# 1.0 Abstract

## Title

Real World Evidence of the Effectiveness of Paritaprevir/r + Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C - An Observational Study in Hungary (VERITAS)

## Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir , ombitasvir, dasabuvir, ribavirin, sustained virological response (SVR), Health Economics and Outcomes Research (HEOR), Patient Reported Outcome (PRO), EuroQol 5 dimension 5 level (EQ-5D-5L), WPAI (Work Productivity and Activity Impairment)

## Rationale and Background

The interferon-free combination regimen of paritaprevir/ritonavir (r) – ombitasvir with or without dasabuvir (ABBVIE REGIMEN) ± ribavirin (RBV) for the treatment of chronic hepatitis C (CHC) has been shown to be safe and effective in randomized controlled clinical trials with strict inclusion and exclusion criteria under well controlled conditions.

The rationale for this observational study was to determine how the efficacy and safety of the ABBVIE REGIMEN as demonstrated in pivotal trials translates into real world everyday clinical settings when used according to local label in Hungary in a clinical practice patient population.

## Research Question and Objectives

What is the effectiveness, PRO and work productivity of the interferon-free ABBVIE REGIMEN ± RBV in patients with CHC in a real life setting across clinical practice patient populations?

Primary Objective

1. To describe in routine clinical practice the effectiveness of the interferon-free PTV/r+OBV±DSV±RBV in patients with CHC as evidenced by SVR12

Secondary Objectives

2. To describe in routine clinical practice the effectiveness of the interferon-free PTV/r+OBV±DSV±RBV in patients with CHC as evidenced by sustained virological response at 24 weeks (≥141 days) after end of treatment (SVR24)
3. To provide real world evidence for predictive factors of virological response
4. To describe the pattern of real world use of the PTV/r+OBV±DSV±RBV with respect to different patient and treatment characteristics
5. To evaluate the influence of adherence on treatment outcome in routine clinical practice
6. To collect information on co-morbidities and concomitant medication in the Hungarian population
7. To describe the tolerability of the PTV/r+OBV±DSV±RBV
8. To document the effect of the PTV/r+OBV±DSV±RBV on PROs and work productivity in the [country] population
9. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization

## Study Design

This was a prospective, multi-center observational study in patients receiving the interferon-free PTV/r+OBV±DSV with or without RBV in Hungary. The prescription of a treatment regimen was at the discretion of the physician in accordance with local clinical practice and label, was made independently from this observational study and preceded the decision to offer the patient the opportunity to participate in this study.

## Subjects and Study Size, Including Dropouts

The target population comprised adult male or female patients with confirmed CHC, genotype 1 or 4, treatment-naïve or treatment-experienced, receiving combination therapy with the interferon-free PTV/r+OBV±DSV±RBV (AbbVie regimen) ± RBV according to standard of care and in line with the local label who voluntarily signed and dated a patient authorization to use and disclose his/her anonymized health data prior to inclusion into the study.

In total, 244 patients were enrolled into the study. One patient never started treatment, thus the safety population (SP) and the target population (TP) included 243 patients. In the TP there were 5 patients with genotype 1a who not received RBV and they were excluded from core population (CP, number of patients: 238). Reasons from excluded from Core with sufficient follow-up (CPSFU12, number of patients: 233) were failure to return for 4 patients, and other not further specified for one patient. Reasons from excluded from Core with sufficient follow-up (CPSFU24, number of patients: 232) was no HCV RNA test after 12 weeks EoT for one patient.

## Variables and Data Sources

Primary Variable

- The percentage of patients achieving SVR12 (HCV RNA <50 IU/mL 12 weeks [i.e. ≥70 days]after the last actual dose of the PTV/r+OBV±DSV±RBV)

Secondary Variables

- The percentage of patients achieving SVR 24 (HCV RNA <50 IU/mL 24 weeks [i.e. ≥141 days] after the last actual dose of the ABBVIE REGIMEN (PTV/r+OBV±DSV±RBV)
- Type of treatment regimen (PTV/r+OBV±DSV±RBV, intended and actual combination, dose and duration)
- Adherence
    - Percentage of the DAA dose taken in relation to the target dose of DAA (cumulative dose taken divided by target dose in percent)
    - Percentage of the RBV dose taken in relation to the target dose of RBV (cumulative dose taken divided by target dose in percent)
    - Percentage of missed RBV treatment days in relation to the target number of RBV treatment days.
- The number and percentage of co-morbidities and concomitant medication
- The number and percentage of serious and non-serious adverse events and pregnancy occurrences
- Questionnaires on PROs: e.g. EuroQol 5 dimension 5 level (EQ-5D-5L) questionnaire and work productivity and activity impairment (WPAI) questionnaire prior to treatment initiation, at EoT as well as 12 and 24 weeks after EoT.
- PAM-13, PSP satisfaction and utilization questionnaires

## Results

In total, 244 patients were enrolled into the study. One patient never started treatment, thus the safety population (SP) and the target population (TP) included 243 patients. In the TP there were 5 patients with genotype 1a who not received RBV and they were excluded from core population (CP, number of patients: 238). Reasons from excluded from Core with sufficient follow-up at Post Treatment (PT) Week 12 (CPSFU12, number of patients: 233) were failure to return for 4 patients, and other not further specified for one patient. Reasons from excluded from Core with sufficient follow-up at PT Week 24 (CPSFU24, number of patients: 232) was no HCV RNA testmore than 12 weeks after EoT for one patient.

**Baseline characteristics**

Median age of patients in the CP was 60 years, 41.6% of participants were male and all patients were white/Caucasian. The most prevalent HCV genotype was genotype 1b (95.4%). Cirrhosis was present in 70.2% of patients and 12.2% had transition to cirrhosis. Treatment experienced patients accounted for 66.0% of the population. Duration of the HCV infection diagnosis was from 0 to 40 years prior to study start (mean (± SD) 9.1 ± 7.70 years, median 7.5). 88.2% patients in the CP did not consume alcohol.

The planned treatment duration was 12 weeks for 228 patients (95.8%). The 3 direct-acting antiviral agents (3-DAA) combination of paritaprevir/r plus ombitasvir plus dasabuvir without RBV was prescribed for the majority of the CP (n: 132, [55.2%]), whereas the 3-DAA regimen in combination with RBV was prescribed for 96 patients (40.3%).

One patient (0.4%) was taking the 3-DAA regimen without RBV for 24 weeks, whereas 9 patients (3.8%) was taking 3-DAA regimen with RBV.

**Effectiveness**

The virological response rate SVR12 was 94.5% (95% CI: [90.9%, 96.8%]) in the CP. The sustained virological response rate in the populations with sufficient follow-up (SVR12 -CPSFU12) data were 96.6% (95% CI: [93.4%, 98.3%] at 12 weeks.

In patients with genotype 1a, and 1b, SVR12 in the CP was 80.0% (95% CI: [49.0%, 94.3%]) and 95.2% (95% CI: [91.6%, 97.3%]), whereas respective SVR12 rates in the CPSFU12 were 80.0% (95% CI: [49.0%, 94.3%]) and 97.3% (95% CI: [94.3%, 98.8%]).

For the patients with cirrhosis SVR12 was 94.0% (95% CI: [89.3%, 96.7%]) in the CP and 95.7% (95% CI: [91.5%, 97.9%]) in the CPSFU12. In the non-cirrhosis group

SVR12 was 95.8% (95% CI: [88.3%, 98.6%]) in the CP and 98.6% (95% CI: [92.2%, 99.7%]) in the CPSFU12.

Reasons for virological failure among 13 SVR12 non-responders reported by the physician were on-treatment virological failure for 2 patients, relapse for 3 patients, death for 3 patients, premature treatment discontinuation for 2 patients and none of the above categories (including patients with missing SVR12 data) for 3 patients; 10 of these patients had cirrhosis.

The sustained virological response rate in the populations with sufficient follow-up (SVR24 -CPSFU12) data were 96.6% (95% CI: [93.3%, 98.2%] at 24 weeks.

In patients with genotype 1a, and 1b, SVR24 (CPSFU24) was 80.0% (95% CI: [49.0%, 94.3%]) and 97.3% (95% CI: [94.2%, 98.8]).

For the patients with cirrhosis SVR24 was 95.7% (95% CI: [91.4%, 97.9%]) in the CPSFU24. In the non-cirrhosis group SVR24 was 98.6% (95% CI: [92.2%, 99.7%]) in the CPSFU24.

Multiple logistic regression methods were used to investigate the impact of baseline factors on SVR24. Only immunologically mediated disease remained statistically significant from the factors. Patients with immunology mediated disease showed lower SVR24 rates than patients without immunologically mediated disease (odds ratio: 0.070, 95% CI: [0.005,0.903].

**Adherence**

For most patients (93.7%) in the CP the adherence rate to AbbVie regimen was greater than 95% and less than or equal to 105%. Similar results were reported in the cirrhosis group (92.8%) and in the non-cirrhosis group (95.8%).

For most patients (78.1%) in the CP the adherence rate to RBV was greater than 95% and less than or equal to 105%. Similar result reported in the cirrhosis group (78.8%) and in the con-cirrhosis group (75.0%).

The association between adherence to AbbVie regimen and SVR24 as well as between adherence to RBV and SVR24 was analyzed using univariate and multiple logistic regression methods including adherence as mandatory factor. Based on these models patients with lower adherence showed lower SVR24 rates compared to patients with higher adherence.

## Patient reported outcomes

### EQ-5D-5L

For the index score and the VAS at 12 weeks after EoT and 24 after EoT, there were slight improvements compared to baseline. Comparing the change between patients administered 3DAA with RBV and those administered 3DAA without RBV ,no relevant difference could be detected for the index score (12 weeks after EoT p=0.4770; 24 weeks after EoT p=0.9219). The difference in change of VAS 24 weeks after EoT and baseline between patients administered 3DAA with RBV and those administered 3DAA without RBV was statistically significant (p=0.0201) but not the difference in change of VAS 12 weeks after EoT and baseline (p=0.0786).

### WPAI

Of the 232 patients in the CP who answered the WPAI at baseline 62.1% were unemployed at baseline. Of the 226 patients who answered WPAI at EoT 61.9 were unemployed at EoT. Of the 221 patients who answered the WPAI both at baseline and EoT 5 unemployed patients at baseline became employed at EoT and 6 employed patients at baseline became unemployed at EoT.

Absenteeism (%) decreased from 5.8±18.7 at baseline to 2.7±13.1 at EoT and 3.7±17.6 at 12 weeks after EoT. At 24 weeks after EoT 5.9±22.6 reported in the CP.

Presenteeism (%) changed from 12.2±21.3 at baseline to 13.9±24.8 at EoT and 7.3±18.4 at 12 weeks after EoT. At 24 weeks after EoT 5.1±15.7 reported in the CP.

TWPI (%) changed from 16.7±27.1 at baseline to 14.7±26.4 at EoT and 10.4±24.5 at 12 weeks after EoT. At 24 weeks after EoT 10.3±26.6 reported in the CP.

TAI (%) changed from 22.9±26.0 at baseline to 23.9±23.7 at EoT and 16.1±23.7 at 12 weeks after EoT. At 24 weeks after EoT 13.3±21.2 reported in the CP.

**PAM-13**

PAM-13 changed from 60.7±11.8 at baseline to 59.8±11.7 at EoT in the CP. No statistically differences in changes between patients administered 3DAA with RBV and those administered 3DAA without RBV.

**Patient Support Program (PSP)**

75.2% of patients participated in the patient support program and found it fully or mostly addressing their needs. The majority of patients utilized materials at least once weekly and reported their level of satisfaction with the program as very good or good.

## Safety

**Exposure to study medication**

The mean duration of AbbVie regimen was 88±20.1 days in the SP. In the 3DAA without RBV mean duration was 87±17.5 days, whereas the mean duration was 90±23.1 in the 3DAA with RBV group. Early discontinuation of AbbVie regimen was reported for 6 patients (2.5%). Two of them were treated with 3DAA without RBV, and 4 patients were treated with 3DAA with RBV. Duration of RBV taken was 85±29.6 days, and it was discontinued earlier than AbbVie regimen for 7 patients.

Unintended medication error or pregnancy was not reported.

**Laboratory data**

For some patients reported potentially clinically significant laboratory values. The analysis revealed 12 patients with very high creatinine, 23 patients with very low

creatinine clearance, 1 patient with very low hemoglobin value, 1 patient with very low platelets, 1 patient with very high ALT and 1 patient with very high AST.

**Adverse events (AE) and serious adverse events (SAE)**

Adverse events were registered in 29 (11.9%) patients (34 events). The proportion of patients with AEs and the number of AEs were higher in the 3DAA+RBV (23 patients [21.9%], 27 events) compared with 3DAA without RBV group (6 patients [4.3%], 7 events). The proportion of patients with AEs and number of events were also higher in the cirrhosis subgroup (22 patients [12.8%], 25 events) in comparison with no-cirrhosis subgroup (7 patients [9.9%], 9 events).

Overall of SP the most affected (>1.0%) SOC was blood and lymphatic system disorders (17 events in 17 [7.0%] patients) followed by infections and infestations (3 events in 3 [1.2%] patients. In the 3DAA+RBV group the most affected (at least 2 events) SOC was blood and lymphatic disorders (17 events in 17 [16.2%]) patients, followed by infections and infestations, hepatobiliary disorders (2 events in 2 patients [1.9%]. In the 3DAA without RBV group only one event per SOC was registered. In the cirrhosis subgroup the most affected (at least 2 events) SOC was blood and lymphatic disorders (11 events in 11 [6.4%]) patients, followed by infections and infestations, hepatobiliary disorders (3 events in 3 patients [1.7%] and hepatobiliary disorders (2 events in 2 patients [1.2%]) . In the non-cirrhosis subgroup blood and lymphatic system disorders was the most affected registered SOC (6 events in 6 patients [8.5%]).

The majority of events was moderate AEs (20 events), 11 events were registered as mild and 3 registered as severe.

5 (2.1%) patients experienced 6 events assessed as related to the therapy with AbbVie regimen (hyperbilirubinaemia [2 events], anemia, enzyme level increased, pruritus, hypotension), whereas 20 (19.0%) patients experienced 21 events assessed as possibly related to RBV (anemia [17 events], diarrhea, fatigue, cough, dermatitis allergic).

3 (1.2%) patients experienced 3 events leading to withdrawal of AbbVie regimen (anemia, sepsis, enzyme level increased), whereas 8 (7.6%) patients experienced 8 events leading to withdrawal of RBV (anemia [4 events], diarrhoea, fatigue, sepsis, dermatitis allergic).

There were 7 SAEs in the study reported in 6 (3.5% ) patients (3DAA without RBV: oedema peripheral, , intervertebral disc disorder, hypertension, hospitalization ; 3DAA + RBV: cardiac failure, anaemia, sepsis). These events were neither related to AbbVie regimen, nor RBV.

For two patients SAE led to death (cardiac failure, sepsis). For one further patient a non-treatment emergent AE led to death (general physical health deterioration).

**Co-morbidities and concomitant medication**

Co-morbidities and/or co-infections were present in 81.5 % of the CP at baseline. Co-infections were only documented for one patient (hepatitis B virus). Liver and/or CHC related co-morbidities (hepatocellular carcinoma, steatosis, alcoholic liver disease, auto-immune hepatitis, cryoglobulinemia, auto-immune skin disease) were reported in 46 (19.3%) patients. Other co-morbidities were present in 190 (79.8%) patients. The most common other co-morbidities (>10%) were type II diabetes mellitus (56 patients [23.5%]) and hypertension (118 patients [49.6%]).

In the SP, 69.5% of patients were receiving concomitant medications. The most frequently (>10%) taken classes of concomitant medications were beta blocking agents (32.1%), ace inhibitors (21.8%), diuretics (17.3%), drugs for peptic ulcer and gastro-oesophageal reflux disease (17.3%), calcium channel blockers (14.0%), blood glucose lowering drugs (11.1%) and mineral supplements (10.3%).

## Discussion

Currently there is limited country specific data available in Hungary on the real world effectiveness of the AbbVie regimen. The present study was set up to close this data gap.

The results of this study support data of the previous interventional and observational studies of the AbbVie regimen. The results of this study demonstrate that treatment of CHC 1 genotype patients with OBV/PTV/r+ DSV± RBV is effective and well tolerated in routine clinical practice. Both regimens help achieve SVR12 and SVR24, with low non-responders rates. No new safety signal was observed.

## Marketing Authorisation Holder(s)

AbbVie Deutschland GmbH& Co. KG [redacted]

## Names and Affiliations of Principal Investigators