# Title Page

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|---|---|
| **Title** | **Real World Evidence Study of the Effectiveness of Paritaprevir/r – Ombitasvir, + Dasabuvir without Ribavirin in Patients with Chronic HCV Gt1b infection and Compensated Liver Cirrhosis in the Russian FederaTion- An ObseRvational, Multi-CeNter Study (CITRIN)** |
| **Protocol Version Identifier** | P16-253 |
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| **Marketing Authorisation Holder(s)** | LLC "AbbVie", Russia, Moscow, Lenigragskoe shosse 16, bild. 1, 125171 |
| **Joint PASS** | Not applicable |
| **Research Question and Objectives** | What is the effectiveness of the interferon-free 3DAA ABBVIE REGIMEN without RBV in patients with chronic HCV Gt1b infection and compensated liver cirrhosis in a real life setting |
| **Country(-ies) of Study** | Russian Federation |
| **Author** | [redacted] |

**This study will be conducted in compliance with this protocol.**

**Confidential Information**

**No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.**

# Marketing Authorisation Holder(s)

| | |
|---|---|
| **Marketing Authorisation Holder(s)** | LLC "AbbVie", Russia, Moscow, Lenigragskoe shosse 16, bild. 1, 125171 |
| **MAH Contact Person** | Not applicable |

# 1.0 Table of Contents

## 2.0 Abbreviations

| | |
|---|---|
| AE | adverse event |
| APRI | AST to platelet ratio index |
| ALT | alanine-aminotransferase |
| AST | aspartate-aminotransferase |
| ABBVIE REGIMEN | Paritaprevir/r – ombitasvir ± dasabuvir |
| BMI | body mass index |
| CA | competent authority |
| CD4 | cluster of differentiation 4 |
| CHC | chronic hepatitis C |
| CI | confidence interval |
| CP | core population |
| DAA | direct-acting antiviral agent |
| DDI | drug-drug interaction |
| EC | ethics committee |
| EDC | electronic data capture |
| eCRF | electronic case report form |
| EoT | end of treatment |
| FIB-4 | Fibrosis-4 Score/Index |
| Hb | Hemoglobin |
| HbA1c | hemoglobin A1c |
| HCV | hepatitis C virus |
| HIV | human immunodeficiency virus |
| ICMJE | International Committee of Medical Journal Editors |
| IEC/IRB | independent ethics committee/- review board |

| | |
|---|---|
| INN | international non-proprietary name |
| INR | international normalized ratio |
| LLoD | lower limit of detection |
| LLoQ | lower limit of quantification |
| MAH | Marketing Authorization Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| NCP | non-core population |
| NS3/NS4A | nonstructural protein 3/nonstructural protein 4A |
| NS5A | nonstructural protein 5A |
| NS5B | nonstructural protein 5B |
| OLT | orthotopic liver transplant |
| PCR | polymerase chain reaction |
| PT | preferred term |
| RBV | Ribavirin |
| RNA | ribonucleic acid |
| SAE | serious adverse event |
| SAP | statistical analysis plan |
| SD | standard deviation |
| SDP | study designated physician |
| SOC | system organ class |
| SP | safety population |
| SVR | sustained virological response |
| SVR12 | SVR at 12 weeks after EoT |
| SVR24 | SVR at 24 weeks after EoT |
| TAI | total activity impairment |
| TP | target population |
| WHO | World Health Organization |

## 3.0 Responsible Parties

**Study Designated Physician (SDP):**

[redacted]

**Protocol Authors:**

[redacted]

**Vendor:**

[redacted]

# 4.0 Abstract

**Title:**

Real World Study of the Effectiveness of Paritaprevir/r – Ombitasvir, + Dasabuvir without Ribavirin in Patients with chronic HCV Gt1b infection and Compensated Liver Cirrhosis in the Russian Federation- An Observational, Multi-Center Study

**Rationale and Background:**

According to the recently published results of TURQUOISE III, Gt1b patients with cirrhosis can be successfully treated with 3D regimen without ribavirin [6]. In this study treatment-naïve and peginterferon/ribavirin treatment-experienced patients received 12 weeks of therapy with ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily) without ribavirin. All 60 patients enrolled in the study completed treatment, and SVR12 was achieved in 100% (95% CI, 94.0 – 100%) of patients. This treatment regime was well tolerated, suggesting a 12-week ribavirin-free regimen is appropriate in this population. The Russian label of AbbVie 3D regimen has been recently changed according to the TURQUOISE III results. This study is designed to assess the real world effectiveness and safety of 3D regimen without RBV in Gt1b patients with compensated cirrhosis in Russia.

**Research Question and Objectives:**
Primary objective:

To describe the effectiveness of the interferon-free 3DAA ABBVIE REGIMEN without RBV in patients with chronic HCV Gt1b infection and compensated liver cirrhosis as evidenced by SVR at 12 weeks after the end of treatment in routine clinical practice.

Secondary objectives:

- To assess the end-of-treatment (EoT) response rate
- To assess the rate of relapse (timeframe for assessing relapse - between EoT and SVR 12)
- To describe the baseline characteristics of patients with HCV GT1b and compensated liver cirrhosis treated with AbbVie 3D regimen.
- To collect information on co-morbidities and concomitant medications in cirrhotic patients in the Russian population
- To describe the tolerability of the AbbVie 3D regimen

**Study Design:**
This is a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN.
The prescription of a treatment regimen is at the discretion of the physician in accordance with local clinical practice and label, is made independently from this observational study and precedes the decision to offer a patient the opportunity to participate in this study.

**Target population:**
ABBVIE REGIMEN will be prescribed by physicians according to the routine clinical practice. Patient can be included in the study if he/she will satisfy the following criteria:
Age ≥ 18

Treatment-naïve or IFN/RBV-experienced adult male or female patients with confirmed CHC Gt1b and compensated liver cirrhosis, receiving therapy with the interferon-free ABBVIE 3D REGIMEN initiated not earlier than 2 weeks before the enrollment or the initiation is planned not later than 2 weeks after the day of enrollment in accordance to standard of care and in line with the current local label.

Patients must voluntarily sign and the Authorization (Consent) for Use/Disclosure of Data form prior to inclusion into the study.

Patient must not be participating or intending to participate in a concurrent interventional therapeutic trial.

**Variables:**
Primary Variable

- The percentage of patients achieving SVR12 (undetectable viral load at 12 week) after the last actual dose of the ABBVIE 3D REGIMEN

Secondary Variables

- Baseline characteristics of patients with HCV Gt1b and compensated liver cirrhosis treated with ABBVIE 3D REGIMEN
- Co-morbidities and concomitant medication
- Serious adverse events and non-serious AEs

**Data Sources:**

Source documents are defined as original documents. The investigator will document patient data in his/her own patient files which will serve as source data for the study.

**Study Size:**

60 patients will be included in this descriptive study without any prior sample size calculation. Convenient sampling methods will be used for patients who attended routine outpatient visits, fulfilled the inclusion/exclusion criteria and had signed a patient authorization form to use and disclose personal health information.

**Data Analysis:**

The core population (CP) is defined as all patients of the target population (TP) (definition see above), who have started the treatment combination recommended in the current local label for their disease characteristics. Patients not receiving the treatment recommended in the local label will be summarized in the non-core population (NCP). In addition, the core population with sufficient follow-up data (CPSFU) is defined as all CP patients, who have (i) evaluable HCV RNA data ≥84days after the last actual dose of the ABBVIE REGIMEN or (ii) a HCV RNA value ≥50 IU/mL at the last measurement or (iii) had HCV RNA <50 IU/mL at the last measurement, but no HCV RNA measurement ≥84 days after the last actual dose of the ABBVIE REGIMEN due to reasons related to safety (e.g. dropped out due to adverse event) or incomplete efficacy information (e.g. virologic failure such as relapse is reported in the electronic case report form (eCRF) but date and value of the corresponding HCV RNA test is missing). The safety population (SP) is defined as all patients who received at least one dose of the ABBVIE REGIMEN.

Descriptive and exploratory statistical methods will be used to analyze the data of the study. All baseline and disease characteristics will be summarized for the CP stratified by the CP analysis groups, which are relevant for scheduled treatment and duration (12 weeks). In addition, baseline summaries will be repeated for the SP and TP without stratification into subgroups. Further details of analysis populations and the CP analysis groups will be specified in the statistical analysis plan (SAP).

The primary effectiveness analysis will be performed for CP patients, stratified by the CP analysis groups. Response rates (i.e. SVR12 rate, end of treatment [EoT] response rate, relapse rate,) will be determined for the various CP analysis groups. The relapse rates will be estimated in patients of the CP analysis groups with EoT response and sufficient HCV RNA measurements post treatment. The relapse rates will be estimated in all patients of the CP analysis groups, who have undetectable HCV RNA measurement at EoT visit. For all rates specified above 95%-confidence intervals (CIs) will be determined using the Clopper-Pearson method.

**Milestones:**
Start of Data Collection: 10-Mar-2017

End of Data Collection: 10-Dec-2017

Final Report of Study Results: 30-Mar-2018

## 5.0 Amendments and Updates

- None.

## 6.0 Milestones

Major study milestones and their planned dates are as follows:

| | |
|---|---|
| Start of Data Collection: | 10-Mar-2017 |
| End of Data Collection: | 10-Dec-2017 |
| Final Report of Study Results: | 30-Mar-2018 |

## 7.0 Rationale and Background

Due to recent advances in antiviral drug development and rapid market entry, DAA-containing regimens have become the standard of care for HCV-infected patients in many countries [1]. Although the significant amount of studies have been already conducted and proven high efficacy and good safety of new regimens there is still a room for optimization of treatment schemes and duration of therapy in selected patient categories. Some easy-to-treat patients may require fewer components in the scheme and/or shorter treatment duration which allow improving tolerability, convenience and cost-efficacy of therapy.

Gt1b is the most prevalent genotype of HCV in Russia representing the majority of patients including those with liver cirrhosis [2]. According to Russian and international guidelines HCV-infected patients with liver cirrhosis require immediate treatment in order to prevent further deterioration of liver function and development of severe life-threatening complications like liver failure and hepatocellular carcinoma [1,3]. IFN-free regimens have significant advantages over IFN-containing regimens in this patient population with regard to efficacy, safety and convenience. As cirrhotic patients are being traditionally qualified as hard-to-treat, RBV is still widely used in this category even within IFN-free combinations. In the meantime despite general good safety profile of DAA combinations RBV can contribute to the development of anemia and other AEs

especially in patients with advanced fibrosis and cirrhosis [4]. Therefore exclusion of RBV from the regimens can improve treatment safety and further decrease the rate of discontinuation which will result in higher cure rate.

AbbVie 3D regimen contains 3 DAAs of different classes: paritaprevir – NS3/4A protease inhibitor boosted by ritonavir, ombitasvir - NS5A inhibitor and dasabuvir - non-nucleotide polymerase inhibitor. In phase III study TURQUOISE II 3D + RBV showed high efficacy and safety in GT1HCV-infected patients with compensated liver cirrhosis [5].

According to the recently published results of TURQUOISE III study Gt1b patients with cirrhosis can be successfully treated with 3D regimen without ribavirin [6]. In this study treatment-naïve and peginterferon/ribavirin treatment-experienced patients received 12 weeks of therapy with ombitasvir/paritaprevir/ritonavir (25/150/100 mg once daily) and dasabuvir (250 mg twice daily). Key inclusion criteria were hemoglobin ≥10 g/dL, albumin ≥2.8 g/dL, platelet count ≥25 x 109/L, creatinine clearance ≥30 ml/min, and Child-Pugh score ≤6. Efficacy was assessed by the percentage of patients achieved sustained virologic response (HCV RNA <25 IU/mL) 12 weeks post-treatment (SVR12). Efficacy and safety were assessed in all patients receiving study drug. Sixty patients with HCV GT1b infection and cirrhosis received treatment. The study population comprised 62% male, 55% treatment-experienced, 83% with IL28B non-CC genotype, 22% with platelet count <90 x 109/L, and 17% with albumin <3.5 g/dL. All 60 patients completed treatment, and SVR12 was achieved in 100% (95% CI, 94.0 – 100%) of patients. The most common adverse events were fatigue (22%), diarrhea (20%), and headache (18%). Only one patient (1.7%) experienced a serious adverse event. Laboratory bnormalities were infrequently observed and not clinically significant. The HCV regimen of ombitasvir/paritaprevir/ritonavir and dasabuvir without ribavirin for 12 weeks achieved 100% SVR12 and was well tolerated in HCV GT1b-infected patients with cirrhosis, suggesting that this 12-week ribavirin-free regimen is sufficient in this population.

Current study was developed in order to assess RWE effectiveness and safety of 3D regimen without RBV in Gt1b patients with compensated cirrhosis in Russia.

# 8.0 Research Question and Objectives

## 8.1 Research Question

- What is the effectiveness of the interferon-free 3DAA ABBVIE REGIMEN without RBV in patients with HCV Gt1b infection and compensated liver cirrhosis in a real life setting?

## 8.2 Objectives

### 8.2.1 Primary Objective

- To describe the effectiveness of the interferon-free 3DAA ABBVIE REGIMEN without RBV in patients with HCV Gt1b infection and compensated liver cirrhosis as evidenced by sustained virological response at 12 weeks after the end of treatment in routine clinical practice.

### 8.2.2 Secondary Objectives

- To describe the end-of-treatment (EoT) response rate
- To assess the rate of relapse (timeframe for assessing relapse - between EoT and SVR 12)
- To describe baseline characteristics of patients with HCV Gt1b and compensated cirrhosis treated with AbbVie 3D regimen.
- To collect information on co-morbidities and concomitant medications in cirrhotic patients in the Russian population
- To describe the tolerability of the ABBVIE REGIMEN

# 9.0 Research Methods

## 9.1 Study Design

This is a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN without RBV. The prescription of a treatment regimen is at the discretion of the physician in accordance with local clinical practice and label, is made independently from this observational study and precedes the decision to offer a patient the opportunity to participate in this study.

Adult patients chronically infected with HCV and compensated liver cirrhosis, receiving the interferon-free ABBVIE REGIMEN will be offered to participate in this study during a routine clinical visit at the participating sites.

After written Authorization (Consent) for Use/Disclosure of Data form has been obtained, patient data including demographic data, HCV disease characteristics, co-morbidities, co-medication, treatment details, and laboratory assessments as recorded in the patient's medical records (source documentation) will be documented in the electronic case report form (eCRF). Patients will be observed for the duration of the ABBVIE REGIMEN therapy and for up to 12 weeks after treatment completion. No patient identifiable information will be captured, a unique patient number will be automatically allocated by the web based eCRF system once the investigator or designee creates a new patient file.

This study is focusing on collecting real-world data. Follow-up visits, treatment, procedures and diagnostic methods will follow physicians' routine clinical practice.

12-week routine treatment regimen will include at least two observational visits (Visit 1 and EoT) plus one 30 days safety follow-up visit and one 12 weeks follow-up visit (SVR12) after the last dose of ABBVIE REGIMEN. Additional observational visits between Visit 1 and EoT can be done in case of clinical necessity and physician decision.

## 9.2 Product Supply

As this is a post-marketing observational study, AbbVie is NOT involved in the product supply since the drug is being used according to the approved market label and is to be prescribed by the physician under usual, current medical practice and is clearly separated from the decision to include the patient in the study.

## 9.3 Setting

For the purpose of this program participants will be recruited and observed in approximately 5-7 national and regional hospitals/outpatient services.

## 9.4 Program Duration

Enrollment will start in March 2017 and continue approximately 6 months and ABBVIE REGIMEN therapy will be administered according to physician's prescription and the local label to all enrolled subjects. All visits of the program will be organized according to routine clinical practice over 12 weeks of treatment period as well as 12 weeks follow-up period to assess the SVR12. All enrolled patients will be followed by a personal or telephone contact at 30 days after their last dose in the study.

## 9.5 Investigator selection criteria

In order to assure credibility of the final results the below listed criteria will be considered during the recruitment process of physician/investigators:

- Physician licensed in infection diseases or gastroenterology;
- Physician is working at a national or regional hospitals or outpatient centers;
- Availability of patient population fulfilling the inclusion/exclusion criteria;
- Ability to appropriately conduct the observational program.

## 9.6 Inclusion Criteria

ABBVIE REGIMEN will be prescribed by physicians according to the routine clinical practice. Patient can be included in the study if he/she will satisfy the following criteria:

1. Age ≥ 18
2. Treatment-naïve or IFN/RBV-experienced adult male or female patients with confirmed CHC Gt1b and compensated liver cirrhosis, receiving therapy with the interferon-free ABBVIE 3D REGIMEN initiated not earlier than 2 weeks before the enrollment or the initiation is planned not later than 2 weeks after the day of enrollment in accordance to standard of care and in line with the current local label.
3. Patients must voluntarily sign and the Authorization (Consent) for Use/Disclosure of Data form prior to inclusion into the study.
4. Patient must not be participating or intending to participate in a concurrent interventional therapeutic trial.

## 9.7 Exclusion Criteria

A patient will not be eligible for this PMOS if he/she fulfils the following criteria:

1. Co-administration RBV with the ABBVIE REGIMEN
2. Patients with Child Pugh B and C cirrhosis
3. Patients with a history of prior DAA therapy
4. Any other contraindications to the administration of ABBVIE REGIMEN according to the label

## 9.8 Description of Activities

The patient visits will be scheduled based on routine clinical practice and prescription of consulting physician. Prescription of ABBVIE REGIMEN is clearly separated from the decision to include the patient in the study. However, it would be included at least two observational visits (Visit 1 and EoT) plus one 30 days safety follow-up visit and one 12 weeks follow-up visit (SVR12) after the last dose of ABBVIE REGIMEN. Additional observational visits between Visit 1 and EoT can be done in case of clinical necessity and physician decision.

Information for patients enrolled within 2 weeks after initiation of ABBVIE REGIMEN is collected at routine patient visits therefore baseline patient data should be taken from medical records.

In total, there will be at least four study visits. Please refer to Table 2for observational documentation.

## Table 2. Program Activities

| **Assessment/ Procedure** (only available data to be collected; no diagnostic or monitoring procedures to be applied to the patients apart from those of routine clinical practice) | **Visit 1** | **Treatment Period** | **Post-treatment (PT) Period** | |
|---|---|---|---|---|
| | | **EoT[b] (on-treatment visits)** | Safety Follow-up Visit [c] | SVR 12 Follow-up Visit |
| Authorization (Consent) for Use/Disclosure of Data form | X[a] | | | |
| Inclusion/Exclusion Criteria | X | | | |
| Demographic information | X | | | |
| IL28B | X | | | |
| Relevant CHC disease characteristics | X | | | |
| Liver fibrosis stage | X | | | |
| CHC treatment history | X | | | |
| HCV genotype and subtype | X | | | |
| HCV RNA samples | X | X | | X |
| Clinical chemistry and hematology | X | X | | X |
| ABBVIE REGIMEN initiation documentation | X | | | |
| ABBVIE REGIMEN adherence | | X | | |
| Concomitant medication | X | X | | X |
| Relevant medical history, co-morbidities | X | | | |
| SAE, non-serious AE and pregnancy reporting | X | X | X | X |

Abbreviations: EoT = End of Treatment (at Week 12 or at premature discontinuation),
PT = Post-Treatment

a Written patient authorization or informed consent must be obtained before any data documentation in the eCRF

b Patients who prematurely discontinue should return to the site to document EoT data

c Tolerability documentation until PT week 4, visit can be done as telephone call contact

Collected data and planned activities within the observational program:

**Visit 1**

- Signing of the Authorization (Consent) for Use/Disclosure of Data form by patient
- Assignment of patient's identification number (two-digit center number + two-digit patient individual enrollment number)
- Inclusion/exclusion criteria verification
- Demographics (sex, age, race)
    - Interleukin 28B (IL28B) genotypes
- CHC disease characteristics
    - Year of diagnosis and probable mode of infection
    - Stage of liver fibrosis
- CHC treatment history
    - Naïve or experienced
- If experienced, most recent prior therapy and outcome Relevant medical history, co-morbidities and co-infections
        - Liver USG, CT scan
        - Last available AFP value
- Concomitant medication
- ABBVIE REGIMEN information

- Laboratory data

| Key clinical chemistry | Remarks |
|---|---|
| ▪ ALT (alanine-aminotransferase) | including upper limit of normal (ULN), |
| ▪ AST (aspartate-aminotransferase) | including ULN, AST to platelet ratio index (APRI) and Fibrosis-4 Score/Index (FIB-4)* will be calculated |
| ▪ γ-GT (gamma-glutamyltransferase) | |
| ▪ Total bilirubin | |
| ▪ Albumin | |
| ▪ Creatinine | creatinine clearance# will be calculated |
| ▪ AFP | |
| Key hematology | |
| ▪ Hb (Hemoglobin) | |
| ▪ Platelets | |
| ▪ Prothrombin time | or international normalized ratio (INR) |
| Virology | |
| ▪ HCV genotype and subtype | |
| ▪ HCV RNA | quantitative/ qualitative HCV RNA by polymerase chain reaction (PCR) test |
| HIV-infected patients only | |
| ▪ CD 4 count (cluster of differentiation 4) | most recent assessment |
| ▪ HIV RNA | in copies/mL |

*derived from patient's age, ALT, AST and platelets
#by Cockcroft-Gault-Formula based on creatinine, gender, age and weight

**End of treatment visit and additional on-treatment visits**

End of treatment visit and additional on treatment visits is scheduled by the physician per routine clinical practice. Likewise treatment, procedures and diagnostic methods will follow physicians' routine clinical practice.

The following will be documented:

- Laboratory data

| Key clinical chemistry | Remarks |
|---|---|
| ▪ ALT | including ULN |
| ▪ AST | including ULN, APRI and FIB-4 will be calculated |
| ▪ γ-GT | |
| ▪ Total bilirubin | |
| ▪ Creatinine | creatinine clearance will be calculated |
| Key hematology | |
| ▪ Hb | |
| ▪ Platelets | |
| Virology | |
| ▪ HCV RNA | quantitative/ qualitative HCV RNA PCR test, see 9.8.1 |
| HIV-infected patients only | |
| ▪ CD 4 count | most recent assessment |
| ▪ HIV RNA | in copies/mL |

- Concomitant medication
- Tolerability (non-serious AEs, SAEs) and pregnancies

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**Safety Follow-up Visit** (personal or telephone contact)

- Tolerability (non-serious AEs, SAEs) and pregnancies

**SVR 12 Follow-up Visit**

Follow-up visit is scheduled by the physician per routine clinical practice. Likewise treatment, procedures and diagnostic methods will follow physicians' routine clinical practice.

The following will be documented:

- Laboratory data

| Key clinical chemistry | Remarks |
|---|---|
| ▪ ALT | including ULN |
| ▪ AST | including ULN, APRI and FIB-4, will be calculated |
| ▪ γ-GT | |
| ▪ Total bilirubin | |
| ▪ Albumin | |
| ▪ Creatinine | creatinine clearance will be calculated |
| Key hematology | |
| ▪ Hb | |
| ▪ Platelets | |
| ▪ Prothrombin time | or INR |
| Virology | |
| ▪ HCV RNA | quantitative/ qualitative HCV RNA PCR test, see 9.8.1 |
| HIV-infected patients only | |
| ▪ CD 4 count | most recent assessment |
| ▪ HIV RNA | in copies/mL |

- Tolerability (non-serious AEs, SAEs)

### 9.8.1 HCV RNA Sample

**HCV RNA sample** – the following needs to be documented:

- **Quantitative** HCV RNA by PCR test
  - Test name and result **in IU/mL**
  - Lower limit of detection (LLoD) **in IU/mL** and lower limit of quantification (LLoQ) **in IU/mL**

- **Qualitative** HCV RNA by PCR test
  - Test name and result **(positive/negative)**
  - LLoD **in IU/mL**

### 9.8.2 Concomitant Medication

**Concomitant medication** - the following will be documented:

- Concomitant medication used from the first dose of ABBVIE REGIMEN until the end of Follow-up period

It should be verified by the treating physician that concomitant medication can be safely administered with the ABBVIE REGIMEN. Some medications may be contraindicated; some may require dose adjustments due to potential for drug-drug interactions (DDIs). The investigator or qualified designee should review the concomitant medication(s) labels and screen concomitant medications at each visit for potential DDIs.

## 9.9 Variables

### 9.9.1 Primary Variable

- The percentage of patients achieving SVR12 (undetectable viral load at 12 week after the last actual dose of the ABBVIE 3D REGIMEN)

### 9.9.2 Secondary Variables

- Baseline characteristics of patients with HCV Gt1b and compensated cirrhosis treated with ABBVIE 3D REGIMEN
- Co-morbidities and concomitant medication
- Serious and non-serious adverse events

## 9.10 Data Sources

Data for the study will be collected within clinical interview with the patient and source document at the center. Source documents will be original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, etc.

## 9.11 Study Size

60 patients will be included in this descriptive study without any priory sample size calculation. Convenient sampling methods will be used for patients who attended routine outpatient visits, fulfilled the inclusion/exclusion criteria and had signed a patient authorization form to use and disclose personal health information.

## 9.12 Data Management

### 9.12.1 Electronic Case Report Forms

Data for this study will be recorded in English by each participating center via an electronic data capture (EDC) system using a web-based eCRF. Examinations, diagnostic measures, laboratory assessments, findings and observations routinely performed in patients with CHC included in this cohort, will be transcribed by the investigator or designee from the source documents into the eCRF. For each enrolled patient, the investigator or designee will create a new patient file in the eCRF and a unique patient number will be automatically allocated by the system.

A comprehensive data validation program utilizing front-end checks in the eCRF will validate the data. Automated checks for data consistency will be implemented, discrepancies need to be solved by the researcher in the eCRF before the module can be completed.

Follow-up on eCRF data for medical plausibility will be done by AbbVie personnel (or their representatives). Queries will be generated in the eCRF for online resolution at the site. The investigator or an authorized member of the investigator's staff will make any necessary data corrections to the eCRF. All change information, including the date and person performing the corrections, will be available via the audit trail, which is part of the EDC system. The principal investigator of each site will finally review the eCRFs for

completeness and accuracy of available data and provide his or her electronic signature and date to the eCRFs as evidence thereof.

Access to the EDC system will be provided for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media (e.g. CD-ROM) and provided to the investigator as a durable record of the site's eCRF data.

### 9.12.2 Assignment of Preferred Terms

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) and will be tabulated by primary MedDRA system organ class (SOC) and preferred term (PT). For treatments, surgical and medical procedures the international non-proprietary name (INN) Drug Terms and Procedures Dictionary will be used.

## 9.13 Data Analysis

### 9.13.1 Analysis Population, Time Windows and Handling of Missing Data

The target population (TP) is defined as all patients who fulfill the inclusion/exclusion criteria. The core population (CP) is defined as all patients of the TP, who have started the treatment combination recommended in the current local label for their disease characteristics. Patients not receiving the treatment recommended in the local label will be summarized in the non-core population (NCP). In addition, the core population with sufficient follow-up data (CPSFU) is defined as all CP patients, who fulfil one of the following criteria:

(1) evaluable HCV RNA data ≥84 days after the last actual dose of the ABBVIE REGIMEN (i.e. data within the SVR12 time window)

(2) a HCV RNA value ≥50 IU/mL at the last measurement post-baseline (i.e. no virological response achieved at the last measurement on-treatment or post-treatment)

(3) HCV RNA <50 IU/mL at the last measurement post-baseline, but no HCV RNA measurement ≥84 days after the last actual dose of the ABBVIE REGIMEN due to reasons related to safety (e.g. dropped out due to AE) or incomplete efficacy information (e.g. virologic failure such as relapse is reported in the eCRF but date and value of the corresponding HCV RNA test is missing). This means only patients who had virological response at their last on-treatment or post-treatment measurement, but had no HCV RNA measurements ≥84 days post-treatment for reasons not related to safety or effectiveness (e.g. lost-to-follow-up or patient not willing to perform an additional HCV RNA test ≥84 days post-treatment) will be excluded from this analysis.

The Safety Population (SP) is defined as all patients who received at least one dose of the ABBVIE REGIMEN.

In accordance with the non-interventional nature of the study all HCV RNA measurements will be performed at the sole discretion of the physician and all HCV RNA measurements have to be entered into the eCRF. All recorded HCV RNA values will be assigned to appropriate time points (Visit 1, additional on-treatment visits (if any), EoT visit, 30 days safety follow-up visit and SVR 12 follow-up visit). The time windows for the assignments will be specified in the statistical analysis plan (SAP).

No data will be imputed for any effectiveness or safety analyses except for the analyses of the HCV RNA endpoints. When there is no HCV RNA value in a visit time window post-baseline, but prior to EoT, the closest values before and after the window, regardless of the value chosen for the subsequent and preceding window, will be used for the flanking imputation described below. If a patient has a missing HCV RNA value at a post-Visit 1

visit prior to EoT but has undetectable HCV RNA (with LLoD ≤50 IU/mL) or unquantifiable, but detectable HCV RNA levels (with LLoQ ≤50 IU/mL) at both the preceding and succeeding measurements, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this patient. In addition, if a patient has an unquantifiable HCV RNA level at the preceding measurement and an undetectable HCV RNA level at the succeeding measurement, or vice versa, the HCV RNA level will be imputed as unquantifiable at this visit for this patient. For virological response at EoT a corresponding backward imputation approach will be applied. This means if HCV RNA is missing at EoT, then unquantifiable or undetectable will be assumed for EoT, if the succeeding HCV RNA value is undetectable or unquantifiable. For SVR12 the single last available HCV RNA measurement ≥84 days post-treatment will be used. Subsequent to this flanking and backward imputation, if the HCV RNA value remains missing at a specific time point, then the patients will be considered as virological failure at this time point (i.e. not undetectable or unquantifiable).

### 9.13.2 Demographics and Disease Characteristics

All baseline and disease characteristics will be summarized for the CP stratified by the CP analysis groups (i.e. based on genotype 1 subtype, fibrosis status, treatment experienced or naïve), which are relevant for scheduled treatment combination (ABBVIE REGIMEN) and duration (12 weeks). In addition, baseline summaries will be repeated for the SP and the TP without stratification into subgroups. Summary statistics (n, mean, median, standard deviation [SD], and range) will be generated for continuous variables (e.g. age and body mass index [BMI]). The number and percentage of patients will be presented for categorical variables (e.g. gender and race). Further details of analysis populations and the CP analysis groups will be specified in the SAP, taking into account the ABBVIE REGIMEN recommended in the current local label for various patient groups.

### 9.13.3 Effectiveness Analysis

The primary effectiveness analysis on clinical outcomes will be performed on all patients in the CP stratified by the CP analysis groups. Due to the non-interventional nature of this study several different methods for determination of the HCV RNA value can be applied. For the purpose of the statistical analysis, a HCV RNA measurement is considered ≤50 IU/mL,

- if a PCR test was used
- and the test result is undetectable and the LLoD of the test is ≤50 IU/mL or the test result is unquantifiable and the LLoQ is ≤50 IU/mL

### 9.13.4 Primary Effectiveness Endpoint

The percentage of patients achieving SVR12 (single last HCV RNA <50 IU/mL 12 weeks [i.e. at least 84 days] after the last actual dose of the ABBVIE REGIMEN) is the primary effectiveness endpoint.

### 9.13.5 Secondary Effectiveness Endpoints

The secondary effectiveness endpoints are:

- The percentage of patients with virological response (HCV RNA <50 IU/mL) at EoT
- 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 relapse (defined as at least one documented HCV RNA <50 IU/mL followed by HCV RNA ≥50 IU/mL during treatment).

- The number and percentage of patients meeting each and any of the following SVR12 non-response categories:
    - Relapse (defined as HCV RNA <50 IU/mL at EoT or at the last on-treatment HCV RNA measurement followed by HCV RNA ≥50 IU/mL post-treatment)
    - Missing SVR12 data and/or none of the above criteria

### 9.13.6 Statistical Methods for Analysis of Effectiveness Variables

The simple percentage of patients achieving SVR12 will be calculated and an exact two-sided 95% confidence interval (CI) of the percentage will be computed based on the Clopper-Pearson method.

Corresponding methods will be used for other response rates (EoT response rate, relapse rate). The relapse rates will be estimated in patients of the CP analysis groups with EoT response and sufficient HCV RNA measurements post-treatment.

These analyses will be of exploratory nature, data driven, and will be repeatedly performed for various CP Analysis Groups, since not each covariate might be predictive in each patient group. Furthermore, the fact that treatment regimens will differ in the various patient groups has to be taken into account, when selecting the patient groups for each MLR analysis. Backward selection procedures will be applied to generate the final MLR models which consider only covariates in the selection procedure with a p-value <0.25 in the corresponding univariate logistic regression analysis. A p-value <0.05 will be used for the covariates to stay in the model in a backward elimination step. Logistic regression methods will also be used to investigate the impact of treatment adherence on SVR12.

### 9.13.7 Clinical Laboratory Data

All reported clinical laboratory test results will be assigned to one of the time points using the time windows specified in the table below.

**Table 1 - Analysis Time Windows**

| Time point | Time Window |
|---|---|
| Visit 1 | Last value prior to start of study treatment (i.e. ≤study day 1) |
| Actual EoT | Study day of last dose<br>(28 days prior to EoT - 14 days post EoT) |
| 12 weeks<br>(day 85 post EoT) | 57 – 112 post EoT |

Mean changes from baseline to each post-baseline visit will be summarized descriptively.

Laboratory data values collected during the treatment period will be categorized as low, normal, or high based on reference ranges used in this study. The number and percent of patients who experience post-baseline shifts during treatment in clinical laboratory values from low/normal to high and high/normal to low based on the reference range will be summarized.

Additional details of the analyses of clinical laboratory data will be specified in the SAP.

### 9.13.8 Tolerability Analysis

All tolerability variables will be summarized using descriptive statistical methods for the SP stratified by type of combination treatment and scheduled treatment duration.

All SAEs, non-serious AEs and pregnancy occurrences are to be reported for patients included in the study. AEs will be coded using MedDRA. The number and percentage of patients with treatment-emergent AEs (i.e. any reported event that begins or worsens in severity after initiation of study drug through 30 days post-study drug dosing) will be

tabulated by primary MedDRA SOC and PT. Corresponding summary tables will be provided for all serious treatment-emergent AEs. The tabulation of the number of patients with treatment-emergent AEs by severity and relationship to study drug will also be provided. Patients reporting more than one AE for a given MedDRA PT will be counted only once for that term using the most severe incident for the severity summary table and the most related for the relationship summary table. Patients reporting more than one type of event within a SOC will be counted only once for that SOC.

Additional details of the analysis of AEs will be specified in the SAP.

## 9.14 Quality Control

The sites will be instructed in the protocol, the functionality and handling of the eCRF, and the requirement to maintain source documents for each patient in the study.

A comprehensive data validation program utilizing front-end checks in the eCRF will validate the data. Automated checks for data consistency will be implemented, discrepancies need to be solved by the researcher in the eCRF before the module can be completed. Follow-up on eCRF data for medical plausibility will be done by AbbVie personnel (or their representatives). The principal investigator of each site will finally review the eCRFs for completeness and accuracy of available data and provide his or her electronic signature and date to eCRFs as evidence thereof.

Continuous monitoring of the study and frequent site telephone contacts will be done by AbbVie or a CRO working on behalf of AbbVie.

## 9.15 Limitations of the Research Methods

The limitations of observational studies, such as uncontrolled confounding by lack of randomization, and difficulties to clearly interpret treatment effects in the context of missing data are well known. Their validity can be increased by accurate outcome

measurements, documentation of the most common confounders, sufficient length of follow-up and by activities to obtain complete recording of available data as well as by searches for missing key data.

The most important outcome measure in this study is HCV RNA. Missing or unrecorded follow-up HCV RNA data can in particular lead to an underestimation of the real SVR rate as compared to the SVR rate of interventional trials. Highly sensitive and quantitative diagnostic tests are required to measure HCV RNA levels in blood. In an observational study each center will be using its own test – either commercially available or so-called "home-brew" tests – which might change from one visit to the next within a patient data set. The challenge is to accurately and consistently document test properties such as the LLoD and the LLoQ to put the results into perspective of prior outcomes from randomized controlled trials with (usually) central laboratory assessments for all trial participants.

### 9.16 Other Aspects

Not applicable.

## 10.0 Protection of Human Subjects

This observational study will be run in compliance with local laws and regulations. Notification/submission to the responsible regulatory authorities, Ethics Committee (EC) and/or Competent Authorities (CAs) will be done as required by local laws and regulations.

The investigator is responsible to ensure that written informed consent will be obtained prior to patient inclusion

To maintain patient confidentiality, no demographic data that can identify the patient will be collected (e.g. initials, date of birth) - only the patient age will be collected. In order to

protect patient identity, a unique number will be assigned to each patient and related study recording.

# 11.0 Management and Reporting of Complaints

A Complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device after it is released for distribution.

Complaints associated with any component of this investigational product must be reported to the Sponsor (Section 11.2.2). For adverse events, please refer to Sections 11.1.1 through 11.1.6. For product complaints, please refer to Section 11.2.

## 11.1 Medical Complaints

### 11.1.1 Adverse Event Definition and Serious Adverse Event Categories

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

**Death of Patient:** An event that results in the death of a patient.

| | |
|---|---|
| **Life-Threatening:** | An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form. |
| **Hospitalization:** | An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility. |
| **Prolongation of Hospitalization:** | An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay. |
| **Congenital Anomaly:** | An anomaly detected at or after birth, or any anomaly that results in fetal loss. |
| **Persistent or Significant Disability/Incapacity:** | An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle). |
| **Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:** | An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. |

### 11.1.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

| | |
|---|---|
| **Mild:** | The adverse event is transient and easily tolerated by the patient. |
| **Moderate:** | The adverse event causes the patient discomfort and interrupts the patient's usual activities. |
| **Severe:** | The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening. |

### 11.1.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

| | |
|---|---|
| **Reasonable Possibility** | An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event. |
| **No Reasonable Possibility** | An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event. |

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

### 11.1.4 Adverse Event Collection Period

Non-serious adverse events and serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days following the intake of the last dose of physician-prescribed treatment.

### 11.1.5 Serious and Non-serious Adverse Event Reporting

In the event of an ***SAE***, the physician will:

- For events from patients using the ABBVIE REGIMEN report to AbbVie within 24 hours of the physician becoming aware of the event by using the eCRF system or notifying the AbbVie contact representatives identified below.

In the event of a ***non-serious AE***, the physician will:

- For events from patients using the ABBVIE REGIMEN report to AbbVie by using the eCRF system.

**Primary contact for SAEs, AEs reporting:**

[redacted]

**Back-up contact for SAEs, AEs reporting:**

[redacted]

### 11.1.6 Pregnancy Reporting

Patients and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the HCV treatment and for 30 days after the end of treatment with DAAs.

In the event of a pregnancy occurrence in the patient, the physician will report to AbbVie within 24 hours of the physician becoming aware of the pregnancy by using the eCRF system or notifying the AbbVie contact person identified in Section 11.1.5.

## 11.2 Product Complaint

### 11.2.1 Definition

A Product Complaint is any Complaint (see Section 11.0 for the definition) related to the biologic or drug component of the product.

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, or packaging issues.

Any information available to help in the determination of causality to the events outlined directly above should be captured.

### 11.2.2 Reporting

Product Complaints concerning the investigational product must be reported to the Sponsor within 24 hours of the study site's knowledge of the event via local Product Complaint reporting practices. Product Complaints occurring during the study will be followed-up to a satisfactory conclusion. All follow-up information is to be reported to the Sponsor (or an authorized representative) and documented in source as required by the Sponsor. Product Complaints associated with adverse events will be reported in the study summary. All other complaints will be monitored on an ongoing basis.

Product complaints involving a non-Sponsor investigational product should be reported to the identified contact or manufacturer, as necessary per local regulations.

Product Complaints may require return of the product with the alleged complaint condition. In instances where a return is requested, every effort should be made by the investigator to return the product within 30 days. If returns cannot be accommodated within 30 days, the site will need to provide justification and an estimated date of return.

The description of the complaint is important for AbbVie in order to enable AbbVie to investigate and determine if any corrective actions are required.

**Primary contact for Product Complaint reporting:**

[redacted]

**Back-up contact for Product Complaint reporting:**

[redacted]

## 12.0 Plans for Disseminating and Communicating Study Results

At the end of this observational study, a report will be written by AbbVie or a CRO working on behalf of AbbVie. The required standard study report template will be followed. This report will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed eCRFs, patient questionnaires, the final study output and study report are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The study results will be submitted to local authorities by the participating countries per local laws and regulations.

The results of this study will be made publicly available on one of the primary registries in the World Health Organization (WHO) Registry Network which meet the requirements of the ICMJE (International Committee of Medical Journal Editors) and through scientific publications. Authorship will be in line with ICMJE' authorship requirements 7.

## 13.0 References

1. EASL Recommendations on Treatment of Hepatitis C 2015. Journal of Hepatology 2015 vol. 63 j 199–236
2. В.П. Чуланов Оценка текущего состояния диагностики и лечения ХГС в России. Доклад на 41-я Научной сессии ЦНИИГ «Расширяя границы» Сателлитный симпозиум «К новому «образу» противовирусной терапии хронического гепатита С» г. Москва, 5 марта 2015 г.
3. Н.Д. Ющук, В.Т. Ивашкин и соавт. Рекомендации по диагностике и лечению взрослых больных гепатитом С. http://www.rsls.ru/ru/for-specialists/recommendations/20-recomend-3. Accessed 24 Apr 2016.

4. Mamta K Jain et al, Role of ribavirin in HCV treatment response: now and in the future. Expert Opin. Pharmacother. (2010) 11(4):673-683
5. Fred Poordad et al. ABT-450/r–Ombitasvir and Dasabuvir with Ribavirin for Hepatitis C with Cirrhosis. N Engl J Med. 2014 May 22;370(21):1973-82.
6. Jordan J. Feld et al. Sustained virologic response of 100% in HCV genotype 1b patients with cirrhosis receiving ombitasvir/paritaprevir/r and dasabuvir for 12 weeks. Journal of Hepatology 2016 vol. 64 j 301–307.
7. International Committee of Medical Journal Editors. Available at http://www.icmje.org/recommendations/browse/roles-and-responsibilities/defining-the-role-of-authors-and-contributors.html; accessed July 07, 2014.

**AbbVie Inc. (AbbVie)**

**Post Marketing Observational Study**

**Protocol (P16-253)**

# Real World Study of the Effectiveness of Paritaprevir/r – Ombitasvir, + Dasabuvir without Ribavirin in Patients with Chronic HCV Gt1b infection and Compensated Liver Cirrhosis in the Russian Federation- An Observational, Multi-Center Study (CITRIN)

[redacted]

16 Jan 2017
Date

10 JAN 2017
Date

16 Jan 2017
Date

JAN 10TH 2017
Date