CENTER FOR DRUG EVALUATION AND RESEARCH

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CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	November 24, 2014
From	Linda L. Lewis, MD Division of Antiviral Products OAP/OND/CDER/FDA
Subject	Cross-Discipline Team Leader Review
NDA/BLA # **Supplement#**	NDA 206619 Original
Applicant	AbbVie
Date of Submission	April 21, 2014
PDUFA Goal Date	December 21, 2014
Proprietary Name / **Established (USAN) names**	Viekira Pak Ombitasvir, paritaprevir, ritonavir, and dasabuvir
Dosage forms / Strength	Ombitasvir, paritaprevir, ritonavir fixed dose combination tablet (12.5 mg/75 mg/50 mg) Co-packaged with dasabuvir (250 mg) Two tablets each packaged in blister cards (1 day's dose)
Proposed Indication(s)	1. Treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis
Recommended:	*Approval – pending completion of facility inspections, with modifications to labeling as described in this review*

1. Introduction

This NDA contains information to support the approval of Viekira Pak™, a new complete treatment regimen for chronic hepatitis C virus (HCV) infection, comprised of ombitasvir (ABT-267), paritaprevir (ABT-450), and ritonavir coformulated as a fixed dose combination tablet co-packaged with dasabuvir (ABT-333) tablets. Viekira Pak represents one of the first generation interferon-free regimens for treatment of chronic HCV and is comprised of three oral direct acting antivirals (DAAs). The regimen was developed and the NDA was submitted by AbbVie, Inc.

Viekira Pak represents a novel product review. This NDA contains three new molecular entities (NMEs): ombitasvir (OMB), an HCV NS5A inhibitor, paritaprevir (PTV), an HCV NS3/4 protease inhibitor, and dasabuvir (DBV), a non-nucleoside HCV NS5B inhibitor. The fixed dose combination (FDC) tablet also includes ritonavir (RTV), a CYP3A, mechanism-based pharmacoenhancer included to boost the exposure of PTV. Most non-clinical and early clinical development was conducted with the individual drugs. The phase 2 clinical development focused on identifying the optimal doses and combinations of the three DAAs in different patient populations. The phase 3 clinical trials confirmed the proposed dose regimens and characterized the safety profile of the slightly different regimens, and treatment durations proposed for approval, including the use of ribavirin in some populations. To our knowledge, this will be the first approval of three NMEs simultaneously in a single NDA.

The NDA contains the results of the nonclinical and clinical development program conducted by AbbVie for the three active component drugs. The submission contains study reports characterizing the chemistry/manufacturing/control (CMC) processes, nonclinical toxicology, in vitro and clinical virology, and clinical pharmacology (including multiple drug-drug interaction studies), in addition to clinical safety and efficacy of the complete regimen. This Cross-Discipline Team Leader's (CDTL's) Review will convey the CDTL's assessment of the major issues pertinent to approvability of the application and will summarize the clinical evidence (efficacy trials, safety database, critical clinical pharmacology data) and key aspects of reviews from other disciplines (microbiology, CMC, nonclinical pharmacology/toxicology).

2. Background

The Centers for Disease Control and Prevention estimates that about 3 million people in the U.S. are living with chronic HCV, many unaware they are infected. Because HCV infection has been shown to be clustered in the "baby boomer" generation and HCV-associated liver disease may take decades to progress, the rates of cirrhosis, liver failure, hepatocellular carcinoma, and liver transplantation are expected to continue to increase over the next 20 years. Previous treatment options have included pegylated alpha interferon injections plus ribavirin combined with a DAA, regimens that were difficult to tolerate and required up to a year of treatment. Sustained virologic response (SVR) rates with these regimens were about 70% for patients with genotype 1 HCV infection, the most common genotype found in the U.S., in the clinical trials but are reported to be substantially lower in clinical practice. The

first of the new all-DAA, interferon-free regimens Harvoni (ledipasvir/sofosbuvir FDC, Gilead Sciences) was approved in October, 2014 on the basis of clinical trials documenting SVR rates > 95%. The Harvoni approval ushered in a new age of HCV treatment.

Viekira Pak represents another all-oral DAA, interferon-free regimen for treatment of genotype 1 (GT1) HCV that provides extremely high SVR rates across a broad population of patients. The Division of Antiviral Products Review Team provided input on the development programs of the three individual drugs under INDs 101636 (DBV), 103526 (PTV), and 108434 (OMB). The Applicant's development program included early explorations of dose response for individual component drugs and explorations of different combinations of the three component drugs. These early phase studies established optimal dosing of each component and the need for all three component drugs to achieve the highest SVR rates in patients with GT1 HCV. AbbVie then conducted a large, multi-arm, phase 2 trial (Study M11-652, AVIATOR) to further explore optimal regimens, including the need for both OMB and DBV, the need for RBV, and durations of treatment in different patient subgroups. The phase 2 development program demonstrated the contribution of each drug in the proposed regimen in different populations as described in detail in both the Statistical and Virology Reviews. The evidence for including all three DAA component drugs was strongest for subjects with GT1a HCV.

The package of clinical trials to be submitted in the NDA was discussed with the Applicant at an End-of-Phase-2 meeting in October, 2012, during which the Review Team voiced some concerns regarding the Applicant's initial phase 3 plan. However, based on the very promising results of the phase 2 M11-652 trial, the 3-DAA regimen was granted Breakthrough Therapy designation in May, 2013. A pre-NDA meeting was held in January, 2014, during which the Review Team agreed on the final nonclinical and clinical NDA package.

The optimal regimens were confirmed in a series of six phase 3 trials designed to characterize the safety and efficacy in key subgroups. In addition to confirming efficacy, the phase 3 clinical trials submitted in the NDA were designed to evaluate different durations of treatment and need for RBV in some subgroups. The proposed trial designs are in accordance with the Draft Guidance for Industry: *Chronic Hepatitis C Virus Infection: Developing Direct-Acting Antiviral Drugs for Treatment* published by the FDA in October, 2013. In the Guidance, FDA recommends an immediate versus deferred, placebo-controlled trial design in subjects not in need of urgent treatment (SAPPHIRE I and II) in order to assess the safety profile of the new regimen. In treatment experienced subjects or those more in need of timely treatment, a dose or treatment duration comparison or a well-justified, pre-specified historical control is also recommended. As shown in Table 1 below, all of the submitted phase 3 trials explore an important comparison that provides evidence for selection of the optimal regimen in key subpopulations.

Table 1: Phase 3 Randomized, Global, Multicenter Trials Conducted with Viekira Pak With or Without Ribavirin (RBV)

Trial	Population	Study Arms (Number of Subjects Treated)

Trial	Population	Study Arms (Number of Subjects Treated)
SAPPHIRE I (double-blind)	GT1 (a and b) TN[a] without cirrhosis	Arm A: VIEKIRA PAK + RBV (473) Arm B: Placebo (158)
SAPPHIRE II (double-blind)	GT1 (a and b) TE[b] without cirrhosis	Arm A: VIEKIRA PAK + RBV (297) Arm B: Placebo (97)
PEARL II (open-label)	GT1b TE without cirrhosis	Arm A: VIEKIRA PAK + RBV (88) Arm B: VIEKIRA PAK (91)
PEARL III (double-blind)	GT1b TN without cirrhosis	Arm A: VIEKIRA PAK + RBV (210) Arm B: VIEKIRA PAK (209)
PEARL IV (double-blind)	GT1a TN without cirrhosis	Arm A: VIEKIRA PAK + RBV (100) Arm B: VIEKIRA PAK (205)
TURQUOISE II (open-label)	GT1 (a and b) TN & TE with cirrhosis	Arm A: VIEKIRA PAK + RBV (12 weeks) (208) Arm B: VIEKIRA PAK + RBV (24 weeks) (172)

[a] TN, treatment naïve was defined as not having received any prior therapy for HCV infection.
[b] TE, treatment-experienced subjects were defined as either: prior relapsers, prior partial responders, or prior null responders to pegIFN/RBV treatment.

In addition, the Review Team agreed that AbbVie could submit within 30 days of the original planned submission date additional data from Study M12-999 conducted in post-liver transplant patients. The Review Team also agreed to allow AbbVie to submit during the review cycle interim results from Study M14-004 (TURQUOISE-I) conducted in with HIV/HCV coinfected patients, although no commitment was made to review the data during this review cycle. The Review Team concluded that if the interim data from Study M14-004 were consistent with the data in HCV mono-infected patients, there would likely be substantial off-label use in coinfected patients and including the data in the NDA review might lead to safer use.

Overall, the material submitted in this NDA provides adequate support for the approval of Viekira Pak for the treatment of chronic GT1 HCV infection including patients with compensated cirrhosis, selected post-liver transplant patients, and HIV/HCV coinfected patients on specific antiretroviral therapy regimens. No substantive disagreements regarding approvability were encountered among members of the Review Team. The conclusions of the DAVP Review Team and consultants will be summarized in the body of this CDTL Review and an overall risk-benefit assessment is provided in Section 13.

3. CMC/Device

The Applicant submitted a complete package of CMC information enabling a thorough review of all three NME drug substances and the drug product. For a complete description of the drug quality review, please refer to the Chemistry Review submitted by Drs. Maotang Zhou, Milton Sloan, and Caroline Strasinger. Dr. Elsbeth Chikhale's Biopharmaceutics Review describes the dissolution testing methodology and the bioavailability/bioequivalence studies used to

bridge development program formulations to the commercial formulations. In addition, Dr. Erika Pfeiler conducted an assessment of the microbial limits applicable to Viekira Pak.

- ***General product quality considerations***

As noted in the introduction to this CDTL Review, Viekira Pak is comprised of two NMEs combined with a pharmacoenhancer in an FDC (OMB, PTV, RTV) copackaged with a third NME (DBV). The CMC reviewers evaluated information on all three NME drug substances, the final drug products, and the copackaged configuration. Because it is an approved product, no substantial review of RTV drug substance was conducted for this NDA. A separate Biopharmaceutics Review addresses dissolution criteria.

Some key physicochemical and manufacturing attributes of the drug substances are summarized from the CMC Review. Dasabuvir is manufactured as a monosodium salt monohydrate that has relatively low solubility. It is produced in a (b) (4) manufacturing process. The specifications for dasabuvir sodium drug substance includes tests for description, identification, assay, impurities, sodium content, residual solvents, (b) (4) water content, residual heavy metals, and microbiological quality. At the time of the NDA submission, adequate stability data were provided to support the proposed retest period of (b) (4) months for dasabuvir drug substance.

Paritaprevir is manufactured as a dihydrate (b) (4)
It has low solubility and moderate permeability (b) (4)
Drug substance specifications include tests for description, identification, (b) (4) assay, impurities, genotoxic impurities, residue on ignition, water, and microbiological attributes. Stability data provided in the NDA supports a retest period of (b) (4) months when stored below (b) (4) C.

Ombitasvir is manufactured in a (b) (4) process that produces a drug substance hydrate that is almost insoluble in water but is soluble in ethanol. In order to improve (b) (4), OMB is manufactured (b) (4) The drug substance specifications include tests for description, identification, (b) (4) assay, impurities, genotoxic impurities, carcinogenic impurities, residue on ignition, water and microbiological attributes. Submitted stability data support a retest period of (b) (4) months when stored below (b) (4) °C.

The proposed drug product consists of coformulated OMB, PTV, and RTV film-coated tablets (12.5 mg/75mg/50 mg) co-packaged with DBV film-coated tablets (250 mg). Drug substances are processed into final tablets and then tested and packaged at different facilities. Quality of the drug products are controlled by tests for description, identity, assay, (b) (4) content uniformity, degradation products, and dissolution. Both final tablets are immediate release tablets that contain commonly used excipients. A single day's dose is packaged in a blister pack in a cardboard wallet configuration containing two FDC tablets to be taken once daily and two DBV tablets to be taken as one tablet twice daily. Seven wallet packs are packaged in

a carton and four weekly cartons are packaged in a larger carton to provide a month's supply suitable for dispensing to the patient. Adequate information was submitted to support the Applicant's proposal for a 24 month expiration dating.

The Biopharmaceutics reviewer evaluated the Applicant's proposed dissolution methods and concluded they were acceptable for both the OMB, PTV, RTV FDC tablet and the DBV tablet. Further she concluded the proposed dissolution acceptance criteria for release were acceptable. She noted that some of the single component and FDC formulations of OMB, PTV, and RTV used during the clinical development program had different PTV bioavailability due to different pharmacoenhancing effects of RTV provided by different formulation. However, there was adequate information submitted to bridge formulations used during product development to the commercial formulations.

Finally, the Product Quality microbiologist conducted an assessment of microbial limits relevant to Viekira Pak manufacture. She agreed with the Applicant's rationale that microbiological quality of the drug product is controlled via a suitable testing protocol. Therefore, a microbial limits release specification for drug product release is not necessary.

- ***Facilities review/inspection***

Because Viekira Pak includes four drug substances (including three NMEs) and two final tablet products, facility inspections were required at multiple sites. One of the sites inspected (b) (4) was issued FDA Form 483 based on two observations related to the Quality System and was designated OAI. The site is in the process of responding to these observations. At the time of writing this CDTL Review, the facility inspections have not been completed and the Office of Compliance has not confirmed an Overall Acceptable recommendation.

- ***Other notable issues (resolved or outstanding)***

The CMC reviewers provided several comments to the Applicant regarding the appropriate labeling of the drug product. Consistent with other recently approved FDC tablets, the Applicant was advised to list the established name as "ombitasvir, paritaprevir, ritonavir" rather than as "ombitasvir/paritaprevir/ritonavir." They also recommended an equivalency statement be included in the DBV description, "Each tablet contains 270.3 mg dasabuvir sodium, hydrate equivalent to 250 mg dasabuvir." The Applicant complied with these recommendations.

As noted above, some of the drug substances are produced (b) (4) At the request of the CMC review team, the Applicant has agreed (b) (4) This will be done under a post-marketing commitment.

Overall, the CMC reviewers concluded that sufficient information was provided in the NDA to assure the quality of the drug substances and the drug product. The Biopharmaceutics reviewer and the Product Quality Microbiology reviewers also recommended approval of the final drug product, the proposed dissolution methods, and the microbiological controls.

However, a final recommendation for approval cannot be provided until all facility inspections have been completed, all 483 observations have been adequately addressed, and an Overall Acceptable recommendation is made by the Office of Compliance.

4. Nonclinical Pharmacology/Toxicology

The Applicant submitted a portfolio of nonclinical study reports describing the results of acute and chronic toxicity studies, genotoxicity studies, carcinogenicity studies and reproductive toxicology studies for the three NMEs (OMB, PTV, and DBV). Complete nonclinical data related to RTV has been reviewed previously; this information was cross-referenced to NDA 22417 for Norvir (RTV) and summarized in the NDA review. Nonclinical studies were not conducted with the full Viekira Pak combination of products, an approach considered acceptable in the ICH M3(R2) guidance. For a complete discussion of the *in vitro* safety assessments and animal toxicology studies, please refer to the Pharmacology/Toxicology Review performed by Dr. Mark Seaton. Key points from the Pharmcology/Toxicology review are summarized in this section.

- ***General nonclinical pharmacology/toxicology considerations (including pharmacologic properties of the product, both therapeutic and otherwise)***

Paritaprevir was evaluated in a series of repeat dose studies in mice, rats and dogs. Early formulations were not well-absorbed in animals but coadministration with RTV increased exposure in all species. The primary target organ for toxicity was the gallbladder in mice and dogs with findings of edema, mixed cell infiltration, epithelial cell necrosis, and increased serum alkaline phosphatase. In rats, exposure of PTV 5 times the clinical dose produced CNS excitation (jumping, head twitching, salivation, mydriasis, etc). In a hERG channel model, high exposures of PTV reduced the hERG channel tail current by < 20%; this was interpreted as a weak effect and not considered a clinical safety concern. Paritaprevir is metabolized primarily by CYP3A in humans and has been shown to inhibit several hepatic transporters (OATP1B1, OATP2B1, OATP1B3, MRP2, and Bile Salt Export Pump), renal transporters (OAT1, OAT3, and MATE2K), in addition to the intestinal transporter BCRP and the widely distributed P-glycopeptide. The most clinically relevant of these transporter interactions is the inhibition of OATP1B1 which is critical in bilirubin transport.

Ombitasvir was evaluated in a series of repeat dose studies in mice, rats, and dogs. Mice and dogs achieved higher systemic exposures than rats and monkeys and were the primary species for chronic dosing studies. Toxicology studies were limited by the minimal solubility of OMB in aqueous solutions. As noted in the Pharmacology/Toxicology Review, no significant toxicological effects were noted in nonclinical studies of OMB given at the maximum feasible doses and at exposures reflecting saturation of absorption. These studies achieved exposure in the animals considered adequate to predict toxicity. The primary target organ for toxicity in mice appeared to be the liver but these effects were observed only in a 2-week study and were not confirmed in the longer studies (1 to 6 months). Minor effects were observed in the small intestine in dogs administered OMB but these findings were not accompanied by any effect on food consumption or body weight. Ombitasvir had no effects on CNS, cardiovascular system,

or respiratory system. Unlike PTV, OMB does not appear to significantly inhibit OATP1B1, OATP1B3, OCT1, OCT2, OAT1, OAT3, MATE1 or MATE2K, P-gp and BCRP.

Dasabuvir was evaluated in a series of repeat dose studies in mice, rats, and dogs. Oral bioavailability of DBV was low in monkeys and rats but high in dogs. In the repeat dose toxicology studies, no specific toxicological effects were noted following DBV dosing. Dasabuvir had no effects on CNS, cardiovascular system, respiratory system, or gastrointestinal system Dasabuvir is metabolized in humans primarily by CYP2C8 with some contribution from CYP3A4 and CYP2D6 but does not appear to interact significantly with transporters.

- ***Carcinogenicity***

Genotoxicity of all three NMEs was evaluated in *in vitro* and *in vivo* assays. Paritaprevir was noted to be negative in a bacterial mutation assay (Ames test) and the *in vivo* rat bone marrow micronucleus test and rat liver Comet test but gave positive results in an *in vitro* human chromosome aberration test. Neither OMB nor DBV was mutagenic (negative Ames tests) or clastogenic in *in vitro* (human lymphocytes) assays and neither induced chromosomal aberrations *in vivo* (mice).

Paritaprevir was evaluated in a six-month oral carcinogenicity study in transgenic mice and a two-year oral carcinogenicity study in rats. No neoplastic lesions were identified in either of these studies after administration of the combination of PTV/RTV. Ombitasvir was evaluated in a six-month transgenic mouse carcinogenicity study and no neoplastic lesions were observed. Dasabuvir was also evaluated in a six-month transgenic mouse study and no neoplastic lesions were identified.

As noted above, RTV nonclinical data has been previously reviewed. These data were briefly summarized in the context of a combined drug regimen to evaluate the possibility of overlapping toxicity. The primary target organs for toxicity in nonclinical studies of RTV were the liver and the eyes. While increased serum transaminases, clinical hepatitis, and jaundice have been reported in patients receiving RTV, the retinal toxicity noted in nonclinical studies has not been observed in patients.

- ***Reproductive toxicology***

Reproductive and developmental toxicity was evaluated in the three NMEs including fertility studies in male and female rats, embryo-fetal developmental studies in mice and rats, and peri- and postnatal developmental studies in rats. The combination of PTV/RTV did not affect fertility of male or female rats and did not produce maternal toxicity, developmental toxicity, or teratogenicity in pregnant rats and their offspring. Reproductive toxicity studies of OMB were conducted in mice because of the higher exposure. No effects on male or female fertility were identified following OMB dosing although it was associated with increased prostate and seminal vesicle weight and decreased testicle weight in male mice. Ombitasvir was neither maternally toxic nor teratogenic in either mice or rabbits. However, in the rabbit embryo-fetal study, skeletal and visceral variations and malformations were observed at a low incidence, considered within the range observed among historical controls. Dasabuvir had no effects on

male or female fertility and elicited no maternal toxicity or teratogenicity in either pregnant rats or rabbits.

- ***Other notable issues (resolved or outstanding)***

Multiple metabolites of OMB were identified in animals, produced via amide hydrolysis, oxidative metabolism, and other pathways. The major human metabolic pathway appears to involve hydrolysis, oxidation, and C-demethylation. Two unique metabolites present at significant levels in human plasma (M29 and M36) were specifically assessed in genetic toxicology assays, repeat dose animal toxicology studies, and reproductive toxicology studies. No significant toxicologic effects of these metabolites were identified.

The Pharmacology/Toxicology reviewer noted that there are no novel excipients in the final drug products. He also concluded that the Applicant's proposed specifications for impurities or degradants that might be present in the drug product are acceptable.

There are no unresolved nonclinical issues from the perspective of the Pharmacology/Toxicology reviewer and he recommended approval of Viekira Pak. A number of revisions were recommended to the nonclinical information proposed for the product label and these were conveyed to the Applicant.

5. Clinical Pharmacology/Biopharmaceutics

Viekira Pak, as a combination regimen or the component drugs, was extensively evaluated to assess its clinical pharmacologic characteristics, to determine dose- and exposure-response relationships, and to identify relevant drug-drug interactions. For a complete discussion of the clinical pharmacology issues, please refer to the Clinical Pharmacology Review submitted by Dr. Vikram Arya and the collaborating team of reviewers (Dr. Seong Jang, Clinical Pharmacology Reviewer, and Drs. Dhananjay Marathe and Jeffry Florian, Pharmacometrics Reviewers). The Clinical Pharmacology Review did not focus on the pharmacologic properties of RTV as a single drug but did evaluate its effect on exposure of PTV in the OMB/PTV/RTV FDC. The following points summarize the conclusions of the Clinical Pharmacology review team.

- ***General clinical pharmacology/biopharmaceutics considerations***

The pharmacologic properties of the component drugs in Viekira Pak have been evaluated in healthy volunteers and subjects with chronic HCV infection. All four component drugs in Viekira Pak are absorbed when dosed orally. All four component drugs are highly bound to plasma proteins. Exposures of PTV and RTV increase greater than dose-proportional; OMB and DBV exposures increase in a dose proportional manner. Steady state exposures of all drugs are achieved in about 12 days of dosing. Exposures of all four component drugs are increased by administration with a moderate or high fat meal, with PTV and OMB increased by up to 211% and 82%, respectively. Dosing recommendations will include instructions to take Viekira Pak with a meal.

All four components of Viekira Pak are metabolized by hepatic enzymes. Ombitasvir is metabolized by amide hydrolysis followed by oxidative metabolism. Paritaprevir is metabolized primarily by CYP3A4; RTV inhibits this metabolism and thereby increases PTV exposure. Ritonavir is itself metabolized by CYP3A and also, to a lesser extent by CYP2D6. Dasabuvir is primarily metabolized by CYP2C8 and, to a lesser extent by CYP3A.

The proposed total daily dose of ABT-267/ABT-450/ritonavir co-formulated tablets is 25 mg/150 mg/100 mg given orally once daily (as two FDC tablets). The proposed total daily dose of ABT-333 is 500 mg (as one 250 mg tablet twice daily).

- ***Drug-drug interactions***

Based on the determination that both PTV is extensively metabolized by CYP3A4, and RTV is a potent inhibitor of CYP3A4, many clinically relevant drug interactions were anticipated by the Applicant. In addition, CYP2D8 plays a major role in DBV metabolism. The Applicant conducted extensive drug-drug interaction studies with the component drugs, OMB/PTV/RTV FDC, or Viekira Pak (25 drug-drug interaction studies). Drug interaction studies were conducted characterizing the effect on various CYP3A4 substrates and the potential for interactions with medications commonly used in patients with HCV infection. In addition, the effects of potent CYP3A induction (carbamazepine) and inhibition (ketoconazole) on drug exposures were assessed. These studies provided adequate information to allow dosing recommendations for Viekira Pak and potentially interacting drugs used in the target population. In addition, some drug-drug interactions were assumed based on RTV's properties as a potent CYP3A4 inhibitor.

The Clinical Pharmacology Review describes the observed or expected drug interactions based on the Review Team's conclusions regarding whether the drug-drug interaction is likely to have serious consequences (recommended contraindicated), whether the drug-drug interaction can be adequately described and managed with dose adjustments, or whether there is no clinically significant interaction. Concomitant use of drugs listed in Table 2 is contraindicated because these drugs are either highly dependent on CYP3A for clearance and elevated plasma concentrations are associated with serious or life-threatening events, strong inducers of CYP3A and CYP2C8 and may lead to reduced efficacy of Viekira Pak, or strong inhibitors of CYP2C8 and may increase dasabuvir plasma concentrations and the risk of QT prolongation. This information will be included in the product label.

Table 2: Drugs that are Contraindicated with VIEKIRA PAK

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Alpha1-adrenoreceptor antagonist	Alfuzosin HCL	Potential for hypotension.
Anticonvulsants	Carbamazepine, phenytoin, phenobarbital	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Antihyperlipidemic agent	Gemfibrozil	Contraindicated with dasabuvir due to an increase in dasabuvir exposures by 10-fold which may increase the risk of QT prolongation.

Drug Class	Drug(s) within Class that are Contraindicated	Clinical Comments
Antimycobacterial	Rifampin	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
Ergot derivatives	Ergotamine, dihydroergotamine, ergonovine, methylergonovine	Acute ergot toxicity characterized by vasospasm and tissue ischemia has been associated with co-administration of ritonavir and ergonovine, ergotamine, dihydroergotamine, or methylergonovine.
Ethinyl estradiol-containing products	Ethinyl estradiol-containing medications such as combined oral contraceptives	Potential for ALT elevations *[see Warnings and Precautions (5.1)]*.
Herbal Product	St. John's Wort *(Hypericum perforatum)*	Ombitasvir, paritaprevir, ritonavir and dasabuvir exposures may decrease leading to a potential loss of therapeutic activity of VIEKIRA PAK.
HMG-CoA Reductase Inhibitors	Lovastatin, simvastatin	Potential for myopathy including rhabdomyolysis.
Neuroleptics	Pimozide	Potential for cardiac arrhythmias.
Non-nucleoside reverse transcriptase inhibitor	Efavirenz	Co-administration of efavirenz based regimens with paritaprevir, ritonavir plus dasabuvir was poorly tolerated and resulted in liver enzyme elevations.
Phosphodiesterase-5 (PDE5) inhibitor	Sildenafil when dosed as REVATIO for the treatment of pulmonary arterial hypertension (PAH)	There is increased potential for sildenafil-associated adverse events such as visual disturbances, hypotension, priapism, and syncope.
Sedatives/hypnotics	Triazolam Orally administered midazolam	Triazolam and orally administered midazolam are extensively metabolized by CYP3A4. Coadministration of triazolam or orally administered midazolam with VIEKIRA PAK may cause large increases in the concentration of these benzodiazepines. The potential exists for serious and/or life threatening events such as prolonged or increased sedation or respiratory depression.

The magnitude and suggested management of drug-drug interactions between one or more components of Viekira Pak and many other drugs are discussed in the Clinical Pharmacology Review. These interactions will be described in Section 7 Drug Interactions and Section 12 Clinical Pharmacology: Pharmacokinetics of the product label. A few of these interactions deserve specific mention.

- Antiretroviral drugs: Coadministration is not recommended with darunavir (decreased darunavir C_{trough}), rilpivirine (increased C_{max}, concern for prolonged QTc), lopinavir/RTV coformulation (increased exposure of PTV and double dose of RTV), and atazanavir/RTV as an evening dose (increased exposure of PTV). Efavirenz is among the contraindicated drugs (see Table 2). The ongoing clinical trial in HIV/HCV co-infected subjects (M14-004) is evaluating a very limited number of antiretroviral regimens.

- Calcineurin inhibitors: Exposures of tacrolimus and cyclosporine are markedly increased when given in combination with Viekira Pak. Management of these products was evaluated in the setting of M12-999 in subjects post-liver transplant and, overall, concomitant drug administration was feasible without serious problems. The Clinical Pharmacology team recommends cyclosporine dose be reduced to 1/5 of the subject's previous dose and levels should be monitored closely. The dose of tacrolimus should be reduced to 0.5 mg weekly beginning the day after initiating Viekira Pak. No dose should be given on the first day of Viekira Pak treatment.
- Proton pump inhibitors: Exposure of omeprazole is decreased with concomitant use of Viekira Pak. The Clinical Pharmacology team recommends avoiding use of omeprazole but if use cannot be avoided, higher doses are needed.
- HMG CoA reductase inhibitors: Exposures of pravastatin and rosuvastatin are increased by Viekira Pak. Upper dose limits or 40 mg and 10 mg, respectively, are recommended to avoid toxicity.

- ***Pathway of elimination***

All of the component drugs of Viekira Pak are excreted in the feces. Very little of the DAA drugs are excreted in the urine (≤ 2%); about 11% of the total RTV dose is excreted in the urine.

- ***Briefly comment on each of the critical intrinsic factors potentially affecting elimination: age, gender, hepatic insufficiency and renal impairment.***

Several intrinsic factors affect the exposures of the component drugs of Viekira Pak. Age > 65 years and female gender were both noted to be significant covariates for drug exposures. After adjusting for other important covariates, the exposures in elderly subjects were found to be 1.1- to 1.3-fold higher than in younger adult subjects. The pharmacokinetics of Viekira Pak components have not been evaluated in pediatric patients. After adjusting for other covariates, exposures in female subjects were found to be 1.2- to 1.8-fold higher than in male subjects. However, these differences were not considered clinically relevant and not dose adjustment is necessary. Neither race nor ethnicity was found to be a significant covariate for drug exposure.

Pharmacokinetics of the four component drugs were evaluated in a single-dose study of uninfected subjects with varying degrees of renal impairment. In subjects with severe renal impairment (not on dialysis), AUC for PTV, RTV, and DBV were increased by 45%, 114%, and 50%, respectively, but OMB AUC was not changed, compared to subjects with normal renal function. These changes in exposure are not thought to be clinically relevant or require dose adjustment.

Hepatic impairment has a major effect on drug exposures of the component drugs. Pharmacokinetics of the component drugs were evaluated in a single-dose study of uninfected subjects with mild, moderate, or severe hepatic impairment. Relative to subjects with normal hepatic function, OMB, PTV and RTV AUCs decreased by 8%, 29% and 34%, respectively, and DBV AUC increased by 17% in subjects with mild hepatic impairment. In subjects with severe hepatic impairment, PTV, RTV and DBV AUCs increased by 945%, 13%, and 325% respectively, and OMB AUC decreased by 54%. The M13-099 clinical trial confirmed that no

dose adjustment was needed in subjects with mild hepatic impairment (Child-Pugh A). However, Viekira Pak will be contraindicated in patients who have severe hepatic impairment (Child-Pugh C) because of the marked increase in exposure of PTV and the resulting increased risk of ALT elevations.

- ***Demographic interactions/special populations***

No other demographic interactions or pharmacokinetic issues in specific populations were identified.

- ***Discuss relevant issues related to clinical pharmacology arising from investigations by gender, age, including pediatrics and geriatrics, and other demographic-based investigations.***

Concomitant administration of Viekira Pak and combination oral contraceptives were evaluated in a specific drug-drug interaction study. This study further characterized modest increases in ethinyl estradiol and norelgestromin/norgestrel exposures when given with Viekira Pak with no changes in exposures of the component drugs. However, a majority of subjects receiving the combination oral contraceptive with Viekira Pak developed ALT elevations compared to none of the subjects who received the progestin alone (without ethinyl estradiol). The association of ethinyl estradiol-containing products and Viekira Pak with elevated ALT is discussed further in Section 8 of this CDTL Review.

- ***Thorough QT study or other QT assessment***

The Applicant conducted a thorough QT study in healthy adult volunteers. Study design was acceptable, with both placebo and active control (moxifloxacin) included. The drug exposures provided by both therapeutic and supratherapeutic doses of Viekira Pak were not associated with QTc prolongation to any clinically relevant extent. This information will be included in the product label.

- ***Exposure-response analyses***

The Pharmacometrics reviewers evaluated exposure-response relationships for both efficacy and key safety parameters for Viekira Pak using data from a large phase 2 trial and the six phase 3 trials. No exposure-response relationship could be determined for SVR12 for any component drug in subjects with GT1b HCV because the response rates were uniformly high. Among subjects with GT1a HCV, there was no identifiable exposure-response relationship observed for DBV exposure and SVR12. For the GT1a population, there were shallow exposure-response relationships between OMB exposure and PTV exposure and SVR12 but the Pharmacometrics reviewer estimated that a 50% decrease in AUC or C_{trough} for either drug may not reduce overall efficacy by a substantial margin.

The exposure-response analyses for safety identified positive relationships for drug-induced rash, ALT elevations, total bilirubin elevations and hemoglobin reductions with PTV. In addition, exposure-response relationships were found for total bilirubin elevations and hemoglobin reductions with RBV, a previously described association. The clinical safety review confirmed that rash events were more frequent with Viekira Pak+RBV use than with placebo and more frequent with Viekira Pak+RBV than with Viekira Pak alone. Pharmacometrics analysis also confirmed that rash events were more frequent in subjects with

higher PTV exposures. Similarly, higher PTV exposures were significantly associated with ALT elevations. A 2-fold increase in PTV exposure increased the odds of ALT > 5 times the upper limit of normal by 1.6-fold. This has clinical implications for subjects with hepatic impairment or any other condition or concomitant medication that substantially increases PTV exposure. A similar association was found between bilirubin elevations and PTV exposure. The predicted impact of a doubling of PTV exposure on any of these laboratory abnormalities in patients with relatively normal hepatic function is expected to be small.

- ***Other notable issues (resolved or outstanding)***

All members of the Clinical Pharmacology and Pharmacometrics review team recommended approval of Viekira Pak with or without RBV for the proposed indication. They agreed with other review groups that the doses of each component drug and the combinations of drugs in the regimen were appropriate. Agreeing on appropriate labeling of drug-drug interactions, including which drugs should be contraindicated and which required dose adjustment or clinical management recommendations, required many discussions with the Applicant. At the time of writing this CDTL Review, there are no major remaining unresolved clinical pharmacology issues but language for some specific drug-drug interactions is still being finalized.

6. Clinical Virology

The Applicant submitted multiple studies and analyses evaluating the antiviral mechanism of action of Viekira Pak or its component drugs, the emergence of resistance substitutions to the component drugs, the effect of baseline polymorphisms on response, and the patterns of cross-resistance with other HCV DAAs. Please refer to the Virology Review submitted by Dr. Patrick Harrington for a detailed discussion of these data and analyses. The main conclusions of his review are summarized below.

- ***General considerations and mechanism of action***

Viekira Pak is comprised of three DAA drugs that block three different steps of the HCV replication cycle. Paritaprevir is the fourth in the class of HCV NS3/4A protease inhibitors that block HCV replication and is active against GT1 HCV (subtypes 1a and 1b) at sub- or low nanomolar concentrations. It has activity against GT1 and GT4 but activity is reduced against GT2 and GT3. In cell culture replicon studies, PTV demonstrated consistent activity against panels of replicons containing NS3 genes from laboratory strains and clinical isolates of GT1a and 1b HCV. Cytotoxicity for replicon cells related to PTV exposure occurred at micromolar concentrations, reflecting a therapeutic index of 39,000 to 116,000 for HCV GT1a and GT1b. In cell culture replicon assays, no antagonism was identified in combination studies with PTV and OMB, DBV, RBV, or interferon-alfa.

Ombitasvir is the second in the class of HCV NS5A inhibitors that block replication and viral assembly/release. It has activity against GT1 (subtypes 1a and 1b) at sub- to low picomolar concentrations. In cell culture replicon studies, OMB had consistent activity against panels of HCV replicons carrying NS5A genes from GT1a and GT1b clinical isolates from DAA treatment-naïve patients, with similar activity observed against GT 2, 3, 4 and 5 isolates. In

these assays, cytotoxicity was observed at micromolar concentrations, reflecting a therapeutic index greater than 2,000,000 for GT1a and 1b replicons. No antagonism was identified in combination studies with OMB and PTV, DBV, RBV, and interferon-alfa.

Dasabuvir is the first in a novel class of non-nucleoside HCV NS5B inhibitor targeting the palm domain of the RNA-dependent, RNA polymerase. It has activity against GT1a and 1b in biochemical and replicon assays at low nanomolar concentrations, with reduced activity against non-GT1 NS5B polymerases. Dasabuvir had consistent activity against panels of replicons containing NS5B genes from GT1a and 1b laboratory strains and clinical isolates from DAA treatment-naïve patients. Cytotoxicity was observed at low micromolar concentrations reflecting a therapeutic index of at least 1,300 for GT1a and GT1b. No antagonism was identified in combination studies with DBV and PTV, OMB, RBV, and interferon-alfa.

Ritonavir has no activity against HCV as demonstrated in cell culture assays evaluating GT1a and 1b replicons.

- ***Emergence of Resistance***

Resistance to all three component DAAs can be selected in cell culture and *in vivo*. As noted in the Virology Review, the major NS3 treatment-emergent substitutions for genotype 1a PTV-selected replicons were Q41R, R155K, D168E/N and I170T/V. The predominant NS3 treatment-emergent substitutions for genotype 1b PTV-selected replicons were R155Q, A156T/V and D168H/V. Paritaprevir activity against GT1a was reduced greater than 3-fold by the following single amino acid substitutions: F43L (19-fold), R155G/K/S/T/V/W (5- to 36-fold), A156T (17-fold), and D168A/E/F/H/N/V/Y (14- to 206-fold). In addition, substitutions V36L/M, Y56H and E357K in combination with R155K or a D168 substitution further reduced HCV susceptibility to PTV. In clinical trials, the most commonly observed NS3/4A treatment-emergent substitutions in subjects with GT1a infection were D168A/V/Y and R155K. Paritaprevir activity against GT1b was reduced greater than 3-fold by the following single amino acid substitutions: R155K (40-fold), A156T (7-fold), and D168A/E/H/K/T/V/Y (4- to 873-fold). In clinical trials, treatment failure and drug resistance emergence were rare for subjects with HCV GT1b infection; the most commonly observed NS3/4A treatment-emergent substitutions were D168A/V and Y56H. A small number of GT1a and GT1b infected subjects who experienced virologic failure unexpectedly had treatment-emergent substitutions in the NS3 helicase domain, and post-marketing studies are planned to characterize the impact of these substitutions on PTV anti-HCV activity.

The predominant NS5A treatment-emergent substitutions for GT1a OMB-selected replicons included M28T/V, Q30R and Y93C/H. In GT1b OMB-selected replicons, single and combination NS5A treatment-emergent substitutions included L28T, L31F/V, Y93H, L28M/V+L31F, L28M+Y93H, R30Q+Y93H, L31F/V+Y93H, and P58A+Y93H. In GT1a replicons, substitutions at positions M28, Q30, L31, H58 and Y93 conferred reduced susceptibility to OMB, sometimes resulting in large reductions (>500-fold) in activity. In clinical trials, the most commonly observed treatment-emergent substitutions in NS5A in subjects with GT1a infection were M28A/T/V and Q30E/K/R. In GT1b replicons, single NS5A substitutions L28T and Y93H conferred 661- and 76-fold reductions in OMB activity

and combinations of substitutions at positions L28, R30, L31, P58 and Y93 conferred 142- to >10,000-fold reductions in OMB activity. In clinical trials, the most commonly observed treatment-emergent substitution in subjects with GT1b infection was Y93H.

The most common NS5B substitutions selected in GT1a replicons by DBV were S556G/N and C316Y. In GT1b replicons, the most commonly selected substitutions included M414T, C316Y, and Y448C/H. Single substitutions at C316Y, M414I/T/V, E446K/Q, Y448C/H, A553T, G554S, S556G/R and Y561H conferred reduced susceptibility to DBV in GT1a replicons while single substitutions C316H/N/Y, S368T, N411S, M414I/T/V, Y448C/H, A553V, S556G and D559G conferred reduced susceptibility in GT1b replicons. In the clinical trials, the most commonly observed treatment-emergent, GT1a NS5B substitution conferring reduced DBV activity was S556G while in GT1b one subject each had treatment-emergent substitutions C316Y+M414I and S556G.

Both the Applicant and the FDA Virology Reviewers conducted an integrated analysis of virologic failure (breakthrough or relapse) and drug resistance across the Viekira Pak clinical development program. Overall, 81/2498 (3.2%) subjects receiving Viekira Pak with or without RBV for treatment durations of 8 to 24 weeks experienced virologic failure (74/1363 (5.4%) in GT1a and 7/1131 (0.6%) in GT1b). Among subjects with GT1a HCV, efficacy was improved and the rate of virologic failure was decreased when RBV was given with Viekira Pak. Because virologic failure is often associated with the emergence of viral populations with resistance-associated substitutions, reducing the rate of virologic failure also effectively reduces the emergence of drug resistance in the treated population. Over 90% of GT1a subjects experiencing virologic failure with a 12 or 24 week treatment duration (the proposed regimens) developed a resistance-associated substitution in at least one antiviral target and over 50% developed resistance-associated substitutions in all three antiviral targets. Among those with GT1b HCV, the addition of RBV had no significant impact on efficacy and virologic failure and emergence of resistance was uncommon.

- ***Cross-resistance***

Based on similar viral targets, cross-resistance is expected between PTV and other NS3/4A protease inhibitors. Substitutions at positions R155 and D168 also emerged in patients failing therapy with boceprevir, telaprevir, and simeprevir and were shown to result in decreased susceptibility of these drugs. Cross-resistance between PTV and drugs in other DAA classes, RBV, or interferon is not expected.

Cross-resistance is expected between OMB and other NS5A inhibitors. Substitutions at positions M/L28, Q/R30, H/P58 or Y93 are associated with reduced susceptibility to OMB and have also been observed in patients failing treatment with other NS5A inhibitors under development. Cross-resistance between OMB and drugs in other DAA classes, RBV, or interferon is not expected.

Cross-resistance is expected between DBV and other nonnucleoside NS5B-palm polymerase inhibitors in development (none currently approved). Cross-resistance is not expected between DBV and interferon, RBV or other DAA classes, including other classes of NS5B polymerase inhibitors.

- ***Notable issues (resolved or outstanding)***

One of the issues that surfaced during reviews of other recent DAAs is the potential impact of naturally occurring polymorphisms in DAA target proteins. The NS3 polymorphism Q80K is present in about 40% of isolates from patients infected with GT1a HCV and was recently shown to decrease response to simeprevir (Olysio™, Janssen). Dr. Harrington assessed the impact of baseline NS3, NS5A and NS5B polymorphisms on treatment outcomes in the phase 2 and phase 3 Viekira Pak clinical trials. In his pooled analysis of the phase 3 trials, he observed that baseline polymorphisms in NS3 (Q80K primarily) and NS5A were minimally enriched in HCV GT1a infected subjects who failed treatment compared to those who achieved SVR, although little or no impact of these polymorphisms was observed in a large phase 2b trial. Polymorphisms in NS5B were uncommon and not enriched in subjects with treatment failure. He concluded that NS3 Q80K and NS5A polymorphisms may have some effect on HCV GT1a response to Viekira Pak+RBV but given the overall low rates of virologic failure in the clinical trials this effect was not substantial.

Although the proposed regimens of Viekira Pak proved to be very effective, the consequences of treatment-emergent resistance-associated substitutions may be substantial. A large proportion of subjects with GT1a failing treatment with Viekira Pak develop resistance-associated substitutions in multiple drug targets. Available phase 2 clinical trial data suggests that resistance-associated substitutions in all three antiviral targets persist for many months after treatment: 59%, 100%,and 69% of subjects with substitutions in NS3, NS5A and NS5B, respectively, still had at least one of these substitutions detected after 24 weeks off treatment and 23%, 100%, and 53% still had substitutions detected after 48 weeks off treatment. Although the data are limited, persistence of the NS5A resistance-associated substitutions is particularly troubling as replacement of viral populations carrying these substitutions was not observed. At present, there are no obvious choices for retreatment of subjects who experience virologic failure with Viekira Pak.

In an Addendum to the Virology Review, Dr. Harrington provided his analysis of the interim virology data from Study M14-004 submitted late in the review cycle. Part 1a of this trial enrolled 63 subjects coinfected with HIV/HCV who were either naïve to treatment or had received prior interferon-based treatment, including those with compensated cirrhosis. Subjects received either 12 or 24 weeks of Viekira Pak with RBV along with antiretroviral treatment. Five subjects failed to achieve SVR, four of whom had virologic failure. All subjects with virologic failure had GT1a; one subject had breakthrough viremia during treatment and three were designated as relapse after completing treatment. Two of the three relapses occurred in non-cirrhotic, treatment-naïve subjects who received 24 weeks of treatment; these subjects do not fit the profile of relapse subjects in other phase 3 trials. Sequencing and phylogenetic analysis of these two subjects' post-treatment isolates strongly suggest both cases represented re-infection rather than post-treatment relapse. Behavioral information from the two subjects appears to confirm this possibility. Assessment of HIV RNA levels during treatment with Viekira Pak failed to identify any negative impact of HCV treatment on ongoing HIV treatment. A total of 10 subjects had transient low level increases in HIV RNA levels ("blips") which resuppressed without changes in antiretroviral regimen. Two additional subjects had detectable HIV RNA during post-treatment follow-up and had not

resuppressed at the last visit. None of the subjects developed resistance-associated substitutions to their antiretroviral drugs. Of interest, was the observation that coinfected subjects demonstrated a trend of decreasing absolute CD4+ T cell counts while on Viekira Pak with RBV. Three subjects developed CD4+ T cells < 200 cells/mm3 or 14% during treatment without evidence of opportunistic infection or other clinical complications. This appeared to be an effect of RBV which has previously been associated with lymphopenia.

The Review Team could not reach final agreement on the whether to recommend 24 weeks of Viekira Pak+RBV for all GT1a patients with cirrhosis. To assist with the final decision, Dr. Harrington evaluated the relapse rates in subjects enrolled in M13-099. He noted that in the 12-week treatment arm, post-treatment relapse was the most common reason for subjects' failure to achieve SVR. Relapses occurred disproportionately among subjects who received 12 weeks compared to those who received 24 weeks of treatment. The results of his analysis are discussed in more detail in Section 7 of this CDTL Review.

Overall, the Virology Reviewer recommended approval of Viekira Pak for the treatment of GT1 HCV infection. Several additional nonclinical virology studies will be requested as post-marketing requirements/commitments to better characterize resistance to the component drugs and cross-resistance (or lack of cross-resistance) with other DAAs.

7. Clinical/Statistical- Efficacy

To support the proposed indication, the Applicant conducted multiple randomized, controlled phase 3 trials (see Table 1) in treatment-naïve and treatment-experienced subjects without cirrhosis and in subjects with compensated cirrhosis. Additional preliminary results were also submitted from ongoing trials in subjects post-liver transplant and HIV/HCV coinfected subjects. For more detailed descriptions of the registrational trial designs, please refer to the Clinical Review provided by Senior Clinical Analyst Russell Fleischer.

Overall, the Clinical and Statistical reviewer's independent analyses confirmed the Applicant's primary efficacy findings and many secondary endpoint analyses for all pivotal clinical trials. Dr. Joy Mele, the Statistical Reviewer, conducted numerous sensitivity analyses and subgroup analyses to assess the robustness of the data and to assist in final regimen selection. Her analyses of primary endpoint for all trials were based on the intent-to-treat population (all subjects randomized and receiving at least one dose of study drug). Only four subjects in the phase 3 database were missing the final post-treatment HCV RNA measurement making imputation of missing data essentially unnecessary. The following points summarize the key findings of the FDA's clinical and statistical reviewers.

The primary efficacy endpoint in all clinical trials was the proportion of subjects achieving SVR12 defined as HCV RNA below the lower limit of quantitation (LLOQ) assessed 12 weeks after the end of study treatment. This represents the FDA's preferred primary endpoint for HCV treatment trials. In all trials, the endpoint was measured using the COBAS TaqMan HCV test (version 2.0) with an LLOQ of 25 IU/mL. Outcomes of subjects not achieving SVR were reported as on-treatment virologic failure ("breakthrough"), post-treatment relapse, or

failure due to other non-virologic reasons (e.g., premature discontinuation, adverse events, lost to follow-up, etc.). The trials will be discussed in this CDTL Review on the basis of the specific comparison being evaluated: placebo-controlled trials, RBV/regimen-controlled trials, and duration comparison trials. This grouping will be carried into product labeling as it provides useful comparisons for clinicians interested in understanding the safety profile of Viekira Pak and the basis for approving specific regimens in specific populations.

Placebo-Controlled Trials: Studies M11-646 (SAPPHIRE-I) and M13-098 (SAPPHIRE-II)

The two randomized, blinded, placebo-controlled trials were intended primarily to evaluate the safety profile of Viekira Pak but additionally to confirm efficacy. M11-646 enrolled non-cirrhotic treatment-naïve subjects with GT1a and GT1b and M13-098 enrolled non-cirrhotic, treatment-experienced subjects with GT1a and GT1b; subjects were randomized to receive either Viekira Pak+RBV or matching placebos for 12 weeks. Subjects in the placebo arms were not expected to spontaneously achieve SVR and were allowed to rollover into active treatment at the end of the blinded 12 week comparison.

The primary efficacy analyses compared the SVR12 for the initially randomized Viekira Pak+RBV arm to pre-specified thresholds based on the historical SVR rates reported in different populations in the telaprevir+peg-interferon+RBV clinical trials. Non-inferiority was tested first based on pre-specified boundaries and, if demonstrated, then superiority was tested. For M11-646, the lower bound of the 95% confidence interval (CI) for SVR was to be greater than 70% in order for the regimen to be considered non-inferior, and greater than 80% to be considered superior. For M13-098, the lower bound of the 95% CI for SVR was to be greater than 60% in order for the regimen to be considered non-inferior, and greater than 70% to be considered superior.

As noted in the Clinical Review, the subjects enrolled in the placebo-controlled trials represented relatively healthy populations of treatment-naïve and treatment-experienced adults. Subjects were predominately White/Caucasian (90%), with 5.5% Black/African American and 2% Asians. The mean age was 50.9 years and 56% of subjects were male. Mean ALT level at study entry was 64-69 U/L across the study arms. Approximately 82% of subjects had HCV RNA > 800,000 IU/mL and 27% had baseline fibrosis stage F2 or F3. Among the treatment-experienced subjects, prior treatment response was distributed between null responders (49%), partial responders (22%), and relapsers (29%). In these trials, GT1a accounted for about 67% of the infections in treatment-naïve subjects and 59% of those in treatment-experienced subjects.

For these placebo-controlled trials, the lower bound of the 95% CI for the SVR12 rates for the Viekira Pak+RBV arms in both trials far exceeded the threshold rates established in the telaprevir +peg-interferon/RBV trials. Results were extremely consistent across major subgroups enrolled. SVR12 rates for Viekira Pak+RBV for 12 weeks in both GT1a and GT1b in both trials and for all subgroups of treatment-experienced subjects were 95-100% as shown in Table 3, abstracted from Dr. Mele's Statistical Review. Non-cirrhotic subjects experienced virologic failure very seldom: only one subject had breakthrough and 16 (2%) subjects relapsed (12 with GT1a HCV). The very small number of documented relapses among the

subjects with GT1b HCV suggests that they might respond very well to a regimen of Viekira Pak without RBV.

Table 3: SVR12 Rates by Study and Study Arm (Placebo-Controlled Trials)

Study	SVR_{12} rate	95% CI[1]	Superiority Threshold
M11-646 TN			
All	456/473 **96%**	94%, 98%	80%
1a	308/322 **96%**	93%, 98%	75%
1b	148/151 **98%**	94%, 99.5%	84%
M13-098 TE			
All	286/297 **96%**	93%, 98%	70%
1a	166/173 **96%**	92%, 98%	65%
1b	120/124 **97%**	92%, 99%	77%
M13-098 TE			
1a Null	83/87 **95%**	89%, 99%	
1a Partial	36/36 **100%**	90%, 100%	
1a Relapser	47/50 **94%**	83%, 99%	
1b Null	56/59 **95%**	86%, 99%	
1b Partial	29/29 **100%**	88%, 100%	
1b Relapser	35/36 **97%**	85%, 100%	

[1]Clopper Pearson exact confidence interval
Source: NDA 206619, Statistical Review, J. Mele, page 34.

Ribavirin/Regimen-Controlled Trials: Studies M13-389 (PEARL-II), M13-961 (PEARL-III), and M14-002 (PEARL-IV)

As noted in Table 1, these trials were designed to compare treatment with Viekira Pak+RBV to Viekira Pak alone in non-cirrhotic subjects: M13-389 in treatment-experienced GT1b subjects, M13-961 in treatment-naïve GT1b, and M14-002 in treatment-naïve GT1a subjects. All subjects were randomized to receive Viekira Pak for 12 weeks with or without RBV. Primary endpoint analysis was conducted after all subjects reached post-treatment week 12 but the trials continue follow-up through post-treatment week 48 in order to confirm durability of response. As noted in the Statistical Review, the primary objective of all three studies was to compare the safety of Viekira Pak+RBV and Viekira Pak and secondly to show that each arm is non-inferior in SVR12 rates to the historical SVR rate of telaprevir + peg-interferon+RBV therapy based on thresholds agreed upon with the DAVP Review Team.

These three trials enrolled populations with similar disease and demographic characteristics and were pooled for efficacy and safety analyses as appropriate. Overall, the pooled population was predominately White/Caucasian (90%), with 8% Black/African American (18% representation in US sites) and about 1% Asian. The mean age was 50.8 years and 51% of subjects were male. Mean ALT level at study entry was 59-75 U/L across the study arms. Approximately 80% of subjects had HCV RNA > 800,000 IU/mL and 33% had baseline fibrosis stage F2 or F3. Among the treatment-experienced subjects, prior treatment response

was relatively equally balanced between null responders (35%), partial responders (29%), and relapsers (36%).

For these RBV/regimen-controlled trials, the lower bound of the confidence interval for the SVR12 rates for all arms in all trials exceeded the threshold rates established in the telaprevir +peg-interferon/RBV trials. SVR12 rates for both Viekira Pak and Viekira Pak+RBV for 12 weeks in all arms were 90-100% as shown in Table 4, taken from Dr. Mele's Statistical Review. These trials demonstrated that subjects with GT1b HCV achieved nearly universal success either with or without RBV in the treatment regimen. None of the non-SVR outcomes among GT1b subjects were due to virologic failure (breakthrough or relapse). Those with GT1a HCV, on the other hand, appeared to derive significant benefit from the addition of RBV to Viekira Pak for 12 weeks, achieving 97-99% SVR12 with that regimen.

Table 4: SVR12 Rates by Study and Study Arm (RBV/Regimen-Controlled Trials)

Study	Viekira Pak+RBV SVR12 Rate (95% CI)[1]	Viekira Pak SVR12 Rate (95% CI)	3DAA+RBV - 3DAA Difference (95% CI)[2]	p-value
M13-389 GT 1b TE	89/91 98% (92%, 100%)	95/95 100% (96%, 100%)	-2% (-6%, +2%)	0.16
M13-961 GT 1b TN	209/210 99.5% (97%, 99.9%)	209/209 100% (98%, 100%)	+0.5% (-1%, +2%)	>0.30
M14-002 GT 1a TN	97/100 97% (94%, 100%)	185/205 90% (86%, 94%)	+6.8% (+1.3%, +12%)	0.035

[1] Clopper Pearson exact confidence interval

[2] Results of MH stratified analysis

Source: NDA 206619, Statistical Review, J. Mele, page 27.

Duration Comparison Trial: M13-099 (TURQUOISE II)

Study M13-099 was designed to compare treatment durations of 12 and 24 weeks in treatment-naïve and treatment-experienced subjects with either GT1a or GT1b HCV and compensated cirrhosis (Child-Pugh Class A). Subjects were randomized in a complicated schema (initially 3:5, then after 200 subjects, 3:1) to either 12 or 24 weeks of Viekira Pak+RBV. The primary efficacy analysis of the study was to compare the 12-week regimen SVR12 rate to the historical SVR12 rate of telaprevir plus pegIFN and RBV using a 2-sided 97.5% CI and a noninferiority margin of 43% and a superiority margin of 54%. Although the primary endpoint provided for calculation of an appropriate sample size and a valid historical comparison, the major interest of the Review Team was the secondary endpoint comparison of the two treatment durations. Although these subjects with Child-Pugh A cirrhosis had relatively stable liver disease with mild hepatic impairment, they still represent a difficult to treat group. The Review Team was concerned that the Applicant's proposed (b) (4)

Subjects enrolling in M13-099 were predominately White/Caucasian (92%); 3% were Black/African Americans and 2% were Asians. The mean age was 57 years, older than that observed in the trials of non-cirrhotic subjects, and 70% were male. In this study, 42% were treatment naïve, about 36% of the treatment-experienced group were prior null responders, and

69% had GT1a HCV. Mean ALT was 99 U/L and 86% had HCV RNA ≥ 800,000 IU/mL. Over half of the subjects in M13-099 were enrolled at North American clinical sites.

Overall, treatment with Viekira Pak+RBV in this population was highly effective but favoring the longer duration of treatment with SVR12 92% for the 12 week regimen and 97% for the 24 week regimen. However, during the review, it became clear that there were differences in SVR across some of the key subgroups as shown in Table 5 (compiled from Dr. Mele's review). As in other clinical trials, subjects with GT1b HCV responded uniformly well to treatment regardless of duration with only a single subject (12 week arm) not achieving SVR due to relapse. Among subjects with GT1a HCV, SVR12 was 89% for the 12 week regimen and 95% for the 24 week regimen. Even among subjects with GT1a, differences in SVR rates were noted across different subgroups based on demographic and disease characteristics although few of these differences were statistically significant.

Table 5: Study M13-099 SVR12 Treatment Differences by Genotype and Treatment Experience

	3DAA+RBV 12 weeks	**3DAA+RBV 24 weeks**	**24 wks-12 wks Trt diff (95%CI)**	**p-value for Int.[1]**
Overall (1a & 1b)	191/208 **92%**	166/172 **96%**	+5% (+0.07%, +10%)[2]	
Overall 1a	124/140 **89%**	115/121 **95%**	+6 % (-0.6%, +13%)	
Baseline HCV RNA By median < 3,630,000 ≥ 3,630,000	 66/74 **89%** 58/66 **88%**	 52/56 **93%** 63/65 **97%**	 +4% (-6%, +13%) +10% (-0.7%, +20%)	>0.3
By tertiles <2,120,000 2,120,000-5,690,000 >5,690,000	 45/48 **90%** 43/47 **91%** 38/45 **84%**	 36/38 **95%** 39/41 **95%** 40/42 **95%**	 +5% (-6%, +16%) +4% (-7%, +14%) +11% (-2%, +23%)	>0.3
Sex Male Female	 89/101 **88%** 35/39 **90%**	 84/89 **94%** 31/32 **97%**	 +6% (-2%, +14%) +7% (-4%, +18%)	>0.3
Median Age years <57 ≥ 57	 67/74 **91%** 57/66 **86%**	 53/56 **95%** 62/65 **95%**	 +4% (-4%, +13%) +9% (-1%, +19%)	>0.3
Median BMI kg/m^2 <28 ≥ 28	 58/67 **87%** 66/73 **90%**	 65/67 (97%) 50/54 (93%)	 +10% (+1%, +20%) +2% (-8%, +12%)	>0.3
Geographic area US & Canada Europe With Site 44318 w/o Site 44318	 76/86 (88%) 48/54 (89%) 5/10 (50%) 119/130 (92%)	 70/76 (92%) 45/45 (100%) 7/7 (100%) 108/114 (95%)	 +4% (-5%, +13%) +11% (+3%, +19%) +50% (+3%, +82%) +3% (-3%, +9.5%)	**0.13** 0.21
Randomization date Before or on 4/8/13[3] After 4/8/13	 47/56 (84%) 77/84 (92%)	 88/92 (96%) 27/29 (93%)	 +12% (+1%, +22%) +1% (-10%, +12%)	0.23

[1]Zelen's exact test of homogeneity was used to test for an interaction; a large p-value indicates homogeneity across the subgroup effects.
[2]MH for the risk difference stratified by genotypes and treatment experience. P=0.055

[3]4/8/2013 is the date the 200th patient was randomized. The randomization scheme (Wk 12 arm to Wk 24 arm) was to change from 3:5 to 3:1 after 200 patients enrolled.
Source: NDA206619, Statistical Review, J. Mele, pages 42-43.

The SVR differences noted were primarily determined by the number of subjects who relapsed following treatment, an event thought to be mediated by duration of active treatment. As noted in the Virology Review, in treatment-naïve, GT1a cirrhotic subjects, failure to achieve SVR was due to post-treatment relapse in 5 subjects (4/64 receiving 12 weeks and 1/56 receiving 24 weeks). All of the subjects in this subgroup who relapsed were IL28B CT or TT genotype. Among the treatment-experienced, GT1a cirrhotic subjects, failure to achieve SVR was due to virologic breakthrough in 4 subjects (1/76 receiving 12 weeks and 3/65 receiving 24 weeks) and to relapse in 8 subjects (all receiving 12 weeks). Relapse in the treatment-experienced group was more likely to occur in subjects who were prior null responders (7/50, 14%). This overall difference in relapse rates of 8.5% (12/76) to 1.5% (1/65) among the GT1a cirrhotic subjects receiving 12 or 24 weeks, respectively, was concerning and suggested that all of this subgroup might benefit from longer treatment.

The Review Team's integrated analysis of SVR rates in subjects with GT1a HCV confirmed that these subjects benefited from more intensive treatment (addition of RBV in non-cirrhotic) and longer therapy (cirrhotics may need 24 weeks) than those with GT1b HCV. Outcomes data such as that displayed Tables 6 and 7 will be included in the product label to provide SVR12 and non-SVR outcome information for this historically more difficult to treat genotype.

Table 6: SVR12 for Genotype 1a-Infected Subjects without Cirrhosis Who Were Treatment-Naïve or Previously Treated with PegIFN/RBV

Trial	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**
GT 1a treatment-naïve	
SAPPHIRE-I SVR12	96% (308/322)
Outcome for subjects w/o SVR12	
On-treatment VF*	<1% (1/322)
Relapse	2% (6/314)
Other	2% (7/322)
PEARL-IV SVR12	97% (97/100)
Outcome for subjects w/o SVR12	
On-treatment VF	1% (1/100)
Relapse	1% (1/98)
Other	1% (1/100)
GT 1a treatment-experienced	
SAPPHIRE-II SVR12	96% (166/173)
Outcome for subjects w/o SVR12	
On-treatment VF	0% (0/173)
Relapse	3% (5/172)
Other	1% (2/173)
SVR12 by Prior pegIFN Experience	

Null Responder	95% (83/87)
Partial Responder	100% (36/36)
Relapser	94% (47/50)

*VF, virologic failure

Table 7: SVR12 for Genotype 1-Infected Subjects with Cirrhosis Who Were Treatment-Naïve or Previously Treated with pegIFN/RBV (TURQUOISE II)

	GT1a	
	VIEKIRA PAK with RBV for 24 Weeks % (n/N)	**VIEKIRA PAK with RBV for 12 Weeks % (n/N)**
Overall SVR12	95% (115/121)	89% (124/140)
Outcome for subjects without SVR12		
On-treatment VF	2% (3/121)	<1% (1/140)
Relapse	1% (1/116)	8% (11/135)
Other	2% (2/121)	3% (4/140)
SVR12 for Naïve	95% (53/56)	92% (59/64)
SVR12 by Prior pegIFN Experience		
Null Responder	93% (39/42)	80% (40/50)
Partial Responder	100% (10/10)	100% (11/11)
Relapser	100% (13/13)	93% (14/15)

*VF, virologic failure

Post-Liver Transplant: M12-999

The Review Team agreed to review late submission of the results of the phase 2 Study M12-999, an open-label, single-arm trial conducted in selected post-liver transplant patients with recurrent HCV infection. Enrolled subjects were at least 1 year post-transplant, had not received treatment for recurrent HCV infection since transplant, had minimal hepatic impairment (Childs-Pugh A), and had liver fibrosis score ≤ F2 on a biopsy performed within 6 months of screening. All subjects received 24 weeks of Viekira Pak+RBV. Because of the observed drug-drug interactions with PTV and RTV, doses of the calcineurin inhibitor drugs were reduced during the trial and levels were monitored carefully.

A total of 34 subjects were enrolled. Seventy-nine percent of subjects were male, 85% were White/Caucasian, and 91% were older than 55 years of age. The majority of subjects were infected with GT1a (85%) and had an IL28B non-CC genotype (76.5%). Mean time since liver transplant was about 48 months. Most subjects were receiving tacrolimus and a minority was receiving cyclosporine.

Although this study was small, the results demonstrated excellent response to treatment with Viekira Pak in a population at high risk of progression of liver disease. Thirty-three of 34 enrolled (97%) achieved SVR; 28/29 subjects with GT1a and 5/5 with GT1b. The only subject who failed to achieve SVR discontinued treatment prematurely due to an adverse

event. No episodes of rejection were identified during the trial and all subjects remained on their calcineurin inhibitor medications.

HIV/HCV Co-infected Subjects (M14-004) – Interim Results

At the pre-NDA meeting, the Applicant asked to be allowed to submit interim results of Study M14-004 evaluating Viekira Pak+RBV in HIV/HCV co-infected subjects late in the review cycle. The Review Team agreed the data could be submitted but did not commit to including the results in this review cycle. In light of Viekira Pak's Breakthrough Therapy designation and the impressive results of M14-004 Part 1a, the Review Team decided to include the study in the NDA review. These reviews are archived as Addendum Clinical, Statistical, and Virology Reviews by the reviewers.

M14-004 Part 1a enrolled HIV/HCV co-infected subjects who had virologic suppression of their HIV on an antiretroviral regimen including either raltegravir or atazanavir plus emtricitabine/tenofovir and a CD4+ cell count > 200 cells/mm^3 (or 14%). Subjects could be either HCV treatment-naïve or treatment-experienced, including those with compensated cirrhosis. Subjects enrolled in the trial were 92% male, 76% White/Caucasian, and had a mean age of 51 years. About 2/3 of subjects were HCV treatment-naïve, about 90% had GT1a HCV, and 20% had cirrhosis. A total of 63 subjects were randomized to receive either 12 or 24 weeks of Viekira Pak+RBV.

HIV/HCV co-infected subjects are historically included in the hard to treat subgroups of chronic HCV. In M14-004 Part 1a, SVR rates in this population were very consistent with those observed in HCV mono-infected subjects in the phase 3 trials. Overall SVR rates were 93.5% for those receiving 12 weeks of treatment and 91% for those receiving 24 weeks. One subject had a virologic breakthrough (24 week arm) and three experienced post-treatment relapse (1 in the 12 week arm and 2 in the 24 week arm), all had GT1a HCV. All subjects with GT1b HCV achieved SVR. As noted in the Virology Review, in general, subjects maintained HIV suppression.

- ***Notable efficacy issues both resolved and outstanding***

In order to assess durability of SVR12, the Virology reviewer conducted an analysis of concordance between SVR12 and later off-treatment follow-up times in the phase 2 study M11-652. In this large, open-label clinical trial, 92% of subjects (526/571) who received various combinations of the DAAs included in Viekira Pak with or without RBV achieved SVR12, and 99% of those who achieved SVR12 maintained their response through 48 weeks post-treatment (SVR48). Adequate data were not available from the phase 3 trials to do a comparable analysis at this time.

Both the statistical reviewer and the clinical reviewer agreed that the evidence supporting Viekira Pak with or without RBV for the treatment of chronic HCV was conclusive and robust and they recommended approval. In placebo-controlled trials, RBV/regimen-controlled trials, and treatment duration comparison trials enrolling broadly representative populations of subjects including those with compensated cirrhosis, Viekira Pak treatment resulted in SVR rates far above those in the historical control trials. Both statistical and clinical reviewers

agreed that the data in subjects with GT1b HCV supports 12 weeks of treatment with Viekira Pak (without RBV) for those without cirrhosis and 12 weeks of treatment with Viekira Pak+RBV for those with compensated cirrhosis. They also agree the data in subjects with GT1a supports treatment with 12 weeks of Viekira Pak+RBV in those without cirrhosis.

(b) (4)

Dr. Mele's subgroup analysis demonstrates that most subgroups had numerically better SVR rates if they received 24 weeks of treatment. Many of these subgroups were small and the CIs were wide, making it difficult to state with certainty that 24 weeks of treatment are warranted in all GT1a cirrhotic subjects.

Although the differences between 12 and 24 week treatment duration were relatively small and not statistically significant, it was difficult to identify any subgroup for which 24 weeks of treatment was not numerically better than 12 weeks. Treatment failure with the Viekira Pak+RBV regimen was associated with the emergence of drug resistance-associated substitutions in NS3, NS5A, and NS5B that could make re-treatment challenging for the foreseeable future. The Review Team was primarily concerned with optimizing treatment for the largest number of patients. However, 24 weeks of treatment will likely provide longer than necessary treatment for many patients and the Review Team discussed many options to identify the subgroups most in need of longer treatment. After reviewing multiple analyses provided by the Applicant following the Mid-Cycle and Late Cycle Meetings, the Review Team decided that the clearest differences in treatment response were those based on prior treatment history (b) (4) However, the Review Team felt strongly that the primary regimen described in the product label for GT1a cirrhotic patients should be Viekira Pak+RBV for 24 weeks. Clinicians can consider a 12 week regimen based on treatment history (i.e., naïve, prior relapse, or prior partial response).

8. Safety

The data collected during the phase 2 program and the six phase 3 clinical trials provided the safety database reviewed for this NDA. For a complete description of these data and the safety analyses, please refer to the Clinical Review submitted by Russell Fleischer, Senior Clinical Analyst. Key findings of his review are summarized below.

- ***Discuss the adequacy of the database, major findings/signals, special studies, foreign marketing experience, if any, and plans for postmarketing as discussed in the Pre-Approval Safety Conference (if NME will be approved)***

The safety data collected during the phase 3 clinical trials was adequate to characterize the safety profile of Viekira Pak with or without RBV for 12 or 24 weeks of treatment in study populations broadly representative of those for whom the product is intended. Smaller clinical trials provided safety data in key subgroups (post-liver transplant patients and HIV/HCV co-infected patients). The safety database included 2,964 subjects who received at least one dose of Viekira Pak in the phase 2 and phase 3 clinical trials. The phase 3 trials contributed 2,060 subjects, 1,888 receiving 12 weeks of Viekira Pak and 172 receiving 24 weeks; 1,551 subjects

received Viekira Pak+RBV and 509 received Viekira Pak alone. The Applicant conducted multiple safety analyses based on different pooling strategies: placebo-controlled trials, RBV/regimen-controlled trials, phase 2 and phase 3trials (All Treated), and pooled phase 1 trials. The FDA safety analysis focused mainly on analysis of the phase 3 trials and evaluated the key comparisons Viekira Pak compared to placebo, Viekira Pak with or without RBV, and Viekira Pak+RBV for 12 or 24 weeks. Significant events such as deaths, serious adverse events (SAEs), and discontinuations due to adverse events (AEs) were reviewed from the entire safety database.

The primary safety issues identified during the review of Viekira Pak included elevation of serum transaminases (specifically ALT), rash events, and the contributions of RBV and longer treatment duration to regimen toxicity. The potential for significant drug-drug interactions is considered a safety issue and is addressed in Section 5. Emergence of resistance is also considered a significant safety issue for all antimicrobial drugs and is addressed in Section 6 of this CDTL Review. No specific special safety studies were conducted. Viekira Pak is not approved for use in any foreign countries, and no foreign post-marketing experience is available.

- ***General discussion of deaths, SAEs, discontinuations due to AEs, general AEs, and results of laboratory tests.***

Overall, the safety profile of Viekira Pak either with or without RBV was acceptable. The addition of RBV to the regimen generally reduced the tolerability of the regimen but did not add substantially to serious toxicity. Lengthening the duration of treatment from 12 to 24 weeks increased the incidence of some reported AEs and laboratory abnormalities but did not substantially affect subjects' ability to complete the regimen.

Seven deaths were reported in the NDA safety database only one of which occurred while the subject was receiving Viekira Pak. The remaining six deaths occurred during post-treatment follow-up and were not thought to be related to study drugs. The on-treatment death is summarized below:

> The subject was a 64 year old female subject with Child-Pugh A cirrhosis enrolled in M13-099 and randomized to receive Viekira Pak+RBV for 12 weeks. Relevant medical history included a history of diabetes mellitus treated with metformin since 1988. At the time of study screening, her dose of metformin was increased by 50% and she received furosemide and spironolactone (reasons for changes not documented). Within the first day of study treatment she was noted to have peripheral edema and was hospitalized on Day 2. Diuretics were increased. On Day 7 she experienced nausea and vomiting and all study drugs were discontinued on Day 8. On Day 10 she was noted to have lactic acidosis and required hemodialysis, followed by multi-organ failure and rhabdomyolysis. On Day 13 she underwent liver transplant. She had a rocky course but lactic acidosis, rhabdomyolysis, and organ failure resolved. She died on Day 94 (81 days post-transplant) with cause of death listed as septic shock, renal failure with bleeding complications. The investigator assessed the original events of nausea, vomiting, and lactic acidosis as being possibly related to study drugs.

The Applicant did not believe this death was related to study drugs but was concerned that the increased doses of metformin and diuretics may have precipitated the lactic acidosis that started the fatal chain of events. The metformin product label contains a Boxed Warning related to risk of lactic acidosis, particularly in the setting of renal dysfunction, liver disease, or hypoperfusion/shock. The histology of the explanted liver was reviewed by an independent hepatic pathologist and thought to be consistent with severe ischemic-hypoxic hepatic necrosis superimposed on cirrhosis and steatosis. The pathologist did not consider the findings suggestive of drug-induced liver injury. After review of the available information, the Review Team agreed with the assessment that metformin was likely the suspect drug.

Serious AEs were reported in 12/643 (2%) subjects enrolled in phase 2 trials and 78/2321 (3%) subjects enrolled in phase 3 trials included in the safety database. Two SAEs reported from the phase 2 trials were considered possibly study drug related: a case of cholecystitis/cholelithiasis requiring cholecystectomy and a case of progressive bilateral knee arthralgia that resolved. In the phase 3 trials, 19 subjects developed SAEs considered by the investigators to be possibly related to study drugs, including the RBV component. These SAEs included: anemia (3), acute respiratory failure (2), abdominal pain, dizziness, nausea, vomiting (2), and possible exacerbation of coronary artery disease with anemia, anemia with shortness of breath, acute renal failure, acute hepatitis with concomitant estrogen use, pruritus/angioedema, arthralgia, cellulitis, and cerebral vascular accident (1 each). For a more complete description of these SAEs, please refer to Mr. Fleischer's Clinical Review, Table 22. Of interest to the Review Team evaluating treatment recommendations, the longer treatment duration evaluated in M13-099 did not appear to be associated with more SAEs.

Retention in the phase 2 and phase 3 trials was good and only about 1% of subjects discontinued study drugs because of AEs. In the phase 2 trials submitted, 12/643 (2%) discontinued due to an AE; 5 were considered possibly related to study drugs. In the phase 3 trials, < 1% of subjects discontinued because of AE; 18 were considered possibly related to study drugs. Nausea, vomiting, palpitations/tachycardia, headache, neuropsychiatric symptoms, anemia, anxiety/agitation, dyspnea, and fever are among the symptoms described in these cases. In Mr. Fleischer's analysis, the inclusion of RBV appeared to increase the risk of discontinuations due to AEs thought to be possibly related to study drugs. Longer duration of treatment in cirrhotic subjects did not increase discontinuations due to AEs (2% in both 12 week and 24 week arms). For a more complete description of the AEs leading to discontinuation, please refer to the Clinical Review, Table 23.

Non-serious clinical AEs were relatively common during treatment with Viekira Pak with and without RBV in the phase 3 clinical trials. The FDA safety analysis focused on three logical safety comparisons based on the design of these clinical trials. Pooling the placebo-controlled trials, M11-646 (SAPPHIRE-I) and M13-098 (SAPPHIRE-II), allowed comparison of subjects receiving Viekira Pak+RBV to untreated subjects with the same disease characteristics. Adverse events occurring in at least 10% of subjects and with at least 5% higher frequency in the Viekira Pak+RBV arm compared to the placebo arm are shown in Table 8. As these events are observed more frequently with study drugs than with placebo, they are considered confirmed adverse drug reactions.

Table 8: Adverse Reactions with ≥5% Greater Frequency Reported in Subjects Treated with VIEKIRA PAK in Combination with Ribavirin Compared to Placebo

	SAPPHIRE I and II	
	VIEKIRA PAK + RBV 12 Weeks N = 770 n (%)	**Placebo 12 Weeks N = 255 n (%)**
Fatigue	263 (34)	67 (26)
Nausea	172 (22)	38 (15)
Pruritus*	138 (18)	17 (7)
Insomnia	108 (14)	19 (8)
Asthenia	104 (14)	17 (7)

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

Pooling the RBV/regimen-controlled trials, M13-389 (PEARL-II), M13-961 (PEARL-III), and M14-002 (PEARL-IV), allowed analysis of the contribution of RBV to the toxicity of Viekira Pak. Table 9 shows the most common AEs occurring with at least 5% higher frequency among subjects receiving Viekira Pak+RBV compared to those receiving Viekira Pak alone. Nausea, pruritus, insomnia, and asthenia were commonly reported across all the study drug arms but also seemed to be more frequent when RBV was added to the regimen. Tables 8 and 9 will be displayed in the Viekira Pak label.

Table 9: Adverse Events with ≥5% Greater Frequency Reported in Subjects Treated with VIEKIRA PAK in Combination with Ribavirin Compared to VIEKIRA PAK

	PEARL II, III and IV	
	VIEKIRA PAK + RBV 12 Weeks N = 401 n (%)	**VIEKIRA PAK 12 Weeks N = 509 n (%)**
Nausea	63 (16)	43 (8)
Pruritus*	51 (13)	35 (7)
Insomnia	49 (12)	26 (5)
Asthenia	36 (9)	20 (4)

*Grouped term 'pruritus' included the preferred terms pruritus and pruritus generalized.

Integrating these two analyses provides an indirect assessment of AEs across placebo, Viekira Pak and Viekira Pak+RBV in non-cirrhotic subjects receiving 12 weeks of study drugs but may be somewhat confounded because rates of AEs appeared to be higher in subjects receiving Viekira Pak+RBV in the placebo-controlled trials than in the RBV/regimen controlled trials. Please see the Clinical Review (Section 7.4.1) for more detailed results of this integrated safety analysis.

- ***Immunogenicity***

As Viekira Pak is comprised of well-characterized small molecules with no biologic components, there are no concerns regarding immunogenicity.

- ***Special safety concerns***

Rash and pruritus were noted as clinical AEs during the Viekira Pak development program. Similar events have been previously noted with some of the approved HCV protease inhibitors (e.g., telaprevir and simeprevir) and PTV was considered the suspect drug, although RBV has also been associated with rash and pruritus. In an FDA pooled analysis, the incidence of rash events was about 25% in non-cirrhotic subjects receiving Viekira Pak+RBV for 12 weeks compared to 7% in those receiving Viekira Pak alone. No severe cutaneous reactions, such as Stevens Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), erythema multiforme (EM) or drug rash with eosinophilia and systemic symptoms (DRESS) were reported. Pruritus was reported more commonly in subjects receiving Viekira Pak+RBV than those receiving Viekira Pak alone in the RBV/regimen-controlled trials and more commonly in subjects receiving Viekira Pak+RBV than in those receiving placebo.

Elevations of serum transaminases, particularly ALT, were identified as a potential toxicity of Viekira Pak relatively late during the development program. In most subjects, treatment with Viekira Pak with or without RBV results in normalization of HCV-related elevated ALT and across the 12 week Viekira Pak regimens, mean ALT decrease by about 50 U/L in both non-cirrhotic and cirrhotic populations. However, approximately 1% of subjects experienced elevations of ALT to > 5 x upper limit of normal (ULN). Because PTV is an inhibitor of OATP1B1 transporter, mild to moderate elevations of bilirubin are also observed during Viekira Pak use, complicating the interpretation of elevated ALT. The Applicant identified 32 case subjects from across the Viekira Pak development program who developed ALT >3 x ULN and total bilirubin >2 x ULN or ALT levels >5 x ULN and total bilirubin <2 x ULN. They convened a panel of experts in hepatic toxicity[1] to adjudicate these cases, blinded to treatment assignment. Among these subjects, all but one were receiving Viekira Pak+RBV. Mean time to ALT elevation was 20 days (range 8-57). These ALT elevations were generally asymptomatic, occurred during the first 4 weeks of treatment, and resolved in spite of ongoing therapy within two to eight weeks. Among the adjudicated cases, 26 subjects continued their assigned Viekira Pak regimen without change, three subjects interrupted study drugs temporarily, and three subjects discontinued study drugs. Twenty-eight of 32 (87.5%) subjects achieved SVR. The expert panel concluded that none of the 32 cases met the criteria for Hy's Law, because the bilirubin elevations generally preceded the peak ALT elevations and were predominately indirect bilirubin. However, the panel did consider 25/32 cases at least possible drug-induced liver injury, describing them as hepatocellular drug-induced liver injury with adaptation. Seven of the cases referred to the expert hepatic panel were in women receiving concomitant systemic estrogen-containing medications.

The Applicant identified a higher proportion of ALT elevations (>5 x ULN) among women receiving estrogen-containing medications as phase 2 development was ending and phase 3 trials were beginning. At that time, the Applicant prohibited estrogen-containing

[1] AbbVie's Expert Hepatic Panel included: (b) (4)

contraceptives in the ongoing phase 3 trials and initiated a drug-drug interaction study with Viekira Pak and combination ethinyl estradiol/norethindrone oral contraceptive. The study was terminated early when a high proportion of the healthy volunteers experienced ALT elevations. The NDA safety analysis confirmed that up to 27% of women receiving concomitant ethinyl estradiol (mostly as oral contraceptives) in the phase 3 trials experienced elevated ALT. A Warning describing "Increased Risk of ALT Elevations" will be included in the Viekira Pak label and clinicians will be instructed to monitor ALT during the first four weeks of treatment and as clinically indicated thereafter. The use of concomitant ethinyl estradiol-containing medications will be contraindicated during Viekira Pak treatment. Although women receiving other estrogens did not appear to have an increased risk, the number of subjects receiving these medications was limited.

An association of RBV with anemia has been well characterized in other HCV drug development programs and is understood to be due to RBV-induced hemolysis. Reductions in RBV dose are commonly required and instructions for these dose adjustments are described in RBV product labels. In the placebo-controlled and RBV/regimen-controlled trials, about 7% of subjects receiving Viekira Pak+RBV experienced dose adjustments. One subject receiving Viekira Pak alone had dose adjustment of the RBV-placebo. In M13-099, dose reductions were made in 8% of subjects in the 12 week arm compared to 13% of those in the 24 week arm. In both arms, the primary reason for RBV dose adjustment/reduction was anemia or decreased hemoglobin. As has been described in other treatment regimens, reduction in RBV dose did not have an adverse impact on treatment success, with 98.5% of subjects who experienced dose reduction achieving SVR12.

As noted above, PTV is known to be an inhibitor of the cellular transporter OATP1B1 involved in bilirubin transport. Consequently, use of Viekira Pak leads to predictable increases in serum bilirubin, primarily indirect bilirubin. In the phase 3 trials, elevated bilirubin levels were observed within the first few weeks of treatment and resolved without treatment interruption by the end of treatment or shortly after. Addition of RBV, known to cause hemolysis appeared to contribute significantly to the bilirubin elevations. As noted in the Clinical Review, there was a significant increase in mean bilirubin levels in subjects treated with Viekira Pak+RBV (+1.75 mg/dL) compared to Viekira Pak alone (+0.6 mg/dL). The rates and severity of these bilirubin increases were greater in subjects with cirrhosis. Table 10 taken from the Clinical Review shows the maximum bilirubin elevation by toxicity grade across the phase 3 trials integrated analysis. None of the reported clinical events of jaundice were considered serious and none led to discontinuation of study drugs. None of the subjects receiving Viekira Pak alone or placebo had clinical findings related to bilirubin elevations.

Table 10: Maximum On-Treatment Bilirubin Elevations, Phase 3 Trials

	Viekira Pak + RBV X 12 weeks Non-cirrhotic N=1165	Viekira Pak X 12 weeks Non-cirrhotic N=509	PBO[1] N=254	Viekira Pak + RBV X 12 weeks Cirrhotic N=208	Viekira Pak + RBV X 24 weeks Cirrhotic N=172
G1 (>ULN-1.5 x ULN)	274 (23)	45 (9)	8 (3)	58 (28)	53 (31)

G2 (>1.5-3.0 x ULN)	215 (18)	29 (6)	2 (<1)	58 (28)	65 (38)
G3 (>3.0-10 x ULN)	42 (4)	2 (<1)	0	28 (13.5)	9 (5)
G4 (>10 x ULN)	1 (<1)	1 (<1)	0	0	0

1 During Double-Blind treatment period
Source: NDA 206619, Clinical Review, R. Fleischer, page 100.

- ***Discussion of notable safety issues (resolved or outstanding)***

The Clinical reviewer considered the safety profile of Viekira Pak with or without RBV acceptable. None of the identified risks of rash events, elevated ALT or bilirubin, or anemia were unpredicatable or unmanageable and none preclude approval. He strongly recommended routine monitoring of liver-related laboratory tests early during treatment and careful follow-up of any significant ALT abnormalities and this approach was discussed with the Applicant. Description of ALT elevations, particularly among women taking concomitant ethinyl estradiol-containing oral contraceptives, will be included in the product label in a specific Warning ("Increased Risk of ALT Elevations") as well as in the Adverse Reactions, Clinical Trials section. Concomitant use of ethinyl estradiol-containing medications will be contraindicated. In addition, the occurrence of rash and pruritus, elevated bilirubin, and anemia and decreased hemoglobin will also be described in the Adverse Reactions section.

As part of the discussion surrounding management of liver-related laboratory abnormalities, we requested advice from DAVP's resident hepatologist, Dr. Poonam Mishra. Dr. Mishra provides consultation on possible hepatotoxicity signals for DAVP and other review divisions within CDER/OND. She reviewed the analyses related to ALT and bilirubin and the Expert Hepatic Panel's Liver Safety Assessment Report. She agreed with the Review Team's plan to describe ALT and bilirubin elevations and provide guidance on monitoring and management in the product label. In addition, she recommended utilizing established post-marketing observational cohorts to further characterize the possible pattern of hepatic injury related to Viekira Pak. For further details, please refer to Dr. Mishra's Memorandum dated October 6, 2014.

9. Advisory Committee Meeting

An Advisory Committee was not considered warranted as Viekira Pak was granted Breakthrough Therapy designation on the basis of the dramatic treatment responses observed in the phase 2 trial M11-652. The results of the six phase 3 trials confirmed the overall highly favorable risk-benefit assessment for Viekira Pak with or without RBV in broadly representative study populations.

10. Pediatrics

Chronic HCV infection is much less common in pediatric patients than in adults but drug development is still needed in this area as current treatment recommendations for pediatric patients relies on peg-interferon plus RBV. To date, the Applicant has not begun a pediatric development program but they have submitted an initial pediatric study plan (iPSP) which has

been reviewed and agreed upon by DAVP and the FDA Pediatric Review Committee (PeRC). They propose to conduct clinical trials in pediatric subjects with GT1 HCV to assess pharmacokinetics, safety, and antiviral activity (as measured by SVR12) of Viekira Pak with or without RBV. (b) (4) In addition, they plan to assess long-term follow-up to confirm durability of response and characterize resistance in subjects who do not achieve SVR.

At the time of NDA submission the Applicant requested a deferral of these pediatric studies on the basis that the adult studies were completed and ready for approval. The Applicant also requested a waiver in pediatric patients younger than 3 years of age on the basis that the product would not provide meaningful therapeutic benefit and is unlikely to be used in a substantial number of patients in this age group. The Review Team agreed with this request. A diagnosis of chronic HCV infection is difficult to establish definitively in patients young pediatric patients. Spontaneous resolution of HCV infection, depending on mode of transmission and genotype, occurs in pediatric patients generally up to age 4, and the risk of progression of liver disease in HCV-infected patients prior to age 3 is very low. Among perinatally infected patients, an estimated 20-30% will have spontaneous clearance of HCV and clearance is most likely in the first 2-3 years of life. Therefore, we anticipate very few pediatric patients younger than 3 years of age will require treatment for chronic HCV infection. The deferral and waiver requests were presented to the PeRC on October 15, 2014 and were approved.

A pediatric Written Request has not been issued for Viekira Pak.

The approval of Viekira Pak will trigger required pediatric studies under PREA. These PREA post-marketing requirements incorporate the studies outlined in the iPSP and are as follows:

2830-1 Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection.

Final Protocol Submission: July 31, 2015
Trial Completion: April 30, 2019
Final Report Submission: August 31, 2019

2830-2 Collect and analyze long-term safety data for subjects enrolled in the pediatric ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) pharmacokinetic, safety, and antiviral efficacy study(ies). Data collected should include at least 3 years of follow-up in order to characterize the durability of response to ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) and the long-term safety including growth assessment, sexual maturation, and characterization of resistance associated substitutions in viral isolates from subjects failing therapy.

Final Protocol Submission: July 31, 2015
Trial Completion: April 30, 2022

Final Report Submission: August 30, 2022

11. Other Relevant Regulatory Issues

There were few regulatory issues that warrant specific mention. No data quality or integrity concerns were identified during the review.

- ***Financial disclosures***

Financial disclosure information for the investigators participating in the phase 3 clinical trials was reviewed by the Clinical reviewer (see Section 9.4 of the Clinical Review). Of the 300 investigators included, ten were identified by the Applicant as having disclosable financial interests/arrangements. Mr. Fleischer noted the Applicant took steps to minimize potential bias due to potential financial interests and arrangements by employing randomized study designs with no site enrolling large numbers of subjects that could influence results and utilizing a primary endpoint that included an objective laboratory measurement (HCV RNA). He concluded the disclosed financial interests/arrangements did not raise questions about the integrity of study data and did not affect approvability of the application.

- ***Other GCP issues***

The Applicant stated that all clinical trials were conducted in accordance with the International Conference on Harmonization (ICH) and Good Clinical Practice (GCP) guidelines. All protocols were submitted to the investigational review boards (IRBs) or ethics committees as appropriate for participating investigators.

- ***DSI audits***

The Clinical Inspection Summary notes that eight clinical investigators' sites representing four of the phase 3 clinical trials were selected by the Review Team for inspection by the Office of Scientific Investigation. Inspections were conducted at seven of these sites (four domestic and three international); the inspection in Israel was cancelled due to travel restrictions at the time of the scheduled inspection. One site in France contributed a relatively large number of subjects to M13-099 (N=24 enrolled). This site accounted for a disproportionate number of GT1a treatment failures in the 12 week treatment arm of the trial, with 5/10 (50%) achieving SVR compared to 7/7 in the 24 week arm. No deficiencies were identified at this site that explained the poorer results in the shorter treatment arm. OSI concluded the data from all inspected sites appeared to be acceptable to support the application.

- ***Other discipline consults***

A consult was obtained from the Pediatric and Maternal Health Staff (PMHS) to gain their opinion regarding the best way to communicate risk of hepatotoxicity with concomitant use of Viekira Pak and estrogen-containing medications and other pregnancy-related labeling. The PMHS consultant recommended Viekira Pak be labeled with a pregnancy category B classification (no concerning animal embryo-fetal effects but no adequate and well-controlled studies in pregnant women). The consultant provided labeling recommendations which are aligned with the proposed final Pregnancy and Lactation Labeling Rule which is currently in

the clearance process. PMHS also agreed with the Review Team's recommendation to contraindicate use of ethinyl estradiol-containing products.

12. Labeling

Although many aspects of labeling are complete, some issues remain to be negotiated at the time of writing this CDTL Review. Key aspects of labeling are summarized below.

- ***Proprietary name***

The proprietary name Viekira Pak was submitted for the coformulated OMB, PTV, RTV tablets copackaged with DBV tablets and was reviewed by staff from the Division of Medication Error Prevention and Risk Management (DMEPA). The proposed name was found to be acceptable and the Applicant was informed of the decision on August 22, 2014.

- ***Address important issues raised by brief discussion of OPDP and OSE Division comments.***

No specific issues were raised by either OPDP or OSE other than those already discussed in this CDTL Review.

- ***Physician labeling***

Discussion of final labeling language is ongoing with the Applicant. Recommended wording for selected sections of the label not described in other parts of this CDTL as of the time of writing this review are shown below.

The Review Team and the Applicant agreed on the following language for the Indications and Usage section of the label:

> VIEKIRA PAK with or without ribavirin is indicated for the treatment of patients with genotype 1 chronic hepatitis C virus (HCV) infection including those with compensated cirrhosis.
>
> Limitation of Use:
>
> VIEKIRA PAK is not recommended for use in patients with decompensated liver disease *[see Use in Specific Populations (8.7), and Clinical Pharmacology (12.3)]*.

As noted in the Dosage and Administration section of the label, the recommended oral dosage of VIEKIRA PAK is two ombitasvir, paritaprevir, ritonavir tablets once daily (in the morning) and one dasabuvir tablet twice daily (morning and evening). Table 11 below contains the Review Team's recommended regimens for different patient populations. These dosage recommendations are extended to HCV/HIV-1 co-infected patients. In addition, Viekira Pak+RBV for 24 weeks is recommended for selected, stable post-liver transplant patients.

Table 11: Treatment Regimen and Duration by Patient Population (Treatment Naïve or Interferon-Experienced)

Patient Population	Treatment*	Duration
Genotype 1a,	VIEKIRA PAK + ribavirin	12 weeks

without cirrhosis		
Genotype 1a, with cirrhosis	VIEKIRA PAK + ribavirin	24 weeks**
Genotype 1b, without cirrhosis	VIEKIRA PAK	12 weeks
Genotype 1b, with cirrhosis	VIEKIRA PAK + ribavirin	12 weeks

*Note: Follow the genotype 1a dosing recommendations in patients with an unknown genotype 1 subtype or with mixed genotype 1 infection.
**VIEKIRA PAK administered with ribavirin for 12 weeks may be considered for some patients based on prior treatment history [*see Clinical Studies (14.3)]*.

In addition to the contraindications for patients with severe hepatic impairment or concomitant use of certain drugs, we recommend Viekira Pak be contraindicated in patients who have known hypersensitivity to ritonavir. This contraindication may apply to HIV/HCV do-infected patients who have previously received a RTV-containing antiretroviral regimen.

Routine monitoring of ALT levels in all patients receiving Viekira Pak are recommended and ALT elevations are described in the Warnings and Precautions section of the label as follows:

Increased Risk of ALT Elevations
During clinical trials with VIEKIRA PAK with or without ribavirin, elevations of ALT to greater than 5 times the upper limit of normal (ULN) occurred in approximately 1% of all subjects *[see Adverse Reactions (6.1)]*. ALT elevations were typically asymptomatic, occurred during the first 4 weeks of treatment, and declined within two to eight weeks of onset with continued dosing of VIEKIRA PAK with or without ribavirin.
These ALT elevations were significantly more frequent in female subjects who were using ethinyl estradiol-containing medications such as combined oral contraceptives, contraceptive patches or contraceptive vaginal rings. Ethinyl estradiol-containing medications must be discontinued prior to starting therapy with VIEKIRA PAK *[see Contraindications (4)]*. Alternative methods of contraception (e.g, progestin only contraception or non-hormonal methods) are recommended during VIEKIRA PAK therapy. Ethinyl estradiol-containing medications can be restarted approximately 2 weeks following completion of treatment with VIEKIRA PAK.
Women using estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens used in hormone replacement therapy had a rate of ALT elevation similar to those not receiving any estrogens (1%). However, due to the limited number (n=87) of subjects taking these others estrogens, caution is warranted for co-administration with VIEKIRA PAK.
Hepatic laboratory testing should be performed during the first 4 weeks of starting treatment and as clinically indicated thereafter. If ALT is found to be elevated above baseline levels, it should be repeated and monitored closely:

- Patients should be instructed to consult their health care professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces.

- Consider discontinuing VIEKIRA PAK if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue VIEKIRA PAK if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or INR.

An additional Warning and Precaution is recommended to ensure clinicians are aware that HIV/HCV co-infected patients should be on a suppressive antiretroviral regimen when on Viekira Pak.

- ***Carton and immediate container labels (if problems are noted)***

Carton and container labels have been reviewed by the Chemistry review team and the Division of Medication Error Prevention and Analysis (DMEPA) and found to be acceptable.

- ***Patient labeling/Medication guide (if considered or required)***

Because the product label will contain Warnings and Precautions, a Medication Guide will be recommended. The draft Medication Guide is being reviewed by the Patient Labeling Team but this review is not yet complete.

13. Recommendations/Risk Benefit Assessment

- ***Recommended Regulatory Action***

I concur with the conclusions of the multi-disciplinary Review Team and recommend Viekira Pak with or without ribavirin be approved for the treatment of chronic HCV (genotype 1) infection, including patients with compensated cirrhosis. The package of submitted phase 3 clinical trials met the regulatory standard required for approval and all trials achieved their efficacy objectives. These trials demonstrated that use of Viekira Pak was both safe and effective.

Although there are no clinical or other discipline findings that would preclude approval, approval of Viekira Pak is contingent upon successful completion of all inspections and adequate resolution of any deficiencies identified as determined by the Office of Compliance.

- ***Risk Benefit Assessment***

Viekira Pak with or without RBV will become the second all-oral regimen for the treatment of chronic GT1 HCV infection. After review of the data supporting the approval of Viekira Pak (ombitasvir, paritaprevir, ritonavir, and dasabuvir) as a treatment regimen for chronic HCV infection, it was clear that the potential benefits of Viekira Pak far outweighed the potential risks. Previously approved treatment regimens of direct acting antivirals plus peg-interferon and ribavirin achieved SVR in about 70-75% of treatment-naïve patients and far fewer of those who had already failed an interferon-based regimen. In multiple trials of Viekira Pak with or without RBV in both treatment-naïve and treatment-experienced subjects, SVR was achieved in 97-100% of non-cirrhotic subjects with GT1b HCV infection with 12 weeks of treatment. The data definitively demonstrated that RBV was not needed to achieve these dramatic results. In non-cirrhotic subjects with GT1a HCV infection, SVR was achieved in 94-97% of those

receiving Viekira Pak+RBV and 90% of those receiving Viekira Pak alone for 12 weeks. Thus, for GT1a HCV, the addition of RBV to the regimen was beneficial. Reductions in RBV dose for safety or tolerability reasons had no impact on ultimate treatment success.

In a large clinical trial enrolling subjects with compensated cirrhosis (Child-Pugh A), the treatment outcomes were almost as good as those in non-cirrhotic subjects. Among subjects with GT1b HCV receiving Viekira Pak+RBV for 12 or 24 weeks, 98-100% achieved SVR, supporting the recommendation for a 12 week treatment course for GT1b infection. Again, history of past treatment made no difference in response rates in subjects with this genotype. Small differences in SVR rates were identified among cirrhotic subjects with GT1a HCV receiving 12 or 24 weeks of treatment. The overall SVR rates for GT1a-infected subjects were 92% and 96% for those receiving 12 or 24 weeks, respectively. Although the differences between 12 and 24 week treatment duration were small and not statistically significant, it was difficult to identify any subgroup for which 24 weeks of treatment was not numerically better than 12 weeks. These differences in SVR were predominately driven by differences in post-treatment relapse, an event shown to be influenced by treatment duration in other drug development programs, leading the Review Team to consider Viekira Pak+RBV for 24 weeks the optimal regimen for cirrhotic GT1a patients. The trial data suggested that the subgroup with the clearest difference between 12 and 24 week treatment was the group of GT1a prior null responders, but we did not have confidence that we could identify other patient subgroups who would benefit substantially from the longer regimen. Thus, the recommendation for 24 weeks of Viekira Pak+RBV in cirrhotic patients GT1a HCV will include a caveat that clinicians can consider a 12 week regimen in some subjects based on prior treatment history.

Smaller trials enrolling cohorts of previously difficult to treat subjects reinforced the conclusion that Viekira Pak represents a true breakthrough in HCV treatment. An initial cohort of carefully selected, stable, post-liver transplant subjects with recurrent chronic HCV achieved 97% SVR. Similarly, the first cohorts in a trial comparing 12 or 24 weeks of treatment in HIV/HCV co-infected subjects demonstrated SVR rates of 93% and 91%, respectively. These treatment outcomes approach those observed in subjects without HIV.

The substantial treatment benefits are accompanied by relatively low potential for risk. The overall safety profile of Viekira Pak with or without RBV for either 12 or 24 weeks was acceptable and the identified safety signals appear to be manageable. The toxicity warranting most concern was elevation in serum ALT that appeared to be associated with the paritaprevir component of Viekira Pak. Elevations of ALT were most frequent among women receiving concomitant ethinyl estradiol-containing oral contraceptives but were also observed in about 1% of other subjects receiving the drugs. The Review Team considered these ALT elevations potentially indicative of drug-induced liver injury but noted that almost all subjects continued their assigned treatment without clinical consequences and ALT subsequently returned to normal. Risk can be mitigated by prohibiting concomitant use of ethinyl estradiol-containing products during treatment with Viekira Pak and monitoring ALT levels during the first four weeks of treatment. The product label will provide some guidelines for management of persistently elevated ALT levels.

Other safety signals include an increased risk of rash events and pruritus, anemia, and elevated bilirubin levels. A majority of the adverse events reported in the clinical trials were characterized as mild and very few led to discontinuation of drugs. To date, there have been no cases of serious skin reactions such as Stephens-Johnson Syndrome, erythema multiforme, or toxic epidermal necrolysis reported with Viekira Pak. Many of the reported adverse events appeared to be increased by the addition of RBV to the Viekira Pak regimen and have been previously described with RBV use in other regimens. About 6% of subjects receiving RBV in the clinical trials underwent RBV dose reduction, primarily because of anemia or decreased hemoglobin, but only three subjects received transfusions and five received erythropoietin. Importantly, rates of adverse events and laboratory abnormalities were not substantially higher in subjects receiving Viekira Pak+RBV for 24 weeks compared to 12 weeks.

Overall, the risk-benefit assessment strongly favors approval of Viekira Pak for use with or without RBV. The noted safety signals will be monitored in the post-marketing period. Perhaps the most critical question remaining is how to manage the small proportion of patients who fail this treatment regimen as retreatment options may be extremely limited for the foreseeable future.

- ***Recommendation for Postmarketing Risk Evaluation and Management Strategies***

Based on the overall safety profile of Viekira Pak, a REMS is not recommended. A Medication Guide will be required to ensure that patients have access to important safety information and instructions for use of Viekira Pak in consumer-friendly language.

- ***Recommendation for other Postmarketing Requirements and Commitments***

In order to further characterize resistance to Viekira Pak and cross-resistance with other DAAs, the Review Team has recommended the following virology-related postmarketing studies. As resistance in HCV is considered a significant safety issue, the first study recommendation will be a PMR under FDAAA.

1. Conduct the following site-directed mutant HCV replicon phenotype analyses:
   - Sofosbuvir activity against HCV replicons carrying NS5B substitutions associated with dasabuvir resistance: C316Y (GT1a and GT1b) and S556G (GT1a).
   - Dasabuvir activity against HCV replicons carrying the following NS5B substitutions: L159F (GT1a and GT1b), V321A (GT1a and GT1b), M423I (GT1a), I482T (GT1a) and A486V (GT1b).
   - Paritaprevir activity against HCV replicons carrying substitutions in the NS3 helicase (e.g., P334S, S342P, V406A/I, T449I, P470S) that emerged in virologic failure subjects treated with the 3-DAA ± RBV regimen; evaluate the impact of these substitutions alone and in combination with other key resistance-associated substitutions (e.g., R155K or D168x) that were often detected in combination.

2. In addition, the sponsor has agreed to the following virology PMC:
   Submit a complete report for ongoing clinical Study M13-102, "A Follow-up Study to Assess Resistance and Durability of Response to AbbVie Direct-Acting Antiviral

Agent (DAA) Therapy in Subjects Who Participated in Phase 2 or 3 Clinical Studies for the Treatment of Chronic Hepatitis C Virus (HCV) Infection."

As part of our ongoing efforts to characterize safety and efficacy of Viekira Pak in different patient populations we have requested the following final study reports of clinical trials that are either ongoing or planned at the time of this review.

3. Submit the final clinical study report and datasets for the ongoing Phase 3 clinical trial M11-646 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

4. Submit the final clinical study report and datasets for the Phase 3 clinical trial M13-098 entitled "A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection."

5. Submit the final clinical study report and datasets for the Phase 3 clinical trial M13-099 entitled "A Randomized, Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT- 333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

6. Submit the final clinical study report and datasets for the Phase 3 clinical trial M13-961 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

7. Submit the final clinical study report and datasets for the Phase 3 clinical trial M13-389 entitled "A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection."

8. Submit the final clinical study report and datasets for the Phase 3 clinical trial M14-002 entitled "A Randomized, Double-Blind, Controlled Study to Evaluate the Efficacy and Safety of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin (RBV) in Treatment-Naïve Adults with Genotype 1a Chronic Hepatitis C Virus (HCV) Infection."

9. Submit a final clinical study report and datasets for the ongoing clinical trial M14-226 entitled "An Open-Label Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir with or without Ribavirin (RBV) in

Treatment-Naïve Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection, with Severe Renal Impairment or End-Stage Renal Disease."

10. Submit a final clinical study report and datasets for the ongoing clinical trial M14-227 entitled "An Open-Label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 and ABT-333 with Ribavirin in Adults with Genotype 1 Chronic Hepatitis C Virus Infection and Decompensated Cirrhosis." Based on recommendations from the OND Safety Review Team and discussion with the primary NDA reviewers, the request for this study report will be made a PMR.

11. Submit a final clinical study report and datasets for the ongoing clinical trial M12-999 entitled "Open-label, Phase 2 Study to Evaluate the Safety and Efficacy of the Combination of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adult Liver Transplant Recipients with Genotype 1 Hepatitis C Virus (HCV) Infection."

12. Submit a final clinical study report and datasets for the ongoing clinical trial M14-004 entitled "A Randomized, Open-label Study to Evaluate the Safety and Efficacy of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Coadministered with Ribavirin (RBV) in Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection and Human Immunodeficiency Virus, Type 1 (HIV-1) Coinfection."

13. Submit a final clinical study report and datasets for the ongoing clinical trial M14-490 entitled "An Open-Label, Single-Arm Study to Evaluate the Safety and Efficacy of Ombitasvir/ABT-450/Ritonavir and Dasabuvir in Adults with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection and Cirrhosis."

The pediatric PMRs required under PREA are described in Section 10 of this review.

- ***Recommended Comments to Applicant***

There are no additional comments that need to be conveyed to the Applicant.

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

/s/

LINDA L LEWIS
11/24/2014