

NO EVIDENCE OF R7128 DRUG RESISTANCE AFTER UP TO 4 WEEKS TREATMENT OF GT 1, 2 AND 3 HEPATITIS C VIRUS INFECTED INDIVIDUALS



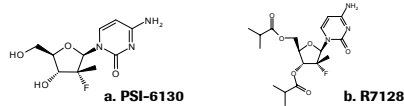
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Introduction

- PSI-6130 (β-D-deoxy-2'-fluoro-2'-C-methylcytidine, figure 1a) is a potent inhibitor of HCV RNA replication *in vitro*¹
- PSI-6130 has demonstrated potent activity against HCV replicons containing NS5B genes derived from genotype 1a and 1b clinical isolates²
- In vitro* replicon studies have identified the NS5B polymerase amino acid substitution S282T, responsible for a 3 to 4-fold decrease in susceptibility to PSI-6130 *in vitro*²
- R7128, a prodrug of PSI-6130 (figure 1b), has demonstrated potent antiviral efficacy after 2 weeks monotherapy in treatment-experienced HCV GT 1 infected patients and after 4 weeks therapy in combination with pegylated interferon alpha 2a and ribavirin in GT 1 infected treatment-naïve patients and in GT 2/3 infected treatment-experienced patients^{3,4,5}

Figure 1. Structures of PSI-6130 (a) and R7128 (b)



Objectives of the study

- The aim of the study was to:
 - monitor the emergence of drug resistance to R7128 *in vivo*, through sequence and phenotypic analysis,
 - determine whether the NS5B S282T substitution exists in the patient's quasispecies at low frequency (clonal analysis),
 - determine the frequency of S282T in a patient's quasispecies necessary to observe a decrease in PSI-6130 sensitivity.

Methods

Study Design

- Multiple oral doses of R7128 were administered as monotherapy to 40 GT 1 HCV infected patients (doses of 750 mg QD, 1500 mg QD, 750 mg BID, and 1500 mg BID administered orally for 14 days) and as combination therapy with the standard of care (SOC) to 81 GT 1 and 25 GT 2/GT 3 HCV infected patients (doses of 500 mg, 1000 mg, 1500 mg BID administered orally for 28 days)
- Serum samples for HCV RNA quantification and resistance monitoring were collected through the study

Definitions of clinical responses and criteria for viral resistance evaluation

- Identify patients who showed:
 - Non-Response:** Viral load decrease ≤ 0.5 log₁₀ IU/ml from baseline and/or viral load ≥ 1000 IU/ml at end of ≥ 4 week combination treatment
 - Partial Response:** Initial viral load decrease followed by stabilization
 - Viral Load Rebound:** Initial viral load decrease ≥ 0.5 log₁₀ IU/ml followed by a sustained viral load rebound ≥ 0.5 log₁₀ IU/ml from nadir while on R7128 treatment

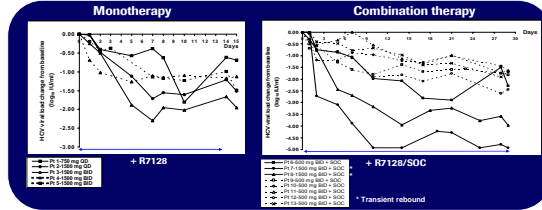
Viral resistance evaluation for R7128 14 Day Monotherapy or 28 Day Combination

- 6/117 R7128-treated patients showed an HCV viral load rebound
- 7/117 R7128-treated patients showed a partial response

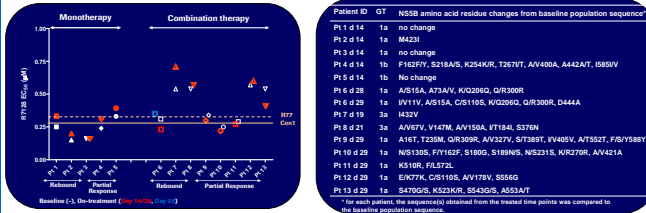
	Dose [mg]	R7128 [n]	VL Rebound [n]	VL Rebound from nadir [log ₁₀ IU/ml]	VL Partial Response [n]	VL Continuous Decline [n]
GT 1	750 QD	8 (2 SOC)	1	1.2	0	7
	1500 QD	8 (2 SOC)	1	0.5	0	7
	750 BID	8 (2 SOC)	0		0	8
	1500 BID	8 (2 SOC)	0		2	6
	500 mg BID + SOC	20 (5 SOC)	1	0.6	8	8
	1000 mg BID + SOC	25 (6 SOC)	0		0	25
	1500 mg BID + SOC	20 (5 SOC)	0		0	20
	1500 mg BID + SOC	20 (5 SOC)	0		0	20
	GT 2/3 1500 mg BID + SOC	20 (5 SOC)	2*	0.6-0.7*	0	18

* Transient rebound

Viral load kinetics of patients evaluated for R7128 resistance

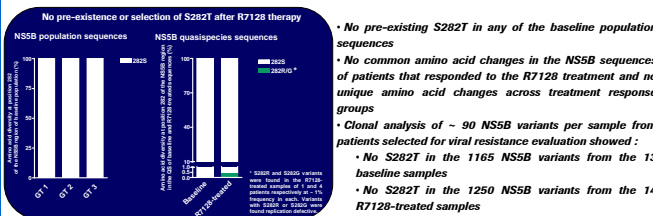


No resistance to R7128 *in vivo* after 14 day Monotherapy or 28 days of Combination therapy

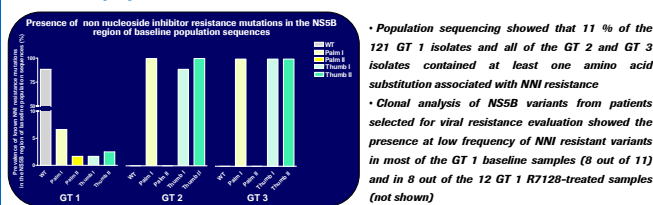


* On treatment samples are as sensitive to R7128 as baseline samples and reference replicons (Con1 and H77) • No S282T, nor common amino acid substitution(s), observed in any treated samples at the population level

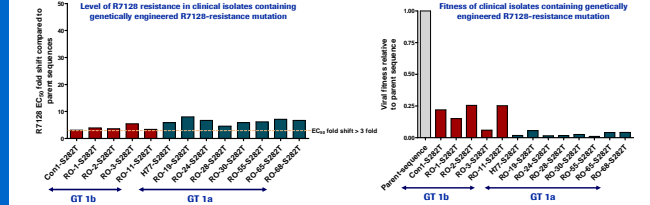
NS5B population and clonal sequencing showed no pre-existence or selection of S282T after 14 Day Monotherapy or 28 Day Combination Therapy



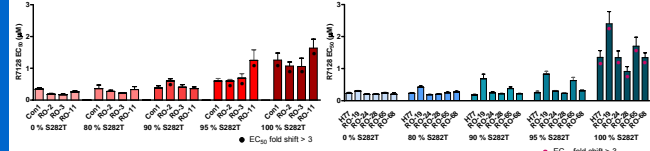
NS5B population and clonal sequencing showed the presence of non nucleoside polymerase inhibitor resistant variants



Engineered S282T resistance mutation confers low level resistance and low fitness in genetically diverse NS5B clinical isolates



S282T needs to be present at a frequency of ~90% in the viral quasispecies to observe a ~3-fold decrease in R7128 sensitivity



- The introduction of S282T resulted in a severe reduction in the replication capacity in all GT 1 isolates. A 3- to 7-fold reduction in sensitivity to R7128 was observed for all S282T mutant replicons
- In all GT 1 isolates, a decrease in sensitivity was observed only when the S282T mutation is present at a high proportion in the population (above 90%)

Conclusions

- R7128, prodrug of PSI-6130 has shown potent antiviral efficacy in monotherapy with a dose-dependent HCV RNA decrease through 14 days in all dose groups.
- In combination therapy with the current standard of care, mean HCV RNA reductions of 5.0 log₁₀ IU/ml in GT 1, 2 and 3 patients were observed at 1000 and 1500 mg BID
- No evidence for development of viral resistance to R7128 after 2 weeks or 4 weeks of therapy was observed
- No S282T variants were found in baseline or R7128-treated patients at population or quasispecies level, confirming the high barrier to resistance to this nucleoside polymerase inhibitor in short-term studies
- The introduction of S282T resulted in a severe reduction of the replication capacity in all GT 1 isolates and a reduction in sensitivity to R7128 (3- to 7-fold)
- In all GT 1 isolates, a decrease in sensitivity was observed only when the S282T mutation is present at a high proportion in the population (above 90%)

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