analysis will help identify patient cohorts who are more likely to respond to treatment and lead to commercial adoption of >26% in eligible patients, per our HBV prescriber survey. Additional clinical trials will help elucidate bepirovirsen's role in future treatment combinations including, combination with JNJ-3989 (siRNA).

Will siRNA + Newer Immunomodulator Combos or Additional Recent Breakthroughs Match Bepirovirsen efficacy?

Bepirovirsen has achieved durable functional cure without an added immunomodulator, relative to siRNAs which have sought combination with interferon or newer

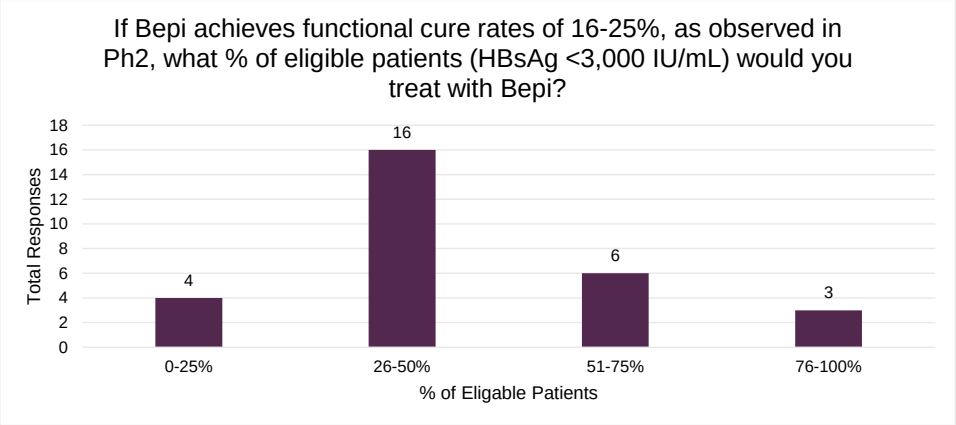
immunomodulators and is considered most likely 'backbone' of future combinations, per our survey. While data appears to show bepirovirsen has an innate advantage over siRNAs given its intrinsic immunomodulatory mechanism, data from VIR and ROG-SWX have highlighted combo data of siRNAs with immunomodulators like peg-IFN, TLR7 agonists, and HBV therapeutic vaccines that show higher rates of surface antigen loss and more sustained response vs. siRNA monotherapy. Newer siRNAs (**VIR**, **ROG-SWX**, **NOVO.B**, **ABUS**, **GSK**) and immunomodulators look to improve upon pegIFN including checkpoint inhibition, TLR agonists (**GILD**, **ROG-SWX**, **Primmune Therapeutics** [private]), and therapeutic vaccines (**BRII-B, VBIV**, **Viravaxx** [private], **BRNS**, **HOOK**). Additional classes of Hepatitis B targeted therapies such as monoclonal antibodies (**VIR**, **Bluejay Therapeutics** [private]), HBsAg inhibitors (**Replicor** [private]), and capsid inhibitors (**ENTA**, **ALGS**, **ASMB**) could be additive as part of a combo regimen. *For our EASL 2024 Hepatitis B & D coverage, please view EASL 2024 Field Report: Viral Hepatitis Updates Recap.*

Genome Editing for HBV — In Pursuit of the "Holy Grail"

The potential of a curative genome editing approach to HBV is the "holy grail" of Hepatitis B treatment. If the Hepatitis B virus can be fundamentally **epigenetic silenced** or ARCUS cleaved (**DTIL**) in a durable manner, genome editing could offer a one-and-done option for CHB. Extra hepatic reservoirs of the Hepatitis B virus do exist, particularly within bone marrow and other lymphatic tissues. However, this does not appear to be a concern for LNP-based liver directed treatment, as these extra hepatic reservoirs are viewed as non-replicative and of uncertain significance in regard to target effect.

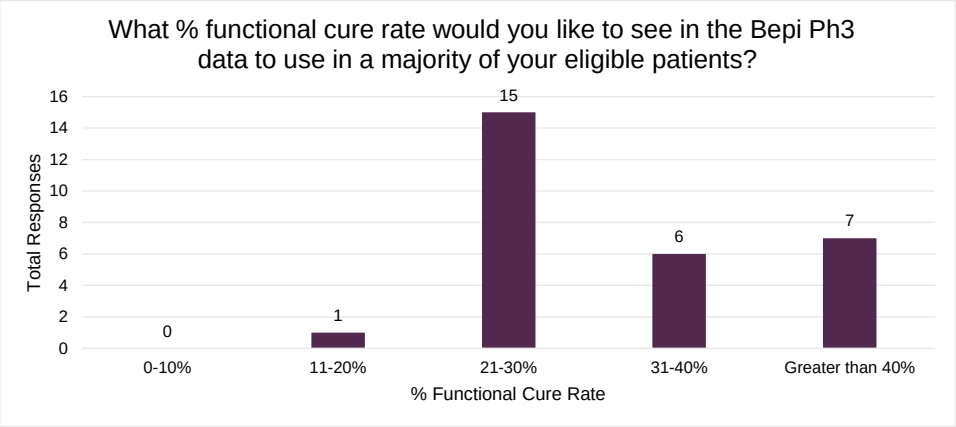
Hepatitis B Prescriber Survey

Figure 1 - 86% of physicians indicate at least 26% treatment rate should Bepi recapitulate Ph2 data



Source: Guggenheim Securities, LLC

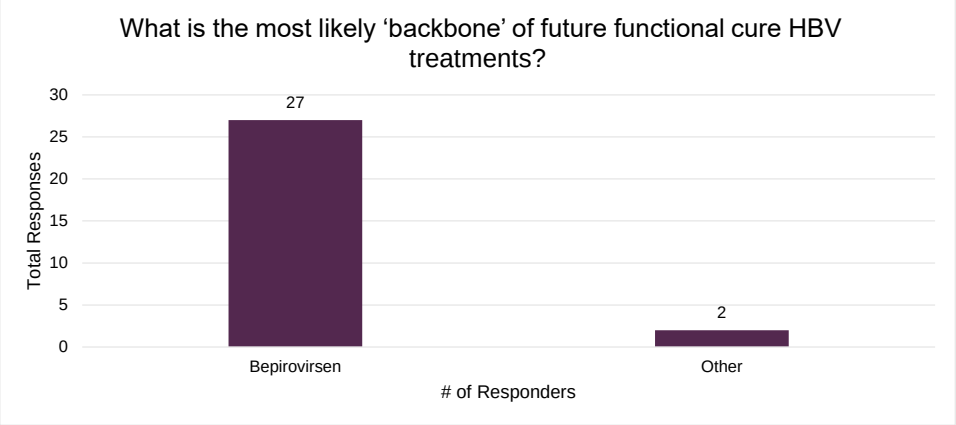
Figure 2 - A functional cure rate of 21%+ appears preferred to polled physicians



Source: Guggenheim Securities, LLC

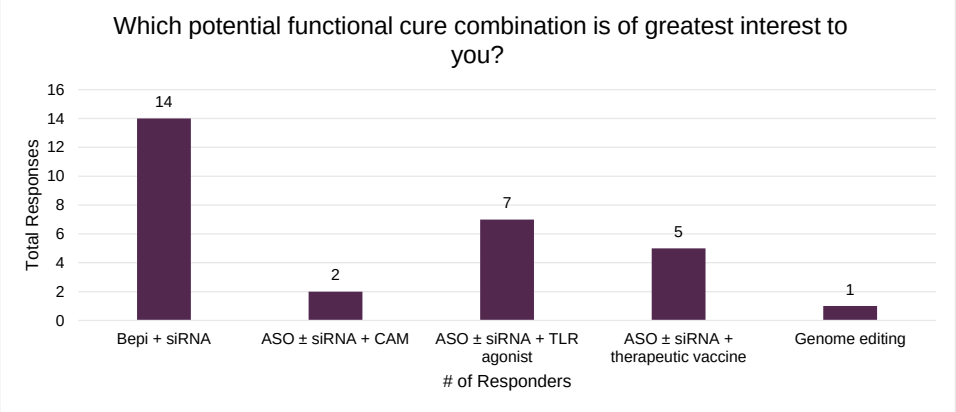
Figure 3 - Bepirovirsen is the most likely future backbone

Other responses include gene editing approaches (N=1) and therapeutic vaccine (N=1)



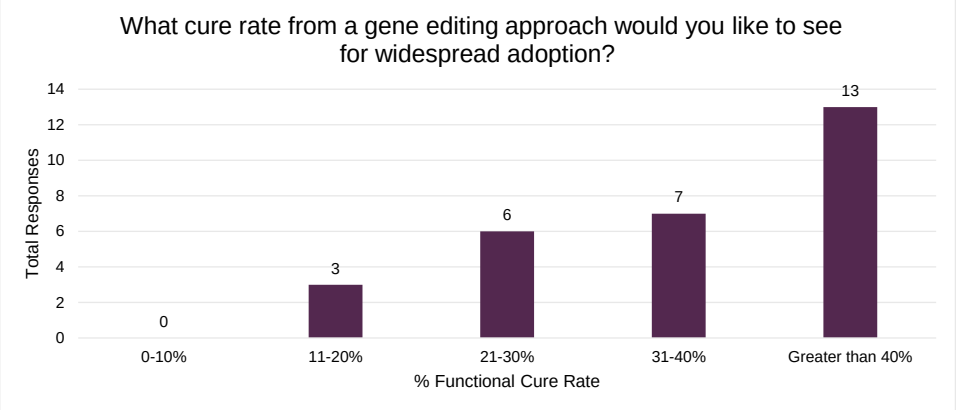
Source: Guggenheim Securities, LLC

Figure 4 - Bepi + siRNA is the combination of greatest interest to prescribers



Source: Guggenheim Securities, LLC

Figure 5 - Physicians would like to see a 21%+ functional cure rate for future gene editing approaches



Source: Guggenheim Securities, LLC

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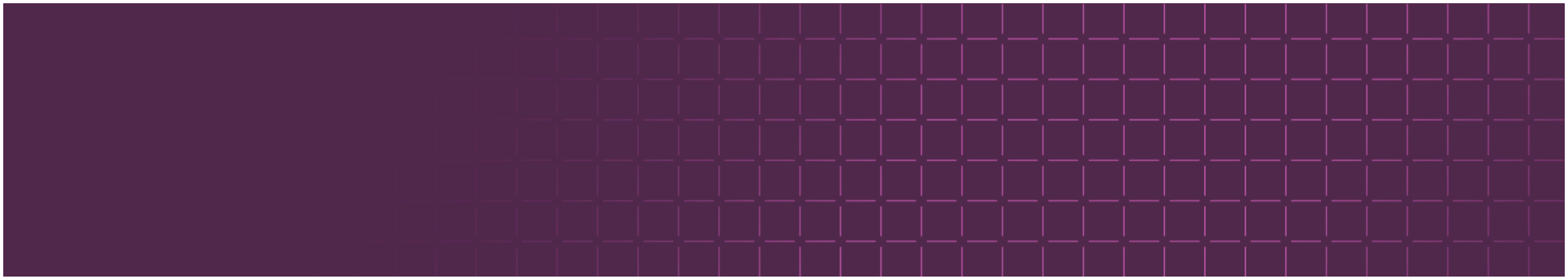

Hepatitis B

The Pursuit of Functional Cures with Bepirovirsen and Targeted Combinations

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Debjit Chattopadhyay
Analyst
929-788-0332
Debjit.Chattopadhyay@guggenheimpartners.com

Seamus Fernandez
Analyst
617-859-4637
Seamus.Fernandez@guggenheimpartners.com

Robert Finke
Vice President
929-788-0393
Robert.Finke@guggenheimpartners.com

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Executive Summary

Key Takeaways: The Pursuit of Functional Cures in a Large, Unmet, Market

Bepirovirsen highlights the potential of HBV suppression and immune-mediated medicines in Hepatitis B, validating the achievement of functional cures above standard-of-care rates

- Phase 2b data from bepirovirsen demonstrate functional cures in 16-25% of patients with low baseline Hepatitis B surface antigen (HBsAg)
- Current standard of care suppresses HBsAg but only induces functional cures in 1-4% of patients

Hepatitis B has become an area of high strategic interest, as global Biopharma increases investment and SMID-cap Biotech companies explore cutting edge modalities

- GSK / IONS view bepirovirsen as a "backbone" to its Hepatitis B efforts, with estimated peak sales of > $2B annually
- Multiple classes of medicines with recent breakthroughs have provided encouraging results, including: (1) RNAi-based therapy with either ASO or siRNA; (2) S antigen lowering monoclonal antibodies, capsid assembly modulators; and (3) immunomodulators, including therapeutic vaccines, PD-1/PD-L1 inhibitors, TLRs agonists, and novel interferons; while (4) preclinical DNA and epigenetic editing approaches may offer one-time curative approaches

Addressing the Unmet Need in Chronic Hepatitis B

- Standard of care, particularly nucleos(t)ide analogues (NA), have made HBV a treatable and controllable disease. However, despite treatment advances, HBV infection remains broadly incurable, with approximately 300M (per CDC) people infected worldwide. It is estimated ~35% of infections are diagnosed in the US, ~25% in Europe, and ~50% in Japan
- Infected individuals face an elevated risk of liver fibrosis, cirrhosis, and hepatocellular carcinoma, with more than 800,000 deaths attributed to HBV-related complications annually

Key Takeaways: Hep B Prescriber Survey Results and EASL 2024 Highlights

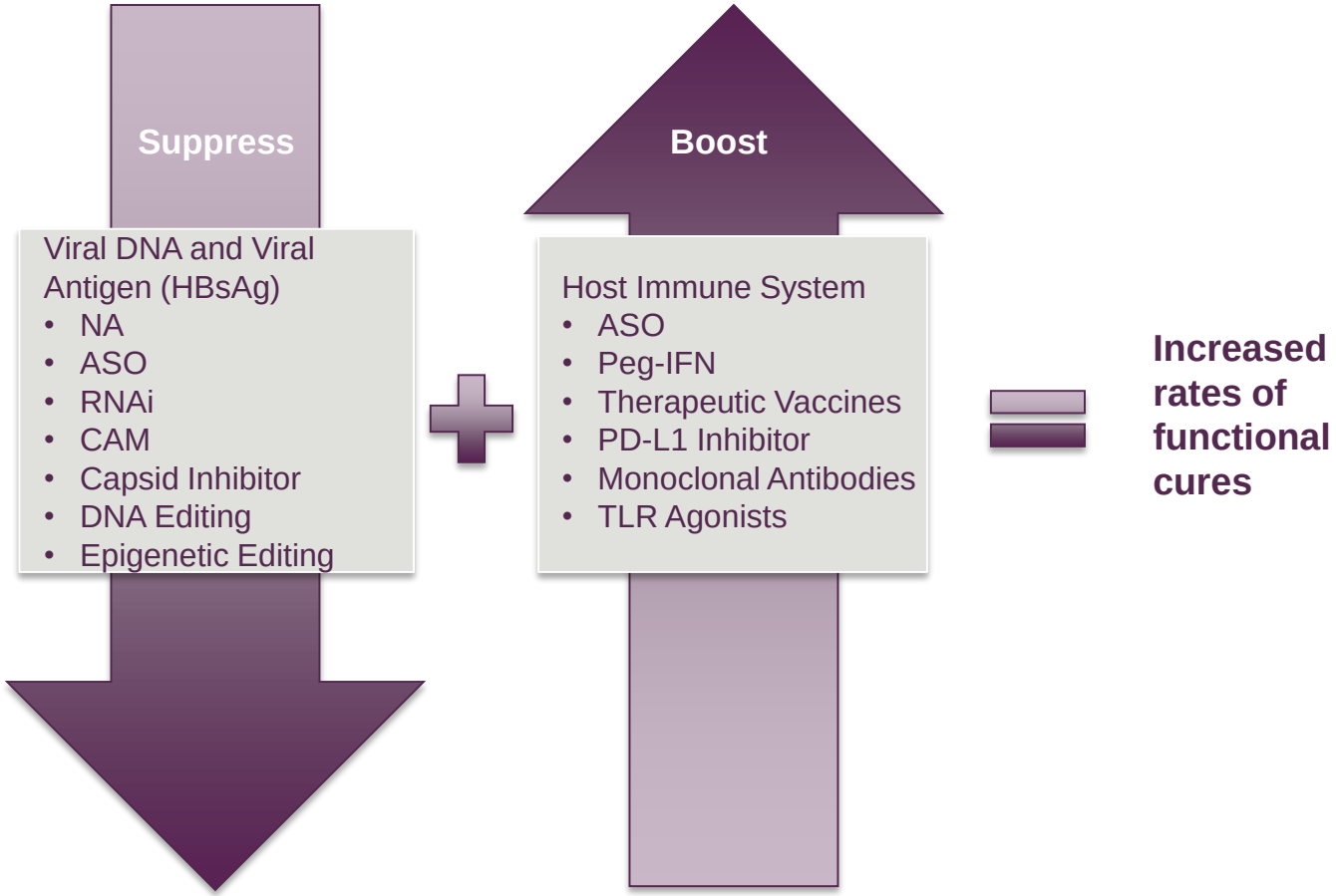
We conducted a propriety survey of Hepatitis B prescribers to gauge interest in bepirovirsen

- Across 29 prescribers, who on average treat 86 HBV patients, 93% of prescribers view bepirovirsen as the most likely future 'backbone' of functional cure HBV treatments
- Should the bepirovirsen Ph3 program recapitulate Ph2 (functional cure rates of 16-25%), 86% of prescribers would treat at least 26-50% of their eligible HBV patients
- Most prescribers (97%) would like to see a functional cure rate of >20% to use bepirovirsen in a majority of their eligible patients

EASL 2024 Takeaways – ASO / siRNA combinations with immunotherapies lead the development landscape

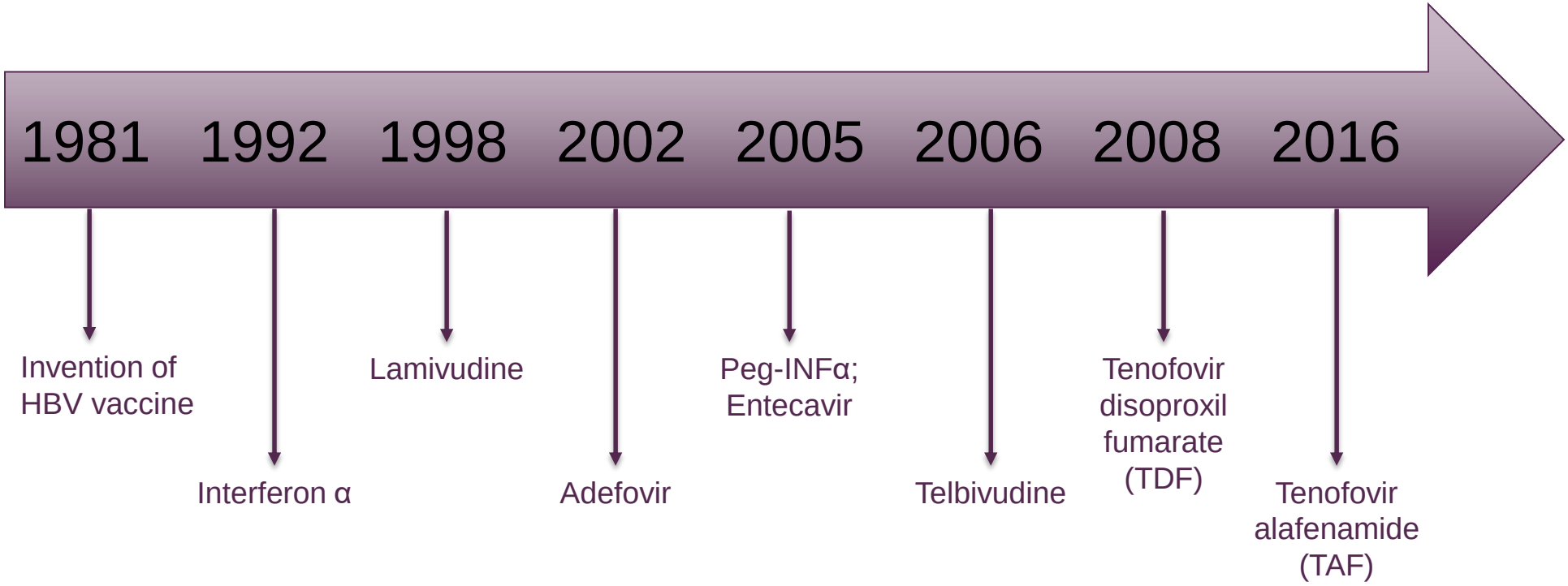
- Effects of combining siRNA with PD-1 appear minimal during on-treatment periods, per the JNJ-3989 / nivolumab OCTOPUS-1 trial. On safety, overall the nivolumab dose was low, though there were 2 cases of reversible TSH elevation that led to withdrawal of PD-1 administration
- Effects of combining JNJ-3989 (siRNA) with a DNA vaccine, JNJ-0535, demonstrated NA treatment stopping in 7 (30%) of patients, and enhanced CD4 and/or CD8 polypositive HBV-specific T-cells in 33% of patients. However, no patients achieved HBsAg seroclearance
- HBV targeted siRNA xalnesiran (ROG-SWX), PIRANGA Ph2 Trial - siRNA + immunomodulator (pegIFN or TLR7) - show best responses with + pegIFN combo through 48 weeks post end of treatment. Across all arms, HBsAg loss and seroconversion were observed only in participants with HBsAg < 1000 IU/mL. HBsAg seroconversion at its 48-week follow-up was 17% (vs. 20% at 24-weeks)

Functional Cure Success Will Likely Involve HBV Suppression and Immune System Activation



Source: Guggenheim Securities LLC and ABUS corporate report

Development and Approval of HBV Therapies in the US



Potential Future HBV Therapies and Estimated Approvals

- Bepirovirsen – 2027
- Bepirovirsen + JNJ-3989 – Late 2020s
- ASO ± siRNA + immunomodulator – Early 2030s
- ARCUS Editing – Early 2030s
- Epigenetic Editing – 2030s

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8707465/pdf/microorganisms-09-02607.pdf

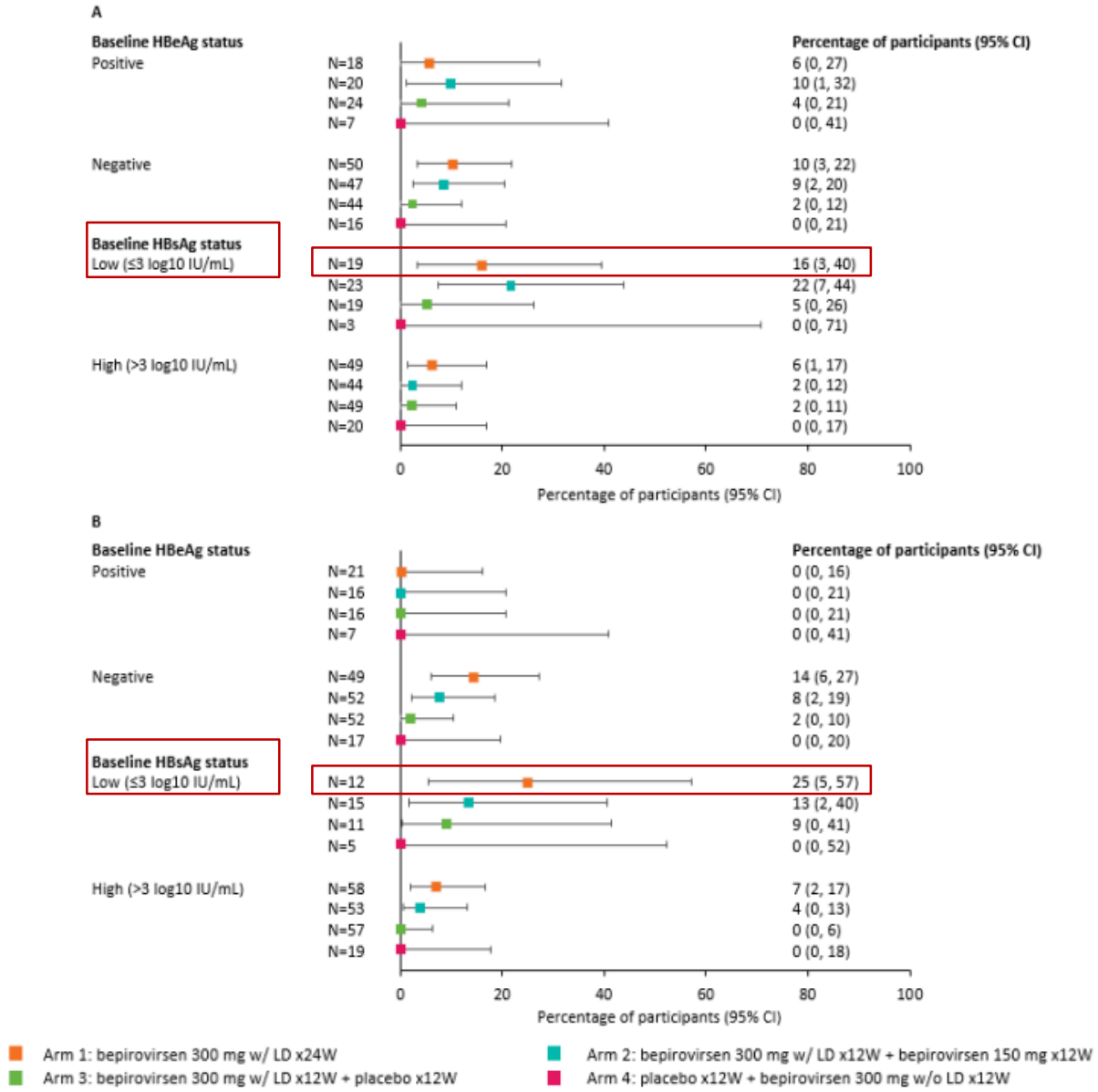
Functional Cure Clinical Data - Bepirovirsen Data Review

Bepirovirsen Induced Functional Cures in 16-25% of Patients with Low Baseline HBsAg

Proportion of Participants (A) On-NA and (B) Not-on-NA Achieving Primary Outcome in bepirovirsen Ph2b B-Clear Trial

In the Ph2 B-Clear Study, the composite primary outcome was a Hepatitis B surface antigen (HBsAg) level below the limit of detection and an HBV DNA level below the limit of quantification maintained for 24 weeks after the planned end of bepirovirsen treatment, without newly initiated antiviral medication.

In the group receiving bepirovirsen 300mg for 24 weeks, a total of 16% of the participants receiving NA therapy and 25% of participants not receiving NA therapy with a low HBsAg level (≤3,000 IU/mL) at baseline had a primary-outcome event, as compared with 6% and 7% of participants, respectively, with a high HBsAg level (>3,000 IU/mL) at baseline.



Source: https://pubmed.ncbi.nlm.nih.gov/36346079/

Bepirovirsen; Genotype A and D May Be More Responsive

Results of the bepirovirsen Ph 2b B-Together Study

	Overall N=108						
Genotype	A	B	C	D	E	H[a]	Undetermined
N	9 (8%)	3 (3%)	26 (24%)	10 (9%)	5 (5%)	1 (<1%)	54 (50%)
Mean HBsAg (log IU/mL) at baseline	3.55	3.49	3.29	3.36	3.31		3.28
Mean reduction HBsAg (log IU/mL) at EOT	−2.90	−1.74	−1.51	−2.11	−1.42		−1.56
Mean reduction HBsAg (log IU/mL) at OT-W24	−1.90	−1.06	−0.92	−1.90	−0.95		−1.54
Number (%) of participants achieving PE[b]	2/9 (22%)	0/3	1/26 (4%)	2/10 (20%)	1/5 (20%)	0/1	7/54 (13%)

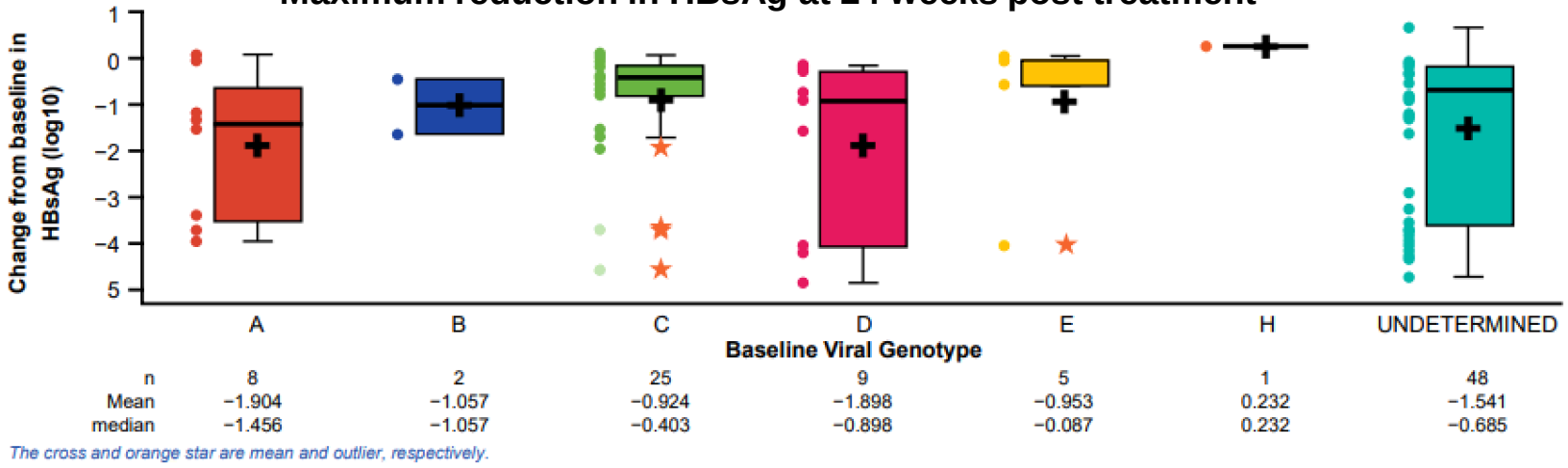
[a]Mean HBsAg data not included for GT with N ≤1 (i.e., Arm 2 GT-B, GT-H); [b]Denominator indicates number of participants with data available at OT-W24.

Participants with genotype C had the lowest baseline mean HBsAg level (3.29 log10 IU/mL) and genotype A had the highest (3.55 log10 IU/mL).

Participants with genotype A and genotype D had the greatest mean reduction in HBsAg at OT-W24 (-1.90 log10 IU/mL) and genotype C had the least (-0.92 log10 IU/mL) following bepirovirsen and peg-IFN.

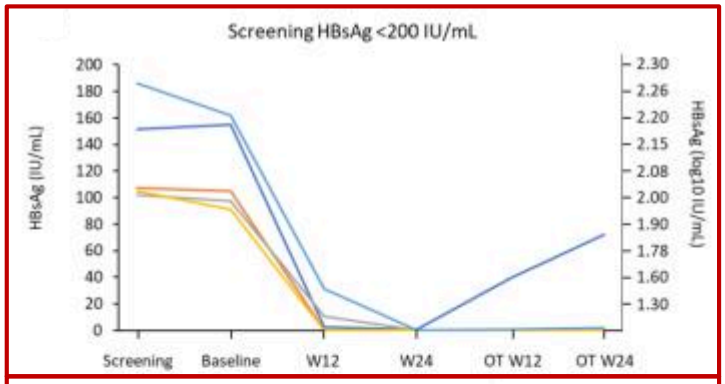
Baseline genotype data was insufficient to perform a robust statistical analysis of response by genotype.

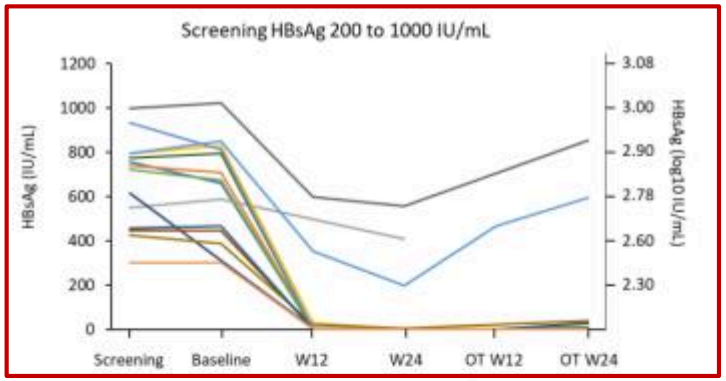
Maximum reduction in HBsAg at 24 weeks post treatment

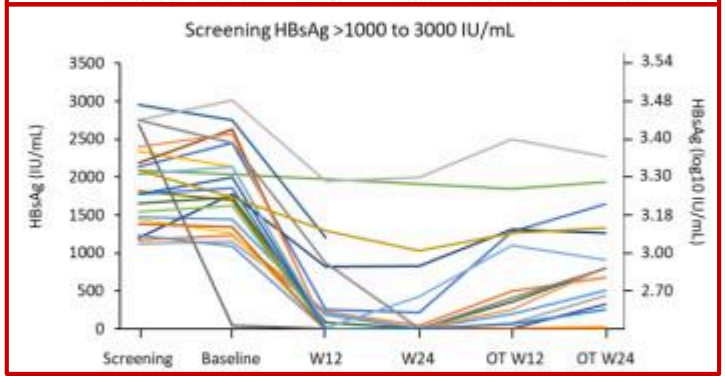


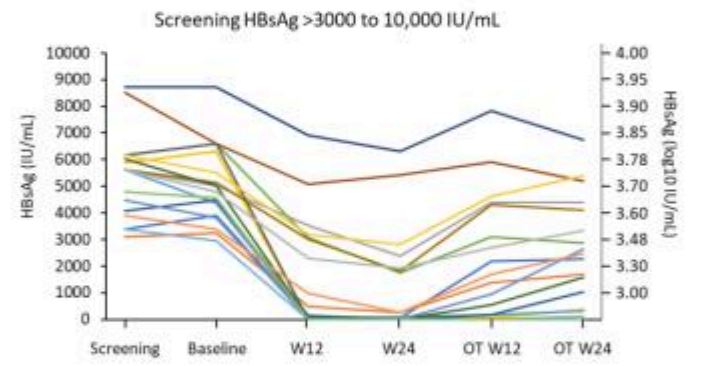
Source: GSK / IONS 2023 AASLD Poster

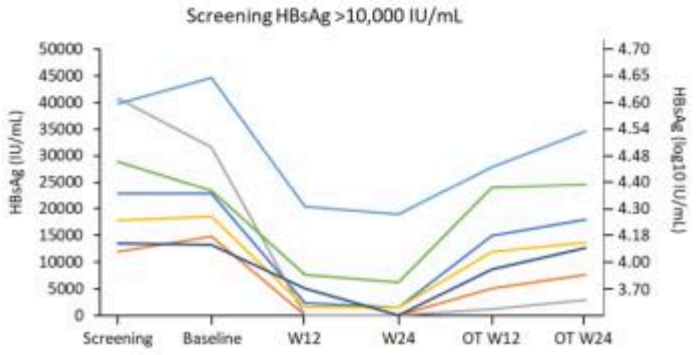
Individual Participant Time-Course HBsAg Levels in the On-NA Population Reveal Correlation between Baseline HBsAg Levels and Bepi Response







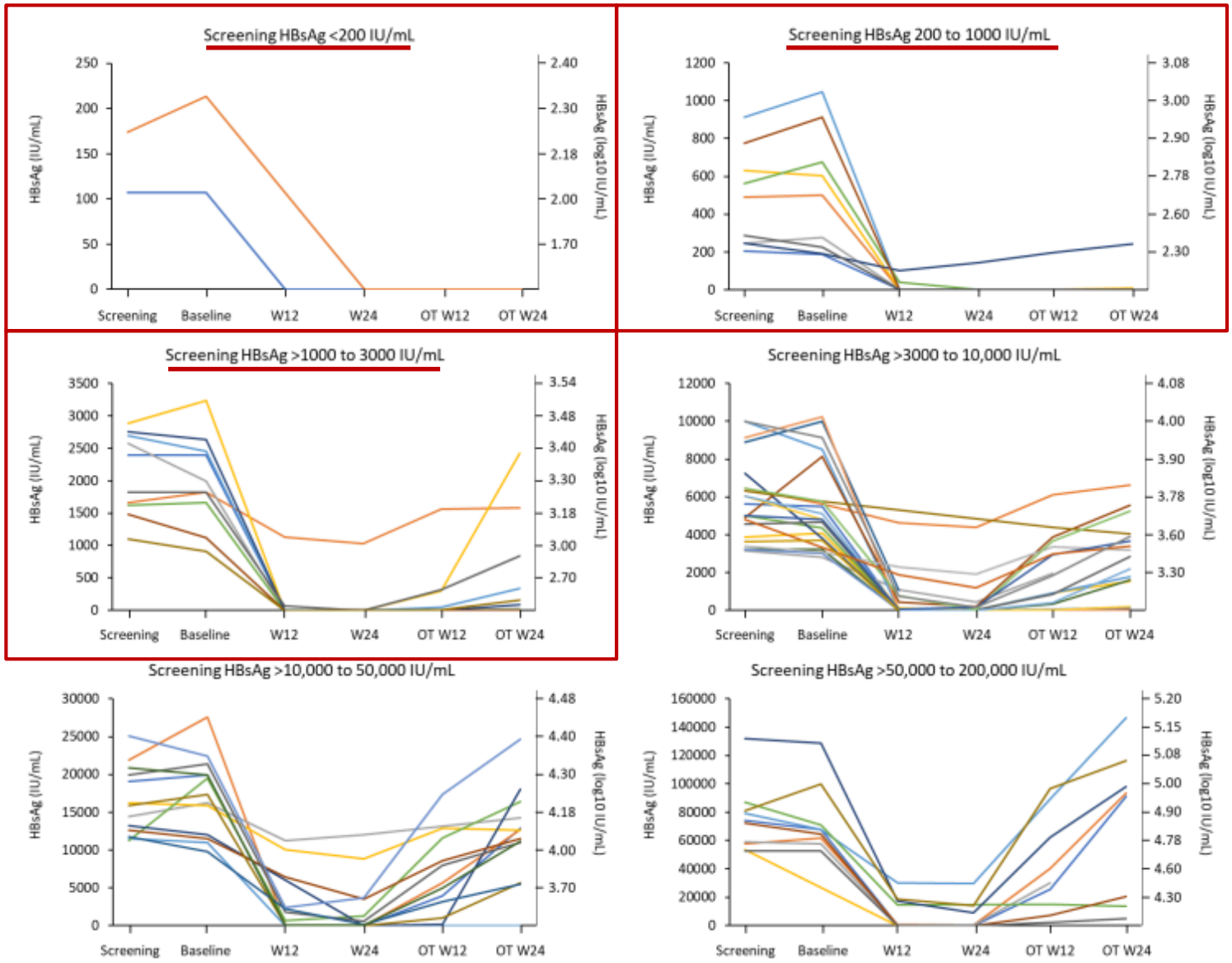




Individuals with HBsAg < 3,000 IU/mL respond better to bepirovirsen treatment compared to individuals with HBsAg > 3,000 IU/mL.

Source: https://pubmed.ncbi.nlm.nih.gov/36346079/

Individual Participant Time-Course HBsAg Levels in the Not-on-NA Population Similarly Correlated Between Baseline HBsAg Levels and Bepi Response



Source: https://pubmed.ncbi.nlm.nih.gov/36346079/

Bepirovirsen; Hepatobiliary Laboratory Findings

Laboratory criteria	On-NA population (n=226)	Not-on-NA population (n=230)
N	225	227
ALT ≥3x ULN and BIL ≥2x ULN	0	2 (<1)
ALT ≥3x ULN and INR ≥1.5	0	0
ALT ≥3x ULN	39 (17)	93 (41)

Note: The upper limit of the normal range (ULN) for alanine aminotransferase (ALT) is 40 IU per liter for men and 33 IU per liter for women.

Of the 226 participants, 39 (17%) receiving NA therapy and 93 (41%) not receiving NA therapy had a transient increase in the ALT ≥3 times the ULN. At baseline, most participants (91% of those receiving NA therapy and 70% of those not receiving NA therapy) had an ALT level at or below the ULN.

Source: https://pubmed.ncbi.nlm.nih.gov/36346079/

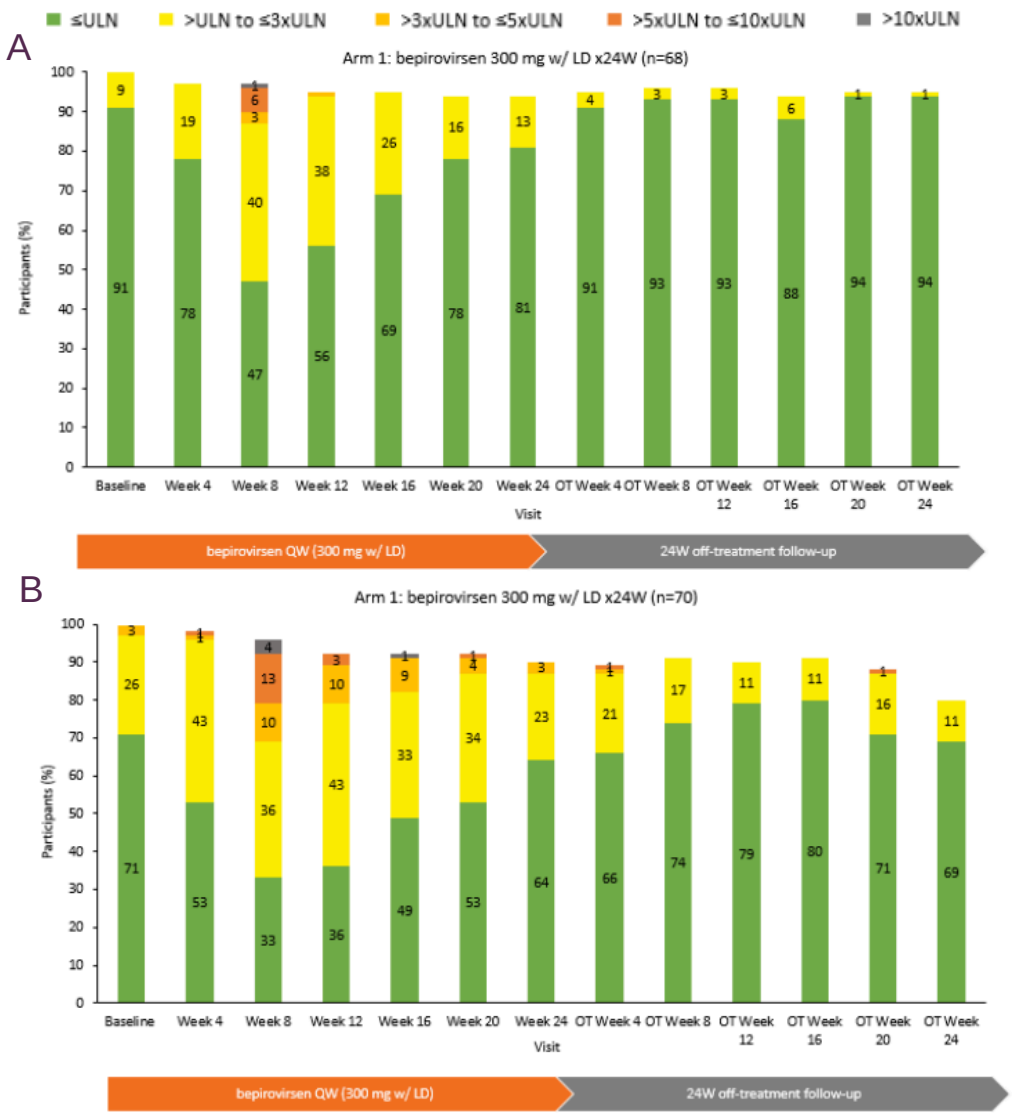
Proportion of Participants Within ALT Categories Over Time—Per our KOL LFT <5x ULN Not a Concern in Non-Fibrotic HBV Patients

In the bepirovirsen Ph IIb trial, B-Clear, the research team analyzed ALT elevations over treatment course (≤ULN, >ULN to ≤3xULN, >3xULN to ≤5xULN, >5xULN to ≤10xULN, >10xULN).

Participants exhibit peak ALT elevations around 8-weeks post treatment initiation.

On-NA patients (A) have less ALT elevations with shorter duration, compared to non-on-NA population (B).

Only 6% of patients had ALT >5xULN in on-NA patients and 13% >5xULN in not-on-NA patients, with return below 5xULN within one week.



Source: https://pubmed.ncbi.nlm.nih.gov/36346079/

HBsAg Loss is ~85% Durable in Extended Follow Up in Systematic Review of Available HBV Treatments

Durability of HBsAg loss in observational studies

Type of therapy	No. of studies	Pre-defined timepoints					
		Week 24	Week 48	Week 96	Week 144	Week 192	Week 240
NA (any)	4	88% *(n=1)*	88, 96%*, and 98% *(n=3)*	88, 93%*, and 96% *(n=3)*	88, 93%*, and 95% *(n=3)*	78% *(n=1)*	78% *(n=1)*
IFN (any)	1	–	69% *(n=1)*	87% *(n=1)*	64% *(n=1)*	–	–
Peg-IFN ± NA	1	80% *(n=1)*	80% *(n=1)*	77% *(n=1)*	–	–	–
NA/Peg-IFN ± NA	1	87% *(n=1)*	85% *(n=1)*	82% *(n=1)*	81% *(n=1)*	72% *(n=1)*	72% *(n=1)*
Untreated	1	–	98% *(n=1)*	96% *(n=1)*	95% *(n=1)*	–	–

*Median values.

A systematic review of studies in people with chronic HBV infection was conducted to assess durability of HBsAg loss. In the clinical trials (n=9), durability of HBsAg loss remained >85% for most studies.

Source: https://gskusmedicalaffairs.com/docviewer.html?cmd=GSKMedicalInformation&medcommid=REF--ALL-005370&token=23108-c6bf0fe6-20cb-437b-881b-3fafce531fe7&dns=gsk-medcomms.veevavault.com

Bepirovirsen Ph3 Design – Enrollment Completed June 2024

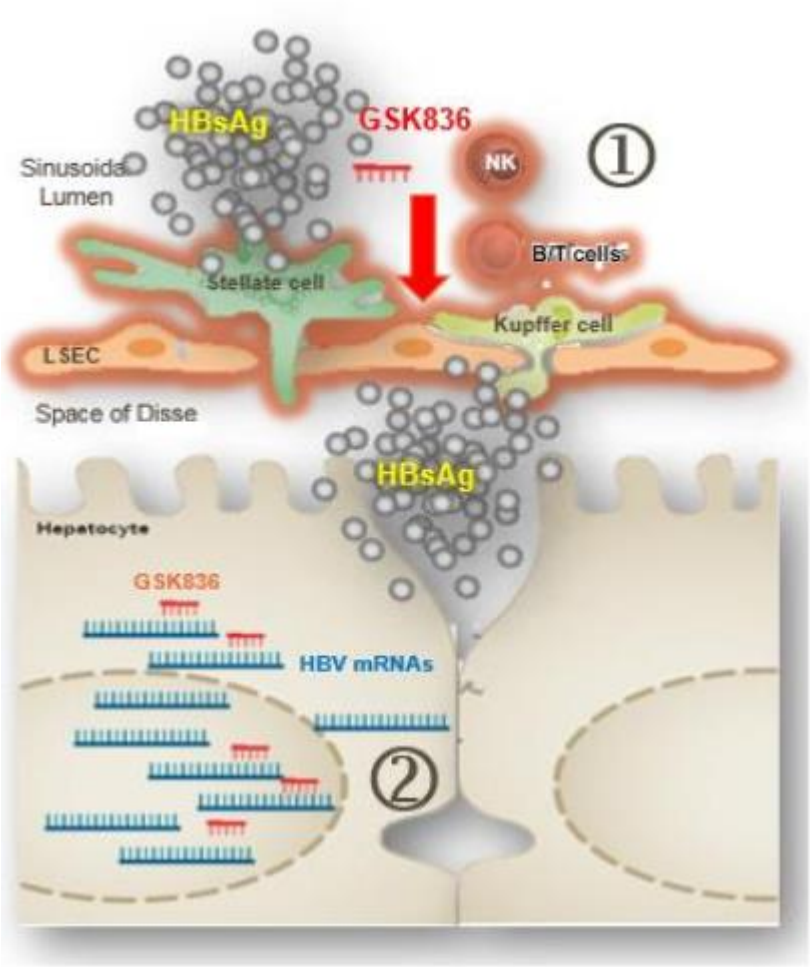
	B-WELL 1 - NCT05630807	B-WELL 2 - NCT05630820
Phase	III	III
Patient	Non-cirrhotic nucleos(t)ide analogue treated patients with CHB	Non-cirrhotic nucleos(t)ide analogue treated patients with CHB
Subjects	941	859
Treatment arms	Arm A: bepirovirsen for 24 weeks Arm B: placebo	Arm A: bepirovirsen for 24 weeks Arm B: placebo
Description	Ph3 multicenter, randomized, double blind, placebo controlled	Ph3 multicenter, randomized, double blind, placebo controlled
Timeline	Trial start: Q1 2023 Data anticipated: 2026	Trial start: Q1 2023 Data anticipated: 2026
Key endpoints	# of participants achieving functional cure with baseline HBsAg ≤ 3000 IU/mL	# of participants achieving functional cure with baseline HBsAg ≤ 3000 IU/mL

- Participants who have documented chronic HBV infection ≥6 months prior to screening and currently receiving stable NA therapy defined as no changes to their NA regimen from at least 6 months prior to screening and with no planned changes to the stable regimen over the duration of the study
- The arms will be stratified based on HBsAg level (HBsAg ≥ 0 IU/mL to ≤1000 IU/mL or > 1000 IU/mL to ≤3000 IU/mL) at screening
- Plasma or serum HBV DNA concentration must be adequately suppressed, defined as plasma or serum HBV DNA <90 IU/mL
- Baseline alanine aminotransferase (ALT) ≤2 × upper limit of normal (ULN)

Source: https://clinicaltrials.gov/study/NCT05630807; https://clinicaltrials.gov/study/NCT05630820

Bepirovirsen Mechanisms of Action

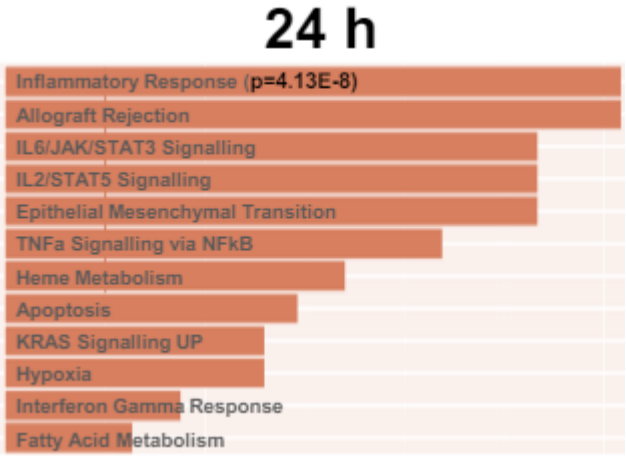
(1) Bepirovirsen (GSK836) may be preferentially distributed to non-parenchymal cells, conferring immune activation of pattern recognition receptors activation (TLR7 and TLR8).

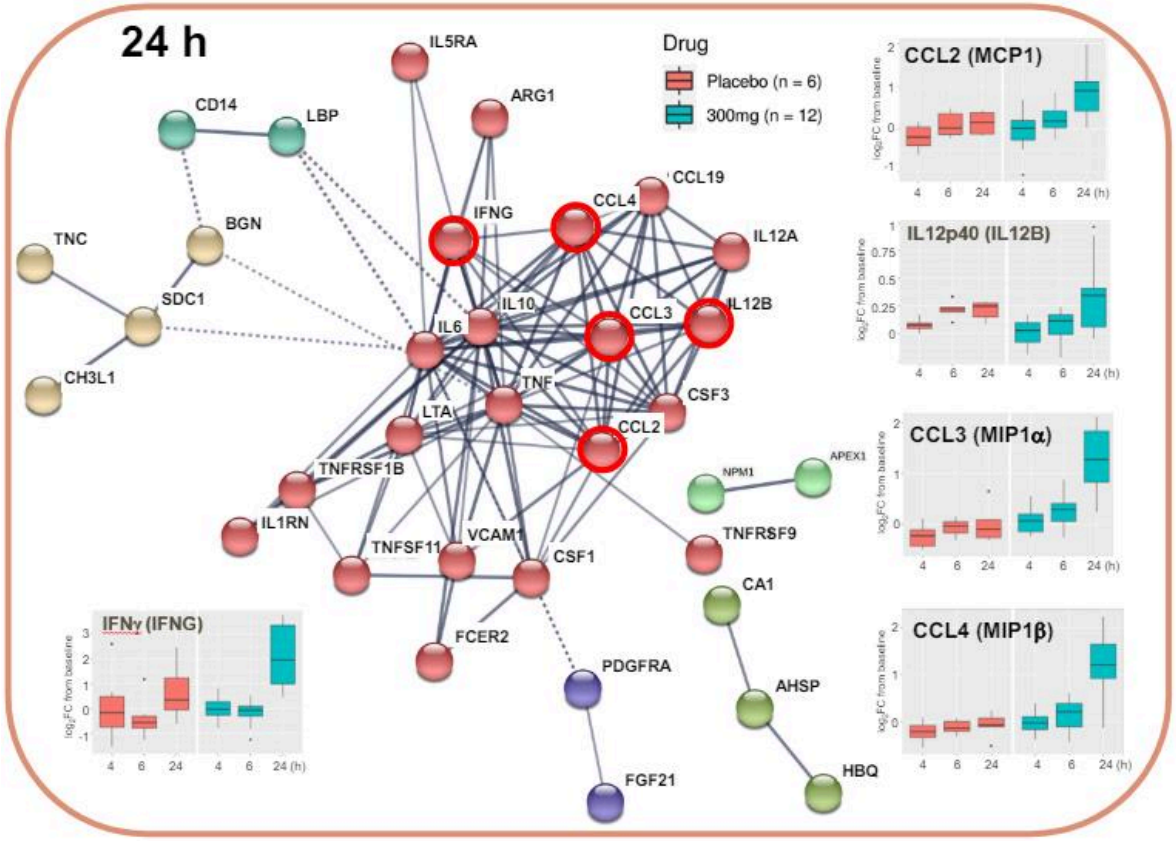


(2) Bepirovirsen provides inhibition of HBV mRNA via standard ASO mechanisms in hepatocytes.

Source: https://www.postersessiononline.eu/173580348_eu/congresos/ILC2022/aula/-SAT_439_ILC2022.pdf

Bepirovirsen Induces Immune Response Within 24 hrs Post-Treatment

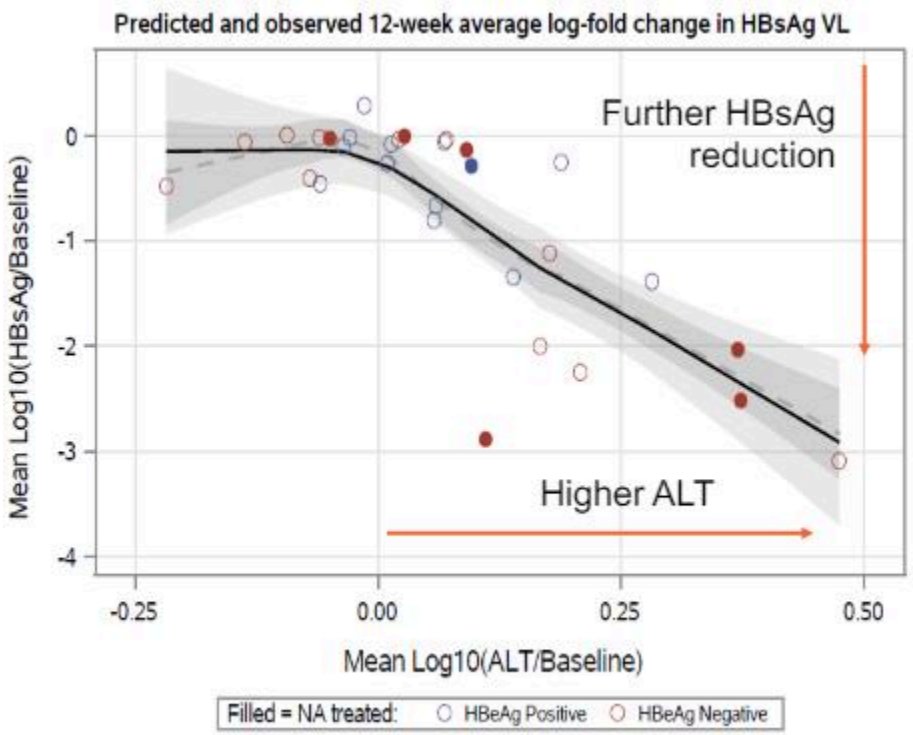


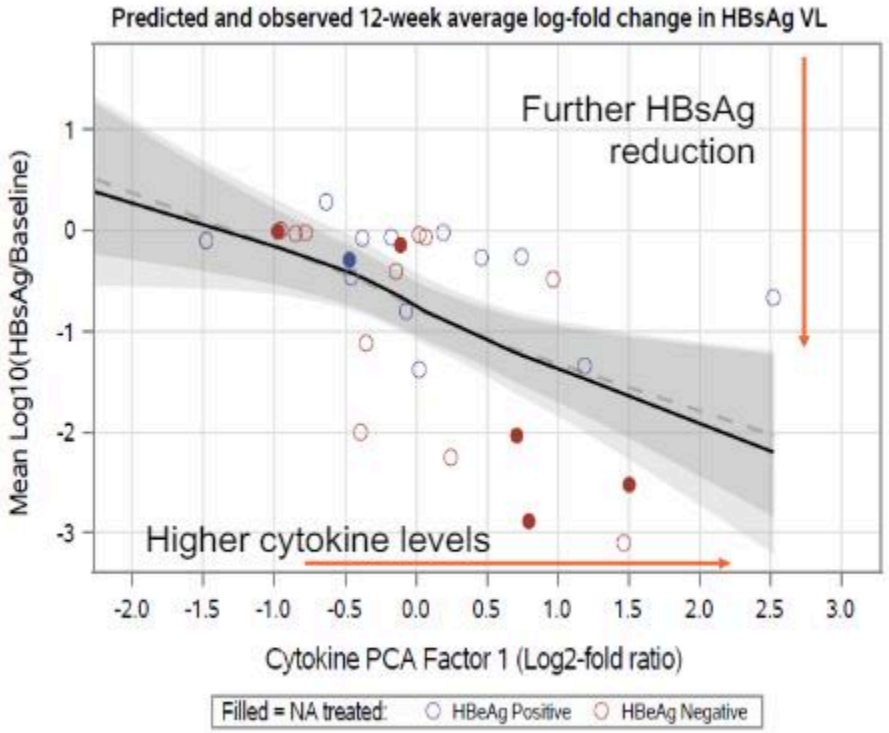


Serum markers upregulated at 24 hours suggest inflammatory response to bepirovirsen with activation of innate and adaptive immune cells. These include: inflammatory cytokines (IFN-g, TNF); recruitment of monocyte/macrophage, NK, and T cells (CCL2, CCL3, CCL4, CCL19); activation of macrophages and neutrophils (CSF1, CSF3) and T cells (IL-12B, CCL19); and lymphocyte activation (TNFSRF9 (T cell), FCER2 (B cell), TNFSF11).

Source: https://www.postersessiononline.eu/173580348_eu/congresos/ILC2022/aula/-SAT_439_ILC2022.pdf

HBsAg Reduction Correlated with ALT Flare and TLR8 Cytokines Activation





ALT flares are highly correlated with HBsAg response (left) and HBsAg reduction trends with greater induction of TLR8 cytokines (right).

Note: TLR8 cytokines measured include: CCL11, CCL2 (MCP-1), CCL20, CCL3, CCL4, CCL5, CCL8 (MCP-2), CSF3, CXCL10, CXCL8, CXCL9, IFN, IL10, IL12p40 (IL12B), IL18, IL1A, IL1B, IL1RN, IL6, and TNF.

Source: https://www.postersessiononline.eu/173580348_eu/congresos/ILC2022/aula/-SAT_439_ILC2022.pdf

GSK obtains exclusive license for the siRNA JNJ-3989 to expand the development of bepirovirsen
- Review of JNJ-3989 Data and License Rationale

JNJ-3989 Ph 2b REEF-1—Virological Suppression Occurs Following siRNA Treatment

The efficacy and safety of the siRNA JNJ-3989 with NA treatment with-or-without the capsid assembly modulator (CAM) JNJ-6379 for the treatment of chronic hepatitis B across 470 patients in the Ph 2b trial REEF-1.

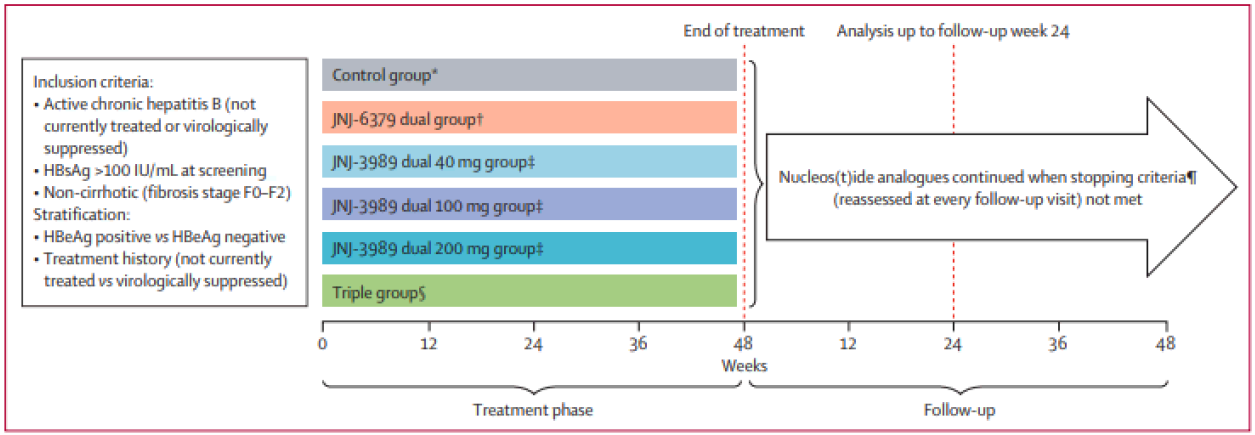
Median baseline HBsAg values were between 3.6 log10 IU/mL and 3.9 log10 IU/mL across treatment groups.

63% of patients were virologically suppressed and 70% were HBeAg negative at baseline.

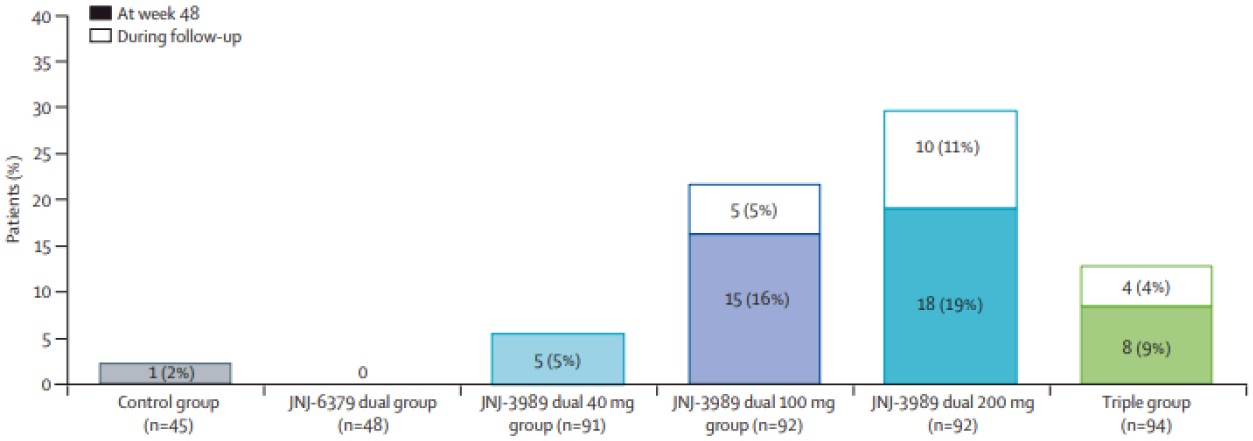
At week 48, the following met the primary endpoint of NA-stopping criteria (ALT <3xULN, HBV DNA < LLOQ, HBeAg negative, HBsAg <10 IU/mL). 5% in the JNJ-3989 dual 40 mg group, 16% in the JNJ-3989 dual 100 mg group, 19% in the JNJ-3989 dual 200 mg group, 9% in the triple group, and 2% in the control group; no patients in the JNJ-6379 (CAM) dual group met stopping criteria.

At the follow-up week 24 analysis, 19 (4%) of 464 additional patients had met NA stopping criteria.

REEF-1 Trial Design



Percentage of patients meeting NA-stopping criteria at week 48 and during the 24-week follow-up



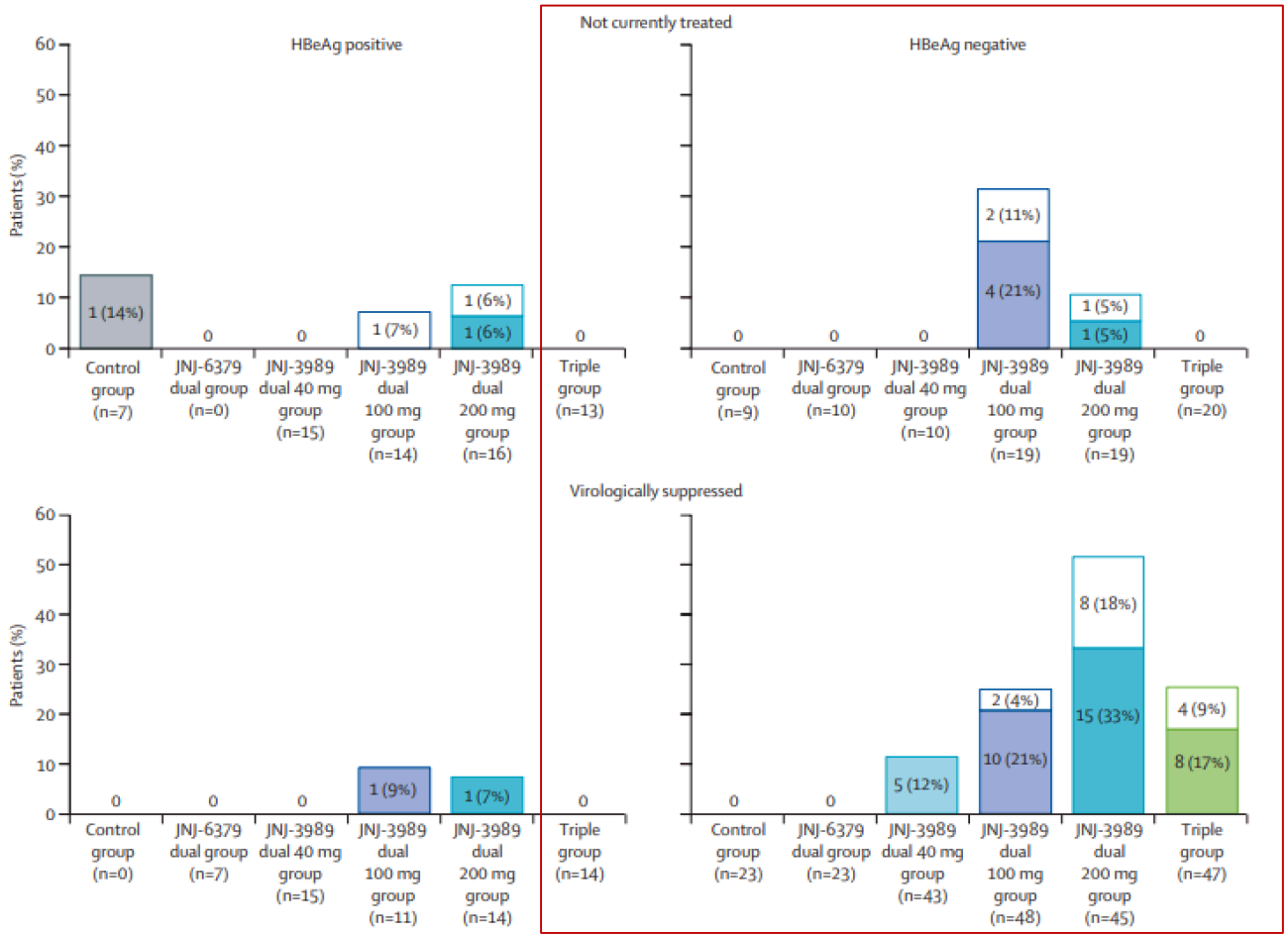
Source: https://pubmed.ncbi.nlm.nih.gov/37442152/

JNJ-3989—HBeAg-Negative Participants Respond Better to siRNA Treatment than HBeAg-Positive Participants

38 (81%) patients who met the NA-stopping criteria at week 48 were virologically suppressed and HBeAg negative at baseline. Only a small number of patients from other subgroups met NA-stopping criteria at week 48.

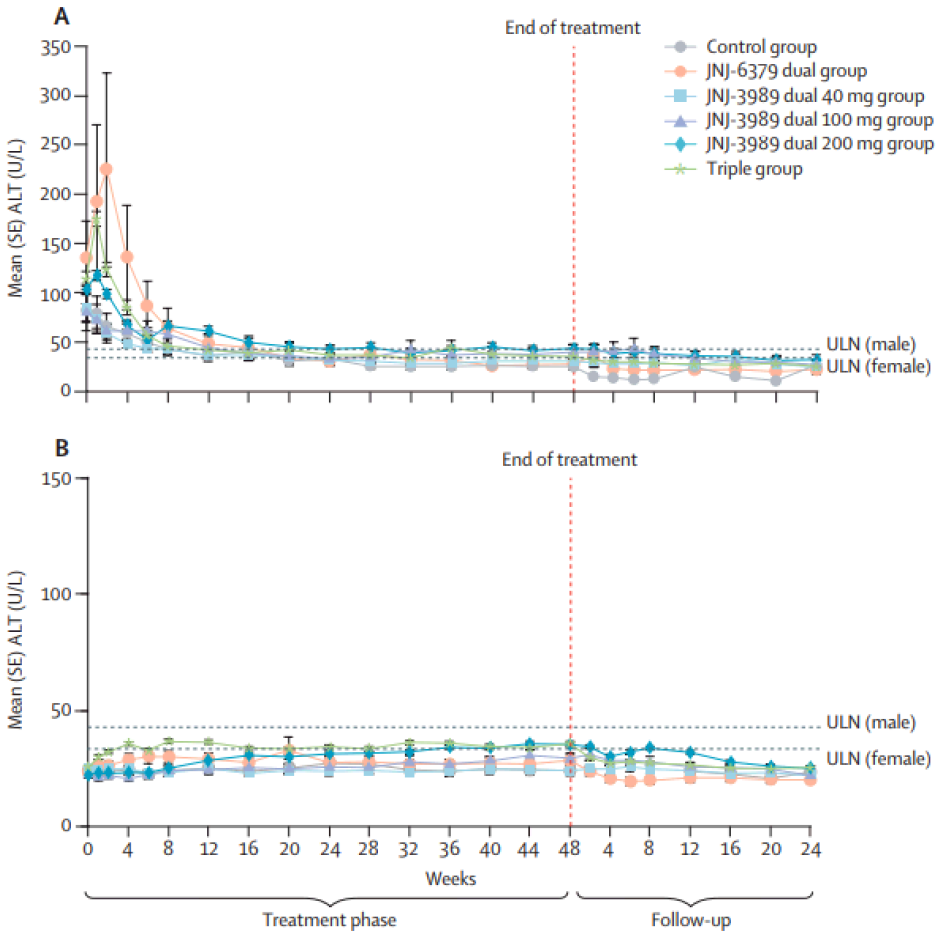
Substantial HBsAg reductions were observed with JNJ-3989 treatment. However, functional cure (off-treatment HBsAg seroclearance) was not reached with the treatments evaluated.

Percentage of patients meeting NA-stopping criteria at week 48 and during the 24-week follow-up by stratification factors



Source: https://pubmed.ncbi.nlm.nih.gov/37442152/

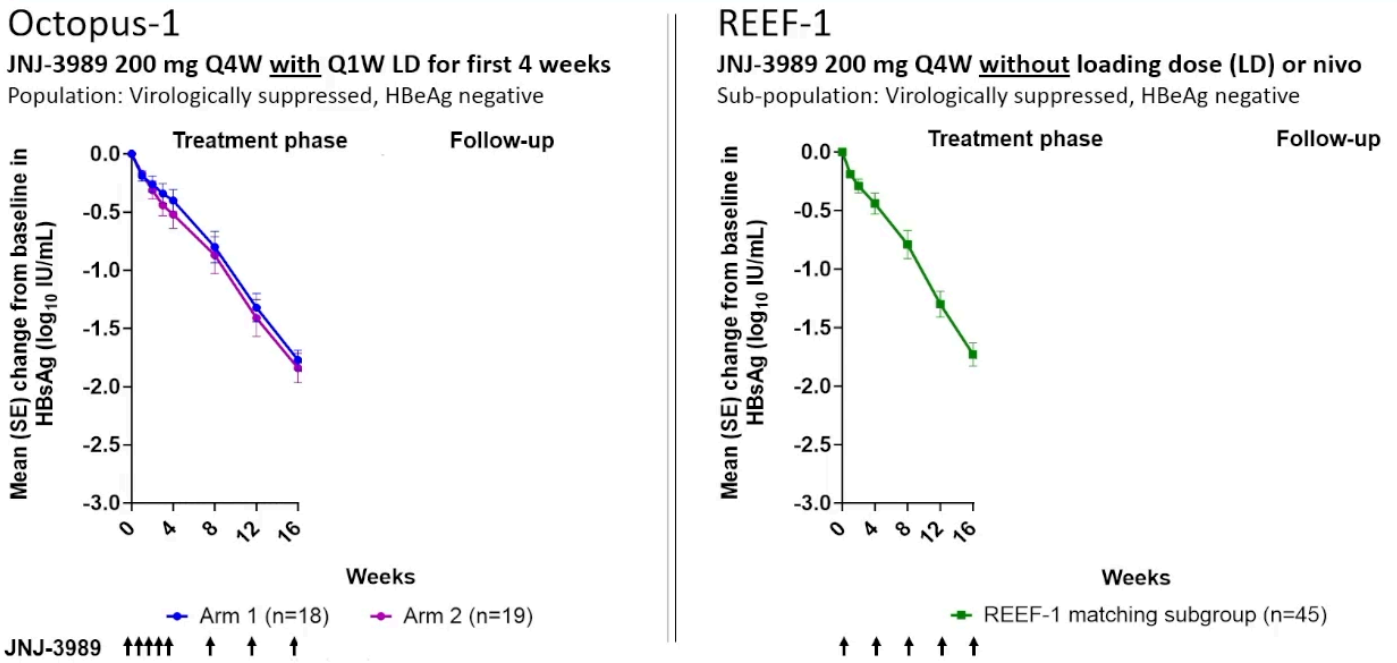
JNJ-3989—ALT Profile Suggests Combination With Bepirovirsen is Feasible



Mean ALT profiles over time in patients who were not currently treated (top) and patients who were virologically suppressed (bottom), reveal limited ALT elevation following siRNA treatment in patients with virologically suppressed CHB.

Source: https://pubmed.ncbi.nlm.nih.gov/37442152/

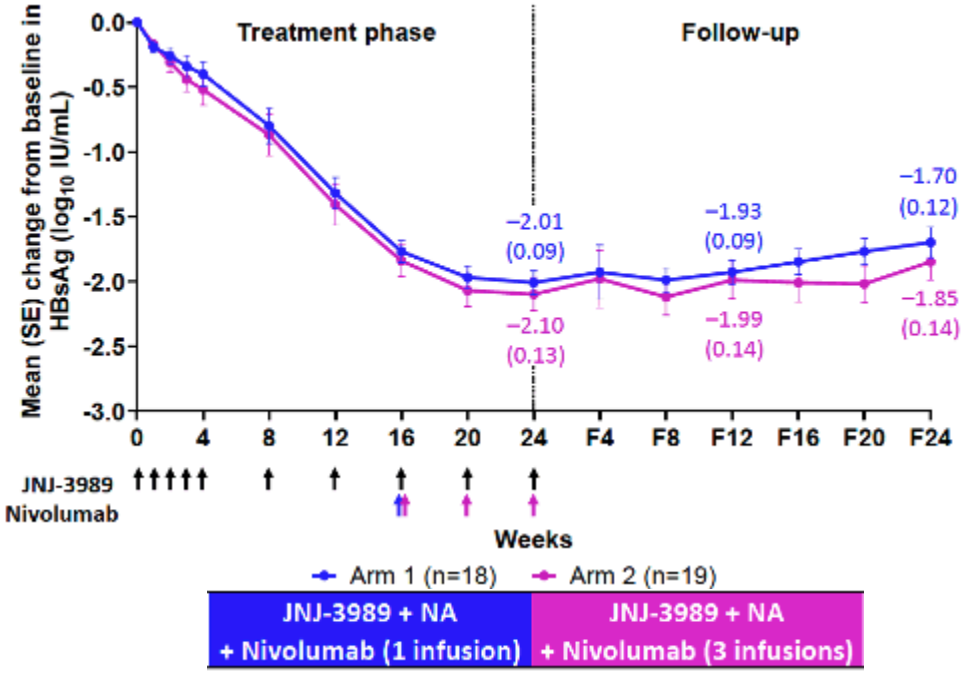
In the Ph 2 Octopus-1 Study, JNJ-3989 Loading Dose Did Not Lead to HBsAg Declines

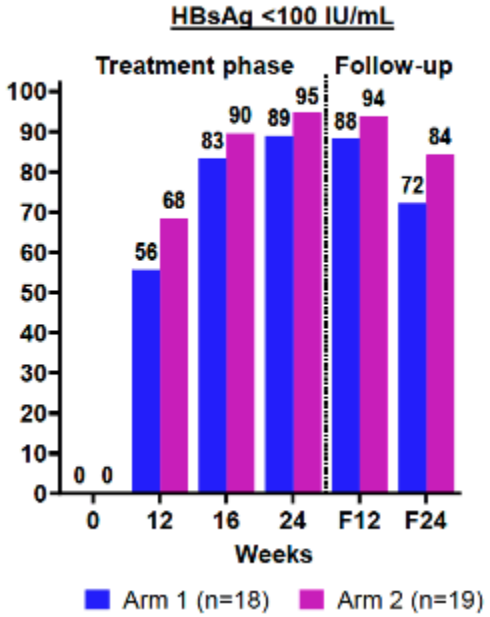


Increased dose frequency of JNJ-3989 (200 mg Q4W with Q1W loading dose for first 4-weeks) was safe and well tolerated but did not improve HBsAg declines. Mild increases of ALT were observed earlier in Octopus-1 (with loading dose) than REEF-1 (without loading dose).

Source: JNJ EASL 2024 Presentation

In the Octopus-1 Study, Adding Nivolumab Did Not Add to HBsAg Declines





The addition of nivolumab at low dose with >80% receptor occupancy did not improve the HBsAg declines of JNJ-3989+NA. No participant met the primary endpoint of HBsAg < LLOQ.

After two events of temporary TSH suppression, it was deemed nivolumab infusions added no clear benefit and the protocol was amended to remove nivolumab from the study.

Source: JNJ EASL 2024 Presentation

JNJ-3989, 100 to 400 mg Q4W Resulted in HBsAg Reductions >−1 log10 IU/ml From Baseline

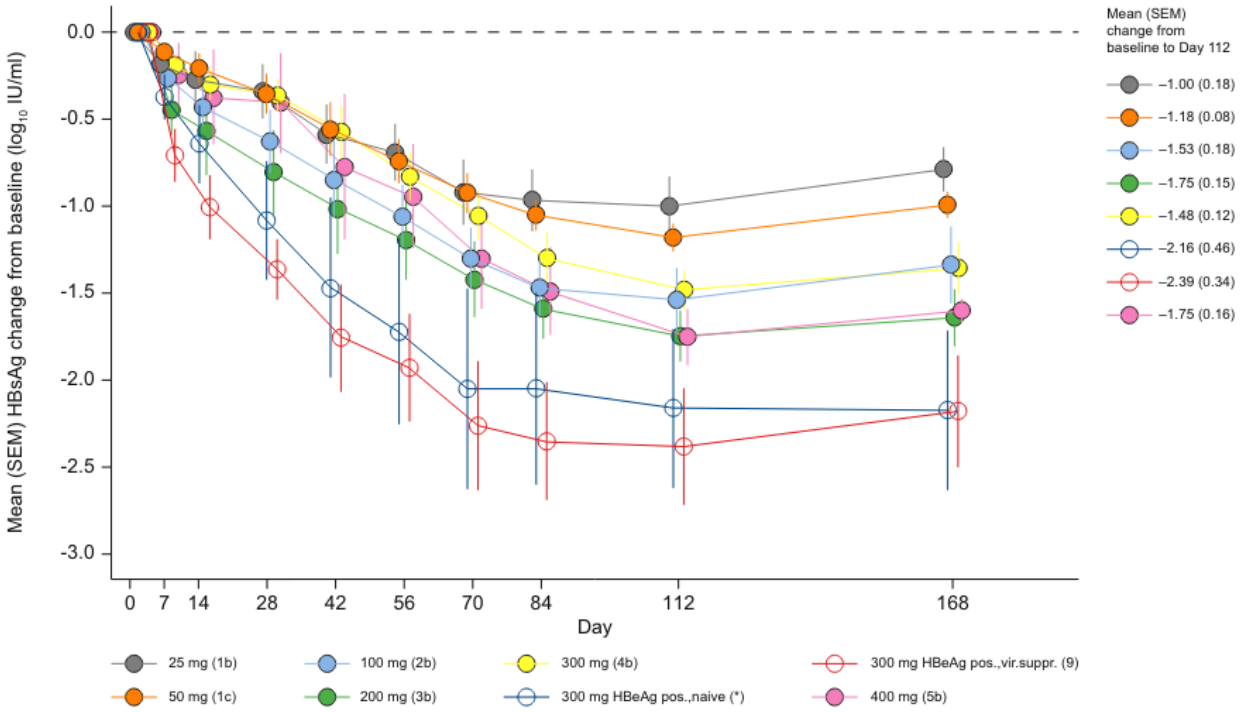
In a separate Ph2 trial, patients with chronic Hepatitis B were administered siRNA JNJ-3989 plus an NA.

Median HBsAg at baseline (log10 IU/ml) was 3.14.

Smaller reductions in mean HBsAg were observed with 25 mg (1.00 log10 IU/ml) and 50 mg (1.18 log10 IU/ml) vs. 100 to 400 mg (1.48 to 2.39 log10 IU/ml) JNJ-3989 dosing.

Dose response appeared to plateau above 100 mg.

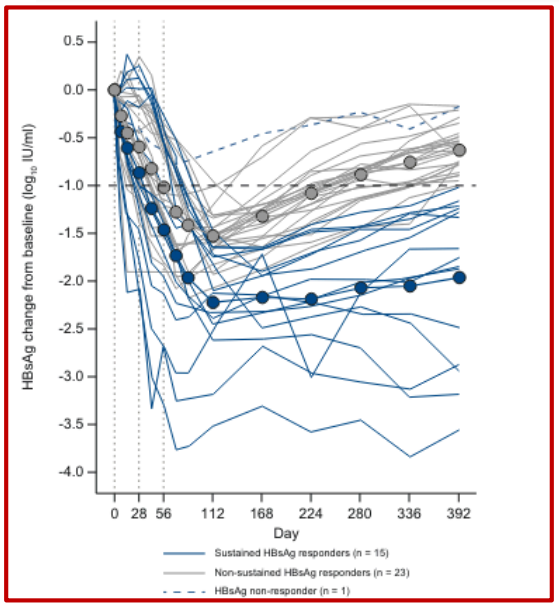
75% of patients (30/40) had <100 IU/mL at day 112, of those who received 100mg to 400mg JNJ-3989.

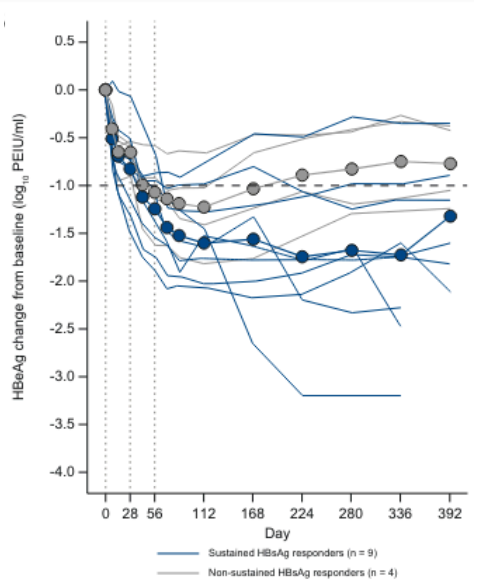


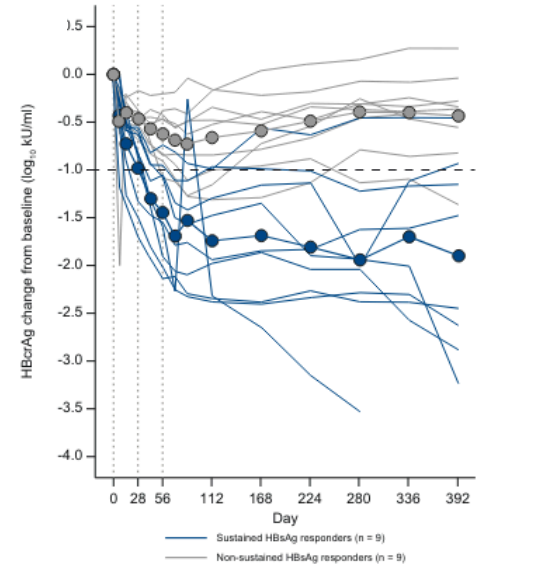
Source: https://pubmed.ncbi.nlm.nih.gov/35870702/

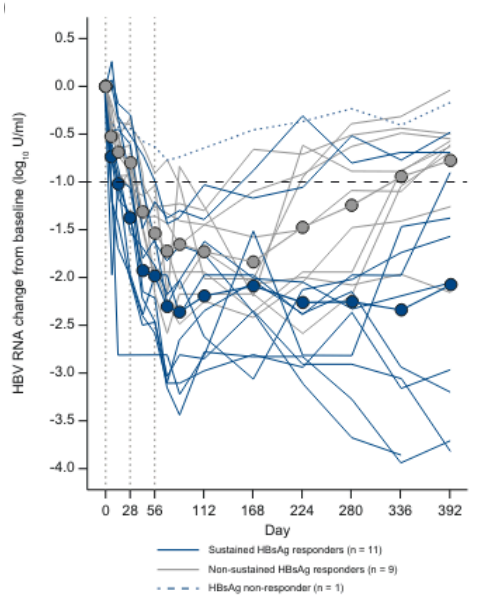
15/39 Patients Maintained > 1 log10 IU/ml HBsAg Reduction Through Day 392

The mean HBsAg reductions were 1.96 log10 IU/ml in sustained responders and 0.63 log10 IU/ml in non-sustained responders







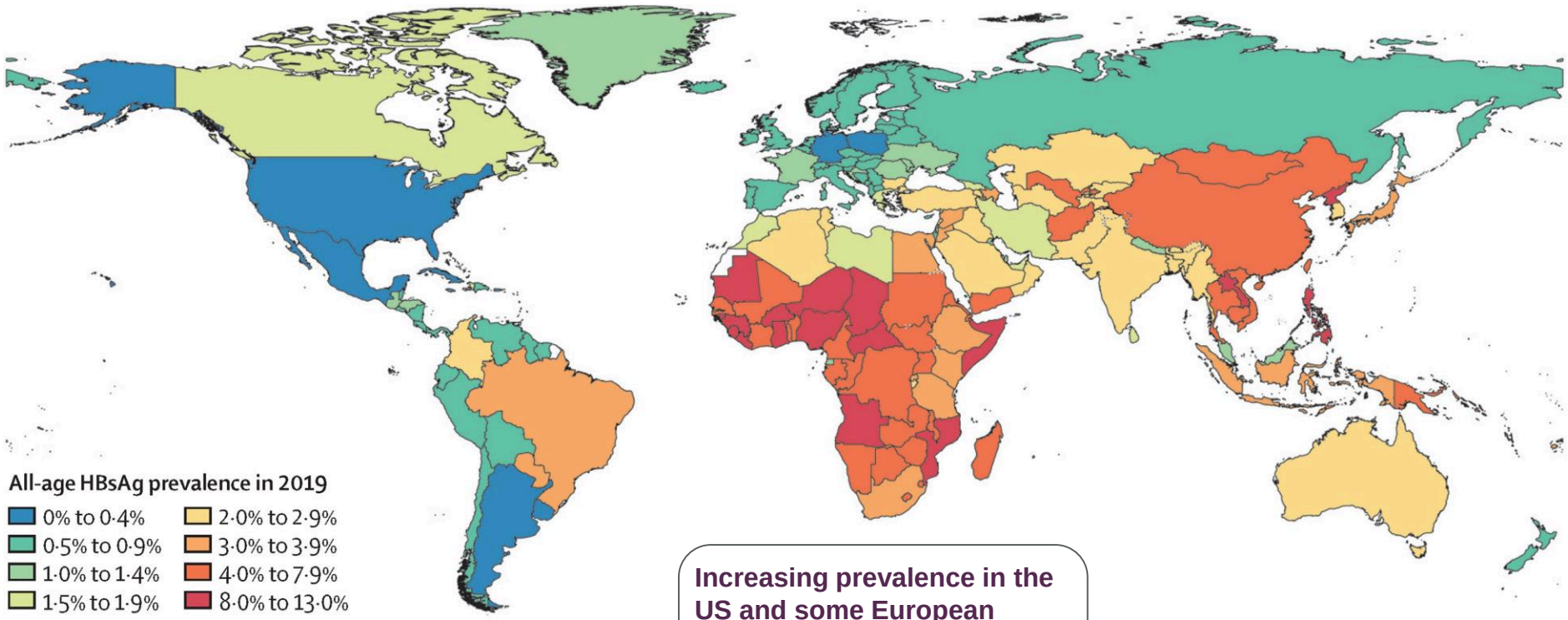


Source: https://pubmed.ncbi.nlm.nih.gov/35870702/

HBV Commercial Opportunity
- A view of the Current Clinical Landscape

Chronic HBV Epidemiology and Public Health Burden

- Worldwide there are approximately 300 million chronic HBsAg carriers
- In 2013, there were 686,000 reported deaths from HBV-related liver disease and HCC
- CHB remains a global public health issue and diagnosis remains low. Diagnosis rates are approximately 35% in the US, 25% in Europe and 50% in Japan. Recently, the CDC published guidelines that suggest that adults should be tested for Hepatitis B



Source: EASL HBV 2020 Update; https://doi.org/10.1016/S0140-6736(22)01468-4

Increasing prevalence in the US and some European countries:

- Migration from high endemic countries

US Hepatitis B Epidemiology

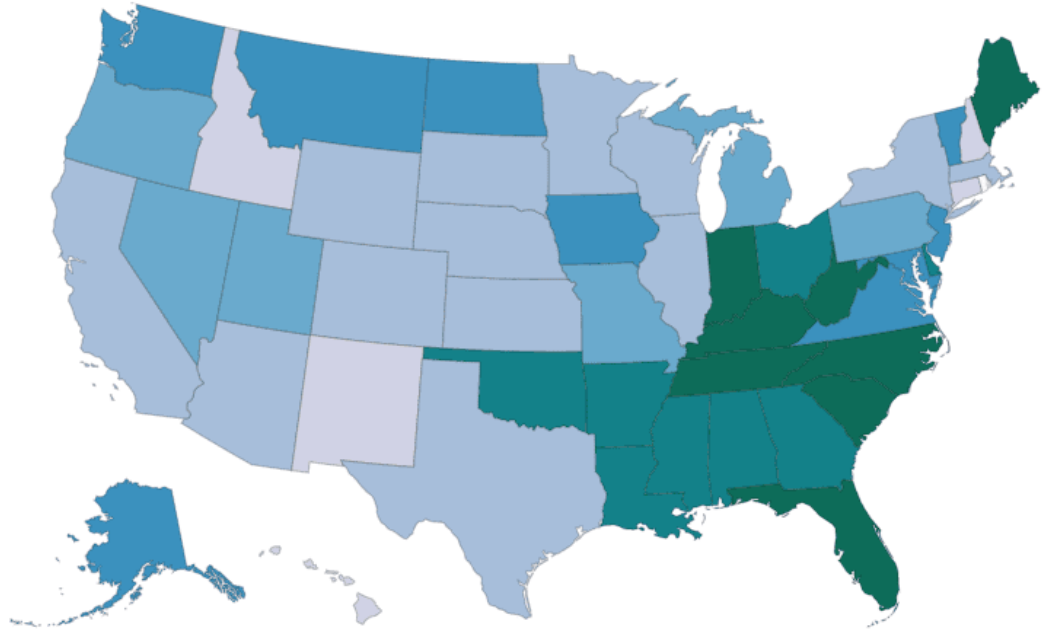
There are an estimated 850,000 to 2.2M people infected with chronic HBV in the US.

Of the chronic population, 15% - 25% die prematurely from cirrhosis or liver cancer.

Asian Americans account for approximately 50% of all US chronic HBV cases.

The CDC estimates there are approximately 4,000 reported acute HBV cases annually, and approximately 20,000 to 25,000 estimated acute HBV infections annually. Per the CDC, the number of estimated cases of acute Hepatitis B is determined by multiplying the number of reported cases by a factor that is adjusted for under-ascertainment and under-reporting; the number of estimated cases is typically about 6.5-fold higher than reported cases.

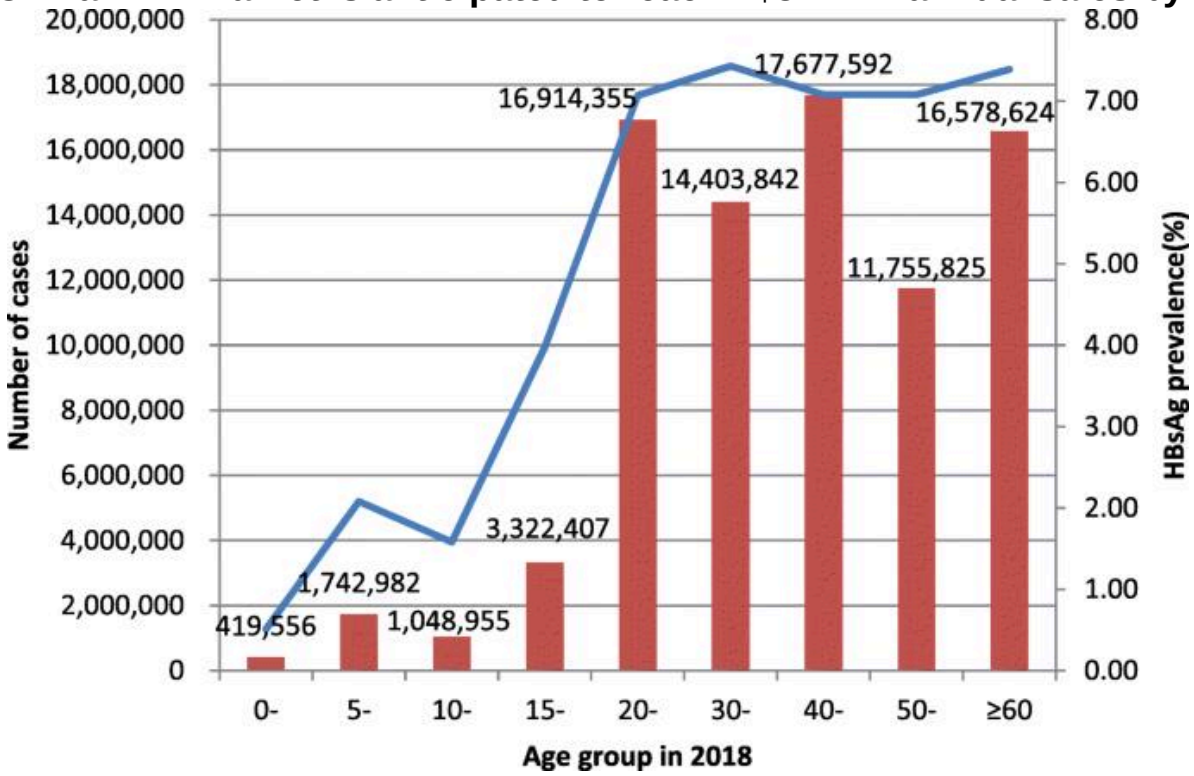
Rates of Reported Acute Hepatitis B Virus: Rates of Reported Cases, by State or Jurisdiction, United States, 2022



Source: Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. https://www.cdc.gov/nchhstp/atlas/index.htm. Accessed [2024].

China is One of the Largest Markets for HBV

The China HBV market is anticipated to reach ~$3.4B in annual sales by 2029



Number of HBV infected & treated people in China:

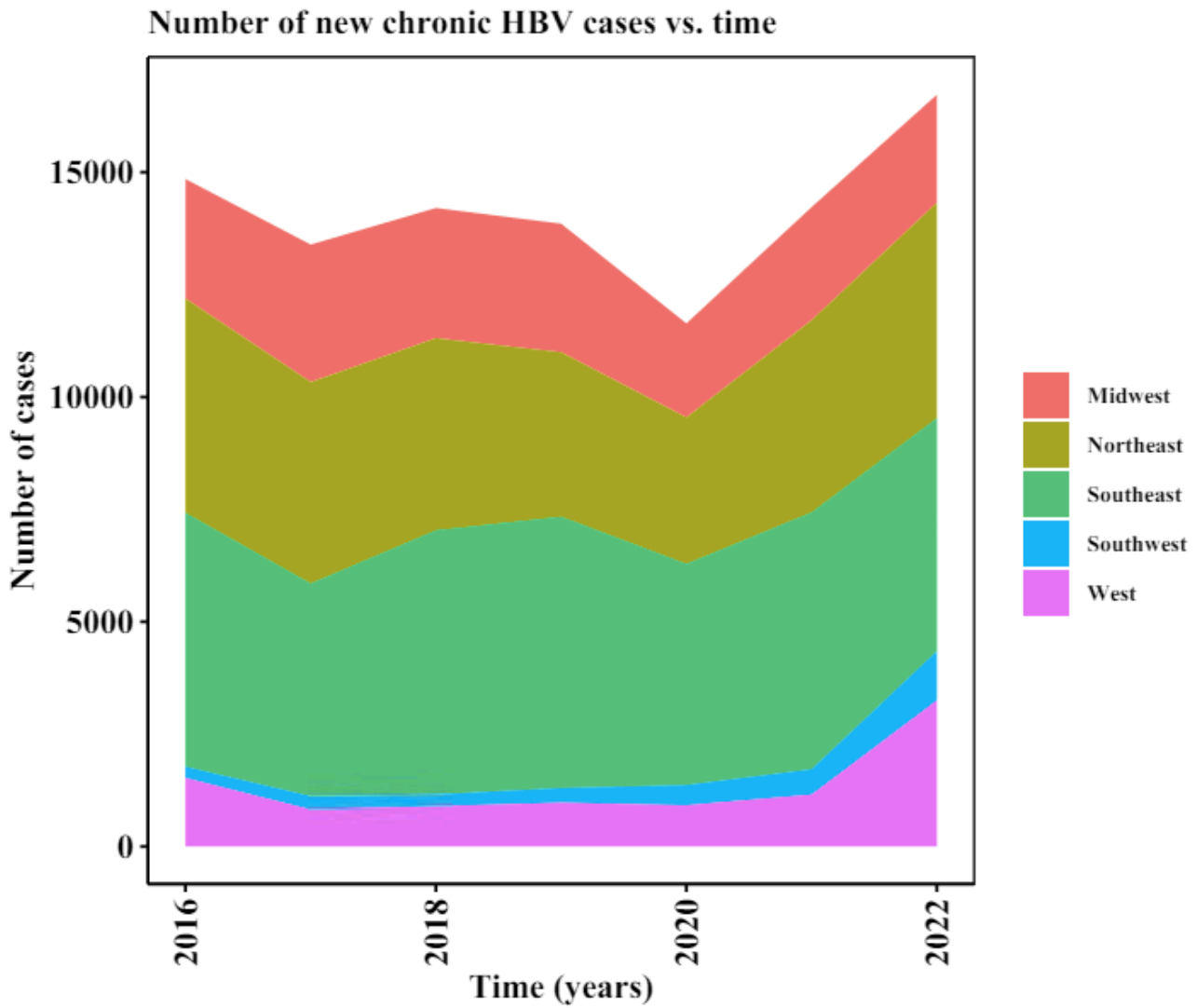
Infected with HBV: ~79M
Require treatment per guidelines: ~75M
Receiving antiviral treatment: ~11M

Social Pressures of HBV Infection in China

In a survey of 797 HBV patients in China;
Denied jobs due to HBV: 20%
Denied health insurance due to HBV: 14.7%

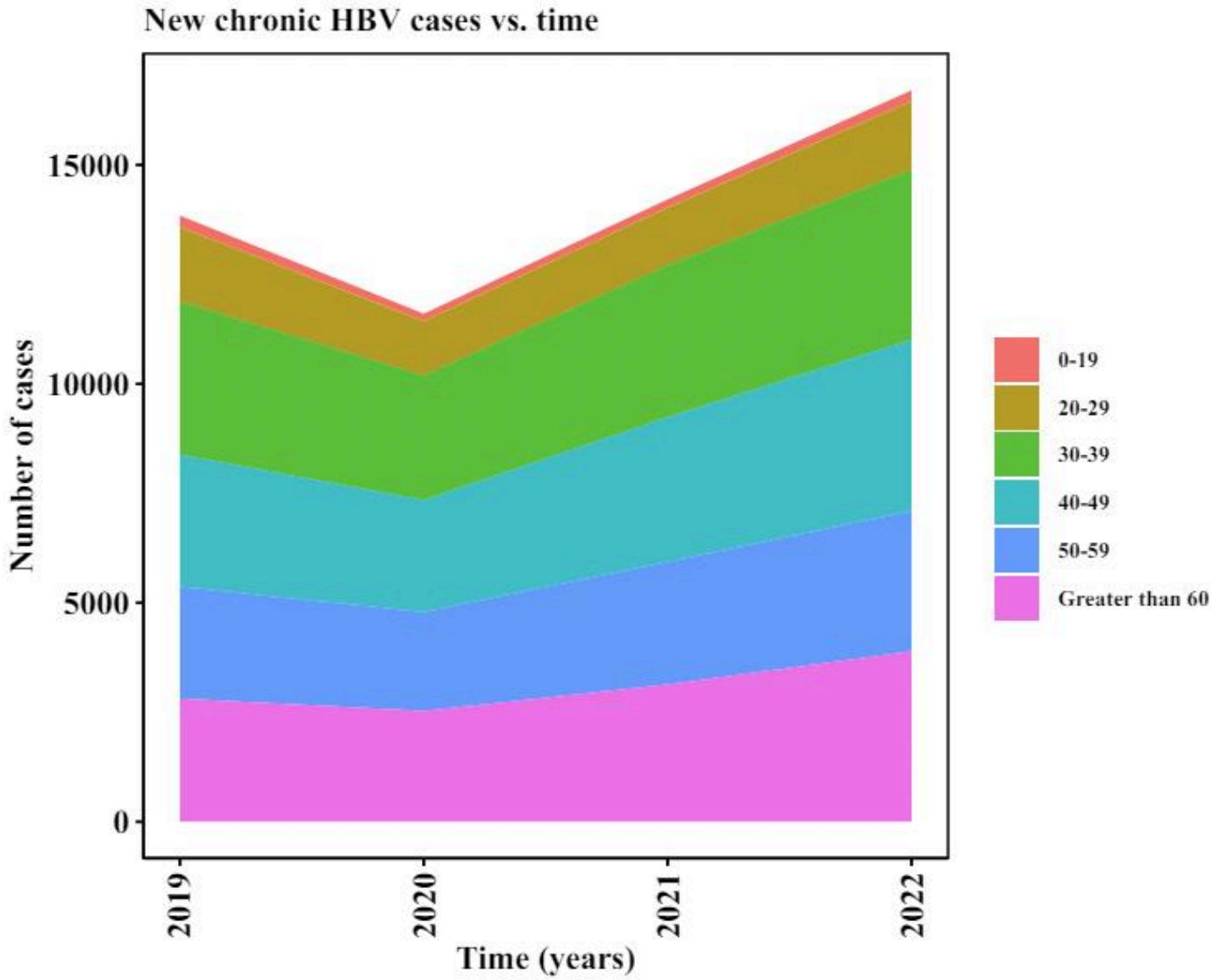
Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6751646/; BRII Bio corporate report;) 2017 survey on discrimination against chronic HBV patients in China conducted by the Chinese Foundation for Hepatitis Prevention and Control

CDC Estimated New Chronic HBV Cases Per Year on the Rise



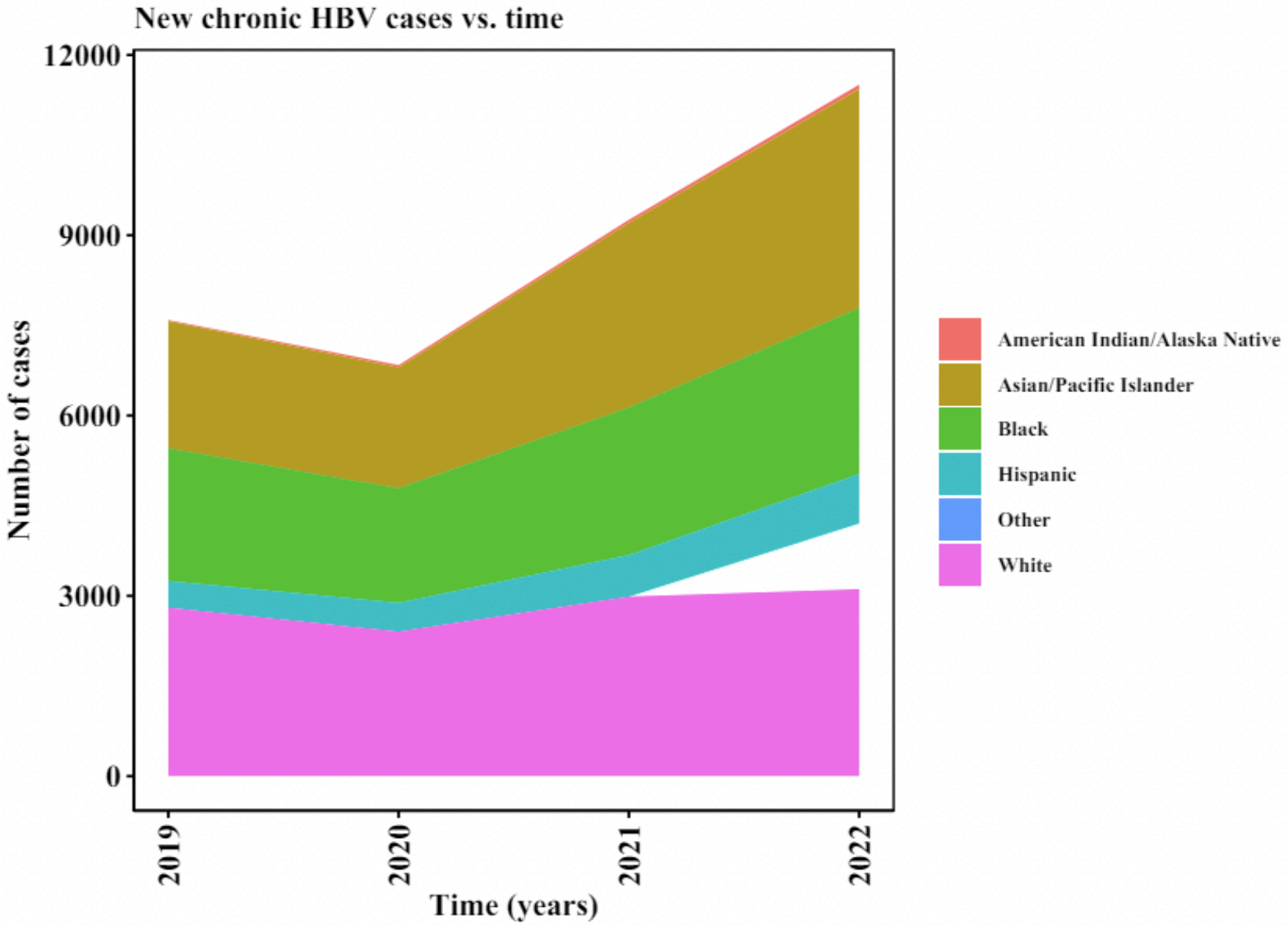
Source: Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. https://www.cdc.gov/nchhstp/atlas/index.htm. Accessed [2024].

CDC Estimated New Chronic HBV Cases to Be ~15,000 Annually in the US



Source: Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. https://www.cdc.gov/nchhstp/atlas/index.htm. Accessed [2024].

US New Chronic HBV Cases Stratified by Ethnicity



Source: Centers for Disease Control and Prevention. NCHHSTP AtlasPlus. https://www.cdc.gov/nchhstp/atlas/index.htm. Accessed [2024].

Mechanism of Action of HBV Medicines Under Development

Treatment Classes	Mechanism of action	Types
Drugs targeting HBV life cycle		
Entry inhibitors	Blockage of liver-specific bile acid transporter (NTCP)	Inhibitors of NTCP; NMAb
Capsid assembly modulators	Interfere with capsid formation and disrupt encapsulation of pgRNA	CAMs
Post-transcriptional control inhibitors	Post-transcriptional gene silencing by inhibition of the translation of viral proteins	siRNAs, ASOs
HBsAg release inhibitors	Intracellular degradation of HBsAg via proteasomal and lysosomal degradation	NAPs
Immunomodulators		
Innate immune activator	Stimulation of innate immunity through TLRs and RIG-I	TLRs agonist, RIG-I agonists
Adaptive immune activator	Blocking the PD-1/PD-L1 pathway to reverse T-cell exhaustion; stimulation of hist's immune response to generate CD4 and CD8 HBV-specific T cells	Checkpoint inhibitors; therapeutic vaccines

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10354584/pdf/WJG-29-3964.pdf

siRNA Therapeutics in Development for HBV - Interferes and Destroys Viral RNA

Drug	Mechanism	Company	Ticker	Clinical Stage
VIR-2218 (Elebsiran)	RNAi gene silencer	Vir Biotech	VIR	Phase II
Xalnesiran (RG6346)	RNAi gene silencer	Dicerna with Roche	RHHBY / NVO	Phase II
Imdurisan (AB-729)	RNAi gene silencer	Arbutus Biopharma	ABUS	Phase II
BW-20507	RNAi gene silencer	Argo Biopharma Australia	Private	Phase II
ALG-125755	RNAi gene silencer	Aligos Therapeutics	ALGS	Holding for new partner
BB-103	RNAi gene silencer	Benitec, Australia	BNTC	Preclinical
JNJ-3989 (ARO-HBV)	RNAi gene silencer	GSK, USA	GSK	Phase II

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Gene Editing Excision in Development for HBV – Intended to Destroy HBV DNA

Drug	Mechanism	Company	Ticker	Clinical Stage
PBGENE-HBV	ARCUS platform	Precision Bio	DTIL	Preclinical
EBT107	CRISPR/Cas 9	Excision Bio	Private	Preclinical

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Entry Inhibitors, HBsAg Inhibitors, and ASOs in Development for HBV

Drug	Mechanism	Company	Ticker	Clinical Stage
Entry Inhibitors - Interferes with HBV Getting into Liver Cells				
Bulevirtide (Hepcludex)	Entry inhibitor	Gilead	GILD	Phase III

Drug	Mechanism	Company	Ticker	Clinical Stage
HBsAg Inhibitors - Interferes with production of HBV surface antigen (sAg)				
REP 2139	sAg inhibitor	Replicor, Canada	Private	Phase II

Drug	Mechanism	Company	Ticker	Clinical Stage
ASOs - Binds to the viral mRNA to prevent it from turning into viral protein				
Bepirovirsen	HBV Antisense	GSK, USA	GSK / IONS	Phase III

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Capsid or Core Inhibitors in Development for HBV

Drug	Mechanism	Company	Ticker	Clinical Stage
EDP-514	Capsid inhibitor	Enanta Pharma	ENTA	Phase I
ALG-000184	Capsid inhibitor	Aligos Therapeutics	ALGS	Phase I
ABI-H4334	Capsid inhibitor	Assembly Biosciences	ASMB	Phase I

Source: https://www.hepb.org/treatment-and-management/drug-watch/

HBV Therapeutic Vaccines – Used to Stimulate the Immune System

Drug	Mechanism	Company	Ticker	Clinical Stage
VBI-2601 (BRII-179)	Therapeutic vaccine	VBI Vaccines	VBIV	Phase II
VVX001	Therapeutic vaccine	Viravaxx	Private	Phase II
GSK 3528869A	Therapeutic vaccine	GSK	GSK	Phase II
VTP-300	Therapeutic vaccine	Barinthus Biotherapeutics	BRNS	Phase II
CVI-HBV-002	Therapeutic vaccine	Cha Vaccine Institute, S. Korea	Private	Phase I/II
HB-400 (GS2829/GS6779)	Therapeutic vaccine	HOOKIPA Pharma with Gilead	GILD / HOOK	Phase I
ISA104	Therapeutic vaccine	ISA Pharma, The Netherlands	Private	Phase I
VRON-0200	Therapeutic vaccine	Viron Therapeutics, USA	Private	Phase I
CLB-3000	Therapeutic vaccine	Clear B Therapeutics	Private	Phase I
CARG-201	Therapeutic vaccine	CaroGen	Private	Preclinical
PRGN-2013	Therapeutic vaccine	Precigen	PGEN	Preclinical
HBV vaccine	Therapeutic vaccine	Astrivax, Belgium	Private	Preclinical

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Innate Immune System Activators in Development for HBV

Drug	Mechanism	Company	Ticker	Clinical Stage
Selgantolimod (GS9688)	TLR-8 agonist	Gilead Sciences	GILD	Phase II
Ruzotolimod (RG7854)	TLR-7 agonist	Roche	RHHBY	Phase II
GSK 5251738	TLR-8 agonist	Gilead	GILD	Phase I
PRTX007	TLR-7 agonist	Primmune Therapeutics, USA	Private	Phase I

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Monoclonal Antibodies in Development for HBV - Neutralize or Bind the HBV Proteins to Reduce Infection

Drug	Mechanism	Company	Ticker	Clinical Stage
VIR-3434	Monoclonal antibody	Vir Biotech	VIR	Phase II
Burfiralimab (IgG4)	Monoclonal antibody	ImmuneMed, South Korea	Private	Phase II
BJT-778	Monoclonal antibody	Blue Jay Therapeutics, USA	Private	Phase I
RG6449	Monoclonal antibody	Roche	RHHBY	Phase I

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Additional HBV Drugs in Development – Checkpoint Inhibitors and Immunotherapies

Drug	Mechanism	Company	Ticker	Clinical Stage
RG6084	PDL1 inhibitor	Roche	RHHBY	Phase II
AB-101	PDL1 inhibitor	Arbutus	ABUS	Phase I
IMC-I109V	T-cell Receptor	Immunocore	IMCR	Phase I
GSK 4388067A	Targeted immunotherapy	GSK	GSK	Phase II
GSK 3965193	PAPD5/PAPD7 inhibitor	GSK	GSK	Phase I
AB359	CD8 IL-2 immunotherapy	Asher Biotherapeutics, USA	Private	Preclinical
BJT-628	Small molecule	Blue Jay Therapeutics, USA	Private	Preclinical

Source: https://www.hepb.org/treatment-and-management/drug-watch/

Drug Combinations in Recent HBV Clinical Trials have Demonstrated Substantial HBsAg Decline, However Only Bepi Demonstrates Meaningful HBsAg Loss

Drug class	Drug	Patients	Time on therapy (wk)	Efficacy	Safety
ASO + NA	**Bepirovirsen ± NA**	**457**	**12-24**	**HBsAg < LoQ in 28%-29% and HBsAg loss in 9%-10% after 24 wk of EoT**	**Injection site reactions; few cases of grade 3-4 ALT flares**
NA +/- CAM	NA vs NA + JNJ-6379	232	24-48	HBsAg decline 0.25 log IU/mL vs. 0.41 log IU/mL	No major AE
siRNA +/- NA	AB-729 vs NA + AB-729	43	8	HBsAg decline 2.03 log IU/mL monotherapy	Injection site reactions; ALT flares
NTCP inhibitor + Peg-IFN	Bulevirtide + Peg-IFN in HDV-HBV co-infection	90	48	HBsAg loss 26.7% in one arm vs. 0% in the other	Related to Peg-IFN; injection site reactions
NA + TLR agonist	NA + TLR7 agonist (GS-9620)	162	24	No changes in HBsAg	Some grade 3 AE with higher doses (few treatment discontinuations)
NA + TLR agonist	NA + TLR8 agonist (selgantolimod)	48	24	HBsAg loss 5% at week 48	Mild and transient gastrointestinal AE
NA + checkpoint inhibitors	NA + PD-1 inhibitor (nivolumab)	12	1 dose (24 follow up)	HBsAg reduction 0.48 log IU/mL (HBsAg loss in 5%)	No major AE
NA + checkpoint inhibitors	NA + PD-L1 inhibitor (Menvafolimab)	48	24	HBsAg decline 0.38 log IU/mL (HBsAg loss in 19%)	Grade 1 and 2 ALT flares
NA + siRNA +/- CAM	NA + JNJ-3989 (siRNA) +NA ± JNJ-6379 (CAM)	117	48	HBsAg decline 2.1 log IU/mL in double vs. 1.8 log IU/mL in triple combination	No major AE
NAP + NA + Peg-IFN	REP2139 or REP 2165 + NA + Peg-IFN	40	48	15 / 18 HBsAg response > 1 log	Related to Peg-IFN
siRNA + NA +/- Peg-IFN	VIR 2218 (siRNA) + NA +/- Peg-IFN	80	24	HBsAg decline 2.03 log IU/mL in dual arm vs. 2.55 log IU/mL in triple arm (HBsAg < 100 IU/mL in 95% and HBsAg < 10 IU/mL in 55%)	Related to Peg-IFN

Source:https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10354584/pdf/WJG-29-3964.pdf

Chronic Hepatitis B Serology
-Understanding a Broad Unmet Need

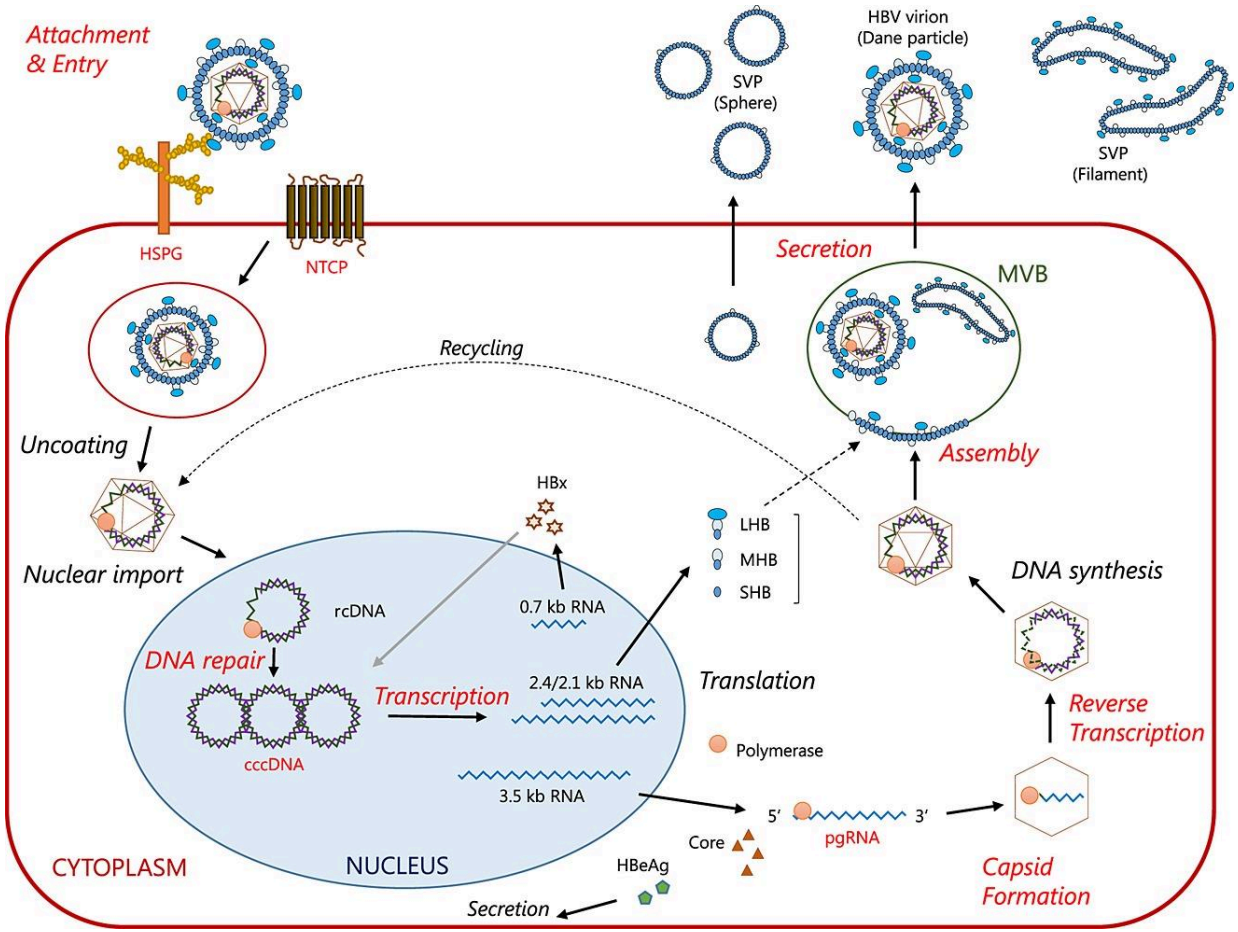
Hepatitis B Virus Life Cycle

The HBV genome is a relaxed-circular DNA (rcDNA), which is converted into covalently closed circular DNA (cccDNA) in infected hepatocytes. cccDNA produce HBV RNAs mainly of 3.5 Kb, 2.4 Kb, 2.1 Kb, or 0.7 Kb in size. Hbe is produced by the translation of the 3.5 Kb preC mRNA.

HBV enters host cells through surface receptors including heparan sulfate proteoglycans (HSPGs).

cccDNA resides episomally, and functions as a template for viral replication over the long term, with a half-life of up to 9-months in HBV patients.

HBV RNA can undergo capsid formation, followed by reverse transcription and DNA synthesis to form HBV virion particles. These particles can be secreted from the host cell.



Source: https://pubmed.ncbi.nlm.nih.gov/26776362/

Genotypes of HBV – Genotypes A & B Most Responsive to Treatment

Some patients with chronic Hep B have widely fluctuating HBV-DNA levels that may vary from undetectable to >2,000,000 IU/mL. Thus, serial monitoring of HBV-DNA levels is important.

HBV exists in ten genotypes (A-J). Genotypes A-H are present in the US, and A, B, and C are the most prevalent. Genotype A (vs B, C, D) is associated with greater rates of HBeAg and HBsAg loss with IFN therapy.

HBV genotype B is associated with more sustained remission, less hepatic necroinflammation, slower progression to cirrhosis, and lower rate of HCC development vs. genotype C.

HBV genotype: A and B genotypes are more likely to achieve HBeAg and HBsAg loss with peg-IFN than non-A or non-B genotypes.

Genotypes	Subtypes	Geographic location
A	A1	Sub-Saharan Africa
	A2	Northern Europe
	A3	Western Africa
B	B1	Japan
	B2-5	East Asia, Taiwan, China, Indonesia, Vietnam, Philippines
	B6	Alaska, Northern Canada, Greenland
C	C1-3	Taiwan, China, Korea and Southeast Asia.
	C4	Australia
	C5	Philippines, Vietnam
D	D1-5	Africa, Europe, Mediterranean countries and India
E		Restricted to West Africa
F	F1-4	Central and South America
G		France, Germany and the United States
H		Central America
I		Vietnam and Laos
J		Japan

Clinical significance of HBV genotypes

Geographical distribution
- A – Northwest Europe and North America
- B – SE Asia
- C – Far East
- D – Mediterranean basin, India, Middle East

Spontaneous HBeAg seroconversion
- B earlier than C

Activity of liver disease and risk of progression to cirrhosis
- C>B

Response to IFN
- A better than D
- B better than C

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/; https://www.natap.org/2003/oct/100203_1.htm; https://pubmed.ncbi.nlm.nih.gov/23183198/

Characteristics of Different Phases of Chronic Hepatitis B

CHB Stage	Phase 1	Phase 2	Phase 3	Phase 4	Phase 5
CHB Stage (alternative nomenclature)	Immune tolerant (HBeAg-positive)	Immune active (HBeAg-positive; immune reactive phase)	Immune inactive (HBeAg-negative; low replication phase)	Immune active HBeAg negative (HBeAg-negative; reactivation phase)	Resolved CHB (HBeAg loss phase)
Characteristics					
HBsAg	High	High/intermediate	Low	Intermediate	Negative
HBeAg	Positive	Positive	Negative	Negative	Negative
HBV DNA level	$>10^6$ –10^7 IU/mL	$>2x10^4$ IU/mL	<2,000 IU/mL	>2,000 IU/mL	Undetectable
ALT level	Persistently normal	Elevated	Persistently normal	Elevated	Normal
Histological activity	None/minimal	Moderate/severe	Minimal	Moderate/severe	None

Note: HBV DNA > 10^6 IU/mL per AASLD, $>10^7$ IU/mL per KASL and EASL

Guidelines recommend treatment of patients with cirrhosis and those with HBeAg-positive or HBeAg-negative active disease.

Guidelines do not recommend routine treatment in the immune-tolerant phase. These patients are usually below the age of 30-40 and at low risk of near-term liver cirrhosis or HCC, and current treatments rarely result in functional cure.

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7641563/; https://pubmed.ncbi.nlm.nih.gov/31713892/

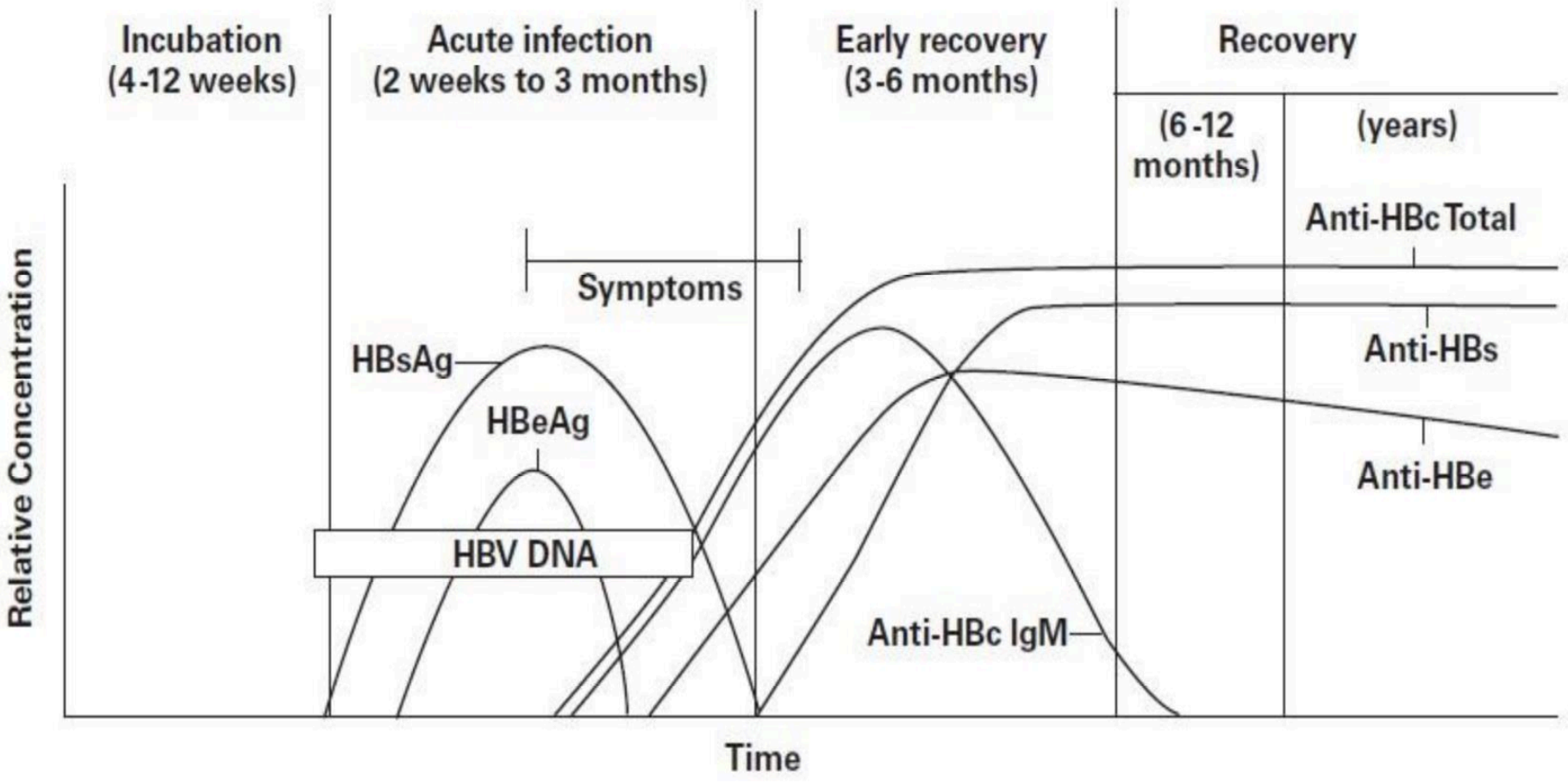
Characteristics of Different Antigens / Immune Response of Chronic Hepatitis B

	HBsAg	HBeAg	Anti-HBc	Anti-HBe	Anti-HBs	HBV DNA
Acute infection	+/- *	+	+	-	-	+
Past infection	-	-	+	+/-	+	-
Occult HBV	-	-	+	-	-	+
Chronic HBV	+	+	+	-	-	+
Pre-core mutant	+	-	+	+	-	+
Healthy carrier	+	-	+	+	-	-
Memo	**HBsAg surface antigen = current infection**	**Envelop Ag (HBeAg) = infectious**	**Infected, unknown timing**	**Envelope antibody = recovery from acute infection**	**Surface antibody = immunity**	**Viral DNA is marker of viral activity**

* May be negative in acute infections where HBsAg is below LOD

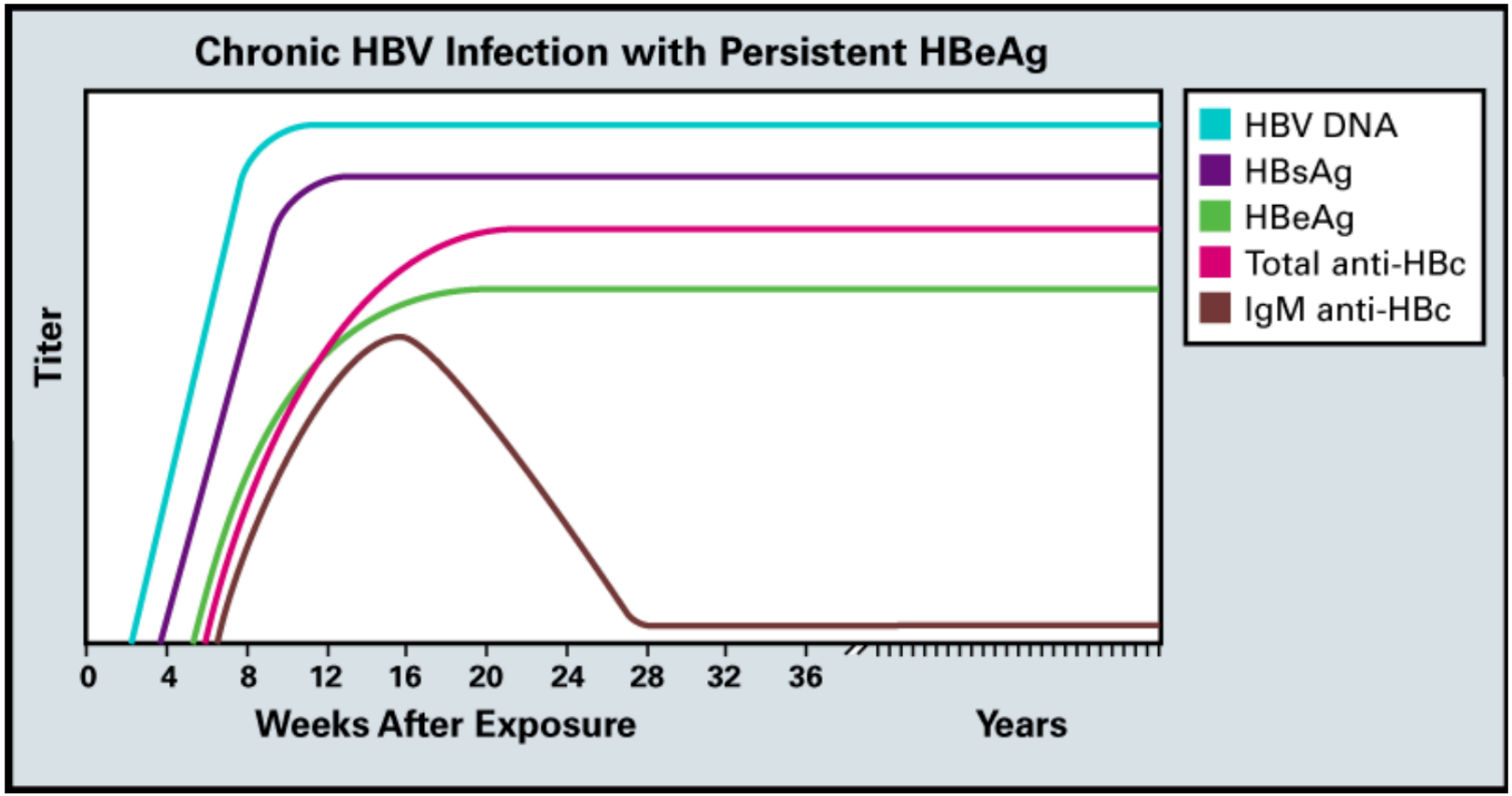
Source: https://epi.dph.ncdhhs.gov/cd/lhds/manuals/cd/conference/docs/HepatitisBSurveillanceandInvestigation.pdf

Serology of Acute Infection Which Resolves



Source: https://epi.dph.ncdhhs.gov/cd/lhds/manuals/cd/conference/docs/HepatitisBSurveillanceandInvestigation.pdf

Serology of Chronic Infection With Persistent HBeAg



Source: https://epi.dph.ncdhhs.gov/cd/lhds/manuals/cd/conference/docs/HepatitisBSurveillanceandInvestigation.pdf

Incidence of HCC in High Risk Groups With HBV

Group	Incidence of HCC (%/year)
Asian male; HBV > age 40	0.4–0.6
Asian female; HBV > age 50	0.3–0.6
HBV with HCC family history	Higher than without family history
African/North American Blacks with HBV	HCC occurs at younger age
HBV cirrhosis	3–8
HCV cirrhosis	3–5

- Over 50% of HCC cases worldwide are related to chronic HBV, accounting for approximately 700,000 to 800,000 new cases of HCC annually
- The annual incidence of HCC is estimated at less than 1% for non-cirrhotic patients and between 3-8% for patients with cirrhosis
- HCC risk associated with HBV is lower in the US vs. Asian-Pacific and sub-Saharan Africa
- 55% of all HCC cases worldwide stem from China

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5401856/

Comparison of HCC Risk in CHB Patients Treated with ETV vs. TDV

First Author	Race	Country	Mean Age (yr)	Males ETV	Males TDF	Total Patient	ETV	TDF	HCC in ETV	HCC in TDF	Cirrhosis before ETV	Cirrhosis before TDF	HbeAg Pos ETV	HbeAg Pos TDF	HBV DNA Baseline ETV	HBV DNA Baseline TDF
				n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	(Log IU/mL)	(Log IU/mL)
Riveiro-Barciela [52]	Caucasian	Spain	50 ± 13	139 (74.3)	305 (71.9)	611	187 (31)	424 (69)	**3 (1.6)**	**11 (2.5)**	64 (34.2)	133 (31.4)	34 (18.2)	67 (15.8)	4.9 ± 2.4	3.8 ± 2.3
Seung Up Kim [51]	Asian	South Korea	48.4 ± 11.7	889 (59.9)	913 (64.6)	2897	1484 (51.2)	1413 (48.7)	**138 (9.2)**	**102 (7.2)**	499 (33.6)	411 (29.1)	758 (51.1)	694 (49.1)	5.7 ± 2.1	5.4 ± 2.1
Jonggi Choi [49]	Asian	Korea	48.8 ± 10.5	965 (61.9)	692 (60.6)	2701	1560 (57.7)	1141 (42.2)	**115 (7.3)**	**39 (3.4)**	935 (59.9)	653 (57.2)	853 (54.7)	641 (56.2)	6.7	6.4
Sung Won Lee [57]	Asian	South Korea	47	926 (58.5)	841 (58.4)	3022	1583 (52.3)	1439 (47.6)	**84 (5.3)**	**50 (3.5)**	567 (35.82)	483 (33.56)	974 (61.5)	823 (57.1)	6.49 (5.28, 7.67)	6.41 (5.34, 7.49)
Terry Cheuk-Fung Yip [60]	Asian	China	52.9 ± 13.2	18,094 (47.3)	591 (45.1)	29,350	28,041 (95.5)	1309 (4.5)	**1386 (4.9)**	**8 (0.6)**	3822 (13.6)	38 (2.9)	8317 (29.7)	721 (55.1)	5.3 ± 2.2	4.9 ± 2.7
Ingyoon Ha [56]	Asian	South Korea	45	558 (61)	266 (63)	1340	921 (68.7)	419 (31.2)	**82 (8.9)**	**24 (5.7)**	259 (28)	39 (9.3)	488 (53)	261 (62)	6.36	6.67
George V. Papatheodoridis [55]	Caucasian	Europe	52 ± 14	538 (70)	827 (71)	1951	772 (39.5)	1163 (59.6)	**50 (6.5)**	**93 (8)**	166 (21.5)	358 (30.8)	110 (14.2)	233 (20)	-	-

HCC rates vary between 0.6% and 9.2% on NA therapy depending on ethnicity and underlying cirrhosis

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8878376/

HBV Replication, ALT, and Fibrosis Status in HBsAg-positive Persons

Region	HBV DNA		Abnormal ALT	
	Proportion of people with HBeAg	Proportion of people with >2,000 IU/mL	Proportion of people with >20,000 IU/mL	Proportion of people with ALT>ULN	Proportion of people with ALT >2 times ULN
Americas	12.8%	12.9%	6.4%	34.7%	6.4%
Europe	13.7%	31.4%	13.3%	54.9%	13.3%
World Wide	17.7%	28.2%	10.1%	30.8%	11.0%

Region	Proportion of HBsAg-positive patients with selected stages of liver fibrosis		
	F2	F3	F4 (cirrhosis)
Americas	5%	6%	7.3%
Europe	37%	18%	14.2%
World Wide	21%	18%	9.5%

Approximately 9% of HBsAg-positive participants had cirrhosis, and 10% had HBV DNA exceeding 20,000 IU/mL. Around one third had raised ALT levels on at least one occasion. Estimates of treatment eligibility according to guidelines varied between 12% - 25%.

Source: https://pubmed.ncbi.nlm.nih.gov/33197397/

Current HBV Treatment Guidance - Standard of Care Is Not Curative

Treatment Is Primarily Based on the Combination of 3 Criteria: HBV DNA, Serum ALT, and Severity of Liver Disease

EASL 2020 Guidelines

Recommendations	Grade of evidence	Grade of recommendation
Should be treated		
• Patients with HBeAg-positive or -negative chronic hepatitis B*	I	1
• Patients with cirrhosis, any detectable HBV DNA, regardless of ALT level	I	1
• Patients with HBV DNA >20,000 IU/mL and ALT >2x ULN, regardless of severity of histological lesions	II-2	1
May be treated		
• Patients with HBeAg-positive chronic HBV infection† >30 years old, regardless of severity of liver histological lesions	III	2
Can be treated		
• Patients with HBeAg-positive or -negative chronic HBV infection and family history of HCC or cirrhosis and extrahepatic manifestations‡	III	2

*Defined by HBV DNA >2,000 IU/ml, ALT >ULN and/or at least moderate liver necroinflammation or fibrosis;
†Defined by persistently normal ALT and high HBV DNA levels;
‡Even if typical treatment indications are not fulfilled

Grade of evidence: I – randomized controlled trial; II-2 - Cohort or case-control analytical studies; III - Opinions of respected authorities, descriptive epidemiology
Grade of recommendation: 1 – Strong recommendation; 2 – Weaker recommendation

Source: EASL 2020 Guidelines

Takeaways From the 2019 EASL-AASLD HBV Treatment Endpoints Conference

1. A “functional” cure is achievable and should be defined as sustained HBsAg loss (based on assays with lower limit of detection [LLOD] ~0.05 IU/mL) in addition to undetectable HBV DNA 6 months post-treatment.
   - Covalently closed circular (ccc) DNA is still present in the liver in very small amounts or in a transcriptionally inactive state, and integrated HBV DNA is still present. Thus, HBV reactivation can occur spontaneously or upon immunosuppression.
2. The primary endpoint of phase III trials should be functional cure; HBsAg loss with or without anti-HBs seroconversion 6 months after treatment, plus HBV DNA to undetectable levels.
   - HBsAg loss in ≥15% of patients is deemed clinically significant by GSK.
3. Sustained virologic suppression (undetectable serum HBV DNA) without HBsAg loss 6 months after discontinuation of treatment would be an intermediate goal.
4. Demonstrated validity for the prediction of sustained HBsAg loss was considered the most appropriate criterion for the approval of new HBV assays to determine efficacy endpoints.
5. Clinical trials aimed at HBV functional cure should initially focus on patients with HBeAg-positive or -negative chronic hepatitis, who are treatment-naïve or virally suppressed on nucleos(t)ide analogues.
6. A hepatitis flare associated with an increase in bilirubin or international normalized ratio should prompt temporary or permanent cessation of an investigational treatment.
7. New treatments must be as safe as existing nucleos(t)ide analogues.

Source: https://pubmed.ncbi.nlm.nih.gov/31713892/

Efficacy of Approved First-Line Antiviral Therapies in Adults with HBeAg Negative Treatment-Naïve Chronic Hep B

HBeAg Negative	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate	Tenofovir Alafenamide
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)	19 (<80 IU/mL)	90-91 (<50-60 IU/mL)	93 (<60 IU/mL)	90 (<29 IU/mL)
% Normalization ALT	59	78-88	76	81
% HBsAg loss	**4**	**0-1**	**0**	**<1**

Note: Not head-to-head comparisons

Current treatment options induce HBsAg loss (functional cure) in only 1-4% of HBeAg negative patients.

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Efficacy of Approved First-Line Antiviral Therapies in Adults with HBeAg Positive Treatment-Naïve Chronic Hep B

HBeAg Positive	Peg-IFN	Entecavir	Tenofovir Disoproxil Fumarate	Tenofovir Alafenamide
% HBV-DNA suppression (cutoff to define HBV-DNA suppression)	8-14 (<80 IU/mL)	61 (<50-60 IU/mL)	76 (<60 IU/mL)	73 (<29 IU/mL)
% HBeAg loss	32-36	22-25	-	22
% HBeAg seroconversion	29-36	21-22	21	18
% Normalization ALT	34-52	68-81	68	-
% HBsAg loss	**2-7**	**4-5**	**8**	**1**

Note: Not head-to-head comparisons

Current treatment options induce HBsAg loss (functional cure) in only 1-4% of HBeAg positive patients.

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Comparison of PegIFN vs. NA Therapy

Features	PegIFN	ETV, TDF, TAF
Route of administration	Subcutaneous injections	Oral
Treatment duration	48 weeks	Long-term until HBsAg loss
Tolerability	Low	High
Long-term safety concerns	Very rarely persistence of on-treatment AEs	Probably not
Contraindications	Many	None
Strategy	Induction of a long-term immune control	Inhibition of viral replication
Level of viral suppression	Moderate	Universally high
Effect on HBeAg loss	Moderate	Low in first year, moderate over long term
Effect on HBsAg levels	Variable	Low
Risk of relapse after treatment cessation	Low for those with sustained response 6–12 months after therapy	Moderate if consolidation treatment provided after HBeAg seroconversion. High for HBeAg-negative disease
Early stopping rules	Yes	No
Risk of viral resistance	No	Minimal to none

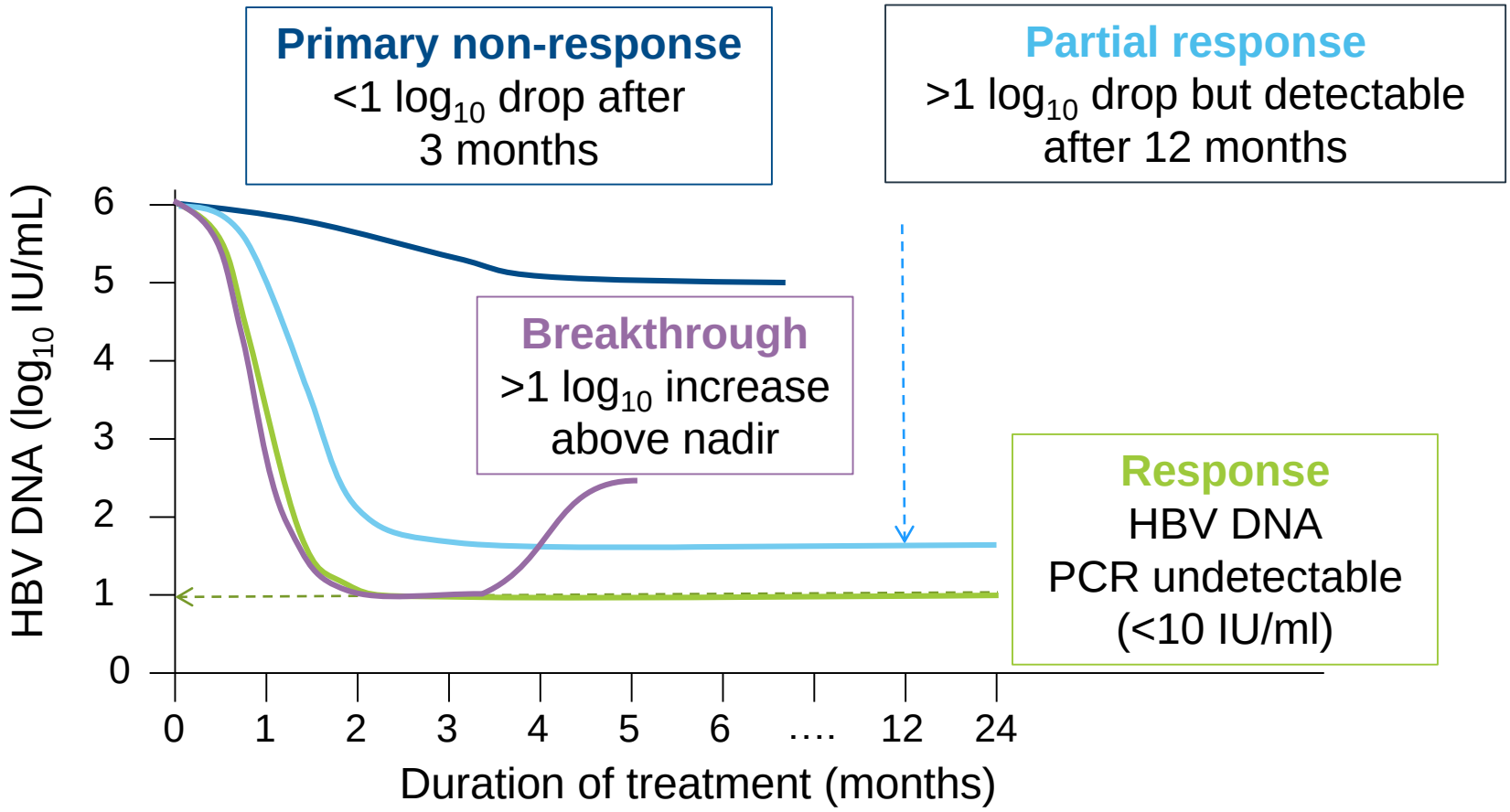
*Source:*EASL CPG HBV. J Hepatol 2017;67:370–98/ EASL HBV 2020 Report

Framing Response to Treatment

Responses	NA therapy	PegIFNα therapy	Functional Cure (Bepirovirsen and PBGENE-HBV)
Virological (on-treatment)	**Response:** HBV DNA <10 IU/ml **Primary non-response:** <1 log_{10} decrease in HBV DNA after 3 months of therapy **Partial response:** HBV DNA decreased by >1 log_{10} but still detectable after ≥12 months of therapy in compliant patients **Breakthrough:** confirmed HBV DNA increase of >1 log_{10} above on-therapy nadir	**Response:** HBV DNA <2,000 IU/ml	Functional cure is achievable and should be defined as sustained HBsAg loss (based on assays with lower limit of detection [LLOD] ~0.05 IU/mL) in addition to undetectable HBV DNA 6 months post-treatment
Virological (off-treatment)	**Sustained response:** HBV DNA <2,000 IU/ml for ≥12 months after end of therapy		
Serological	HBeAg loss and development of anti-HBe (for HBeAg positive patients) HBsAg loss and development of anti-HBs		
Biochemical	ALT normalization (confirmed by ALT determination at least every 3 months for at least 1 year post-treatment)		
Histological	Decrease in necroinflammatory activity without worsening in fibrosis compared with pre-treatment histological findings		

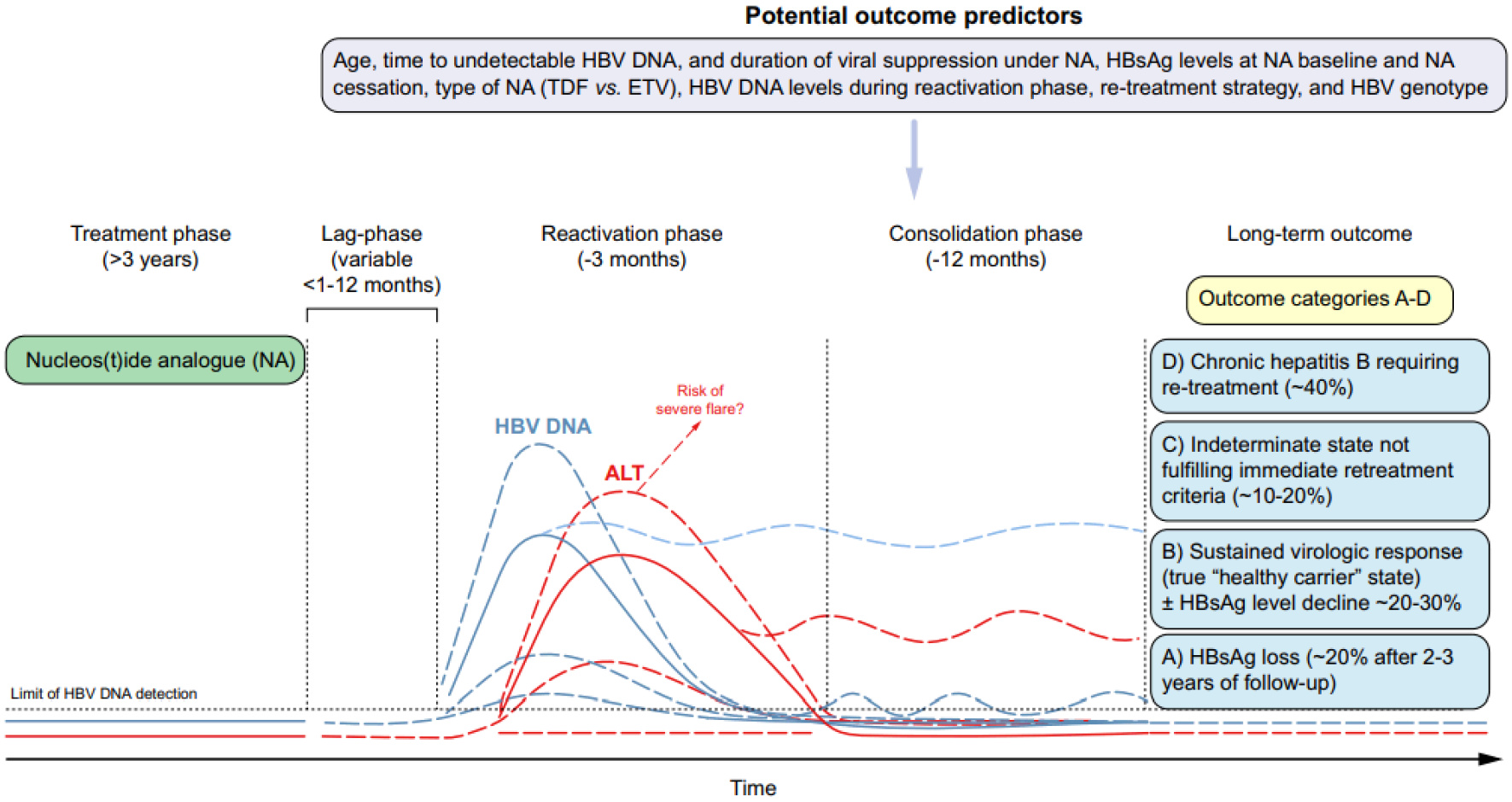
*Source:*EASL CPG HBV. J Hepatol 2017;67:370–98/ EASL HBV 2020 Report

Time Course of Potential Viral Responses to NA Therapy



*Source:*EASL CPG HBV. J Hepatol 2017;67:370–98/ EASL HBV 2020 Report

Potential Outcomes in Patients with HBeAg-negative CHB After NA Treatment Discontinuation



Virologic relapse (HBV DNA >2,000 IU/mL and clinical relapse (HBV DNA >2,000 IU/mL and ALT >2x ULN) are common when NA treatment is discontinued.

Source: https://pubmed.ncbi.nlm.nih.gov/31713892/

EASL Patient Monitoring Recommendations

Monitoring recommendations
ALT and serum HBV DNA • All patients treated with NAs
Renal monitoring • Patients at risk of renal disease treated with any NA • All patients treated with TDF, regardless of renal risk
Switch to ETV or TAF • Should be considered in patients on TDF at risk of development of, and/or with, underlying renal or bone disease
Long-term surveillance recommendations
HCC surveillance recommended • All patients under effective long-term NA therapy
HCC surveillance mandatory • All patients with cirrhosis or with moderate or high HCC risk scores at the onset of NA therapy

*Source:*EASL CPG HBV. J Hepatol 2017;67:370–98/ EASL HBV 2020 Report

Cessation Criteria for CHB Treatment

	KASL	AASLD	EASL	APASL
HBeAg-Positive	1) HBsAg loss 2) HBeAg loss or seroconversion with 12 months consolidation plus undetectable HBV DNA	1) HBeAg seroconversion with 12 months consolidation plus undetectable HBV DNA 2) Treat until HBsAG is lost	1) HBsAg loss with or without anti-HB seroconversion 2) HBeAg seroconversion with 12 months consolidation plus undetectable HBV DNA	1) HBeAg seroconversion with 12 months consolidation (preferably 3 years) 2) HBsAg loss or seroconversion
HBeAg-Negative	1) HBsAg loss	1) Indefinite 2) May be considered after HBsAg loss	1) HBsAg loss with or without seroconversion 2) May be considered after > 3 years virological suppression after NA therapy	1) HBsAg loss or seroconversion 2) Undetectable HBV DNA for at least 2 years on 3 separate occasions, each 6 months apart

Note: KASL, Korean Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, Asian-Pacific Association for the Study of the Liver
Note: In liver cirrhosis patients, indefinite treatment is generally recommended

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7641563/

Recommendations for Treatment of Patients With HBeAg-Negative, Immune-Active CHB

AASLD 2018 Hepatitis B Guidance

Patients with HBeAg-Negative, Immune-Active Adults With Chronic Hepatitis B

- AASLD recommends indefinite antiviral therapy for adults with HBeAg-negative, immune-active CHB
- Antiviral therapy is not recommended for persons without cirrhosis who are HBeAg-negative with normal ALT activity and low-level viremia (<2,000 U/mL; “inactive” CHB)

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Recommendations for Treatment of Patients with Immune-Active Disease

AASLD 2018 Hepatitis B Guidance

Patients with Immune Active Disease

- Antiviral therapy (peg-IFN, entecavir, or tenofovir) is recommended for adults with immune-active CHB (HBeAg-negative or HBeAg-positive) to decrease the risk of liver-related complications
  - Note: Immune-active CHB is defined by an elevation of ALT ≥2x the ULN or evidence of significant histologic disease plus elevated HBV DNA above 2,000 IU/mL (HBeAg-negative) or above 20,000 IU/mL (HBeAg-positive)
- Therapy is recommended for persons with immune-active CHB and cirrhosis if HBV DNA is >2,000 IU/mL, regardless of ALT level
- Head-to-head comparisons of antiviral therapies fail to show superiority of one therapy over another in achieving risk reduction in liver-related complications
- For patients treated with peg-IFN, 48 weeks' duration is used in most studies and is preferred. This treatment duration yields HBeAg seroconversion rates of 20%-31% and sustained off-treatment HBV-DNA suppression of <2,000 IU/mL in 65% of persons who achieve HBeAg to anti-Hbe seroconversion. The combination of peg-IFN has not yielded higher rates of off-treatment serological or virological responses and is not recommended
- Treatment with antivirals does not eliminate the risk of HCC, and surveillance for HCC should continue in persons who are at risk

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Recommendations for Treatment of Patients with Immune-Tolerant Disease

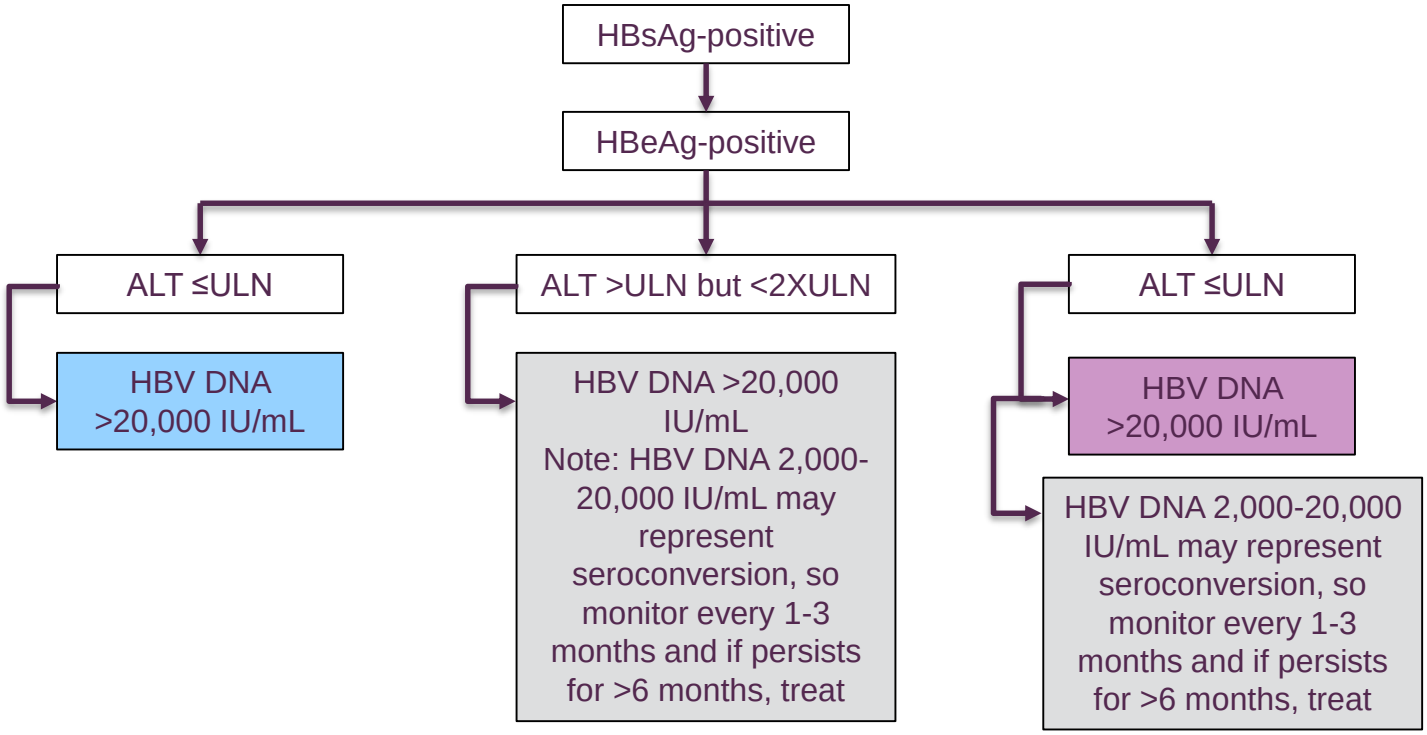
AASLD 2018 Hepatitis B Guidance

Patients with Immune-Tolerant Adults With Chronic Hepatitis B

- AASLD recommends against antiviral therapy for adults with immune-tolerant CHB
- Note: Immune-tolerant status should be defined by ALT levels, utilizing 35 U/L for men and 25 U/L for women as ULN rather than local laboratory ULN
- ALT levels should be tested at least every 6 months for adults with immune tolerant CHB to monitor for potential transition to immune-active or immune-inactive CHB
- Antiviral therapy is recommended in adults >40 years of age with normal ALT and elevated HBV DNA (1,000,000 IU/mL) and liver biopsy specimen showing significant necroinflammation or fibrosis
- Moderate-to-severe necroinflammation or fibrosis on a liver biopsy specimen is a reason to consider initiation of antiviral therapy if other causes of liver disease are excluded

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Treatment Flow Chart for HBsAg-Positive Persons Without Cirrhosis & HBeAg-Positive



Recommendations:

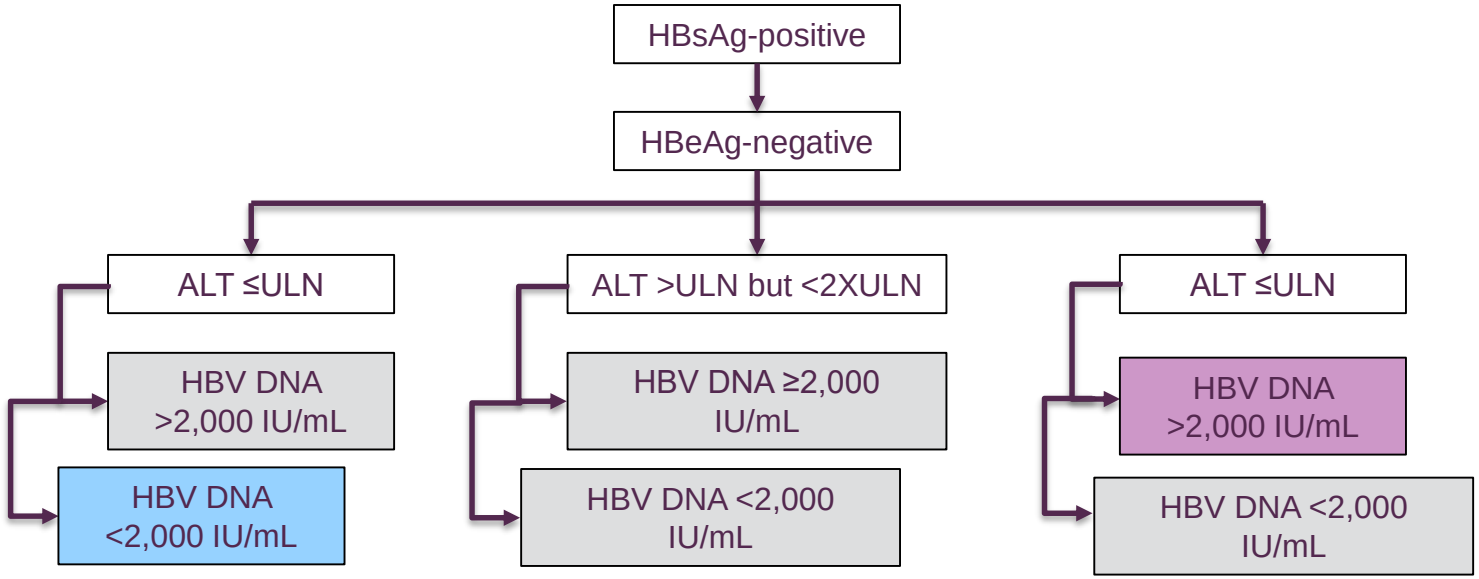
Treat

Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBeAg every 6-12 months

Exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If other causes of ALT>ULN exclude and elevations persists, treat, especially if age >40

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Treatment Flow Chart for HBsAg-Positive Persons Without Cirrhosis & HBeAg-Negative



Recommendations:

Treat

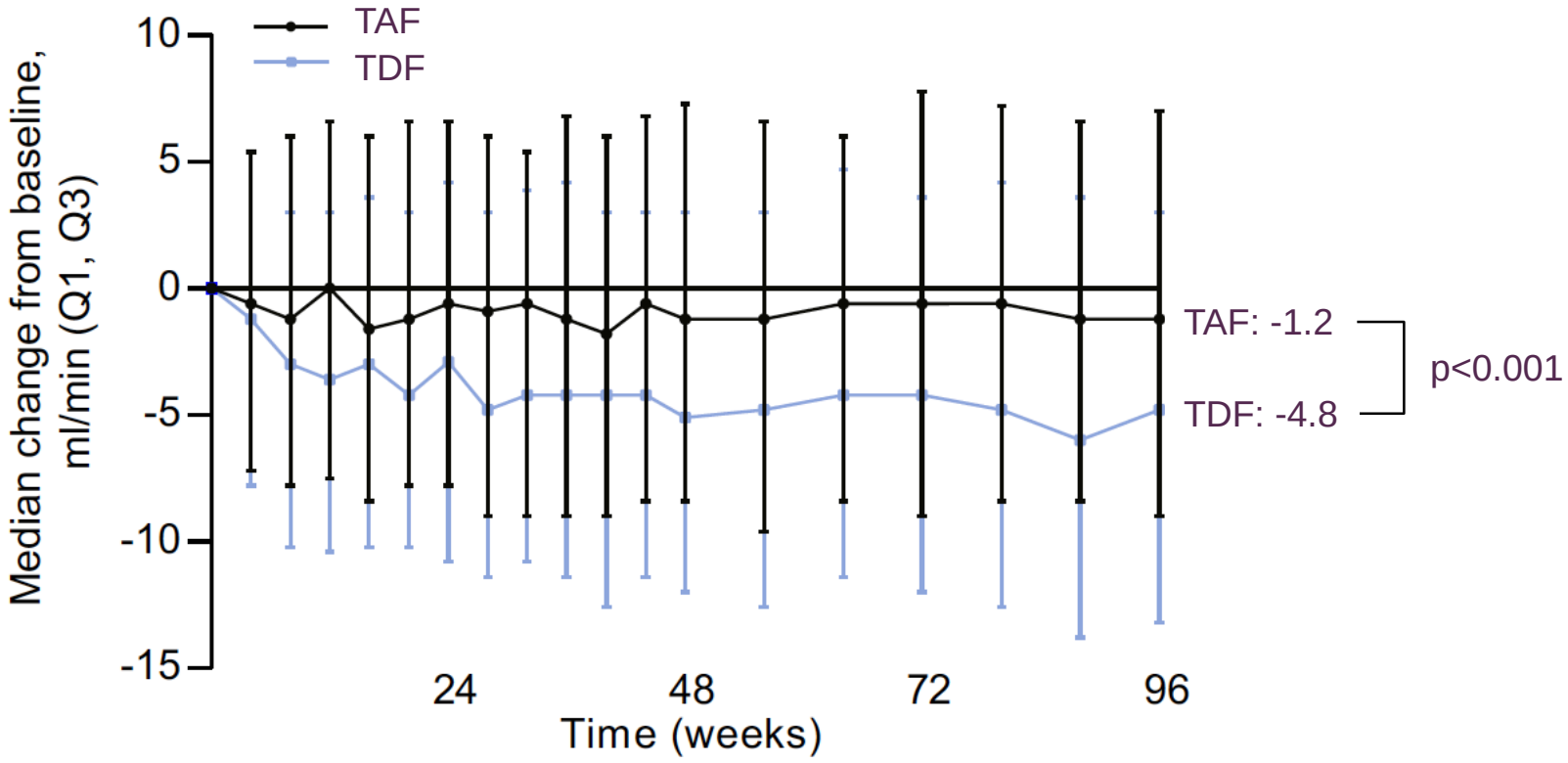
Do not treat. Monitor with ALT and HBV DNA levels every 3-6 months and HBsAg annually

If ALT <ULN, monitor ALT and HBV DNA every 3 months for 1 year, then every 6 months.
If ALT elevated, exclude other causes of ALT elevation and assess disease severity with non-invasive tests and/or liver biopsy. If staging indicates ≥F2 or ≥A3, treat. If persistent ALT>ULN with HBV DNA ≥2000 IU/mL, treat, especially if age >40

Source: https://pubmed.ncbi.nlm.nih.gov/29405329/

Tenofovir alafenamide (TAF) vs. Tenofovir disoproxil fumarate (TDF) Change in eGFR in HBV Patients

Median change from baseline in eGFR over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)

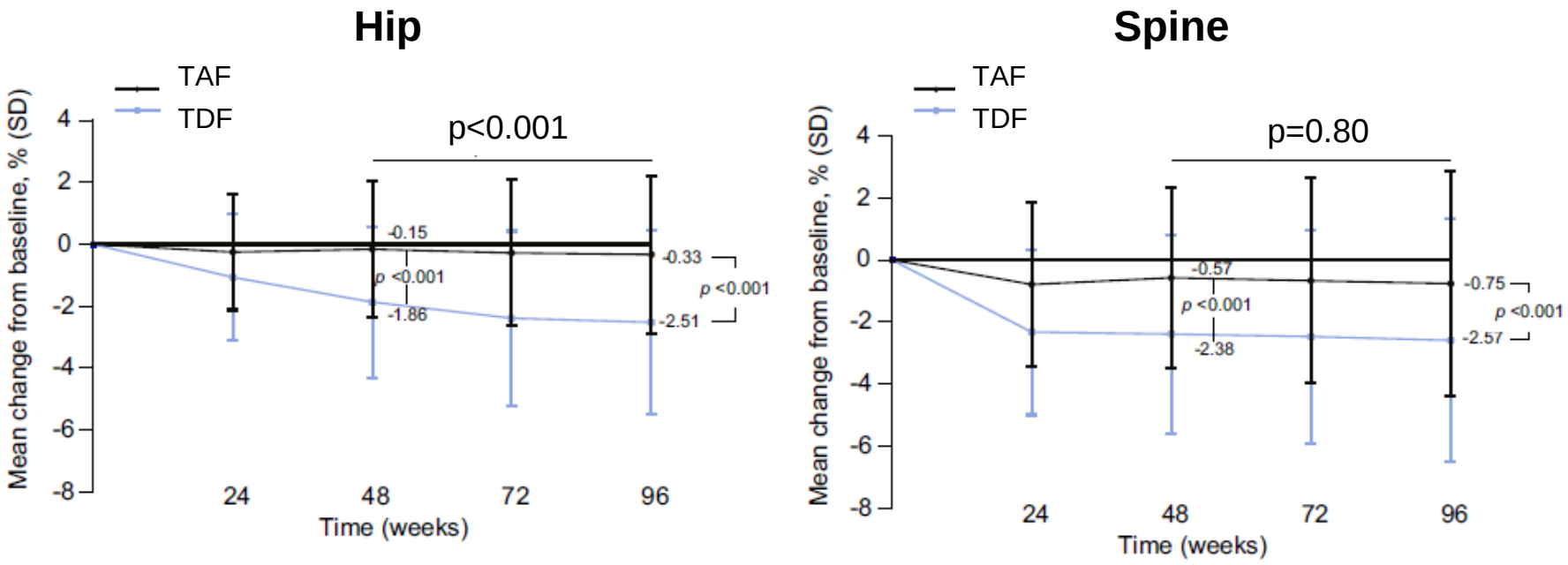


TAF leads to an approximate -1.2% change in eGFR from baseline over 96 weeks vs. -4.8% change in eGFR from baseline for TDF.

*Source:*Agarwal K, et al. J Hepatol 2018;68:672□81/ EASL HBV 2020 Report

Tenofovir alafenamide (TAF) vs. Tenofovir disoproxil fumarate (TDF) Change in BMD in HBV Patients

Median change from baseline in BMD over 96 weeks
TAF 25 mg (n=866) vs. TDF 300 mg (n=432)



TAF leads to an approximate -0.33% change in hip BMD from baseline over 96 weeks vs. -2.51% change in spine BMD from baseline for TDF.

*Source:*Agarwal K, et al. J Hepatol 2018;68:672□81/ EASL HBV 2020 Report

Partial Virological Response During CHB Treatment Definitions

	KASL	AASLD	EASL	APASL
Partial response definition	Decreased but detectable level of HBV DNA after at least 48 weeks of therapy using high genetic barrier drugs (24 weeks for low genetic barrier drugs)	Plateau in the decline of HBV DNA and/or failure to achieve an undetectable HBV DNA level after 96 weeks of therapy	Decrease in HBV DNA level of more than 1 $\log_{10}$ IU/mL but HBV DNA remains detectable after at least 12 months of therapy	Reduction of serum HBV DNA level >1 log IU/mL but still detectable at 24 weeks of therapy

Note: KASL, Korean Association for the Study of the Liver; AASLD, American Association for the Study of Liver Diseases; EASL, European Association for the Study of the Liver; APASL, Asian-Pacific Association for the Study of the Liver

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7641563/

Assessment of ALT Elevations During CHB Treatment

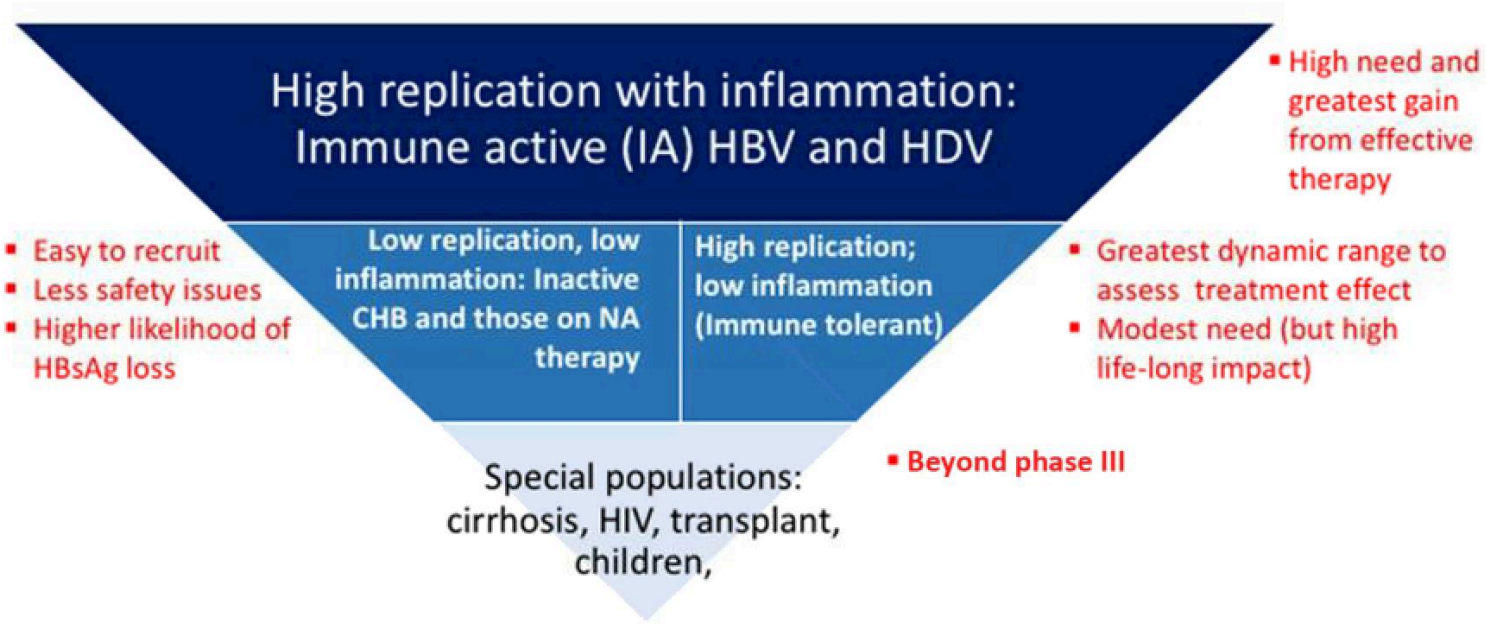
ALT elevations represent a major concern in HBV drug development. Due to known elevated liver enzymes at baseline, guidelines have proposed a new evaluation matrix based on baseline and post-treatment ALT levels. Elevations associated with an increase in bilirubin, INR, or hepatic decompensation require discontinuation of treatment.

Guidelines Stopping Criteria in HBV Patients with ALT Flares During Treatment

Baseline ALT Value	Elevation During Treatment
1 to < 2x ULN	>5x from baseline and > 10x ULN
2x to less than 5x ULN	>3x from baseline
≥ 5x ULN	>2x from baseline

Source: https://pubmed.ncbi.nlm.nih.gov/31713892/

Prioritization of Patient Populations for Clinical Trials

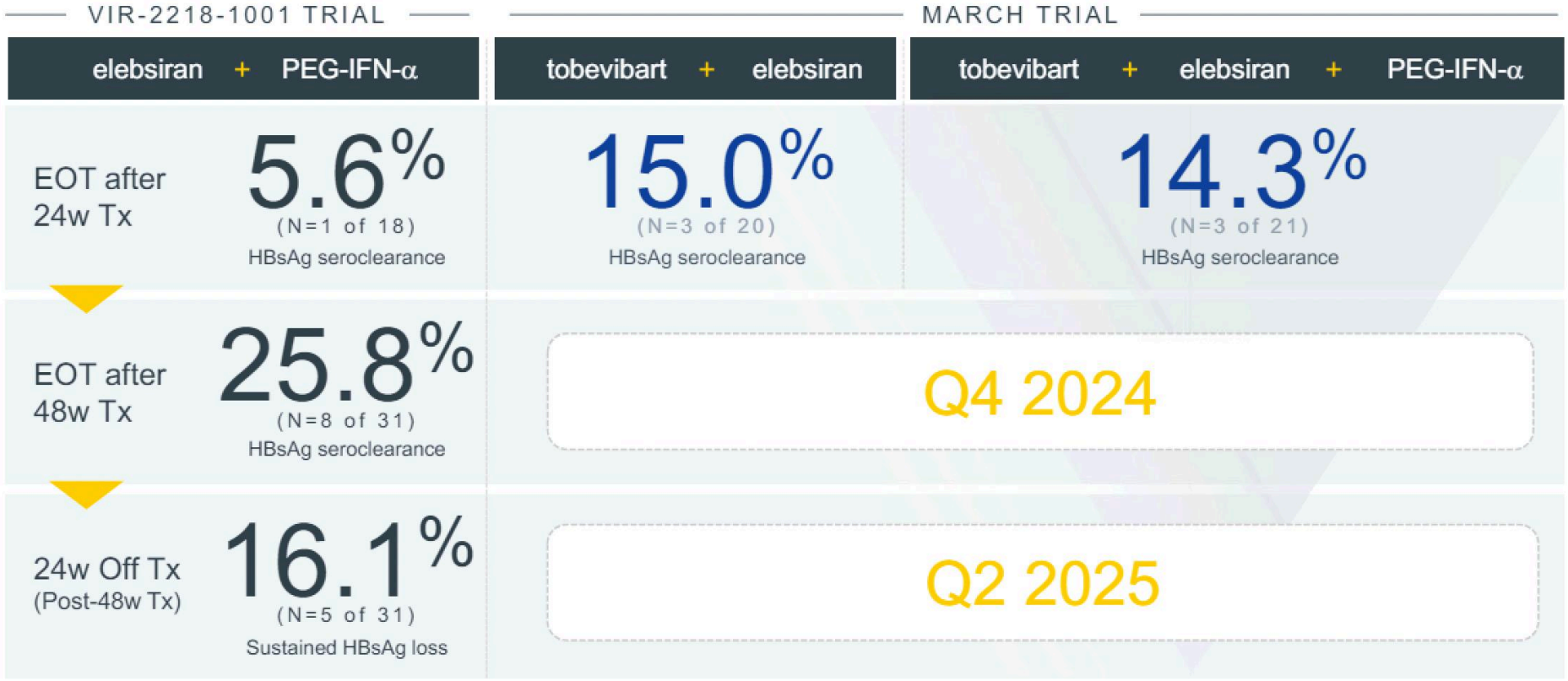


- Patients with immune-active CHB, high levels of HBV replication >20,000 IU/mL, and hepatic inflammation have the greatest immediate need for treatment
- Patients with HBeAg-positive infection (immune tolerant phase), who have low risk of liver complications, specifically if less than 30 years old, may benefit from a finite therapy with high rate of HBsAg loss. Most of this group are without fibrosis, thus functional cure would likely prevent long-term liver complications
- Due to potential heterogeneity, consideration should be given to baseline HBsAg, HBV DNA or ALT levels, HBeAg status, combination of treatments, and genotype stratification during trial design

Source: https://pubmed.ncbi.nlm.nih.gov/31713892/

Can siRNA + Immunomodulator Combos Match Bepi?
- Data from VIR, ROG-SWX and EASL 2024

VIR: Utilizing Two Approaches with Potential for Achieving a Functional Cure (1/3)

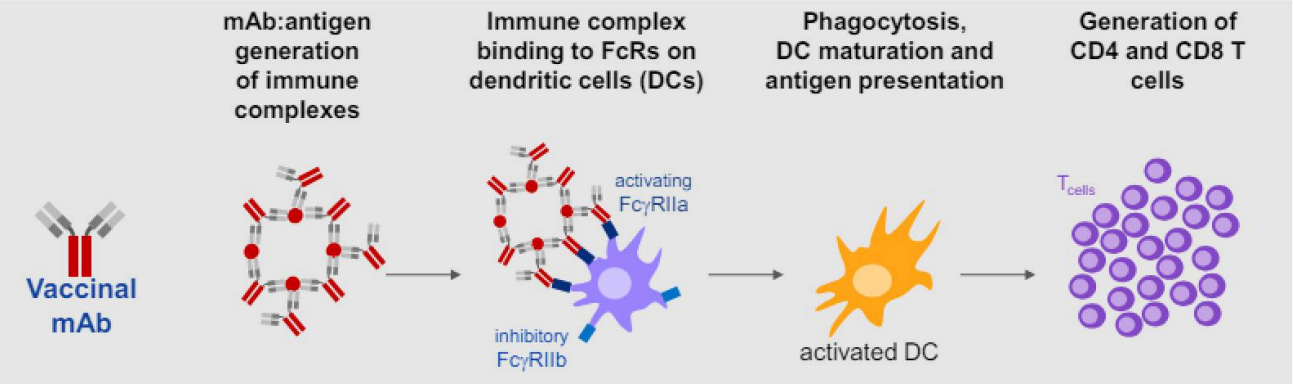


Vir's approach includes: Tobevibart (neutralizing mAb engineered for immune engagement) + Elebsiran (siRNA) with or without Peg-IFN. Data indicate 3x increase in HBsAg seroclearance adding Tobevibart on top of elebsiran – potentially implying immunoactivity components of the mAb.

Vir plants to update MARCH Trial data sets in Q4 2024 and Q2 2025, respectively.

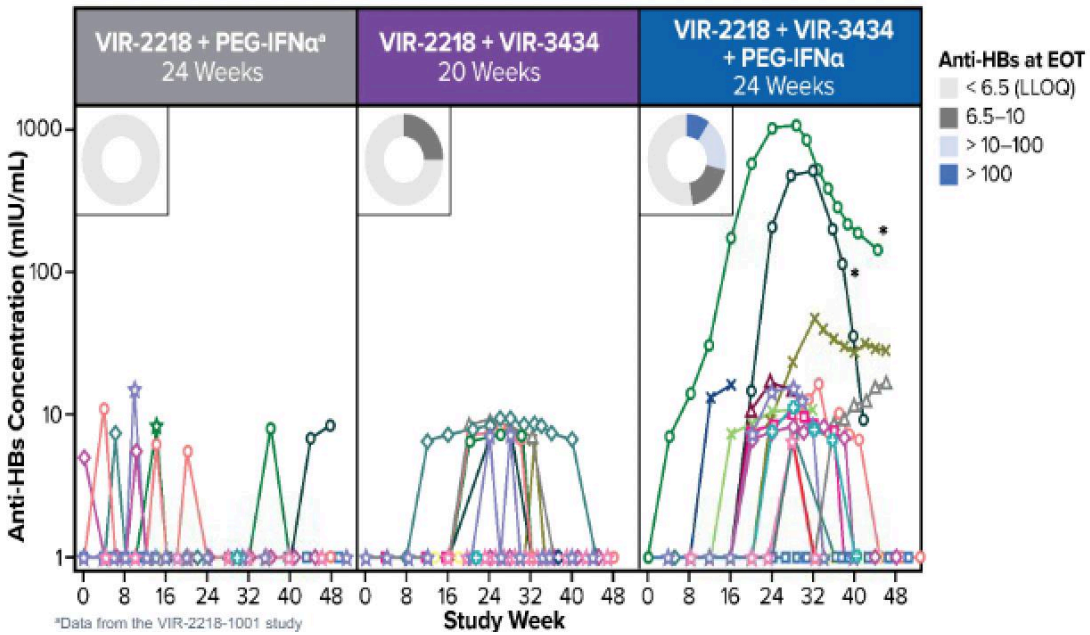
Source: VIR Corporate Presentation

VIR: mAb Immune Complex Generation may Enhance Immunostimulation (2/3)



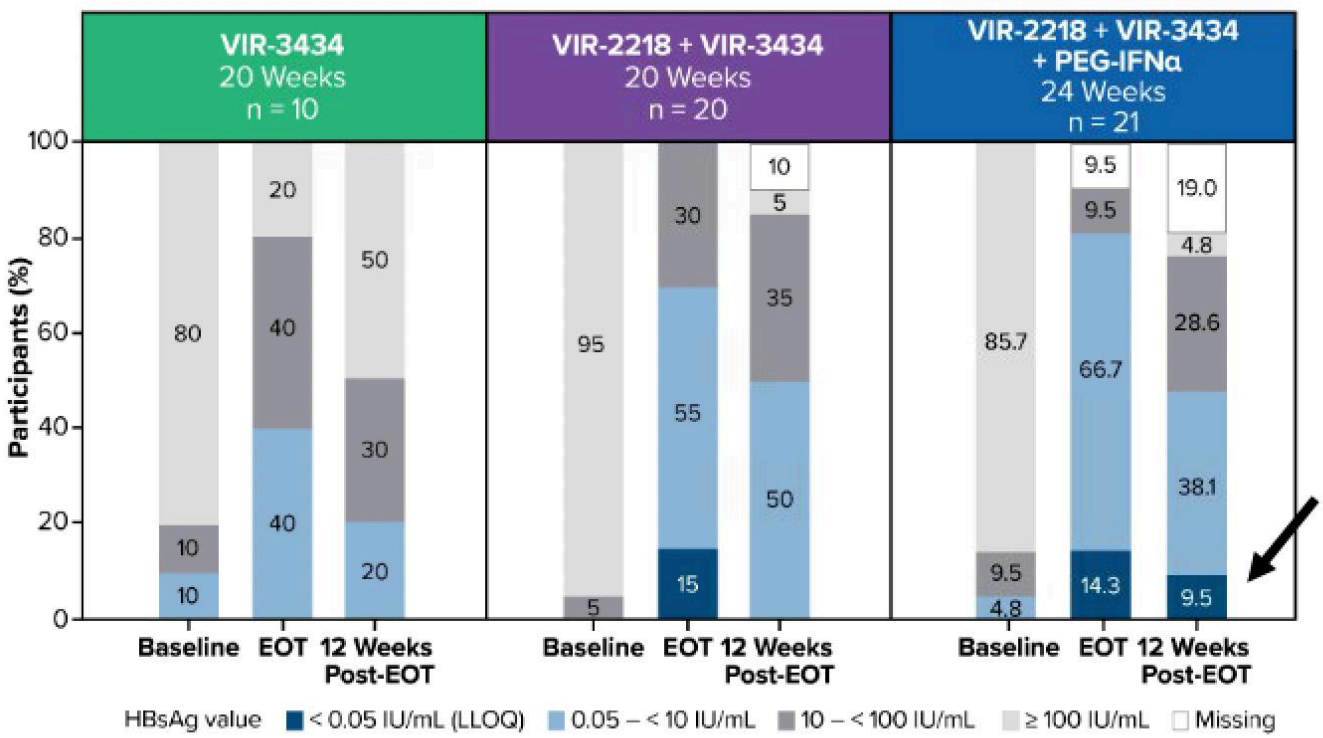
Tobevibart may contain natural immunostimulatory properties based on mAb:antigen immune complexes leading to generation of CD4 and CD8 T cells.

Available data suggests VIR-2218 (elebsiran; siRNA) combined with VIR-3434 (tobevibart; mAb) elicits a similar immune response vs. siRNA + Peg-IFN. The highest anti-HBs concentrations were observed in the 2 participants in the VIR-2218 + VIR-3434 + PEG-IFNα cohort who maintained HBsAg loss through 12 weeks post end of treatment.



Source: VIR Corporate Presentation

VIR: Peg-IFN on Top of VIR-2218 (Elebsiran; siRNA) + VIR-3434 (Tobevibart; mAb) May be Necessary to Drive Sustained Functional Cures Based on Preliminary Data (3/3)



EOT, end of treatment; HBsAg, hepatitis B surface antigen; LLOQ, lower limit of quantitation.

Per the company:

At 12 weeks post-EOT, 2 participants in the VIR-2218 + VIR-3434 + PEG-IFNα cohort maintained HBsAg loss; *all other participants with HBsAg loss at EOT experienced a rebound*

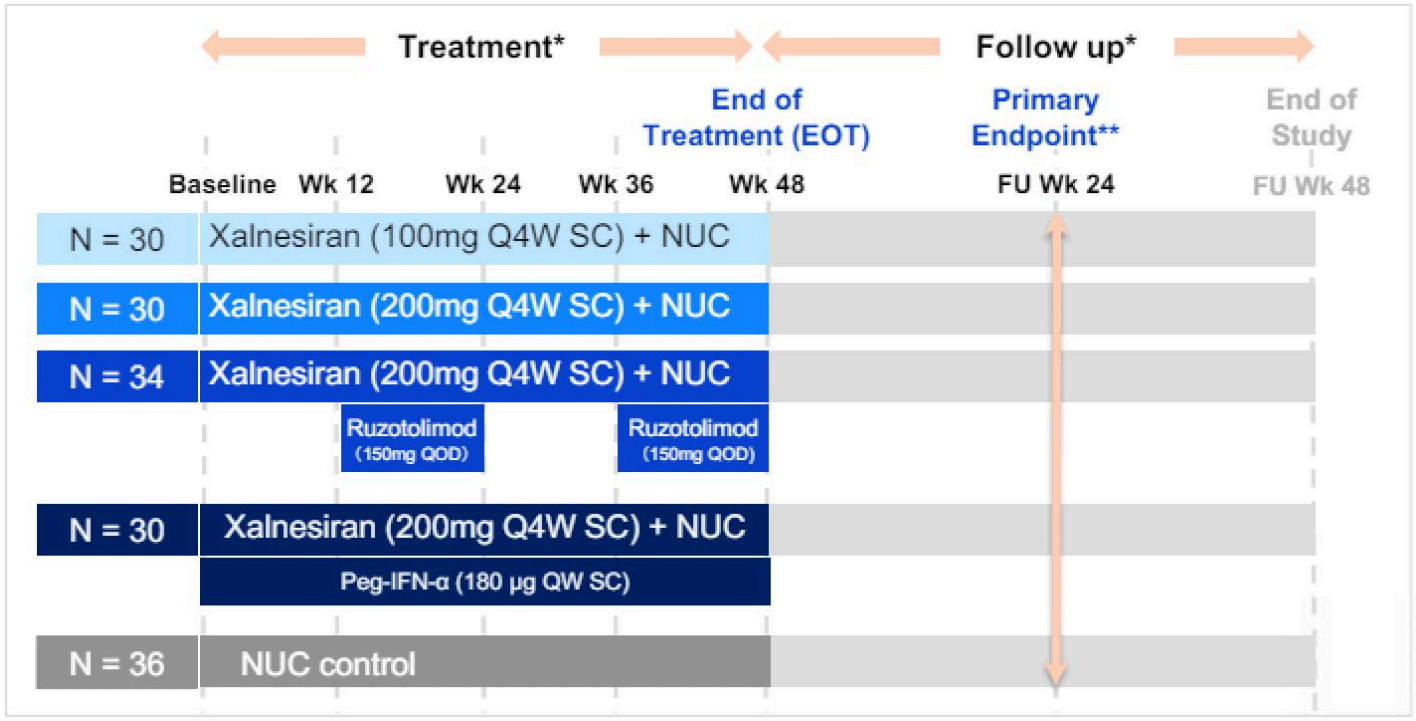
Source: VIR Corporate Presentation

Roche: Primary Endpoint Results from the Phase 2, Randomized, Controlled, Adaptive, Open-Label Platform Study (PIRANGA) (1/2)

PIRANGA Trial Design

Participants

- CHB infection ≥6 months
- On NUC (ETV or TDF or TAF) monotherapy for ≥12 months
- HBV DNA below the LLOQ or <20 IU/mL
- ALT <1.5 x ULN
- Non-cirrhotic



Roche examined the combination of Xalnesiran (HBV siRNA) plus immunomodulators, including:

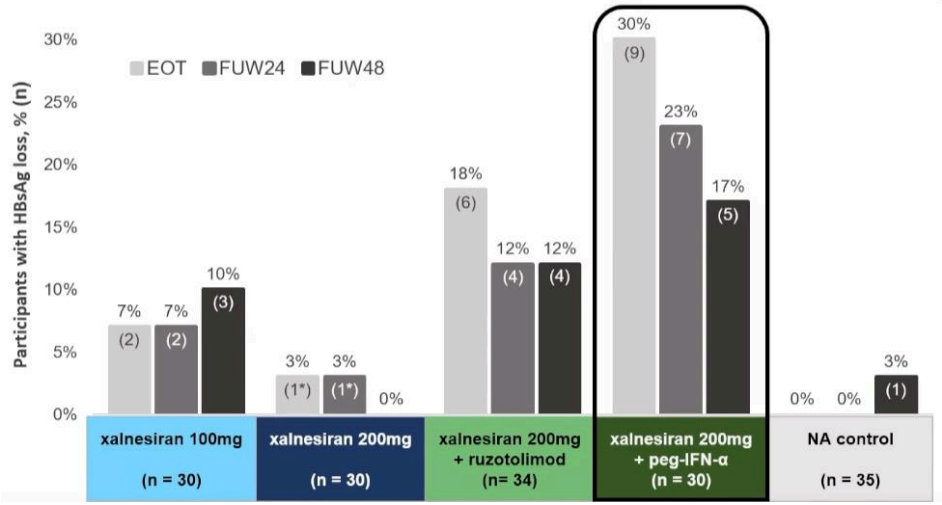
1) Ruzotolimod (TLR7 agonist) - Double pro-drug selectively activated in the liver designed to stimulate cytokine production and dendritic cell activation, or;
2) Peg-IFN – To inducer innate antiviral immune response.

The primary endpoint was percentage of participants with HBsAg loss at 24 weeks post end of treatment.

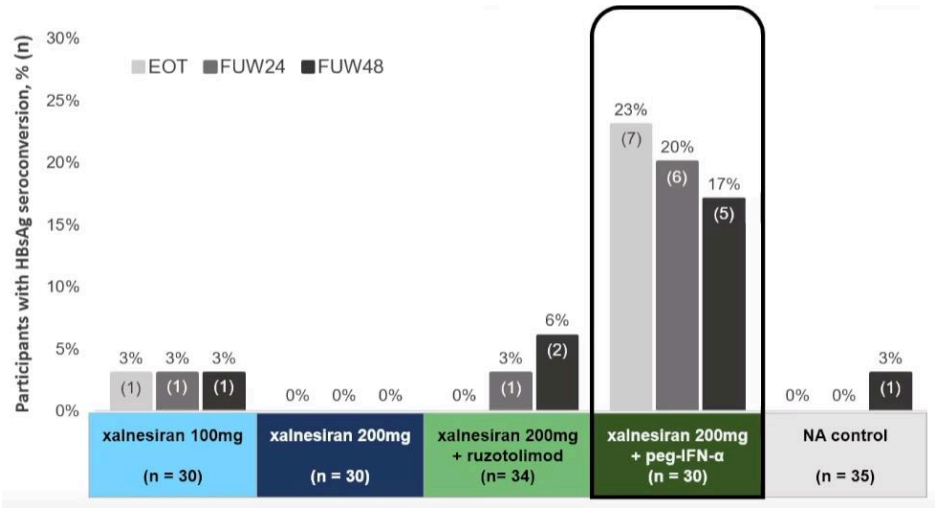
Source:https://medically.roche.com/content/dam/pdmahub/restricted/oncology/apasl-2024/APASL-2024-presentation-hou-efficacy-and-safety-of-xalnesiran.pdf

Roche: HBsAg Loss Observed only in Participants with Baseline HBsAg <1000 IU/mL (2/2)

HBsAg loss at EOT and through 48-week post-treatment follow-up



HBsAg seroconversion at EOT, and at follow-up weeks 24 and 48



All participants with HBsAg loss had undetectable HBV RNA by 24 weeks post end of treatment.

HBsAg loss observed only in participants with baseline HBsAg <1000 IU/mL.

HBsAg seroconversion at 48 weeks post end of treatment included:

- n=5 xalnesiran+Peg-IFN
- n=2 xalnesiran+ruzotolimod
- n=1 xalnesiran 100mg

Roche's siRNA appears to perform best in combination with Peg-IFN.

Source:Roche EASL 2024 presentation

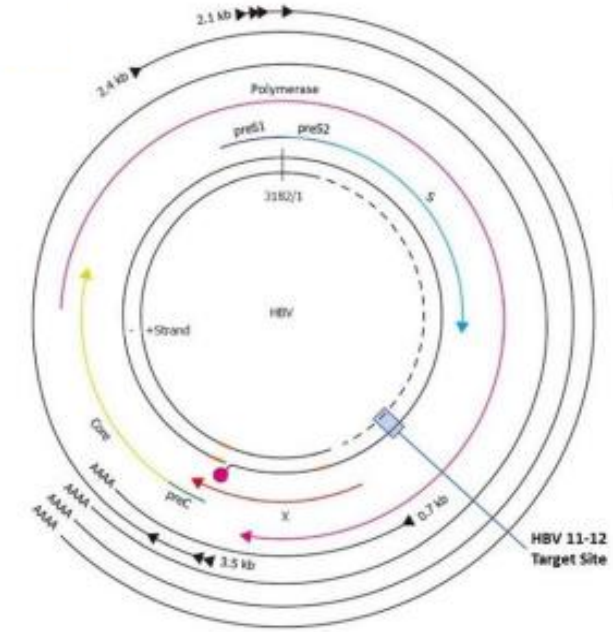
PBGENE-HBV
- The Potential of Curative HBV Editing

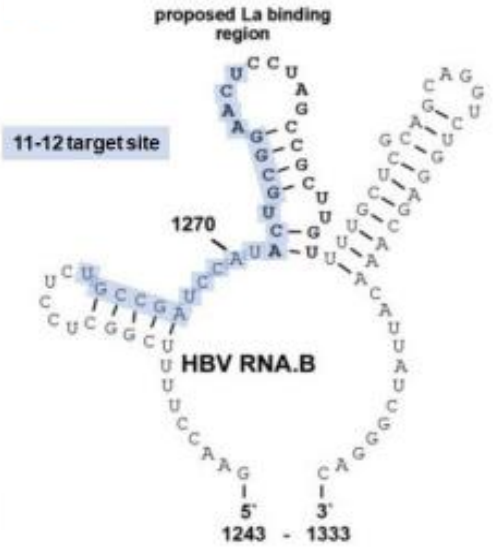
PBGENE-HBV's Target Site Conserved Across >92% of Isolates Across Genotypes

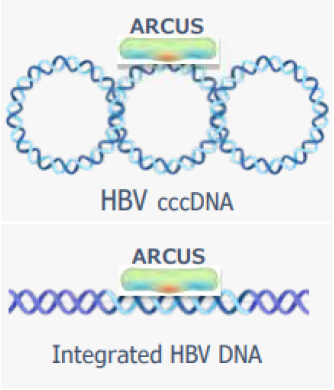
Precision's ARCUS editor recognizes a highly conserved sequence in cccDNA that is present in greater than 92% of isolates across genotypes.

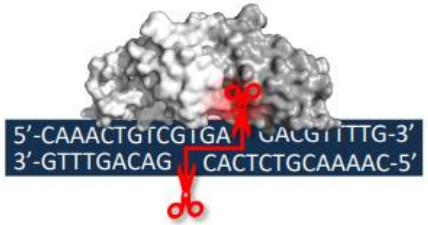
Targeted sequence in integrated HBV DNA (bp 1,259-1,280) is highly conserved across viral variants.

ARCUS recognizes its target in the 23S rRNA gene, eliminating cccDNA and inactivating integrated HBV DNA to produce durable antigen loss.







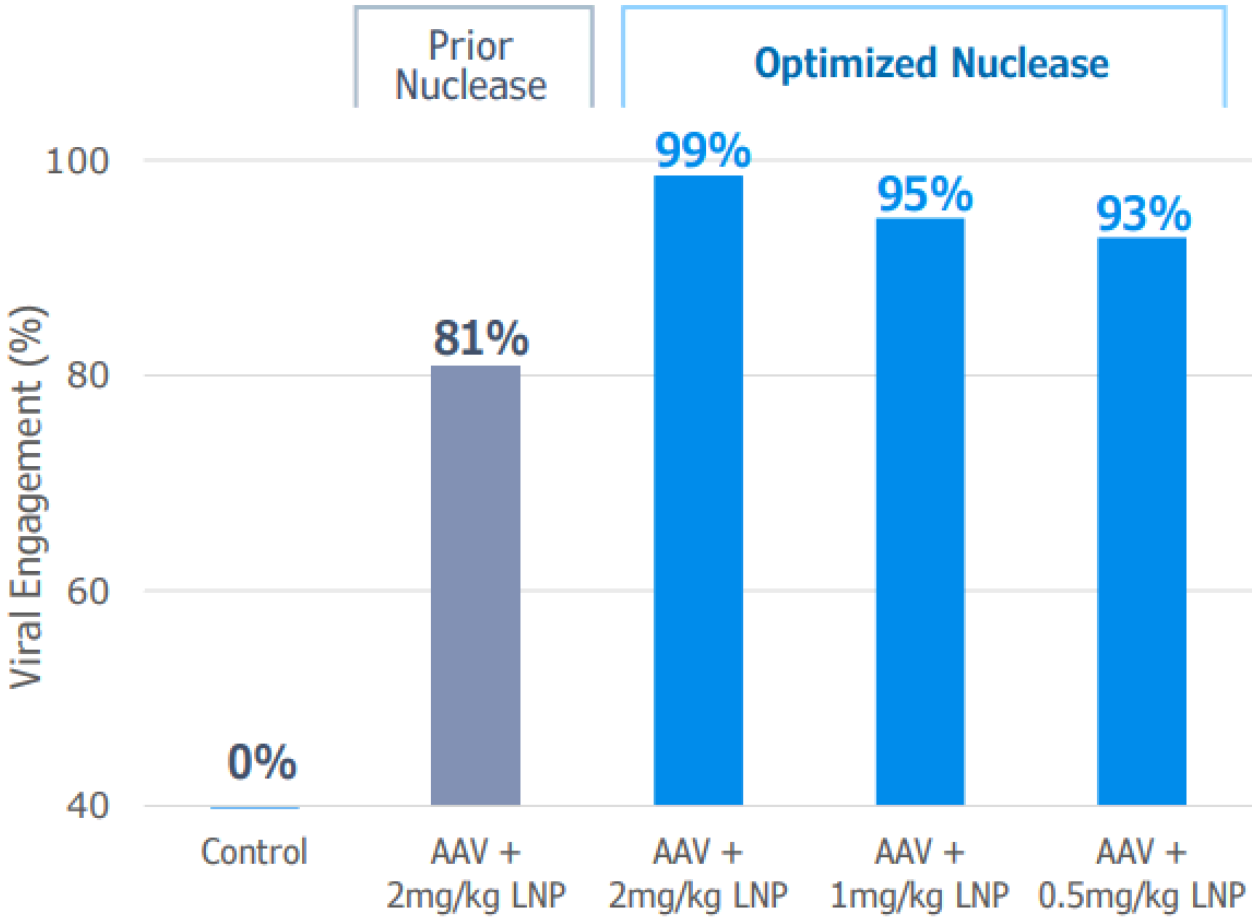


Source: DTIL AASLD 2023 Poster; DTIL Corporate Deck

Final Optimized Clinical Candidate (PBGENE-HBV) Demonstrates Up to 99% Viral Engagement

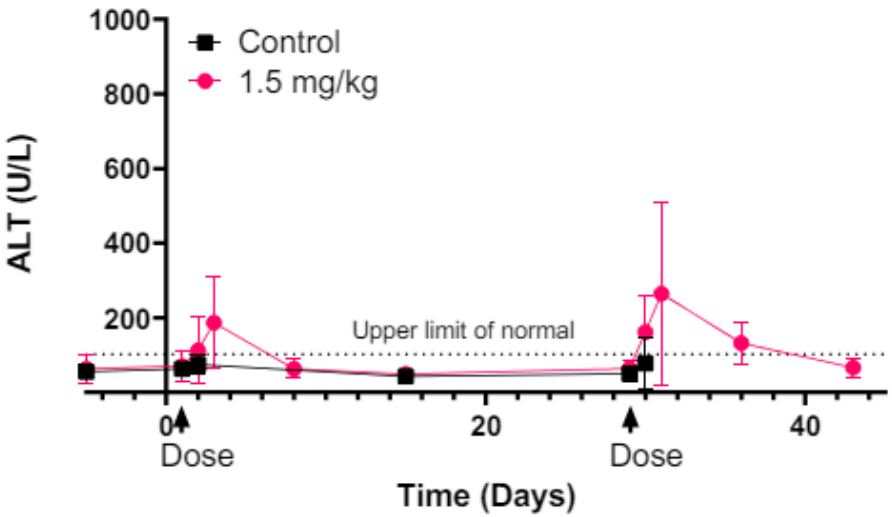
- NHPs were administered AAVs containing HBV cccDNA, with subsequent 2 doses of PBGENE-HBV.
- The optimized PBGENE-HBV ARCUS editor resulted in 81% eliminated cccDNA and 18% indels of cccDNA, measured at day 90.
- We anticipate PBGENE-HBV will be the first gene editor tailored for multi-course treatment in humans.

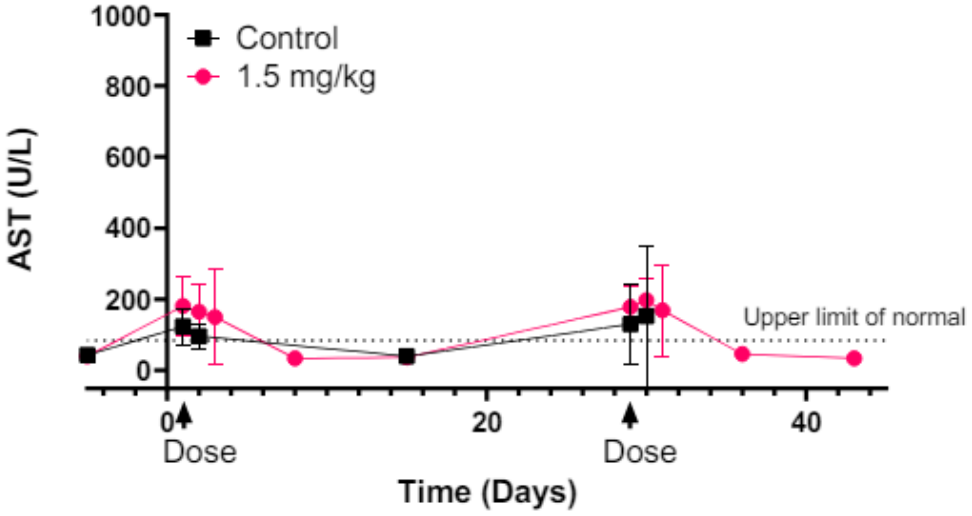
2 Doses of PBGENE-HBV 42 Days Apart in NHPs

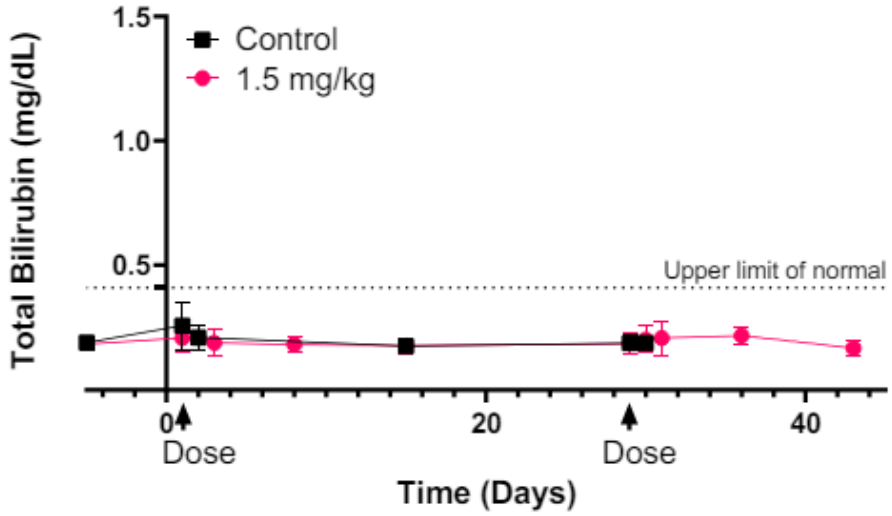


Source: DTIL Corporate Deck

Dual-Course PBGENE-HBV Results in Transient ALT/AST Elevations





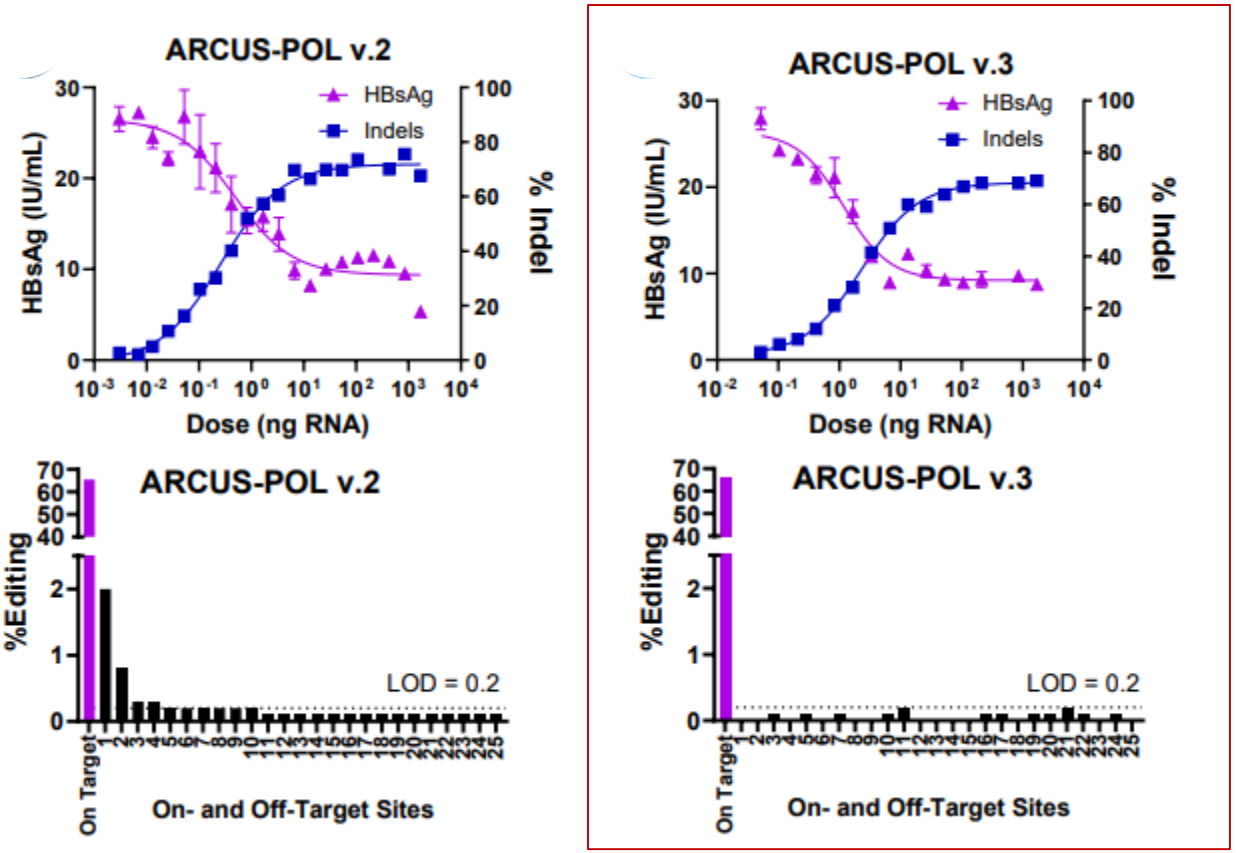


DTIL examined the safety of dual-course PBGENE-HBV in an NHP model. Transient ALT and AST elevations were observed following LNP +/- ARCUS administration, which returned to baseline approximately 7 days after therapeutic administration.

Of note, there was no incremental ALT/AST elevation following the second dose of LNP injection, suggesting no memory-based immune response to ARCUS editors.

Source: https://precisionbiosciences.com/wp-content/uploads/2024/06/PBGENEHBV-EASL-2024-poster_final.pdf

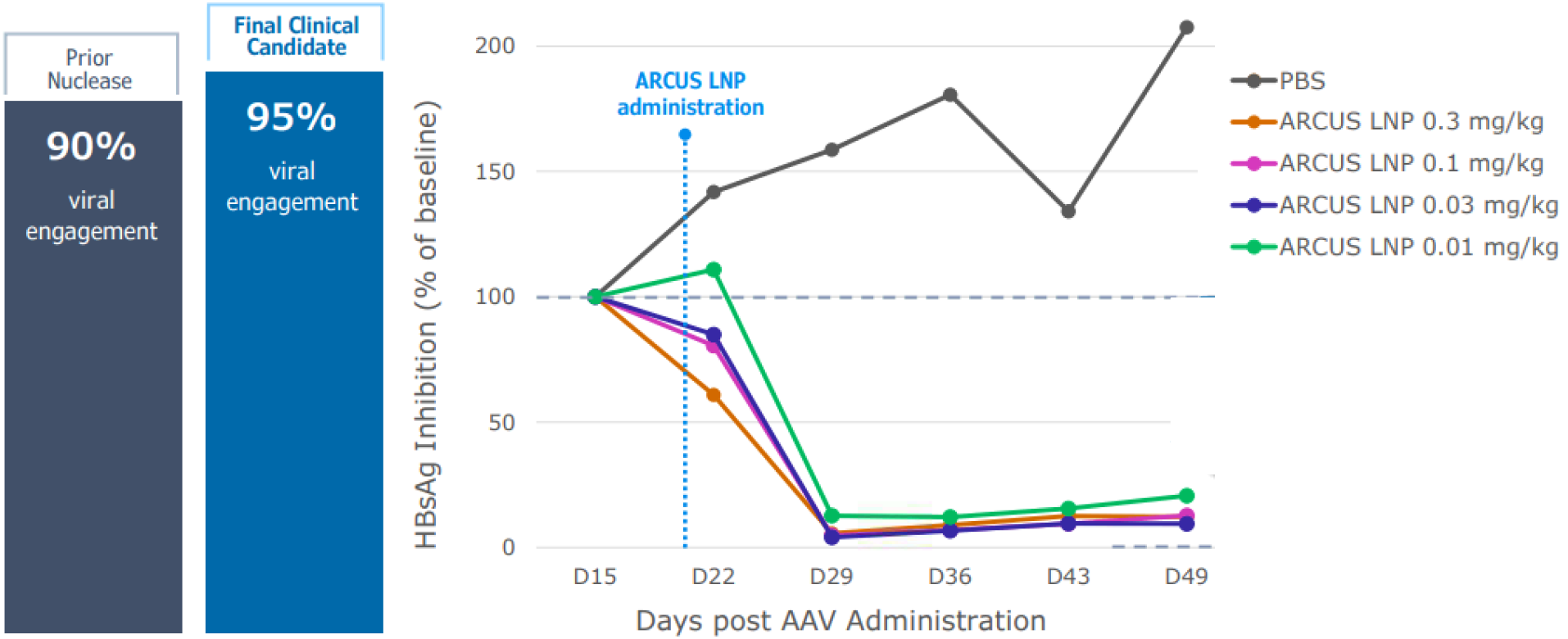
PBGENE-HBV Final Clinical Candidate Optimized for Enhanced Specificity



ARCUS-POL v.3 editor maintains on-target potency and achieves no off-target editing across 384 potential off-target sites. Prior generation ARCUS-POL v.2 demonstrated considerably higher off-target editing.

Source: DTIL AASLD 2023 Poster

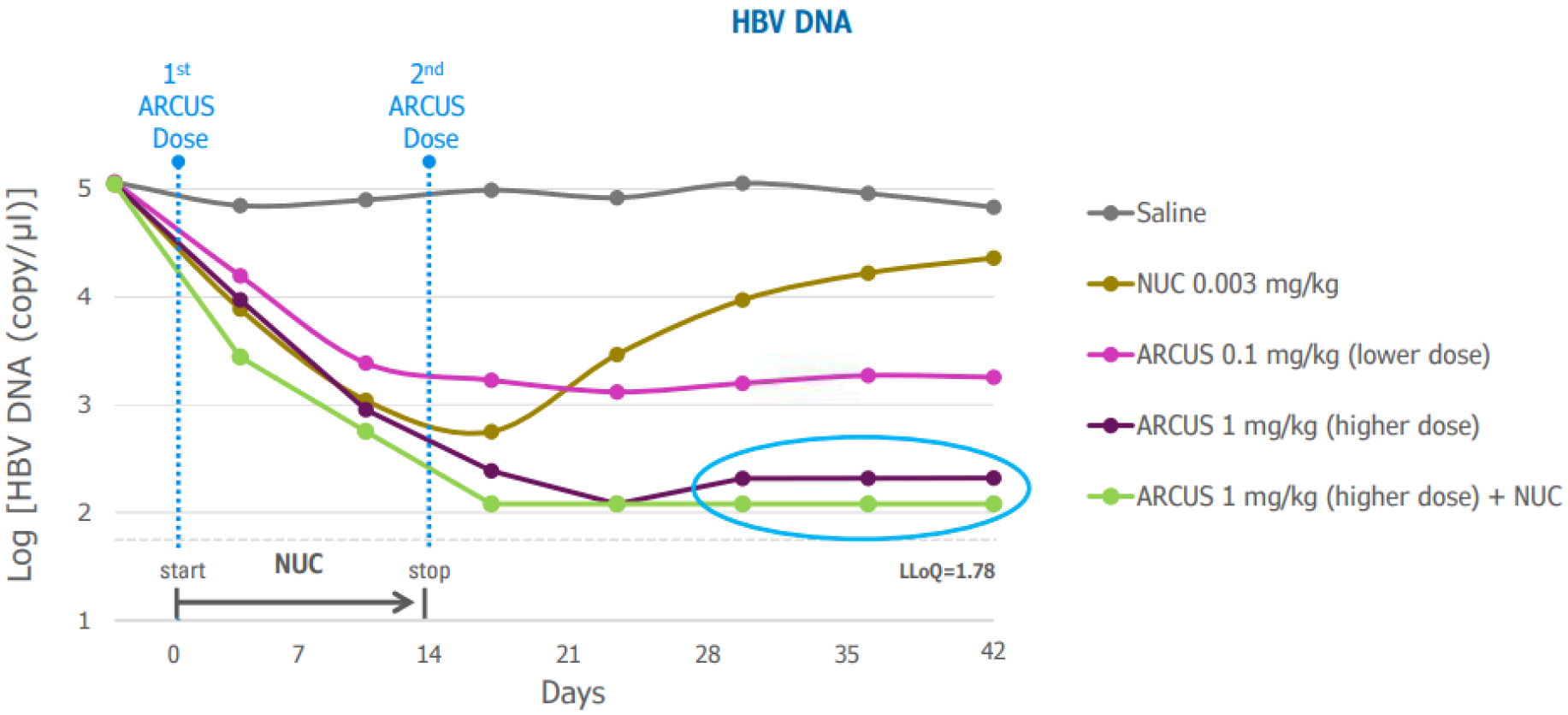
In Episomal Mouse Model, PBGENE-HBV Resulted in 95% HBsAg Reduction



PBGENE-HBV was administered at day 21 post AAV administration. Treatment demonstrated 95% viral engagement (elimination and inactivation through indels) and 95% HBsAg reduction.

Source: DTIL Corporate Deck

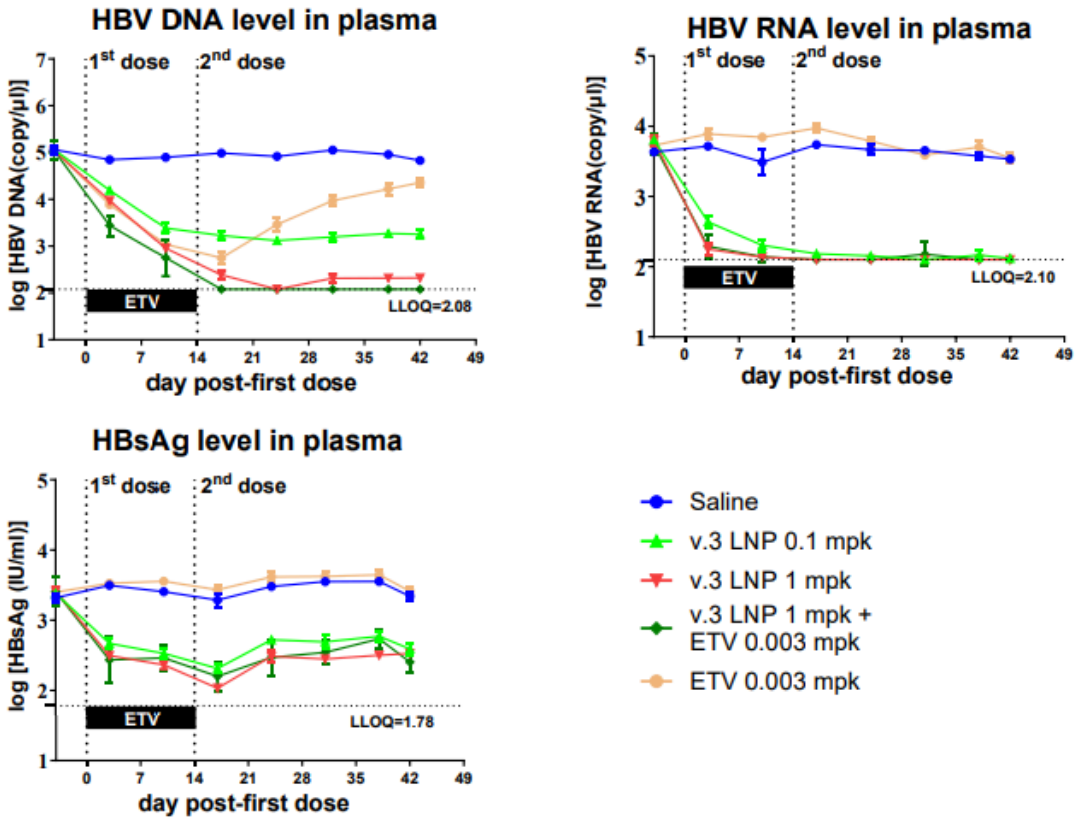
In Transgenic Mouse Model, PBGENE-HBV Resulted in Significant HBV DNA Reduction



PBGENE-HBV was administered twice, 14 days apart. Treatment durably reduced HBV DNA (as measured in plasma) after stopping nucleos(t)ide analog.

Source: DTIL Corporate Deck

Fully Optimized ARCUS-POL v.3 Durably Reduces HBV DNA, HBV RNA, and HBsAg in Transgenic HBV Mouse Model



Mice were administered two doses of ARCUS-POL v.3 fourteen days apart or in combination with a 14-day course of entecavir. HBV DNA and HBV RNA reached the LLOQ, and HBsAg trended toward the LLOQ.

Source: DTIL AASLD 2023 Poster

Select Public and Private Chronic Hepatitis B Focused Companies

Arbutus Biopharma (ABUS): Complementary Mechanisms to Pursue an HBV Cure

Select Members of Management

- CEO: Michael J. McElhaugh
- CFO: David C. Hastings
- CSO: Michael J. Sofia PhD
- CMO: Karen Sims, MD, PhD

Company Description

Leveraging the proven track record of success established with the team's expertise in understanding and treating viral infections by discovering and developing a differentiated pipeline of therapies targeting chronic HBV.

Source: ABUS corporate presentation

Aligos Therapeutics (ALGS): Building a Pipeline of Potentially Best-in-Class Drug Candidates for Chronic Liver Diseases and Viral Infections

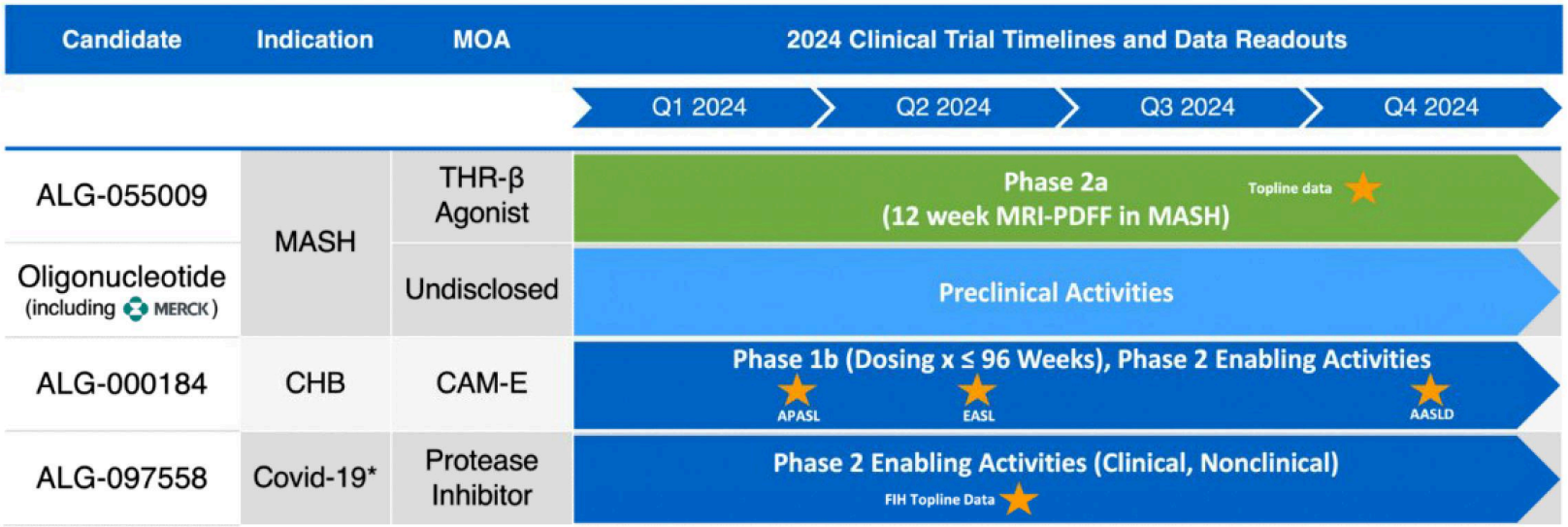
ALIGOS THERAPEUTICS

Select Members of Management

- CEO: Lawrence M. Blatt, Ph.D., M.B.A.
- CFO: Lesley Ann Calhoun
- CSO: Julian Symons, D.Phil.

Company Description

Aligos is building a pipeline of potentially best-in-class drug candidates. These drug candidates target multiple clinically validated mechanisms of action and are designed to become transformative treatment options for MASH and viral diseases.



Source: ALGS corporate presentation

Assembly Bio (ASMB): Focused on Transforming Treatment of Serious Viral Diseases

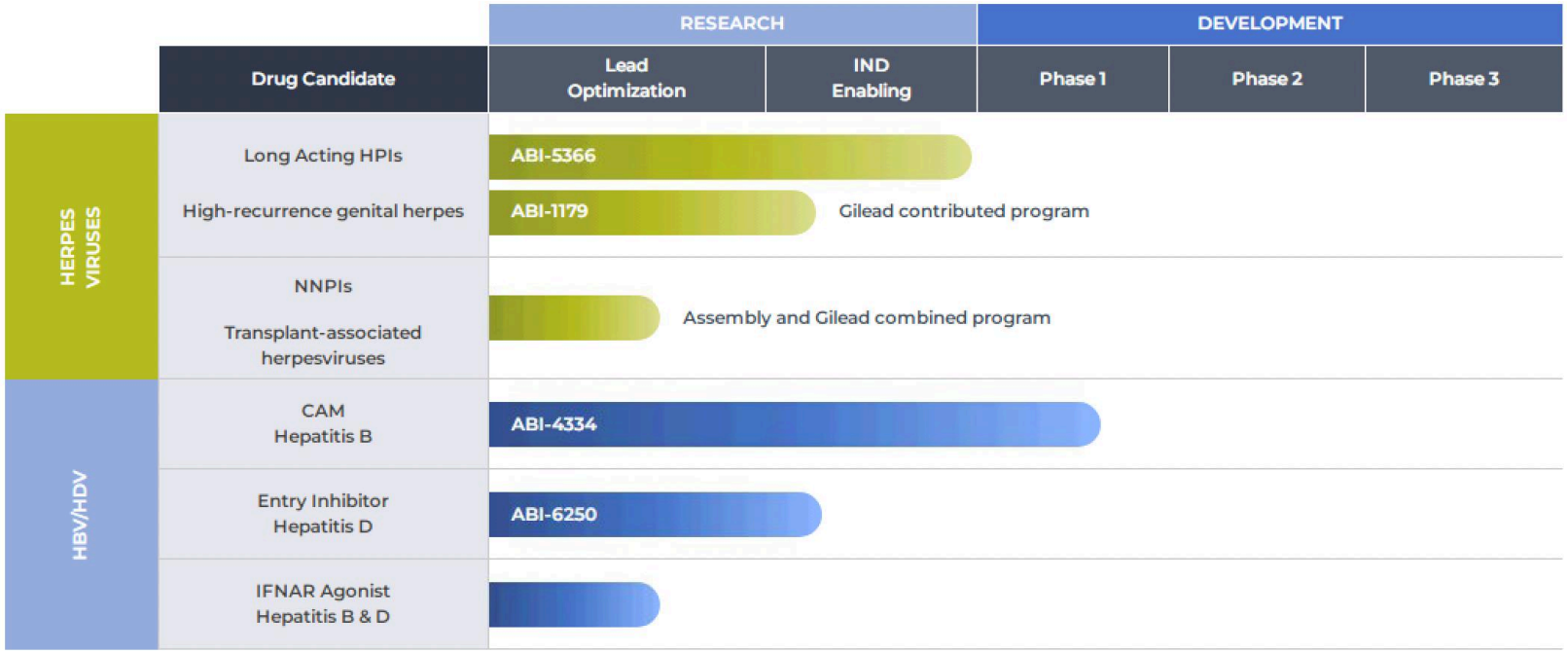
assemblybio

Select Members of Management

- CEO: Jason Okazaki
- CSO: William Delaney, PhD
- CMO: Anuj Gaggar, MD, PhD

Company Description

Assembly's pipeline includes a clinical-stage therapeutic candidate for the treatment of chronic HBV and development candidates for the treatment of high-recurrence genital herpes and chronic HDV.



HPI: Helicase-primase inhibitor; NNPI: Non-nucleoside polymerase inhibitor; CAM: Capsid assembly modulator; IFNAR: Interferon-α receptor

Source: ENTA corporate presentation

HOOKIPA Pharma (HOOK): Leveraging Modular Arenavirus Platform to Develop Product Candidates for Multiple Cancers and Infectious Diseases

Select Members of Management

- CEO: Joern Aldag
- CFO: Reinhard Kandera
- CSO: Klaus Orlinger
- COO: Roman Necina

Company Description

HOOKIPA Pharma Inc. is a clinical-stage biopharmaceutical company focused on developing novel immunotherapies to fight cancer and chronic infectious disease.

Source: HOOK corporate presentation

Precision BioSciences (DTIL): Developing PBGENE-HBV for the Treatment of Patients with Chronic Hepatitis B

PRECISION BIOSCIENCES

Select Members of Management

- CEO: Michael Amoroso
- CFO: Alex Kelly
- CRO: Jeff Smith, Ph.D.

Company Description

Precision BioSciences is a clinical stage biotechnology company dedicated to improving life with its novel and proprietary ARCUS genome editing platform.

PROGRAM	INDICATION	TISSUE	TARGET	EDIT TYPE / DELIVERY	RESEARCH	IND-ENABLING	CLINICAL	PARTNER
PBGENE-HBV	Chronic hepatitis B	Liver	HBV	Elimination/LNP				
PBGENE-PMM	m3243 primary mitochondrial myopathy	Muscle	PMM	Elimination/AAV				
PBGENE-DMD	Duchenne muscular dystrophy	Muscle	DMD	Excision/AAV		Returning to Precision Under Assessment		
PBGENE-LIVER	Undisclosed	Liver	—	Insertion/—				
PBGENE-CNS	Undisclosed	CNS	—	—				
iECURE-OTC*	Ornithine transcarbamylase deficiency	Liver	OTC	Insertion/AAV				ECURE
PBGENE-NVS	Sickle cell disease/ beta thalassemia	HSCs	—	Insertion/—				NOVARTIS

*iECURE-OTC also named ECUR-506 under investigation in the OTC-HOPE study

Source: DTIL corporate presentation

Barinthus Biotherapeutics (BRNS): Harnessing its Range of Proprietary Viral Vector and Synthetic Platform Technologies

Select Members of Management

- CEO: Bill Enright
- CFO: Gemma Brown
- CSO: Dr. Nadège Pelletier

Company Description

Barinthus Biotherapeutics is a clinical-stage biopharmaceutical company developing novel T cell immunotherapeutics that guide the immune system to overcome chronic infectious diseases, autoimmunity and cancer.

Program	Product Candidate*	Therapeutic For	Preclinical	Phase 1	Phase 2	Phase 3	Status/Anticipated Upcoming Milestones
Infectious Disease Programs	VTP-300	Chronic Hepatitis B Virus (HBV) infection					Phase 2b & Phase 2a interim analysis (Q2 2024)
	VTP-200	Persistent Human Papillomavirus (HPV) infection					Phase 1b/2 complete, analysis ongoing
Autoimmune Programs	VTP-1000	Celiac disease					Phase 1 initiation (Q3 2024)
Cancer Programs	VTP-800/850	Prostate cancer					Phase 1/2 futility data (2025)

Program	Product Candidate		Partner	Preclinical	Phase 1	Phase 2	Phase 3	Marketed	Barinthus Bio Rights	Status/Anticipated Upcoming Milestones
Cancer Programs	VTP-600	NSCLC/Squamous Esophageal cancer therapeutic in combo. with checkpoint inhibitor + chemo	Ludwig Cancer Research; Cancer Research UK						Worldwide (76% of Sub.)	Phase 1/2a ongoing
Prophylactic Programs	VTP-500	MERS	University of Oxford; CEPI						Worldwide	Initiation of Phase 2
	VTP-400	Zoster	CanSinoBIO						Worldwide (excl. China)	Phase 1 ongoing

Data supporting proof-of-concept announced; ChAdOx only; Existing human clinical data; Near-term proof-of-concept readout

ChAdOx + MVA; SNAP-TI

Source: BRNS corporate presentation

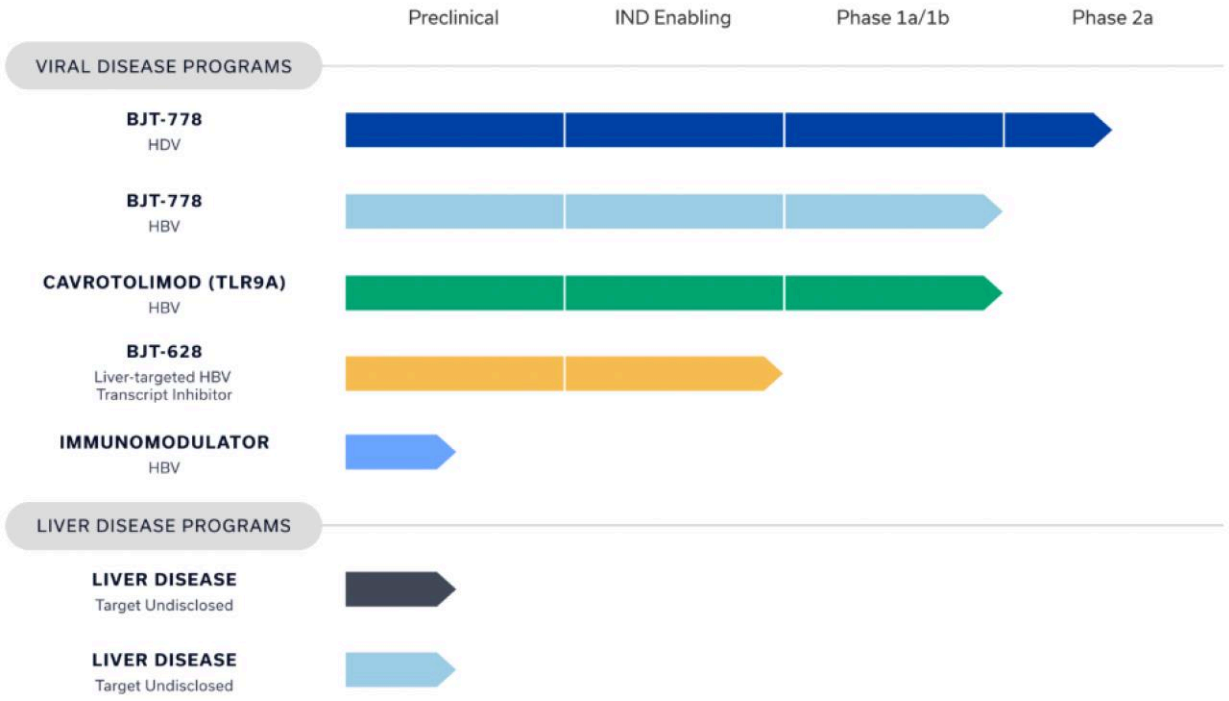
Bluejay Therapeutics (Private): Lead Program, BJT-778, is a Best-in-Class mAb Against Hepatitis B Surface Antigen (anti-HBsAg mAb)

Select Members of Management

- CEO: Keting Chu
- CSO: Dr. Hassan Javanbakht
- CMO: Nancy Shulman

Company Description

Bluejay is discovering life-changing medicines and cures for people with viral and liver diseases, starting with chronic Hepatitis B and chronic Hepatitis D.



Source: Bluejay Therapeutics corporate website

Replicor (Private): Clinical-Stage Biopharmaceutical Company Developing Nucleic Acid Polymers (NAPs)

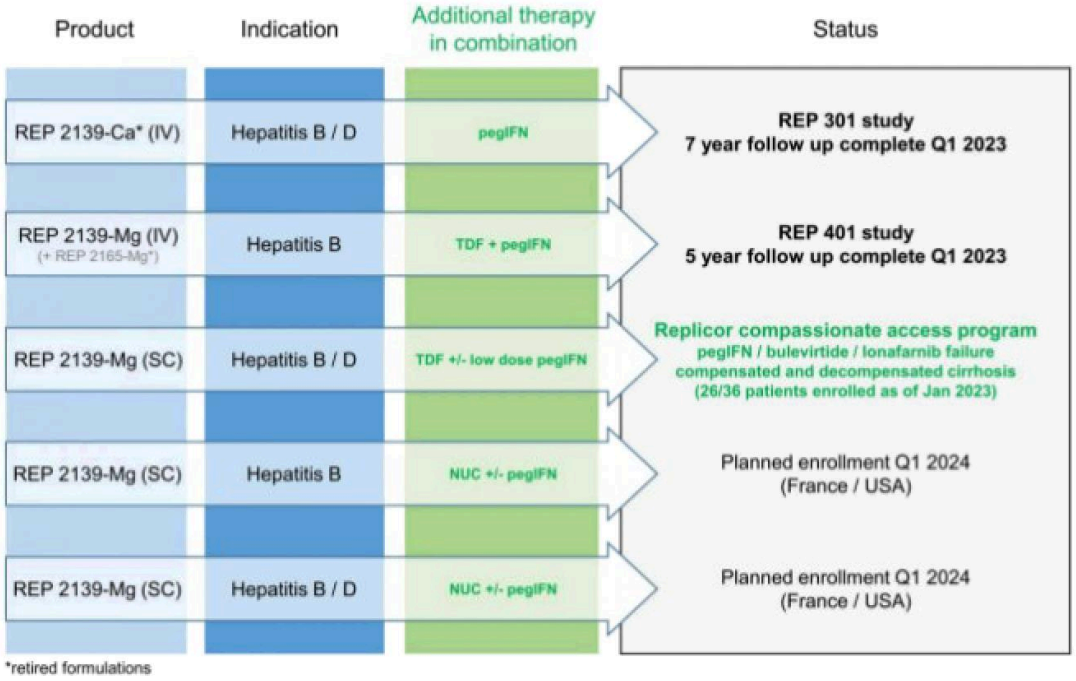
Select Members of Management

- CEO / CMO: Michel Bazinet, M.D.
- CSO: Andrew Vaillant, Ph.D.
- VP Administration: Léo Bazinet, B.A.A.

Company Description

Replicor has focused its efforts on developing a cure for HBV and HDV with REP 2139-based combination therapies.

Phase II clinical study timeline



Source: Replicor corporate website

Viravaxx (Private): Preventive and Therapeutic Vaccines and Diagnostics for Hepatitis B, SARS-CoV-2, HIV, RSV and Rhinovirus

viravaxX

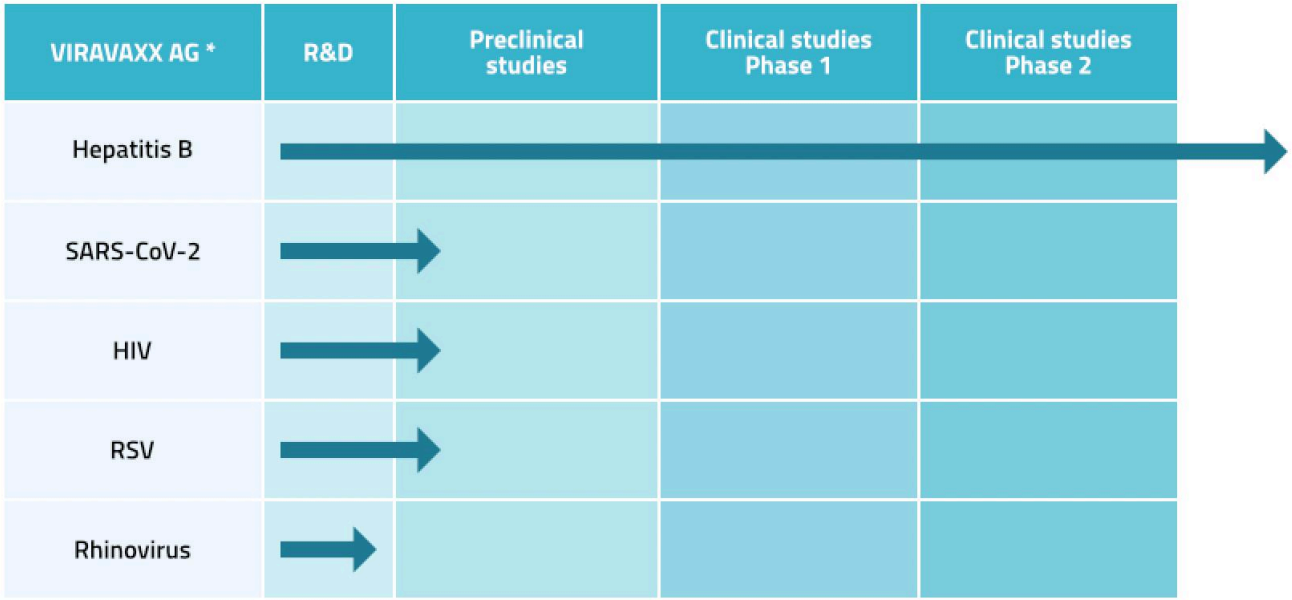
Select Members of Management

- CEO: Dr. Walter Baumann

Company Description

Viravaxx AG is a privately held company based in Vienna, Austria, with a flagship vaccine against Hepatitis B. The newly developed vaccine is a step towards the therapeutic as well as prophylactic use of vaccination against chronic Hepatitis B. The vaccine has already been tested successfully in clinical studies.

NEW VACCINES AND DIAGNOSTICS



Source: Viravaxx corporate website

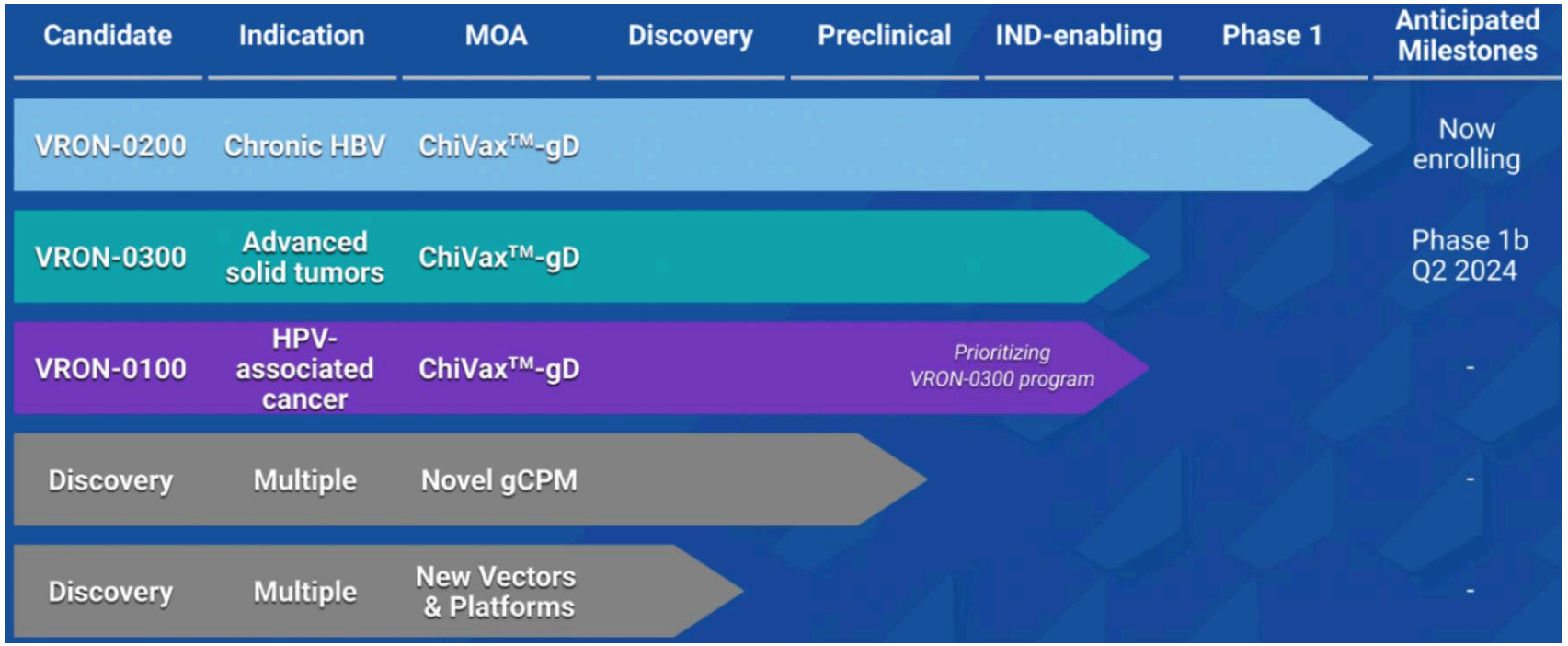
Virion Therapeutics (Private): T Cell-Based Immunotherapies for Cancer and Infectious Diseases

Select Members of Management

- CEO: Andrew D. Luber, Pharm.D.
- COO: Sue Currie, Ph.D.
- CTO: Paula MacDonald

Company Description

Virion Therapeutics is a clinical-stage company developing novel T cell-based immunotherapies for cancer and chronic infectious diseases, utilizing genetically encoded checkpoint modifiers (CPM) to enhance and broaden CD8+ T cell responses to a tumor or chronic infection.



Source: Viron Therapeutcs corporate website

ClearB Therapeutics (Private): Engineered Bionanoparticles (BNPs) of Hepatitis B Surface Antigen (HBsAg) Delivering Clearance Epitope Target Inserts

CLEARB THERAPEUTICS

Select Members of Management

- CEO: Aileen Rubio, PhD
- CTO: Bharat Dixit, PhD
- CMO: Chris Stevens, MD

Company Description

ClearB is working to develop therapeutic vaccines designed to redirect patients' immune systems toward functional cure of Hepatitis B.

Trial registered on ANZCTR

Registration number	ACTRN12623000841673
Ethics application status	Approved
Date submitted	14/07/2023
Date registered	4/08/2023
Date last updated	1/11/2023
Date data sharing statement initially provided	4/08/2023
Type of registration	Prospectively registered

Titles & IDs

Public title	Study to Evaluate the Safety, Tolerability, Immunogenicity and Antiviral Activity of Multiple Doses of CLB-3000 in participants with Chronic Hepatitis B
Scientific title	An Open-Label Phase 1b Study Evaluating the Safety, Tolerability, Immunogenicity and Antiviral Activity of Multiple Doses of CLB-3000 in Subjects with Chronic Hepatitis B
Secondary ID [1]	CLB-3000-1-001
Universal Trial Number (UTN)	
Trial acronym	
Linked study record	

Source: ClearB corporate website

CaroGen (Private): Immunotherapy Company Employing a Virus-Like Vesicle (VLV) Platform Technology

CaroGen Corporation
Creating a Wave of Transformative Medicines...

Select Members of Management

- CEO: Bijan Almassian, PhD
- CSO: Valerian Nakaar, PhD
- CMO: Deborah Church, MD

Company Description

CaroGen is creating a wave of potentially transformative, first-in-class immunotherapeutics designed to engage the body's immune system to both recognize and fight off infectious diseases and cancer.

Source: CaroGen corporate website

ANALYST CERTIFICATION

By issuing this research report, each Guggenheim Securities, LLC ("Guggenheim Securities") research analyst whose name appears in this report hereby certifies that (i) all of the views expressed in this report accurately reflect the research analyst's personal views about any and all of the subject securities or issuers discussed herein and (ii) no part of the research analyst's compensation was, is, or will be directly or indirectly related to the specific recommendations or views expressed by the research analyst.

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BUY (B) - Describes stocks that we expect to provide a total return (price appreciation plus yield) of 10% or more within a 12-month period.

NEUTRAL (N) - Describes stocks that we expect to provide a total return (price appreciation plus yield) of between plus 10% and minus 10% within a 12-month period.

SELL (S) - Describes stocks that we expect to provide a total negative return (price appreciation plus yield) of 10% or more within a 12-month period.

NR - The investment rating and price target have been temporarily suspended. Such suspensions are in compliance with applicable regulations and/or Guggenheim Securities, LLC policies.

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Monitor - Describes stocks whose company fundamentals and financials are being monitored, and for which no financial projections or opinions on the investment merits of the company are provided.

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Guggenheim Securities Equity Research & Equities Teams

Consumer Equity Research

Automotive
Ron Jewsikow 212.823.6581
Ronald.Jewsikow@guggenheimpartners.com

Food Retailers; Consumables Retail/Distribution
John Heinbockel 212.381.4135
John.Heinbockel@guggenheimpartners.com

Hardlines Retail
Steven Forbes, CFA, CPA 212.381.4188
Steven.Forbes@guggenheimpartners.com

Restaurants
Gregory Francfort, CFA 212.518.9182
Gregory.Francfort@guggenheimpartners.com

Retailing/Department Stores & Specialty Softlines
Robert Drbul 212.823.6558
Robert.Drbul@guggenheimpartners.com

Consumer Equities Team

Consumer Sector Specialist
Carey Kaufman 504.299.3424
Carey.Kaufman@guggenheimpartners.com

Power & Energy Transition Equity Research

Energy Technology & Industrial Technology
Joseph Osha, CFA 415.852.6468
Joseph.Osha@guggenheimpartners.com

Power & Utilities
Shahriar Pourreza, CFA 212.518.5862
Shahriar.Pourreza@guggenheimpartners.com

Technology & Media Equity Research

Entertainment & Digital Media
Michael Morris, CFA 804.253.8025
Michael.Morris@guggenheimpartners.com

IT Services
Jonathan Lee 212.518.5388
Jonathan.Lee@guggenheimpartners.com

Media & Live Entertainment
Curry Baker 804.253.8029
Curry.Baker@guggenheimpartners.com

Software
John DiFucci 212.518.9670
John.DiFucci@guggenheimpartners.com

Howard Ma 512.354.3458
Howard.Ma@guggenheimpartners.com

Raymond McDonough, CFA 212.518.9704
Raymond.McDonough@guggenheimpartners.com

Technology & Media Equities Team

TMT Sector Specialist
Seth Ostrie 212.518.9547
Seth.Ostrie@guggenheimpartners.com

Healthcare Equity Research

Biotechnology
Debjit Chattopadhyay, Ph.D. 212.823.6584
Debjit.Chattopadhyay@guggenheimpartners.com

Kelsey Goodwin 617.859.4621
Kelsey.Goodwin@guggenheimpartners.com

Eddie Hickman, Ph.D. 212.518.9904
Eddie.Hickman@guggenheimpartners.com

Michael Schmidt, Ph.D. 617.859.4636
Michael.Schmidt@guggenheimpartners.com

Yatin Suneja 212.518.9565
Yatin.Suneja@guggenheimpartners.com

Diagnostics & Life Sciences Tools
Subbu Nambi, Ph.D. 617.859.4609
Subbu.Nambi@guggenheimpartners.com

Global Biopharmaceuticals
Vamil Divan, M.D. 212.823.6543
Vamil.Divan@guggenheimpartners.com

Seamus Fernandez 617.859.4637
Seamus.Fernandez@guggenheimpartners.com

Evan Wang 212.651.9756
Evan.Wang@guggenheimpartners.com

Healthcare IT & Services
Jack Wallace 212.518.9620
Jack.Wallace@guggenheimpartners.com

Healthcare Equities Team

Healthcare Sector Specialist - New York
Whitney Wolfe 212.518.9630
Whitney.Wolfe@guggenheimpartners.com

Healthcare Sector Specialist - San Francisco
Daniel Donner 415.671.4385
Daniel.Donner@guggenheimpartners.com

Equities Management

Stefano Natella, Head of Equities	212.292.4700
Jeffrey Cohen, Head of Sales	212.292.4762
Dante Ferrarie, Head of Trading	212.518.3331
Craig Peckham, Head of Research	212.292.4765

Sales and Trading Offices

New York	212.292.4700
San Francisco	415.852.6451
Boston	617.859.4626
Richmond	804.253.8052