

# Potent Antiviral Activity Observed with PSI-7851, a Novel Nucleotide Polymerase Inhibitor for HCV, Following Multiple Ascending Oral Doses for 3 Days in Patients with Chronic HCV Infection

Abstract  
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Eric Lawitz<sup>1</sup>, Maribel Rodriguez-Torres<sup>2</sup>, Jill M. Denning<sup>3</sup>, Efsevia Albanis<sup>3</sup>, William Symonds<sup>3</sup>, and M. Michelle Berrey<sup>3</sup>

1. Alamo Medical Research, Ltd, San Antonio, TX, USA, 2. Fundación de Investigación de Diego, Santurce, PR, USA, 3. Pharmasset, Inc., Princeton, NJ, USA.

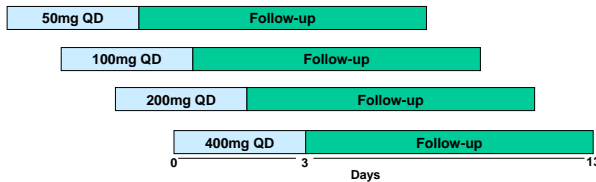
## Background

The nucleoside 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  $\beta$ -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 step<sup>1</sup>. 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.

## MAD 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



### Design

- Multiple oral doses of PSI-7851 (50mg, 100mg, 200mg or 400mg) were administered once daily for 3 days
- 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

- PSI-7851 and metabolites were assayed in plasma and urine using a validated LC-MS/MS assay
- PK parameters were calculated using WinNonlin (Ver. 5.2)

## Study Population

### Key Inclusion/Exclusion Criteria

- Chronic infection with HCV Genotype 1
  - HCV RNA  $\geq$  50,000 IU/mL
- Naïve to immunomodulatory or nucleoside/tide treatment
- ALT and AST screening measurement < 5x ULN
- Non-cirrhotic

Table 1. Baseline Demographics and Parameters

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 <sup>2</sup> )	25.2	28.5	28.5	31.3	26.3
Race					
Caucasian	6	6	6	5	5
African American	2	2	2	3	3
Ethnicity					
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 <sub>10</sub> IU/ml)	6.2	6.6	6.1	6.2	6.4

## Clinical Safety

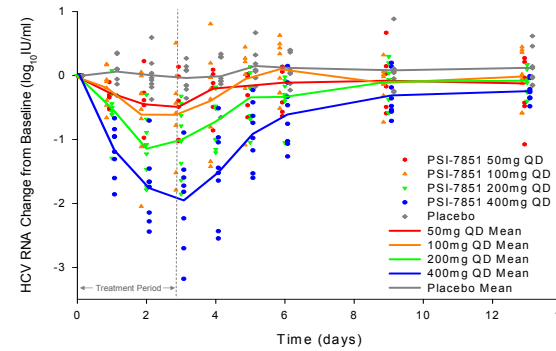
- No maximum tolerated dose identified
- No premature drug discontinuations
- The most commonly reported AEs are summarized in Table 2
- A total of 26 adverse events were reported
- 4 AEs were considered possibly/probably drug-related
- All drug-related AEs were considered mild to moderate in severity
- No dose-related trends in AEs or laboratory abnormalities were apparent
- No clinically significant changes were reported for vital signs or ECGs

Table 2. Adverse Events (% Subjects within cohort) by  $\geq$  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

## MAD Results

Figure 1. 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 log<sub>10</sub> 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 log<sub>10</sub> 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 2. PSI-7851 HCV RNA Response at Day 3 Compared with RG7128<sup>2,3</sup>

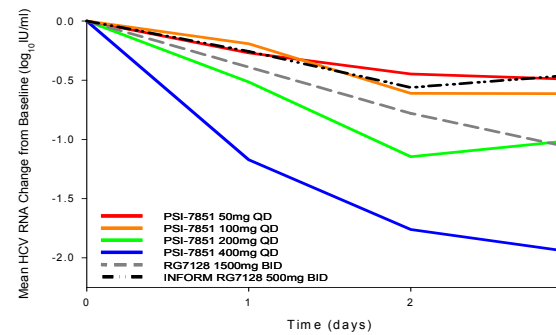


Figure 3. Similar Antiviral Activity of PSI-7851 400mg QD Against GT 1A and 1B

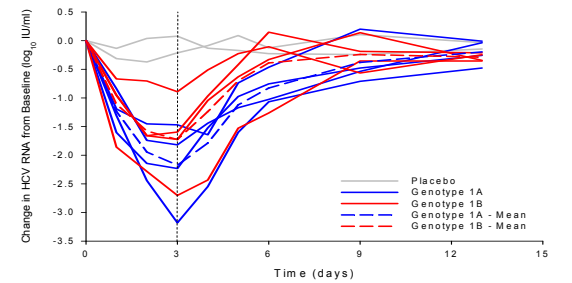
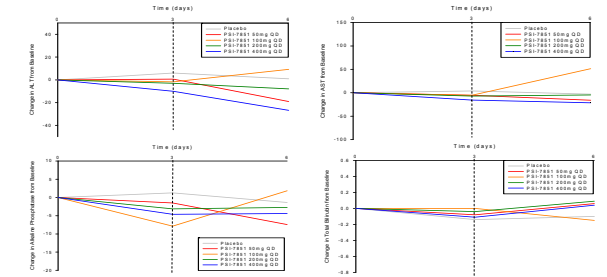


Figure 4. Trend Towards Improvement in Biochemical Parameters Assessing Liver Function



## Conclusions

- PSI-7851 administered as monotherapy at doses up to 400mg over 3 days was generally well-tolerated
- PSI-7851 demonstrated dose-dependent suppression of HCV RNA up to a mean 1.95 log<sub>10</sub> IU/mL reduction
- Observed antiviral activity exceeds the change from baseline estimated at Day 3 from the RG7128 monotherapy trial of -1.07 log<sub>10</sub> IU/mL following 1500mg BID<sup>3</sup>, which demonstrated an 85% RVR in combination with SOC<sup>4</sup>
- These results support continued development of PSI-7851 for the treatment of chronic HCV infection in combination with SOC or as a component of a small molecule combination

1. Furman, et al. 15th Intl Symposium on HCV, Oct 2008, San Antonio, TX  
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 3. Reddy, et al. LB#9, AALSD, 2007  
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