AT-527, a purine nucleotide prodrug, exhibits potent pan-genotypic antiviral activity in HCV-infected subjects with cirrhosis

X.J. ZHOU[1], E. BERLIBA[2], M. BOGUS[2], F. VANHOUTTE[3], P.J. BERGHMANS[3], S. GOOD[1], A. MOUSSA[1], K. PIETROPAOLO[1], R. MURPHY[1,4] and J.P. SOMMADOSSI[1]

[1]Atea Pharmaceuticals, Inc., Boston, MA, USA, [2]ARENSIA Exploratory Medicine, Republican Clinical Hospital, Chisinau, Moldova, [3]SGS Life Sciences, Antwerp, Belgium and [4]Northwestern University, Chicago, IL, USA

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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 and highly differentiated antiviral profile compared to sofosbuvir (SOF) (1,2). AT-527 was well tolerated in healthy subjects and non-cirrhotic (NC) HCV-infected subjects, with similar plasma pharmacokinetics (PK) between the populations (3). AT-527 exhibited profound genotype (GT)-independent antiviral activity following 550 mg (free base) QD dosing for 7 days in NC GT1b and NC GT3 HCV-infected subjects (4). Despite the approval of multiple DAA regimens, treatment of cirrhotic subjects remains challenging. Here we report the safety, PK and antiviral activity of AT-527 in cirrhotic HCV-infected subjects in comparison to NC subjects.

Methods

- Treatment-naïve subjects with Child-Pugh A (CPA) cirrhosis and HCV RNA ≥ 5 $\log_{10}$ received open-label AT-527 550 mg QD for 7 days. HCV-infected subjects with GT 1, 2, 3, 4, 5 or 6 were eligible. Cirrhosis was confirmed by Fibroscan® > 12.5 kPa.
- Plasma levels of AT-273, nucleoside metabolite of the active triphosphate (TP) of AT-527, were measured using LC-MS/MS; HCV RNA was quantified using COBAS® AmpliPrep/TaqMan® HCV Test v2.0 with a limit of quantitation (LOQ) of 15 IU/mL.
- Data for cirrhotic subjects are summarized with comparison to previously reported data obtained from NC GT1b and NC GT3 subjects who received the same dose and duration of AT-527.
  - As PK was not impacted by GT, subjects with differing GTs were pooled based on cirrhosis status for the PK analysis.
  - Data obtained from the previously reported lower dose cohorts were used in the E_{max} model.

Results

Demographics

	AT-527 550 mg x 7 days		
	NC GT1b (N=6)	NC GT3 (N=6)	Cirrhotic (N=6)
Age, mean yrs (range)	45 (29-62)	38 (30-44)	53 (39-63)
Weight, mean kg (range)	68.8 (57.1-94.0)	75.3 (59.8-94.2)	80.7 (65.0-105.0)
Male/Female, n	2/4	6/0	2/4
Caucasian, n	6	6	6
HCV RNA, mean $\log_{10}$ IU/mL (range)	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	0/0/6	3#/1/2
ALT, mean U/L (range)	45.7 (10-79)	87.8 (46-170)	42.5 (24-63)
Fibroscan®, mean kPa (range)	6.2 (3.3-9.6)	6.9 (4.5-11.0)	20.6 (13.8-31.6)

#Two subjects (one NC and one cirrhotic) had GT1 w/undetermined sub-type.

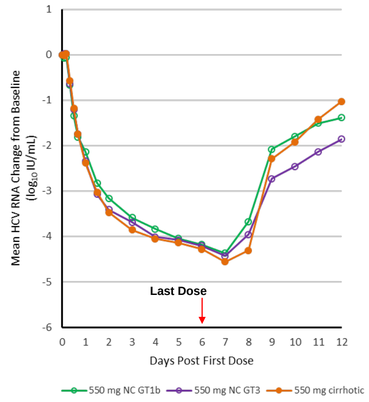
- **Compared to NC subjects, HCV-infected subjects with cirrhosis were older with higher baseline Fibroscan® results.**
- **NC GT3-infected subjects and cirrhotic subjects had slightly higher baseline viral loads.**

Safety Summary

Most common AEs (reported in > 1 subject), n (%)	AT-527 550 mg x 7 days		
	NC GT1b (N=6)	NC GT3 (N=6)	Cirrhotic (N=6)
Blood cholesterol increased	2 (33)	2 (33)	1 (17)
Blood triglycerides increased	1 (17)	1 (17)	1 (17)
Platelet count decreased	0	0	2 (33)

- **No serious adverse events, dose-limiting toxicities or premature discontinuations**
- **Comparable safety across cohorts**
- **One asymptomatic, isolated grade 4 elevation of triglycerides occurred in a NC GT3-infected subject three days after last dose, which was assessed as unrelated to study drug. All other AEs were mild or moderate in intensity.**
- **Two cirrhotic subjects had AEs of platelet count decreased (86 x 10^9/L and 87 x 10^9/L) which were assessed as unrelated to study drug by the investigator. As these subjects also had platelet counts below the lower limit of normal prior to dosing, the investigator assessed the events as probably related to underlying cirrhosis and disease activity.**
  - **Thrombocytopenia was not observed in any other subjects; mean/individual platelet counts were stable over time across all other cohorts.**
- **No clinically relevant or dose related patterns in vital signs or ECGs.**

Mean HCV RNA Change After Multiple Doses of AT-527 550 mg



NC=Non-cirrhotic

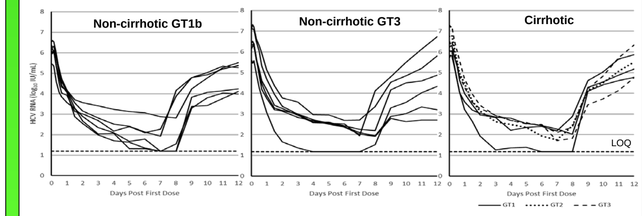
Maximum HCV RNA Change

Maximum Reduction ($\log_{10}$ IU/mL)	AT-527 550 mg x 7 days		
	NC GT1b (N=6)	NC GT3 (N=6)	Cirrhotic (N=6)
Mean±SD	4.4±0.712	4.5±0.262	4.6±0.485
Individual	3.5, 4.0, 4.1, 4.3#, 5.2, 5.3	4.2, 4.4, 4.4, 4.5, 4.5, 5.0	GT1: 4.0#, 4.0, 4.5 GT2: 5.0 GT3: 4.8, 5.2

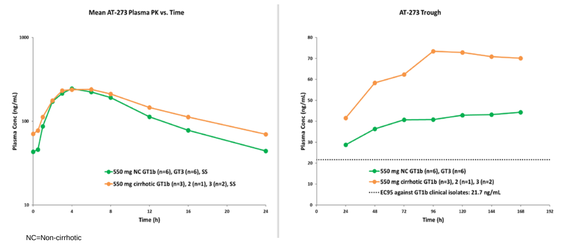
#Undetermined sub-type.

- **In CPA cirrhotic HCV-infected subjects, mean maximum HCV RNA reduction was 4.6 $\log_{10}$ IU/mL after 7 days of dosing with AT-527 550 mg. These results were similar to those previously observed in the NC cohorts, with mean maximum HCV RNA reductions of 4.4 $\log_{10}$ IU/mL for NC GT1b and 4.5 $\log_{10}$ IU/mL for NC GT3.**
- **Similar to the NC cohorts, viral load reduction was rapid with a mean HCV RNA reduction of 2.4 $\log_{10}$ IU/mL after the first dose in cirrhotic subjects.**
- **AT-527 exhibited equally potent antiviral activity regardless of genotype or cirrhosis status**

Individual HCV RNA After Multiple Doses of AT-527 550 mg



Plasma PK and Trough Profiles of AT-273 at Steady-State After Multiple Doses of AT-527 550 mg



NC=Non-cirrhotic

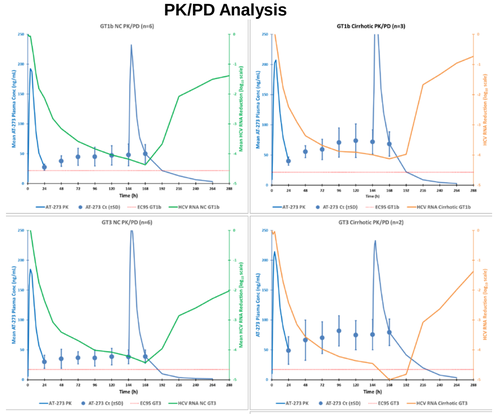
PK Parameters for AT-273 at Steady-State After Multiple Doses of AT-527 550 mg

Dose (mg/d)	C_{max} (ng/mL)	T_{max} (h)	AUC_τ (ng/mLxh)	$T_{1/2}$ (h)	C_τ (ng/mL)
NC (n=12)	248±77.3	4.0 (4.0-6.0)	2978±818	28.4±15.7	44.3±14.1
Cirrhotic (n=6)	255±95.4	6.0 (4.0-6.0)	3569±1214	24.4±9.81	70.1±18.2

NC=Non-cirrhotic
Values are reported as mean ± SD, except tor T_{max} where median (range) is reported.

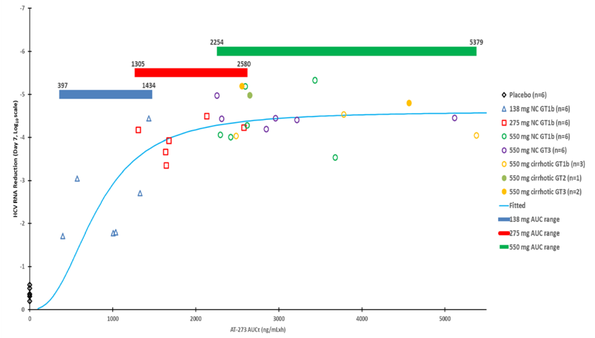
- **AT-511, the free base of AT-527, was rapidly and well absorbed with estimated fraction absorbed approximating 50% based on urinary recovery (data not shown).**
- **AT-273, the nucleoside metabolite of the active TP, exhibited dose-proportional plasma PK with a long half-life supporting QD dosing.**
- **Upon repeat QD dosing of AT-527, steady state of AT-273 was reached after 3-4 days in each of the cohorts.**
- **PK of AT-273 was similar in non-cirrhotic and cirrhotic subjects.**

PK/PD Analysis



- From first dose, AT-273 trough levels exceeded EC_{95} of AT-511 in inhibiting replicons containing HCV GT1b (~22 ng/mL), GT2 (~12 ng/mL) and GT3 (~18 ng/mL) constructs of clinical isolates.
  - Leading to profound early response
- Steady-state AT-273 troughs in cirrhotic subjects were 3- to 6-fold the EC_{95} values.

E_{max} Model: Relationship Between AT-273 AUC_τ and HCV RNA Change from Baseline After 7 Days of AT-527 Treatment



NC=Non-cirrhotic

- **E_{max} model predicts AT-273 exposures ≥ 2000 ng/mLxh will result in maximal viral load reduction of at least 4 log after 7 days of QD dosing with AT-527.**
- **550 mg dose results in AT-273 AUC_τ consistently above this exposure threshold.**
  - **Lower bound of 95% C.I. excludes 2000 ng/mLxh**

Conclusions

- As in non-cirrhotic subjects, AT-527 550 mg was well tolerated after multiple doses in Child-Pugh A cirrhotic HCV-infected subjects.
- As in non-cirrhotic subjects, rapid and potent pan-genotypic antiviral activity was observed in HCV-infected subjects with cirrhosis (including cirrhotic subjects with GT3 infection), with mean HCV RNA reduction of 2.4 $\log_{10}$ IU/mL after a single dose and mean maximum HCV RNA reduction of 4.6 $\log_{10}$ IU/mL after 7 days of dosing with AT-527 550 mg.
- PK in cirrhotic subjects was similar to non-cirrhotic subjects.
- PK/PD analysis indicated that antiviral activity correlated with plasma exposure of AT-273.
  - From the first dose of AT-527, plasma levels of the nucleoside metabolite AT-273 exceeded its EC_{95} in inhibiting replicons containing HCV GT1b, GT2 or GT3 constructs of clinical isolates, leading to profound early viral response.
- E_{max} modeling demonstrated that a dose of 550 mg QD will result in maximal viral load reduction.
- These data support Phase 2 clinical development of AT-527.

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