AVL-192, Potency against HCV NS3 mutants allows for replicon clearance as a monotherapy and in combination studies

M. Hagel; D. Niu; T. St. Martin; M. Sheets; L. Qiao; P. Chaturvedi; M. Labenski, M. Nacht; R. Petter; J. Singh; W. Westlin.

Avila Therapeutics Inc. 100 Beaver Street, Waltham, MA USA 02453

Abstract

The current manuscript demonstrates that a covalent inhibitor of NS3, AVL-192, exhibits significantly increased potency and prolonged duration of action. Using both HCV NS3 replicon systems, we observed potent activity against the drug-resistant, genotype 1b replicon-derived NS3 mutant, S139A, and enhanced activity against NS3 genotypes 1a and 2a. Potency increases as a monotherapy and in combination with IFN+AVL-192, with a time-dependent mode of action that delivers potent inhibition on the order of minutes to hours. The combination of AVL-192 and IFN-α demonstrates improved viral clearance compared to IFN-α alone, with additive viral clearance observed for genotypes 2 and 3. In addition, AVL-192 exhibits a unique profile, which differentiates it as a potential best-in-class therapeutic.

AVL-192 Achieves Replicon Clearance as a Monotherapy and in Combination with IFN-α or NSSB Inhibitor

AVL-192 is selective against host proteases and potent in the presence of human serum proteins

AVL-192 has a time-dependent mode of action that delivers potent and rapid inhibition of WT NS3/4A and importantly retains potency against drug-resistant mutant NS3/4A proteases.

AVL-192 is able to inhibit the protease long after the compound is removed, offering the benefits of less frequent dosing.

AVL-192 is highly selective and spares host proteases.

AVL-192 as monotherapy is curative in the replicon clearance assay.

In combination with standard of care IFN-α or an NSSB inhibitor, AVL-192 prevents breakthrough due to resistance.

AVL-192 has a unique mode of action that offers a potency and selectivity profile that highlights it as a potential best in class therapeutic.