HCV viral kinetic analysis predicts shorter treatment duration with AT-527, a purine nucleotide prodrug with potent pan-genotypic antiviral activity in HCV-infected subjects regardless of cirrhosis status

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Background

AT-527 is a novel modified guanosine nucleotide prodrug inhibitor of the hepatitis C virus (HCV) NS5B polymerase, with a favorable/highly differentiated profile compared to sofosbuvir (1,2). A clinical trial evaluating AT-527 administered as a single agent for 7 days was successfully completed, allowing for the HCV viral kinetic analysis presented herein (3).

Methods

- Subjects and Data: HCV RNA data obtained from 30 subjects in the 7-day study who received active AT-527 doses were used for the viral kinetic analyses (3):
  - Part C: Treatment-naïve (TN) non-cirrhotic (NC) subjects with genotype (GT) 1b HCV (n=6/dose) received AT-527 escalating doses of 138, 275 or 550 mg QD for 7 days (expressed as approximate free base equivalent).
  - Part D: TN NC GT3 subjects (N=6) received the 550 mg dose QD for 7 days.
  - Part E: TN cirrhotic GT1b (n=3), GT2 (n=1) or GT3 (n=2) subjects received the 550 mg dose QD for 7 days.

Key Baseline Characteristics

	Part C – GT1b NC			Part D – GT3 NC	Part E – Cirrhotic
	138 mg (N=6)	275 mg (N=6)	550 mg (N=6)	550 mg (N=6)	550 mg (N=6)
HCV RNA, mean (range) $\log_{10}$ IU/mL	5.8 (5.2-6.5)	6.2 (5.4-6.9)	6.1 (5.5-6.5)	6.5 (5.6-7.2)	6.4 (5.7-7.3)
Genotype 1b/2/3, n	6/0/0	6/0/0	6/0/0	0/0/6	3/1/2

- HCV RNA Samples:
  - Serial samples were collected prior to (0 h on study day 1) and post treatment initiation at 2, 4, 8, 12, 16, 24, 36, 48, 72, 96, 120 and 144 h (days 1-7 during dosing) and daily after completion of dosing on days 8 to 13, as well as on day 35.
  - HCV RNA levels were quantified using COBAS® AmpliPrep TaqMan® v2.0, with a lower limit of quantitation (LLQ) of 15 IU/mL (or 1.18 $\log_{10}$ IU/mL).
- Viral Kinetic Modeling and Simulation:
  - HCV viral load decline under AT-527 treatment and rebound after treatment completion was assumed to follow the standard model as described by the differential equations below (4,5):

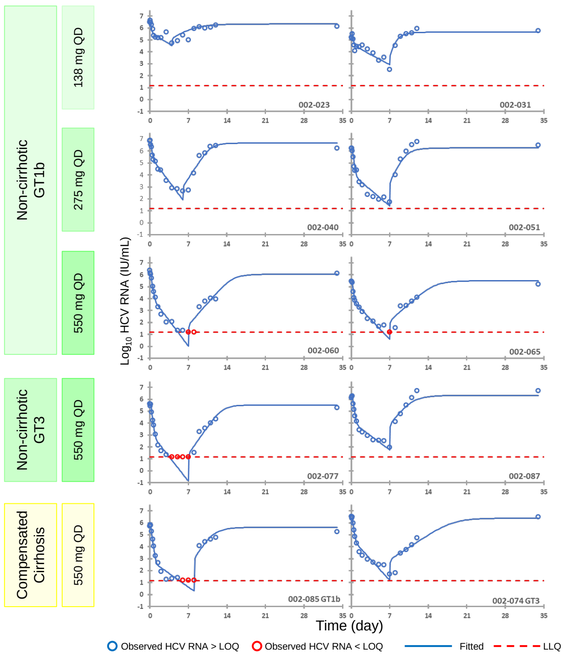
$$\frac{dT}{dt} = s - dT - \beta VT$$
$$\frac{dI}{dt} = \beta T_0 V - \delta I$$
$$\frac{dV}{dt} = (1-\varepsilon)pI - cV$$

  - Where T is the number of target hepatocytes susceptible to infection, I is the number of productively infected hepatocytes and V is the viral load. Susceptible hepatocytes are produced at rate s and die at rate d. *De novo* infection of cells occurs at rate β and the infected cells are lost at rate δ. HCV virions are produced at rate p per hepatocyte and cleared at rate c per virion.
  - Effectiveness of AT-527 in blocking viral replication is defined by ε ($0 \leq \varepsilon \leq 1$). Upon dosing completion, where $\varepsilon = 0$, viral load starts to rebound.
  - Parameter estimates and associated interindividual variability were obtained using a maximum-likelihood method by the stochastic approximation expectation-maximization (SAEM) algorithm implemented in MonolixSuite 2019R1 (Lixoft, Orsay, France).
  - Simulation was performed using Simulx for the 550 mg daily dose to estimate time to reach LLQ and cure. The latter is defined as HCV RNA < 1 IU in the entire extracellular body fluid (roughly 13.5 L): 7.5×10^{-5} or -4.13 $\log_{10}$ IU/mL.

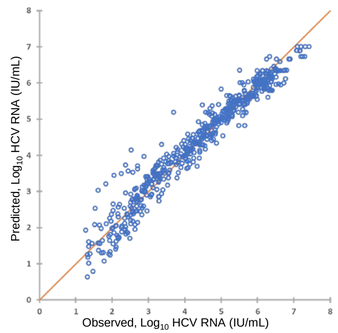
Results

Viral Kinetic Modeling

- A model incorporating pharmacologic delay (τ) as well as AT-527 dose as a covariate of (ε) was found to best describe the observed data.
- Goodness-of-Fit
  - Representative individual fitted vs. observed viral kinetics



- Predicted vs. observed HCV RNA



Population Viral Kinetic Parameter Estimates

Parameter	$\log_{10} V_0$ (IU/mL)	δ (d^{-1})	c (h^{-1})	τ (h)	ε
Estimate (±SE)	6.07±0.079	1.02±0.067	0.340±0.019	4.03±0.26	0.994±0.001

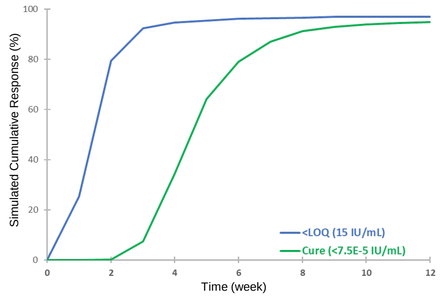
Summary (mean±SD) Individual Viral Kinetic Parameters by Cohort/Dose

Cohort	N	$\log_{10} V_0$ (IU/mL)	δ (d^{-1})	$T_{1/2}$ cell (d)	c (h^{-1})	$T_{1/2}$ HCV (h)	τ (h)	ε
138 mg GT1b NC	6	5.75±0.45	1.22±0.50	15.0±4.33	0.394±0.059	1.79±0.25	4.08±0.12	0.888±0.042
275 mg GT1b NC	6	6.12±0.34	1.22±0.44	16.0±8.24	0.335±0.030	2.09±0.18	3.84±0.19	0.976±0.013
All 550 mg	18	6.16±0.40	0.98±0.23	18.2±5.48	0.331±0.061	2.14±0.43	4.10±0.17	0.992±0.006
Overall	30	6.07±0.44	1.07±5.67	17.1±0.32	0.344±0.053	2.06±0.32	4.04±0.17	

- Viral kinetic parameter estimates were consistent across cohorts, except for ε, the effectiveness of AT-527 in blocking viral production: the 550 mg dose resulted in the highest ε which is in agreement with up to a mean of 2.4 $\log_{10}$ reduction of HCV viral load observed in the first 24 h after dosing in the 550 mg cohorts, regardless of genotypes or cirrhosis status (3).
- The estimated loss rate of infected hepatocytes (δ), about 1 d^{-1}, with AT-527 alone was faster than 0.35 day^{-1} with sofosbuvir (4). This higher loss rate with AT-527 leads to an estimated infected cell half-life of approximately 17 h, as compared to 48 h with sofosbuvir.
- The estimated clearance rate constant of HCV virions (c) and half-life were ~0.35 h^{-1} and 2.0 h respectively across cohorts. These results are in agreement with previously published data (5).
- The pharmacologic delay (τ) was estimated to be around 4 h. This is consistent with AT-527 being a nucleotide prodrug that requires multistep activation to its active triphosphate. This delay is in agreement with the plasma T_{max} (4-5 h) of AT-273, nucleoside surrogate of the intracellular active triphosphate of AT-527.

Simulation

- Simulation was performed with subjects receiving a 550 mg QD dosing regimen of AT-527 as a single agent to assess treatment duration required to achieve a cure, defined as plasma HCV RNA < 1 IU/mL (-4.13 $\log_{10}$/mL). Time to reach plasma HCV RNA < LLQ was also evaluated.

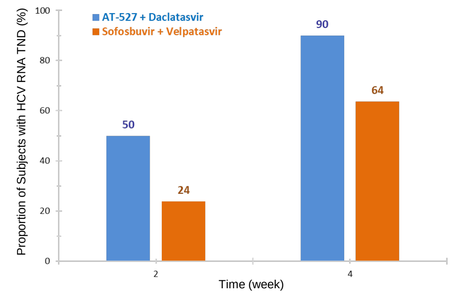


Simulation results showed that with AT-527 as a single agent at 550 mg/day:

- About 80% and 95% of subjects would have plasma HCV RNA < LLQ by wk 2 and 4 respectively.
- Approximately 80% and >90% of subjects would achieve a cure with 6 and 8 wks of treatment, regardless of HCV genotype or cirrhosis status.

On-Treatment Response from an On-Going Phase II Study of AT-527 plus Daclatasvir

- AT-527 plus daclatasvir was well-tolerated for 8-12 weeks in HCV GT1 treatment-naïve subjects (N=10).
- High proportions of subjects achieved HCV RNA target not detected (TND) at week 2 (50%) and week 4 (90%), with all subjects achieving TND at end of treatment. These on-treatment response rates are much higher than those observed with sofosbuvir plus velpatasvir (6).
- The very rapid early viral kinetics with AT-527 plus daclatasvir allowed for an 8 week treatment duration in all but one subject. SVR results are pending.



Conclusions

- Viral kinetic analysis based on data generated from 7-day dosing of AT-527 as a single agent suggests that >90% of all patients should be cured with 8 weeks of treatment.
- Interim data from an on-going pilot study with AT-527 plus daclatasvir, the only commercially available standalone NS5A inhibitor, suggest that high cure rates and shorter treatment duration may be achieved with a AT-527 containing regimen, as compared to sofosbuvir-containing regimens.
- A highly effective single-tablet once daily pan-genotypic short treatment regimen with less drug-drug-interaction potential will greatly simplify the care for chronic hepatitis C especially in patients with cirrhosis.

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