AT-527, a pan-genotypic purine nucleotide prodrug, exhibits potent antiviral activity in subjects with chronic hepatitis C

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Abstract THU-341

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Introduction

AT-527 is a novel salt form purine nucleotide prodrug NS5B polymerase inhibitor in clinical development for treatment of chronic hepatitis C virus (HCV) infection. AT-527 possesses a favorable and highly differentiated antiviral profile compared to sofosbuvir (SOF). AT-511, free base of AT-527, showed potent antiviral activity *in vitro* against wild-type clinical isolates with EC_{95} <80 nM in all HCV genotypes, being ~10- to 14-fold more potent than SOF in genotype 1 and 3 replicons. AT-511 maintained activity against SOF-resistant S282T single and S282T/L159F double variants with ~50-fold greater potency than SOF (1,2).

Aim and Methods

- Aim: Safety/tolerability, pharmacokinetics (PK) and antiviral activity
- Methods: Multiple part study evaluating single oral doses up to 367 mg (400 mg salt form) in healthy subjects (Part A), single doses up to 550 mg (600 mg salt form) in non-cirrhotic (NC) genotype (GT) 1 HCV-infected subjects (Part B) and multiple doses up to 550 mg once daily (QD) for 7 days in NC GT1 HCV-infected subjects (Part C). Ongoing cohorts are evaluating 550 mg QD for 7 days in NC GT3 (Part D) and Child-Pugh A (CPA) cirrhotic GT1/3 (Part E) HCV-infected subjects.
- Parts A/C: placebo (pbo)-controlled and double-blinded; Parts B/D: open-label
- Doses reflect AT-511 free base equivalent, with dose of AT-527 salt form referenced above in parenthesis.
- HCV-infected subjects were treatment-naïve with HCV RNA ≥ 5 $\log_{10}$ IU/mL. Cirrhosis confirmed by prior liver biopsy or Fibroscan > 12.5 kPa.
- Plasma levels of AT-273, nucleoside metabolite of the active triphosphate (TP), measured using LC-MS/MS; HCV RNA quantified using COBAS® AmpliPrep/TaqMan® HCV Test v2.0 with a limit of quantitation (LOQ) of 15 IU/mL.
- Part A/partial Part B data (low dose cohorts) were previously reported (3). Here we summarize:
  - Part B (GT1b, non-cirrhotic): antiviral activity data from the high single dose cohort (n=3)
  - Part C (GT1b, non-cirrhotic): data from all multiple dose cohorts (n=8/cohort)
  - Part D (GT3, non-cirrhotic): data from 4 of up to 6 subjects planned (ongoing)
  - Part E (GT1b or 3, CPA cirrhotic): data from 2 of up to 6 subjects planned (ongoing)

Results

Demographics

	Part C* – GT1b			Part D – GT3	Part E – Cirrhotic
	138 mg or Pbo x 7 days (N=8)	275 mg or Pbo x 7 days (N=8)	550 mg or Pbo x 7 days (N=8)	550 mg x 7 days (N=4)	550 mg x 7 days (N=2)
Age, mean yrs (range)	45 (31-64)	44 (31-58)	43 (29-62)	39 (30-44)	48 (42-53)
Weight, mean kg (range)	86.5 (60.7-121.0)	76.1 (62.5-106.0)	68.0 (56.0-94.0)	76.8 (68.3-94.2)	71.0 (68.5-73.4)
Male/Female, n	6/2	4/4	3/5	4/0	1/1
Caucasian, n	8	8	8	4	2
HCV RNA, mean $\log_{10}$ IU/mL	5.9	6.3	6.0	6.6	6.4
Genotype 1b/3, n	8/0	8/0	8#/0	0/4	1/1

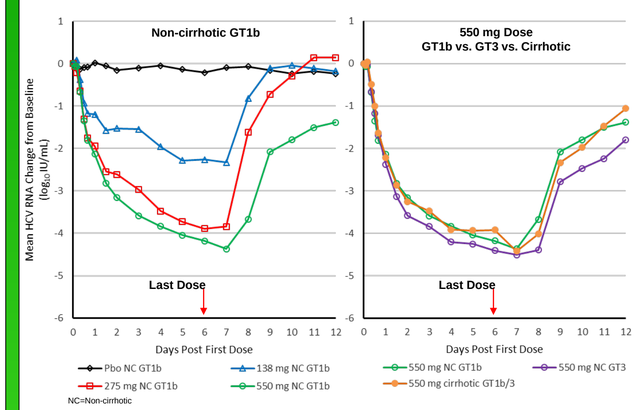
*6 active:2 pbo pooled in each cohort to preserve blind, as study ongoing ; #1 subject had GT1 w/undetermined sub-type

Safety Summary

AE, n (%)	Part C – GT1b				Part D – GT3	Part E – Cirrhotic
	Pbo x 7 days (N=6)	138 mg x 7 days (N=6)	275 mg x 7 days (N=6)	550 mg x 7 days (N=6)	550 mg x 7 days (N=4)	550 mg x 7 days (N=2)
Subjects experiencing at least one AE	4 (67)	3 (50)	3 (50)	2 (33)	2 (50)	1 (50)
Serious AE	0	0	0	0	0	0
Grade ≥ 3 AE	0	0	0	0	1 (25)	0

- **No serious adverse events, dose-limiting toxicities or premature discontinuations**
- **No relationship to dose with reported adverse events (AEs)**
- **One asymptomatic, isolated grade 4 elevation in triglycerides three days after last dose, assessed as unrelated to study drug. All other AEs were mild or moderate in intensity.**
- **No clinically significant changes in vital signs or ECGs.**

Mean HCV RNA Change After Multiple Doses of AT-527

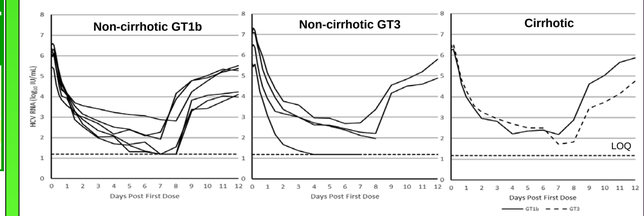


Maximum HCV RNA Change

Maximum Reduction ($\log_{10}$ IU/mL)	Part B – GT1b	Part C – GT1b				Part D – GT3	Part E – Cirrhotic
	550 mg x 1 day (N=3)	Pbo x 7 days (N=6)	138 mg x 7 days (N=6)	275 mg x 7 days (N=6)	550 mg x 7 days (N=6)	550 mg x 7 days (N=4)	550 mg x 7 days (N=2)
Mean±SD	2.3±0.255	0.4±0.136	2.6±1.071	4.0±0.416	4.4±0.709	4.6±0.272	4.4±0.541
95% C.I.	--	0.2-0.5	1.5-3.7	3.5-4.4	3.7-5.1	4.1-5.0	--

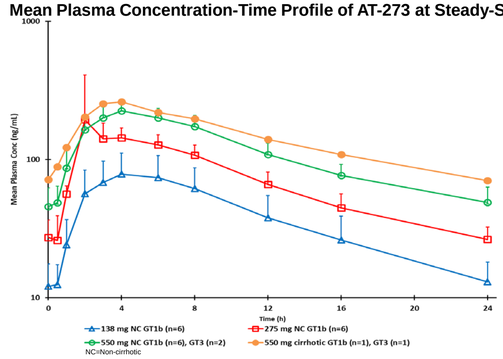
- **In Part B, a single 550 mg dose of AT-527 administered to non-cirrhotic GT1b HCV-infected subjects (n=3) resulted in mean maximum HCV RNA reduction of 2.3 $\log_{10}$ IU/mL. Individual maximum HCV RNA reductions were 2.1, 2.3 and 2.6 $\log_{10}$ IU/mL.**
- **In Part C, dose-related antiviral activity was observed after 7 days of dosing, with mean maximum HCV RNA reduction up to 4.4 $\log_{10}$ IU/mL in non-cirrhotic GT1b HCV-infected subjects.**
  - **50% of subjects achieved HCV RNA < LOQ**
- **In Part D, potent antiviral activity was observed in non-cirrhotic GT3 HCV-infected subjects, with mean maximum HCV RNA reduction of 4.6 $\log_{10}$ IU/mL.**
  - **Mean HCV RNA reduction was 2.4 $\log_{10}$ IU/mL after the first dose**
  - **One subject achieved HCV RNA < LOQ within four days after the first dose**
- **In ongoing Part E, antiviral activity in CPA cirrhotic HCV-infected subjects was similar to non-cirrhotic GT1b and GT3 cohorts.**

Individual HCV RNA After 550 mg AT-527 Dosing



- **AT-527 exhibited equally potent antiviral activity regardless of genotype or cirrhosis status**

Mean Plasma Concentration-Time Profile of AT-273 at Steady-State



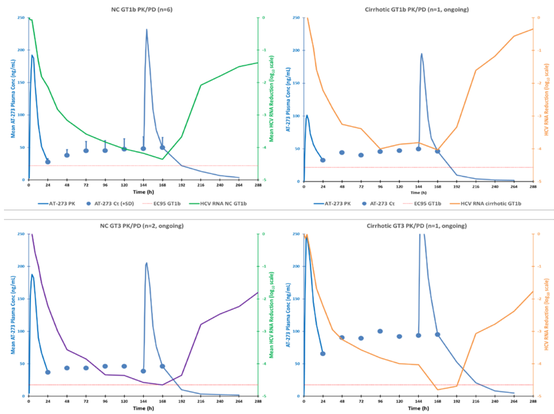
PK Parameters for AT-273 at Steady-State

Dose (mg/d)	C_{max} (ng/mL)	T_{max} (h)	AUC_τ (ng/mLxh)	$T_{1/2}$ (h)	C_τ (ng/mL)
138 NC (n=6)	81.1±33.9	4.0 (4.0-8.0)	962±409	14.0±7.77	12.8±4.5
275 NC (n=6)	220±203	4.0 (2.0-6.0)	1828±453	27.3±16.9	26.1±7.6
550 NC (n=8)	226±43.5	4.0 (4.0-6.0)	2813±550	31.9±10.8	46.2±14.1
550 Cirrhotic (n=2)	195, 326	4.0, 4.0	2483, 4567	21.2, 40.1	45.7, 93.9

NC=Non-cirrhotic
Values are reported as mean ± SD, except for T_{max} where median (range) is reported.
Individual data shown for the two cirrhotic subjects.

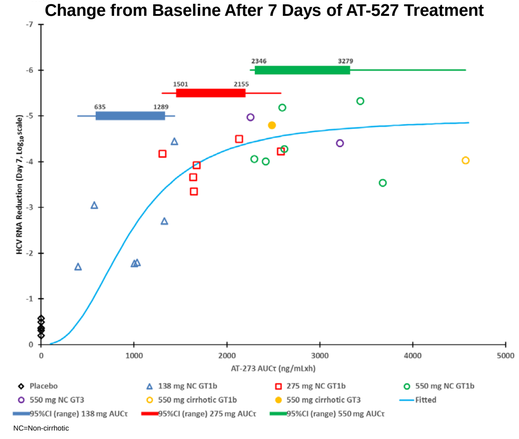
- **AT-511, the free base of AT-527, was rapidly and well absorbed with estimated fraction absorbed approximating 50% based on urine recovery (data not shown).**
- **AT-273, the nucleoside metabolite of the active TP, exhibited dose-proportional plasma PK with a long half-life supporting QD dosing.**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

PK/PD Analysis



- **Steady state plasma trough levels of AT-273 after 550 mg QD AT-527 dosing consistently exceeded the EC_{95} of AT-511 in inhibiting replicons containing HCV GT1b (~21.7 ng/mL) and GT3 (17.5 ng/mL) constructs of clinical isolates.**

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



- **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

- AT-527 was well tolerated after multiple doses in HCV-infected subjects.
- Potent antiviral activity was observed in non-cirrhotic GT1b HCV-infected subjects, with mean maximum HCV RNA reductions of 2.3 $\log_{10}$ IU/mL after a single dose and 4.4 $\log_{10}$ IU/mL after 7 days of dosing with 550 mg AT-527.
- Potent antiviral activity was also observed in non-cirrhotic GT3 HCV-infected subjects, with mean maximum HCV RNA reductions of 4.6 $\log_{10}$ IU/mL after 7 days of dosing with 550 mg AT-527.
- Preliminary data in HCV-infected subjects with cirrhosis suggest similar potent antiviral activity of AT-527.
- After multiple oral doses, plasma exposure of AT-273, the nucleoside metabolite of the active TP, was dose-proportional with a long half-life ($T_{1/2}$ >30 h) supporting QD dosing.
  - PK was similar in non-cirrhotic and cirrhotic subjects.
- PK/PD analysis indicated that antiviral activity correlated with plasma exposure of AT-273.
- E_{max} modeling demonstrates that doses of 550 mg QD will result in maximal viral load reduction.
- These data support Phase 2 clinical development of AT-527, which has best-in-class potential.

References

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Acknowledgements

The authors would like to thank the subjects who participated in this study. In addition, thanks to the staff at SGS Life Sciences and ARENSIA Exploratory Medicine.

Disclosures: XJZ, SG, AM, KP and JPS are employees of Atea Pharmaceuticals. RM is a consultant to Atea Pharmaceuticals.