Efficacy and Safety of the siRNA JNJ-3989 and/or the Capsid Assembly Modulator JNJ-6379 for the Treatment of Chronic Hepatitis B Virus Infection : Results From the Phase 2b REEF-1 Study

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- Professor Yuen is the Chair & Deputy Head of the Department of Medicine and the Chief of the Division of Gastroenterology & Hepatology at the University of Hong Kong
- His current research interests include:
  - Novel antiviral and immunomodulatory agents for HBV
  - Treatment effects on HBV DNA–host integration
  - Development of emerging biomarkers for overt and occult HBV infection
  - Disease interaction between HBV and NAFLD

Presenter Disclosures

- Man-Fung Yuen reports being an advisor/consultant for and/or having received grant/research support from AbbVie, Aligos Therapeutics, Antios Therapeutics, Arbutus Biopharma, Arrowhead Pharmaceuticals, Assembly Biosciences, Bristol Myers Squibb, Clear B Therapeutics, Dicerna Pharmaceuticals, Finch Therapeutics, Fujirebio, Gilead Sciences, GlaxoSmithKline, Immunocore, Janssen, Merck Sharp and Dohme, Roche, Silverback Therapeutics, Spring Bank Pharmaceuticals, and Sysmex Corporation

REEF-1: Introduction

- JNJ-3989 is an siRNA that targets all HBV RNAs, thereby reducing levels of all viral proteins
- JNJ-6379 is a CAM-N that inhibits viral replication by inducing the formation of non-infectious viral particles consisting of empty nucleocapsids
- JNJ-3989, with or without JNJ-6379, has demonstrated strong HBsAg decline[1]
- The Phase 2b REEF-1 study assessed the efficacy and safety of 48 weeks of JNJ-3989 and/or JNJ-6379 in combination with NA in patients with CHB

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

1. Gane E, et al. European Association for the Study of the Liver (EASL) Digital International Liver Conference; August 27-29, 2020.

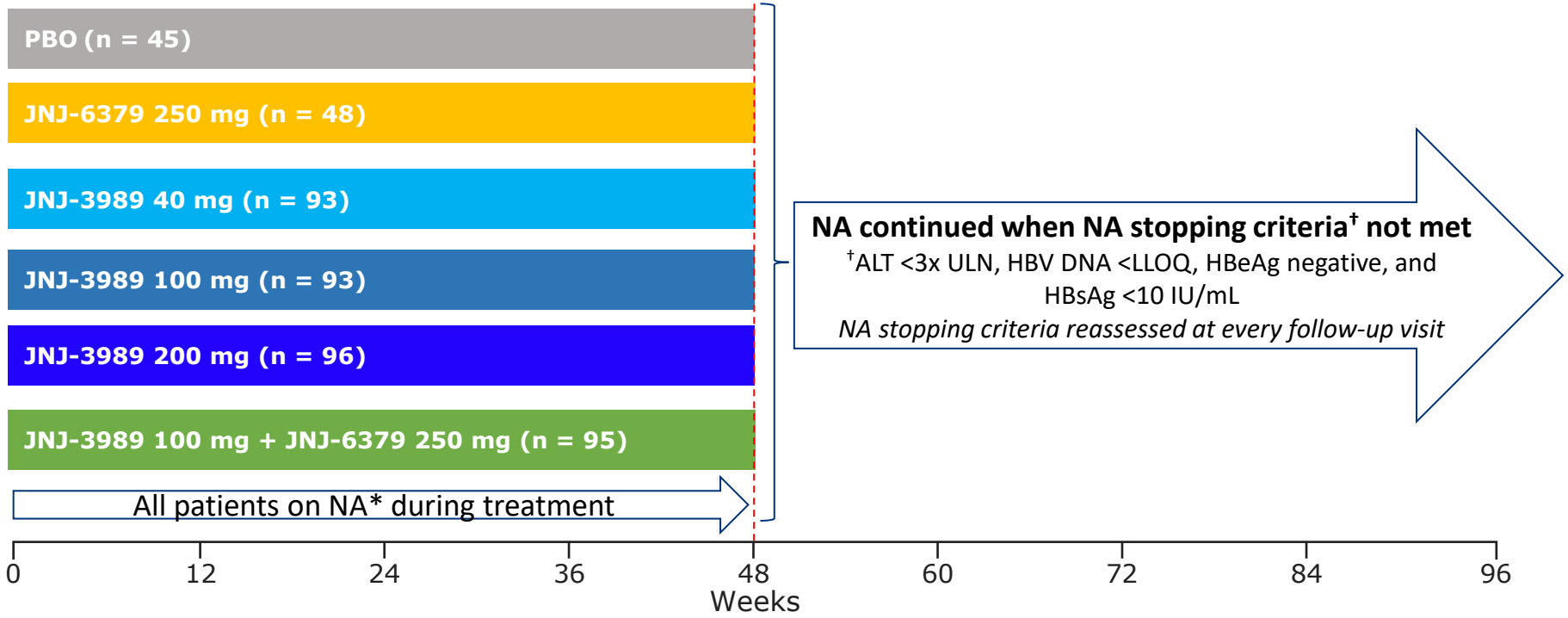
REEF-1: Study Design

Inclusion criteria:

- Active CHB (NCT or NA suppressed)
- HBsAg >100 IU/mL at screening
- Non-cirrhotic (Fibrosis Stage F0-F2)

Stratification:

- HBeAg positive vs negative
- Treatment History (NCT vs VS)



Primary endpoint: Proportion of patients meeting NA stopping criteria (ALT <3x ULN, HBV DNA <LLOQ, HBeAg negative, and HBsAg <10 IU/mL) at EOT

*NA = entecavir (ETV)/tenofovir disoproxil fumarate (TDF)/tenofovir alafenamide (TAF).

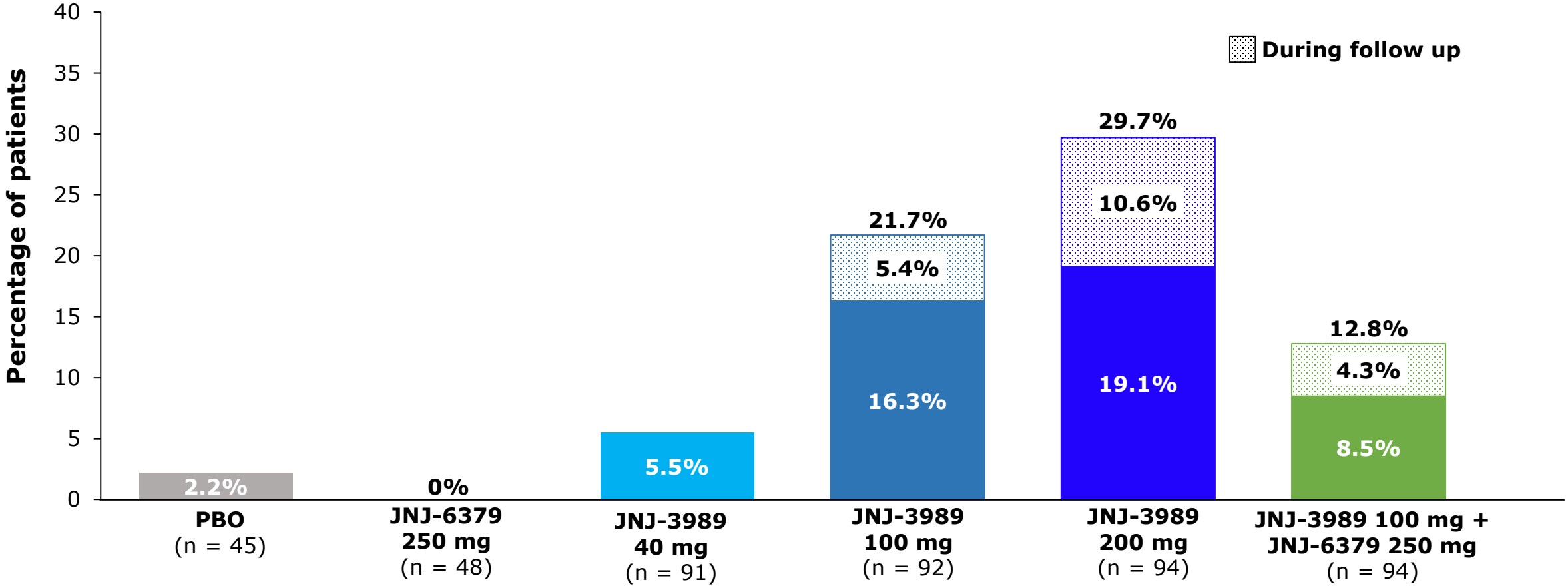
ALT, alanine aminotransferase; EOT, end of treatment; HBeAg, hepatitis B e antigen; LLOQ, lower limit of quantitation; NCT, not currently treated; PBO, placebo; ULN, upper limit of normal; VS, virologically suppressed under NA treatment.

REEF-1: Demographics and Baseline Characteristics

Baseline Mean Values	PBO (n = 45)	JNJ-6379 (n = 48)	JNJ-3989 40 mg (n = 93)	JNJ-3989 100 mg (n = 93)	JNJ-3989 200 mg (n = 96)	JNJ-3989 100 mg + JNJ-6379 (n = 95)
Male, %	56	77	66	59	64	75
Asian, %	33	42	46	42	41	37
Age, years	44	44	42	43	43	43
Treatment history, NCT, %	36	38	37	37	38	36
HBeAg positive, %	29	31	32	28	31	30
HBsAg, $\log_{10}$ IU/mL	3.8	3.6	3.8	3.7	3.8	3.7
ALT, U/L	44.9	65.5	47.0	43.7	53.0	57.2
Liver stiffness,* kPa	5.4	5.3	5.4	5.3	5.3	5.3

*Measured with FibroScan.

REEF-1: Percentage of Patients Meeting NA Stopping Criteria* at Week 48



Data shown are for missing as nonresponse analysis.
*Primary endpoint: ALT <3× ULN, HBV DNA <LLOQ, HBeAg negative, and HBsAg <10 IU/mL.

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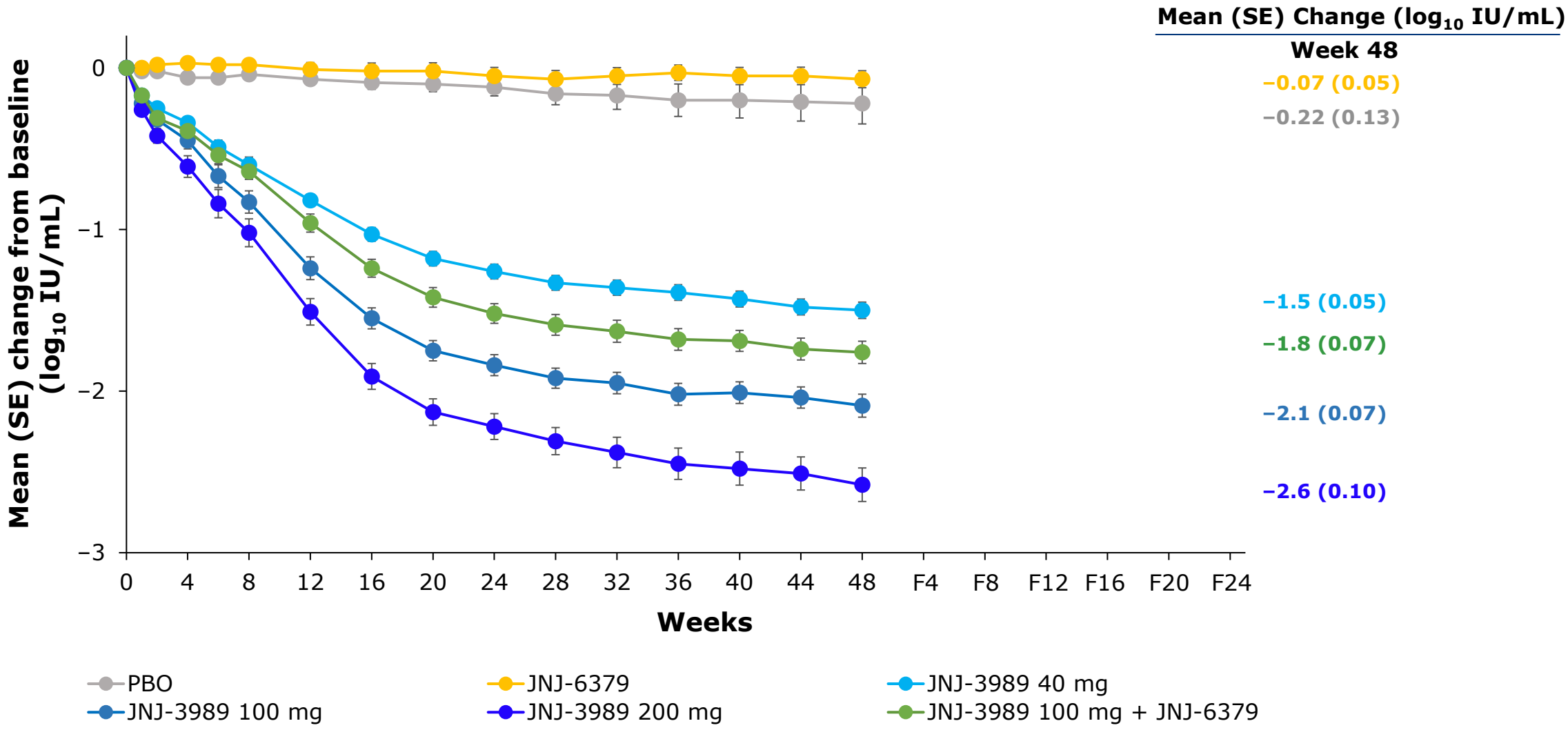
REEF-1: HBsAg Over Time



FU, follow up; SE, standard error.

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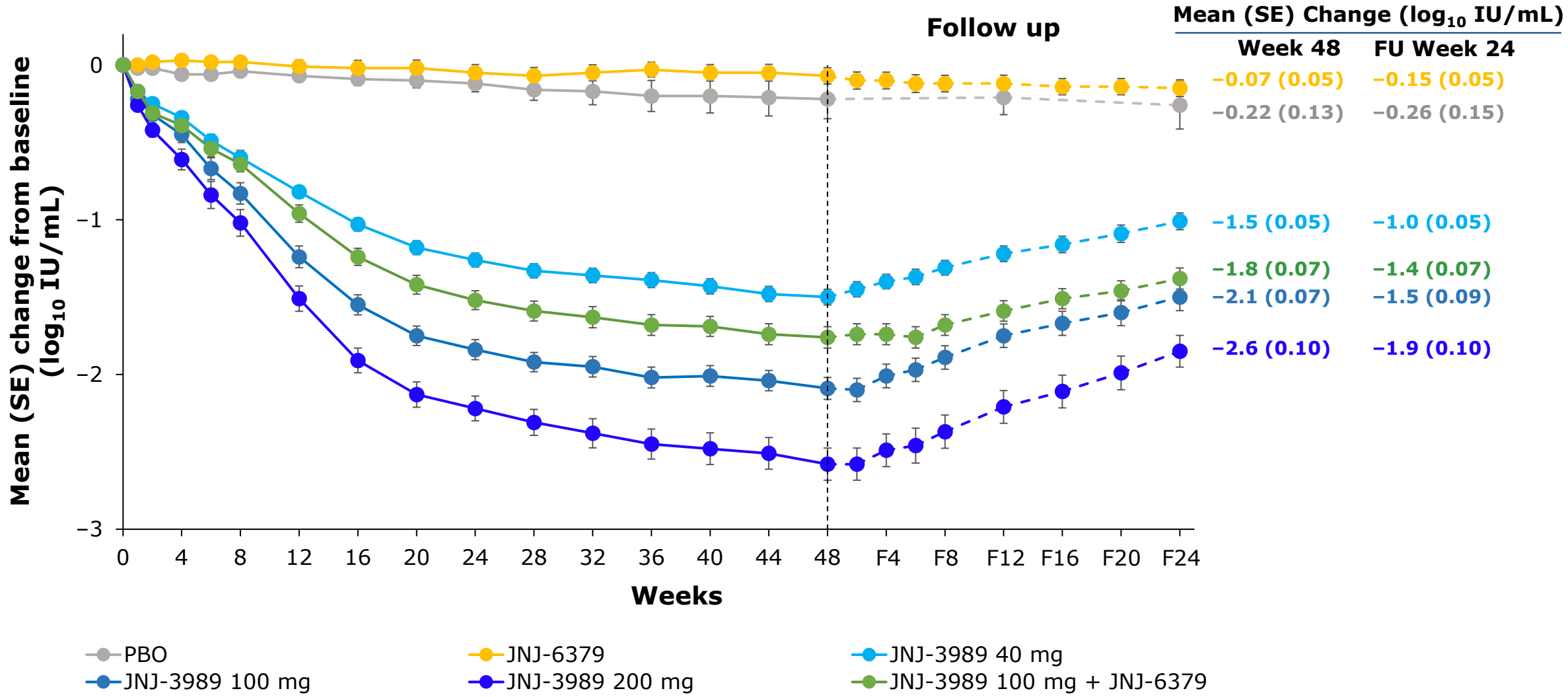
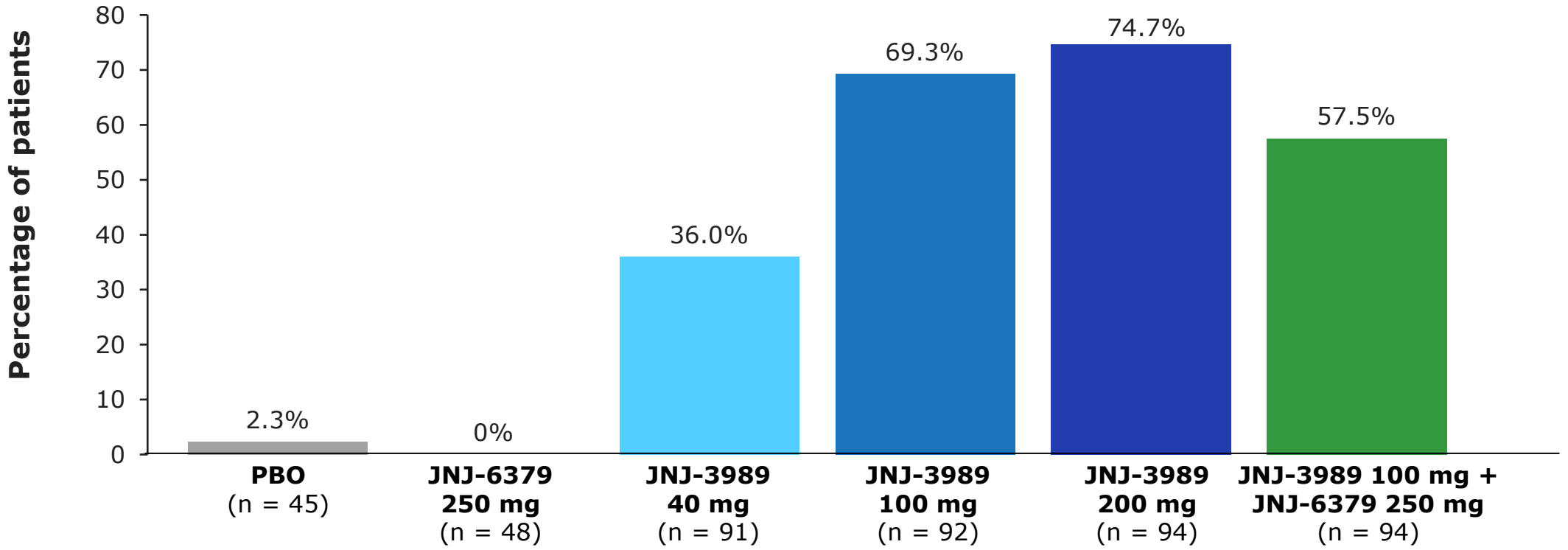
REEF-1: HBsAg Over Time



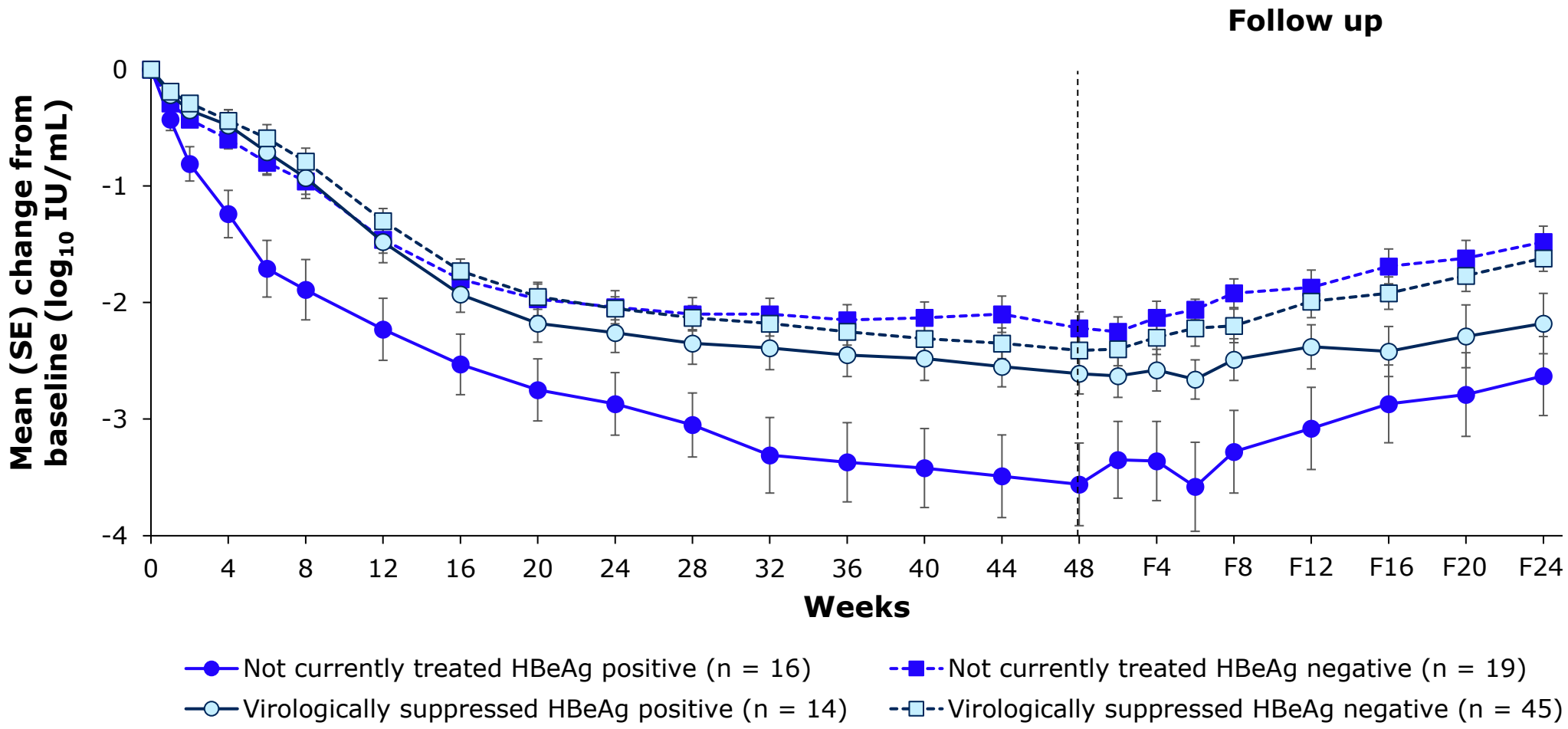
- No patient in the active treatment arms achieved functional cure at follow-up Week 24

FU, follow up; SE, standard error.

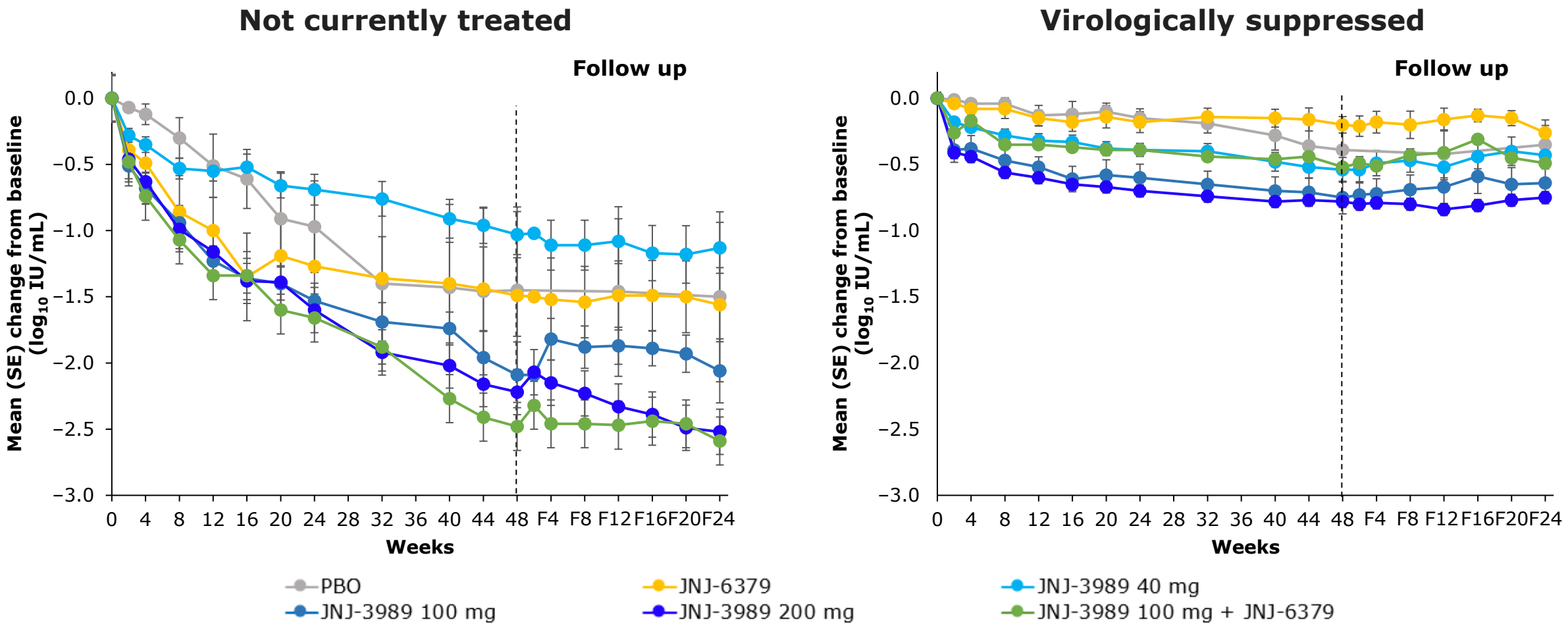
REEF-1: Percentage of Patients Achieving HBsAg <100 IU/mL at Week 48



REEF-1: HBsAg Over Time by Stratification Factors (JNJ-3989 200 mg)



REEF-1: HBeAg Over Time in Treatment History Subgroups

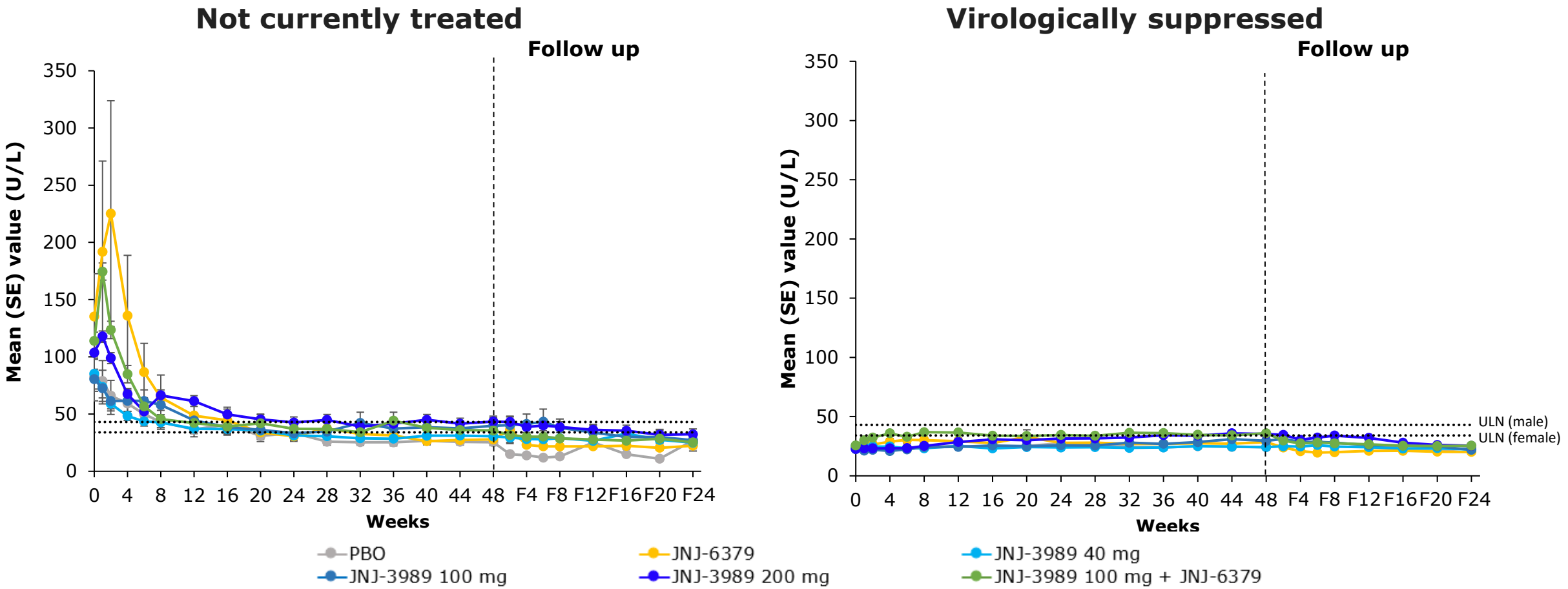


REEF-1: Adverse Events During Double-blind Phase (Up to Week 48)

	PBO (n = 45)	JNJ-6379 (n = 48)	JNJ-3989 40 mg (n = 93)	JNJ-3989 100 mg (n = 93)	JNJ-3989 200 mg (n = 96)	JNJ-3989 100 mg + JNJ-6379 (n = 95)
Percentage of patients with 1 or more (%):						
AEs	66.7	85.4	74.2	71.0	64.6	71.6
Related AEs	20.0	43.8	30.1	28.0	32.3	34.7
AEs leading to death	0	0	0	0	0	0
Serious AEs	0	4.2	1.1	2.2	3.1	2.1
Serious AEs related to study treatment	0	0	0	0	1.0	1.1
AEs leading to discontinuation of JNJ-6379 and/or JNJ-3989	0	2.1	2.2	0	0	2.1
Grade 3 or 4 AEs	4.4	14.6	6.5	2.2	5.2	7.4

AE, adverse event.

REEF-1: ALT Profiles Over Time



- 13/470 (2.8%) patients reported ALT flares during double-blind treatment; 7/96 patients in the JNJ-3989 200 mg arm had on-treatment ALT flares
- 1 patient in the JNJ-3989 200 mg arm experienced an ALT flare post-treatment after stopping NA

*ALT flare: confirmed ALT ≥3× ULN and ≥3× nadir (ie, lowest value observed up to the start of the flare).

REEF-1: Summary and Conclusion

- A dose dependent response to JNJ-3989 (siRNA) was observed
- JNJ-3989 200 mg (highest dose) arm at Week 48:
  - 19.1% patients met primary endpoint (NA stopping criteria)
  - Greatest reduction of HBsAg levels from baseline (2.6 $\log_{10}$ IU/mL)
  - 74.7% of achieved HBsAg <100 IU/mL
- All regimens within this long-term study were generally well tolerated and safe
- Combination studies involving different mechanisms of action are ongoing

Acknowledgments

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