



VIRAL KINETICS MODELING OF SHORT-TERM MONOTHERAPY DATA OF ACH-1625, AN HCV PROTEASE INHIBITOR

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ABSTRACT

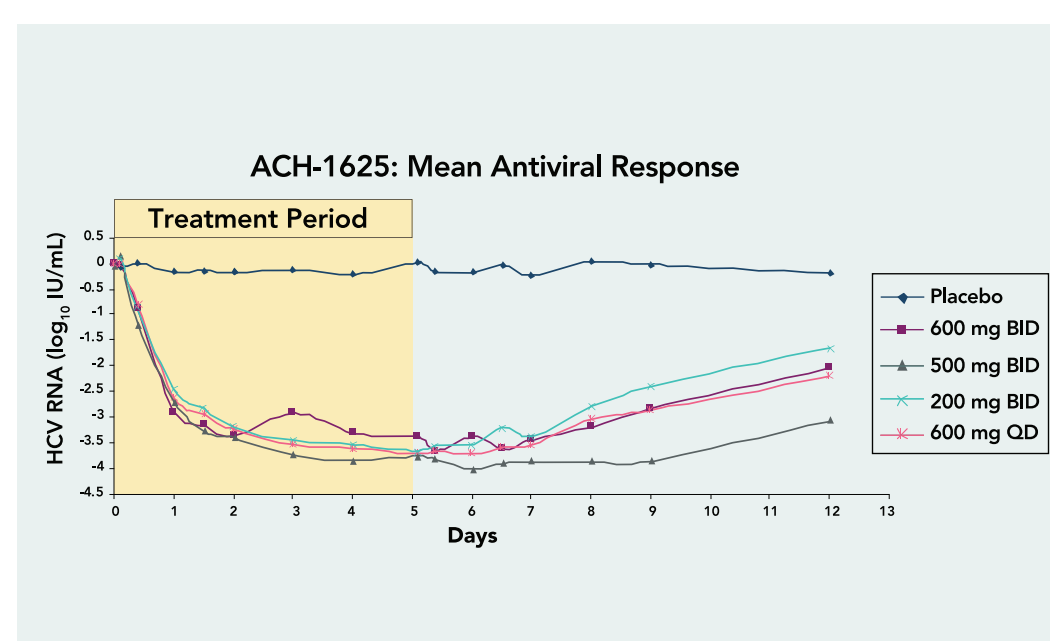
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INTRODUCTION

- HCV NS3 serine protease is a prime target of new therapies that have the potential to improve SVR rates and/or lower adverse events in patients with chronic hepatitis C when combined with standard of care (SOC).
- ACH-1625 is a potent, linear, noncovalent inhibitor of HCV NS3 protease. It binds to NS3 protease slowly and tightly with an inhibition constant at steady state (K_i^*) of 0.06 nM (GT-1b). It binds with similar potency to all genotypes (1-2; 4-6), except genotype 3.
- The mean EC_{50} value in a cell line harboring the GT-1b/Con-1 subgenomic replicon is 11 nM.
- Mutations causing resistance to ACH-1625 500 and 600 mg BID monotherapy have been identified at amino acid positions 155, 156, and 168 of NS3; despite the presence of resistant variants and drug plasma levels significantly below EC_{50} , ACH-1625 suppressed viral replication through the end of follow-up.¹
- Some mutations associated with resistance to other NS3 protease inhibitors are not cross-resistant to ACH-1625.
- ACH-1625 distributes rapidly and selectively to liver, partly due to transporter-mediated uptake.²
- ACH-1625 is safe and well tolerated at doses up to 2000 mg/day for 4.5 days duration.³
- Administration of ACH-1625 in HCV patients at doses of 200, 500, and 600 mg BID for 4.5 days and 600 mg QD for 5 days resulted in 3.86, 4.25, 3.94, and 3.81 \log_{10} mean maximum drops, of plasma HCV RNA, respectively (Figure 1).
- ACH-1625 demonstrates prolonged viral suppression, with HCV levels reduced $>1.5 \log_{10}$ 7 days after discontinuing treatment (Figure 1).
- Robust antiviral effects support once-daily dosing.¹
- ACH-1625 in combination with pegylated interferon alfa-2a and ribavirin (SOC) is currently being studied in a phase II clinical trial.

FIGURE 1. MEAN CHANGE FROM BASELINE IN HCV RNA



OBJECTIVE

- The primary objective of this work was to analyze the hepatitis C viral load decline after administration of ACH-1625 and estimate the drug efficiency.
- A second objective was to aid the dose selection of ACH-1625 to be used in combination with SOC (phase II clinical trial).

STUDY DESIGN

- HCV-infected genotype-1 patients with $>10^5$ HCV RNA at baseline, ALT $<5X$ ULN, and either naïve to prior interferon/ribavirin (IFN/RBV) therapy or have relapsed, not responded, or had an incomplete response to prior IFN/RBV treatment.
- Patients in 4 groups of 9 each were randomized to receive 4.5 or 5 days of placebo or ACH-1625 at daily doses 200, 500, or 600 mg BID or 600 mg QD.
- HCV RNA was obtained through day 12 with Cobas AmpliRep/Cobas TaqMan HCV test (LLOQ 45 IU/mL, LLOD 15 IU/mL) (Roche Molecular Diagnostics, Pleasanton, California).

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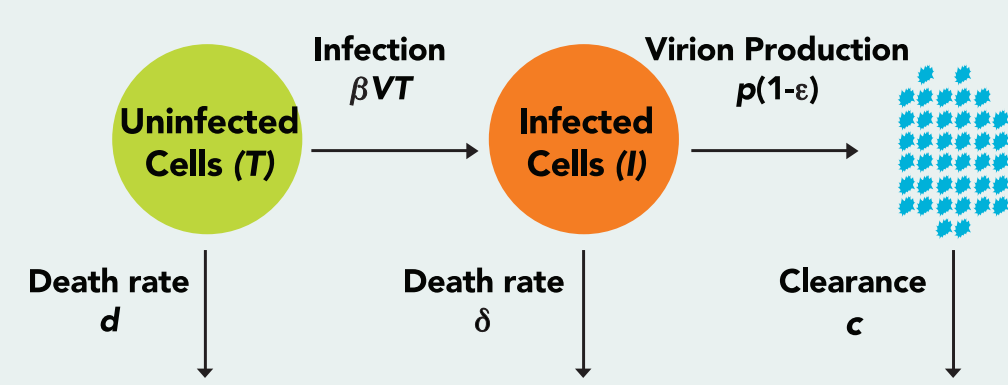
DISCLOSURES

AA, BZ, MH, and MD are employees of Achillion Pharmaceuticals, Inc.

METHODS

- HCV RNA data from subjects treated with ACH-1625 were analyzed by applying a single population viral dynamics model as described by Neumann et al⁴ (Figure 2).

FIGURE 2. VIRAL DYNAMICS MODEL



Uninfected hepatocytes become infected at a steady rate that is determined by free viral load (V), number of uninfected cells (T), and the rate of new cell infection (β). These infected cells produce virions at a constant rate (p), which are cleared from the serum at a constant rate (c). Uninfected and infected cells die at rates d and δ , respectively. Protease inhibitors inhibit virion production by the efficiency (ϵ).

- Viral kinetics parameters were estimated by solving the following equation

$$V(t) = V_0 [1 - \epsilon + \epsilon e^{-c(t-\tau)}] \quad t > \tau$$

V_0 : initial viral load c : virion clearance rate constant
 ϵ : drug efficiency τ : time delay

- These estimates of ϵ , c , and τ were substituted in the following equation to estimate the infected cell death rate constant (δ)

$$V(t) = V_0 \{ [Ae^{-\lambda_1(t-\tau)}] + [(1-A)e^{-\lambda_2(t-\tau)}] \} \quad t > \tau$$

$$\lambda_{1,2} = 1/2 \{ (c+\delta) \pm [(c-\delta)^2 + 4(1-\epsilon)c\delta]^{1/2} \}, \text{ and}$$

$$A = (\epsilon c - \lambda_2) / (\lambda_1 - \lambda_2)$$

λ_1 : slope of phase-1 of viral decay
 λ_2 : slope of phase-2 of viral decay

- The virion production rate (p) was computed as $p = cV_0L$
 L : volume of extracellular fluid in the human body
- Subsequently, the probability distribution pattern of each viral kinetics parameter in the patient population was determined following treatment with ACH-1625 or pegylated interferon alfa-2a.
- Viral kinetics parameters were then assigned at random in a set of 1000 patients *in silico* within probability distribution patterns identified. Subsequently, simulations were run to estimate viral load in these *in silico* patients at day 28 of combination (pegylated interferon alfa-2a and several doses of ACH-1625) treatment.
- Viral load estimates at day 28 were used as the criterion for selecting ACH-1625 doses for phase II clinical trial.
- Programming codes for viral kinetics modeling and simulations were developed in Matlab 7.9.0 (MathWorks, Natick, MA).

RESULTS

- All dose cohorts of ACH-1625 demonstrated a sharp phase-1 decline that is reflected in the high drug efficiency observed (Figures 3 through 6 and tables 1 and 2).

FIGURE 3. ACH-1625: 600 mg BID VIRAL DECAY: PHASE-1

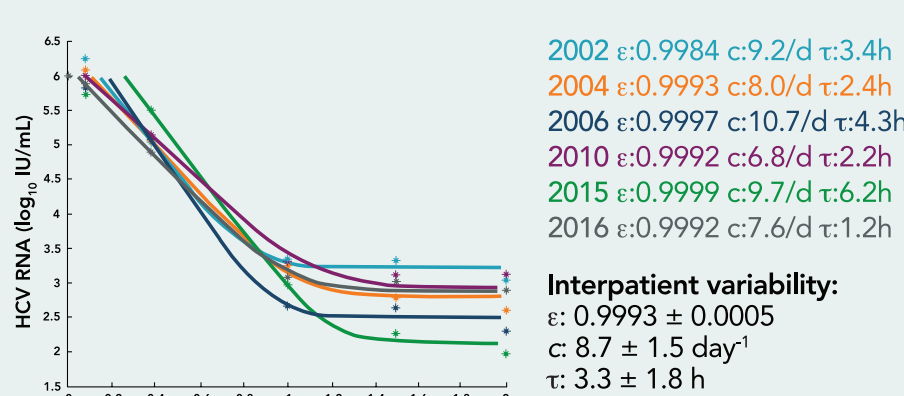


FIGURE 4. ACH-1625: 500 mg BID VIRAL DECAY: PHASE-1

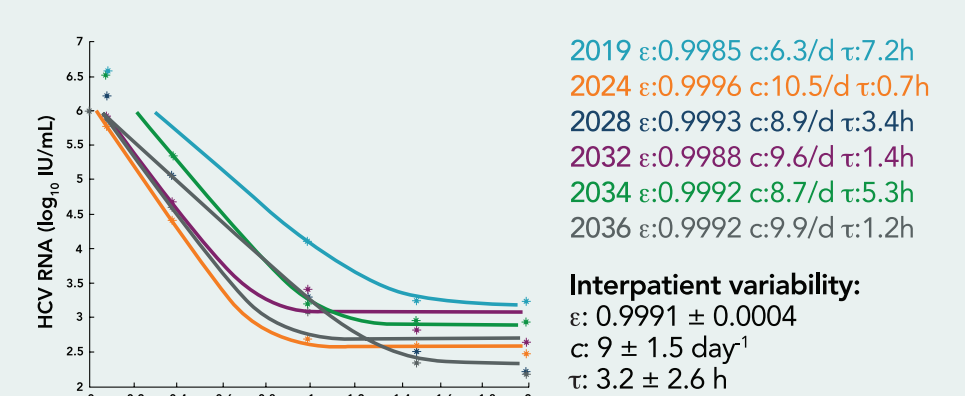


FIGURE 5. ACH-1625: 200 mg BID VIRAL DECAY: PHASE-1

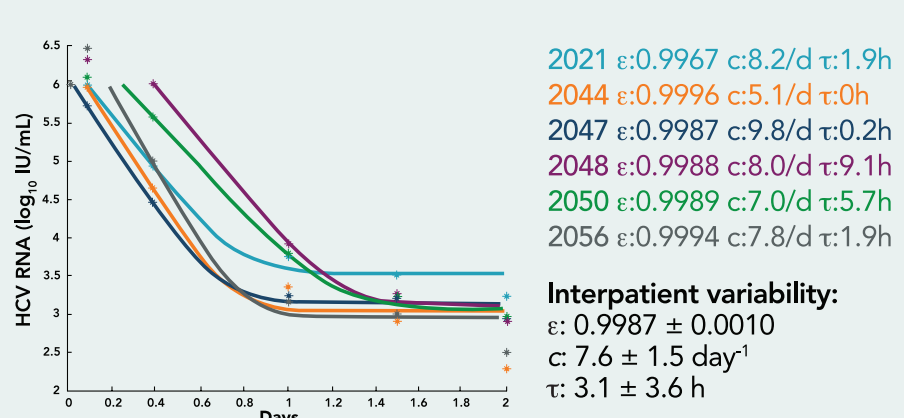


FIGURE 6. ACH-1625: 600 mg QD VIRAL DECAY: PHASE-1

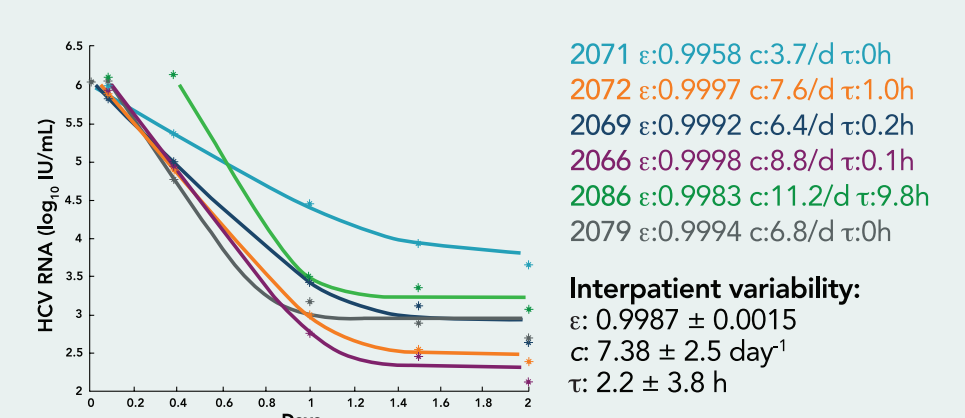


Table 1. Drug Efficiency and Time Delay

	600 mg BID	500 mg BID	200 mg BID	600 mg QD
Efficiency (ϵ)	0.9993 \pm 0.0005	0.9991 \pm 0.0005	0.9985 \pm 0.009	0.9987 \pm 0.0015
Time delay (τ)	3.3 \pm 1.8 h	3.2 \pm 2.6 h	3.8 \pm 3.3 h	2.9 \pm 3.7 h

Table 2. Treatment Independent Viral Kinetics Parameters

Parameter	Estimate
Virion clearance rate (c)	8.2 \pm 1.8 day ⁻¹
Infected cell death rate (δ)	0.21 \pm 0.17 day ⁻¹
Virion production rate (p)	1.5 X 10 ¹¹ \pm 2.0 X 10 ¹¹ day ⁻¹

- When combined with pegylated interferon alfa-2a, ACH-1625 at 400 mg QD or 800 mg QD is predicted to increase RVR >2 -fold as compared with SOC.

CONCLUSIONS

- Viral kinetics parameters obtained from modeling of ACH-1625 monotherapy are robust and demonstrate high drug efficiency.
- Antiviral therapy with ACH-1625 in combination with SOC is predicted to enhance achievement of RVR in HCV patients.
- Treatment estimates are consistent with results from other HCV protease inhibitors and indicate that ACH-1625 has the potential to significantly improve EVR and SVR when incorporated into regimens that are currently the SOC for chronic hepatitis C.^{5,6}
- ACH-1625 is currently undergoing a Phase II, randomized, double-blind, placebo-controlled trial to evaluate the safety, tolerability, and antiviral activity of oral ACH-1625 in combination with SOC.