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Abstract

Background: R7128 is a prodrug of PSI-6130, an oral cytidine nucleoside analog polymerase inhibitor, currently in development for the treatment of chronic HCV infection by Pharmasset and Roche. This study assessed safety, tolerability and pharmacokinetics of R7128 and its metabolites in healthy volunteers after single ascending doses.

Methods: Single oral doses of R7128 (500-9000 mg) were administered to 46 healthy subjects. PK and safety assessments were conducted throughout the study period. Subjects were enrolled in 5 sequential dose groups (500 mg, 1500 mg, 4500 mg, 6000 mg, and 9000 mg); 6 active and 2 placebo subjects per group, and one food effect group (1500 mg); 6 active.

Results: Nineteen (19) adverse events were reported, including headache (3), sunburn (2), sore throat (2) and nasal congestion (2); all were mild to moderate, none were dose dependent, and no gastrointestinal AEs were observed. There were no clinically significant changes in vital signs, ECGs, hematology, or other laboratory parameters. Plasma exposure to R7128 was negligible; exposure to PSI-6130 and PSI-6206 (RO2433), the uridine metabolite of PSI-6130, increased with increasing doses of R7128. Terminal half-life was approximately 5h for PSI-6130 and 19h for PSI-6206 (RO2433). Food increased exposure of PSI-6130 by approximately 20%. **Conclusion:** Single ascending doses of R7128 were well-tolerated in this study. The PK profile indicates good exposure to the active moiety, PSI-6130, and no dose-related adverse events or laboratory abnormalities were observed. Based upon these results, a multiple dose study of R7128 was initiated in HCV-infected genotype 1 subjects, who previously failed interferon therapy.

Methods

Study Design

- Single oral doses of R7128 were administered to 46 healthy subjects in 5 sequential dose groups (500 mg, 1500 mg, 4500 mg, 6000 mg, and 9000 mg) and one food effect group (1500 mg)
- 6 active and 2 placebo subjects per group for the dose escalation groups
- 6 active for the food effect group

Safety Assessments

- Physical exam, clinical laboratory tests, electrocardiograms (ECGs), and adverse events (AEs) assessments were performed throughout the study.

PK Assessments

- Serial blood samples were collected up to 72h post dose.

Sample Analysis

- Plasma and urine PSI-6130 and PSI-6206 concentrations were determined by a validated LC/MS assay.

PK Analysis

- PK parameters were estimated using non-compartmental methods

Statistical Analysis

- PK parameters were summarized by dose level using descriptive statistics

Results

Table 1: Demographics

N	Sex	Race	Age (y)	Weight (kg)	Height (cm)	BMI (kg/m ²)
46	Males: 45 Females: 1	Caucasian: 42 Maori: 2 Malay: 1	18 - 51	68.5 - 106.5	160 - 191	21 - 32.5

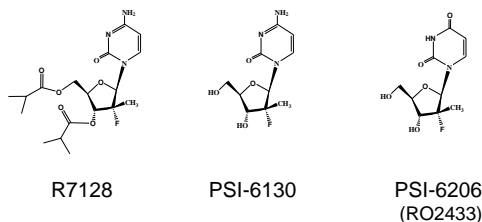
Clinical Safety

- No severe or serious clinical AEs have been reported. No subjects discontinued R7128 due to an adverse event.
- The most commonly reported AEs with R7128 were headache (3), sunburn (2), nasal congestion (2), and sore throat (2), followed by dermatitis, dry mouth, euphoria, inflammation at ECG electrode, ganglion right foot, inflammation – right eye, inflammation cannula site, intermittent lightheadedness, somnolence and pharyngeal ulcer (1 report each)
- All AEs were mild to moderate.
- No 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 serial ECGs, including no QTc prolongation beyond 500 ms.

Table 2: Selected Pharmacokinetic Parameters Following Single Doses of R7128

Analyte	Dose of R7128 (mg)	C _{max} (µg/mL)	Median t _{max} (h)	t _{1/2} (h)	AUC(0-∞) (µg ^h /mL)
PSI-6130	500	4.5 ± 0.8	0.9	4.84 ± 0.4	22.7 ± 3.6
	1500	7.5 ± 1.9	2.0	5.57 ± 0.8	58.6 ± 9.4
	4500	10.9 ± 4.8	2.0	5.59 ± 0.4	103 ± 35
	1500 + food	8.9 ± 1.2	3.0	5.16 ± 0.8	71.3 ± 9.2
	6000	18.1 ± 4.7	2.5	5.88 ± 0.7	152 ± 54
	9000	25.8 ± 5.9	4.0	6.5 ± 0.3	280 ± 80
PSI-6206	500	0.199 ± 0.1	3.0	17.0 ± 1.3	3.6 ± 1.1
	1500	0.454 ± 0.1	4.0	18.1 ± 5.2	10.1 ± 1.7
	4500	0.65 ± 0.2	7.0	14.3 ± 2.6	19.4 ± 3.1
	1500 + food	0.54 ± 0.2	5.0	19.8 ± 3.2	10.2 ± 1.5
	6000	1.36 ± 0.6	3.5	18.9 ± 6.8	29.3 ± 6.9
	9000	1.25 ± 0.6	6.0	30.3 ± 25.2	43.6 ± 14.4

Chemical Structures



Results, Continued

Figure 1: Concentration/Time Profiles of PSI-6130 Following Single, Oral Doses of R7128

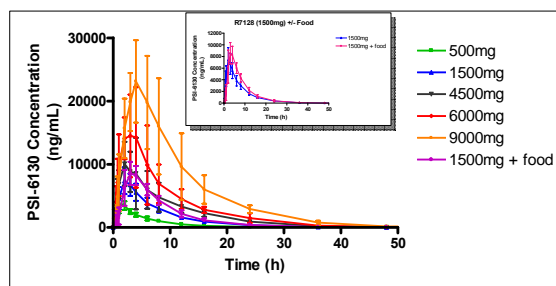


Figure 2: Concentration/Time Profiles of PSI-6206 Following Single, Oral Doses of R7128

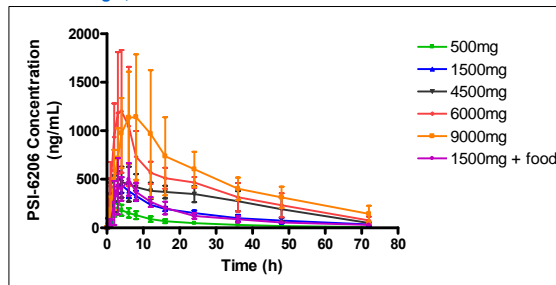
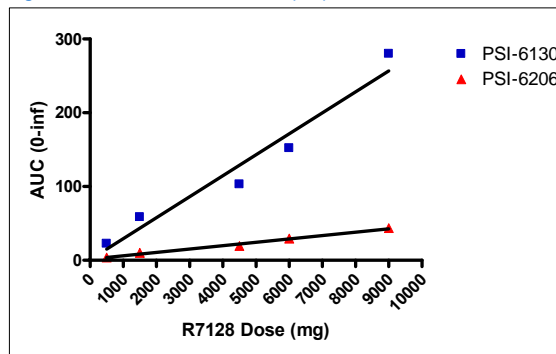


Figure 3: R7128 Dose Versus AUC (0-∞)



Conclusions

- R7128, when administered to healthy volunteers as a single oral dose at up to 9000 mg, is generally safe and well-tolerated
- The PK profile indicates good exposure to the active moiety, PSI-6130.
- No dose-dependant adverse events or laboratory abnormalities were observed.
- Based upon these results, a multiple dose study of R7128 was initiated in HCV-infected genotype 1 subjects.