

## High Rapid Virologic Response (RVR) with PSI-7977 Daily Dosing plus PEG-IFN/RBV in a 28-day Phase 2a Trial

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## Conclusions

- RVR rates of 88-94% were observed with PSI-7977/SOC in treatment-naïve, HCV GT-1 subjects, far superior to placebo/SOC (21% RVR)
- The regimen of PSI-7977 + SOC was well-tolerated with no dose-limiting toxicities identified; the incidence and severity of lab abnormalities and AEs was similar to SOC alone
- Following cessation of PSI-7977, the durability of antiviral response was greatest in the 200 and 400 mg groups
- No viral resistance to PSI-7977 has been detected to date
- Results from this study supported initiation of a 12 week study of PSI-7977 200 and 400 mg with SOC compared with SOC alone
- PSI-7977 antiviral efficacy in GT-1 subjects in the current study coupled with broad genotype *in vitro* activity support the exploration of PSI-7977 in all HCV genotypes

# Background

The nucleoside/tide analog polymerase inhibitor class has been shown to have significant potential for the treatment of chronic hepatitis C infection due to promising clinical efficacy, safety and a high barrier to resistance. PSI-7977 is a phosphoramidate prodrug of  $\beta$ -D-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-monophosphate (PSI-6206 monophosphate). PSI-7977 has enhanced antiviral potency over earlier nucleoside analogs, achieves high liver to plasma ratios of key metabolites in preclinical studies and has the potential to be dosed once daily.

# Objectives

To assess the safety, tolerability, pharmacokinetics and antiviral activity of PSI-7977 (100 to 400 mg daily) for 28 days, in combination with Standard of Care (SOC; PEG-IFN and RBV) in treatment-naïve, HCV genotype 1 (GT-1) infected patients.

# Methods

## Study Design

- Double-blind, randomized, placebo-controlled, dose-ranging, parallel-group study with subjects assigned to one of three daily doses of PSI-7977 (100, 200 or 400 mg) or placebo for 28 days, co-administered with SOC
- Enrolled subjects had GT-1 infection with HCV RNA  $\geq 5 \log_{10}$  IU/mL, were HCV treatment-naïve, and were non-cirrhotic per recent liver biopsy
- Randomization was stratified by IL28B status (rs1299860) for C/C vs. any T allele
- SOC was comprised of peginterferon alfa-2a (Pegasys®) and ribavirin and dosed according to the package inserts for GT-1
  - SOC was continued for 48 weeks
- All subjects were assessed for RVR (HCV RNA < limit of detection [LOD] at Day 28), and subjects are being followed for SVR12 and SVR24

## Safety Assessments

- Physical exams, vital signs, clinical labs, ECGs, and AEs

## Virology Assessments

- Plasma HCV RNA measured by Roche COBAS TaqMan HCV test (LOD < 15 IU/mL; limit of quantitation < 43 IU/mL)
- Samples were collected for HCV resistance testing

# Subject Disposition

- 7 US sites enrolled 63 subjects
- Baseline demographics were similar across groups (Table 1)
- 62 subjects completed the study through 28 days
  - One subject who received PSI-7977 200 mg QD/SOC was lost to follow-up at Day 14, with no AEs reported at the time of loss to follow-up

**Table 1. Subject Demographics and Baseline Data by Treatment**

	100 mg (n = 16)	200 mg (n = 18)	400 mg (n = 15)	Placebo (n = 14)
Male, n (%)	11 (69)	10 (56)	11 (73)	11 (79)
Caucasian (n)	15	16	12	14
Median age (y)	45.0	44.0	45.0	48.5
Mean BMI (kg/m <sup>2</sup> )	28.2	26.8	27.4	30.7
HCV 1a/1b (n)	14/2	16/2	12/3	10/4
HCV RNA (log <sub>10</sub> IU/mL)	6.64	6.28	6.49	6.48
IL28B C/C, n (%)	4 (25)	5 (28)	4(27)	4 (29)
HOMA-IR <3 (%) range	9 (56) 1.0-24.3	13 (72) 0.7-122.6	7 (47) 0.5-19.7	7 (50) 1.3-5.7
No/minimal fibrosis (F0-1)	9 (56)	10 (56)	9 (60)	10 (71)
Portal fibrosis (F1-2)	6 (38)	4 (22)	4 (27)	2 (14)
Bridging fibrosis (F3)	1 (12)	4 (22)	2 (13)	2 (14)

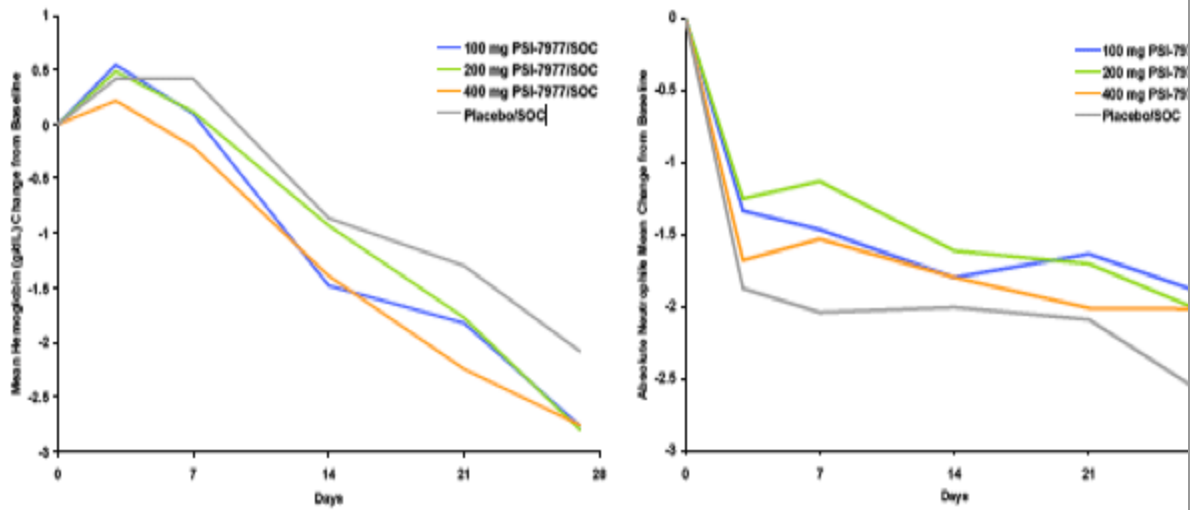
# Safety

- No SAEs or discontinuations due to adverse events
- All AEs were of mild or moderate intensity and were reported with similar frequency across treatment groups (Table 2)
- No Grade 4 lab abnormalities; Grade 3 lab abnormalities were limited to hemoglobin (2 subjects each in 200 and 400 mg groups), neutropenia (1 subject each in pbo and 400 mg, 2 subjects each in 200 mg and 400 mg), hypophosphatemia (1 subject each in placebo and 100 mg group)
- Dose-dependent decreases in ALT levels were observed coincident with HCV RNA declines (Figure 2)
- No significant changes in vital signs and ECG parameters

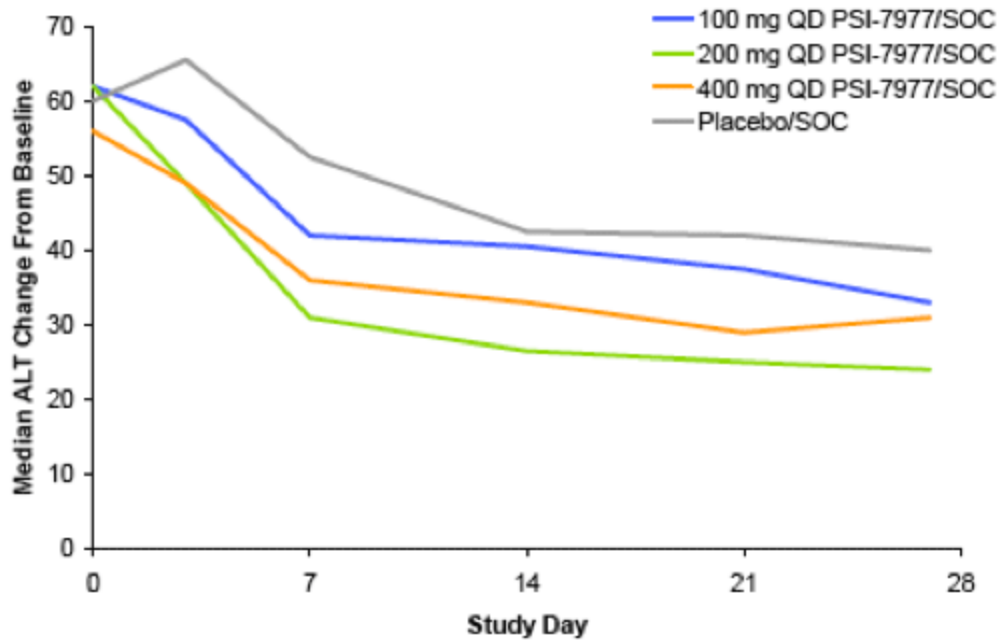
**Table 2. Most Commonly Reported Drug-related Adverse Events**

	100 mg (n = 16)	200 mg (n = 18)	400 mg (n = 15)	Placebo (n = 14)
<b>Subjects with at least 1 AE, n (%)</b>	2 (13)	5 (28)	5 (33)	6 (42)
Nausea	1 (6)	1 (6)	4 (27)	2 (14)
Fatigue	0	1 (6)	0	1 (7)
Dizziness	0	0	1 (7)	2 (14)
Headache	1 (6)	1 (6)	2 (13)	0

**Figure 1. Hemoglobin and ANC: Change from Baseline**



**Figure 2. Median Decline in ALT with PSI-7977/SOC or Placebo/SOC**



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