

Antiviral Activity, Pharmacokinetics, Safety, and Tolerability of PSI-7851, a Novel Nucleotide Polymerase Inhibitor for HCV, Following Single and 3 Day Multiple Ascending Oral Doses in Healthy Volunteers and Patients with Chronic HCV Infection

Abstract
LB#17

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Background

The nucleotide polymerase inhibitor class has been shown to have significant potential for the treatment of chronic hepatitis C infection due to clinical potency, safety and a high barrier to resistance. PSI-7851, a second generation nucleotide analog, is a phosphoramidate prodrug of β -D-2'-deoxy-2'-fluoro-2'-C-methyluridine 5'-monophosphate (PSI-6206 monophosphate). *In vitro*, PSI-6206 does not demonstrate antiviral activity in the replicon assay because it can not be phosphorylated to the monophosphate form. However metabolism studies in primary human hepatocytes demonstrated that the monophosphate of PSI-6206 can be phosphorylated to the corresponding triphosphate. The triphosphate form of PSI-6206 (PSI-7409) is a potent inhibitor of the HCV NS5B RNA-dependent RNA polymerase. Therefore, PSI-7851 was developed to overcome this non-productive phosphorylation step¹. PSI-7851 has enhanced antiviral potency over first generation nucleoside analogs, achieves high liver to plasma ratios of key metabolites in preclinical studies and has the potential to be dosed once daily.

SAD Methods

Objective

- To investigate the safety, tolerability, and pharmacokinetics of PSI-7851 and metabolites following single oral administration in healthy subjects

Study Design

- PSI-7851 or placebo was administered to 42 healthy adult subjects with 8 active and 2 placebo per dose level in an alternating panel design
- Subjects were enrolled across 4 cohorts, 3 of which received 2 doses of PSI-7851, while the 4th cohort received the 800mg dose
- Doses included: 25mg, 50mg, 100mg, 200mg, 400mg and 800mg
- A 50mg solution dose was also evaluated
- Safety and PK review prior to each dose escalation

Safety Assessments

- Physical exams, vital signs, clinical laboratory assessments, ECGs, and adverse events

PK Assessments

- Drug concentrations were measured in plasma and urine following each dose
- PSI-7851 and metabolites were assayed in plasma and urine using a validated LC-MS/MS assay
- PK parameters were calculated using WinNonlin (Version 5.2)

SAD Results

Table 1: Demographics

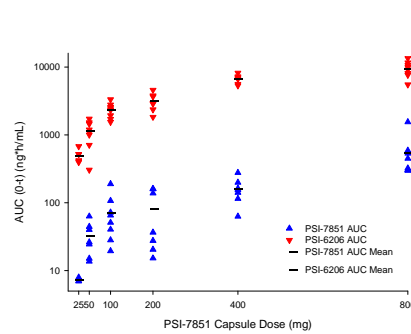
N	Sex (%)	Race	Mean Age (y)	Mean Weight (kg)	Mean Height (cm)	Mean BMI (kg/m ²)
42	Males: 29 (69) Females: 13 (31)	White: 37 Black: 4 Asian: 1	29.5	78.5	175.1	25.5

Clinical Safety

- No maximum tolerated dose identified
- No severe or serious clinical AEs reported
- The most commonly reported AEs were erythema (19) or pruritus (5) at telemetry pad sites
- All AEs were mild to moderate
- No dose-related trends in laboratory abnormalities were apparent
- No treatment-emergent grade 2 or higher labs were reported
- No clinically significant changes were reported for vital signs or ECGs

SAD Results

Figure 1. Plasma PSI-7851 and PSI-6206 Concentrations



- PSI-7851 exposure was generally low, with the majority of the systemic drug exposure from PSI-6206, the nucleoside metabolite.
- Dose proportionality was not found for the dosage range studied (25mg to 800mg)
- PSI-6206 Exposure (C_{max} and AUC) for the solution was approximately 18% higher than the capsule formulation
- Pharmacokinetic results demonstrate a systemic exposure profile consistent with rapid uptake of the drug by the liver

MAD Methods

Objectives

- To assess the safety, tolerability and pharmacokinetics of PSI-7851 in treatment-naïve HCV Genotype 1-infected patients after once daily dosing for 3 days
- To evaluate the viral dynamics as measured by changes in plasma HCV RNA in treatment naïve HCV Genotype 1-infected patients after daily dosing of PSI-7851 for 3 days
- To monitor for the development of viral resistance

Study Design

- Multiple oral doses of PSI-7851 (50mg, 100mg, 200mg or 400mg) were administered once daily for 3 days
- Patients had chronic HCV genotype 1 infection, were treatment-naïve and had no evidence of hepatic cirrhosis
- 10 patients per cohort with 8 receiving active and 2 receiving placebo
- Safety and PK review prior to each dose escalation

Safety Assessments

- Physical exams, vital signs, clinical laboratory assessments, ECGs, and adverse events

Virology Assessments

- Plasma HCV RNA measured by Roche COBAS TaqMan HCV™
- Samples for HCV genotype and resistance testing

PK Assessments

- Drug concentrations were measured in plasma and urine following each dose on Study Days 1 and 3
- PSI-7851 and metabolites were assayed in plasma and urine using a validated LC-MS/MS assay
- PK parameters were calculated using WinNonlin (Version 5.2)

MAD Results

Table 2. Demographics

Demographics	Placebo (N=8)	50mg (n=8)	100mg (n=8)	200mg (n=8)	400mg (n=8)
Male	8	6	7	7	8
Female	0	2	1	1	0
Age (mean yrs)	47	38	43	46	41
Weight (mean kgs)	75.7	80.8	84.0	96.4	74.0
BMI (mean kg/m ²)	25.2	28.5	28.5	31.3	26.3
Caucasian	6	6	6	5	5
African American	2	2	2	3	3
Hispanic or Latino	3	7	7	5	6
Not Hispanic or Latino	5	1	1	3	2
Genotype 1a	7	8	6	6	4
Genotype 1b	1	0	2	2	4
Baseline HCV RNA (median log ₁₀ IU/ml)	6.2	6.6	6.1	6.2	6.4

Clinical Safety

- No maximum tolerated dose identified
- No premature drug discontinuations
- 28 adverse events were reported
- 4 AEs were considered possibly/probably drug-related
- The most commonly reported AEs are summarized in Table 3
- All drug-related AEs were considered mild to moderate in severity
- No dose-related trends in AEs or laboratory abnormalities were apparent
- No clinically significant changes were reported for vital signs or ECGs

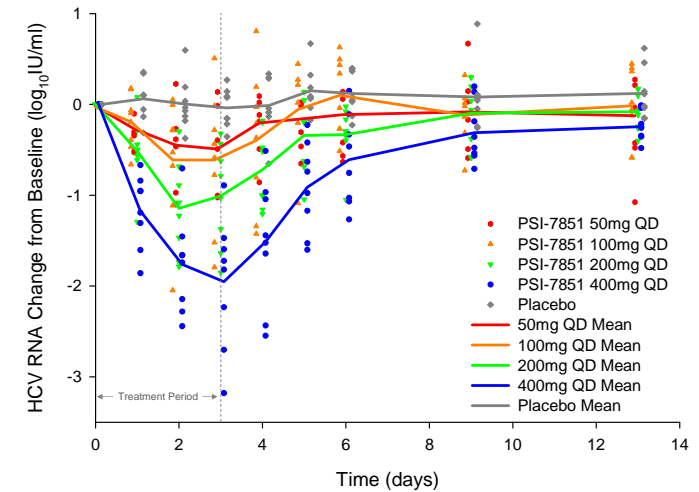
Table 3. Adverse Events (% Subjects within cohort) by Treatment Reported by ≥2 Subjects

Adverse Event	Placebo (N=8)	50mg (n=8)	100mg (n=8)	200mg (n=8)	400mg (n=8)
Total Number of AEs	3	12	3	8	2
Headache	0	2 (25%)	0	3 (38%)	0
Elevated CK	0	1 (13%)	1 (13%)	0	0
Urinary Tract Infection	0	1 (13%)	0	1 (13%)	0
Anemia	0	1 (13%)	1 (13%)	0	0
Abdominal Pain	0	2 (25%)	0	0	0

Table 4. Selected Pharmacokinetic Parameters Following Multiple Doses of PSI-7851 on Day 3

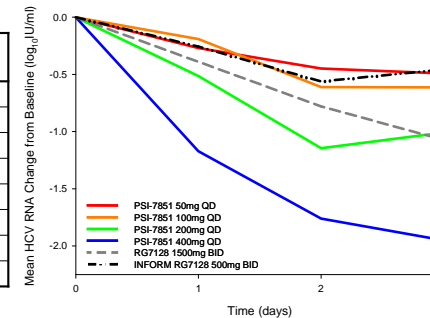
Analyte	Dose of PSI-7851 (mg)	C _{max} (ng/mL)	Median t _{max} (h)	t _{1/2} (h)	AUC(0-∞) (ng·h/mL)
PSI-7851	50mg QD	16.5	1.5	1.7	68.5
	100mg QD	41.4	1.5	1.1	101.7
	200mg QD	58.5	1.0	1.0	165.9
	400mg QD	61.3	1.0	1.1	280.2
PSI-6206	50mg QD	109.7	3.5	4.8	928.3
	100mg QD	213.1	3.0	11.7	2382.0
	200mg QD	329.9	3.5	7.6	3317.1
	400mg QD	322.2	3.0	18.3	5815.5

Figure 2. PSI-7851 HCV RNA Change from Baseline by Cohort



- HCV-RNA declined in a dose dependent manner after 3 days of monotherapy, with mean changes from baseline of -0.04, -0.49, -0.61, -1.01, and -1.95 log₁₀ IU/mL in the placebo, 50, 100, 200 and 400mg QD cohorts, respectively
- Median changes in HCV RNA from baseline were similar with -0.04, -0.44, -0.51, -0.91, and -1.72 log₁₀ IU/mL in the placebo, 50, 100, 200 and 400mg QD cohorts, respectively
- There were no pre-existing or treatment emergent S282T mutations detected, nor was there evidence of viral resistance following 3 days of monotherapy based upon population sequencing of the NS5B region

Figure 3. PSI-7851 HCV RNA Response at Day 3 Compared with RG7128^{2,3}



Conclusions

- PSI-7851 at single doses up to 800mg and as monotherapy up to 400mg administered over 3 days was generally well-tolerated with no maximum tolerated doses identified
- PSI-7851 demonstrated potent, dose-dependent suppression of HCV RNA up to a mean 1.95 log₁₀ IU/mL reduction when administered as monotherapy in QD doses up to 400 mg for 3 days
- This level of antiviral activity exceeds the change from baseline estimated at Day 3 from the RG7128 monotherapy trial of -1.07 log₁₀ IU/mL following 1500mg BID², which demonstrated an 85% RVR in combination with pegylated interferon and ribavirin⁴
- These results support continued development of PSI-7851 for the treatment of chronic HCV infection in combination with pegylated interferon and ribavirin or as a component of a small molecule combination

Disclosures

Maribel Rodriguez-Torres - Grant/Research Support: Pharmasset; Eric Lawitz - Grant/Research Support: Pharmasset; Stephen Flach - Grant/Research Support; Jill Denning - Employee: Pharmasset; Efsevia Albanis - Employee: Pharmasset; William Symonds - Employee: Pharmasset; Michelle Berrey - Employee: Pharmasset

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