Novel Therapy for Chronic Hepatitis B

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Last Updated: Oct 20, 2025

Disclosures

In the last two years, I have served on the Data Adjudication Cmte for a non-hepatology investigational drug for Novo Nordisk and the P&T Cmte for Premera

Any conflicts of interest have been mitigated.

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Disclaimer

Funding for this presentation was made possible by 5 TR7HA53202-02-00 from the Human Resources and Services Administration HIV/AIDS Bureau. The views expressed do not necessarily reflect the official policies of the Department of Health and Human Services nor does mention of trade names, commercial practices, or organizations imply endorsement by the U.S. Government. *Any trade/brand names for products mentioned during this presentation are for training and identification purposes only.*

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Objectives

1. To describe the safety and efficacy of siRNA therapy for chronic hep B
2. To describe the safety and efficacy of capsid assembly modulators for chronic hep B

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Background: HIV/HBV Coinfection

- Shared pathways for transmission: IDU, maternal to child, and sexual intercourse
- Globally, 5-20% of people living with HIV also have chronic hep B
  - Depends on geography (more common in sub-Saharan Africa and Asia)
- HIV coinfection significantly worsens natural history of HBV infection
  - Increased risk of chronic HBV
  - Higher HBV viral load and infectivity
  - Accelerated liver disease progression
- Reduced response to HBV treatment
- More reactivation of HBV

Georgios K. Nikolopoulo, Dimitrios Paraskevis, Eleni Hatzitheodorou, Zissis Moschidis, Vana Sypsa, Xenophon Zavitsanos, Victoria Kalapothaki, Angelos Hatzakis, Impact of Hepatitis B Virus Infection on the Progression of AIDS and Mortality in HIV-Infected Individuals: A Cohort Study and Meta-Analysis, *Clinical Infectious Diseases*, Volume 48, Issue 12, 15 June 2009, Pages 1763–1771, https://doi.org/10.1086/599110

Why is it so hard to cure hepatitis B

- **High levels of HBsAg production** → immune exhaustion
- **cccDNA** → difficult for immune system and antivirals to penetrate, remains even after sAg loss
- **Integrated HBV DNA into host** → occurs early in course of infection, leads to de novo hepatocarcinogenesis

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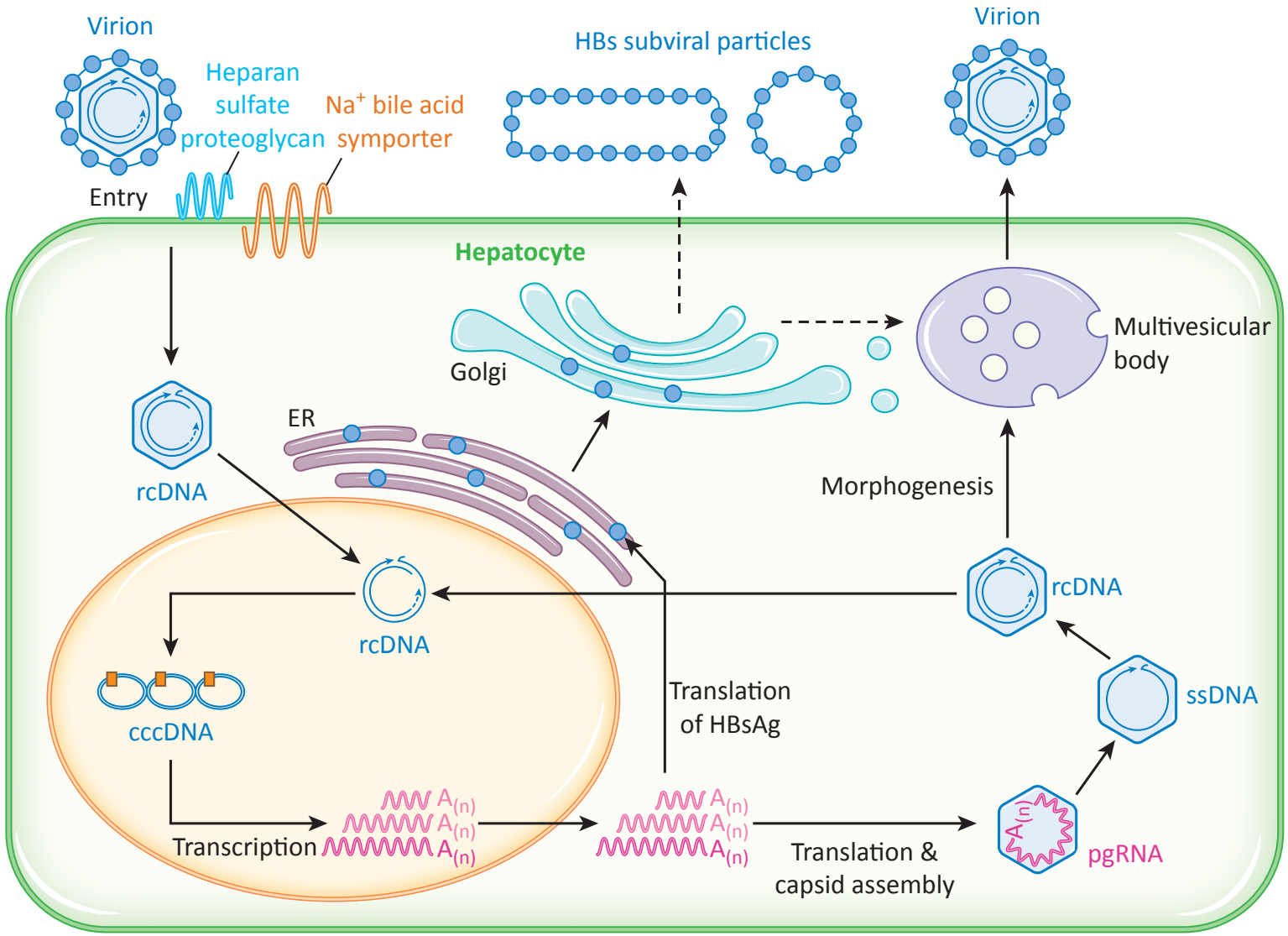
Review of HBV Lifecycle



C Shih, et al
Trends in Microbiology, April 2018, Vol.26, No. 4

siRNA: Multiple Mechanisms of Action

1. Targeting HBV RNA:

- siRNAs are designed to be complementary to specific sequences within HBV RNA, including pgRNA and mRNA.

2. RNA Interference (RNAi):

- Once inside the cell, siRNAs are processed by the cell's machinery into a RNA-induced silencing complex (RISC).

3. mRNA Degradation:

- The RISC complex, containing the siRNA, then binds to the target HBV mRNA, leading to mRNA degradation and silencing of the targeted gene.

4. Reduced Viral Protein Production:

- By reducing the levels of HBV mRNA, siRNAs effectively lower the production of viral proteins, including HBsAg, HBcAg, HBeAg, and HBV polymerase.

5. Suppression of Viral Replication:

- Reduced viral protein production leads to a decrease in viral replication, including the suppression of HBV cccDNA, the stable form of HBV DNA responsible for its persistence.

6. Potential Immune Reconstitution:

- By significantly reducing HBV viral antigens, siRNAs may indirectly enhance the host's immune response against the virus, which is a key advantage over other antiviral treatments that may only suppress viral replication but not directly target the viral reservoir.

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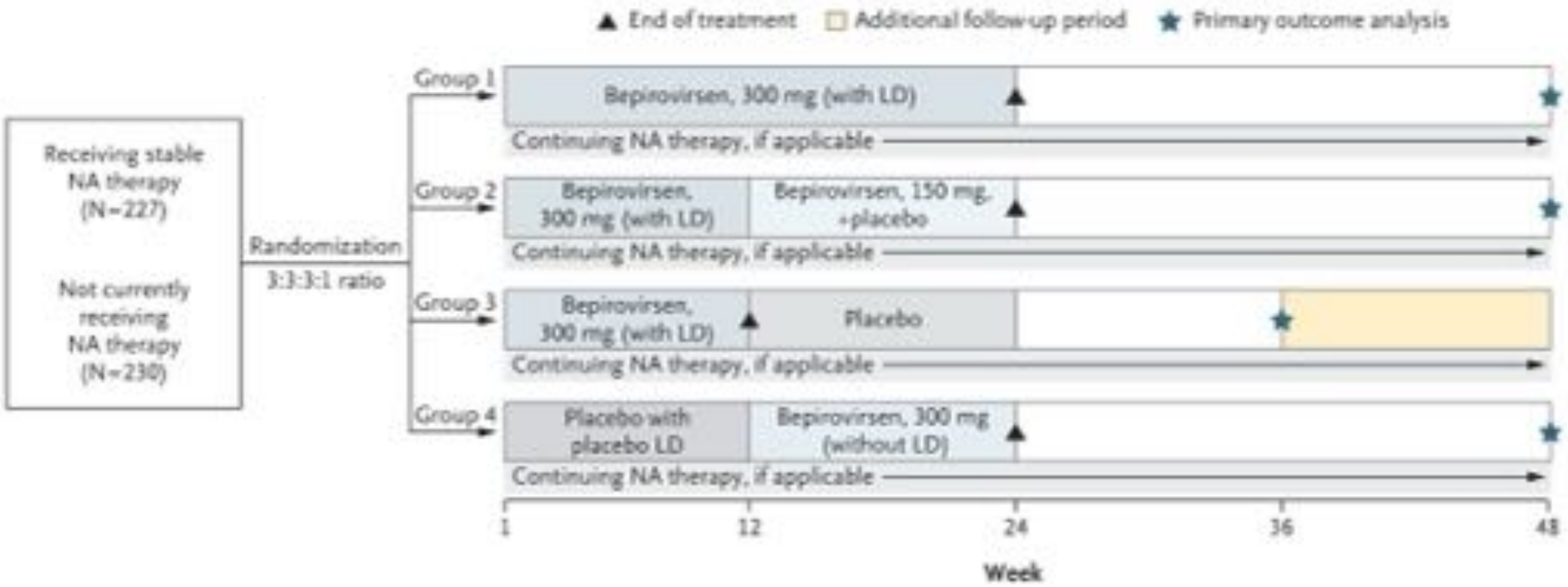
Phase 2 Study of Bepirovirsen



Eligibility: adults, qsAg>100 Iu/ml, if on NA HBV DNA <90 IU/ml and ALT <2xULN, if NA naïve HBV DNA>2000 IU/ml and ALT <3xULN, no HIV, HDV or HCV, no cirrhosis

Yuen M-F et al. N Engl J Med 2022;387:1957-1968

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Results

Table 2. Primary Outcome (Intention-to-Treat Population).*

Variable	Receiving NA Therapy				Not Receiving NA Therapy			
	Group 1 (N=68)	Group 2 (N=68)	Group 3 (N=68)	Group 4 (N=23)	Group 1 (N=70)	Group 2 (N=68)	Group 3 (N=68)	Group 4 (N=24)
Primary-outcome event — no. of participants (%)†	6 (9)	6 (9)	2 (3)	0	7 (10)	4 (6)	1 (1)	0
Point estimate of response — % (95% credible interval)	9 (0–31)	9 (0–43)	3 (0–16)	2 (0–8)‡	10 (0–38)	6 (0–25)	2 (0–6)‡	2 (0–8)‡

* Participants were randomly assigned (in a 3:3:3:1 ratio) to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). Loading doses of bepirovirsen (300 mg, in groups 1, 2, and 3) or placebo (in group 4) were administered on days 4 and 11.

† The primary outcome was an HBsAg level below the lower limit of detection (0.05 IU per milliliter) and an HBV DNA level below the lower limit of quantification (20 IU per milliliter) maintained for 24 weeks after the planned end of bepirovirsen treatment, without newly initiated antiviral medication.

‡ Shown are point estimates and credible intervals from post hoc unstratified Bayesian analysis owing to nonconvergence of the prespecified stratified Bayesian hierarchical model. Additional details are provided in the Methods section in the Supplementary Appendix.

Among patients with baseline qsAg <3000 Iu/ml, 12-25% had durable sAg loss and HBV DNA suppression

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Safety Data

Adverse Event	Receiving NA Therapy				Not Receiving NA Therapy			
	Group 1 (N=68)	Group 2 (N=67)	Group 3 (N=68)	Group 4 (N=23)	Group 1 (N=70)	Group 2 (N=67)	Group 3 (N=68)	Group 4 (N=24)
	number of participants (percent)							
Visits at wk 1–12 (when group 4 received placebo)								
Any adverse event	53 (78)	57 (85)	52 (76)	10 (43)	63 (90)	55 (82)	59 (87)	13 (54)
Any grade 3 or 4 adverse event†	5 (7)	9 (13)	5 (7)	0	10 (14)	9 (13)	7 (10)	0
Any serious adverse event‡	1 (1)	1 (1)	3 (4)	0	3 (4)	0	0	0
Adverse events of special interest§								
Injection-site reaction	38 (56)	47 (70)	43 (63)	3 (13)	50 (71)	41 (61)	46 (68)	3 (12)
Vascular inflammation and complement activation	24 (35)	31 (46)	30 (44)	1 (4)	45 (64)	38 (57)	42 (62)	6 (25)
Thrombocytopenia	12 (18)	9 (13)	11 (16)	3 (13)	21 (30)	17 (25)	19 (28)	4 (17)
Increased ALT level	7 (10)	10 (15)	6 (9)	0	15 (21)	12 (18)	11 (16)	1 (4)
Renal injury	2 (3)	6 (9)	6 (9)	0	5 (7)	3 (4)	9 (13)	1 (4)
All visits								
Any adverse event	56 (82)	59 (88)	53 (78)	16 (70)	65 (93)	60 (90)	62 (91)	19 (79)
Any adverse event leading to discontinuation of trial agent	2 (3)	3 (4)	3 (4)	0	3 (4)	1 (1)	5 (7)	0
Any grade 3 or 4 adverse event†	7 (10)	11 (16)	8 (12)	0	16 (23)	15 (22)	13 (19)	4 (17)
Any serious adverse event‡	1 (1)	1 (1)	4 (6)	0	6 (9)	2 (3)	3 (4)	0
Adverse events of special interest§								
Injection-site reaction	41 (60)	49 (73)	43 (63)	11 (48)	52 (74)	41 (61)	49 (72)	12 (50)
Vascular inflammation and complement activation	30 (44)	34 (51)	31 (46)	10 (43)	49 (70)	40 (60)	46 (68)	12 (50)
Thrombocytopenia	19 (28)	16 (24)	12 (18)	6 (26)	32 (46)	21 (31)	21 (31)	6 (25)
Increased ALT level	7 (10)	10 (15)	6 (9)	6 (26)	20 (29)	18 (28)	16 (24)	5 (21)
Renal injury	4 (6)	9 (13)	6 (9)	2 (9)	7 (10)	6 (9)	9 (13)	3 (12)

Participants were randomly assigned (in a 3:3:3:1 ratio) to receive weekly subcutaneous injections of bepirovirsen at a dose of 300 mg for 24 weeks (group 1), bepirovirsen at a dose of 300 mg for 12 weeks then 150 mg for 12 weeks (group 2), bepirovirsen at a dose of 300 mg for 12 weeks then placebo for 12 weeks (group 3), or placebo for 12 weeks then bepirovirsen at a dose of 300 mg for 12 weeks (group 4). Loading doses of bepirovirsen (300 mg, in groups 1, 2, and 3) or placebo (in group 4) were administered on days 4 and 11. In group 2, one participant receiving NA therapy and one not receiving NA therapy did not receive any bepirovirsen treatment and were therefore not included in the safety population.

Adverse events were graded according to the Division of AIDS Table for Grading the Severity of Adult and Pediatric Adverse Events, corrected version 2.1. Grade 1 indicates a mild event, grade 2 a moderate event, grade 3 a severe event, grade 4 a potentially life-threatening event, and grade 5 death.

A serious adverse event is defined as an adverse event that, at any dose of bepirovirsen or placebo, results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or clinically significant disability or incapacity, or is a congenital anomaly or birth defect.

The adverse events of special interest were defined according to standardized *Medical Dictionary for Regulatory Activities* (MedDRA) queries or MedDRA high-level terms or individual preferred terms (see Table S9 in the Supplementary Appendix). The adverse event of special interest "vascular inflammation and complement activation" included preferred terms such as injection-site pruritus and injection-site swelling. Injection-site reactions were the most commonly reported events in the trial.

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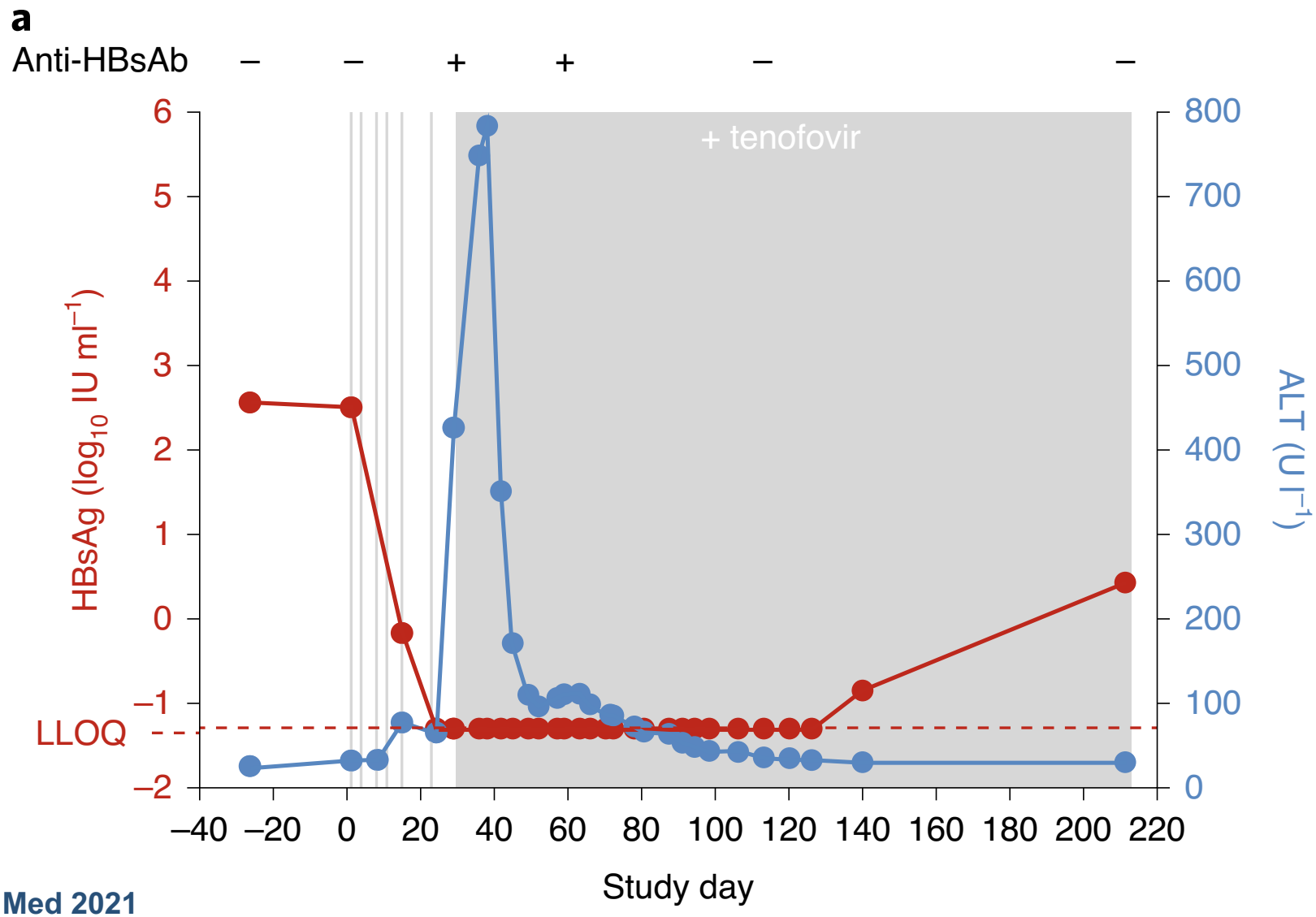
ALT Flares



Yuen MF, et al. Nature Med 2021

Findings

- In this phase 2b trial, bepirovirsen at a dose of 300 mg per week for 24 weeks resulted in sustained HBsAg and HBV DNA loss in 9 to 10% of participants with chronic HBV infection
- ALT flares happen on bepirovirsen, typically at time of sAg clearance
- Being on a NA and having a baseline quant sAg <3000 IU/ml are predictive of response
- Larger and longer trials are ongoing, enrollment complete

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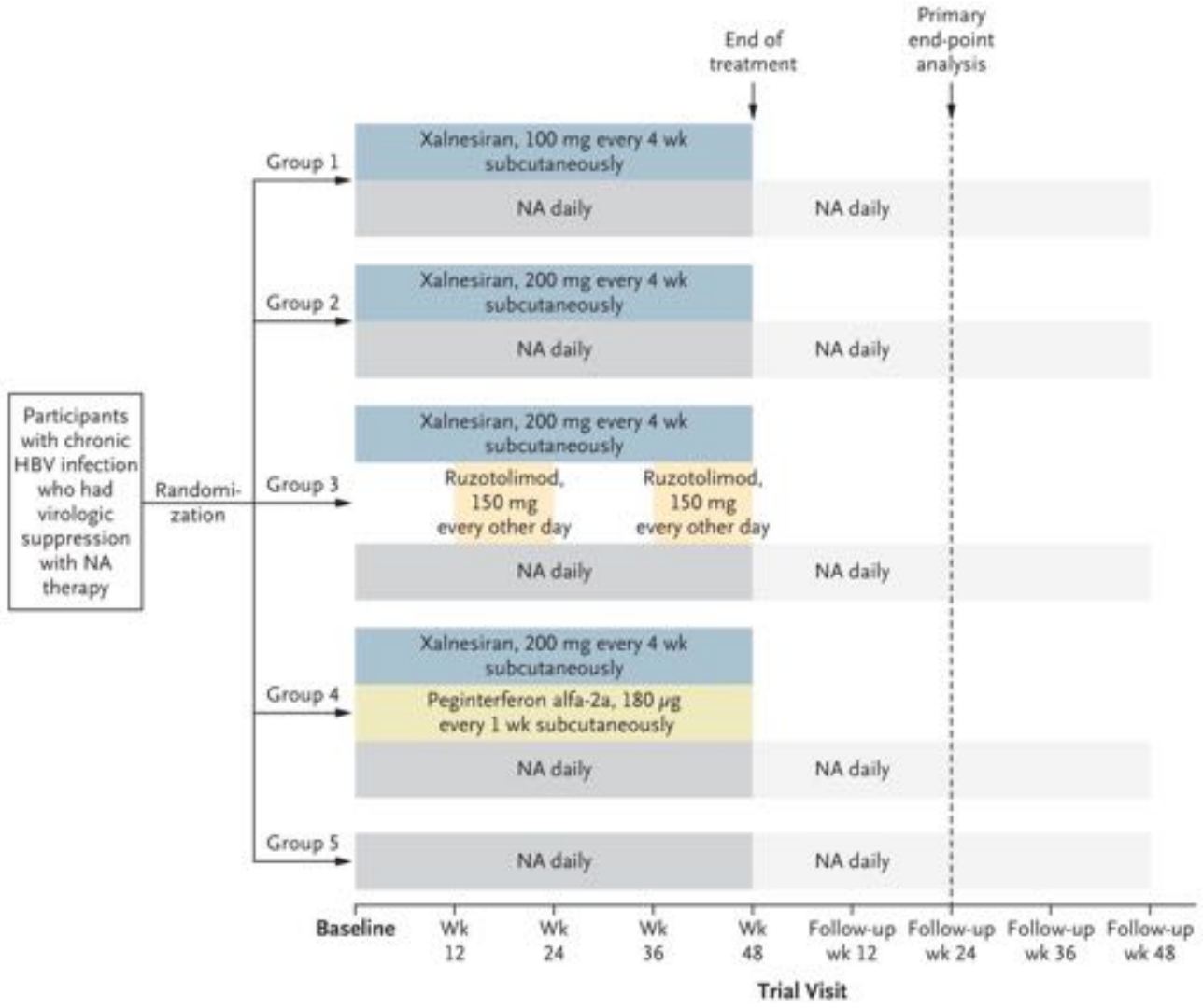
siRNA + immunomodulator: Xalnesiran



Hou J et al. N Engl J Med 2024;391:2098-2109

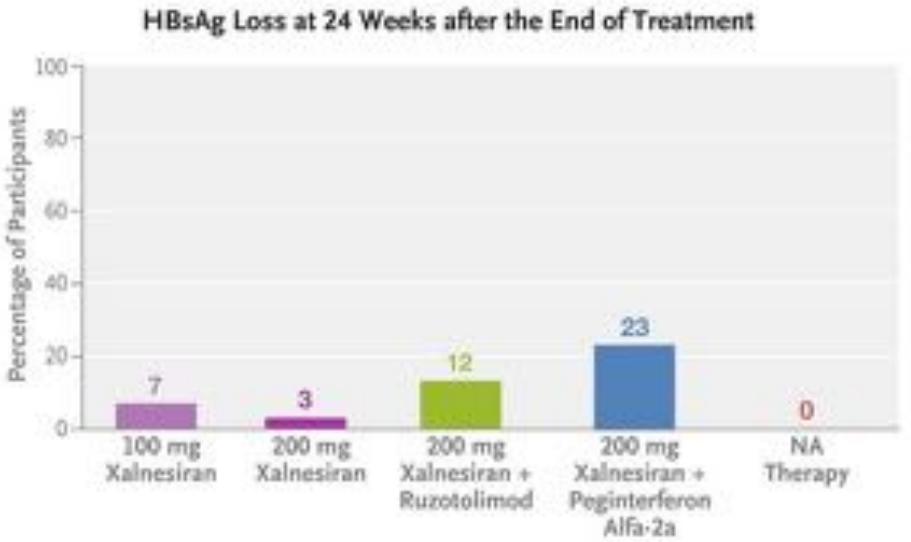
Results

The NEW ENGLAND JOURNAL of MEDICINE

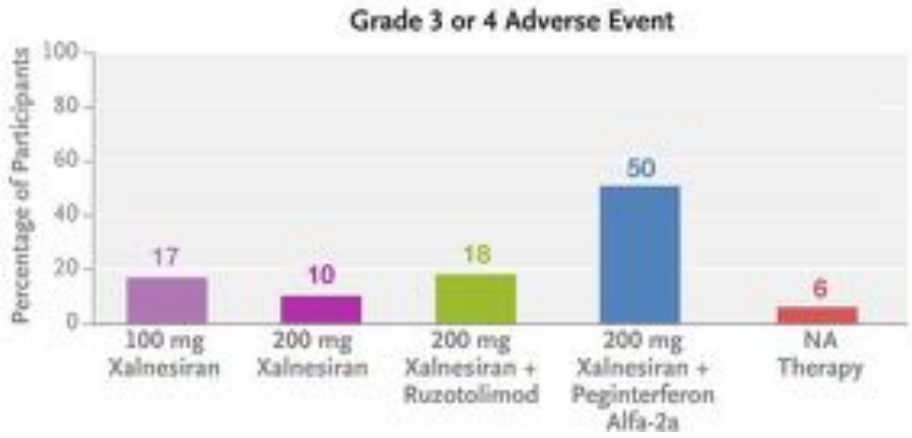
RESULTS

The percentage of participants with HBsAg loss at 24 weeks after treatment ended was highest with xalnesiran plus ruzotolimod and xalnesiran plus peginterferon alfa-2a.

HBsAg seroconversion (a secondary end point) occurred most often with xalnesiran plus peginterferon alfa-2a.



Grade 3 or 4 adverse events were not uncommon; the most frequent such event was an elevated alanine aminotransferase level, which was most often observed in the group treated with xalnesiran plus peginterferon alfa-2a.



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siRNA treatment summary

- See an initial sAg decline (up to 2-4 log after 48 weeks) but then plateaus
- Need to combine with other agents
- Rebound if stop therapy but see lower pre-set level of HBV DNA and sAg

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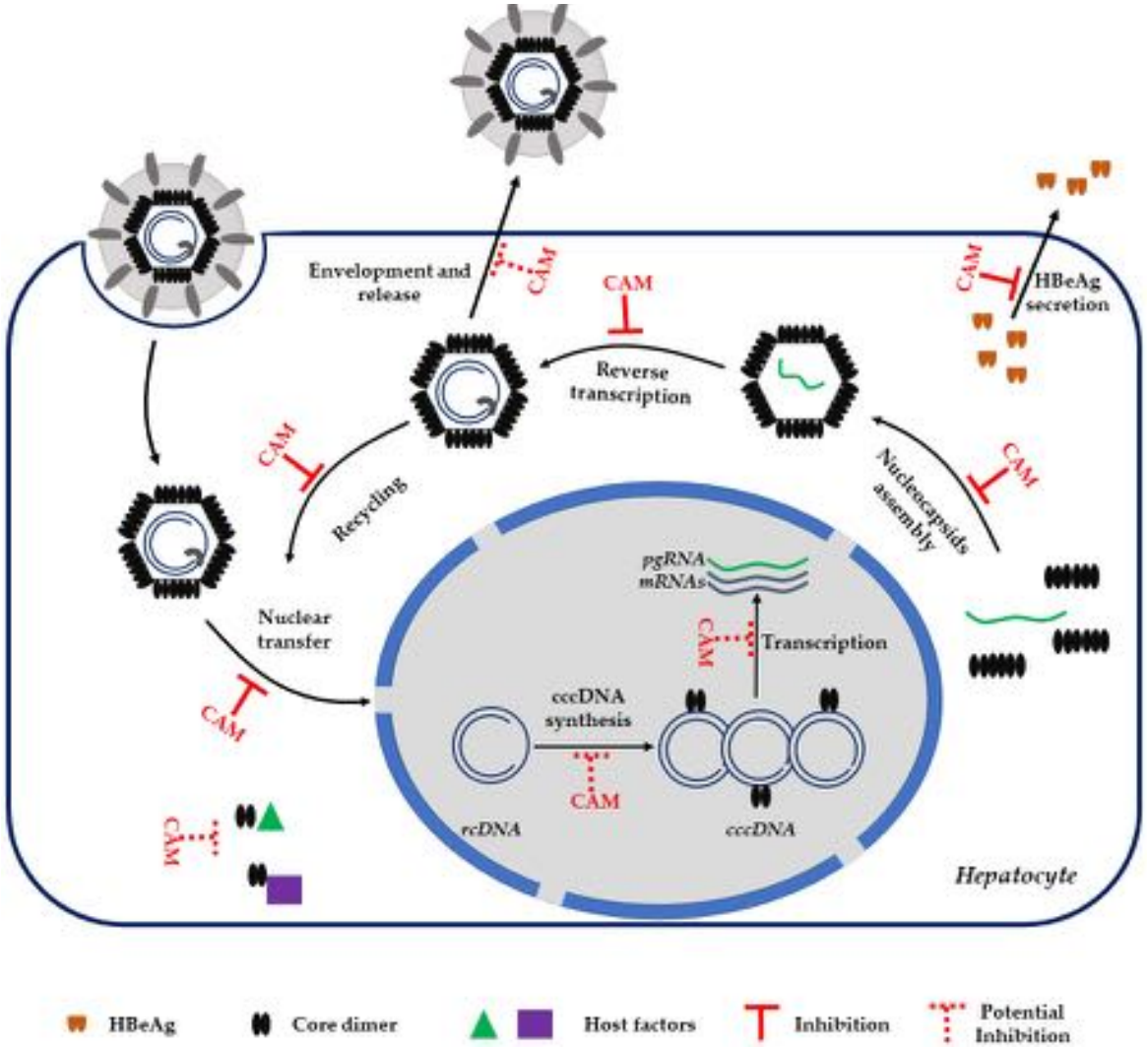
Capsid Assembly Modulator: Mechanism of Action

- Core protein modulates almost every step of the HBV life cycle; hence, it represents an attractive target for the development of new antiviral therapies.
- The primary MoA of CAM is to drive the nucleocapsid mis-assembly.



Source: V. Taverniti. *J. Clin. Med.* 2022, *11*, 1349. https://doi.org/10.3390/jcm11051349

Clinical Trials with CAMs: JNJ-56136379

Hepatology

Original research

Randomised phase 2 study (JADE) of the HBV capsid assembly modulator JNJ-56136379 with or without a nucleos(t)ide analogue in patients with chronic hepatitis B infection

Harry L A Janssen,[1,2] Jinlin Hou ,[3] Tarik Asselah ,[4] Henry L Y Chan,[5] Fabien Zoulim ,[6] Yasuhito Tanaka,[7] Ewa Janczewska,[8] Ronald G Nahass,[9] Stefan Bourgeois,[10] Maria Buti,[11] Pietro Lampertico ,[12,13] Oliver Lenz,[14] Thierry Verbinnen,[14] Joris Vandenbossche,[14] Willem Talloen,[14] Ronald Kalmeijer,[15] Maria Beumont,[15] Michael Biermer ,[14] Umesh Shukla[15]

Source: Janssen HLA, Hou J, Asselah T, *et al*. *Gut* 2023;72:1385–1398.

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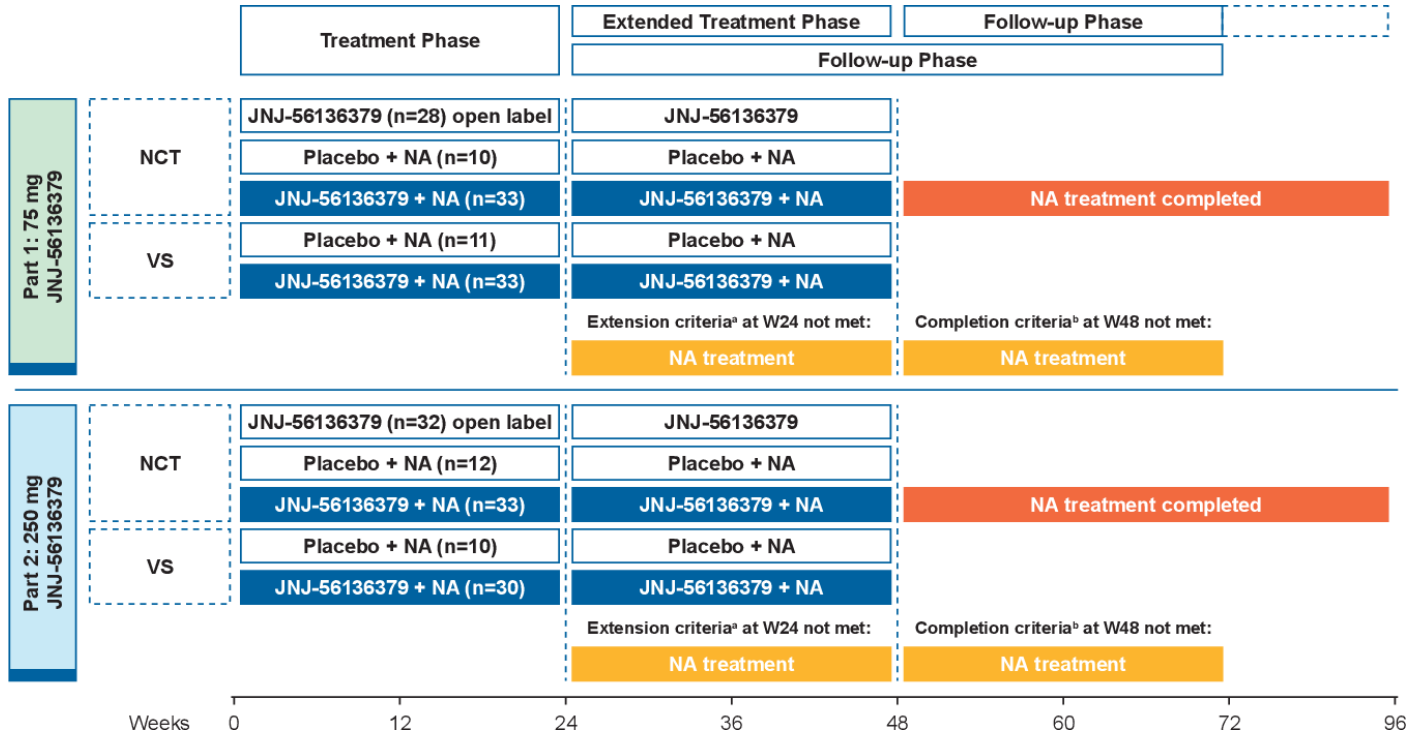
Study Design

- Phase 2, randomized, placebo-controlled trial of both eAg+ and eAg- chronic hep B adult patients
- With and without a nucleoside analog (NA: Entecavir or TDF)
- NCT = not currently on therapy
- VS = virally suppressed
- No cirrhosis
- Outcome: >1 log decline in qsAg after 24 wks



Results

	Treatment group				
	Pooled placebo + NA	JNJ-56136379 75 mg open label	JNJ-56136379 75 mg + NA	JNJ-56136379 250 mg open label	JNJ-56136379 250 mg + NA
Participants randomised and treated N=232 (100%)	**N=43 (100%)**	**N=28 (100%)**	**N=66 (100%)**	**N=32 (100%)**	**N=63 (100%)**
Completed Week 24 study treatment	**41 (95.3%)**	**15 (53.6%)**	**65 (98.5%)**	**30 (93.8%)**	**57 (90.5%)**
Entered treatment extension phase	**33 (76.7%)**	**3 (10.7%)**	**43 (65.2%)**	**20 (62.5%)**	**48 (76.2%)**
Reason for not entering treatment extension phase*					
No virologic response by Week 20	7 (16.3%)	11 (39.3%)	22 (33.3%)	10 (31.3%)	9 (14.3%)
No consent to participate in treatment extension phase	2 (4.7%)	2 (7.1%)	0	1 (3.1%)	1 (1.6%)
Completed treatment extension	**31 (72.1%)**	**0**	**41 (62.1%)**	**18 (56.3%)**	**46 (73.0%)**
Discontinued treatment extension	**2 (4.7%)**	**3 (10.7%)**	**2 (3.0%)**	**2 (6.3%)**	**2 (3.2%)**
Withdrawal by participant	1 (2.3%)	0	1 (1.5%)	0	1 (1.6%)
Adverse events	0	0	1 (1.5%)	1 (3.1%)	0
Non-compliance with study drug	1 (2.3%)	0	0	0	1 (1.6%)
Lack of efficacy	0	1 (3.6%)	0	0	0
Other reasons	0	2 (7.1%)	0	1 (3.1%)	0

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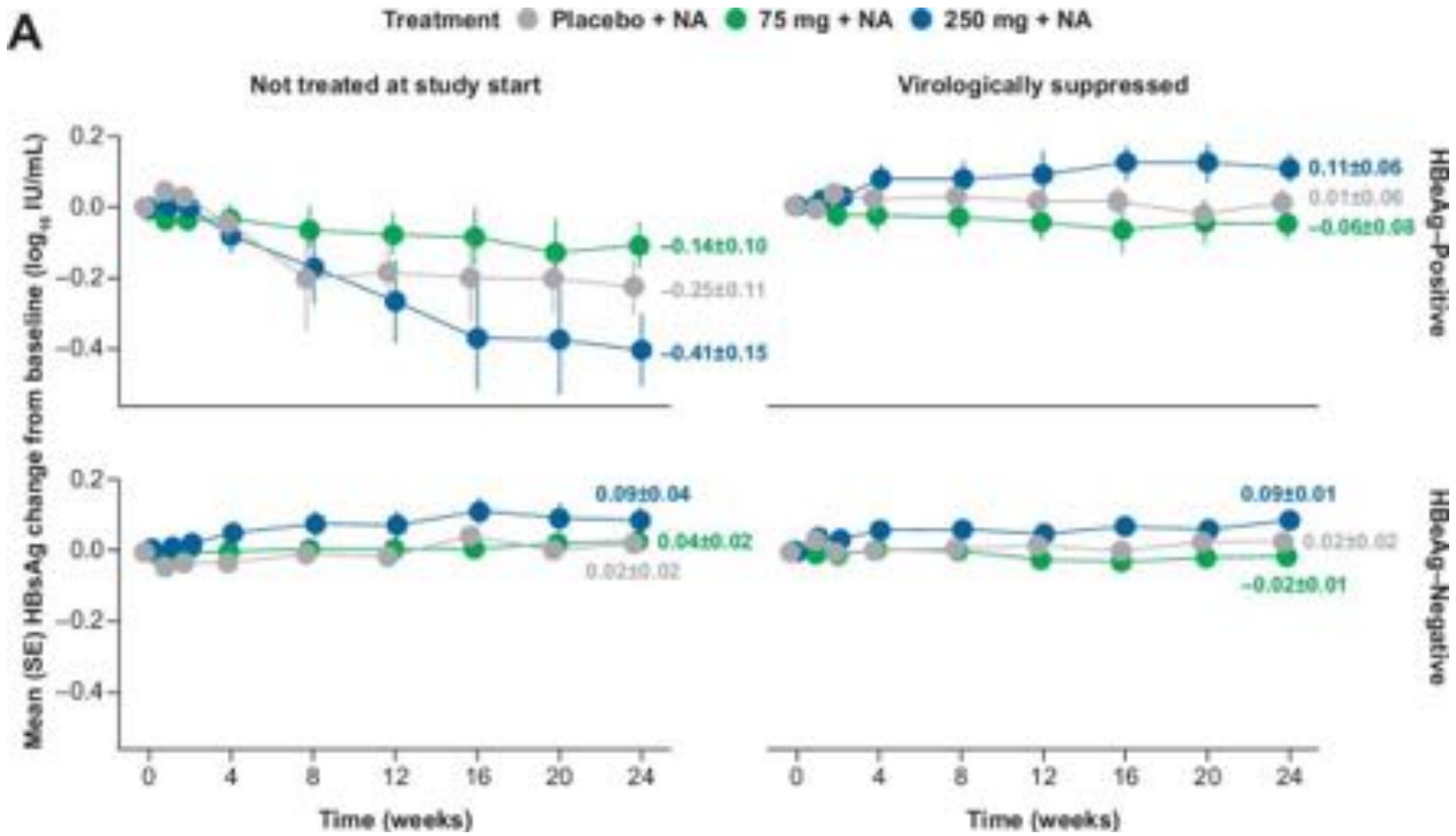
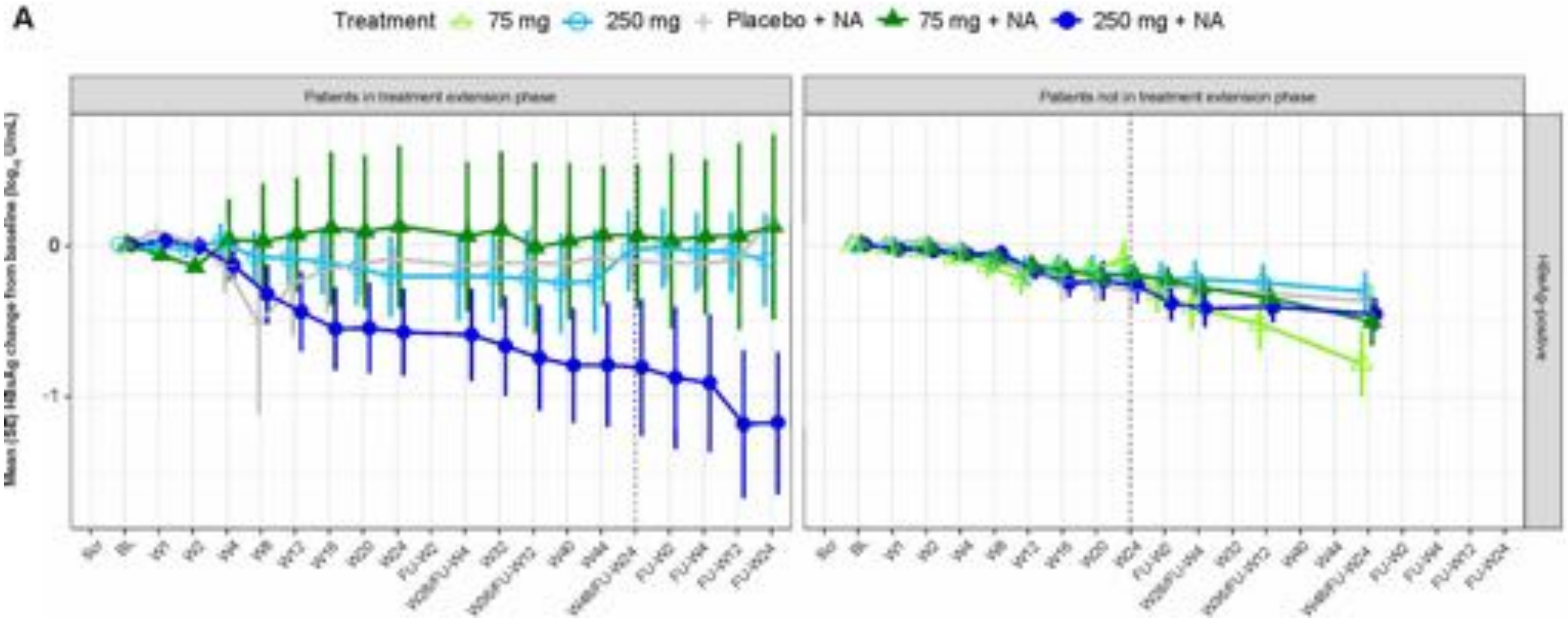
Results: Biggest benefit in eAg+ and higher dosage



Results: Longer Tail



Results: Safety

- Most treatment-emergent AEs were Grade 1 or 2
- Two patients on CAM discontinued treatment due to AEs
  - streptococcal toxic shock syndrome, acute cardiac failure, myocarditis and muscle necrosis
  - weight loss
- Seventeen patients had ≥Grade 3 AEs (13 (7%) in the pooled JNJ-56136379 treatment versus four (9%) in the pooled placebo+NA arms)
- Most commonly increased ALT and aspartate aminotransferase (AST) (six (3%) and five (3%) patients, respectively) in the pooled JNJ-56136379 treatment arms versus no patients in the pooled placebo+NA arm
- None of the eight reported SAEs were considered related to study treatment

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Conclusion

"In patients with non-cirrhotic CHB, JNJ- 56136379+NA showed pronounced reductions in HBV DNA and HBV RNA, limited HBsAg or HBeAg declines in patients who are NCT HBeAg positive, and was well tolerated, but no clear benefit with regards to efficacy of JNJ-56136379 over NA was observed."

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Summary

- Capsid assembly modulators represent a viable new antiviral target with potential long tail
- ALT flares will be more common
- Stay tuned for results of phase 2 trials!
- Check out Hep B foundation for latest on hep B drugs in development: https://www.hepb.org/treatment-and-management/drug-watch/

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Treatment Paradigm: Combination Therapy

TDF
TAF
Entecavir

siRNA
Entry inhibitor
Capsid inhibitor
Antisense molecule

Therapeutic vaccine
Monoclonal Ab
TLR 8 or 9 agonist
Interferon
Checkpoint inhibitor

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Summary

- Promising improvement in HBV therapy with surface Ag clearance rates approaching 25-30% after one year
- More complicated!
- More expensive-will pharma continue antiviral development?
- Interferon coming back?
- Importance of testing for quant sAg for future therapies

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Acknowledgment

This Mountain West AIDS Education and Training (MWAETC) program is supported by the Health Resources and Services Administration (HRSA) of the U.S. Department of Health and Human Services (HHS) as part of award 5 TR7HA53202-02-00 totaling $2,820,772 with 0% financed with non-governmental sources.

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