Efficacy and Safety of Finite 48-week Treatment With the siRNA JNJ-3989 and the Capsid Assembly Modulator JNJ-6379 in HBeAg Negative Virologically Suppressed Chronic Hepatitis B Patients: Results from the REEF-2 Study

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REEF-2: Introduction

- JNJ-3989 is an siRNA that targets all HBV RNAs, thereby reducing levels of all viral proteins[1]
- JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of structurally normal, non-infectious viral particles consisting of empty nucleocapsids[2]
- In the REEF-1 study (NCT03982186), JNJ-3989, with or without JNJ-6379, demonstrated strong dose-dependent HBsAg decline in a 48-week regimen[3]
- In virologically suppressed, NA-treated, non-cirrhotic, HBeAg negative CHB patients, discontinuation of NA treatment may result in increased rates of functional cure (HBsAg seroclearance), especially in the subset of patients with low HBsAg levels at the end of treatment[4]
- The REEF-2 study (NCT04129554) assessed the efficacy and safety of 48 weeks of the combination of JNJ-3989, JNJ-6379, and NA in this population, with 48 weeks of follow-up after discontinuation of all treatment
  - Here, we report Follow-up Week 24 data

CAM-N, capsid assembly modulator - normal capsid structure; CHB, chronic hepatitis B; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; NA, nucleos(t)ide analogues; siRNA, small interfering RNA.

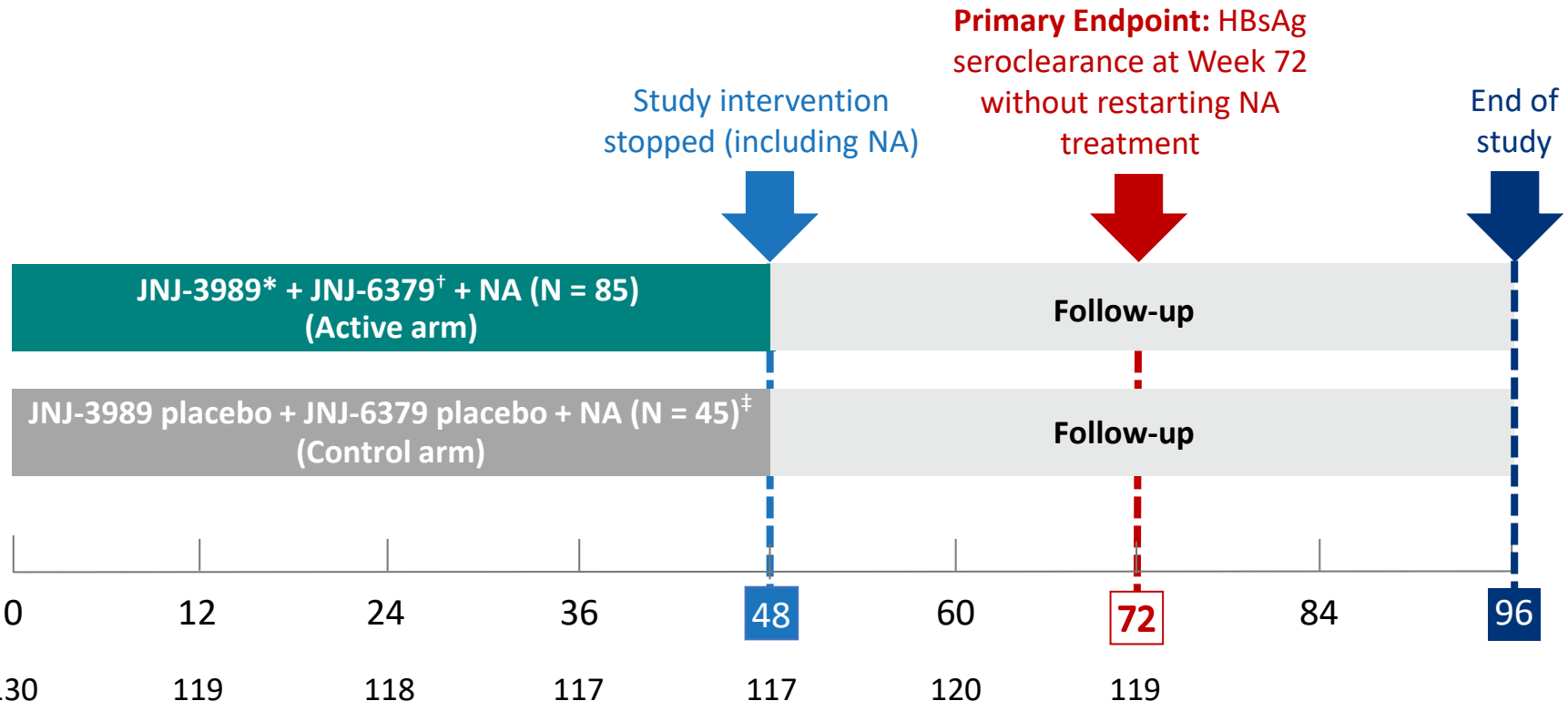
1. Yuen MF, et al. Submitted. 2022. 2. Berke JM, et al. *Antimicrob Agents Chemother*. 2020; 64(5):e02439-19. 3. Yuen MF, et al. AASLD: The Liver Meeting; Nov, 2021; abstract LO10. 4. Van Bommel F and Berg, T. *Hepatology Commun*. 2021;0:1-17.

REEF-2 (NCT04129554): Study Design

NA Suppressed/HBeAg negative
CHB who received NA treatment ≥2 years
ALT <2.0 ULN, HBV DNA <60 IU/mL
HBsAg >100 IU/mL at screening
Non-cirrhotic (Fibrosis Stage F0-F2)

NA = ETV/TDF/TAF according to label

7 Countries in Europe



HBsAg seroclearance defined as HBsAg <LLOQ (0.05 IU/mL)
*200 mg SC every 4 weeks; †250 mg PO daily.

All analyses were performed for the ITT population.

ETV, entecavir; ITT, intention-to-treat; LLOQ, lower limit of quantitation; PO, oral; SC, subcutaneous; TAF, tenofovir alafenamide; TDF, tenofovir disoproxil fumarate; ULN, upper limit of normal.

‡Referred to as NA treatment.

REEF-2: NA Retreatment Criteria

After stopping NA treatment (Week 48), participants were to restart NA treatment:

- If the below results were confirmed at least 4 weeks apart:
  - HBeAg seroreversion
  - Post-treatment increases in HBV DNA >2,000 IU/mL and ALT >5× ULN
  - Post-treatment increases in HBV DNA >20,000 IU/mL
- Immediately, in case of signs of decreasing or impaired liver function based on laboratory findings or clinical assessment

Additional retreatment criteria were added to the protocol during the course of the study:*

- Immediately with an HBV DNA value >100,000 IU/mL (irrespective of confirmation and/or ALT increase)

*Prompted by a single patient in the control arm who experienced severe liver deterioration and had to undergo transplant after stopping NA even though NA retreatment began in accordance with retreatment criteria in the original protocol.

REEF-2: Demographics and Baseline Characteristics

Percentages or Mean Value (SD)	Placebo + NA (Control)	JNJ-3989 + JNJ-6379 + NA (Active)	Total
N	45	85	130
Demographics			
Female vs. Male (%)	35.6/64.4	31.8/68.2	33.1/66.9
Age, years	47.4 (10.55)	45.3 (10.10)	46.0 (10.27)
White (%)	66.7	65.9	66.2
Disease Characteristics			
HBsAg, $\log_{10}$ IU/mL	3.49 (0.703)	3.43 (0.530)	3.45 (0.594)
HBV DNA <LLOQ (%)*	100	100	100
HBV RNA <LOD (%)†	97.7	92.8	94.4
HBcrAg <LLOQ (%)‡	75.0	65.9	69.0
ALT, U/L	23.9 (10.75)	24.2 (10.89)	24.1 (10.80)
Fibroscan score, kPa	5.02 (1.301)	5.23 (1.482)	5.16 (1.420)
Duration of NA at study entry, years	8.1 (4.48)	8.4 (4.79)	8.3 (4.67)
Stratification Factors			
Asian vs. Non-Asian (%)	17.8/82.2	21.2/78.8	20.0/80.0
Type of NA: ETV vs. TDF/TAF (%) §	37.8/62.2	38.8/61.2	38.5/61.5
HBsAg level: <1,000 vs. ≥1,000 IU/mL (%)	24.4/75.6	20.0/80.0	21.5/78.5

ALT, alanine transaminase; HBcrAg, hepatitis B core related antigen.
*HBV DNA, LLOQ = 20 IU/mL. †HBV RNA, LOD = 2.49 $\log_{10}$ cp/mL. ‡HBcrAg, LLOQ = 3.0 $\log_{10}$ U/mL. §2 patients were on TAF.

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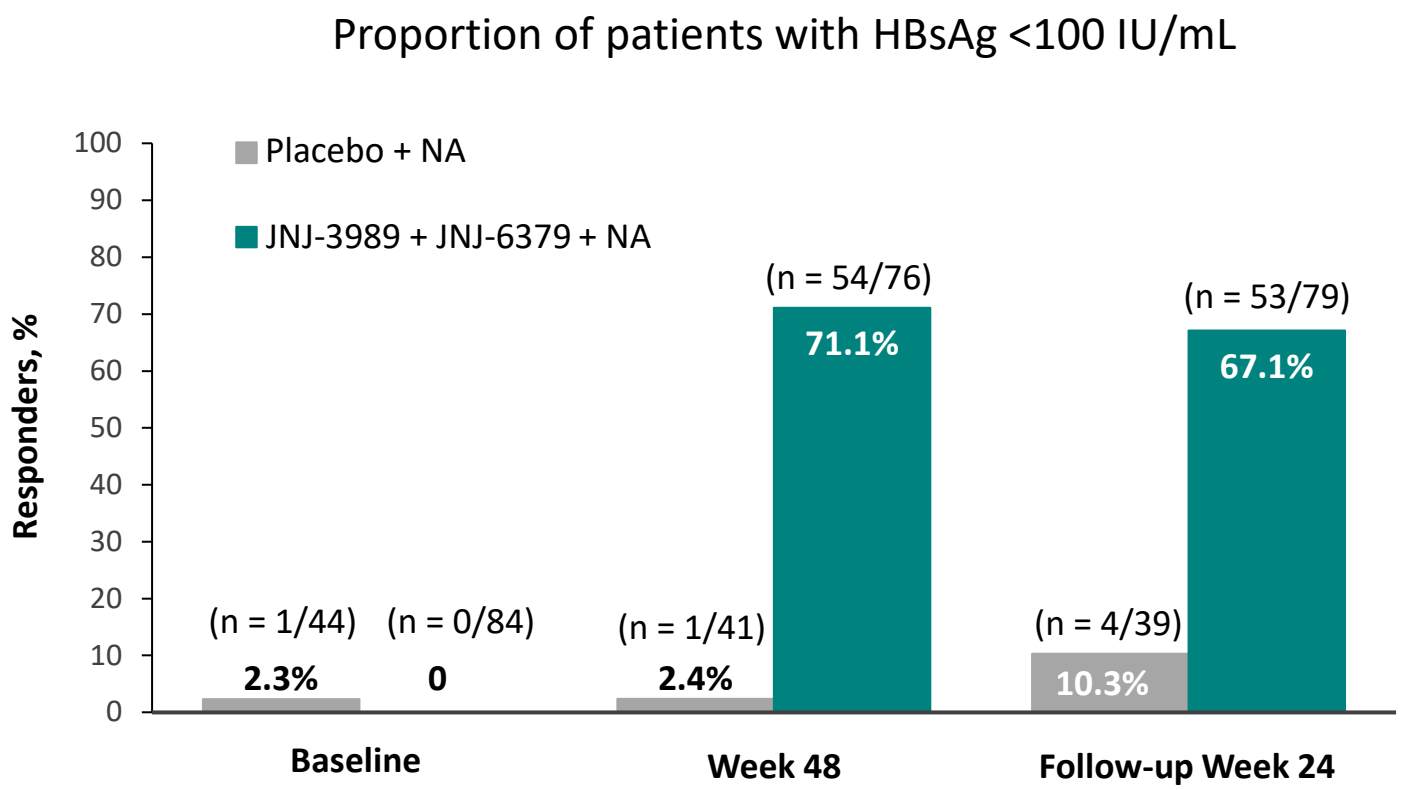
REEF-2: Primary Endpoint and Proportion of Patients With HBsAg <100 IU/mL

No patients achieved the primary endpoint of HBsAg seroclearance* at Follow-up Week 24 without restarting NA treatment, in either treatment arm



*HBsAg seroclearance defined as HBsAg <LLOQ (0.05 IU/mL).

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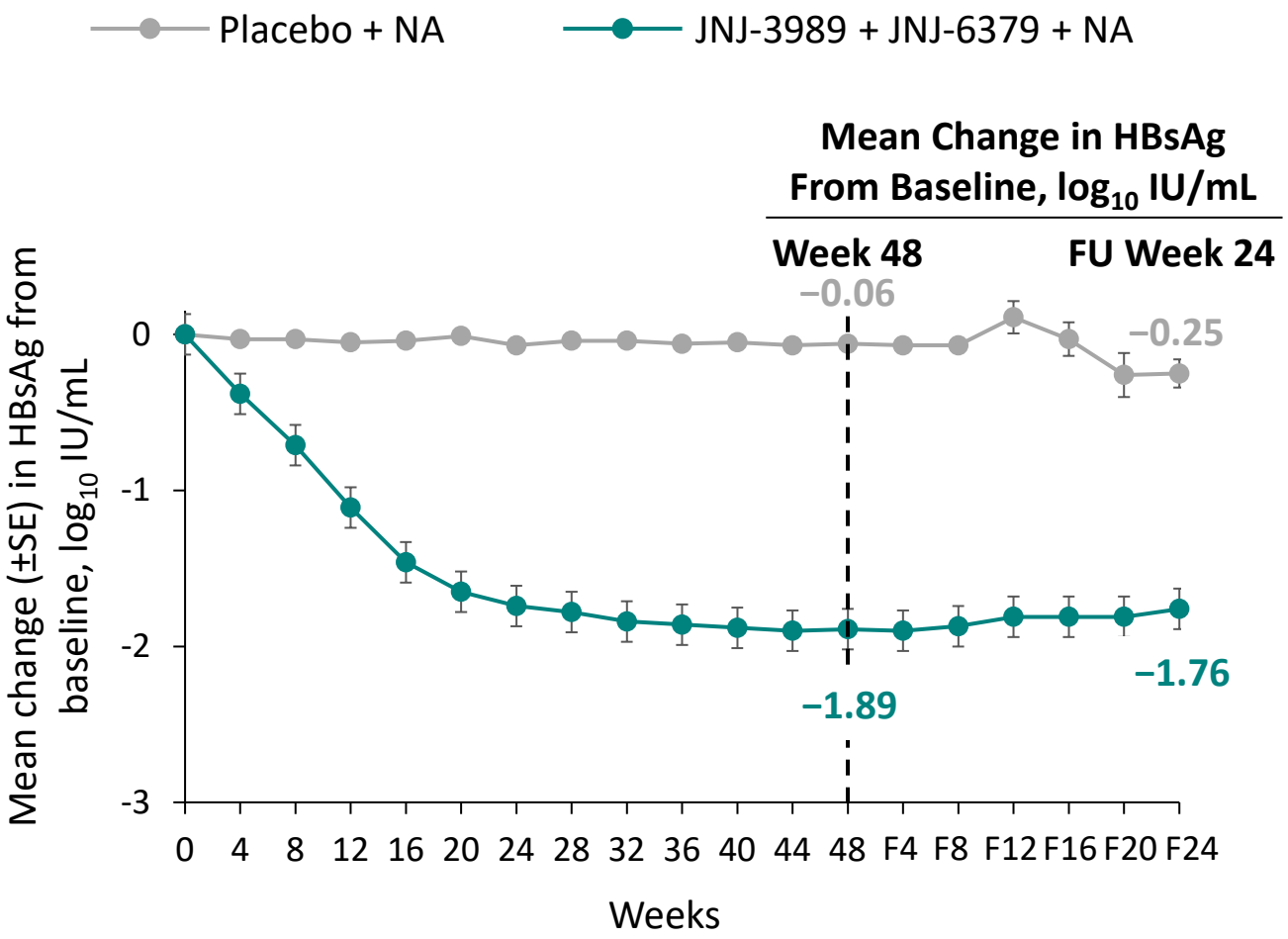
REEF-2: Change in HBsAg Over Time



Change in HBsAg from Week 48 to FU Week 24

Patients, n (%)	Placebo + NA (N = 40)	JNJ-3989 + JNJ-6379 + NA (N = 76)
Decrease: >0.2 log_{10} IU/mL	13 (32.5)	13 (17.1)
Stable: Within ±0.2 log_{10} IU/mL	25 (62.5)	31 (40.8)
Increase: >0.2 log_{10} IU/mL	2 (5.0)	32 (42.1)

57.9% of patients in the JNJ-3989 + JNJ-6379 + NA arm had declining or stable HBsAg levels off treatment

FU, follow-up; SE, standard error.

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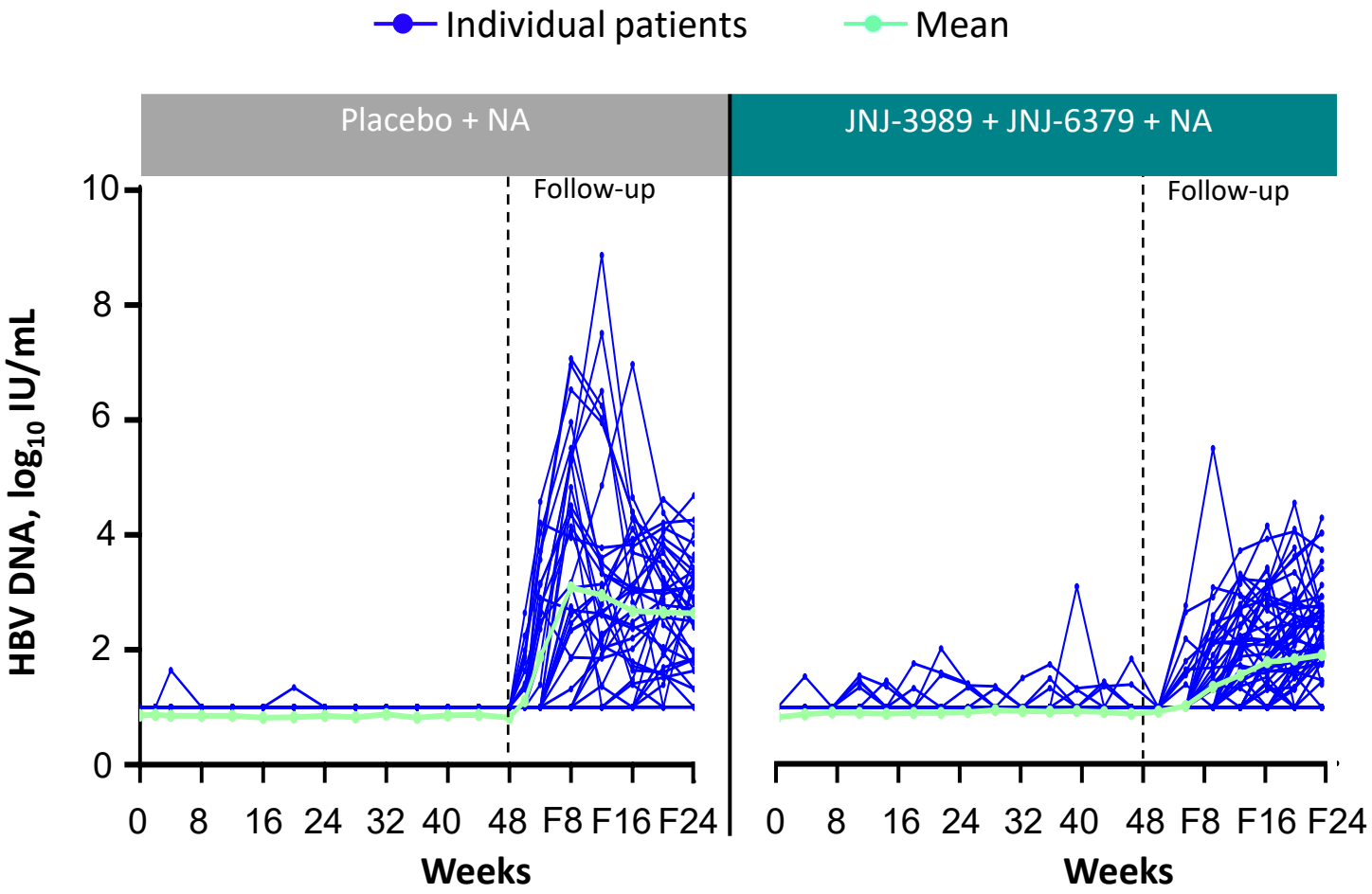
REEF-2: HBV DNA Over Time in Individual Patients

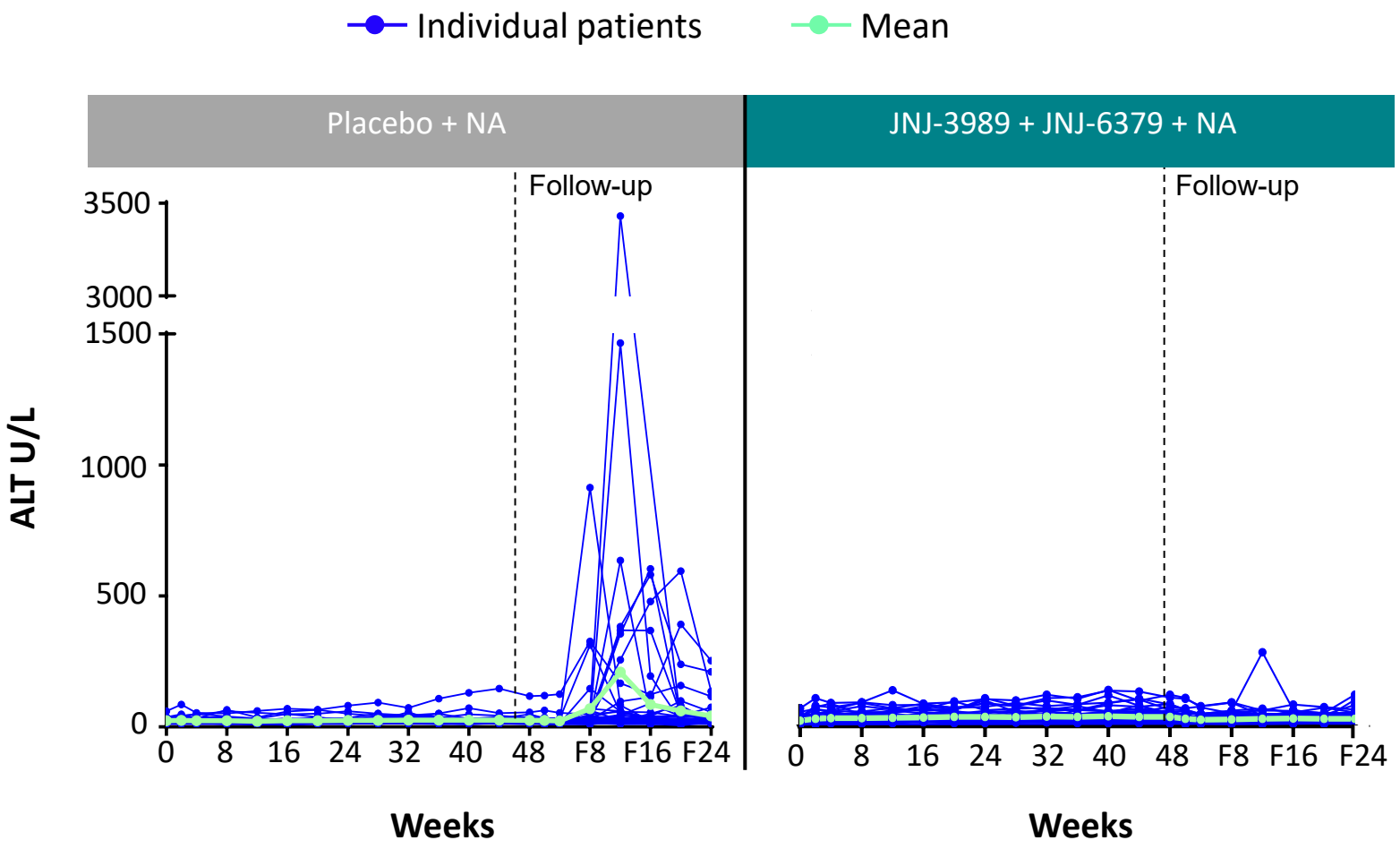


Patients with off-treatment virologic relapse* during 24 weeks of FU, n (%)	Placebo + NA (N = 41)	JNJ-3989 + JNJ-6379 + NA (N = 77)
HBV DNA >200 and ≤2,000 IU/mL	9 (22.0)	18 (23.4)
HBV DNA >2,000 and ≤20,000 IU/mL	11 (26.8)	10 (13.0)
HBV DNA >20,000 IU/mL	14 (34.1)	5 (6.5)

Patients with HBV DNA suppression at FU Week 24, n (%)	Placebo + NA (N = 31†)	JNJ-3989 + JNJ-6379 + NA (N = 74†)
HBV DNA <2,000 IU/mL	20 (64.5)	68 (91.9)
HBV DNA <LLOQ	3 (9.7)	25 (33.8)
HBV DNA <LLOQ and HBsAg <100 IU/mL	2 (6.5)	22 (29.7)

In each figure panel, the green line is the mean for all patients. LLOQ = 20 IU/mL. FU24, Follow-up Week 24.
*Virologic relapse: confirmed HBV DNA > peak threshold. †The FU Week 24 numbers are only among patients without NA treatment (re-treatment or never stopped), thus excluding 7 and 5 patients from the control and active arms, respectively.

REEF-2: ALT Over Time in Individual Patients



ALT flare during 24 weeks of FU, n (%)	Placebo + NA (N = 42)	JNJ-3989 + JNJ-6379 + NA (N = 83)
≥3 × ULN and ≥ 3 × nadir*	10 (23.8)	2 (2.4)

ALT peak level during 24 weeks of FU, n (%)	Placebo + NA	JNJ-3989 + JNJ-6379 + NA
<3 × ULN	27 (66)	74 (96)
≥3 × ULN to <5 × ULN	2 (5)	1 (1)
≥5 × ULN to <10 × ULN	4 (10)	1 (1)
≥10 × ULN	8 (20)	1 (1)
Total†	41 (100)	77 (100)

In each figure panel, the green line is the mean for all patients.
*Confirmed ALT ≥3 × ULN and ≥3 × nadir (i.e., lowest value observed up to the start of the flare). †Note: Restricted to patients who stopped NA at end of double-blind phase.

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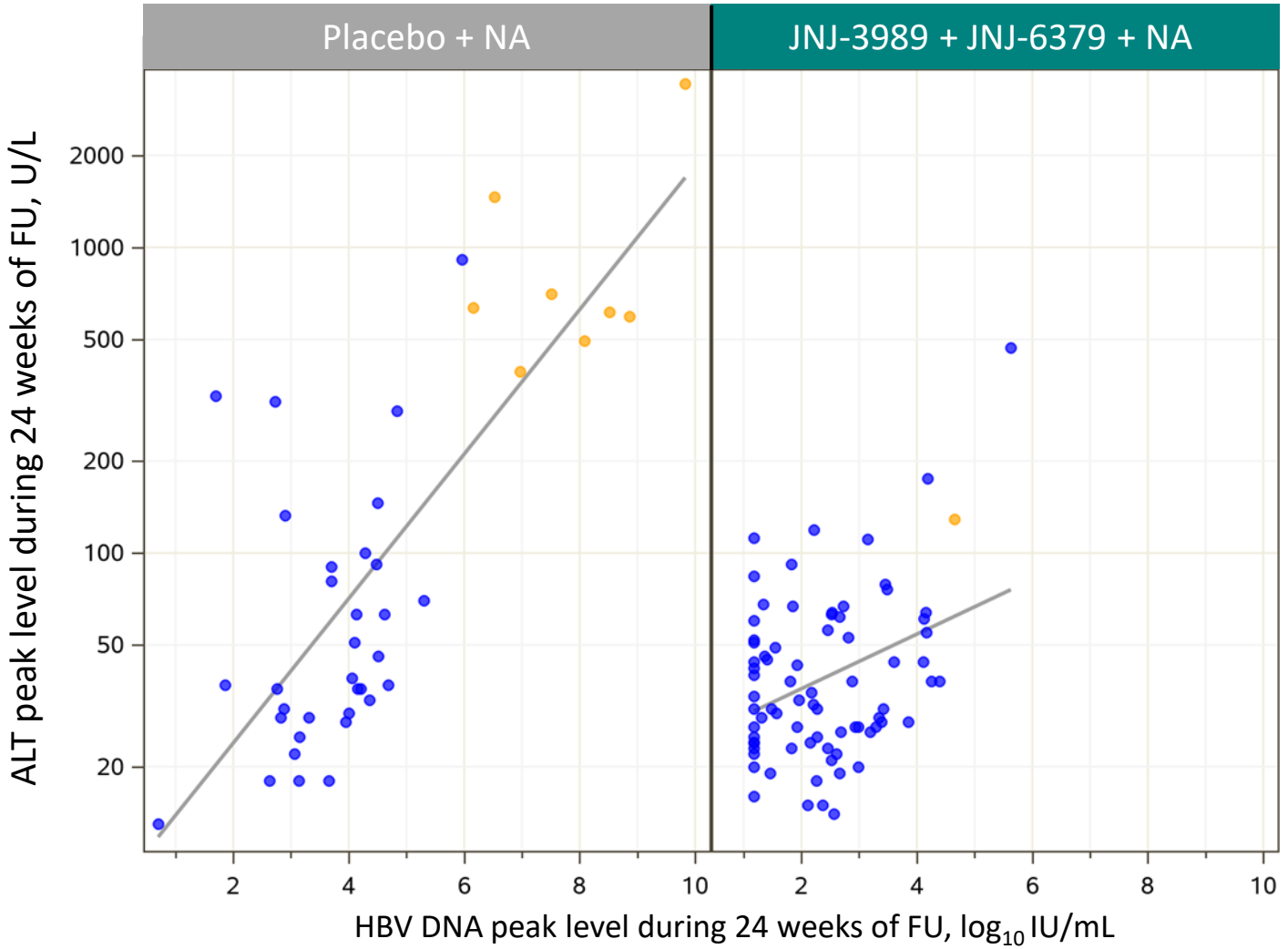
REEF-2: Peak Follow-up Phase ALT versus HBV DNA



Restarted NA

Did not restart NA

Linear regression

NA restarted during 24 weeks of FU, n (%)	Placebo + NA (N = 44)	JNJ-3989 + JNJ-6379 + NA (N = 77)
	8 (19.5)	1 (1.3)*

ALT values are displayed in U/L but spaced logarithmically. Note: Restricted to patients who stopped NA at the end of the double-blind phase.

*One patient in the active group restarted NA after diagnosis of cholangiocarcinoma (HBV DNA 2130 IU/ml; ALT 5xULN at time of NA restart).

REEF-2: Safety

	48 Week Treatment Phase		Off-treatment Follow-up Phase	
	Placebo + NA (N = 45)	JNJ-3989 + JNJ-6379 + NA (N = 85)	Placebo + NA (N = 41)	JNJ-3989 + JNJ-6379 + NA (N = 84)
Patients with ≥1 AEs, %	71.1	81.2	68.3	56.0
Related AEs	33.3	44.7	2.4	1.2
JNJ-3989/Placebo	26.7	40.0	2.4	1.2
JNJ-6379/Placebo	24.4	42.4	2.4	1.2
NA (ETV/TDF/TAF)	6.7	11.8	0	1.2
AEs leading to death, %	0	0	0	0
SAEs, %	2.2	2.4	7.3	2.4
Related SAEs	0	0	2.4*	0
AEs leading to discontinuation of JNJ-6379 and/or JNJ-3989, %	2.2	3.5	–	–
Grade 3 or 4 AEs, %	4.4	15.3	17.1	7.1
Related Grade 3 or 4 AEs	0	7.1	2.4	1.2
eGFR decreased†	0	7.1	0	0
ALT increased	0	0	9.8	2.4

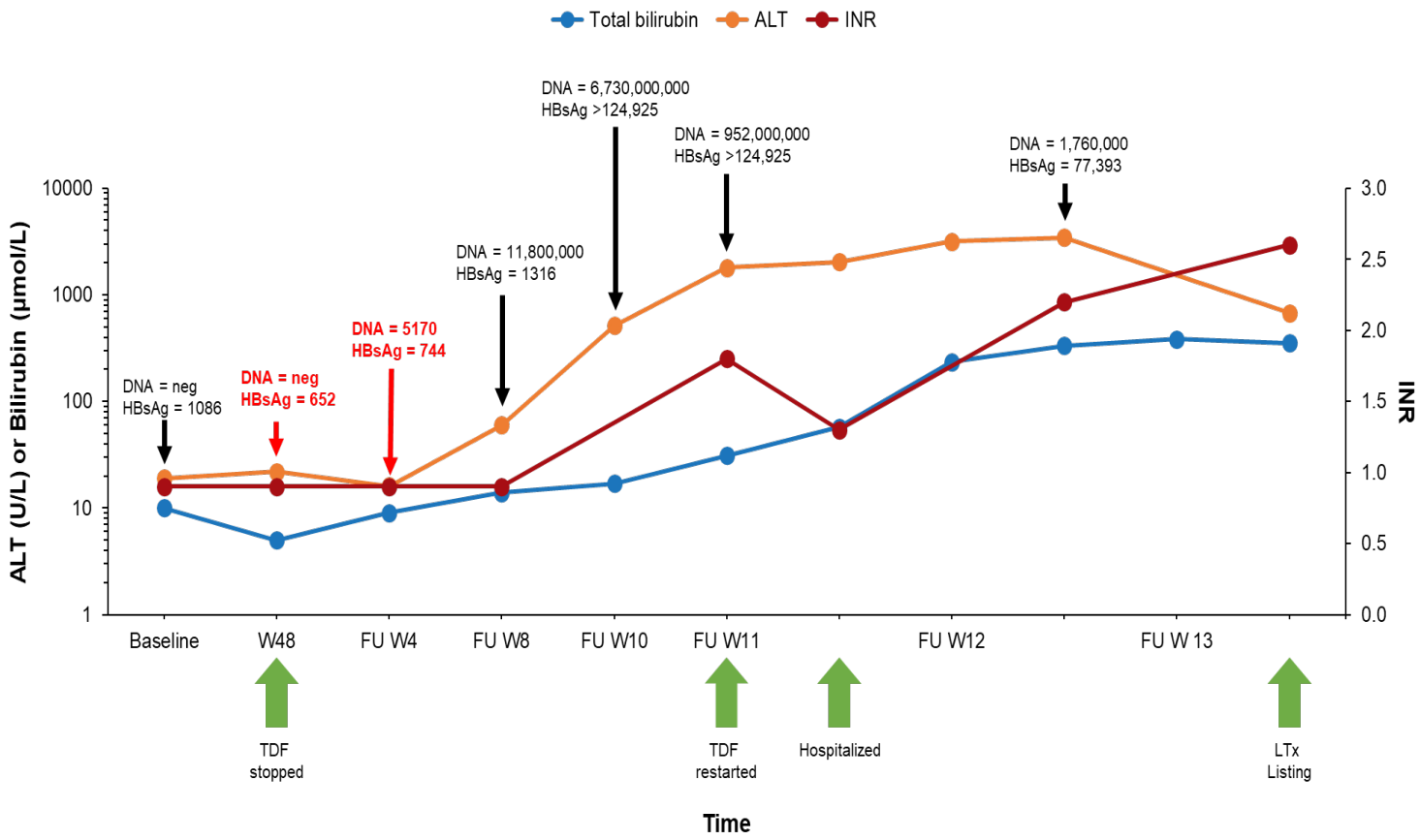
AE, adverse event; eGFR, estimated glomerular filtration rate; SAE, serious adverse event.

*1 patient experienced severe acute liver failure after stopping NA that was considered related to study procedure.

†Likely due to JNJ-6379 based on its known profile; this was reversible at the end of therapy.

REEF-2: Subacute Liver Failure Following NA Withdrawal

- 54-year-old, Asian male with stable TDF treatment for 8 years prior to screening
- NA only treatment arm
- Follow-up Week 11: rise in HBV DNA and ALT after stopping NA prompted NA retreatment, with jaundice, coagulopathy, and sub-acute liver failure
- Super-urgent listing and liver transplant required, with complete recovery
- Prompted an amendment to retreatment criteria: HBV DNA >5 $\log_{10}$ IU/mL requires immediate retreatment irrespective of ALT increase



HBV DNA and HBsAg values shown as IU/mL.

Agarwal et al. *J Hepatol.* 2022;77(1):245-248. doi: 10.1016/j.jhep.2022.03.006.

REEF-2: Summary

- In this European study of virologically suppressed HBeAg negative non-cirrhotic CHB patients, 48-week treatment with JNJ-3989 + JNJ-6379 + NA or Placebo + NA did not lead to HBsAg seroclearance 24 weeks after stopping all treatment

- **At Week 48**, JNJ-3989 + JNJ-6379 + NA showed a robust reduction in HBsAg:
  - Mean reduction of 1.89 $\log_{10}$ IU/mL
  - 71.6% of patients achieved HBsAg <100 IU/mL

- **At Follow-up Week 24**, JNJ-3989 + JNJ-6379 + NA showed pronounced off-treatment HBsAg and HBV DNA suppression and rarely resulted in ALT flares:
  - 29.7% of patients had HBV DNA <LLOQ and HBsAg <100 IU/mL
  - 91.9% of patients had HBV DNA <2000 IU/mL
  - 67.1% of patients had HBsAg <100 IU/mL
  - 2.4% of patients had ALT flares during follow-up

- Rates of SAEs and AEs leading to treatment discontinuation of JNJ-3989 and/or JNJ-6379 were low for both treatment arms, and there were no AEs leading to death

- One patient in the control arm had severe HBV reactivation that required liver transplant
  - Careful design of retreatment criteria is important in studies assessing the NA stopping concept

REEF-2: Conclusions

- Greater and more durable off-treatment virologic control was observed in patients who received the JNJ-3989 based regimen versus NA alone

- The absence of ‘functional cure’ at Follow-up Week 24 suggests the need for combining JNJ-3989 + NA with other mechanisms of action

- Results from Follow-up Week 48 are forthcoming

REEF-2: Countries and Sites

Italy

- Pietro Andreone – *Modena*
- Maurizia Rossana Brunetto – *Pisa*
- Pietro Lampertico – *Milano*
- Gloria Taliani – *Rome*

Poland

- Jacek Gasiorowski – *Wroclaw*
- Waldemar Jakub Halota – *Bydgosczcz*
- Maria Hlebowicz – *Gdansk*
- Ewa Janczewska – *Myslowice*

Spain

- Maria Buti – *Barcelona*
- Jose Luis Calleja – *Madrid*
- Javier Crespo Garcia – *Santander*
- Moises Diago – *Valencia*
- Inmaculada Fernandez – *Madrid*
- Xavier Forns – *Barcelona*

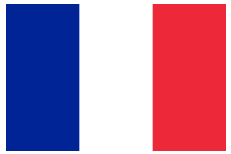
United Kingdom

- Andrew Ustianowski – *Manchester*
- Kosh Agarwal – *London*
- Patrick Kennedy – *London*
- Daniel Forton – *London*
- David Mutimer – *Birmingham*
- Stephen Barclay – *Glasgow*

Belgium

- Stefan Bourgeois – *Antwerp*
- Frederik Nevens – *Leuven*
- Hans Van Vlierberghe – *Gent*
- Thomas Vanwolleghem – *Antwerp*

France



- Tarik Asselah – *Clichy*
- Marc Bourliere – *Marseille*
- Jean-Pierre Bronowicki – *Nancy*
- Caroline Jezequel – *Rennes*
- Stanislas Pol – *Paris*
- Fabien Zoulim – *Lyon*
- Didier Samuel – *Villejuif*

Germany

- Markus Cornberg– *Hannover*
- Julian Schulze zur Wiesch – *Hamburg*
- Annette Grambihler – *Mainz*
- Cristoph Neumann-Haefelin – *Freiburg*
- Michael Sabranski – *Hamburg*
- Kathrin Sprinzl – *Frankfurt*
- Florian van Bömmel – *Leipzig*
- Heiner Wedemeyer – *Essen*

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