PHARMACOKINETICS/PHARMACODYNAMICS (PK/PD) OF COMBINATION RG7227 AND RG7128 THERAPY FROM INFORM-1 DEMONSTRATES SIMILAR EARLY HCV VIRAL DYNAMICS WHEN RG7227 IS COMBINED WITH EITHER PEG-IFN/RIBAVIRIN (SOC) OR RG7128

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Background

INFORM-1 is evaluating a nucleoside polymerase inhibitor (RG7128) and protease inhibitor (RG7227) in combination, offering the potential for a potent, all oral, interferon-free regimen with a high barrier to resistance. *In vitro* HCV replicon experiments demonstrate that the combination of RG7128 and RG7227 is additive, without cross resistance, and the addition of RG7128 prevents the emergence of RG7227 resistance.[1] The INFORM-1 clinical study has confirmed that a twice-daily combination of RG7128 and RG7227 results in significant reductions in HCV RNA, without the emergence of resistance.

Objective

To evaluate and compare the PK/PD relationships for RG7227 when combined with either RG7128 or standard of care (SOC).

Methods

The PK/PD and viral kinetics of patients receiving RG7227 in combination with either a) RG7128 (INFORM-1) or b) SOC PEG-IFN/RBV (NSHC-003[2]) were evaluated.

Study design

INFORM-1 was a randomized, double-blind, placebo controlled, dose ranging study of RG7128 and RG7227 in adult patients with chronic hepatitis C (CHC) genotype 1.

Treatment-naive (Cohorts A–D, and G), -experienced (Cohort E), or null responder (Cohort F) patients were randomized to escalating doses of RG7128 (500 or 1000 mg bid) and RG7227 (100 or 200 mg tid or 600 or 900 mg bid) for 13 days. Frequent on-treatment samples were taken to assess the pharmacokinetics and viral kinetics of the combination.

The study designs of INFORM-1 and NSHC-003 were generally similar; SOC treatment was initiated 24 hours prior to the first dose of R7227 in NSHC-003.

Pharmacokinetic/Pharmacodynamic and statistical methods

Concentration-response relationships were evaluated using nonlinear regression with an Emax-type model. A bi-phasic mixed effects model was used to describe the viral kinetic profiles. The individual parameter estimates were then used to compute alpha phase half-life, length of alpha phase and the slope of the beta phase.

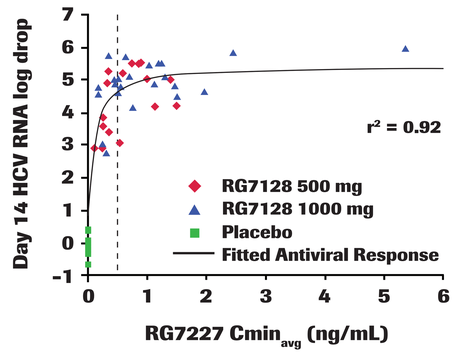
Results

Treatment with RG7128 + RG7227 resulted in potent viral suppression with median reductions in HCV RNA ranging from 4.8 to 5.2 $\log_{10}$ at the higher dose cohorts.[3] No resistance has been detected by phenotypic analysis or by population sequencing and clonal analysis.[4]

Exposure-Response Relationships

Cmin concentrations appear to be the pharmacodynamically linked variable for RG7227 antiviral activity. The relationship between RG7227 average Cmin ($Cmin_{avg}$), defined as the mean Cmin for each patient across all PK sampling days, and $\log_{10}$ HCV RNA change from baseline is shown in **Figure 1**.

Figure 1: Fitted antiviral response in treatment naive patients receiving RG7128 + RG7227



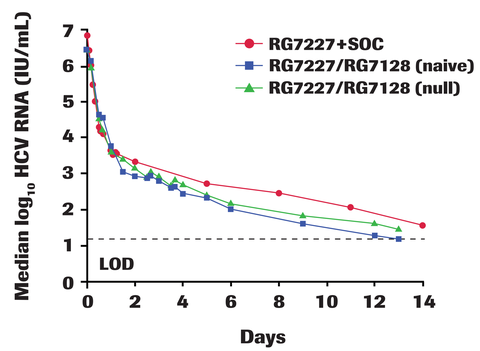
The PK/PD of RG7227 is similar when combined with either RG7128 or SOC: E_{max} (95% CI) and EC_{50} for a) RG7227 + RG7128 was 5.4 (4.99–5.85) $\log_{10}$ and 0.08 (0.04–0.13) ng/mL, respectively; and for b) RG7227 + SOC was 5.2 (4.74–5.60) $\log_{10}$ and 0.03 (-0.05–0.10) ng/mL, respectively.

As shown in **Figure 1**, all patients with an RG7227 $Cmin_{avg} > 0.5$ ng/mL achieved significant decreases in HCV RNA (median ~5.0 $\log_{10}$) by end of DAA treatment, irrespective of RG7128 dose. At RG7227 $Cmin_{avg} < 0.5$ ng/mL, it appears that the higher RG7128 dose (1000 mg) may be beneficial. Patients with an RG7227 $Cmin_{avg} < 0.5$ ng/mL achieved a median -3.6 $\log_{10}$ reduction in HCV RNA from baseline with 500 mg RG7128, compared to a -4.7 $\log_{10}$ reduction with 1000 mg.

Viral Kinetics

RG7227 demonstrated similar early viral kinetic profiles when administered in combination with either 1000 mg RG7128 or SOC **(Figure 2)**.

Figure 2: Viral kinetic profile of 900 mg bid RG7227 plus either SOC or 1000 mg bid RG7128 in naive or null Responders



Similar alpha phase VK profiles were observed with RG7227 added to either RG7128 or SOC (~3.5 logs in the first 48hr); both regimens provide highly potent inhibition of viral production. Differences in study designs between INFORM-1 and NSHC-003 (24h induction with SOC in NSHC-003) complicate direct comparisons of the alpha phase between these two studies.

The combination of RG7227 + RG7128 displayed similar beta phase viral kinetic slopes compared to RG7227 + SOC, suggesting that the IFN-free small molecule combination has potent direct antiviral activity and similarly contributes to the clearance of infected hepatocytes **(Table 1)**.

If combination with a nucleoside analogue such as RG7128 can prevent emergence of protease inhibitor resistance over longer treatment periods, treatment with RG7227 + RG7128 (with or without ribavirin) may result in a sustained virological response (SVR) in CHC.

Table 1: Median (MAD^) alpha-half-life, length of alpha phase, beta-phase slopes and % undetectable for RG7227 added to either RG7128 or SOC

RG7227 Dose	Combination	Alpha half-life (hours)	Length of Phase 1 (hours)	Beta slope (-HCVRNA Log_{10}/week)	< LLOD (%)
100 mg tid - naive	SOC			0.92 (0.49)	13
	500 mg RG7128	4.07 (1.21)	34.88 (4.16)	0.79 (0.25)	13
	1000 mg RG7128	2.72 (0.29)	30.69 (4.37)	1.23 (0.32)	29
200 mg tid - naive	SOC			1.70 (0.44)	50
	500 mg RG7128	2.98 (0.31)	32.83 (0.53)	1.22 (0.34)	25
	1000 mg RG7128	2.62 (0.13)	29.75 (1.65)	1.10 (0.21)	25
naive 600 mg bid - TE	SOC			1.12 (0.48)	13
	1000 mg RG7128	2.52 (0.23)	27.22 (4.08)	0.74 (0.43)	13
900 mg bid - naive	SOC			1.17 (0.34)	14
	1000 mg RG7128	2.53 (0.26)	29.11 (2.18)	1.13 (0.46)	63
900 mg bid-null	1000 mg RG7128	2.34 (0.19)	25.25 (2.52)	0.94 (0.17)	25

^Median Absolute Deviation
*Treatment Experienced
LLOD : lower limit of detection (<15 IU/mL for INFORM-1 and < 9.3 IU/mL NHSC-003)

Conclusions

- RG7128 demonstrated a dose-dependent enhancement of RG7227 antiviral activity, which was particularly evident at low RG7227 Cmin
- The high barrier to resistance provided by a nucleoside polymerase inhibitor is likely important for sustained suppression in protease inhibitor-containing DAA combinations
- The addition of RG7128 to RG7227 provided similar PK/PD and early viral kinetic profiles compared to the addition of SOC to RG7227
- The similarities in beta phase slopes when RG7227 is added to either SOC or RG7128 demonstrates similar viral suppression which is sustained over 2 weeks
- These results support the continued clinical development of this novel, all-oral twice daily direct-acting antiviral combination in the absence of interferon

References

1. Nájera I, McCown M, Leveque V, et al. Silibinin inhibits HCV replication in vitro. J Hepatol 2009: 50 (Suppl 1): S346
2. Zeuzem S, Sulkowski M, Lawitz E, et al. Efficacy and safety of albinterferon alfa-2b in combination with ribavirin in treatment-naive, chronic hepatitis C genotype 1 (CHC G1) patients. J Hepatol 2009: 50 (Suppl 1): S377
3. Gane EJ, Roberts SK, Stedman CA, et al. Combination Therapy With A Nucleoside Polymerase (R7128) And Protease (R7227/ITMN-191) Inhibitor In HCV:Safety, Pharmacokinetics, And Virologic Results From INFORM-1. Hepatology 2009; 50 (4; Suppl 1):394A–395A
4. Pogam S, Chhabra M, Ali, S, et al. Combination therapy with nucleoside polymerase (RG7128) and protease (RG7227) inhibitors in genotype 1 HCV infected patients: interim resistance analysis of INFORM-1 cohorts A–D. Hepatology 2009; 50 (4; Suppl 1):1037A

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