1.0 Title Page

Clinical Study Protocol M14-748

An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)

Incorporating Administrative Change 1 Amendments 1, 1.01, 2 and 3

AbbVie Investigational Product:	Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir
Date:	21 August 2017
Development Phase:	Part 1: Phase 2 Part 2: Phase 3
Study Design:	Open-label combination drug study
EudraCT Number:	2015-000111-41
Investigators:	Multicenter. Investigator information is on file at AbbVie.
Sponsor:	AbbVie Inc.*

Sponsor/Emergency Contact:	Therapeutic Area Scientific Director [redacted] Infectious Diseases Development [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Mobile: Fax:	Therapeutic Area Medical Director [redacted] Infectious Diseases Development [redacted] 1 North Waukegan Road North Chicago, IL 60064 Phone: [redacted] Mobile: Fax:

* The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority.

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

Previous Protocol Versions

Protocol	Date
Original	15 March 2015
Amendment 1	23 July 2015
Amendment 1.01	28 January 2016
Administrative Change 1	20 May 2016
Amendment 2	07 July 2016

The purpose of this amendment is to:

- Remove pellets formulation from the study, and change all endpoints to remove the pellet formulation.

  Rationale: *The inclusion of the pellet formulation introduces additional variability into the analysis of therapeutic exposure by age and weight among a relatively small number of subjects in each age and weight group, so it is preferable to establish the PK, safety and efficacy using one formulation.*

- Remove APRI from study procedures.

  Rationale: *Liver fibrosis is determined with Fibrotest, Fibroscan or liver biopsy. APRI measurement is redundant to the test mentioned above and therefore has been removed.*

- Update contraceptive language in the protocol further.

  Rationale: *Contraceptive recommendations were edited to align with regulatory guidance and to ensure patient safety. Section 5.2.1, Inclusion Criteria, Criterion 3 and 4 updated to add contraceptive practices. Inclusion criteria clarify which female subjects require pregnancy testing for participation in the study. Section 5.2.2, Exclusion Criteria, Criterion 1 and 11 define acceptable approaches for women who plan pregnancy and males who should refrain from sperm donation during the trial. Section 5.2.4, Contraception Recommendations and Pregnancy Testing, added to provide greater detail regarding contraceptive practice, in alignment with regulatory guidance.*

- Addition of Exclusion Criterion 12 in Section 5.2.2, Exclusion Criteria.

  Rationale: *Exclusion Criterion 12 has been added to the protocol to clarify weight limit for subjects in the 3 to 8 year old age group. Children weighing <15 kg represent a very small subpopulation in the 3 to 8 year old age group. In this population, drug dosing is particularly challenging, and the variability in dosing can lead to a higher level variability in PK. In addition, there is a lack of significant urgency for treating the HCV infection in younger children. The alternative of allowing subjects to grow to a higher weight prior to treatment offers more benefit.*

- Update Virologic Failure criteria.

  Rationale: *Due to the high sensitivity of the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 assay currently used in Study M14-748, the LLOQ is 15 IU/mL. A small fluctuation of the HCV RNA level around LLOQ, for example, a current value of 16 IU/mL after previously achieving <15 IU/mL, may occur within the assay variability. Therefore, the current virologic breakthrough criteria of "HCV RNA ≥ LLOQ after achieving LLOQ previously" may include subjects, who have responded to treatment. In addition, using virologic breakthrough criteria of "HCV RNA ≥ 100 IU/mL after previously achieved LLOQ" is consistent with the recent AbbVie HCV studies, where the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0 assay was used to define LLOQ.*

- Reduction of Long Term Follow Up period.

  Rationale: *In accordance with EMA guidance "Report of the paediatric hepatitis C therapy expert meeting" document, thus the study long term period has been simplified in the frequency of visits and the total duration reduced.*

- Correct inconsistencies and typographical errors throughout the protocol.

An itemized list of all changes made to this protocol amendment can be found in Appendix F.

1.2 Synopsis

AbbVie Inc.	**Protocol Number:** M14-748
Name of Study Drug: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Phase of Development:** 2/3
Name of Active Ingredient: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Date of Protocol Synopsis:** 21 August 2017
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)	
Objectives: To assess the pharmacokinetics of OBV, PTV, RTV, and DSV with or without RBV in treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects in Part 1. To assess the efficacy (percentage of subjects achieving SVR_{12} [defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study drug]) or SVR_{24} [defined as HCV RNA < LLOQ 24 weeks after the last actual dose of study drug]) and safety of OBV, PTV, RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV genotype 1 (GT1) or genotype 4 (GT4)-infected treatment-naïve and prior IFN (IFN or peg-IFN with or without RBV) treatment-experienced, cirrhotic and non-cirrhotic pediatric subjects in Part 1 and Part 2. To assess the durability of response for subjects who achieved SVR, to assess the emergence and persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure, and to assess the impact of OBV, PTV, RTV with or without DSV and with or without RBV on growth and development in Part 3, the long-term follow-up of approximately 2.5 years.	
Investigator: Global, multicenter trial: Investigator information is on file at AbbVie.	
Study Sites: Up to 30 sites globally.	
Study Population: **Part 1:** Treatment-naïve, non-cirrhotic, GT1-infected pediatric patients ≥ 3 to 17 years of age **Part 2:** Treatment-naïve and IFN (IFN or peg-IFN with or without RBV) treatment-experienced HCV GT1 or GT4-infected pediatric subjects ≥ 12 to 17 years of age with or without compensated cirrhosis **Part 3 (Long-term follow-up):** All subjects who take at least one dose of study drug and complete the Post-Treatment (PT) Week 24 visit in Part 1 or Part 2.	
Number of Subjects to be Enrolled: Approximately 62 subjects will be enrolled in total into two Parts. Part 1: Approximately 36 treatment-naïve, non-cirrhotic, GT1 subjects. Part 2: Approximately 26 subjects ≥ 12 to 17 years of age treatment-naïve or prior IFN treatment-experienced, cirrhotic or non-cirrhotic with GT1 or GT4 HCV infection.	

Methodology:

The study aims to assess three formulations in the pediatric population. The approved adult 3D (OBV/PTV/RTV and DSV) regimen formulation and the approved adult 2D (OBV/PTV/RTV) regimen formulation will be administrated in subjects who are in the ≥ 12 to 17 years old age group with weight greater than 45 kg and willing to swallow the adult formulation. The mini-tablet formulation will be administered in subjects who are in the ≥ 3 – 8 and ≥ 9 – 11 age groups to identify the optimal or final doses.

Part 1 mini-tablet is designed to allow for dose adjustment on an ongoing basis, based on available pharmacokinetic and clinical data to achieve therapeutic exposures that have been safe and efficacious in adult subjects. Area under the concentration curve (AUC) from the intensive PK sampling at Week 2 will be the primary measure for dose adjustment, which will be compared with the range of the geometric means and the range of individual values across Phase 1/2/3 studies in adults that had intensive PK data (see Section 5.1). C_{max} and C_{trough} will be considered for safety and efficacy using the same rules. Part 2 (Safety and Efficacy) will use the adult formulation if the results from the adult formulation in Part 1 are satisfactory. In Part 1 and Part 2, the treatment duration is either 12 weeks or 24 weeks and all pediatric subjects who receive at least 1 dose of study drug will be followed for 24 weeks in the post-treatment period after completing or prematurely discontinuing the study treatment. All pediatric subjects who complete the Post-Treatment (PT) Week 24 visit in either Part 1 or Part 2 will be followed in Part 3 (Long-term Follow-up) for 144 weeks.

Part 1 (Pharmacokinetic Study):

Approximately 36 treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects will be enrolled. In the ≥ 12 to 17 year age group, 12 subjects will receive the standard adult formulation; in the ≥ 3 to 8 and ≥ 9 to 11 year age groups, at least 12 subjects will receive the mini-tablet formulation. Up to 12 additional subjects may be enrolled to receive the mini-tablet formulation in Part 1 if needed to adequately characterize the pharmacokinetics of a particular age group or subgroup. Subjects in the ≥ 12 to 17 year age group who are ≥ 45 kg and willing to swallow the adult formulations will begin enrollment before subjects in the younger age groups. The starting drug regimen is defined by HCV sub-genotype. All HCV sub-genotype 1b (GT1b) subjects will receive study medication (OBV/PTV/RTV and DSV) without RBV for 12 weeks as shown below. All subjects with a HCV GT1 non-b infection will receive study medication with weight based RBV for 12 weeks.

Methodology (Continued):

Part 1 (Pharmacokinetic Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, and Week 12. At Week 2 and Week 8, the morning dose of study drug will be administered in the clinic at approximately 24 hours after the prior morning dose. At Week 2, the evening doses will be administered in the clinic following the 12 hour PK draw and the morning doses at Week 2 + 1 day will be administered in the clinic following the 24 hour PK draw. PT visits will occur at PT Weeks 4, 12, and 24.

PK samples will be collected at the following timepoints from each subject:

- Day 1: 4 hours postdose (the morning doses will be administered in the clinic)
- Week 2: 2, 4, 8, 12 and 24 hours postdose (the morning doses, the evening doses following the 12 hour PK draw and the morning doses following the 24 hour PK draw will be administered in the clinic)
- Week 4: a PK sample (regardless of the dosing time)
- Week 8: a trough PK sample (i.e., prior to the morning dose, which will be administered in the clinic)
- Week 12: a PK sample (regardless of the dosing time)

Based on assessment of Week 2 intensive pharmacokinetic and clinical data, dose adjustments and/or dose adjustments for subsequently enrolled subjects may be performed.

Part 2 (Safety/Efficacy Study):

Approximately 16 HCV GT1-infected and approximately 10 HCV GT4-infected treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced pediatric subjects in the ≥ 12 to 17 age group will be enrolled.

Subjects with GT1 infection will receive the 3D tablet formulation approved for adults (with or without RBV) and the subjects with GT4 infection will receive the 2D tablet formulation approved for adults with RBV. RBV will be administered weight based as tablets or as solution per local RBV label. The regimen and duration will be determined according to HCV genotype, sub-genotype and cirrhosis status.

Methodology (Continued):
Part 2 (Safety/Efficacy Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir (approved adult 3D formulation)	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	12 weeks
Genotype 1a,* with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin (approved adult 2D formulation plus RBV)	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24. The latter 3 visits at Weeks 16, 20 and 24 are required for subjects with compensated cirrhosis taking study drug for 24 weeks. PT visits will occur at PT Weeks 4, 12, and 24.

One PK sample (regardless of the dosing time) will be collected at each visit for each subject in Part 2.

The following criteria will be considered evidence of virologic failure during treatment. Pediatric subjects demonstrating any of the following should be discontinued from study drug:

- Confirmed increase from nadir (defined as 2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir) in HCV RNA at any time point
- Confirmed HCV RNA $\geq$ 100 IU/ml (defined as 2 consecutive HCV RNA measurements $\geq$ 100 IU/ml) at any point after achieving HCV RNA < LLOQ

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met, the subject will discontinue study treatment, if applicable. If the Investigator feels that a subject who meets one of these criteria should still remain on study treatment, the subject would only be allowed to remain on treatment with approval of the AbbVie Study TA SD/TA MD.

Part 3 (Long-Term Follow-Up):

All subjects who have completed Post-Treatment Week 24 in either Part 1 or Part 2 of the study will be followed to assess the durability of viral response, for the emergence and persistence of resistant viral variants, and for SAEs related to study drug for an additional 120 weeks in the Long-term Follow-up period. Study visits will occur at Post-Treatment Weeks 36, 48, 96, and 144.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 3 to 17 years of age and weight ≥ 15 kg at time of enrollment.
2. Willingness to participate in the study for up to 42 months.
3. HCV infection demonstrated by positive anti-HCV Ab and HCV RNA ≥ 1000 IU/mL at the time of screening.
4. Screening laboratory results indicating HCV genotype 1 for enrollment into Part 1 and genotype 1 or 4 for enrollment into Part 2.
5. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.

Main Exclusion:

1. Women who are pregnant, breastfeeding, or are considering becoming pregnant.
2. Use of known strong inducers and inhibitors (e.g., gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in subjects receiving dasabuvir, or strong or moderate inducers of CYP3A, within 2 weeks or 10 half-lives, whichever is longer, of the respective medication/supplement prior to study drug administration.
3. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-HIV antibody (HIV Ab) test.
4. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFNs or RBV or receipt of any investigational product within 6 weeks prior to study drug administration.

Investigational Products:

Weight < 45 kg or eligible but not willing to swallow the adult formulations: Part 1	
paritaprevir	1.0 mg mini-tablet
ritonavir	1.0 mg mini-tablet
ombitasvir	0.3 mg mini-tablet
dasabuvir	3.08 mg mini-tablet
ribavirin	40 mg/mL oral solution

Weight ≥ 45 kg who are ≥ 12 to 17 years old and willing to swallow the adult formulations:	
ombitasvir/paritaprevir/r	12.5/75/50 mg tablet
dasabuvir	250 mg tablet
Ribavirin	200 mg tablet

Doses:

Part 1 Mini-Tablet:

Initial dosing based on body weight at time of Screening:

	≥ 15 to 29 kg	≥ 30 to 44 kg	≥ 45 kg
paritaprevir (QD)	50 mg	100 mg	150 mg
ritonavir (QD)	35 mg	70 mg	100 mg
ombitasvir (QD)	10 mg	15 mg	25 mg
dasabuvir (BID)	100 mg	150 mg	250 mg
Ribavirin solution	Per local label		

Part 2:

Only adult formulation and RBV tablets if required will be provided to subjects who are in the ≥ 12 – 17 year old age group with weight equal and greater than 45 kg and willing to swallow the adult formulations.

Mode of Administration: Oral

Reference Therapy: Not applicable

Dose: Not applicable

Mode of Administration: Not applicable

Duration of Treatment:

Part 1: Pediatric subjects will receive OBV, PTV, RTV, DSV with or without RBV for 12 weeks.

Part 2: Pediatric subjects will receive OBV, PTV, RTV with or without DSV and with or without RBV for 12 weeks or 24 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each treatment and Post-Treatment Period visit in all three parts of the study.

Pharmacokinetic:

Plasma concentrations of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, RTV and RBV (if applicable) will be determined at each study visit for each subject for the treatment periods of Part 1 and Part 2.

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests and vital signs. Growth and development will be assessed relative to age specific norms.

Statistical Methods:

The pharmacokinetic analysis will be performed separately for Part 1 and Part 2. For population pharmacokinetic analyses, data from Part 1 and Part 2 will be combined if needed. All efficacy, safety, growth and development outcomes will be assessed across Parts 1 and 2 of the study with summaries by formulation, age and weight group, totaled across all subjects, and totaled across adult formulations (OBV/PTV/RTV + RBV and OBV/PTV/RTV and DSV ± RBV). Analyses on durability of response, resistance, growth and development outcomes, and patient-reported outcomes will be performed through Post-Treatment Week 24 in Parts 1 and 2 and after Post-Treatment Week 24 for all subjects in Part 3.

An interim analysis will occur once all subjects complete PT Week 12 or prematurely discontinue from the study. Final analysis will occur after the completion of the whole study.

Efficacy:

The primary pharmacokinetic endpoints are C_{max} and AUC following dosing on Week 2, and trough concentration (C_{trough}) following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

The primary efficacy endpoint is the percentage of subjects with SVR_{12} among all subjects. The percentage of subjects achieving SVR_{12} will be calculated along with the 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} across all subjects must be greater than 67% to show superiority to pegIFN and RBV as described in Section 8.2.

Statistical Methods (Continued):

Efficacy (Continued):

The main secondary endpoints are:

1. The percentage of subjects who achieve SVR_{12} summarized by formulation, age and weight group and across all subjects.
2. The percentage of subjects who achieve SVR_{24} by formulation, age and weight group, across all the subjects, and across all subjects on the adult formulations;
3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

For the secondary efficacy endpoints, the simple percentage will be calculated along with the 2-sided 95% confidence interval. For both primary and secondary endpoints, the normal approximation to the binomial distribution will be used if the rate is not 0% or 100%, otherwise the Wilson's score method will be used to calculate the confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%.

Resistance:

For subjects with virologic failure and HCV RNA > 1000 IU/mL, the variants at each amino acid position (by population, deep, and/or clonal nucleotide sequencing) at available post baseline time points compared to baseline and prototypic reference standard sequences will be summarized by DAA target genes and accompanying listings will be provided.

Safety:

All safety analysis will be done by age and weight group separately for each formulation, for all subjects, and for all subjects on the adult formulations.

The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by MedDRA system organ class and preferred term. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by grade (Grades 1 – 5) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects with potentially clinically significant values during treatment will be calculated.

Growth and Development:

All growth and development analyses will be done by age group separately for each formulation, for all subjects, and for all subjects on the adult formulations. The following growth and development endpoints will be calculated at applicable study visits.

- Growth rate at each post baseline visit (defined as change in height over change in age from the previous visit)
- Height z score
- Waist circumference
- Tanner staging

Statistical Methods (Continued):

Pharmacokinetic:

Plasma concentrations and pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV, if applicable, will be tabulated for each subject and summarized as appropriate by formulation, weight range or age group.

Individual plasma concentrations or pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV may be used for safety or efficacy evaluation if needed.

Additional analyses may be conducted as needed.

1.3 List of Abbreviations and Definition of Terms

Abbreviations

2D	Ombitasvir, Paritaprevir, Ritonavir
3D	Ombitasvir, Paritaprevir, Ritonavir, Dasabuvir
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AUC	Area under the concentration curve
aPTT	Activated partial thromboplastin time
AST	Aspartate aminotransferase
BID	Twice Daily
BMI	Body mass index
BUN	Blood urea nitrogen
CI	Confidence interval
CrCl	Creatinine clearance
CRF	Case report form
CYP3A	Cytochrome P450 3A
DAA	Direct-acting antiviral agent
DDI	Drug-drug interaction
DNA	Deoxyribonucleic acid
DSV	Dasabuvir
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EDC	Electronic data capture
EOT	End of treatment
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
GGT	Gamma-glutamyltransferase
GT	Genotype
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
hCG	Human chorionic gonadotropic

HCV	Hepatitis C virus
HCV Ab	Hepatitis C virus antibody
HIV Ab	Human immunodeficiency virus antibody
ICH	International Conference on Harmonization
IEC	Independent ethics committee
IFN	Interferon
IL28B	Interleukin 28B
IMP	Investigational Medical Product
INR	International normalized ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IU	International units
IUD	Intrauterine Device
LCB	Lower confidence bound
LLN	Lower limit of normal
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LTFU	Long-Term Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
ND	New Drug
NS3	Nonstructural viral protein 3
NS4A	Nonstructural viral protein 4A
NS5A	Nonstructural viral protein 5A
NS5B	Nonstructural viral protein 5B
OATP1B1	Organic anion transporting polypeptide 1B1
OBV	Ombitasvir
PCR	Polymerase chain reaction
pegIFN	Pegylated-interferon alfa-2a or 2b
PIP	Pediatric Investigational Plan
PK	Pharmacokinetic
POR	Proof of Receipt
PRO	Patient Reported Outcomes
PSP	Pediatric Study Plan

PT	Post-Treatment
PTV	Paritaprevir
QD	Once daily
RBC	Red blood cells
RBV	Ribavirin
RNA	Ribonucleic acid
RT-PCR	Reverse transcriptase PCR
RTV	Ritonavir
SAE	Serious adverse event
SAS	Statistical Analysis System
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOC	System Organ Class
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained virologic response
SVR_{12}	Sustained virologic response 12 weeks Post-Treatment
SVR_{24}	Sustained virologic response 24 weeks Post-Treatment
TA MD	Therapeutic Area Medical Director
TA SD	Therapeutic Area Scientific Director
ULN	Upper limit of normal
USPI	United States Proscribing Information
WBC	White blood cells
WOCBP	Women of Childbearing Potential

Definition of Terms

Study Drugs	Ombitasvir, Paritaprevir, Ritonavir, ± Dasabuvir, ± RBV
Screening Period	Up to 42 days prior to Study Day 1
Study Day 1	First day a subject takes study drugs
Treatment Period (TP)	Baseline/Study Day 1 through last dose of study drugs
Post-Treatment Period (PTP)	Day after the last dose of study drugs through Post-Treatment Week 24
Long-Term Follow-Up (LTFU)	Day after Post-Treatment Week 24 visit through Post-Treatment Week 144 or Post-Treatment Discontinuation

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3.0 Introduction

Hepatitis C viral (HCV) infection is a global health problem, with 170 million individuals chronically infected worldwide and at risk of developing liver cirrhosis, hepatocellular carcinoma, or both.[2] Children represent only a small proportion of the hepatitis C virus (HCV) infected population. Nevertheless, a substantial number of children have chronic HCV infection and are at risk for complications. According to a recent report which approximated 115 million HCV infected persons in the world, 11 million of them were younger than 15 years of age. It has been estimated that the global health care costs for HCV-infected children and their families are hundreds of millions of dollars annually.[3]

In pediatric populations, the natural history of disease varies based on factors such as the route of transmission, age at time of infection, and the presence of comorbidities such as hematologic malignancy or immunosuppression. The 3 most important routes of HCV infection for pediatric patients are vertical transmission, transfusion of contaminated blood products, and injection drug use. As infection via contaminated blood products has essentially disappeared in countries with adequate hygienic facilities due to improvements to the safety of the blood supply in the early 1990s and injection drug use in the pediatric population occurs among adolescents and young adults, vertical transmission has become the predominant mode of HCV transmission to pediatric patients in the developed world.[4] The rate of perinatal transmission presently ranges from 5% to 13% in children born to HCV-infected mothers.[5-9]

Spontaneous viral clearance in vertically infected children seems to be dependent on genotype and was found to range from 2.4% – 25%.[10,11] Beyond the age of 4 years, spontaneous viral clearance seems to become rather unlikely.[10] Patients who do not clear the virus within the first years of life will develop chronic hepatitis C. Overall, the cumulative probability of progression to chronicity is approximately 80%.[12,13]

Chronic hepatitis C appears as a mild, indolent infection in most pediatric patients, with low rates of disease progression over 10 to 35 years.[11,14,15] Of perinatally-infected children, approximately 20% experience spontaneous viral clearance, 50% develop

chronic asymptomatic infection (with intermittent viremia, usually normal alanine aminotransferase [ALT] levels, and rare hepatomegaly), and 30% develop chronic active infection.[13] The most severe sequelae of chronic HCV, including progressive hepatic fibrosis, cirrhosis, liver failure, and hepatocellular carcinoma (HCC) occur significantly less frequently in pediatric patients than in adults with chronic HCV infection. The frequency of advanced fibrosis and cirrhosis appear to increase with increasing age, and both are uncommon in younger children.[14,16] In a study of 359 viremic untreated HCV-infected pediatric patients, progression to advanced liver disease occurred in 1.8% of the 332 patients with persistent viremia, at a mean of 9.6 years.[10] HCC has rarely been reported in adolescents.[17] Cirrhosis has been reported in pediatric series at frequencies ranging from < 2%[10,14,16] to as high as 8%; however, the latter rate was reported from a quaternary referral center in the US, which likely over-represents the prevalence of advanced disease in the pediatric population.[18] Cirrhosis appears to be extremely uncommon in patients less than 6 years of age.[10,11,14,16,18,19]

Currently available treatments for pediatric chronic hepatitis C are interferon-α (IFN) or pegylated interferon-α (pegIFN) and ribavirin (RBV). SVR rates of pegIFN in combination with ribavirin in patients with genotype 1 have been reported in several pediatric studies and ranged from 44% to 59%. Achieving SVR in children with genotype 2 and 3 was very successful and yielded rates of more than 90%.

Combinations of direct-acting antiviral agents (DAAs) targeting different steps of viral replication have been shown to significantly improve HCV treatment compared to interferon-containing regimens for HCV genotype 1 infection by increasing SVR rates, 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 are expected to significantly reduce the public health burden of this disease. However, limitations still exist particularly in patients with comorbid conditions and in difficult-to-cure patients with advanced liver disease including those with cirrhosis. None of the DAA combination therapies are currently approved for pediatric patients.

AbbVie's Ombitasvir/Paritaprevir/r (OBV/PTV/RTV) and Dasabuvir (DSV), Also Known as the 3D Regimen

AbbVie's IFN-free 3D regimen for the treatment of chronic HCV GT 1 infection includes 3 DAAs targeting different steps in HCV replication. Ombitasvir is a nonstructural protein 5A (NS5A) inhibitor; paritaprevir is a NS3/NS4A protease inhibitor co-administered with the pharmacokinetic enhancer, ritonavir (paritaprevir/r); and dasabuvir is a NS5B non-nucleoside polymerase inhibitor.

The safety and efficacy of OBV/PTV/RTV 25/150/100 mg once daily and DSV 250 mg twice daily was evaluated in six Phase 3 randomized, multicenter, clinical trials (Studies M11-646, M13-098, M13-389, M13-961, M14-002 and M13-099) in more than 2,300 adult subjects with chronic HCV GT1 infection who received the 3D regimen with or without ribavirin for 12 or 24 weeks, including one trial exclusively in subjects with compensated cirrhosis.

Subjects with HCV GT1a infection without cirrhosis treated with the 3D regimen with RBV for 12 weeks in Studies M11-646, M13-098 and M14-002 had a median age of 53 years (range: 18 to 70); 63% of the subjects were male; 90% were White; 7% were Black/African American; 8% were Hispanic or Latino; 72% had IL28B non-CC genotype; 85% had baseline HCV RNA levels of at least 800,000 IU/mL. The efficacy results from Studies M11-646, M13-098 and M14-002 are listed in Table 1.

Table 1. SVR_{12} for HCV Genotype 1a-Infected Subjects Without Cirrhosis Who Were Treatment-Naïve or Previously Treated With PegIFN/RBV

	3D + RBV for 12 Weeks % (n/N)
GT1a Treatment-Naïve	
M11-646 (SAPPHIRE-I) SVR_{12}	96% (308/322)
Outcome for subjects without SVR_{12}	
On treatment virologic failure	< 1% (1/322)
Relapse	2% (6/314)
Other	2% (7/322)
M14-002 (PEARL IV) SVR_{12}	97% (97/100)
Outcome for subjects without SVR_{12}	
On treatment virologic failure	1% (1/100)
Relapse	1% (1/98)
Other	1% (1/100)
GT1a Treatment-Experienced	
M13-098 (SAPPHIRE-II) SVR_{12}	96% (166/173)
Outcome for subjects without SVR_{12}	
On treatment virologic failure	0% (0/173)
Relapse	3% (5/172)
Other	1% (2/173)
SVR_{12} by Prior pegIFN/RBV Experience	
Null Responder	95% (83/87)
Partial Responder	100% (36/36)
Relapser	94% (47/50)

Subjects with HCV GT1b infection without cirrhosis were treated with the 3D regimen with or without RBV for 12 weeks in Studies M13-389 and M13-961. Subjects had a median age of 52 years (range: 22 to 70); 47% of the subjects were male; 93% were White; 5% were Black/African American; 2% were Hispanic or Latino; 83% had IL28B non-CC genotype; 77% had baseline HCV RNA levels of at least 800,000 IU/mL. The efficacy results for subjects treated with the 3D regimen without RBV from Studies M13-389 and M13-961 are listed in Table 2.

Table 2. SVR_{12} for HCV Genotype 1b-Infected Subjects Without Cirrhosis Who Were Treatment-Naïve or Previously Treated With PegIFN/RBV

	3D for 12 Weeks % (n/N)
GT1b Treatment-Naïve	
M13-961 (PEARL-III) SVR_{12}	100% (209/209)
Outcome for subjects without SVR_{12}	
On treatment virologic failure	0% (0/210)
Relapse	0% (0/210)
Other	0% (0/210)
GT1b Treatment-Experienced	
M13-389 (PEARL-II) SVR_{12}	100% (91/91)
Outcome for subjects without SVR_{12}	
On treatment virologic failure	0% (0/91)
Relapse	0% (0/91)
Other	0% (0/91)
SVR_{12} by Prior pegIFN/RBV Experience	
Null Responder	100% (32/32)
Partial Responder	100% (26/26)
Relapser	100% (33/33)

The 3D regimen in combination with RBV was evaluated in Study M13-099 in 380 HCV GT1a and 1b-infected subjects with compensated cirrhosis who were either treatment-naïve or did not achieve SVR with prior treatment with pegIFN/RBV. Subjects were randomized to receive 3D + RBV for either 12 or 24 weeks. Treated subjects had a median age of 58 years (range: 21 to 71); 70% of the subjects were male; 95% were White; 3% were Black/African American; 12% were Hispanic or Latino; 82% had IL28B non-CC genotype; 86% had baseline HCV RNA levels of at least 800,000 IU/mL; 15% had platelet counts of less than 90×10^9/L; 50% had albumin less than 4.0 mg/dL. The efficacy results from Study M13-099 are presented in Table 3.

The safety and efficacy of the 3D regimen without RBV for 12 weeks was evaluated in Study M14-490 (TURQUOISE-III) in 60 HCV GT1b-infected subjects with compensated

cirrhosis, who were either treatment-naïve or prior pegIFN/RBV treatment-experienced. All subjects (100%) achieved SVR_{12}. No patients discontinued treatment due to adverse events. Based on these results treatment guidelines from AASLD have been updated to recommend the 3D regimen without RBV for 12 weeks in GT1b-infected subjects with compensated cirrhosis, and the US label was updated accordingly (Table 3).

Table 3. SVR_{12} for HCV Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV

	GT 1a		GT 1b	
M13-099 (TURQUOISE-II) and M14-490 (TURQUISE-III)	**3D + RBV for 24 Weeks % (n/N)**	**3D + RBV for 12 Weeks % (n/N)**	**3D + RBV for 12 Weeks % (n/N)**	**3D Without RBV for 12 Weeks % (n/N)**
SVR_{12}	95% (115/121)	89% (124/140)	99% (67/68)	100% (60/60)
Outcome for subjects without SVR_{12}				
On treatment virologic failure	2% (3/121)	< 1% (1/140)	0% (0/68)	0% (0/60)
Relapse	1% (1/116)	8% (11/135)	1% (1/68)	0% (0/60)
Other	2% (2/121)	3% (4/140)	0% (0/68)	0% (0/60)
SVR_{12} for Treatment-naive	95% (53/56)	92% (59/64)	100% (22/22)	100% (27/27)
SVR_{12} by Prior pegIFN/RBV Experience				100% (33/33)
Null Responder	93% (39/42)	80% (40/50)	100% (25/25)	100% (25/25)
Partial Responder	100% (10/10)	100% (11/11)	86% (6/7)	100% (5/5)
Relapser	100% (13/13)	93% (14/15)	100% (14/14)	100% (3/3)
Other Failures[+]	-	-	-	100% (18/18)

[+] Other types of pegIFN/RBV failures includes non-response, relapse/breakthrough, and other pegIFN failures.

The safety of 3D + RBV was assessed in 770 subjects in two placebo-controlled trials (Studies M11-646 and M13-098). Adverse reactions that occurred more often in subjects treated with 3D + RBV compared to placebo were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. The majority of the adverse reactions were mild in severity. Two percent of subjects experienced a serious adverse event (SAE) and the

proportion of subjects who permanently discontinued treatment due to adverse reactions was less than 1%.

The safety of the 3D regimen with and without RBV was assessed in 401 and 509 subjects, respectively, in three clinical trials (Studies M13-389, M13-961 and M14-002). Pruritus, nausea, insomnia, and asthenia were identified as adverse events occurring more often in subjects treated with 3D + RBV. The majority of adverse events were mild to moderate in severity. The proportion of subjects who permanently discontinued treatment due to adverse events was less than 1% for both 3D + RBV and 3D alone.

The safety of 3D + RBV was assessed in 380 subjects with compensated cirrhosis who were treated for 12 (n = 208) or 24 (n = 172) weeks duration in Study M13-099. The type and severity of adverse events in subjects with compensated cirrhosis was comparable to non-cirrhotic subjects in other Phase 3 trials. Fatigue, skin reactions and dyspnea occurred at least 5% more often in subjects treated for 24 weeks. The majority of adverse events occurred during the first 12 weeks of dosing in both treatment arms. Most of the adverse events were mild to moderate in severity. The proportion of subjects treated with 3D + RBV for 12 and 24 weeks with SAEs was 6% and 5%, respectively and 2% of subjects permanently discontinued treatment due to adverse events in each treatment arm.

Approximately 1% of subjects treated with the 3D regimen with and without RBV in Phase 3 studies experienced post-baseline serum ALT levels greater than 5 times the upper limit of normal (ULN) after starting treatment. The incidence increased to 25% (4/16) among women taking a concomitant ethinyl estradiol-containing medication. The incidence of ALT elevations greater than 5 times ULN among women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy, was 1.7% (1/59). ALT elevations were typically asymptomatic, generally occurred during the first 4 weeks of treatment (mean time 20 days, range: 8 – 57 days) and most resolved with ongoing therapy. Elevations in ALT were generally not associated with bilirubin elevations.

Post-baseline elevations in bilirubin at least 2 × ULN were observed in 15% of subjects who received 3D + RBV compared to 2% in those who received 3D alone. These bilirubin increases were predominately indirect and related to the inhibition of the bilirubin transporters OATP1B1/1B3 by paritaprevir and ribavirin-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 serum ALT elevations.

In summary, the 3D regimen, with or without RBV, was well tolerated with a low discontinuation rate. Adverse events were typically mild, and many of the adverse events and laboratory abnormalities observed were attributable to the presence of RBV. Transient, asymptomatic serum ALT elevations were observed at a low rate, were not associated with hepatic dysfunction and generally resolved with ongoing treatment.

A detailed discussion of the preclinical toxicology, metabolism, pharmacokinetics and drug-drug interactions can be found in the Investigator's Brochures and prescribing information for ombitasvir/paritaprevir/r and dasabuvir, and prescribing information for ribavirin.

AbbVie's Ombitasvir/Paritaprevir/r (OBV/PTV/RTV), Also Known as the 2D Regimen

AbbVie's IFN-free 2D regimen includes ombitasvir and paritaprevir/r. The 2D program is composed of one Phase 2b trial for HCV sub-genotype 1b and genotype 4 in the US and Europe (Study M13-393, also known as PEARL-I), one Phase 2a trial for genotypes 1, 2, and 3 in the US (Study M12-998), one Japanese Phase 2b trial for HCV sub-genotype 1b and genotype 2 (Study M12-536), and two Japanese Phase 3 trials for HCV sub-genotype 1b and genotype 2 (Studies M13-004 and M14-153).

HCV Genotype 4

While GT4 infection accounts for only approximately 1% of HCV infections in the United States (US), in parts of Europe the prevalence of GT4 among all HCV-infected people is

as high as 10% to 24% in some areas.[20-24] HCV GT4 infection is common in the Middle East and Sub-Saharan Africa. In Egypt, it is responsible for almost 90% of HCV infections.[20-25]

Efficacy and safety data are available from the cohorts of non-cirrhotic genotype 4-infected adult subjects participating in the Phase 2 Study M13-393 (PEARL-I) who were administered ombitasvir 25 mg, paritaprevir 150 mg and ritonavir 100 mg once daily with or without RBV for 12 weeks. SVR_{12} rates of 91% were observed among non-cirrhotic genotype 4-infected treatment-naïve subjects who received the 2D without RBV regimen for 12 weeks. When non-cirrhotic HCV genotype 4-infected treatment-naïve subjects were administered the 2D regimen with RBV, SVR_{12} rates of 100% were achieved. Among non-cirrhotic HCV genotype 4-treatment-experienced subjects receiving the 2D regimen with RBV for 12 weeks, the SVR_{12} rate was 100%.

Safety data from these cohorts of non-cirrhotic genotype 4-infected subjects demonstrate the 12-week 2D regimen with or without RBV was generally well tolerated, with no subject discontinuing study drug due to a treatment-emergent adverse event. The only treatment-emergent adverse events that occurred in ≥ 10.0% of subjects in all 3 treatment groups were asthenia and headache. This adverse event profile is consistent with the more robust placebo-controlled and regimen-controlled analysis sets of the Phase 3 3D + RBV treatment regimen from which asthenia, nausea, fatigue, insomnia, and pruritus were identified as adverse drug reactions.

Overall, the percentage of HCV genotype 4-infected subjects in any treatment group who experienced a protocol defined potentially clinically significant or Grade 3 hematology or chemistry value was low. These findings are also consistent with the observations from the Phase 3 studies evaluating the 3D + RBV treatment regimen.

The 2D regimen was subsequently evaluated in genotype 4-infected treatment-naïve or prior pegIFN/RBV treatment-experienced cirrhotic adult subjects following 12 weeks, 16 weeks and 24 weeks treatment durations (Study M11-665, AGATE-I). High SVR_{12} rates of 97% and 98% were achieved for the 12 week and 16 week treatment arms,

suggesting no added benefit to SVR observed with an additional 4 weeks of treatment for the 16-week arm. The regimen was generally well tolerated, with no patient discontinuing treatment due to adverse events.

Hepatic Decompensation

In late 2015, several cases of hepatic decompensation were reported in patients treated post-marketing with 2D or 3D with or without RBV, some of which resulted in fatalities or necessitated liver transplants. These occurrences were observed in patients who already had advanced or decompensated cirrhosis prior to starting treatment. Although complete information on baseline clinical status and laboratory values was infrequently available, patients with severe outcomes of death or liver transplantation generally had evidence of more advanced cirrhosis and portal hypertension. Laboratory findings (when available) associated with events of hepatic decompensation and hepatic failure were characterized by the acute onset of rising direct serum bilirubin levels with additional clinical signs and symptoms of hepatic decompensation, typically without associated ALT elevations. The label was subsequently updated to contraindicate 3D and 2D in patients with decompensated cirrhosis (i.e., CPB or CPC). The current study is intended to evaluate the pharmacokinetics, safety, efficacy and the long-term outcomes of ombitasvir, paritaprevir, ritonavir with or without dasabuvir and with or without ribavirin in pediatric subjects with genotype 1 or 4 chronic hepatitis C with or without compensated cirrhosis. Subjects with current evidence or a prior history of liver decompensation are excluded from this study.

3.1 Differences Statement

The combination of OBV/PTV/RTV with or without DSV and with or without RBV has been thoroughly studied and is approved in the US and several countries in EU for the treatment of HCV GT1 and GT4-infected adults. This is the first study to evaluate the pharmacokinetics, efficacy and safety of OBV/PTV/RTV with or without DSV and with or without RBV in HCV-infected pediatric subjects (under age 18). The study population for Part 1, the pharmacokinetic study, will include GT1-infected subjects who are

non-cirrhotic and treatment-naïve. Part 2, the safety and efficacy study, will include GT1 and GT4 subjects who are treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced with or without compensated cirrhosis. In Part 3, long-term safety and efficacy will be evaluated for 144 weeks.

3.2 Benefits and Risks

Part 1 of this study is a Phase 2 study in which eligible HCV GT1-infected pediatric subjects will receive OBV, PTV, RTV and DSV with or without RBV for 12 weeks. Part 2 of this study is a Phase 3 study in which eligible genotype 1 or 4-infected subjects will receive OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks depending on HCV genotype, sub-genotype and cirrhosis status. OBV/PTV/RTV and DSV with or without RBV was evaluated in > 2300 adult subjects with HCV GT1 infection in six Phase 3 studies. OBV/PTV/RTV and DSV with or without RBV achieved SVR_{12} greater than 97% overall in HCV GT1-infected subjects, including those with compensated cirrhosis, with the label recommended regimens. OBV/PTV/RTV with or without RBV was evaluated in 135 adult subjects with HCV GT4 infection in a Phase 2 study. Similarly high SVR_{12} rates (100%) were observed in this study with OBV/PTV/RTV with RBV.

OBV/PTV/RTV and DSV with or without RBV was well tolerated in the Phase 3 studies in genotype 1-infected adults with discontinuation due to AEs approximately 1%. Adverse events that are known and those not previously described, may occur as detailed in the informed consent and assent for this study. In addition, subjects may experience inconvenience or discomfort related to the study visits or study procedures.

Post-marketing cases of hepatic decompensation were reported in patients treated with OBV/PTV/RTV with or without DSV with or without RBV, some of which resulted in fatalities or necessitated liver transplants. These occurrences were observed in patients who already had highly advanced or decompensated cirrhosis prior to starting treatment. In this study, patients with a history of or existing decompensation will not be included in the study. Other risks associated with OBV/PTV/RTV with or without DSV and with or

without RBV include the risks of toxicity and virologic failure. Adverse events associated with treatment have been limited and manageable based on the results from the Phase 2/3 studies. Given the potential high rate of cure in HCV GT1 and GT4-infected subjects, the risk-benefit profile is favorable.

3.3 Pediatric Study Plan and Pediatric Investigational Plan

The original Study M14-748 study design was developed in accordance with the Pediatric Study Plan (PSP) and Pediatric Investigational Plan (PIP) for OBV/PTV/RTV and DSV for the treatment of Hepatitis C virus infection.[6,20,27]

The Pediatric Committee (PDCO) of the European Medicines Agency (EMA) issued a positive opinion on the PIP for the OBV/PTV/RTV and DSV on November 08, 2013. Upon AbbVie request, a waiver was granted for the pediatric population younger than 3 years of age "on the grounds that the specific medicinal product does not represent a significant benefit over existing treatment for pediatric patients" in this age group. In addition, both the PK and safety and efficacy study were granted deferrals to begin after approval of OBV/PTV/RTV and DSV in adults with GT1 infection.

Similarly, the initial PSP for OBV/PTV/RTV and DSV, dated December 19, 2013, provided a waiver for the pediatric population younger than 3 years of age and a deferral to begin the PK and safety/efficacy studies in pediatric populations after the approval of OBV/PTV/RTV and DSV in adults with GT1 infection. The initial PSP was revised to include GT4-infected subjects and agreed upon by the FDA on December 19, 2014. This revision also included a waiver for the pediatric population younger than 3 years of age and a deferral of pediatric assessments in the pediatric population younger than 18 years of age for the 2D regimen until after approval of the NDA for GT4 infection.

4.0 Study Objective

Primary Objective(s):

- To assess the pharmacokinetics of different OBV, PTV, RTV and DSV formulations with or without RBV in treatment-naïve, non-cirrhotic, GT 1 HCV-infected pediatric subjects in Part 1.
- To assess the efficacy (percentage of subjects with SVR_{12}) and safety of OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV GT1 or GT4-infected treatment-naïve and treatment-experienced pediatric subjects with and without compensated cirrhosis in Part 1 and Part 2.

Secondary Objective(s):

- To evaluate the percentage of subjects with SVR_{12} by formulation, age and weight group and across all subjects on the adult formulations.
- To evaluate the percentage of subjects with SVR_{24} and the percentage of subjects with ALT normalization by the end of treatment, by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

5.0 Investigational Plan

5.1 Overall Study Design and Plan: Description

In Part 1 of this study eligible HCV GT1-infected, treatment-naïve, non-cirrhotic pediatric subjects will receive OBV, PTV, RTV with DSV and with or without RBV for 12 weeks. Part 2 of this study is a Phase 3 study in which eligible GT1 or 4-infected treatment-naïve or prior IFN (or IFN or pegIFN with or without RBV) treatment-experienced pediatric subjects without cirrhosis or with compensated cirrhosis will receive OBV/PTV/RTV with or without DSV and with or without RBV for 12 or 24 weeks depending on HCV genotype, sub-genotype and cirrhosis status. Part 1 is designed to allow for dose adjustment (details are provided below in *Dose Adjustment Considerations for Part 1*

[Pharmacokinetic Study]) on an ongoing basis based on available pharmacokinetic and clinical data to achieve therapeutic exposures that have been demonstrated to be safe and efficacious in adult subjects. Part 2 will evaluate the adult formulations in treatment-naïve and IFN treatment-experienced HCV GT1 or GT4-infected adolescents with or without compensated cirrhosis. Both Parts 1 and 2 will consist of a Screening Period (Section 5.1.1), a Treatment Period (Section 5.1.2), and a 24-week Post-Treatment Period (Section 5.1.3) (Section 5.1.4). Subjects who prematurely discontinue study treatment in Part 1 will be followed in the Post-Treatment Period in Part 1. Similarly subjects who prematurely discontinue study treatment in Part 2 will be followed in the Post-Treatment Period in Part 2. After completing the Post-Treatment Period in Part 1 or Part 2, the subjects will be followed in Part 3 for 144 weeks. Subjects who prematurely discontinue from the Post-Treatment Period in Part 1 or Part 2 or from Part 3 will be discontinued from the study.

Part 1

In Part 1, the primary objectives are to assess the pharmacokinetics, efficacy and safety of OBV, PTV, RTV and DSV with or without RBV in HCV GT1-infected, treatment-naive pediatric subjects. Part 1 will include approximately 36 subjects. At least 12 subjects will enroll in each of the 3 age year groups, ≥ 3 to 8, ≥ 9 to 11, and ≥ 12 to 17. Enrollment will begin with pediatric subjects ≥ 12 to 17 years old who are ≥ 45 kg and willing to swallow the OBV/PTV/RTV and DSV adult formulations. After acceptable pharmacokinetic, efficacy and safety data are available from at least 6 subjects from the ≥ 12 to 17 age group who receive the adult regimen, subjects ages ≥ 9 to 11 will begin enrollment to be administered the mini-tablet formulations. After acceptable pharmacokinetic, efficacy and safety data are available from at least 6 subjects from the ≥ 9 to 11 age group (at least 4 of which have a body weight of 15 to 44 kg) subjects ages ≥ 3 to 8 will be enrolled and administered the mini-tablets. In the ≥ 3 to 8 year age group, at least 2 subjects each from subgroups ≥ 3 to 5 and ≥ 6 to 8 years old will be enrolled to ensure that there is adequate information for dosing recommendations for the entire ≥ 3 to 8 age group. Up to approximately 12 additional pediatric subjects may be enrolled to

receive the mini-tablet formulation in Part 1 if needed to adequately characterize the pharmacokinetics and determine the final dose strength for a particular age group or subgroup. Subjects will be followed in Part 1 of the study through Post-Treatment Week 24.

In summary, children who are ≥ 12 to 17 years old with weight ≥ 45 kg and willing to swallow the adult formulations will use the adult formulations of OBV/PTV/RTV with DSV. All other children ≥ 3 to 11 years of age will be dosed with the pediatric mini-tablet formulation. For subjects that are not willing to swallow the RBV tablets and are not taking the adult formulations of the DAAs, RBV will be provided as a 40 mg/mL oral solution.

Dose Adjustment Considerations for Part 1

For each subject, the initial dose of DAAs will be based on the subject's body weight at Screening. No dose adjustments of DAAs or RBV will be made as a consequence of weight change during the treatment period. Dose adjustments may be implemented during the treatment period based on available data and enrollment. When preliminary pharmacokinetic and clinical data (following Week 2 intensive PK sampling or Week 8 trough sample) from approximately 6 subjects in the age group are available, these data will be used to adjust doses, if needed, for subjects who have been enrolled and for subjects who are subsequently enrolled in the respective age group. The data from age groups of ≥ 3 to 8 and ≥ 9 to 11 years old may be combined for final analyses if exposures from these 2 groups are comparable to each other.

For each of the analytes (OBV, PTV, RTV, or DSV), the geometric mean and individual values of AUC from these pediatric subjects from the Week 2 intensive PK sampling will be compared with the range of geometric means and the range of individual AUCs across Phase 1/2/3 studies in adults that had intensive pharmacokinetic data. Dose adjustments may be made for each component of the DAA regimen if the respective geometric mean AUC in pediatric subjects is outside the geometric mean range in adults and/or at least 2 of 6 pediatric subjects have individual AUCs outside of the individual range in adults. In

addition, if data are available from fewer than 6 subjects and if at least 2 of these subjects have individual AUCs outside of the individual range in adults, dose adjustment might be considered for the age group.

AUC will be the primary measure for dose adjustment. C_{max} and C_{trough} will be considered for safety and efficacy using the same rules.

Additional criteria may be considered for making dose adjustment decisions for Part 1 to ensure safe and efficacious exposures. Subjects who take at least one dose of the study drug will be followed in Part 1 of the study through Post-Treatment Week 24 to assess SVR_{12} and SVR_{24}.

Part 2

In Part 2, the primary objectives are to further evaluate the safety and efficacy (percentage of treatment-naïve or treatment-experienced subjects achieving SVR_{12}) of OBV/PTV/RTV and DSV with or without RBV in HCV GT1-infected pediatric subjects and OBV/PTV/RTV in GT4-infected pediatric subjects with or without compensated cirrhosis. Part 2 will enroll approximately 16 HCV GT1infected and 10 GT4 infected, treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced pediatric subjects ages ≥ 12 to 17 years of age. Enrollment in Part 2 will begin once dosing recommendations of OBV, PTV, RTV and DSV are available for the ≥ 12 to 17 year-old age group based on the pharmacokinetic and clinical data from Part 1 of the study. Subjects who take at least one dose of the study drug will be followed in Part 2 of the study through Post-Treatment Week 24 to assess SVR_{12} and SVR_{24}.

Part 3 (Long-Term Follow-Up Period)

In Part 3, the objectives are to assess the durability of response for subjects who achieved SVR, to assess the persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure and to assess the impact of OBV/PTV/RTV with or without DSV co-administered with or without RBV on growth and development. All pediatric subjects who complete the PT Week 24 visit in Part 1 or

Part 2 will be automatically enrolled into Part 3 and followed for up to 144 weeks. Subjects will return to their study site for their scheduled visits on an outpatient basis. Subjects with virologic failure are allowed to use any other approved treatments for their HCV infection, if appropriate, while participating in the Long-term Follow-up study; however that therapy would be provided outside the context of this study and needs to be captured in source documents and entered into EDC by site personnel.

Fibrosis Assessment

An assessment of liver fibrosis is mandatory prior to enrollment. Subjects, with no history of cirrhosis, who have not had a liver biopsy or FibroScan within 24 months prior to screening, will undergo a non-invasive FibroTest to determine presence or absence of cirrhosis.

Subjects will be considered to be non-cirrhotic based on a liver biopsy within 24 months prior to screening demonstrating the absence of cirrhosis (e.g., a Metavir Score of 3 or less, Ishak score of 4 or less) or, if a liver biopsy is unavailable, a historical Fibroscan® result < 14.6 kPa within 24 months prior to screening. If neither historical result is available, a screening FibroTest score of < 0.75 can be used to demonstrate absence of cirrhosis.

Subjects will be considered to have cirrhosis based on previous histologic diagnosis of cirrhosis on a liver biopsy at any time prior to screening (e.g., Metavir Score of > 3 [including 3 – 4 or 3/4], Ishak score of > 4) or, if a liver biopsy is unavailable, a historical FibroScan score ≥ 14.6 kPa or a screening FibroTest ≥ 0.75 (Table 4).

Table 4. Baseline Fibrosis Stage

Baseline Fibrosis Stage, Metavir Equivalents	Liver Biopsy Metavir, Batts-Ludwig, Knodell, IASL, Scheuer, or Laennec Score	Liver Biopsy Ishak Score	FibroScan (kPa)	FibroTest
F0 – F1	0 or 1	0, 1, or 2	< 8.8	< 0.49
F2	2	3	≥ 8.8 to < 9.6	0.49 to < 0.59
F3	3	4	≥ 9.6 to < 14.6	0.59 to < 0.75
F4	4	5 or 6	≥ 14.6	≥ 0.75

The resulting fibrosis status (F0-F3 noncirrhotic, F4 cirrhotic) and HCV genotype/sub-genotype will be documented via recording in the Interactive Response Technology (IRT) system for each subject to determine the duration and regimen of the study drug for each subject.

Subjects will be considered treatment-naïve if they have never received any antiviral treatment for hepatitis C virus infection.

Subjects will be considered treatment-experienced if they have received prior IFN (IFN or pegIFN with or without RBV) excluding DAAs. Subjects with prior treatment with IFN will be categorized as one of the following:

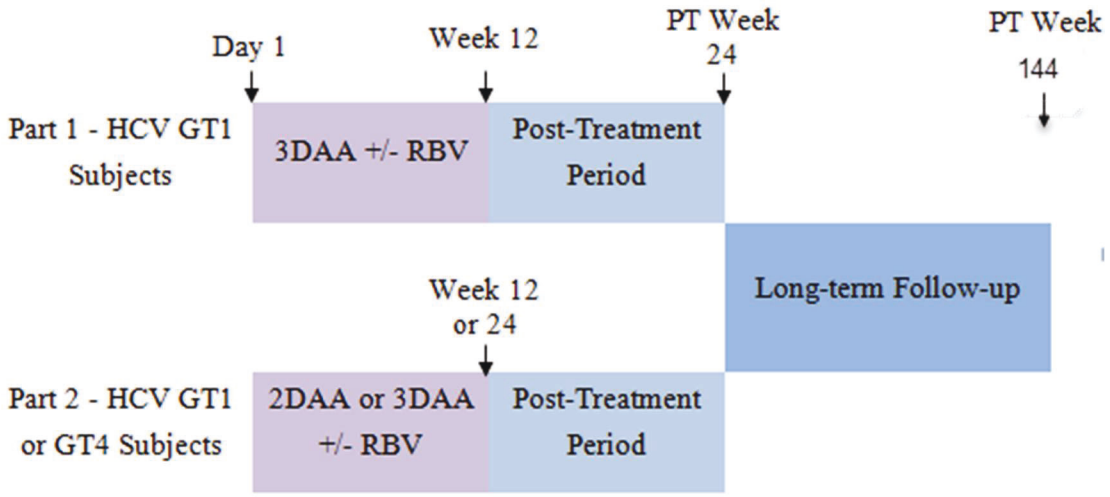
- Non-responder: HCV RNA detected at the end of a prior IFN, IFN/RBV or pegIFN/RBV treatment course (except for breakthrough, which is captured separately). These subjects are further categorized as:
  - Null-responder: failed to achieve a 1 $\log_{10}$ IU/mL reduction in HCV RNA by Week 4 or a 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior IFN, IFN/RBV or pegIFN/RBV treatment course;
  - Partial responder: achieved at least 2 $\log_{10}$ IU/mL reduction in HCV RNA by Week 12 during a prior IFN, IFN/RBV or pegIFN/RBV treatment course but failed to achieve HCV RNA undetectable at the end of treatment;

- Unknown or unable to specify: insufficient data to categorize as null or partial responder.

- Breakthrough: confirmed ≥ 1 $\log_{10}$ IU/mL increase from nadir or achieved HCV RNA undetectable (or unquantifiable) during a prior IFN, IFN/RBV or pegIFN/RBV treatment course but HCV RNA was quantifiable during or at the end of treatment.
- Relapser: achieved HCV RNA undetectable at the end of a prior IFN, IFN/RBV or pegIFN/RBV treatment course but HCV RNA was detectable following cessation of therapy.
- Unknown/other IFN-experienced: subject received a prior IFN, IFN/RBV or pegIFN/RBV treatment course and reason for not achieving SVR is unknown or other than above.

After meeting the eligibility criteria, subjects will be enrolled to 12 weeks of treatment in Part 1 or either 12 or 24 weeks of treatment in Part 2.

Figure 1. Study Schematic



The study is designed to enroll approximately 62 subjects to meet scientific, regulatory and clinical objectives without enrolling an undue number of subjects in alignment with

ethical considerations. Therefore, if the target number of subjects has been enrolled, there is a possibility that additional subjects in screening will not be enrolled.

5.1.1 Screening

At the Screening Visit for Part 1 or Part 2, parent(s)/guardian(s) must provide written (signed and dated) informed consent and the subject must provide assent (as appropriate for age and country) respectively, prior to any study specific procedures on the subject.

Subjects will receive a unique subject number via the IRT system and will undergo the study procedures identified in Section 5.3.1 associated with the Screening Visit. The investigator or his/her designated and qualified representatives will evaluate whether the subject meets all of the eligibility criteria specified in Section 5.2.1 and Section 5.2.2 for the Part in which they are enrolling during the period from the Screening Visit through Study Day 1 prior to dosing and record the results of this assessment and the details of the informed consent and assent process in the subject's medical records.

Eligible subjects have up to 42 days following the Screening Visit to enroll into Part 1 or Part 2 of the study. There is no screening period for Part 3 (Long-term Follow-up). Part 3 will start the day after the PT Week 24 Visit in Part 1 or Part 2.

5.1.1.1 Rescreening

Subjects who have any of the following results are ineligible to rescreen or have other exclusionary laboratory parameters retested: an exclusionary HCV genotype, a positive hepatitis B surface antigen (HBsAg), positive human immunodeficiency virus (HIV) antibody or confirmed pregnancy.

Subjects who meet all eligibility criteria with the exception of **up to three (3)** exclusionary laboratory parameters may repeat laboratory testing once within the 42-day screening period without prior AbbVie approval. Subjects being retested because of exclusionary laboratory parameter(s) must have the related panel(s) repeated

(e.g., bilirubin requires a repeat chemistry panel) within the same screening period and all eligibility criteria must be met on the repeated panels.

Subjects may be rescreened only once as follows:

- Subjects who have more than 3 exclusionary laboratory results require approval from the AbbVie Therapeutic Area Medical Director prior to rescreening.
- Eligible subjects who fail to enroll within 42 days of screening, regardless of the reason for falling outside the 42-day screening window.

For subjects who do not meet the study eligibility criteria, the site personnel must register the subject as a screen failure in both IRT and electronic data capture (EDC) systems.

5.1.2 Treatment Period (TP)

After meeting all the eligibility criteria, subjects will be enrolled to a study regimen according to their HCV sub-genotype for Part 1 (Table 5) or to a study regimen and study duration according to their HCV genotype, sub-genotype and cirrhosis status in Part 2 (Table 6).

Table 5. Treatment Regimen and Duration – Part 1

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

In Part 1, treatment-naïve HCV GT1-infected subjects without cirrhosis will receive OBV, PTV, RTV and DSV with or without RBV for 12 weeks according to Table 5. In Part 2, HCV GT1 and GT4-infected subjects with and without compensated cirrhosis who are either treatment-naïve or previously treated with IFN (IFN or pegIFN with or without

RBV) will receive OBV/PTV/RTV with or without DSV and with or without RBV according to Table 6. The treatment duration will be 12 or 24 weeks depending on their genotype, subgenotype and cirrhosis status. Details regarding enrollment in Part 1 and Part 2 are outlined in Section 5.1 (Overall Study Design and Plan: Description).

Table 6. Treatment Regimen and Duration – Part 2 (For Subjects ≥ 12 – 17 Years of Age)

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks
Genotype 1a,* with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

The site will enter subject's genotype and sub-genotype (GT1b/GT1 non-b/GT4) and fibrosis stage in the IRT system in order to obtain the subject's treatment regimen and duration.

OBV, PTV, RTV, DSV (if applicable) and RBV (if applicable) will be administered as described in Section 5.5.1 (Treatments Administered). Subjects and their parent(s)/guardian(s) will receive instructions about the study drugs at the Day 1 Visit. The study drugs will be dispensed at the visits as indicated in Appendix C.

After enrollment, all subjects will continue to return to the site on an outpatient basis for the study visits and procedures as identified in Appendix C. Subjects could also return to the site for an unscheduled study visit for additional safety assessments if the investigator feels it is necessary. Sites should ensure that subjects adhere to the study visits listed in Appendix C. Subjects who cannot complete their study visit per the visit schedule should

ensure they do not run out of study drug prior to their next study visit. Compliance is critical to ensure adequate drug exposure.

Virologic failure criteria will be evaluated and applied by the Investigator as detailed in Section 5.4.3.

Subjects who prematurely discontinue from the Treatment Period should return for a Treatment Discontinuation Visit and undergo the study procedures as outlined in Appendix C and as described in Section 5.3.1.1. Ideally, this should occur on the day of study drug discontinuation, but is recommended to be no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy if applicable. Following completion or premature discontinuation of study drug treatment, all subjects in either Part 1 or Part 2 will be followed in the associated Post-Treatment Period of Part 1 or Part 2.

5.1.3 Post-Treatment Period of Part 1 and Part 2

All subjects who receive at least one dose of the study drug will enter into the Post-Treatment Period of Part 1 or Part 2. The 24-week Post-Treatment Period of Parts 1 and 2 will include the visits through Post-Treatment Week 24 as outlined in Appendix C. Subjects who prematurely discontinue during the Post-Treatment Period should return to the site for a discontinuation visit and undergo the study procedures as outlined in Appendix C.

5.1.4 Long-Term Follow-Up Period

All subjects who complete the Post-Treatment Week 24 visit will automatically be enrolled into Part 3 – the Long-term Follow-up Period and return to the site on an outpatient basis for the study visits and procedures as identified in Appendix C. The Long-term Follow-up Period will begin the day following the Post-Treatment Week 24 visit and last for 144 weeks as outlined in Appendix C. Subjects may also return to the site for an unscheduled study visit for additional safety assessments if the investigator feels it is necessary.

The Long-term Follow-up Period will assess safety, antiviral response, and growth and development.

Growth and development will be assessed using waist circumference, Tanner Pubertal Staging, height standardized score, and growth rate defined as the change in height over change in age from the previous visit.

5.2 Selection of Study Population

The study population in Part 1 consists of HCV genotype 1-infected pediatric subjects without cirrhosis who are naïve to HCV treatment. The study population in Part 2 consists of HCV genotype 1- or 4-infected pediatric subjects with or without compensated cirrhosis, who are treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced.

Subjects who meet the inclusion criteria and who do not meet any of the exclusion criteria will be eligible for enrollment into the study.

5.2.1 Inclusion Criteria

1. Male or female ≥ 3 to 17 years of age with weight ≥ 15 kg at time of enrollment.
2. Willingness to participate in the study for up to 42 months.
3. If female, subject must either be pre-menarche and not sexually active, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) OR for Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).
4. If male subject and sexually active with female partner(s) of childbearing potential, subject must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1 and for up to 9 months after stopping study drug (or as directed

by the local RBV label if receiving RBV) or from Study Day 1 through 30 days after last dose of study drug for subjects whose study regimen does not include RBV.

5. HCV infection demonstrated by positive anti-HCV Ab and HCV RNA ≥ 1000 IU/mL at the time of screening.
6. Screening laboratory results indicating HCV genotype 1 for enrollment into Part 1 and genotype 1 or 4 for enrollment into Part 2.
7. Subject has never received antiviral treatment (including IFN or pegIFN with or without RBV) for hepatitis C infection (treatment-naïve subjects) for Part 1 or Part 2, or subject must have completed their IFN based (IFN or pegIFN with or without RBV only) hepatitis C treatment at least 6 months prior to enrollment into Part 2.
8. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.
9. Females of childbearing potential must have a negative serum pregnancy test result at Screening, and a negative urine pregnancy test at Study Day 1. Females of non-childbearing potential (as defined above) at Screening do not require pregnancy testing.

Rationale for Inclusion Criteria

1, 2, 5 – 7	To select the appropriate subject population with sufficient disease severity for evaluation
3, 4, 9	RBV has known teratogenic effects
8	In accordance with harmonized Good Clinical Practice (GCP)

5.2.2 Exclusion Criteria

A subject will be excluded from the study if he/she meets any of the following criteria:

1. Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).
2. Use of known strong inducers and inhibitors (e.g., gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in subjects receiving dasabuvir, or strong or moderate inducers of CYP3A, medications listed below, or medications contraindicated for ritonavir or RBV (for those that receive RBV), within 2 weeks or 10 half-lives, whichever is longer, of the respective medication prior to study drug administration including but not limited to:

Table 7. Medications Contraindicated for Use with the Study Drug Regimen

Alfuzosin	Ethinyl estradiol-containing	Pimozide
Astemizole	medications	Ranolazine
Atorvastatin	Fusidic Acid	Rifampin
Blonanserin	Gemfibrozil[a]	Salmeterol
Carbamazepine	Lovastatin	Sildenafil[b]
Cisapride	Lurasidone	Simvastatin
Colchicine[c]	Methylergonovine	St. John's Wort
Dihydroergotamine	Midazolam (oral)	Terfenadine
Dronedarone	Phenobarbital	Triazolam
Efavirenz	Phenytoin	
Ergotamine		
Ergonovine		

a. Strong CYP2C8 inhibitors (e.g., gemfibrozil) and CYP2C8 inducers are not contraindicated with ombitasvir, paritaprevir and ritonavir (for GT4 subjects).

b. When used for the treatment of pulmonary arterial hypertension.

c. When used in patients with renal or hepatic impairment.

Note: Not all medications contraindicated with ribavirin are listed above. Refer to the most current package inserts or product labeling of ribavirin for a complete list of contraindicated medications.

For medications contraindicated with AbbVie's 2D and 3D regimen, refer to the recommended prescribing information section of the approved local product labels in countries where the regimen contained in this study (i.e., ombitasvir/paritaprevir/ritonavir with or without dasabuvir) has received marketing authorization. If locally approved labels are not available, refer to the following Contraindicated Medication list:

3. Clinically significant abnormalities or co-morbidities, other than HCV infection that make the subject an unsuitable candidate for this study or treatment with RBV (if applicable) in the opinion of the investigator.
4. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-HIV antibody (HIV Ab) test.
5. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFNs or RBV or receipt of any investigational product within 6 weeks prior to study drug administration.
6. History of solid organ transplant.
7. Prior or current use of any investigational or commercially available anti-HCV agents other than IFN, pegIFN or RBV, including telaprevir, boceprevir, sofosbuvir, ombitasvir, dasabuvir, paritaprevir, ledipasvir, daclatasvir, simeprevir, elbasvir, grazoprevir or an investigational DAA.
8. Screening laboratory analyses showing any of the following abnormal laboratory results:
    - Albumin < 2.8 g/dL
    - Hemoglobin < 10 g/dL
    - Platelets < 25,000 cells per mm^3
    - Total bilirubin > 3.0 mg/dL

9. Any current or past clinical evidence of Child-Pugh B or C Classification (Child-Pugh Score ≥ 7) or clinical history of liver decompensation such as ascites (noted on physical exam), variceal bleeding or hepatic encephalopathy.
10. Confirmed presence of hepatocellular carcinoma indicated on imaging techniques such as computed tomography (CT) scan or magnetic resonance imaging (MRI) within 3 months prior to Screening or on an ultrasound performed at Screening for subjects with cirrhosis (a positive ultrasound result will be confirmed with CT scan or MRI).
11. Male subject who is considering fathering a child or donating sperm during the study or for approximately 120 days after stopping study drug if receiving DAAs only, or for up to 9 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Rationale for Exclusion Criteria

1, 3, 7, 8, 10, 11	To ensure safety of the subjects throughout the study
2	To avoid bias for the evaluation of efficacy and safety by concomitant use of other medications
4 – 6, 9	To avoid bias for the evaluation of efficacy and safety

5.2.3 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the subject is receiving from 2 weeks prior to enrollment through 30 days post-dosing, must be recorded along with the reason for use, date(s) of administration including start and end dates, and dosage information including dose, route and frequency.

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drugs. Only medications taken for SAEs assessed as related to the study drugs and treatment of HCV will be recorded thereafter.

The AbbVie Therapeutic Area Medical Director should be contacted if there are any questions regarding concomitant or prior therapies.

5.2.3.1 Prior HCV Therapy

Part 1 will include only subjects that are treatment-naïve. For Part 2, prior or current use of any investigational or commercially available anti-HCV agents other than IFN, pegIFN or RBV, including telaprevir, boceprevir, sofosbuvir, ombitasvir, dasabuvir, paritaprevir, ledipasvir, daclatasvir, simeprevir, elbasvir, grazoprevir or an investigational DAA excludes a subject from this study. Subjects who previously participated in trials of investigational anti-HCV agents may be enrolled if they can produce documentation that they received only placebo.

Treatment experienced subjects must have discontinued previous therapy at least 6 months prior to the Screening Visit in order to be eligible for the study.

5.2.3.2 Concomitant Therapy

Subjects must be able to safely discontinue any prohibited medications within 2 weeks or 10 half-lives of the medication, whichever is longer, prior to initial study drug administration and through 2 weeks following discontinuation of study drugs. Parent(s)/legal guardian(s) and the pediatric subject must review and sign the informed consent and assent respectively prior to discontinuing any prohibited medications for the purpose of meeting study enrollment criteria.

The investigator or a qualified designee should confirm that a concomitant medication can be safely administered with DAAs (including ritonavir) and RBV (if applicable). Some medications may require dose adjustments due to potential for drug-drug interactions.

The investigator or qualified designee should review concomitant medication(s) label(s), the locally approved labels for ombitasvir, paritaprevir, ritonavir, dasabuvir (if applicable) and ribavirin (if applicable) and http://www.hep-druginteractions.org/ to screen concomitant medications at each visit for potential drug-drug interactions (DDI) with study drugs. Additionally, the site should document their DDI review in the subject's source.

Subjects using systemic ethinyl estradiol-containing contraceptive therapy have a higher risk for elevated ALT levels. Subjects using these kinds of medications must discontinue them at least 2 weeks prior to initial study drug administration. Subjects may replace the systemic ethinyl estradiol-containing contraceptive with a highly effective progestin-only hormonal contraceptive method or with another highly effective contraceptive method.

During the Post-Treatment Period, investigators should reassess concomitant medications. Subjects may resume previously prohibited medications or revert to pre-study doses, at a minimum of 2 weeks following discontinuation of study drugs, if applicable.

5.2.3.3 Prohibited Therapy

In addition to the medications listed in Table 7, use of known strong or moderate inducers of CYP3A (for GT1 and GT4 subjects receiving OBV/PTV/RTV with or without DSV), or strong inducers and inhibitors of CYP2C8 (only for GT1 subjects receiving OBV/PTV/RTV with DSV) are prohibited within 2 weeks or 10 half-lives of the medication, whichever is longer, prior to the initial dose of study drugs and through the first 2 weeks after the subject has completed study drugs in the Treatment Period.

Subjects must be able to safely discontinue any prohibited medications. Subjects must be consented prior to discontinuing any prohibited medications for the purpose of meeting study enrollment criteria. During the Post-Treatment Periods of Part 1 and Part 2, investigators should reassess prohibited medications and subjects may resume previously prohibited medications or revert to pre-study doses, at a minimum of 2 weeks following discontinuation of study drugs, if applicable.

5.2.4 Contraception Recommendations and Pregnancy Testing

The contraception recommendations in this paragraph are summarized in relation to the potential risk of the investigational products used in this study. All female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Principal Investigator, or who are of child-bearing potential should undergo pregnancy testing according to Section 5.3.1.1.

If female, subject must be:

- Pre-menarche and not sexually active, or
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), or
- Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).
    - Progestogen-only hormonal contraception (injectable or implantable) associated with inhibition of ovulation, initiated at least 1 month prior to Study Day 1.
    - Bilateral tubal occlusion/ligation.
    - Vasectomized partner(s), provided the vasectomized partner has received medical assessment of the surgical success and is the sole sexual partner of the WOCBP trial participant.
    - Intrauterine device (IUD).
    - Intrauterine hormone-releasing system (IUS).
    - True abstinence: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Listed methods of contraception achieve a failure rate of less than 1% per year when used perfectly (consistently and correctly). For oral hormonal contraceptives, failure rates can increase up to 9% with typical use (including inconsistent or incorrect use).

Note: Contraceptive methods with low user dependency are implantable progesterone only hormonal contraception, IUD, IUS, bilateral tubal occlusion, and vasectomized partner.

If required per local practices, male or female condom with or without spermicide OR cap, diaphragm or sponge with spermicide should be used in addition to one of the birth control methods listed above (excluding true abstinence).

If male, subjects must be

- Prepubertal and not sexually active, or
- surgically sterile (vasectomy with medical assessment confirming surgical success), or
- have a female partner who is postmenopausal or permanently sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy), or
- if sexually active with female partner(s) of childbearing potential must agree to practice contraception with a method listed below from Study Day 1 and for up to 9 months after stopping study drug (or as directed by the local RBV label if receiving RBV) or from Study Day 1 and continue for 120 days after last dose of study drug for subjects whose study regimen does not include RBV.
- Condom use in combination with one additional birth control method.
- True abstinence: Refraining from heterosexual intercourse – when this is in line with the preferred and usual lifestyle of the subject. (Note: Periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 120 days after the end of treatment if taking DAAs only, or for 9 months after the last dose of RBV (or per local RBV label).

5.3 Efficacy Pharmacokinetic, Pharmacogenetic and Safety Assessments/Variables

5.3.1 Efficacy and Safety Measurements Assessed and Flow Chart

Study procedures described are listed in the following section of this protocol and are summarized in tabular format in Appendix C.

5.3.1.1 Study Procedures

The study procedures outlined in Appendix C are discussed in detail in this section with the exception of the assessment of concomitant medications (Section 5.2.3), and the collection of adverse event information (Section 6.1.4). All study data will be recorded in the subject's source documentation and then on the appropriate eCRFs, with the exception of laboratory data which will be provided to the Sponsor electronically from the laboratory(ies).

Informed Consent/Assent

Signed study-specific informed consent and assent (as appropriate for age and country) will be obtained from the parent(s)/guardian(s) and subject before any study procedures are performed. If a subject becomes of legal age during the course of the study, the subject will need to be consented using the approved informed consent form. Details about how informed consent and assent will be obtained and documented are provided in Section 9.3.

RBV Information

Subjects taking RBV will be given the RBV Medication Guide (where applicable/locally available).

Medical History

A complete medical history, including history of tobacco, nicotine containing products and alcohol use, will be taken from each subject during the Screening Visit. An updated

medical history will be obtained prior to study drug administration and will serve as the baseline for clinical assessment.

Physical Examination

A complete physical examination will be performed at visits specified in Appendix C. A symptom-directed physical examination may be performed at any other visit, when necessary.

The physical examination performed on Study Day 1 will serve as the baseline physical examination for clinical assessment. Any significant physical examination findings after the first dose will be recorded as adverse events.

Vital Signs, Weight, Height and Waist Circumference

Body temperature, blood pressure, pulse, body weight, height, and waist circumference will be measured at the visits specified in Appendix C, or upon subject discontinuation. Blood pressure and pulse rate will be measured after the subject has been sitting for at least 3 minutes. The vital signs performed on Study Day 1 will serve as the baseline for clinical assessment. Height will be measured standing without shoes using a stadiometer. Waist circumference will be measured using a flexible tape at the level of the iliac crest at the end of expiration.

12-Lead Electrocardiogram

The ECG obtained at Screening will serve as the baseline assessment. The ECG should be performed prior to blood collection. An ECG can be performed at subsequent visits if deemed clinically.

The ECGs will be evaluated by an appropriately trained physician at the site ("local reader"). The local reader from the site will sign, and date ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

Only the local reader's evaluation of the ECG will be collected and documented in the subject's source. The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

Clinical Laboratory Tests

Samples will be obtained at a minimum for the clinical laboratory tests outlined in Table 8 at the visits indicated in Appendix C.

An overview about the volume of blood drawn for each of the study visits is listed in Appendix D of this protocol. The Investigator/designee should refer to the local recommendations on blood drawn in pediatric patients (e.g., the guide on *"Ethical Considerations for Clinical Trials on Medical Products With the Paediatric Population" or "Blood Drawing For Human Subject Research" by Duke University*). The Investigator/designee should document exceptions to the local blood loss recommendations in the subject's source along with a justification as appropriate.

At the Study Day 1 visit, a blood sample is to be collected prior to the first dose of study drug which is to be administered during the visit. Subjects should be reminded to eat prior to their first dose of study drug after the sample is collected (e.g., suggest they bring a light snack). Fasting status will be recorded in the source documents and on the laboratory requisition. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement prior to the initial dose of study drug.

A certified central laboratory will be utilized to process and provide results for the clinical laboratory tests. Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory chosen for this study. The certified

laboratory chosen for this study is Covance. Samples will be sent to the following address:

North and South American sites:

Covance Central Laboratory Services
8211 SciCor Drive
Indianapolis, IN 46214-2985 USA
Tel. (317) 271-1200
Fax: (317) 273-4030

European sites:

Covance Central Laboratory Services
Rue Moïse-Marcinhes 7
1217 Meyrin/Genève-CH
Tel: +41 58-822-7000
Fax: +41 58-822-6999

Table 8. Clinical Laboratory Tests

Hematology	Clinical Chemistry	Additional Tests
Hematocrit Hemoglobin Red Blood Cell (RBC) count White Blood Cell (WBC) count Neutrophils Bands, if detected Lymphocytes Monocytes Basophils Eosinophils Platelet count (estimate not acceptable) ANC Prothrombin Time/INR Activated partial thromboplastin time (aPTT) Reticulocyte count	Blood Urea Nitrogen (BUN) Creatinine Total bilirubin[a,b] Direct and indirect bilirubin Serum glutamic-pyruvic transaminase (SGPT/ALT) Serum glutamic-oxaloacetic transaminase (SGOT/AST) Alkaline phosphatase Sodium Potassium Calcium Inorganic phosphorus Uric acid Cholesterol Total protein Glucose Triglycerides Albumin[a] Chloride Bicarbonate Magnesium Gamma-glutamyl transferase (GGT)[a] Creatinine clearance (Cockcroft Gault calculation for subjects ≥ 12 years old and Schwartz formula for those < 12 years old) Alpha2-macroglobulinb Haptoglobin[b] Apolipoprotein A1[b]	HBsAg[c] Anti-HCV Ab[c] Anti-HIV Ab[c] FSH[c] Urine and Serum Human Chorionic Gonadotropin (hCG)[d] HCV RNA IL28B[c] HCV genotype and sub-genotype[c] Pharmacogenetic sample (optional)
Urinalysis		
Specific gravity Ketones pH Protein Blood Glucose Urobilinogen Bilirubin Leukocyte esterase Microscopic (reflex)		

a. Also a component of the Child-Pugh Assessment.

b. Also a component of FibroTest.

c. Performed only at Screening. FSH will be taken for female subjects aged ≥ 9 to 17 years old.

d. Serum and urine pregnancy testing only required for female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the PI, or who are of child-bearing potential.

Acceptability Questionnaire

For each subject who is taking the mini-tablet formulation, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form. The parent(s)/guardian(s) of the subject will be asked of their overall impression towards the dosage form and the administration via dosing

vehicle to the subject; such as duration of administration, volume of dosing vehicle, swallowability, and the convenience of administration.

The questionnaire will be completed at the visits as indicated in Appendix C. The parent(s)/guardian(s) will indicate their answers on the questionnaire, which will be kept as part of the study record and copied into EDC by site personnel. Site personnel will encourage completion of the questionnaire at all applicable visits and will ensure that a response is entered for all items.

Pregnancy Test

Females of non-childbearing potential (either pre-menarche and not sexually active or permanently surgically sterile as defined above in Section 5.2.4) at Screening do not require pregnancy testing. All female subjects who are experiencing menses or are nearing sexual maturation in the opinion of the Principal Investigator, or who are of child-bearing potential:

- A serum pregnancy test will be performed at the Screening visit only and analyzed by the central laboratory.
- Pregnancy testing will be performed as specified in Appendix C regardless of treatment regimen.
- Subjects that receive a RBV containing regimen will have pregnancy tests performed monthly throughout the Treatment Period and through Post-Treatment Week 16 or 4 months after the discontinuation of RBV, or according to the local RBV label and/or local treatment guidelines for RBV.
- Subjects receiving DAAs only should have urine pregnancy testing done through Post-Treatment Week 4.
- Urine pregnancy testing will be performed on-site during the study visit if there is a scheduled visit. The pregnancy result will be captured in the source document and recorded in the eCRF by site personnel. If there is not a scheduled study visit, subjects may either have pregnancy testing performed at the site as an unscheduled study visit or a urine pregnancy test may be conducted by the subject at home with a pregnancy test kit provided by the

site. If a urine pregnancy test is performed at home, site personnel should contact these female study subjects to capture the results of any study-related pregnancy tests in the source records only.

- If a urine pregnancy result is positive, a confirmatory hCG serum test should be collected and sent to the central lab.

Concomitant Medication Assessment

Use of medications (prescription or over-the-counter, including vitamins, herbal supplements, and vaccines) from the time of signing the consent, through the Treatment Period and 30 days after study drugs are stopped must be recorded in the source and eCRF at each study visit indicated in Appendix C (Treatment Period and Post-Treatment Period). Thereafter, only medications taken for SAEs assessed as related to study drugs and treatment of HCV will be recorded in the eCRF at each study visit indicated in Appendix C (Post-Treatment Period). The investigator or his/her designated and qualified representatives should review concomitant medication(s) label(s), the locally approved labels for ombitasvir, paritaprevir, ritonavir, dasabuvir (if applicable), and ribavirin (if applicable) and http://www.hep-druginteractions.org/ to screen concomitant medications at each visit for potential drug interaction with study drugs. The site should document their DDI review in the source and maintain it in the subject's study file. The sites should refer to Section 5.2.3 (Prior, Concomitant, and Prohibited Therapy).

Hepatitis and HIV Screen

HBsAg (hepatitis B surface antigen), anti-HCV Ab and anti-HIV Ab will be performed at Screening. A positive anti-HIV Ab test must be confirmed. The investigator or his/her representatives must discuss any local reporting requirements to local health agencies with the subject's parent(s)/legal guardian(s). The site will report these results per local regulations, if necessary.

HCV Genotype and Sub-Genotype

Plasma samples for HCV genotype and sub-genotype will be collected at Screening. Genotype and sub-genotype will be assessed using the Versant HCV Genotyping assay (LiPA 2.0). If the Versant LiPA 2.0 assay is resulted as "unable to genotype" then the HCV genotype will be determined by Sanger sequencing of NS5B region on Applied Biosystems 3500XL.

HCV RNA Levels

Plasma samples for HCV RNA levels will be collected as indicated in Appendix C and analyzed using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0. For this assay, the lower limit of quantification (LLOQ) is 15 IU/mL.

Historical Liver Biopsy or FibroScan or Screening Fibro Test

An assessment of liver fibrosis is mandatory prior to enrollment. Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will undergo a non-invasive FibroTest at Screening to determine presence or absence of cirrhosis.

Subjects will be considered to be non-cirrhotic based on a liver biopsy within 24 months prior to screening demonstrating the absence of cirrhosis (e.g., a Metavir Score of 3 or less, Ishak score of 4 or less) or, if a liver biopsy is unavailable, a historical Fibroscan® result < 14.6 kPa within 24 months prior to screening. If neither historical result is available, a screening FibroTest score of < 0.75 can be used to demonstrate absence of cirrhosis.

Subjects will be considered to have cirrhosis based on previous histologic diagnosis of cirrhosis on a liver biopsy (e.g., Metavir Score of > 3 [including 3 – 4 or 3/4], Ishak score of > 4) or a historical FibroScan score of ≥ 14.6 kPa or a screening FibroTest result of ≥ 0.75.

Longitudinal Fibrotest

All subjects will undergo assessment of FibroTest at Screening or Day 1 and FibroTest at PT Weeks 24, and 144. Any subject that does not have a FibroTest performed during Screening will have them performed at Day 1.

Child-Pugh Score and Category

The Child-Pugh score will be calculated and documented prior to Day 1 Visit for cirrhotic subjects only. Subjects who were considered to be non-cirrhotic at the screening visit but identified as cirrhotic (according to definitions listed here) during the screening process will return to the site prior to the baseline visit for Child-Pugh assessment.

The Child-Pugh score uses five clinical measures of liver disease (3 laboratory parameters and 2 clinical assessments). Child-Pugh score will be determined at the screening visit as indicated in Appendix C. The Child-Pugh score will be automatically calculated prior to Day 1 by EDC RAVE once the investigator or designated site personnel enters the subject's parameters (as listed in Table 9). A total score of 5 – 6 is considered Class A (compensated disease); 7 – 9 is Class B (significant functional compromise); and 10 – 15 is Class C (decompensated disease).

Table 9. Child-Pugh Classification of Severity of Cirrhosis

	Points Assigned for Observed Findings		
	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.

Hepatocellular Carcinoma Screening: Liver Ultrasound

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver will be performed as indicated in Appendix C for subjects with compensated cirrhosis only.

Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

A positive ultrasound result suspicious for HCC during the treatment or Post-Treatment Period will be confirmed with CT scan or MRI.

HCV Resistance Testing Plasma Sample

A plasma sample for baseline HCV resistance testing will be collected on Day 1. HCV resistance testing is required for all subjects who meet virologic failure criteria at the visits indicated in Appendix C. Specific instructions for preparation and storage of the samples will be provided by the central laboratory, the Sponsor, or its designee.

Tanner Pubertal Stage

The Tanner Pubertal Stage will be calculated for all subjects ages ≥ 9 to 17 and documented at the visits indicated in Appendix C. Boys will be rated on a 5-point scale (Tanner Stage 1 – 5) for genital development and pubic hair growth. Girls will be rated on a 5-point scale (Tanner Stage 1 – 5) for breast development as well as pubic hair growth (Appendix E). Once a child reaches Tanner Stage 5, the test will not be repeated.

Patient Reported Outcomes (PRO) Instrument (EQ-5D-3L with EQ VAS)

Subjects will complete the PRO instrument, EQ-5D-3L with EQ VAS, with the assistance of a parent/guardian (where allowed per local regulatory guidelines) on the study days specified in Appendix C. The PRO should be administered as the first procedure at each visit. Subjects will be instructed to follow the instructions provided with the instrument and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are unable (too young) to read or understand the instrument may have their parent(s)/guardian(s) read the questionnaire to them. Site personnel will encourage completion of each instrument at all applicable visits and will ensure that a response is entered for all items.

The EQ-5D-3L is a health state instrument that evaluates preference for health status (utility). The 5 items in the EQ-5D-3L comprise 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), each of which are rated on 3 levels of severity. Subjects also rate their perception of their overall health on a separate visual analog scale (VAS). Health status captured by EQ-5D-3L relates to the respondent's

situation at the time of completion. Completion of the EQ-5D-3L should require approximately 5 minutes. Subjects who are older than 7-years of age (at Day 1) and are able to read and understand the questions should complete the questionnaire by themselves. For subjects who are 7-years of age or younger (at Day 1) or who are not comfortable with reading the questions, their parent(s)/guardian(s) should read the questionnaires to them and record their response for each item.

Assignment of Subject Numbers

A subject number is assigned at screening via IRT system. Subject numbers will be unique 5-digit numbers and will begin with 11001, with the first digit representing the part of initial enrollment (Part 1 or Part 2); the next 2 digits will represent the investigative site and the last 2 digits representing the subjects at that site. Enrolled subjects will keep their subject number throughout the study.

Study Drug Dispensation

Study drugs will be dispensed at the visits as indicated in Appendix C.

Study Drug Dosing Card

Study drug dosing cards will be dispensed to subjects in Part 1 and Part 2 at the study visits indicated in Appendix C. Parent(s)/legal guardian(s) and the subject will be instructed by the site to record the date and time (to the nearest minute) of the 2 study drug doses prior to each scheduled visit in the treatment periods including evening dose (other than Day 1). The subject must bring the completed study drug dosing card with them to each visit. Site personnel will record the information from the completed dosing card into the eCRF and file the completed dosing card in the subject's source documents. In the event that the dosing card is not available, the site may obtain dosing information via parent(s)/legal guardian(s) and/or subject interview and record this information into the eCRF and into the subject's source documents.

Ribavirin Diary

At Day 1, the principal investigator or designee will provide the parent(s)/legal guardian(s) with a Ribavirin Diary in case the subject is taking the RBV solution formulation. The principal investigator or designee will complete the header of the RBV diary and instruct the parent(s)/legal guardian(s) on the completion of the diary. The parent(s)/legal guardian(s) must bring the completed RBV diary to each of the study visits. The principal investigator or designee will transcribe the information from the RBV diary into the RAVE system.

Study Drug Compliance

At the Study Drug accountability visits noted in Appendix C, the returned study drug including RBV will be accounted for by the study site and recorded electronically. Additional information regarding treatment compliance can be found in Section 5.5.6.

5.3.1.2 Blood Samples for Pharmacogenetic Analysis

IL28B Sample

One (required) 2 mL whole blood sample for deoxyribonucleic acid (DNA) isolation will be collected from each subject at screening for Interleukin 28B (IL28B) pharmacogenetic analysis and related markers. If the sample is not collected at this visit, it may be collected at any time throughout the study. This sample will not be used for any testing other than IL28B genotypes.

Specific instructions for sample collection and storage will be provided by the central laboratory, the Sponsor, or its designee.

Optional Sample for Pharmacogenetic DNA Analysis

One 3 mL whole blood sample for DNA isolation will be collected on Day 1 (Treatment Periods Part 1 and Part 2) from each subject who signed the assent form (as per local requirements) and whose parent(s)/guardian(s) have signed the informed consent to provide the optional sample for pharmacogenetic analysis. If the optional

pharmacogenetic sample is not collected at Day 1, it may be collected at any other visit during the study. The Investigator/designee should follow their local recommendations on blood drawn for the PG sample collection during the Treatment Period. The procedure for obtaining and documenting informed consent is discussed in Section 9.3. The sample collection tubes will minimally be labeled with "PG-DNA," protocol number and subject number. Samples will be shipped frozen to AbbVie or a designated laboratory for DNA extraction and long-term storage. Specific instructions for preparation and storage of archive pharmacogenetic samples will be provided by the central laboratory, AbbVie, or its designee. AbbVie will store the DNA samples in a secure storage space with adequate measures to protect confidentiality. The samples will be retained while research on OBV, PTV, DSV, (or drugs for the treatment of HCV) continues but no longer than 20 years.

5.3.1.3 Meals and Dietary Requirement

Subjects should be reminded that, in order to maximize absorption, each dose of the study drugs should be taken with food. Subjects whose visits occur prior to the morning dose of study drugs should be instructed to not have a full meal before the visits, so that study drugs can be taken with food during the visits.

All study drugs should be dosed together and administered with food, i.e., the morning dose of OBV, PTV, RTV, DSV (if applicable) and RBV(if applicable) should be taken together with food and the evening dose of DSV (if applicable) and RBV (if applicable) should be taken together with food.

5.3.2 Drug Concentration Measurements

5.3.2.1 Collection of Samples for Analysis

Blood samples for pharmacokinetic assay of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, as well as RTV and RBV (if applicable) will be collected by venipuncture at each study visit indicated in Appendix C.

Part 1

Subjects enrolled into Part 1 may undergo dose adjustments based on available pharmacokinetic and clinical data. Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, and Week 12. At Week 2 and Week 8, the morning dose of study drug will be administered in the clinic at approximately 24 hours after the prior morning dose. At Week 2, the evening doses of DSV and RBV (if applicable) will be administered in the clinic following the 12 hour PK draw and the Week 2 + 1 day morning doses of study drug will be administered in the clinic following the 24 hour PK draw. PK samples will be collected at the following timepoints for each subject:

- Day 1: 4 hours post-dose (the morning doses will be administered in the clinic)
- Week 2: 2, 4, 8, 12 and 24 hours post-dose (the morning doses, the evening doses following the 12 hour PK draw and the morning doses following the 24 hour PK draw will be administered in the clinic)
- Week 4: a PK sample (regardless of the dosing time)
- Week 8: a trough PK sample (i.e., prior to the morning dose, which will be administered in the clinic)
- Week 12: a PK sample (regardless of the dosing time)

The time that each blood sample is collected will be recorded to the nearest minute on the lab requisitions.

Part 2

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20 and Week 24. The latter 3 visits, Weeks 16, 20 and 24, are required for subjects with GT1a HCV infection and compensated cirrhosis receiving 24 weeks of treatment.

One PK sample (regardless of the dosing time) will be collected at each treatment visit for each subject in Part 2.

The time that each blood sample is collected will be recorded to the nearest minute on the lab requisitions.

For Part 1, the maximum amount of blood drawn will be approximately 18.3 mL during a 24-hour period (at Week 2) and approximately 55.8 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

For Part 2, the maximum amount of blood drawn after Day 1 (25.8 mL) will be approximately 11.7 mL during any 24-hour period and approximately 49.2 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

5.3.2.2 Handling/Processing of Samples

Specific instructions for collection of blood samples and subsequent preparation and storage of the plasma samples for the pharmacokinetic assays of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, RTV and RBV will be provided by the central laboratory, the Sponsor, or its designee.

5.3.2.3 Disposition of Samples

The frozen plasma samples for the pharmacokinetic assays of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, RTV and RBV will be packed in dry ice sufficient to last during transport, and transferred from the study site to the central laboratory.

Specific instructions for shipping to the analytical lab from the central laboratory will be provided by the central laboratory, the Sponsor, or its designee.

The central laboratory will then ship the plasma samples to:

Sample Receiving
Dept. R43F, Bldg. AP13A, Room 2310
c/o: Delivery Services
1150 S. Northpoint Blvd.
Waukegan, IL 60085

Phone: (847) 937-0889
Fax: (847) 938-9898
Email: sample.receiving@abbvie.com

An inventory of the samples included will accompany the package and an electronic copy of the Manifests (including subject number, study day, the time of sample collection and barcode) will be sent to the contact person at sample.receiving@abbvie.com.

5.3.2.4 Measurement Methods

Plasma concentrations of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV will be determined using validated analytical methods under the supervision of the Drug Analysis Department at AbbVie. Plasma concentrations of possible metabolites of OBV, PTV, and other metabolites of DSV may also be determined using validated or non-validated methods.

5.3.3 Efficacy Variables

5.3.3.1 Primary Variables

The primary PK endpoints from Part 1 are:

- C_{max} and AUC following dosing on Week 2, and trough concentration following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

The primary efficacy endpoint is:

- The percentage of subjects with SVR_{12} among all subjects.

5.3.3.2 Secondary Variables

The secondary efficacy endpoints in Parts 1 and 2 are:

- The percentage of subjects with SVR_{12} by formulation, age and weight group and across all subjects on the adult formulations.
- The percentage of subjects with SVR_{24} by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.
- The percentage of treatment-naïve subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

5.3.4 Safety Variables

The following safety evaluations will be analyzed during the study: adverse event monitoring and vital signs, physical examination, and laboratory test assessments. Growth and development outcomes of growth rate, height relative to age, waist circumference and Tanner stage will also be assessed.

5.3.5 Pharmacokinetic Variables

Individual plasma concentrations of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV (if applicable) will be measured for Part 1 and Part 2.

Values for the pharmacokinetic parameters of OBV, PTV, RTV, DSV, DSV M1 metabolite, and RBV (if applicable) including the C_{max}, T_{max}, C_{trough}, and area under the concentration curve (AUC) will be determined by noncompartmental methods using data from subjects in Part 1.

Additional parameters may be determined if useful in the interpretation of the data.

5.3.6 Pharmacogenetic Variables

IL28B status will be determined for each subject and analyzed as a factor contributing to the subject's response to study treatment. These IL28B genotype results may be analyzed as part of a multi-study assessment of IL28B and response to study drug treatment. The results may also be used for the development of diagnostic tests related to IL28B and study treatment, or drugs of these classes.

DNA samples from subjects, where the subject has provided assent (per local regulations) and subject's parent(s)/guardian(s) have signed the informed consent to additional pharmacogenetic analysis, may be sequenced and data analyzed for genetic factors contributing to the disease or to the subject's response to OBV, PTV, DSV in terms of pharmacokinetics, efficacy, tolerability, and safety. Such genetic factors may include genes for drug metabolizing enzymes, drug transport proteins, genes within the target pathway, genes believed to be related to the disease or to drug response. Some genes currently insufficiently characterized or unknown may be understood to be important at the time of analysis. The samples may be analyzed as part of a multi-study assessment of genetic factors involved in the response to OBV, PTV, DSV, drugs of this class, or the disease state. The samples may also be used for the development of diagnostic tests related to OBV, PTV, DSV, drugs of this class, or the disease state. The results of pharmacogenetic analyses may not be reported with the study summary.

5.4 Removal of Subjects from Therapy or Assessment

5.4.1 Discontinuation of Individual Subjects

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

If a subject prematurely discontinues during the Treatment Period, Post-Treatment Period or the Long-term Follow-up Period, the procedures outlined for the applicable Premature

D/C Visit should be completed as defined in Appendix C. Ideally for study drug discontinuation, this should occur on the day of study drug discontinuation, but no later than 2 days after their final dose of study drug and prior to the initiation of any other anti-HCV therapy. However, these procedures should not interfere with the initiation of any new treatments or therapeutic modalities that the investigator feels are necessary to treat the subject's condition. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment. The last dose of any study drug and reason for discontinuation from the Treatment Period will be recorded in the EDC system.

If a subject has an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range at the time of study drug discontinuation, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the Treatment Period, the administration of RBV (if applicable) to that subject must be discontinued immediately and DAAs may be continued at the principal investigator's discretion after discussion with the subject and parent(s)/guardian(s), if the benefit of continuing DAAs is felt to outweigh the potential risk. Specific instructions regarding subject pregnancy can be found in Section 6.1.6. Subjects will be monitored for SVR in the Post-Treatment Period as described in Section 5.1.3. The investigator is also encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if applicable.

5.4.2 Discontinuation of Entire Study

AbbVie may terminate this study prematurely, either in its entirety or at any study site, for reasonable cause provided that written notice is submitted in advance of the intended termination. The investigator may also terminate the study at his/her site for reasonable cause, after providing written notice to AbbVie in advance of the intended termination.

Advance notice is not required by either party if the study is stopped due to safety concerns.

If AbbVie terminates the study for safety reasons, AbbVie will immediately notify the investigator by telephone and subsequently provide written instructions for study termination.

5.4.3 Discontinuation of Subjects Meeting Virologic Failure Criteria

The following criteria will be considered evidence of virologic failure during the study treatment period. Pediatric subjects demonstrating any of the following should be discontinued from study drug:

- Confirmed increase from nadir (defined as 2 consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) in HCV RNA at any time point
- Confirmed HCV RNA ≥ 100 IU/ml (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/ml) at any point after achieving HCV RNA < LLOQ

Confirmatory testing, where required, should be completed as soon as possible. Also, when confirmation is required, the subject should remain on study treatment until the virologic failure has been confirmed.

If any of the above criteria are met during the study treatment period, the subject should discontinue study treatment but continue in the PT Period. If the investigator believes the virologic failure is due to study drug interruption and/or is compliance related, the AbbVie Study TA SD/TA MD should be contacted to discuss alternative management.

5.5 Treatments

5.5.1 Treatments Administered

Each dose of open-label DAA study drugs (ombitasvir, paritaprevir, ritonavir and dasabuvir) and ribavirin will be dispensed in the form of tablets, mini-tablets, or as an oral solution (RBV only). Study drugs will be dispensed at the visits listed in Appendix C.

Adult Formulations:

Ombitasvir/paritaprevir/r will be provided by the Sponsor as 12.5 mg/75 mg/50 mg tablets. Ombitasvir/paritaprevir/r will be taken orally as 2 tablets every morning which corresponds to an ombitasvir 25 mg/paritaprevir 150 mg/ritonavir 100 mg dose QD.

Dasabuvir will be provided by the Sponsor as 250 mg tablets. Dasabuvir will be taken orally as 1 tablet twice daily, which corresponds to a 250 mg dose BID.

RBV: Parts 1 and 2

RBV will also be provided to the investigator by the Sponsor for use in this study. RBV will be provided as 200 mg tablets for subjects that are willing to swallow those tablets. For subjects that are not willing to swallow the RBV tablets and not taking the adult formulations of the DAAs, RBV will be provided as a 40 mg/mL oral solution. Management of RBV in renally impaired patients (CrCl < 50 mL/min) will be left to the physician's discretion in consultation with the Therapeutic Area Medical Director.

Part 1 Mini-Tablet:

Ombitasvir, paritaprevir and ritonavir will be provided by the Sponsor as separate 0.3 mg, 1.0 mg, and 1.0 mg mini-tablets. Ombitasvir, paritaprevir and ritonavir will be taken orally and will be dosed QD based on body weight.

Dasabuvir will be provided by the Sponsor as 3.08 mg mini-tablet. Dasabuvir will be taken orally and will be dosed BID based on body weight.

The mini-tablets are packed in unit doses and are to be administered at once. The legal guardian(s) should be counselled by site to check that the study drug bottles have been emptied completely into the dosing vehicle to assure the complete dose is taken by the subject. Ombitasvir, Paritaprevir, Ritonavir will be taken orally and will be dosed QD based on body weight. Dasabuvir will be taken orally and will be dosed BID based on body weight.

On the morning of Study Day 1, at the site, subjects will be administered study drugs by the study site personnel and receive instructions for self-administration of all study drugs from the Day 1 evening dose of dasabuvir or Study Day 2 through Study Week 12 of the Treatment Period. The date and time of administration of the first dose of each drug will be recorded in the source and eCRF.

Following enrollment, the site will use the IRT system for drug dispensation. Study drugs must not be dispensed without contacting the IRT system, and only for subjects enrolled in the study through the IRT system.

All subjects who receive at least one dose of study drugs who fail to achieve virologic suppression, or who experience virologic breakthrough on DAA therapy will be discontinued from treatment and enter the Post-Treatment Period, unless alternative management is agreed to with AbbVie Study TA SD/TA MD. The investigator can prescribe another regimen, as deemed appropriate, which will not be provided or reimbursed by AbbVie.

5.5.2 Identity of Investigational Products

Information regarding the study drugs to be used in this study is presented in Table 10.

Table 10. Identity of Investigational Products

Part	Investigational Product	Manufacturer	Mode of Administration	Formulation	Strength
1 & 2	Ombitasvir/paritaprevir/ ritonavir	AbbVie	Oral	Tablets	12.5/75/50 mg
1 & 2	Dasabuvir	AbbVie	Oral	Tablets	250 mg
1	Ombitasvir	AbbVie	Oral	Mini-tablets	0.3 mg
1	Paritaprevir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Ritonavir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Dasabuvir	AbbVie	Oral	Mini-tablets	3.08 mg
1 & 2	Ribavirin	Kadmon/ AbbVie	Oral	Tablets	200 mg
1	Ribavirin	Merck	Oral	Solution	40 mg/mL
2	Ribavirin	MSD Sharp & Dohme	Oral	Solution	40 mg/mL

5.5.2.1 Packaging and Labeling

Part 1: Ombitasvir/paritaprevir/ritonavir tablets, dasabuvir tablets, all mini-tablets, RBV tablets or oral solution will all be provided in bottles. Each bottle will be labeled as required per country requirement. Labels must remain affixed to the bottles.

Part 2: Adult formulation ombitasvir/paritaprevir/ritonavir tablets and dasabuvir tablets will be provided in bottles. Ribavirin tablets and oral solution will be provided in bottles. All products will be labeled as required per country requirement and labels must remain affixed.

All blank spaces (if applicable) on the study drug labels should be completed by site staff prior to dispensing to subjects.

5.5.2.2 Storage and Disposition of Study Drugs

All study drugs, with the exception of the ribavirin oral solution, must be stored at controlled room temperature (15° to 25°C/59° to 77°F) according to labeled storage conditions. Ribavirin oral solution should be stored at refrigerated or controlled room temperature (2° to 30°C/36° to 86°F).

Part 1: Ombitasvir 0.3 mg, paritaprevir 1.0 mg, ritonavir 1.0 mg and dasabuvir 3.08 mg mini-tablets will be supplied to the site in bottles.

Mini-tablets can be administered in a dosing vehicle (e.g., applesauce, see dosing card for instructions).

RBV for both Part 1 and 2: RBV tablets and solution will be administered according to the local RBV label and provided by the sponsor to the sites. A dosing syringe for the RBV solution intake will be provided by the sponsor to the sites.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or returned to the AbbVie. Upon receipt of study drugs, the site will acknowledge receipt within the IRT system.

5.5.3 Method of Assigning Subjects to Treatment Groups

At the Screening Visit, all subjects will be assigned a unique subject number through the use of IRT. For subjects who do not meet the study selection criteria (or who are unable to enroll before enrollment has closed), the site personnel must contact the IRT system and identify the subject as a screen failure.

First, the subjects in the ≥ 12 to 17 year age group of Part 1 who are ≥ 45 kg and willing to swallow the adult formulations will be enrolled, then sequential enrollment into the other age groups of Part 1 will start (Section 5.1). Enrollment in Part 2 will begin once dosing recommendations of OBV, PTV, RTV and DSV are available for the ≥ 12 to 17 year-old age group based on the pharmacokinetic and clinical data from Part 1 of the study (Section 5.1). Subjects who are enrolled will retain their subject number assigned at the Screening Visit throughout the study. For enrollment of eligible subjects into the study, the site will utilize the IRT system in order to receive unique study drug kit numbers according to the regimen assigned (Table 5 and Table 6). In Part 1, the study drug kit numbers will be assigned to daily doses assigned to a site according to schedules

computer-generated before the start of the study by the AbbVie Data and Statistical Sciences Department.

In Part 1 of the study, caps on the number of subjects in each group in IRT will be employed to ensure that approximately 12 subjects in each age group are enrolled.

In Part 2 of the study, caps on GT1 and GT4 subjects will be employed in IRT to ensure that approximately 10 genotype 4-infected subjects regardless of prior treatment experience and cirrhotic status are enrolled.

Contact information and user guidelines for IRT use will be provided to each site.

5.5.4 Selection and Timing of Dose for Each Subject

Selection of the doses for this study is discussed in Section 5.6.5. The daily dose assigned to each subject in Part 1 will be assigned by IRT according to the formulation used and the weight of the subject. In Part 2, the study drugs will be provided in unit doses and the number of unit doses to be administered per day will be assigned by IRT according to the formulation used (to be determined from Part 1) and the weight of the subject.

Study drug dosing will be initiated at the Study Day 1 Visit. OBV, PTV, RTV will be dosed QD and DSV (if applicable) will be dosed BID. Thus with normal dosing, 1 dose of OBV, PTV, RTV and DSV (if applicable) should be taken in the morning, and 1 dose of DSV should be taken in the evening. RBV (if applicable) will be dosed according to the local label. RBV dose modifications will be assessed by the Investigator following the RBV Dose Modification Guideline (Table 12), taking into account the subject's clinical and safety parameters in conjunction with the Therapeutic Area Medical Director.

All study drugs should be dosed together and administered with food at approximately the same time in the morning every day, i.e., the AM dose of OBV, PTV, RTV, DSV (if applicable) and RBV (if applicable) should be taken together with food and the PM dose of DSV (if applicable) and RBV (if applicable) should be taken together and with food.

5.5.5 Blinding

This is an open-label study.

5.5.6 Treatment Compliance

The investigator or his/her designated and qualified representatives will administer/dispense study drug only to subjects enrolled in the study in accordance with the protocol. The study drug must not be used for reasons other than that described in the protocol.

All study drugs will be dispensed to subjects by study-site personnel under the direction of the investigator. At the start of the study, each subject along with their parent(s)/guardian(s) should receive counseling regarding the importance of dosing adherence with the treatment regimen with regard to virologic response and potential development of resistance. The start and stop dates of all study drugs will be recorded in the source documents and eCRFs. When dosing mini-tablets, the bottles should be checked thoroughly to ensure that no mini-tablets remained inside the bottle.

During the Treatment Period, subjects will be instructed to bring all study drug units (full, partial or empty) to the study site at each study visit. The study site personnel will inspect the contents of the study drug bottles and account for the returned study drug electronically at each Study Drug Accountability visit indicated in Appendix C. If poor adherence is noted, the subject and parent(s)/guardian(s) should be counseled and this should be documented in the subject's source document.

5.5.7 Drug Accountability

The investigator or his/her representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating the Proof of Receipt (POR) or similar document and via recording in the IRT system. A current (running) and accurate inventory of study drug will be kept per subject by the investigator. An overall accountability of the study drug will be performed and verified by the AbbVie monitor throughout the Treatment Period. The monitor will review study

drug accountability on an ongoing basis. Final accountability will be verified by the monitor at the end of study drug treatment at the site.

During the study, should an enrolled subject misplace or damage a study drug unit, the IRT system must be contacted and informed of the misplaced or damaged study drug. If the study drug unit is damaged, the subject will be requested to return the remaining study drug to the site. Replacement study drug may only be dispensed to the subject by contacting the IRT system. Study drug replacement(s) and an explanation of the reason for the misplaced or damaged study drug(s) will be documented within the subject's source. Date of the first dose and the last dose of the regimen will be documented in the subject's source documents and recorded on the appropriate eCRF.

The return status of each study drug unit and the date of reconciliation will be documented at Study Drug Accountability Visits in Appendix C.

Detailed instructions regarding study drug accountability are provided below.

Adult Formulations and RBV Tablets Part 1 and Part 2

The number of tablets of each type of study drug returned in each bottle will be noted in the IRT system and on a drug accountability log (if appropriate). Labels must remain affixed to the bottles.

Mini-Tablet Formulation (Part 1)

The status of each returned mini-tablet bottle will be noted in the IRT system and on a drug accountability log (if appropriate). The Investigator/designee must document the status of the returned bottles as full/sealed or empty or unsealed but not empty in the IRT system. Labels must remain affixed to the bottles.

RBV Solution Part 1

The status of each returned RBV solution bottle will be noted in the IRT system and on a drug accountability log (if appropriate). The Investigator/designee must document the

status of the returned RBV solution bottle as full/sealed or empty or unsealed but not empty in the IRT system. Labels must remain affixed to the bottles. Supporting drug accountability data will be transcribed by the Investigator/designee from the RBV solution diary into the EDC system.

Upon completion of or discontinuation from the Treatment Period, all original study drug units (containing unused study drugs) will be returned to the Sponsor (or designee) or destroyed on site. All destruction procedures will be according to instructions from the Sponsor and according to local regulations following completion of drug accountability procedures. All empty original study drug units shall be disposed of onsite following completion of study drug accountability and reconciliation procedures. Labels must remain attached to the study drug units.

5.6 Discussion and Justification of Study Design

5.6.1 Discussion of Study Design and Choice of Control Groups

The combination regimen of OBV, PTV, RTV, with DSV (GT1) or without DSV (GT4) and with RBV (GT1a and GT4) or without RBV (GT1b) for 12 or 24 weeks (GT1a cirrhotic subjects only) is currently approved in adults in several countries including the US and in the EU. The dose, durations, and regimens have been optimized for a given HCV genotype/sub-genotype and cirrhosis/non-cirrhosis status in adults. These same durations and regimens are anticipated to be similarly successful in children as long as the drug exposures are comparable, so further regimen/duration exploration is not warranted. In addition, no interferon-free regimens are approved for use in children; the approved standard of care (pegIFN/RBV) has notably lower efficacy rates and a worse safety profile than the interferon-free DAA regimens and requires a longer treatment duration, making a comparative study unethical and difficult to enroll. A non-randomized parallel study design with regimens/duration and drug exposure comparable to the recommended adult regimens is the best method for evaluation.

5.6.2 Appropriateness of Measurements

Standard pharmacokinetic, statistical, clinical, and laboratory procedures will be utilized in this study. HCV RNA assays are standard and validated. The EQ-5D-3L instrument is standard in the literature and thoroughly validated in studies of the pediatric population and in pediatric subjects who have chronic health conditions.

5.6.3 Justification of Primary and Secondary Endpoint Success Criteria

According to the Highlights of Prescribing Information of PEGASYS®, the SVR_{24} rate was 47% among 45 treatment-naïve pediatric subjects with HCV GT1 in the NV17424 trial.[1] To show that the DAA regimen is superior to this current standard of care by 20%, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%.

For the secondary endpoints of the percentage of subjects with SVR_{12} by formulation, age and weight group, the percentage of subjects with SVR_{24}, and the percentage of subjects with ALT normalization during treatment, the simple percentage will be calculated along with a 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%. ALT normalization is defined as the percentage of subjects with ALT at or below the upper limit of normal (ULN) at the final treatment visit among subjects with ALT > ULN at baseline, and will be presented along with a 2-sided 95% confidence interval.

5.6.4 Suitability of Subject Population

This study plans to enroll both HCV treatment-naïve and IFN (IFN and pegIFN with or without RBV) treatment-experienced subjects from ≥ 3 to 17 years old with genotype 1 or 4 HCV infection as agreed upon in the PIP and PSP. The older subjects who are willing to swallow the adult formulations and are ≥ 45 kg will be studied with the adult coformulated tablets. For the younger children in the ≥ 3 to 8 and ≥ 9 to 11 year old age groups, a mini-tablet formulation of all the DAAs and RTV will be used for ease of

administration. In addition, RBV oral solution will be available in the study for children who cannot take the RBV tablets.

5.6.5 Selection of Doses in the Study

In the Pediatric Investigation Plans (PIP) and the Pediatric Study Plan (PSP) for ombitasvir/paritaprevir/ritonavir and dasabuvir, the proposed pediatric doses were based on providing comparable exposures to adult subjects.

AbbVie has recently developed separate mini-tablet formulations for ombitasvir, paritaprevir, ritonavir and dasabuvir for use in Part 1 of the present study.

The mg/kg doses as proposed in the PIP and PSP were used to calculate mg doses for a given weight range for each of the age groups. While this approach involved some approximation of doses, it provides a simplified approach and is expected to help reduce potential dispensing and dosing errors while meeting the objectives of the weight based dosing. This approach is further supported by the wide margin of safety/efficacy for each DAA.

In the global Phase 3 program, 30 adult HCV GT1-infected subjects had body weight ranging from 42 to 49 kg. The exposures of ombitasvir, paritaprevir, ritonavir and dasabuvir in these subjects were within the ranges of exposures in subjects who had body weight of at least 50 kg. The established safety and efficacy of the 3D regimen in adults would support the use of the same adult dose of ombitasvir/paritaprevir/ritonavir 25/150/100 mg QD and dasabuvir 250 mg BID in children who weigh at least 42 kg. For the present study, children who weigh at least 45 kg will be dosed with adult dose if they are willing to swallow the adult formulations.

For Part 1 of the present study, the proposed doses by body weight range for subjects administered the adult formulation or the mini tablet formulation are shown in Table 11.

Table 11. Proposed DAA and Ritonavir Doses for Subjects Administered the Adult Formulation or Mini Tablet Formulation

	Body Weight		
	15 to 29 kg	**30 to 44 kg**	**≥ 45 kg**
Paritaprevir (QD)	50 mg	100 mg	150 mg
Ritonavir (QD)	35 mg	70 mg	100 mg
Ombitasvir (QD)	10 mg	15 mg	25 mg
Dasabuvir (BID)	100 mg	150 mg	250 mg

For Part 1, enrollment will start with pediatric subjects ≥ 12 to 17 years old who are ≥ 45 kg and willing to swallow the adult formulations. The pharmacokinetic and clinical data will be used to confirm appropriate exposure in this age group. Dose adjustments will be made if necessary to ensure safe and efficacious exposures that are comparable to the adult population.

Enrollment in Part 2 will only begin after the recommendations of adult 3D formulation are determined ≥ 12 to 17 years based on the pharmacokinetic, safety and efficacy data from Part 1 of the study.

Details on the dose adjustment considerations for Part 1, the enrollment sequence in Part 1, and the considerations for enrollment in Part 2 are provided in Section 5.1.

5.6.6 Maximum Dose

For Part 1, the maximum dose of OBV, PTV and RTV will not exceed 25 mg, 150 mg, and 100 mg per day for 12 weeks. The maximum dose of DSV will not exceed 500 mg per day for 12 weeks. For subject receiving RBV, the maximum RBV dose will not exceed 1200 mg, divided twice daily for 12 weeks.

For Part 2, the maximum dose of OBV, PTV and RTV will not exceed 25 mg, 150 mg, and 100 mg per day for 12 or 24 weeks depending on HCV genotype, sub-genotype and cirrhosis status. For HCV GT1-infected subjects, the maximum dose of DSV will not

exceed 500 mg per day for 12 or 24 weeks. For subject receiving RBV, the maximum RBV dose will not exceed 1200 mg, divided twice daily for 12 or 24 weeks.

6.0 Complaints

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

For adverse events, please refer to Sections 6.1 through 6.1.7.6.

6.1 Medical Complaints

The investigator will monitor each subject for clinical and laboratory evidence of adverse events on a routine basis throughout the study. The investigator will assess and record any adverse event in detail including the date of onset, event diagnosis (if known) or sign/symptom, severity, time course (end date, ongoing, intermittent), relationship of the adverse event to study drug, and any action(s) taken. For serious adverse events considered as having "no reasonable possibility" of being associated with study drug, the investigator will provide an "Other" cause of the event. For adverse events to be considered intermittent, the events must be of similar nature and severity. Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded.

All adverse events will be followed to a satisfactory conclusion.

6.1.1 Definitions

6.1.1.1 Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore

be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) 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 protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Worsening in severity of a reported adverse event should be reported as a new adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events only if they result in discontinuation from the study, necessitate therapeutic medical intervention, (meets protocol specific criteria [see Section 6.1.7 regarding toxicity management]) and/or if the investigator considers them to be adverse events.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition or the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

6.1.1.2 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event (SAE) within 24 hours of the site being made aware of the serious adverse event.

Death of Subject	An event that results in the death of a subject.
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 or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or admission to an outpatient facility.
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 subject. 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 subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, 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.

For serious adverse events with the outcome of death, the date and cause of death will be recorded on the appropriate case report form.

6.1.2 Adverse Event Severity

The investigator will rate the severity of each adverse event according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE Version 4).

The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is available from the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf and is to be used in the grading of adverse events. Below are the general grading categories. However, the investigator should always search NCI CTC AE for a given diagnostic/symptomatic AE term to identify and apply specific grading details for that AE entity.

Grading System for Adverse Events *(a semi-colon indicates 'or' within the description of the grade).*

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL*
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**
Grade 4	Life-threatening consequences; urgent intervention indicated
Grade 5	Death related to AE

ADL = Activities of Daily Living

* Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.

** Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.1.3 Relationship to Study Drug

The investigator will use the following definitions to assess the relationship of the adverse event to the use of (OBV/PTV/RTV with or without DSV) and to the use of RBV (if applicable):

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the study drug and the adverse event.

No Reasonable Possibility	An adverse event where there is no evidence to suggest a causal relationship between the study drug and the adverse event.

For causality assessments, events assessed as having a reasonable possibility of being related to the study drug will be considered "associated." Events assessed as having no reasonable possibility of being related to study drug will be considered "not associated." In addition, when the investigator has not reported a causality or deemed it not assessable, AbbVie will consider the event associated.

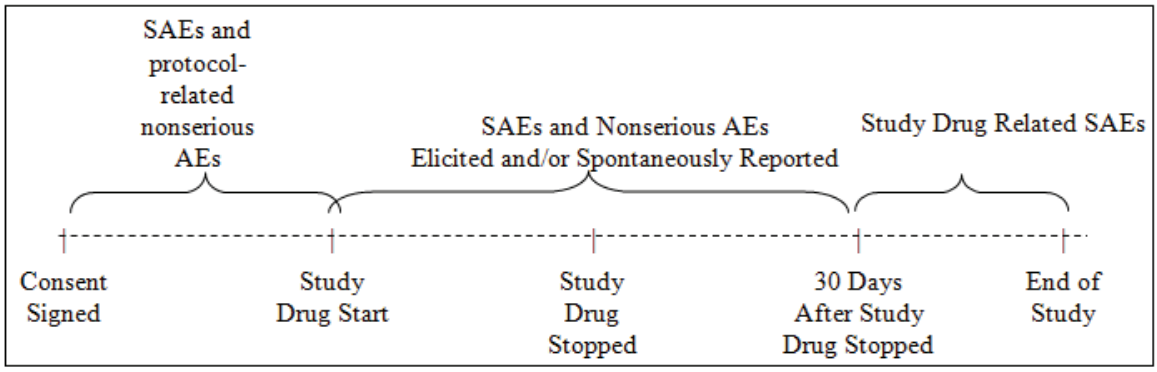
If an investigator's opinion of no reasonable possibility of being related to study drug is given, an "Other" cause of event must be provided by the investigator for the serious adverse event.

6.1.4 Adverse Event Collection Period

All serious adverse events as well as protocol-related nonserious adverse events (e.g., infection at venipuncture site) will be collected from the time the parent(s)/guardian(s) and subject signs the study-specific informed consent and assent (as appropriate for age and country) respectively until study drug administration. From the time of study drug administration until 30 days following discontinuation of study drug treatment has elapsed, all adverse events and serious adverse events will be collected, whether solicited or spontaneously reported by the subject. From 30 days following discontinuation of study drug administration until the end of study, only serious adverse events deemed related to study drug by the investigator will need to be collected.

Adverse event information will be collected as shown in Figure 2.

Figure 2. Adverse Event Collection



6.1.5 Adverse Event Reporting

In the event of a SAE, whether associated with study drug or not, the Investigator will notify Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. For SAEs that occur prior to the site having access to the RAVE® system or if RAVE is not operable, the forms should be faxed or emailed to Clinical Pharmacovigilance within 24 hours of the site being made aware of the SAE.

FAX to: +1 (847) 938-0660

Email: PPDINDPharmacovigilance@AbbVie.com

For safety concerns, contact the Antiviral Safety Team at:

Antiviral Safety Management
Dept. R48S, Bldg. AP30-3
AbbVie Inc.
1 North Waukegan Road
North Chicago, IL 60064
Office: (847) 938-1870
Email: SafetyManagement_Virology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Telephone Contact Information:
Office:
Mobile:
Fax:
Email: [redacted]

In case of subject safety concerns or medical emergencies, where the primary Therapeutic Area Medical Director be unavailable, please call the following central back-up number:

Phone: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC. The reference document used for SUSAR reporting in the EU countries will be the most current version of the Investigator's Brochure.

6.1.6 Pregnancy

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, which is defined as from Study Day 1 until 30 days after the last dose of study drug if subjects do not take RBV, or from Study Day 1 until 6 months for WOCBP and 9 months for males after the last dose of the study drug containing RBV (or per local RBV label).

Pregnancy in a study subject must be reported to the AbbVie within 1 working day of the site becoming aware of the pregnancy. Subjects who report a positive pregnancy test during the Treatment Period must be notified to stop RBV (if applicable) immediately. Administration of DAAs may be continued at the investigator's discretion after discussion with the subject, if the benefit of continuing therapy is felt to outweigh the potential risk (as allowed per local guidance) (Section 5.4.1).

Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected for pregnancies occurring up to 30 days after the end of treatment with DAAs only, or through Post-Treatment Week 28 (or per local RBV label) after the last dose of RBV for treatment with DAAs plus RBV. The investigator is encouraged to report the pregnancy information to the voluntary RBV Pregnancy Registry, if RBV is included within the regimen.

Subjects who discontinue study medications due to pregnancy will be monitored for SVR in the Post-Treatment Period as described in Section 5.4.1.

Pregnancy in a study subject is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a serious adverse event and must be reported to the Sponsor within 24 hours of the site becoming aware of the event.

6.1.7 Toxicity Management

For the purpose of medical management, all adverse events and laboratory abnormalities that occur during the study must be evaluated by the investigator. All adverse events and laboratory abnormalities will be managed and followed to a satisfactory clinical resolution. The table of clinical toxicity grades "National Cancer Institute Common Terminology Criteria for Adverse Events, Version 4" is to be used in the grading of adverse events and laboratory abnormalities which is available on the Cancer Therapy Evaluation Program (CTEP) website at: http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

A drug-related toxicity is an adverse event or laboratory value outside of the reference range that is judged by the investigator or the Sponsor as having a "reasonable possibility" of being related to the study drug (Section 6.1.3). A toxicity is deemed "clinically significant" based on the medical judgment of the investigator. Laboratory abnormalities will be managed as deemed clinically appropriate by the investigator until satisfactory resolution.

Investigators should avoid interrupting study drugs for more than 7 consecutive days. The Investigator should ensure that any study drug interruptions or RBV (if applicable) dose modifications and associated adverse events are promptly entered into the appropriate eCRFs.

The toxicity management guidelines below should be followed throughout the Treatment Period of the study.

6.1.7.1 Grade 1 or 2 Laboratory Abnormalities and Mild or Moderate Adverse Events

Subjects who develop a mild or moderate adverse event or Grade 1 or 2 laboratory abnormality, other than those discussed separately in Section 6.1.7.4 (Management of Decreases in Hemoglobin) for subjects receiving RBV, Section 6.1.7.5 (Management of ALT Elevations), and Section 6.1.7.6 (Creatinine Clearance) may continue study drugs with follow-up per study protocol and in accordance with local standard of care.

6.1.7.2 Grade 3 or 4 Laboratory Abnormalities

With the exception of Grade 3 or higher abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides, or glucose (in subjects with a history of diabetes), if a subject experiences a Grade 3 or greater abnormal laboratory parameter during the Treatment Period, the abnormal laboratory test should be repeated. If the Grade 3 or greater abnormality is confirmed, the investigator should assess whether the abnormality can be managed medically without interruption of study drug, or whether study drugs should be interrupted and the laboratory parameter followed until it improves.

If study drugs are interrupted and restarted and the abnormality recurs, then study drugs should be permanently discontinued.

Decreases in serum hemoglobin or in calculated creatinine clearance or elevations of serum ALT should be managed according to the guidance in Section 6.1.7.4, Section 6.1.7.5, and Section 6.1.7.6 below. Grade 3 or greater abnormalities of total bilirubin, uric acid, phosphorus, total cholesterol, triglycerides or glucose (in subjects with a history of diabetes) should be managed medically as appropriate and do not require confirmation or study drug interruption unless deemed necessary by the investigator.

6.1.7.3 Severe Adverse Events or Serious Adverse Events

If a subject experiences a severe adverse event (Grade 3+) or a serious adverse event that the investigator considers to have a reasonable possibility of relationship to study drug, the investigator should assess whether the adverse event can be managed medically without interruption of study drug, or whether study drugs should be interrupted until the event improves. If study drugs are interrupted and restarted and the adverse event recurs, then study drugs should be permanently discontinued.

If a subject experiences a severe adverse event (Grade 3+) or serious adverse event that is considered unrelated (no reasonable possibility) to the study drugs, it is not necessary to interrupt study drugs unless an interruption is required because of the nature of the event (e.g., unable to take oral medications).

The investigator should ensure that all serious adverse events are reported to AbbVie within 24 hours of awareness. Serious adverse event follow-up information, including associated dose interruptions (or discontinuations), must be reported to AbbVie within 24 hours of awareness by entering updated SAE information into the appropriate eCRFs.

Severe adverse events and any associated dose interruptions (or discontinuations) should be entered into the appropriate eCRFs.

6.1.7.4 Management of Decreases in Hemoglobin

For subjects not receiving ribavirin:

Hemoglobin decreases should be managed according to grade based on the guidance in Section 6.1.7.1 and Section 6.1.7.2 above.

For subjects receiving ribavirin:

Decreases in hemoglobin are a well characterized side effect of ribavirin exposure. If a subject receiving the standard dose of RBV experiences a hemoglobin decrease meeting one of the criteria outlined in Table 12, a confirmatory test should be performed. If the hemoglobin decrease is confirmed, the management guidelines in Table 12 should be followed. Management will be different for subjects without a history of known cardiac disease and subjects with known cardiac disease. Subjects experiencing decreases in hemoglobin that do not meet the criteria outlined in Table 12 may need hemoglobin evaluations at more frequent intervals at the discretion of the investigator.

In subjects with creatinine clearance less than 50 mL/min, RBV should be interrupted if subject experiences a confirmed decrease in hemoglobin to less than 10 g/dL. In these subjects, decreases in hemoglobin should be managed at the discretion of the investigator and as medically appropriate.

Use of hematologic growth factors (such as erythropoietin or filgrastim) or blood transfusions are permitted at the discretion of the investigator. Management of hematologic growth factor therapy is the responsibility of the Investigator, and growth factors will not be provided by AbbVie.

Alternate management of hemoglobin decreases outside of these criteria is permitted with approval of the AbbVie Therapeutic Area Medical Director.

Table 12. Ribavirin Dose Modification Guidelines in Management of Hemoglobin Decreases

Subjects with Creatinine Clearance ≥ 50 mL/min		
	Reduce RBV Daily Dose[a] if:	**Interrupt RBV[b] if:**
Hemoglobin in Patients with No Cardiac Disease	< 10 g/dL	< 8.5 g/dL
Hemoglobin in Patients with History of Stable Cardiac Disease	≥ 2 g/dL decrease in hemoglobin during any 4 week treatment period (permanent dose reduction)	< 12 g/dL despite 4 weeks at reduced RBV dose

a. Reduce RBV daily dose in accordance with local RBV prescribing information/product label or per the discretion of the investigator.

b. If the abnormality is reversed, RBV may be restarted at the discretion of the investigator and in accordance with local RBV prescribing information/product label.

6.1.7.5 Management of ALT Elevations

Transient asymptomatic grades 3 – 4 ALT elevations have been observed in approximately 1% of subjects receiving paritaprevir/r-containing regimens. If a subject experiences a post-baseline increase in ALT to > 5 × ULN that is increased from the previous measurement, the subject should have a confirmatory ALT measurement performed.

If the ALT increase is confirmed to be > 5 × ULN and increased from the previous measurement, the recommendations below should be followed:

- Evaluate for alternative etiology of ALT elevation: update medical history and concomitant medications eCRF (if applicable), and obtain additional testing as appropriate.
- Manage the subject as medically appropriate.
- Repeat ALT, AST, total and fractionated bilirubin, alkaline phosphatase and
- INR within 1 week. Repeat liver chemistries as indicated until resolution.
- Consider discontinuing study drugs if ALT level is persistently > 10 × ULN.
- Discontinue study drugs if the following is observed at any time:

- Increasing direct bilirubin, increasing INR, or onset of symptoms/signs of hepatitis.

Alternate management of ALT increases is permitted with approval of the AbbVie Therapeutic Area Medical Director.

6.1.7.6 Creatinine Clearance

If calculated creatinine clearance (by Schwartz formula for children aged 3 to < 12 years and Crockcroft-Gault formula for children ≥ 12 years) is confirmed to have decreased to < 50 mL/minute, medical evaluation should include a full review of current medications, including those taken on an as needed basis, those which are sold over the counter and any dietary and herbal supplements, and appropriate dose reduction or discontinuation based on impaired renal function should be done (if applicable). Ribavirin dose should be adjusted according to local RBV prescribing information/product label or per the discretion of the investigator. Alternative management of RBV dose in the setting of reduced renal function will require approval of the AbbVie Therapeutic Area Medical Director.

Schwartz formula (children 3 to < 12 years old):

GFR Estimate = [Height (cm) × 0.55] /
[Serum creatinine (μmol/L) × 0.01131]

Crockcroft-Gault formula (Children ≥ 12 years old):

CrCl = [(140 – Age) × Mass (in kg) × (0.85 if female)] /
[72 × Serum creatinine (in mg/dL)]

The investigator should also consider whether drug-drug interactions with concomitant medications may have contributed to the decrease in creatinine clearance, and whether discontinuation or substitution of the possible interacting drug might be needed. For example, drug interactions between DAAs and some antihypertensive medications could

potentially increase exposures of the antihypertensive, which may lead to reduction in renal function. If anti-hypertensive medications are adjusted, vital signs should be monitored to ensure appropriate blood pressure control. Refer to Section 5.2.3 for additional information regarding drug-drug interactions.

If creatinine clearance improves, the site should perform all necessary readjustment of any dose modifications that have been made. If creatinine clearance improves to above the level that triggered the RBV dose reduction, RBV dose may be increased accordingly.

The Investigator should ensure that any concomitant medication changes, RBV dose reductions, and study drug discontinuations, as well as consequent related adverse events are entered into the appropriate eCRFs.

7.0 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol. The principal investigator is responsible for complying with all protocol requirements, and applicable global and local laws regarding protocol deviations. If a protocol deviation occurs (or is identified) after a subject has been enrolled, the principal investigator is responsible for notifying Independent Ethics Committee (IEC)/Independent Review Board (IRB) regulatory authorities (as applicable), and the following AbbVie Clinical Personnel:

Primary Contact US/PR:	Primary Contact OUS:	Secondary Contact:
[redacted] 1 North Waukegan Road North Chicago, IL 60064 Office: [redacted] Fax:	[redacted] Medical Department Avenida de Burgos, 91 28050 Madrid, Spain Office: [redacted] Fax:	[redacted] AbbVie Deutschland GmbH & Co. KG Knollstrasse 67061 Ludwigshafen, Germany Office: [redacted] Fax:

Such contact must be made as soon as possible to permit a review by AbbVie to determine the impact of the deviation on the subject and/or the study.

8.0 Statistical Methods and Determination of Sample Size

8.1 Statistical and Analytical Plans

The pharmacokinetic analysis will be performed separately for Part 1 and Part 2. For population pharmacokinetic analyses, data from Part 1 and Part 2 will be combined if needed. The efficacy, resistance, growth and development and safety analyses will be performed across Parts 1 and 2 combined. Analyses on durability of response, resistance, growth and development outcome, patient-reported outcome, and clinical outcomes will be performed through Post-Treatment Week 24 in Parts 1 and 2 and after Post-Treatment Week 24 for all subjects who enter Part 3.

An interim analysis will occur once all subjects complete PT Week 12 or prematurely discontinue from the study. Final analysis will occur after the completion of the whole study.

SAS® (SAS Institute, Inc., Cary, NC) for the UNIX operating system will be used for all analyses. All statistical tests and all confidence intervals will be two-sided with an α level of 0.05.

The intention-to-treat populations, ITT will consist of all subjects who receive at least one dose of study drug in Part 1 or Part 2 of the study. The intention-to-treat population for Part 3, ITT-3, will consist of all subjects who enter Part 3.

Efficacy endpoints and growth and development outcomes will be summarized across Parts 1 and 2 for the ITT population. Growth outcomes including standardized height, waist circumference, Tanner pubertal stage, and growth rate as defined in protocol Section 5.3.1.1 will be summarized through Post-Treatment Week 24 in Parts 1 and 2 and through the end of Long-term Follow-up in Part 3, for ITT-3.

No data will be imputed for any efficacy or safety analyses except for analyses of the SVR endpoints. For EQ-5D-3L health state index, no imputation will be performed for missing items.

HCV RNA values will be selected for the SVR_{12} and SVR_{24} analyses based on defined visit windows. When there is no HCV RNA value in a visit window based on defined visit windows, 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 subject has a missing HCV RNA value at a post-baseline visit but with undetectable or unquantifiable HCV RNA levels at both the preceding value and succeeding value, the HCV RNA level will be considered undetectable or unquantifiable, respectively, at this visit for this subject. For SVR_{12} and SVR_{24} analysis, if there is no value in the appropriate window but there is an HCV RNA value after the window, then it will be imputed into the SVR_{12} or SVR_{24} window, respectively. Subsequent to this flanking imputation, if a subject is missing a value for the visit window associated with the analysis, the subject will be imputed as a visit failure (i.e., not undetectable or unquantifiable).

The 95% confidence interval for any simple percentage (e.g., SVR_{12}, SVR_{24}, and percentage of subjects with ALT normalization) will be calculated using normal approximation to the binomial distribution if the percentage is not 0% or 100%; otherwise, Wilson's score method will be used.

Detailed statistical methods for all endpoints will be provided in the Statistical Analysis Plan (SAP).

8.1.1 Demographics

Demographics and baseline characteristics will be summarized by age and weight group separately for each formulation, for all subjects and for all subjects on the adult formulations in the ITT and ITT-3 populations. The baseline value refers to the last non-missing measurement collected before the first dose of study drug is received in Part 1 and on or before Day 1 in Part 2. Demographics include age, birth year, weight, height, body mass index (BMI), height z score (height z score will be calculated using WHO published height-for-age z-score tables), waist circumference, gender, race, ethnicity, geographic region and country. Baseline characteristics will include HCV genotype and sub-genotype (1a, 1b, 1-other and 4 if applicable), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), IFN treatment history if applicable (treatment-naïve or IFN-based treatment-experienced [prior non-responder {null responder, partial responder, or other unable to specify}, breakthrough, relapse, and interferon experienced-other]), baseline platelets (< 90 or $\geq 90 \times 10^9$/L), baseline albumin (< 35 or ≥ 35 g/L), baseline HCV RNA levels (continuous) and ($< 800{,}000$ IU/mL or $\geq 800{,}000$ IU/mL, baseline fibrosis stage [F0-1, F2, F3, F4]), baseline Fibrotest score, baseline Child-Pugh score (non-cirrhotic, 5, 6, or > 6), tobacco use (user, ex-user, or non-user) status, alcohol use (drinker, ex-drinker, or non-drinker) status, and baseline Tanner pubertal staging – genital (males only), breast (females only), and pubic hair development. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and height z-score). The number and percentage of subjects will be presented for categorical variables (e.g., gender and race).

8.1.2 Efficacy

Efficacy analyses will be performed across Part 1 and Part 2 using the ITT population.

Plasma HCV RNA levels will be determined for each sample collected by the central laboratory using the COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0. For this assay, the lower limit of quantification (LLOQ) and the lower limit of detection are 15 IU/mL. HCV RNA results that are detectable but not quantifiable are reported as "HCV RNA is detected, less than 15 IU/mL HCV RNA." HCV RNA results for which no HCV RNA is detected are reported as "HCV RNA not detected."

8.1.2.1 Primary Efficacy Endpoint Across Parts 1 and 2

The primary efficacy endpoint is the percentage of subjects with SVR12 among all subjects. The 95% confidence interval for the SVR rate will be calculated.

To evaluate the hypothesis that the percentage of HCV pediatric subjects treated with ombitasvir/paritaprevir/r, with or without dasabuvir with or without RBV who achieve SVR_{12} is superior to the historical SVR rate for the pediatric population treated with pegIFN and RBV, the lower bound of the 2-sided 95% CI of the percentage of subjects with SVR_{12} must be greater than 67% (Section 5.6.3).

8.1.2.2 Secondary Efficacy Endpoints Across Parts 1 and 2

1. The percentage of subjects who achieve SVR_{12} by formulation, age and weight group, and across all subjects on the adult formulations.
2. The percentage of subjects who achieve SVR_{24} by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.
3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation, age, and weight group, across all subjects, and across all subjects on the adult formulations.

The percentage of subjects with SVR_{12} or SVR_{24} and the percentage of subjects with ALT normalization during treatment, the simple percentage will be calculated along with the 2-sided 95% confidence intervals. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%. ALT normalization is defined as the percentage of subjects with ALT at or below the ULN at the final treatment visit among all treatment naïve subjects with ALT > ULN at baseline, and will be presented along with 95% confidence intervals.

8.1.2.3 Additional Efficacy Endpoints Across Parts 1 and 2

The following efficacy endpoints will be analyzed by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations:

1. The percentage of subjects with virologic failure during treatment;
2. The percentage of subjects with Post-Treatment relapse (including $Relapse_{12}$ as defined at the end of this section);
3. Change from baseline to all post-baseline visits in Fibrotest score.

If the dose of the mini-tablets is adjusted for any age or weight group during the study, any subjects administered the dose considered not acceptable will be removed in a sensitivity analysis of SVR_{12} among subjects administered acceptable doses of OBV, PTV, RTV and DSV.

All rates of SVR, ALT normalization, virologic failure on treatment and relapse will be presented with 2-sided 95% confidence intervals.

On-treatment virologic failure is breakthrough or failure to suppress during treatment. Breakthrough is defined as confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurement > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment. Failure to suppress during treatment is defined as all on-treatment values of HCV RNA

≥ LLOQ with at least 6 weeks (defined as active study drug duration ≥ 36 days) of treatment.

$Relapse_{12}$ defined as confirmed HCV RNA ≥ LLOQ between end of treatment and 12 weeks after last actual dose of active study drug (up to and including the SVR_{12} assessment time point) for a subject with HCV RNA < LLOQ at Final Treatment Visit who completes treatment. Completion of treatment is defined as a study drug duration ≥ 77 days for a subject assigned to 12 weeks of treatment and ≥ 154 days for a subject assigned to 24 weeks of treatment).

The change from baseline to each post baseline visit of collection for Fibrotest will be summarized descriptively.

8.1.2.4 Subgroup Analysis of Parts 1 and 2

The percentage of subjects with SVR_{12} will be presented along with the 2-sided 95% confidence interval for the following subgroups if applicable.

- Age (≥ 3 – 8, ≥ 9 – 11, and ≥ 12 – 17 years);
- HCV genotype and sub-genotype (1a, 1b, other 1, and 4);
- Presence of compensated cirrhosis (yes/no);
- Treatment IFN (IFN or pegIFN with or without RBV) experience if applicable (treatment naïve, prior non-responder, prior breakthrough, prior relapse, and interferon experienced-other);
- IL28B genotype (CC or non-CC), (CC, CT, or TT);
- Sex (male or female);
- Baseline Child-Pugh Score (non-cirrhotic, 5 or ≥ 6);
- Baseline fibrosis stage (F0-F1, F2, F3 or F4);
- Baseline HCV RNA level (< 800,000 IU/mL or ≥ 800,000 IU/mL);
- Race (Black versus non-black);
- Ethnicity (Hispanic/Latino versus none);
- Height z-score (< –1, –1 to 1 or > 1);

- Drug compliance (< 80% versus ≥ 80%).

For cirrhotic subjects, the following subgroups will be presented:

- Baseline platelets (< 90, ≥ 90 × 10^9/L)
- Baseline albumin (< 35, ≥ 35 g/L)
- Any of platelets < 90 × 10^9/L and albumin < 35 g/L

The two-sided 95% confidence intervals will be produced if there are at least 10 subjects in the subgroups.

8.1.2.5 Treatment Failures

Across Parts 1 and 2, the number and percentage of subjects overall, on the adult formulations, and on the mini-tablet formulation meeting each and any of the following SVR_{24} and SVR_{12} non-response categories will summarized. The summary might also be subgrouped by age and weight group, and HCV genotypes/sub-genotypes.

1. On-treatment virologic failure (breakthrough or fail to suppress)
2. Relapse (with further breakdown by relapse vs reinfection based on HCV RNA population sequence)
3. Premature study drug discontinuation with no on-treatment virologic failure
4. Missing SVR data (SVR_{24} or SVR_{12})
5. Other

8.1.3 Growth and Development

The following growth and development endpoints will be calculated through Post-Treatment Week 24 in Parts 1 and 2 for the ITT population, and in Part 3 for the ITT-3 population for later visits.

- Growth rate at each post baseline visit (defined as change in height over change in age from the previous visit)
- Height z score[27]
- Waist circumference
- Tanner staging

For growth rate and height z score, summary statistics (N, mean and SD together, median and range together) will be provided at each applicable post baseline visit for all and by gender for each pre-defined age group separately. For height z score only, summary statistics of change from baseline (N, mean and SD together, median and range together) will be summarized over time at each applicable study visit for all and by gender for each pre-defined age group separately. Change from baseline in waist circumference, weight and height will be summarized together with other vital signs such as temperature and blood pressure. Listings of Tanner staging for each applicable subject over applicable timepoints will be produced.

8.1.4 Patient Reported Outcomes

During Treatment and Post-Treatment, health utility values will be assessed using the EQ-5D-3L instrument. The health state data measured by EQ-5D-3L will not be analyzed until validated weights are available for pediatric subjects to convert health states to a single summary index.

For subjects enrolled in Part 1 and 2 (ITT), summary statistics at each visit and on the change from baseline to each visit (n, mean, SD, minimum and maximum) of EQ VAS score will be provided. In particular, for each of the three visits – EOT, PT Week 12 and PT Week 24, the mean change from baseline in EQ VAS score, will be analyzed using ANCOVA with appropriate baseline fibrosis stage, gender, and age group as factors, and baseline EQ VAS score and SVR status as covariates. For subjects enrolled in Part 3 (ITT-3), summary statistics at each visit and the change from baseline to each applicable post-baseline visit (n, mean, SD, minimum and maximum) in EQ VAS score will be provided.

8.1.5 Acceptability Questionnaire

For each subject taking the mini-tablet formulation, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form at the visits indicated in Appendix C.

The number and percentage of subjects with each categorical answer marked will be presented for each question in the acceptability questionnaire at each applicable treatment visit overall, by age and weight group. Listings of acceptability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced.

8.1.6 Safety

All subjects who receive at least one dose of study drug will be included in the safety analyses. The safety analysis will be carried out for all subjects by formulation, age and weight group, for all subjects on the adult formulation. A listing of any SAEs recorded in Part 3 will be included.

8.1.6.1 Adverse Events

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent adverse events (i.e., any 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 System Organ Class (SOC) and preferred term (PT). The tabulation of the number of subjects with treatment-emergent adverse events by grade (Grades 1 – 5) and relationship to study drug also will be provided.

Additional analyses will be performed if useful and appropriate.

8.1.6.2 Clinical Laboratory Data

Clinical laboratory tests will be summarized at each visit. The baseline value will be the last measurement prior to the initial dose of study drug. 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 of the laboratory used in this study. The number and percentage of subjects who experience post-baseline shifts during treatment in clinical laboratory values from low/normal to high and high/normal to low based on the normal range will be summarized.

In addition, the number and percentage of subjects with post-baseline values meeting pre-specified criteria for Potentially Clinically Significant laboratory values during treatment will be summarized. Additional analyses will be performed if useful and appropriate.

8.1.6.3 Vital Signs Data

Mean changes in temperature, systolic and diastolic blood pressure, pulse, weight, height, and waist circumference from Day 1 to each post baseline visit will be summarized descriptively. Number and percentage of subjects with post-baseline values meeting pre-defined criteria for Potentially Clinically Significant vital signs values during treatment will be summarized.

8.1.7 Resistance Analysis

All subjects who receive at least 1 dose of study drug in Part 1 or Part 2 will be followed to monitor the development and persistence of antiviral drug resistance by population, deep, and/or clonal sequencing (in subjects who experience virologic failure).

The genes of interest for sequencing in this study are those encoding NS3 amino acids 1 to 181, NS5A amino acids 1 to 215, and (only in subjects receiving DSV) NS5B amino acids 300 to 591. For each DAA target, resistance-associated signature amino acid

variants will be identified by AbbVie Clinical Virology. Only samples with an HCV RNA level of ≥ 1000 IU/mL will undergo sequence analysis in order to allow accurate assessment of the products of amplification. Therefore if the HCV RNA level at the time of virologic failure is < 1000 IU/mL, the sample closest in time after the failure with an HCV RNA level ≥ 1000 IU/mL will be used if available.

The prototypic reference strains with their associated GenBank Accession IDs for sequence analyses are GT1a-H77 (NC_004102) and 1b-Con1 (AJ238799). For genotype 4, ED43 (GenBank Accession ID GU814265) will be used for all samples except those identified by phylogenetic analysis as sub-genotype 4d, for which genotype 4d strain QC382 (GenBank Accession ID FJ462437) will be used. A 329 nucleotide region of NS5B will be PCR amplified and sequenced from the baseline sample from all genotype 4-infected subjects. Phylogenetic analysis will be conducted on the resulting sequences in order to accurately determine the genotype 4 sub-genotype.[29]

The following definitions will be used in the resistance analyses:

- Baseline variant: a variant (by population or deep sequencing) in a baseline sample determined by comparison of the amino acid sequence of the baseline sample to the appropriate prototypic reference amino acid sequence for a given DAA target (NS3, NS5A, or NS5B).
- Post-baseline variant by population or deep sequencing: an amino acid variant in a post-baseline time point sample that was not detected at baseline and is detectable by population or deep sequencing.
- Post-baseline variant by clonal sequencing: a variant at a signature resistance associated amino acid position that was not present by population or deep sequencing at baseline in a subject that is detected in a post-baseline sample by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).
- Linked variant by population or deep sequencing: variants at 2 or more signature resistance-associated amino acid amino acid positions identified within a target by population or deep sequencing, and no mixture of amino acids is detected at any of those positions.

- Post-baseline variant by clonal sequencing: a variant at a signature resistance-associated amino acid position that was not present by population or deep sequencing at baseline in a subject that is detected in a post-baseline sample by clonal sequencing in at least 2 clones from that sample (among the subset of subjects for whom clonal sequencing is performed).

For subjects who have population or deep sequencing performed on baseline samples, a listing by subject of all baseline variants relative to the appropriate prototypic reference sequence at signature resistance-associated amino acid positions will be provided for each DAA target. In addition, a summary of the number and percentage of subjects with each baseline variant at a signature resistance-associated amino acid position within each target by HCV sub-genotype out of the total number of baseline samples sequenced will also be provided.

The following analyses will be performed on the samples from subjects who experience virologic failure and have post-baseline resistance data available.

The HCV amino acid sequence as determined by population or deep sequencing at the time of virologic failure or the sample closest in time after virologic failure with an HCV RNA level of $\geq$ 1000 IU/mL will be compared with the baseline sequence and with the appropriate prototypic reference amino acid sequence. A listing by subject of all post-baseline variants at signature resistance-associated amino acid positions detected by population or deep sequencing relative to the baseline amino acid sequences will be provided for each DAA target. In addition, a listing by subject of all post-baseline variants (by population or deep sequencing) at signature resistance-associated amino acid positions relative to the appropriate prototypic reference amino acid sequences will be provided.

Linkage between variants at signature resistance-associated amino acid positions by population or deep sequencing will also be evaluated. A listing by subject and time point of the linked variants will be provided.

For the subset of samples for which clonal sequencing is performed, the amino acid variants determined by clonal sequencing will be summarized by counting the number of clones whose amino acid sequence at signature resistance-associated positions does not match that of the population baseline sequence by subject at each time point and amino acid position, out of the total number of clones analyzed. Listings by subject of post-baseline variants at signature resistance-associated positions detected by clonal sequencing (≥ 2 clones per sample) will be provided for each DAA target.

For all subjects who experience virologic failure for whom resistance analyses are performed, the persistence of resistance-associated substitutions at signature resistance associated amino acid positions for each target will be assessed by population, deep, and/or clonal sequencing at Post-Treatment Week 24 and at various time points during the LTFU period. However, if resistance-associated variants are not detected in a given target for a subject at the time of virologic failure, then that target may not be sequenced in subsequent samples from that subject. Listings by subject and time point of all variants at signature resistance-associated amino acid positions relative to the baseline amino acid sequence will be provided for each DAA target.

All summaries may also be subgrouped by age group.

8.1.8 Pharmacokinetic and Exposure-Response Analyses

Plasma concentrations of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV will be tabulated and summarized as appropriate by formulation, weight range or age group for subjects in Part 1 and Part 2.

Values for the pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV including the C_{max}, T_{max}, C_{trough}, and AUC will be tabulated and summarized formulation, weight range or age group for subjects in Part 1. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Plasma concentration data from Part 1 and Part 2 of this study may be combined with data from other studies and analyzed using the following general methodology.

Population pharmacokinetic analyses may be performed using the actual sampling time relative to dosing. Pharmacokinetic models will be built using a non-linear mixed-effect modeling approach with the NONMEM software. The structure of the starting pharmacokinetic model will be based on the pharmacokinetic analysis of data from previous studies. Apparent oral clearance (CL/F) and apparent volume of distribution (V/F) of the PK analytes will be the pharmacokinetic parameters of major interest in the NONMEM analyses. If necessary, other parameters, including the parameters describing absorption characteristics, may be fixed if useful in the analysis.

Once an appropriate base pharmacokinetic model (including inter- and intra-subject error structure) is developed, empirical Bayesian estimates of individual model parameters will be calculated by the posterior conditional estimation technique using NONMEM.

Relationship between exposure and clinical observations (antiviral activity) will be explored. Exposure-response relationships for primary and secondary efficacy variables and/or some safety measures of interest may also be explored.

The relationship between exposure (e.g., population pharmacokinetic model predicted concentrations over time or average concentrations or AUC or trough concentrations of the individual model-predicted pharmacokinetic profiles, or some other appropriate measure of exposure) and antiviral activity will be explored using graphical and/or logistic regression analyses.

Additionally, relationship between exposure and safety endpoints of interest may also be explored. Additional analyses will be performed if useful and appropriate.

8.2 Determination of Sample Size

The sample size of 36 subjects in Part 1 will adequately characterize the pharmacokinetics of the AbbVie DAAs to enable dose selection in pediatric subjects.

According to the Prescribing Information of PEGASYS, the SVR_{24} rate was 47% among 45 treatment-naïve pediatric subjects with HCV GT1 in the NV17424 trial. To show that

the DAA regimen is superior to this current standard of care by 20% in Parts 1 and 2, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%. For the primary efficacy endpoint of the percentage of subjects with SVR_{12}, if it is assumed 90% subjects would achieve SVR_{12} then 50 or more subjects would have > 90% power to have a lower bound of 2-sided confidence interval based on normal approximation to the binomial distribution > 67%.

8.3 Randomization Methods

There is no randomization in this study. Enrolled subjects will receive treatment per the planned study schematic outlined in Section 5.1.2.

9.0 Ethics

9.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Good Clinical Practice (GCP) requires that the clinical protocol, any protocol amendments, the Investigator's Brochure, the informed consent/assent and all other forms of subject information related to the study (e.g., advertisements used to recruit subjects) and any other necessary documents be reviewed by an IEC/IRB. The IEC/IRB will review the ethical, scientific and medical appropriateness of the study before it is conducted. IEC/IRB approval of the protocol, informed consent/assent and subject information and/or advertising, as relevant, will be obtained prior to the authorization of drug shipment to a study site.

Any amendments to the protocol will require IEC/IRB approval prior to implementation of any changes made to the study design. The investigator will be required to submit, maintain and archive study essential documents according to ICH GCP.

Any serious adverse events that meet the reporting criteria, as dictated by local regulations, will be reported to both responsible Ethics Committees and Regulatory Agencies, as required by local regulations. During the conduct of the study, the investigator should promptly provide written reports (e.g., ICH Expedited Reports, and

any additional reports required by local regulations) to the IEC/IRB of any changes that affect the conduct of the study and/or increase the risk to subjects. Written documentation of the submission to the IEC/IRB should also be provided to AbbVie.

9.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, International Conference on Harmonization (ICH) guidelines, applicable regulations and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the clinical investigator are specified in Appendix A.

9.3 Subject Information and Consent

The investigator or his/her representative will explain the nature of the study to the subject's parent(s)/legal guardian(s) and answer all questions regarding this study. Pediatric subjects will be included in all the discussions in order to obtain written assent. Prior to any study-related screening procedures being performed on the subject, the informed consent statement will be reviewed and signed and dated by subject's parent(s)/legal guardian(s) and the person who administered the informed consent, and any other signatories according to local requirements. Additionally, in keeping with each institution's IEC requirements, if applicable, an informed assent form will also be obtained by each subject, as appropriate for age and country, prior to any study-related procedures being performed. If a subject becomes of legal age during the course of the study, that subject will need to be consented using the approved informed consent form. A copy of the informed consent form and assent form will be given to the subject and subject's parent(s)/legal guardian(s) and the originals will be placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent and assent (if applicable) were obtained prior to any study-related procedures and that the subject and parent(s)/legal guardian(s) received signed copies of the informed consent and assent forms.

Information regarding incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Optional pharmacogenetic analysis will only be performed if the subject has provided assent, as appropriate for age and country, and the subject's parent(s)/guardian(s) have voluntarily signed and dated the pharmacogenetic informed consent, approved by an IRB/IEC, after the nature of the testing has been explained and the subject and their parent(s)/guardian(s) have had an opportunity to ask questions. The subject's parent(s)/guardians(s) must have signed and dated the pharmacogenetic informed consent before the optional pharmacogenetic testing is performed. If the parent(s)/guardian(s) do not provide consent or subject does not provide assent, as appropriate for age and country, to the optional pharmacogenetic testing, it will not impact the subject's participation in the study.

10.0 Source Documents and Case Report Form Completion

10.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, subjects' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents.

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

10.2 Case Report Forms

Case report forms (CRF) must be completed for each subject screened/enrolled in this study. These forms will be used to transmit information collected during the study to

AbbVie and regulatory authorities, as applicable. The CRF data for this study are being collected with an electronic data capture (EDC) system called Rave® provided by the technology vendor Medidata Solutions Incorporated, NY, USA. The EDC system and the study-specific electronic case report forms (eCRFs) will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, Medidata, while the validation of the study-specific eCRFs will be conducted by AbbVie and will be maintained in the Trial Master File at AbbVie.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by investigative site personnel in the EDC system. All data entered into the eCRF will be supported by source documentation.

The investigator or an authorized member of the investigator's staff will make any necessary 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. For any correction, a reason for the alteration will be provided. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by AbbVie personnel (or their representatives). AbbVie (or their representatives) will also be allowed access to all source documents pertinent to the study in order to verify eCRF entries. The principal investigator will review the eCRFs for completeness and accuracy and provide his or her electronic signature and date to eCRFs as evidence thereof.

Medidata will provide access to the EDC system for the duration of the trial 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 (CD-ROM, etc.) and provided to the investigator at that time as a durable record of the site's eCRF data. It will be possible for the investigator to make paper printouts from that media.

11.0 Data Quality Assurance

Computer logic and manual checks will be created to identify items such as inconsistent study dates. Any necessary corrections will be made to the eCRF.

12.0 Use of Information

Any optional pharmacogenetic research that may be done using DNA samples from this study will be experimental in nature and the results will not be suitable for clinical decision-making or patient management. Hence, the investigator, the subject, nor the subject's physician (if different than the investigator) will be informed of individual subject optional pharmacogenetic results, should analyses be performed, nor will anyone not directly involved in this research. Correspondingly, genetic researchers will have no access to subject identifiers. Individual results will not be reported to anyone not directly involved in this research other than for regulatory purposes. Aggregate pharmacogenetic information from this study may be used in scientific publications or presented at medical conventions. Pharmacogenetic information will be published or presented only in a way that does not identify any individual subject.

13.0 Completion of the Study

The investigator will conduct the study in compliance with the protocol and complete the study within the timeframe specified in the contract between the investigator and AbbVie. Continuation of this study beyond this date must be mutually agreed upon in writing by both the investigator and AbbVie. The investigator will provide a final report to the IEC/IRB following conclusion of the study, and will forward a copy of this report to AbbVie or their representative.

The investigator must retain any records related to the study according to local requirements. If the investigator is not able to retain the records, he/she must notify AbbVie to arrange alternative archiving options.

AbbVie will select the signatory investigator from the investigators who participate in the study. Selection criteria for this investigator will include level of participation as well as significant knowledge of the clinical research, investigational drug and study protocol. The signatory investigator for the study will review and sign the final study report in accordance with the European Agency for the Evaluation of Medicinal Products (EMEA) Guidance on Investigator's Signature for Study Reports.

The end-of-study is defined as the date of the last subject's last visit.

14.0 Investigator's Agreement

1. I have received and reviewed the Investigator's Brochure for Paritaprevir, Ritonavir, Ombitasvir, Dasabuvir and the product labeling for RBV.
2. I have read this protocol and agree that the study is ethical.
3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.
4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.
5. I agree that all electronic signatures will be considered the equivalent of a handwritten signature and will be legally binding.

Protocol Title:	An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)
Protocol Date:	21 August 2017

Signature of Principal Investigator _____ Date _____

Name of Principal Investigator (printed or typed) _____

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29. Koletzki D, Dumont S, Vermeiren H, et al. Development and evaluation of an automated hepatitis C virus NS5B sequence-based subtyping assay. Clin Chem Lab Med. 2010;48(8):1095-102.

Appendix A. Responsibilities of the Clinical Investigator

Clinical research studies sponsored by AbbVie are subject to the Good Clinical Practices (GCP) and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement in Section 14.0 of this protocol, the investigator is agreeing to the following:

1. Conducting the study in accordance with the relevant, current protocol, making changes in a protocol only after notifying AbbVie, except when necessary to protect the safety, rights or welfare of subjects.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., independent ethics committee [IEC] or institutional review board [IRB]) review and approval of the protocol and amendments.
4. Reporting adverse experiences that occur in the course of the investigation(s) to AbbVie and the site director.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical investigation and all amendments.

9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.

10. Following the protocol and not make any changes in the research without ethics committee approval, except where necessary to eliminate apparent immediate hazards to human subjects.

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Global Drug Supply
		Clinical
		Statistics
		Clinical
		Bioanalysis

Appendix C. Study Activities

Study Activities – Treatment Period – Parts 1 and 2

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			Premature D/C from Treatment[c]
	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	
Informed Consent[d]	X									
RBV medication guide[e]	X									
Medical History	X	X[f]								
Physical Exam[g]	X	X		X	X	X			X	X
Vital Signs, Weight, Height, Waist Circumference	X	X[h]	X	X	X	X	X	X	X	X
ECG	X		X[i]							
Pregnancy Test (serum [s] urine [u])[j]	X (s)	X (u)		X (u)	X(u)	X (u)	X (u)	X (u)	X (u)	X (u)
Hematology/Chemistry/Urinalysis/Coagulation Panel[k]	X	X	X	X	X	X	X	X	X	X
FSH[l]	X									
HBsAg, Anti-HCV Ab, Anti-HIV Ab	X									
HCV Genotype and Sub-genotype	X									
IL28B Sample	X									

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			Premature D/C from Treatment[c]
	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	
Historical Liver Biopsy or FibroScan assessment or Screening FibroTest for liver cirrhosis[m]	X									
Longitudinal Fibrotest		X[n]								
Child Pugh Score[o]	X									
HCC Assessment: Liver ultrasound[p]	X									X
Concomitant Medication Assessment[q]	X	X	X	X	X	X	X	X	X	X
Adverse Event Assessment[r]	X	X	X	X	X	X	X	X	X	X
Study Drugs Dispensation[s]		X	X	Weeks 4, 6, 8, 10		X[t]	X	X		
Dispense/Collect/Review Study Drug Dosing Card[u]		X	X	X	X	X	X	X	X	X
Study Drug Accountability and/or Review of Study Drug Adherence			X	Weeks 4, 6, 8, 10[s]		X	X	X	X	X
RBV Solution Diary Dispense/Collect/Record[v]		X	X	Weeks 4, 6, 8, 10		X	X	X	X	X
PK Sampling[w]		X	X	X	X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X	X	X	X
Assignment of Subject Number via IRT[x]	X									
Enrollment		X								

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			
	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	Premature D/C from Treatment[c]
HCV Resistance Sample[y]		X								
Tanner Pubertal Stage[z]		X								
Patient Reported Outcome[aa]		X	X	X	X	X	X	X	X	X
Acceptability Questionnaire[bb]			X			X			X	X
Pharmacogenetic Sample (optional)[cc]		X								
Drug compliance review[dd]		X	X	X	X	X				X

D/C = Discontinuation; EOT (End of Treatment) = Final Treatment Visit; Day 1 = Baseline Visit

* Treatment for 24 weeks is applicable for all subjects with genotype 1 non-b compensated cirrhosis.

a. All procedures to be performed prior to first dose.

b. Treatment Duration Study Visits:
   - Subjects assigned to 12 weeks of treatment will complete the procedures from the screening visit through the Week 12/EOT visit.
   - Subjects assigned to 24 weeks of treatment will complete the procedures from the screening visit through the Week 24/EOT. Subjects will complete a Week 12 Study Visit as an interim visit.

c. Subjects that prematurely discontinue from the Treatment Period should return to the site to complete the Premature D/C from Treatment visit procedures.

d. Prior to performing any screening or study-specific procedures, parent(s)/guardian(s) will sign an informed consent for the study. Additionally an assent from the subject will be obtained to meet the institution's IEC requirements, as applicable.

e. Where applicable/locally available.

f. Medical history will be updated at the Day 1 Visit prior to study drug administration and will serve as the Baseline for clinical assessment.

g. A symptom-directed physical examination may be performed at any other visit, when necessary.

h. Height and waist circumference will be measured at baseline only during treatment.

i. Part 1 only.

j. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving RBV should have urine pregnancy testing done monthly starting from Day 1 (Baseline) through PT Week 16 after RBV discontinuation or per local label. Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving DAA only should have urine pregnancy testing done thru Post-Treatment Week 4.

k. Non-cirrhotic subjects: Coagulation panel performed only at Day 1 and as clinically indicated.
Cirrhotic subjects: Coagulation panel is required at all treatment visits.

l. FSH for all female subjects aged ≥ 9 to 17 years old.

m. Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will have a screening FibroTest to determine the presence or absence of cirrhosis for the purpose of treatment assignment. Subjects who have a liver biopsy or FibroScan indicating cirrhosis at any time in the past will not need a Fibrotest to be performed at screening as evidence of cirrhosis.

n. Perform a Fibrotest at Day 1 for any subject who did not have a FibroTest done during Screening.

o. Applies only to subjects with cirrhosis. The Child-Pugh score will be calculated in the EDC RAVE system. Subjects who were considered to be non-cirrhotic at the Screening visit but identified as cirrhotic (according to definitions listed in Section 5.3.1.1) during the screening period will return to the site prior to the baseline visit for Child-Pugh assessment.

p. HCC assessment for subjects with compensated cirrhosis only: Liver ultrasound will be performed at the screening visit. Liver ultrasound testing will occur yearly after Day 1.
Subjects with a historical negative liver ultrasound, CT or MRI (within 3 months prior to screening) are not required to undergo a screening ultrasound.

q. The local study drug labels and http://www hep-druginteractions.org/ should be utilized to evaluate concomitant medications for potential DDI.

r. See specific information regarding the adverse event collection in Section 6.1.4.

s. Part 1: Study drugs will be dispensed every 2 weeks for subjects receiving the mini-tablets with study visit procedures occurring at Day 1, Weeks 2, 4, 6, 8 and 10. Subjects receiving the adult formulation will have drug dispensed at Study Day 1 and Weeks 4 and 8 for 12-week treatment.
Part 2: Study drug dispensed every 4 weeks at regularly scheduled visits at Day 1 and Weeks 4 and 8 for 12-week treatment and Day 1 and Weeks 4, 8, 12, 16, and 20 for 24-week treatment. Drug accountability will be performed at each drug dispensation visit as outlined for mini-tablet, pellet and adult formulations.

t. Study drugs are only dispensed at Week 12 for subjects who will receive 24 weeks of treatment.

u. Dosing card is filled out with date and time (to the nearest minutes) of the 2 doses before PK draws in Part 1 and Part 2. Do not dispense the dosing card at Week 12 visit of Part 1 and at the Week 12 visit for subjects assigned to 12 weeks of treatment in Part 2 (Section 5.3.1.1).

v. Only for Subjects taking RBV Solution
Part 1: Dispensed/Collected every 2 weeks for subjects receiving the mini-tablets with RBV with study visit procedures occurring at Day 1, Weeks 2, 4, and 8.
Part 2: Dispensed/Collected every 4 weeks at regularly scheduled visits at Day 1 and Weeks 4 and 8 for 12-week treatment and Day 1 and Weeks 4, 8, 12, 16, and 20 for 24-week treatment.

w. In Part 1, intensive PK sampling will be done at Week 2 and sparse PK sampling at other visits (Section 5.3.2.1), while sparse PK sampling will be done at all PK visits in Part 2 (Section 5.3.2.1).

x. The Subject will retain the subject number throughout the course of the study.

y. Resistance sample will be collected at Day 1 and upon meeting virologic failure criteria.

z. The Tanner Pubertal stage is assessed for subjects aged ≥ 9 to 17 years old. Tanner staging will not be repeated once the child reaches Tanner Stage 5.

aa. The PRO should be administered as the first study procedure at each visit.

bb. Subjects taking the mini-tablet/pellet formulations only.

cc. Parent(s) or legal guardian(s) and subjects must provide written informed consent and assent (as appropriate for age and country) respectively for the optional pharmacogenetic substudy. If the optional pharmacogenetic DNA sample is not collected at Day 1, it may be collected at any other visit during the study. The investigative site should follow the volume of blood drawn guidance as outlined in Section 5.3.1.1 for the PG sample collection.

dd. Sites will inspect the returned study drug containers at every visit to determine drug compliance. Sites will counsel legal guardian(s) in case of non-drug compliance. See Section 5.5.6 for more details.

Study Activities – Post-Treatment – Parts 1, 2 and 3

Activity	Post-Treatment (PT)						
	Post-Treatment Period of Parts 1 and 2 (PTP)			Part 3: Long-Term Follow-Up (LTFU)			Premature D/C
	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96, and 144	
Vital Signs, Weight, Height, Waist Circumferences[a]	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X	(Weeks 12, 16)					X
Longitudinal Fibrotest			X			X[c]	
Hematology/Chemistry/Urinalysis[d]/Coagulation Panel	X						X
HCC Assessment: Liver Ultrasound[e]			X			X	X
Concomitant Medication Assessment[f]	X	X	X	X	X	X	X
Adverse Event Assessment[g]	X	X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample[h]							
Tanner Pubertal Stage[i]		X		X		X[j]	X
Patient Reported Outcome[k]	X	X	X	X	X	X	X

D/C = Discontinuation

a. Height and Waist circumference will be measured at PT Weeks 12, 36, 96 and 144 only.

b. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving DAAs only should have urine pregnancy testing done thru Post-Treatment Week 4.

Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving RBV should have urine pregnancy testing done monthly starting from Day 1 (Baseline) through PT Week 16 after RBV discontinuation or per local label.

At the PT Visit 16subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

c. FibroTest will be performed at PT Weeks 24 and 144.
d. Urinalysis will not be conducted after the Post-Treatment Week 4 visit.
e. HCC assessment for subjects with compensated cirrhosis only: Liver ultrasound testing will occur yearly.
f. Only medications taken for SAEs assessed as related to study drugs and treatment of HCV will be collected after 30 days post-dosing.
g. Nonserious AEs and all SAEs will be collected until 30 days post dosing. Only drug-related SAEs will be collected thereafter. See Section 6.1.4.
h. Resistance samples are only collected at the confirmation visit for patients that potentially meet virologic failure criteria.
i The Tanner Pubertal stage is assessed for subjects aged ≥ 9 to 17 years old. Tanner staging will not be repeated once the child reaches Tanner Stage 5.
j. Tanner Pubertal Staging only performed at PT Weeks 12, 36, 96 and 144.
k. The PRO should be administered as the first study procedure at each visit.

Appendix D. Estimated Blood Loss for Pediatric Subjects

Treatment Period – Part 1:

	Treatment Period (TP)						
	Treatment Visits – All Subjects						
Estimated Whole Blood Drawn (mL) – using Pediatric tubes	**Screening**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12 or EOT**	**Premature D/C from Treatment**
	19.8	25.8	18.3	11.7	10.3	11.7	12.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	29.0	29.8	20.5	14.3	12.5	14.3	16.8

Treatment Period – Part 2:

	Treatment Period (TP)				
	Treatment Visits – All Subjects				Premature D/C from Treatment
Estimated Whole Blood Drawn (mL) – using	Screening	Day 1	Wk 2, 4, 8, 12, 16 and 20	Wk 24 or EOT	
Pediatric tubes	19.8	25.8	11.7	12.8	12.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	29.0	29.8	14.3	16.8	16.8

Post-Treatment – Part 3:

	Post-Treatment (PT)						
	Post-Treatment Period of (PTP)			Part 3: Long-Term Follow-Up (LTFU)			
Estimated Whole Blood Drawn (mL) – using	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96*, and 144	Premature D/C
Pediatric tubes	8.7	6.0	20.7	16.0	17.1	20.7*/17.1	20.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	12.3	6.0	23.5	16.0	18.5	23.5*/18.5	24.8

Appendix E. Tanner Pubertal Stage

Boys – development of external genitalia

Stage 1: Prepubertal

Stage 2: Enlargement of scrotum and testes; scrotum skin reddens and changes in texture

Stage 3: Enlargement of penis (length at first); further growth of testes

Stage 4: Increased size of penis with growth in breadth and development of glans; testes and scrotum larger, scrotum skin darker

Stage 5: Adult genitalia

Girls – breast development

Stage 1: Prepubertal

Stage 2: Breast bud stage with elevation of breast and papilla; enlargement of areola

Stage 3: Further enlargement of breast and areola; no separation of their contour

Stage 4: Areola and papilla form a secondary mound above level of breast

Stage 5: Mature stage: projection of papilla only, related to recession of areola

Boys and girls – pubic hair

Stage 1: Prepubertal (can see velus hair similar to abdominal wall)

Stage 2: Sparse growth of long, slightly pigmented hair, straight or curled, at base of penis or along labia

Stage 3: Darker, coarser and more curled hair, spreading sparsely over junction of pubes

Stage 4: Hair adult in type, but covering smaller area than in adult; no spread to medial surface of thighs

Stage 5: Adult in type and quantity, with horizontal distribution ("feminine")

Appendix F. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Section 1.2 Synopsis
Previously read:

AbbVie Inc.	**Protocol Number:** M14-748
Name of Study Drug: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Phase of Development:** 2/3
Name of Active Ingredient: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Date of Protocol Synopsis:** 07 July 2016
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)	
Objectives: To assess the pharmacokinetics of OBV, PTV, RTV, and DSV with or without RBV in treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects in Part 1. To assess the efficacy (percentage of subjects achieving SVR_{12} [defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study drug]) or SVR_{24} [defined as HCV RNA < LLOQ 24 weeks after the last actual dose of study drug]) and safety of OBV, PTV, RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV genotype 1 (GT1) or genotype 4 (GT4)-infected treatment-naïve and prior IFN (IFN or peg-IFN with or without RBV) treatment-experienced, cirrhotic and non-cirrhotic pediatric subjects in Part 1 and Part 2. To assess the durability of response for subjects who achieved SVR, to assess the emergence and persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure, and to assess the impact of OBV, PTV, RTV with or without DSV and with or without RBV on growth and development in Part 3, the long-term follow-up of approximately 3.5 years.	
Investigator: Global, multicenter trial: Investigator information is on file at AbbVie.	
Study Sites: Up to 30 sites globally.	
Study Population: **Part 1:** Treatment-naïve, non-cirrhotic, GT1-infected pediatric patients ≥ 3 to 17 years of age **Part 2:** Treatment-naïve and IFN (interferon or pegylated-interferon with or without RBV) treatment-experienced HCV GT1 or GT4-infected pediatric subjects ≥ 12 to 17 years of age with or without compensated cirrhosis **Part 3 (Long-term follow-up):** All pediatric subjects who take at least one dose of study drug and complete the Post-Treatment (PT) Week 24 visit in Part 1 or Part 2.	

Number of Subjects to be Enrolled:

Approximately 74 subjects will be enrolled in total into two Parts. Part 1: Approximately 48 treatment-naïve, non-cirrhotic, GT1 subjects. Part 2: Approximately 26 treatment-naïve or prior IFN treatment-experienced, cirrhotic or non-cirrhotic subjects with GT1 or GT4.

Methodology:

The study aims to assess four formulations in the pediatric population. The approved adult 3D regimen formulation and the approved adult 2D regimen formulation will be administrated in subjects who are in the 12 to 17 years old age group with weight greater than 45 kg and willing to swallow the adult formulation. These formulations will be the final dose formulations for this age group if satisfactory safety and efficacy profiles are observed. The mini-tablet formulation will be administered in subjects who are in the 3 – 8 and 9 – 11 age groups to identify the optimal or final doses. The pellet formulation will be administrated also in these two age groups after final doses are identified. The pellet formulation will be the final dose formulation for the two age groups if satisfactory safety and efficacy profile is observed.

Part 1 mini-tablet is designed to allow for dose adjustment on an ongoing basis, based on available pharmacokinetic and clinical data to achieve therapeutic exposures that have been safe and efficacious in adult subjects. Area under the concentration curve (AUC) from the intensive PK sampling at Week 2 will be the primary measure for dose adjustment, which will be compared with the range of the geometric means and the range of individual values across Phase 1/2/3 studies in adults that had intensive PK data (see Section 5.1). C_{max} and C_{trough} will be considered for safety and efficacy using the same rules. Part 2 (Safety and Efficacy) will use the adult formulation if the results from the adult formulation in Part 1 are satisfactory. In Part 1 and Part 2, the treatment duration is either 12 weeks or 24 weeks and all pediatric subjects who receive at least 1 dose of study drug will be followed for 24 weeks in the post-treatment period after completing or prematurely discontinuing the study treatment. All pediatric subjects who complete the Post-Treatment (PT) Week 24 visit in either Part 1 or Part 2 will be followed in Part 3 (Long-term Follow-up) for an additional 168 weeks.

Part 1 (Pharmacokinetic Study):

Approximately 48 treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects will be enrolled. In the ≥ 12 to 17 year age group, 12 subjects will receive the standard adult formulation; in the ≥ 3 to 8 and ≥ 9 to 11 year age groups, at least 6 subjects will receive the mini-tablet formulation and at least 6 subjects will receive the pellet formulation). Up to 12 additional subjects may be enrolled to receive the mini-tablet formulation in Part 1 if needed to adequately characterize the pharmacokinetics of a particular age group or subgroup. Subjects in the ≥ 12 to 17 year age group who are ≥ 45 kg and willing to swallow the adult formulations will begin enrollment before subjects in the younger age groups. The starting drug regimen is defined by HCV sub-genotype. All HCV sub-genotype 1b subjects will receive study medication without RBV for 12 weeks as shown below. All subjects with a HCV GT1 non-b infection will receive study medication with weight based RBV for 12 weeks.

Methodology (Continued):

Part 1 (Pharmacokinetic Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, and Week 12. At Week 2 and Week 8, the morning dose of study drug will be administered in the clinic at approximately 24 hours after the prior morning dose. At Week 2, the evening doses will be administered in the clinic following the 12 hour PK draw and the morning doses at Week 2 + 1 day will be administered in the clinic following the 24 hour PK draw. PT visits will occur at PT Weeks 4, 12, and 24.

PK samples will be collected at the following timepoints from each subject:

- Day 1: 4 hours postdose (the morning doses will be administered in the clinic)
- Week 2: 2, 4, 8, 12 and 24 hours postdose (the morning doses, the evening doses following the 12 hour PK draw and the morning doses following the 24 hour PK draw will be administered in the clinic)
- Week 4: a PK sample (regardless of the dosing time)
- Week 8: a trough PK sample (i.e., prior to the morning dose, which will be administered in the clinic)
- Week 12: a PK sample (regardless of the dosing time)

Based on assessment of Week 2 intensive pharmacokinetic and clinical data, dose adjustments and/or dose adjustments for subsequently enrolled subjects may be performed.

Part 2 (Safety/Efficacy Study):

Approximately 16 HCV GT1-infected and approximately 10 HCV GT4-infected treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced pediatric subjects in the ≥ 12 to 17 age group will be enrolled.

Subjects with GT1 infection will receive the 3D formulations approved for adults (with or without RBV) and the subjects with GT4 infection will received the 2D formulation approved for adults with RBV in Part 2. RBV dosing will be weight-based at 1000 or 1200 mg divided twice daily or per local RBV label. The regimen and duration will be determined according to HCV genotype, sub-genotype and cirrhosis status.

Methodology (Continued):
Part 2 (Safety/Efficacy Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir (approved adult 3D formulation)	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	12 weeks
Genotype 1a,* with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin (approved adult 2D formulation plus RBV)	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24. The latter 3 visits at Weeks 16, 20 and 24 are required for subjects with compensated cirrhosis taking study drug for 24 weeks. PT visits will occur at PT Weeks 4, 12, and 24.

One PK sample (regardless of the dosing time) will be collected at each visit for each subject in Part 2.

The following criteria will be considered evidence of virologic failure during treatment. Pediatric subjects demonstrating any of the following should be discontinued from study drug:

- Confirmed increase from nadir (defined as 2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir) in HCV RNA at any time point
- Confirmed HCV RNA $\geq$ LLOQ (defined as 2 consecutive HCV RNA measurements $\geq$ LLOQ) at any point after achieving HCV RNA < LLOQ
- Failure to achieve HCV RNA < LLOQ on or before Week 6

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met, the subject will discontinue study treatment, if applicable. If the Investigator feels that a subject who meets one of these criteria should still remain on study treatment, the subject would only be allowed to remain on treatment with approval of the AbbVie Study TA SD/TA MD.

Part 3 (Long-Term Follow-Up):

All subjects who have completed Post-Treatment Week 24 in either Part 1 or Part 2 of the study will be followed to assess the durability of viral response, for the emergence and persistence of resistant viral variants, and for SAEs related to study drug for an additional 168 weeks in the Long-term Follow-up. Study visits will occur at Post-Treatment Weeks 36, 48, 72, 96, 120, 144, 168, and 192.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 3 to 17 years of age at time of enrollment.
2. Willingness to participate in the study for up to 50 months.
3. HCV infection demonstrated by positive anti-HCV Ab and HCV RNA ≥ 1000 IU/mL at the time of screening.
4. Screening laboratory results indicating HCV genotype 1 for enrollment into Part 1 and genotype 1 or 4 for enrollment into Part 2.
5. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.

Main Exclusion:

1. Women who are pregnant, breastfeeding, or are considering becoming pregnant.
2. Use of known strong inducers and inhibitors (e.g., gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in subjects receiving dasabuvir, or strong or moderate inducers of CYP3A, within 2 weeks or 10 half-lives, whichever is longer, of the respective medication/supplement prior to study drug administration.
3. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-HIV antibody (HIV Ab) test.
4. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFNs or RBV or receipt of any investigational product within 6 weeks prior to study drug administration.

Investigational Products:

Weight < 45 kg or eligible but not willing to swallow the adult formulations: Part 1	
paritaprevir	1.0 mg mini-tablet
ritonavir	1.0 mg mini-tablet
ombitasvir	0.3 mg mini-tablet
dasabuvir	3.08 mg mini-tablet
ribavirin	40 mg/mL oral solution

Weight < 45 kg: Final pellet dosage strength: Part 1	
ombitasvir/paritaprevir/ritonavir	ombitasvir/paritaprevir/ritonavir X1/X2/X3 mg pellets
dasabuvir	dasabuvir X4 mg pellets
ribavirin	40 mg/mL oral solution

Weight ≥ 45 kg who are ≥ 12 to 17 years old and willing to swallow the adult formulations:	
ombitasvir/paritaprevir/r	12.5/75/50 mg tablet
dasabuvir	250 mg tablet
ribavirin	200 mg tablet

Doses:

Part 1:

Initial dosing based on body weight at time of Screening:

	≤ 14 kg	15 to 29 kg	30 to 44 kg	≥ 45 kg
paritaprevir (QD)	35 mg	50 mg	100 mg	150 mg
ritonavir (QD)	25 mg	35 mg	70 mg	100 mg
ombitasvir (QD)	5 mg	10 mg	15 mg	25 mg
dasabuvir (BID)	50 mg	100 mg	150 mg	250 mg
ribavirin	Per local label			

The doses for ombitasvir/paritaprevir/r and dasabuvir pellet dosing in Part 1 will be determined from Part 1 mini-tablet dosing.

Part 2:

Only adult formulation will be provided to subjects who are in the 12 – 17 year old age group with weight greater than 45 kg and willing to swallow the adult formulations.

Mode of Administration: Oral

Reference Therapy:	Not applicable
Dose:	Not applicable
Mode of Administration:	Not applicable

Duration of Treatment:

Part 1: Pediatric subjects will receive OBV, PTV, RTV, DSV with or without RBV for 12 weeks.

Part 2: Pediatric subjects will receive OBV, PTV, RTV with or without DSV and with or without RBV for 12 weeks or 24 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each treatment and Post-Treatment Period visit in all three parts of the study.

Pharmacokinetic:

Plasma concentrations of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, RTV and RBV (if applicable) will be determined at each study visit for each subject for the treatment periods of Part 1 and Part 2.

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests and vital signs. Growth and development will be assessed relative to age specific norms.

Statistical Methods:

The pharmacokinetic analysis will be performed separately for Part 1 and Part 2. For population pharmacokinetic analyses, data from Part 1 and Part 2 will be combined if needed. All efficacy, safety, growth and development outcomes will be assessed across Parts 1 and 2 of the study with summaries by formulation and age group, totaled across the final dose formulations (2D + RBV, 3D ± RBV, and pellets), and totaled across adult formulations (2D + RBV and 3D ± RBV). Analyses on durability of response, resistance, growth and development outcomes, and patient-reported outcomes will be performed through Post-Treatment Week 24 in Parts 1 and 2 and after Post-Treatment Week 24 for all subjects in Part 3.

An interim analysis will occur once all subjects complete PT Week 12 or prematurely discontinue from the study. Final analysis will occur after the completion of the whole study.

Efficacy:

The primary pharmacokinetic endpoints are C_{max} and AUC following dosing on Week 2, and trough concentration (C_{trough}) following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

The primary efficacy endpoint is the percentage of subjects with SVR_{12} among the subjects who receive the final dose formulations. The final dose formulations are the adult formulations used in either Part 1 and/or Part 2 (3D ± RBV and 2D + RBV) and the coated pellet formulation to be used in Part 1 only. The percentage of subjects achieving SVR_{12} will be calculated across all subjects on the final dose formulations along with the 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} on the final dose formulations must be greater than 67% to show superiority to pegIFN and RBV as described in Section 8.2.

Statistical Methods (Continued):

Efficacy (Continued):

The main secondary endpoints are:

1. The percentage of subjects who achieve SVR_{12} summarized by formulation and age group and across all subjects on the adult formulations.
2. The percentage of subjects who achieve SVR_{24} by formulation and age group, across all the subjects on the final dose formulations, and across all subjects on the adult formulations;
3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation and age group, across all subjects on the final dose formulations, and across all subjects on the adult formulations.

For the secondary efficacy endpoints, the simple percentage will be calculated along with the 2-sided 95% confidence interval. For both primary and secondary endpoints, the normal approximation to the binomial distribution will be used if the rate is not 0% or 100%, otherwise the Wilson's score method will be used to calculate the confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate in subjects on the final dose formulations will also be compared to 67%.

Resistance:

For subjects with virologic failure and HCV RNA > 1000 IU/mL, the variants at each amino acid position (by population, deep, and/or clonal nucleotide sequencing) at available post baseline time points compared to baseline and prototypic reference standard sequences will be summarized by DAA target genes and accompanying listings will be provided.

Safety:

All safety analysis will be done by age group separately for each formulation, for all subjects on the final dose formulations, and for all subjects on the adult formulations.

The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by MedDRA system organ class and preferred term. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by grade (Grades 1 – 5) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects with potentially clinically significant values during treatment will be calculated.

Growth and Development:

All growth and development analyses will be done by age group separately for each formulation, for all subjects on the final dose formulations, and for all subjects on the adult formulations. The following growth and development endpoints will be calculated at applicable study visits.

- Growth rate at each post baseline visit (defined as change in height over change in age from the previous visit)
- Height z score
- Waist circumference
- Tanner staging

Statistical Methods (Continued): **Pharmacokinetic:** Plasma concentrations and pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV, if applicable, will be tabulated for each subject and summarized as appropriate by formulation, weight range or age group. Individual plasma concentrations or pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV may be used for safety or efficacy evaluation if needed. Additional analyses may be conducted as needed.

Has been changed to read:

AbbVie Inc.	**Protocol Number:** M14-748
Name of Study Drug: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Phase of Development:** 2/3
Name of Active Ingredient: ombitasvir, paritaprevir, ritonavir, dasabuvir, ribavirin	**Date of Protocol Synopsis:** 21 August 2017
Protocol Title: An Open-Label, Multicenter Study to Evaluate the Pharmacokinetics, Safety, and Efficacy of Ombitasvir (OBV), Paritaprevir (PTV), Ritonavir (RTV) With or Without Dasabuvir (DSV) and With or Without Ribavirin (RBV) in Pediatric Subjects With Genotype 1 or 4 Chronic Hepatitis C Virus (HCV) Infection (ZIRCON)	
Objectives: To assess the pharmacokinetics of OBV, PTV, RTV, and DSV with or without RBV in treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects in Part 1. To assess the efficacy (percentage of subjects achieving SVR_{12} [defined as HCV RNA < LLOQ 12 weeks after the last actual dose of study drug]) or SVR_{24} [defined as HCV RNA < LLOQ 24 weeks after the last actual dose of study drug]) and safety of OBV, PTV, RTV with or without DSV and with or without RBV for 12 or 24 weeks in HCV genotype 1 (GT1) or genotype 4 (GT4)-infected treatment-naïve and prior IFN (IFN or peg-IFN with or without RBV) treatment-experienced, cirrhotic and non-cirrhotic pediatric subjects in Part 1 and Part 2. To assess the durability of response for subjects who achieved SVR, to assess the emergence and persistence of specific HCV amino acid variants associated with drug resistance in subjects who experienced virologic failure, and to assess the impact of OBV, PTV, RTV with or without DSV and with or without RBV on growth and development in Part 3, the long-term follow-up of approximately 2.5 years.	
Investigator: Global, multicenter trial: Investigator information is on file at AbbVie.	
Study Sites: Up to 30 sites globally.	

Study Population:

Part 1: Treatment-naïve, non-cirrhotic, GT1-infected pediatric patients ≥ 3 to 17 years of age

Part 2: Treatment-naïve and IFN (IFN or peg-IFN with or without RBV) treatment-experienced HCV GT1 or GT4-infected pediatric subjects ≥ 12 to 17 years of age with or without compensated cirrhosis

Part 3 (Long-term follow-up): All subjects who take at least one dose of study drug and complete the Post-Treatment (PT) Week 24 visit in Part 1 or Part 2.

Number of Subjects to be Enrolled:

Approximately 62 subjects will be enrolled in total into two Parts. Part 1: Approximately 36 treatment-naïve, non-cirrhotic, GT1 subjects. Part 2: Approximately 26 subjects ≥ 12 to 17 years of age treatment-naïve or prior IFN treatment-experienced, cirrhotic or non-cirrhotic with GT1 or GT4 HCV infection.

Methodology:

The study aims to assess three formulations in the pediatric population. The approved adult 3D (OBV/PTV/RTV and DSV) regimen formulation and the approved adult 2D (OBV/PTV/RTV) regimen formulation will be administrated in subjects who are in the ≥ 12 to 17 years old age group with weight greater than 45 kg and willing to swallow the adult formulation. The mini-tablet formulation will be administered in subjects who are in the ≥ 3 – 8 and ≥ 9 – 11 age groups to identify the optimal or final doses.

Part 1 mini-tablet is designed to allow for dose adjustment on an ongoing basis, based on available pharmacokinetic and clinical data to achieve therapeutic exposures that have been safe and efficacious in adult subjects. Area under the concentration curve (AUC) from the intensive PK sampling at Week 2 will be the primary measure for dose adjustment, which will be compared with the range of the geometric means and the range of individual values across Phase 1/2/3 studies in adults that had intensive PK data (see Section 5.1). C_{max} and C_{trough} will be considered for safety and efficacy using the same rules. Part 2 (Safety and Efficacy) will use the adult formulation if the results from the adult formulation in Part 1 are satisfactory. In Part 1 and Part 2, the treatment duration is either 12 weeks or 24 weeks and all pediatric subjects who receive at least 1 dose of study drug will be followed for 24 weeks in the post-treatment period after completing or prematurely discontinuing the study treatment. All pediatric subjects who complete the Post-Treatment (PT) Week 24 visit in either Part 1 or Part 2 will be followed in Part 3 (Long-term Follow-up) for 144 weeks.

Part 1 (Pharmacokinetic Study):

Approximately 36 treatment-naïve, non-cirrhotic, HCV GT1-infected pediatric subjects will be enrolled. In the ≥ 12 to 17 year age group, 12 subjects will receive the standard adult formulation; in the ≥ 3 to 8 and ≥ 9 to 11 year age groups, at least 12 subjects will receive the mini-tablet formulation. Up to 12 additional subjects may be enrolled to receive the mini-tablet formulation in Part 1 if needed to adequately characterize the pharmacokinetics of a particular age group or subgroup. Subjects in the ≥ 12 to 17 year age group who are ≥ 45 kg and willing to swallow the adult formulations will begin enrollment before subjects in the younger age groups. The starting drug regimen is defined by HCV sub-genotype. All HCV sub-genotype 1b (GT1b) subjects will receive study medication (OBV/PTV/RTV and DSV) without RBV for 12 weeks as shown below. All subjects with a HCV GT1 non-b infection will receive study medication with weight based RBV for 12 weeks.

Methodology (Continued):

Part 1 (Pharmacokinetic Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b, without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, and Week 12. At Week 2 and Week 8, the morning dose of study drug will be administered in the clinic at approximately 24 hours after the prior morning dose. At Week 2, the evening doses will be administered in the clinic following the 12 hour PK draw and the morning doses at Week 2 + 1 day will be administered in the clinic following the 24 hour PK draw. PT visits will occur at PT Weeks 4, 12, and 24.

PK samples will be collected at the following timepoints from each subject:

- Day 1: 4 hours postdose (the morning doses will be administered in the clinic)
- Week 2: 2, 4, 8, 12 and 24 hours postdose (the morning doses, the evening doses following the 12 hour PK draw and the morning doses following the 24 hour PK draw will be administered in the clinic)
- Week 4: a PK sample (regardless of the dosing time)
- Week 8: a trough PK sample (i.e., prior to the morning dose, which will be administered in the clinic)
- Week 12: a PK sample (regardless of the dosing time)

Based on assessment of Week 2 intensive pharmacokinetic and clinical data, dose adjustments and/or dose adjustments for subsequently enrolled subjects may be performed.

Part 2 (Safety/Efficacy Study):

Approximately 16 HCV GT1-infected and approximately 10 HCV GT4-infected treatment-naïve or IFN (IFN or pegIFN with or without RBV) treatment-experienced pediatric subjects in the ≥ 12 to 17 age group will be enrolled.

Subjects with GT1 infection will receive the 3D tablet formulation approved for adults (with or without RBV) and the subjects with GT4 infection will receive the 2D tablet formulation approved for adults with RBV. RBV will be administered weight based as tablets or as solution per local RBV label. The regimen and duration will be determined according to HCV genotype, sub-genotype and cirrhosis status.

Methodology (Continued):
Part 2 (Safety/Efficacy Study) (Continued):

Patient Population	Treatment	Duration
Genotype 1b with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir (approved adult 3D formulation)	12 weeks
Genotype 1a,* without cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	12 weeks
Genotype 1a,* with compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + dasabuvir + ribavirin (approved adult 3D formulation plus RBV)	24 weeks
Genotype 4 with or without compensated cirrhosis	ombitasvir + paritaprevir + ritonavir + ribavirin (approved adult 2D formulation plus RBV)	12 weeks

* Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 sub-genotype or with mixed genotype 1 infection.

Study treatment visits will occur at Day 1, Week 2, Week 4, Week 8, Week 12, Week 16, Week 20, and Week 24. The latter 3 visits at Weeks 16, 20 and 24 are required for subjects with compensated cirrhosis taking study drug for 24 weeks. PT visits will occur at PT Weeks 4, 12, and 24.

One PK sample (regardless of the dosing time) will be collected at each visit for each subject in Part 2.

The following criteria will be considered evidence of virologic failure during treatment. Pediatric subjects demonstrating any of the following should be discontinued from study drug:

- Confirmed increase from nadir (defined as 2 consecutive HCV RNA measurements $> 1 \log_{10}$ IU/mL above nadir) in HCV RNA at any time point
- Confirmed HCV RNA $\geq$ 100 IU/ml (defined as 2 consecutive HCV RNA measurements $\geq$ 100 IU/ml) at any point after achieving HCV RNA < LLOQ

Confirmatory testing should be completed as soon as possible. If any of the above criteria are met, the subject will discontinue study treatment, if applicable. If the Investigator feels that a subject who meets one of these criteria should still remain on study treatment, the subject would only be allowed to remain on treatment with approval of the AbbVie Study TA SD/TA MD.

Part 3 (Long-Term Follow-Up):

All subjects who have completed Post-Treatment Week 24 in either Part 1 or Part 2 of the study will be followed to assess the durability of viral response, for the emergence and persistence of resistant viral variants, and for SAEs related to study drug for an additional 120 weeks in the Long-term Follow-up period. Study visits will occur at Post-Treatment Weeks 36, 48, 96, and 144.

Diagnosis and Main Criteria for Inclusion/Exclusion:

Main Inclusion:

1. Male or female ≥ 3 to 17 years of age and weight ≥ 15 kg at time of enrollment.
2. Willingness to participate in the study for up to 42 months.
3. HCV infection demonstrated by positive anti-HCV Ab and HCV RNA ≥ 1000 IU/mL at the time of screening.
4. Screening laboratory results indicating HCV genotype 1 for enrollment into Part 1 and genotype 1 or 4 for enrollment into Part 2.
5. Parent or legal guardian with the willingness and ability to provide written informed consent and subject willing and able to give assent, as appropriate for age and country.

Main Exclusion:

1. Women who are pregnant, breastfeeding, or are considering becoming pregnant.
2. Use of known strong inducers and inhibitors (e.g., gemfibrozil) of cytochrome P450 2C8 (CYP2C8) in subjects receiving dasabuvir, or strong or moderate inducers of CYP3A, within 2 weeks or 10 half-lives, whichever is longer, of the respective medication/supplement prior to study drug administration.
3. Positive test result for Hepatitis B surface antigen (HbsAg) or anti-HIV antibody (HIV Ab) test.
4. Current enrollment in another interventional clinical study, previous enrollment in this study, prior or current use of any investigational or commercially available anti-HCV agents other than IFNs or RBV or receipt of any investigational product within 6 weeks prior to study drug administration.

Investigational Products:

Weight < 45 kg or eligible but not willing to swallow the adult formulations: Part 1	
paritaprevir	1.0 mg mini-tablet
ritonavir	1.0 mg mini-tablet
ombitasvir	0.3 mg mini-tablet
dasabuvir	3.08 mg mini-tablet
ribavirin	40 mg/mL oral solution

Weight ≥ 45 kg who are ≥ 12 to 17 years old and willing to swallow the adult formulations:	
ombitasvir/paritaprevir/r	12.5/75/50 mg tablet
dasabuvir	250 mg tablet
Ribavirin	200 mg tablet

Doses:

Part 1 Mini-Tablet:

Initial dosing based on body weight at time of Screening:

	≥ 15 to 29 kg	≥ 30 to 44 kg	≥ 45 kg
paritaprevir (QD)	50 mg	100 mg	150 mg
ritonavir (QD)	35 mg	70 mg	100 mg
ombitasvir (QD)	10 mg	15 mg	25 mg
dasabuvir (BID)	100 mg	150 mg	250 mg
Ribavirin solution	Per local label		

Part 2:

Only adult formulation and RBV tablets if required will be provided to subjects who are in the ≥ 12 – 17 year old age group with weight equal and greater than 45 kg and willing to swallow the adult formulations.

Mode of Administration: Oral

Reference Therapy: Not applicable

Dose: Not applicable

Mode of Administration: Not applicable

Duration of Treatment:

Part 1: Pediatric subjects will receive OBV, PTV, RTV, DSV with or without RBV for 12 weeks.

Part 2: Pediatric subjects will receive OBV, PTV, RTV with or without DSV and with or without RBV for 12 weeks or 24 weeks.

Criteria for Evaluation:

Efficacy:

Plasma HCV RNA (IU/mL) will be assessed at each treatment and Post-Treatment Period visit in all three parts of the study.

Pharmacokinetic:

Plasma concentrations of OBV, possible OBV metabolites, PTV, possible PTV metabolites, DSV, DSV M1 metabolite, other possible DSV metabolites, RTV and RBV (if applicable) will be determined at each study visit for each subject for the treatment periods of Part 1 and Part 2.

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical examinations, clinical laboratory tests and vital signs. Growth and development will be assessed relative to age specific norms.

Statistical Methods:

The pharmacokinetic analysis will be performed separately for Part 1 and Part 2. For population pharmacokinetic analyses, data from Part 1 and Part 2 will be combined if needed. All efficacy, safety, growth and development outcomes will be assessed across Parts 1 and 2 of the study with summaries by formulation, age and weight group, totaled across all subjects, and totaled across adult formulations (OBV/PTV/RTV + RBV and OBV/PTV/RTV and DSV ± RBV). Analyses on durability of response, resistance, growth and development outcomes, and patient-reported outcomes will be performed through Post-Treatment Week 24 in Parts 1 and 2 and after Post-Treatment Week 24 for all subjects in Part 3.

An interim analysis will occur once all subjects complete PT Week 12 or prematurely discontinue from the study. Final analysis will occur after the completion of the whole study.

Efficacy:

The primary pharmacokinetic endpoints are C_{max} and AUC following dosing on Week 2, and trough concentration (C_{trough}) following dosing on Week 2 and Week 8 for OBV, PTV, DSV, and RTV.

The primary efficacy endpoint is the percentage of subjects with SVR_{12} among all subjects. The percentage of subjects achieving SVR_{12} will be calculated along with the 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the percentage of subjects with SVR_{12} across all subjects must be greater than 67% to show superiority to pegIFN and RBV as described in Section 8.2.

The main secondary endpoints are:

1. The percentage of subjects who achieve SVR_{12} summarized by formulation, age and weight group and across all subjects.
2. The percentage of subjects who achieve SVR_{24} by formulation, age and weight group, across all the subjects, and across all subjects on the adult formulations;
3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

For the secondary efficacy endpoints, the simple percentage will be calculated along with the 2-sided 95% confidence interval. For both primary and secondary endpoints, the normal approximation to the binomial distribution will be used if the rate is not 0% or 100%, otherwise the Wilson's score method will be used to calculate the confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%.

Resistance:

For subjects with virologic failure and HCV RNA > 1000 IU/mL, the variants at each amino acid position (by population, deep, and/or clonal nucleotide sequencing) at available post baseline time points compared to baseline and prototypic reference standard sequences will be summarized by DAA target genes and accompanying listings will be provided.

Statistical Methods (Continued):

Safety:

All safety analysis will be done by age and weight group separately for each formulation, for all subjects, and for all subjects on the adult formulations.

The number and percentage of subjects reporting treatment-emergent adverse events will be tabulated by MedDRA system organ class and preferred term. Tabulations will also be provided in which the number of subjects reporting an adverse event (MedDRA preferred term) is presented by grade (Grades 1 – 5) and relationship to study drugs.

Change from baseline in laboratory tests and vital sign measurements to each time point of collection will be summarized descriptively. Laboratory test and vital sign values that are potentially clinically significant, according to predefined criteria, will be identified and the number and percentage of subjects with potentially clinically significant values during treatment will be calculated.

Growth and Development:

All growth and development analyses will be done by age group separately for each formulation, for all subjects, and for all subjects on the adult formulations. The following growth and development endpoints will be calculated at applicable study visits.

- Growth rate at each post baseline visit (defined as change in height over change in age from the previous visit)
- Height z score
- Waist circumference
- Tanner staging

Pharmacokinetic:

Plasma concentrations and pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV, if applicable, will be tabulated for each subject and summarized as appropriate by formulation, weight range or age group.

Individual plasma concentrations or pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV may be used for safety or efficacy evaluation if needed.

Additional analyses may be conducted as needed.

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Abbreviations
Delete: "APRI"

APRI Aspartate Aminotransferase to Platelet Ratio Index

Section 1.3 List of Abbreviations and Definition of Terms
Subsection Definition of Terms
"Long-Term Follow-Up (LTFU)" previously read:

Long-Term Follow-Up (LTFU) Day after Post-Treatment Week 24 visit through Post-Treatment Week 168 or Post-Treatment Discontinuation

Has been changed to read:

Long-Term Follow-Up (LTFU)	Day after Post-Treatment Week 24 visit through Post-Treatment Week 144 or Post-Treatment Discontinuation

Section 3.0 Introduction
Subsection AbbVie's 3D Regimen
Subsection title previously read:

AbbVie's 3D Regimen

Has been changed to read:

AbbVie's Ombitasvir/Paritaprevir/r (OBV/PTV/RTV) and Dasabuvir (DSV), Also Known as the 3D Regimen

Section 3.0 Introduction
Subsection AbbVie's 3D Regimen
Second paragraph previously read:

The safety and efficacy of ombitasvir/paritaprevir/r 25/150/100 mg once daily and dasabuvir 250 mg twice daily (3D regimen) was evaluated in six Phase 3 randomized, multicenter, clinical trials (Studies M11-646, M13-098, M13-389, M13-961, M14-002 and M13-099) in more than 2,300 adult subjects with chronic HCV GT1 infection who received the 3D regimen with or without ribavirin for 12 or 24 weeks, including one trial exclusively in subjects with compensated cirrhosis.

Has been changed to read:

The safety and efficacy of OBV/PTV/RTV 25/150/100 mg once daily and DSV 250 mg twice daily was evaluated in six Phase 3 randomized, multicenter, clinical trials (Studies M11-646, M13-098, M13-389, M13-961, M14-002 and M13-099) in more than 2,300 adult subjects with chronic HCV GT1 infection who received the 3D regimen with or without ribavirin for 12 or 24 weeks, including one trial exclusively in subjects with compensated cirrhosis.

Section 3.0 Introduction
Subsection AbbVie's 2D Regimen
Subsection title previously read:

AbbVie's 2D Regimen

Has been changed to read:

AbbVie's Ombitasvir/Paritaprevir/r (OBV/PTV/RTV), Also Known as the 2D Regimen

Section 3.1 Differences Statement
Last sentence previously read:

In Part 3, long-term safety and efficacy will be evaluated in a 168-week long-term follow-up period.

Has been changed to read:

In Part 3, long-term safety and efficacy will be evaluated for 144 weeks.

Section 3.3 Pediatric Study Plan and Pediatric Investigational Plan
Last paragraph, first sentence previously read:

Similarly, the initial PSP for 3D, dated December 19, 2013, provided a waiver for the pediatric population younger than 3 years of age and a deferral to begin the PK and safety/efficacy studies in pediatric populations after the approval of OBV/PTV/RTV and DSV in adults with GT1 infection.

Has been changed to read:

Similarly, the initial PSP for OBV/PTV/RTV and DSV, dated December 19, 2013, provided a waiver for the pediatric population younger than 3 years of age and a deferral to begin the PK and safety/efficacy studies in pediatric populations after the approval of OBV/PTV/RTV and DSV in adults with GT1 infection.

Section 4.0 Study Objective
Subsection Secondary Objective(s):
Previously read:

- To evaluate the percentage of subjects with SVR_{12} by formulation and age group and across all subjects on the adult formulations.
- To evaluate the percentage of subjects with SVR_{24} and the percentage of subjects with ALT normalization by the end of treatment, by formulation and age group, across all subjects on the final dose formulations, and across all subjects on the adult formulations.

Has been changed to read:

- To evaluate the percentage of subjects with SVR_{12} by formulation, age and weight group and across all subjects on the adult formulations.
- To evaluate the percentage of subjects with SVR_{24} and the percentage of subjects with ALT normalization by the end of treatment, by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

Section 5.1 Overall Study Design and Plan: Description
First paragraph, first sentence previously read:

Part 1 of this study is a Phase 2 study in which eligible HCV GT1-infected, treatment-naïve, non-cirrhotic pediatric subjects will receive OBV, PTV, RTV with DSV and with or without RBV for 12 weeks.

Has been changed to read:

In Part 1 of this study eligible HCV GT1-infected, treatment-naïve, non-cirrhotic pediatric subjects will receive OBV, PTV, RTV with DSV and with or without RBV for 12 weeks.

Section 5.1 Overall Study Design and Plan: Description
First paragraph, eighth sentence previously read:

After completing the Post-Treatment Period in Part 1 or Part 2, the subjects will be followed in Part 3 for 168 weeks.

Has been changed to read:

After completing the Post-Treatment Period in Part 1 or Part 2, the subjects will be followed in Part 3 for 144 weeks.

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>Part 1</u>
First paragraph previously read:

In Part 1, the primary objective is to assess the pharmacokinetics of OBV, PTV, RTV and DSV with or without RBV in HCV GT1-infected, treatment-naive pediatric subjects. Part 1 will include approximately 36 subjects. At least 12 subjects will enroll in each of the 3 age year groups, ≥ 3 to 8, ≥ 9 to 11, and ≥ 12 to 17. Enrollment will begin with pediatric subjects ≥ 12 to 17 years old who are ≥ 45 kg and willing to swallow the 3D adult formulations. After acceptable pharmacokinetic and safety data are available from at least 6 subjects from the ≥ 12 to 17 age group who receive the adult 3D regimen, subjects ages ≥ 9 to 11 will begin enrollment to be administered the mini-tablet formulations. After acceptable pharmacokinetic and safety data are available from at least 6 subjects from the ≥ 9 to 11 age group (at least 4 of which have a body weight of 15 to 44 kg) subjects ages ≥ 3 to 8 will be enrolled in the mini-tablets. In the ≥ 3 to 8 year age group, at least 4 subjects each from subgroups ≥ 3 to 5 and ≥ 6 to 8 years old will be enrolled to ensure that there is adequate information for dosing recommendations for the entire ≥ 3 to 8 age group. Up to 12 additional pediatric subjects may be enrolled in Part 1 if needed to adequately characterize the pharmacokinetics and determine the final dose strength for a particular age group or subgroup. After the doses are established for the ≥ 9 to 11 and ≥ 3 to 8 age groups using the mini-tablets, at least 6 additional subjects in each of the age groups will be enrolled and administered the co-formulated pellet formulation if

available to establish the PK, safety and efficacy of this formulation. Subjects will be followed in Part 1 of the study through Post-Treatment Week 24.

Has been changed to read:

In Part 1, the primary objectives are to assess the pharmacokinetics, efficacy and safety of OBV, PTV, RTV and DSV with or without RBV in HCV GT1-infected, treatment-naive pediatric subjects. Part 1 will include approximately 36 subjects. At least 12 subjects will enroll in each of the 3 age year groups, ≥ 3 to 8, ≥ 9 to 11, and ≥ 12 to 17. Enrollment will begin with pediatric subjects ≥ 12 to 17 years old who are ≥ 45 kg and willing to swallow the OBV/PTV/RTV and DSV adult formulations. After acceptable pharmacokinetic, efficacy and safety data are available from at least 6 subjects from the ≥ 12 to 17 age group who receive the adult regimen, subjects ages ≥ 9 to 11 will begin enrollment to be administered the mini-tablet formulations. After acceptable pharmacokinetic, efficacy and safety data are available from at least 6 subjects from the ≥ 9 to 11 age group (at least 4 of which have a body weight of 15 to 44 kg) subjects ages ≥ 3 to 8 will be enrolled and administered the mini-tablets. In the ≥ 3 to 8 year age group, at least 2 subjects each from subgroups ≥ 3 to 5 and ≥ 6 to 8 years old will be enrolled to ensure that there is adequate information for dosing recommendations for the entire ≥ 3 to 8 age group. Up to approximately 12 additional pediatric subjects may be enrolled to receive the mini-tablet formulation in Part 1 if needed to adequately characterize the pharmacokinetics and determine the final dose strength for a particular age group or subgroup. Subjects will be followed in Part 1 of the study through Post-Treatment Week 24.

Section 5.1 Overall Study Design and Plan: Description
Subsection <u>Part 1</u>
Second paragraph, second sentence previously read:

All other children < 12 years of age will be dosed with either a pediatric mini-tablet formulation or pediatric co-formulated pellets.

Has been changed to read:

All other children ≥ 3 to 11 years of age will be dosed with the pediatric mini-tablet formulation.

Section 5.1 Overall Study Design and Plan: Description
Subsection Part 1
Heading "Dose Adjustment Considerations for Part 1"
First paragraph, second sentence previously read:

No dose adjustments of DAAs will be made as a consequence of weight change during the treatment period.

Has been changed to read:

No dose adjustments of DAAs or RBV will be made as a consequence of weight change during the treatment period.

Section 5.1 Overall Study Design and Plan: Description
Subsection Part 2
First sentence previously read:

In Part 2, the primary objectives are to evaluate the safety and efficacy (percentage of treatment-naïve or treatment-experienced subjects achieving SVR_{12}) of OBV/PTV/RTV and DSV with or without RBV in HCV GT1-infected subjects and OBV/PTV/RTV in GT4-infected pediatric subjects with or without compensated cirrhosis.

Has been changed to read:

In Part 2, the primary objectives are to further evaluate the safety and efficacy (percentage of treatment-naïve or treatment-experienced subjects achieving SVR_{12}) of OBV/PTV/RTV and DSV with or without RBV in HCV GT1-infected pediatric subjects and OBV/PTV/RTV in GT4-infected pediatric subjects with or without compensated cirrhosis.

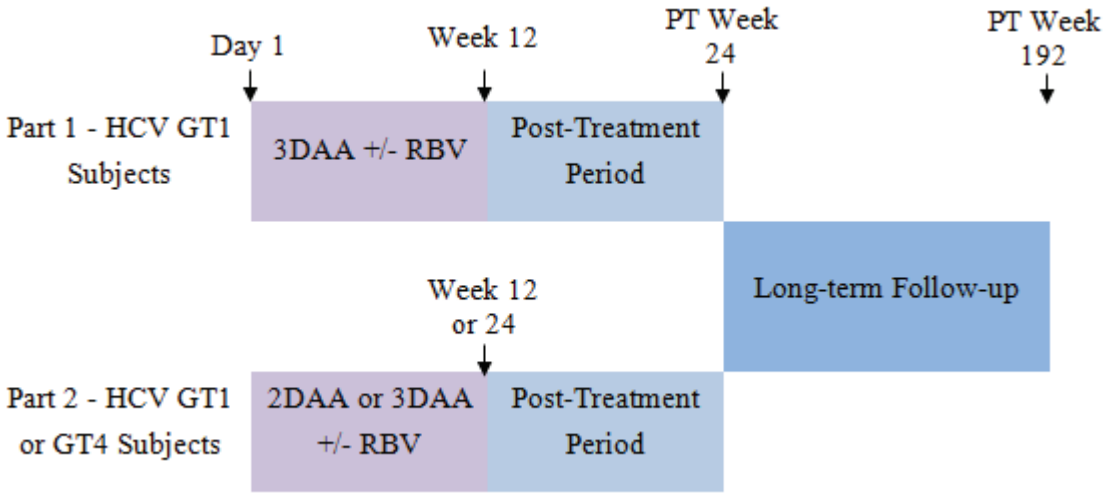
Section 5.1 Overall Study Design and Plan: Description
Subsection Part 3 (Long-Term Follow-Up Period)
Second sentence previously read:

All pediatric subjects who complete the PT Week 24 visit in Part 1 or Part 2 will be automatically enrolled into Part 3 and followed for up to 168 weeks.

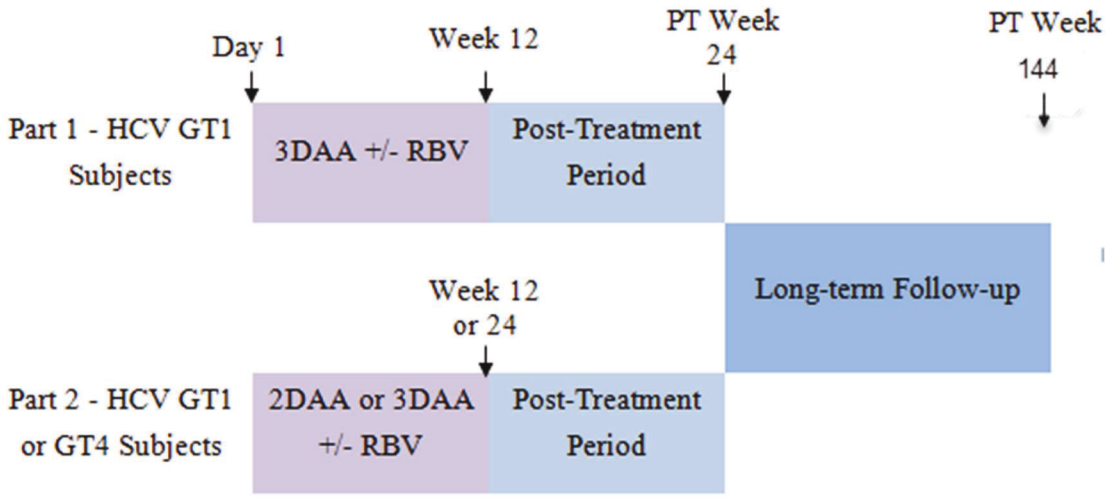
Has been changed to read:

All pediatric subjects who complete the PT Week 24 visit in Part 1 or Part 2 will be automatically enrolled into Part 3 and followed for up to 144 weeks.

Figure 1. Study Schematic
Previously read:



Has been changed to read:



Section 5.1 Overall Study Design and Plan: Description
Subsection <u>Fibrosis Assessment</u>
Last paragraph, first sentence previously read:

The study is designed to enroll approximately 74 subjects to meet scientific, regulatory and clinical objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Has been changed to read:

The study is designed to enroll approximately 62 subjects to meet scientific, regulatory and clinical objectives without enrolling an undue number of subjects in alignment with ethical considerations.

Table 6. Treatment Regimen and Duration – Part 2
Table title previously read:

Treatment Regimen and Duration – Part 2

Has been changed to read:

Treatment Regimen and Duration – Part 2 (For Subjects ≥ 12 – 17 Years of Age)

Section 5.1.4 Long-Term Follow-Up Period
First paragraph, second sentence previously read:

The Long-term Follow-up Period will begin the day following the Post-Treatment Week 24 visit and last for 168 weeks as outlined in Appendix C.

Has been changed to read:

The Long-term Follow-up Period will begin the day following the Post-Treatment Week 24 visit and last for 144 weeks as outlined in Appendix C.

Section 5.2.1 Inclusion Criteria
Criterion 1, 2, 3 and 4 previously read:

1. Male or female ≥ 3 to 17 years of age at time of enrollment.

2. Willingness to participate in the study for up to 50 months.

3. If female, subject must either be pre-menarche and not sexually active, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) OR for Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 4 months after stopping study drug if receiving RBV (or as directed by local RBV label).

4. If male subject and sexually active with female partner(s) of childbearing potential, subject must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1 and for up to 7 months after stopping study drug (or as directed by the local RBV label if receiving RBV) or from Study Day 1 through 30 days after last dose of study drug for subjects whose study regimen does not include RBV.

Has been changed to read:

1. Male or female ≥ 3 to 17 years of age with weight ≥ 15 kg at time of enrollment.

2. Willingness to participate in the study for up to 42 months.

3. If female, subject must either be pre-menarche and not sexually active, permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy or hysterectomy) OR for Women of Childbearing Potential (WOCBP) practicing at least one protocol specified method of birth control (Section 5.2.4), starting at Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).

4. If male subject and sexually active with female partner(s) of childbearing potential, subject must agree to practice the protocol specified contraception (Section 5.2.4), from Study Day 1 and for up to 9 months after stopping study drug (or as directed by the local RBV label if receiving RBV) or from Study Day 1 through 30 days after last dose of study drug for subjects whose study regimen does not include RBV.

Section 5.2.2 Exclusion Criteria
Criterion 1 previously read:

Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after stopping study drug (if not receiving RBV), or for up to 4 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Has been changed to read:

Female subject who is pregnant, breastfeeding or is considering becoming pregnant during the study or for approximately 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Table 7. Medications Contraindicated for Use with the Study Drug Regimen
Previously read:

Alfuzosin	Ethinyl estradiol-containing	Pimozide
Astemizole	medications	Rifampin
Blonanserin	Fusidic Acid	Salmeterol
Carbamazepine	Gemfibrozil[a]	Sildenafil[b]
Cisapride	Lovastatin	Simvastatin
Dihydroergotamine	Methylergonovine	St. John's Wort
Efavirenz	Midazolam (oral)	Terfenadine
Ergotamine	Phenobarbital	Triazolam
Ergonovine	Phenytoin	

a. Strong CYP2C8 inhibitors (e.g., gemfibrozil) and CYP2C8 inducers are not contraindicated with ombitasvir, paritaprevir and ritonavir (for GT4 subjects).

b. When used for the treatment of pulmonary arterial hypertension.

Note: Not all medications contraindicated with ribavirin are listed above. Refer to the most current package inserts or product labeling of ribavirin for a complete list of contraindicated medications.

Has been changed to read:

Alfuzosin	Ethinyl estradiol-containing	Pimozide
Astemizole	medications	Ranolazine
Atorvastatin	Fusidic Acid	Rifampin
Blonanserin	Gemfibrozil[a]	Salmeterol
Carbamazepine	Lovastatin	Sildenafil[b]
Cisapride	Lurasidone	Simvastatin
Colchicine[c]	Methylergonovine	St. John's Wort
Dihydroergotamine	Midazolam (oral)	Terfenadine
Dronedarone	Phenobarbital	Triazolam
Efavirenz	Phenytoin	
Ergotamine		
Ergonovine		

a. Strong CYP2C8 inhibitors (e.g., gemfibrozil) and CYP2C8 inducers are not contraindicated with ombitasvir, paritaprevir and ritonavir (for GT4 subjects).

b. When used for the treatment of pulmonary arterial hypertension.

c. When used in patients with renal or hepatic impairment.

Note: Not all medications contraindicated with ribavirin are listed above. Refer to the most current package inserts or product labeling of ribavirin for a complete list of contraindicated medications.

Section 5.2.2 Exclusion Criteria
Criterion 11 previously read:

Male subject who is considering fathering a child or donating sperm during the study or for approximately 120 days after stopping study drug if receiving DAAs only, or for up to 7 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Has been changed to read:

Male subject who is considering fathering a child or donating sperm during the study or for approximately 120 days after stopping study drug if receiving DAAs only, or for up to 9 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Section 5.2.4 Contraception Recommendations and Pregnancy Testing
Second paragraph, third bullet previously read:

Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 4 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Has been changed to read:

Practicing at least one of the following methods of birth control, on Study Day 1 (or earlier) through at least 30 days after stopping study drug (if not receiving RBV), or for up to 6 months after stopping study drug if receiving RBV (or as directed by local RBV label).

Section 5.2.4 Contraception Recommendations and Pregnancy Testing
Sixth paragraph, fourth bullet previously read:

if sexually active with female partner(s) of childbearing potential must agree to practice contraception with a method listed below from Study Day 1 and for up to 7 months after stopping study drug (or as directed by the local RBV label if receiving RBV) or from

Study Day 1 and continue for 120 days after last dose of study drug for subjects whose study regimen does not include RBV.

Has been changed to read:

if sexually active with female partner(s) of childbearing potential must agree to practice contraception with a method listed below from Study Day 1 and for up to 9 months after stopping study drug (or as directed by the local RBV label if receiving RBV) or from Study Day 1 and continue for 120 days after last dose of study drug for subjects whose study regimen does not include RBV.

Section 5.2.4 Contraception Recommendations and Pregnancy Testing
Last paragraph previously read:

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 120 days after the end of treatment if taking DAAs only, or for 7 months after the last dose of RBV (or per local RBV label).

Has been changed to read:

Additionally, male subjects must agree not to donate sperm from Study Day 1 through 120 days after the end of treatment if taking DAAs only, or for 9 months after the last dose of RBV (or per local RBV label).

Table 8. Clinical Laboratory Tests
Column "Clinical Chemistry"
Delete:

Alpha fetoprotein

Section 5.3.1.1 Study Procedures
Subsection <u>Acceptability Questionnaires</u>
Subsection title previously read:

Acceptability Questionnaires

Has been changed to read:

Acceptability Questionnaire

Section 5.3.1.1 Study Procedures
Subsection <u>Acceptability Questionnaires</u>
First paragraph, first sentence previously read:

For each subject who is taking the mini-tablet or pellet formulations, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form.

Has been changed to read:

For each subject who is taking the mini-tablet formulation, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form.

Section 5.3.1.1 Study Procedures
Subsection <u>Historical Liver Biopsy or FibroScan or Screening Fibro Test</u>
First paragraph, last sentence previously read:

Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will undergo a non-invasive FibroTest and APRI at Screening to determine presence or absence of cirrhosis.

Has been changed to read:

Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will undergo a non-invasive FibroTest at Screening to determine presence or absence of cirrhosis.

Section 5.3.1.1 Study Procedures
Subsection Historical Liver Biopsy or FibroScan or Screening Fibro Test
Heading "Longitudinal Fibrotest and APRI"
Heading title and text previously read:

Longitudinal Fibrotest and APRI

All subjects will undergo assessment of FibroTest and APRI at Screening or Day 1 and FibroTest and APRI at PT Weeks 24, 96 and 192. Any subject that does not have a FibroTest and APRI performed during Screening will have them performed at Day 1.

Has been changed to read:

Longitudinal Fibrotest

All subjects will undergo assessment of FibroTest at Screening or Day 1 and FibroTest at PT Weeks 24, and 144. Any subject that does not have a FibroTest performed during Screening will have them performed at Day 1.

Section 5.3.1.1 Study Procedures
Subsection Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein
Subsection title previously read:

Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein

Has been changed to read:

Hepatocellular Carcinoma Screening: Liver Ultrasound

Section 5.3.1.1 Study Procedures
Subsection Hepatocellular Carcinoma Screening: Liver Ultrasound and Alpha Fetoprotein
First paragraph previously read:

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver and alpha fetoprotein testing will be performed as indicated in Appendix C for subjects with compensated cirrhosis only.

Has been changed to read:

In order to monitor for the presence of hepatocellular carcinoma (HCC), an ultrasound of the liver will be performed as indicated in Appendix C for subjects with compensated cirrhosis only.

Section 5.3.1.1 Study Procedures
Subsection Ribavirin Diary
Add: new subsection title and text

Ribavirin Diary

At Day 1, the principal investigator or designee will provide the parent(s)/legal guardian(s) with a Ribavirin Diary in case the subject is taking the RBV solution formulation. The principal investigator or designee will complete the header of the RBV diary and instruct the parent(s)/legal guardian(s) on the completion of the diary. The parent(s)/legal guardian(s) must bring the completed RBV diary to each of the study visits. The principal investigator or designee will transcribe the information from the RBV diary into the RAVE system.

Section 5.3.2.1 Collection of Samples for Analysis
Subsection Part 2
Fourth and fifth paragraph previously read:

For Part 1, the maximum amount of blood drawn for pharmacokinetic samples will be approximately 10 mL during a 24-hour period (at Week 2) and approximately 14 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

For Part 2, the maximum amount of blood drawn for pharmacokinetic samples will be approximately 2 mL during any 24-hour period and approximately 6 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

Has been changed to read:

For Part 1, the maximum amount of blood drawn will be approximately 18.3 mL during a 24-hour period (at Week 2) and approximately 55.8 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

For Part 2, the maximum amount of blood drawn after Day 1 (25.8 mL) will be approximately 11.7 mL during any 24-hour period and approximately 49.2 mL during a 30-day period (from Day 1 to Week 4) as indicated in Appendix D.

Section 5.3.3.1 Primary Variables
Last paragraph and bullet list previously read:

The primary efficacy endpoint from Parts 1 and 2 is:

- The percentage of treatment-naïve subjects with SVR_{12} among subjects on the final dose formulations.

Has been changed to read:

The primary efficacy endpoint is:

- The percentage of subjects with SVR_{12} among all subjects.

Section 5.3.3.2 Secondary Variables
Bullet list previously read:

- The percentage of subjects with SVR_{12} by formulation and age group and across all subjects on the adult formulations.
- The percentage of subjects with SVR_{24} by formulation and age group, across all subjects on the final dose formulations, and across all subjects on the adult formulations.
- The percentage of treatment-naïve subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline by formulation and age group, across all subjects on the final dose formulations, and across all subjects the an adult formulations.

Has been changed to read:

- The percentage of subjects with SVR_{12} by formulation, age and weight group and across all subjects on the adult formulations.
- The percentage of subjects with SVR_{24} by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.
- The percentage of treatment-naïve subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

Section 5.4.3 Discontinuation of Subjects Meeting Virologic Failure Criteria
Second and third bullet previously read:

- Confirmed HCV RNA ≥ LLOQ (defined as 2 consecutive HCV RNA measurements ≥ LLOQ) at any point after achieving HCV RNA < LLOQ
- Failure to achieve HCV RNA < LLOQ on or before Week 6

Has been changed to read:

- Confirmed HCV RNA ≥ 100 IU/ml (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/ml) at any point after achieving HCV RNA < LLOQ

Section 5.4.3 Discontinuation of Subjects Meeting Virologic Failure Criteria
Delete: second paragraph

The sites should contact the subjects who have HCV RNA ≥ LLOQ at the Week 4 visit and have them return to the site at Week 6 for an unscheduled visit for HCV RNA testing. Only subjects with HCV RNA ≥ LLOQ at the Week 4 visit need to return to the site for an unscheduled blood draw for HCV RNA at Week 6. If an inadequate virologic response at Week 6 is due to noncompliance or incorrect dosing or there is no evidence of virologic breakthrough, the study investigator may consider continuing treatment with the permission of the Study TA SD/TA MD.

Section 5.5.1 Treatments Administered
First and second paragraph previously read:

Each dose of open-label DAA study drugs (ombitasvir, paritaprevir, ritonavir and dasabuvir) and ribavirin will be dispensed in the form of tablets, mini-tablets, pellets, or as an oral solution (RBV only). Study drugs will be dispensed at the visits listed in Appendix C.

Note on dosage form nomenclature: In the iPSPs and Study M14-748 protocol, the pediatric dosage form was previously referred to as either mini-tablets or granules. AbbVie has now determined the correct nomenclature for the pediatric dosage form to be "mini-tablets" for the administration of separate, individual components of the 3D regimen (ombitasvir, paritaprevir, ritonavir and dasabuvir) and "pellets" for the administration of co-formulated ombitasvir/paritaprevir/r with dasabuvir and will use this terminology for all new documents, but legacy documents or legacy investigational drug product labeling will not be revised.

Has been changed to read:

Each dose of open-label DAA study drugs (ombitasvir, paritaprevir, ritonavir and dasabuvir) and ribavirin will be dispensed in the form of tablets, mini-tablets, or as an oral solution (RBV only). Study drugs will be dispensed at the visits listed in Appendix C.

Section 5.5.1 Treatments Administered
Subsection <u>Part 1 Mini-Tablet and Pellet Formulations:</u>
Subsection title previously read:

Part 1 Mini-Tablet and Pellet Formulations:

Has been changed to read:

Part 1 Mini-Tablet:

Section 5.5.1 Treatments Administered
Subsection Part 1 Mini-Tablet and Pellet Formulations:
Add: new third paragraph

The mini-tablets are packed in unit doses and are to be administered at once. The legal guardian(s) should be counselled by site to check that the study drug bottles have been emptied completely into the dosing vehicle to assure the complete dose is taken by the subject. Ombitasvir, Paritaprevir, Ritonavir will be taken orally and will be dosed QD based on body weight. Dasabuvir will be taken orally and will be dosed BID based on body weight.

Section 5.5.1 Treatments Administered
Subsection Part 1 Mini-Tablet and Pellet Formulations:
Delete: fifth paragraph

Once the final dose strength for the mini-tablets has been determined, enrollment into pellet dosing will be open upon sponsor notification.

Section 5.5.1 Treatments Administered
Subsection Part 1 Mini-Tablet and Pellet Formulations:
Delete: seventh and eighth paragraph previously read:

A fixed dose pellet combination formulation containing ombitasvir/paritaprevir/r and a dasabuvir pellet formulation will be provided by the Sponsor as pellets per unit dose packaging. The unit dose strength of ombitasvir/paritaprevir/r and dasabuvir will be determined with dose selection based on mini-tablet dosing in Part 1. Ombitasvir/paritaprevir/r will be taken orally and will be dosed QD based on body weight.

Dasabuvir will be taken orally and will be dosed BID based on body weight.

Section 5.5.2 Identity of Investigational Products
Previously read:

Information regarding the study drugs to be used in this study is presented in Table 10.

Table 10. Identity of Investigational Products

Part	Investigational Product	Manufacturer	Mode of Administration	Formulation	Strength
1 & 2	Ombitasvir/paritaprevir/ ritonavir	AbbVie	Oral	Tablets	12.5/75/50 mg
1 & 2	Dasabuvir	AbbVie	Oral	Tablets	250 mg
1	Ombitasvir	AbbVie	Oral	Mini-tablets	0.3 mg
1	Paritaprevir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Ritonavir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Dasabuvir	AbbVie	Oral	Mini-tablets	3.08 mg
1	Ombitasvir/paritaprevir/ ritonavir	AbbVie	Oral	Pellets	X1/X2/X3 mg*
1	Dasabuvir	AbbVie	Oral	Pellets	X4* mg
1 & 2	Ribavirin	Kadmon/ AbbVie	Oral	Tablets	200 mg
1	Ribavirin	Merck	Oral	Solution	40 mg/mL
2	Ribavirin	MSD Sharp & Dohme	Oral	Solution	40 mg/mL

* The unit dose strength of ombitasvir, paritaprevir, ritonavir and dasabuvir will be determined with dose selection based on Part 1.

Has been changed to read:

Information regarding the study drugs to be used in this study is presented in Table 10.

Table 10. Identity of Investigational Products

Part	Investigational Product	Manufacturer	Mode of Administration	Formulation	Strength
1 & 2	Ombitasvir/paritaprevir/ ritonavir	AbbVie	Oral	Tablets	12.5/75/50 mg
1 & 2	Dasabuvir	AbbVie	Oral	Tablets	250 mg
1	Ombitasvir	AbbVie	Oral	Mini-tablets	0.3 mg
1	Paritaprevir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Ritonavir	AbbVie	Oral	Mini-tablets	1.0 mg
1	Dasabuvir	AbbVie	Oral	Mini-tablets	3.08 mg
1 & 2	Ribavirin	Kadmon/ AbbVie	Oral	Tablets	200 mg
1	Ribavirin	Merck	Oral	Solution	40 mg/mL
2	Ribavirin	MSD Sharp & Dohme	Oral	Solution	40 mg/mL

Section 5.5.2.1 Packaging and Labeling
First paragraph
Delete: third sentence

Pellets will be provided in unit dose packaging.

Section 5.5.2.1 Packaging and Labeling
Last paragraph previously read:

All blank spaces on the study drug labels should be completed by site staff prior to dispensing to subjects.

Has been changed to read:

All blank spaces (if applicable) on the study drug labels should be completed by site staff prior to dispensing to subjects.

Section 5.5.2.2 Storage and Disposition of Study Drugs
Third and fourth paragraph previously read:

Ombitasvir/paritaprevir/r pellets and dasabuvir pellets will be supplied to the sites in unit dose packaging.

Mini-tablets and pellets can be administered in a dosing vehicle (e.g., applesauce, see dosing card for instructions).

Has been changed to read:

Mini-tablets can be administered in a dosing vehicle (e.g., applesauce, see dosing card for instructions).

Section 5.5.3 Method of Assigning Subjects to Treatment Groups
Second paragraph, first sentence previously read:

First, the subjects in the ≥ 12 to 17 year age group of Part 1 who are ≥ 45 kg and willing to swallow the adult formulations will be enrolled, then other groups of Part 1 will be enrolled (Section 5.1).

Has been changed to read:

First, the subjects in the ≥ 12 to 17 year age group of Part 1 who are ≥ 45 kg and willing to swallow the adult formulations will be enrolled, then sequential enrollment into the other age groups of Part 1 will start (Section 5.1).

Section 5.5.6 Treatment Compliance
Second paragraph
Add: new last sentence

When dosing mini-tablets, the bottles should be checked thoroughly to ensure that no mini-tablets remained inside the bottle.

Section 5.5.6 Treatment Compliance
Last paragraph, second sentence previously read:

The study site personnel will inspect the contents of the study drug units and account for the returned study drug electronically at each Study Drug Accountability visit indicated in Appendix C.

Has been changed to read:

The study site personnel will inspect the contents of the study drug bottles and account for the returned study drug electronically at each Study Drug Accountability visit indicated in Appendix C.

Section 5.5.7 Drug Accountability
Subsection Adult Formulation and RBV Tablets Part 1 and Part 2
Subsection title previously read:

Adult Formulation and RBV Tablets Part 1 and Part 2

Has been changed to read:

Adult Formulations and RBV Tablets Part 1 and Part 2

Section 5.5.7 Drug Accountability
Subsection Mini-Tablets and Pellets (Part 1)
Subsection title and text previously read:

Mini-Tablets and Pellets (Part 1)

The status of each returned mini-tablet and pellet container will be noted in the IRT system and on a drug accountability log (if appropriate). The Investigator/designee must document the status of the returned containers as full/sealed or empty or unsealed but not empty in the IRT system. Labels must remain affixed to the bottles.

Has been changed to read:

Mini-Tablet Formulation (Part 1)

The status of each returned mini-tablet bottle will be noted in the IRT system and on a drug accountability log (if appropriate). The Investigator/designee must document the status of the returned bottles as full/sealed or empty or unsealed but not empty in the IRT system. Labels must remain affixed to the bottles.

Section 5.6.3 Justification of Primary and Secondary Endpoint Success Criteria
Previously read:

According to the Highlights of Prescribing Information of PEGASYS®, the SVR_{24} rate was 47% among 45 treatment-naïve pediatric subjects with HCV GT1 in the NV17424 trial.[1] To show that the DAA regimen is superior to this current standard of care by 20%, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate in subjects on the final dose formulations in the study must be greater than 67%.

For the secondary endpoints of the percentage of subjects with SVR_{12}, the percentage of subjects with SVR_{24}, and the percentage of subjects with ALT normalization during treatment, the simple percentage will be calculated along with a 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate in subjects treated with a final dose formulation in the study will also be compared to 67%. ALT normalization is defined as the percentage of subjects with ALT at or below the upper limit of normal (ULN) at the final treatment visit among subjects with ALT > ULN at baseline, and will be presented along with a 2-sided 95% confidence interval.

Has been changed to read:

According to the Highlights of Prescribing Information of PEGASYS®, the SVR_{24} rate was 47% among 45 treatment-naïve pediatric subjects with HCV GT1 in the NV17424 trial.[1] To show that the DAA regimen is superior to this current standard of care by 20%, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%.

For the secondary endpoints of the percentage of subjects with SVR_{12} by formulation, age and weight group, the percentage of subjects with SVR_{24}, and the percentage of subjects with ALT normalization during treatment, the simple percentage will be calculated along with a 2-sided 95% confidence interval. The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%. ALT normalization is defined as the percentage of subjects with ALT at or below the

upper limit of normal (ULN) at the final treatment visit among subjects with ALT > ULN at baseline, and will be presented along with a 2-sided 95% confidence interval.

Section 5.6.4 Suitability of Subject Population
Third sentence previously read:

For the younger children in the ≥ 3 to 8 and ≥ 9 to 11 year old age groups, a mini-tablet or pellet formulation of all the DAAs and RTV will be used for ease of administration.

Has been changed to read:

For the younger children in the ≥ 3 to 8 and ≥ 9 to 11 year old age groups, a mini-tablet formulation of all the DAAs and RTV will be used for ease of administration.

Section 5.6.5 Selection of Doses in the Study
Fifth paragraph previously read:

For Part 1 of the present study, the proposed doses by body weight range are shown in Table 11.

Has been changed to read:

For Part 1 of the present study, the proposed doses by body weight range for subjects administered the adult formulation or the mini tablet formulation are shown in Table 11.

Table 11. Proposed DAA and Ritonavir Doses for Pediatric Population
Table title and table previously read:

Table 11. Proposed DAA and Ritonavir Doses for Pediatric Population

	Body Weight			
	≤ 14 kg	**15 to 29 kg**	**30 to 44 kg**	**≥ 45 kg**
Paritaprevir (QD)	35 mg	50 mg	100 mg	150 mg
Ritonavir (QD)	25 mg	35 mg	70 mg	100 mg
Ombitasvir (QD)	5 mg	10 mg	15 mg	25 mg
Dasabuvir (BID)	50 mg	100 mg	150 mg	250 mg

Has been changed to read:

Table 12. Proposed DAA and Ritonavir Doses for Subjects Administered the Adult Formulation or Mini Tablet Formulation

	Body Weight		
	15 to 29 kg	**30 to 44 kg**	**≥ 45 kg**
Paritaprevir (QD)	50 mg	100 mg	150 mg
Ritonavir (QD)	35 mg	70 mg	100 mg
Ombitasvir (QD)	10 mg	15 mg	25 mg
Dasabuvir (BID)	100 mg	150 mg	250 mg

Section 6.1.6 Pregnancy
First paragraph previously read:

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, starting with Study Day 1 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) for males or through Post-Treatment Week 28 (or per local RBV label) for WOCBP and/or consistent with local treatment guidelines for RBV.

Has been changed to read:

Subjects and their partners should avoid pregnancy and males should avoid sperm donation throughout the course of the study, which is defined as from Study Day 1 until 30 days after the last dose of study drug if subjects do not take RBV, or from Study Day 1 until 6 months for WOCBP and 9 months for males after the last dose of the study drug containing RBV (or per local RBV label).

Section 7.0 Protocol Deviations
Contact information previously read:

Primary Contact:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Fax:

Secondary Contact:

[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen, Germany

Office: [redacted]
Fax:

Has been changed to read:

Primary Contact US/PR:

[redacted]
1 North Waukegan Road
North Chicago, IL 60064

Office: [redacted]
Fax:

Primary Contact OUS:

[redacted]
Medical Department
Avenida de Burgos, 91
28050 Madrid, Spain

Office: [redacted]
Fax:

Secondary Contact:

[redacted]
AbbVie Deutschland GmbH & Co. KG
Knollstrasse
67061 Ludwigshafen, Germany

Office: [redacted]
Fax:

Section 8.1.1 Demographics
First sentence previously read:

Demographics and baseline characteristics will be summarized by age group separately for each formulation, for all subjects on the final dose formulations (defined as the adult formulations used in either Part 1 and/or Part 2 (3D ± RBV and 2D + RBV) and the coated pellet formulation to be used in Part 1 only) and for all subjects on the adult formulations in the ITT and ITT-3 populations.

Has been changed to read:

Demographics and baseline characteristics will be summarized by age and weight group separately for each formulation, for all subjects and for all subjects on the adult formulations in the ITT and ITT-3 populations.

Section 8.1.1 Demographics
Fourth sentence previously read:

Baseline characteristics will include HCV genotype and sub-genotype (1a, 1b, 1-other and 4 if applicable), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), IFN treatment history if applicable (treatment-naïve or IFN-based treatment-experienced [prior non-responder {null responder, partial responder, or other unable to specify}, breakthrough, relapse, and interferon experienced-other]), baseline platelets (< 90 or ≥ 90 × 10^9/L), baseline albumin (< 35 or ≥ 35 g/L), baseline alpha fetoprotein (< 20 or ≥ 20 ng/mL), baseline HCV RNA levels (continuous) and (< 800,000 IU/mL or ≥ 800,000 IU/mL, baseline fibrosis stage [F0-1, F2, F3, F4]), baseline Fibrotest score, baseline APRI, baseline Child-Pugh score (non-cirrhotic, 5, 6, or > 6), tobacco use (user, ex-user, or non-user) status, alcohol use (drinker, ex-drinker, or non-drinker) status, and baseline Tanner pubertal staging – genital (males only), breast (females only), and pubic hair development. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and height z-score).

Has been changed to read:

Baseline characteristics will include HCV genotype and sub-genotype (1a, 1b, 1-other and 4 if applicable), IL28B genotype ([CC, CT, or TT] and [CC or non-CC]), IFN treatment history if applicable (treatment-naïve or IFN-based treatment-experienced [prior non-responder {null responder, partial responder, or other unable to specify}, breakthrough, relapse, and interferon experienced-other]), baseline platelets (< 90 or ≥ 90 × 10^9/L), baseline albumin (< 35 or ≥ 35 g/L), baseline HCV RNA levels (continuous) and (< 800,000 IU/mL or ≥ 800,000 IU/mL, baseline fibrosis stage [F0-1, F2, F3, F4]), baseline Fibrotest score, baseline Child-Pugh score (non-cirrhotic, 5, 6, or

> 6), tobacco use (user, ex-user, or non-user) status, alcohol use (drinker, ex-drinker, or non-drinker) status, and baseline Tanner pubertal staging – genital (males only), breast (females only), and pubic hair development. Summary statistics (N, mean, median, SD, and range) will be generated for continuous variables (e.g., age and height z-score)

Section 8.1.2.1 Primary Efficacy Endpoint Across Parts 1 and 2
First paragraph, first sentence previously read:

The primary efficacy endpoint is the percentage of subjects with SVR12 among all subjects on the final dose formulations.

Has been changed to read:

The primary efficacy endpoint is the percentage of subjects with SVR_{12} among all subjects.

Section 8.1.2.2 Secondary Efficacy Endpoints Across Parts 1 and 2
Numbered list previously read:

1. The percentage of subjects who achieve SVR_{12} by formulation and age group, and across all subjects on the adult formulations.

2. The percentage of subjects who achieve SVR_{24} by formulation and age group, across all subjects on the final dose formulations and across all subjects on the adult formulations.

3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation and age group, across all subjects on the final dose formulations and across all subjects on the adult formulations.

Has been changed to read:

1. The percentage of subjects who achieve SVR_{12} by formulation, age and weight group, and across all subjects on the adult formulations.

2. The percentage of subjects who achieve SVR_{24} by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations.

3. The percentage of subjects with ALT normalization during treatment, defined as ALT ≤ ULN at the final treatment visit for subjects with ALT > ULN at baseline, by formulation, age, and weight group, across all subjects, and across all subjects on the adult formulations.

Section 8.1.2.2 Secondary Efficacy Endpoints Across Parts 1 and 2
Last paragraph, second sentence previously read:

The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects on the final dose formulations in the study will also be compared to 67%.

Has been changed to read:

The lower bound of the 2-sided 95% confidence interval of the SVR_{24} rate across all subjects in the study will also be compared to 67%.

Section 8.1.2.3 Additional Efficacy Endpoints Across Parts 1 and 2
First paragraph previously read:

The following efficacy endpoints will be analyzed by formulation and age group, across all subjects on the final dose formulations and across all subjects on the adult formulations:

Has been changed to read:

The following efficacy endpoints will be analyzed by formulation, age and weight group, across all subjects, and across all subjects on the adult formulations:

Section 8.1.2.3 Additional Efficacy Endpoints Across Parts 1 and 2
Item 3 previously read:

3. Change from baseline to all post-baseline visits in Fibrotest score and APRI.

Has been changed to read:

3. Change from baseline to all post-baseline visits in Fibrotest score.

If the dose of the mini-tablets is adjusted for any age or weight group during the study, any subjects administered the dose considered not acceptable will be removed in a sensitivity analysis of SVR_{12} among subjects administered acceptable doses of OBV, PTV, RTV and DSV.

Section 8.1.2.3 Additional Efficacy Endpoints Across Parts 1 and 2
Third paragraph, second sentence previously read:

Breakthrough is defined as confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurement > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment.

Has been changed to read:

Breakthrough is defined as confirmed HCV RNA ≥ 100 IU/mL after HCV RNA < LLOQ during treatment, or confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurement > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment.

Section 8.1.2.3 Additional Efficacy Endpoints Across Parts 1 and 2
Last paragraph previously read:

The change from baseline to each post baseline visit of collection for Fibrotest and APRI will be summarized descriptively.

Has been changed to read:

The change from baseline to each post baseline visit of collection for Fibrotest will be summarized descriptively.

Section 8.1.2.4 Subgroup Analysis of Parts 1 and 2
First paragraph previously read:

For subjects on the final dose formulations the number and percentage of subjects with SVR_{12} will be presented along with the 2-sided 95% confidence interval for the following subgroups if applicable.

Has been changed to read:

The percentage of subjects with SVR_{12} will be presented along with the 2-sided 95% confidence interval for the following subgroups if applicable.

Section 8.1.2.4 Subgroup Analysis of Parts 1 and 2
Second paragraph, third and fourth bullet previously read:

- Baseline alpha fetoprotein (< 20, ≥ 20 ng/mL)
- Any of platelets < 90×10^9/L, albumin < 35 g/L, or alpha fetoprotein ≥ 20 ng/mL, or none of the three

Has been changed to read:

- Any of platelets < 90×10^9/L and albumin < 35 g/L

Section 8.1.2.5 Treatment Failures
First paragraph previously read:

Across Parts 1 and 2, the number and percentage of subjects on final dose formulations, on the adult formulations and on the mini-tablet formulation meeting each and any of the following SVR_{24} and SVR_{12} non-response categories will summarized. The summary might also be subgrouped by age group and HCV genotypes/sub-genotypes.

Has been changed to read:

Across Parts 1 and 2, the number and percentage of subjects overall, on the adult formulations, and on the mini-tablet formulation meeting each and any of the following

SVR_{24} and SVR_{12} non-response categories will summarized. The summary might also be subgrouped by age and weight group, and HCV genotypes/sub-genotypes.

Section 8.1.5 Acceptability Questionnaire
Previously read:

For each subject taking the mini-tablet/pellet formulations, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form at the visits indicated in Appendix C.

Separately for mini-tablet and pellet formulations, the number and percentage of subjects with each categorical answer marked will be presented for each question in the acceptability questionnaire at each applicable treatment visit overall, by age group, and by weight group. Listings of acceptability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced separately for each part.

Has been changed to read:

For each subject taking the mini-tablet formulation, the parent(s)/guardian(s) of the subject will complete an Acceptability Questionnaire to provide feedback on the perception of the dosage form at the visits indicated in Appendix C.

The number and percentage of subjects with each categorical answer marked will be presented for each question in the acceptability questionnaire at each applicable treatment visit overall, by age and weight group. Listings of acceptability questionnaire results and comments for each applicable subject over applicable treatment visits will be produced.

Section 8.1.6 Safety
Second sentence previously read:

The safety analysis will be carried out for all subjects in Parts 1 and 2 by formulation and age group, for all subjects on the final dose formulations, for all subjects on the adult formulations, and for all subjects on the mini-tablet formulation.

Has been changed to read:

The safety analysis will be carried out for all subjects by formulation, age and weight group, for all subjects on the adult formulation.

Section 8.1.8 Pharmacokinetic and Exposure-Response Analyses
First, second and third paragraph previously read:

Plasma concentrations of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV will be tabulated and summarized for subjects in Part 1 and Part 2 by age group and overall.

Values for the pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV including the C_{max}, T_{max}, C_{trough}, and AUC will be tabulated and summarized for subjects in Part 1 by age group and overall. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Plasma concentration data from Part 1 and Part 2 of this study may be combined with data from other studies and analyzed using the following general methodology.

Has been changed to read:

Plasma concentrations of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV will be tabulated and summarized as appropriate by formulation, weight range or age group for subjects in Part 1 and Part 2.

Values for the pharmacokinetic parameters of OBV, PTV, DSV, DSV M1 metabolite, RTV and RBV including the C_{max}, T_{max}, C_{trough}, and AUC will be tabulated and summarized formulation, weight range or age group for subjects in Part 1. Additional parameters or summaries may be determined if useful in the interpretation of the data.

Section 8.2 Determination of Sample Size
Last paragraph, second and third sentence previously read:

To show that the DAA regimen is superior to this current standard of care by 20% in Parts 1 and 2, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate in

subjects treated with a final dose formulation in the study must be greater than 67%. For the primary efficacy endpoint of the percentage of subjects with SVR_{12} out of all subjects dosed with a final dose formulation, if it is assumed 90% subjects would achieve SVR_{12} then 50 subjects would have > 90% power to have a lower bound of 2-sided confidence interval based on normal approximation to the binomial distribution > 67%.

Has been changed to read:

To show that the DAA regimen is superior to this current standard of care by 20% in Parts 1 and 2, the lower bound of the 2-sided 95% confidence interval of the SVR_{12} rate across all subjects in the study must be greater than 67%. For the primary efficacy endpoint of the percentage of subjects with SVR_{12}, if it is assumed 90% subjects would achieve SVR_{12} then 50 or more subjects would have > 90% power to have a lower bound of 2-sided confidence interval based on normal approximation to the binomial distribution > 67%.

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	Pharmacokinetics
		Clinical
		Clinical
		Global Drug Supply
		Clinical
		Statistics
		Clinical
		Bioanalysis

Has been changed to read:

Name	Title	Functional Area
[redacted]		Pharmacokinetics
		Clinical
		Clinical
		Global Drug Supply
		Clinical
		Statistics
		Clinical
		Bioanalysis

Appendix C. Study Activities
Subsection <u>Study Activities – Treatment Period – Parts 1 and 2</u>
Activity "Longitudinal Fibrotest & APRI" previously read:

Longitudinal Fibrotest & APRI

Has been changed to read:

Longitudinal Fibrotest

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Delete: Activity "HCC Assessment: Alpha fetoprotein[p]"

	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			
Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	Premature D/C from Treatment[c]
HCC Assessment: Alpha fetoprotein[p]	X								X	X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Activity "HCV RNA Samples" previously read:

	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			
Activity	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	Premature D/C from Treatment[c]
HCV RNA Samples	X	X	X	X[x]	X	X	X	X	X	X

Has been changed to read:

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			
	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	Premature D/C from Treatment[c]
HCV RNA Samples	X	X	X	X	X	X	X	X	X	X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Add: Activity "Drug compliance review[dd]"

Activity	Treatment Period (TP)									
	Treatment Visits – All Subjects						Treatment Visits – 24-Week*			
	Screening	Day 1[a]	Wk 2	Wk 4	Wk 8	Wk 12 or EOT[b]	Wk 16	Wk 20	Wk 24 (EOT)[b]	Premature D/C from Treatment[c]
Drug compliance review[dd]		X	X	X	X	X				X

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Table note "m." and "n." previously read:

m. Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will have a screening FibroTest and APRI to determine the presence or absence of cirrhosis for the purpose of treatment assignment. Subjects who have a liver biopsy or FibroScan indicating cirrhosis at any time in the past will not need a Fibrotest and APRI to be performed at screening as evidence of cirrhosis.
n. Perform a Fibrotest and APRI at Day 1 for any subject who did not have a FibroTest and APRI done during Screening.

Has been changed to read:

m. Subjects with no history of cirrhosis who have not had a liver biopsy or Fibroscan within 24 months prior to screening, will have a screening FibroTest to determine the presence or absence of cirrhosis for the purpose of treatment assignment. Subjects who have a liver biopsy or FibroScan indicating cirrhosis at any time in the past will not need a Fibrotest to be performed at screening as evidence of cirrhosis.
n. Perform a Fibrotest at Day 1 for any subject who did not have a FibroTest done during Screening.

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Table note "p.," first paragraph
Delete: last sentence

Alpha fetoprotein testing will occur every 6 months.

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Table note "s.," first paragraph
First sentence previously read:

Part 1: Study drugs will be dispensed every 2 weeks for subjects receiving the mini-tablets or pellets with study visit procedures occurring at Day 1, Weeks 2, 4, 6, 8 and 10.

Has been changed to read:

Part 1: Study drugs will be dispensed every 2 weeks for subjects receiving the mini-tablets with study visit procedures occurring at Day 1, Weeks 2, 4, 6, 8 and 10.

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Table note "v.," second paragraph previously read:

Part 1: Dispensed/Collected every 2 weeks for subjects receiving the pellets with RBV with study visit procedures occurring at Day 1, Weeks 2, 4, and 8.

Has been changed to read:

Part 1: Dispensed/Collected every 2 weeks for subjects receiving the mini-tablets with RBV with study visit procedures occurring at Day 1, Weeks 2, 4, and 8.

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Delete: table note "x."

Subjects who fail to achieve HCV RNA < LLOQ at Week 4 will return at Week 6 for an unscheduled visit to assess HCV RNA.

Appendix C. Study Activities
Subsection Study Activities – Treatment Period – Parts 1 and 2
Add: table note "dd."

Sites will inspect the returned study drug containers at every visit to determine drug compliance. Sites will counsel legal guardian(s) in case of non-drug compliance. See Section 5.5.6 for more details.

Appendix C. Study Activities
Subsection Study Activities – Post-Treatment – Parts 1, 2 and 3
Previously read:

Activity	Post-Treatment (PT)						
	Post-Treatment Period of Parts 1 and 2 (PTP)			Part 3: Long-Term Follow-Up (LTFU)			Premature D/C
	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 72, 96, 120, 144, 168, and 192	
Vital Signs, Weight, Height, Waist Circumferences[a]	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X	(Weeks 12, 16)					X
Longitudinal Fibrotest and APRI			X			X[c]	
Hematology/Chemistry/Urinalysis[d]/Coagulation Panel	X						X
HCC Assessment: Liver Ultrasound[e]			X			X	X
HCC Assessment: Alpha fetoprotein[e]			X		X	X	X
Concomitant Medication Assessment[f]	X	X	X	X	X	X	X
Adverse Event Assessment[g]	X	X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample[h]			X	X	X	X	X
Tanner Pubertal Stage[i]		X		X		X[j]	X
Patient Reported Outcome[k]	X	X	X	X	X	X	X

D/C = Discontinuation

a. Height and Waist circumference will be measured at PT Weeks 12, 36, 72, 120, and 192 only.

b. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving DAAs only should have urine pregnancy testing done thru Post-Treatment Week 4.

c. Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving RBV should have urine pregnancy testing done monthly starting from Day 1 (Baseline) through PT Week 16 after RBV discontinuation or per local label.

d. At the PT Visit 16subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

e. FibroTest and APRI will be performed at PT Weeks 96 and 192.

f. Urinalysis will not be conducted after the Post-Treatment Week 4 visit.

g. HCC assessment for subjects with compensated cirrhosis only: Liver ultrasound testing will occur yearly. Alpha fetoprotein testing will occur every 6 months.

h. Only medications taken for SAEs assessed as related to study drugs and treatment of HCV will be collected after 30 days post-dosing.

i. Nonserious AEs and all SAEs will be collected until 30 days post dosing. Only drug-related SAEs will be collected thereafter. See Section 6.1.4.

j. Resistance samples are only collected for patients that meet virologic failure criteria.

k. The Tanner Pubertal stage is assessed for subjects aged ≥ 9 to 17 years old. Tanner staging will not be repeated once the child reaches Tanner Stage 5.

l. Tanner Pubertal Staging only performed at PT Weeks 72, 120 and 192.

m. The PRO should be administered as the first study procedure at each visit.

Has been changed to read:

Activity	Post-Treatment (PT)						
	Post-Treatment Period of Parts 1 and 2 (PTP)			Part 3: Long-Term Follow-Up (LTFU)			Premature D/C
	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96, and 144	
Vital Signs, Weight, Height, Waist Circumferences[a]	X	X	X	X	X	X	X
Urine Pregnancy Test[b]	X	(Weeks 12, 16)					X
Longitudinal Fibrotest			X			X[c]	
Hematology/Chemistry/Urinalysis[d]/Coagulation Panel	X						X
HCC Assessment: Liver Ultrasound[e]			X			X	X
Concomitant Medication Assessment[f]	X	X	X	X	X	X	X
Adverse Event Assessment[g]	X	X	X	X	X	X	X
HCV RNA Samples	X	X	X	X	X	X	X
HCV Resistance Sample[h]							
Tanner Pubertal Stage[i]		X		X		X[j]	X
Patient Reported Outcome[k]	X	X	X	X	X	X	X

D/C = Discontinuation

a. Height and Waist circumference will be measured at PT Weeks 12, 36, 96 and 144 only.

b. A positive urine pregnancy test requires a confirmatory serum test. (Refer to Section 5.3.1.1 [Pregnancy Test] for additional details.) Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving DAAs only should have urine pregnancy testing done thru Post-Treatment Week 4.

Females who are experiencing menses or are nearing sexual maturation in the opinion of the PI or who are of childbearing potential who are receiving RBV should have urine pregnancy testing done monthly starting from Day 1 (Baseline) through PT Week 16 after RBV discontinuation or per local label.

At the PT Visit 16subjects may have an unscheduled office visit for pregnancy testing or elect to perform the tests at home with test kits provided by the site. Additional testing may be required per local RBV label.

c. FibroTest will be performed at PT Weeks 24 and 144.
d. Urinalysis will not be conducted after the Post-Treatment Week 4 visit.
e. HCC assessment for subjects with compensated cirrhosis only: Liver ultrasound testing will occur yearly.
f. Only medications taken for SAEs assessed as related to study drugs and treatment of HCV will be collected after 30 days post-dosing.
g. Nonserious AEs and all SAEs will be collected until 30 days post dosing. Only drug-related SAEs will be collected thereafter. See Section 6.1.4.
h. Resistance samples are only collected at the confirmation visit for patients that potentially meet virologic failure criteria.
i The Tanner Pubertal stage is assessed for subjects aged ≥ 9 to 17 years old. Tanner staging will not be repeated once the child reaches Tanner Stage 5.
j. Tanner Pubertal Staging only performed at PT Weeks 12, 36, 96 and 144.
k. The PRO should be administered as the first study procedure at each visit.

Appendix D. Estimated Blood Loss for Pediatric Subjects
Previously read:

Treatment Period – Part 1:

	Treatment Period (TP)							
	Treatment Visits – All Subjects							
Estimated Whole Blood Drawn (mL) – using Pediatric tubes	**Screening**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 6**	**Wk 8**	**Wk 12 or EOT**	**Premature D/C from Treatment**
	21.2	29.2	38.3	23.7	6.0	22.3	23.7	24.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	29.0	31.8	40.5	26.3	6.0	24.05	26.3	28.8

Post-Treatment – Parts 1 and 3:

	Post-Treatment (PT)						
	Post-Treatment Period of Parts 1 (PTP)			Part 3: Long-Term Follow-Up (LTFU)			
Estimated Whole Blood Drawn (mL) – using Pediatric tubes	**PT Wk 4**	**PT Wk 12**	**PT Wk 24**	**PT Wk 36**	**PT Wk 48**	**PT Wks 72, 96*, 120, 144, 168, and 192***	**Premature D/C**
	19.7	16.0	20.7	16.0	17.1	17.1/*20.7	20.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	22.3	16.0	23.5	16.0	18.5	18.5/*23.5	24.8

Has been changed to read:

Treatment Period – Part 1:

	Treatment Period (TP)						
	Treatment Visits – All Subjects						
Estimated Whole Blood Drawn (mL) – using Pediatric tubes	**Screening**	**Day 1**	**Wk 2**	**Wk 4**	**Wk 8**	**Wk 12 or EOT**	**Premature D/C from Treatment**
	19.8	25.8	18.3	11.7	10.3	11.7	12.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	29.0	29.8	20.5	14.3	12.5	14.3	16.8

Treatment Period – Part 2:

	Treatment Period (TP)				
	Treatment Visits – All Subjects				Premature D/C from Treatment
Estimated Whole Blood Drawn (mL) – using	Screening	Day 1	Wk 2, 4, 8, 12, 16 and 20	Wk 24 or EOT	
Pediatric tubes	19.8	25.8	11.7	12.8	12.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	29.0	29.8	14.3	16.8	16.8

Post-Treatment – Part 3:

	Post-Treatment (PT)						
	Post-Treatment Period of (PTP)			Part 3: Long-Term Follow-Up (LTFU)			
Estimated Whole Blood Drawn (mL) – using	PT Wk 4	PT Wk 12	PT Wk 24	PT Wk 36	PT Wk 48	PT Wks 96*, and 144	Premature D/C
Pediatric tubes	8.7	6.0	20.7	16.0	17.1	20.7*/17.1	20.8
Estimated Whole Blood Drawn (mL) – using Standard tubes	12.3	6.0	23.5	16.0	18.5	23.5*/18.5	24.8