

Potent Antiviral Activity of the Nucleoside HCV Inhibitor, R7128, in Prior IFN Nonresponders

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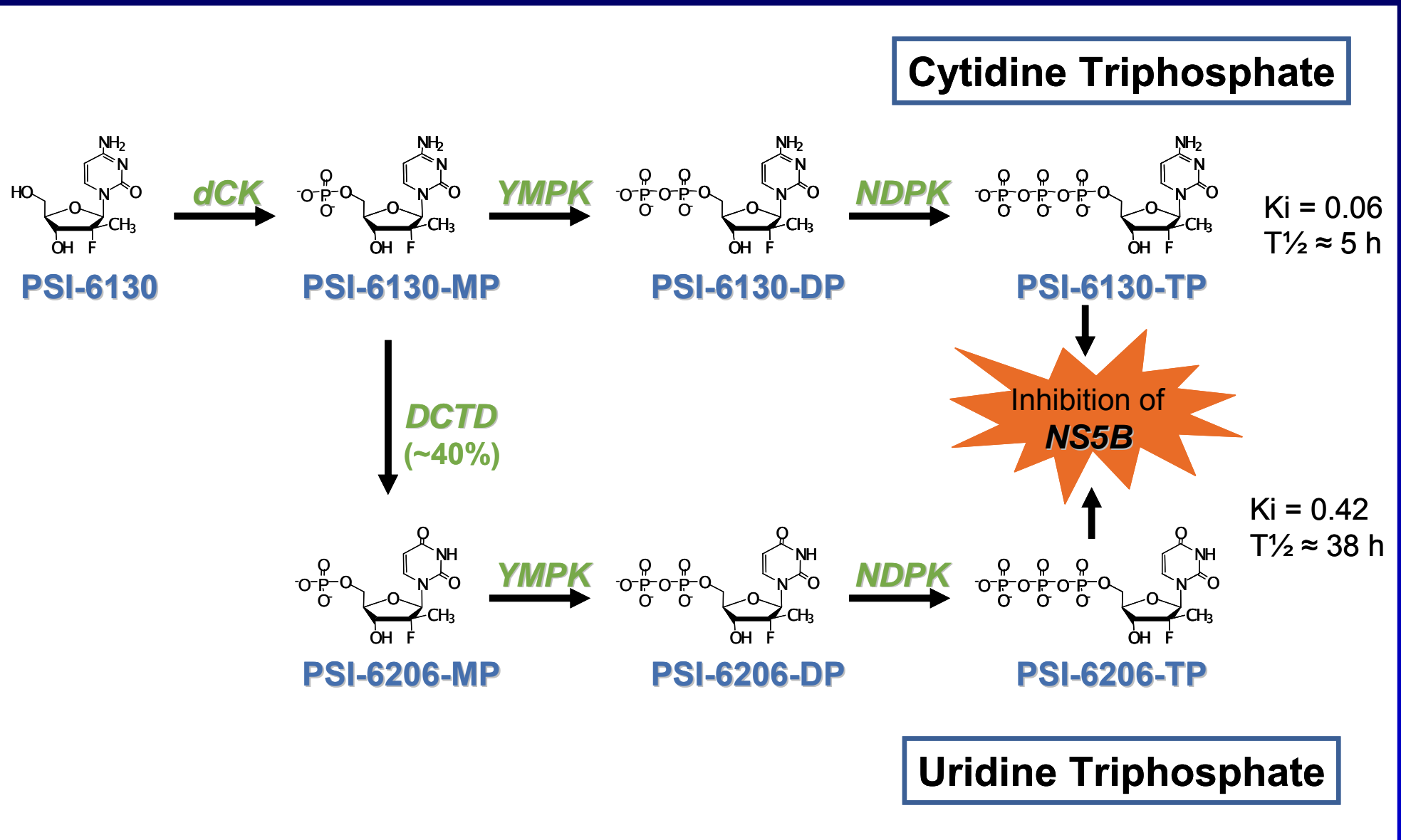
HepDart

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R7128 is a Specific Nucleoside Polymerase Inhibitor of HCV

- R7128 is a prodrug of PSI-6130 (*Pharmasset & Roche*)
- Favorable in vitro characteristics
 - Demonstrates potent activity against GT-1a and GT-1b clinical isolates
 - Additive in combination with interferon and other HCV inhibitors
 - Retains activity against known polymerase mutations
 - Chain terminator
 - Orally bioavailable
- Single ascending oral dose study in healthy volunteers (*completed*)
- 14-day multiple ascending oral dose study in HCV patients who failed interferon (*completed*)
- Ongoing 4-week combination study of R7128 with peginterferon alpha-2a and ribavirin in treatment-naïve patients

R7128 (PSI-6130) is metabolized intracellularly to two HCV polymerase inhibitors



Source: Murakami E, et al. 14th International Symposium on Hepatitis C Virus and Related Viruses, Glasgow, Scotland, September 2007.

Phase I Study Design: Single Ascending Dose in Healthy Volunteers

R7128
500mg

Follow-up

R7128
1500mg

Follow-up

R7128
4500mg

Follow-up

R7128
1500mg
w/ food

Follow-up

R7128
6000mg

Follow-up

Sequential enrollment of cohorts
following safety/PK review.

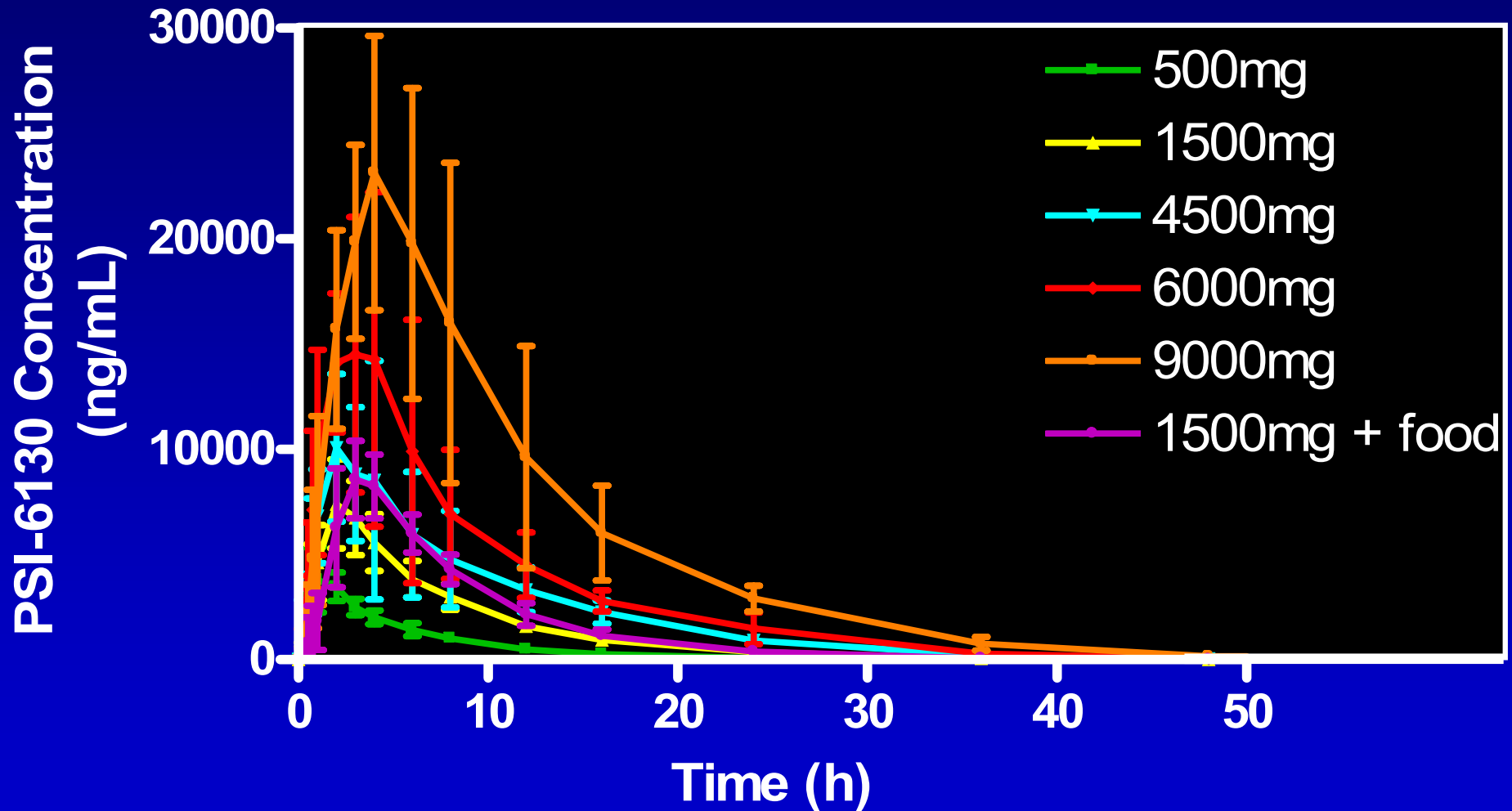
R7128
9000mg

Follow-up

Phase 1: Single Ascending Dose Study

- Objective
 - To assess the safety, tolerability, pharmacokinetics and food effect of R7128 in healthy volunteers
- Design
 - Single-center, randomized, double-blind
 - Patient population
 - 6 active and 2 placebo subjects per group
 - 6 active for the food effect group
 - Safety Assessments
 - Physical exam, clinical laboratory tests, electrocardiograms, and adverse events
 - PK Assessments
 - Serial blood samples collected up to 72h post-dose

R7128 Efficiently Delivers PSI-6130 to the Systemic Circulation



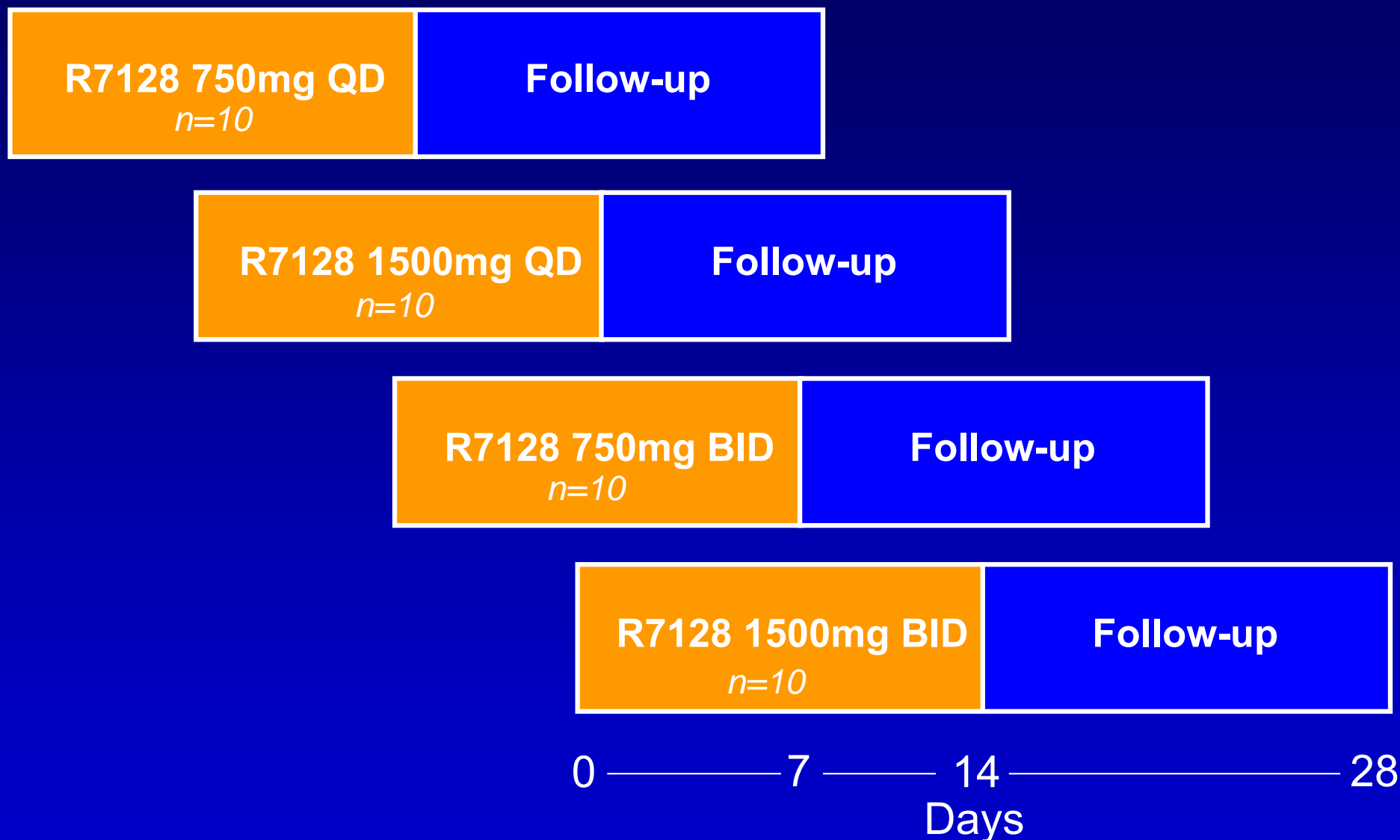
R7128 Demonstrated Safety and Tolerability with No Clinically Significant Adverse Events

- No maximum tolerated dose identified in this study
- No serious or treatment limiting adverse events (SAEs)
- Nineteen AEs, including headache, sunburn, sore throat and nasal congestion
- All AEs were mild to moderate, none were related to dose
- No gastrointestinal AEs were observed
- No clinically significant changes in hematologic or other laboratory parameters

Phase 1: Multiple Ascending Dose Study

- Objectives
 - To evaluate safety, tolerability, pharmacokinetics and preliminary antiviral activity
- Design
 - Multi-center, randomized, double-blind
 - Patient population
 - Treatment-experienced HCV Genotype 1-infected patients
 - 8 active and 2 placebo per dose group
 - Study Assessments
 - Physical exam, clinical laboratory tests, ECG, and adverse events
 - Serial samples for HCV RNA (COBAS TaqMan HCV™) and PK throughout
 - Samples for HCV NS5B resistance testing

Phase I Study Design: Multiple Ascending Dose *HCV treatment experienced patients*



Sequential enrollment of cohorts following safety/PK review
8 active/2 placebo subjects per cohort

Study Population – Key Inclusion Criteria

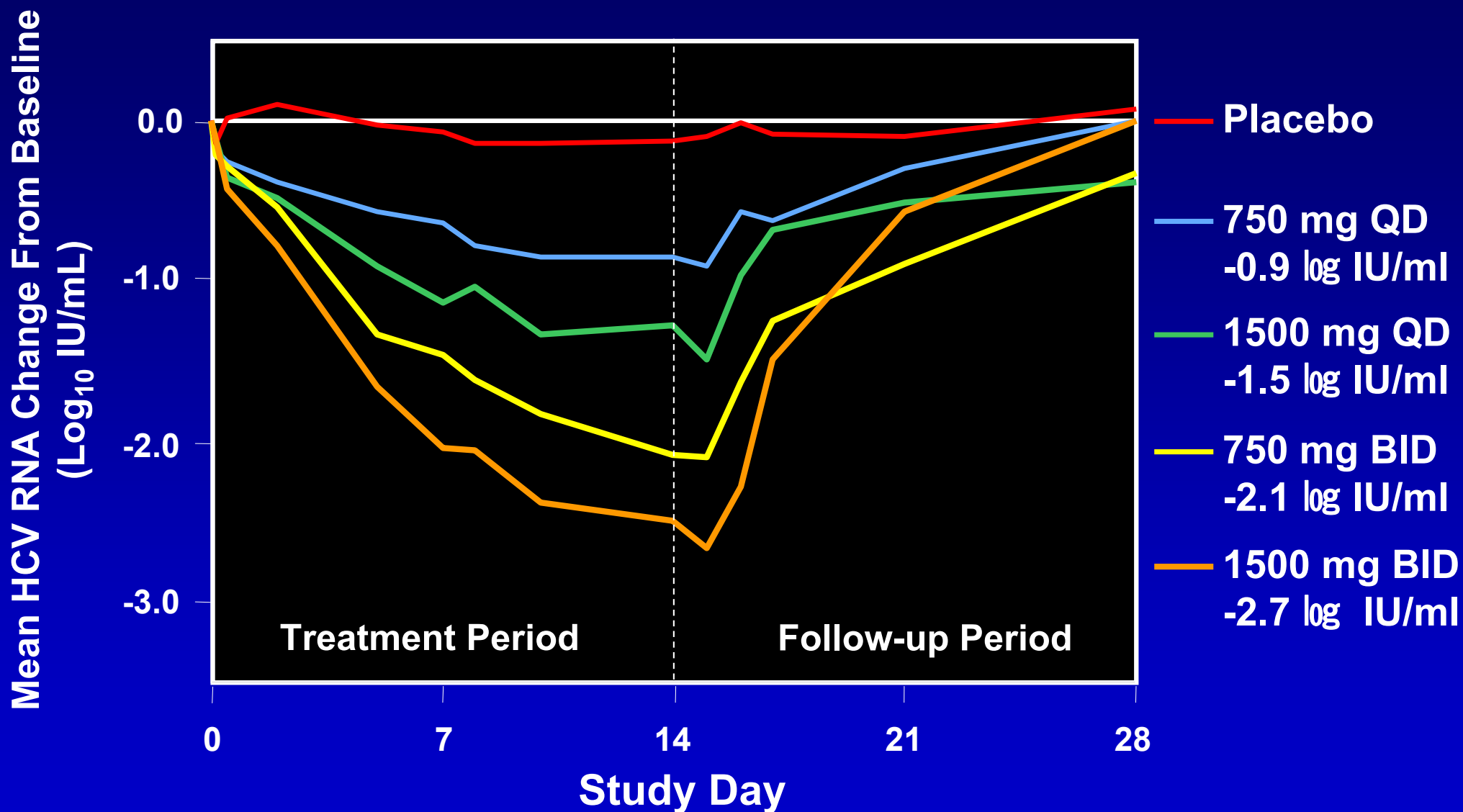
- HCV Genotype 1
 - Baseline HCV RNA $\geq 10^5$ IU/mL
- ALT and AST screening measurement $< 3x$ ULN
- Previously failed interferon alpha with or without ribavirin
 - non-response or relapse
 - Antiviral therapy > 6 months prior to screening
 - patients who discontinued because of AEs (especially hematological AEs) not to be included
- Liver biopsy within 36 months
 - No cirrhosis

Baseline Demographics

	Placebo	750mg QD	1500 mg QD	750 mg BID	1500 mg BID
n	8	8	8	8	8
Sex: M:F	6:2	4:4	5:3	5:1	5:3
Race:					
Black	0	2	1	0	2
Caucasian	7	6	4	1	5
Other ¹	1	0	3	7	1
Age (mean years)	49	51	48	50	46
Weight (mean kg)	89	79	81	83	75
BMI (mean kg/m ²)	28	27	27	29	25
HCV RNA Genotype 1a:1b	7:1	7:1	5:3	7:1	4:4
Baseline HCV RNA (log ₁₀ IU/mL)	6.71	6.63	6.64	6.53	6.34

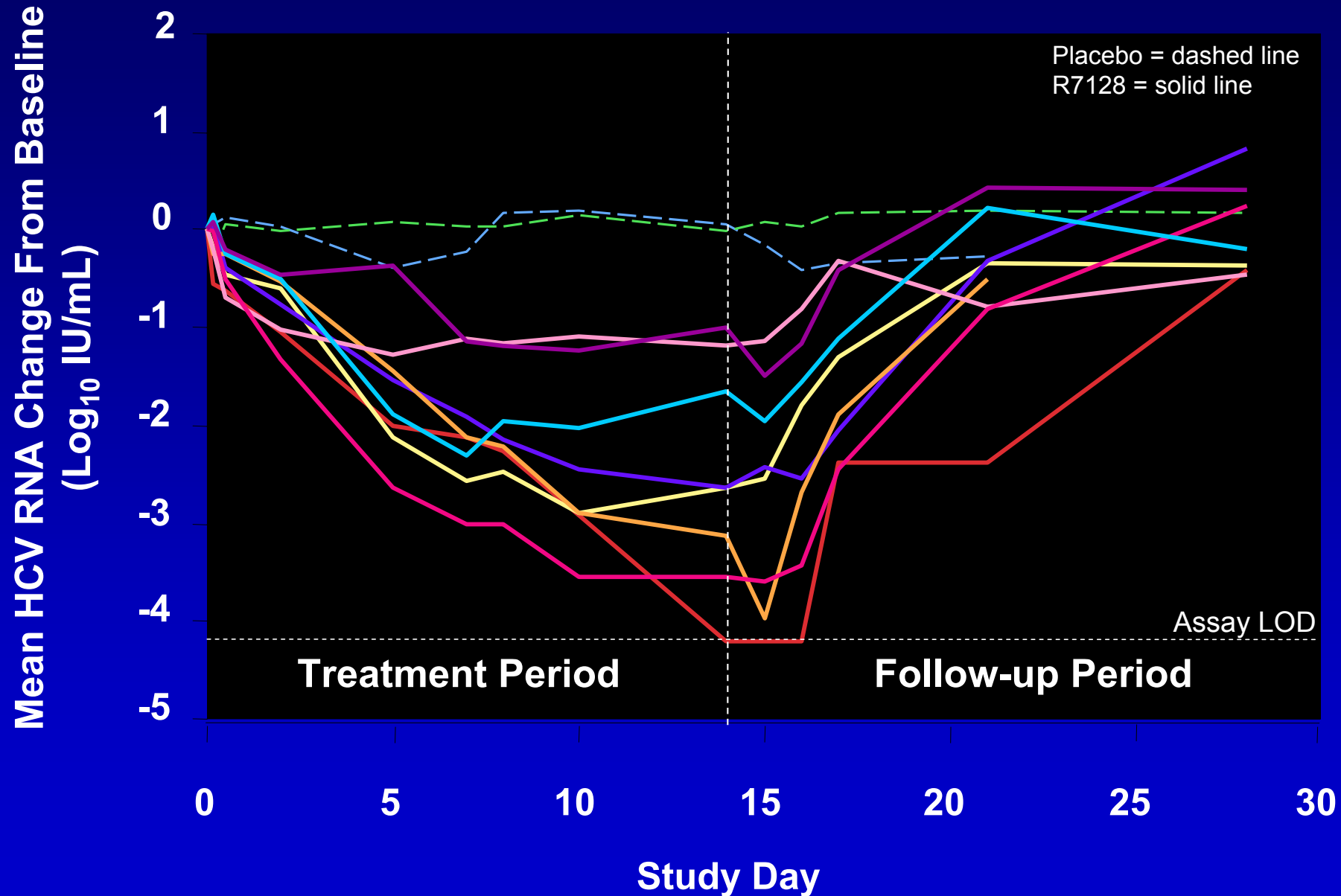
1. 'Other' race includes: Black Hispanic, Hispanic, Samoan, White Latino, White/Black/Hispanic

R7128 Demonstrated a 2.7 log₁₀ Mean HCV RNA Decrease with 1500 mg BID Dose

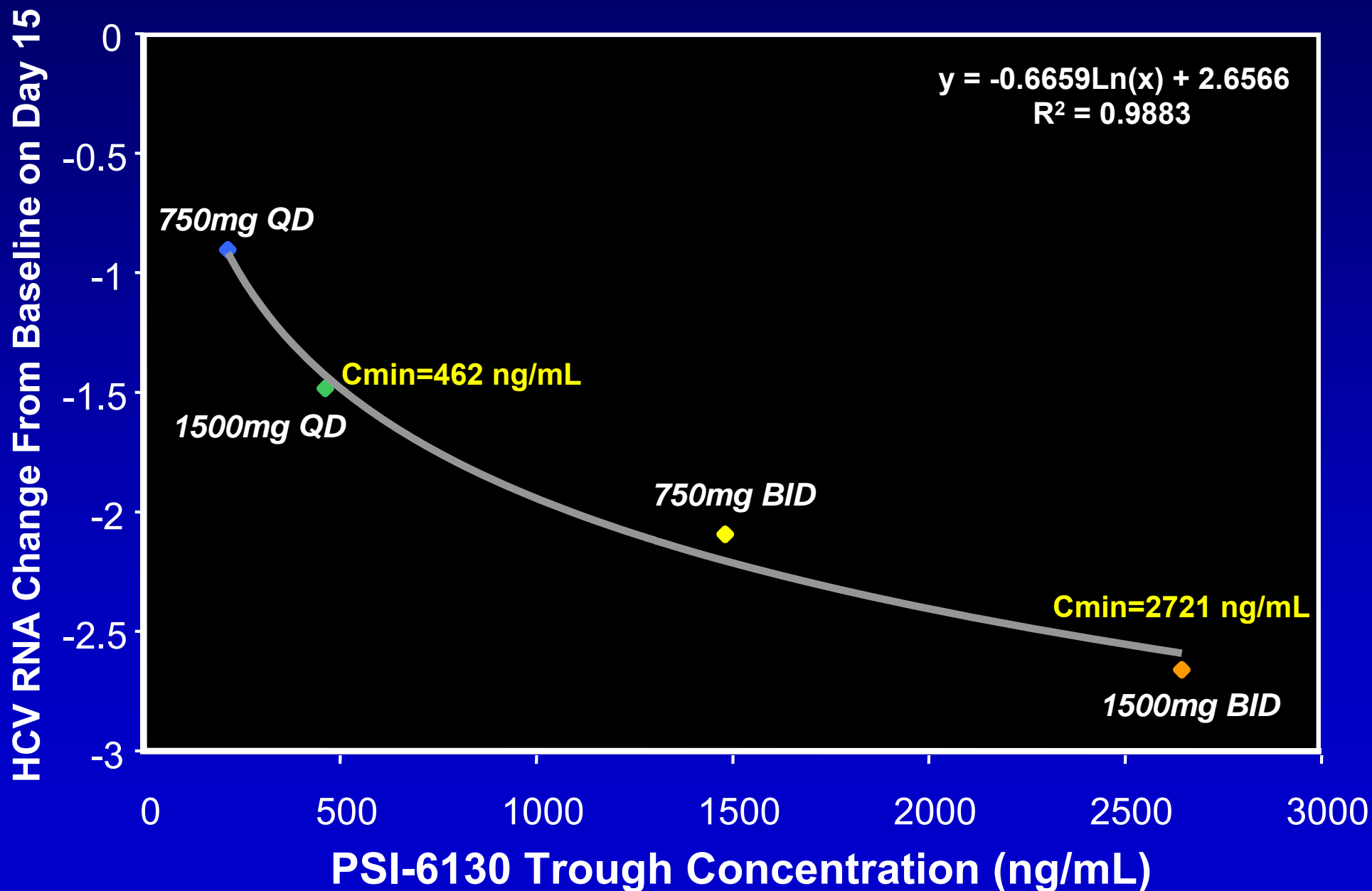


No Evidence of Viral Rebound During 14 Days of Monotherapy

Plasma HCV RNA: Individual Mean Log₁₀ (IU/mL) Change from Baseline in Cohort 4 (1500mg BID)



Dose-related Antiviral Activity Observed Following 14 Days of Monotherapy with R7128



Most Commonly Reported Adverse Events

>5% of Subjects Overall

	Placebo QD/BID N=8	750mg QD N=8	1500mg QD N=8	750mg BID N=8	1500mg BID N=8
Total Number of AEs	34	18	6	13	14
Headache	4 (11.8%)	4 (22.2%)	1 (16.7%)	3 (23.1%)	5 (35.7%)
Diarrhea	4 (11.8%)	0	1 (16.7%)	0	0
Dry Mouth	1 (2.9%)	2 (11.1%)	0	0	1 (7.1%)
Nausea	1 (2.9%)	1 (5.6%)	0	1 (7.7%)	0
Fatigue	0	1 (5.6%)	0	0	1 (7.1%)
Tiredness	0	0	0	0	2 (14.3%)
Upper Respiratory Tract Infection	0	1 (5.6%)	0	1 (7.7%)	0

Individual AEs reported as: n(% of total AEs)

No serious AEs Reported, the majority were mild in intensity

Additional Safety Parameters

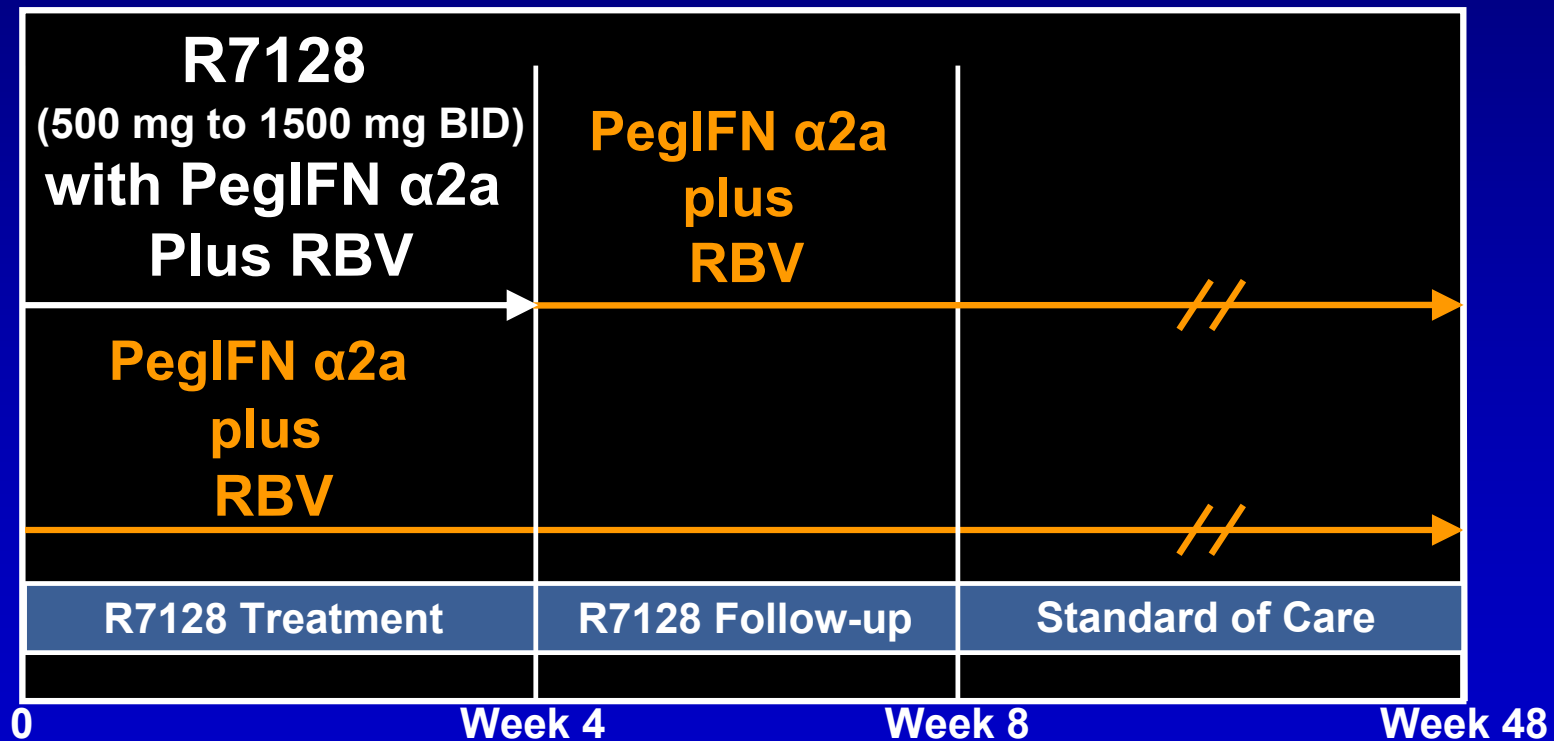
- There were no clinically significant changes noted in other measured parameters across the treatment groups
- No trends in laboratory abnormalities
- No treatment related grade ≥ 2 lab abnormalities
- 78% of patients with abnormal ALT values and who received R7128, had normal values by Day 14
- No clinically significant ECG changes
 - no QTc prolongation beyond 500ms

R7128 Conclusions

- R7128 demonstrated significant anti-HCV activity across a range of doses in a prior IFN non-responder population
- R7128, a nucleoside analog HCV polymerase inhibitor, can deliver sufficient antiviral potency via monotherapy to suppress replication below the level of detection (<15 IU/mL)
- No maximum tolerated dose was identified in the single or multiple-dose studies
- Lack of clinical rebound provides early evidence of high genetic barrier for nucleoside inhibitors of NS5b polymerase
- Safe and acceptable adverse effect profile to date

R7128 Combination Study Enrolling

Preliminary Evaluation of Safety, Tolerability, Pharmacokinetics and Antiviral Activity of R7128 with Pegasys plus Copegus
Up to 75 treatment-naïve patients with HCV genotype 1 infection



Interim Results 1Q 2008

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