Title Page

Title	Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C - An Observational Study in Belgium
Protocol Version Identifier	Protocol Belgium Version 2.0 (9 June 2015)
Date of Last Version of Protocol	n.a.
Research Question and Objectives	What is the effectiveness and the influence of adherence on treatment outcome of the interferon-free regimen of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in patients with CHC in a real life setting across clinical practice patient populations?
Country(-ies) of Study	Belgium
Main Author	[redacted]
Marketing Authorization Holder(s)	Abbvie sa/nv, Avenue Einstein 14, 1300 Wavre, Belgium

This study will be conducted in compliance with this protocol and all applicable local regulatory requirements

1.0 Table of Contents

2.0 Abbreviations

Paritaprevir/r	Paritaprevir/ritonavir
AE	adverse event
APRI	AST to platelet ratio index
AFP	alfa fetoprotein
ALT	alanine-aminotransferase
AST	aspartate-aminotransferase
ABBVIE REGIMEN	Paritaprevir/r – ombitasvir ± dasabuvir
ANCOVA	analysis of covariance
BMI	body mass index
BMQ	beliefs medication questionnaire
CA	competent authority
CD4	cluster of differentiation 4
CHC	chronic hepatitis C
CI	confidence interval
CNI	calcineurin
CP	core population
CPFSU	core population with sufficient follow-up data
CT	computer tomography
DAA	direct-acting antiviral agent
DDI	drug-drug interaction
EC	ethics committee
EDC	electronic data capture
eCRF	electronic case report form
EMA	European Medicines Agency
EoT	end of treatment
FDA	Food and Drug Administration

FIB-4	Fibrosis-4 Score/Index
γ-GT	gamma-glutamyltransferase
HCC	hepatocellular carcinoma
HCP	health care provider
Hb	hemoglobin
HbA1c	hemoglobin A1c
HBV	hepatitis B virus
HCV	hepatitis C virus
HDL	high-density lipoprotein
HIV	human immunodeficiency virus
HOMA	homeostasis model assessment
HVPG	hepatic venous pressure gradient
ICMJE	International Committee of Medical Journal Editors
IEC/IRB	independent ethics committee/- review board
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IgM	Immunoglobulin M
INN	international non-proprietary name
INR	international normalized ratio
LDL	low-density lipoprotein
LLoD	lower limit of detection
LLoQ	lower limit of quantification
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
MLR	multiple logistic regression
MRI	magnetic resonance imaging
NCP	non-core population
NS3/NS4A	nonstructural protein 3/nonstructural protein 4A
NS5A	nonstructural protein 5A

NS5B	nonstructural protein 5B
OATP	organic anion-transporting polypeptide
OLT	orthotopic liver transplant
PAM-13	Patient Activation Measure 13
PCR	polymerase chain reaction
pegIFN	pegylated interferon
PRO	patient reported outcome
PSP	patient support program
PT	preferred term
RBV	ribavirin
RF	rheumatoid factor
RNA	ribonucleic acid
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SDP	study designated physician
SNP	single nucleotide polymorphism
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
TWP	total work productivity impairment
VAS	visual analogue scale
WHO	World Health Organization

3.0 Responsible Parties

Study Designated Physician (SDP):

[redacted]

Protocol Authors:

[redacted]

Vendor:

- IST GmbH, Soldnerstrasse 1, D-68219 Mannheim, Germany
  www.istgmbh.com

4.0 Abstract

Title:

Real World Evidence of the Effectiveness of Paritraprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C
An Observational Study in Belgium.

Rationale and Background:

The interferon-free combination regimen of Paritaprevir/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 ABBVIE REGIMEN is expected to be first available in Belgium for the treatment of CHC in 2015.

The rationale for this observational study is to determine how the efficacy and safety of the ABBVIE REGIMEN as demonstrated in pivotal trials translates into real world everyday clinical settings, which means evaluating its effectiveness. Whereas efficacy can be defined as a measure of the capacity of a treatment to produce the desired effect in a controlled environment, such as in a randomized controlled trial, effectiveness is the extent to which a drug achieves its intended effect in the usual clinical setting. Effectiveness trials typically have limited exclusion criteria and will involve the broader patient populations in routine clinical practice and per local label which might include patients with heterogenous compliance patterns and patients with significant comorbid conditions and could be used to model and disseminate best practices. Effectiveness research allows for external patient-, provider-, and system-level factors and can therefore be more relevant for health-care decisions by both providers in practice and policy-makers.

This observational study is the first effectiveness research examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Belgium in a clinical practice patient population.

During the last decade when dual therapy with pegylated interferon (pegIFN) plus RBV was standard of care for the treatment of CHC, the discovery of predictive factors for virological response and the subsequent development of treatment algorithms marked a milestone in patient care for CHC. As a consequence, treatment could be effectively targeted to patients most likely to respond. Interestingly, many of the now well established predictors of response to pegIFN/RBV and first generation direct acting anitvirals (DAAs) in combination with pegIFN/RBV were not predictive of outcome in the development trials of the ABBVIE REGIMEN ± RBV. This observational study may play an important part in bridging the data gaps. It may help identify predictive factors of response that are important in real world treatment settings and thus, could assist in further optimizing treatment with the interferon-free ABBVIE REGIMEN ± RBV in the future.

The label of the ABBVIE REGIMEN ± RBV will vary according to hepatitis C virus (HCV) genotype/subtype and stage of liver disease. It is therefore relevant to understand the pattern of use and outcome in daily clinical practice. In addition, this study will provide data on the impact of adherence on treatment outcomes in everyday settings, which may help treating physicians

to improve the management of patients under their care.

The aim of this observational study is to provide evidence of the effectiveness and of the influence of adherence on treatment outcome of the ABBVIE REGIMEN ± RBV in a real world setting across clinical practice patient populations.

Research Question and Objectives:

What is the effectiveness and the influence of adherence on treatment outcome 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 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 describe the pattern of real world use of the ABBVIE REGIMEN ± RBV with respect to different patient and treatment characteristics
4. To evaluate the influence of adherence on treatment outcome in routine clinical practice
5. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization
6. To assess viral resistance patterns

Study Design:

This is a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN ± 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 the patient the opportunity to participate in this study.

Target Population:

Patients are eligible for observation in this cohort if the following applies:

- Treatment-naïve or -experienced adult male or female patients with confirmed CHC, genotype 1 or 4, receiving combination therapy with the interferon-free ABBVIE REGIMEN ± RBV according to standard of care and in line with the current local label
- If RBV is co-administered with the ABBVIE REGIMEN, it has been prescribed in line with the current local label (with special attention to contraception requirements and contraindication during pregnancy)
- Patients must voluntarily sign and date an informed consent 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 (HCV RNA <50 IU/mL 12 weeks [i.e. ≥70 days]

after the last actual dose of the ABBVIE REGIMEN)
Secondary Variables

- Type of treatment regimen (± Dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Adherence

*A period of **7 days in a row** of missed intake of the **ABBVIE Regimen** during the time between documented first dose and last dose will issue a medication error report*

  - 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

- PAM-13, BMQ, PSP satisfaction and utilization questionnaires
- Portal hypertension in cirrhotic patients as assessed by hepatic venous pressure gradient (HVPG) and/or clinical symptoms prior to treatment initiation, at EoT, as well as 12 and 24 weeks after EoT
- Resistant virus variants at post-baseline time points compared to baseline

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:

In phase III studies investigating the interferon-free ABBVIE REGIMEN ± RBV, SVR12 rates of at least 90% were observed, even in difficult-to-treat CHC patients (e.g. cirrhotic G1a treatment experienced patients). To describe in routine clinical practice the effectiveness of the ABBVIE REGIMEN ± RBV in patients with CHC, a precise estimate of the SVR12 rates in the core population of this study should be achieved (see Data Analysis for the definition of the core population).

If the SVR12 rate is at least 90% then with 417 evaluable patients the width of the 95% confidence interval (CI) based on Clopper-Pearson method will not be wider than 6%. If the SVR12 rate is at least 95%, then 238 patients are sufficient for a width of 6%, and the width of the 95%CI will be ≤ 6% if at least 334 evaluable patients can be included. Taken into consideration that about 5% of the patients enrolled, might be not evaluable in the core population 440 patients should be enrolled during the planned inclusion period of 24 months.

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 ≥70 days 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 ≥70 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 (based on genotype 1 subtype, fibrosis status, treatment experienced or naïve), which are relevant for scheduled treatment combination (± dasabuvir, ± RBV) and duration (12 or 24 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, viral breakthrough) 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. Viral breakthrough rates will be estimated in all patients of the CP analysis groups, who have at least one undetectable HCV RNA measurement on treatment and at least one on-treatment or EoT measurement thereafter. For all rates specified above 95%-confidence intervals (CIs) will be determined using the Clopper-Pearson method.

Univariate and multiple logistic regression (MLR) methods will be used to investigate the impact of various explanatory covariates (e.g. demographic and disease characteristics, co-morbidities, type of treating institution, and prior treatment for CHC and response outcome in treatment experienced patients) on SVR12. These analyses will be of exploratory nature, data driven, and will be 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 will 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.

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

Milestones:

Start of Data Collection:	Sept 2015
End of Data Collection:	Aug 2018
Final Report of Study Results:	July 2019

5.0 Amendments and Updates

- None

6.0 Milestones

- Start of Data Collection: Sept 2015
- End of Data Collection: Aug 2018
- Final Report of Study Results: July 2019

7.0 Rationale and Background

7.1 Background

Infection with the hepatitis C virus (HCV) is associated with considerable morbidity and mortality [1] and is a leading cause of chronic liver disease, cirrhosis, and hepatocellular carcinoma (HCC), as well as the most common indication for liver transplantation in many countries [2]. Around 60-85% of subjects exposed to HCV do not clear the virus and go on to develop chronic disease [3] [4]. Chronic hepatitis C (CHC) affects an estimated 2-3% of the world's population - equaling approximately 130-210 million individuals [5] [6]. The prevalence varies markedly from one geographic area to another ranging from 0.1-1% in Western Europe to 1-2% in Latin America and up to 4.9% in some regions of Eastern Europe [7] [8] [9] [10].

HCV demonstrates a high degree of genetic variability and has been classified into seven major genotypes (and a large number of subtypes) the distribution of which varies globally [11]. Genotypes 1 through 3 are found worldwide; the other genotypes have a more restricted distribution, genotype 4 is found predominantly in the Middle East, Central Africa, and Egypt; genotype 5 in South Africa; and genotype 6 mainly in Asia. HCV genotypes 1a and 1b are the most common forms, accounting for 60% of HCV infections worldwide [12] [13] [14] [15].

HCV is primarily transmitted by parenteral exposures to contaminated blood, most frequently by injection drug use, exposures in health-care settings and inadequate infection-control practices (tattoo, piercing). Occupational, perinatal and sexual exposure can also result in transmission of HCV [16] [17]. Since the early 1990's routine blood screening protocols have been introduced in most countries and as a consequence

transmission of the virus is rarely seen following receipt of blood, blood products or through organ transplants.

The natural course of CHC leads to progressive fibrosis and can eventually lead to cirrhosis of the liver over the course of 20-30 years in approximately 15-30% of infected individuals [18]. Once patients become cirrhotic, around 6% per year are expected to develop hepatic decompensation (ascites, encephalopathy, variceal hemorrhage, hepatorenal syndrome, or hepatic synthetic dysfunction) and around 3% per year will develop HCC [19]. Over the same time frame, between 4 and 5% of patients can be expected to require liver transplantation or die [19] [20]. Progression is not necessarily a linear process and can be accelerated by a number of factors including the age of the patient, duration of HCV infection, male gender, alcohol consumption and co-infection with other viruses such as hepatitis B virus (HBV) and human immunodeficiency virus (HIV) [4] but also by concomitant steatosis and obesity. Comorbid conditions can impact CHC treatment eligibility, safety, tolerability and efficacy of therapy [21] [22].

The burden of advanced liver disease varies widely across countries and is dependent upon several factors including chronic HCV prevalence and age distribution (and duration of infection) of those infected [23]. Due to an aging cohort of patients and an associated increase in the incidence of severe liver disease, the burden of CHC will continue to increase. In persons 30–49 years of age, the prevalence of the disease is 3–fold higher than in other age groups. By 2020, the rates of HCC and liver-related deaths among individuals with CHC are expected to increase by 81% and 180%, respectively [24].

The eradication of the virus, defined as the absence of HCV ribonucleic acid (RNA) in serum (as shown by a sensitive test) at the end of treatment (EoT) and 12-24 weeks later (sustained virological response [SVR]), is the therapeutic goal of CHC treatment [25] [26] [27] and is generally accepted as a virological cure, thus, eventually preventing the aforementioned complications [26] [27].

Achieving an SVR was associated with significant reduction in all-cause death compared to patients who did not achieve SVR (5-year mortality rate in HCV genotype 1-infected patients: 6.7% vs 14.4%, respectively) [28]. In another study the 10-year cumulative all-cause mortality rate was 8.9% in patients with SVR and 26.0% without SVR ($p<0.001$), the liver-related mortality or transplantation was 1.9% with SVR and 27.4% without SVR ($p<0.001$), the rate of HCC was 5.1% with and 21.8% without SVR ($p<0.001$), and the rate of patients experiencing liver failure was 2.1% with and 29.9% ($p<0.001$) without SVR [29]. Patients with SVR following treatment with pegylated interferon (pegIFN) with or without RBV have also shown improvement in liver histology and a reduction in liver-related death in several studies [30] [31] [32]. Moreover, patients with compensated

cirrhosis who achieve SVR essentially eliminate their subsequent risk of decompensation, may achieve histologic regression, and decrease their risk of HCC by two-thirds [33] [34] [35].

In the 1980's and 1990's interferon alfa was the first drug to show activity against HCV. However, the effectiveness of interferon monotherapy in the treatment of CHC infection was generally unsatisfactory resulting in an overall SVR rate across genotypes of <20% [36] [37]. Combination therapy with interferon plus ribavirin (RBV) improved SVR rates but still overall rates across genotypes remained below 50% [38] [39]. Following the introduction of long-acting interferons (peginterferon alfa-2a and peginterferon alfa-2b [i.e. pegIFNs]) in combination with RBV more than a decade ago, further advances have been made in efficacy with overall rates of SVR up to 54-63% [39] [40] [41]. SVR rates vary substantially by HCV genotype with genotype 1 being the most difficult-to-treat, thus requiring longer treatment periods to obtain SVR with interferon-based dual therapy. SVR rates up to around 50% can be achieved in patients with genotype 1 whereas for genotypes 2 and 3 cure rates of up to 80% can be achieved [41].

Treatment with pegIFN and RBV is associated with considerable, often treatment-limiting toxicities including cytopenias, neuro-psychiatric disorders and influenza-like symptoms.

In 2011 the first direct-acting antivirals (DAAs), specifically the protease inhibitors boceprevir and telaprevir, have been approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for treatment of HCV genotype 1. These first generation DAAs have significantly improved efficacy with rates of SVR reported as high as 63-75% among treatment-naïve HCV genotype 1 individuals [42] [43] [44]. However, these DAAs must be used in combination with pegIFN and RBV as triple combination therapy and the tolerability profile is further impaired by additional DAA specific adverse effects such as rash, pruritus, dysgeusia and anemia [42] [43] [44]. Treatment regimens with these DAAs are rather complicated with the necessity of futility rules and a response guided therapy duration of up to 48 weeks in selected patients.

Since 2014 the new standard of care for genotype 1 is pegIFN and RBV combined with either the nonstructural protein 3/nonstructural protein 4A (NS3/4A) protease inhibitor simeprevir or the nucleotide nonstructural protein 5B (NS5B) polymerase inhibitor sofosbuvir [45] [46].

Simeprevir is a NS3/4A protease inhibitor which was approved by the FDA at the end of 2013 and by the EMA in May 2014. In the phase III studies QUEST 1 and 2 treatment-naïve patients with genotype 1 yielded SVR rates of 80%, around 90% of these patients were eligible for truncated therapy of 24 weeks in a response guided treatment setting [47] [48]. Very similar results were reported for patients with prior relapse in the

PROMISE trial [49]. In the ATTAIN study 771 treatment-experienced partial and null-responder patients were randomized to either simeprevir plus pegIFN and RBV or telaprevir plus pegIFN and RBV. Although efficacy rates were similar (SVR was 55% and 54%, respectively) the safety profile of simeprevir was significantly improved, in particular with regards to anemia (13% vs. 37%) and pruritus (31% vs. 43%), while serious adverse events (SAEs) were reported by 2% and 9% of patients, respectively [50].
Notably, among patients infected with HCV genotype 1a the presence of a common Q80K polymorphism (pre-existing resistance-associated variant or not) results in significantly reduced response rates and thus, it is recommended that patients infected with HCV genotype 1a are screened for this mutation, and if the respective variant is present, consideration is given to selecting an alternative therapy [51].

Sofosbuvir acts as an RNA chain terminator within the catalytic site of the NS5B polymerase. It was approved by the FDA in December 2013 and by the EMA in January 2014 for treatment of genotype 1, 4, 5, and 6 along with pegIFN plus RBV and in genotype 2 and 3 patients as an interferon-free regimen with RBV only.

In the NEUTRINO phase III trial with sofosbuvir plus pegIFN/RBV in 326 treatment-naïve genotype 1, 4, 5 and 6 patients, the overall SVR was 90% (92% in genotype 1a and 82% in genotype 1b; 80% in cirrhotic patients) with a tolerability profile similar to pegIFN plus RBV. One further advantage of this triple treatment regimen is the treatment duration of just 12 weeks [52].

Data on the interferon-free combination of sofosbuvir plus RBV in treatment-naïve patients with genotype 1 are only available from small trials and results are somewhat inconsistent. When given for a duration of 24 weeks SVR rates of 50-68% have been reported and this regimen is currently only recommended for patients who cannot take pegIFN [45] [46] [53] [54].

Thus, currently available approved treatment regimens are not optimal for many patients and there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment and/or decrease the need for pegIFN as components of CHC therapy, ideally with shorter treatment duration.

Combinations of multiple DAAs targeting different steps of viral replication have the potential to significantly improve CHC treatment compared to current therapies by increasing SVR rates, eliminating interferon as a component of therapy, increasing the safety and tolerability of treatment, shortening duration of therapy and simplifying the treatment algorithm. In addition, wider application of DAA therapy and better responses with combination DAA regimens could significantly reduce the public health burden of this disease.

AbbVie's interferon-free regimen for the treatment of CHC includes 3 DAAs targeting different steps in HCV replication. paritaprevir is a NS3/4A protease inhibitor with nanomolar potency *in vitro* and is co-administered with low-dose ritonavir, an inhibitor of the cytochrome P-450 enzyme CYP3A4. As a pharmacologic enhancer of paritaprevir, ritonavir co-administration with paritaprevir (paritaprevir/r) results in higher drug exposures than administration of paritaprevir alone [55]. Ombitasvir (ABT-267) is a nonstructural protein 5A (NS5A) inhibitor with picomolar potency *in vitro*, and dasabuvir (ABT-333) is a NS5B non-nucleoside polymerase inhibitor with nanomolar potency *in vitro*.

The 3 DAA combination of paritaprevir/r – ombitasvir plus dasabuvir with or without RBV has been initially evaluated in 6 Phase III studies with genotype 1 infected patients (SAPPHIRE-I [56], SAPPHIRE-II [57], PEARL-II [58], PEARL-III [59], PEARL-IV [59], TURQUOISE-II [60]).

Therapy for 12 weeks with the above regimen in non-cirrhotic patients resulted in the following SVR rates 12 weeks after EoT (SVR12):

Table 1 - SVR12 rates in clinical trials:

Population and treatment duration	Genotype	SVR12 ABBVIE REGIMEN + RBV	SVR12 ABBVIE REGIMEN alone
Non-cirrhotic, treatment-naïve (12 weeks)	1a	95-97% (SAPPHIRE-I, PEARL-IV)	90% (PEARL-IV)
	1b	98-99.5% (SAPPHIRE-I, PEARL-III)	99% (PEARL-III)
Non-cirrhotic, treatment-experienced (12 weeks)	1a	96% (SAPPHIRE-II)	n.a.
	1b	97% (SAPPHIRE-II, PEARL-II)	100% (PEARL-II)

These results suggest that the ABBVIE REGIMEN with RBV is the optimal regimen for genotype 1a infected patients, while patients with genotype 1b do not require RBV.

The TURQUOISE-II [60] study explored the efficacy of the ABBVIE REGIMEN in the traditionally most difficult-to-treat cirrhotic patients. This large study enrolled exclusively genotype 1 infected patients with cirrhosis, including treatment-naïve and treatment-experienced individuals. All patients received the ABBVIE REGIMEN with RBV and were

randomized to 12 or 24 weeks of therapy. Overall 92% and 96% of patients achieved SVR following treatment for 12 or 24 weeks, respectively. Analysis of subgroups demonstrated that the small difference in SVR between treatment arms was due largely to the subgroup of genotype 1a treatment-experienced prior null responders treated for 12 weeks who achieved an SVR of 80%. This subgroup of patients achieved an SVR of 93% when treated for 24 weeks. Among genotype 1a infected patients, partial responders and relapsers had higher SVR rates than null responders in the 12 week treatment group, while similar SVR rates were seen among the null responders, partial responders and relapsers treated for 24 weeks, suggesting that the longer duration of 24 weeks is required only for cirrhotic genotype 1a null responders. SVR rates were very high across all subgroups in genotype 1b treatment-experienced patients treated for 12 and 24 weeks.

The ABBVIE REGIMEN has been studied with and without RBV in over 2,300 patients in Phase III trials across a variety of patient populations including those with compensated cirrhosis. Based on Phase III data, the ABBVIE REGIMEN, with or without RBV, was well tolerated with a low discontinuation rate. Adverse events (AEs) were typically mild, and many of the AEs and laboratory abnormalities reported were attributable to the presence of RBV. However, these AEs were much milder than observed when RBV was given in combination with interferon. Transient, asymptomatic serum alanine aminotransferase (ALT) elevations were observed at a low rate, were not associated with hepatic dysfunction and generally resolved with ongoing treatment. A disproportionate number of the cases were in women on concurrent ethinyl estradiol-containing therapy (i.e., contraceptives or hormone replacement) and discontinuation of the hormonal therapy with continuation or brief interruption of the ABBVIE REGIMEN led to resolution in serum ALT elevation. Transient elevations in serum bilirubin (predominantly indirect) were observed in subjects receiving the ABBVIE REGIMEN with RBV, related to the inhibition of the bilirubin transporters, organic anion-transporting polypeptides (OATPs) 1B1/1B3, by paritaprevir and RBV-induced hemolysis. Bilirubin elevations occurred after initiation of treatment, peaked by study Week 1, and generally resolved with ongoing therapy. Bilirubin elevations were not associated with aminotransferase elevations. The frequency of indirect bilirubin elevations was lower among subjects who did not receive RBV.

Response of CHC genotype 4 was assessed in the phase II study PEARL-I in which 86 treatment-naīve patients were randomized to the 2 DAA combination of paritaprevir/r – ombitasvir with vs. without RBV for 12 weeks. The SVR was 100% with RBV vs. 91% without RBV [61]. No serious SAEs or AEs leading to discontinuation were reported.

These results from pivotal studies are encouraging and the new interferon-free regimens might provide physicians with the armamentarium to cure the vast majority of patients

infected with CHC. However, the medical community is expecting data which show how these results translate into routine clinical practice particularly after the experience with the first protease inhibitors which were available to physicians and where the outcome in everyday life and especially the tolerability was far less favorable in certain difficult-to-treat patient subgroups than expected from the development trials [62] [63].

7.2 Rationale

The ABBVIE REGIMEN ± RBV for the treatment of 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 ABBVIE REGIMEN is expected to be first available in Belgium for the treatment of CHC in 2015.

The rationale for this observational study is to determine how the efficacy and safety of the ABBVIE REGIMEN as demonstrated in pivotal trials translates into real world everyday clinical settings, evaluating its effectiveness. Whereas efficacy can be defined as a measure of the capacity of a treatment to produce the desired effect in a controlled environment, such as in a randomized controlled trial, effectiveness is 'the extent to which a drug achieves its intended effect in the usual clinical setting' [64]. Effectiveness trials typically have limited exclusion criteria and will involve the broader patient populations in routine clinical practice, treated per local label, which might include patients with heterogenous compliance patterns and patients with significant comorbid conditions and could be used to model and disseminate best practices. Effectiveness research allows for external patient-, provider-, and system-level factors and can therefore be relevant for health-care decisions by both providers in practice and policy-makers [65].

This observational study is the first effectiveness research examining the ABBVIE REGIMEN ± RBV, used according to local label, under real world conditions in Belgium in clinical practice patient population.

During the last decade when dual therapy with pegIFN plus RBV was standard of care for the treatment of CHC, management of patients and clinical outcome were improved following the discovery of predictive factors of virological response, often in observational studies with large data bases [66]. Thus treatment could be targeted to patients most likely to respond and futile treatment stopped in patients with a low likelihood of virological cure. HCV genotype and subtype, baseline viral load, fibrosis stage, age, treatment exposure and on-treatment virological response proved to be useful predictors for the eradication of HCV in everyday clinical practice [27]. More recently the discovery

of a genetic disposition of the Interleukin 28B (IL28B) single nucleotide polymorphism (SNP) contributed further to our understanding of virological responses to treatment [67]. For new interferon-free treatment regimens knowledge of predictive factors of virological response is extremely sparse and several of the now well established predictors of response were not initially identified through analyses of the development trials. This observational study may play an important part in bridging the data gaps and could help identify predictive factors of virological response in everyday clinical settings which were not detected in interventional trials and which could be used to further optimize treatment with the interferon-free ABBVIE REGIMEN in the future.

The label of the ABBVIE REGIMEN will vary according to HCV genotype/subtype and stage of liver disease. It is therefore relevant to understand the pattern of use and outcome in daily clinical practice. In addition, this study will provide data on the impact of adherence on treatment outcomes in everyday settings, which may help treating physicians to improve the management of patients under their care.

The aim of this observational study is to provide evidence of the effectiveness and of the influence of adherence on treatment outcome of the ABBVIE REGIMEN ± RBV in a real world setting across clinical practice patient populations.

8.0 Research Question and Objectives

8.1 Research Question

What is the effectiveness and the influence of adherence on treatment outcome of the interferon-free ABBVIE REGIMEN ± RBV in patients with CHC in a real life setting across clinical practice patient populations?

8.2 Objectives

8.2.1 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 SVR12

8.2.2 Secondary Objectives

2. To provide real world evidence for predictive factors of virological response
3. To describe the pattern of real world use of the ABBVIE REGIMEN ± RBV with respect to different patient and treatment characteristics

4. To evaluate the influence of adherence on treatment outcome in routine clinical practice
5. To evaluate the contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization
6. To assess viral resistance patterns

9.0 Research Methods

9.1 Study Design

This is a prospective, multi-center observational study in patients receiving the interferon-free ABBVIE REGIMEN with or 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 the patient the opportunity to participate in this study.

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

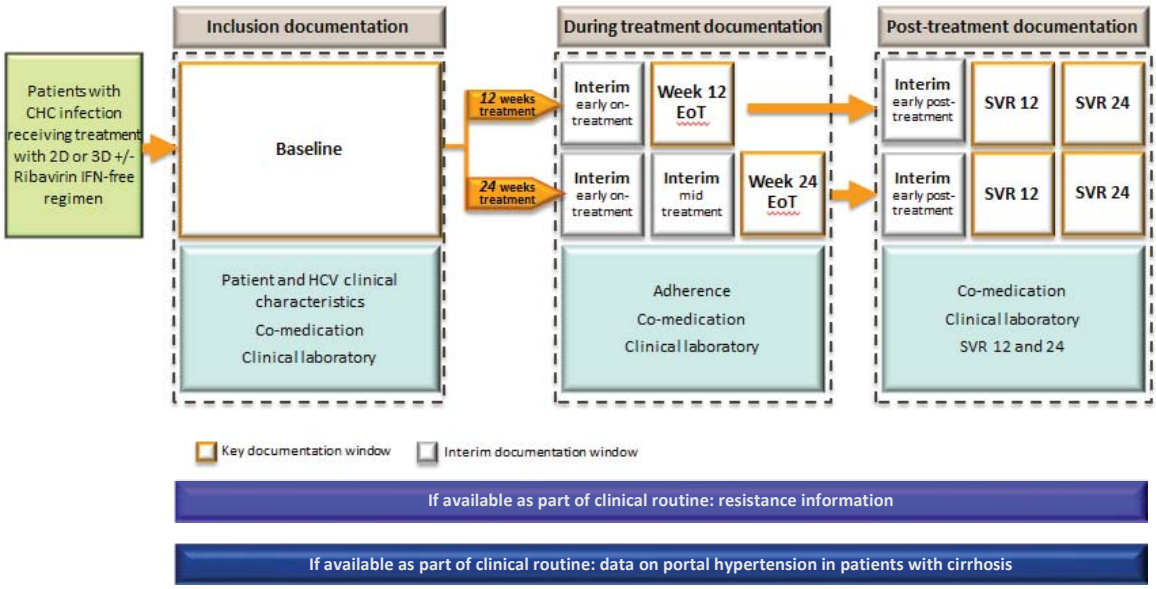
After written informed consent has been obtained, patient data including demographic data, HCV disease characteristics, co-morbidities, co-medication, treatment details, and laboratory assessments as recorded in the patient's medical records (source documentation) will be documented in the electronic case report form (eCRF). Patients will be observed for the duration of the ABBVIE REGIMEN therapy and for up to 24 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. The observational study period entails the following data collection schemes, data documented will be those closest to the time windows as indicated in Figure 1:

- 12-week treatment regimen: four visits plus two interim data collection windows
- 24-week treatment regimen: four visits plus three interim data collection windows

This schedule is based on the anticipated regular follow-up for patients undergoing treatment for CHC.

Figure 1 - Study Flowchart



9.2 Setting

For overall research design and observational documentation schedule refer to Sections 9.1 and 9.4.1 as well as to Figure 1.

9.2.1 Target Population

Patients are eligible for observation in this cohort if the following applies:

- Treatment-naïve or -experienced adult male or female patients with confirmed CHC, genotype 1 or 4, receiving combination therapy with the interferon-free ABBVIE REGIMEN ± RBV according to standard of care and in line with the current local label
- If RBV is co-administered with the ABBVIE REGIMEN, it has been prescribed in line with the current local label (with special attention to contraception requirements and contraindication during pregnancy)
- Patients must voluntarily sign and date an informed consent prior to inclusion into the study
- Patient must not be participating or intending to participate in a concurrent interventional therapeutic trial

9.2.2 Study Duration

This is a prospective, observational study. The inclusion period will be approximately 24 months and the observational period of the study will be from baseline visit until 24 weeks post-treatment.

The observational period for patients receiving 12 weeks of ABBVIE REGIMEN will be max. 36 weeks (12 weeks treatment and 24 weeks post-treatment observation) and for patients receiving 24 weeks of ABBVIE REGIMEN the observational period will be max. 48 weeks (24 weeks treatment and 24 weeks post-treatment observation).

9.2.3 Termination Criteria

For patients who terminate the ABBVIE REGIMEN prematurely for whatever reason the EoT eCRF page should be filled in and the reason for treatment discontinuation should be documented. If the reason for ABBVIE REGIMEN discontinuation is due to an SAE, the event must be reported to AbbVie within 24 hours of physician awareness (see Section 11.5).

If, in such patients, there is evidence of virological response during therapy or at EoT, the SVR12 and SVR24 pages should be completed if respective data is available.

9.2.4 Investigator Selection Criteria

University centers and outpatient clinics qualified by training and experience in the management of patients with CHC will be selected to participate in this study. The AbbVie Affiliate Medical Director will ensure that sites participating in the study are representative of the medical practice in the country, have the ability to conduct the study and their availability of the target patient population. The type of the participating treating institute will be documented in the eCRF.

9.3 Variables

9.3.1 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 ABBVIE REGIMEN)

9.3.2 Secondary Variables

- Type of treatment regimen (± Dasabuvir, ± RBV, intended and actual combination, dose and duration)
- Adherence
  *A period of **7 days in a row** of missed intake of the **ABBVIE Regimen** during the time between documented first dose and last dose will issue a medication error report.*
  - 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
- PAM-13, BMQ, PSP satisfaction and utilization questionnaires
- Portal hypertension in cirrhotic patients as assessed by hepatic venous pressure gradient (HVPG) and/or clinical symptoms prior to treatment initiation, at EoT, as well as 12 and 24 weeks after EoT
- Resistant virus variants at post-baseline time points compared to baseline

9.4 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. Data are collected from the source documents for each patient in the study, consisting of medical records containing demographic data, medical, treatment and diagnostic documentation and laboratory assessments.

The investigator(s)/institution(s) will permit study-related monitoring, audits, independent ethics committee/- review board (IEC/IRB) review, and regulatory inspection(s), providing direct access to source data documents.

9.4.1 Data to be Documented

This observational study covers three documentation periods, see Figure 1. An overview on data to be collected throughout the study is summarized in **Table 2**.

After the patient has signed an informed consent, the following data will be documented in the eCRF, if available from the patient charts based on assessments done in physicians' routine clinical practice.

9.4.1.1 Inclusion Documentation

The following will be documented:

- Demographic information
  - Interleukin 28B (IL28B) genotypes
- CHC disease characteristics
  - Year of diagnosis and 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
- Concomitant medication, see 9.4.1.5
- ABBVIE REGIMEN ± RBV

- 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, see 9.4.1.4
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

- Data on portal hypertension (for patients with cirrhosis only): HVPG or clinical assessments (e.g. splenomegaly, presence of esophageal varices, gastric varices, surrogate lab markers, CT, MRI)
- Viral resistance (blood for viral sequencing)
- PAM-13, BMQ

9.4.1.2 During Treatment Documentation

Follow-up visits are 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 9.4.1.4
HIV-infected patients only	
▪ CD 4 count	most recent assessment
▪ HIV RNA	in copies/mL

- Concomitant medication, see 9.4.1.5
- Adherence to ABBVIE REGIMEN ± RBV (ABBVIE REGIMEN - % of target dose taken and RBV Y/N)
  *A period of **7 days in a row** of missed intake of the **ABBVIE Regimen** during the time between documented first dose and last dose will issue a medication error report.*
- Tolerability (sAEs and AEs, see 11.5) and pregnancies (see 11.6)
- Data on portal hypertension (for patients with cirrhosis only): HVPG or clinical assessments (e.g. splenomegaly, presence of esophageal varices, surrogate lab markers, CT, MRI) (EoT only)
- Viral resistance (blood for viral sequencing) (EoT only)
- PSP satisfaction and utilization questionnaires, PAM-13 and BMQ: only at EOT/premature discontinuation

9.4.1.3 Post-Treatment Documentation

Follow-up visits are 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 9.4.1.4
HIV-infected patients only	
▪ CD 4 count	most recent assessment
▪ HIV RNA	in copies/mL

- Tolerability (sAEs, see 11.4) and pregnancies (see 11.6)
- Data on portal hypertension (for patients with cirrhosis only): HVPG or clinical assessments (e.g. splenomegaly, presence of esophageal varices, surrogate lab markers, CT, MRI)
- Viral resistance (blood for viral sequencing)
- PSP Satisfaction and utilization questionnaires

Table 2 - Data Documentation Schedule

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)	Baseline	Treatment Period			Post-treatment (PT) Period		
		On-treatment visits	Mid treatment visit for pts receiving 24 weeks of therapy	EoT[b]	Early PT visit	SVR 12 visit	SVR 24 visit
Informed consent	X[a]						
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	X	X	X	X
Clinical chemistry and hematology	X	X	X	X	X	X	X
ABBVIE REGIMEN initiation documentation	X						
ABBVIE REGIMEN adherence		X	X	X			
Concomitant medication	X	X	X	X			
Relevant medical history, co-morbidities	X						
sAE, AE and pregnancy reporting	X	X	X	X	X[c]	X[d]	X[d]
For patients receiving RBV: Evidence, in accordance with local label, that female patient or female partner of male patient is not pregnant	X						
Data on portal hypertension in patients with cirrhosis	X			X		X	X
Viral resistance sample	X			X		X	X
BMQ, PAM-13	X			X			
PSP evaluation		X	X	X	X	X	

Abbreviations: EoT = End of Treatment (at Week 12 or 24 or at premature discontinuation), PT = Post-Treatment

a Written 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

d Pregnancy reporting for patients treated with DAA plus RBV

9.4.1.4 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**

9.4.1.5 Concomitant Medication

Concomitant medication - the following will be documented:

- Concomitant medication used from the time when the decision is made to initiate treatment with the ABBVIE REGIMEN until after the last dose

It should be verified by the treating physician that concomitant medication can be safely administered with the ABBVIE REGIMEN (including ritonavir) and RBV. Some medications may be contra-indicated, 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.

9.4.1.6 Standardized Assessment Tools

Patient Activation Measure – (PAM-13)

PAM 13 is a measure used to assess the patient knowledge, skill, and confidence for self-management. It should require approximately 7 minutes to complete and is presented in Annex 1.

Beliefs Medication Questionnaire – (18-item BMQ)

The 18-item BMQ consists of 18 questions used to screen for patients' beliefs, attitudes and concerns about their medication.

The BMQ should require approximately 10 minutes to complete and is presented in Annex 2.

Patient Support Program (PSP) Questionnaire

The PSP utilization and satisfaction assessment will evaluate the frequency of utilization and patient's overall satisfaction with their respective Patient Support Program.

The PSP questionnaire should require approximately 2-5 minutes to complete and is presented in Annex 3-4.

9.5 Study Size

In phase III studies investigating the interferon-free ABBVIE REGIMEN ± RBV, SVR12 rates of at least 90% were observed, even in difficult-to-treat CHC patients (e.g. cirrhotic G1a treatment experienced patients). To describe in routine clinical practice the effectiveness of the ABBVIE REGIMEN ± RBV in patients with CHC, a precise estimate of the SVR12 rates in the core population of this study should be achieved (see Section **Error! Reference source not found.** for the definition of the core population).

As obvious from **Error! Reference source not found.**, if the SVR12 rate is at least 90%, then with 417 evaluable patients the width of the 95% confidence interval (CI) will not be wider than 6%. If the SVR12 rate is at least 95%, then 238 patients are sufficient for a width of 6%, and the width of the 95%CI will be ≤ 5% if at least 334 evaluable patients can be included. Taken into consideration that about 5% of the patients enrolled might be not evaluable in the core population 440 patients should be enrolled during the planned inclusion period of 24 months.

Table 3 Width of 95% Confidence Interval for SVR12

Number of patients	SVR12 rates	95% Confidence Interval*		
		Lower Limit	Upper Limit	Width
417	90%	86.71	92.71	6.00%
238	95%	91.41	97.40	5.99%
334	95%	92.08	97.08	5.00%

* exact two-sided 95% confidence interval according Clopper-Pearson

9.6 Data Management

9.6.1 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. Only data specified in the protocol will be entered 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.

Original Questionnaires will be collected from the sites by Abbvie.

9.6.2 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.

9.7 Data Analysis

9.7.1 Analysis Population, Time Windows and Handling of Missing Data

The target population (TP) is defined as all patients who fulfill the criteria specified in Section 9.2.1. 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 ≥70 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 ≥70 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 ≥70 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 ≥70 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 (baseline, on-treatment visits, EoT visit, post-

treatment visits). 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-baseline 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 ≥70 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 considered as virological failure at this time point (i.e. not undetectable or unquantifiable).

9.7.2 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 ± RBV) and duration (12 and 24 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.

9.7.3 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

9.7.3.1 Primary Effectiveness Endpoint

The percentage of patients achieving SVR12 (single last HCV RNA <50 IU/mL 12 weeks [i.e. at least 70 days] after the last actual dose of the ABBVIE REGIMEN) is the primary effectiveness endpoint.

9.7.3.2 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 breakthrough (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:
    - On-treatment virologic failure (breakthrough [defined as above] or failure to suppress [each measured on-treatment HCV RNA value ≥50 IU/mL])
    - 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)

- Premature study drug discontinuation with no on-treatment virologic failure
- Missing SVR12 data and/or none of the above criteria

9.7.3.3 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, viral breakthrough). The relapse rates will be estimated in patients of the CP analysis groups with EoT response and sufficient HCV RNA measurements post-treatment. Viral breakthrough rates will be estimated in all patients of the CP analysis groups, who have at least one undetectable HCV RNA measurement on-treatment and at least one on-treatment or EoT measurement thereafter.

Univariate and multiple logistic regression (MLR) methods will be used to investigate the impact of the following explanatory covariates on SVR12:

- Key demographic information
- Mode of CHC infection
- HCV RNA level at baseline
- Most recent stage of liver fibrosis
- HCV genotype and subtype (if available)
- Type of treating institute
- Liver and/or CHC related co-morbidities
- Key clinical chemistry and hematology laboratory variables at baseline
- In treatment experienced patients only:
  - Most recent prior treatment for CHC
  - Outcome of most recent prior CHC treatment

Further details and additional covariates will be specified in the SAP.

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.

9.7.4 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 4 - Analysis Time Windows

Phase	Time point	Time Window
Pre-Treatment	Baseline	Last value prior to start of study treatment (i.e. ≤study day 1)
		Study day during treatment period (Study day 1 = first treatment day)
Treatment Weeks	4 (day 29)	15 - 42
	8 (day 57)	43 - 70
	12 (day 85)	71 - 98
	16 (day 113)	99 - 126
EoT	Actual EoT	Study day of last dose (28 days prior to EoT - 14 days post EoT)
Post Treatment	4 weeks (day 29 post EoT)	15 – 56 post EoT
	12 weeks (day 85 post EoT)	57 – 112 post EoT
	24 weeks (day 169 post EoT)	141 – 196 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.

9.7.5 PSP, PAM and BMQ

The contribution of the patient support program (PSP) to disease control, treatment continuation over time, patient satisfaction and PSP utilization will be analyzed using descriptive and exploratory statistical methods. Appropriate frequency tables will summarize all corresponding variables of the PSP questionnaire (see ANNEX 3 and 4) over time stratified by ABBVIE REGIMEN arms. In addition, multiple logistic regression (MLR) analysis will be performed to investigate the association between the use of the PSP and the patient satisfaction variables of the PSP questionnaire with the probability to treatment completion. These MLRs will be performed similar to the MLRs for SVR12 (see Section 9.7.3.3. Additional details will be specified in the SAP.

The Patient Activation Measure (PAM) 13 item scale is a measure used to assess the patient knowledge, skill, and confidence for self-management. Each of the 13 items can be answered with one of four possible response options, which are “disagree strongly” (1), “disagree” (2), “agree” (3), “agree strongly” (4).

Based on responses to the 13-item measure, the score is calculated by adding up the raw scores (range of the sum: 13 – 52) and mapping up the value onto a scale of 0–100 indicating strength of agreement with the 13 items (100 *(sum - 13) / (52 - 13)).The final score can be assigned to one of the four levels of activation. A higher score indicates that the patient is likely to participate more actively in health care processes and takes more responsibility for his or her health.

In case of missing item values, the mean value of the available items will be used for replacement. However, if there are less than nine items answered, no summary score will be calculated.

A summary table will show descriptive statistics (n, mean, median, SD, minimum and maximum) for the summary score at baseline and the post-baseline time points, as well as changes from baseline. In addition analysis of covariance (ANCOVA) will be applied to investigate the effect of the different ABBVIE REGIMENS (± RBV and duration) on the summary score using the corresponding baseline value as covariates. Further details will be specified in the SAP.

The 18-item Beliefs Medication Questionnaire (BMQ) consists of 18 questions used to screen for patients’ beliefs, attitudes and concerns about their medication. The 18 items are rated on a Likert scale from 1=strongly disagree to 5 = strongly agree and the 18 items are summarized into 4 scale scores: necessity of their medication, medication-related concerns, general medication-related harm and general medication overuse. The total score of each BMQ subscale will be calculated.

The same statistical methods as specified above for BMQ will be applied for the BMQ subscales.

9.7.6 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 (see Section 11.0 and 9.2.3). 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.

9.7.7 Interim Assessments

One interim analysis is planned as soon as the first 200 patients have completed the study and their data are sufficiently cleaned. It is expected, that the vast majority of the patients in this interim analysis (about 95%) will have been treated for 12 weeks. Further details will be specified in the SAP.

9.8 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 (see Section 9.4).

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.

9.9 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.

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 Adverse Events/Adverse Reactions

PRO data are not considered a potential source of adverse reactions. However, participating sites should review the PRO data and if a possible product-related event (including a suspected adverse reaction) is noted, the HCP must determine whether the event is related to the ABBVIE REGIMEN ± RBV (or any other AbbVie authorized product) and if so, it should be reported to AbbVie.

Medication errors (this refers to any unintentional error in the prescribing, dispensing, or administration of a medicinal product while in control of the HCP, patient or consumer) should be reported by the HCP to AbbVie.

The relevant AbbVie Pharmacovigilance contact details are specified below:

Name: Abbvie Belgium Pharmacovigilance department

Address: Avenue Einstein 14, 1300 Wavre, Belgium

[redacted]

11.1 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 AE 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 AE.

If an AE 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.

11.2 Severity

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

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

11.3 Relationship to Pharmaceutical Product

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

Reasonable Possibility	An AE where there is evidence to suggest a causal relationship between the product and the AE.
No Reasonable Possibility	An AE where there is no evidence to suggest a causal relationship between the product and the AE.

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

11.4 Serious Adverse Event Collection Period

SAEs will be reported to AbbVie from the time the physician obtains the patient's informed consent until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

11.5 Serious and non-serious Adverse Event Reporting

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

- For events from patients using the ABBVIE REGIMEN ± RBV (or any other AbbVie authorized product) report to AbbVie within 24 hours of the physician becoming aware of the event by using the eCRF system or notifying the AbbVie contact person identified in Section 11.0.
- For events from patients using a non-AbbVie product - notify the Marketing Authorization Holder (MAH) of the product within 24 hours of the physician becoming aware of the event.

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

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

11.6 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 only, or for 7 months after the last dose of RBV (or per local RBV label) and/or consistent with local treatment guidelines for RBV.

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 11.0.

The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if RBV is included within the regimen.

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, interim assessments, 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 [68].

13.0 References

[1] Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 2012; 380: 2095-128.

[2] Chen SL, Morgan TR. The natural history of hepatitis C virus (HCV) Infection. Int J Med Sci 2006; 3: 47-52.

[3] Hoofnagle JH. Course and outcome of hepatitis C. Hepatology 2002; 36 (Suppl 1): S21-9.

[4] Di Bisceglie AM. Natural history of hepatitis C: its impact on clinical management. Hepatology 2000; 31: 1014-8.

[5] Pawlotsky JM. Hepatitis C virus: from discovery to eradication in 40 years? Clin Microbiol Infect 2011; 17: 105-6.

[6] Lavanchy D. Evolving epidemiology of hepatitis C virus. Clin Microbiol Infect 2011; 17: 107-15.

[7] WHO. Weekly epidemiological record. 2000; 75, 17-28. Available at http://www.who.int/docstore/wer/pdf/2000/wer7503.pdf.

[8] Szabo SM, Bibby M, Yuan Y et al. The epidemiologic burden of hepatitis C virus infection in Latin America. Ann Hepatol 2012; 11: 623-35.

[9] Pereira LMMB, Martelli CMT, Moreira RC et al. Prevalence and risk factors of hepatitis C virus infection in Brazil, 2005 through 2009: a cross-sectional study. BMC Infect Dis 2013; 13: 1-12.

[10] Eurosurveillance 2003; 8 (5): 99-118.

[11] Smith DB, Bukh J, Kuiken C, et al. Expanded classification of hepatitis C virus into 7 genotypes and 67 subtypes: updated criteria and genotype assignment web resource. Hepatology 2014; 59: 318-27.

[12] US Department of Health and Human Services - Centers for Disease Control and Prevention. Recommendations for prevention and control of hepatitis C virus (HCV) infection and HCV related chronic disease. CDC Report1998; 47: 1-39

[13] Houghton M. Hepatitis C viruses. In: Fields BN, Knipe DM, Howley PM, eds, Fields Virology (3rd ed). Philadelphia: Lippincott - Raven, 1996: 1035-58.

[14] Global surveillance and control of hepatitis C. Report of a WHO Consultation organized in collaboration with the Viral Hepatitis Prevention Board, Antwerp, Belgium. J Viral Hepat 1999; 6: 35-47.

[15] WHO. HCV genotypes. Available at http://www.who.int/csr/disease/hepatitis/whocdscsrlyo2003/en/index2.html#genome; accessed July 07, 2014.

[16] Prati D. Transmission of hepatitis C virus by blood transfusions and other medical procedures: a global review. J Hepatol 2006; 45: 607-16.

[17] Central and Eastern European Harm Reduction Network (CEEHRN). Hepatitis C among drug users in the new EU member states and neighborhood: Recommendations for action. CEEHRN brochure/leaflet 2006. Available at http://www.aidsactioneurope.org/clearinghouse/topics/hepatitis-c-among-drug-users-new-eu-member-states-and.

[18] Alberti A, Chemello L, Benvegnù L. Natural history of hepatitis C. J Hepatol 1999; 31 (Suppl 1): 17-24.

[19] Alazawi W, Cunningham M, Dearden J, Foster GR. Systematic review: outcome of compensated cirrhosis due to chronic hepatitis C infection. Aliment Pharmacol Ther 2010; 32: 344-55.

[20] Brown RS. Hepatitis C and liver transplantation. Nature 2005; 436: 973-78.

[21] Villano SA, Vlahov D, Nelson KE, Cohn S, Thomas DL. Persistenc of viremia and the importance of long-term follow-up after acute hepatitis C infection. Hepatology 1999; 29: 908-14.

[22] Thomas DL, Astemborski J, Rai RM, et al. The natural history of hepatitis C virus infection: host, viral, and environmental factors. JAMA 2000; 284: 450-6.

[23] Dore GJ, Ward J, Thursz M. Hepatitis C disease burden and strategies to manage the burden (Guest Editors Mark Thursz, Gregory Dore and John Ward). J Viral Hepat 2014; 21 (Suppl 1): 1-4.

[24] Davis GL, Albright JE, Cook SF, Rosenberg DM. Projecting future complications of chronic hepatitis C in the United States. Liver Transpl 2003; 9: 331-8.

[25] Strader DB, Wright T, Thomas DL, Seeff LB. AASLD practice guidelines: diagnosis, management, and treatment of hepatitis C. Hepatology 2004; 39: 1147-70.

[26] Dienstag LJ, McHutchison JG. American gastroenterological association technical review on the management of hepatitis C. Gastroenterology 2006; 130: 231-64.

[27] Ghany MG, Strader DB, Thomas DL, Seeff LB. AASLD practice guidelines: diagnosis, management, and treatment of hepatitis C: an update. Hepatology 2009; 49: 1335-74.

[28] Backus LI, Boothroyd DB, Phillips BR, et al. A sustained virologic response reduces risk of all-cause mortality in patients with hepatitis C. Clin Gastroenterol Hepatol 2011; 9: 509-16.

[29] Van der Meer AJ, Veldt BJ, Feld JJ, et al. Association between sustained virological response and all-cause mortality among patients with chronic hepatitis C and advanced hepatic fibrosis. JAMA 2012; 308: 2584-93.

[30] Everson GT, Balart L, Lee SS, et al. Histological benefits of virological response to peginterferon alfa-2a monotherapy in patients with hepatitis C and advanced fibrosis or compensated cirrhosis. Aliment Pharmacol Ther 2008; 27: 542-51.

[31] Poynard T, McHutchison JG, Manns M, et al. Impact of pegylated interferon alfa-2b and ribavirin on liver fibrosis in patients with chronic hepatitis C. Gastroenterology 2002; 122: 1303-13.

[32] Shiffman M, Hofmann CM, Thompson EB, et al. Relationship between biochemical, virologic and histologic response during interferon treatment of chronic hepatitis C. Hepatology 1997; 26: 780-5.

[33] Bruno S, Stroffolini T, Colombo M, et al. Sustained virological response to interferon-alpha is associated with improved outcome in HCV-related cirrhosis: a retrospective study. Hepatology 2007; 45: 579-87.

[34] Di Bisceglie AM, Shiffman M, Everson GT, et al. Prolonged antiviral therapy with peginterferon to prevent complications of advanced liver disease associated with hepatitis C: results of the hepatitis C antiviral long-term treatment against cirrhosis (HALT-C) trial. Hepatology 2007; 46 (Suppl S1): 290A.

[35] Camma C, Di Bona D, Schepis F, et al. Effect of peginterferon alfa-2a on liver histology in chronic hepatitis C: a meta-analysis of individual patient data. Hepatology 2004; 39: 333-42.

[36] McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. Hepatitis Interventional Therapy Group. NEJM 1998; 339: 1485-92.

[37] Zeuzem S, Feinman SV, Rasenack J, et al. Peginterferon α-2a in patients with chronic hepatitis C. NEJM 2000; 343: 1666-72.

[38] Poynard T, McHutchison JG, Goodman Z, Ling MH, Albrecht J. Is an “à la carte” combination interferon alfa-2b plus ribavirin regimen possible for the first line treatment in patients with chronic hepatitis C? Hepatology 2000; 31: 211-8.

[39] Fried MW, Shiffman M, Reddy KR, et al (for the PEGASYS® International Study Group). Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. NEJM 2002; 347: 975-82.

[40] Manns M, McHutchison JG, Gordon SC et al. PegInterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomized trial. Lancet 2001; 358: 958-65.

[41] Hadziyannis SJ, Sette H Jr, Morgan TR et al. Peginterferon-alpha 2a and ribavirin combination therapy in chronic hepatitis C: a randomized study of treatment duration and ribavirin dose. Ann Intern Med 2004; 140: 346-55.

[42] Jacobson IM, McHutchison JG, Dusheiko GM et al. Telaprevir in combination with peginterferon and ribavirin in genotype 1 HCV treatment-naive patients: final results of phase 3 ADVANCE study. Hepatology 2010; 52 (Suppl S1): 427A.

[43] Sherman KE, Flamm SL, Afdhal NH et al. Telaprevir in combination with peginterferon alfa2b and ribavirin for 24 or 48 weeks in treatment-naive genotype 1 HCV patients who achieved an extended rapid viral response: final results of Phase 3 ILLUMINATE study. Hepatology 2010; 52 (Suppl S1): 401A.

[44] Poordad F, McCone J, Bacon BR et al. Boceprevir (BOC) combined with peginterferon alfa-2b/ribavirin (P/R) for treatment-naive patients with hepatitis C (HCV) genotype 1: SPRINT-2 final results. Hepatology 2010; 52 (Suppl S1): 402A.

[45] EASL Recommendations on Treatment of Hepatitis C 2014. J Hepatol 2014; doi: 10.1016/j.jhep.2014.05.001 (Epub ahead of print).

[46] AASLD. Recommendations for Testing, Managing, and Treating Hepatitis C. 2014: 1-50. Available at http://www.hcvguidelines.org/sites/default/files/full_report.pdf.

[47] Jacobson IM, Dore G, Foster G et al. Simeprevir with pegylated interferon alfa 2a plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-1): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet 2014; doi: 10.1016/S0140-6736(14)60494-3 (Epub ahead of print).

[48] Manns M, Marcellin P, Poordad F, et al. Simeprevir with pegylated interferon alfa 2a or 2b plus ribavirin in treatment-naive patients with chronic hepatitis C virus genotype 1 infection (QUEST-2): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2014; doi: 10.1016/S0140-6736(14)60538-9 (Epub ahead of print).

[49] Forns X, Lawitz E, Zeuzem S, et al. Simeprevir with Peginterferon and ribavirin leads to high rates of SVR in patients with HCV genotype 1 who relapsed after previous therapy: a phase 3 trial. Gastroenterology. 2014; 146: 1669-79.

[50] Reddy KR, Zeuzem S, Zoulim F, et al. A Phase III randomised, double-blind study to evaluate the efficacy, safety and tolerability of simeprevir vs telaprevir in combination with pegylated interferon and ribavirin in chronic hepatitis C virus genotype 1 treatment-experienced patients: the ATTAIN study. Abstract APASL 2014 Brisbane, Australia. Available at http://www.natap.org/2014/APASL/APASL_20.htm.

[51] Full prescribing information Olysio. Available at http://www.olysio.com/shared/product/olysio/prescribing-information.pdf; accessed February 09, 2014.

[52] Lawitz E, Mangia A, Wyles D, et al. Sofosbuvir for previously untreated chronic hepatitis C infection. NEJM 2013; 368: 1878-87.

[53] Lalezari L, Nelson D, Hyland R, et al. Once daily sofosbuvir plus ribavirin for 12 and 24 weeks in treatment-naive patients with HCV infection: the QUANTUM study. J Hepatol 2013; 58 (Suppl 1): S346.

[54] Osinusi A, Meissner EG, Lee YJ, et al. Sofosbuvir and ribavirin for hepatitis C genotype 1 in patients with unfavorable treatment characteristics: a randomized clinical trial. JAMA 2013; 310: 804-11.

[55] Menon RM, Klein CE, Lawal AA, et al. Pharmacokinetics and tolerability of the HCV protease inhibitor ABT-450 following single ascending doses in healthy adult volunteers with and without ritonavir. Abstract of HepDART 2009, Kohala Coast, Hawaii, USA. Available at http://www.natap.org/2009/hepDART/hepDART_03.htm.

[56] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r ombitasvir and dasabuvir with ribavirin. NEJM 2014; 370: 1594-603.

[57] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r-ombitasvir and dasabuvir with ribavirin. NEJM 2014; 370: 1604-14.

[58] Andreone P, Colombo MG, Enejosa JV, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology 2014; doi: 10.1053/j.gastro.2014.04.045 (Epub ahead of print).

[59] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r-ombitasvir and dasabuvir with or without ribavirin for HCV. NEJM 2014; 370: 1983-92.

[60] Poordad F, Hezode C, Trinh R, et al. ABT-450/r-ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. NEJM 2014; 370: 1973-82.

[61] Hezode C, Marcellin P, Pol S, et al. Results from the phase 2 PEARL-I study: interferon-free regimens of ABT-450/R + ABT-267 with or without ribavirin in patients with HCV genotype 4 infection. J Hepatol 2014; 60 (Suppl 1): S24.

[62] Hezode C, Fontaine H, Dorival C et al. Effectiveness of telaprevir or boceprevir in treatment-experienced patients with HCV genotype 1 infection and cirrhosis. Gastroenterology 2014; 147: 132-42.

[63] Colombo M, Fernández I, Abdurakhmanov D, et al. Safety and on-treatment efficacy of telaprevir: the early access programme for patients with advanced hepatitis C. Gut 2014; 63: 1150-8.

[64] Marley J. Efficacy, effectiveness, efficiency. Aust Prescr 2000; 23: 114-5.

[65] Singal AG, Higgins PDR, Waljee AK. A primer on effectiveness and efficacy trials. Clin Trans Gastroenterol 2014; 5 (e45): 1-4.

[66] Marcellin P, Cheinquer H, Curescu M, et al. High sustained virologic response rates in rapid virologic response patients in the large real-world PROPHESYS cohort confirm results from randomized clinical trials. Hepatology 2012; 56: 2039-50.

[67] Thompson AJ, Muir AJ, Sulkowski MS, et al. IL28B polymorphism improves viral kinetics and is the strongest pre-treatment predictor of SVR in HCV-1 patients. Gastroenterology 2010; 139: 120-9.

[68] 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.

Annex 1. PAM-13 Questionnaire Sample

Below are some statements that people sometimes make when they talk about their health. Please indicate how much you agree or disagree with each statement as it applies to you personally by circling your answer. Your answers should be what is true for you and not what you think others might want you to say.

If the statement does not apply to you, circle N/A.

1.	When all is said and done, I am the person who is responsible for taking care of my health	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
2.	Taking an active role in my own health care is the most important thing that affects my health	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
3.	I am confident I can help prevent or reduce problems associated with my health	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
4.	I know what each of my prescribed medications do	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
5.	I am confident that I can tell whether I need to go to the doctor or whether I can take care of a health problem myself	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
6.	I am confident that I can tell a doctor concerns I have even when he or she does not ask	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
7.	I am confident that I can follow through on medical treatments I may need to do at home	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
8.	I understand my health problems and what causes them	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
9.	I know what treatments are available for my health problems	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
10.	I have been able to maintain (keep up with) lifestyle changes, like eating right or exercising	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
11.	I know how to prevent problems with my health	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
12.	I am confident I can figure out solutions when new problems arise with my health	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)
13.	I am confident that I can maintain lifestyle changes, like eating right and exercising, even during times of stress	Disagree Strongly (1)	Disagree (2)	Agree (3)	Agree Strongly (4)	N/A (5)

DRAFT Version 0.03/CBA BG

Annex 2. Beliefs Medication Questionnaire

Beliefs Medication questionnaire (18-item BMQ) BMQ general

Your views about medicines prescribed for you.

- We would like to ask you about your personal views about medicines prescribed for you.
- These are statements other people have made about their medicines.
- Please indicate the extent to which you agree or disagree with them by ticking the appropriate box.
- There are no right or wrong answers. We are interested in your personal views.

	Strongly disagree	disagree	uncertain	agree	Strongly agree
1. Doctors use too many medicines					
2. Doctors place too much trust on medicines					
3. If doctors had more time with patients they would prescribe fewer medicines					
4. Natural remedies are safer than medicines					
5. Medicines do more harm than good					
6. People who take medicines should stop their treatment for a while every now and then					
7. Most medicines are addictive					
8. All medicines are poisons					

Beliefs Medication questionnaire (18-item BMQ) BMQ specific

	Strongly disagree	disagree	uncertain	agree	Strongly agree
9. My health, at present, depends on my medicine					
10. Having to take my medicine worries me					
11. My life would be impossible without my medicine					
12. I sometimes worry about long term effects of my medicine					
13. Without my medicine I would be very ill					
14. My medicine is a mystery to me					
15. My health in the future will depend on my medicine					
16. My medicine disrupts my life					
17. I sometimes worry about becoming too dependent on my medicine					
18. My medicine protects me from becoming worse					

Annex 3. Patient Support Program (PSP) Utilization Questionnaire

12 weeks treatment: At Interim early post-treatment visit
24 weeks treatment: At Interim mid treatment visit and Interim early post-treatment visit

Since the last visit, have you utilized any components from the AbbVie Patient Support Program?

☐ No
→ Please ignore questions below and return questionnaire to your physician or study nurse

☐ Yes
↓

Please specify service(s) used:

● ☐ **Personal support** (e.g. Care Coach)

▲ ☐ **Educational and information material** (e.g. magazines, leaflets, diaries)

✖ ☐ Printed
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

✚ ☐ Online
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

■ ☐ **Additional digital and mobile resources**

★ ☐ Web-portal
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

O ☐ App
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

⬢ ☐ Reminders

♥ ☐ Other

Annex 4. Patient Support Program (PSP) Utilization and Satisfaction Questionnaire

12 weeks treatment: At Interim early on-treatment visit, week 12 EoT visit and SVR 12 visit
24 weeks treatment: At Interim early on-treatment visit, week 24 EoT visit and SVR 12 visit

Since the last visit, have you utilized any components from the AbbVie Patient Support Program?

☐ No
→ Please ignore questions below and return questionnaire to your physician or study nurse

☐ Yes
→ What is your level of satisfaction of the AbbVie Patient Support Program in general?
☐ Very good
☐ Good
☐ Satisfactory
☐ Poor
→ Did the Program address your needs? ☐ Yes, fully ☐ Yes, mostly ☐ No

Please specify service(s) used:

● ☐ **Personal support** (e.g. Care Coach)
→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

▲ ☐ **Educational and information material** (e.g. magazines, leaflets, diaries)

✖ ☐ Printed
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

✚ ☐ Online
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

■ ☐ Additional digital and mobile resources

★ ☐ Web-portal
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

● ☐ App
→ Please specify how often used: ☐ Usually daily
☐ Several times per week
☐ Usually once weekly
☐ Less than once weekly

→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Not satisfactory

⬢ ☐ Reminders
→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

♥ ☐ Other
→ Please specify your level of satisfaction: ☐ Very good
☐ Good
☐ Satisfactory
☐ Poor

Annex 5. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
Parameter	**1**	**2**	**3**
Total bilirubin, µmol/L (mg/dL)	<34.2 (<2)	34.2 – 51.3 (2 – 3)	>51.3 (>3)
Serum albumin, g/L (g/dL)	>35 (>3.5)	28 – 35 (2.8 – 3.5)	<28 (<2.8)
INR	<1.7	1.7 – 2.3	>2.3
Ascites*	None	Slight	Moderate to severe
Hepatic encephalopathy**	None	Grade 1 or 2 (or suppressed with medication)	Grade 3 or 4 (or refractory)

* None.
Slight ascites = Ascites detectable only by ultrasound examination.
Moderate ascites = Ascites manifested by moderate symmetrical distension of the abdomen.
Severe ascites = Large or gross ascites with marked abdominal distension.

** Grade 0: normal consciousness, personality, neurological examination, electroencephalogram.
Grade 1: restless, sleep disturbed, irritable/agitated, tremor, impaired handwriting, 5 cps waves.
Grade 2: lethargic, time-disoriented, inappropriate behavior, asterixis, ataxia, slow triphasic waves.
Grade 3: somnolent, stuporous, place-disoriented, hyperactive reflexes, rigidity, slower waves.
Grade 4: unarousable coma, no personality/behavior, decerebrate, slow 2 to 3 cps delta activity

14.0 Protocol Signature Page

AbbVie
Post Marketing Observational Study
Protocol P15-650

Real World Evidence of the Effectiveness of Paritaprevir/r – Ombitasvir, ± Dasabuvir, ± Ribavirin in Patients with Chronic Hepatitis C - An Observational Study Belgium

[redacted]

18 June 2015
Date

18 June 2015
Date

18 June 2015
Date

18 June 2015
Date

09 JUL 2015
Date