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APPLICATION NUMBER:

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MEDICAL REVIEW(S)

REVIEW of 4-MONTH SAFETY UPDATE

Date submitted: June 23, 2015
Date completed: June 30, 2015
Reviewer: Russell Fleischer, PA-C, MPH

NDA 207931 TECHNIVIE TABLETS (SN-13)

The current submission contains a 4-month safety update to augment the review of NDA 207931 for Technivie Tablets for treatment of adults with HCV genotype 4 infection without cirrhosis. There were no new safety signals identified and as such no changes to the conclusions reached in the primary review of the NDA, or draft labeling, are warranted.

Of note, the Applicant reported SVR24 rates for all genotype 4 subjects in Study M13-393. Of the 91 subjects treated with Technivie Tablets + ribavirin, all 91 (100%) maintained virologic suppression through the follow-up week 24 time period. Two subjects treated with Technivie Tablets alone who had SVR12 were either lost to follow-up or withdrew due to biliary adenocarcinoma; the overall SVR24 for this group was 86% (38/44). These data will be proposed for inclusion in labeling.

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/s/

RUSSELL D FLEISCHER
07/14/2015

JOINT CLINICAL, STATISTICAL AND VIROLOGY REVIEW

Application Type	NDA
Application Number(s)	207931
Priority or Standard	Priority
Submit Date(s)	February 25, 2015
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Division / Office	DAVP/OAP
Reviewer Name(s)	Russell Fleischer, PA-C, MPH Karen Qi, PhD Patrick Harrington, PhD
Review Completion Date	June 17, 2015
Established Names	Ombitasvir, paritaprevir, ritonavir
Trade Name	Technivie™ Tablets
Therapeutic Class	HCV NS5A inhibitor and HCV NS3/4A protease inhibitor
Applicant	AbbVie, Inc.
Formulation(s)	Co-formulated tablets
Dosing Regimen	2-ombitasvir, paritaprevir, ritonavir co-formulated tablets once daily with meals co-administered with or without weight-based ribavirin for 12 weeks
Indication(s)	Adults
Intended Population(s)	Treatment naïve and pegIFN + ribavirin experienced patients with GT4 HCV infection without cirrhosis

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

This NDA provides clinical data from an ongoing phase 2 study that support the approval of a currently approved NS3/4A protease inhibitor (ABT-450, paritaprevir) co-formulated with ritonavir + an NS5A inhibitor (ABT-267, ombitasvir) co-administered with or without ribavirin (RBV) for treatment of patients with Genotype 4 (GT4) chronic hepatitis C (CHC) virus infection without cirrhosis, including those who failed to respond to a previous course of pegylated interferon and RBV (pegIFN/RBV) therapy.

Ombitasvir and paritaprevir (with a third drug dasabuvir) are components of Viekira Pak™, which was approved in December 2014 for treatment of GT1 infection. Based on a review of the current clinical trial data, the clinical, statistical and virology reviewers recommend that this NDA be approved. If approved, the co-formulated tablets of ombitasvir/paritaprevir/ritonavir will be packaged and distributed under the trade-name Technivie™ Tablets.

1.2 Risk Benefit Assessment

Historical sustained virologic response (SVR) rates in HCV GT4-infected subjects treated with pegIFN/RBV are similar to those observed for GT1-infected patients, and as such, GT4 has traditionally been considered a more difficult to treat genotype. The available results of Study M13-393 demonstrate the regimen of ombitasvir/paritaprevir/ritonavir (2-DAA) + RBV for 12 weeks resulted in 100% virologic response rates (SVR12, defined as unquantifiable HCV RNA at Post-Treatment Week 12) in non-cirrhotic GT4-infected subjects with favorable disease characteristics who were treatment naïve or previously treated with pegIFN/RBV. In treatment naïve subjects treated with the 2-DAA regimen alone, the efficacy was 91%. Although this response rate was lower in subjects who did not receive RBV, the Division is providing an option for treatment with the 2-DAAs alone because there are some patients who cannot take or tolerate RBV.

There are no data available in GT4-infected subjects with cirrhosis, HCV recurrence following a liver transplant, or with HIV/HCV co-infection. Once data from ongoing studies evaluating the 2-DAA + RBV regimen in these populations of GT4-infected subjects becomes available, the indication and recommended regimen(s) may be amended.

The safety profile of the 2-DAA + RBV regimen is similar to that of Viekira Pak regimen and appears manageable. The most common treatment-emergent adverse events reported by GT4-infected subjects treated with 2-DAA + RBV were: headache, asthenia, fatigue, nausea, and insomnia.

In the majority of subjects, ALT levels rapidly decreased to within normal levels by treatment week four to six that persisted following completion of treatment. Four percent of GT4 subjects treated with the 2-DAA + RBV regimen experienced post-baseline ALT elevations $\geq$2.5 - 5.0 X ULN, (Grade $\geq$2), and none $\geq$5.0 X ULN (Grade 3). There were no clinical Hy's law cases based

on review by an independent hepatic expert panel. All subjects experienced improvement or resolution by the Final Treatment Visit or by PTW4, and, in all cases, the ALT elevation resolved with continued 2-DAA treatment. A WARNING describing monitoring and management recommendations for transaminitis is contained in the Viekira Pak label and will be included in the Technivie Tablets label.

In addition, based on data reviewed in NDA 206619, there is a substantially increased risk of transaminitis when Viekira Pak is co-administered with estrogen estradiol-containing products. It is believed this interaction is driven by paritaprevir, but no specific mechanism of action has been proven. In Study M13-393 concomitant use of estrogen-containing oral contraceptives was not allowed. As with Viekira Pak, co-administration of estrogen estradiol-containing products and Technivie Tablets will be contraindicated.

Paritaprevir is a known inhibitor of the bilirubin transporter OATP1B1, which leads to asymptomatic elevations of predominantly indirect bilirubin levels. Mean increases in total bilirubin were observed in Groups 4 and 6 who were treated with 2-DAA + RBV (+0.11 mg/dL), whereas mean decreases were observed in groups treated with 2-DAA without RBV: - 0.16 mg/dL in Group 1. The mean increase in indirect bilirubin in subjects treated with RBV was +0.12 mg/dL while there was a mean decrease of -0.06 mg/dL in those who did not receive RBV. There were no differences in the proportions of males and females with elevated bilirubin levels. In the current study, 11% (15/135) of GT4-infected subjects had an on treatment total bilirubin level elevation $\geq$Grade 2; 14/15 subjects were in groups that received RBV. In general, maximum bilirubin increases were observed at Week 1 (day 8), levels either stabilized or decreased during treatment, and were generally at baseline or below baseline levels by Post-Treatment Week 4.

Rash and pruritus were observed in 10% of GT4-infected subjects treated with the 2-DAA + RBV regimen. Paritaprevir is an NS3/4A HCV protease inhibitor, and skin and skin structure adverse events have been reported in subjects treated with other approved protease inhibitors and RBV. In addition, RBV is associated with an increased frequency of rash and pruritus. The majority of events were graded as mild or moderate in severity and responded to treatment with topical or oral corticosteroids, oral antihistamines and/or other over-the-counter topical agents. No subject discontinued RBV or interrupted or discontinued the DAAs, there were no skin-related SAEs and no severe cutaneous reactions, such as SJS, TEN, EM or DRESS were reported.

The most important adverse event related to RBV is hemolytic anemia. The addition of RBV caused a mean -2.1 g/dL decrease in hemoglobin levels from baseline during treatment compared to a mean -0.5 g/dL decrease among subjects that did not receive RBV. Five GT4-infected subjects treated with Technivie Tablets + RBV underwent a RBV dose modification due to anemia/reduced hemoglobin, and these modifications did not negatively impact SVR12 rates. Fatigue, nausea, asthenia, insomnia, pruritus, and hyperbilirubinemia (likely due to hemolysis) occurred with higher frequency in subjects who received RBV.

Cytochrome P450 (CYP) 3A is the primary contributor to the metabolism of paritaprevir. Paritaprevir is co-formulated with a low dose of ritonavir (RTV) which is a potent inhibitor of CYP3A4 in order to increase paritaprevir's C_{max} and maintain plasma half-life thereby increasing its intracellular half-life and potentiating its antiviral activity. There are a significant number of

drugs that are listed as either contraindicated or to be used with caution with Viekira Pak, and the same recommendations should apply to Technivie Tablets.

Technivie Tablets can be administered to patients with mild hepatic impairment (Childs-Pugh A, <6). Exposures of paritaprevir are increased in patients with moderate hepatic impairment (Childs-Pugh B), and like Viekria Pak, Technivie Tablets should not be recommended for use patients with Childs-Pugh B hepatic impairment. Both products are contraindicated in patients with severe liver impairment (Childs-Pugh C). Viekira Pak and Technivie Tablets can be administered to patients with varying degrees of renal impairment, but it is unknown if use of these products in patients with on hemodialysis will be safe; (b) (4)

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None; all the components of Technivie™ Tablets are currently approved.

1.4 Recommendations for Postmarket Requirements and Commitments

Recommended post-market requirements and commitments include:

- Assess the safety and efficacy of Technivie Tablets/RBV in subjects with GT4 infection and compensated cirrhosis.
- Characterize the persistence of viral populations with paritaprevir or ombitasvir resistance-associated substitutions in HCV GT4 infected subjects who experienced virologic failure with ombitasvir/paritaprevir/ritonavir with or without ribavirin.
- Characterize the cell culture antiviral activity of ombitasvir against representative HCV subtype 4b isolates, including those with amino acid variability (relative to subtypes 4a and 4d) at NS5A positions 30 and 93.

2 Introduction and Regulatory Background

2.1 Product Information

ABT-450 (paritaprevir, PTV) is an HCV NS3/4A protease inhibitor and ABT-267 (ombitasvir, OBV) is an HCV NS5A inhibitor. Together they target and disrupt multiple stages of the hepatitis C virus (HCV) life cycle. Ritonavir (RTV) is an HIV-1 protease inhibitor which in low doses is a potent inhibitor of CYP3A4. Ritonavir is co-administered with paritaprevir to increase its exposure and plasma half-life.

2.2 Currently Available Treatments for Proposed Indications

HCV is a small positive-strand ribonucleic acid (RNA) virus in the *Flaviviridae* family. At least seven HCV genotypes have been identified, numbered 1 to 7 (Smith et al., 2014). This NDA seeks approval for the use of ombitasvir/paritaprevir/ritonavir in the treatment of chronic HCV Genotype 4 (GT4) infection without cirrhosis.

HCV GT4 is uncommon in the U.S. but is prevalent in other parts of the world. According to recent reviews by Gower et al., 2014 and Messina et al., 2015, HCV GT4 is particularly prevalent in the Middle East and certain regions of Africa (Figure 1). In the U.S./North America, it is estimated that 1-6% of HCV infected patients are infected with HCV GT4.

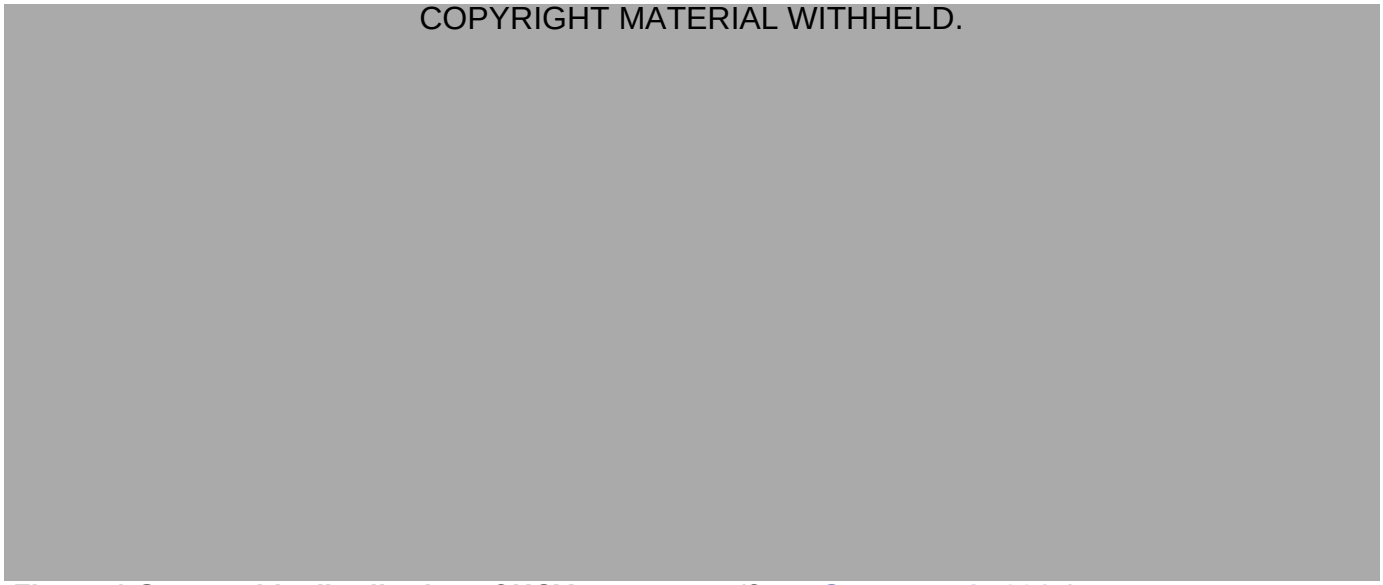


Figure 1 Geographic distribution of HCV genotypes (from Gower et al., 2014)

HCV GT4 is extremely diverse, with at least 17 confirmed subtypes (Smith et al., 2014). The prevalence of specific HCV GT4 subtypes in the U.S. is unknown. The worldwide geographic distribution of HCV GT4 subtypes in general is unclear and not well described in the literature, with the exception of a few published local/regional analyses. Furthermore, some published studies have used inadequate methods to determine HCV GT4 subtype (e.g., Ntagirabiri et al., 2014). HCV GT4a was most common in one recent study of clinical trial subjects of Egyptian ancestry enrolled at a single U.S. study site (Ruane et al., 2015). One study in the Netherlands identified predominantly subtypes 4a and 4d, and the authors similarly found that HCV GT4a was primarily found in Egyptian immigrants (de Bruijne et al., 2009). A recent small study of telaprevir in HCV GT4 infected subjects in France identified mostly subtypes 4a, 4c and 4d (De Meyer et al., 2014). In the United States, genotype 1 is the most common, accounting for 70 to 80 percent of infections. Although representing only 1-6% of HCV infections, treatment of GT4 has been challenging with few drugs demonstrating significant efficacy.

There are currently no interferon-free therapies approved for treatment of GT4 infection; only IFN-based regimens of IFN, peg-IFN with ribavirin, and IFN/RBV with or without the NS5B polymerase sofosbuvir (Sovaldi®) are approved for treatment of GT4 infection in the United States.

2.3 Availability of Proposed Active Ingredient in the United States

Ombitasvir, paritaprevir, ritonavir co-formulated tablets are currently approved and available in the U.S. as a component of Viekira Pak™, which also includes a third co-packaged anti-HCV drug, dasabuvir.

2.4 Important Safety Issues with Consideration to Related Drugs

The combination of ombitasvir, paritaprevir, and ritonavir are components of Viekira Pak, which is approved for treatment of patients with HCV GT1 infection. Important adverse events observed in subjects treated with Viekira Pak, and probably related to paritaprevir, include: transaminitis and hyperbilirubinemia.

In subjects receiving Viekira Pak with ribavirin, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving Viekira Pak without ribavirin, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia.

In addition, because ritonavir is a strong inhibitor of CYP3A, there are a significant number of concomitant medications that should not be used with Viekira Pak because they may result in known or potentially significant drug interactions and loss of therapeutic effect.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

Individual INDs for paritaprevir and ombitasvir were submitted in 2010. Initial Phase 1 studies were directed at determination of individual product safety, tolerability, pharmacokinetics and early antiviral activity. Subsequently, and based on results from individual product studies, these two DAAs (plus a third agent, dasabuvir) were evaluated in various combinations with and without ribavirin and/or peg-IFN. The outcomes of these early studies led to the development of a large Phase 2 study that investigated optimal doses, combinations and durations of the 3-DAA combination with and without RBV in GT1-infected patients.

In parallel, the Applicant expressed interest in exploring treatment of patients with GT4 infection using ombitasvir, paritaprevir, and ritonavir (2-DAA) with and without RBV, and without dasabuvir, which had minimal activity against this genotype in a biochemical assay. A new IND for the 2-DAA combination was submitted and the combination was granted breakthrough therapy status in May, 2014. A Pre-NDA meeting for the 2-DAA combination took place on October 9, 2014, and the NDA was submitted February 25, 2015.

2.6 Other Relevant Background Information

None

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The submission was complete, there were no quality or integrity issues, and all databases were useable.

3.2 Compliance with Good Clinical Practices

No inspections were conducted as most US investigators for Study M13-393 were recently inspected for GCP and found to be NAI or enrolled too few subjects to be in a position to influence the study results. Most ex-US investigators were in Europe, Eastern Europe and Russia, and, again, each enrolled too few subjects, that would have influenced the study data, to warrant inspection.

3.3 Financial Disclosures

Financial disclosure documentation was reviewed. There were no instances where a single investigator had significant impact on the conduct or outcomes of Study M13-393. See Appendix 9.4 for the Clinical Investigator Financial Disclosure Review.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Technivie™ Tablets (ombitasvir, paritaprevir, ritonavir) are pink-colored, film-coated, oblong biconvex shaped tablets containing 12.5 mg ombitasvir, 75 mg paritaprevir and 50 mg of ritonavir debossed with “AV1” on one side.

The proposed daily regimen is: 2 ombitasvir, paritaprevir, ritonavir tablets once daily with food. The full daily regimen is co-packaged and dispensed in a monthly carton for a total of 28 days of therapy. Each monthly carton contains four weekly cartons, and each weekly carton contains seven daily dose packs. Technivie Tablets should be stored at or below 30°C (86°F).

No quality inspections of manufacturing and testing sites were required as these sites were inspected during review of the Viekira Pak™NDA (NDA 206619).

4.2 Clinical Microbiology (Virology)

This section summarizes the nonclinical virology characteristics of paritaprevir and ombitasvir, including mechanism of action, cell culture antiviral activity, and resistance characteristics in cell culture. Clinical virology analyses of study M13-393 are summarized in Section 6.1.
Paritaprevir (ABT-450, PTV) is an HCV NS3/4A protease inhibitor. In a biochemical assay, PTV inhibited the activity of a recombinant HCV GT4a NS3/4A protease enzyme with an IC_{50} value of 0.16 nM. Paritaprevir inhibited the replication of stable and transient HCV replicons carrying an NS3 gene region from a single HCV GT4a isolate with EC_{50} values of 0.09 nM and 0.05 nM, respectively. In a transient replicon assay, PTV inhibited a replicon carrying an NS3 gene region from a single HCV GT4d isolate with an EC_{50} value of 0.015 nM. As described in the Viekira Pak™ label, paritaprevir inhibited stable HCV replicons derived from HCV genotype 1a, 1b, 2a, 3a and 6a isolates with EC_{50} values of 1.0 nM, 0.21 nM, 5.3 nM, 19 nM and 0.68 nM, respectively.

Selection of an HCV GT4a-derived replicon for resistance to PTV resulted in the emergence of NS3 substitutions R155C, A156T/V and D168H/V. The most common resistance-associated substitution was D168V, detected in 25 of 36 clones analyzed. These substitutions individually conferred 40- to 323-fold reductions in PTV anti-HCV activity against the HCV genotype 4a-derived replicon (Table 1; derived from R&D/13/636 and R&D/14/0817). Selection of GT4d replicons for resistance to PTV was not conducted, but the NS3 Y56H and D168V substitutions that emerged in virologic failure subjects in M13-393 were shown to confer reduced PTV anti-HCV activity when re-engineered into a genotype 4d-based replicon (Table 1). These substitutions (or positions) associated with PTV resistance in HCV GT4a and GT4d are also associated with HCV GT1 resistance to PTV and other NS3/4A protease inhibitors.

Table 1 Paritaprevir activity against HCV GT4 replicons with NS3 site-directed substitutions

GT4 Subtype	Substitution(s)	EC_{50} value (Mean nM)	Fold-Change in EC_{50} value
4a	WT	0.048	
	R155C	2.8	59
	A156T	1.9	40
	A156V	7.4	155
	D168H	12	252
	D168V	15	323
4d	WT	0.015	
	Y56H	0.12	8
	D168V	4.7	313
	Y56H + D168V	188	12,533

Ritonavir (RTV) is an HIV-1 protease inhibitor which in low doses is a potent inhibitor of CYP3A4. RTV is co-administered with paritaprevir to increase its exposures and maintain plasma half-life thereby increasing its intracellular half-life and potentiating its antiviral activity (see also Section 4.4.3).

Ombitasvir (ABT-267, OBV) is an HCV NS5A inhibitor. The mechanism of action of OBV has been characterized in HCV replicon activity and drug resistance selection studies, although the precise mechanism of NS5A inhibition and the resulting inhibition of HCV replication is unclear. Based on drug resistance mapping, NS5A inhibitors like OBV appear to target primarily the N-terminus of the protein. Cell culture and viral RNA kinetic modeling studies have indicated that NS5A inhibitors also impact HCV assembly or release. Ombitasvir inhibited the replication of a stable HCV replicon carrying an NS5A gene region from a single GT4a isolate with an EC_{50} value of 1.7 pM. In a transient HCV replicon assay, OBV inhibited the replication of a replicon carrying an NS5A gene region from single HCV GT4d isolate with an EC_{50} value of 0.38 pM. OBV inhibited a panel of transient HCV GT4a-derived replicons with a range of EC_{50} values of 0.10 pM to 0.36 pM (n=9). As described in the Viekira Pak™ label, OBV had EC_{50} values of 14 pM, 5.0 pM, 12 pM, 4.3 pM, 19 pM, 3.2 pM and 366 pM against replicon cell lines representing genotypes 1a, 1b, 2a, 2b, 3a, 5a and 6a, respectively.

Selection of an HCV GT4a-derived replicon for resistance to OBV resulted in the emergence of an NS5A L28V substitution in 21/21 evaluated clones, which conferred a 21-fold reduction in OBV anti-HCV activity (Table 2; derived from R&D/13/635 and R&D/14/0817). Selection of GT4d replicons for resistance to OBV was not conducted, but the NS5A L28V substitution that emerged in 2 virologic failure subjects in M13-393 conferred a 310-fold reduction in OBV anti-HCV activity when re-engineered into a genotype 4d-based replicon (Table 2). The third virologic failure subject had treatment-emergent L28S + M31I. While M31I conferred only a modest 2.5-fold reduction in OBV activity, the L28S single substitution and L28S + M31I combined substitutions could not be evaluated for their impact on OBV activity due to poor replication capacity of the replicons.

Table 2 Ombitasivir activity against HCV GT4 replicons with NS5A site-directed substitutions

GT4 Subtype	Substitution(s)	EC_{50} value (Mean pM)	Fold-Change in EC_{50} value
4a	WT	0.35	
	L28V	8	21
4d	WT	0.38	
	L28S	nd	nd
	L28V	118	310
	M31I	0.96	2.5
	M31L	0.39	1
	T58A	0.53	1.4
	T58P	0.42	1.1
	T58S	0.52	1.4
	L28S + M31I	nd	nd
	L28V + T58S	289	760

nd, no data due to poor replication capacity.

Ribavirin is a guanosine analogue that enhances the efficacy of anti-HCV treatment by mechanism(s) that are not fully understood. Ribavirin may interfere with viral RNA replication or increase the genome mutation frequency during replication.

4.3 Preclinical Pharmacology/Toxicology

The preclinical Pharmacology/Toxicology for each DAA was extensively reviewed in NDA 206619.

Reproductive Toxicity: Neither of the DAAs demonstrated effects in reproductive parameters of male or female rats and there were no maternal nor test article-related effects on survival, growth, sexual maturation, learning/memory, or reproduction in F1 generation rats. RBV can cause significant teratogenic and/or embryocidal effects; pregnancy must be avoided during RBV treatment and up to 6-months post-treatment. Because RBV will be a recommended component of treatment for patients with GT4 infection, pregnancy should be avoided during administration of Technivie Tablets.

4.4 Clinical Pharmacology

The proposed 2-DAA regimen for marketing is: two ombitasvir/paritaprevir/ritonavir (12.5/75/50 mg) co-formulated tablets administered once daily with meals. The Clinical Pharmacology of paritaprevir and ombitasvir were extensively reviewed in NDA 206619.

4.4.1 Mechanism of Action

Paritaprevir (combined with low-dose ritonavir, ABT-450/r) is an HCV NS3/4A protease inhibitor and ombitasvir (ABT-267) is an NS5A replication complex inhibitor. Administered together, these agents have a direct effect on multiple stages of the HCV viral life-cycle (see Section 4.2 above for additional details).

4.4.2 Pharmacodynamics

Individually, in subjects infected with GT1, there was a ~4.0 $\log_{10}$ IU/mL reduction in HCV RNA from baseline following 3 days of monotherapy with paritaprevir/r. The 25 mg dose of ombitasvir provided a ~3.10 $\log_{10}$ IU/mL reduction from baseline in HCV RNA following three days of monotherapy.

In Study M13-393 following co-administration of the 2-DAAs at their proposed doses for marketing, paritaprevir/r 150/100 mg and ombitasvir 25 mg QD, there were rapid reductions in HCV RNA and steady-state exposures were comparable to exposures observed when each agent was administered separately in other trials.

4.4.3 Pharmacokinetics

The pharmacokinetics of paritaprevir/ritonavir, ombitasvir was extensively evaluated in NDA 206619. The following provides a brief summary.

Paritaprevir is primarily eliminated in the bile with minimal renal elimination (<1%), with a terminal half-life of 5-8 hours. There is a supra-proportional increase (~5-fold) in exposure when co-administered with ritonavir, and a ~2-fold accumulation following multiple daily dosing, with exposures ~30-300% (50-200 mg) higher in HCV-infected subjects than in healthy subjects. Cytochrome P450 CYP3A4 is the primary contributor to the metabolism of ABT-450 and CYP3A5 to a lesser extent, and it is a substrate and inhibitor of various uptake and efflux transporters (P-gp, BCRP, OATP1B1). ABT-450's inhibition of the organic anion transporting polypeptide transporter OATP1B1 appears to contribute to clinical indirect hyperbilirubinemia.

The exposure of paritaprevir is increased 2- to 3-fold higher under non-fasting relative to fasting conditions. Thus, it is recommended that it be administered with food.

Ritonavir (RTV) is a potent inhibitor of CYP3A4 and an inhibitor of P-gp and BCRP, and increases paritaprevir exposures to maintain plasma half-life thereby increasing its intracellular half-life.

Ombitasvir is highly bound to plasma proteins (>99%), primarily eliminated in the bile with minimal renal elimination (<1%), has a terminal half-life of ~24 hours, and has linear pharmacokinetics with minimal accumulation after multiple dosing. Ombitasvir undergoes amide hydrolysis; minor CYP3A4 contribution, and does not induce CYP1A2 or 3A4 mRNA and is a substrate and inhibitor of P-gp and BCRP. Administration of ombitasvir under nonfasting conditions resulted in 93% and 62% increase in C_{max} and AUC values, respectively, relative to fasting conditions.

Drug-drug Interactions: A large number of drug-drug interaction studies were conducted with the 3- and 2-DAA combinations. Paritaprevir/r interacts with many concomitantly administered drugs, which could impact the pharmacokinetic and pharmacodynamics of the DAAs or the concomitant drugs possibly leading to a negative impact on safety and/or efficacy. CYP3A4 is the primary contributor to the metabolism of paritaprevir, and it is co-formulated with a low dose of ritonavir (50 mg) which is a potent inhibitor of CYP3A4. Based on the presence of ritonavir there are a substantial number of drugs for which co-administration is contraindicated or that should be used with caution with this regimen. Ombitasvir does not appear to contribute to the drug-drug interactions observed.

Hepatic Impairment: The results of a hepatic impairment study conducted with paritaprevir, ombitasvir and dasabuvir demonstrated that no dose adjustment is required in subjects with mild hepatic impairment (CTP-A <6) as changes in DAA exposures were not considered to be clinically significant. Among subjects with more advanced hepatic impairment (CPT-B and C), changes in paritaprevir exposures were significantly higher: exposure of paritaprevir was 62% higher in moderate impaired subjects, and in severely impaired subjects paritaprevir exposures were 920% higher, compared to subjects with normal hepatic function.

Reviewer comment: There are no data assessing safety with the 2-DAA combination in patients with hepatic impairment. However, it is expected that the pharmacokinetic changes will be consistent and likely driven by paritaprevir. Therefore, it seems reasonable to allow the 2-DAA combination to be used in subjects with mild, well-compensated hepatic impairment (Childs-Pugh A <6), not recommended in subjects with moderate hepatic impairment (Childs-Pugh B), and contraindicated in subjects with severe hepatic impairment (Childs-Pugh C).

Renal Impairment: The results of a renal impairment study demonstrated no dose adjustment is required in subjects with mild, moderate or severe renal impairment.

5 Sources of Clinical Data

5.1 Studies/Clinical Trials

This NDA is primarily supported by a single Phase 2 clinical trial (M13-393) entitled “A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of Coadministration of ABT-450 (paritaprevir) with Ritonavir (ABT-450/r) and ABT-267 (ombitasvir) in Adults with Chronic Hepatitis C Virus Infection (PEARL-I).”

The study is ongoing and was conducted in 181 HCV GT1b-infected adults with and without compensated cirrhosis and 135 non-cirrhotic HCV GT4-infected subjects.

5.2 Review Strategy

Study M13-393 included both HCV GT1b and GT4 infected adults. The Applicant is only requesting approval of the 2-DAA combination of ombitasvir and paritaprevir/ritonavir in GT4-infected patients. As such, the efficacy of the 2-DAA regimen in patients with GT1b infection will only be briefly summarized in this review, and where appropriate, safety information from this population will be integrated.

5.3 Discussion of Individual Studies/Clinical Trials

This NDA relies on the results of a single Phase 2 trial conducted in 135 subjects infected with HCV GT4 and supportive data from the approved NDA 206619 which demonstrated robust efficacy of the 2-DAAs plus a third drug (dasabuvir) with and without RBV in >2300 subjects with GT1 infection.

6 Review of Efficacy

Efficacy Summary

6.1 Indication

The Applicant's proposed indication reads: TRADENAME is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection.

6.1.1 Methods

Study M13-393 is an ongoing Phase 2 study that was initially designed to evaluate open-label paritaprevir/r + ombitasvir with and without RBV for 12 weeks in treatment-naïve and pegIFN/RBV-experienced HCV GT1b-infected cirrhotic and non-cirrhotic subjects and GT4-infected non-cirrhotic subjects. The primary endpoint is the percentage of subjects achieving SVR12 defined as HCV RNA less than the lower limit of quantification (<LLOQ) 12 weeks after the last actual dose of study drug.
This was a multicenter study conducted at 46 sites in the United States (US), Puerto Rico, France, Hungary, Italy, Poland, Romania, Spain and Turkey. The first subject's first Screening Visit: 14 August 2012; first subject's first dose of study drug: 12 September 2012; last subject's last dose of study drug: 03 March 2014; last subject's last visit for primary endpoint of SVR12-: 06 June 2014; and, database lock for this interim clinical study report: 18 June 2014. Figure 2 below displays the study design and planned sample size for each treatment arm.

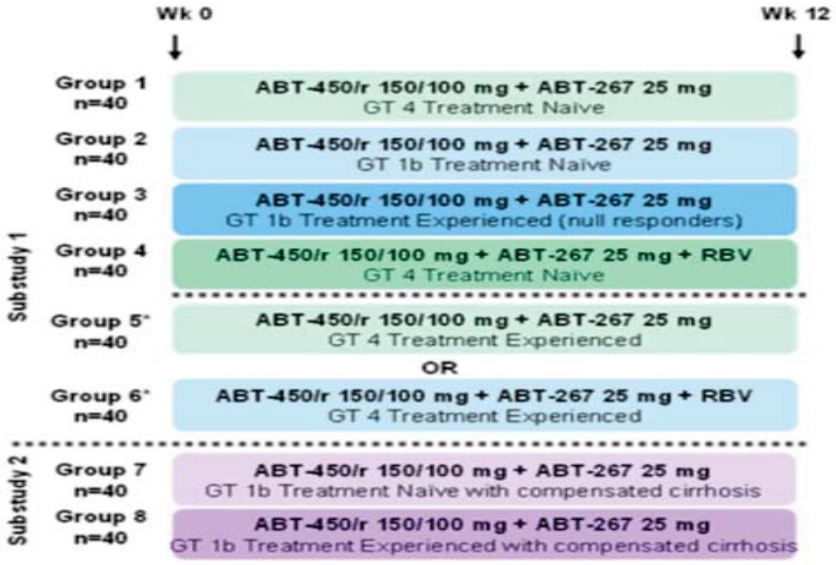


Figure 2 M13-393 Study Design

The study was subsequently modified to not enroll subjects into Group 5 (GT4 treatment experienced to be treated with paritaprevir/r/ombitasvir without RBV) because preliminary data showed that two of 10 treatment naïve GT4 subjects in Group 1 (paritaprevir/r/ombitasvir without RBV) experienced virologic failure: one breakthrough and one relapse.

The final three GT4 groups were:

- Group 1: Treatment naïve subjects treated with ombitasvir/paritaprevir/ritonavir x 12 weeks
- Group 4: Treatment naïve subjects treated with ombitasvir/paritaprevir/ritonavir + RBV x 12 weeks
- Group 6: Prior pegIFN/RBV non-responders treated with ombitasvir/paritaprevir/ritonavir + RBV x 12 weeks

Please note that the eligible GT4 treatment naïve subjects were randomized in a 1:1 ratio into Group 1 or Group 4. The randomization was stratified by IL28B genotype (CC vs. non-CC).

Outcome Measures

The primary efficacy outcome was sustained virologic response at Post-Treatment Week 12 (SVR12). In the GT4 treatment arms, plasma samples for HCV RNA levels were collected at screening, baseline, Weeks 1-4, 6, 8, 10 and 12. Plasma HCV RNA levels were determined for each sample collected by the central laboratory using the FDA approved Roche COBAS TaqMan® real-time reverse transcriptase polymerase chain reaction assay v2.0. The lower limit of quantification (LLOQ) of this assay is 25 IU/mL.

As mentioned above, the primary efficacy endpoint is the percentage of subjects with SVR12. The secondary efficacy endpoints included the following three variables:

1) SVR24, i.e., HCV RNA < LLOQ 24 weeks after the last actual dose of study drug
2) On-treatment virologic failure, i.e., confirmed HCV RNA ≥ LLOQ after HCV RNA < LLOQ during treatment, confirmed increase from nadir in HCV RNA (two consecutive HCV RNA measurements > 1 $\log_{10}$ IU/mL above nadir) at any time point during treatment or HCV RNA > LLOQ persistently during treatment with at least 6 weeks of treatment (study drug duration ≥ 36 days). A single rebound value (≥ LLOQ or > 1 $\log_{10}$ IU/mL above nadir) followed by lost to follow-up was also considered an on-treatment virologic failure
3) Post-treatment relapse

Efficacy analyses were performed on all subjects who received at least one dose of study drug.

Study Subjects

To be enrolled, GT4-infected subjects were to have been:

- Male or female between 18 and 70 years, inclusive, at time of enrollment, with chronic HCV genotype 4 and plasma HCV RNA level >10,000 IU/mL at Screening.

- **Treatment-naïve:** Subject has never received antiviral treatment for hepatitis C infection (Groups 1 and 4);

OR

- **Prior null responders:** Subject has documentation that they previously received pegIFN/RBV for at least 10 weeks and failed to achieve a 2 $\log_{10}$ IU/mL HCV RNA decrease at Week 12 (Weeks 10 – 16) (Group 6);

OR

- **Partial responder:** received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved ≥ 2 $\log_{10}$ IU/mL reduction in HCV RNA at Week 12 (Weeks 10 – 16), but failed to achieve HCV RNA undetectable at the end of treatment (Group 6);

OR

- **Relapser:** received at least 36 weeks of pegIFN/RBV for the treatment of HCV, and HCV RNA was undetectable at the end of treatment but detectable within 52 weeks of treatment follow-up (Group 6).

- Body Mass Index (BMI) is from ≥ 18 to < 38 kg/m2. BMI is calculated as weight in kilograms (kg) divided by the square of height measured in meters (m).
- Liver biopsy within 24 months prior to screening or during screening demonstrating the absence of cirrhosis. Only in the absence of a biopsy within the 24 months prior to screening or during screening:
    - a screening FibroTest score of ≤ 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) ≤ 2; or
    - a screening FibroScan® result of < 9.6 kPa.

Females were to be:

- practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle)

- sexually active with female partners only
- not of childbearing potential, defined as:
    - postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or
        - surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s);
- of childbearing potential and sexually active with male partner(s): currently using at least one effective method of birth control at the time of screening and two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents), starting with Study Day 1 and for 7 months after stopping study drug or as directed by the RBV label (Group 4 and Group 6 only), as applicable (Note: Hormonal contraceptives, including oral, topical, injectable or implantable [hormone eluting intrauterine devices [IUDs] varieties, were not allowed during study drug treatment).

Females were required to have negative results for pregnancy tests performed:

- at Screening on a serum specimen obtained within 35 days prior to initial study drug administration, and
- on a urine specimen obtained on Study Day 1 (prior to dosing).

Sexually active males had to be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential had to agree to practice two effective forms of birth control (as outlined in the subject information and consent form or other subject information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local RBV label (Group 4 and Group 6 only), as applicable.

6.1.2 Demographics

One-hundred thirty five HCV GT4-infected subjects were enrolled: 42 into Group 1, 44 into Group 4 and 49 in Group 6. Demographic and some disease characteristics were generally matched across the three treatment groups with most subjects being male (65%) and Caucasian (90%), mean age of 48.2 years, 58% $\geq$50 years of age, 3% $\geq$65 years of age, 86% had a BMI <30 kg/m^2. all subjects had a Childs-Pugh score $\leq$6; 77% had F0-F1 fibrosis, 16% had F2 fibrosis, 7% F3 fibrosis and <1% F4 fibrosis (see Table 3 and Table 4).

As to be expected, P/R treatment experienced subjects in Group 6 had a higher percentage of subjects with HIV-RNA ≥800,000 IU/mL than treatment-naïve subjects in Group 1 and a higher percentage of subjects with F3 fibrosis than treatment-naïve subjects in Groups 1 and 4. In addition treatment-naïve subjects in Group 1 had a lower percentage of subjects with HCV subtype 4a/c/d and treatment-naïve subjects in Groups 1 and 4 had a higher percentage of subjects with the Il28B CC genotype compared to P/R treatment experienced subjects in Group 6.

The Versant® HCV Genotype Inno-LiPA v2.0 assay (Siemens Healthcare Diagnostics, Tarrytown, NY) was used to determine HCV genotype for enrollment. In addition, because the

screening assay does not reliably identify HCV GT4 subtypes, GT4 subtypes were identified retrospectively based on nucleotide sequencing and phylogenetic analysis.

Table 3 Demographic characteristics of GT4-infected subjects

	Group 1 PTV/r + OBV Tx-naïve (N=44)	Group 4: PTV/r + OBV + RBV Tx-naïve (N=42)	Group 6: PTV/r + OBV + RBV P/R-Exp. (N=49)
Gender			
Female	20 (45.5%)	14 (33.3%)	13 (26.5%)
Male	24 (54.5%)	28 (66.7%)	36 (73.5%)
Race			
White	37 (84.1%)	38 (90.5%)	45 (91.8%)
Black	6 (13.6%)	3 (7.1%)	3 (6.1%)
Other	0	1 (2.4%)	1 (2.0%)
Multi-race	1 (2.3%)	0	0
Age (year)			
Mean (SD)	48.9 (10.0)	44.2 (12.7)	50.9 (10.1)
Median (Q1, Q3)	50.5 (44.0, 56.0)	48.5 (35.0, 54.0)	52.0 (48.0, 56.0)
< 65 years	42 (95.5%)	41 (97.6%)	48 (98.0%)
≥ 65 years	2 (4.6%)	1 (2.4%)	1 (2.0%)
Weight (kg)			
Mean (SD)	72.6 (15.3)	74.3 (13.0)	79.4 (14.6)
Median (Q1, Q3)	70.8 (62.5, 80.0)	72.0 (64.7, 82.0)	80.0 (70.0, 87.0)
BMI (kg/m^2)			
Mean (SD)	24.9 (3.8)	24.8 (3.6)	26.8 (3.7)
Median (Q1, Q3)	24.5 (21.9, 27.5)	24.1 (22.0, 27.4)	26.5 (24.3, 28.7)
< 30 kg/m^2	39 (88.6%)	37 (88.1%)	40 (81.6%)
≥ 30 kg/m^2	5 (11.4%)	5 (11.9%)	9 (18.4%)
Country			
United States	6 (13.6%)	6 (14.3%)	7 (14.3%)
France	21 (47.7%)	17 (40.5%)	16 (32.7%)
Italy	5 (11.4%)	4 (9.5%)	7 (14.3%)
Poland	4 (9.1%)	7 (16.7%)	5 (10.2%)
Spain	8 (18.2%)	8 (19.1%)	14 (28.6%)

Table 4 Disease characteristics of GT4-infected subjects

	Group 1 PTV/r + OBV Tx-naïve (N=44)	Group 4: PTV/r + OBV + RBV Tx-naïve (N=42)	Group 6: PTV/r + OBV + RBV P/R-Exp. (N=49)
HCV subtype (by screening assay)			
4a/c/d	21 (47.7%)	26 (61.9%)	32 (65.3%)
4e	0	0	1 (2.0%)
4f	3 (6.8%)	3 (7.1%)	0
4h	1 (2.3%)	0	1 (2.0%)
4 (not reported)	19 (43.2%)	13 (31.0%)	15 (30.6%)
IL28 B genotype			
CC	12 (27.3%)	11 (26.2%)	6 (12.2%)

CT	24 (54.6%)	26 (61.9%)	32 (65.3%)
TT	8 (18.2%)	5 (11.9%)	11 (22.5%)
Baseline HCV RNA (log_{10} IU/mL)			
Mean (SD)	6.1 (0.6)	6.1 (0.6)	6.3 (0.5)
Median (Q1, Q3)	6.1 (5.6, 6.5)	6.1 (5.8, 6.5)	6.3 (5.9, 6.5)
< 800,000 IU/mL	17 (38.6%)	12 (28.6%)	12 (24.5%)
≥ 800,000 IU/mL	27 (61.4%)	30 (71.4%)	37 (75.5%)
Response to prior pegIFN/RBV treatment			
Null responder	n/a	n/a	23 (46.9%)
Partial responder	n/a	n/a	9 (18.4%)
Relapser	n/a	n/a	17 (34.7%)
Fibrosis stage			
F0 – F1	38 (86.4%)	33 (78.6%)	33 (67.4%)
F2	4 (9.1%)	6 (14.3%)	11 (22.5%)
F3	2 (4.6%)	2 (4.8%)	5 (10.2%)
F4	0	1 (2.4%)	0

Reviewer comment: GT4 is the predominant HCV genotype in persons from Egypt, and no subjects in this trial were of Egyptian heritage. It is not expected, however, that a different response would be observed in Egyptian and non-Egyptian patients infected with HCV GT4.

6.1.3 Subject Disposition

Of the 135 HCV GT4 subjects enrolled and treated, 133 completed their assigned dosing regimen. Reasons for study drug and study discontinuations are shown in Table 5.

Table 5 Disposition of GT4 infected subjects

	Group 1 PTV/r + OBV Tx-naïve	**Group 4: PTV/r + OBV + RBV Tx-naïve**	**Group 6: PTV/r + OBV + RBV P/R-Exp.**
Number randomized	44	42	49
Number treated	44 (100%)	42 (100%)	49 (100%)
Discontinued study drug	2 (4.5%)	0	0
Virologic failure	1 (2.3%)	0	0
Lost to follow-up	1 (2.3%)	0	0
Discontinued study	3 (6.8%)	1 (2.4%)	0
Withdrew consent	1 (2.3%)	0	0
Lost to follow-up	2 (4.5%)	1 (2.4%)	0

6.1.4 Analysis of Primary Endpoint

The primary efficacy endpoint was SVR12. This is a well-established primary endpoint that has been vetted by FDA and is used in all trials of anti-HCV therapies. All efficacy analyses were performed on the all treated population, defined as all subjects who were randomized and received at least one dose of study drug.

In the primary efficacy analysis, the applicant planned to use a logistic regression model with treatment group, baseline $\log_{10}$ HCV RNA level, and IL28B genotype (CC, or non-CC) as predictors to compare SVR12 rate between Groups 1 and 4. If the logistic regression analysis could not be completed due to complete or quasi-separation, then the applicant would use the stratum-adjusted Mantel-Haenszel (MH) proportion with continuity-corrected variance, adjusting for IL28B genotype (i.e., the stratifier used for randomization). In addition, the applicant calculated the exact 95% CI using the Clopper-Pearson method for SVR12 rate in each arm. The applicant conducted similar analyses for the secondary efficacy endpoint of SVR24.

The applicant's results for the primary efficacy endpoint of SVR12 rate are displayed in Table 6. For GT4 treatment-naive (TN) subjects, the SVR12 rate in Group 1 was approximately 91% compared with 100% in Group 4. The SVR12 rate in Group 6 for GT4 treatment-experienced (TE) subjects was 100%. Among the four subjects in Group 1 who did not achieve SVR12, one subject had on-treatment virologic failure due to rebound, one discontinued study drug prematurely due to lost to follow up (the patient discontinued the study drugs three days after initial dosing), and two experienced virologic relapses at post-treatment Weeks 4 and 8 respectively.

Table 6 SVR12 rates and reasons for non-response in GT4-infected subjects

	Group 1 PTV/r + OBV Tx-naïve N=44	**Group 4 PTV/r + OBV + RBV Tx-naïve N=42**	**Group 6 PTV/r + OBV + RBV P/R-Exp. N=49**
SVR12 [95% CI]	40/44 (91%) [78.3%, 97.5%]	42/42 (100) [91.6%, 100.0%]	49/49 (100) [92.7%, 100.0%]
Reasons for non-response			
-On-treatment failure	1 (2%)	0	0
-Relapse	2 (5%)	0	0
-Premature dc	1 (2%)	0	0

The Applicant carried out statistical inferential analyses to compare the SVR12 rate between Groups 1 and 4 in GT4 TN subjects (Table 7). The logistic regression model did not converge due to a quasi or incomplete separation of data. The unadjusted SVR12 rate in Group 1 was statistically significantly lower than the rate in Group 4 since the 95% CI for the treatment difference did not cover zero. Similar results were obtained when the MH method was used; however, the upper bound of the 95% CI for the treatment difference after adjusting for IL28B genotype was slightly greater than zero.

Table 7 Applicant's primary efficacy endpoint comparison between Groups 1 and 4

	Group 1 2-DAA TN	Group 4 2-DAA + RBV TN	Comparison (Group 1 versus Group 4)		
			Logistic Regression[1] P value	Unadjusted Difference (95% CI)[2]	Stratum-Adjusted Difference (95% CI)[3]
SVR12	90.9% (40/44)	100% (42/42)	NA	-9.1% (-17.6%, -0.6%)	-9.2% (-19.6%, 1.3%)

Source: Table 23 in Clinical Study Report for M13-393
[1]Treatment group, baseline log_{10}HCV RNA level and IL28B genotype (CC or non-CC) were used as predictors in the logistic regression model.
[2]The 95% CI was constructed using the Clopper-Pearson Exact method.
[3]The treatment difference and its 95% CI were obtained using stratum-adjusted Mantel-Haenszel method with continuity-corrected variance, adjusting for IL28B genotype (CC or non-CC).

The FDA statistical reviewer applied the Fisher's exact test to compare difference between Groups 1 and 4 (p-value = 0.12). Furthermore, the reviewer was concerned about the performance of the applicant's MH test due to very small cell counts (i.e., only four subjects did not achieve SVR12 and all were in Group 1). Therefore, the reviewer carried out the exact Cochran-Armitage permutation test to compare treatment Groups 1 and 4 adjusted for IL28B genotype (p-value = 0.11).

It was noticed that all of the four subjects in Group 1 who did not have SVR12 had IL28B non-CC genotype (Table 8). Therefore, the SVR12 rates were 100% for both groups in IL28B CC subjects, but Group 1 was worse than Group 4 (87.5% vs. 100%) among IL28B non-CC subjects (exact p-value = 0.11 based on Fisher's exact test). The interaction between treatment and the subgroup defined by IL28B genotype appeared not to be statistically significant due to the large extent of overlap between the two exact 95% CIs. Therefore, it is not possible to conclude that adding RBV to PTV/r + OBV is only beneficial in non-CC subjects.

Table 8 FDA reviewer's results for SVR12 by IL28B in Group 1 and Group 4

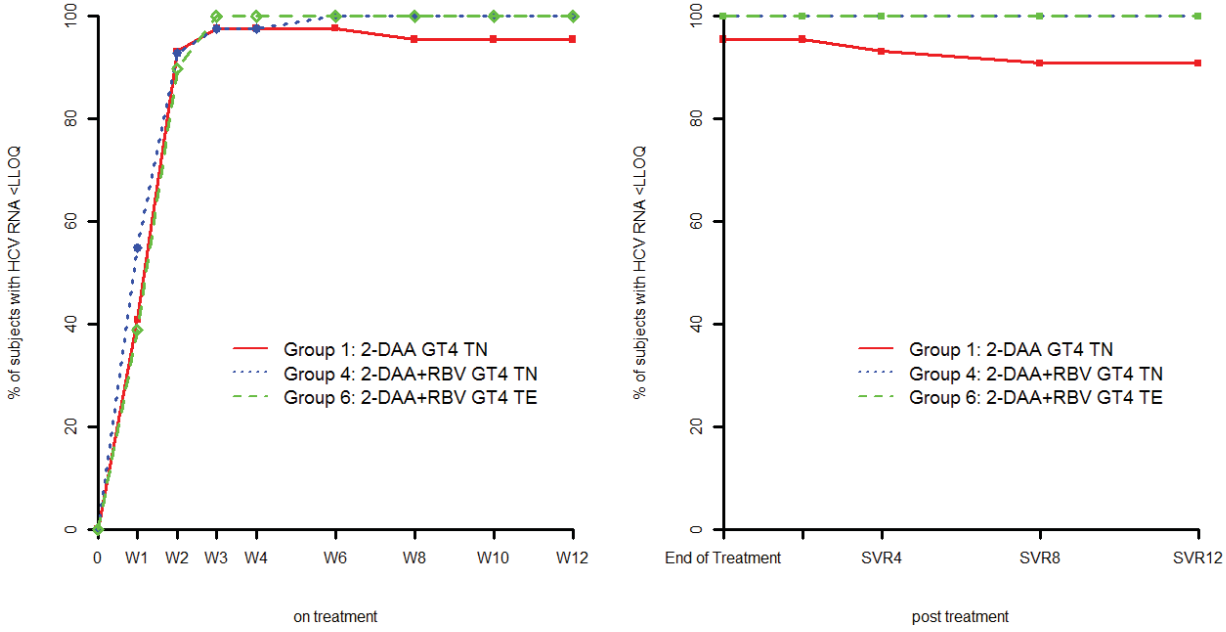
	Group 1 PTV/r + OBV Tx-naive N=44	Group 4 PTV/r + OBV + RBV Tx-naïve N=42	Proportion Difference (Exact 95% CI)[1]
IL28B			
CC	100% (12/12)	100% (11/11)	0% (-25.3%, 26.6%)
Non-CC	87.5% (28/32)	100% (31/31)	-12.5% (-29.7%, -0.7%)

[1]based on inverting a two-sided test

The FDA reviewer calculated and plotted the percent of subjects with HCV RNA < LLOQ at each visit during the study using backward imputation (Figure 3). The graphs illustrate that more than 95% of subjects had responded by about Week 3 in all three groups and a difference

between 2-DAA (Group 1) and 2-DAA+RBV (Groups 4 and 6) was observed approximately from Week 6 through 12 weeks post treatment.

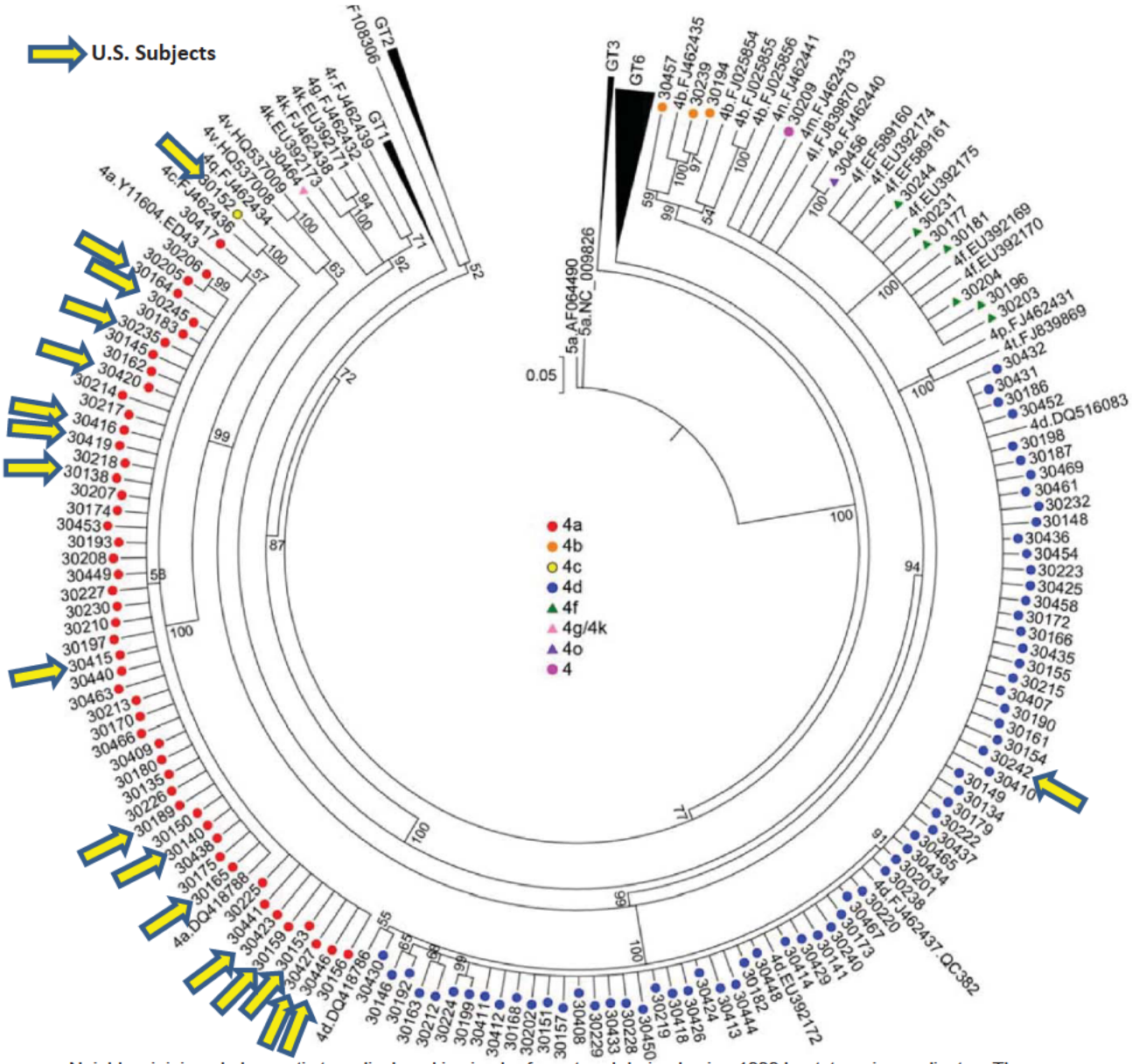
Figure 3 FDA reviewer's results for percent of subjects with HCV RNA < LLOQ at each visit (All Treated, Backward Imputation)



- **Response by GT4 subtypes**

As noted above HCV GT4 is extremely heterogeneous, with at least 17 confirmed subtypes (Smith et al., 2014), and the HCV genotype screening assay does not adequately determine HCV genotype 4 subtypes. Therefore, phylogenetic analyses of HCV population sequences were conducted to determine HCV GT4 subtype. Phylogenetic analyses were conducted for 132 HCV GT4 infected subjects: 43/44, 40/42, and 49/49 of the subjects in Groups 1, 4, and 6, respectively. Subtype assignment was based on a consensus of results from analyses of NS3/4A, NS5A and NS5B. Baseline samples were not available for 3 subjects to conduct phylogenetic analyses (SUBJIDs: 30136, 30137, 30178, all achieved SVR12).

Figure 4 (CSR pg. 254) provides a representation of the phylogenetic analyses, based on full length NS5A sequences. Table 9 (provided by the Applicant in SDN-009) illustrates a high concordance of subtype assignment based on the individual NS3/4A, NS5A and NS5B genome regions, supporting the sponsor's approach to assign HCV subtype based on the consensus of all three regions analyzed (e.g., for cases where results were missing for one region). The investigational Versant® HCV Genotype Inno-LiPA v2.0 assay used for identification of HCV GT4 at Screening did not accurately or consistently determine HCV GT4 subtype, confirming that this assay should not be used for HCV GT4 subtype determination.



Neighbor-joining phylogenetic tree displayed in circular format and derived using 1000 bootstrapping replicates. The genetic distance scale bar indicates the number of nucleotide substitutions per site between full-length NS5A sequences. The arrows indicate data from U.S. study site subjects.

Figure 4 Determination of HCV GT4 subtype by phylogenetic analysis

Table 9 Concordance of HCV GT4 subtype assignment based on phylogenetic analysis of three different HCV genome regions

GT4 Subtype by LiPA 2.0	GT4 Subtype for Resistance Analyses	Phylogenetic Analysis N[a]			Total Number of Subjects
		NS5B	NS3/4A	NS5A	
4, 4h, or 4a/4c/4d	4a	50	50	50	50
4	4b	3	2[b]	3	3
4	4c	1	1	1	1
4 or 4a/4c/4d	4d	68	68	68	68
4 or 4f	4f	5[c]	7	7	7
4	4g/4k	1 (4g)	1 (4g or 4k)	1 (4g or 4k)	1
4e	4o	1	1	1	1
4	4	1 (4m or 4p)	1 (4)	1 (4)	1
4 or 4a/4c/4d	No sample[d]	3	3	3	3

a. Genotype and subtype are listed in parenthesis for each target if there were discrepancies in the phylogenetic subtype assignment between targets.
b. One sample could not be amplified for NS3/4A.
c. Two samples could not be amplified for NS5B.
d. Baseline samples for 3 subjects were not available for analysis.

As summarized in Table 10, the most commonly observed GT4 subtypes were 4a and 4d. In the U.S., 16/18 (89%) subjects with available data were infected with HCV subtype 4a. The 19 U.S. subjects, including 1 subject without GT4 subtype determined by phylogenetic analysis, were enrolled across 10 different study sites. The denominator for percentage calculation is number of subjects with available data (n=132 total, n=18 U.S.).

Table 10 HCV GT4 subtypes in M13-393 based on phylogenetic analysis (consensus results from NS3/4A, NS5A and NS5B)

GT 4 Subtypes	Number of Subjects N=132
4 (i.e., analyzed, but not determined)	1 (1%)
4a	50 (38%)
4b	3 (2%)
4c	1 (1%)
4d	68 (52%)
4f	7 (5%)
4g/4k	1 (1%)
4o	1 (1%)
Not Reported	3
GT 4 Subtypes (U.S.)	**Number of Subjects N=18**
4a	16 (89%)
4c	1 (6%)
4d	1 (6%)

Table 11 provides a breakdown of HCV GT4 subtypes by study site country.

Table 11 Subjects' HCV GT4 subtypes, based on phylogenetic analysis, according study site location

COUNTRY	GT4 Subtype	N
U.S.	4A	16
	4C	1
	4D	1
	Not Reported	1
Spain	4A	7
	4D	20
	4F	1
	Not Reported	2
France	4 (not determined)	1
	4A	26
	4B	3
	4D	16
	4F	6
	4G/4K	1
	4O	1
Italy	4A	1
	4D	15
Poland	4D	16

Table 12 summarizes SVR12 rates according to GT4 subtype based on phylogenetic analysis. All 3 subjects who experienced virologic failure in Group 1 (no RBV) were infected with HCV subtype 4d, and were from non-U.S. study sites.

Table 12 SVR12 rates in M13-393 according to HCV GT4 subtype, determined based on phylogenetic analysis

GT4 Subtype	Group 1 PTV/r + OBV Tx-naïve	Group 4: PTV/r + OBV + RBV Tx-naïve	Group 6: PTV/r + OBV + RBV P/R-Exp.
4a	21/21 (100%)	13/13 (100%)	16/16 (100%)
4b	0/1[1]	1/1	1/1
4c	ND	1/1	ND
4d	13/16 (81%)[2]	22/22 (100%)	30/30 (100%)
4f	4/4 (100%)	3/3 (100%)	ND
4g/4k	ND	ND	1/1
4o	ND	ND	1/1
4 (subtype not determined)	1/1	ND	ND
Not reported	1/1 (100%)	2/2 (100%)	ND
All Subtypes	**40/44 (91%)**	**42/42 (100%)**	**49/49 (100%)**
U.S. Sites Only			
4a	6/6 (100%)	3/3 (100%)	7/7 (100%)
4c	ND	1/1	ND

4d	ND	1/1	ND

[1]HCV GT4b infected subject (30194) discontinued treatment early for non-virologic reasons.
[2]All three subjects experienced virologic failure (2 relapse, 1 breakthrough).
ND, no data

- **Virologic Failure**

Drug resistance analyses included population nucleotide sequence analysis of full length NS3/4A and NS5A. Only samples with an HCV RNA level of ≥1,000 IU/mL underwent sequence analysis. For virologic failure isolates, if the HCV RNA level at the time of virologic failure was <1,000 IU/mL the sample closest to the time of failure with an HCV RNA level ≥1,000 IU/mL was analyzed.

Four subjects did not achieve SVR12, all in Group 1 (no RBV). Table 13 summarizes the reasons for treatment failure for these 4 subjects. Three of the 4 subjects experienced virologic failure (relapse or breakthrough), and 1 subject failed treatment for non-virologic reasons. The 3 subjects who experienced virologic failure were infected with HCV GT4d (see also resistance analyses in the next section). The increase in virologic failure in Group 1 may have been driven by the lack of RBV in the treatment regimen. Note that all 3 virologic failure subjects also had relatively high HCV RNA levels at baseline, with a median of 6.9 $\log_{10}$ IU/mL (range 6.5-7.0 $\log_{10}$ IU/mL).

Table 13 HCV GT4 subjects who did not achieve SVR12 in M13-393

USUBJID	Treatment Dur. (Days)	EOT <LLOQ	Relapse	Comments
M13393-44317-30228	84	Y*	Y	Relapse
M13393-44318-30194	30	N		Premature discontinuation, HCV RNA never suppressed (HCV RNA 3,560 at Day 3, no subsequent data)
M13393-44365-30182	81	N		Virologic Breakthrough at Week 8
M13393-45484-30238	84	Y*	Y	Relapse

*HCV RNA Target Not Detected.

- **Resistance Analysis**

NS3/4A

Baseline NS3 amino acid sequences at positions associated with resistance to NS3/4A protease inhibitors were relatively conserved across HCV GT4 subtypes (Table 14). There were insufficient numbers of subjects with polymorphisms at NS3 positions of interest to detect a substantial difference in polymorphism frequency between U.S. and non-U.S. study subjects. Of note, a Q80K polymorphism is common in GT1a and is associated with reduced efficacy for some NS3/4A protease inhibitors, but position Q80 was 100% conserved in HCV GT4a and GT4d infected subjects in M13-393. The NS3 positions most commonly associated with PTV

resistance in HCV GT1 infected subjects (Y56, R155, D168) were 100% conserved at baseline for all subjects in M13-393.

Table 14 Baseline variability at NS3 positions potentially associated with resistance to NS3/4A protease inhibitors for subjects in M13-393, according to HCV GT4 subtype

			NS3 Positions Potentially Associated with Resistance: Variability from Reference Sequence										
GT4 Subtype	**Reference Sequence**	**N**	**36**	**43**	**54**	**55**	**56**	**80**	**132**	**155**	**156**	**168**	**170**
4a	ED43	50			S (2/50)	A (1/50)			L (2/50)				I (6/50)
4d	QC382	68											
4b	ED43	2						K (1/2)	L (1/2)				
4c	ED43	1											
4f	ED43	7											
4g/4k	ED43	1							L (1/1)				
4o	ED43	1											
4	ED43	1			S (1/1)								I (1/1)
4a (U.S.)	ED43	16			S (2/16)				L (1/16)				I (3/16)
4a (non-U.S.)	ED43	34				A (1/34)			L (1/34)				I (3/34)
4a-ED43 Reference			**L**	**F**	**T**	**V**	**Y**	**Q**	**I**	**R**	**A**	**D**	**V**
4d-QC382 Reference			**L**	**F**	**T**	**V**	**Y**	**Q**	**I**	**R**	**A**	**D**	**V**
1a-H77 Reference			**V**	**F**	**T**	**V**	**Y**	**Q**	**I**	**R**	**A**	**D**	**I**
1b-Con1 Reference			**V**	**F**	**T**	**V**	**Y**	**Q**	**V**	**R**	**A**	**D**	**V**

The 3 subjects who experienced virologic failure in M13-393 were infected with HCV GT4d. In HCV GT4d infected subjects, no baseline polymorphisms were observed at NS3 positions previously associated with resistance to NS3/4A protease inhibitors, and therefore the impact of baseline NS3 polymorphisms on treatment efficacy cannot be assessed.

All 3 virologic failure subjects had treatment-emergent NS3 D168V, which was a key substitution associated with treatment failure in HCV GT1 infected subjects (Table 15). A Y56H substitution, which is also associated with PTV resistance in GT1, emerged with D168V in Subject 30182 who experienced virologic breakthrough. The D168V substitution alone confers a 313-fold reduction in PTV cell culture anti-HCV activity. The Y56H + D168V combination causes a >12,000-fold reduction in PTV activity.

A few other amino acid substitutions were observed in individual subjects at NS3/4A positions not known to be associated with resistance to NS3/4A protease inhibitors. Of note, a I/V107I mixture change (V107 is the reference/consensus) was observed in Subject 30182. A V107I substitution was previously noted as a minor boceprevir resistance-associated substitution (see boceprevir label). Since the change was from a mixture at Baseline in a single subject, and the subject also had treatment-emergent Y56H + D168V which confer clear phenotypic resistance

to PTV, the potential role of V107I in PTV resistance is unclear but should continue to be monitored in other trials of NS3/4A protease inhibitors in HCV GT4 infected subjects.

Table 15 Treatment-emergent NS3 substitutions in 3 GT4d virologic failure subjects (all from Group 1-no RBV)

USUBJID	Virologic Failure Cat.	VISIT	Y56	D168
M13393-44317-30228	Relapse	BASELINE		
		PTW4		V
M13393-44365-30182	Breakthrough	BASELINE		
		TW8	H	V
M13393-45484-30238	Relapse	BASELINE		
		PTW8		V

NS5A

As observed in HCV GT1, variability in GT4 NS5A amino acid sequences was observed at multiple positions previously described as being associated with resistance to NS5A inhibitors (Table 16). Note that some of the NS5A positions included in Table 16 are not major resistance-associated positions or consistently associated with NS5A inhibitor resistance (e.g., 54, 62), but are shown for completeness. The “wild-type” consensus sequences at certain positions (e.g., 30, 54) appear to differ across certain subtypes. Importantly, the detection frequencies for NS5A polymorphisms in GT4a sequences did not differ by geographic location (U.S. versus non-U.S.), supporting the pooling of efficacy results for subjects infected with HCV GT4a independent of geographic location. Also note regarding the reference sequences: (1) the GT4a consensus at position 62 (E, glutamic acid) differs from the ED43 reference (D, aspartic acid), and (2) the GT4d consensus at position 58 (P, proline) differs from the QC382 reference (T, threonine). Finally, it is also noted that the consensus (based on only 3 isolates) in HCV subtype 4b included unusual sequences at key NS5A inhibitor resistance-associated positions 30 (serine, S) and 93 (histidine, H), raising concerns that this subtype is naturally less susceptible to OBV or other NS5A inhibitors.

Table 16 Baseline variability at NS5A positions potentially associated with resistance to NS5A inhibitors for subjects in M13-393, according to HCV GT4 subtype

			NS5A Positions Potentially Associated with Resistance: Variability from Reference Sequence*										
GT4 Subtype	**Reference Sequence**	**N**	**24**	**28**	**29**	**30**	**31**	**32**	**54**	**58**	**62**	**92**	**93**
4a	ED43	50		M (8/50)		R (3/50)				L (1/50)	E (47/50)		
4d	QC382	68		M (1/68)			L (3/68)		R (1/68)	P (47/68), A/P (1/68), A (1/68), S (1/68)	G (1/68), Q (1/68)		
4b	ED43	3				S (2/3)			N (3/3)	S (1/3) T (1/3)	E (3/3)		H (2/3)
4c	ED43	1				R (1/1)					Q (1/1)		
4f	ED43	7				R (7/7)	L (1/7)				E (6/7), N (1/7)		
4g/4k	ED43	1				C (1/1)	L (1/1)		N (1/1)		Q (1/1)		
4o	ED43	1		M (1/1)		T (1/1)					N/S (1/1)		
4	ED43	1				R (1/1)	L (1/1)				A (1/1)		
4a (U.S.)	ED43	16		M (3/16)		R (1/16)				L (1/16)	E (14/16)		
4a (Non-U.S.)	ED43	34		M (5/34)		R (2/34)					E (33/34)		
4a-ED43 Reference			**K**	**L**	**P**	**L**	**M**	**P**	**H**	**P**	**D**	**A**	**Y**
4d-QC382 Reference			**K**	**L**	**P**	**R**	**M**	**P**	**H**	**T**	**E**	**A**	**Y**
1a-H77 Reference			**K**	**M**	**P**	**Q**	**L**	**P**	**H**	**H**	**E**	**A**	**Y**
1b-Con1 Reference			**Q**	**L**	**P**	**R**	**L**	**P**	**Q**	**P**	**Q**	**A**	**Y**

*Underline indicates changes from reference that reflect the consensus of baseline sequences (subtypes with n≥3) in the dataset.

The only NS5A polymorphisms (at the positions noted above) observed in the 3 HCV GT4d infected subjects who experienced virologic failure were at position 58, which is clearly a polymorphic position. One subject each had the following amino acids detected at this position: P58, T58 and S/T58. The S58 sequence, detected in Subject 30238, was not detected in any other HCV GT4d infected subjects and was enriched from the S/T mixture at the time of virologic failure. This subject also had a treatment-emergent L28V substitution (treatment-emergent resistance summarized below). In cell culture, the T58S substitution by itself was not associated with reduced OBV activity, and contributed a ~2-fold increase in OBV EC_{50} value when present in combination with L28V; L28V alone conferred a 310-fold reduction in OBV activity. Given that the T58S polymorphism was detected only in a single subject and had a minimal impact on OBV cell culture anti-HCV activity, its contribution towards virologic failure in Subject 30238 is unclear. Nevertheless, this position should continue to be monitored in other studies of HCV GT4 infected subjects.

Each of the 3 virologic failure subjects had treatment-emergent substitutions at position L28 (L28S or L28V) (Table 17). Subject 30228 also had a treatment-emergent M31I substitution. As noted above, enrichment of S/T58S was observed in Subject 30238. No other amino acid

changes relative to reference were observed at known NS5A inhibitor resistance-associated positions for these 3 subjects. The impact of the L28S substitution, with or without M31I, could not be evaluated due to poor replication capacity of the chimeric HCV replicon carrying these substitutions. An M31I substitution alone conferred a modest 2.5-fold reduction in OBV activity. Several other amino acid changes were observed in single subjects at positions not previously associated with resistance to NS5A inhibitors, primarily in highly polymorphic regions beyond the N-terminal 100 amino acids of NS5A.

Table 17 Treatment-emergent NS5A substitutions in 3 GT4d virologic failure subjects (all from Group 1-no RBV)

USUBJID	Virologic Failure Cat.	VISIT	L28	M31	T58
M13393-44317-30228	Relapse	BASELINE			P
		PTW4	S	I/M	P
M13393-44365-30182	Breakthrough	BASELINE			
		TW8	V		
M13393-45484-30238	Relapse	BASELINE			S/T
		PTW8	V		S

Persistence of Resistance-Associated Substitutions

No data are currently available addressing the persistence of paritaprevir and ombitasvir resistance-associated substitutions in subjects with HCV GT4 infection. In clinical trial M13-393, subjects are to be followed through Post-Treatment Week 48 for resistance assessments.

As described in the Viekira Pak™ label, in HCV GT1 infected subjects who experienced virologic failure with the 3-DAA ± RBV regimen, persistence of ombitasvir and paritaprevir resistance-associated substitutions could be detected by population and clonal nucleotide sequence analyses (assay sensitivity approximately 5-10%) through at least 24 weeks of follow-up in most subjects. Ombitasvir resistance-associated substitutions in NS5A persisted in 100% of subjects with available data through Post-Treatment Week 48. Paritaprevir resistance-associated substitutions persisted in 59% of subjects through Post-Treatment Week 24, and in 20% of subjects through Post-Treatment Week 48. See the Viekira Pak™ label for additional details.

Cross-resistance

No NS3/4A protease inhibitors or NS5A inhibitors are currently approved for HCV GT4. Nevertheless, based on cross-resistance patterns in GT1 and the common paritaprevir and ombitasvir resistance-associated positions in GT1 and GT4, at least some degree of cross-resistance is expected within the NS3/4A protease inhibitor class and within the NS5A inhibitor class.

6.1.6 Other Endpoints

As all subjects in Groups 4 and 6 achieved SVR12 and, there were no other clinically relevant endpoints to evaluate.

6.1.7 Subpopulations

Assessment of response by subpopulation is moot since all subjects in Groups 4 and 6 achieved SVR12.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

All subjects treated with the 2-DAA/RBV regimen achieved SVR12 following 12 weeks of treatment. Therefore, the recommended duration of dosing for GT4-infected subjects without cirrhosis is 12 weeks.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

- **SVR12/SVR24 Concordance**

Of the 131 subjects who achieved SVR12 in M13-393, 79 subjects had SVR24 outcome results, of whom all 79 (100%) achieved SVR24. These subjects all came from Treatment Groups 1 and 4, as Group 6 had not completed the Post-Treatment Week 24 visit at the time of database lock. Three subjects in Groups 1 and 4 who achieved SVR12 did not have available SVR24 outcome data.

6.1.10 Additional Efficacy Issues/Analyses

Summary of efficacy in GT4-infected subjects

The results of Study M13-393 demonstrate a high SVR rate in a small number of reasonably healthy HCV-infected subjects who underwent intensive monitoring and adherence support. It is recognized that the 100% SVR rate for the 2-DAA + RBV regimen is unlikely to persist once the regimen enters routine clinical practice.

The SVR rate in subjects who did not receive RBV was somewhat lower and likely due to the lack of RBV, which has been demonstrated to decrease rates of virologic relapse. There are patients for whom RBV is not recommended (e.g., advanced cardiovascular disease or pre-existing anemia/hemoglobinopathies). Further, the subjects who did respond in this group all had IL28B CC genotype and HCV GT4 subtype 4a; both groups were relatively small and assessment of these parameters will unlikely be incorporated into routine clinical care. Based on the 100% (21/21) SVR12 rate for Group 1 subjects infected with HCV genotype 4a, the most common GT4 subtype represented at US study sites, the 2-DAA alone (no RBV) regimen may be a reasonable treatment option for non-cirrhotic US patients who cannot use or tolerate RBV. Therefore, given the findings of this study, it would be reasonable to allow a consideration of treating a GT4-infected patient with the 2-DAA alone regimen as long as the patient is made aware of the risk of a lower response and treatment-emergent drug resistance that may limit future re-treatment options.

HCV GT4-infected subjects with cirrhosis were not enrolled into this trial, and no recommendation on treatment of this population can be made.

Summary of efficacy in GT1b-infected subjects

SVR12 rates for the GT1b-infected subjects are shown in Table 18.

Table 18 SVR12 rates for GT1b-infected subjects

n/N (%)	Group 2 TN No cirrhosis 2-DAA x 12 weeks	Group 3 Null No cirrhosis 2-DAA x 12 weeks	Group 7 TN Cirrhosis 2-DAA x 24 weeks	Group 8 TE Cirrhosis 2-DAA x 24 weeks
SVR12	40/42 (95)	36/40 (90)	46/47 (98)	50/52 (96)
Virologic failure	0	1	0	0
Relapse	0	3	0	1
Premature discontinuation	1	0	1	0
Missing SVR12	1	0	0	1

Reviewer comment: The SVR12 results in HCV GT1b-infected subjects in Study M13-393, considering the results of other Phase 2/3 trials of the 3-DAA (Viekira Pak) ± RBV regimen, suggest that in those with prior pegIFN/RBV failure, the relapse rate may be mitigated with the addition of a third DAA or the addition of RBV. In addition, extending treatment to 24 weeks is unlikely to be a viable regimen for marketing as there are more effective regimens administered for less time than are currently available. In general these data do not support a recommendation for the 2-DAA regimen in GT1b-infected patients.

7 Review of Safety

Safety Summary

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The single trial, M13-393, formed the basis of the safety review. In this trial, a total of 316 subjects were enrolled at 46 sites: 135 subjects were non-cirrhotic HCV GT4-infected (Groups 1, 4, and 6), 82 subjects were non-cirrhotic HCV GT1b-infected (Groups 2 and 3), and 99 subjects were GT1b-infected with compensated cirrhosis (Groups 7 and 8).

Direct comparisons of GT4 and GT1b-infected subjects is challenging as no GT1b-infected subject received ribavirin. The safety profile of the GT1b subjects was reviewed and the safety profile was generally consistent with the known safety profile of the DAAs; no new adverse events were reported and the frequency of reported events was similar. Since review of GT1b subjects is not germane to the approval of Technivie Tablets for treatment of GT4 infection, they will not be discussed any further.

Paritaprevir/ombitasvir/rtionaivr ± RBV were administered to >2300 subjects with GT1 infection and salient safety information from that NDA will referenced as it applies to the current application. However, direct comparisons are difficult as all subjects in NDA 206619 received a third DAA.

7.1.2 Categorization of Adverse Events

Treatment-emergent AEs were defined as any event that began or worsened in severity after initiation of study drug through 30 days after the last dose of study drug. Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 16.0.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Not applicable as the NDA is based on data from a single trial.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The 135 GT4-infected subjects were exposed to study treatment for a median of 84 days. The doses used were those currently approved for treatment of patients infected with GT1.

7.2.2 Explorations for Dose Response

Explorations for dose response were conducted prior to submission of the GT1 NDA, and support the proposed dosing in subjects with GT4 infection.

7.2.3 Special Animal and/or In Vitro Testing

Not applicable.

7.2.4 Routine Clinical Testing

Routine clinical testing for adverse clinical and laboratory events was comprehensive. Adverse events, serious and non-serious, were collected beginning after the informed consent form was signed through the Safety follow-up assessment. Adverse events were recorded regardless of the suspected cause of the event. Study visits occurred at Treatment Weeks 1, 2, 4, 6, 8, 10, and 12, and Post-Treatment Weeks 2, 4, 8, 12, 24, 36, and 48. Unscheduled visits were conducted for premature discontinuation from treatment and as needed to assess progression and/or resolution of events.

Safety evaluations included clinical laboratory assessments, clinical evaluation of vital signs, physical examinations, ECGs, and the subjective reporting of adverse events. For each adverse event, the following information was collected: description, classification of “serious” or “not

serious," date of first occurrence and date of resolution (if applicable), severity, causal relationship (possible, probably or definite), action taken, outcome, and concomitant or other treatment given. Similar requirements were in place for laboratory abnormalities as adverse events. Grading of hematology and clinical chemistry abnormalities were adapted from the National Cancer Institute's Common Terminology Criteria for Adverse Events v4.0 (CTCAE). Many laboratory parameters were reported in SI units, and these values were converted by this reviewer and presented in US Conventional Units.

7.2.5 Metabolic, Clearance, and Interaction Workup

See above and review of NDA 206619.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Paritaprevir is a protease inhibitor (PI) and there are currently two other PIs approved: boceprevir and simeprevir. A third PI, telaprevir, was recently withdrawn from the US market. Telaprevir and simeprevir are associated with skin and skin structure reactions. Further, co-administration of boceprevir and telaprevir with pegIFN/RBV leads to high rates of anemia and anemia-related adverse events. Unlike these other PIs, paritaprevir inhibits the OATB1 transporter which results in hyperbilirubinemia (primarily indirect), and is associated with more frequent elevations in hepatic transaminase levels. Ombitasvir is one of two currently approved NS5A inhibitors, the other being ledipasvir.

The fixed-dose combination of ombitasvir, paritaprevir, ritonavir plus a separate NS5b non-nucleoside inhibitor (dasabuvir) with and without ribavirin was approved in December 2014 (3-DAA $\pm$ RBV). Important adverse events observed in subjects treated with this regimen include: transaminitis and hyperbilirubinemia. The labeling for this regimen contains a Warning related to transaminitis and the requirement for liver test monitoring during treatment. Further, in subjects receiving the 3-DAA + RBV regimen, the most commonly reported adverse reactions (greater than 10% of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia and asthenia. In subjects receiving the 3-DAAs alone, the most commonly reported adverse reactions (greater than or equal to 5% of subjects) were nausea, pruritus and insomnia.

7.3 Major Safety Results

7.3.1 Deaths

No deaths were reported in GT4-infected subjects.

7.3.2 Nonfatal Serious Adverse Events

Five of 135 GT4-infected subjects (4%) reported SAEs of which only one was on-treatment. The other four were reported within 30-days of completing study drugs, and none were considered by the investigators or Applicant to be related to study drugs.

- One subject in Group 1 with trauma following a motorcycle accident (on-treatment)
- Two subjects in Group 1 with back pain/spondylolisthesis and adenocarcinoma of the pancreas/cholangitis
- One subject in Group 4 with rotator cuff syndrome
- One subject in Group 6 with breast cancer

7.3.3 Dropouts and/or Discontinuations

No GT4-infected subjects discontinued dosing or the trial due to adverse events.

7.3.4 Significant Adverse Events

Two GT4-infected subjects reported severe adverse events: one subject in Group 6 with hyperbilirubinemia and one in Group 4 with headache.

7.3.5 Submission Specific Primary Safety Concerns

Abnormalities in Liver Function

- **Transaminase Elevations**

Transaminitis occurred in approximately 1% of subjects treated with Viekira Pak; this risk increased to 27% among females taking a concomitant estradiol or ethylene estradiol medication. The current Viekira Pak labeling carries a Warning that all subjects be monitored for ALT elevations during treatment, and co-administration of estradiol and ethylene estradiol containing medications are contraindicated. In Study M13-393, use of estradiol and ethylene estradiol containing medications were also not allowed.

No GT4 subjects had ≥Grade 3 ALT elevations (see Table 19), and no hepatotoxicity-related treatment-emergent adverse events were reported.

Table 19 Treatment-emergent ALT elevations

N (%)	2-DAA N=44	2-DAA + RBV N=91
ALT ≥Grade 2 (≥2.5 – 5 x ULN)	0	4 (4)
ALT ≥Grade 3 (≥5.0 – 10 x ULN)	0	0

- **Bilirubin Elevations**

Paritaprevir inhibits the organic anion transporting polypeptide transporter OATP1B1 which leads to predominantly indirect hyperbilirubinemia. In addition, ribavirin-induced hemolytic anemia can contribute to the occurrence of increased indirect bilirubin levels.

Mean increases in total bilirubin were observed in Groups 4 and 6 who were treated with 2-DAA + RBV (+0.11 mg/dL), whereas mean decreases were observed in groups treated with 2-DAA without RBV:- 0.16 mg/dL in Group 1. The greatest mean increase was at Week 1 (+0.58 mg/dL for Groups 4 + 6) and mean decreases from baseline were observed after the end of treatment by Post-Treatment Week 2.

In the Viekira Pak NDA, on-treatment elevations of total bilirubin levels ≥Grade 2 (≥1.5 – 3.0 x ULN) were reported in 23-43% of subjects treated with the 3-DAA + RBV compared to 8% when RBV was not included in the regimen. In study M13-393, 11% (15/135) of GT4-infected subjects had an on treatment total bilirubin level elevation ≥Grade 2; 14/15 subjects were in groups that received RBV.

Three subjects in Group 6 (GT4 treatment experienced; 2-DAA + RBV x 12 weeks) had potentially clinically significant on-treatment total bilirubin elevations:

- Subject 30464 was a 60 year old male. This subject had a normal bilirubin at baseline which increased to Grade 3 on Day 8. The subject also complained of asthenia, fatigue and myalgia. No change was made to study drugs and the bilirubin decreased to Grade 2 by the end of treatment.
- Subject 30469 was a 39 year old male. This subject had a Grade 2 bilirubin at baseline which increased to Grade 3 on Day 8. No change was made to study drugs and the bilirubin decreased to normal by the end of treatment.
- Subject 30446 was a 60 year old male. This subject had a normal bilirubin at baseline which increased to Grade 3 on Day 8. The subject also complained of fatigue. No change was made to study drugs and the bilirubin decreased to normal by the end of treatment.

Reviewer comment: Increases in bilirubin levels appear consistent with the inhibitory effect of paritaprevir on the bilirubin transporter OATP1B1 and with the addition of ribavirin to the regimen and with the pattern observed in the review of NDA 206691.

- **Combined Transaminase and Bilirubin Elevations**

An independent expert hepatic panel reviewed a single case of a GT4-infected subject who experienced elevations in both transaminase and bilirubin levels:

- Subject 30417 was a 58 year old White male in Group 6 (GT4 TE non-cirrhotic treated with 2-DAA + RBV x 12 weeks). At baseline his ALT was 66 U/L and total bilirubin was 0.64 mg/dL. On Day 8, the bilirubin was 49. On Day 22 the ALT was 135 U/L. On Day 85 the ALT was 46 and total bilirubin was 1.34 mg/dL. The subject also experienced an adverse event of moderate hemolytic anemia on Day 8.No action was taken with the study drugs. The panel's assessment was this was possible DILI with adaptation, however, the ALT increase was small (trivial) and transient. The rise in indirect bilirubin was attributed to study drugs but not considered to be DILI. Because the rise in bilirubin preceded the rise in ALT, and because the bilirubin was predominantly indirect, this was not a potential Hy's law case.

- **Skin and Skin Structures**

Rash and pruritus were observed in subjects treated with the 3-DAA regimen in Phase 2 and 3 trials in NDA 206619. Paritaprevir is an NS3/4A HCV protease inhibitor, and skin and skin structure adverse events have been reported in subjects treated with other approved protease

inhibitors and RBV. In addition, RBV alone is associated with an increased frequency of rash and pruritus.

The Applicant conducted a special analysis to evaluate the potential for the 3-DAA regimen to cause significant adverse events in the skin and skin structure organ class. Rash-related adverse events were evaluated using a pre-specified (MedDRA) query (CMQ) and the severe cutaneous reactions standardized MedDRA query (SMQ). As in NDA 206619, the two most frequently reported events were rash and pruritus.

In GT4 subjects, the frequency of skin events was 9% (4/44) among those who did not receive RBV and 12% (11/91) among those who did. In Group 1 (-RBV) there were four subjects with six events: pruritus (1), rash and pruritus (1), photosensitivity and rash (1), and nasal allergy/hypersensitivity (1). In Groups 4 and 6 (+RBV), there were 10 subjects with 12 events: pruritus (5), rash (2), rash and pruritus (1), eczema (1), allergic dermatitis (1), and erythema (1).

The majority of events were graded as mild or moderate in severity and responded to treatment with topical or oral corticosteroids, oral antihistamines and/or other over-the-counter topical agents. There were no serious skin events such as SJS, DRESS or TEN reported. No subject discontinued RBV or interrupted or discontinued the DAAs.

Anemia

The primary toxicity of ribavirin is hemolytic anemia. The frequency of anemia in Groups 4 and 6 was 5% (5/91), which was comparable to the frequency observed in non-cirrhotic subjects treated with 3-DAA + RBV in NDA 206619 (6.5%). Only one subject in Group 6 had a hemoglobin level <8.0 g/dL.

The mean reduction in hemoglobin levels in subjects who received RBV (Groups 4 and 6) was -2.1 g/dL compared to -0.5 g/dL in Group 1 (no RBV). The decrease in hemoglobin occurred primarily during the first 4 weeks of treatment, and remained stable during the remainder of the Treatment Period and then returned to near baseline levels by Post-Treatment Week 4. A corresponding increase in reticulocytes with the decrease in hemoglobin was also observed, which returned to near baseline levels at Post-Treatment Week 4.

The five subjects in Groups 4 and 6 with low hemoglobin levels were managed with RBV dose modifications; no subject received erythropoietin or a blood transfusion, and no subjects interrupted or discontinued RBV. All five completed a full course of treatment, and all achieved SVR12.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Headache, asthenia, fatigue, nausea, and insomnia were the most common treatment-emergent adverse events among the GT4 subjects treated with Technivie Tablets + RBV (Table 20). This adverse event profile is consistent with that of Viekira Pak + RBV, for which pruritus, nausea, fatigue, asthenia, insomnia, and anemia were identified as adverse events.

Table 20 Treatment-emergent adverse events in >10% of GT4 subjects

N (%)	Group 1 2-DAA Treatment-naïve N=44	Group 4 2-DAA + RBV Treatment-naïve N=42	Group 6 2-DAA + RBV Treatment-experienced N=49
Diarrhea	2 (4.5)	6 (14)	3 (6)
Nausea	4 (9)	7 (17)	6 (12)
Asthenia	11 (25)	10 (24)	16 (33)
Fatigue	3 (7)	5 (12)	9 (18)
Irritability	3 (7)	6 (14)	2 (4)
Myalgia	0	0	5 (10)
Headache	13 (29.5)	14 (33)	14 (29)
Insomnia	2 (4.5)	4 (9.5)	8 (16)
Pruritus	2 (4.5)	1 (2)	5 (10)

7.4.2 Laboratory Findings

Please see above for a discussion of ALT, bilirubin, and hemoglobin abnormalities. The Applicant focused the assessment of laboratory abnormalities on those deemed "potentially clinically significant;" most of which met the threshold of being ≥Grade 3 abnormalities. Most laboratory abnormalities were single values. No laboratory parameters were identified that warranted special monitoring or management during treatment with the 2-DAAs.

Hematology Parameters

The only hematology abnormalities were a single subject in Group 4 with hemoglobin <8.0 g/dL, and two subjects, and one each in Groups 4 and 6 with a total neutrophil count <1 x 10^9/L.

Chemistry Parameters

Abnormalities in clinical chemistry parameters were infrequent and no patterns were observed.

7.4.3 Vital Signs

There were no clinically relevant changes in vital signs observed.

7.4.4 Electrocardiograms (ECGs)

The Applicant previously conducted a Thorough QT (TQT) study (Study M12-680) that demonstrated the 2-DAAs (with a third DAA, dasabuvir) did not meet the threshold for QTcF prolongation based on ICH E14 guidelines at therapeutic or supratherapeutic doses.

There was one event of a treatment-emergent clinically significant abnormal ECG finding: Subject 30170 in Group 1 (GT4, treatment naïve, 2-DAA). This subject had a history of hypertension. On Day 86 the subject had atrial fibrillation that was considered clinically significant. The investigator reported the atrial fibrillation as an AE (Days 58 – 252+) that was mild, not related to study drug, not serious, and did not result in study drug interruption or

discontinuation. The atrial fibrillation started on Day 58, was ongoing as of Day 252 (Post-Treatment Day 194), and was treated with medication.

7.4.5 Special Safety Studies/Clinical Trials

No special safety studies were required or conducted.

7.4.6 Immunogenicity

None of the drugs in the regimen are immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

All subjects received the same dose of study medications.

7.5.2 Time Dependency for Adverse Events

Adverse events occurred at all times during dosing with the 2-DAAs either with or without RBV. Hyperbilirubinemia and anemia occurred early in treatment, typically within the first 1-4 weeks of dosing, generally stabilized and returned toward baseline levels by end of treatment or soon thereafter (by PTW4). Transaminitis also typically occurred early during treatment, days 8-43, and usually resolved by the end of treatment.

7.5.3 Drug-Demographic Interactions

None identified.

7.5.4 Drug-Disease Interactions

None identified.

7.5.5 Drug-Drug Interactions

The interaction profile for the 3-DAA and 2-DAA regimens have been extensively characterized, There are a substantial number of drug-drug interactions (see Section 4.4.3 above and the review of NDA 206619), which resulted in contraindications and recommendations for dose modifications of many other drugs (dose modifications of the DAAs is not possible). The following is a list of contraindicated medications:

Alfuzosin, Astemizole, Blonanserin, Carbamazepine, Cisparide, Dihydroergotamine, Efavirenz, Ergotamine, Ergonovine, Ethinyl estradiol-containing medications, Fusidic Acid,Lovastatin, Methylergonovine, Midazolam (oral), Phenobarbital, Phenytoin, Pimozide, Rifampin, Salmeterol, Sildenafil (when used for treatment of PAH), Simvastatin, St. John's Wort, Terfenadine, and Triazolam.

Differences in dosing recommendations between Technivie Tablets and Viekira Pak based on drug-drug interactions exist for rosuvastatin (dose should not exceed 20 mg/day with Technivie Tablets), digoxin (dose should be reduced by 30-50% with Technivie Tablets), and gemfibrozil (no adjustment required with Technivie Tablets).

Additional drug-drug interaction studies conducted with the 2-DAAs are summarized in Dr. Vikram Ayra's Clinical Pharmacology review.

7.6 Additional Safety Evaluations

Not applicable.

7.6.1 Human Carcinogenicity

Neither DAA demonstrated mutagenic or carcinogenic potential in vitro.

7.6.2 Human Reproduction and Pregnancy Data

No pregnancies have been reported in Study M13-393.

Pregnancy should be avoided during treatment with Technivie™ Tablets due to RBV's significant teratogenic and/or embryocidal effects. Females of childbearing potential ensure they use adequate forms of birth control while receiving RBV, and for at least 6 months after stopping RBV. Females are to have negative results for pregnancy tests performed prior to treatment. Males are to be abstinent from sexual intercourse, surgically sterile or agree to practice two effective forms of birth control throughout RBV dosing and for 6 months after the last dose of study drug.

As discussed in Section 7.3.5 above, use of estrogen-containing hormonal contraceptives was disallowed during the conduct of the trial due the risk of excessive transaminitis, and will be contraindicated for use with this regimen.

7.6.3 Pediatrics and Assessment of Effects on Growth

There is a study plan in place to assess the safety and efficacy of the 2-DAA/RBV regimen in pediatric patients with GT4 infection.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

See the review of NDA 206619.

7.7 Additional Submissions / Safety Issues

There were no additional safety submissions or issues identified in the review of this NDA.

8 Postmarket Experience

An abbreviated review evaluated adverse events associated with the use of Viekira Pak that were detected in a data mining search. The Division of Antiviral Products (DAVP) consulted the Division of Pharmacovigilance II (DPV II) to identify adverse events reported in patients receiving Viekira Pak as part of the approval process of Technivie Tablets for the treatment of genotype 4 chronic HCV infection. The data mining review of the most frequently reported PTs with the use of Viekira Pak did not identify any new safety concerns. The PTs were all labeled (i.e., hyperbilirubinemia, pruritus, insomnia, fatigue, headache, rash, nausea) or disease related (i.e., jaundice, ascites, anemia), and did not identify any new safety concerns or deaths that can be attributed to Viekira Pak use.

9 Appendices

9.1 Literature Review/References

The Applicant has published the final results of Study M13-393:

Hézode C, Asselah T, Reddy KR, Hassanein T, Berenguer M, Fleischer-Stepniewska K, Marcellin P, Hall C, Schnell G, Pilot-Matias T, Mobashery N, Redman R, Vilchez RA, Pol S. **Ombitasvir plus paritaprevir plus ritonavir with or without ribavirin in treatment-naive and treatment-experienced patients with genotype 4 chronic hepatitis C virus infection (PEARL-I): a randomised, open-label trial.** Lancet. 2015 Mar 30. pii: S0140-6736(15)60159-3. doi: 10.1016/S0140-6736(15)60159-3. [Epub ahead of print]

9.2 Labeling Recommendations

The following represent recommendations on various sections of the draft Technivie Tablets label:

Indication

The Applicant's proposed indication reads: TECHNIVIE TABLETS is indicated in combination with ribavirin for the treatment of patients with genotype 4 chronic hepatitis C virus (HCV) infection.

Reviewer comment: The proposed indication is too broad as it implies that the 2-DAA combination can be used in any GT4 infected patients. For example, there are no data in this application on use of this combination in patients with cirrhosis.

Dosage and Administration

The Dosage and Administration section provides a recommendation that TECHNIVIE TABLETS (without ribavirin) may be considered in some patients.

Reviewer comment: Inclusion of this caveat should be acceptable with the addition of "in patients who cannot take or tolerate ribavirin."

Adverse Events

The frequency and pattern of ALT elevations, bilirubin elevations and decreases in hemoglobin levels were generally similar to those reviewed in NDA 206619 and described in the approved labeling for Viekira Pak, and this same information should be included in the Technivie Tablets label.

Clinical Pharmacology

New information about drug-drug interactions with the 2-DAA regimen are included in the various clinical pharmacology tables.

Clinical Virology

A number of editorial comments are suggested and will be conveyed to the Applicant.

Clinical Trials

The clinical trials section provides a generally accurate discussion of the trial design and outcomes by treatment arms. A number of editorial comments are suggested and will be conveyed to the Applicant.

9.3 Advisory Committee Meeting

Not applicable.

9.4 Clinical Investigator Financial Disclosure Review

Application Number: 207931

Submission Date(s): 02/25/2015

Applicant: AbbVie

Product: ombitasvir, paritaprevir, ritonavir fixed-dose tablets

Reviewer: Russell Fleischer, PA-C, MPH

Date of Review: 04/20/2015

Covered Clinical Study (Name and/or Number): M13-393

Was a list of clinical investigators provided:	Yes X	No ☐ (Request list from applicant)
Total number of investigators identified: 48		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 4		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)):		

Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: 4 Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes X	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes X	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes X	No ☐ (Request explanation from applicant)

The Applicant has adequately disclosed financial interests/arrangements with clinical investigators as recommended in the guidance for industry *Financial Disclosure by Clinical Investigators*. There were no interests/arrangements or investigators who are sponsor employees that raise questions about the integrity of the data.

Specifically, the Applicant took steps to minimize potential bias of clinical investigators from financial interests and arrangements by utilizing randomized study designs with no site enrolling numbers of subjects so high as to influence results. The primary endpoint for all of the covered studies included an objective laboratory endpoint of HCV RNA. In addition the Phase 3 studies also utilized an independent Data Safety Monitoring Board (DSMB) and an Independent Hepatic Expert Panel for impartial monitoring of safety.

In summary, the disclosed financial interests/arrangements did not appear to affect the approvability of this application.

The following investigators who participated in Study M13-393 hold financial interests required to be disclosed:

- (b) (6) received significant payments having total value in excess of $25,000, other than payments for conducting clinical studies. The site enrolled (b) (6)
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APPEARS THIS WAY ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL D FLEISCHER
06/18/2015

PATRICK R HARRINGTON
06/18/2015

XIAOJING K QI
06/19/2015

JULIAN J O REAR
06/19/2015

FRASER B SMITH
06/19/2015

JEFFREY S MURRAY
06/19/2015

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 207931 **Applicant: AbbVie** **Stamp Date: 2/26/2014**

Drug Name: ombitasvir/paritaprevir/ritonavir **NDA/BLA Type: Priority**

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.*, Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2).	(b)(1)			
505(b)(2) Applications					
13.	If appropriate, what is the reference drug?			X	
14.	Did the applicant provide a scientific bridge demonstrating the relationship between the proposed product and the referenced product(s)/published literature?				
15.	Describe the scientific bridge (e.g., BA/BE studies)			X	
DOSE					
16.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)?			X	Doses are the same as currently approved
EFFICACY					
17.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? Pivotal Study #1: Study M13-393: Comparison of	X			The Division agreed that a single trial in the proposed population would be adequate

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
	ombitasvir/paritaprevir/ritonavir with or without ribavirin in GT4 infected adults without cirrhosis Indication: Treatment of adults with GT 4 chronic hepatitis C virus infection without cirrhosis				given the extensive data available in other genotypes. There was no expectation that safety would differ based on genotype.
18.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X			
19.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	X			
20.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?	X			
SAFETY					
21.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	X			
22.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	X			These data were submitted and reviewed in NDA 206619
23.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
24.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?			X	Duration of treatment is 12 weeks
25.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?	X			Data from over 3000 patients treated with these agents have been reviewed
26.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	X			
27.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	NA	Comment
28.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
OTHER STUDIES					
29.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	X			
30.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			X	
PEDIATRIC USE					
31.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			
ABUSE LIABILITY					
32.	If relevant, has the applicant submitted information to assess the abuse liability of the product?	X			
FOREIGN STUDIES					
33.	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?	X			
DATASETS					
34.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
35.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
36.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
37.	Are all datasets to support the critical safety analyses available and complete?	X			
38.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
CASE REPORT FORMS					
39.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
40.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	X			
FINANCIAL DISCLOSURE					
41.	Has the applicant submitted the required Financial Disclosure information?	X			
GOOD CLINICAL PRACTICE					
42.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __YES___

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

CLINICAL FILING CHECKLIST FOR NDA/BLA or Supplement

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

None.

Russell Fleischer, PA-C, MPH	03/25/2015
Reviewing Medical Officer	Date
Linda Lewis, MD	03/25/2015
Clinical Team Leader	Date

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL D FLEISCHER
06/17/2015