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Back

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 β-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 ≥ 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^2)	28.2	26.8	27.4	30.7
HCV 1a/1b (n)	14/2	16/2	12/3	10/4
HCV RNA ($\log_{10}$ 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) Portal fibrosis (F1-2) Bridging fibrosis (F3)	9 (56) 6 (38) 1 (12)	10 (56) 4 (22) 4 (22)	9 (60) 4 (27) 2 (13)	10 (71) 2 (14) 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)
Subjects with at least 1 AE, n (%)	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

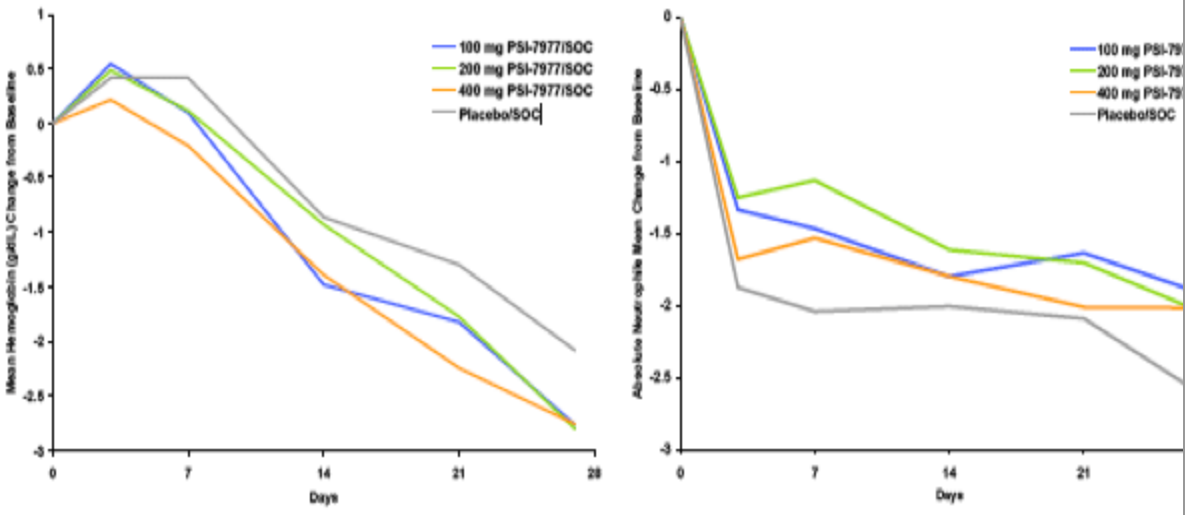
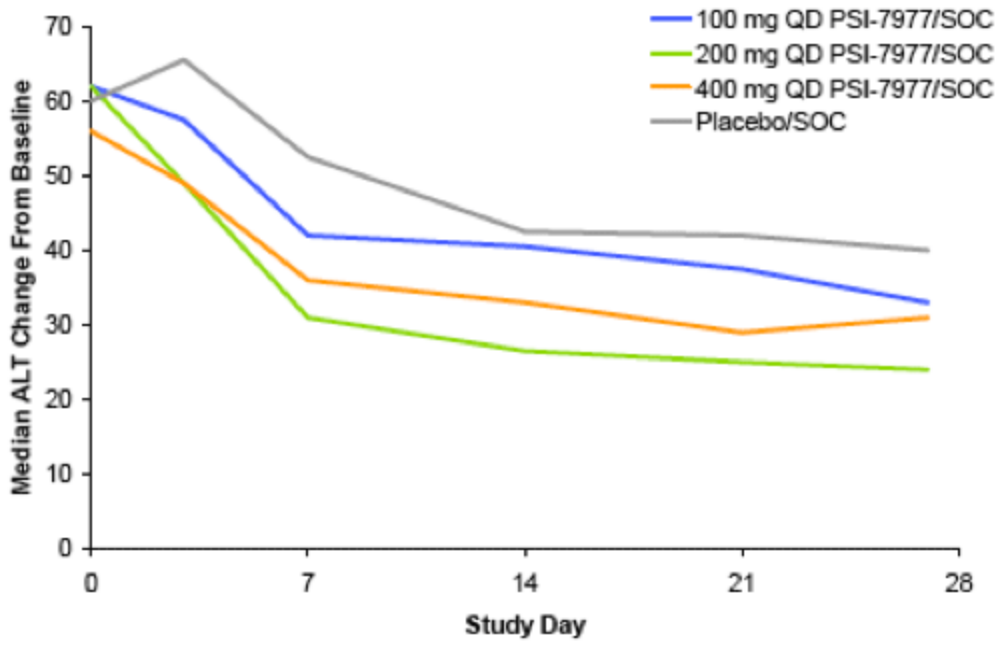


Figure 2. Median Decline in ALT with PSI-7977/SOC or Placebo/SOC



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