# Drug Interactions Between Hepatoprotective Agents Ursodeoxycholic Acid or Glycyrrhizin and Ombitasvir/Paritaprevir/Ritonavir in Healthy Japanese Subjects

Jiuhong Zha, PhD[1]; Prajakta S. Badri, PhD[1]; Bifeng Ding, MS[1]; Naotaka Uchiyama, PhD[2]; Katia Alves, MD[1]; Lino Rodrigues-Jr, MD[1]; Rebecca Redman, MD[1]; Sandeep Dutta, PhD[1]; and Rajeev M. Menon, PhD[1]

[1]*AbbVie Inc, North Chicago, Illinois; and* [2]*AbbVie GK, Japan Development, Tokyo, Japan*

## ABSTRACT

**Purpose:** The 2 direct-acting antiviral combination (2D) of ombitasvir and paritaprevir (coadministered with ritonavir) is being evaluated for the treatment of chronic hepatitis C virus infection in Japan. Ursodeoxycholic acid (UDCA) and glycyrrhizin (GCR) are hepatoprotective agents widely used in Japan. A drug-drug interaction (DDI) study was conducted to guide dosing recommendations for UDCA and GCR when coadministered with the 2D regimen.

**Methods:** DDIs between the 2D regimen (ombitasvir/paritaprevir/ritonavir 25/150/100 mg orally once daily) and UDCA (50 mg orally 3 times daily) or GCR (80 mg intravenously once daily) were evaluated in a 2-arm, multiple-dose study in 24 Japanese healthy subjects under fed conditions. Pharmacokinetic and safety evaluations were performed when UDCA or GCR and the 2D regimen were administered alone and during coadministration. Exposures from coadministration of the 2D regimen plus UDCA or GCR versus the 2D regimen, UDCA, or GCR alone were compared using repeated-measures analyses of natural logarithms of the maximum plasma concentration ($C_{max}$) and area under the curve (AUC).

**Findings:** After coadministration of the 2D regimen and UDCA, steady-state exposures ($C_{max}$ and AUC) of ombitasvir, paritaprevir, and ritonavir showed a $\leq$9% change, and UDCA exposures showed a $\leq$20% change compared with administration alone. When the 2D regimen and GCR were coadministered, steady-state exposures of ombitasvir, paritaprevir, and ritonavir were not affected ($\leq$9% change), GCR AUC increased by 49%, and GCR $C_{max}$ was unaffected ($<$1% change).

**Implications:** No dose adjustment is needed for UDCA, GCR, or the 2D regimen when UDCA or GCR is coadministered with the 2D regimen in hepatitis C virus–infected patients under fed conditions. Clinical monitoring of patients using GCR is recommended due to an approximately 50% increase in GCR AUC when coadministered with the 2D regimen. (*Clin Ther.* 2015;37:2560–2571) 

**Key words:** drug interactions, glycyrrhizin, ombitasvir, paritaprevir, ritonavir, ursodeoxycholic acid.

## INTRODUCTION

Approximately 1.5 million to 2.0 million people in Japan and >150 million people worldwide are chronically infected with hepatitis C virus (HCV).[1–3] HCV genotype 1 is the most common genotype worldwide.[4] In Japan, HCV subtype 1b is most prevalent.[5] It accounts for approximately 70% of HCV infections, followed by subtypes 2a and 2b, which account for the remaining 20% and 10% of HCV infections, respectively.[6] Individuals chronically infected with HCV are at risk of dying of liver cirrhosis and/or liver cancer.[1]

Ombitasvir (formerly known as ABT-267) and paritaprevir (formerly known as ABT-450) are direct-acting antiviral agents (DAAs) being evaluated as a combination 2D regimen for treatment of chronic HCV infection in Japan. These DAAs have distinct, nonoverlapping mechanisms of action against HCV. Ombitasvir is a nonstructural protein (NS) 5A inhibitor, and paritaprevir, administered with a low dose of

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ritonavir as a pharmacokinetic enhancer, is an NS3/4A protease inhibitor identified by AbbVie and Enanta as a lead compound for clinical development. The 2D regimen of ombitasvir/paritaprevir/ritonavir is being evaluated for the treatment of Japanese patients infected with HCV subtype 1b and genotype 2.[7,8]

In Japan, use of the hepatoprotective agents ursodeoxycholic acid (UDCA) and glycyrrhizin (GCR) in patients with chronic liver disease is common. These hepatoprotective agents are used to reduce transaminase levels but do not target the HCV and progression of disease. UDCA is a naturally occurring bile acid found in small quantities in human plasma. Formulated UDCA is used for the improvement of liver function in HCV infection,[9] for the dissolution and prevention of gallstones, and for the treatment of primary biliary cirrhosis, among other indications.[10–14] GCR is a glycosylated saponin found in the roots of *Glicyrrhiza* species (licorice). GCR is used for the improvement of abnormal hepatic function in patients with chronic liver disease and for other indications.[9,15]

The metabolic and transporter profiles (substrate specificity, induction, and inhibition) of these hepatoprotective agents and the 2D regimen of ombitasvir/paritaprevir/ritonavir overlap. UDCA has been shown to be an inducer of the cytochrome P450 (CYP) 3A subfamily.[16,17] In addition, UDCA amidate metabolites are actively transported across the canalicular membrane into bile via the bile salt export pump.[18] In vitro studies have shown that GCR is a potent P-glycoprotein inhibitor and that its active metabolite, glycyrrhetinic acid (GCA), is an inhibitor of P-glycoprotein and multidrug resistance–associated protein 1.[19] GCR also has shown modest CYP3A induction.[20] Paritaprevir and ritonavir are bile salt export pump inhibitors and may cause inhibition of transportation of bile acids such as UDCA.[21] In addition, CYP3A4 is involved in the disposition of paritaprevir and ritonavir, and P-glycoprotein is involved in the disposition of paritaprevir, ritonavir, and ombitasvir.[21] Thus, there is potential for pharmacokinetic interactions between the 2D regimen and UDCA or GCR.

The present study was conducted in Japanese healthy subjects to evaluate the potential pharmacokinetic interactions between the 2D regimen and UDCA or GCR to guide dosing recommendations for HCV-infected patients who choose to use hepatoprotective agents during treatment with the 2D regimen.

## SUBJECTS AND METHODS

This was an open-label, Phase I study conducted at a single site in Japan. The study was conducted in accordance with Good Clinical Practice guidelines and ethical principles that have their origin in the Declaration of Helsinki. The protocol was approved by the institutional review board, and written informed consent was obtained from each subject before any study-related procedures were performed.

### Subjects

Japanese men and women between the ages of 20 and 55 years with a body mass index (BMI) of at least 18.5 $kg/m^2$ but $<25.0$ $kg/m^2$ and in general good health were eligible to enroll. Subjects who tested positive for hepatitis A virus IgM, hepatitis B surface antigen, HCV antibody, or HIV antibodies were not allowed to participate in the study. Subjects must not have used any of the following before study drug administration: tobacco or nicotine-containing products within 6 months, known inhibitors or inducers of CYP3A or organic anion transporting polypeptide 1B1 within 1 month, food containing licorice or licorice derivatives or any preparations containing GCR or glycyrrhizinic acid within 2 weeks, or alcohol within 72 hours.

### Study Design

The study consisted of 2 independent arms (n = 12 per arm) that received UDCA (Urso, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan) 50 mg orally 3 times daily (arm 1) or GCR (Stronger Neo-Minophagen C, Minophagen Pharmaceutical Co, Ltd, Tokyo, Japan) 80 mg IV for 20 (ranging from 18 to 22) minutes once daily (arm 2), alone or in combination with ombitasvir/paritaprevir/ritonavir 25/150/100 mg (2 coformulated 12.5/75/50 mg tablets once daily) (**Figure 1**). Standardized meals providing approximately 2200 calories per day (approximately 40% of calories from fat and up to 45% of calories from carbohydrates) were consumed throughout the study. All doses of ombitasvir/paritaprevir/ritonavir and GCR were taken or administered in the morning, approximately 30 minutes after the start of breakfast. Doses of UDCA were taken approximately 30 minutes after the start of breakfast, lunch, and dinner. On days when subjects received UDCA or GCR together with ombitasvir/paritaprevir/ritonavir, the doses were administered at the same time. The dose of ombitasvir/paritaprevir/ritonavir