A Phase 1a Study of AT-527, a Novel Pan-Genotypic Purine Nucleotide Prodrug Inhibitor of Hepatitis C Virus (HCV)

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Background

Despite the high burden of hepatitis C virus (HCV) infection globally, there remains only a single nucleoside analog (sofosbuvir, SOF) available for use in combination with other direct-acting antivirals. The duration of SOF-containing regimens is 12 weeks for most populations. AT-527 is the salt form of a novel purine nucleotide analog prodrug in clinical development for the treatment of chronic HCV infection. The active triphosphate (TP) metabolite of AT-527 is a potent and specific inhibitor of the HCV NS5B polymerase (1,2). Unique structure modifications have conferred AT-527 with pharmacologic and antiviral properties that are differentiated from other anti-HCV nucleosides. AT-511, the free base of AT-527, was > 10-fold more active than SOF in Huh-7 cells bearing the genotype (GT) 1b replicon, with an EC_{95} of ~25nM. AT-511 showed potent pan-genotypic anti-HCV activity *in vitro* with up to 14-fold greater potency than SOF against clinical isolates harboring wild-type GT 1-4 HCV. AT-511 maintains its activity against the HCV S282T variant, with ~50-fold greater potency than SOF. GLP toxicology studies provided > 200-fold safety margin at the clinical starting dose.

Methods

Part A

- Design: Single ascending dose study; randomized, placebo (pbo)-controlled and double-blinded
- Population: Healthy male and female subjects, 18-65 years old
- Objectives: Safety/tolerability and pharmacokinetics (PK)

Cohort	Population	N (active: pbo)	AT-527 Dose (free base)	Status
1a	Healthy	6:2	50 (45) mg x 1	Complete
2a	Healthy	6:2	100 (90) mg x 1	Complete
3a	Healthy	6:2	200 (180) mg x 1	Complete
4a	Healthy	6:2	400 (360) mg x 1	Complete

Part B

- Design: Single ascending dose study; open-label
- Population: Treatment-naïve, GT1 HCV-infected subjects, HCV RNA ≥ 5 $\log_{10}$ IU/mL, non-cirrhotic
- Objectives: Safety/tolerability, PK and antiviral activity

Cohort	Population	N	AT-527 Dose (free base)	Status
1b	GT1 HCV-Infected	3	100 (90) mg x 1	Complete
2b	GT1 HCV-Infected	3	300 (270) mg x 1	Complete
3b	GT1 HCV-Infected	3	400 (360) mg x 1	Ongoing

- Clinical doses above are expressed in terms of the AT-527 salt, with the approximate AT-511 free base equivalent in parenthesis.

Results

Demographics – Part A, Healthy Subjects

	50 mg or pbo (N=8)	100 mg or pbo (N=8)	200 mg or pbo (N=8)	400 mg or pbo (N=8)
Age, mean (range) (yrs)	51 (38-65)	50 (26-63)	49 (30-65)	50 (23-65)
Weight, mean (range) (kg)	71.9 (62.5-82.3)	75.8 (53.1-93.5)	68.7 (55.2-81.1)	78.1 (61.9-93.7)
Male/Female (n)	4/4	4/4	4/4	5/3
Caucasian (n)	8	8	8	8

Demographics – Part B, HCV-Infected Subjects

	100 mg (N=3)	300 mg (N=3)
Age, mean (range) (yrs)	44 (37-53)	52 (46-55)
Weight, mean (range) (kg)	63.4 (51.0-80.0)	84.7 (67.0-107.0)
Male/Female (n)	2/1	0/3
Caucasian (n)	3	3
HCV RNA, mean ($\log_{10}$ IU/mL)	6.1	5.7
Genotype 1a/1b (n)	0/3	0/3

Adverse Events in ≥ 2 Subjects (Blinded) – Part A, Healthy Subjects

	50 mg or pbo (N=8)	100 mg or pbo (N=8)	200 mg or pbo (N=8)	400 mg or pbo (N=8)
Headache	2	2	3	2
Low back pain	0	2	2	2
Diarrhea	2	0	0	0
Nausea	1	1	0	1

Adverse Events – Part B, HCV-Infected Subjects

	100 mg (N=3)	300 mg (N=3)
Headache	2	0
Urinary tract infection	1	0

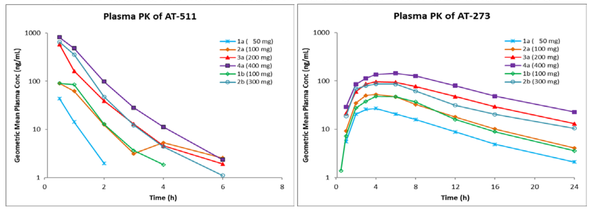
- ❖ **As the study and data management activities are ongoing, active and placebo recipients were pooled within each Part A cohort to preserve the study blind.**
- ❖ **No serious adverse events or premature discontinuations; all adverse events (AEs) were mild/moderate in intensity; no dose-related patterns were evident, including laboratory parameters, vital signs and ECGs.**

PK of AT-511 (Free Base) and AT-273 (Nucleoside Metabolite of Active TP) after a Single Dose of AT-527

	Dose (mg)	C_{max} (ng/mL)	T_{max} (h)	AUC_{tot} (ng/mLxh)	$T_{1/2}$ (h)	C_{24h} (ng/mL)
Part A, Healthy Subjects						
AT-511	50	46.4±17.6	0.5 (0.5-0.5)	36.4±12.3	0.32±0.02	--
	100	156±96.3	0.5 (0.5-1.0)	167±110	0.53±0.24	--
	200	818±443	0.5 (0.5-3.0)	656±255	0.71±0.16	--
	400	1194±401	0.5 (0.5-1.0)	1108±326	0.86±0.15	--
AT-273	50	27.9±5.62	3.5 (3.0-4.0)	285±69.4	7.07±4.59	2.28±0.95
	100	56.6±14.0	4.0 (3.0-6.0)	663±242	17.7±14.7	4.45±1.87
	200	111±38.8	5.0 (3.0-6.0)	1524±497	15.9±7.95	13.7±5.09
	400	153±49.4	6.0 (4.0-8.0)	2342±598	15.6±6.37	23.5±6.31
Part B, HCV-Infected Subjects						
AT-511	100	212±32.0	0.5 (0.5-1.0)	179±54.4	0.54±0.12	--
	300	871±590	0.5 (0.5-1.0)	818±475	0.67±0.14	--
AT-273	100	50.2±15.4	6.0 (4.0-6.0)	538±103*	8.4±4.3*	3.60±0.40
	300	96.9±38.9	6.0 (3.0-6.0)	1131±273*	8.1±2.4*	10.9±3.51

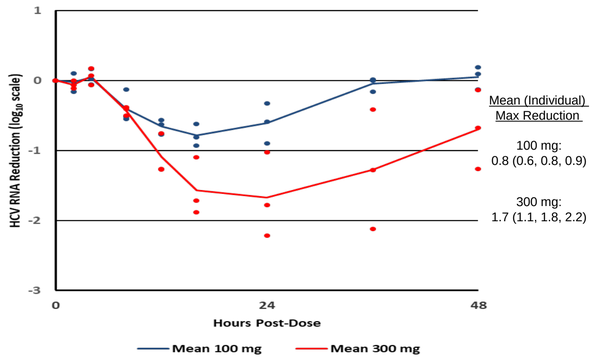
Values are reported as mean ± SD, except for T_{max} where median (range) is reported. *Based on 24-hr profile.

Mean Plasma Concentration-Time Profiles of AT-511 and AT-273



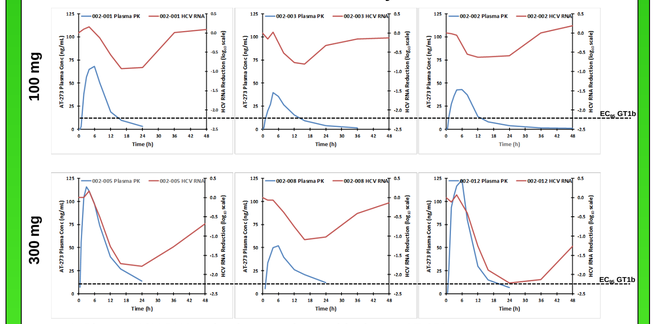
- ❖ **AT-511 was quickly absorbed and rapidly/extensively metabolized.**
- ❖ **AT-273, the guanosine nucleoside considered a surrogate of intracellular phosphates including the active TP, was a major metabolite and exhibited sustained plasma concentrations.**
- ❖ **Plasma exposure of AT-511 was dose-related while exposure of AT-273 was mostly dose-proportional in the studied dose range.**
- ❖ **PK was comparable in healthy subjects and HCV-infected subjects.**

Mean and Individual HCV RNA Change from Baseline After a Single Dose of AT-527



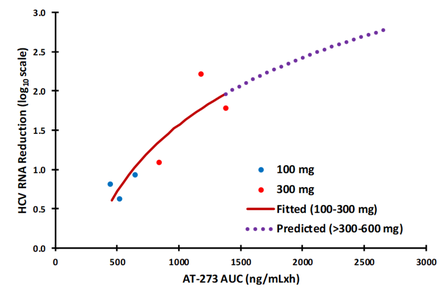
- ❖ **A single 300 mg dose of AT-527 (270 mg free base equivalent) resulted in significant antiviral activity in GT1b HCV-infected subjects, with a mean maximum HCV RNA reduction of 1.7 $\log_{10}$ IU/mL.**

Individual PK/PD Analysis

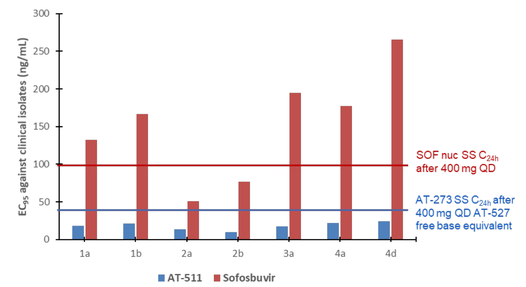


- ❖ **Plasma HCV RNA reduction correlates with plasma AT-273 exposure.**
- ❖ **Viral response is sustained with AT-273 plasma concentrations > EC_{95} against GT1b.**

Predicted Maximum HCV RNA Reduction vs. AT-273 AUC Achievable after a Single Dose of AT-527 up to 600 mg



Predicted Steady-State Trough Levels of AT-273 Exceed AT-511 EC_{95} against Clinical Isolates of HCV GT 1-4



- ❖ **Predicted steady-state (SS) trough plasma levels (C_{24h}) of AT-273 after 400 mg QD free base equivalent dosing of AT-527 exceed the *in vitro* EC_{95} of AT-511 against all tested clinical isolates of GT 1-4 HCV-infected patients.**
  - **SS C_{24h} levels of SOF clinical dose (400 mg QD) only cover clinical isolates of GT2.**

Conclusions

- ➢ AT-527 was well tolerated after a single dose in both healthy and HCV-infected subjects.
- ➢ After single oral doses, plasma exposure of AT-273, the nucleoside metabolite of the active nucleotide, was mostly dose-proportional over the studied dose range.
- ➢ PK parameters were comparable in both healthy and HCV-infected subjects.
- ➢ Significant antiviral activity was observed in GT1b HCV-infected subjects after a single 300 mg dose of AT-527 (270 mg free base equivalent), with a mean maximum HCV RNA reduction of 1.7 $\log_{10}$ IU/mL.
  - This compares to ~2 $\log_{10}$ IU/mL reduction after 1 day of 400 mg SOF monotherapy in GT1a HCV-infected subjects (3).
- ➢ PK/PD analysis indicated that antiviral activity correlated with plasma exposure of AT-273, predicting a more profound viral response at higher drug exposure.
  - Predicted steady-state troughs of AT-273 after 400 mg QD AT-527 free base equivalent exceed the *in vitro* EC_{95} of AT-511 against all tested clinical isolates of GT 1-4 HCV patients, suggesting that AT-527 will have potent pan-genotypic antiviral activity.
- ➢ Higher doses are being evaluated in Part B of this ongoing study. These data support initiation of a 7-day proof-of-concept study, in which QD doses of AT-527 will be evaluated as a single agent in HCV-infected subjects.

References

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