**AT-337, AT-511 and its Salt Form, AT-527: Novel Potent and Selective Pan-genotypic Nucleotide Prodrug Inhibitors of HCV Polymerase**

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**Introduction**

Hepatitis C virus (HCV) infection remains a global concern with approximately 170 million patients chronically infected worldwide. Although HCV treatment outcomes have been considerably improved, current treatments still require 12 weeks of treatment. More potent DAAAs could significantly shorten treatment duration and improve compliance while achieving high SVR rates across genotype and disease stage. Nucleoside analogs with potent pan-genotypic activity and higher barrier to drug resistance are considered hallmarks in the treatment of HCV infection. Previously reported results (1) with AT-337 and AT-511, novel purine-based nucleotide prodrugs with both base and sugar modifications, demonstrated activity against HCV genotypes 1b and favorable pharmacokinetics in rats and monkeys. Here we report potent pan-genotypic activities and additional in vitro selectivity of these compounds, as well as the in vivo pharmacokinetics and formation of the active analog triphosphates after oral administration of AT-527, a salt form of AT-511.

**Methods**

A panel of replicons containing the NS5B sequences from various HCV genotypes derived from 6 laboratory reference strains (GT1a, 1b, 2a, 3a, 4a and 5a) and from 8 HCV patient plasma samples (GT1a, 1b, 2a, 3a, 4a, 4d, 5a, and 6a) as well as replicons containing wild-type or sofosbuvir-resistant mutants (FRV) from laboratory constructs (1aC103I, 1aS282T, 1aL286F, 1aS282T, 1bL286F and 2aL159F) and from clinical isolates (1aS282T, 1aL286F, 1aS282T and 1bL286F) were used to determine the IC50 and/or IC95 values for AT-337, AT-511 and sofosbuvir. IC50 values for AT-337 and AT-511 were determined by monitoring the waning nucleoside triphosphates of sofosbuvir, INX-189, and AT-511 and AT-511 by human mitochondrial RNA-dependent DNA polymerase (POLRMT) as determined according to published methods (2).

**Results**

**Potential Activities of AT-337 and AT-511 Against Sofosbuvir Resistant Variants**

AT-337 and AT-511 maintain their activities against the HCV S282T variant, with 40-to 124-fold greater potency than sofosbuvir.

**IC50 Values for AT-511 and sofosbuvir Resistant Variants**

IC50 values for AT-511 and sofosbuvir resistant variants (1aS282T, 1aL286F, 1aS282T and 1bL286F) were determined according to published methods (2).

**Plasma Profiles of AT-511 and AT-273 (metabolite of the active TP) in Rats Given Single 500 mg/kg Oral Doses of AT-527 (salt form of AT-511)**

**Plasma Profiles of AT-511 and AT-273 (metabolite of the active TP) in Monkeys Given Single 30, 100 or 300 mg/kg Oral Doses of AT-527 (salt form of AT-511)**

**Plasmatic Pharmacokinetic Parameters for AT-337 and AT-527 in Rats and Monkeys Given Single Oral Doses of AT-527 (salt form of AT-511)**

**Plasmatic Pharmacokinetic Parameters for AT-337 and AT-527 in Rats and Monkeys Given Single Oral Doses of AT-527 (salt form of AT-511)**

**Significant liver levels of the active TP were obtained in both rats and monkeys at all doses and undetectable heart levels indicate selective liver formation of the active TP.**

**Conclusions**

- AT-337 and AT-511 are potent pan-genotypic inhibitors of HCV and are 6- to 33-fold more inhibitory of HCV replication in vitro than sofosbuvir.
- AT-337 and AT-511 maintain their activities against the HCV S282T variant, with 40- to 124-fold greater potency than sofosbuvir.
- AT-337 and AT-511 are not metabolized to mutagenic nucleobases by recombinant human CYP3A4, in contrast to the purine-based nucleoside produgs PSi-661, PSI-938 and PSI-198.
- AT-337 and AT-511 are not likely to affect mitochondrial integrity since their active triphosphates are poorly incorporated by human mitochondrial RNA polymerase with an efficiency similar to that of the triphosphate of sofosbuvir.
- The high levels of AT-9010 observed in liver and the long half-lives of AT-273 in plasma suggest that AT-9010 continues to increase up to the highest dose tested, reflecting substantial formation of AT-511 in these species.
- The high levels of AT-9010 observed in liver and the long half-lives of AT-511 in plasma of rats and monkeys dosed orally with AT-527 suggest clinical antiviral activity with once daily dosing. The undetectable levels of AT-9010 in heart is indicative of liver-specific formation of the active triphosphate.
- INDACTa-Enabling studies with AT-511 and ongoing.

**References**


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