

Antiviral Activity of the Non-Nucleoside Polymerase Inhibitor, HCV-796, in Combination with Pegylated Interferon Alfa-2b in Treatment-Naïve Patients With Chronic Hepatitis C Virus

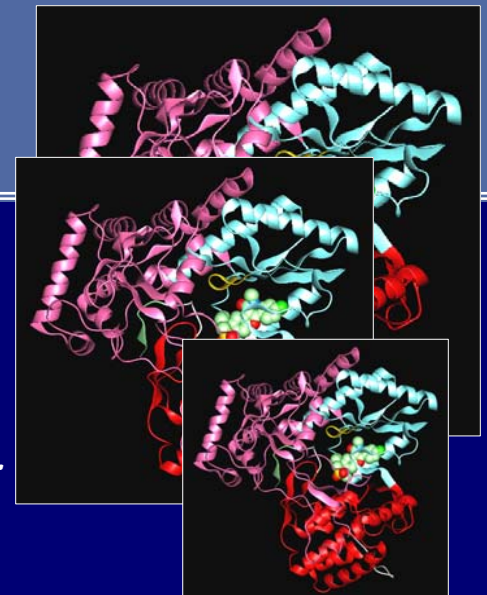
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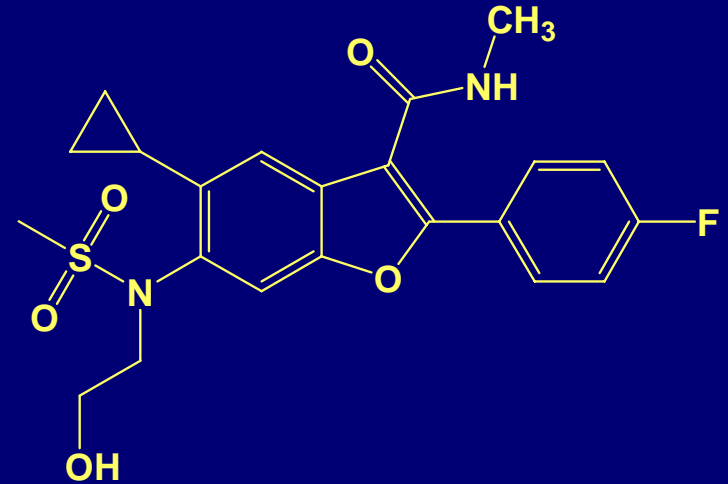
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HCV-796 Background

Preclinical

- Chemical Class: Benzofuran
- Orally bioavailable
- Target: HCV NS5B RdRp
- Mechanism: Non-competitive allosteric inhibitor (Non-nucleoside)
- *In vitro*:
 - Active against RdRp Enzyme (Genotypes 1, 2, 3, 4)
 - Replicon Activity:
 - 1a replicon: $EC_{50} = 4.5 \pm 2.0$ nM
 - 1b replicon: $EC_{50} = 8.6 \pm 4.0$ nM
- *In vivo*: antiviral activity in chimeric mice infected with HCV



Study Design

- Randomized, double-blind, placebo-controlled dose-ranging study
- Subjects with chronic HCV infection
 - HCV treatment-naïve; any HCV genotype
- Day -1 and Day 7: PEG-IFN
 - pegylated interferon alfa-2b; 1.5 µg/kg/dose
- Days 1-14: HCV-796 or placebo
 - 100, 250, 500, or 1000 mg BID
- Objectives: Safety, PK, Antiviral activity

Study Population

Key Entry Criteria

- Age 18 to 64 years
- Treatment-naïve subjects with chronic HCV
- Any HCV genotype
- No other known causes of liver disease
- No advanced or decompensated liver disease
- Plasma HCV RNA $\geq 10^4$ IU/mL at screening
- Human immunodeficiency virus (HIV) negative
- ALT less than 5x upper limit of normal

Methods

- All subjects monitored as inpatients during the 14-day treatment period
- Baseline HCV genotyping
 - TRUEGENE® HCV 5'NC Genotyping Kit (Bayer HealthCare)
- Plasma HCV RNA Assessments by PCR
 - AMPLICOR HCV MONITOR (Roche Diagnostics)
- Standard safety assessments
- PK profiles Day 1 and Day 14

Demographics / Baseline Characteristics

HCV-796 Dose (mg)	PEG	100 + PEG	250 + PEG	500 + PEG	1000 + PEG
n	19	12	10	12	12
Age (y) Median	52	51	50	50	52
Gender (n) M / F	17 / 2	10 / 2	9 / 1	9 / 3	7 / 5
Wt (kg) Median	82	76	69	83	95
Race (n) White	15	8	9	11	9
Black	4	3	1	-	1
Other	-	1	-	1	2
HCV genotype 1 (%)	68	58	67	67	67
Baseline HCV RNA (log ₁₀) Median	6.7	6.4	6.2	6.3	6.7

HCV-796 Plasma PK

Parameters on Day 14

	Mean (SD)			
	C _{max} (ng/mL)	AUC ₀₋₁₂ (ng·hr/mL)	t _{1/2} (hr)	AUC D14 / D1
100 mg Q12	674 (157)	6074 (1526)	50 (14)	4.0
+ PEG	643 (139)	5737 (1108)	50 (14)	4.0
250 mg Q12	1043 (185)	9348 (1789)	42 (14)	3.0
+ PEG	1076 (302)	9278 (2887)	39 (12)	2.8
500 mg Q12	1575 (239)	14360 (1833)	42 (11)	3.8
+ PEG	1546 (510)	13546 (4487)	48 (27)	2.6
1000 mg Q12	2186 (764)	20046 (7633)	54 (29)	4.2
+ PEG	1936 (406)	17474 (3008)	50 (17)	2.1

Safety

- Safety profile of HCV-796 + PEG was generally consistent with known effects of interferons
 - Virtually all subjects had headache, chills, myalgia, or fever – most starting on Day -1 after first dose of PEG
- No dose-limiting toxicities identified across the range of study doses
- Serious AEs:
 - PEG: (1) pneumonia [Day 15]
 - 1000 mg + PEG: (1) seizure, rhabdomyolysis [Day 1]

Adverse Events

Most Common AEs

HCV-796 Dose (mg)	PEG	100 + PEG	250 + PEG	500 + PEG	1000 + PEG
n	19	12	10	12	12
Headache, %	84	83	70	83	92
Chills, %	53	58	70	75	67
Myalgia, %	53	42	60	83	67
Fever, %	58	33	80	42	33
Back pain, %	16	33	70	75	17
Arthralgia, %	16	25	30	25	17
Pain, %	11	25	10	8	33
Rash, %	5	25	10	17	33

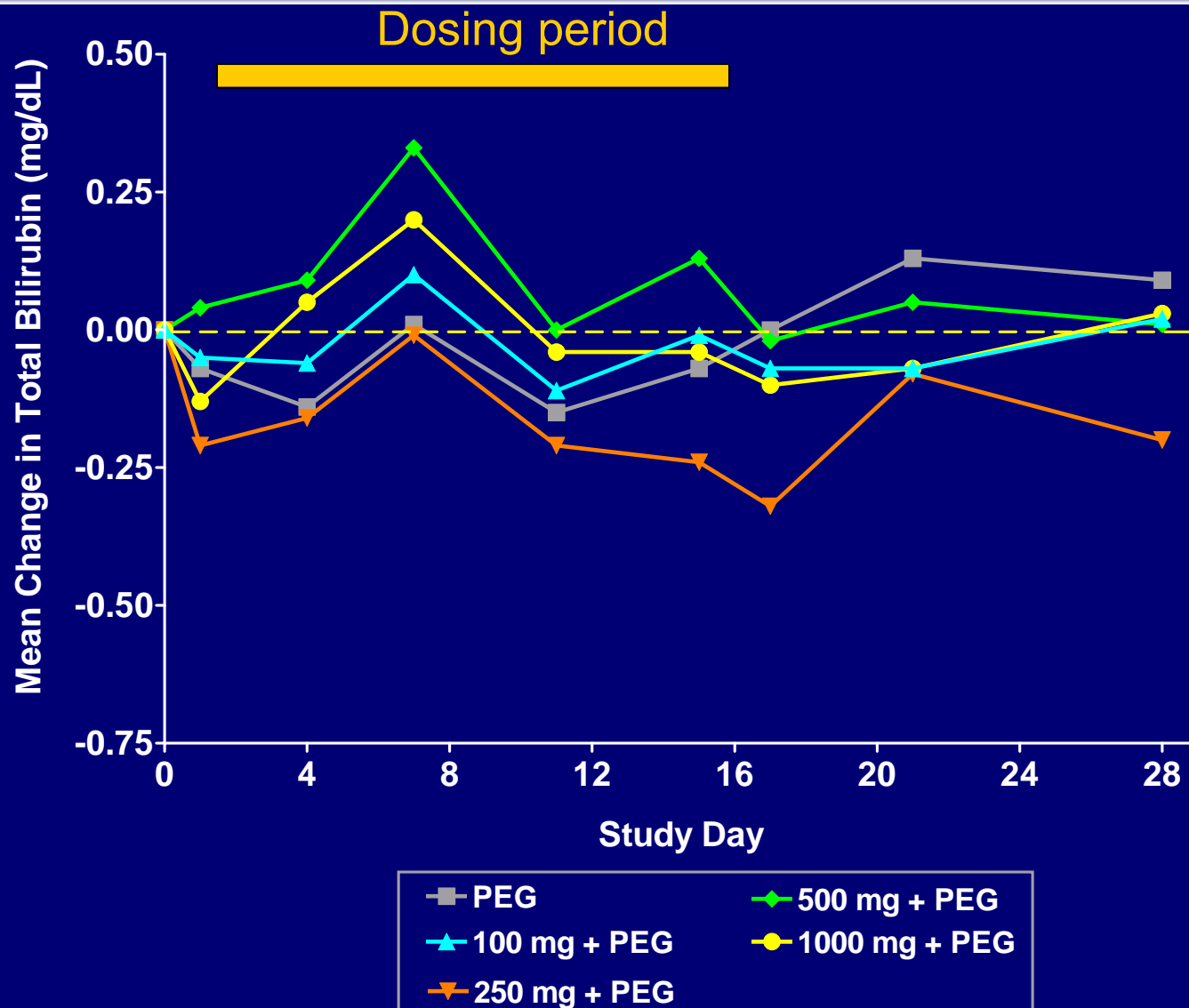
Shown are events reported in > 15% of all subjects receiving HCV-796.

Subject Disposition Through End of Treatment

	D/C for AE	D/C for other reason	On-Rx data @ Day 14
PEG	1 • hypertension	–	15
100 mg +PEG	–	2 • withdrew consent	10
250 mg +PEG	–	1 • low baseline HCV RNA	9
500 mg +PEG	–	–	12
1000 mg +PEG (a)	1 seizure/rhabdomyolysis, Day 1 → cohort discontinued		
1000 mg +PEG (b)	2 • rash • vasovagal syncope	–	10

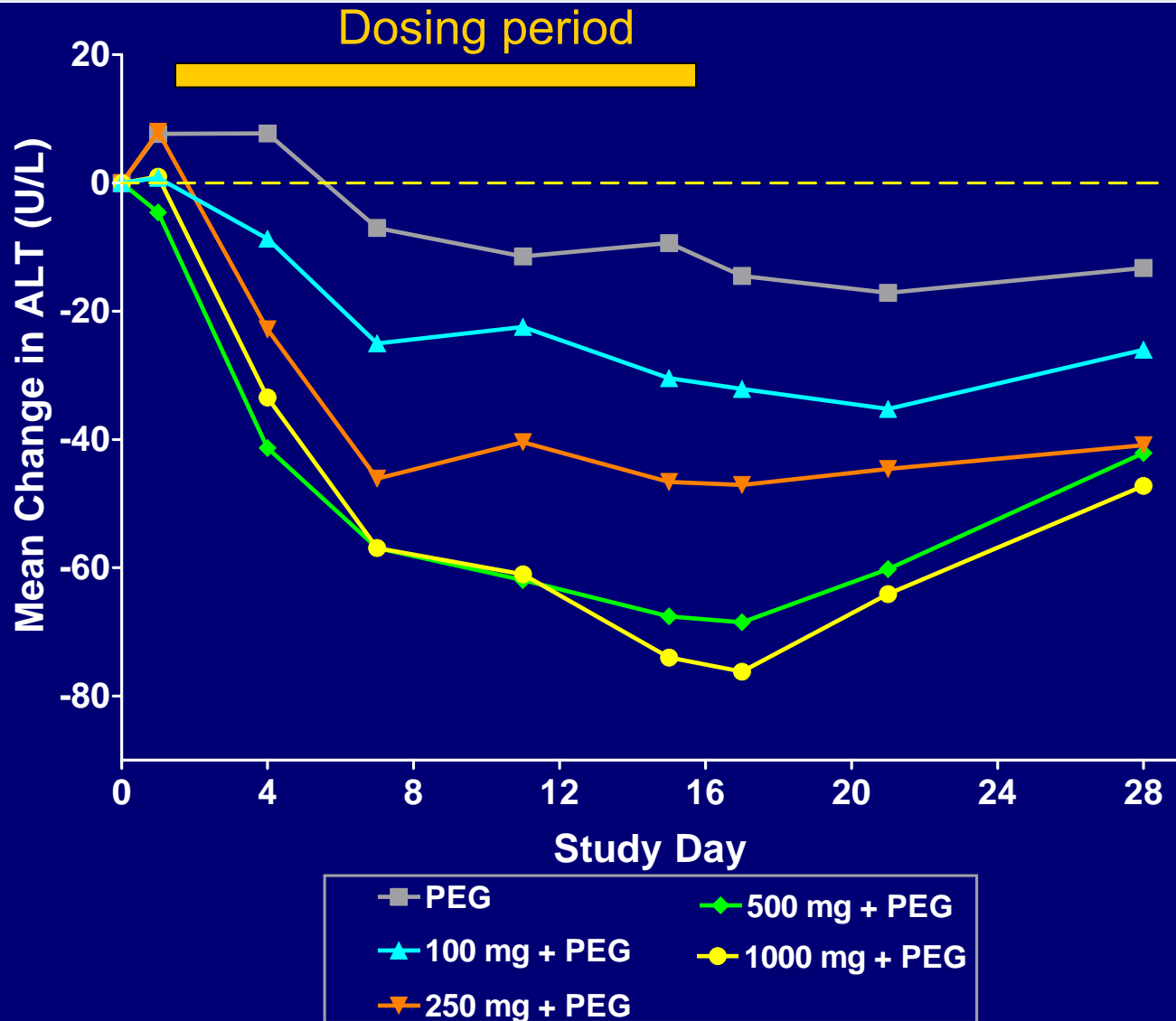
Total Bilirubin

Change From Baseline



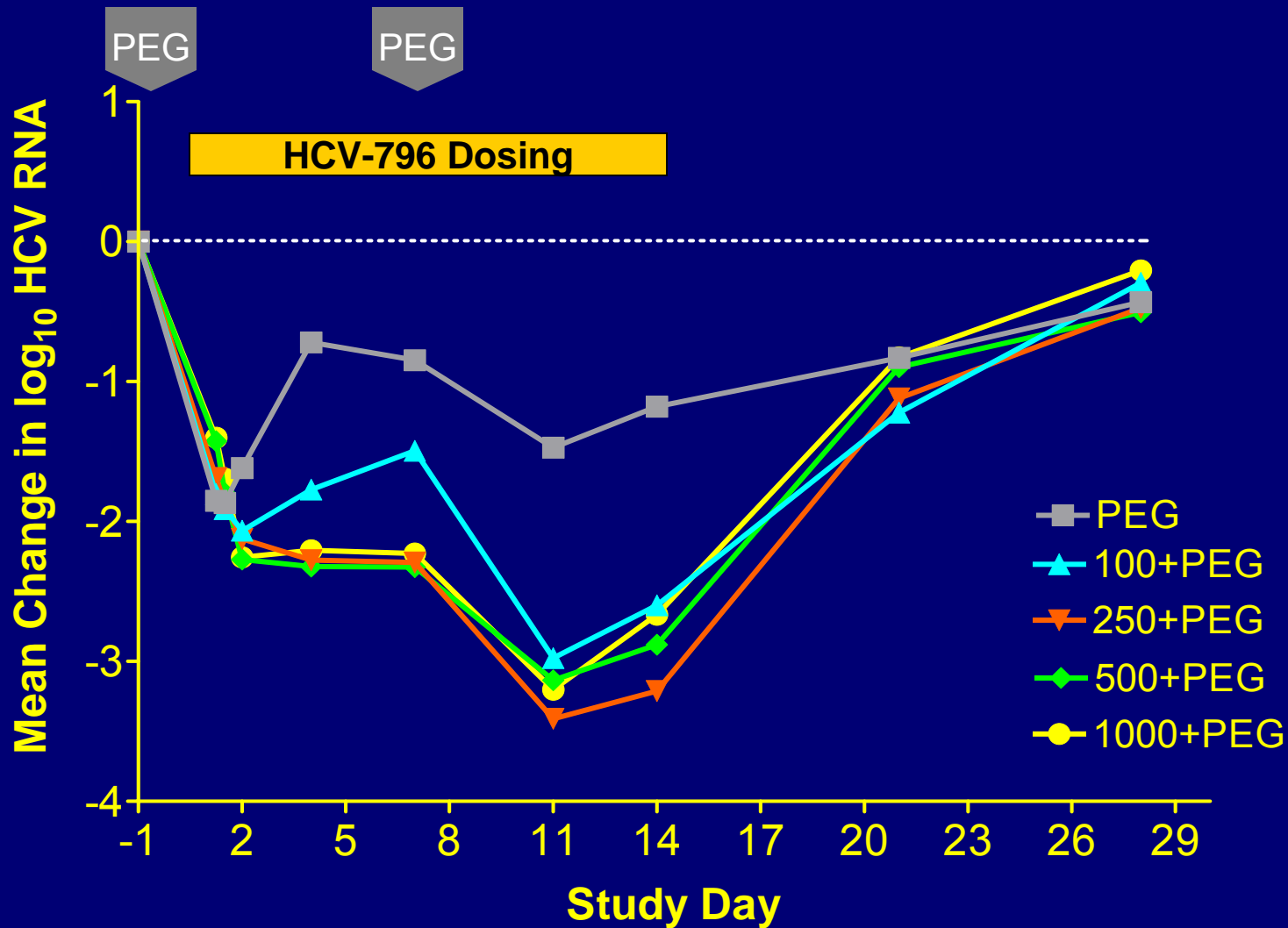
ALT

Change From Baseline



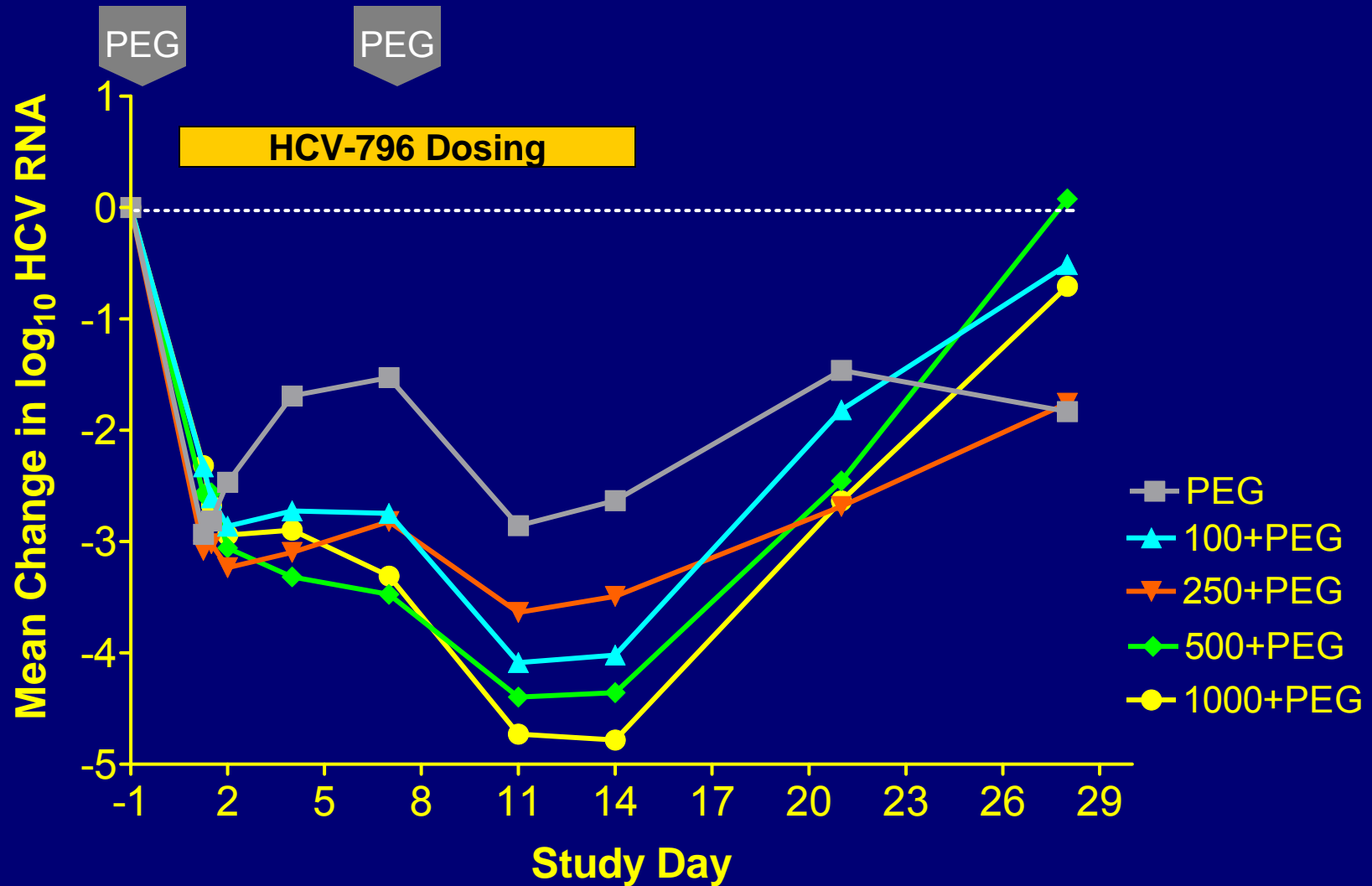
HCV RNA Change from Baseline

Genotype 1



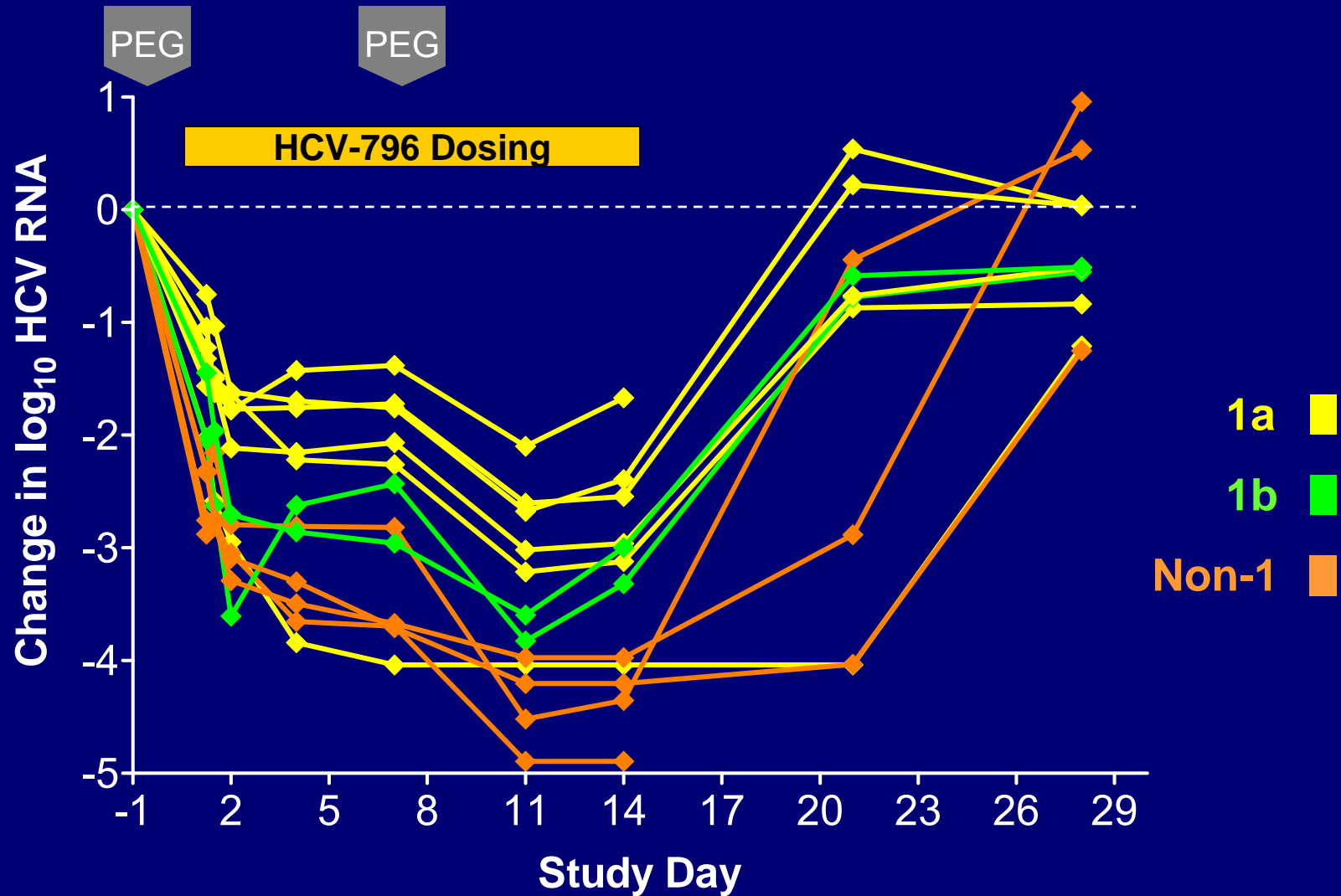
HCV RNA Change from Baseline

Genotype non-1



HCV RNA Change from Baseline

Individuals: 500 mg + PEG



HCV-RNA Reductions

Change from Baseline at Day 14, All Genotypes

% Subjects With ↓ in log₁₀ HCV RNA

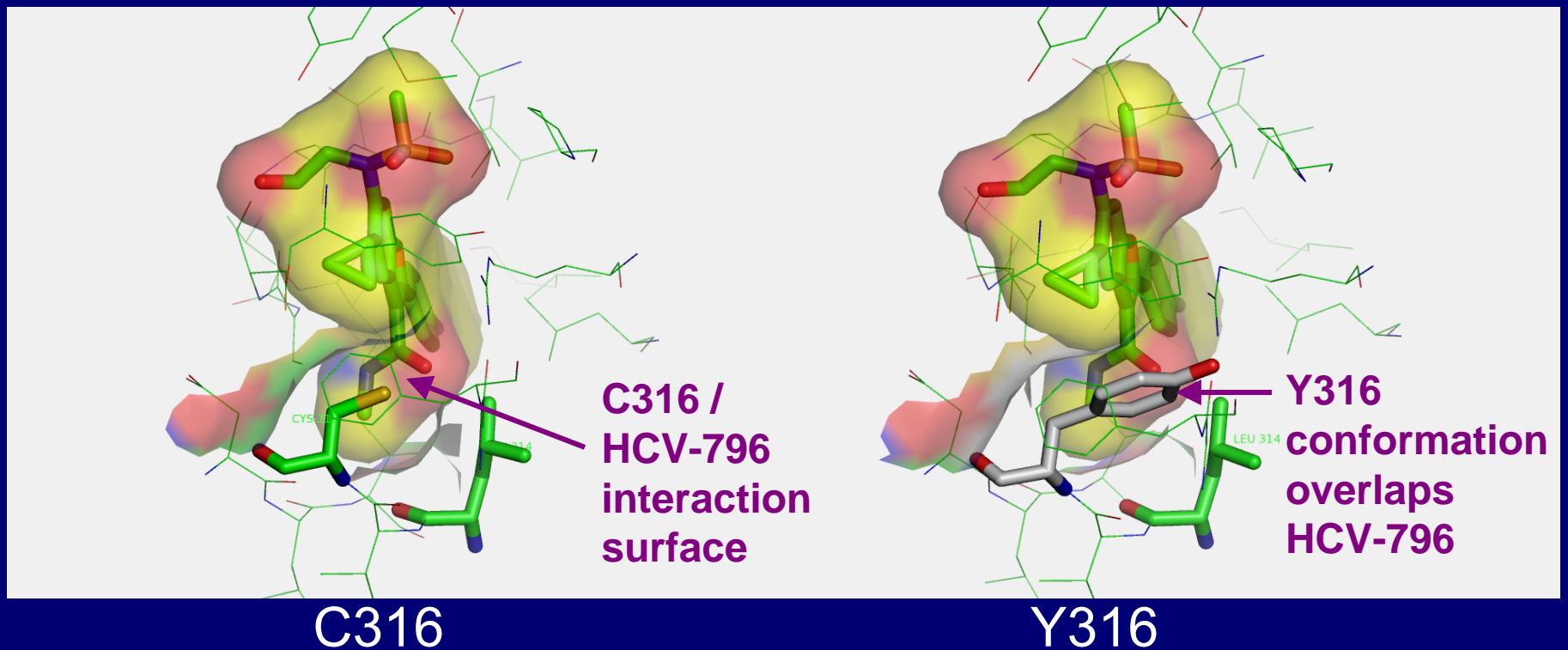
	n	≥ 2 log	≥ 3 log	BQL
PEG	15	6 (40%)	2 (13%)	2 (13%)
100 mg +PEG	10	7 (70%)	7 (70%)	2 (20%)
250 mg +PEG	9	7 (78%)	6 (67%)	3 (33%)
500 mg +PEG	12	11 (92%)	8 (67%)	4 (33%)
1000 mg +PEG	10	7 (70%)	7 (70%)	3 (30%)

BQL = below quantification limits (< 50 IU/mL)

HCV Genetic Sequencing

Background: C316Y variant

- *In vitro*, selection of resistant replicons maps to a number of variants within the binding pocket including C316Y
- In subjects treated for 14 days with HCV-796 monotherapy, on-therapy increases in HCV RNA levels were associated with emergence of C316Y



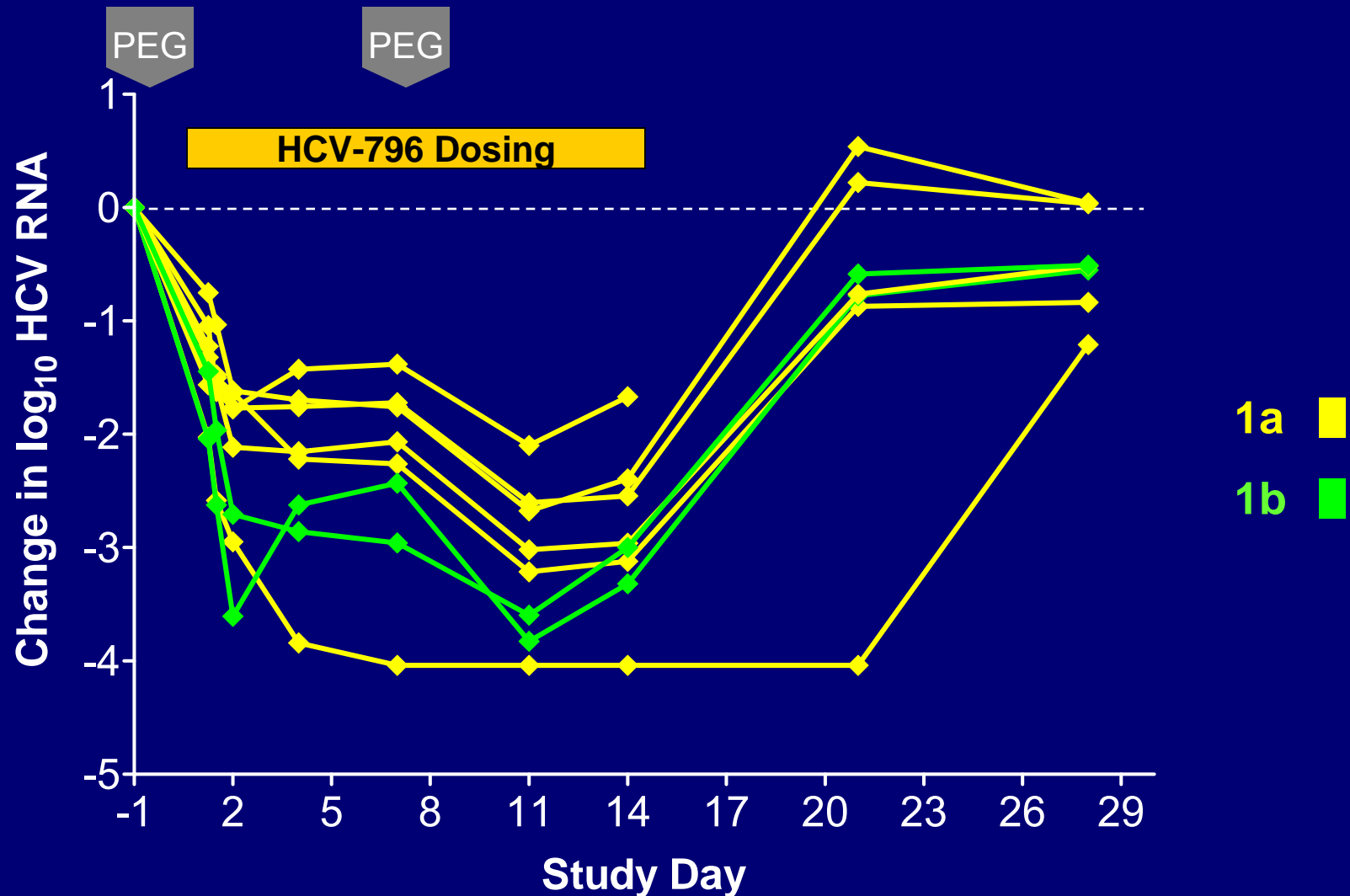
HCV Genetic Sequencing

Preliminary Analyses

- Samples tested from combination therapy groups:
 - HCV genotype 1a or 1b subjects treated to Day 14
 - Baseline, Day 7, End of treatment (Day 14)
- NS5B sequencing: 36 subjects (11 PEG, 25 HCV-796 + PEG)
 - Baseline: no variants at position 316 detected
 - During or end of treatment:
 - PEG: no changes at 316
 - HCV-796 + PEG: C316Y detected in 7 (28%; 3 1a, 4 1b)
 - Unclear association with response pattern over the 14 days of treatment

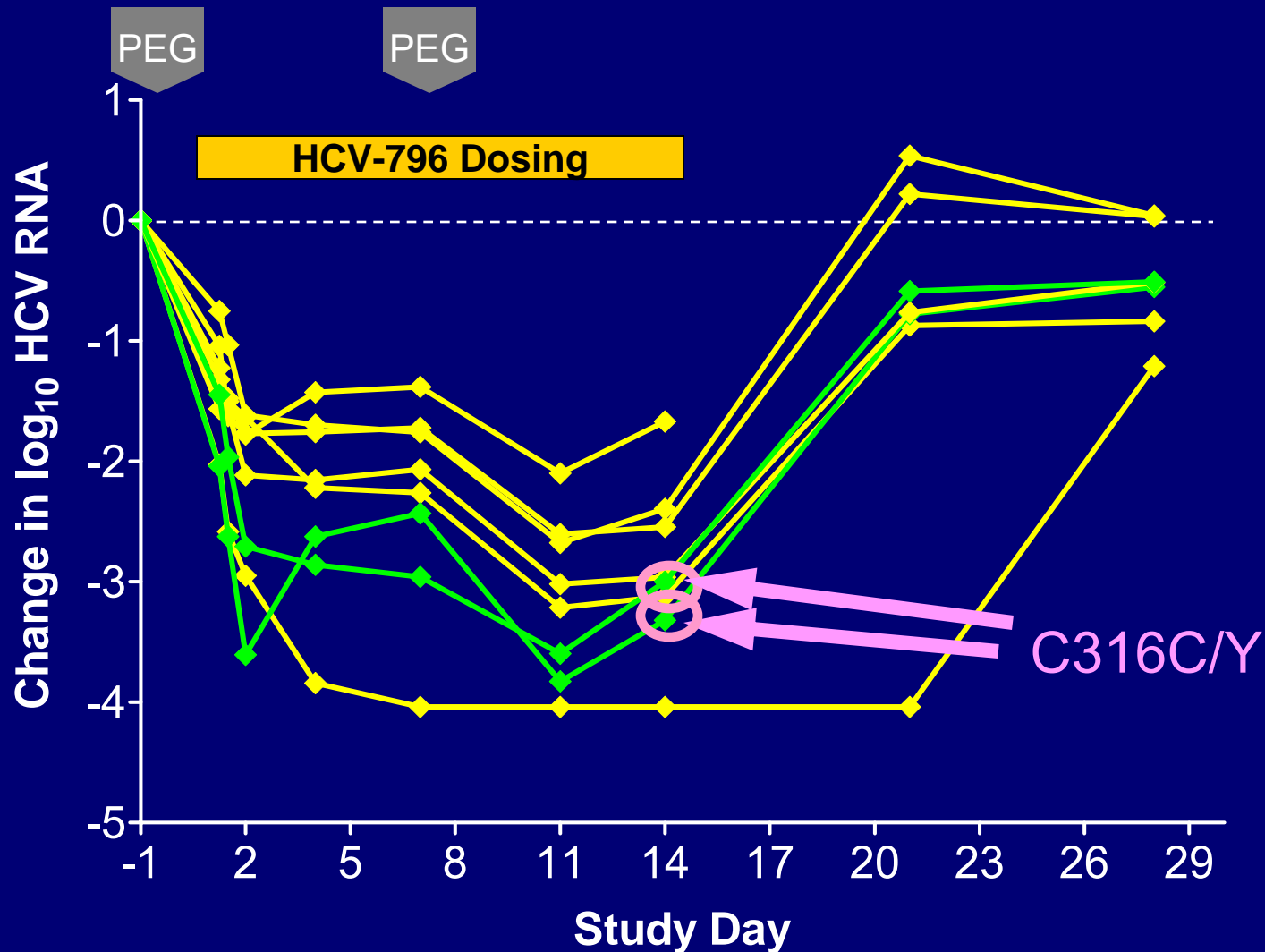
HCV RNA Change from Baseline

Individuals: 500 mg + PEG



HCV RNA Change from Baseline

Individuals: 500 mg + PEG



Conclusions

- HCV-796 + PEG displays clinical antiviral activity that is greater than that of HCV-796 or PEG alone:
 - Across multiple HCV genotypes
 - Similar responses observed at HCV-796 doses ≥ 250 mg Q12
- HCV-796 was well tolerated when added to PEG
 - AEs generally consistent with known effects of interferons
 - No dose-limiting toxicities across the range of study doses
- NS5B sequencing identified C316Y variant in a subset of subjects treated with HCV-796 + PEG, but not clearly associated with virologic response pattern
 - Implication to be determined in more long-term studies
- Phase 2 study of combination therapy ongoing

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