DATA SHEET

1. PRODUCT NAME

ZEPATIER® 50mg/100mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 50 mg elbasvir and 100 mg grazoprevir.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ZEPATIER is a fixed-dose combination tablet containing elbasvir and grazoprevir for oral administration.

Beige-coloured, oval-shaped tablet debossed with “770” on one side and plain on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZEPATIER is indicated for the treatment of Chronic Hepatitis C genotypes 1, 3 or 4 infection in adults.

4.2 Dose and method of administration

Dose

ZEPATIER is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. The recommended dosage of ZEPATIER is one tablet taken orally once daily with or without food.

Treatment regimen and duration of therapy

Table 1 below provides the recommended ZEPATIER treatment regimen and duration based on the patient population and genotype in HCV mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis.

Table 1: Recommended dosage regimens and durations for ZEPATIER for treatment of chronic hepatitis C infection in patients with or without cirrhosis

Treatment[Þ]	**Duration**
Treatment-Naïve or Treatment-Experienced* Relapsers - Genotype 1 or 4	
ZEPATIER	12 weeks *(8 weeks may be considered in treatment-naïve genotype 1b[†] patients without significant fibrosis or cirrhosis[‡])*
Treatment-Experienced* On-Treatment Virologic Failures[§] - Genotype 1 or 4	
Genotype 1b[†] ZEPATIER	 12 weeks
Genotype 1a or 4 ZEPATIER with ribavirin [¶,#]	 16 weeks
Treatment-Naïve - Genotype 3	
ZEPATIER with sofosbuvir	12 weeks

[Þ]Refer to the prescribing information of the medicinal products that are used in combination with ZEPATIER for specific dosing instructions.
*Genotype 1 or 4 patients who have failed treatment with peginterferon alfa + ribavirin or genotype 1 patients who failed peginterferon alfa + ribavirin + boceprevir, simeprevir, or telaprevir.
[†]Includes patients with known genotype 1 subtypes other than 1a or 1b.
[‡]Patients without clinically significant fibrosis or cirrhosis as determined by liver biopsy (i.e., METAVIR F0-F2) or by non-invasive tests.
[§]On-treatment virologic failures are patients who have had a null response, partial response, virologic breakthrough or rebound, or intolerance to prior treatment.
[¶]In clinical trials, the dose of ribavirin was weight-based (<66 kg = 800 mg/day, 66 to 80 kg = 1000 mg/day, 81 to 105 kg = 1200 mg/day, >105 kg = 1400 mg/day) administered in two divided doses with food. For further information on ribavirin dosing and dose modifications, refer to the ribavirin prescribing information.
[#]Patients with severe renal impairment (estimated Glomerular Filtration Rate [eGFR] <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD) should receive ZEPATIER without ribavirin *(See section 4.2)*.

Missed dose

In case a dose of ZEPATIER is missed and it is within 16 hours of the time ZEPATIER is usually taken, the patient should be instructed to take ZEPATIER as soon as possible and then take the next dose of ZEPATIER at the usual time. If more than 16 hours have passed since ZEPATIER is usually taken, then the patient should be instructed that the missed dose should NOT be taken and to take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.

Special populations

Renal impairment

In genotype 1 or 4 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with end stage renal disease (ESRD), including patients on dialysis, administer ZEPATIER without ribavirin according to the treatment duration in Table 1 *(*see section 4.4: *Renal impairment)*. In genotype 1a or 4 patients with severe renal impairment or with ESRD who experienced on treatment-failure during prior peginterferon alfa + ribavirin or interferon only treatment, 12 weeks treatment duration of ZEPATIER may be considered.

The safety and efficacy of ZEPATIER with sofosbuvir in genotype 3 patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with ESRD, including patients on dialysis, have not been established.

Hepatic impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to a lack of clinical safety and efficacy experience in this patient population and the expected increase in grazoprevir plasma concentration. ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to the expected significant increase in grazoprevir plasma concentration *(see section 4.3 and 4.4: Hepatic impairment).*

The safety and efficacy of ZEPATIER have not been established in patients awaiting liver transplant or in liver transplant recipients. The plasma concentration of grazoprevir is increased if ZEPATIER is co-administered with cyclosporine. Co-administration with cyclosporine is contraindicated *(see section 4.3).*

HCV/HBV (hepatitis B virus) co-infection

The safety and efficacy of ZEPATIER have not been studied in HCV/HBV co-infected patients. For dosing recommendations of HBV medicinal products, *see section 4.5 and Table 2: Potentially significant drug interactions.*

Paediatric patients

Safety and efficacy of ZEPATIER have not been established in paediatric patients less than 18 years of age.

Geriatric patients

No dosage adjustment of ZEPATIER is recommended in geriatric patients *(see section 4.4: Use in elderly).*

Method of administration

For oral use.

The film-coated tablets should be swallowed whole and may be taken with or without food (*see section 5.2*)

4.3 Contraindications

- ZEPATIER is contraindicated in patients with known hypersensitivity to elbasvir, grazoprevir, or any of its components (see *section 6.1)*.
- ZEPATIER is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to a lack of clinical safety and efficacy experience in this patient population and the expected increase in grazoprevir plasma concentration. ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) due to the expected significantly increased grazoprevir plasma concentration and the increased risk of alanine aminotransferase (ALT) elevations *(see section 4.4: Hepatic impairment)*.
- ZEPATIER is contraindicated with medicines that inhibit organic anion transporting polypeptide 1B (OATP1B) that are known or expected to significantly increase grazoprevir plasma concentrations, such as atazanavir, darunavir, lopinavir, saquinavir, tipranavir, or cyclosporine, due to the increased risk of ALT elevations *(see section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions and 4.5)*.
- ZEPATIER is contraindicated with medicines that are strong inducers of cytochrome P450 3A (CYP3A), such as phenytoin, carbamazepine, or St. John's Wort *(Hypericum perforatum),* or with efavirenz due to the expected significant decreases in elbasvir and grazoprevir plasma concentrations and the loss of virologic response *(see section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions and 4.5)*.
- ZEPATIER is contraindicated with rifampin because of an initial significant increase in grazoprevir plasma concentration on coadministration (due to OATP1B inhibition), followed by decreases in elbasvir and grazoprevir plasma concentrations during continued coadministration (due to strong CYP3A induction).

If ZEPATIER is administered with ribavirin or sofosbuvir, the contraindications to ribavirin or sofosbuvir also apply to this combination regimen. Refer to the ribavirin or sofosbuvir prescribing information for a list of contraindications for ribavirin or sofosbuvir.

4.4 Special warnings and precautions for use

Risk of hepatitis B virus reactivation in patients co-infected with HCV and HBV

Hepatitis B virus (HBV) reactivation has been reported in HCV/HBV co-infected patients who were undergoing or had completed treatment with HCV direct acting antivirals, and who were not receiving HBV antiviral therapy. Some cases have resulted in fulminant hepatitis, hepatic failure and death. Cases have been reported in patients who are hepatitis B surface antigen (HBsAg) positive and also in patients with serologic evidence of resolved HBV infection (i.e., HBsAg negative and hepatitis B core antibody (anti-HBc) positive). HBV reactivation has also been reported in patients receiving certain immunosuppressant or chemotherapeutic agents; the risk of HBV reactivation associated with treatment with HCV direct acting antivirals may be increased in these patients.

HBV reactivation is characterised as an abrupt increase in HBV replication manifesting as a rapid increase in serum HBV DNA level. In patients with resolved HBV infection reappearance of HBsAg can occur. Reactivation of HBV replication may be accompanied by hepatitis, i.e., increase in aminotransferase levels; and, in severe cases, increases in bilirubin levels, liver failure, and death can occur.

Test all patients for evidence of current or prior HBV infection by measuring HBsAg and anti-HBc before initiating HCV treatment with ZEPATIER. In patients with serologic evidence of HBV infection, monitor for clinical and laboratory signs of hepatitis flare or HBV reactivation during HCV treatment with ZEPATIER and during post-treatment follow-up. Initiate appropriate patient management for HBV infection as clinically indicated.

Increased risk of ALT elevations

During clinical trials with ZEPATIER with or without ribavirin, <1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Higher rates of late ALT elevations occurred in females (2% [11/652]), Asians (2% [4/165]), and subjects aged ≥65 years (2% [3/187]) *(see section 4.8)*.

Hepatic laboratory testing should be performed prior to therapy at treatment week 8 and as clinically indicated. For patients receiving 16 weeks of therapy, additional hepatic laboratory testing should be performed at treatment week 12.

- Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discoloured faeces.
- Consider discontinuing ZEPATIER if ALT levels remain persistently greater than 10 times the ULN.
- Discontinue ZEPATIER if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated bilirubin, alkaline phosphatase, or International Normalised Ratio (INR).

Risks associated with ribavirin combination:

If ZEPATIER is administered with ribavirin, the warnings and precautions for ribavirin, including the pregnancy avoidance warning, also apply to this combination regimen. Refer to the ribavirin prescribing information for a list of warnings and precautions for ribavirin.

Risks associated with sofosbuvir combination:

If ZEPATIER is administered with sofosbuvir, the warnings and precautions for sofosbuvir, also apply to this combination regimen. Refer to the sofosbuvir prescribing information for a list of warnings and precautions for sofosbuvir.

Risk of adverse reactions or reduced therapeutic effect due to drug Interactions

OATP1B inhibitors:

Co-administration of ZEPATIER and OATP1B inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations is contraindicated (*see section 4.3 and 4.5*).

Strong CYP3A inducers or efavirenz:

The concomitant use of ZEPATIER and strong CYP3A inducers or efavirenz may significantly decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER. Therefore, the use of ZEPATIER with strong CYP3A inducers or efavirenz is contraindicated *(see section 4.3 and 4.5)*.

Moderate CYP3A inducers:

The concomitant use of ZEPATIER and moderate CYP3A inducers may decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of ZEPATIER. Therefore, the use of ZEPATIER with moderate CYP3A inducers is not recommended *(see section 4.5: Effects of other drugs on ZEPATIER and Table 2)*.

Strong CYP3A inhibitors:

The concomitant use of ZEPATIER and strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended *(see section 4.5: Effects of other drugs on ZEPATIER and Table 2).*

See **Table 2 Potentially significant drug interactions** for steps to prevent or manage these possible and known significant drug interactions, including dosing recommendations *(see section 4.5)*. Consider the potential for drug interactions prior to and during ZEPATIER therapy; review concomitant medications during ZEPATIER therapy; and monitor for the adverse reactions associated with the concomitant drugs *(see section 4.5)*.

If ZEPATIER is co-administered with ribavirin or sofosbuvir, the information for ribavirin or sofosbuvir with regard to contraception, pregnancy testing, pregnancy, breast-feeding, and fertility also applies to this combination regimen (refer to the prescribing information of the co-administered medicinal product for additional information).

Use in the elderly

No overall differences in safety or efficacy were observed between subjects aged 65 years and over and younger subjects, but greater sensitivity of some older individuals cannot be ruled out.

Higher elbasvir and grazoprevir plasma concentrations were observed in subjects aged 65 years and over. No dosage adjustment of ZEPATIER is recommended in geriatric patients.

Genotoxicity

Elbasvir and grazoprevir were not genotoxic in a battery of *in vitro* or *in vivo* assays, including microbial mutagenesis, chromosomal aberration in Chinese Hamster Ovary cells, and in *in vivo* rat micronucleus assays.

If ZEPATIER is administered in a regimen containing ribavirin or sofosbuvir, the information for ribavirin or sofosbuvir on mutagenesis also applies to this combination regimen *(see prescribing information for ribavirin* or sofosbuvir*)*.

Carcinogenicity

Carcinogenicity studies with elbasvir or grazoprevir have not been conducted.

If ZEPATIER is administered in a regimen containing ribavirin or sofosbuvir, the information for ribavirin or sofosbuvir on carcinogenesis also applies to this combination regimen *(see prescribing information for ribavirin or sofosbuvir)*.

Gender

Higher elbasvir and grazoprevir plasma concentrations were observed in females compared to males. No dose adjustment of ZEPATIER is recommended based on gender.

Race

Higher elbasvir and grazoprevir plasma concentrations were observed in Asians compared to Whites. No dose adjustment of ZEPATIER is recommended based on race/ethnicity.

Renal impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild, moderate, or severe renal impairment. No dosage adjustment of ZEPATIER is recommended in patients who are on dialysis (including haemodialysis or peritoneal dialysis).
In patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2) or with ESRD, including patients on dialysis, administer ZEPATIER without ribavirin (see *section 4.2).*

Hepatic impairment

No dosage adjustment of ZEPATIER is recommended in patients with mild hepatic impairment (Child-Pugh A). ZEPATIER is contraindicated in patients with moderate hepatic impairment (Child-Pugh B) due to a lack of clinical safety and efficacy experience in this population and the expected increase in grazoprevir exposure of 5-fold. ZEPATIER is contraindicated in patients with severe hepatic impairment (Child-Pugh C) based on the expected significant increase in grazoprevir exposure of approximately 12-fold (see *section 4.2 and 4.3).*

Other HCV genotypes

The efficacy of ZEPATIER has not been established in patients infected with HCV genotypes 2, 5 and 6 (see *section 4.1).*

Paediatric population

Safety and efficacy of ZEPATIER have not been established in paediatric patients less than 18 years of age.

4.5 Interaction with other medicines and other forms of interaction

See *section 4.3 and 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions*.

As ZEPATIER contains elbasvir and grazoprevir, interactions that have been identified with these agents individually may occur with ZEPATIER (*see section 5.2: Drug Interaction Studies*).

Effects of other drugs on ZEPATIER

Grazoprevir is a substrate of OATP1B drug transporters. Co-administration of ZEPATIER with OATP1B inhibitors that are known or expected to significantly increase grazoprevir plasma concentrations is contraindicated *(see section 4.3).*

Elbasvir and grazoprevir are substrates of CYP3A and P-gp. Co-administration of strong inducers of CYP3A or efavirenz with ZEPATIER may significantly decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of ZEPATIER with strong CYP3A inducers or efavirenz is contraindicated *(see section 4.3).*

Co-administration of moderate inducers of CYP3A with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of ZEPATIER with moderate CYP3A inducers is not recommended *(see section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions and Table 2)*.

Co-administration of ZEPATIER with strong CYP3A inhibitors increases elbasvir and grazoprevir plasma concentrations. Co-administration of ZEPATIER with certain strong CYP3A inhibitors is not recommended (see *section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions and Table 2)*. Co-administration of ZEPATIER with P-gp inhibitors is expected to have a minimal effect on the plasma concentrations of ZEPATIER.

Effects of ZEPATIER on other drugs

Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates. Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak, but not clinically relevant, CYP3A inhibitor in humans. Therefore, no dose adjustment is required for CYP3A substrates when co-administered with ZEPATIER.

Elbasvir has minimal intestinal P-gp inhibition in humans and grazoprevir is not a P-gp inhibitor in vitro. Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER. Elbasvir and grazoprevir are not OATP1B inhibitors in humans. Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, esterases (CES1, CES2, and CatA), organic anion transporters (OAT)1 and OAT3, and organic cation transporter (OCT)2 are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolised by CYP isoforms based on *in vitro* data.

As liver function may change during treatment with ZEPATIER, a close monitoring of INR values is recommended in patients treated with vitamin K antagonists.

Established and other potential drug interactions

If dose adjustments of concomitant medications are made due to treatment with ZEPATIER, doses should be readjusted after administration of ZEPATIER is completed.

Table 2 provides a listing of established or potentially clinically significant drug interactions. The drug interactions described are based on studies conducted with either ZEPATIER, the components of ZEPATIER (elbasvir [EBR] and grazoprevir [GZR]) as individual agents, or are predicted drug interactions that may occur with ZEPATIER *(see section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions)*.

Table 2: Potentially significant drug interactions: Alteration in dose may be recommended based on results from drug interaction studies or predicted interactions*

Concomitant Drug Class: Drug Name	Effect on Concentration†	Clinical Comment
Antibiotic: nafcillin	↓ EBR ↓ GZR	Co-administration of ZEPATIER with nafcillin, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
Antifungals: ketoconazole‡	↑ EBR ↑ GZR	Concomitant use of systemic ketoconazole and ZEPATIER increases grazoprevir exposure and may increase the overall risk of hepatotoxicity; co-administration of ketoconazole is not recommended.
Endothelin Antagonist: bosentan	↓ EBR ↓ GZR	Co-administration of ZEPATIER with bosentan, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
Immunosuppressants: tacrolimus‡	↑ tacrolimus	Co-administration of ZEPATIER with systemic tacrolimus increases the concentrations of tacrolimus. Frequent monitoring of tacrolimus whole blood concentrations, changes in renal function, and tacrolimus-associated adverse events upon the initiation of co-administration is recommended.
HIV Medications:		
etravirine	↓ EBR ↓ GZR	Co-administration of ZEPATIER with etravirine, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.
elvitegravir/cobicistat/ emtricitabine/tenofovir disoproxil fumarate‡ or alafenamide (fixed-dose combination)	↑ GZR ↑ EBR	Co-administration of ZEPATIER with the fixed-dose combination of elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate or alafenamide resulted in or may result in increases in EBR and GZR concentrations. Co-administration with ZEPATIER is not recommended.
HMG-CoA Reductase Inhibitors#:		
atorvastatin‡	↑ atorvastatin	Co-administration of EBR and GZR with atorvastatin increases the concentrations of atorvastatin. The dose of atorvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.#
rosuvastatin‡	↑ rosuvastatin	Co-administration of EBR and GZR with rosuvastatin increases the concentrations of rosuvastatin. The dose of rosuvastatin should not exceed a daily dose of 10 mg when co-administered with ZEPATIER.#
fluvastatin lovastatin simvastatin	↑ fluvastatin ↑ lovastatin ↑ simvastatin	Co-administration of ZEPATIER with these statins has not been studied but may increase the concentrations of these statins. The dose of fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg when co-administered with ZEPATIER.#
Kinase Inhibitor sunitinib	↑ sunitinib	Co-administration of ZEPATIER with sunitinib may increase sunitinib concentrations leading to an increased risk of sunitinib-associated adverse events. Use with caution.
Wakefulness-Promoting Agents: modafinil	↓ EBR ↓ GZR	Co-administration of ZEPATIER with modafinil, a moderate CYP3A inducer, may decrease EBR and GZR concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration is not recommended.

*This table is not all inclusive.
†↓ = decrease, ↑ = increase.
‡These interactions have been studied in healthy adults.

[#]*See section 4.5: Drugs without clinically significant interactions with ZEPATIER* for a list of HMG Co-A reductase inhibitors without clinically relevant interactions with ZEPATIER.

Drugs without clinically significant interactions with ZEPATIER

The interaction between the components of ZEPATIER (elbasvir or grazoprevir) or ZEPATIER and the following drugs were evaluated in clinical studies, and no dose adjustments are needed when ZEPATIER is used with the following drugs individually: acid reducing agents (proton pump inhibitors, H2 blockers, antacids), buprenorphine/naloxone, digoxin, dolutegravir, methadone, mycophenolate mofetil, oral contraceptive pills, phosphate binders, pitavastatin, pravastatin, prednisone, raltegravir, ribavirin, rilpivirine, tenofovir disoproxil fumarate, and sofosbuvir.

No clinically relevant drug-drug interaction is expected when ZEPATIER is co-administered with abacavir, emtricitabine, entecavir, and lamivudine.

4.6 Fertility, pregnancy and lactation

Pregnancy: ZEPATIER (Pregnancy Category B1)

There are no adequate and well-controlled studies with ZEPATIER in pregnant women. No effects on embryo-foetal development were observed in rats or rabbits at elbasvir or grazoprevir exposures higher than exposures in humans at the recommended clinical dose. Because animal reproduction studies are not always predictive of human response, ZEPATIER should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus.

Elbasvir:

No effects on embryo-foetal development or maternal toxicity have been observed in rats or rabbits when dams were administered elbasvir up to the highest dose tested during early embryonic development (rats), organogenesis (rats and rabbits), or perinatal period (rats). In the rat and rabbit, AUC exposure to elbasvir was approximately 9- and 17-fold, respectively, the exposure in humans at the recommended clinical dose. In both species, elbasvir has been shown to cross the placenta.

Grazoprevir:

No effects on embryo-foetal development or maternal toxicity have been observed in rats or rabbits when dams were administered grazoprevir up to the highest dose tested during early embryonic development (rats), organogenesis (rats and rabbits), or perinatal period (rats). In the rat and rabbit, AUC exposure to grazoprevir was approximately 79- and 39-fold, respectively, the exposure in humans at the recommended clinical dose. In both species, grazoprevir has been shown to cross the placenta.

Breast-feeding

There are no human data to assess whether ZEPATIER is excreted in human breast milk. Elbasvir and grazoprevir are excreted in the milk of lactating rats. Concentrations of elbasvir were higher and concentrations of grazoprevir were lower in breast milk than maternal plasma in rats. No effects on postnatal development were observed in nursing rats when lactating dams were exposed to elbasvir or grazoprevir.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for ZEPATIER and any potential adverse effects on the breastfed child from ZEPATIER or from the underlying maternal condition.

Elbasvir:

No effects on postnatal development in nursing rats and no maternal toxicity have been observed when lactating dams were administered elbasvir up to the highest dose tested. AUC exposure to elbasvir was approximately 9-fold the exposure in humans at the recommended clinical dose. Elbasvir has been shown to be excreted into the milk of lactating rats. Elbasvir was excreted into the milk of lactating rats with concentrations 4-fold that of the maternal plasma concentrations.

Grazoprevir:

No effects on postnatal development in nursing rats and no maternal toxicity have been observed when lactating dams were administered grazoprevir up to the highest dose tested. AUC exposure to grazoprevir was approximately 79-fold the exposure in humans at the recommended clinical dose. Grazoprevir has been shown to be excreted into the milk of lactating rats. Grazoprevir was excreted into the milk of lactating rats with concentrations <1-fold of the maternal plasma concentrations.

Fertility

No human data on the effect of elbasvir or grazoprevir on fertility are available. No effects on mating, female or male fertility, or early embryonic development were observed in rats up to the highest dose tested. AUC exposure to elbasvir and grazoprevir was approximately 7- and 108-fold, respectively, the exposure in humans at the recommended clinical dose.

4.7 Effects on ability to drive and use machines

ZEPATIER (administered alone or in combination with ribavirin) is not likely to have an effect on the ability to drive and use machines. Patients should be informed that fatigue has been reported during treatment with ZEPATIER (see *section 4.8)*.

4.8 Undesirable effects

If ZEPATIER is administered with ribavirin or sofosbuvir, refer to the prescribing information for ribavirin or sofosbuvir for a list of ribavirin or sofosbuvir-associated adverse reactions.

Clinical trials experience

Adults

The safety of ZEPATIER was assessed based on 2 placebo-controlled trials and 8 uncontrolled Phase 2 and 3 clinical trials in approximately 2000 subjects with chronic hepatitis C infection with compensated liver disease (with or without cirrhosis).

Adverse reactions in subjects receiving ZEPATIER alone

C-EDGE TN was a Phase 3 placebo-controlled trial in treatment-naïve (TN) subjects. Adverse reactions (adverse events assessed as causally related by the investigator, all grades) occurring in C-EDGE TN at ≥5% frequency in subjects treated with ZEPATIER for 12 weeks are presented in Table 3. No subjects treated with ZEPATIER or placebo had serious adverse reactions. The proportion of subjects treated with ZEPATIER or placebo who permanently discontinued treatment due to adverse reactions was <1% and 1%, respectively.

Adverse reactions occurring in a pooled analysis of Phase 2 and 3 clinical trials at ≥5% frequency in subjects treated with ZEPATIER for 12 weeks are presented in Table 3. The majority of the adverse reactions were mild in severity. No subjects treated with ZEPATIER had serious adverse reactions. The proportion of subjects who permanently discontinued treatment due to adverse reactions was <1%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

Table 3: Adverse reactions occurring at ≥5% frequency in subjects with chronic hepatitis C infection treated with ZEPATIER for 12 weeks in C-EDGE TN or with ZEPATIER for 12 weeks in the pooled phase 2 and 3 clinical trials

	C-EDGE TN		**Pooled***
	ZEPATIER N=316 % (n) 12 weeks	**Placebo N=105 % (n) 12 weeks**	**ZEPATIER N=834 % (n) 12 weeks**
Nervous system disorders			
Headache	10% (31)	9% (9)	10% (86)
Gastrointestinal disorders			
Nausea	4% (14)	5% (5)	5% (43)
General disorders and administration site conditions			
Fatigue	11% (35)	10% (10)	11% (94)

*Includes C-WORTHY, C-SCAPE, C-SALT, C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and P058

The type and severity of adverse reactions were comparable among subjects treated with 8, 12 or 16 weeks of ZEPATIER.

Adverse reactions in subjects receiving ZEPATIER with ribavirin

C-EDGE TE was a Phase 3 open-label trial in treatment-experienced (TE) subjects. Adverse reactions occurring in C-EDGE TE at ≥5% frequency in subjects treated with ZEPATIER with ribavirin for 16 weeks are presented inTable 4. The majority of the adverse reactions were mild in severity. The proportion of subjects treated with ZEPATIER with ribavirin with serious adverse reactions was <1%. The portion of subjects who permanently discontinued treatment due to adverse reactions was 2%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.

Table 4: Adverse reactions occurring at ≥5% frequency in subjects with chronic hepatitis C infection treated with ZEPATIER + ribavirin for 16 weeks in C-EDGE TE

	C-EDGE TE
	ZEPATIER + Ribavirin **N=106** **% (n)** **16 weeks**
Blood and lymphatic system disorders	
Anaemia	16% (17)
Haemoglobin decreased	7% (7)
Psychiatric disorders	
Insomnia	6% (6)
Nervous system disorders	
Headache	17% (18)
Respiratory, thoracic and mediastinal disorders	
Dyspnoea	8% (9)
Dyspnoea exertional	6% (6)
Gastrointestinal disorders	
Nausea	12% (13)
Dyspepsia	6% (6)
Vomiting	6% (6)
Skin and subcutaneous tissue disorders	
Pruritus	9% (10)
Musculoskeletal and connective tissue disorders	
Myalgia	6% (6)
General disorders and administration site conditions	
Fatigue	25% (27)
Asthenia	8% (9)

Laboratory abnormalities in subjects receiving ZEPATIER with or without ribavirin

Serum late ALT elevations

During clinical trials with ZEPATIER with or without ribavirin, regardless of treatment duration, <1% (13/1690) of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8 (mean onset time 10 weeks, range 6-12 weeks). These late ALT elevations were typically asymptomatic. Most late ALT elevations resolved with ongoing therapy with ZEPATIER or after completion of therapy (*see section 4.4: Increased risk of ALT elevations)*. The frequency of late ALT elevations was higher in subjects with higher grazoprevir plasma concentration *(see section 4.5)*. The incidence of late ALT elevations was not affected by treatment duration. Cirrhosis was not a risk factor for late ALT elevations.

Serum bilirubin elevations

During clinical trials with ZEPATIER with or without ribavirin, regardless of treatment duration, elevations in bilirubin at greater than 2.5 times ULN were observed in 6% of subjects receiving ZEPATIER with ribavirin compared to <1% in those receiving ZEPATIER alone. These bilirubin increases were predominately indirect and generally observed in association with ribavirin co-administration. Bilirubin elevations were typically not associated with serum ALT elevations.

Decreased haemoglobin

During clinical trials with ZEPATIER with or without ribavirin, the mean change from baseline in haemoglobin levels in subjects treated with ZEPATIER for 12 weeks was –0.3 g/dL and with ZEPATIER with ribavirin for 16 weeks was approximately –2.2 g/dL. Haemoglobin declined during the first 8 weeks of treatment, remained low during the remainder of treatment, and normalised to baseline levels during follow-up. Less than 1% of subjects treated with ZEPATIER with ribavirin had haemoglobin levels decrease to less than 8.5 g/dL during treatment. No subjects treated with ZEPATIER alone had a haemoglobin level less than 8.5 g/dL.

ZEPATIER in subjects with HCV/HIV-1 co-infection

ZEPATIER and ZEPATIER with ribavirin were assessed in 298 subjects with HCV/HIV-1 co-infection. The type and severity of adverse reactions in subjects with HCV/HIV-1 co-infection were comparable to subjects without HCV/HIV-1 co-infection. Median increase in CD4+ T-cell counts of 32 cells/mm^3 was observed at the end of 12 weeks of treatment with ZEPATIER alone. Median decrease in CD4+ T-cell counts of 135 cells/mm^3 was observed at the end of 16 weeks of treatment with ZEPATIER with ribavirin. No subject experienced an AIDS-related opportunistic infection.

ZEPATIER in subjects with advanced chronic kidney disease

The safety of elbasvir and grazoprevir in comparison to placebo in subjects with advanced chronic kidney disease (CKD) (severe renal impairment or ESRD, including patients on dialysis) and genotype 1 chronic hepatitis C infection with compensated liver disease (with or without cirrhosis) was assessed in 235 subjects (C-SURFER). The adverse reactions occurring at ≥5% frequency in subjects treated with ZEPATIER for 12 weeks are presented in Table 5. The majority of the adverse reactions were mild in severity. The proportion of subjects treated with ZEPATIER or placebo with serious adverse reactions was 0% and <1%, respectively, and 0% and 3% of subjects permanently discontinued treatment due to adverse reactions in each treatment arm.

Table 5: Adverse reactions occurring at ≥5% frequency in subjects with advanced CKD and chronic hepatitis C infection treated with ZEPATIER in C-SURFER

	ZEPATIER N=122 % (n) 12 weeks	**Placebo N=113 % (n) 12 weeks**
Nervous system disorders		
Headache	11% (14)	5% (6)
Gastrointestinal disorders		
Nausea	11% (14)	8% (9)
General disorders and administration site conditions		
Fatigue	5% (6)	8% (9)

Adverse Reactions in Subjects Receiving ZEPATIER with Sofosbuvir

The safety of ZEPATIER with sofosbuvir in treatment-naïve subjects with chronic hepatitis C infection was assessed in 143 subjects (C-SWIFT). No adverse reactions were reported at a greater than 5% frequency. The most commonly reported adverse reactions ≥2% of subjects were nausea (2%) and headache (3%). No subjects treated with ZEPATIER with sofosbuvir had serious adverse reactions and no subjects permanently discontinued treatment due to adverse reactions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions

http://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Human experience of overdose with ZEPATIER is limited. No specific antidote is available for overdose with ZEPATIER. In case of overdose, it is recommended that the patient be monitored for any signs or symptoms of adverse reactions and appropriate symptomatic treatment instituted.

Haemodialysis does not remove elbasvir or grazoprevir since elbasvir and grazoprevir are highly bound to plasma protein.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia) or 0800 764 766 (New Zealand).

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antivirals for systemic use; direct acting antivirals, other antivirals. ATC code: not yet assigned.

Mechanism of action

ZEPATIER is a fixed-dose combination of elbasvir and grazoprevir which are direct-acting antiviral agents against the hepatitis C virus (see *section 5.1: Pharmacodynamic effects, Microbiology, Mechanism of Action*)

Pharmacodynamic effects

Cardiac electrophysiology

Thorough QT studies have been conducted for elbasvir and grazoprevir.

The effect of elbasvir 700 mg on the QTc interval was evaluated in a randomised, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 42 healthy subjects. At a plasma concentration 3 to 4 times the therapeutic plasma concentration, elbasvir does not prolong QTc to any clinically relevant extent.

The effect of grazoprevir 1600 mg on QTc interval was evaluated in a randomised, single-dose, placebo- and active-controlled (moxifloxacin 400 mg) 3-period crossover thorough QT trial in 41 healthy subjects. At a plasma concentration 40 times the therapeutic plasma concentration, grazoprevir does not prolong QTc to any clinically relevant extent.

Microbiology

Mechanism of action

ZEPATIER combines two direct-acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles to target HCV at multiple steps in the viral lifecycle.

Elbasvir is an inhibitor of HCV NS5A, which is essential for viral RNA replication and virion assembly. The mechanism of action of elbasvir has been characterised based on cell culture antiviral activity and drug resistance mapping studies.

Grazoprevir is an inhibitor of the HCV NS3/4A protease which is necessary for the proteolytic cleavage of the HCV encoded polyprotein (into mature forms of the NS3, NS4A, NS4B, NS5A, and NS5B proteins) and is essential for viral replication. In a biochemical assay, grazoprevir inhibited the proteolytic activity of the recombinant NS3/4A protease enzymes from HCV genotypes 1a, 1b, 2, 3, 4, 5, and 6, with IC_{50} values ranging from 4 to 690 pM.

Antiviral activity

In HCV replicon assays, the EC_{50} values of elbasvir against full-length replicons from genotypes 1a, 1b, 2a, 3a, 4, 5, and chimeric replicons from genotype 6, were 0.004 nM, 0.003 nM, 0.003 nM, 0.14 nM, 0.0003 nM, 0.001 nM, and 0.009 nM, respectively. The median EC_{50} values of elbasvir against chimeric replicons encoding NS5A sequences from clinical isolates were 0.005 nM for genotype 1a (range 0.003-0.009 nM; N=5), 0.009 nM for genotype 1b (range 0.005-0.010 nM; N=4), 1.85 nM for genotype 2 (range 0.003-20 nM; N=6), 0.02 nM for genotype 3a (range 0.01-0.33 nM; N=9), 0.0007 nM for genotype 4 (range 0.0002-34 nM; N=14), 0.0007 nM for genotype 5 (range 0.0004-43 nM; N=11), and 0.016 nM for genotype 6 (range 0.002-2.7 nM; N=11).

In HCV replicon assays, the EC_{50} values of grazoprevir against full-length replicons from genotypes 1a, 1b, 2, 3, 4, and 5, and chimeric replicons from genotype 6, were 0.4 nM, 0.5 nM, 2.3 nM, 35 nM, 0.3 nM, 1.5 nM, and 0.9 nM, respectively.

The median EC_{50} values of grazoprevir against chimeric replicons encoding NS3/4A sequences from clinical isolates were 0.8 nM for genotype 1a (range 0.4-5.1 nM; N=10), 0.3 nM for genotype 1b (range 0.2-5.9 nM; N=9), 2.9 nM for genotype 2 (range 2.3-3.7 nM; N=3), 5.85 nM for genotype 3 (range 2.1-7.6 nM; N=6), 0.2 nM for genotype 4 (range 0.11-0.33 nM; N=5), 1.5 nM for genotype 5 (range 0.4-6.6 nM; N=5), and 0.2 nM for genotype 6 (range 0.1-0.9 nM; N=9).

Evaluation of elbasvir in combination with grazoprevir, ribavirin, or sofosbuvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells. Evaluation of grazoprevir in combination with ribavirin or sofosbuvir showed no antagonistic effect in reducing HCV RNA levels in replicon cells.

Resistance

In cell culture

HCV replicons with reduced susceptibility to elbasvir and grazoprevir have been selected in cell culture for genotypes 1a, 1b, 3 and 4.

For elbasvir, in HCV genotype 1a replicons, single NS5A substitutions Q30D/E/H/R, L31M/V and Y93C/H/N reduced elbasvir antiviral activity by 6- to 2000-fold. In genotype 1b replicons, single NS5A substitutions L31F and Y93H reduced elbasvir antiviral activity by 17-fold. In genotype 3 replicons, single NS5A substitution Y93H reduced elbasvir antiviral activity by 485-fold. In genotype 4 replicons, single NS5A substitutions L30S, M31V, and Y93H reduced elbasvir antiviral activity by 3- to 23-fold. In general, in HCV genotype 1a, 1b or 4 replicons, combinations of elbasvir resistance-associated substitutions further reduced elbasvir antiviral activity.

For grazoprevir, in HCV genotype 1a replicons, single NS3 substitutions D168A/E/G/S/V reduced grazoprevir antiviral activity by 2- to 81-fold. In genotype 1b replicons, single NS3 substitutions F43S, A156S/T/V, and D168A/G/V reduced grazoprevir antiviral activity by 2- to 375-fold. In genotype 3 replicons, single NS3 substitutions N77S, V163I, Q168R and Q178R reduced grazoprevir antiviral activity by 3- to 7-fold. In genotype 4 replicons, single NS3 substitutions D168A/V reduced grazoprevir antiviral activity by 110- to 320-fold. In general, in

HCV genotype 1a, 1b or 4 replicons, combinations of grazoprevir resistance-associated substitutions further reduced grazoprevir antiviral activity.

In clinical studies

In a pooled analysis of genotype 1 or 4 subjects treated with regimens containing ZEPATIER or elbasvir + grazoprevir with or without ribavirin in Phase 2 and 3 clinical trials, resistance analyses were conducted for 50 subjects who experienced virologic failure and had sequence data available (6 with on-treatment virologic failure, 44 with post-treatment relapse).

Treatment-emergent substitutions observed in the viral populations of these subjects based on genotypes are shown in Table 6. Treatment-emergent substitutions were detected in both HCV drug targets in 23/37 (62%) genotype 1a, 1/8 (13%) genotype 1b and 2/5 (40%) genotype 4 subjects.

Table 6: Treatment-emergent amino acid substitutions in the pooled analysis of ZEPATIER with and without ribavirin regimens in phase 2 and phase 3 clinical trials

Target	**Emergent Amino Acid Substitutions**	**Genotype 1a N = 37 % (n)**	**Genotype 1b N = 8 % (n)**	**Genotype 4 N = 5 % (n)**	
NS5A	Any of the following NS5A substitutions: M/L28A/G/T/S* Q30H/K/R/Y, L/M31F/M/I/V, H/P58D, Y93H/N/S	81% (30)	88% (7)	100% (5)	
	M/L28A/G/T/S	19% (7)	13% (1)	60% (3)	
	Q30H/K/Y	14% (5)	--	--	
	Q30R	46% (17)	--	--	
	L/M31M/F/I/V[†]	11% (4)	25% (2)	40% (2)	
	H/P58D[‡]	5% (3)	--	20% (1)	
	Y93H/N/S	14% (5)	63% (5)	20% (1)	
NS3	Any of the following NS3 substitutions: V36L/M, Y56F/H, V107I, R155I/K, A156G/M/T/V, V158A, D168A/C/E/G/N/V/Y, V170I	78% (29)	25% (2)	40% (2)	
	V36L/M	11% (4)	--	--	
	Y56F/H	14% (5)	13% (1)	--	
	V107I	3% (1)	13% (1)	--	
	R155I/K	5% (2)	--	--	
	A156T	27% (10)	13% (1)	20% (1)	
	A156G/V/M	8% (3)	--	60% (3)	
	V158A	5% (2)	--	--	
	D168A	35% (13)	--	20% (1)	
	D168C/E/G/N/V/Y	14% (5)	--	20% (1)	

	V170I	--	--	20% (1)	

*Reference sequences for NS5A at amino acid 28 are M (genotype 1a) and L (genotype 1b and genotype 4a and 4d).
†Reference sequences for NS5A at amino acid 31 are L (genotype 1a and genotype 1b) and M (genotype 4a and 4d).
‡Reference sequences for NS5A at amino acid 58 are H (genotype 1a) and P (genotype 1b and genotype 4a and 4d).

In an analysis of genotype 3 subjects treated with ZEPATIER and sofosbuvir for 12 weeks in a Phase 2 clinical study, one subject experienced relapse. This subject had a treatment-emergent NS5A Y93H substitution.

***In vitro* cross resistance**

Elbasvir is active *in vitro* against genotype 1a NS5A substitutions, M28V and Q30L, genotype 1b substitutions, L28M/V, R30Q, L31V, Y93C, and genotype 4 substitution, M31V which confer resistance to other NS5A inhibitors. In general, other NS5A substitutions conferring resistance to NS5A inhibitors may also confer resistance to elbasvir. NS5A substitutions conferring resistance to elbasvir may reduce the antiviral activity of other NS5A inhibitors. Elbasvir is fully active against substitutions conferring resistance to NS3/4A protease inhibitors.

Grazoprevir is active *in vitro* against the following genotype 1a NS3 substitutions which confer resistance to other NS3/4A protease inhibitors: V36A/L/M, Q41R, F43L, T54A/S, V55A/I, Y56F, Q80K/R, V107I, S122A/G/R/T, I132V, R155K, A156S, D168N/S, I170T/V. Grazoprevir is active *in vitro* against the following genotype 1b NS3 substitutions conferring resistance to other NS3/4A protease inhibitors: V36A/I/L/M, Q41L/R, F43S, T54A/C/G/S, V55A/I, Y56F, Q80L/R, V107I, S122A/G/R, R155E/K/N/Q/S, A156G/S, D168E/N/S, V170A/I/T. Some NS3 substitutions at A156 and at D168 confer reduced antiviral activity to grazoprevir as well as to other NS3/4A protease inhibitors. Grazoprevir is fully active against resistance-associated variants selected by NS5A inhibitors.

The substitutions associated with resistance to NS5B inhibitors are susceptible to elbasvir or grazoprevir.

Persistence of resistance-associated substitutions

The persistence of elbasvir and grazoprevir treatment-emergent amino acid substitutions in NS5A and NS3 respectively, was assessed in genotype 1-infected subjects in Phase 2 and 3 trials whose virus had treatment-emergent resistance-associated substitution in the drug target, and with available data through at least 24 weeks post-treatment.

Treatment-emergent NS5A resistance-associated substitutions were generally more persistent than NS3 resistance-associated substitutions. Among genotype 1-infected subjects who had one or more treatment-emergent NS5A resistance-associated substitutions, these substitutions became undetectable at follow-up week 12 in only 5% (2/44) of subjects and 0% (0/12) of subjects with follow-up week 24 data.

Among genotype 1-infected subjects with treatment-emergent NS3 resistance-associated substitutions, these substitutions became undetectable at follow-up week 24 in 67% (10/15) of subjects based on population sequencing.

Due to the limited number of genotype 3- and 4-infected subjects with treatment-emergent NS5A and NS3 resistance-associated substitutions, trends in persistence of treatment-emergent substitutions in these genotypes could not be established.

Effect of baseline HCV polymorphisms on treatment response

Analyses in Phase 2 and 3 clinical studies of ZEPATIER, or elbasvir + grazoprevir, with or without ribavirin were conducted to explore the association between baseline NS5A and/or NS3 polymorphisms and treatment response among subjects who achieved SVR or experienced

virologic failure (*see section 5.3)* and for whom baseline sequences were available. Baseline NS5A polymorphism at position 28, 30, 31, 58, and 93 were evaluated. Compared to a reference HCV genotype 1a replicon, the following NS5A substitutions reduced elbasvir antiviral activity by greater than 5-fold: M28T/A, Q30E/H/R/G/K/D, L31M/V/F, H58D, and Y93C/H/N. Baseline NS3 polymorphisms at position 36, 54, 55, 56, 80, 107, 122, 132, 155, 156, 158, 168, 170, and 175 were evaluated.

Genotype 1a

In pooled analyses of genotype 1a-infected subjects, baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were identified in 6% (29/491) of treatment-naïve subjects and 8% (26/334) of treatment-experienced subjects. Among treatment-naïve subjects, SVR was achieved in 98% (432/439) of subjects without baseline NS5A polymorphisms and 55% (16/29) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.* Among treatment-experienced subjects, SVR was achieved in 99% (291/295) of subjects without baseline NS5A polymorphisms and 50% (13/26) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms, including Q80K, prior to the start of therapy did not impact treatment response among genotype 1a-infected subjects.

Genotype 1b

In pooled analyses, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve genotype 1b-infected subjects. NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro* were detected in 14% (36/259) of treatment-experienced subjects. SVR was achieved in 100% (223/223) of subjects without baseline NS5A polymorphisms and 86% (31/36) of subjects with baseline NS5A polymorphisms that confer greater than 5-fold reduction of elbasvir antiviral activity *in vitro.*

In pooled analyses, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among genotype 1b-infected subjects.

Genotype 4

In pooled analyses, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among genotype 4-infected subjects.

In pooled analyses, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve, genotype 4-infected subjects. Baseline NS3 polymorphisms were identified by population sequencing in 19% (7/36) of treatment-experienced genotype 4-infected subjects. In these subjects, SVR was achieved in 100% (7/7) of subjects with baseline NS3 polymorphisms compared with 86% (25/29) in those without baseline NS3 polymorphism.

Genotype 3

In a Phase 2 study (C-SWIFT) of ZEPATIER with sofosbuvir, presence of NS5A polymorphisms prior to the start of therapy did not impact treatment response among genotype 3-infected subjects. Baseline NS5A polymorphisms were identified by population sequencing in 12% (3/25) of treatment-naive genotype 3-infected subjects. In these subjects, SVR was achieved in 100% (3/3) of subjects with baseline NS5A polymorphisms compared with 95% (21/22) in those without baseline NS5A polymorphism.

In this analysis, presence of NS3 polymorphisms prior to the start of therapy did not impact treatment response among treatment-naïve, genotype 3-infected subjects.

No subject had NS5B polymorphisms detected at baseline.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of elbasvir and grazoprevir have been evaluated in non-HCV-infected adult subjects and in HCV-infected adult subjects. Elbasvir pharmacokinetics were similar in healthy subjects and HCV-infected subjects and were approximately dose-proportional over the range of 5-100 mg once daily. Grazoprevir oral exposures are approximately 2-fold greater in HCV-infected subjects as compared to healthy subjects. Grazoprevir pharmacokinetics increased in a greater than dose-proportional manner over the range of 10-800 mg once daily in HCV-infected subjects. Ribavirin or sofosbuvir co-administration with ZEPATIER had no clinically relevant impact on plasma AUC and C_{max} of elbasvir and grazoprevir compared to administration of ZEPATIER alone. Based on the population pharmacokinetic modelling in non-cirrhotic, HCV-infected subjects, the geometric mean steady-state elbasvir AUC_{0-24} and C_{max} at 50 mg were 2180 nM•hr and 137 nM, respectively, and the geometric mean steady-state grazoprevir AUC_{0-24} and C_{max} at 100 mg were 1860 nM•hr and 220 nM, respectively. Following once daily administration of ZEPATIER to HCV-infected subjects, elbasvir and grazoprevir reached steady state within approximately 6 days.

Absorption

Following administration of ZEPATIER to HCV-infected subjects, elbasvir peak plasma concentrations occur at a median T_{max} of 3 hours (range of 3 to 6 hours); grazoprevir peak plasma concentrations occur at a median T_{max} of 2 hours (range of 30 minutes to 3 hours). The absolute bioavailability of elbasvir is estimated to be 32%, and grazoprevir is estimated to be 10 to 40%.

Effect of food

Relative to fasting conditions, the administration of a single dose of ZEPATIER with a high-fat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in decreases in elbasvir AUC_{0-inf} and C_{max} of approximately 11% and 15%, respectively, and increases in grazoprevir AUC_{0-inf} and C_{max} of approximately 1.5-fold and 2.8-fold, respectively. These differences in elbasvir and grazoprevir exposure are not clinically relevant; therefore, ZEPATIER may be taken without regard to food.

Distribution

Elbasvir and grazoprevir are extensively bound (>99.9% and 98.8%, respectively) to human plasma proteins. Both elbasvir and grazoprevir bind to human serum albumin and α1-acid glycoprotein. Plasma protein binding is not meaningfully altered in patients with renal or hepatic impairment.

In preclinical distribution studies, elbasvir distributes into most tissues including the liver, whereas grazoprevir distributes predominantly to the liver likely facilitated by active transport through the OATP1B liver uptake transporter.

Metabolism

Elbasvir and grazoprevir are partially eliminated by oxidative metabolism, primarily by CYP3A. No circulating metabolites of either elbasvir or grazoprevir were detected in human plasma.

Excretion

The geometric mean apparent terminal half-life (% geometric mean coefficient of variation) is approximately 24 (24%) hours at 50 mg elbasvir and approximately 31 (34%) hours at 100 mg grazoprevir in HCV-infected subjects. The primary route of elimination of elbasvir and grazoprevir is through faeces with almost all (>90%) of radiolabeled dose recovered in faeces compared to <1% in urine.

Special populations

Renal impairment

The pharmacokinetics of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with severe renal impairment (eGFR <30 mL/min/1.73 m^2) with or without haemodialysis and also in HCV-infected subjects with severe renal impairment with or without haemodialysis.

Relative to non-HCV-infected subjects with normal renal function (eGFR >80 mL/min/1.73 m^2), elbasvir and grazoprevir AUC values were increased by 86% and 65%, respectively, in non-HCV-infected subjects with severe renal impairment who were not on dialysis. Relative to subjects with normal renal function, elbasvir and grazoprevir AUC values were unchanged in non-HCV-infected subjects with dialysis-dependent, severe renal impairment. Elbasvir and grazoprevir are highly bound to plasma protein. Elbasvir and grazoprevir are not removed by haemodialysis. Concentrations of elbasvir were not quantifiable in the dialysate samples. Less than 0.5% of grazoprevir was recovered in dialysate over a 4-hour dialysis session. Elbasvir and grazoprevir are not expected to be removed by peritoneal dialysis.

In population pharmacokinetic analysis, elbasvir AUC was 25% higher in dialysis-dependent subjects and 46% higher in non-dialysis-dependent subjects with severe renal impairment compared to elbasvir AUC in subjects without severe renal impairment. In population pharmacokinetic analysis in HCV-infected subjects, grazoprevir AUC was 10% higher in dialysis-dependent subjects and 40% higher in non-dialysis-dependent subjects with severe renal impairment compared to grazoprevir AUC in subjects without severe renal impairment.

Overall, changes in exposure of elbasvir and grazoprevir in HCV-infected subjects with renal impairment with or without dialysis are not clinically relevant. Therefore, no dosage adjustment of ZEPATIER is recommended in HCV-infected subjects with renal impairment regardless of dialysis status *(see section 4.2: Renal insufficiency and 4.4: Renal Impairment)*

Hepatic impairment

The pharmacokinetics (PK) of elbasvir and grazoprevir were evaluated in non-HCV-infected subjects with mild hepatic impairment (Child-Pugh Category A [CP-A], score of 5-6), moderate hepatic impairment (Child-Pugh Category B [CP-B], score of 7-9) and severe hepatic impairment (Child-Pugh Category C [CP-C], score of 10-15). In addition, the pharmacokinetics of elbasvir and grazoprevir were also evaluated in HCV-infected subjects with mild hepatic impairment (CP-A) or moderate hepatic impairment (CP-B).

Elbasvir $AUC_{0\text{-}inf}$ was decreased by 40% in non-HCV-infected subjects with mild hepatic impairment (CP-A) compared to matching healthy subjects. In non-HCV-infected subjects with mild hepatic impairment, grazoprevir steady-state $AUC_{0\text{-}24}$ was increased 70% compared to matching healthy subjects. Population PK analyses of HCV-infected subjects in Phase 2 and 3 studies demonstrated that elbasvir steady-state AUC was similar in HCV-infected subjects with mild hepatic impairment compared to subjects without hepatic impairment. Grazoprevir steady-state $AUC_{0\text{-}24}$ increased by approximately 65% in subjects with compensated cirrhosis compared to non-cirrhotic subjects. Based on these data, no dosage adjustment of ZEPATIER

is recommended in HCV-infected subjects with mild hepatic impairment (CP-A), including those with compensated cirrhosis.

Elbasvir AUC decreased by 28% in non-HCV-infected subjects with moderate hepatic impairment (CP-B) compared to matched healthy subjects. Elbasvir steady-state AUC was similar in HCV-infected subjects with moderate hepatic impairment compared to subjects without hepatic impairment. Compared to healthy matched subjects, grazoprevir steady-state AUC_{0-24} was increased 5-fold in non-HCV-infected subjects with moderate hepatic impairment. ZEPATIER is contraindicated in HCV-infected subjects with moderate hepatic impairment (CP-B) due to lack of clinical safety and efficacy experience in this population and the expected increase in grazoprevir exposure.

Elbasvir AUC_{0-inf} is decreased by 12% in non-HCV-infected subjects with severe hepatic impairment (CP-C) compared to matching healthy subjects. Grazoprevir steady-state AUC_{0-24} was increased 12-fold in non-HCV-infected subjects with severe hepatic impairment compared to healthy matched subjects. ZEPATIER is contraindicated in HCV-infected subjects with severe hepatic impairment (Child-Pugh C) based on the significant increase in grazoprevir exposure observed in non-HCV-infected subjects with severe hepatic impairment *(see section 4.3 and 4.4: Hepatic impairment)*.

Gender

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 50% and 30% higher, respectively, in females compared to males. Therefore, no dose adjustment of ZEPATIER is recommended based on sex.

Race

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 15% and 50% higher, respectively, for Asians compared to Whites. Population pharmacokinetics estimates of exposure of elbasvir and grazoprevir were comparable between Whites and Black/African Americans. Therefore, no dose adjustment of ZEPATIER is recommended based on race/ethnicity.

Paediatric

The pharmacokinetics of ZEPATIER in paediatric patients less than 18 years of age have not been established.

Geriatric

In population pharmacokinetic analyses, elbasvir and grazoprevir AUCs are estimated to be 16% and 45% higher, respectively, in >65-year-old subjects compared to subjects less than 65 years of age. No dose adjustment of ZEPATIER is recommended based on age *(see section 4.4: Use in elderly and 4.2: Geriatric patients)*.

Weight/BMI

In population pharmacokinetic analyses, there was no effect of weight on elbasvir pharmacokinetics. Grazoprevir AUC is estimated to be 15% higher in a 53 kg subject compared to a 77 kg subject. This change is not clinically relevant for grazoprevir. Therefore, no dose adjustment of ZEPATIER is recommended based on weight/BMI.

Drug interaction studies

Drug interaction studies were performed in healthy adults with elbasvir, grazoprevir, or co-administered elbasvir and grazoprevir and drugs likely to be co-administered or drugs commonly used as probes for pharmacokinetic interactions. Table 7 summarises the effects of co-administered drugs on the exposures of the individual components of ZEPATIER (elbasvir and grazoprevir). Table 8 summarises the effects of the individual components of ZEPATIER on the exposures of the co-administered drugs. For information regarding clinical recommendations, (*see section 4.4: Risk of adverse reactions or reduced therapeutic effect due to drug interactions and 4.5).*

Elbasvir and grazoprevir are substrates of CYP3A/P-gp, but the role of intestinal P-gp in the absorption of elbasvir and grazoprevir is minimal. Co-administration of moderate and strong CYP3A/P-gp inducers with ZEPATIER may decrease elbasvir and grazoprevir plasma concentrations, leading to reduced therapeutic effect of ZEPATIER. Co-administration of strong CYP3A inhibitors with ZEPATIER may increase elbasvir and grazoprevir plasma concentrations (see Table 7).

Grazoprevir is a substrate of OATP1B. Co-administration of ZEPATIER with drugs that inhibit OATP1B transporters may result in a clinically relevant increase in grazoprevir plasma concentrations.

Elbasvir is not a CYP3A inhibitor *in vitro* and grazoprevir is a weak CYP3A inhibitor in humans. Co-administration with grazoprevir resulted in a 34% increase in plasma exposure of midazolam and a 43% increase in plasma exposure of tacrolimus (see Table 8 and 2).

Clinically significant drug interactions with ZEPATIER as an inhibitor of other CYP enzymes, UGT1A1, and esterases (CES1, CES2, and CatA), are not expected, and multiple-dose administration of elbasvir or grazoprevir is unlikely to induce the metabolism of drugs metabolised by CYP isoforms based on *in vitro* data. A clinical interaction study with montelukast confirmed that grazoprevir is not a CYP2C8 inhibitor (CYP isoform with lowest *in vitro* IC_{50}).

Elbasvir has minimal intestinal P-gp inhibition in humans, and does not result in clinically relevant increases in concentrations of digoxin (a P-gp substrate), with an 11% increase in plasma AUC (see Table 8). Grazoprevir is not a P-gp inhibitor *in vitro*. Therefore, P-gp substrates may be administered without dose adjustment when co-administered with ZEPATIER.

Elbasvir and grazoprevir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of co-administered BCRP substrates. Neither grazoprevir nor elbasvir are inhibitors of OATP1B in humans (*see section 4.5)*.

Table 7: Drug interactions: changes in pharmacokinetics of elbasvir or grazoprevir in the presence of co-administered drug

Co-Administered Drug	**Regimen of Co-Administered Drug**	**Regimen of EBR and/or GZR**	**N**	**Geometric Mean Ratio [90% CI] of EBR and GZR PK with/without Co-Administered Drug (No Effect=1.00)**			
					AUC*	**C_{max}**	**C24**
Antifungal							
Ketoconazole	400 mg once daily	EBR 50 mg single-dose	7	EBR	1.80 (1.41, 2.29)	1.29 (1.00, 1.66)	1.89 (1.37, 2.60)
	400 mg once daily	GZR 100 mg single-dose	8	GZR	3.02 (2.42,	1.13 (0.77,	--

					3.76)	1.67)	
Antimycobacterial							
Rifampin	600 mg single-dose IV	EBR 50 mg single-dose	14	EBR	1.22 (1.06, 1.40)	1.41 (1.18, 1.68)	1.31 (1.12, 1.53)
	600 mg single-dose PO	EBR 50 mg single-dose	14	EBR	1.17 (0.98, 1.39)	1.29 (1.06, 1.58)	1.21 (1.03, 1.43)
	600 mg PO once daily	GZR 200 mg once daily	12	GZR	0.93 (0.75, 1.17)	1.16 (0.82, 1.65)	0.10 (0.07, 0.13)
	600 mg IV single-dose	GZR 200 mg single-dose	12	GZR	10.21 (8.68, 12.00)	10.94 (8.92, 13.43)	1.77 (1.40, 2.24)
	600 mg PO single-dose	GZR 200 mg once daily	12	GZR	8.35 (7.38, 9.45)[†]	6.52 (5.16, 8.24)	1.62 (1.32, 1.98)
HCV Antiviral							
EBR	20 mg once daily	GZR 200 mg once daily	10	GZR	0.90 (0.63, 1.28)	0.87 (0.50, 1.52)	0.94 (0.77, 1.15)
GZR	200 mg once daily	EBR 20 mg once daily	10	EBR	1.01 (0.83, 1.24)	0.93 (0.76, 1.13)	1.02 (0.83, 1.24)
HIV Protease Inhibitor							
Atazanavir/ ritonavir	300 mg/ 100 mg once daily	EBR 50 mg once daily	10	EBR	4.76 (4.07, 5.56)	4.15 (3.46, 4.97)	6.45 (5.51, 7.54)
	300 mg/ 100 mg once daily	GZR 200 mg once daily	12	GZR	10.58 (7.78, 14.39)	6.24 (4.42, 8.81)	11.64 (7.96, 17.02)
Darunavir/ ritonavir	600 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	1.66 (1.35, 2.05)	1.67 (1.36, 2.05)	1.82 (1.39, 2.39)
	600 mg/ 100 mg twice daily	GZR 200 mg once daily	13	GZR	7.50 (5.92, 9.51)	5.27 (4.04, 6.86)	8.05 (6.33, 10.24)
Lopinavir/ ritonavir	400 mg/ 100 mg twice daily	EBR 50 mg once daily	10	EBR	3.71 (3.05, 4.53)	2.87 (2.29, 3.58)	4.58 (3.72, 5.64)
	400 mg/ 100 mg twice daily	GZR 200 mg once daily	13	GZR	12.86 (10.25, 16.13)	7.31 (5.65, 9.45)	21.70 (12.99, 36.25)
Ritonavir[‡]	100 mg twice daily	GZR 200 mg single-dose	10	GZR	2.03 (1.60, 2.56)	1.15 (0.60, 2.18)	1.88 (1.65, 2.14)
HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	50 mg single-dose	EBR 50 mg +	12	EBR	0.98	0.97	0.98

		GZR 200 mg once daily			(0.93, 1.04)	(0.89, 1.05)	(0.93, 1.03)
	50 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	GZR	0.81 (0.67, 0.97)	0.64 (0.44, 0.93)	0.86 (0.79, 0.93)
Raltegravir	400 mg single-dose	EBR 50 mg single-dose	10	EBR	0.81 (0.57, 1.17)	0.89 (0.61, 1.29)	0.80 (0.55, 1.16)
	400 mg twice daily	GZR 200 mg once daily	11	GZR	0.89 (0.72, 1.09)	0.85 (0.62, 1.16)	0.90 (0.82, 0.99)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	600 mg once daily	EBR 50 mg once daily	10	EBR	0.46 (0.36, 0.59)	0.55 (0.41, 0.73)	0.41 (0.28, 0.59)
	600 mg once daily	GZR 200 mg once daily	12	GZR	0.17 (0.13, 0.24)	0.13 (0.09, 0.19)	0.31 (0.25, 0.38)
Rilpivirine	25 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	EBR	1.07 (1.00, 1.15)	1.07 (0.99, 1.16)	1.04 (0.98, 1.11)
	25 mg once daily	EBR 50 mg + GZR 200 mg once daily	19	GZR	0.98 (0.89, 1.07)	0.97 (0.83, 1.14)	1.00 (0.93, 1.07)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	300 mg once daily	EBR 50 mg once daily	10	EBR	0.93 (0.82, 1.05)	0.88 (0.77, 1.00)	0.92 (0.81, 1.05)
	300 mg once daily	GZR 200 mg once daily	12	GZR	0.86 (0.65, 1.12)	0.78 (0.51, 1.18)	0.89 (0.78, 1.01)
HIV Fixed-Dose Combination Regimen							
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	150 mg/ 150 mg/ 200 mg/ 300 mg once daily	EBR 50 mg/ GZR 100 mg once daily	21	EBR	2.18 (2.02, 2.35)	1.91 (1.77, 2.05)	2.38 (2.19, 2.60)
		EBR 50 mg/ GZR 100 mg once daily	21	GZR	5.36 (4.48, 6.43)	4.59 (3.70, 5.69)	2.78 (2.48, 3.11)
Immunosuppressant							
Cyclosporine	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.98 (1.84, 2.13)	1.95 (1.84, 2.07)	2.21 (1.98, 2.47)
	400 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	15.21 (12.83, 18.04)	17.00 (12.94, 22.34)	3.39 (2.82, 4.09)
Mycophenolate mofetil	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.07 (1.00, 1.14)	1.07 (0.98, 1.16)	1.05 (0.97, 1.14)

	1000 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	0.74 (0.60, 0.92)	0.58 (0.42, 0.82)	0.97 (0.89, 1.06)
Prednisone	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	EBR	1.17 (1.11, 1.24)	1.25 (1.16, 1.35)	1.04 (0.97, 1.12)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	14	GZR	1.09 (0.95, 1.25)	1.34 (1.10, 1.62)	0.93 (0.87, 1.00)
Tacrolimus	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	EBR	0.97 (0.90, 1.06)	0.99 (0.88, 1.10)	0.92 (0.83, 1.02)
	2 mg single-dose	EBR 50 mg + GZR 200 mg once daily	16	GZR	1.12 (0.97, 1.30)	1.07 (0.83, 1.37)	0.94 (0.87, 1.02)
Opioid-Substitution Therapy							
Buprenorphine/naloxone	8 mg/2 mg single-dose	EBR 50 mg single-dose	15	EBR	1.22 (0.98, 1.52)	1.13 (0.87, 1.46)	1.22 (0.99, 1.51)
	8-24 mg/ 2-6 mg once daily	GZR 200 mg once daily	12	GZR	0.80 (0.53, 1.22)	0.76 (0.40, 1.44)	0.69 (0.54, 0.88)
Methadone	20-120 mg once daily	EBR 50 mg once daily	10	EBR	1.71 (1.16, 2.51)	1.93 (1.30, 2.86)	1.86 (1.22, 2.83)
	20-150 mg once daily	GZR 200 mg once daily	12	GZR	1.03 (0.53, 1.97)	0.88 (0.36, 2.14)	0.77 (0.56, 1.04)
Acid-Reducing Agent							
Famotidine	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.92, 1.18)	1.11 (0.98, 1.26)	1.03 (0.91, 1.17)
	20 mg single-dose	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.10 (0.95, 1.28)	0.89 (0.71, 1.11)	1.12 (0.97, 1.30)
Pantoprazole	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	EBR	1.05 (0.93, 1.18)	1.02 (0.92, 1.14)	1.03 (0.92, 1.17)
	40 mg once daily	EBR 50 mg/ GZR 100 mg single-dose	16	GZR	1.12 (0.96, 1.30)	1.10 (0.89, 1.37)	1.17 (1.02, 1.34)
Phosphate Binder							
Calcium acetate	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	EBR	0.92 (0.75, 1.14)	0.86 (0.71, 1.04)	0.87 (0.70, 1.09)
	2668 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.79 (0.68, 0.91)	0.57 (0.40, 0.83)	0.77 (0.61, 0.99)
Sevelamer	2400 mg single-	EBR 50 mg +	12	EBR	1.13	1.07	1.22

carbonate	dose	GZR 100 mg single-dose			(0.94, 1.37)	(0.88, 1.29)	(1.02, 1.45)
	2400 mg single-dose	EBR 50 mg + GZR 100 mg single-dose	12	GZR	0.82 (0.68, 0.99)	0.53 (0.37, 0.76)	0.84 (0.71, 0.99)
Statin							
Atorvastatin	20 mg single-dose	GZR 200 mg once daily	9	GZR	1.26 (0.97, 1.64)	1.26 (0.83, 1.90)	1.11 (1.00, 1.23)
Pitavastatin	1 mg single-dose	GZR 200 mg once daily	9	GZR	0.81 (0.70, 0.95)	0.72 (0.57, 0.92)	0.91 (0.82, 1.01)
Pravastatin	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	EBR	0.98 (0.93, 1.02)	0.97 (0.89, 1.05)	0.97 (0.92, 1.02)
	40 mg single-dose	EBR 50 mg + GZR 200 mg once daily	12	GZR	1.24 (1.00, 1.53)	1.42 (1.00, 2.03)	1.07 (0.99, 1.16)
Rosuvastatin	10 mg single-dose	EBR 50 mg + GZR 200 mg single-dose	11	EBR	1.09 (0.98, 1.21)	1.11 (0.99, 1.26)	0.96 (0.86, 1.08)
	10 mg single-dose	GZR 200 mg once daily	11	GZR	1.16 (0.94, 1.44)	1.13 (0.77, 1.65)	0.93 (0.84, 1.03)
	10 mg single-dose	EBR 50 mg + GZR 200 mg once daily	11	GZR	1.01 (0.79, 1.28)	0.97 (0.63, 1.50)	0.95 (0.87, 1.04)

Abbreviations: EBR, elbasvir ; GZR, grazoprevir; IV, intravenous; PO, oral; EBR + GZR, administration of EBR and GZR as separate tablets; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet
*$AUC_{0\text{-}inf}$ for single-dose, $AUC_{0\text{-}24}$ for once daily
†$AUC_{0\text{-}24}$
‡Higher doses of ritonavir have not been tested in a drug interaction study with GZR

Table 8: Drug interactions: changes in pharmacokinetics for co-administered drug in the presence of elbasvir, grazoprevir, or co-administered elbasvir and grazoprevir

Co-Administered Drug	**Regimen of Co-Administered Drug**	**EBR or/and GZR Administration**	**EBR or/and GZR Regimen**	**N**	**Geometric Mean Ratio [90% CI] of Co-Administered Drug PK with/without EBR or/and GZR (No Effect=1.00)**		
					AUC*	**C_{max}**	**C_{trough}†**
P-gp Substrate							
Digoxin	Digoxin 0.25 mg single-dose	EBR	50 mg once daily	18	1.11 (1.02, 1.22)	1.47 (1.25, 1.73)	--
CYP3A Substrate							
Midazolam	Midazolam 2 mg single-dose	GZR	200 mg once daily	11	1.34 (1.29,	1.15 (1.01, 1.31)	--

					1.39)		
CYP2C8 Substrate							
Montelukast	Montelukast 10 mg single-dose	GZR	200 mg once daily	23	1.11 (1.01, 1.20)	0.92 (0.81, 1.06)	1.39 (1.25, 1.56)
HCV Antiviral							
GS-331007	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.13 (1.05, 1.21)	0.87 (0.78, 0.96)	1.53 (1.43, 1.63)
Sofosbuvir	Sofosbuvir 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	2.43 (2.12, 2.79)‡	2.27 (1.72, 2.99)	--
HIV Protease Inhibitor							
Atazanavir/ ritonavir	Atazanavir 300 mg/ ritonavir 100 mg once daily	EBR	50 mg once daily	8	1.07 (0.98, 1.17)	1.02 (0.96, 1.08)	1.15 (1.02, 1.29)
	Atazanavir 300 mg/ ritonavir 100 mg once daily	GZR	200 mg once daily	11	1.43 (1.30, 1.57)	1.12 (1.01, 1.24)	1.23 (1.13, 1.34)
Darunavir/ ritonavir	Darunavir 600 mg/ ritonavir 100 mg twice daily	EBR	50 mg once daily	8	0.95 (0.86, 1.06)	0.95 (0.85, 1.05)	0.94 (0.85, 1.05)
	Darunavir 600 mg/ ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.11 (0.99, 1.24)	1.10 (0.96, 1.25)	1.00 (0.85, 1.18)
Lopinavir/ ritonavir	Lopinavir 400 mg/ ritonavir 100 mg twice daily	EBR	50 mg once daily	9	1.02 (0.93, 1.13)	1.02 (0.92, 1.13)	1.07 (0.97, 1.18)
	Lopinavir 400 mg/ ritonavir 100 mg twice daily	GZR	200 mg once daily	13	1.03 (0.96, 1.16)	0.97 (0.88, 1.08)	0.97 (0.81, 1.15)
HIV Integrase Strand Transfer Inhibitor							
Dolutegravir	Dolutegravir 50 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.16 (1.00, 1.34)	1.22 (1.05, 1.40)	1.14 (0.95, 1.36)
Raltegravir	Raltegravir 400 mg single-dose	EBR	50 mg single-dose	10	1.02 (0.81, 1.27)	1.09 (0.83, 1.44)	0.99 (0.80, 1.22)§
	Raltegravir 400 mg twice daily	GZR	200 mg once daily	11	1.43 (0.89, 2.30)	1.46 (0.78, 2.73)	1.47 (1.08, 2.00)
HIV Non-Nucleoside Reverse Transcriptase Inhibitor							
Efavirenz	Efavirenz	EBR	50 mg once	7	0.82	0.74 (0.67,	0.91

	600 mg once daily		daily		(0.78, 0.86)	0.82)	(0.87, 0.96)
	Efavirenz 600 mg once daily	GZR	200 mg once daily	11	1.00 (0.96, 1.05)	1.03 (0.99, 1.08)	0.93 (0.88, 0.98)
Rilpivirine	Rilpivirine 25 mg once daily	EBR + GZR	50 mg + 200 mg once daily	19	1.13 (1.07, 1.20)	1.07 (0.97, 1.17)	1.16 (1.09, 1.23)
HIV Nucleotide Reverse Transcriptase Inhibitor							
Tenofovir disoproxil fumarate	Tenofovir disoproxil fumarate 300 mg once daily	EBR	50 mg once daily	10	1.34 (1.23, 1.47)	1.47 (1.32, 1.63)	1.29 (1.18, 1.41)
	Tenofovir disoproxil fumarate 300 mg once daily	GZR	200 mg once daily	12	1.18 (1.09, 1.28)	1.14 (1.04, 1.25)	1.24 (1.10, 1.39)
	Tenofovir disoproxil fumarate 300 mg once daily	EBR/GZR	50 mg + 100 mg once daily	13	1.27 (1.20, 1.35)	1.14 (0.95, 1.36)	1.23 (1.09, 1.40)
HIV Fixed-Dose Combination Regimen							
Elvitegravir/ cobicistat/ emtricitabine/ tenofovir disoproxil fumarate	Elvitegravir 150 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.10 (1.00, 1.21)	1.02 (0.93, 1.11)	1.31 (1.11, 1.55)
	Cobicistat 150 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.49 (1.42, 1.57)	1.39 (1.29, 1.50)	--
	Emtricitabine 200 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.07 (1.03, 1.10)	0.96 (0.90, 1.02)	1.19 (1.13, 1.25)
	Tenofovir disoproxil fumarate 300 mg once daily	EBR/GZR	50 mg / 100 mg once daily	22	1.18 (1.13, 1.24)	1.25 (1.14, 1.37)	1.20 (1.15, 1.26)
Immunosuppressant							
Cyclosporine	Cyclosporine 400 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	0.96 (0.90, 1.02)	0.90 (0.85, 0.97)	1.00 (0.92, 1.08)[§]
Mycophenolic acid	Mycophenolate mofetil 1000 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	0.95 (0.87, 1.03)	0.85 (0.67, 1.07)	--
Prednisolone	Prednisone 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	1.08 (1.01, 1.16)	1.04 (0.99, 1.09)	--
Prednisone	Prednisone 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	14	1.08 (1.00, 1.17)	1.05 (1.00, 1.10)	--

Tacrolimus	Tacrolimus 2 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.43 (1.24, 1.64)	0.60 (0.52, 0.69)	1.70 (1.49, 1.94)[§]
Oral Contraceptive							
Ethinyl estradiol (EE)	0.03 mg EE/ 0.15 mg LNG single-dose	EBR	50 mg once daily	20	1.01 (0.97, 1.05)	1.10 (1.05, 1.16)	--
		GZR	200 mg once daily	20	1.10 (1.05, 1.14)	1.05 (0.98, 1.12)	--
Levonorgestrel (LNG)		EBR	50 mg once daily	20	1.14 (1.04, 1.24)	1.02 (0.95, 1.08)	--
		GZR	200 mg once daily	20	1.23 (1.15, 1.32)	0.93 (0.84, 1.03)	--
Opioid Substitution Therapy							
Buprenorphine	Buprenorphine 8 mg/Naloxone 2 mg single-dose	EBR	50 mg once daily	15	0.98 (0.89, 1.08)	0.94 (0.82, 1.08)	0.98 (0.88, 1.09)
	Buprenorphine 8-24 mg/ Naloxone 2-6 mg once daily	GZR	200 mg once daily	12	0.98 (0.81, 1.19)	0.90 (0.76, 1.07)	--
R-Methadone	Methadone 20-150 mg once daily	EBR	50 mg once daily	10	1.03 (0.92, 1.15)	1.07 (0.95, 1.20)	1.10 (0.96, 1.26)
		GZR	200 mg once daily	12	1.09 (1.02, 1.17)	1.03 (0.96, 1.11)	--
S-Methadone		EBR	50 mg once daily	10	1.09 (0.94, 1.26)	1.09 (0.95, 1.25)	1.20 (0.98, 1.47)
		GZR	200 mg once daily	12	1.23 (1.12, 1.35)	1.15 (1.07, 1.25)	--
Statin							
Atorvastatin	Atorvastatin 10 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	16	1.94 (1.63, 2.33)	4.34 (3.10, 6.07)	0.21 (0.17, 0.26)
	Atorvastatin 20 mg single-dose	GZR	200 mg once daily	9	3.00 (2.42, 3.72)	5.66 (3.39, 9.45)	--
Pitavastatin	Pitavastatin 1 mg single-dose	GZR	200 mg once daily	9	1.11 (0.91, 1.34)	1.27 (1.07, 1.52)	--
Pravastatin	Pravastatin 40 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	1.33 (1.09, 1.64)[¶]	1.28 (1.05, 1.55)	--

Rosuvastatin	Rosuvastatin 10 mg single-dose	EBR + GZR	50 mg + 200 mg once daily	12	2.26 (1.89, 2.69)[#]	5.49 (4.29, 7.04)	0.98 (0.84, 1.13)
		GZR	200 mg once daily	12	1.59 (1.33, 1.89)[#]	4.25 (3.25, 5.56)	0.80 (0.70, 0.91)

Abbreviations: EBR, elbasvir; GZR, grazoprevir; EBR + GZR, administration of EBR and GZR as separate tablets; EBR/GZR, administration of EBR and GZR as a single fixed-dose combination tablet
*AUC_{0-inf} for single-dose administration; AUC_{0-24} for once daily administration; AUC_{0-12} for twice daily administration
[†]C24 for once daily administration; C12 for twice daily administration
[‡]N=14
[§]C12
[¶]N=10
[#]N=8

5.3 Preclinical safety data

The safety and efficacy of ZEPATIER or elbasvir + grazoprevir were evaluated in 8 clinical trials in approximately 1800 subjects with genotype (GT) 1, 3, 4, or 6 chronic hepatitis C (CHC) infection with compensated liver disease (with and without cirrhosis). An overview of the trials is provided in Table 9.

Table 9: Trials conducted with ZEPATIER

Trial	**Population**	**Study Arms and Duration (Number of Subjects Treated)**
C-EDGE TN (double-blind)	GT 1, 4, 6 TN with or without cirrhosis	• ZEPATIER for 12 weeks (N=316) • Placebo for 12 weeks (N=105)
C-EDGE COINFECTION (open-label)	GT 1, 4, 6 TN with or without cirrhosis HCV/HIV-1 co-infection	• ZEPATIER for 12 weeks (N=218)
C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Chronic Kidney Disease	• EBR* + GZR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
C-WORTHY (open-label)	GT 1, 3 TN with or without cirrhosis TE Null Responder with or without cirrhosis TN HCV/HIV-1 co-infection without cirrhosis	• EBR* + GZR*for 8, 12, or 18 weeks (N=31, 136, and 63, respectively) • EBR* + GZR*+ RBV[†] for 8, 12, or 18 weeks (N=60, 152, and 65, respectively)
C-SCAPE (open-label)	GT 4, 6 TN without cirrhosis	• EBR* + GZR* for 12 weeks (N=14) • EBR* + GZR* + RBV[†] for 12 weeks (N=14)

C-EDGE TE (open-label)	GT 1, 4, 6 TE with or without cirrhosis with or without HCV/HIV-1 co-infection	• ZEPATIER for 12 or 16 weeks (N=105, and 105, respectively) • ZEPATIER + RBV[†] for 12 or 16 weeks (N=104 and 106, respectively)
C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen[‡] with or without cirrhosis	• EBR* + GZR* + RBV[†] for 12 weeks (N=79)
C-SWIFT (open-label)	GT 1, 3 TN with or without cirrhosis	• ZEPATIER + sofosbuvir[§] for 8 or 12 weeks in GT 3 (N= 15 and N=26, respectively) • ZEPATIER + sofosbuvir[§] for 4, 6 or 8 weeks in GT 1 (N=31, 50, and 21, respectively)

GT = Genotype
TN = Treatment-Naïve
TE = Treatment-Experienced (failed prior treatment with interferon [IFN] or peginterferon alfa [peg-IFN] with or without ribavirin (RBV) or were intolerant to prior therapy)
* EBR = elbasvir 50 mg; GZR = grazoprevir 100 mg; EBR + GZR = co-administered as single agents
[†]RBV was administered at a total daily dose of 800 mg to 1400 mg based on weight (see *section 4.2: Treatment regimen and duration of therapy*)
[‡] Failed prior treatment with boceprevir, telaprevir, or simeprevir in combination with peg-IFN + RBV
[§] Sofosbuvir dose was 400 mg once a day

- C-EDGE TN was a randomised, double-blind, placebo-controlled trial in treatment-naïve subjects with genotype 1, 4, or 6 infection with or without cirrhosis. Subjects were randomised in a 3:1 ratio to: ZEPATIER for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with ZEPATIER for 12 weeks (deferred treatment group).
- C-EDGE COINFECTION was an open-label trial in treatment-naïve HCV/HIV-1 co-infected subjects with genotype 1, 4, or 6 infection with or without cirrhosis. Subjects received ZEPATIER for 12 weeks.
- C-SURFER was a randomised, double-blind, placebo-controlled trial in subjects with genotype 1 infection, with or without cirrhosis, with CKD Stage 4 (eGFR 15-29 mL/min/1.73 m^2) or Stage 5 (eGFR <15 mL/min/1.73 m^2), including subjects on haemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or peg-IFN ± RBV therapy. Subjects were randomised in a 1:1 ratio to one of the following treatment groups: EBR + GZR for 12 weeks (immediate treatment group) or placebo for 12 weeks followed by open-label treatment with EBR + GZR for 12 weeks (deferred treatment group). In addition, 11 subjects received open-label EBR + GZR for 12 weeks (intensive PK arm).
- C-WORTHY was a multi-arm, multi-stage, randomised, open-label trial which included subjects with genotype 1 or 3 infection who were treatment-naïve or who had failed prior therapy with peg-IFN ± RBV therapy. In the stage evaluating shorter duration of therapy in subjects with genotype 1b infection without cirrhosis, subjects were randomised in a 1:1 ratio to EBR + GZR with or without RBV for 8 weeks. In the stage evaluating subjects with genotype 3 infection without cirrhosis who were treatment-naïve, subjects were randomised to EBR + GZR with RBV for 12 or 18 weeks. In the other stages, subjects with GT 1 infection with or without cirrhosis who were treatment-naïve (with or without HCV/HIV-1 co-infection) or who were peg-IFN + RBV null responders, were randomised to EBR + GZR with or without RBV for 8, 12 or 18 weeks.

- C-SCAPE was a randomised, open-label trial which included treatment-naïve subjects with genotype 4 or 6 infection without cirrhosis. Subjects were randomised in a 1:1 ratio to EBR + GZR for 12 weeks or EBR + GZR + RBV for 12 weeks.
- C-EDGE TE was a randomised, open-label trial in subjects with genotype 1, 4, or 6 infection, with or without cirrhosis, with or without HCV/HIV-1 co-infection, who had failed prior therapy with peg-IFN + RBV therapy. Subjects were randomised in a 1:1:1:1 ratio to one of the following treatment groups: ZEPATIER for 12 weeks, ZEPATIER + RBV for 12 weeks, ZEPATIER for 16 weeks, or ZEPATIER + RBV for 16 weeks.
- C-SALVAGE was an open-label trial in subjects with genotype 1 infection, with or without cirrhosis, who had failed prior treatment with boceprevir, simeprevir, or telaprevir in combination with peg-IFN + RBV. Subjects received EBR + GZR + RBV for 12 weeks.
- C-SWIFT was an open-label trial of ZEPATIER + sofosbuvir in treatment-naïve subjects with genotype 1 or 3 infection. Non-cirrhotic genotype 3 infected subjects, were randomised (1:1) to 8 or 12 weeks of treatment, and cirrhotic genotype 3 infected subjects received 12 weeks of treatment. Non-cirrhotic genotype 1 infected subjects, were randomised (1:1) to 4 or 6 weeks of treatment, and cirrhotic genotype 1 infected subjects were randomised (1:1) to 6 or 8 weeks of treatment.

Sustained virologic response was the primary endpoint in all trials and was defined as HCV RNA less than lower limit of quantification (LLOQ) at 12 weeks after the cessation of treatment (SVR). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU/mL, with the exception of C-WORTHY and C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU/mL.

Clinical trials in treatment-naïve subjects with genotype 1 or 4 chronic hepatitis C infection

Treatment-naïve subjects with genotype 1, 4, or 6 chronic hepatitis C infection treated with ZEPATIER for 12 weeks in C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-WORTHY, and C-SCAPE had a median age of 53 years (range: 20 to 82); 67% of the subjects were male; 67% were White; 21% were Black or African American; 8% were Hispanic or Latino; mean body mass index was 26 kg/m^2; 66% had baseline HCV RNA levels greater than 800,000 IU/mL; 18% had cirrhosis; 68% had non-C/C IL28B alleles (CT or TT); 33% had HCV/HIV-1 co-infection; and 91% had genotype 1, 7% had genotype 4 and 2% had genotype 6 chronic hepatitis C infection.

Table 10 presents treatment outcomes for ZEPATIER in treatment-naïve subjects from C-EDGE TN, C-EDGE COINFECTION, C-SURFER, C-WORTHY, and C-SCAPE trials and from the pooled data from these trials. In trials C-EDGE TN and C-SURFER, the treatment outcomes for subjects treated with ZEPATIER in the immediate treatment groups and intensive PK arm are presented. In the C-WORTHY and C-SCAPE trials, the addition of RBV to the regimens was not shown to improve the treatment outcomes. Therefore, only the 12 weeks treatment arms without RBV are presented in Table 10..

Table 10: Treatment outcomes after 12 weeks of treatment in treatment-naïve subjects with or without cirrhosis, with genotype1 or 4 chronic hepatitis C infection

Trial	**C-EDGE TN**	**C-EDGE COINFECTION (HCV/HIV-1 Co-Infection)**	**C-SURFER (CKD Stages 4-5, including dialysis)**	**C-WORTHY**	**C-SCAPE**	**All Studies**
Regimen	**ZEPATIER 12 Weeks N=306**	**ZEPATIER 12 Weeks N=217**	**EBR + GZR 12 Weeks N=101**	**EBR + GZR 12 Weeks N=103**	**EBR + GZR 12 Weeks N= 10**	**N=737**
Overall SVR	95% (291/306)	95% (206/217)	95% (96/101)	94% (97/103)	90% (9/10)	95% (699/737)
Outcome for subjects without SVR						
On-treatment Virologic Failure*	<1% (1/306)	0% (0/217)	0% (0/101)	2% (2/103)	0% (0/10)	<1% (3/737)
Relapse	3% (10/306)	3% (7/217)	0% (0/101)	2% (2/103)	0% (0/10)	3% (19/737)
Other†	1% (4/306)	2% (4/217)	5% (5/101)	2% (2/103)	10% (1/10)	2% (16/737)
SVR by Genotype						
GT 1a	92% (144/157)	94% (136/144)	98% (52/53)	93% (67/72)	------	94% (399/426)
GT 1b‡	98% (129/131)	96% (43/45)	92% (44/48)	97% (30/31)	------	96% (246/255)
GT 4	100% (18/18)	96% (27/28)	------	------	90% (9/10)	96% (54/56)
SVR by Cirrhosis status						
Non-cirrhotic§	94% (223/236)	94% (171/182)	95% (92/97)	93% (69/74)	90% (9/10)	94% (564/599)
Cirrhotic	97% (68/70)	100% (35/35)	100% (4/4)	97% (28/29)	------	98% (135/138)
SVR by HIV status						
HCV mono-infected	95% (291/306)	------	95% (96/101)	97% (71/73)	90% (9/10)	95% (467/490)
HCV/HIV-1 co-infected	------	95% (206/217)	------	87% (26/30)	------	94% (232/247)

*Includes subjects with virologic breakthrough.
†Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
‡Includes genotype 1 subtypes other than 1a or 1b.
§Includes 1 subject with cirrhosis status of “unknown” in C-SCAPE.

No HIV-1 infected subjects switched their antiretroviral therapy regimen due to loss of plasma HIV-1 RNA suppression. In treatment-naïve subjects, treatment outcomes were consistent in subjects with or without compensated cirrhosis and in subjects with or without HCV/HIV-1 co-infection. Treatment outcomes were consistent in subjects with or without advanced CKD, including subjects on haemodialysis.

Clinical trial with 8-week treatment in treatment-naïve subjects without cirrhosis with genotype 1b chronic hepatitis C infection

In the C-WORTHY trial, treatment-naïve subjects with genotype 1b CHC without cirrhosis were treated with EBR + GZR with or without RBV for 8 weeks. In subjects treated with EBR + GZR without RBV, the subjects had a median age of 56 years (range: 28 to 71); 42% of the subjects were male; 81% were White; 19% were Black or African American; 3% were Hispanic or Latino; mean body mass index was 28 kg/m^2; 87% had baseline HCV RNA levels greater than 800,000 IU/mL; and 90% had non-C/C IL28B alleles (CT or TT). By liver biopsy or non-invasive tests, all were non-cirrhotic and 94% (29/31) had METAVIR scores of F0-F2 and the other 2 subjects had a METAVIR score of F3.

Overall SVR was achieved in 94% (29/31) in treatment-naïve subjects with genotype 1b without cirrhosis who received EBR + GZR for 8 weeks. Two of the thirty-one subjects did not achieve SVR due to relapse. SVR was achieved in 97% (28/29) of subjects with METAVIR scores of F0-F2 and 50% (1/2) subjects with METAVIR score of F3. The addition of RBV was not shown to improve the treatment outcomes observed with EBR + GZR.

Clinical trials in treatment-experienced subjects with genotype 1 or 4 chronic hHepatitis C infection

C-EDGE TE trial – treatment-experienced subjects who failed prior Peg-IFN with RBV therapy

In the C-EDGE TE trial, treatment-experienced subjects who failed prior Peg-IFN with RBV therapy with genotype 1, 4, or 6 chronic hepatitis C infection had a median age of 56 years (range: 19 to 77); 65% of the subjects were male; 68% were White; 17% were Black or African American; 9% were Hispanic or Latino; mean body mass index was 27 kg/m^2; 75% had baseline HCV RNA levels greater than 800,000 IU/mL; 35% had cirrhosis; 79% had non-C/C IL28B alleles (CT or TT); and 5% had HCV/HIV-1 co-infection; and 90% had genotype 1, 9% had genotype 4, and 1% had genotype 6 chronic hepatitis C infection.

Treatment outcomes in subjects treated with ZEPATIER with or without RBV for 12 or 16 weeks are presented in Table 11.

Table 11: C-EDGE TE trial: Treatment outcomes after 12 or 16 weeks of treatment in treatment-experienced subjects who failed prior Peg-IFN with RBV with or without cirrhosis, with genotype 1 or 4 chronic hepatitis C infection

Regimen	ZEPATIER 12 weeks N=105	ZEPATIER + RBV 12 weeks N=104	ZEPATIER 16 weeks N=101	ZEPATIER + RBV 16 weeks N=104
Overall SVR	92% (97/105)	94% (98/104)	93% (94/101)	97% (101/104)
Outcome for subjects without SVR				
On-treatment Virologic Failure*	0% (0/105)	0% (0/104)	2% (2/101)	0% (0/104)
Relapse	6% (6/105)	6% (6/104)	4% (4/101)	0% (0/104)
Other†	2% (2/105)	0% (0/104)	1% (1/101)	3% (3/104)
SVR by Genotype				
GT 1a	90% (55/61)	93% (56/60)	94% (45/48)	95% (55/58)
GT 1b‡	100% (35/35)	97% (28/29)	96% (46/48)	100% (38/38)
GT 4	78% (7/9)	93% (14/15)	60% (3/5)	100% (8/8)
SVR by Cirrhosis status				
Non-cirrhotic	94% (64/68)	97% (67/69)	92% (60/65)	96% (65/68)
Cirrhotic	89% (33/37)	89% (31/35)	94% (34/36)	100% (36/36)
SVR by Response to Prior HCV Therapy				
On-treatment Virologic Failure¶	89% (62/70)	91% (60/66)	92% (60/65)	95% (63/66)
Relapser	100% (35/35)	100% (38/38)	94% (34/36)	100% (38/38)
SVR by HIV status				
HCV mono-infected	92% (91/99)	94% (93/99)	94% (89/95)	97% (97/100)
HCV/HIV-1 co-infected	100% (6/6)	100% (5/5)	83% (5/6)	100% (4/4)

*Includes subjects with virologic breakthrough or rebound.
†Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
‡Includes genotype 1 subtypes other than 1a or 1b.
¶Includes null responders and partial responders.

Overall SVR was achieved in 92% and 97% of subjects receiving ZEPATIER for 12 weeks and ZEPATIER + RBV for 16 weeks, respectively. SVR was 100% in prior relapsers who received ZEPATIER for 12 weeks, regardless of genotype or presence of cirrhosis. SVR was 100% in genotype 1b subjects who received ZEPATIER for 12 weeks, regardless of the presence of cirrhosis or response to prior HCV therapy.

Among genotype 1a or 4, null or partial responders, the highest response was achieved with the administration of ZEPATIER + RBV for 16 weeks. In subjects receiving ZEPATIER + RBV for 16 weeks, treatment outcomes were consistent in subjects with or without cirrhosis, and no subject failed due to virologic failure. Among genotype 1a or 4, null or partial responders, SVR was achieved in 93% of subjects receiving ZEPATIER + RBV for 16 weeks; 90% in subjects

receiving ZEPATIER alone for 16 weeks; 90% in subjects receiving ZEPATIER + RBV for 12 weeks; and 84% in subjects receiving ZEPATIER alone for 12 weeks.

No HIV-1 virological failures were observed in subjects who failed prior peg-IFN + RBV with HCV/HIV-1 co-infection. In treatment-experienced subjects, treatment outcomes were consistent in subjects with or without compensated cirrhosis and in subjects with or without HCV/HIV-1 co-infection.

C-SALVAGE trial – Treatment-experienced subjects who failed prior Peg-IFN + RBV + HCV protease inhibitor therapy (boceprevir, simeprevir, or telaprevir)

In the C-SALVAGE trial, subjects who failed prior peg-IFN + RBV with an HCV protease inhibitor with genotype 1 infection with or without cirrhosis treated with EBR + GZR + RBV for 12 weeks had a median age of 55 years (range: 23 to 75); 58% of the subjects were male; 97% were White; 3% were Black or African American; 15% were Hispanic or Latino; mean body mass index was 28 kg/m^2; 63% had baseline HCV RNA levels greater than 800,000 IU/mL; 43% had cirrhosis; 97% had non-C/C IL28B alleles (CT or TT); and 46% had baseline NS3 resistance-associated substitutions.

Overall SVR was achieved in 96% (76/79) of subjects receiving EBR + GZR + RBV for 12 weeks. Four percent (3/79) of subjects did not achieve SVR due to relapse. Treatment outcomes were consistent in genotype 1a and genotype 1b subjects, in subjects with different response to previous HCV therapy, and in subjects with or without cirrhosis. Treatment outcomes were consistent in subjects with or without NS3 resistance-associated substitutions at baseline *(see section 5.1: Microbiology, Resistance)*.

Based on the lack of impact of baseline NS3 resistance-associated substitutions on treatment outcomes, and efficacy analyses among treatment-experienced subjects in the C-SALVAGE and C-EDGE TE trials, the recommended treatment regimen for treatment-experienced patients who have failed peg-IFN + RBV with boceprevir, simeprevir or telaprevir is as follows: for genotype 1 relapsers, administer ZEPATIER for 12 weeks; for genotype 1b prior on-treatment virologic failures, administer ZEPATIER for 12 weeks; and for genotype 1a prior on-treatment virologic failures, administer ZEPATIER + RBV for 16 weeks (*see section 4.2)*.

<u>Clinical trial in subjects with advanced chronic kidney disease with genotype 1 chronic hepatitis C infection</u>

In the C-SURFER trial, subjects with genotype 1 infection, with or without cirrhosis, with advanced CKD Stage 4 (eGFR 15-29 mL/min/1.73 m^2) or Stage 5 (eGFR <15 mL/min/1.73 m^2), including subjects on haemodialysis, who were treatment-naïve or who had failed prior therapy with IFN or peg-IFN ± RBV therapy had a median age of 58 years (range: 31 to 76); 75% of the subjects were male; 50% were White; 45% were Black or African American; 11% were Hispanic or Latino; 57% had baseline HCV RNA levels greater than 800,000 IU/mL; 75% were on dialysis; 6% had cirrhosis; and 72% had non-C/C IL28B alleles (CT or TT).

Treatment outcomes in subjects treated with ZEPATIER for 12 weeks in the immediate treatment group and intensive PK arm are presented in Table 12.

Table 12: C-SURFER Trial: Treatment outcomes in subjects with advanced chronic kidney disease who were treatment-naïve or had failed prior IFN or Peg-IFN ± RBV, with or without cirrhosis, with genotype 1 chronic hepatitis C Infection

Regimen	**EBR + GZR** **12 weeks** **N=122***
Overall SVR	94% (115/122)[†]
Outcome for subjects without SVR	
On-treatment Virologic Failure	0% (0/122)
Relapse	<1% (1/122)
Other[‡]	5% (6/122)
SVR by Genotype	
GT 1a	97% (61/63)
GT 1b[§]	92% (54/59)
SVR by Cirrhosis status	
Non-cirrhotic	95% (109/115)
Cirrhotic	86% (6/7)
SVR by Prior HCV Treatment Status	
Treatment-naïve	95% (96/101)
Treatment-experienced	90% (19/21)
SVR by Dialysis Status	
No	97% (29/30)
Yes	93% (86/92)
SVR by Chronic Kidney Disease Stage	
Stage 4	100% (22/22)
Stage 5	93% (93/100)

*Includes subjects in the intensive PK arm
[†]SVR was achieved in 99% (115/116) of subjects in the pre-specified primary analysis population, which excluded subjects not receiving at least one dose of study treatment and those with missing data due to death or early study discontinuation for reasons unrelated to treatment response.
[‡]Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.
[§]Includes genotype 1 subtypes other than 1a or 1b.

Clinical trial in treatment-naïve subjects with genotype 3 chronic hepatitis C infection

In the C-SWIFT study, treatment naïve subjects with genotype 3 CHC with or without cirrhosis treated with ZEPATIER + sofosbuvir for 8 or 12 weeks had a median age of 52 years (range: 26 to 69); 71% of the subjects were male; 100% were White; 49% were Hispanic or Latino; mean body mass index was 29 kg/m^2; 51% had baseline HCV RNA levels greater than or equal to 800,000 IU/mL; 29% had cirrhosis; and 63% had non-C/C IL28B alleles (CT or TT). Treatment outcomes are presented in Table 13.

Table 13: C-SWIFT Study: Treatment outcomes in treatment-naïve subjects, with or without cirrhosis, with genotype 3 chronic hepatitis C infection

Regimen	**ZEPATIER + Sofosbuvir 8 Weeks N=15**	**ZEPATIER + Sofosbuvir 12 Weeks N=26**
Overall SVR	93% (14/15)	92% (24/26)
Outcome for subjects without SVR		
On-treatment Virologic Failure	0% (0/15)	0% (0/26)
Relapse	7% (1/15)	4% (1/26)
Other*	0% (0/15)	4% (1/26)
SVR by Cirrhosis status		
Non-cirrhotic	93% (14/15)	100% (14/14)
Cirrhotic	-----	83% (10/12)

*Other includes subjects who discontinued due to adverse event, lost to follow-up, or subject withdrawal.

Overall SVR was achieved in 92% (24/26) in treatment-naïve subjects with genotype 3 with or without cirrhosis who received ZEPATIER with sofosbuvir for 12 weeks and in 93% (14/15) treatment-naïve subjects without cirrhosis who received ZEPATIER with sofosbuvir for 8 weeks. Based on the overall results, including SVR in patients with cirrhosis, a 12 week regimen of ZEPATIER with sofosbuvir is recommended for treatment-naïve subjects with genotype 3 with or without cirrhosis.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

The tablets include the following inactive ingredients: sodium lauryl sulfate, tocofersolan, copovidone, hypromellose, microcrystalline cellulose, mannitol, lactose, croscarmellose sodium, sodium chloride, colloidal anhydrous silica, and magnesium stearate. The tablets are film-coated with a coating material containing the following inactive ingredients: lactose, hypromellose, titanium dioxide, glycerol triacetate, iron oxide yellow, iron oxide red, ferrosoferric oxide, and carnauba wax.

6.2 Incompatabilities

Not applicable

6.3 Shelf life

Store ZEPATIER below 30°C.

6.4 Special precautions for storage

Store ZEPATIER in the original blister package until use to protect from moisture.

6.5 Nature and contents of container

The tablets are packaged into a carton containing two cardboard wallets, each cardboard wallet containing 14-count tablets within Al/Al blisters. Each carton contains a total of 28 tablets.

6.6 Special precautions for disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

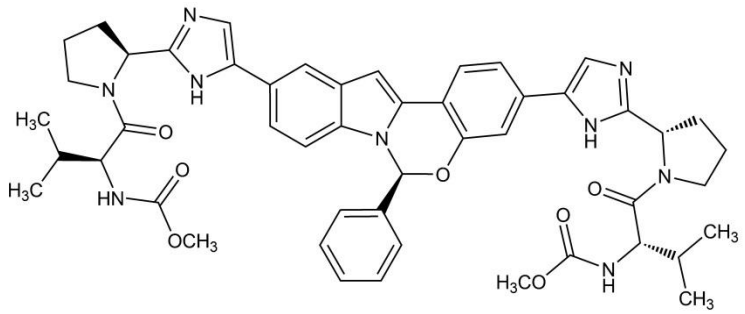
Further information

Chemistry

Elbasvir:

Elbasvir is an HCV NS5A inhibitor. It is practically insoluble in water (<0.1 mg/mL) and very slightly soluble in ethanol (0.2 mg/mL), but is very soluble in ethyl acetate and acetone.

Elbasvir has the following structural formula:



CAS registry number: 1370468-36-2

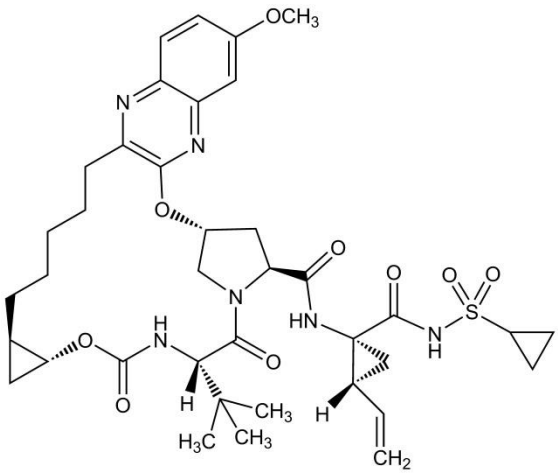
Elbasvir has the following chemical name: Dimethyl *N*,*N*′-([(6*S*)-6-phenylindolo[1,2-*c*][1,3]benzoxazine-3,10-diyl]bis{1*H*-imidazole-5,2-diyl-(2*S*)-pyrrolidine-2,1-diyl[(2*S*)-3-methyl-1-oxobutane-1,2-diyl]})dicarbamate.

It has a molecular formula of $C_{49}H_{55}N_9O_7$ and a molecular weight of 882.02.

Grazoprevir:

Grazoprevir is a hepatitis C virus (HCV) NS3/4A protease inhibitor. It is practically insoluble in water (<0.1 mg/mL) but is freely soluble in ethanol and some organic solvents (e.g., acetone, tetrahydrofuran and N,N-dimethylformamide).

Grazoprevir has the following structural formula:



CAS registry number: 1350514-68-9

Grazoprevir has the following chemical name: (1a*R*,5*S*,8*S*,10*R*,22a*R*)-*N*-[(1*R*,2*S*)-1-[(Cyclopropylsulfonamido)carbonyl]-2-ethenylcyclopropyl]-14-methoxy-5-(2-methylpropan-2-yl)-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro-8*H*-7,10-methanocyclopropa[18,19][1,10,3,6]dioxadiazacyclononadecino[11,12-*b*]quinoxaline-8-carboxamide.

It has a molecular formula of $C_{38}H_{50}N_6O_9S$ and a molecular weight of 766.90.

7. MEDICINE SCHEDULE

Prescription Only Medicine

8. SPONSOR

Merck Sharp & Dohme (NZ) Limited

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Newmarket Auckland

New Zealand

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9. DATE OF FIRST APPROVAL

01 December 2016

10. DATE OF REVISION OF THE TEXT

22 May 2017

SUMMARY TABLE OF CHANGES

Date	Change
March 2017 (CCDS-032017)	Added risk of HBV re-activation in patients co-infected with HCV and HBV Added close monitoring of INR values is recommended in patients treated with vitamin K antagonists Added information on effect on driving and using machines Reformat data sheet;
22 May 2017	Added section on reporting of suspected adverse reactions