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 550 mg once daily (QD) 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) 1-infected subjects without cirrhosis received 550 mg AT-527 and 60 mg daclatasvir QD. 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 ≥ 4 $\log_{10}$ at screening with a lack of cirrhosis confirmed by Fibroscan® ≤ 12.5 kPa or liver biopsy within the prior year.
- Safety was assessed via adverse events (AEs), vital signs, electrocardiograms (ECGs) and standard safety laboratory tests.
- Viral kinetics 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.
- Resistance-associated variants (RAVs) present within the NS5A and NS5B gene regions were assessed using next-generation sequencing techniques (10% sensitivity threshold).
  - Phenotypic analysis was also performed on selected samples of the single subject who failed to achieve SVR12, comparing activity of AT-527 and SOF.

Results

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

Demographics and Baseline Characteristics

	8 weeks N=9	12 weeks N=1	Total N=10
Mean age, yrs (range)	39 (26-57)	44	39 (26-57)
Mean BMI, kg/m² (range)	26.7 (19.6-34.9)	25.5	26.6 (19.6-34.9)
Male/Female, n (%) / n (%)	7 (78) / 2 (22)	1 (100) / 0 (0)	8 (80) / 2 (20)
Race, n (%)			
White	5 (56)	0	5 (50)
Black	4 (44)	1 (100)	5 (50)
Treatment-naïve, n (%)	9 (100)	1 (100)	10 (100)
Mean HCV RNA, $\log_{10}$ IU/mL (range)	6.8 (6.0-7.5)	6.7	6.8 (6.0-7.5)
Mean ALT, U/L (range)	60 (22-134)	181	72 (22-181)
Mean Fibroscan®, kPa (range)	6.8 (3.9-10.1)	7.6	6.8 (3.9-10.1)
HCV genotype, n (%)			
1a	5 (56)	1 (100)	6 (60)
1b	4 (44)	0	4 (40)

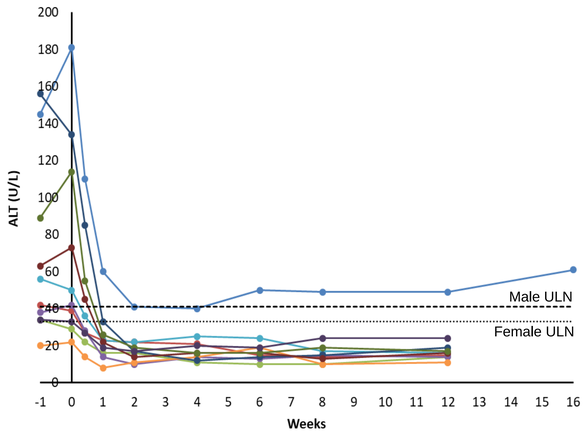
- Demographics of enrolled subjects reflected the HCV population in participating countries, including Belgium, Mauritius, and Moldova.
  - Fifty percent (50%) of subjects were of African origin and 50% were of European origin.
- All subjects were treatment-naïve with high baseline viral load (≥800,000 IU/mL).

Adverse Events

AEs, n (%)	8 weeks N=9	12 weeks N=1	Total N=10
Abdominal pain	1 (11)	0	1 (10)
Abdominal pain upper	1 (11)	0	1 (10)
Cough	1 (11)	0	1 (10)
Headache	2 (22)	1 (100)	3 (30)
Lipase increased	2 (22)	0	2 (20)
Nausea	1 (11)	0	1 (10)
Rhinorrhea	1 (11)	0	1 (10)

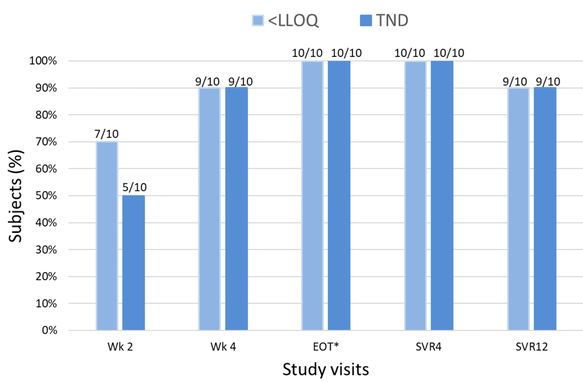
- All subjects completed the treatment period, with no premature discontinuations.
- No serious adverse events occurred on the study.
- AEs were mostly mild, transient and resolved with continued dosing of study drugs.
- One subject had an asymptomatic, isolated grade 4 elevation of lipase at the week 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)



- ALT and AST (not displayed) decreased rapidly upon initiation of dosing with AT-527 and daclatasvir.
- Subjects normalized ALT by week 2 and maintained near nadir levels throughout the dosing and post-treatment period.
- There were no clinically significant changes in bilirubin or any patterns observed for other safety laboratory parameters.

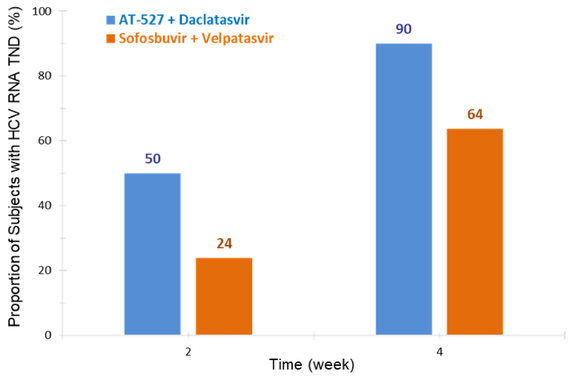
% of Subjects <LLOQ and TND by Study Visit



*End of treatment (EOT) = 8 wks for 9 subjects and 12 wks for 1 subject

- Viral load decreased rapidly, with the majority of subjects achieving plasma HCV RNA < LLOQ by week 2.
- Nine of 10 subjects achieved HCV RNA < LLOQ by week 4 and stopped treatment at week 8, as per the protocol.
- Nine of the 10 subjects achieved SVR12.
  - One GT 1b-infected subject who was target not detected (TND) by week 2, received 8 weeks of treatment, achieved SVR4 and then experienced virologic relapse at post-treatment week 12.

On-Treatment Response Rates Compared to SOF/VEL



- AT-527 plus daclatasvir on-treatment response rates were higher than those observed with sofosbuvir plus velpatasvir (3).

Resistance 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 and SVR12 (only a 1.1 and 0.8-fold shift, respectively, in EC_{50} compared to reference). Compared to sofosbuvir, the EC_{50} and EC_{90} 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/C316H/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 2 (and 50% achieving TND by week 2).
- Nine of the ten subjects achieved SVR12, with a single subject with multiple RAVs/variants at baseline who experienced virologic relapse.
- 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.

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