ONCE DAILY DUAL-NUCLEOTIDE COMBINATION OF PSI-938 AND PSI-7977 PROVIDES 94% HCV RNA < LOD AT DAY 14: FIRST PURINE/PYRIMIDINE CLINICAL COMBINATION DATA (THE NUCLEAR STUDY)

Abstract #1370

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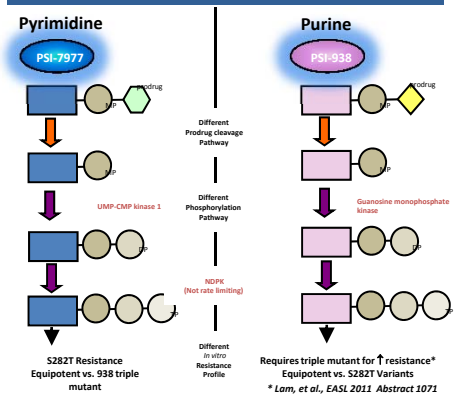
Background

The purine PSI-352938 (PSI-938) was created to be an optimal partner DAA for the pyrimidine PSI-7977. The nucleotides employ different prodrug cleavage pathways, largely independent phosphorylation pathways, competition with separate endogenous nucleotide pools (purine/pyrimidine) and complementary resistance profiles (Sofia *J Med Chem* 2010, Lam *AAC* 2010, Reddy *Bio Med Chem Ltr* 2010). This study is the first proof of concept for the combination of 2 nucleotides for the treatment of HCV infection.

Figure 1. PSI-7977 and PSI-938 are Complementary Nucleotides for Combination Therapy

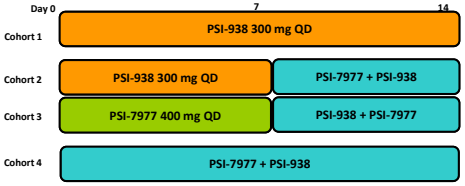


** Lam, et al., EASL 2011 Abstract 1071*

Objectives

To determine the safety, pharmacokinetic interaction and impact on antiviral activity of PSI-938 and PSI-7977 administered as monotherapy or in combination for 7-14 days.

Design



- Forty HCV GT1, treatment-naïve subjects
  - 8 active and 2 placebo per cohort
- Sequential enrollment into Cohort 1, Cohorts 2/3 and Cohort 4
- HCV RNA >50,000 IU/mL, no evidence of cirrhosis
- PSI-938 300 mg QD and PSI-7977 400 mg QD
- Safety, PK, viral kinetics, and resistance monitored throughout
- All subjects offered full course of peg-interferon (Peg-IFN) and ribavirin (RBV) on study day 15

Results

Table 1. Subject Demographics and Baseline Characteristics

	Cohort 1 (n = 8)	Cohort 2 (n = 8)	Cohort 3 (n = 8)	Cohort 4 (n = 8)	Placebo (n = 8)
Male (n)	5	7	7	6	7
Caucasian (n)	7	5	5	5	6
Median age (y)	46	43	41	48	39
Mean BMI (kg/m^2)	28	26	28	28	29
Median (Q1,Q3) HCV RNA ($\log_{10}$ IU/mL)	6.9 (6.2,7.5)	6.3 (5.8,6.7)	6.3 (5.9,6.6)	6.2 (5.7,6.8)	5.9 (5.2,6.6)
HCV 1a/1b (n)	6/2	8/0	8/0	7/1	7/1

SAFETY

- No discontinuations or serious adverse events
- 28 AEs reported in 16/32 subjects receiving active treatment
- Five AEs considered possibly related to active study drug
  - Headache [2], fatigue, non cardiac chest pain, dizziness
  - AEs were mild in intensity
- Two AEs considered possibly related to placebo
  - Increased pruritus and headache
- No dose- or duration-related toxicities were identified
- No clinically significant treatment-emergent changes in laboratory parameters, vital signs or ECGs
- No treatment-emergent grade 4 laboratory abnormalities
- 47% had abnormal ALT at baseline, all normalized during study

Table 2. Summary of Individual HCV RNA Data and Follow-on Therapy Across All Cohorts

	Subject	Study Day: Baseline	1	3	5	7	10	14	16
Cohort 1	201	7.43	4.75	3.23	3.14	2.84	2.16	1.41	1.62
	202	5.16	2.77	< LOD	< LOD	< LOD	< LOD	< LOD	
	203	6.60	3.90	2.55	2.34	2.19	1.30	< LOD	< LOD
	205	5.81	3.54	2.45	2.03	< LOD	< LOD	< LOD	< LOD
	206	6.93	4.78	3.06	2.73	2.25	1.57	< LOD	
	207	6.97	4.99	3.46	3.05	2.85	2.27	1.97	
	209	7.48	4.87	4.00	3.54	3.12	2.97	2.71	
	210	7.49	4.84	3.47	3.07	2.80	2.20	1.72	
Cohort 2	221	6.96	4.39	2.87	2.56	2.13	1.51	< LOD	
	224	5.45	2.77	< LOD	< LOD	< LOD	< LOD	< LOD	< LOD
	229	6.29	4.16	2.40	1.70	1.30	< LOD	< LOD	
	230	6.13	3.77	1.75	< LOD	< LOD	< LOD	< LOD	
	231	5.44	n.d.	2.75	2.39	2.23	1.48	< LOD	
	233	6.88	4.78	3.45	2.86	2.63	2.24	< LOD	
	238	6.54	4.05	2.66	2.41	1.36	1.57	< LOD	
	239	6.36	4.38	3.15	2.69	2.35	1.51	< LOD	
Cohort 3	222	4.98	3.03	< LOD	< LOD	< LOD	< LOD	< LOD	
	223	6.98	4.59	3.14	2.74	2.31	1.93	1.62	
	225	5.89	3.71	2.32	1.81	< LOD	< LOD	< LOD	
	228	5.80	3.78	1.53	1.67	< LOD	< LOD	< LOD	
	232	7.51	5.78	4.26	3.44	2.67	1.46	< LOD	
	234	6.51	4.59	3.87	3.44	2.53	< LOD	< LOD	
	235	6.55	4.41	2.05	1.63	1.26	< LOD	< LOD	
	240	5.54	n.d.	2.06	1.46	< LOD	< LOD	< LOD	
Cohort 4	261	6.37	3.71	2.71	2.43	2.16	2.09	1.59	< LOD
	262	6.26	3.31	2.37	2.11	1.56	< LOD	< LOD	< LOD
	264	5.54	3.05	1.92	1.75	1.51	< LOD	< LOD	< LOD
	265	5.71	3.18	2.53	1.76	1.30	1.18	< LOD	< LOD
	266	6.09	3.34	1.65	1.30	< LOD	< LOD	< LOD	
	268	6.83	3.89	3.18	2.90	2.37	1.89	< LOD	
	269	7.48	4.28	2.91	2.67	2.33	2.26	1.48	
	270	6.27	3.78	2.77	2.59	2.35	2.12	1.20	< LOD

PSI-938 | PSI-7977 | PSI-938/PSI-7977 | Washout | PI/FN/RBV

- HCV RNA declined rapidly in a biphasic manner in all subjects
- Individual subjects reached the assay limit of detection (LOD, <15 IU/mL) in as few as 3 days. This correlated with baseline HCV RNA and did not differ by treatment

Results

Table 3. Summary of Antiviral Response by Cohort

Median (Q1,Q3) HCV RNA Change from Baseline and Number of Subjects with HCV RNA <15 IU/mL (LOD) by Cohort

	Day 7 # < LOD	Day 7 Median [Q1,Q3]	Day 14 # < LOQ	Day 14 # < LOD	Day 14 Median [Q1,Q3]	Total[1] # < LOD
Cohort 1	2	-4.5 (-4.3,-4.7)	5	4	-5.2 (-4.8,-5.8)	4/8 (50%)
Cohort 2	2	-4.6 (-4.2,-5.0)	8	8	-5.2 (-4.8,-5.5)	8/8 (100%)
Cohort 3	4	-4.7 (-4.3,-4.8)	8	7	-5.0 (-4.6,-5.4)	7/8 (88%)
Cohort 4	1	-4.4 (-4.2,-4.8)	8	5	-5.0 (-4.7,-5.3)	7/8 (88%)[2]

94%

92%

1. Cumulative total of individuals whose HCV RNA reached < LOD as a result of the study treatment
2. Includes 2 additional subjects whose HCV RNA reached < LOD on Day 16

Figure 2. Median [Q1,Q3] HCV RNA Change from Baseline

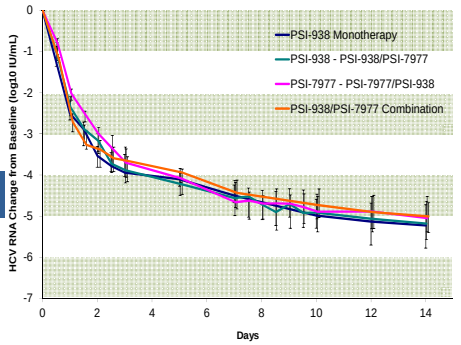
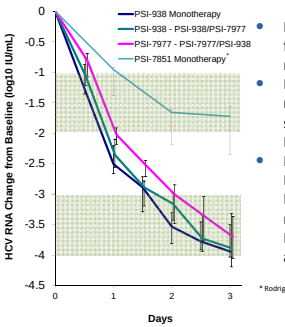


Figure 3. Comparison of Monotherapy Antiviral Responses with PSI-7851, PSI-7977 and PSI-938 (Median, [Q1,Q3])



- PSI-7977 is a single isomer found in PSI-7851, a mixture of 2 isomers
- PSI-7977 monotherapy resulted in greater viral suppression at Day 3 than PSI-7851 at Day 3
- Monotherapy with either PSI-938 at 300 mg QD or PSI-7977 at 400 mg QD resulted in 3.7 to 3.9 $\log_{10}$ IU/mL declines in HCV RNA after 3 days

* Rodriguez-Torres, et al. Abst. LB17, AASLD, Nov. 2009

Results

Figure 4. HCV RNA Change from Baseline by Cohort

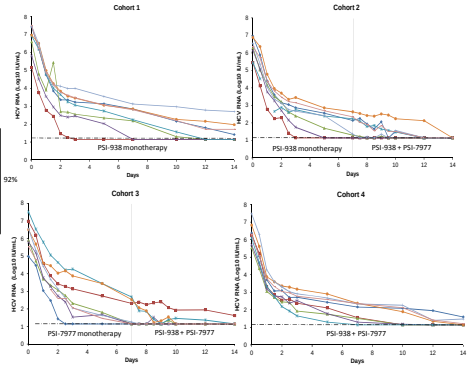
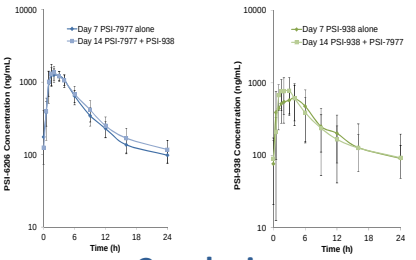


Figure 5. Pharmacokinetic Interaction Data



Conclusions

- PSI-938 and PSI-7977 as monotherapy and in combination were generally safe and well tolerated over 7-14 days
- Significant antiviral activity was observed with rapid α-phase reductions followed by continued β-phase reductions until the end of treatment or assay LOD was reached
- Of note, PSI-7977 monotherapy produced HCV RNA reductions over 7 days which were similar to PSI-938
- No viral breakthrough was observed during therapy
- No significant PK interaction between PSI-938 and PSI-7977 was observed
- Data support progression to a Phase 2 combination study including PSI-938 and PSI-7977

Disclosures

E.L., M.R.T. - Grant/Research Support: Pharmasset; J.D.; M.C.; D.C.; W.S.; M.B. - Employee: Pharmasset; L.Mc. - Consultant

Presented at the 46th Annual Meeting of the European Association for the Study of the Liver, EASL, March 30, 2011 – April 3, 2011, Berlin, Germany