Hepatitis C Clinical Trials Program Overview

VIEKIRA PAK™, (ombitasvir, paritaprevir and ritonavir tablets; dasabuvir tablets) with or without ribavirin (RBV), is indicated for the treatment of adult patients with genotype 1 chronic hepatitis C virus infection, including those with compensated cirrhosis.[1]

LIMITATION OF USE: VIEKIRA PAK is not recommended for use in patients with decompensated liver disease.

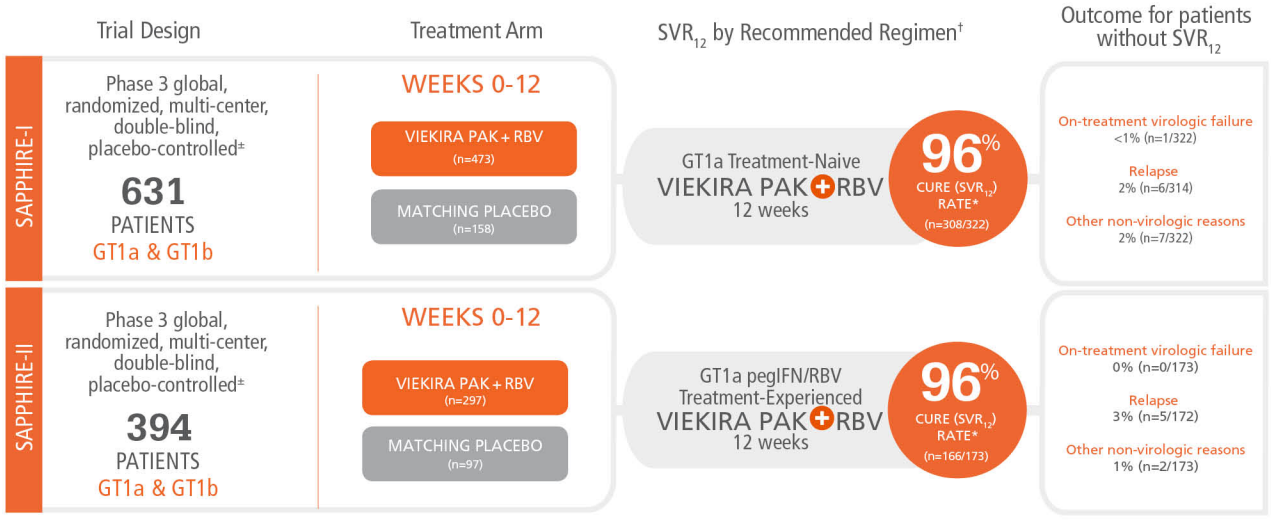
SAFETY CONSIDERATIONS[1]: When VIEKIRA PAK is administered with RBV, the contraindications, warnings and precautions (particularly pregnancy avoidance), and adverse reactions for RBV also apply to this combination regimen. Refer to the RBV prescribing information. VIEKIRA PAK is contraindicated in patients with severe hepatic impairment and in patients with known hypersensitivity to ritonavir. VIEKIRA PAK is contraindicated with certain drugs that are highly dependent on CYP3A for clearance; strong inducers of CYP3A or CYP2C8; and strong inhibitors of CYP2C8. ALT elevations >5x ULN occurred in 1 percent of all subjects and were significantly more frequent in females using ethinyl estradiol-containing medications, which are contraindicated. Perform hepatic lab testing on all patients. HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.[1]

Clinical Trials: VIEKIRA PAK in Chronic Genotype 1 (GT1) Hepatitis C Virus (HCV)

The approval of VIEKIRA PAK is supported by a robust clinical development program designed to study the safety and efficacy of the regimen in more than 2,300 enrolled patients with GT1 HCV across 25 countries. The program consisted of six pivotal Phase 3 studies, which demonstrated that VIEKIRA PAK with or without RBV achieved SVR_{12} in 95-100 percent of GT1a and GT1b hepatitis C patients, when taken according to the recommended dosing regimen and was evaluated in two Phase 2 studies. VIEKIRA PAK was studied in chronic GT1 HCV, including one trial exclusively in patients with cirrhosis with mild hepatic impairment (Child-Pugh A), liver transplant recipients (with normal hepatic function and mild fibrosis) and patients co-infected with HCV and HIV-1.[1]

VIEKIRA PAK with or without Ribavirin (RBV) Clinical Trials Overview

The SAPPHIRE-I and SAPPHIRE-II studies were conducted to evaluate the rate of sustained virologic response (SVR) with VIEKIRA PAK with RBV in adult patients without cirrhosis who were either new to therapy (SAPPHIRE-I) or had failed previous treatment with pegylated interferon (pegIFN) and RBV (SAPPHIRE-II).



* Virologic cure is defined as a sustained virologic response (SVR), which is when the virus is no longer detectable in the patient's blood three months after treatment (SVR_{12}).[2]

† Patients randomized to active treatment received ombitasvir, paritaprevir, ritonavir (25/150/100mg QD) and dasabuvir (250mg BID) +/- RBV (1000 or 1200mg determined by body weight; divided BID).[1]

± For additional study design information for SAPPHIRE-I and SAPPHIRE-II, see page 4.

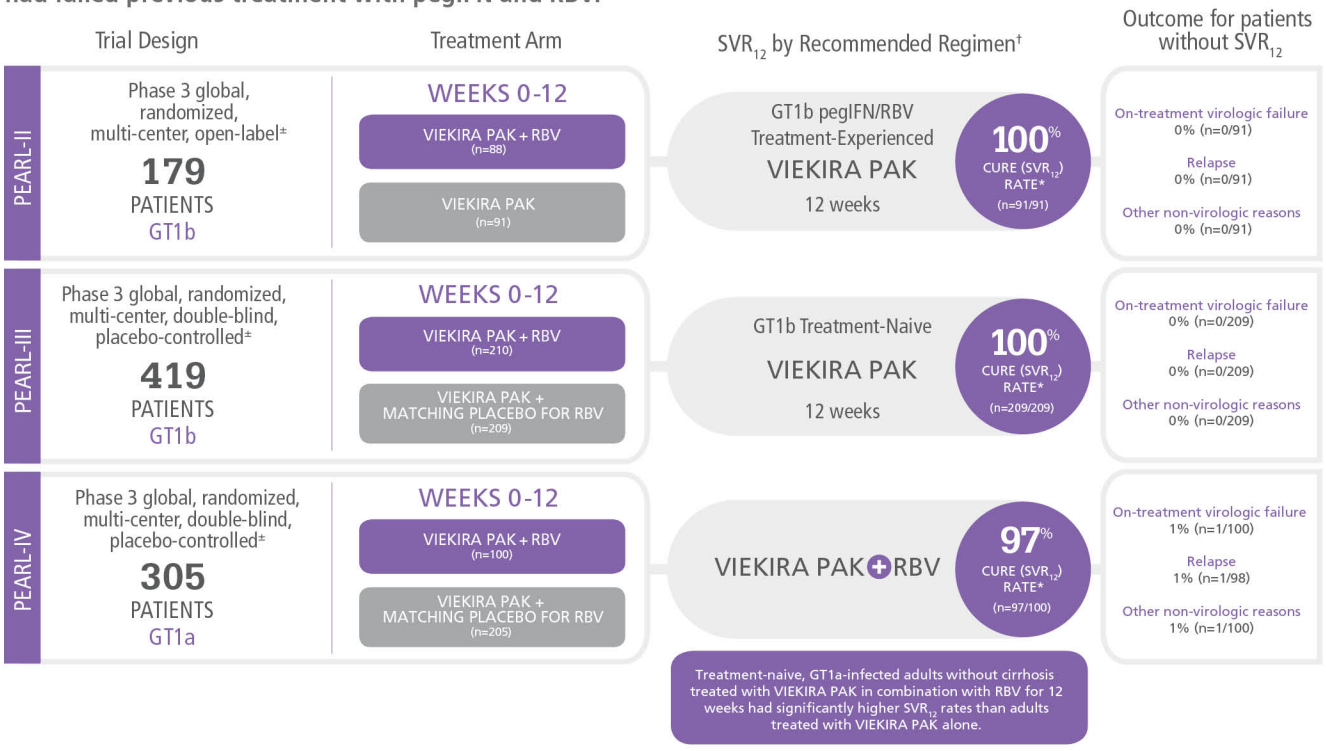
VIEKIRA PAK Important Safety Information

RISKS ASSOCIATED WITH RIBAVIRIN (RBV) COMBINATION TREATMENT

If VIEKIRA PAK is administered with RBV, the contraindications, warnings and precautions (particularly pregnancy avoidance), and adverse reactions for RBV also apply to this combination regimen. Refer to the RBV prescribing information.

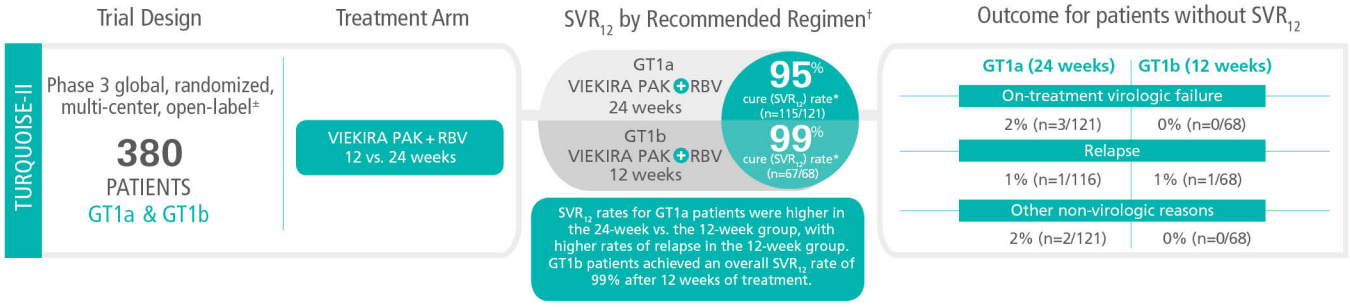
continued on next page

The PEARL-II, PEARL-III, and PEARL-IV studies sought to determine if adults without cirrhosis could be treated with VIEKIRA PAK without the use of RBV. Patients in PEARL-III and PEARL-IV were new to therapy, and patients in PEARL-II had failed previous treatment with pegIFN and RBV.



* Virologic cure is defined as a sustained virologic response (SVR), which is when the virus is no longer detectable in the patient's blood three months after treatment (SVR_{12}).[2]
† Patients randomized to active treatment received ombitasvir, paritaprevir, ritonavir (25/150/100mg QD) and dasabuvir (250mg BID) +/- RBV (1000 or 1200mg determined by body weight; divided BID).[1]
± For additional study design information for PEARL-II, PEARL-III and PEARL-IV, see page 4.

VIEKIRA PAK was studied in a dedicated Phase 3 clinical trial of patients with mild (Child-Pugh A) cirrhosis. The TURQUOISE-II study was conducted to determine the appropriate length of treatment for those patients (12 or 24 weeks).



* Virologic cure is defined as a sustained virologic response (SVR), which is when the virus is no longer detectable in the patient's blood three months after treatment (SVR_{12}).[2]
† Patients randomized to active treatment received ombitasvir, paritaprevir, ritonavir (25/150/100mg QD) and dasabuvir (250mg BID) +/- RBV (1000 or 1200mg determined by body weight; divided BID).[1]
± For additional study design information for TURQUOISE-II, see page 4.

VIEKIRA PAK Important Safety Information (continued)

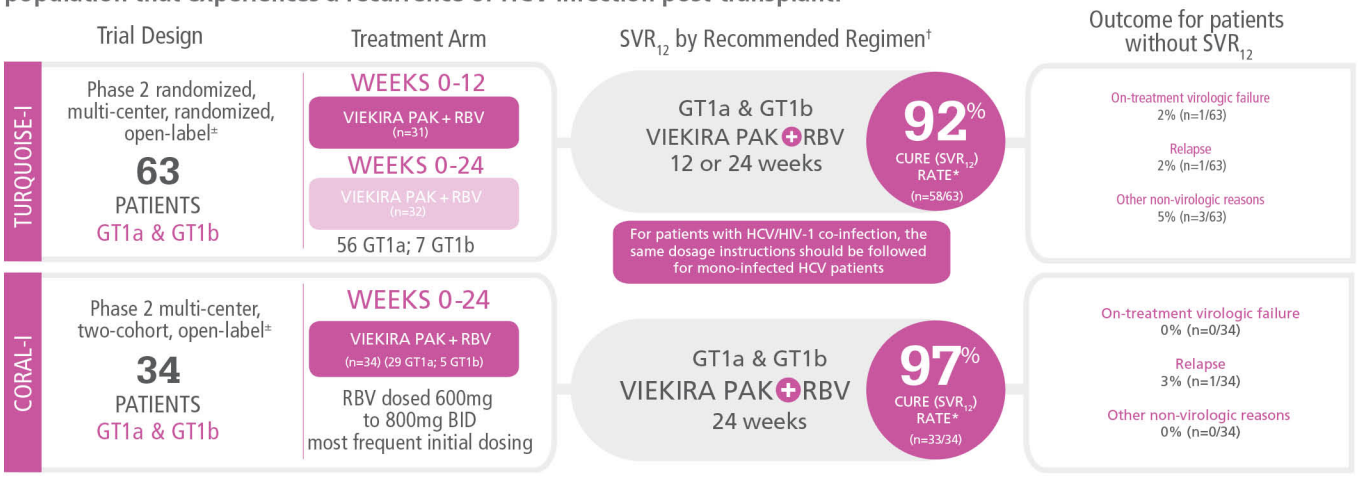
CONTRAINDICATIONS

VIEKIRA PAK is contraindicated:

- In patients with severe hepatic impairment due to risk of potential toxicity.
- With drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious and/or life-threatening events; strong inducers of CYP3A or CYP2C8, which may lead to reduced efficacy of VIEKIRA PAK; and strong CYP2C8 inhibitors, which may increase dasabuvir levels and the risk of QT prolongation.

continued on next page

VIEKIRA PAK + RBV was studied in certain additional patient populations, including chronic GT1a or GT1b HCV patients co-infected with HIV-1, and in patients who had received a liver transplant with normal hepatic function and mild fibrosis. TURQUOISE-I was conducted to evaluate the efficacy and safety of VIEKIRA PAK + RBV in patients with HCV/HIV-1 co-infection. CORAL-I studied the efficacy and safety of VIEKIRA PAK in patients who received liver transplants, a population that experiences a recurrence of HCV infection post-transplant.



* Virologic cure is defined as a sustained virologic response (SVR), which is when the virus is no longer detectable in the patient's blood three months after treatment (SVR_{12}).[2]

† Patients in TURQUOISE-I randomized to active treatment received ombitasvir, paritaprevir, ritonavir (25/150/100mg QD) and dasabuvir (250mg BID) +/- RBV (1000 or 1200mg determined by body weight; divided BID).[1]

± For additional study design information for TURQUOISE-I and CORAL-I, see page 5.

VIEKIRA PAK Clinical Trial Design Summaries

PHASE 2 AND 3 STUDY BACKGROUND INFORMATION

SAFETY ASSESSMENTS adverse events were assessed at each study visit and were collected from the start of study drug administration until 30 days after last dose.[3-7]

HEPATITIS C VIRUS (HCV) RIBONUCLEIC ACID (RNA) MEASUREMENT plasma HCV RNA levels were measured using an assay with a lower limit of detection (LLOD) 15 IU/mL and the lower limit of quantification (LLOQ) of 25 IU/mL.[3-7]

ON-TREATMENT VIROLOGIC FAILURE was defined as confirmed HCV RNA ≥25 IU/mL after HCV RNA <25 IU/mL during treatment, confirmed >1 $\log_{10}$ IU/mL increase in HCV RNA from nadir or HCV RNA persistently ≥25 IU/mL with at least six weeks of treatment.[1]

POST-TREATMENT RELAPSE was defined as confirmed HCV RNA ≥25 IU/mL between the final visit during the treatment period and 12 weeks after the last dose of study drug, for patients assigned to 12 or 24 weeks of treatment, respectively.[1]

TREATMENT NAIVE PATIENTS were defined as not having received any prior therapy for HCV infection.[1]

TREATMENT-EXPERIENCED PATIENTS were defined as either: prior relapsers, prior partial responders or prior null responders to pegylated interferon/ribavirin (pegIFN/RBV) treatment.[1]

VIEKIRA PAK Important Safety Information (continued)

- With the following drugs: alfuzosin HCL; carbamazepine, phenytoin, phenobarbital; gemfibrozil; rifampin; ergotamine, dihydroergotamine, ergonovine, methylergonovine; ethinyl estradiol-containing medicines, such as many oral contraceptives; St. John's wort (Hypericum perforatum); lovastatin, simvastatin; pimozide; efavirenz; sildenafil (when dosed as Revatio* for pulmonary arterial hypertension); triazolam and oral midazolam.
- In patients with known hypersensitivity (e.g., toxic epidermal necrolysis or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations:

- Elevations of ALT to >5x the ULN occurred in 1 percent of all subjects in clinical trials and were significantly more frequent in females using ethinyl estradiol-containing medications. In female patients, discontinue ethinyl estradiol-containing medications prior to starting therapy and use alternative methods of contraception during therapy (e.g., progestin only or non-hormonal contraception). Use caution when co-administering VIEKIRA PAK with estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens.
- Perform hepatic lab testing on all patients during the first 4 weeks of treatment and as clinically indicated thereafter. If ALT is elevated above baseline levels, repeat testing and monitor closely. Patients should be instructed to consult their doctor 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 >10x 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.

continued on next page

VIEKIRA PAK Clinical Trial Design Summaries

NON-CIRRHOTIC PHASE 3 TRIALS

The clinical trial program included five randomized, global, multi-center Phase 3 trials conducted to evaluate the safety and efficacy of VIEKIRA PAK +/- RBV in different non-cirrhotic patient populations described below. In each study, RBV dose adjustments were performed according to the RBV labeling.[1]

SAPPHIRE-I was a placebo-controlled trial of VIEKIRA PAK + RBV in treatment-naive non-cirrhotic adults, 18 to 70 years of age, with genotype 1a or genotype 1b (GT1a or GT1b) chronic HCV infection. Exclusion criteria included: hepatitis B virus (HBV) or human immunodeficiency virus (HIV) co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. Patients were randomized in a 3:1 ratio to 12 weeks of treatment with VIEKIRA PAK + RBV (n=473) or matching placebos (n=158). Primary endpoint: SVR_{12} for patients initially randomized to active treatment. Secondary efficacy endpoints included SVR_{12} according to HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse. Patients randomized to the placebo arm for the first 12 weeks then received open-label VIEKIRA PAK + RBV for the subsequent 12 weeks.[1,3]

SAPPHIRE-II was a placebo-controlled trial of VIEKIRA PAK + RBV in treatment-experienced non-cirrhotic adults, 18 to 70 years of age, with GT1a or GT1b chronic HCV infection. Exclusion criteria included: prior failed triple therapy with pegIFN/RBV + a protease inhibitor, HBV or HIV co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. Patients were randomized in a 3:1 ratio to 12 weeks of treatment with VIEKIRA PAK + RBV (n=297) or matching placebos (n=97). Primary endpoint: SVR_{12} for patients initially randomized to active treatment. Secondary efficacy endpoints included SVR_{12} according to HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse. Patients randomized to the placebo arm for the first 12 weeks then received open-label VIEKIRA PAK + RBV for the subsequent 12 weeks.[1,4]

PEARL-II was an open-label trial of VIEKIRA PAK +/- RBV in treatment-experienced non-cirrhotic adults, 18 to 70 years of age, with GT1b chronic HCV infection. Exclusion criteria included: prior failed triple therapy with pegIFN/RBV + a protease inhibitor, HBV or HIV co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. Patients were randomized in a 1:1 ratio to 12 weeks of treatment with VIEKIRA PAK + RBV or VIEKIRA PAK alone, of which 88 and 91 patients were included in the intent-to-treat efficacy population, respectively. Primary endpoint: SVR_{12}. Secondary efficacy endpoints included assessing the non-inferiority of VIEKIRA PAK without RBV to VIEKIRA PAK + RBV, virologic failure during treatment, and post-treatment relapse.[1,5]

PEARL-III was a controlled trial of VIEKIRA PAK +/- RBV in treatment-naive non-cirrhotic adults, 18 to 70 years of age, with GT1b chronic HCV infection. Exclusion criteria included: HBV or HIV co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. Patients were randomized in a 1:1 ratio to 12 weeks of treatment with VIEKIRA PAK + RBV (n=210) or VIEKIRA PAK + matching placebo for RBV (n=209). Primary endpoint: SVR_{12}. Secondary efficacy endpoints included assessing the non-inferiority of VIEKIRA PAK without RBV to VIEKIRA PAK + RBV, virologic failure during treatment, and post-treatment relapse.[1,6]

PEARL-IV was a controlled trial of VIEKIRA PAK +/- RBV in treatment-naive non-cirrhotic adults, 18 to 70 years of age, with GT1a chronic HCV infection. Exclusion criteria included: HBV or HIV co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. Patients were randomized in a 1:2 ratio to 12 weeks of treatment with VIEKIRA PAK + RBV (n=100) or VIEKIRA PAK + matching placebo for RBV (n=205). Primary endpoint: SVR_{12}. Secondary efficacy endpoints included assessing the non-inferiority of VIEKIRA PAK without RBV to VIEKIRA PAK + RBV, virologic failure during treatment, and post-treatment relapse.[1,7]

CIRRHOTIC PHASE 3 TRIAL

TURQUOISE-II was a randomized, global, multi-center, open-label Phase 3 trial conducted to evaluate the safety and efficacy of VIEKIRA PAK + RBV exclusively in treatment-experienced or treatment-naïve adults with compensated cirrhosis (Child-Pugh A), 18 to 70 years of age, with GT1a or GT1b chronic HCV infection. Eligible patients had documentation of cirrhosis by means of liver biopsy (Metavir score >3 or Ishak score >4) or FibroScan result (≥14.6 kPa within six months before screening or during screening), a Child-Pugh Class A score of <7 at screening, and no current or past clinical evidence of Child-Pugh Class B or C disease. Key eligibility criteria were a platelet count ≥60,000/mm^3, a serum albumin level ≥2.8 g/dL, a total bilirubin level <3 mg/dL, an INR ≤2.3, and a serum alpha-fetoprotein level ≤100 ng/mL. Exclusion criteria included: patients with prior failed therapy with a treatment regimen that included VIEKIRA PAK or other direct-acting antiviral agents, HBV or HIV co-infection, a recent history of drug or alcohol abuse, or hepatocellular carcinoma. Patients were randomly assigned in a ratio of approximately 1:1 to 12 weeks (n=208) or 24 weeks (n=172) of treatment with VIEKIRA PAK + RBV and stratified based on whether or not they received previous pegIFN/RBV treatment. RBV dose adjustments were performed according to the RBV labeling. Primary endpoint: SVR_{12}. The key secondary efficacy endpoint was the percentage of patients with a SVR_{12} in the 24-week group as compared with the 12-week group. Other secondary efficacy endpoints included SVR_{12} according to HCV genotype (1a or 1b), virologic failure during treatment, and post-treatment relapse.[1,7]

PHASE 2 STUDIES

TURQUOISE-I was an open-label clinical trial conducted to evaluate the safety and efficacy of 12 or 24 weeks of treatment with VIEKIRA PAK + RBV in 63 patients co-infected with GT1 HCV and HIV-1. Patients were on a stable HIV-1 antiretroviral treatment (ART) regimen that included tenofovir disoproxil fumarate plus emtricitabine or lamivudine, administered with ritonavir boosted atazanavir or raltegravir. Patients on atazanavir stopped the ritonavir component of their HIV-1 ART regimen upon initiating treatment with VIEKIRA PAK + RBV. Atazanavir was taken with the morning dose of VIEKIRA PAK. The ritonavir component of the HIV-1 ART regimen was restarted after completion of treatment with VIEKIRA PAK + RBV.[1]

CORAL-I was an open-label study conducted to evaluate the safety and efficacy of VIEKIRA PAK + RBV in 34 liver transplant recipients who were ≥12 months post-transplantation with recurrent HCV GT1-infection. All patients had not received treatment for HCV after transplantation and had normal hepatic function and a Metavir fibrosis score of F2 or lower. All patients were taking a stable immunosuppressant regimen based on either tacrolimus or cyclosporine. Exclusion criteria included: use of everolimus or sirolimus within two months of screening visit, HBV or HIV co-infection, a recent history of drug or alcohol abuse, and use of specified concomitant medications, including those contraindicated for use with RBV and ritonavir. All patients received 24 weeks of treatment with VIEKIRA PAK + RBV. Primary endpoint: SVR_{12}. Secondary assessments included the percentage of patients with a SVR at post-treatment week 24, virologic failure during

VIEKIRA PAK Important Safety Information

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions:

- The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK and possible development of resistance, or adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

HCV/HIV-1 Co-infected Patients: Risk of HIV-1 Protease Inhibitor Drug Resistance:

- The ritonavir component of VIEKIRA PAK is an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance. To reduce this risk, HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.

ADVERSE REACTIONS

In subjects receiving VIEKIRA PAK with RBV, the most commonly reported adverse reactions (>10 percent of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. In subjects receiving VIEKIRA PAK without RBV, the most commonly reported adverse reactions (≥5 percent of subjects) were nausea, pruritus, and insomnia.

**Revatio® is a trademark of its respective owner and not a trademark of AbbVie Inc. The makers of this brand are not affiliated with and do not endorse AbbVie Inc. or its products.

VIEKIRA PAK Important Safety Information

RISKS ASSOCIATED WITH RIBAVIRIN (RBV) COMBINATION TREATMENT

If VIEKIRA PAK is administered with RBV, the contraindications, warnings and precautions (particularly pregnancy avoidance), and adverse reactions for RBV also apply to this combination regimen. Refer to the RBV prescribing information.

CONTRAINDICATIONS

VIEKIRA PAK is contraindicated:

- In patients with severe hepatic impairment due to risk of potential toxicity.
- With drugs that are highly dependent on CYP3A for clearance and for which elevated plasma levels are associated with serious and/or life-threatening events; strong inducers of CYP3A or CYP2C8, which may lead to reduced efficacy of VIEKIRA PAK; and strong CYP2C8 inhibitors, which may increase dasabuvir levels and the risk of QT prolongation.
- With the following drugs: alfuzosin HCL; carbamazepine, phenytoin, phenobarbital; gemfibrozil; rifampin; ergotamine, dihydroergotamine, ergonovine, methylergonovine; ethinyl estradiol-containing medicines, such as many oral contraceptives; St. John's wort (Hypericum perforatum); lovastatin, simvastatin; pimozide; efavirenz; sildenafil (when dosed as Revatio* for pulmonary arterial hypertension); triazolam and oral midazolam.
- In patients with known hypersensitivity (e.g., toxic epidermal necrolysis or Stevens-Johnson syndrome) to ritonavir.

WARNINGS AND PRECAUTIONS

Increased Risk of ALT Elevations:

- Elevations of ALT to >5x the ULN occurred in 1 percent of all subjects in clinical trials and were significantly more frequent in females using ethinyl estradiol-containing medications. In female patients, discontinue ethinyl estradiol-containing medications prior to starting therapy and use alternative methods of contraception during therapy (e.g., progestin only or non-hormonal contraception). Use caution when co-administering VIEKIRA PAK with estrogens other than ethinyl estradiol, such as estradiol and conjugated estrogens.
- Perform hepatic lab testing on all patients during the first 4 weeks of treatment and as clinically indicated thereafter. If ALT is elevated above baseline levels, repeat testing and monitor closely. Patients should be instructed to consult their doctor 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 >10x 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.

Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions:

- The concomitant use of VIEKIRA PAK and certain other drugs may result in known or potentially significant drug interactions, some of which may lead to loss of therapeutic effect of VIEKIRA PAK and possible development of resistance, or adverse reactions from greater exposures of concomitant drugs or components of VIEKIRA PAK.

HCV/HIV-1 Co-infected Patients: Risk of HIV-1 Protease Inhibitor Drug Resistance:

- The ritonavir component of VIEKIRA PAK is an HIV-1 protease inhibitor and can select for HIV-1 protease inhibitor resistance. To reduce this risk, HCV/HIV-1 co-infected patients should also be on a suppressive antiretroviral drug regimen.

ADVERSE REACTIONS

In subjects receiving VIEKIRA PAK with RBV, the most commonly reported adverse reactions (>10 percent of subjects) were fatigue, nausea, pruritus, other skin reactions, insomnia, and asthenia. In subjects receiving VIEKIRA PAK without RBV, the most commonly reported adverse reactions (≥5 percent of subjects) were nausea, pruritus, and insomnia.

** Revatio® is a trademark of its respective owner and not a trademark of AbbVie Inc. The makers of this brand are not affiliated with and do not endorse AbbVie Inc. or its products.

References

[1] VIEKIRA PAK [package insert]. North Chicago, IL: AbbVie Inc.

[2] European Association for the Study of the Liver. Clinical Practice Guidelines: Management of hepatitis C virus infection. Journal of Hepatology. 2014; vol. 60: 392–420.

[3] Feld JJ, Kowdley KV, Coakley E, et al. Treatment of HCV with ABT-450/r—ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1594-1603 [and supplementary appendix].

[4] Zeuzem S, Jacobson IM, Baykal T, et al. Retreatment of HCV with ABT-450/r—ombitasvir and dasabuvir with ribavirin. N Engl J Med. 2014;370:1604-1614.

[5] Andreone P, Colombo M, Enejosa J, et al. ABT-450, ritonavir, ombitasvir, and dasabuvir achieves 97% and 100% sustained virologic response with or without ribavirin in treatment-experienced patients with HCV genotype 1b infection. Gastroenterology. 2014;147:359-365 [and supplementary appendix].

[6] Ferenci P, Bernstein D, Lalezari J, et al. ABT-450/r—ombitasvir and dasabuvir with or without ribavirin for HCV. N Engl J Med. 2014;370:1983-1992 [and supplementary appendix].

[7] Poordad F, Hezode C, Trinh R, et al. ABT-450/r—ombitasvir and dasabuvir with ribavirin for hepatitis C with cirrhosis. N Engl J Med. 2014;370:1973-1982 [and supplementary Wappendix].

[8] Kwo P, Mantry P, Coakley E, et al. An interferon-free antiviral regimen for HCV after liver transplantation. N Engl J Med. 2014; 1-8. doi: 10.1056/NEJMoa1408921.