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Pharmacokinetics, Safety, and Tolerability of Single and Multiple Doses of ABT-493: A First-In-Human Study

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ABSTRACT

ABT-493 is a hepatitis C virus nonstructural protein 3/4A protease inhibitor with pangenotypic antiviral activity. This study investigated the pharmacokinetics, safety, and tolerability of single and multiple ascending doses of ABT-493 and the effect of food and ritonavir coadministration on ABT-493 pharmacokinetics in healthy adults. In the blinded, randomized, placebo-controlled phase 1 single- and multiple-dose portions of the study, ABT-493 25-800 mg were evaluated as single doses, and 200, 400, and 800 mg were evaluated as multiple doses. The effect of food and ritonavir was assessed in a crossover unblinded fashion. ABT-493 pharmacokinetic parameters were estimated using noncompartmental methods. ABT-493 25-800 mg showed a greater than dose-proportional increase in exposures. Minimal accumulation ($\leq$15%) was observed after ABT-493 200- and 400-mg multiple dosing; higher accumulations (approximately 80%) were observed after the 800-mg dose. ABT-493 harmonic mean half-life was 6-9 hours. Food had a minimal effect on ABT-493 exposures. All adverse events were assessed by the investigator as mild to moderate in severity, no serious adverse events were reported, and no subjects discontinued from the study. No clinically significant laboratory tests, vital signs, or electrocardiogram values were reported. A maximum tolerated dose was not reached.

Introduction

Hepatitis C virus (HCV) infection is a global health problem, with 130-150 million individuals infected worldwide.[1] Depending on the presence of cofactors, such as alcohol consumption, diabetes mellitus, older age of acquisition, human immunodeficiency virus (HIV) coinfection, or coinfection with other hepatotropic viruses, between 10% and 40% of patients with chronic HCV infection will develop cirrhosis. Cirrhosis caused by HCV is the most common indication for liver transplantation, and HCV infection from the host HCV disease in the new graft is nearly universal, with 20%-40% of untreated liver transplant recipients experiencing cirrhosis within 5 years of transplant.[2,3] Death related to the complications of cirrhosis in HCV patients may occur at an incidence of approximately 4% per year; hepatocellular carcinoma occurs in this population at an estimated incidence of 1%-5% per year. Patients diagnosed with hepatocellular carcinoma have a 33% probability of death during the first year.[4] Successful eradication of HCV has been shown to significantly reduce the risk of disease progression and related mortality and the development of hepatocellular carcinoma.[5-8]

To meet the need for more efficacious and better tolerated anti-HCV treatment regimens compared to previous pegylated interferon and ribavirin combination treatment, a number of direct-acting antiviral agent (DAA) small molecules, including several nonstructural (NS) protein 3/4A protease inhibitors, have been developed or are currently in development. Two non–protease-based therapies for HCV were approved in 2013 (sofosbuvir, a nucleotide analog NS5B polymerase inhibitor) and 2014 (ledipasvir, an NS5A inhibitor, in combination with sofosbuvir).[9,10] In 2014, a potent NS3/4 protease inhibitor, paritaprevir, in combination with an NS5A inhibitor, ombitasvir, and a NS5B inhibitor, dasabuvir, with or without ribavirin was approved for treatment of HCV genotype 1 infection.[11] These combination therapies allowed for the complete removal of pegylated interferon from the HCV treatment paradigm. Although these new DAA combination therapies drastically shortened the treatment duration with high efficacy and tolerability, the first-generation interferon-free DAA regimens had a lower resistance barrier and were approved mainly for HCV genotype 1 infection. In early 2016, a potent NS3/4 protease inhibitor, grazoprevir, in combination with

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an NS5A inhibitor, elbasvir, with or without ribavirin was approved for the treatment of HCV genotype 1 and 4 infections,[12] and velpatasvir, a potent NS5A inhibitor, in combination with sofosbuvir with or without ribavirin, was approved for the treatment of HCV genotype 1, 2, 3, 4, 5, or 6 infections.[13] Limitations of the current regimens include the requirement of ribavirin for some populations, significant drug interactions, and limited options for patients with severe renal impairment or with end-stage renal disease.[9-13] Thus, there is still an unmet medical need for a potent pangenotypic regimen across all HCV genotypes in subpopulations.

ABT-493 is a pangenotypic NS3/4A protease inhibitor that was identified by AbbVie, Inc. (North Chicago, IL) and Enanta Pharmaceuticals, Inc. (Watertown, MA).[14] In nonclinical studies, ABT-493 demonstrates acceptable pharmacokinetic behavior and is well absorbed and primarily eliminated via biliary excretion as unchanged parent drug with limited metabolism. ABT-493 has a substantially improved *in vitro* virologic profile compared to earlier generation HCV NS3/4A protease inhibitors, with potent *in vitro* antiviral activity (concentration required for 50% effect [EC_{50}] = 0.85-2.7 nM) across multiple HCV genotypes.[15] Of note, ABT-493 is potent (EC_{50} = 1.6 nM) against genotype 3a, whereas many other NS3/4A protease inhibitors have much lower potency against genotype 3a.[16] ABT-493 also exhibits a high genetic barrier to resistance in major genotypes (e.g., R155 or D168 variants in HCV genotype 1).[15] In a monotherapy study, ABT-493 has shown strong antiviral effect of 3.8-4.3 $\log_{10}$ viral load decline after once-daily doses of 100-700 mg for 3 days.[17]

Thus, ABT-493 has a potential to cure all major types of HCV infections in combination with other DAAs. Here, we are presenting the results from the first-in-human study assessing the pharmacokinetics, safety, and tolerability of single and multiple escalating doses of ABT-493 in healthy adult subjects. In addition, the effect of food and ritonavir coadministration on the pharmacokinetics and safety of ABT-493 in healthy adult subjects was assessed.

Methods

The study was conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The study protocol was approved by the institutional review board (Vista Health System, Waukegan, IL). Written informed consent was obtained from each subject before any study-related procedures were performed.

Subjects

Adult men and women (postmenopausal or surgically sterile) aged 18-55 years and in general good health were eligible to be enrolled in the study. Subjects were excluded if they had a positive test for hepatitis A, B, or C or HIV or had alanine aminotransferase (ALT) or aspartate aminotransferase levels above the upper limit of normal on screening laboratory tests. Subjects were not eligible if they had used or consumed any of the following before study drug administration: any tobacco or nicotine products within 6 months; any investigational product within 42 days (or 10 half-lives, whichever was longer); any drug by injection within 30 days; any over-the-counter prescription medication, vitamin, or herbal supplement within 14 days (or 5 half-lives, whichever was longer); any grapefruit, grapefruit products, Seville oranges, or starfruit within 3 days; or any alcohol within 3 days.

Study Design

This phase 1, single-center study consisted of 3 substudies. Substudy 1 was a randomized, double-blind, placebo-controlled study to assess the pharmacokinetics, safety, and tolerability and of single escalating doses of ABT-493 in healthy subjects; substudy 2 was a randomized, double-blind, placebo-controlled study to assess the pharmacokinetics, safety, and tolerability of multiple escalating doses of ABT-493 for 10 days in healthy subjects; and substudy 3 was an open-label, 3-period crossover study of ABT-493 in healthy subjects to assess the effect of food and ritonavir coadministration on ABT-493 pharmacokinetics. In substudy 3, periods 1 and 2, subjects were randomly assigned to receive ABT-493 under either fasting or nonfasting conditions; in period 3, all subjects received ABT-493 with ritonavir under nonfasting conditions.

The starting dose of ABT-493 25 mg in substudy 1 was selected based on the no-observed-adverse-effect-level (NOAEL) exposure from rat and dog studies per regulatory guidance. Dose escalation proceeded after evaluation of the pharmacokinetic, safety, and tolerability data from the preceding group. The final maximum dose was selected such that the anticipated human maximum observed plasma concentration (C_{max}) and area under the plasma concentration–time curve (AUC) did not exceed the NOAEL exposures.

The doses selected for substudy 2 were based on exposures observed in substudy 1. ABT-493 pharmacokinetic parameters characterized in substudy 1 were used to identify an initial dose for substudy 2.

Ritonavir is widely recognized to be a potent inhibitor of cytochrome P450 (CYP) 3A, and it also inhibits transporters including organic anion-transporting polypeptide (OATP) 1B1, OATP1B3, p-glycoprotein (P-gp), and breast cancer resistance protein (BCRP). The coadministration of ABT-493 and ritonavir under nonfasting conditions was evaluated in substudy 3 to assess the drug–drug interaction potential of ABT-493 when coadministered with other potent liver enzyme or transporter inhibitors. The dose selected for substudy 3 was based on safety, tolerability, and pharmacokinetic data from substudy 1.

Study Drug Treatments

All study drugs (ABT-493, placebo, and ritonavir) were administered orally under nonfasting conditions, with the exception of the fasting portion of substudy 3. Subjects received a standardized diet providing approximately 40% of the daily calories from fat and no more than 45% of calories from carbohydrates (approximately 2200 calories/day) for all meals during confinement with the exception of the omission of breakfast in the fasting portion of substudy 3. ABT-493 doses ranged from 25 to 800 mg in the single-dose substudy, from 200 to 800 mg in the multiple-dose substudy, and were 200 mg in the food effect substudy.

Assessments

Pharmacokinetics

In substudy 1, blood samples for measurement of ABT-493 concentrations were collected before the morning dose on study day 1 and then 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 60, and 72 hours after dose. In substudy 2, blood samples were collected before the morning dose on study day 1 and then 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, and 16 hours after dose. Trough samples were then collected before the morning ABT-493 dose on study days 2, 3, 5, 7, 8, and 9. On study day 10, blood samples were collected before the morning dose and then 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 16, 24, and 72 hours after dose. In substudy 3, blood samples were collected in each period before the morning dose on study day 1 and then 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 30, 36, 48, 60, and 72 hours after dose. Urine samples for measurement of ABT-493 concentrations were collected in substudy 2 only. Urine was collected over the