Long-Term Clinical Outcomes in HCV Genotype 1-Infected Patients Receiving Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir & Ribavirin: First Interim Safety and Efficacy Results From TOPAZ-I

K Agarwal, GB Gaeta, SS Lee, E Dumas, A Streinu-Cercel, E Scott, RJ Andrade, AM Perez-Rios, G George, I Bakulina, R Marinholo, R Ozams, M Charafeddine, L Liu, T Pilot-Matias, K Howieson, A Jay, D Cohen, F Zouloumis1

1Institute of Liver Studies, King’s College Hospital; 2London Clinical Research Trust; 3London, England; 4King’s College University of Cali, Cali, Colombia; 5University of Alberta, Edmonton, Alberta, Canada; 6Wymark Hospital, North Chicago, Illinois, United States; 7Carol Davila University of Medicine and Pharmacy, Na Călărași, Romania; 8Charité – Universitätsmedizin Berlin, Berlin, Germany; 9University Hospital of Malaga, IMIB, REH, Alcalá de Andalucía, Spain; 10Centro de Investigación Farmacéutica Especializada SC Guadalajara, Mexico; 11Westmead Hospital, Westmead Institute for Medical Research and the University of Sydney, Sydney, Australia; 12Research Institute for Gastroenterology, Moscow, Russia; 13Hospital Santa Maria, Medical School of Lisbon, Lisbon, Portugal; 14Department of Infectious Diseases, Cerrahpaşa Medical School, Istanbul University, Istanbul, Turkey

1Institutional de la Santé et de la Recherche Médicale, Paris, France

Presented at the 67th Annual Meeting of the American Association for the Study of Liver Diseases, November 11-15, 2015, Boston, Massachusetts

BACKGROUND

HCV-infected individuals are at risk for advanced clinical outcomes, such as liver cirrhosis and hepatocellular carcinoma (HCC), resulting in increased liver-related mortality and increased health-care costs. 

• The overall three direct-acting antiviral (DAA) regimes of interest in TOPAZ-I were Ombitasvir/Paritaprevir/Ritonavir (OPR); Dasabuvir/Ribavirin (D/R); and Dasabuvir/Paritaprevir/Ritonavir (D/PR).

• In light of the emerging evidence that HCV genotype (GT) 4 infection is more difficult to treat than other HCV genotypes, we assessed the impact of interferon-free DAA treatment on long-term outcomes in GT 4–infected patients who achieve a sustained virologic response (SVR).

OBJECTIVES

• To assess the efficacy (as measured by SVR) and safety of a 12-week regimen of OPR ± RIBV in OPR-naive, GT 4–infected patients with or without cirrhosis.

• To evaluate the impact of GT 4 on the long-term progression of cirrhosis.

• To evaluate the long-term progression of fibrosis among patients receiving a 12-week regimen of OPR ± RIBV, as change from baseline in liver stiffness determined by transient elastography (M resilence monitor). (Figure 1)

METHODS

STUDY DESIGN

• TOPAZ-I (NCT02136246) was a Phase 3b, open-label, multicenter study to evaluate the efficacy and safety of a 12-week regimen of OPR ± RIBV in OPR-naive, GT 4–infected patients with or without cirrhosis. Patients were randomly assigned 1:1:1 to receive either OPR ± RIBV or D/R or D/PR. The study followed a 9-week on-treatment period and a 3-month post-treatment (PT) period. (Figure 2)

• The study included 1386 participants with documented chronic HCV GT 1 infection, of whom 100 (7.2%) were GT 4–infected: 3 GT1b-infected patients were cirrhotic (n = 97) and 77 were non-cirrhotic (n = 202) patients were treated with OPR ± RIBV, and 3 GT1b-infected patients were cirrhotic (n = 97) and 77 were non-cirrhotic (n = 202) patients were treated with D/R or D/PR. (Figure 3)

• The primary endpoint is the incidence of all-cause death during the study period; the primary SVR endpoint is SVR12. Secondary endpoints included: (1) 14 VF. Baseline characteristics Description of outcome events

• 1 case of acute renal failure with ascites following an event of pyelonephritis, leading to multiorgan failure.

• 2 cases of HCC: both in patients with Child-Pugh grade B cirrhosis and a forced expiratory volume in 1 second (FEV1)/predicted forced expiratory volume in 1 second (FVC) ≥70%.

• 1 case of uncontrolled hypertension.

• 1 case of severe depression.

• 1 case of acute respiratory distress syndrome.

• 1 case of non-Hodgkin lymphoma.

• 1 case of severe pericarditis.

• 1 case of acute myocardial infarction.

• 1 case of acute renal failure.

• 1 case of diplopia.

• 1 case of atrial fibrillation.

• 1 case of acetaminophen-induced liver injury.

• 1 case of osteomyelitis.

• 1 case of urosepsis.

• 1 case of severe congestive heart failure.

• 1 case of unstable angina.

• 1 case of Clostridium difficile infection.

• 1 case of severe wound infection.

• 1 case of severe sepsis.

• 1 case of pneumonia leading to multiple organ failure.

• 1 case of severe non-Hodgkin lymphoma.

• 1 case of severe cerebral palsy.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.

• 1 case of severe acute respiratory distress syndrome.

• 1 case of severe acute kidney injury.

• 1 case of severe neutropenia.

• 1 case of severe acute respiratory failure.

• 1 case of severe septic shock.
Predictors of Improvement in Glomerular Filtration Rate Among Patients Treated With Ombitasvir/Paritaprevir/r and Dasabuvir With or Without Ribavirin

D Bernstein,3 A Tran,9 P Martin,9 K Kowdley,4 A Tran,9 D Bernstein,5 DE Cohen,1 B Benjelloun,1 IM Jacobson1

Background: We previously reported that treatment of HCV genotype (GT) 1–infected patients with all D5K and regimens of PPAR-α agonist, dasabuvir boosted with ritonavir, and dasabuvir (DPV) was associated with a decreased rate of chronic kidney disease (CKD)1 in treatment-naive patients with advanced histology, particularly those with a baseline (BL) eGFR ≤60 mL/min/1.73 m²,1 but not in treatment-experienced (EX) patients.2 In the 7 clinical trials that had available BL urinalysis, 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the end of treatment (EOT) with DPV without and with ribavirin (RBV), respectively.3,4 This report examines the predictors of an increase of ≥10 mL/min/1.73 m² in eGFR from baseline (INCREASE in eGFR FROM BASELINE) and the predictors of an increase of ≥20 mL/min/1.73 m² in eGFR from baseline (DECREASE in eGFR FROM BASELINE) in SAPPHIRE-I and -II Seven Clinical Trials.

INCREASE in eGFR FROM BASELINE

Table 2. Patients With a Post-baseline eGFR Increase ≥20 mL/min/1.73 m² at End of Treatment

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 1479</th>
<th>n (%)</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>769</td>
<td>119 (8)</td>
<td>2.1 1.2–3.9</td>
<td>.009</td>
</tr>
<tr>
<td>Nausea</td>
<td>769</td>
<td>19 (2)</td>
<td>3.1 1.2–7.7</td>
<td>.018</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>769</td>
<td>8 (1)</td>
<td>5.5 1.1–26.2</td>
<td>.036</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>769</td>
<td>5 (0)</td>
<td>0.4 0.1–1.8</td>
<td>.280</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>769</td>
<td>1 (0)</td>
<td>7.3 0.2–131</td>
<td>.404</td>
</tr>
</tbody>
</table>

DECREASE in eGFR FROM BASELINE

Table 1. Baseline Characteristics of 2733 Patients Treated With OBV/PTV/r + DSV ± RBV in the Pooled Analysis

<table>
<thead>
<tr>
<th>Variable</th>
<th>N = 2022</th>
<th>n (%), median (IQR)</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>1989</td>
<td>1129 (57)</td>
<td>1.1 0.9–1.4</td>
<td>.320</td>
</tr>
<tr>
<td>Nausea</td>
<td>1989</td>
<td>28 (1)</td>
<td>1.9 0.7–5.0</td>
<td>.194</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>1989</td>
<td>18 (1)</td>
<td>2.5 1.2–5.1</td>
<td>.015</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>1989</td>
<td>2 (1)</td>
<td>2.5 0.9–7.7</td>
<td>.049</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>1989</td>
<td>0 (0)</td>
<td>5.2 0.1–151</td>
<td>.070</td>
</tr>
</tbody>
</table>

RESULTS

The analysis of safety outcomes included deaths and adjudicated serious adverse events (SAEs).

CONCLUSIONS

A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the end of treatment (EOT) with DPV without and with RBV, respectively.3,4 In the 7 clinical trials that had available BL urinalysis, 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the EOT with DPV without and with RBV, respectively.3,4

PREDICTORS OF CKD IMPROVEMENT

Table 4. Logistic Regression Analysis in 7 Clinical Trials – Excluding RUBY-I and TURQUOISE-III

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>2.1 1.2–3.9</td>
<td>.009</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1 1.2–7.7</td>
<td>.018</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>5.5 1.1–26.2</td>
<td>.036</td>
</tr>
</tbody>
</table>

DISCLOSURES

Disclosure statements are available with the online version of this report.

REFERENCES

1. The Standardized MedDRA Queries (SMQ) search terms: acute renal failure (SMQ20000003) and CKD (SMQ20000213).
2. Grade and severity of all laboratory abnormalities were defined as per the Standard MedDRA Queries (SMQ) search term "acute renal failure" (SMQ20000003) and "acute liver failure" (SMQ20000515). The Standard MedDRA Queries (SMQ) search term "acute renal failure" (SMQ20000003) and "acute liver failure" (SMQ20000515).
3. A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the EOT with DPV without and with RBV, respectively.3,4
4. A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the EOT with DPV without and with RBV, respectively.3,4

CONCLUSIONS

A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the end of treatment (EOT) with DPV without and with RBV, respectively.3,4

PREDICTORS OF eGFR IMPROVEMENT

Table 3. Adverse Events in 210% of Patients in Any Subgroup

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>2.1 1.2–3.9</td>
<td>.009</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1 1.2–7.7</td>
<td>.018</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>5.5 1.1–26.2</td>
<td>.036</td>
</tr>
</tbody>
</table>

DISCLOSURES

Disclosure statements are available with the online version of this report.

REFERENCES

1. The Standardized MedDRA Queries (SMQ) search terms: acute renal failure (SMQ20000003) and CKD (SMQ20000213).
2. Grade and severity of all laboratory abnormalities were defined as per the Standard MedDRA Queries (SMQ) search term "acute renal failure" (SMQ20000003) and "acute liver failure” (SMQ20000515). The Standard MedDRA Queries (SMQ) search term "acute renal failure” (SMQ20000003) and "acute liver failure” (SMQ20000515).
3. A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the EOT with DPV without and with RBV, respectively.3,4
4. A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the EOT with DPV without and with RBV, respectively.3,4

CONCLUSIONS

A total of 18% (486/2663) of patients had an increase of ≥10 mL/min/1.73 m² in eGFR at the end of treatment (EOT) with DPV without and with RBV, respectively.3,4

PREDICTORS OF CKD IMPROVEMENT

Table 4. Logistic Regression Analysis in 7 Clinical Trials – Excluding RUBY-I and TURQUOISE-III

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR 95% CI</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>History of diabetes</td>
<td>2.1 1.2–3.9</td>
<td>.009</td>
</tr>
<tr>
<td>Nausea</td>
<td>3.1 1.2–7.7</td>
<td>.018</td>
</tr>
<tr>
<td>≥Grade 3 ALT</td>
<td>5.5 1.1–26.2</td>
<td>.036</td>
</tr>
</tbody>
</table>
OBJECTIVE

The objective of the TOVA study was to evaluate the efficacy and safety of the 3D ± RBV regimen in patients with GT1a HCV infection, including those with cirrhosis (F3-F4) and coinfection with HIV.

STUDY DESIGN

The TOVA trial was a prospective, randomized, open-label, multicenter study conducted at 26 sites in the United States (Table 1). Patients were randomly assigned to receive either 3D ± RBV, 24 weeks (n = 16), or 3D ± RBV, 48 weeks (n = 93/96) in the modified ITT population (mITT). The primary endpoint was SVR12 in the mITT population. Participants were included regardless of prior treatment history and coinfection with HIV (Table 2A). The inclusion of patients with cirrhosis was based on real-world evidence showing that SVR rates are lower in these patients compared with those without cirrhosis. The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and Good Clinical Practice guidelines (ICH E6 R2). The trial was sponsored by AbbVie Inc. and conducted under a protocol approved by the Institutional Review Board at each site.

RESULTS

A total of 115 patients were screened and 99 were enrolled and received ≥1 dose of study drug (Figure 1). In the mITT population, 93/96 patients (93/96) achieved SVR12 (93/96) in the mITT population, and 97/100 patients (97/100) met the ITT population endpoint criteria, which excluded patients who discontinued treatment due to virologic failure (Figure 5). Figure 1. Study Flow

Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D ± RBV, 24 weeks (n = 16)</th>
<th>3D ± RBV, 48 weeks (n = 93/96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median (range)</td>
<td>52 (19–76)</td>
<td>50 (19–79)</td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>75 (100)</td>
<td>61 (77)</td>
</tr>
<tr>
<td>Race, Black or African American</td>
<td>37 (37)</td>
<td>24 (29)</td>
</tr>
<tr>
<td><strong>Virologic characteristics</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Virologic subtype</td>
<td>GT1a</td>
<td>GT1a</td>
</tr>
<tr>
<td>Fibrosis stage, n (%)</td>
<td>F0–F1</td>
<td>F0–F1</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of IDU, n (%)</td>
<td>59 (60)</td>
<td>47 (52)</td>
</tr>
<tr>
<td>History of psychiatric disorder, n (%)</td>
<td>9 (9)</td>
<td>17 (20)</td>
</tr>
<tr>
<td><strong>Co-infections</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIV co-infection, n (%)</td>
<td>2 (2)</td>
<td>2 (2)</td>
</tr>
</tbody>
</table>

TREATMENT ADHERENCE

• Treatment adherence was high, with 16–90% patients classified as adherent to each component of the 10a RBV regimen (Table 2A).

Table 2. Characteristics of Patients Who Experienced Virologic Failure

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D ± RBV, 24 weeks (n = 16)</th>
<th>3D ± RBV, 48 weeks (n = 93/96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adherence</td>
<td>96%</td>
<td>92%</td>
</tr>
</tbody>
</table>

SAFETY

• A total of 97 patients (86%) experienced an AE (Table 4). 46 AE were assessed as possibly related to DAA therapy (mental state disturbance, insomnia, fatigue), and 38 patients (34%) had a Grade 3 laboratory abnormality. The most common laboratory abnormality was reduced hemoglobin (Table 4).

Table 3. Summary of Clinical Laboratory Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D ± RBV, 24 weeks (n = 16)</th>
<th>3D ± RBV, 48 weeks (n = 93/96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laboratory parameter n/N (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT †</td>
<td>20 (20)</td>
<td>33 (35)</td>
</tr>
<tr>
<td>AST †</td>
<td>20 (20)</td>
<td>33 (35)</td>
</tr>
<tr>
<td>Total bilirubin †</td>
<td>21 (21)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Hemoglobin †</td>
<td>10 (10)</td>
<td>10 (10)</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• In HCV GT1a–infected US adults, >12–24-week treatment with 3D ± RBV resulted in an overall ITT SVR12 rate of 94%, which was higher than that observed in real-world observational studies.

Table 5. Summary of Clinical Laboratory Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>3D ± RBV, 24 weeks (n = 16)</th>
<th>3D ± RBV, 48 weeks (n = 93/96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>AEs</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>51 (51)</td>
<td>60 (64)</td>
</tr>
<tr>
<td>Grade 2</td>
<td>9 (9)</td>
<td>16 (17)</td>
</tr>
<tr>
<td>Grade 3</td>
<td>6 (6)</td>
<td>18 (20)</td>
</tr>
</tbody>
</table>

ACKNOWLEDGEMENTS

AbbVie sponsored the study, contributed to the design, participated in the collection, analysis, and interpretation of data, and contributed to the writing or reviewing of the manuscript. The author was responsible for the decision to submit the manuscript for publication. All authors approved the final manuscript as submitted.
RUBY-II: Efficacy and Safety of a Ribavirin-Free Ombitasvir/Paritaprevir/Ritonavir ± Dasabuvir Regimen in Patients With Severe Renal Impairment or End-Stage Renal Genotype 1a or 4 Infection

Edward Gane1, Ricardo Sola2, Eric Cohen3, Stuart K Roberts4, Jacob George5, Richard Skoen6, Stephen Riordan7, Nilofar Mobashery8, Manal Abumim9, Daniel E Cohen10, Kosh Agarwal

1Auckland City Hospital, Auckland, New Zealand; 2Hospital del Mar, Barcelona, Barcelona, Spain; 3AbbVie Inc., North Chicago, Illinois, United States; 4Ridley Hospital, Melbourne, Australia; 5Westmead Hospital, Westmead Institute for Medical Research and University of Sydney, New South Wales, Sydney, Australia; 6Royal Brisbane and Women's Hospital, Brisbane, Australia; 7Australian Institute of Medical Research and Australian National University, ACT, Australia; 8Institute of Liver Studies, King's College Hospital NHS Foundation Trust; London, United Kingdom

Background

- Many direct-acting antiviral (DAA) therapies are renally metabolized or excreted (eg, sofosbuvir) or have increased exposures in patients with severe renal impairment. As a result, these therapies are not recommended for patients with an estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m².
- By contrast, ombitasvir (OBV), paritaprevir (PTV), ritonavir (r), and dasabuvir (DSV) are all hepatatically metabolized and, therefore, require no dose adjustment in patients with any degree of renal impairment.
- OBV/PTV/r ± DSV-containing regimens have been shown to retain efficacy regardless of baseline resistance-associated polymorphisms,9 unlike the combination of grazoprevir and elbasvir, which often requires resistance profiling before treatment.
- In the phase 3b RUBY-I study, patients with stage 4 or 5 chronic kidney disease (CKD) who received this 3-DAA regimen had OBV/PTV/r and DSV exposures comparable to those observed in patients with healthy renal function, and 18/19 (95%) patients completed treatment and follow-up achieved sustained virologic response at post-treatment Week 12 (SVR12).10

Methods

- Exclusion

  - Age <18 years
  - Chronic infection with HCV GT1a or GT4
  - Stage 4 or 5 CKD, including hemodialysis or peritoneal dialysis
  - Absence of cirrhosis (META VIR score ≥3 or equivalent)
  - No prior HCV treatment experience
  - Coinfection with hepatitis B or human immunodeficiency virus
  - Current or past clinical evidence of cirrhosis
  - Albumin <3.5 g/dL, hemoglobin <8 g/dL, platelets <120,000 cells per μL, total bilirubin ≥3 mg/dL, or international normalized ratio ≥2.3

- Prior phase 3 trial of OBV/PTV/r + DSV suggested that GT1a-infected patients outside the US may have a higher SVR rate when treated with OBV/PTV/r + DSV, possibly related to the lower prevalence of the Q80K polymorphism outside the US.11 In this study, glycopeptidase F (GS-F) values were moderated in part by lowering abacavir at 12 weeks post-treatment.12

- Phase 3b study: RUBY-II

  - Objective: To examine the efficacy and safety of the RBV-free regimen of OBV/PTV/r + DSV in patients with stage 4 or 5 CKD (receiving dialysis) with chronic HCV GT1a or 4 infection.

- Inclusion

  - Patients with stage 4 or 5 CKD receiving dialysis with chronic HCV GT1a or 4 infection

- Study Design

  - A multinational, open-label, randomized, phase 3 study (NCT02610491) of 60 patients (13 with GT1a and 5 with GT4 infection) were enrolled at 8 study sites in Australia, New Zealand, Spain, and the United Kingdom

- Baseline demographics are shown in Table 1

- SVR12 was analyzed in all patients who received at least 1 dose of the study drugs (intent-to-treat [ITT] population); a modified ITT (mITT) population for patients with non-virologic failures was also evaluated.

- Adverse events (AEs) and laboratory abnormalities were assessed in all patients who received at least 1 dose of study drugs.

- A total of 18 patients (13 with GT1a and 5 with GT4 infection) were enrolled at 8 study sites in Australia, New Zealand, Spain, and the United Kingdom

- Baseline demographics are shown in Table 1

- The overall mITT SVR12 was 100% (17/17) in patients with HCV GT4 infection discontinued drug treatment at Week 2 to undergo elective renal transplantation and did not achieve SVR12

- Adverse events and laboratory abnormalities

  - Table 2

- Serious AEs occurred in 4 patients; these events (reversible renal transplant, worsening hypertension, gastroenteritis, and pulmonary edema) were assessed as not related to study drugs by the investigator

- Two patients prematurely discontinued study drugs

  - One HCV GT1a-infected patient discontinued study drug treatment Day 77 due to elevated alanine aminotransferase (grade 3 ≥5 × upper limit of normal and ≥2 × baseline); patient still achieved SVR12

  - One HCV GT4-infected patient underwent elective renal transplantation, withdrew consent at treatment Week 2, and did not achieve SVR12

References


Preliminary Results From TOPAZ-III: A Phase 3b Study Evaluating the Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir ± Ribavirin in Brazil With HCV Genotype 1 Infection and Advanced Fibrosis/ Cirrhosis


INTRODUCTION

• In the Brazilian population, the prevalence of chronic hepatitis C (HCV) infection is approximately 2.2%, with genotype 1b being the most common at all regions.

• Bebiv® universal healthcare system offers low treatment for citizens with chronic hepatitis C including individuals with HIV, neutropenia, chronic or obstructive pulmonary disease, diabetes/mellitus, hemolytic anemias, collagen-vascular disease, and fibrosis (METAVIR F4 or above or greater than 10 years METAVIR stage F4).

• Phase 3 trials of AbbVie’s all-oral, direct-acting antivirals (DAA) regimen of ombitasvir/paritaprevir/ritonavir (OPR) (approved by ANVISA, Brazil) and dasabuvir (piRNA), have demonstrated high rates of sustained virologic response at post-treatment Week 12 (SVR12) in GT1 infected patients with or without compensated cirrhosis.

• The majority of patients were white (82.9%), male (55.4%), and had a BMI (25.4 kg/m²). One hundred and sixty years of age (70.2%) (Table 1)

• Approximately half (54.1%) of patients received prior IFN-based therapy (including individuals with HIV/AIDS) (Table 1).

• Safety data were analyzed using descriptive statistics and confirmatory analysis was performed with a 2-sided 95% confidence interval.

RESULTS

BASELINE CHARACTERISTICS

• The study enrolled 222 individuals across 16 study centers in Brazil; 85.5% (222/260) completed treatment.

• The majority of patients were white (82.9%), male (55.4%), and had a BMI (25.4 kg/m²). One hundred and sixty years of age (70.2%) (Table 1)

• Approximately half (54.1%) of patients received prior IFN-based therapy (including individuals with HIV/AIDS) (Table 1). A total of 178 (80.8%) were treatment naïve (96% vs 97%, respectively) (Figure 3).

• SVR12 rates were similar between the subgroups with METAVIR F3 and F4 Fibrosis (87% vs 90%, respectively) (Figure 3).

EFFICACY

• The SVR12 rate was 56.0% (24/42) with a 5% confidence interval of (51.5%, 61.5%) in the overall ITT population (Figure 2).

• Eight patients did not achieve SVR12 (Table 2).

• Two patients did not achieve SVR12 (Table 2)

• One experienced on-treatment virologic failure (breakthrough – Week 12).

• One experienced post-treatment virologic failure (breakthrough – Week 12).

• One patient was missing SVR2 data due to premature study discontinuation 

• No virologic breakthrough events (BTs) were observed in this study (96% vs 97%, respectively) (Figure 3).

EFFICACY OF 12- OR 24-WEEK TREATMENT WITH 3-DAA ± RBV By Genotype and Fibrosis Stage

Table 1. TOPAZ-III Demographic and Baseline Characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment-naive</th>
<th>Prior IFN-based</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>46.0 (20.3)</td>
<td>52.0 (15.6)</td>
<td>0.039</td>
</tr>
<tr>
<td>Gender (male)</td>
<td>35 (25.6)</td>
<td>24 (23.5)</td>
<td>0.747</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.3 (4.9)</td>
<td>26.0 (5.0)</td>
<td>0.064</td>
</tr>
<tr>
<td>Baseline platelet counts</td>
<td>163 (80, 400)</td>
<td>153 (80, 400)</td>
<td>0.463</td>
</tr>
<tr>
<td>Baseline AST</td>
<td>36 (12, 78)</td>
<td>36 (12, 78)</td>
<td>0.887</td>
</tr>
<tr>
<td>Baseline ALT</td>
<td>27 (12, 59)</td>
<td>31 (15, 74)</td>
<td>0.352</td>
</tr>
<tr>
<td>Baseline bilirubin</td>
<td>0.7 (0.3, 1.7)</td>
<td>0.8 (0.3, 2.1)</td>
<td>0.272</td>
</tr>
<tr>
<td>Baseline total bilirubin</td>
<td>1.6 (1.0, 4.0)</td>
<td>1.6 (1.0, 4.0)</td>
<td>0.820</td>
</tr>
<tr>
<td>Baseline alkaline phosphatase</td>
<td>160 (97, 300)</td>
<td>269 (204, 450)</td>
<td>0.043</td>
</tr>
<tr>
<td>Baseline gamma glutamyl transferase</td>
<td>100 (50, 300)</td>
<td>100 (50, 300)</td>
<td>0.391</td>
</tr>
</tbody>
</table>

Table 2. Resistance Data for Virologic Failures

<table>
<thead>
<tr>
<th>Drug</th>
<th>Baseline Resistance</th>
<th>Post-treatment Resistance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ombitasvir</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Paritaprevir</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Ombitasvir + Paritaprevir</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

Table 3. FibroScan Percent Change From Baseline

<table>
<thead>
<tr>
<th>Fibrosis Stage</th>
<th>Baseline Mean</th>
<th>12-weeks Mean</th>
<th>Mean Change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F3</td>
<td>174.3</td>
<td>146.9</td>
<td>-27.4</td>
<td>0.002</td>
</tr>
<tr>
<td>F4</td>
<td>207.5</td>
<td>153.3</td>
<td>-54.2</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4. Summary of Adverse Events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Total AEs</th>
<th>Grade 3 AEs</th>
<th>Grade 4 AEs</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>All drug discontinuations</td>
<td>23 (10.5%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>0.685</td>
</tr>
<tr>
<td>Death</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Liver failure</td>
<td>1 (0.5%)</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Renal failure</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>1.000</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>1 (0.5%)</td>
<td>0 (0%)</td>
<td>1 (0.5%)</td>
<td>1.000</td>
</tr>
</tbody>
</table>

CONCLUSIONS

• Treatment with 3-DAA ± RBV in treatment-naive and experienced individuals resulted in 96% SVR12 rates in HCV GT1-infected Brazilian patients with bridging fibrosis (METAVIR F3 or above) for both 12 and 24 weeks through the study.

• Achieving SVR12 reduced liver cirrhosis in individuals with advanced fibrosis or cirrhosis.

• 3-DAA ± RBV was well tolerated and had a similar safety profile in Brazilian patients when compared to other global studies.

REFERENCES


ACKNOWLEDGMENTS

• The authors wish to thank all the patients that participated in this study and all the members of the clinical research organizations (CROs) that made this study possible.

• The authors also wish to thank the Advisory Board of Viral Hepatitis for their support and guidance throughout this study.

DISCLOSURES

• AbbVie (PIRUS Ph. D. C.) and Enanta (PIRUS Ph. D. C.) made the materials available for study, the study was conducted by: Nael H. A. Elbashir (PIRUS Ph. D. C.) and the data was analyzed by: Nael H. A. Elbashir (PIRUS Ph. D. C.)

• The study was designed, performed, and analyzed by: Nael H. A. Elbashir (PIRUS Ph. D. C.) and the data was analyzed by: Nael H. A. Elbashir (PIRUS Ph. D. C.)

• AbbVie employees may hold stock or stock options in AbbVie.

Presented at the 67th Annual Meeting of the American Association for the Study of Liver Diseases, November 11–15, 2016, Boston, Massachusetts
METHODS

Background

The 3 direct acting antiviral (DAAs) combination (3D) of paritaprevir/ritonavir/ombitasvir (NS5A protease inhibitor) identified by Abbott and Merck and dosed with (ritonavir), ombitasvir/paritaprevir/ritonavir (NS5A inhibitor) and daclatasvir (NS5B polymerase inhibitor) in ribavirin (RBV) was evaluated with ≥200,000 copies/mL (HCV) genotype 1 infected subjects as part of 6 phase 3 trials and was generally well tolerated with a 12-week sustained virologic response (SVR12) of 92% to 100% in patients with or without cirrhosis.1 The 3D regimen (ombitasvir/paritaprevir/ritonavir and daclatasvir) 3 weight based RBV was supported by the treatment of HIV genotype 1 (GT1) infection.

Rationale

With the potent 3D regimen, RBV dose reduction is expected to improve tolerability with minimal impact on efficacy.

Objectives

• To predict the efficacy (percent 12-week sustained virologic response [SVR12]) and
• To predict the safety event rates (total bilirubin [TBIL] elevation and hemoglobin [Hgb] reduction) of the 3D regimen + low dose (600 mg) RBV (3D + LDR) compared to the 3D regimen + weight based (1000 to 1200 mg daily) RBV (3D + WBR).

Methods

Datasets

In general, the studies (in Table 1) enrolled:

• GT1 HCV-infected subjects who were 18 years or older and are either HCV treatment naïve or treatment experienced with previous interferon (IFN) or pegylated IFN + RBV therapy.
• Studies excluded subjects who had a positive test result for hepatitis B or human immunodeficiency virus or recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that could preclude adherence to the study protocol.

Efficacy endpoint

• Data from GT1a subjects from four Phase 3 and Phase 2a studies (20 mg or 3D + WBR; N = 1215) were included in the analysis (Table 1). All the GT1a subjects included in the dataset were treated with the regimens for 12 weeks except for cirrhotic responders (3D treatment-naïve) who were treated for 24 weeks.

• Subjects who discontinued prematurely due to non-virologic reasons (adverse events or withdrawal of informed consent) irrespective of whether they achieved SVR24, or those with missing SVR24 data (loss to follow-up) were excluded from the analysis.

Safety data

Data from GT1a and GT1b subjects from six Phase 3 studies and one Phase 2 study (10 mg and 20 mg; N = 2340) were included in the analysis (Table 1).

Table 1: List of Studies with Efficacy and Safety Data Included in the Analyses

<table>
<thead>
<tr>
<th>Phase Study</th>
<th>Treatment Regimen</th>
<th>N = No. of Patients</th>
<th>N = No. of Events</th>
<th>% of Patients</th>
<th>% of Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3</td>
<td>GT1a treatment-naïve 3D regimen + RBV</td>
<td>139</td>
<td>1103</td>
<td>100</td>
<td>91%</td>
</tr>
<tr>
<td></td>
<td>GT1b treatment-naïve 3D regimen + RBV</td>
<td>0</td>
<td>43</td>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td></td>
<td>GT1a treatment-naïve 3D regimen + RBV</td>
<td>298</td>
<td>355</td>
<td>100</td>
<td>92%</td>
</tr>
<tr>
<td></td>
<td>GT1b treatment-naïve 3D regimen + RBV</td>
<td>204</td>
<td>380</td>
<td>100</td>
<td>95%</td>
</tr>
<tr>
<td></td>
<td>GT1a treatment-experienced + RBV</td>
<td>313</td>
<td>626</td>
<td>100</td>
<td>85%</td>
</tr>
<tr>
<td></td>
<td>GT1a treatment-experienced + RBV</td>
<td>172</td>
<td>351</td>
<td>100</td>
<td>94%</td>
</tr>
<tr>
<td>Phase 2</td>
<td>GT1a treatment-naïve 3D regimen + RBV</td>
<td>232</td>
<td>22</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td></td>
<td>GT1a treatment-experienced + RBV</td>
<td>310</td>
<td>60</td>
<td>99%</td>
<td>89%</td>
</tr>
</tbody>
</table>

Efficacy Analyses

• Multiple linear logistic regression model was developed (SAS 9.2) to establish the relationship between SVR12, and SVR12 values of DAA regimens for the GT1 infected subjects only.

• Age, weight, body mass index (BMI), sex, ethnicity, baseline viral load, IL28B genotype, CC (non-C or CC) +3D GT1, prior treatment experience (Natural, treatment experienced) and compensated liver cirrhosis (Child-Pugh A) were included as covariates.

• Backward elimination procedure was used to select the covariates. Relevant covariates were included in the final model based on statistical and clinical significance.

• The Hosmer-Lemeshow test was used to assess the goodness of fit of the logistic regression model. The model chi-square value (p = 0.05) indicates that the logistic regression model fits the data well. The final model was used to predict the SVR12, for the 3D + LDR compared to the 3D + WBR for the following 4 subpopulations: predictions for the 3D + LDR were conducted at 50% of the geometric mean value of RBV (IVR) from the 3D + WBR.

• P0: Non-cirrhotic females with 2.72 cc genotype (easy-to-use)
P1: Non-cirrhotic males with 2.6 cc genotype
P2: Cirrhotic females with 2.72 cc genotype
P3: Cirrhotic males with 2.6 cc genotype

• In addition to the above, efficacy analysis was done excluding AVIRO protocol study which included 2D and 3D regimens administered with different formulations compared to the marketed formulations used in other studies.

Safety Analyses

• Separate MMR models for the relationship between safety incidence rates (by severity for total bilirubin elevation and hemoglobin reduction) and area under the concentration time curve (AUC) values were developed (SAS 9.1.5).

• In the analyses, the predictor variables were logarithmic values of the following: AUCs for paritaprevir, ombitasvir, dasabuvir, ritonavir, and RBV derived from population pharmacokinetic analyses, treatment effects (no RBV versus RBV or placebo versus active treatment), and covariates including age, weight, sex, study effects, use of escape or genotype changing containing medication, and baseline status of the safety variable.

• Forward selection procedure was used to select the pharmacokinetic variables and covariates based on the Bayesian Information Criterion (BIC).

• The final model was used to predict the grade 3 total bilirubin elevation and grade 2 hemoglobin reduction for the 3D + LDR compared to the 3D + WBR predictions for the 3D + LDR were conducted at 40% to 60% of RBV AUC value from the 3D + WBR regimen.
GEODE-II: Efficacy and Safety of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With Low-Dose Ribavirin QD in Patients With Genotype 1a Chronic Hepatitis C Virus Infection Without Cirrhosis

Fred Poonard1, Shahvari Sedghi2, Paul J. Pockros1, Natanjan Ravendranath3, Robert Reinold4, Michael R Lucey5, Michael Epstein6, Leslie Bank7, David Bernstein8, Roy Trinh9, Preethi Krishnan10, Tami Pillet-Mapas11, Alkeshant R Polegato12, Rajveeth Kumar Pothapachan13, Kristina Unnerve14, Marisol Martinez15, David R Nelson16

1Texas Liver Institute, University of Texas Health Science Center, San Antonio, Texas, United States; 2Associate Professor of Medicine and Surgery, Mercer University School of Medicine, Macon, Georgia, United States; 3Division of Gastroenterology/Hepatology, Scripps Clinic, La Jolla, California, United States; 4Department of Infectious Diseases, University Hospitals, Cleveland, Ohio, United States; 5Division of Gastroenterology/Hepatology, Department of Medicine, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, United States; 6Annie Arundel Medical Center, Digestive Disorders, Annapolis, Maryland, United States; 7Principal Investigators’ Group, Regional Clinical Research Center, New York, United States; 8Hofstra Northwell School of Medicine, Manhasset, New York, United States; 9Abbvie Inc., North Chicago, Illinois, United States; 10Abbvie Deutschland GmbH & Co. KG, Ludwigshafen, Germany; 11Department of Medicine, Gam clf, Barcelona, Spain

BACKGROUND
- Ritonavir does not have an
- • Evaluate the safety and efficacy of Ombitasvir-speciﬁc and Ombitasvir-prothrombin activator complex
- • The direct antiviral agents (DAAs) ombitasvir/paritaprevir/ritonavir (3-DAA) administered combination is associated with improved virological response (VR) and a lower rate of severe adverse events (SAEs).
- • Hepatitis C virus (HCV) genotype 1a treatment guidelines recommend that RBV is administered in combination with a 3-DAA regimen.

OBJECTIVE
- To evaluate the safety and efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With Low-Dose Ribavirin QD in treatment-naive and treatment-experienced genotype 1a patients without cirrhosis.

METHODS
- Patients with GT1a infection without cirrhosis received 140 mg/105 mg/50 mg once daily for 12 weeks with low-dose RBV (600 mg once daily) for 12 weeks in a randomized, multicenter, double-blind, placebo-controlled study (PEARL-IV)4
- Treatment guidelines recommend that RBV is administered according to weight, where patients weighing ≤10 kg receive 100 mg/day, 10–20 kg 150 mg/day, and >20 kg 300 mg/day.

RESULTS
- Patients with GT1a infection were randomized to receive 3-DAA + full dose RBV (n = 213) or 3-DAA + low dose RBV (n = 213).

SAFETY
- Most adverse events (AEs) were mild or moderate in severity (75.2% vs 82.8%).
- Grade 3+ liver enzyme increases were observed in 39.6% of patients receiving full dose RBV and 94.7% of patients receiving low dose RBV.

PHARMACOKINETICS
- Though plasma concentrations of OBV, PTV, C316Y, M414I/T/V, E446K/Q, Y448C/H, C451R, A553T, Q80K (3-fold increase in EC50) was evaluated separately
- Treatment guidelines recommend that RBV is administered in combination with a 3-DAA regimen.
- Ombitasvir-specific and Ombitasvir-prothrombin activator complex
- The direct antiviral agents (DAAs) ombitasvir/paritaprevir/ritonavir (3-DAA) administered combination is associated with improved virological response (VR) and a lower rate of severe adverse events (SAEs).
- Hepatitis C virus (HCV) genotype 1a treatment guidelines recommend that RBV is administered in combination with a 3-DAA regimen.
AbbVie’s
Khatri
RBV
Vierling
Estimation
An
OBV
Renal Function, N (%)
Age (years)
without cirrhosis or with compensated cirrhosis with Stage 4
or previous
treatment or previous pegylated
Ribavirin
Lamivudine/Entecavir
obstipation
Stage 4 CKD
or ESRD (eGFR = 15 to
60 mL/min) or ESRD
(>10 to 15 hours post
dosing in Stage 4 CKD
or ESRD subjects or 12
hours post-dosing in
Stage 4 CKD and
ESRD subjects). The
treatment regimens for RBVII are shown below.

METHODS

To assess the pharmacokinetics (PK) of OBV, PTV, RTV, and DSV and
Ribavirin (RBV) exposures were generally within the range of those
observed in subjects with normal renal function or mild renal
impairment.

There were no clinically meaningful decreases in venous versus
arterial concentrations (≤ 17% decrease) for OBV, PTV, RTV, and
Ribavirin suggesting that hemodialysis does not extract DAAs or RTV
from the bloodstream. Ribavirin versus simultaneous collection during
hemodialysis started approximately 5 hours after the morning dose.

To date, subjects from RUBY I and RUBY II are shown
Figure 3
and AUC values for subjects with Stage 4 CKD or ESRD are combined from RUBY
I and RUBY II studies. N=12 for
Phase 3/3b Studies.

The exposures of OBV, PTV, RTV and DSV in HCV infected subjects with
Stage 4 CKD or ESRD were comparable to the exposures of these
 compounds in subjects with normal renal function or mild renal
impairment.

ERYC is an ongoing, open label
study of DAAs, RTV and RBV during hemodialysis
The study was designed to determine if the
DAAs, RTV and RBV exposures were not meaningfully
influenced by hemodialysis and to assess the
pharmacokinetics of OBV, PTV, RTV, and DSV in
subjects with Stage 4 CKD or ESRD. Subjects could participate in the
day for those receiving
hemodialysis treatment at the same
facility who had been identified for inclusion
in the study by the treating physician.

The studies were funded by AbbVie.

The authors declare competing financial interests in one or more
studies within the scope of this publication. SD is an employee of
AbbVie and may own Abbvie stock or stock options.

The subjects were treated as intent to treat subjects.

There were no statistically
significant differences in
exposures between those
who were on dialysis
and those who were not.

The study was conducted
in accordance with the
WMA Declaration of Helsinki.

Diana L. Shuster, Rajeev M. Menon, Bifeng Ding, Hong Li, Eric Cohen, Daniel E. Cohen, Sandeep Dutta, Jiuhong Zha

1 AbbVie’s all-oral IFN-free, direct-acting antiviral (DAAs) regimens include ombitasvir (OBV; NS5a inhibitor), paritaprevir (PTV; NS5a/NS5b protease inhibitor), elbasvir (EVR; NS5b RNA polymerase inhibitor), and dasabuvir (DSV; NS5B inhibitor). Abbott and Enzon, Inc.; Roivant (RTV) and daclatasvir (DAA, NS5A non-structural protein inhibitor) 2 Shafter is a registered trade name for thesolariel x protein inhibitor; 3 Shafter is a trade name for the solariel A genotype 3a

AbbVie, North Chicago, IL, USA, Clinical Pharmacology and Modeling, Amgen, Thousand Oaks, CA, USA

AbbVie, North Chicago, IL, USA, Biometrics, Abbvie, North Chicago, IL, USA, Infectious Diseases Development, Abbvie, North Chicago, IL, USA

CONCLUSIONS

• The exposures of OBV, PTV, RTV and DSV in HCV infected subjects with Stage 4 CKD or ESRD were comparable to the exposures of these compounds in subjects with normal renal function or mild renal impairment.

• OBV, PTV and DSV plasma concentrations are not notably affected during hemodialysis.

• These data support the conclusion that no dose adjustment is necessary for OBV, PTV, and DSV when administered to HCV infected subjects with Stage 4 CKD or ESRD.

• RBV exposures based on 290 mg QD dosing in Stage 4 CKD and ESRD subjects were comparable with exposures observed in HCV infected subjects without Stage 4 CKD or ESRD receiving the regular dose of ribavirin.

REFERENCES


ACtNOWLEDGMENTS

The authors appreciate the scientific writing and editorial contributions of Chagrin BioSciences, an arm of Medivate, and the authors acknowledge the assistance of the authors in the preparation of this manuscript. LBS is an employee of Medivate and a member of the scientific writing team.

PUBLICATION ETHICS

Medivate is a professional services company with expertise in scientific and medical writing. LBS is an employee of Medivate. The views and opinions expressed in this paper are those of the authors and do not necessarily reflect those of Medivate or its parent company, China Medical System Ltd. The authors declare competing financial interests in one or more studies within the scope of this publication.
**RUBY-I: Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir With or Without Ribavirin in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection With Severe Renal Impairment or End-Stage Renal Disease**


**INTRODUCTION**

- Ombitasvir/paritaprevir/r + dasabuvir (OBV/PTV/r + DSV) is approved for the treatment of GT1a (with or without RBV) and GT1b HCV infection, including patients with compensated cirrhosis.
- However, only limited clinical data have been published on the safety and efficacy of this regimen in patients with severe renal dysfunction, including those on dialysis.
- In the first cohort of the RUBY-I study, observed rates of sustained virological response (SVR) at 12 weeks post-treatment and 24 weeks after discontinuation of treatment (SVR12) were consistent with those reported in patients without kidney disease.

**OBJECTIVE**

- Evaluate the safety and efficacy of OBV/PTV/r + DSV ± RBV for 12 or 24 weeks in GT1 HCV-infected patients with severe renal impairment or end-stage renal disease, including those on dialysis.

**METHODS**

- **Study Design**: Multi-targeted 3 Direct-acting Antiviral Regimens (3-DAA).
- **PARTICIPANTS**: All patients were enrolled at 15 study sites in the US.
- **STUDY ASSESSMENTS**: Safety and efficacy data were available from the second cohort of RUBY-I, which includes patients with parenchymal cirrhosis or those who failed prior peginterferon/RBV treatment.

**RESULTS**

- **Participants**: 40 patients were enrolled in 15 study sites in the US – 15 (35/46%) of patients had compensated cirrhosis – 83% (36/44) of patients had CKD stage 5, and 69% (30/44) were on dialysis.

**EFFICACY**

- **SVR12 was achieved by 40/48 (96%) patients**: 27/28 in Arm C, 39/45 in Arm A, and 11/11 in Arm E (Figure 2).

**SAFETY**

- **Most AEs**: Mild or moderate in severity (Table 3).
- **AEs of anemia occurred only in patients receiving RBV**: – Of the 19 cases of anemia, 11 were mild, 4 were moderate, and 4 were severe.

**RESULTS (CONTINUED)**

- **SVR12 Rates for the 3 Groups of Patients Enrolled in This Study as Well as the Total**: (Figure 2).

**SUMMARY AND CONCLUSIONS**

- The regimen was generally well-tolerated for this group of patients with severe renal disease, with acceptable adherence to a 1:1 DAA/RBV ratio for 12 or 24 weeks.
- A large proportion of patients on RBV required RBV dose modifications.
- Most AEs were mild or moderate in severity.

**REFERENCES**

- 1. Viekira Pak prescribing information. [viekirapak.com](http://viekirapak.com).

**ACKNOWLEDGMENTS**

- The study was supported by AbbVie.
- The authors acknowledge the following for their contributions: J Vierling: Consultant/Advisor: Asana, Bayer, Biothergen, DE Cohen, T Podsadecki; Contractor: Medtronic, Merck, Novartis, Presidio, Roche, Santaris; Advisory Committee: Hyperion, Intercept, Novartis; Speaker: Gilead, Medtronic, Merck, Novartis, Presidio, Roche, Santaris, Theravance, Vertex.
- M Lawitz: Consultant/Advisor: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Pegasys, Regeneron, Roche, Santaris; Speaker: AbbVie, Boehringer Ingelheim, Gilead, Pegasys, Roche, Santaris, Theravance, Vertex.
- D Bernstein: Consultant/Advisor: Asana, Bayer, Biothergen, DE Cohen, T Podsadecki; Speaker: Asana, Bayer, Biothergen, DE Cohen, T Podsadecki.
- PS Mantry: Consultant/Advisor: Merck, Novartis, Presidio, Roche, Santaris, Theravance, Vertex.
- E Lawitz: Consultant/Advisor: AbbVie, Boehringer Ingelheim, Bristol-Myers Squibb, Gilead, Pegasys, Regeneron, Roche, Santaris; Speaker: AbbVie, Boehringer Ingelheim, Gilead, Pegasys, Roche, Santaris, Theravance, Vertex.

**DISCLOSURES**

- All authors report no relevant conflicts of interest in connection with the design, conduct, analyses, and interpretation of this study or the decision to submit it for publication.
- The authors report no relevant financial or professional associations or interests that might pose a potential conflict of interest in connection with the submission of this study.
Evaluate the safety and efficacy of Ombitasvir/Paritaprevir/ritonavir and dasabuvir in Asian adults with genotype 1b chronic hepatitis C virus infection — A randomised, double-blind, placebo-controlled study.

INTRODUCTION

In Asia, more than 60 million people may be chronically infected with the hepatitis C virus (HCV).

The prevalence of chronic HCV infection in China was found to be greater than in the Americas and Europe combined.

HCV genotype 1b (GT1b) is the most prevalent sub-genotype in China.

Despite recent advances in the development of oral, direct-acting antiviral (DAA) agents for HCV infection, GT1b remains a significant challenge in China.

A total of 650 participants were randomised to receive either Arm A: Ombitasvir/Paritaprevir/ritonavir (3-DAA) or Arm B: Placebo (Table 1).

Paritaprevir (PTV, formerly ABT-450) is a potent HCV NS3/4A protease inhibitor

### Key Eligibility Criteria

- **Primary Endpoint**: SVR12
- **Secondary Endpoint**: Safety

### Methods

**Participants**: Ombitasvir/Paritaprevir/ritonavir boosted with ritonavir (3-DAA) or placebo for 12 weeks.

**Outcome Measures**: Safety

**Efficacy**: SVR12

**Safety**: All adverse events (AEs) leading to drug discontinuation

**Primary Endpoints**: SVR12

**Secondary Endpoints**: Safety

**Safety Assessment**: All AEs are to be followed up for 48 weeks

### Results

SVR12 rates were 99.0%, 100%, and 100% in Arm A treatment-naive patients, 100%, 100%, and 100% in Arm A treatment-experienced patients, 99.0%, 100%, and 100% in Arm B treatment-naive patients, and 99.0%, 100%, and 100% in Arm B treatment-experienced patients.

**Efficacy**: SVR12 was achieved in 100% of 60 Chinese treatment-naive patients and 100% of 60 treatment-experienced patients. The primary end-point of the 95% confidence interval was 1.2% above the 80% success threshold for treatment-naive patients and the 75% success threshold for treatment-experienced patients.

The SVR12 rates were 99.0%, 100.0%, and 100.0% in Arm A treatment-naive patients and 99.0%, 100.0%, and 100.0% in Arm A treatment-experienced patients from each cohort.

### Conclusion

Ombitasvir/Paritaprevir/ritonavir and dasabuvir for 12 weeks achieved a high cure rate in GT1b-infected Asian patients, supporting their use in clinical practice.

### Acknowledgements

The authors thank the patients, their families, and health care providers for their contributions to this study. The authors also thank the employees of the study centres, the nurses and study staff for their excellent participation and support during the trial. The authors would like to acknowledge the contribution of the Data Management and Coordinating Centre (DMCC) and the Statistical Analysis and Coordinating Centre (SACC) at Abbott Laboratories, North Chicago, Illinois, USA.

### References


**Disclosure**

All authors or any company at which any author is employed have declared no financial interest.

**Conflict of Interest**

The authors have no personal or professional conflicts of interest in these studies.

**Funding**

All authors or any company at which any author is employed have declared no financial interest in these studies.
ONXY-II: Safety and Efficacy of Ombitasvir/Paritaprevir/Ritonavir and Dasabuvir Coadministered With Ribavirin in Asian Adults With Genotype 1b Chronic Hepatitis C Virus Infection and Compensated Cirrhosis

Lai Wei1, Guiqiang Wang2, Yan Luo3, Chi-Jen Chu4, Seung Woon Paik5, Jinlin Hou6, Jun Cheng7, Qing Xie8, Zhongping Duan9, Jia-Horng Kao10, Bo Fu3, Niloufar Mobashery3, Jeong Heo11

4. Risks and benefits of a study being compared with those of standard care for the condition under study
5. Choice and standard use of diagnostic tests in a clinical trial
6. Appropriate methods for evaluating treatment efficacy

METHODS

Onyx-II is an ongoing Phase 3, multicenter, single-arm trial conducted in China, South Korea, and Taiwan. Patients received the 3-DAA (OBR/PTV/r + DSV ± RBV) regimen for 12 weeks and were followed for 24 weeks after treatment completion. The primary efficacy objective for the intent-to-treat (ITT) population was SVR12 in patients with compensated cirrhosis.

RESULTS

The study included 113 patients with compensated cirrhosis from China, South Korea, and Taiwan. SVR12 was achieved by 100% of patients treated with the 3-DAA regimen. No treatment-related serious adverse events were reported. The most common adverse events were nausea and pruritus.

Efficacy

SVR12 was achieved by 100% of patients. The lower bound of the 95% confidence interval (95% CI) was above the 95% confidence threshold; therefore, the 95% CI was expressed as a proportion of the historical telephonic plus (THP) cutoff (Figure 2).

Table 1. Abnormal Laboratory Results Exclusion Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>China</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total bilirubin (μmol/L)</td>
<td>24 (3) ± 18</td>
<td>26 (3) ± 33</td>
<td>26 (3) ± 24</td>
<td>25 (4) ± 22</td>
</tr>
<tr>
<td>Direct bilirubin (μmol/L)</td>
<td>11 (2) ± 12</td>
<td>12 (2) ± 13</td>
<td>12 (2) ± 11</td>
<td>12 (2) ± 12</td>
</tr>
<tr>
<td>ALT (U/L)</td>
<td>28 (6) ± 30</td>
<td>23 (3) ± 28</td>
<td>23 (3) ± 19</td>
<td>23 (3) ± 23</td>
</tr>
<tr>
<td>AST (U/L)</td>
<td>23 (3) ± 27</td>
<td>19 (3) ± 22</td>
<td>19 (3) ± 17</td>
<td>19 (3) ± 19</td>
</tr>
</tbody>
</table>

Table 2. Patient Demographics and Baseline Characteristics

<table>
<thead>
<tr>
<th>Country</th>
<th>N (%)</th>
<th>Age (yr)</th>
<th>Sex (%)</th>
<th>HCV Genotype/subgenotype (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>China</td>
<td>63 (68)</td>
<td>61.0 ± 12.0</td>
<td>43 (68)</td>
<td>44 (70)</td>
</tr>
<tr>
<td>South Korea</td>
<td>21 (48)</td>
<td>61.0 ± 12.0</td>
<td>10 (48)</td>
<td>15 (71)</td>
</tr>
<tr>
<td>Taiwan</td>
<td>20 (55)</td>
<td>60.0 ± 12.0</td>
<td>11 (55)</td>
<td>13 (65)</td>
</tr>
</tbody>
</table>

Table 3. Treatment-emergent Adverse Events

<table>
<thead>
<tr>
<th>Event</th>
<th>China</th>
<th>South Korea</th>
<th>Taiwan</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pruritus</td>
<td>6 (10)</td>
<td>4 (19)</td>
<td>6 (30)</td>
<td>16 (15)</td>
</tr>
<tr>
<td>Blood bilirubin increased</td>
<td>23 (37)</td>
<td>2 (10)</td>
<td>1 (5)</td>
<td>26 (25)</td>
</tr>
</tbody>
</table>

SAFETY

Most AEs were mild in severity.

Conclusions

The 3-DAA regimen was well tolerated and achieved high SVR12 rates in patients with compensated cirrhosis.

REFERENCES


ACKNOWLEDGMENTS

The authors acknowledge the contributions of all physicians, nurses, and other study personnel who participated in the trial. The authors also acknowledge the editorial support from Melissa Green, PhD, of AbbVie.

CONCLUSIONS

1. SVR12 was achieved by 100% of patients enrolled in this study.
2. The regimen was well tolerated; AEs were mostly mild.
3. One patient had AEs leading to study drug discontinuation.
4. One serious AE in the Chinese cohort was assessed as being RBV-related but not DAA-related.
5. Post-baseline laboratory abnormalities with a severity grade ≥3 were rare.
6. The efficacy and safety profiles observed in this Asian regional Phase 3 study are similar to those in the global Phase 3 studies.

DISCLOSURES

None of the authors have a financial relationship with a commercial entity that has an interest in the subject of this manuscript.