SUPPORTING MATERIAL

Randomized Trial of Interferon- and Ribavirin-Free Ombitasvir/Paritaprevir/Ritonavir in Treatment-Experienced HCV-Infected Patients

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Paritaprevir (ABT-450) was identified by AbbVie and Enanta as a lead compound for clinical development.

Planned Analyses of the Primary Endpoint, SVR_{24}

Within the subtype 1b cohort, the effects of treatment duration (12 weeks versus 24 weeks) and paritaprevir dose (100 mg versus 150 mg) were to be tested using a logistic regression model with baseline $\log_{10}$ HCV RNA level, treatment duration (12 or 24 weeks), paritaprevir dose, and prior treatment response (null responder, partial responder) as predictors. Within the genotype 2 cohort, the effect of paritaprevir dose (100 vs 150 mg) was to be tested using a logistic regression model with baseline $\log_{10}$ HCV RNA level, paritaprevir dose, and prior treatment response (null responder, partial responder, relapser) as predictors. For each comparison within each HCV genotype, the odds ratio, 95% confidence interval for the odds ratio, and the *P* value were to be presented. However, the logistic regression could not be performed due to a quasi or complete separation of data.

Additionally, for the HCV subtype 1b cohort, the stratum-adjusted Mantel-Haenszel (MH) method controlling for the baseline variables treatment duration (12 or 24 weeks; when testing for paritaprevir dose), paritaprevir dose (100 mg or 150 mg; when testing for treatment duration), and prior treatment response (null responder, partial responder), were to be applied for the comparisons of SVR_{24} between paritaprevir doses and between 12-week and 24-week treatment regimens. For the HCV genotype 2 cohort, the stratum-adjusted Mantel-Haenszel (MH) method, controlling for the baseline variable prior treatment response (null responder, partial responder), was to be applied for the comparison of SVR_{24} between paritaprevir doses.

The stratum-adjusted Mantel-Haenszel (MH) method was only to be utilized when there were at least 3 subjects in each treatment arm in each strata. If such condition was not met, the Fisher exact test was performed instead.

Imputation Methods

For RVR, EOTR, and SVR, missing HCV RNA values were imputed using a flanking imputation approach, with subsequent backward imputation performed for SVR endpoints. After performing these imputations, patients with missing data were counted as failures. All other efficacy and safety endpoints were summarized using observed data (no imputation).

Table 1. Main Inclusion and Exclusion Criteria

Inclusion Criteria

- Aged between 18 and75 years, inclusive
- Chronic HCV infection[a] for at least 6 months before study enrollment
- Must have been a HCV subtype 1b-infected null responder[b] or partial responder[c] or a HCV genotype 2-infected null responder, partial responder, or relapser[d]
- Absence of liver cirrhosis[e]
- Plasma HCV RNA level greater than 10,000 IU/mL

Exclusion Criteria

- Females who were pregnant or planned to become pregnant, or breastfeeding
- History of severe, life-threatening sensitivity to any drug
- Use of any herbal supplements or medicines or ursodeoxycholic acid or S-Adenosyl methionine 2 weeks before the first dose of study medication and throughout the treatment period
- Drug or alcohol abuse within 6 months before study drug administration that could interfere with protocol adherence
- Positive test for hepatitis B surface antigen or anti-HIV antibodies
- Use of any form of hormonal contraceptives or use of any medication contraindicated for use with ritonavir within 2 weeks prior to study drug administration
- Use of strong inhibitors or inducers of CYP3A and OATP1B1 within 4 weeks of study drug administration
- Positive urine drug test result for opiates, barbiturates, amphetamines, cocaine, benzodiazepines, phencyclidine, propoxyphene, or alcohol, with the exception of a positive screen, associated with documented short-term use or chronic stable use of a prescribed medication in that class, when approved by the Medical Monitor
- Any clinically significant abnormality other than HCV infection that made the patient an unsuitable candidate for the study in the opinion of the investigator
- History of uncontrolled seizures[f] or diabetes,[g] diagnosis of or suspected cancer, or history of cancer other than basal cell skin cancer or cervical carcinoma in the past 5 years
- Any current or past clinical evidence of cirrhosis
- Any active or inactive cause of liver disease, other than chronic HCV infection
- Any of the following abnormal laboratory results at screening:
    - ALT greater than 5 times the ULN;
    - AST greater than 5 times the ULN;
    - Calculated creatinine clearance <50 mL/min
    - Albumin < LLN;
    - Prothrombin time/international normalized ratio greater than 1.5[h]
    - Hemoglobin less than the LLN
    - Platelets with levels less than the LLN for patients who did not have a liver

biopsy in the previous 24 months evaluated by Metavir, Ishak, or New Inuyama scores or for patients with a liver biopsy and a METAVIR or New Inuyama fibrosis score of 3 or an Ishak fibrosis score of 4; platelets with levels below 120,000 cells per mm^3 for patients with a METAVIR or New Inuyama fibrosis score of less than 3 or an Ishak fibrosis score less than 4. Absolute neutrophil count less than 1500 cells/μL;

- Indirect bilirubin greater than 1.5 × the ULN and direct bilirubin greater than ULN.

- Clinically significant abnormal electrocardiogram or QTcF greater than 450 msec at screening
- History of gastric surgery, vagotomy, bowel resection, or any surgical procedure that might interfere with gastrointestinal motility, pH, or absorption or use of acid secretion inhibitors within 7 days before the first dose of study drug and throughout the study
- Therapy with another investigational agent within 10 half-lives of the product or a minimum of 6 weeks before administration of study drug
- Current enrollment in another clinical study, previous enrollment in this study, or previous use of any investigational (including previous exposure to ombitasir or paritaprevir) or commercially available anti-HCV agent other than IFN-based therapy (IFN alpha, INF beta, or pegIFN) with or without RBV unless the patient can produce documentation that they received placebo
- Use of colony-stimulating factors or erythropoietin within 2 months of screening
- If the investigator considered, for any reason, that the patient was not a suitable candidate to receive ombitasir, paritaprevir or ritonavir

CYP3A=cytochrome P450 3A; INF=international normalized ratio; OATP1B1=organic anion transporting polypeptide 1B1; QTcF= QT interval corrected for heart rate (QTc) using Fridericia's correction formula; ULN= upper limit of normal

[a]Chronic infection was defined as having a positive test for anti-HCV antibodies or HCV RNA at least 6 months before screening and testing positive for HCV RNA and anti-HCV antibody at the time of screening or testing positive for anti-HCV antibodies and HCV RNA at screening and having a liver biopsy that was consistent with chronic HCV infection.

[b]Patients who had a 2 $\log_{10}$ IU/mL reduction in HCV RNA levels at week 12 after at least 10 weeks of treatment with pegIFN/RBV combination therapy.

[c]Patients who had of at least a 2 $\log_{10}$ IU/mL reduction in HCV RNA at week 12 after a minimum of 20 weeks of treatment with pegIFN/RBV.

[d]Patients with undetectable levels of HCV RNA after at the end of at least 1course of pegIFN/RBV treatment and who had detectable HCV RNA levels within 24 weeks after the end of that treatment.

[e]As assessed by liver biopsy at least 24 months before screening or during screening (eg, a METAVIR or New Inuyama fibrosis score no greater than 3 or an Ishak fibrosis score of no more than 4). If a liver biopsy was not available in the previous 24 months, absence of cirrhosis was assessed by 1 of the following during the screening period: a FibroTest score of no greater than 0.72 and an aspartate aminotransferase to platelet ratio of no greater than 2; a Fibroscan (31) result of less than 9.6 kPa; or a Discriminant score of less than 0, according to the formula: 0.124 × [gamma-globulin (%)] + 0.001 × [hyaluronate] [μg l(-1)]-0.075 × [platelet × (10(4) counts per mm(3))]-0.413 × gender [male, 1; female, 2] - 2.005).

[f]Seizure disorders not controlled by medication.

[g]Defined as a hemoglobin A1c level greater than 8.0%.

[h]Patients with a known inherited blood disorder and INR > 1.5 could be enrolled with permission of the Medical Monitor .

Table 2. SVR_{24} by Subtype in Patients With HCV Genotype 2 Infection Subtype, n/N, (%, 95% CI)

	12 weeks	12 weeks
Subtype by LiPA	**OBV*/PTV/r 100/100**	**OBV*/PTV/r 150 /100**
2b	2/8	3/8
	(25, 3.2–65.1)	(37.5, 8.5–75.5)
Not 2b	9/11	10/10
	(81.8, 48.2–97.7)	(100, 69.1–100)
Subtype by phylogenetic analysis		
1b	1/1	1/1
	(100, 2.5–100)	(100, 2.5–100)
2a	9/11	9/9
	(81.8, 48.2–97.7)	(100, 66.4–100)
2b	1/7	3/8
	(14.3, 0.4–57.9)	(37.5, 8.5–75.5)

HCV=hepatitis C virus; OBV=ombitasvir; PTV=paritaprevir; r=ritonavir; SVR_{24}=sustained virologic response at post-treatment week 24.
*Dose: 25 mg.

Table 3. Treatment-Emergent AEs by Paritaprevir Dose and Duration

	12 Weeks		24 Weeks	
Parameter, n (%)	**OBV*/PTV/r 100/100 (n=37[†])**	**OBV*/PTV/r 150/100 (n=36[‡])**	**OBV*/PTV/r 100/100 (n=19[§])**	**OBV*/PTV/r 150/100 (n=18[§])**
Any AE	28 (75.7)	31 (86.1)	16 (84.2)	15 (83.3)
Any serious AE	1 (2.7)	2 (5.6)	2 (10.5)	0
AE leading to study drug discontinuation	0	1 (2.8)	0	0
Common AEs[‖]				
Nasopharyngitis	6 (16.2)	13 (36.1)	4 (21.1)	9 (50.0)
Headache	5 (13.5)	6 (16.7)	3 (15.8)	1 (5.6)
Rash	0	1 (2.8)	2 (10.5)	3 (16.7)

AE=adverse event; OBV=ombitasvir; PTV=paritaprevir; r=ritonavir.
* Dose: 25 mg.
[†] GT1b, n=18; GT2, n=19.
[‡]GT1b, n=19; GT2, n=18.
[§]GT1b patients only.
[‖] Incidence >15% in any group.

Table 4. Potentially Clinically Significant* Chemistry and Hematologic Values of Interest During Treatment

	12 Weeks		24 Weeks	
	OBV†/PTV/r 100/100 (n=37‡)	**OBV†/PTV/r 150/100 (n=36§)**	**OBV†/PTV/r 100/100 (n=19‖)**	**OBV†/PTV/r 150/100 (n=18‖)**
Hemoglobin <10 g/dL	1 (2.7)	0	0	0
Total bilirubin ≥2x ULN	0	0	0	1 (5.6)
ALT >5x the ULN and ≥2x baseline	0	0	0	0
AST >5x the ULN and 2x baseline	0	0	0	0
ALP >1.5x the ULN	0	1 (2.8)	0	0
Creatinine clearance <50 mL/min	0	2 (5.6)	2 (10.5)	2 (11.1)
GFR <50 mL/min/BSA	3 (8.1)	1 (2.8)	2 (10.5)	3 (16.7)
BUN >5x the ULN	0	0	0	0
Uric acid >713.8 µmol/L	0	0	0	0

ALP=alkaline phosphatase; ALT=alanine transaminase; BSA=body surface area; BUN=blood urea nitrogen; GFR=glomerular filtration rate; OBV=ombitasvir; PTV=paritaprevir; r=ritonavir; ULN=upper limit of normal.
*Based on the medical judgment of the investigator.
†Dose: 25 mg.
‡GT1b, n=18; GT2, n=19.
§GT1b, n=19; GT2, n=18.
‖GT1b patients only.