

# Antiviral Activity of the Non-Nucleoside Polymerase Inhibitor, HCV-796, in Patients With Chronic Hepatitis C Virus: Preliminary Results From a Randomized, Double-Blind, Placebo-Controlled, Ascending Multiple Dose Study

*Priyamvada Chandra,<sup>1</sup> Donald Raible,<sup>1</sup> Dawn Harper,<sup>1</sup>  
John Speth,<sup>1</sup> Stephen Villano,<sup>2</sup> Geraldine Bichier<sup>3</sup>*

*<sup>1</sup>Dept of Clinical Pharmacology, Wyeth Research, Collegeville, PA;*

*<sup>2</sup>Clinical Research & Development, ViroPharma, Incorporated, Exton, PA;*

*<sup>3</sup>Center for Clinical Trials Research, Univ. of Florida, Gainesville, FL*



# HCV-796 Background

## *Preclinical*

- Chemical Class: Benzofuran
- Target: HCV NS5B RNA Dependent RNA Polymerase
- Mechanism: Non-competitive allosteric inhibitor (Non-nucleoside)
- *In vitro* Antiviral Activity:
  - RdRp Enzyme Activity
    - Genotypes 1a & 1b:  $IC_{50} = 0.01 - 0.16 \mu M$
    - Genotypes 2, 3, 4:  $IC_{50} = 0.22 - 1.7 \mu M$
  - Replicon Activity:
    - 1a replicon:  $EC_{50} = 4.5 \pm 2.0 \text{ nM}$
    - 1b replicon:  $EC_{50} = 8.6 \pm 4.0 \text{ nM}$
- *In vivo* Antiviral Activity:
  - $2 \log_{10}$  HCV RNA reduction in chimeric mice infected with HCV

## Study Design

- Randomized, double-blind, placebo-controlled dose-ranging study
- Dosing: 6 ascending dose groups
  - 50, 100, 250, 500, 1000, 1500 mg
  - Twice-daily (Q 12 h) dosing
  - 3:1 allocation (12 active: 4 placebo) per group
- 14 days of dosing
- 4-week post-treatment follow-up
- 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  
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HCV-796 Dose (mg)		50	100	250	500	1000	1500	Placebo
n		12	12	12	14	12	15	25
Age (y)	Median	51	54	48	51	51	50	49
	min, max	32, 59	47, 63	32, 57	20, 64	42, 63	30, 61	39, 60
Gender (n)	M / F	12 / 0	7 / 5	10 / 2	10 / 4	7 / 5	11 / 4	21 / 4
Wt (kg)	Median	79	80	90	84	83	98	80
Race (n)	White	12	11	11	11	10	11	22
	Black	-	-	1	3	1	4	3
	Other	-	1	-	-	1	-	-
Baseline HCV RNA (log <sub>10</sub> )	Median	7.2	7.1	6.5	6.4	6.8	6.7	6.7

# HCV Genotype Distribution

Dose Group	HCV Genotype/Subtype (n)							
	1a	1b	1	2a	2b	3a	4a	?
50 mg Q12	6	2	-	1	1	-	1	1
100 mg Q12	4	3	3	-	-	2	-	-
250 mg Q12	5	2	2	-	2	-	1	-
500 mg Q12	7	1	1	-	2	1	-	2
1000 mg Q12	8	1	-	-	2	-	1	-
1500 mg Q12	7	2	2	-	3	-	-	1
PLACEBO	8	7	2	-	3	2	1	2
Total	45 44%	18 18%	10 10%	1 1%	13 13%	5 5%	4 4%	6 6%

72% genotype 1

# HCV-796 Plasma PK

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## Parameters on Day 14

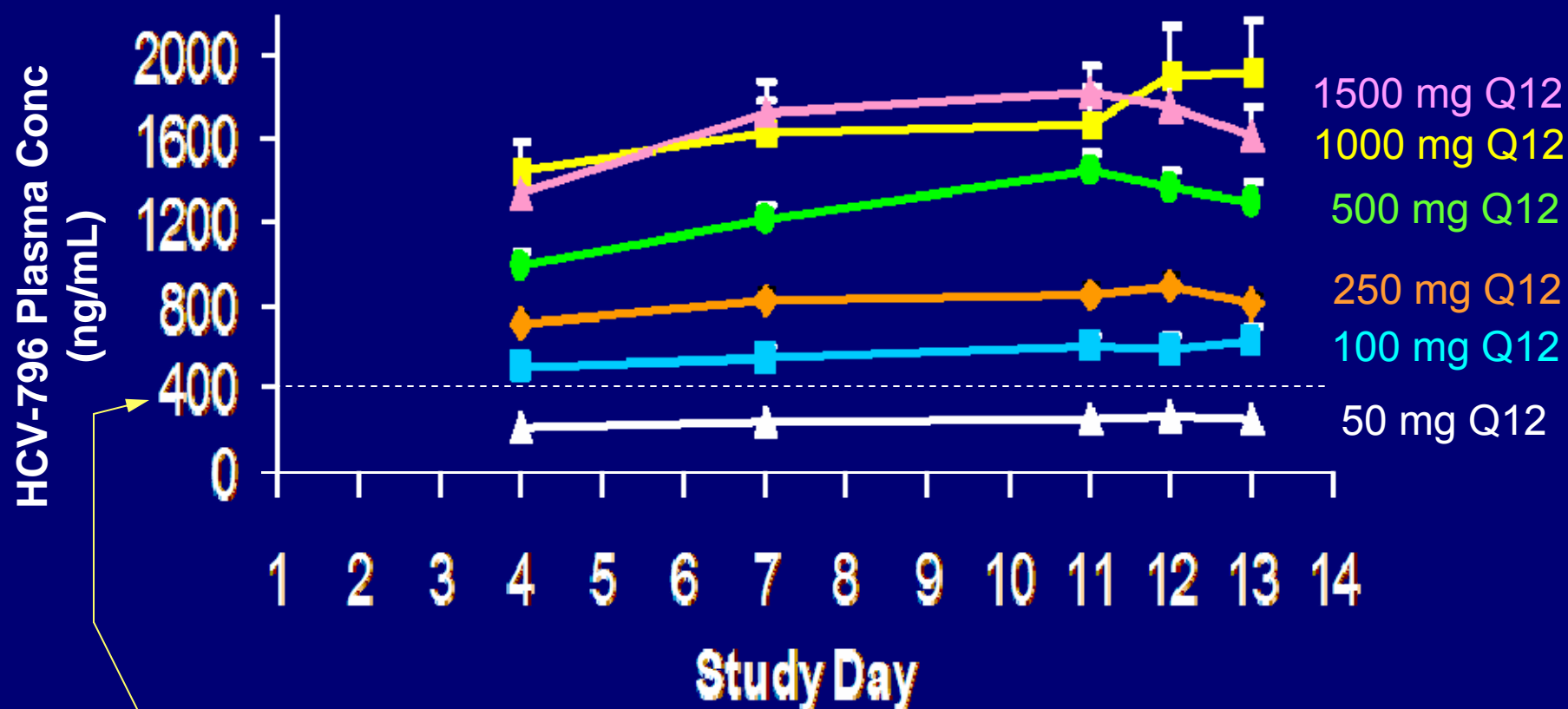
	Mean (SD)			
	C <sub>max</sub> (ng/mL)	AUC 0-12 (ng·hr/mL)	t <sub>1/2</sub> (hr)	AUC Day 14/Day 1
50 mg Q12	329 (71)	2966 (689)	47 (22)	3.9
100 mg Q12	674 (157)	6074 (1526)	50 (14)	3.7
250 mg Q12	1043 (185)	9348 (1789)	42 (14)	3.0
500 mg Q12	1575 (239)	14360 (1833)	42 (11)	3.8
1000 mg Q12	2186 (764)	20046 (7633)	54 (29)	4.2
1500 mg Q12	1917 (405)	19749 (4749)	46 (15)	3.1

HCV-796 t<sub>max</sub> is ~ 2-3 hours

# HCV-796 PK

## Trough Plasma Concentrations

N = 12/group; mean  $\pm$  SE

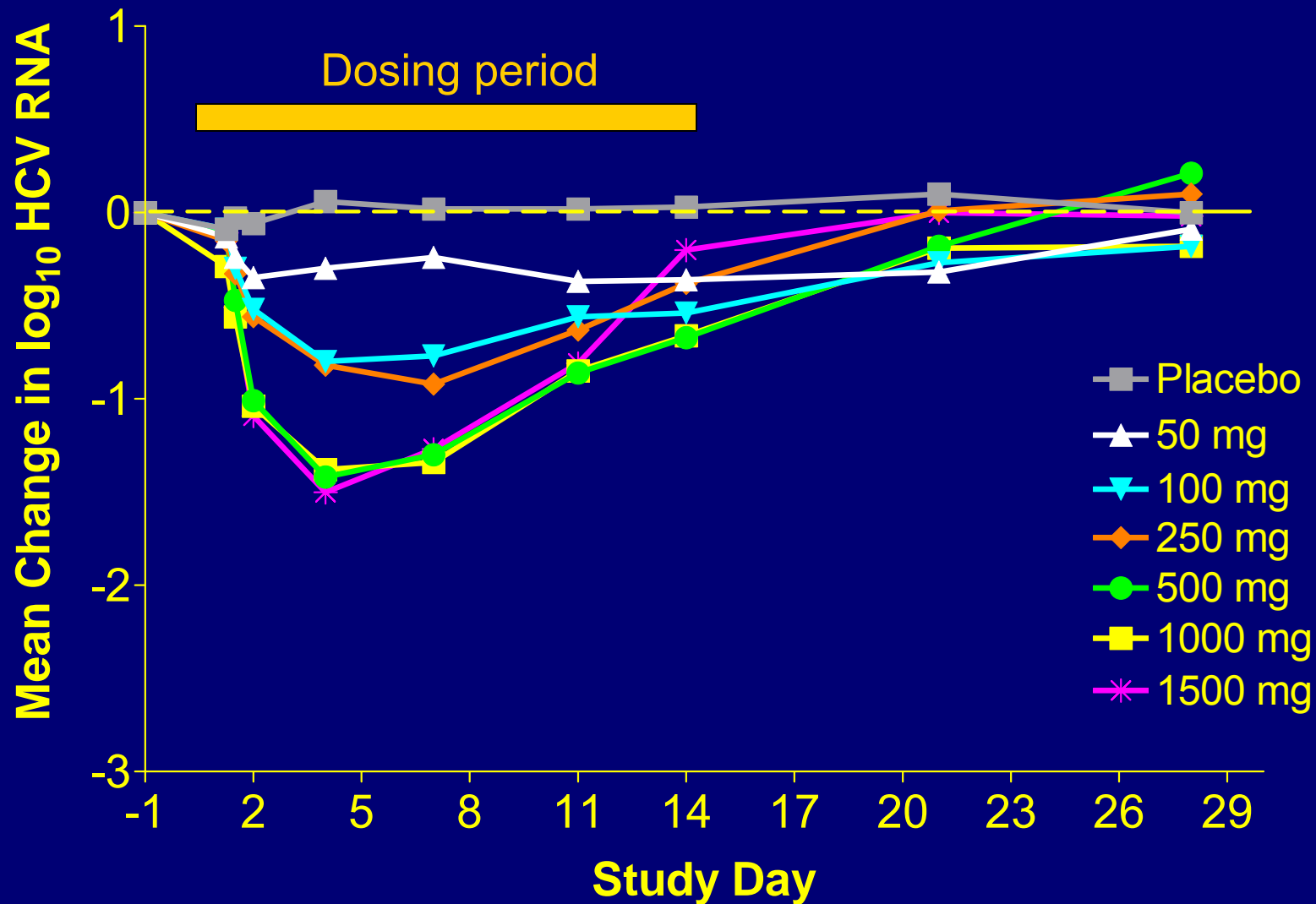


Target concentration based on preclinical antiviral activity

# HCV RNA Change from Baseline

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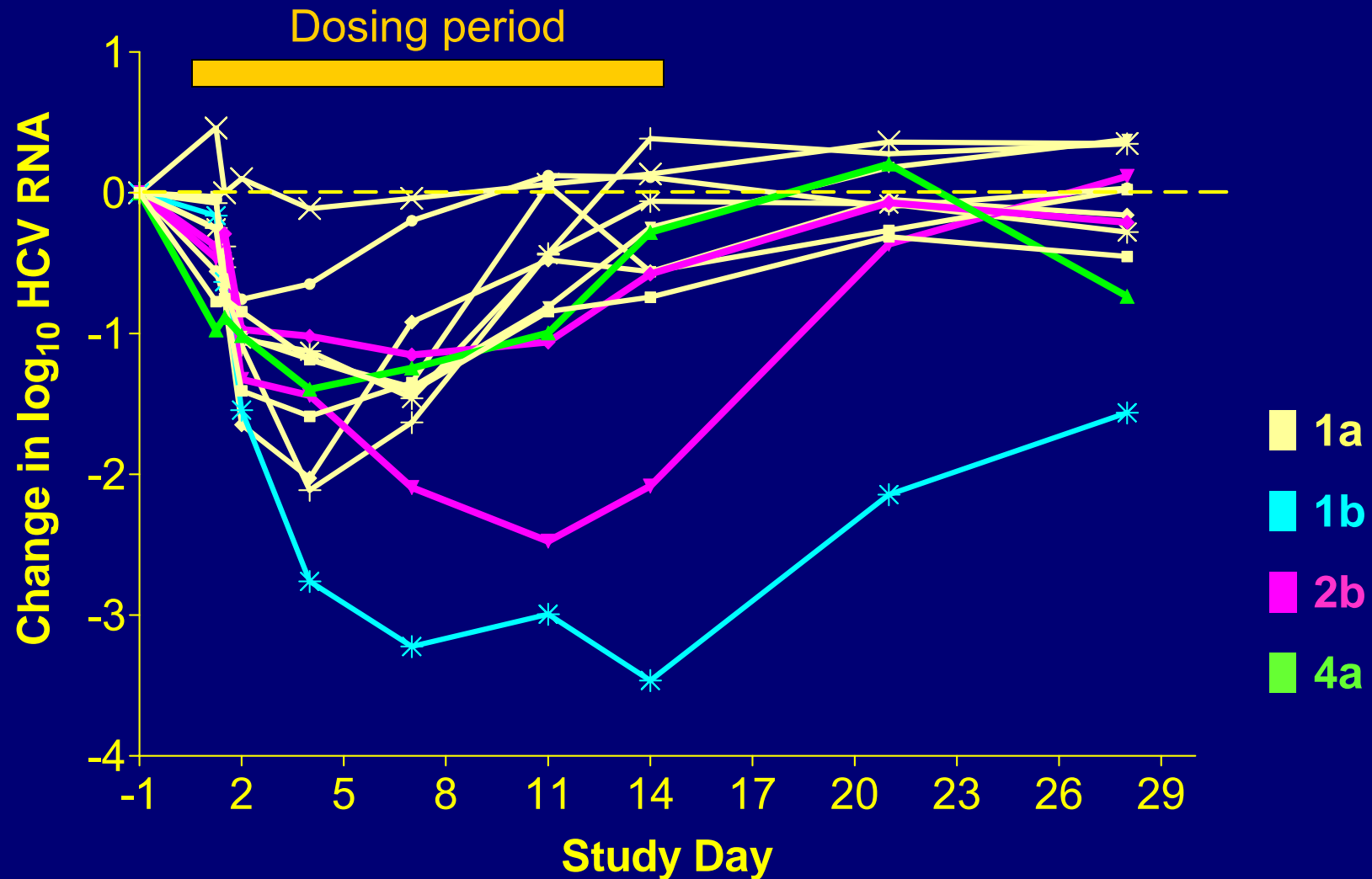
*All subjects*



# HCV RNA Change from Baseline

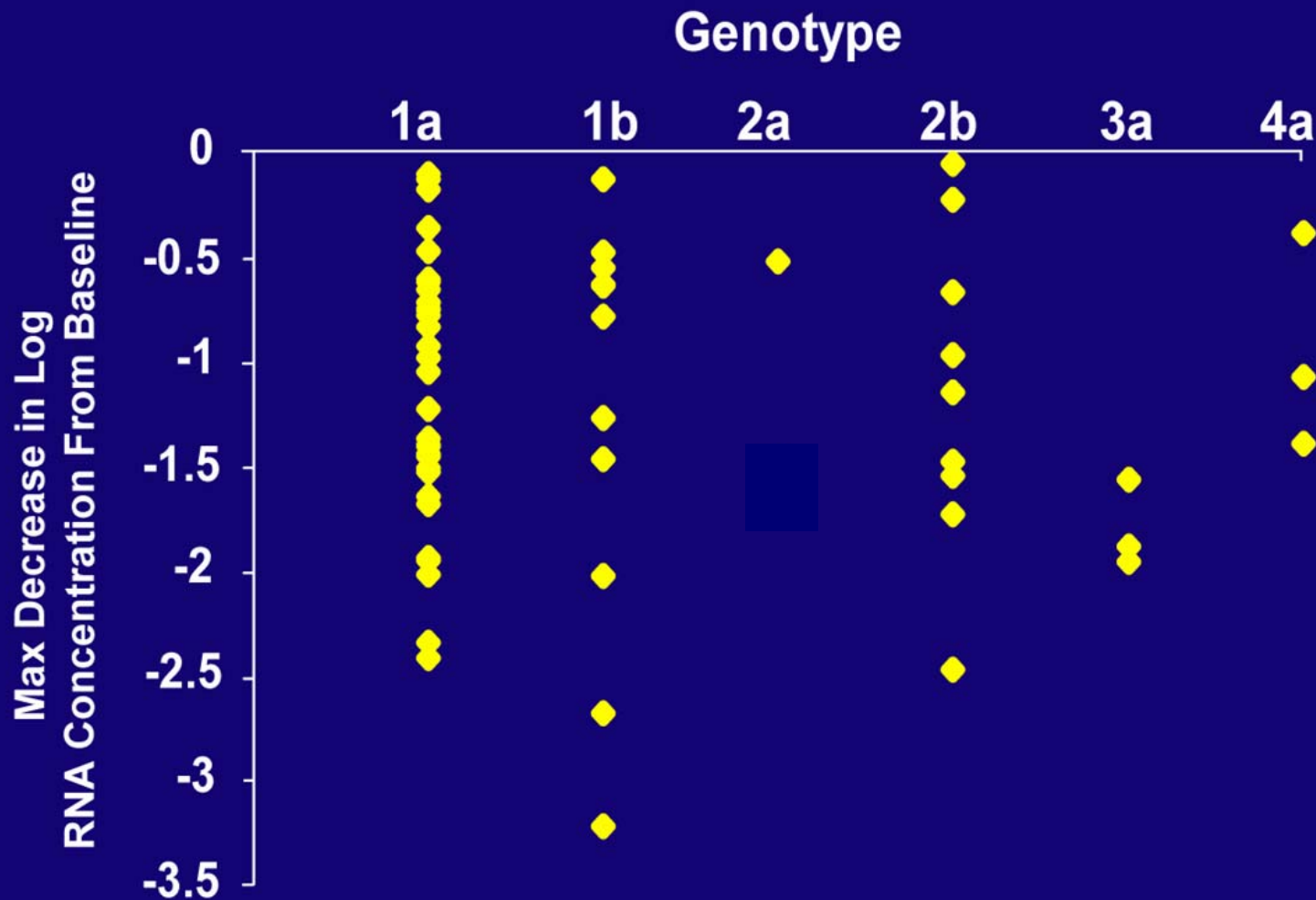
## 1000 mg Q12 Dose Group

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# Maximum ↓ in HCV RNA By Genotype

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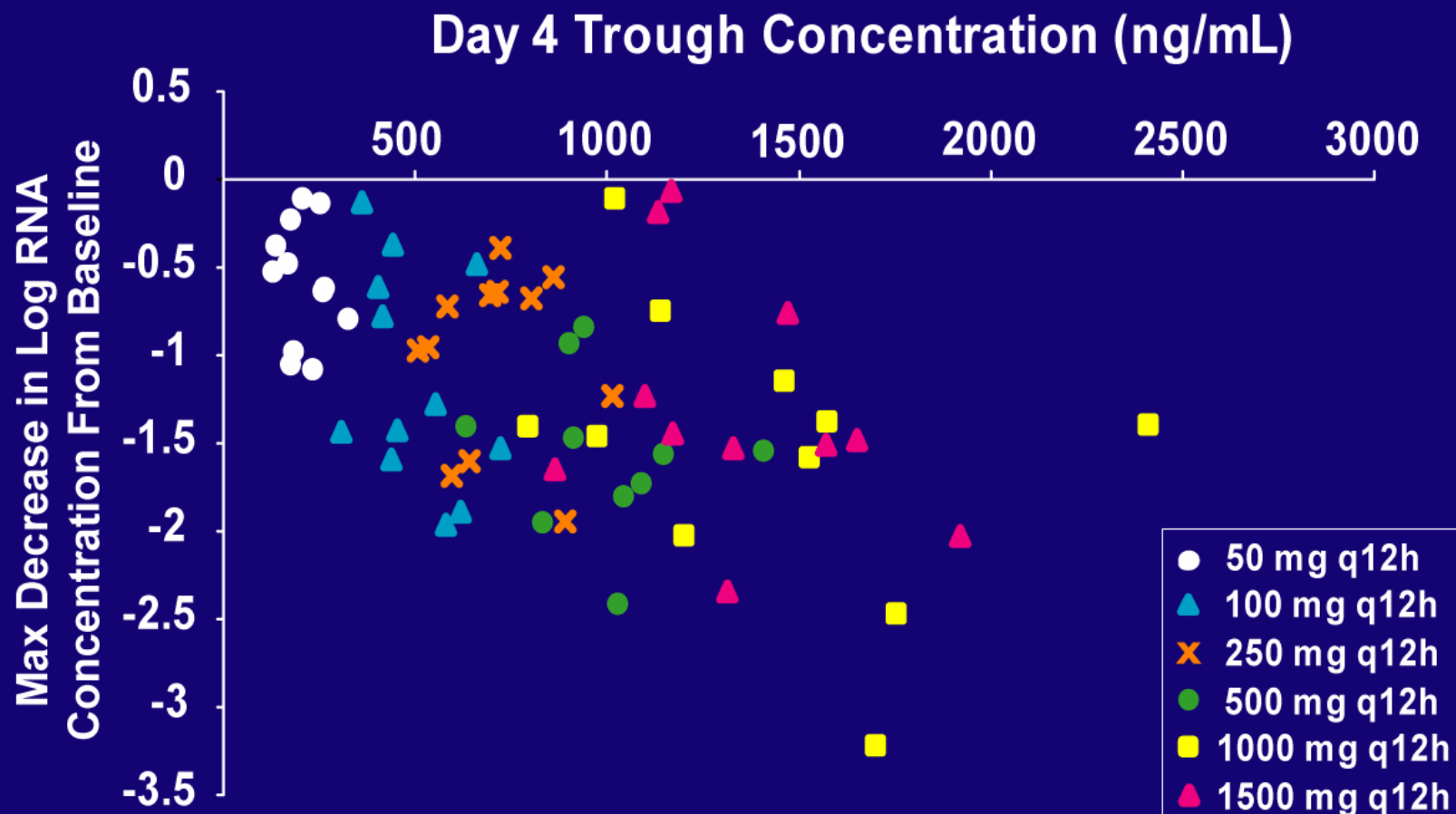
# HCV-RNA Reductions

## Maximum Change Over 14 Days

% Subjects With Maximum ↓ From Baseline in log<sub>10</sub> HCV RNA

	n	≥ 1 log	≥ 1.5 log	≥ 2 log
Placebo	25	0	0	0
50 mg Q12	12	2 (17%)	0	0
100 mg Q12	12	7 (58%)	4 (33%)	0
250 mg Q12	12	4 (33%)	3 (25%)	0
500 mg Q12	14	12 (86%)	9 (64%)	3 (21%)
1000 mg Q12	12	10 (83%)	5 (42%)	4 (33%)
1500 mg Q12	15	13 (87%)	9 (60%)	4 (27%)

# Maximum ↓ in HCV RNA vs. Day 4 Trough Concentrations of HCV-796



# Safety

- HCV-796 was generally well tolerated
- No dose-limiting toxicities identified across the range of study doses
- No serious adverse events
- Discontinuations due to AEs:
  - Placebo: (1) poorly controlled hypertension (preexisting)
  - 500 mg: (1) elevated TSH level
  - 1500 mg: (1) elevated unconjugated bilirubin (3.7 mg/dL)

# Adverse Events

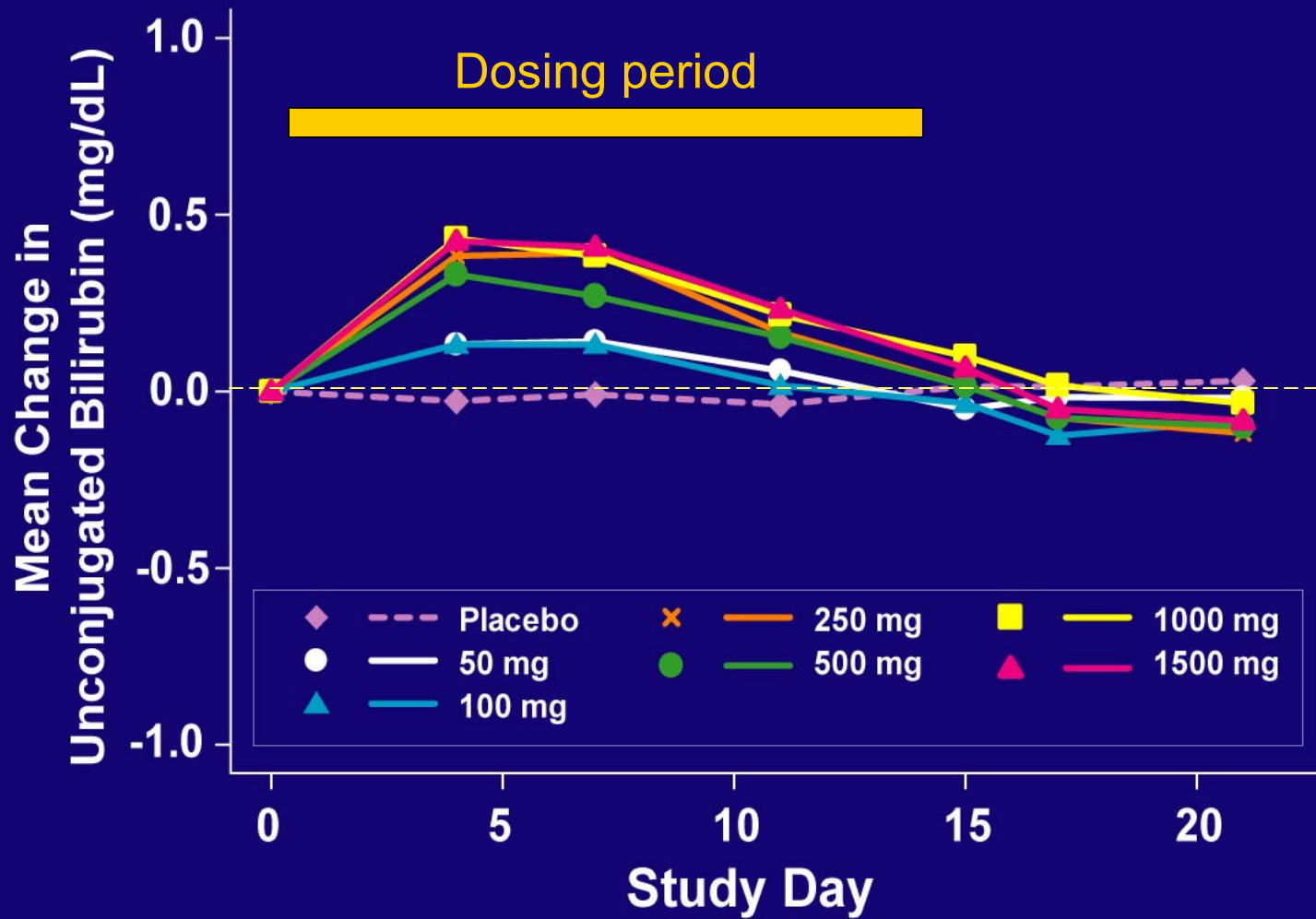
## Most Common AEs

HCV-796 Dose (mg)	Placebo	50	100	250	500	1000	1500
n	25	12	12	12	14	12	15
Headache, %	32	58	42	42	36	42	60
Constipation, %	12	8	8	25	21	17	40
Back pain, %	8	17	25	17	21	0	13
Diarrhea, %	0	0	17	0	0	25	20
Abdominal pain, %	8	0	17	0	21	0	7
Pain, %	4	0	8	0	7	17	13
Pruritus, %	8	0	17	0	7	17	0
Rash, %	4	0	8	0	7	25	0

Shown are events reported in > 6% of all subjects receiving HCV-796.

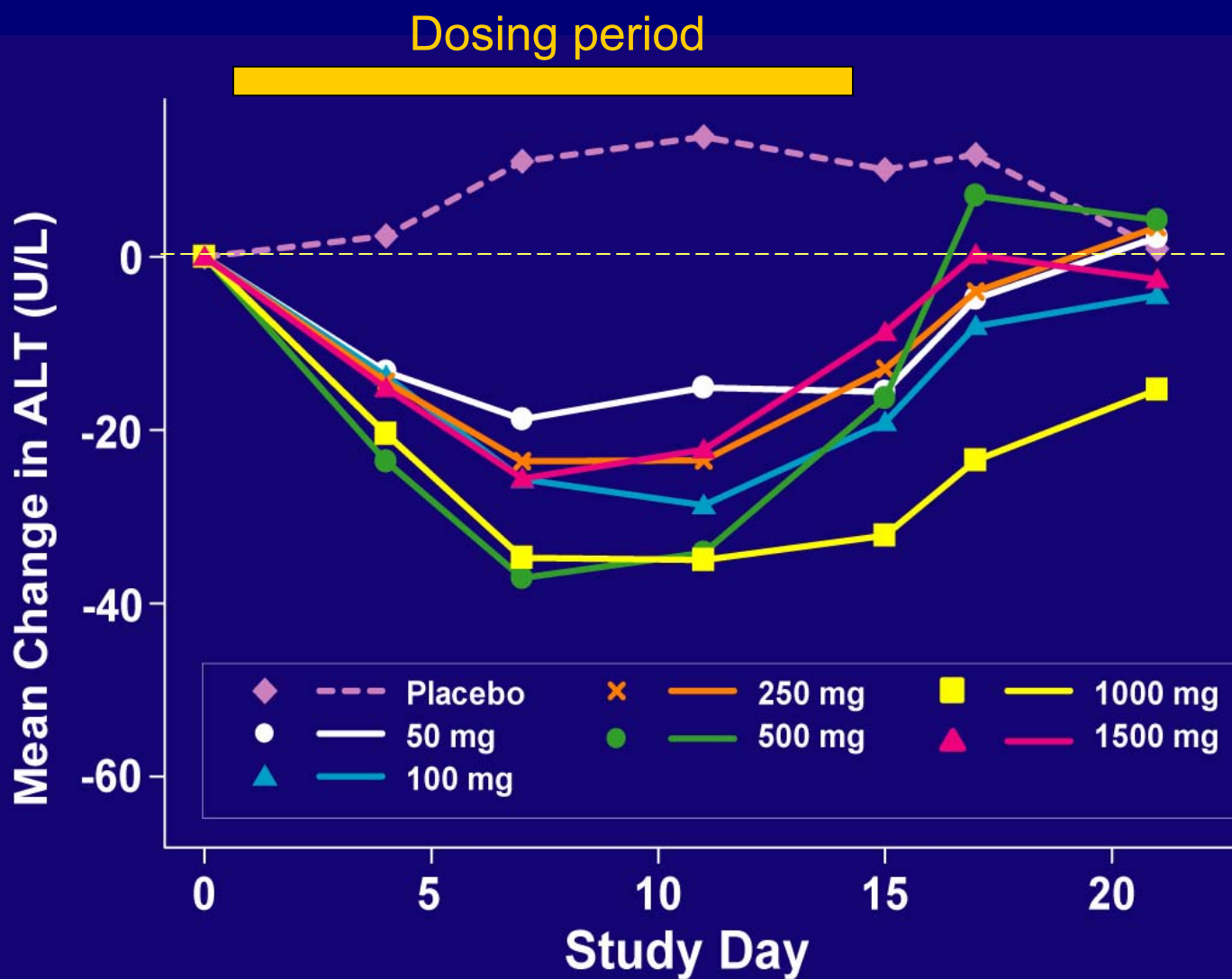
# Bilirubin (Unconjugated) Change From Baseline

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# ALT

## Change From Baseline



## Conclusions

- HCV-796 displays dose-related antiviral activity:
  - Across multiple HCV genotypes
  - Peak response achieved at the 500 – 1000 mg Q12 dose
- Exposure (PK) is less than dose-proportional with increasing dose, with plateau at the 1000 mg Q12 dose
- Genetic sequencing of HCV NS5B is ongoing, with focus on subjects with “breakthrough” virologic response pattern
- HCV-796 was well tolerated
  - no dose-limiting toxicities across the range of study doses
  - mild-moderate headache was the most common adverse event
  - ALT decrease temporally associated with antiviral activity
- Study of combination therapy with PEG-interferon ongoing

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