2.0 Synopsis

AbbVie Inc.	**Individual Study Table Referring to Part of Dossier:**	**(For National Authority Use Only)**
Name of Study Drug: Ombitasvir, paritaprevir (ABT-450), ritonavir, dasabuvir, ribavirin	**Volume:** **Page:**	
Name of Active Ingredient: Ombitasvir: Dimethyl ([(2S,5S)-1-(4-tert-butylphenyl) pyrrolidine-2,5-diyl]bis{benzene-4,1-diylcarbamoyl(2S)pyrrolidine-2,1-diyl[(2S)-3-methyl-1-oxobutane-1,2-diyl]})biscarbamate hydrate Paritaprevir: (2R,6S,12Z,13aS,14aR,16aS)-N-(cyclopropylsulfonyl)-6-{[(5-methylpyrazin-2-yl)carbonyl]amino}-5,16-dioxo-2-(phenanthridin-6-yloxy)-1,2,3,6,7,8,9,10,11,13a,14,15,16,16a-tetradecahydrocyclopropa[e]pyrrolo[1,2-a][1,4]diazacyclopentadecine-14a(5H)-carboxamide hydrate ritonavir: [5S-(5R*,8R*,10R*,11R*)]10-Hydroxy-2-methyl-5-(1-methylethyl)-1-[2-(1-methylethyl)-4-thiazolyl]-3,6-dioxo-8,11-bis(phenylmethyl)-2,4,7,12-tetraazatridecan-13-oic acid, 5-thiazolylmethyl ester Dasabuvir (ABT-333): Sodium 3-(3-*tert*-butyl-4-methoxy-5-{6-[(methylsulfonyl)amino]naphthalene-2-yl}phenyl)-2,6-dioxo-3,6-dihydro-2H-pyrimidin-1-ide hydrate (1:1:1) Ribavirin: 1-β-D-ribofuranosyl-1*H*-1,2,4-triazole-3-carboxamide		

Title of Study:

An Exploratory Study to Evaluate Immune Restoration Following Removal of Viral Antigen in Treatment-Naïve and Treatment-Experienced Adults with Genotype (GT) 1a Chronic Hepatitis C Virus (HCV) Infection Administered Ombitasvir/ABT-450/Ritonavir with Dasabuvir and Ribavirin (RBV) for 12 Weeks

Investigator: Raymond T. Chung, MD

Study Site: A single center in the United States

Publications: 1 abstract

Studied Period (Years):
First Subject First Visit: 04 June 2015
Last Subject Last Visit: 02 December 2016

Phase of Development: 3b

Objectives:

The primary objective of this study was to evaluate the role of direct acting antiviral agent (DAA) treatment leading to sustained virologic response 12 weeks post-dosing (SVR_{12}) on the changes from baseline in interferon (IFN)-stimulated gene (ISG) expression in peripheral blood mononucleated cells (PBMCs) in hepatitis C virus (HCV) genotype (GT) 1a-infected adult subjects.

The exploratory objectives of this study were to evaluate the role of DAA treatment leading to SVR_{12} on the changes from baseline in interleukin-10 (IL-10) and interferon gamma-induced protein 10 (IP-10) (cleaved and uncleaved) levels in plasma, expression levels of T-cell inhibitory receptors and memory markers on HCV-specific CD8 T-cells (treatment-naïve subjects only) in HCV GT1a-infected adult subjects, and to compare the baseline and changes from baseline in ISG expression in PBMCs, expression levels of T-cell inhibitory receptors and memory markers on HCV-specific CD8 T-cells, and T-cell phenotype and function in the blood and liver, between HCV GT1a-infected treatment-naïve and prior pegIFN/RBV treatment-experienced subjects achieving SVR_{12}.

Methodology:

This was an exploratory, open-label, single-center study evaluating the immune restoration following removal of viral antigen by ombitasvir/paritaprevir/ritonavir and dasabuvir coadministered with RBV for 12 weeks. The study was to enroll approximately 40 HCV GT1a treatment-naïve adults and previous pegylated-interferon (pegIFN)/RBV-experienced adults without cirrhosis. The study consisted of a screening period that lasted up to 42 days, a 12-week Treatment Period and a 24-week Post-Treatment Period. The final analysis occurred after all enrolled subjects completed the Post-Treatment Period or prematurely discontinued from the study. Efficacy evaluations occurred throughout the Treatment and Post-Treatment Periods. If virologic failure criteria were met, the findings were to be discussed with the investigator and reviewed by AbbVie.

Number of Subjects (Planned and Analyzed):

Approximately 40 subjects were planned to be enrolled. Twenty-five subjects were enrolled in the study and received at least 1 dose of study drug.

Diagnosis and Main Criteria for Inclusion:

Male or female, at least 18 years of age at time of screening.

Chronic HCV GT1a-infected adult subjects without cirrhosis, who were treatment-naïve or prior pegIFN/RBV treatment-experienced.

Test Product, Dose/Strength/Concentration, Mode of Administration and Lot Number:

Investigational Product	Manufacturer	Mode of Administration	Dosage Form	Strength	Bulk Lot Number
Ombitasvir/ paritaprevir/ Ritonavir	AbbVie	Oral	Tablet	12.5 mg/ 75 mg/ 50 mg	13-005537
Dasabuvir	AbbVie	Oral	Tablet	250 mg	14-002089
Ribavirin	DSM Pharmaceuticals, Inc. for Kadmon Pharmaceuticals, LLC	Oral	Tablet	200 mg	14-001215

Duration of Treatment:

Subjects received ombitasvir/paritaprevir/ritonavir and dasabuvir coadministered with RBV for 12 weeks

Reference Therapy, Dose/Strength/Concentration and Mode of Administration and Lot Number:

Not applicable

Criteria for Evaluation

Efficacy:

The change in key ISG expression in PBMCs was assessed from baseline to Post-Treatment Week 12. Plasma HCV ribonucleic acid (RNA) (IU/mL) was assessed at each Treatment and Post-Treatment Visit.

Pharmacogenetic:

Interleukin 28B (IL28B) status was determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. Deoxyribonucleic acid (DNA) samples may have been sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to ombitasvir/paritaprevir/ritonavir and dasabuvir, other study treatment, in terms of pharmacokinetics, efficacy, tolerability, and safety. Messenger RNA samples from subjects may have been analyzed for RNA expression levels contributing to the subject's response to study treatment, in terms of pharmacokinetics, pharmacodynamics, efficacy, tolerability and safety. Analysis may have included quantifying RNA levels from IFN-stimulated pathways, or other families believed to be related to drug response. Messenger RNA analysis was limited to studying response to HCV therapy and is not reported in the study report; no other analyses were performed.

Safety:

Safety and tolerability were assessed by monitoring adverse events, physical examinations, clinical laboratory tests, 12-lead electrocardiograms (ECGs), and vital signs.

Statistical Methods

Efficacy:

The primary efficacy endpoint was the change in key ISG expression in PBMCs from baseline to Post-Treatment Week 12 for subjects achieving SVR_{12}. Mean changes from baseline to Post-Treatment Week 12 were summarized for the primary endpoint with the baseline mean, visit mean, change from baseline mean, standard deviation, and median.

The number and percentage of subjects with SVR_{12} were summarized.

Pharmacogenetic:

The analysis of pharmacogenetic samples is considered exploratory, and results are not reported in the clinical study report.

Safety:

The number and percentage of subjects reporting treatment-emergent adverse events were tabulated by Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term. Additional tabulations were provided in which the number of subjects reporting an adverse event (MedDRA preferred term) was presented by severity and relationship to study drug(s).

Changes from baseline in laboratory tests and vital sign measurements to each time point of collection were summarized descriptively. Laboratory test and vital sign values that were potentially clinically significant, according to predefined criteria were calculated.

Summary/Conclusions

Efficacy Results:

For the primary endpoint assessment of change in key ISG expression in PBMCs for subjects achieving SVR_{12}, the mean fold difference at Post-Treatment Week 12 compared with baseline were significantly ($P < 0.05$) different from zero for 28 of the 74 ISGs assessed. Twenty-six (26) of these ISGs were significantly down-regulated compared with their baseline gene expression levels.

SVR_{12} was achieved by 23/25 (92.0%) subjects. Two subjects did not achieve SVR_{12} due to premature discontinuation of study drug. There was no on-treatment virologic failure.

SVR_{24} was achieved by 22/25 (88.0%) subjects. The reasons for nonresponse were premature discontinuation of study drug for 2 subjects and relapse between post treatment Week 12 and 24 for 1 subject.

Pharmacogenetic Results:

The analysis of pharmacogenetic samples is considered exploratory, may be performed by a non-Good Laboratory Practice laboratory, and results are not reported in the clinical study report.

Safety Results:

A 12-week regimen of ombitasvir/paritaprevir/ritonavir with dasabuvir coadministered with RBV was generally well tolerated in the HCV genotype 1a-infected, treatment-naïve or treatment-experienced, noncirrhotic adult subjects in this study. All subjects (100%) experienced 1 or more treatment-emergent adverse events during the Treatment Period, of whom 12 (48%) experienced treatment-emergent adverse events that were considered related to DAA treatment and most events were mild or moderate severity. The most common treatment-emergent adverse events were fatigue, nausea, headache, insomnia, rash, diarrhea, and anxiety.

Summary/Conclusions (Continued)

Safety Results (Continued):

Two subjects experienced serious adverse events (1 with fatal overdose [of heroin] and 1 with anxiety). For both these subjects, the investigator considered the events to have no reasonable possibility of relationship to either DAAs or RBV. In addition to the subject who died, 1 subject discontinued due to nonserious adverse events of worsening fatigue, dyspnea, and chest pain, which were assessed by the investigator as having no reasonable possibility of being related to DAAs and as having a reasonable possibility of being related to RBV.

There were no grade 2 or greater alanine aminotransferase elevations during treatment.

Conclusions:

Down-regulation of ISGs was observed after successful treatment with the 3-DAA + RBV regimen, which suggests at least a partial reversal of the exhausted ISG phenotype and partial restoration of innate immunity after successful removal of HCV viral antigen.

The adverse event profile in this study was generally consistent with that seen in previous studies of ombitasvir/paritaprevir/ritonavir with dasabuvir and RBV.