Clinical Pharmacology Considerations and Clinical Study Designs of HCV Combination Therapies
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Daclatasvir (DCV) a first in class NS5A agent, has formed the basis for all HCV regimens at BMS. Development programs for DCV based regimens have adapted based on the need for new therapies. Initial DCV studies were conducted with an interferon / ribavirin backbone for 48 weeks but with changing treatment and regulatory landscapes and the need to evaluate all oral interferon free regimens and shorter treatment durations, the DUAL regimen (DCV+ASV [aunaprevir] for 24 weeks) was the first all oral direct acting antiviral (DAA) regimen to be marketed in the world with approval in Japan. The TRIO regimen (DCV, ASV, and beclabuvir [BCV]) which is currently under review is to be administered for only 12 weeks. The DCV + sofosbuvir (SOF) regimen which has resulted in significantly improved efficacy, especially for difficult to treat patients has been studied for 12 weeks or for shorter durations and is approved worldwide. As multiple drug regimens have become commonplace in HCV, unique challenges have arisen, specifically when designing clinical pharmacology (CP) studies. Initial CP studies for DCV and ASV were conducted for individual assets with some DDI studies conducted for the combination. Conversely, for the TRIO regimen, all studies including the renal impairment (RI) study were conducted for the regimen.

Modeling and simulation was used extensively both during development and regulatory approval of DCV based regimens. Exposure-response safety and efficacy analysis with viral kinetic modeling was utilized for dose selection for Phase 3 studies. Physiologically based pharmacokinetic modeling was also utilized to justify dosing recommendations for DCV when coadministered with concomitant medications that were not evaluated in the clinic such as verapamil and cobicistat boosted protease inhibitors.

The presentation will discuss the clinical study design aspects of DCV based treatment and the Clinical Pharmacology considerations during development of these regimens, including the role of Modeling and Simulation.