CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Deputy Office Director Decisional Memo

Date	(electronic stamp)
From	John Farley, M.D.,M.P.H.
Subject	Deputy Office Director Decisional Memo
NDA #	206619
Applicant Name	AbbVie
Date of Submission	April 21, 2014
PDUFA Goal Date	December 21, 2014
Proprietary Name / Established (USAN) Name	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)
Proposed Indication	Treatment of genotype 1 chronic hepatitis C infection, including patients with cirrhosis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Russell Fleischer, PA-C, M.P.H.
Statistical Review	Joy Mele, M.S.
Pharmacology Toxicology Review	Mark Seaton, Ph.D., DABT
CMC, Biopharmaceutics, Product Quality Microbiology Reviews	Maotang Zhou, Ph.D., Milton Sloan, Ph.D., Caroline Strasinger, Ph.D., Elsbeth Chikhale, Ph.D., Erika Pfeiler, Ph.D.
Clinical Virology Review	Patrick Harrington, Ph.D.
Clinical Pharmacology Review	Vikram Arya, Ph.D., FCP, Seong Jang, Ph.D., Dhananjay Marathe Ph.D., Jeffry Florian, Ph.D., Islam Younis, Ph.D.
OSI	Antoine El-Hage, Ph.D.
OPDP	Sharon Mills, B.S.N., C.C.R.P., Jessica Fox, Pharm.D., RAC
DMEPA	Kellie Taylor, Pharm.D., M.P.H., Monica Calderon, Pharm.D., BCPS, Irene Chan, Pharm.D., BCPS
DRISK	Felicia Duffy, B.S.N., M.S.Ed
CDTL Review	Linda Lewis, M.D.
Deputy Division Director Review	Jeff Murray, M.D., M.P.H.

OND=Office of New Drugs
CMC= Chemistry, Manufacturing and Controls
OPDP= Office of Prescription Drug Products
OSI= Office of Scientific Investigations
DMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Viekira Pak is a new treatment for chronic hepatitis C virus infection (CHC), comprised of ombitasvir (ABT-267), paritaprevir (ABT-450), and ritonavir co-formulated as a fixed dose combination (FDC) tablet co-packaged with dasabuvir (ABT-333) tablets. Viekira Pak includes 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 FDC tablet also includes ritonavir (RTV), a CYP3A, mechanism-based pharmaco-enhancer included to boost the exposure of PTV.

The proposed indication is treatment of genotype 1 CHC, including patients with cirrhosis. The proposed dosing regimen is two OMB, PTV, RTV 12.5/75/50 mg tablets once daily (in the morning) and one DBV 250 mg tablet twice daily (morning and evening) with a meal. Viekira Pak is to be administered with ribavirin for all genotype 1a patients and genotype 1b patients with cirrhosis. The recommended duration of treatment and the indication for patients with cirrhosis were review issues and are discussed in this Memo.

The review for this NDA relies upon the results of six adequate and well-controlled Phase 3 trials evaluating the efficacy and safety of Viekira Pak with and without ribavirin with treatment durations of 12 or 24 weeks in different genotype 1 CHC patient populations. In addition, the contribution of DBV, OMB, and ribavirin in the Viekira Pak regimen was demonstrated in a large, multi-arm, Phase 2 trial. The review team has reviewed issues pertinent to their respective disciplines with regard to the safety and efficacy of NDA 206619 for the indication proposed. For a detailed discussion of NDA 206619, the reader is referred to individual discipline specific reviews, the Cross-Discipline Team Leader (CDTL) review, and the Deputy Division Director review.

2. Background/Regulatory

The product was developed under INDs 101636, 103526, and 108434.

Based on the promising results of the large, multi-arm Phase 2 trial, Viekira Pak was granted Breakthrough Therapy designation in May 2013.

NDA 206619 was a rolling review with the final component received on April 21, 2014. The NDA was filed on June 20, 2014, and granted a Priority Review to be managed under the PDUFA V program guidelines.

Considering the Breakthrough Therapy designation, the Division agreed that the Applicant could submit within 30 days of the submission date for the final NDA component additional data from Study M12-999 conducted in post-liver transplant patients. The Division also agreed to allow the Applicant to submit during the review cycle primary analysis results from Study M14-004 (TURQUOISE-I) conducted in HIV/HCV co-infected patients.

3. Chemistry Manufacturing and Controls / Product Quality Microbiology

The CMC review team concluded that the NDA provided sufficient information to assure the identity, strength, purity, and quality of the drug product. An overall "Acceptable" recommendation for manufacturing facilities was received from the Office of Compliance, and the CMC review team recommended approval. I conclude that there are no CMC issues precluding approval.

The proposed drug product consists of co-formulated OMB, PTV, and RTV film-coated tablets (12.5 mg/75mg/50 mg) co-packaged with DBV film-coated tablets (250 mg). 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. The CMC reviewers concluded that adequate information was submitted to support the Applicant's proposal for a 24 month expiration dating for the drug product when stored at or below 30°C.

Manufacturing processes, controls, and specifications for each of the drugs substances was deemed acceptable. For RTV, drug substance information was cross-referenced to the Norvir NDA.

In the course of the review, the Applicant agreed to add a test for detection of (b) (4) for each of the three drug substances in the OMB/PTV/RTV tablet. A Post-Marketing Commitment was agreed to by the Agency and Applicant to continue development of a test for (b) (4) with a sensitivity of (b) (4)% in the OMB/PTV/RTV drug product tablet for the release and stability specification.

The Biopharmaceutics reviewer concluded that dissolution methods and acceptance criteria were acceptable. In addition, she concluded that adequate bridging was performed throughout the product development.

The Product Quality Microbiology reviewer concluded that the microbiological quality of the drug product is controlled through a suitable testing protocol and recommended approval.

4. Non-Clinical Pharmacology Toxicology

The Non-Clinical Pharmacology Toxicology reviewer recommended approval. I concur that there are no pharmacology toxicology issues precluding approval.

The gall bladder was identified as a target organ of PTV toxicity in repeat dose studies in mice and dogs. Findings include edema, mononuclear and mixed cell infiltration, and epithelial cell necrosis with increased serum alkaline phosphatase, suggesting biliary effects. PTV was positive in an in-vitro human chromosome aberration test, but negative in a bacterial mutation assay and in two in-vivo genetic toxicology assays. PTV was not

carcinogenic in nonclinical studies. Oral administration to pregnant rats and mice did not result in teratogenicity at systemic exposures exceeding (up to 8x in rats and 98x in mice) expected human exposure. In clinical development, PTV was co-administered with RTV to boost systemic exposures. Non-clinical studies, including carcinogenicity studies in mice and rats, were performed with varying dose levels of both drugs.

In non-clinical studies with RTV alone, the main target organs were liver and retina. Hepatic transaminase elevations, clinical hepatitis, and jaundice have occurred in patients treated with RTV alone or as part of a HIV treatment combination regimen.

No toxicologically significant effects of OMB were noted in non-clinical studies. No clinically significant reproductive toxicity, maternal toxicities, or teratogenicity was observed in non-clinical studies.

No target organs were identified for DBV in non-clinical toxicology studies. DBV was not genotoxic or carcinogenic. There was no clinically significant effect on fertility or maternal toxicity, and teratogenicity was not observed.

Pregnancy Category B is recommended. The reviewer recommended that labeling note that if Viekira Pak is administered with ribavirin, it is contraindicated in pregnant women and in men whose female partners are pregnant.

5. Clinical Pharmacology

The Clinical Pharmacology review team recommended approval. I concur that there are no Clinical Pharmacology issues precluding approval.

No exposure-response relationship was observed for SVR12 for PTV, OMB, or DBV exposures and SVR12 was uniformly high (97-100%) across all exposure quartiles. There was a positive exposure-response relationship for the safety signals of drug induced rash, ALT elevations, total bilirubin elevations and hemoglobin reductions with PTV exposures. A 2-fold increase in PTV exposure increased the odds of ALT > 3 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.

In patients with severe hepatic impairment (Child-Pugh C), PTV and DBV AUC increased by approximately 945% and 325% respectively and OMB AUC decreased by 54%. As described above, a dose response for PTV and ALT elevations was observed. Viekira Pak will be contra-indicated in patients with severe hepatic impairment. In patients with moderate hepatic impairment (Child-Pugh B), PTV AUC increased by 62%. There was not sufficient clinical data in the NDA to support the safety and efficacy of Viekira Pak in patients with Child-Pugh B hepatic impairment. In addition, there was concern that this population may be at higher risk for the significant transaminase elevations observed in some patients in clinical trials (see Section 8). The review team recommended and the Applicant agreed to state in labeling that Viekira Pak is not

recommended in HCV-infected patients with moderate hepatic impairment (Child-Pugh B). In addition, a study to evaluate the safety and efficacy of Viekira Pak in this population post-marketing will be required.

No dose adjustments are recommended for mild, moderate, and severe renal impairment, but no data are available for patients with ESRD.

Based on the results of food effects studies, the review team recommended that Viekira Pak be labeled as "should always be taken with a meal".

PTV is a known inhibitor of the organic anion transporting polypeptide OATP1B1, which is critical in bilirubin transport. Co-administered ribavirin may induce hemolysis contributing to hyperbilirubinemia. Elevation of indirect bilirubin was anticipated and observed in clinical trials.

OMB, PTV, DBV, and RTV are inhibitors of a number of important metabolic enzymes and many drug-drug interactions are expected. Co-administration of Viekira Pak with drugs that are substrates of CYP3A, UGT1A1, BCRP, OATP1B1, or OATP1B3 may result in increased plasma levels of such drugs. PTV and RTV are primarily metabolized by CYP3A enzymes. DBV is primarily metabolized by CYP2C8 enzymes. Co-administration of Viekira Pak with other drugs that inhibit these enzymes may increase concentrations of PTV, RTV, or DBV. Based on drug-drug interaction studies in healthy volunteers and modeling based on those results, the review team recommended contraindication for a number of drugs. The team also recommended that a number of drugs be listed in labeling as "co-administration not recommended", or "dose adjustment /monitoring recommended". This information has been included in labeling.

6. Clinical Virology

The Clinical Virology reviewer found the NDA approvable from a Clinical Virology perspective. I concur that there are no Clinical Virology issues precluding approval.

The reviewer evaluated the effect of baseline HCV polymorphisms on treatment response. While associations were observed for polymorphisms at all 3 targets, the reviewer concluded that given the low virologic failure rates observed with optimal treatment regimens recommended for genotype 1a and 1b patients, the detection of HCV polymorphisms at baseline is expected to have little impact on the likelihood of achieving SVR.

In a pooled analysis of subjects treated with regimens containing OMB, PTV, and DBV with or without ribavirin in Phase 2b and Phase 3 trials, resistance analyses were conducted in 64 subjects who experienced virologic failure. Treatment emergent substitutions were detected in all 3 drug targets in 30 of 57 genotype 1a infected subjects and 1 of 6 genotype 1b infected subjects. Persistence of substitutions was assessed in genotype 1a Phase 2 trials with data available through at least 24 weeks of treatment. For OMB, treatment emergent substitutions in NS5A persisted at detectable levels through at

least post-treatment week 24 in 24 of 24 subjects and through post-treatment week 48 in 18 of 18 subjects. For PTV, treatment emergent substitutions in NS3 persisted at detectable levels through at least post-treatment week 24 in 17 of 29 subjects and through post-treatment week 48 in 5 of 22 subjects. For DBV, treatment emergent substitutions in NS5B persisted at detectable levels through at least post-treatment week 24 in 11 of 16 subjects and through post-treatment week 48 in 8 of 15 subjects.

The reviewer recommended and the Applicant agreed to a PMR to conduct site-directed mutant HCV phenotype analyses of sofosbuvir, DBV, and PTV activity against HIV replicons carrying certain substitutions.

7. Clinical/Statistical Efficacy

The Clinical reviewer, Statistical reviewer, CDTL, and Deputy Division Director all concluded that substantial evidence of efficacy has been provided and I concur.

The results of six Phase 3 trials and one 14-arm Phase 2 study were submitted to demonstrate the efficacy and safety of Viekira Pak (see TABLE 1). Additional studies conducted in specific populations will also be discussed.

TABLE 1: Key Studies Demonstrating Safety and Efficacy
Source: Table 2.1.1 Statistical Review, 3 DAA refers to PTV/RTV, DBV, and OMB

Study	Design	Treatment Period	Follow-up Period	Randomized Arms (ITT N)	Study Population
Phase 2 Study					
M11-652	OL, R, MC	8, 12 and 24 weeks	48 weeks	14 arms (see Table 3.1.1)	GT1 Non-cirrhotic TN & TE null responders
Phase 3 Studies by Design					
Studies comparing 3DAA+RBV versus 3DAA+Placebo					
M13-389 PEARL II	OL, R, MC	12 weeks	48 weeks	3DAA+RBV (88) 3DAA (91)	GT 1b non-cirrhotic TE
M13-961 PEARL III	DB, R, MC	12 weeks	48 weeks	3DAA+RBV (210) 3DAA (209)	GT 1b non-cirrhotic TN
M14-002 PEARL IV	DB, R, MC	12 weeks	48 weeks	3DAA+RBV (100) 3DAA (205)	GT 1a non-cirrhotic TN
Studies comparing 3DAA+RBV versus Placebo					
M11-646 SAPPHIRE I	DB, R, MC	12 weeks	48 weeks	3DAA+RBV (473) Placebo (158)	GT 1 non-cirrhotic TN
M13-098 SAPPHIRE II	DB, R, MC	12 weeks	48 weeks	3DAA+RBV (297) Placebo (97)	GT 1 non-cirrhotic TE
Study comparing duration of treatment for 3DAA+RBV in cirrhotic patients					
M13-099 TURQUOISE II	OL, R, MC	12 weeks and 24 weeks	48 weeks	3DAA+RBV 12 wks (208) 24 wks (172)	GT 1 cirrhotic TE & TN

OL=open label, DB=double-blind, R=randomized, MC=multicenter, Trt=treatment, FU=follow-up off treatment, TE=treatment experienced, TN=treatment naïve, ITT=intent-to-treat population of patients who were randomized and took at least one dose

For each of these trials, the primary outcome is the sustained virologic response (SVR) assessed 12 or 24 weeks post-treatment (SVR12, SVR24).

The Phase 2 study, M11-652 is an open label, 14 arm study designed to examine multiple doses of PTV/RTV in combination with OMB and/or DBV and with or without ribavirin for treatment durations of 8, 12, or 24 weeks in treatment naïve and experienced genotype 1 CHC patients. The primary comparison in the trial was to determine whether 12 weeks of treatment vs. 8 weeks of treatment with PTV, OMB, DBV, and ribavirin was more efficacious based on SVR24. While the difference was not statistically significant, the 12 week regimen had a higher point estimate for SVR24 (93% vs. 84%). The study design also provided information regarding the individual contribution of DBV, OMB, and ribavirin. While the differences were not statistically significant, the results suggested that DBV, OMB, and ribavirin each individually contribute to an increase in SVR rates for genotype 1a patients. While there is not clinical data supporting the individual contribution of PTV/RTV, there is in-vitro data supporting this. I agree with the review team that a clinical trial with a full factorial design (including a single drug arm) would not be acceptable due to resistance risk and concur that the contribution of each drug in the combination has been adequately demonstrated.

The primary analysis population in all Phase 3 trials was the ITT population of all patients randomized who received at least one dose of study drug. The primary efficacy analysis for all Phase 3 trials compared the SVR12 for the test regimen to an historical control treated with telaprevir plus pegylated interferon and ribavirin. Thresholds for specific patient populations (HCV genotype, treatment experience history, presence of cirrhosis) were defined based on the upper bound of the confidence interval for historical SVR rates for the particular patient population.

The SAPPHIRE I and SAPPHIRE II trials were placebo-controlled with a 12 week treatment delay for the placebo arms. One of the main objectives was to evaluate comparative safety during the 12 week treatment period. SVR12 rates for various patient populations enrolled in these trials ranged from 95-100%. The lower bounds of the 95% CI for the trial SVR12 rates were all superior to the historical control threshold for the particular patient population.

For the genotype 1a population without cirrhosis, the results for Trial M14-002 (PEARL IV) demonstrate a statistically significantly higher SVR12 rate (about 7% higher) for the full regimen including RBV compared to PTV/RTV/DBV/OMB alone. For the 1a population with cirrhosis, 24 weeks of treatment was seen to be more beneficial than 12 weeks of treatment in Trial M13-099 (TURQUOISE II) and although the difference was not statistically different, the difference was seen across multiple subgroups. The lower bounds of the 95% CI for SVR12 rates for various patient populations enrolled in these trials were all superior to the historical control threshold for the particular patient population.

TABLE 2: SVR_{12} rates for the 1a population
Source: Table 1.2 Statistical Review, 3 DAA refers to PTV/RTV, DBV, and OMB

M14-002 GT 1a w/o cirrhosis	3DAA+RBV/12 weeks 97/100 97% (94%, 100%)	3DAA/12 weeks 185/205 90% (86%, 94%)	Trt diff (95%CI) +6.8% (+1%, +12%)
M13-099 GT 1a w/ cirrhosis	3DAA+RBV/24 weeks 115/121 95% (97%, 100%)	3DAA+RBV/12 weeks 124/140 89% (81%, 94%)	Trt diff (95%CI) +6% (-1%, +13%)

Based on the findings of Trials M13-389 (PEARL II), M13-961 (PEARL III), and M13-099 (TURQUOISE II), the genotype 1b population required less aggressive treatment with non-cirrhotics adequately treated with PTV/RTV/DBV/OMB without ribavirin and with cirrhotics treated with 12 weeks of treatment with ribavirin. The SVR12 rates for the 1b population were 99% to 100%. The lower bounds of the 95% CI for the SVR12 rates for various patient populations enrolled in these trials were all superior to the historical control threshold for the particular patient population.

TABLE 3: SVR_{12} rates for the 1b population
Source: Table 1.3 Statistical Review, 3 DAA refers to PTV/RTV, DBV, and OMB

M13-389 & M13-961 GT 1b w/o cirrhosis	3DAA+RBV 298/301 99% (97%, 100%)	3DAA 304/304 100% (99%, 100%)	Trt diff (95%CI) -1% (-2%, +1%)
M13-099 GT 1b w/ cirrhosis	3DAA+RBV/24 weeks 51/51 100% (92%, 100%)	3DAA+RBV/12 weeks 67/68 98.5% (91%, 100%)	Trt diff (95%CI) +1% (-6%, +8%)

As discussed above, based on the results of the TURQUOISE II trial, for the 1a population with cirrhosis, 24 weeks of treatment was associated with a higher SVR12 rate than 12 weeks of treatment. The Applicant propose (b) (4) As part of the discussion of this review issue, the Statistical reviewer performed a subgroup analysis of genotype 1a cirrhotic patients. 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. 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. While 24 weeks of treatment will likely provide longer than necessary treatment for some genotype 1a cirrhotic patients, treatment failure with the Viekira Pak+ribavirin 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 (see Section 6). Ultimately, the review team and the Applicant agreed to recommend in labeling a regimen of Viekira Pak + ribavirin for 24 weeks for genotype 1a cirrhotic patients. A footnote will indicate that clinicians can consider a 12 week regimen based on treatment history (i.e., naïve, prior relapse, or prior partial response).

In the six Phase 3 trials, the representation of Black/African-American subjects was considerably lower (range 3-10%) than the proportion of CHC patients in the U.S. who are Black/African-American (approximately 23%). A large proportion of patients in the Phase 3 trials were enrolled in Europe and other parts of the world. For Black/African-American subjects, the SVR12 point estimates were similar to the overall trial

populations, but numbers are small. The review team concluded and I concur that the safety database for Black/African American is insufficient to identify potential unexpected toxicities in this subgroup which may be more vulnerable to drug toxicity based on increased frequencies of certain comorbidities. A clinical trial or observational study in Blacks/African American HCV-infected patients that will evaluate safety and efficacy and allow for comparative analyses with White enrollees in the same trial or observational study will be required post-marketing.

The review team agreed to review late submission of the results of the Phase 2 Trial M12-999, an open-label, single-arm trial conducted in selected post-liver transplant patients with recurrent HCV infection. Thirty-four subjects were enrolled who were at least 1 year post-transplant, had not received treatment for recurrent HCV infection since transplant, were Childs-Pugh A, and had liver fibrosis score $\geq$ 2 on a biopsy. Thirty-three of 34 enrolled (97%) achieved SVR; 28 of 29 subjects with Genotype 1a and 5 of 5 with genotype 1b. A dosing recommendation for liver transplant recipients with normal hepatic function and mild fibrosis will be included in the Dosage and Administration section of labeling.

The team reviewed the primary analysis results from Trial M14-004 Part 1a, which 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%). A total of 63 subjects were randomized to receive either 12 or 24 weeks of Viekira Pak+ribavirin. Overall SVR rates were 93.5% for those receiving 12 weeks of treatment and 91% for those receiving 24 weeks. These results will be included in labeling.

8. Safety

The Clinical reviewer, CDTL, and Deputy Division Director all concluded that there were no safety issues precluding approval and I concur.

At the time of NDA submission, the safety database included 2,964 subjects who received at least one dose of any combination of PTV/RTV, DBV, or OMB with or without ribavirin. The safety data collected during the Phase 3 clinical trials were deemed adequate to characterize the safety profile of Viekira Pak with or without ribavirin for 12 or 24 weeks of treatment in study populations broadly representative of those for whom the product is intended. There were 7 deaths in the safety database and only 1 was on-treatment. The review team concluded that the on-treatment death was likely unrelated to study drug and I concur. In the Phase 3 trials, 19 subjects developed SAEs considered by the investigators to be possibly related to study drugs, including the ribavirin 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). Based on a comparison with the placebo arms in the SAPPHIRE I and II trials, adverse reactions with $\geq$ 10% frequency more common with

Viekira Pak + ribavirin for 12 weeks were: fatigue, nausea, pruritus, insomnia, and asthenia.

Elevations of serum transaminases, particularly ALT, were identified as a potential toxicity of Viekira Pak during the development program. Because PTV is an inhibitor of OATP1B1 transporter, mild to moderate elevations of bilirubin were 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. All but one of these subjects was receiving Viekira Pak + ribavirin. These ALT elevations were generally asymptomatic, occurred during the first 4 weeks of treatment, and resolved in spite of ongoing therapy within 2-8weeks. Among these cases, 26 subjects continued their assigned Viekira Pak regimen without change, 3 subjects interrupted study drugs temporarily, and 3 subjects discontinued study drugs. The Applicant convened a panel of experts in hepatic toxicity to adjudicate these 32 cases, blinded to treatment assignment. 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 of the 32 cases as at least possible drug-induced liver injury, describing them as hepatocellular drug-induced liver injury with adaptation. Dr. Poonam Mishra reviewed the analyses related to ALT and bilirubin and the applicant's expert hepatic panel's 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.

The Applicant had 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. Seven of the 32 cases of hepatoxicity described above were in women receiving concomitant systemic estrogen-containing medications. At the time of identification of the signal, the Applicant prohibited estrogen-containing 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 labeling. Clinicians will be instructed in labeling to discontinue ethinyl estradiol-containing medications prior to starting Viekira Pak and to monitor ALT during the first four weeks of treatment and as clinically indicated thereafter.

A thorough QT study was performed dosing subjects with Viekira Pak at therapeutic doses and supra-therapeutic doses. No significant QTc prolongation effect was observed.

DRISK as well as the review team concluded that no adverse events of particular concern or preclinical safety signals were identified that cannot be effectively communicated through labeling. Because of the need for effective contraception in women receiving a

ribavirin-containing regimen and the risk of hepatotoxicity with or without concomitant use of estrogen-containing therapies (and therefore a need for monitoring), DRISK and the review team concluded that a Medication Guide be included as a part of labeling. DRISK concluded that risk mitigation measures beyond approved labeling which includes a Medication Guide were not warranted.

9. Advisory Committee Meeting

An Advisory Committee was not convened to discuss this NDA as there were no review issues for this product with Breakthrough designation for which Advisory Committee advice was needed.

10. Pediatrics

The Applicant submitted an initial pediatric study plan that was reviewed and agreed upon by the Division and the FDA Pediatric Review Committee (PeRC). The Applicant plans to conduct clinical trials in children with genotype 1 CHC. (b) (4)

At the time of NDA submission the Applicant requested a deferral of 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. The deferral and waiver requests were presented to the PeRC on October 15, 2014 and were approved.

11. Other Relevant Regulatory Issues

Seven clinical investigator sites and the Applicant were inspected. There were no regulatory violations. OSI concluded that the data submitted from these sites was considered acceptable.

There are no unresolved relevant regulatory issues.

12. Labeling

DMEPA found the proprietary name, Viekira Pak, acceptable.

OPDP and DMEPA labeling recommendations were incorporated as appropriate.

Labeling issues discussed in the course of the review and highlighted in this Memo include:

- Limitation of Use in patients with decompensated liver disease
- Contraindication in patients with severe hepatic impairment

- Contraindication of certain drugs which are highly dependent on CYP3A for clearance, strong inducers of CYP3A and CYP2C8, or strong inhibitors of CYP2C8
- A Warning regarding ALT elevations including recommendations to discontinue ethinyl-estradiol containing medications and perform hepatic laboratory testing on all patients during the first 4 weeks of treatment.
- A Medication Guide is included (see Section 8).

13. Decision/Action/Risk Benefit Assessment

Regulatory Action: I concur with the conclusion of the review team and recommend approval of Viekira Pak with or without ribavirin for the treatment of HCV (genotype 1) infection, including patients with compensated cirrhosis.

Risk Benefit Assessment: Viekira Pak with or without ribavirin is the second approved all-oral regimen for the treatment of genotype 1 HCV infection. The high SVR rates observed in both non-cirrhotic and cirrhotic patients regardless of genotype represent a major therapeutic advance compared with previously approved regimens requiring both interferon and ribavirin. The large number of clinical trials submitted provide substantial evidence of efficacy and provide sufficient information to optimize the treatment regimen and duration of therapy recommended for patients based on genotype and the presence or absence of cirrhosis. The overall safety profile was acceptable and the risks identified can be mitigated through labeling including a Medication Guide.

Recommendations for Post-marketing Risk Evaluation and Mitigation Strategies: None

Recommendation for Post-marketing Requirements:

> Evaluate the pharmacokinetics, safety and treatment response (using sustained virologic response as the primary endpoint) of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) in pediatric subjects 3 to less than 18 years of age with chronic hepatitis C virus infection.
>
> 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).
>
> Conduct the site-directed mutant HCV replicon phenotype analyses described in Section 6 of this Memo.
>
> Submit a final report for ongoing observational 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."

Conduct an observational study to investigate the safety and efficacy of ombitasvir, paritaprevir, ritonavir, dasabuvir (Viekira Pak™) in a sufficient number of Blacks/African Americans with and without cirrhosis compared to whites/Caucasians.

Submit the final 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."

Submit the final 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."

Recommendation for Post-marketing Commitments:

The Applicant has agreed to submit the final report and data sets from nine ongoing or recently completed trials.

The Applicant has agreed to develop a test for (b) (4) with a sensitivity of (b) (4)% in the ombitasvir, paritaprevir, ritonavir drug product tablet for the release and stability specification.

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

/s/

JOHN J FARLEY
12/19/2014