Preclinical characterization of CC-31244, a pan-genotypic, potent NS5B non-nucleoside inhibitor for the treatment of chronic hepatitis C

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INTRODUCTION

- Hepatitis C virus is the major cause of chronic liver disease, leading to cirrhosis, liver failure, hepatocellular carcinoma. HCV viruses are classified into 6 genotypes, and 130-180 million people are infected worldwide.
- NS5B non-nucleoside inhibitors are a distinct class of direct acting agents (DAA) for the treatment of HCV. We have developed a novel, pan-genotypic nonnucleoside inhibitor (NNI), CC-31244, which can be used as part of combination DAA therapies. We present here our recent in vitro characterization of CC-31244, binding mode, drug resistance profiles, and pharmacokinetic data.

AIM

- Design and develop novel structure-guided pan-genotypic NS5B NNI leads.
- Demonstrate excellent activity toward known NS5B NNI drug resistant variants.
- Demonstrate good pharmacokinetic and in vitro safety profiles.
- Demonstrate liver targeting activity.

METHODS

Genotype HCV NS5B polymerases (GT1-6) and drug resistant NS5B polymerases were purified for protein crystallization and IC50 determination. NS5B polymerase crystals (GT1, 2, 4, and 6) and cocrystals diffraction at 1.7 – 2.2 Å. Antiviral activity was determined using HCV replicons and chimeric replicon assays. The genetic barrier to resistance in HCV GT1b replicon was measured in resistant colony selection assays using inhibitor concentrations at various multiples over the EC50 value of CC-31244. Safety pharmacology and pharmacokinetic profiles of CC-31244 were determined. X-ray data collection was done at BCSB (ALS), LS-CAT (APS), and SMB (SSRL).

RESULTS

- CC-31244 demonstrates excellent activity against HCV replicons containing NS5B variants identified by CC-31244 resistant colony selection.
- CC-31244 demonstrates pan-genotypic activity against NS5B polymerases of GT 1-6.
- GT1b replicons bearing the NS5B C445F mutation were selected as a major drug resistant variant.
- CC-31244 exhibits good potency against common NNI and Nuc drug resistant variants.
- Based on its favorable preclinical activity and pharmacokinetic characteristics, CC-31244 was selected as a clinical candidate and regulatory submission is scheduled for early 2016.

CONCLUSION

- CC-31244 demonstrates pan-genotypic activity against NS5B polymerases of GT 1-6.
- GT1b replicons bearing the NS5B C445F mutation were selected as a major drug resistant variant.
- CC-31244 exhibits good potency against common NNI and Nuc drug resistant variants.
- Based on its favorable preclinical activity and pharmacokinetic characteristics, CC-31244 was selected as a clinical candidate and regulatory submission is scheduled for early 2016.

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