

Potent Antiviral Response To The HCV Nucleoside Polymerase Inhibitor R7128 For 28 Days With Peg-IFN And Ribavirin: Subanalysis by Race/Ethnicity, Weight and HCV Genotype

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Abstract

Background: R7128 is a potent nucleoside analog inhibitor of HCV polymerase. When administered for 28 days in combination with pegylated interferon and ribavirin, R7128 at 1000mg to 1500mg BID resulted in an >85% RVR.

Methods: The current trial is designed to evaluate R7128 with 180µg peginterferon alfa-2a (PEG-IFN) and 1000-1200mg ribavirin (RBV) for 28 days in treatment-naïve, HCV+ G1 patients. 25 patients (20 active/5 placebo) in Cohort 1 received R7128 500mg BID/placebo with PEG-IFN+RBV; 25 patients (20 active/5 placebo) in Cohort 2 received R7128 1500mg BID/placebo with PEG-IFN+RBV. 31 patients (25 active/6 placebo) in Cohort 3 received R7128 1000mg BID/placebo with PEG-IFN+RBV. Using an analysis of variance method, a model was fitted to look at reductions in viral load at day 29. Baseline HCV RNA, race/ethnicity, weight, BMI and gender were evaluated along with randomized treatment.

Results: 81 subjects were randomized across the 3 cohorts: Analysis of variance was performed on Week 4 HCV RNA change from baseline controlling for different factors such as race/ethnicity, baseline, treatment, sex, weight, and genotype. In patients randomized to receive SOC, 3 (Caucasian) patients in 15 (20%) achieved RVR. In Cohort 1 (R7128 500mg BID) RVR rates were 45% for the Caucasian subjects, 25% for Latinos, 0% (0 of 3) for AA, and 0% Other. In Cohort 2 (R7128 1500mg BID) RVR rates were 90% for the Caucasian subjects, 86% for Latinos, 50% (1 of 2) for AA, and 100% (1 of 1) Other. Two subjects were omitted from this analysis: 1 discontinued therapy on Day 24, and 1 with poor venous access resulting in no Week 4 data. HCV genotype, Weight, BMI and gender were not significant predictors of antiviral response. No serious adverse events were reported, and no differences in AEs were noted by race/ethnicity.

Conclusions: R7128 administered in combination with PEG-IFN/RBV for 28 days demonstrated clinically significant antiviral potency regardless of race/ethnicity, with a numerical improvement in RVR rates in Latino patients who received R7128 1500mg BID. Further studies are planned to fully characterize the incremental benefit of R7128 over SOC with longer durations of treatment in these sub-populations.

Methods

Study Design

- R7128 or placebo was co-administered with PEG-IFN (Pegasys[®]) and RBV (Copegus[®]) for 28 days in 81 treatment naïve subjects with chronic HCV genotype 1
- Randomized treatments included three oral doses of R7128: 500mg, 1000mg, or 1500mg BID
- Within each cohort, subjects were randomized to receive either R7128 (N=20-25) or placebo (N=5-6)

Safety Assessments

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

PK and PD Assessments

- Full PK profiles were obtained for R7128 on days 1 and 28, RBV on day 28, with additional PK samples collected on days 2, 4/5, 7, 10/11, 14, 17/18, 21, 24/25, and 29
- HCV RNA was evaluated at Screening and on days -14, -1, 1, 2, 4/5, 7, 10/11, 14, 17/18, 21, 24/25, 28, 35, 42, 49, and 56

Analysis Methods

- Analysis methods included summary statistics and figures, and analysis of variance. Potential covariates of change from baseline in HCV RNA analyzed included age, weight, BMI, race/ethnicity, baseline HCV RNA, viral subgenotype, dose and dose * race/ethnicity

Results

Table 1. Demographics

Demographics	Placebo (N=16)	500mg BID (N=20)	1000mg BID (N=25)	1500mg BID (N=20)
Male	13	12	18	16
Female	3	8	7	4
Age (median yrs)	47.5	47.5	45.0	51.0
Weight (median kgs)	80.6	85.4	79.1	86.3
BMI (median kg/m ²)	26.4	27.1	24.4	27.9
Caucasian	9	11	21	10
Hispanic	3	3	3	4
African American	2	5	0	5
Asian	1	0	1	0
Other	1	1	0	1
Genotype 1a	11	15	18	15
Genotype 1b	5	5	7	5
Baseline HCV RNA (median log ₁₀ IU/ml)	6.30	6.21	6.22	6.11

- Each Cohort enrolled 25-31 patients with chronic genotype 1a/1b HCV infection
- Baseline characteristics including baseline HCV RNA were similar across all treatment groups
- The adverse events reported by >30% subjects were headache, fatigue, myalgia and nausea. There were no dose-related differences in AE severity or organ system
- No serious adverse event was reported for subjects on R7128: suicidal ideation. This subject had a history of bipolar disorder and previous suicidal ideation prior to IFN treatment
- No significant differences in safety laboratory abnormalities across doses or between active R7128 and placebo were noted
- No clinically significant changes were noted in vital signs; no changes were reported for serial ECGs and no QTc prolongation beyond 500ms was observed

Table 2. Most Commonly Reported Adverse Events (% Subjects within cohort) by Treatment

Adverse Event	Placebo	500mg	1000mg	1500mg
ANEMIA	2(13%)	4(20%)	5(20%)	4(20%)
ANXIETY	1(6%)	4(20%)	6(24%)	3(15%)
ARTHRALGIA	1(6%)	4(20%)	2(8%)	5(25%)
CHILLS	2(13%)	4(20%)	7(28%)	8(40%)
DIARRHEA	2(13%)	5(25%)	5(20%)	4(20%)
DIZZINESS	3(19%)	3(15%)	3(12%)	5(25%)
FATIGUE	6(38%)	4(20%)	13(52%)	9(45%)
HEADACHE	9(56%)	13(65%)	15(60%)	15(75%)
INJECTION SITE ERYTHEMA	3(19%)	6(30%)	5(20%)	3(15%)
INSOMNIA	0(0%)	3(15%)	7(28%)	4(20%)
IRRITABILITY	0(0%)	0(0%)	5(20%)	2(10%)
MYALGIA	3(19%)	8(40%)	3(12%)	5(25%)
NAUSEA	4(25%)	5(25%)	9(36%)	5(25%)
PAIN	3(19%)	2(10%)	6(24%)	2(10%)
PYREXIA	4(25%)	3(15%)	3(12%)	5(25%)
RASH	3(19%)	5(25%)	2(8%)	1(5%)

Results

Figure 1. RVR: Percent of Patients with Plasma HCV RNA <15 IU/ml at Week 4 by Dose

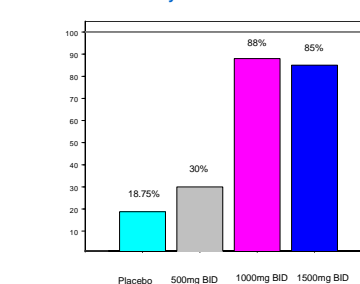


Figure 2. HCV RNA by Viral Subgenotype

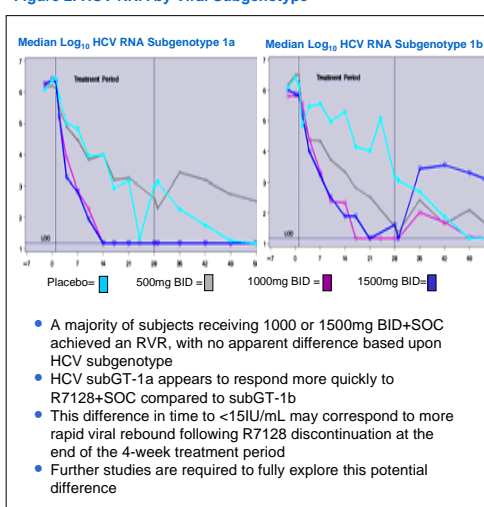
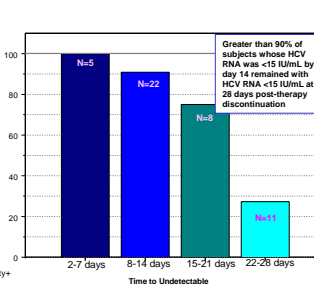


Figure 4: Predictors of Week 4 Change from Baseline in Log₁₀ HCV RNA

Covariates	P >= F
Treatment	<0.0001
Baseline Viral Load	0.0178
Genotype	0.7512
Sex	0.6056
Weight	0.1585
Race/Ethnicity	0.0137
Treatment*Race	0.0208

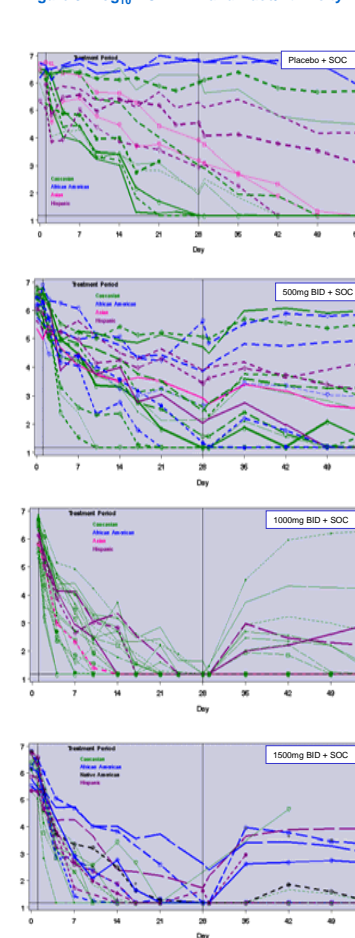
*Model: Day 29 Log₁₀ HCV RNA = Treatment + Baseline + Genotype + Sex + Weight + Race/Ethnicity + Race/Ethnicity * Treatment

Figure 5: Percentage of Week 4 Treated Patients with HCV RNA <15 IU/mL Who Maintain HCV RNA <15 IU/mL at 4 Weeks after Discontinuation of R7128



Results

Figure 3: Log₁₀ HCV RNA and Race/Ethnicity



- African Americans on placebo + SOC had no meaningful HCV RNA reductions in HCV RNA
- No apparent differences in HCV RNA reduction across race/ethnicity with respect to R7128 1000mg BID or 1500mg BID
- Further studies are required to confirm findings and determine clinical impact

Summary

- R7128 demonstrated 88% RVR for the R7128 1000mg BID and 85% RVR for the R7128 1500mg BID dose groups as compared to the expected 10% RVR in the placebo+SOC
- Treatment, baseline viral load, and race/ethnicity were significant contributors to the analysis model evaluating change in HCV RNA
- When R7128 is added to SOC, responses are more consistent across the race/ethnicities versus placebo + SOC
- No significant effects of viral subgenotype, weight, or gender on HCV RNA reduction at Week 4 were noted in those subjects who were randomized to R7128 + SOC
- No dose-related changes in terms of safety and tolerability were noted

Conclusions

- R7128 has demonstrated that short-term treatment with a potent antiviral administered with SOC in treatment-naïve subgenotype 1a and 1b subjects, can result in RVRs in 85-88% of subjects, without any significant safety signals in addition to those anticipated with SOC
- Ethnicities less susceptible to SOC alone demonstrated significant antiviral responses when R7128 1000mg BID or R7128 1500mg BID was part of the regimen. Larger studies are indicated to more fully characterize the potential of R7128 in different populations
- HCV+ patients with historically lower likelihood of response to PEG-IFN/RBV may have an opportunity for improved SVR with addition of R7128 in longer-term studies
- Rebound viremia after discontinuation of R7128 highlights the impact of the nucleoside inhibitor on those patients who were less likely to have responded to current standard-of-care, PEG-IFN/RBV
- R7128 in 28-day studies provides appropriate potency and safety to progress to Phase 2b studies to determine the duration of triple therapy necessary to improve SVR rates in HCV genotype 1a/b treatment-naïve patients

Acknowledgments

- The contributions of the investigators, study coordinators, and especially the patients who participated in the study are gratefully acknowledged

Disclosures

Maribel Rodriguez-Torres - Grant/Research Support: Pharmasset; Ed Gane - Grant/Research Support: Pharmasset; David Nelson - Grant/Research Support: Pharmasset; Ira Jacobson - Grant/Research Support: Pharmasset; Lennox Jeffers - Grant/Research Support: Pharmasset; John G. McHutchison - Grant/Research Support: Pharmasset, Consultant/Adviser: Pharmasset; Amanda Beard - Employee: Pharmasset; Nancy Shulman - Employee: Roche; Sue Walker - Employee: Pharmasset; Efsavia Albanis - Employee: Pharmasset; William Symonds - Employee: Pharmasset; Michelle Berrey - Employee: Pharmasset