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

**X.J. ZHOU**, E. BERLIBA2, F. VANHOUTTE3, M. BOGUS2, P.J. BERGHMANS3, S. GOOD1, A. MOUSSA1, K. PIETROPAOLO1, R. MURPHY1,4 and J.P. SOMMADIOS1

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

**Introduction**

AT-527 is a novel full-term purine nucleotide prodrug composed of 5′-adenosine-5′-triphosphate (ATP) and the 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 detection of 15 IU/mL. This study was designed to evaluate the safety, PK/PD, and antiviral activity of AT-527 in healthy and cirrhotic subjects infected with HCV genotypes 1b, 3, and 4. Aim and Methods

- **Aim:** Safety, tolerability, pharmacokinetics (PK) and antiviral activity
- **Methods:** Doses reflect AT-511 free base equivalent, with dose of AT-527 salt form referenced above in Methods. Part E – GT1b or 3, CPA cirrhotic: data from 2 of up to 6 subjects planned (ongoing); Part D – GT3, non-cirrhotic: data from 4 of up to 6 subjects planned (ongoing); Part C – GT1b, non-cirrhotic: data from all multiple dose cohorts (n=8/cohort).
- **PK/PD analysis:** Indicated that antiviral activity correlated with plasma exposure of AT-273, the 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 detection of 15 IU/mL.
- **Disclosures:** XJZ, SG, AM, KP and JPS are employees of Atea Pharmaceuticals. RM is a consultant to Atea Pharmaceuticals.

**Results**

**Safety Summary**

- **AEs (%)**
  - **Part E – GT1b**: 550 mg: 0/2; 275 mg: 0/2; 138 mg: 0/2; 69 mg: 0/2
  - **Part C – GT1b**: 550 mg: 0/2; 275 mg: 0/2; 138 mg: 0/2; 69 mg: 0/2
  - **Part D – GT3**: 550 mg: 0/2; 275 mg: 0/2; 138 mg: 0/2; 69 mg: 0/2
  - **Part E – GT3**: 550 mg: 0/2; 275 mg: 0/2; 138 mg: 0/2; 69 mg: 0/2
  - **All subjects experiencing at least one AE**: 0/2 NS
  - **Subjects experiencing at least one AE greater than or equal to Grade 3**: 0/2 NS

- **Mean HCV RNA Reduction was 2.4 log10 IU/mL after the first dose**: 50% of subjects achieved HCV RNA < LOQ.

- **Mean HCV RNA Change After Multiple Doses of AT-527**
  - **Non-cirrhotic GT1b**: 550 mg dose: -5.6 log10 IU/mL
  - **GT3**: 550 mg dose: -5.1 log10 IU/mL
  - **Cirrhotic**: 550 mg dose: -4.8 log10 IU/mL

- **PK/PD Analysis**
  - **Emax Model**: Relationship Between AT-273 AUC and HCV RNA Change from Baseline After 7 Days of AT-527 Treatment

**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 3.2 log10 IU/mL, after a single dose and 4.4 log10 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 4.8 log10 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, exceeded a threshold of 0.4 log10 IU/mL per day for all dose levels.**

**References**


2. X.J. Zhou et al. (2017) A Phase 1a Study of AT-527, a Novel Pan-Genotypic Purine Nucleotide Prodrug Inhibitor of HCV Polymerase. Abs. THU-341. Hepatology. 64(1, Suppl): 341A

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