A combination of AT-527, a potent pan-genotypic guanosine nucleotide prodrug, and daclatasvir was well-tolerated and effective in HCV-infected subjects

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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). AT-527 exhibited profound pan-genotypic antiviral activity after 350 mg once daily (OD) dosing for 7 days in HCV-infected patients with and without cirrhosis (2). The pilot phase 2 study was conducted to evaluate the long-term safety and viral kinetics of AT-527 in combination with daclatasvir, the only approved stand-alone NS5A inhibitor.

Methods
• A cohort of 10 treatment-naïve, genotype (GT) 1b- infected subjects without cirrhosis received 350 mg AT-527 and 60 mg daclatasvir OD. The protocol allowed subjects to stop treatment after 8 weeks for those who achieved plasma HCV RNA < lower limit of quantitation (LLOQ) by week 4. Otherwise, subjects were to receive 12 weeks of treatment.
• Enrolled subjects required plasma HCV RNA ≥ 24 IU/mL at screening.
• Safety was assessed via adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests.
• Viremia were evaluated by quantification of plasma HCV RNA using the Roche cobas® HCV quantitative nucleic acid test for use on the cobas® 6800/8800 systems, with a LLOQ of 15 IU/mL.

All subjects completed the treatment period, with no premature discontinuations.

Results
All subjects achieved HCV RNA < LLOQ by week 2. Nine of 10 subjects achieved SVR4 and then experienced virologic relapse at post-treatment week 12.

All subjects completed treatment, nine of whom received 8 weeks of treatment and one of whom received 12 weeks of treatment.

• Enrolled subjects required plasma HCV RNA ≥ 24 IU/mL at screening.

• All subjects were treatment-naïve with high baseline viral load (≥800,000 IU/mL).

• Nine of 10 subjects achieved HCV RNA < LLOQ by week 4 and stopped treatment at week 8, as per the protocol.

• One subject had an asymptomatic, isolated grade 4 elevation of lipase at the week 1 visit, which returned to normal levels four days later with continued dosing. Amylase remained within the normal range.

• One subject had a grade 3 increase in hepatic lipase at treatment week 14.

• No serious adverse events occurred on the study.

• AEs were mostly mild, transient and resolved with continued dosing of study drugs.

• Phenotypic analysis was also performed on selected samples of the single subject who failed to achieve SVR12, comparing activity of AT-527 and SOF.

• All subjects completed the treatment period, with no premature discontinuations.

• No serious adverse events occurred on the study.

• AEs were mostly mild, transient and resolved with continued dosing of study drugs.

• One subject had an asymptomatic, isolated grade 4 elevation of lipase at the week 1 visit, which returned to normal levels four days later with continued dosing. Amylase remained within the normal range.

• There were no clinically significant changes in vital signs or ECG parameters.

• Individual ALT (U/L)

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<tr>
<th></th>
<th>8 weeks</th>
<th>12 weeks</th>
<th>Total</th>
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<tbody>
<tr>
<td>Male</td>
<td>39 (20)</td>
<td>44 (41)</td>
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</tr>
<tr>
<td>Female</td>
<td>35 (32)</td>
<td>30 (32)</td>
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<tr>
<td>Male BMI, kg/m² (range)</td>
<td>26.7 (19.6-34.9)</td>
<td>25.5</td>
<td>26.6 (19.6-34.9)</td>
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Residence Analyses
The single subject who relapsed with GT 1b virus had the following multiple RAVs/variants both at baseline and at the SVR12 timepoint:

• NS5A: R30Q

• NS5B: L159F/A218S/C316N

Phenotypic analysis demonstrated that AT-527 retained the same high potency against clinical isolates obtained from this relapsed subject at baseline (a 1.1- and 0.8-fold shift, respectively, in EC50 compared to reference). Compared to sofosbuvir, the EC50 and EC90 values for AT-527 were >10-fold lower. Thus, the significance of the RAVs in this case is unclear.

• No other subjects had pre-existing NS5A RAVs at baseline.

• Two other subjects with GT 1b virus had pre-existing NS5B RAVs/variants at baseline (1 with A218S/C316N and 1 with A218S/C316N/V321I).

• Both of these subjects achieved SVR12.

• Lower SVR12 rates have been observed with SOF-based regimens in patients with coexisting NS5A and NS5B RAVs (4).

Conclusions
AT-527, a guanosine nucleotide prodrug, combined with daclatasvir, was well-tolerated for treatment durations of up to 12 weeks in subjects chronically infected with HCV.

Other than rapid decreases in ALT and AST upon initiation of dosing, there were no clinically relevant patterns observed for AEs, vital signs, ECGs or safety laboratory parameters.

Despite the use of a first-generation HCV NS5A inhibitor in this study, viral load decreased rapidly, with 70% of subjects achieving plasma HCV RNA < LLOQ by week 4 and stopped treatment at week 8, as per the protocol.

• Nine of the 10 subjects achieved SVR12.

• The very rapid early clearance of HCV RNA observed in this study supports continued evaluation of AT-527 in shortened treatment regimens, ideally with a more potent, next-generation HCV NS5A inhibitor.

References

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