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## 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 Germany (LIFE-C)

### Keywords

Chronic hepatitis C (CHC), non-interventional study, paritaprevir, ombitasvir, dasabuvir, ribavirin, sustained virological response (SVR), Patient Reported Outcome (PRO), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Impairment (WPAI), Pictorial Representation of Illness and Self-Measure (PRISM), Patient Activation Measure (PAM-13)

### 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.

This observational study is one of the first effectiveness studies examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Germany in a clinical practice patient population outside of a strict clinical study setting.

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 and to assess the impact on patient reported outcome (PRO) and work productivity.

### Research Question and Objectives

#### Research Question

What is the effectiveness and PRO or work ability of the interferon-free ABBVIE REGIMEN ± RBV in patients with CHC in a real life setting across different patient populations?

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### Primary Objective

1. To describe in routine clinical practice the effectiveness of the interferon-free ABBVIE REGIMEN ± RBV in patients with CHC as evidenced by sustained virological response at 12 weeks after end of treatment (SVR12)

### Secondary Objectives

2. To provide real world evidence for predictive factors of virological response
3. To document the effect of the ABBVIE REGIMEN ± RBV on PROs and work productivity in the German population
4. To describe the pattern of real world use of the ABBVIE REGIMEN ± 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 describe the tolerability of the ABBVIE REGIMEN ± RBV
7. To collect information on co-morbidities and concomitant medication in the German population

### **Study Design**

This was a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± RBV in Germany. 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. Follow-up visits, treatment, procedures and diagnostic methods followed physicians' routine clinical practice. Data to be documented were those closest to the following time windows: baseline, early on-treatment visit, mid-treatment visit (for patients with a treatment duration of 24 weeks), end of treatment (EoT), early post-treatment and 12, 24 and 48 weeks after the end of treatment (representing SVR12, SVR24 and SVR48).

### **Setting**

This observational study was conducted in 45 medical centers in Germany experienced in the treatment of CHC. First patient entered the study on 3 December 2015, last patient last visit was on 26 March 2018.

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## Subjects and Study Size, Including Dropouts

The eligible 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 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, 472 patients were enrolled into the study. Since treatment was never started in 2 patients, the safety population (SP) and the core population (CP) comprised 470 patients. Thirty seven patients were excluded from the CP to form the core population with sufficient follow-up data regarding SVR12 (CPSFU12) (n=433): 32 patients did not return and 5 patients had no HCV RNA measurement ≥70 days after EoT due to other reasons, not further specified (but not related to virological response or safety).

## Variables and Data Sources

### Primary Variable

- The percentage of patients achieving SVR12 (HCV RNA <50 IU/mL 12 weeks [i.e. ≥70 to 126 days] after the last actual dose of the ABBVIE REGIMEN)

### Main Secondary Effectiveness Variables

- The percentage of patients with virological response (HCV RNA <50 IU/mL) at EoT (defined as last intake of ABBVIE REGIMEN or RBV)
- The percentage of patients with relapse (defined as HCV RNA <50 IU/mL at EoT followed by HCV RNA ≥50 IU/mL)
- The percentage of patients with breakthrough (defined as at least one documented HCV RNA <50 IU/mL followed by HCV RNA ≥50 IU/mL during treatment)

### Further Secondary Variables

- Type of treatment regimen (± dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Adherence
- Serious (SAEs) and non-serious adverse events (AEs) and pregnancy occurrences
- Questionnaires on PROs: Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Work Productivity and Activity Impairment - Hepatitis C (WPAI Hep C), Pictorial

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### Representation of Illness and Self Measure (PRISM) and Patient Activation Measure (PAM)-13

- Co-morbidities and concomitant medication

### Results

Median age of patients in the CP was 53 years, 63.4% of participants were male, ethnic origin was White (95.3%), Asian/Oriental (2.6%), Black (0.6%) and other (1.5%). The most prevalent HCV genotype was genotype 1b (59.1%), followed by genotype 1a (30.6%) and genotype 4 (10%). Cirrhosis was present in 10.2% of patients and 6.6 % had transition to cirrhosis. Treatment experienced patients accounted for 33.6% of the population.

Co-morbidities and/or co-infections were present in 70.0 % of the patients. The most common classes of not liver related co-morbidities were cardiovascular disease (25.1%), psychiatric disorders (10.9%), diabetes mellitus (8.7%) and hypothyroidism (6.6%). HIV co-infection was documented for 6.6% of patients and HBV co-infection for 2.6%.

Concomitant medications were taken by 59.1% of patients. The most frequently reported classes of concomitant medications were drugs used in addictive disorders (13.2%), analgesics (10.9%), beta blockers (10.9%) and drugs for peptic ulcer and gastro-esophageal reflux disease (10.4%).

The planned treatment duration was 12 weeks for the vast majority of patients in this study. The 3 direct-acting antiviral (DAA) regimen of paritaprevir/r plus ombitasvir plus dasabuvir without RBV was prescribed for 55.3% of the CP for 12 weeks, for 1.1% for 8 weeks (all genotype 1b without cirrhosis) and for 1 patient for 24 weeks. The 3DAA regimen in combination with RBV was prescribed for 33.2% of patients for 12 weeks and for 3 patients for 24 weeks. The 2 DAA regimen of paritaprevir/r plus ombitasvir in combination with RBV for 12 weeks was prescribed for 9.6% of patients, all had genotype 4. The vast majority of patients with genotype 1b (93.9%) received the 3DAA regimen without RBV, whereas 96.6% of genotype 1a patients took the 3DAA regimen with RBV. All genotype 4 patients (n=47) except two were treated with the 2DAA regimen with RBV, the remaining two patients received the 3DAA regimen with RBV.

SVR12 was achieved in 88.1% of the CP and in 95.6% of the CPSFU12. For genotype 1a the respective response rates were 77.9% and 93.4%, for genotype 1b 93.9% and 97.0%, for genotype 4 they were 85.1% and 93.0%. In patients with cirrhosis, SVR12 was achieved in 89.6% of the CP and in 95.6% of the CPSFU12. Patients with missing data were considered as non-responders in the

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calculation of SVR12 rates. In the CPSFU, patients with no HCV RNA data  $\geq 70$  days post treatment were excluded from the SVR12 analysis unless data was missing for reasons related to efficacy or safety. Reasons for virological failure among SVR12 non-responders were on-treatment virological failure in 1.3%, relapse in 1.1% and insufficient virological response in 0.4% of patients. One further patient with genotype 1a who was a SVR12 responder was HCV-RNA positive again in the SVR48 time window due to re-infection with genotype 5a.

Patient well-being during and after treatment was assessed by FACIT-F, WPAI Hep C, PRISM and PAM-13 questionnaires. There was a statistically significant improvement in fatigue from baseline to EoT, 12 and 48 weeks after the EoT as assessed by FACIT-F, as well as a statistically significant improvement in the perceived burden of suffering from baseline to 12 and 48 weeks after the EoT as assessed by PRISM questionnaire. The total work productivity impairment (TWP) component of the WPAI showed a slight increase during treatment and a trend towards improvement of work productivity in employed patients 12 and 24 weeks after EoT as compared to baseline. The total activity impairment (TAI) score in the whole study population - either working or not – showed improvement in HRQoL for all time points. There was no change from baseline in PAM-13 scores until end of treatment.

The assessment of liver function tests revealed an improvement from baseline to EoT and to 12 weeks after EoT for alanine-aminotransferase (ALT), ALT ratio, aspartate-aminotransferase (AST), AST ratio and gamma-glutamyltransferase ( $\gamma$ -GT) while there was no relevant change in median total bilirubin, albumin, creatinine and creatinine clearance. Very few patients had Grade 3 or 4 laboratory abnormalities. The analysis revealed three Grade 3 ALT increases, one Grade 3 AST increase and three Grade 3 low hemoglobin values (one of these patients had RBV withdrawn). In addition, three Grade 3 and four Grade 4 low creatinine clearance values were reported, all of these from patients with chronic kidney disease.

Overall, 26.4% of the patients reported at least one treatment-emergent AE. The most common AEs occurring in  $\geq 3\%$  of patients were fatigue (6.8%), headache (4.0%) and pruritus (3.4%). Treatment emergent SAEs were reported by 2.8% of patients. Overall 5 patients died. One patient died during treatment due to methadone overdose and one patient had the treatment stopped due to AE (hepatic cirrhosis) and subsequently died within 30 days after EoT. A death with unknown cause (deemed possibly related to treatment) was reported about 4 months after EoT. Two further patients died more than 2 and 4 months after EoT due to septic shock and cardiac failure, respectively.

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Five patients (1.1%) terminated the ABBVIE REGIMEN prematurely due to 6 AEs including infection, septic shock, anemia, nephrogenic anemia, gastric perforation and hepatic cirrhosis.

## **Discussion**

Currently there is limited country specific data available in Germany on the real world effectiveness of the ABBVIE REGIMEN. The LIFE-C study was set up to close this data gap.

High SVR12 rates were achieved in the CPSFU12, 95.6% overall, 93.4% for genotype 1a, 97.0% for genotype 1b and 93.0% for genotype 4, mirroring results from the clinical trials, including cirrhotic patients with 95.6% SVR12. There was a low number of virological failures. Results from the CP were lower (SVR12 overall 88.1%) e.g. due to missing follow-up information which reflects the non-interventional character of this study.

Analysis of the PRO instruments shows that treatment does not negatively impact fatigue, work productivity or HRQoL overall and that there is a long-term improvement after the EoT. This is one of the first studies showing long-term effects on PROs for up to 48 weeks after the EoT with the ABBVIE REGIMEN. Results of the LIFE-C study regarding PROs are in contrast to well-known assessments of HRQoL in patients receiving interferon-based therapies where usually a clinically important deterioration of HRQoL occurred during treatment.

Treatment was well tolerated with a low number of SAEs and only 1.1% of patients discontinuing the ABBVIE REGIMEN prematurely for safety reasons. No new safety signals were detected.

Overall the present study provides evidence for the high effectiveness and good tolerability of the ABBVIE REGIMEN under real world conditions in the German CHC population.

## **Marketing Authorisation Holder(s)**

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