Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Grazoprevir / Elbasvir

Proprietary Product Name: Zepatier

Sponsor: Merck Sharpe and Dohme (Australia) Pty Limited.

**Date of first round report: 17 December 2015**

**Date of second round report: 15 April 2016**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

# Contents

# List of common abbreviations

| Abbreviation | Meaning |
|---|---|
| AE | adverse event |
| $Ae_{0-24}$ | amount of analyte that is eliminated in urine over 24 hours |
| $AE_D$ | cumulative amount of drug recovered from dialysate samples |
| ALP | alkaline phosphatase |
| ALT | serum alanine aminotransferase |
| AST | aspartate aminotransferase |
| ATV | atazanavir |
| AUC | area under the plasma concentration/time curve |
| $AUC_{0-24}$ | area under the plasma concentration versus time curve over 24 hours |
| $AUC_{0-inf}$ | AUC extrapolated to infinity |
| $AUC_{0-\tau}$ | area under the concentration-time curve from 0 to dosing interval, τ (τ = 24 hours) |
| BCRP | breast cancer resistance protein |
| BID | twice-daily |
| BLOQ | below the lower limit of quantitation |
| BLQ | below the limit of quantitation |
| BMI - | body mass index |
| BMS-790052 | daclatasvir |
| C0 | plasma concentration prior to dosing |
| $C_{24}$ or $C_{24}h$ | plasma concentration 24 hours following the preceding dose |
| $C_2h$ | plasma concentration 2 hours post dosing |
| CatA | cathepsin A |
| CES | carboxylesterase |
| CHC | Chronic hepatitis C |
| CI | Confidence interval |

| Abbreviation | Meaning |
|---|---|
| CKD | Chronic kidney disease |
| CL | clearance |
| CL/F | apparent clearance |
| $CL_D$ | (Dialysis) Clearance estimated from the dialysate data |
| CLr | renal clearance |
| $C_{max}$ | maximum plasma concentration achieved |
| COWS | Clinical Opiate Withdrawal Scale |
| CPK | creatine phosphokinase |
| C-SSRS | Columbia Suicide Severity Rating Scale |
| CWRES | conditional weighted residuals |
| Cτ or Ctrough | trough plasma concentrations |
| DAA | Direct acting antiviral |
| DFC | dry-filled capsule |
| DRV | darunavir |
| EBR | Elbasvir |
| ECG | electrocardiogram |
| ECI | events of clinical interest |
| EE | ethinyl estradiol |
| eGFR | estimated glomerular filtration rate |
| EOT | End of Treatment |
| ESRD | end-stage renal disease |
| EVR | early virologic response |
| F | absolute bioavailability |
| FAS | Full Analysis Set |
| FDC | fixed dose combination |

| Abbreviation | Meaning |
|---|---|
| fe | urinary excretion |
| FFP | fit-for-purpose |
| FMI | final market image |
| Free combination | co-administration of the individual tablets of EBR/GZR given at the same dosage strength as the FDC |
| FSH | follicle-stimulating hormone |
| FW | Follow-up Week |
| geometric CV% | coefficient of variation/variability |
| GM | geometric mean |
| GMR | geometric mean ratio |
| GT | Genotype |
| GT1 | genotype 1 |
| GT3 | genotype 3 |
| GZR | Grazoprevir |
| HBsAg | Hepatitis B surface antigen |
| HCV | Hepatitis C virus |
| HD | haemodialysis |
| HIV | Human immunodeficiency virus |
| IBD | Inherited blood disorders, including haemophilia, thalassemia and sickle cell anaemia |
| ICF | informed consent form |
| IFN | interferon |
| IL28B | Interleukin 28B (interferon, lambda 3) |
| IPRED | geometric means of individual predicted values |
| IV | intravenous |
| IWRES | individually weighted residuals |

| Abbreviation | Meaning |
|---|---|
| LC-MS/MS | liquid chromatographic tandem mass spectrometry |
| LLoQ | Lower limit of quantification |
| LLOQ | lower limit of quantitation |
| ln | natural log |
| LNG | levonorgestrel |
| LPV | lopinavir |
| LS | least squares |
| mFAS | Modified full analysis set |
| MK-5172 | Grazoprevir |
| MK-8742 | Elbasvir |
| MMF | mycophenolate mofetil |
| MPA | mycophenolic acid |
| MPAG | mycophenolic acid glucuronide |
| MRL | Merck |
| NA, N/A | Not applicable |
| NC | Non cirrhotic |
| NONMEM | non-linear mixed effects modelling |
| NR | Null responder |
| NS5A | nonstructural protein 5A - a phosphoprotein that plays a role in HCV RNA replication |
| NS5B | nonstructural protein 5B |
| OATPs | organic anion transporters |
| OC | oral contraceptive |
| OCT | oral compressed tablet |
| OFV | objective function value |
| OST | Opiate substitution therapy |

| Abbreviation | Meaning |
|---|---|
| OTVF | On Treatment Virologic Failure |
| PD | pharmacodynamics |
| PEG | polyethylene glycol |
| peg-IFN | Pegylated interferon alfa |
| PEP | Pooled efficacy population |
| P-gp | P- glycoprotein |
| PI | Protease inhibitor |
| PI/RTV | protease inhibitor/ritonavir |
| PK | pharmacokinetics |
| PMF | preliminary market formulations |
| PMF1 | prototype pre-market formulation 1 |
| PO | per oral (by mouth) |
| PP | Per Protocol |
| PPC | post predictive check |
| PR | Peginterferon alfa + ribavirin |
| PR interval | time from the onset of the P wave to the start of QRS complex (onset of ventricular depolarisation) |
| PRED | geometric means of typical individual predictions |
| PTF | Prior treatment failure |
| QD | once daily |
| QTc | corrected QT interval |
| QTcF | QT interval with Fridericia's Correction |
| QTcP | population-corrected QTc |
| RAP | Resistance Analysis Population |
| RAV | Resistance-associated variant |
| RBV | Ribavirin |

| Abbreviation | Meaning |
|---|---|
| RNA | ribonucleic acid |
| RR | respiratory rate |
| RTV | ritonavir |
| RVR | rapid virologic response |
| SAE | serious adverse event |
| SD | Standard deviation |
| SEM | standard error of the mean |
| SOC | system organ classes |
| SVR | sustained virologic response |
| SVR12 | Sustained virologic response, having plasma HCV RNA <25 IU/mL at 12 weeks after the end of all study therapy after becoming undetectable (TND) at end of treatment |
| SVR24 | Sustained virologic response, having plasma HCV RNA <25 IU/mL at 24 weeks after the end of all study therapy after becoming undetectable (TND) at end of treatment |
| $t_{1/2}$ | apparent half-life |
| TD(q) | Target detected, quantifiable (HCV RNA ≥25 IU/mL) |
| TD(u) | Target detectable, unquantifiable (HCV RNA <25 IU/mL) |
| TE | Treatment experienced |
| TEAE | treatment emergent adverse event |
| $T_{max}$ | time that at which the maximum plasma concentration is obtained |
| TN | Treatment naïve |
| TND | Target not detected (HCV RNA not detected) |
| TRD | Treatment-Related Discontinuation |
| TW | Treatment Week |
| UGT | uridine 5'-diphospho-glucuronosyltransferase |
| ULN | upper limit of normal |

| Abbreviation | Meaning |
|---|---|
| Vd | volume of distribution |
| Vss | apparent volume of distribution at steady state following an intravascular administration |
| Vz/F | apparent volume of distribution |
| WAM | Wald's Approximation Method |
| WBC | white blood cell count |

# 1. Introduction

This is a Category 1 application to register a new chemical entity for treatment of chronic hepatitis C infection in adults (Table 1).

**Table 1: Submission details**

| | |
|---|---|
| **Submission number** | PM-2015-02428-1-2 |
| **Sponsor** | Merck Sharpe and Dohme Pty Ltd. |
| **Trade name** | Zepatier |
| **Active substance** | Grazoprevir/ Elbasvir 100mg/ 50mg |

Zepatier (also known as MK-5172A) is a fixed dose combination of two Direct Acting Antiviral (DAA) agents targeting different and complimentary aspects of Hepatitis C replication:

- Grazoprevir (also known as MK-5172) is a second generation HCV NS3/4A protease inhibitor (PI).
- Elbasvir (also known as MK-8741) is a second generation HCV NS5A inhibitor.

The proposed indication is '*Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity.)*'.

# 2. Clinical rationale

Hepatitis C is the most prevalent blood-borne virus in Australia and it is estimated there are approximately 230, 000 Australians living with Chronic Hepatitis C (CHC) infection. Despite recent TGA registration of several oral DAA regimens for treatment of HCV infection there remains significant unmet medical need and a lack of therapeutic options for several patient subgroups for example, interferon and ribavirin-free regimens for patients with severe renal disease on haemodialysis and patients with HCV genotype 4 or 6. Until 2011, the standard of care treatment for chronic hepatitis C (CHC) infection was peginterferon alfa (peg-IFN) plus ribavirin (RBV) (together, abbreviated as PR) for 24 to 48 weeks and this therapy resulted in SVR in 40-50% and 60-70% of treated GT1/GT4 and GT2/GT3 patients, respectively. However, net benefit of this therapy was limited by major AEs and poor tolerability.

A better understanding of the biology of HCV led to the development of Direct-Acting Antivirals (DAAs), medicines that directly target HCV proteins critical to viral replication. These DAAs inhibit one of three major viral proteins: the NS3/4a protease, the NS5A protein, and NS5B RNA polymerase. Due to genotype-specific differences among these proteins, the potency of DAAs may vary by genotype. The first generation of DAAs, including the NS3/4A protease inhibitors (PIs) boceprevir, telaprevir and simeprevir, were evaluated as add-ons to PR. However, these agents were GT1 specific and also had low potency against commonly-found viral variants. Nevertheless, these PIs/PR regimens increased the proportion of GT1 patients that achieved SVR with 80% achieving SVR12 among treatment-naïve (TN), non-cirrhotic patients.

Since 2013, other DAAs have become available, and there is now clear evidence that interferon-free regimens, consisting of combinations of DAAs targeting different targets in the HCV life cycle, can be highly effective in clearing chronic HCV infection Although these interferon-free regimens were better tolerated, adverse events (AE) related to RBV (for example, anaemia, fatigue, gastrointestinal symptoms) remained. Therapy required administration of multiple tablets daily, as well as stringent pregnancy precautions. An understanding of HCV biology and

the results of the clinical studies with single DAAs suggest that a highly efficacious interferon-free regimen for treatment of HCV infection requires combined therapy with at least two highly potent direct acting antivirals targeting the HCV life-cycle. For example, an 8 or 12 week regimen combining sofosbuvir and the NS5A protein inhibitor (NS5AI) ledipasvir has been demonstrated to result in SVR12 in >90% of TN non-cirrhotic subjects. Among cirrhotics who failed prior PR-based therapies, a 24 week duration, or addition of ribavirin, is needed to achieve SVR12 in >90% of treated patients. Given the diversity of the HCV population as well as the virus types that cause the disease, there is a need for several effective and well-tolerated regimens for treatment of HCV infection.

Grazoprevir (MK-5172 or GZR) is a once-daily PI with a high potency against GT1, GT2, GT4 GT6, with somewhat less potency against GT3; in vitro, it retains high potency against resistance associated variants (RAVs) that are commonly detected among individuals who fail therapies with first generation PIs such as boceprevir, telaprevir, and simeprevir. However, efficacy was lower in cirrhotics and in patients with GT1a infection.

Elbasvir (MK-8742 or EBR) is a once-daily NS5AI with high potency against GT1, GT2a, GT3, GT4, GT5 and GT6; in vitro, it retains potency in the presence of RAVs associated with failure of other NS5A inhibitors such as daclatasvir and ledipasvir.

Pre-clinical data suggested that co-administration of GZR with EBR would create a highly potent regimen for HCV GT1 patients with potential utility in GT3 patients. A fixed-dose combination (FDC) of GZR/EBR has been developed, to improve compliance and convenience with a simple daily dosing regimen, low pill burden of one tablet, low potential for medication error, and no potential for off-label use of individual components. HCV genotype (GT) 1 is the most prevalent genotype in Australia accounting for approximately 55% of infections. The remaining genotype distributions are 5.2% GT2, 36.8% GT3, 1.9% GT4 and 1.6% GT6. In Australia, there is currently no approved therapeutic regimen for treatment of HCV GT4 or GT6 infection that does not require concomitant administration of ribavirin or pegylated interferon. These drugs have poor tolerability and the treatment burden is well documented, resulting in AEs, discontinuation of treatment and failure to achieve 'cure'. Zepatier would address this unmet medical need as it offers peginterferon and ribavirin-free dosing in these patients. This application presents clinical data in HCV GT4 and GT6 infected patients.

HCV has a significant adverse effect on the progression of renal disease and outcomes of renal transplants. HCV infection and Chronic Kidney Disease (CKD) results in a burden of mortality that is greater than the sum of morbidity and mortality caused by each condition alone. There is currently no registered treatment for patients with chronic HCV infection with severe renal impairment receiving haemodialysis. The DAAs currently approved for treatment of HCV infection in Australia are not suitable for use in patients with severe renal disease as these agents are either excreted primarily through the renal pathway (sofosbuvir-based regimens or require co-administration of pegylated interferon and/or ribavirin). In addition to their tolerability limitations, ribavirin exacerbates renal-failure related anaemia. The efficacy and safety of GZR/EBR FDC (Zepatier) has been evaluated in a study (P052) in 225 HCV patients with CKD Stage 4 or 5 of whom 76% were receiving haemodialysis.

The proposed FDC of GZR+EBR (100/50 mg) hopes to address the unmet medical needs for subgroups of HCV-infected subjects such as those with CKD and other 'hard to cure' patients such as with cirrhosis, HIV co-infection, GT4 and GT6.

### 2.1.1. Guidance

The sponsor has sought TGA's support in accelerating the review and registration process based on unmet clinical need in Australia for: treatment of Chronic Hepatitis C in patients with severe renal disease, including those receiving haemodialysis, and the limited therapeutic options for patients with HCV genotypes 4 and 6.

Breakthrough Therapy designation was granted on October 18, 2013 for MK-5172/MK-8742 for the treatment of chronic HCV GT1 infection. This designation was rescinded on April 1, 2015, based on the recent approval of treatment regimens demonstrating SVR12 rates of 94-100% with overall favourable safety profiles in this population. Breakthrough Therapy designation was granted on April 1, 2015 for MK-5172/MK-8742 for the treatment of chronic HCV GT-1 infection in patients with advanced CKD disease on haemodialysis. Breakthrough Therapy designation was also granted on April 1, 2015 for MK-5172/MK- 8742 for the treatment of patients with chronic HCV GT-4 infection.

Regulatory advice on the Clinical Development Program was obtained from the CHMP via a Scientific Advice Procedure on April 29, 2014. The proposed Phase III trials were judged acceptable in terms of patient population, dose selection/treatment duration, primary efficacy endpoint and time point for assessment, statistical analysis approach and criteria for success. Plans for development of a fixed-dose combination tablet were acceptable.

The TGA had communicated via the Planning Letter that a Risk Management Plan is a requirement for this submission and requested the submission of the current EU-RMP with an Australian Specific Annex. This has been provided.

# 3. Contents of the clinical dossier

## 3.1. Scope of the clinical dossier

The submission contained the following clinical information:

- Fifty-nine clinical pharmacology studies, including 59 that provided pharmacokinetic data and 4 that provided pharmacodynamic data.
- Two population pharmacokinetic analyses.
- Nine core efficacy/safety studies as listed below:

  *Two Controlled Phase II/III studies:*

  – P060 'C-EDGE TN' is a Phase III randomised, parallel group, placebo-controlled double-blind clinical study evaluating 12 weeks of GRZ/EBR treatment without RBV in 468 Treatment Naïve subjects infected with HCV GT1, 4 or 6.

  – P052 'C-SURFER' is a Phase II/III, randomised, parallel group placebo controlled, double-blinded clinical study evaluating 12 weeks of treatment with GRZ+EBR without RBV in 235 subjects with Renal Failure infected with HCV GT1, including some diabetic subjects.

  *Two Uncontrolled Phase III studies:*

  – P061 'C-EDGE COINFXN' is a Phase III unblinded open-label single-arm study evaluating 12 weeks of GRZ/EBR treatment without RBV in 218 subjects co-infected with HIV and HCV GT 1, 4 or 6.

  – P068 'C-EDGE TE' is a Phase III randomised, open-label, parallel group, placebo-controlled clinical study evaluating 12 or 16 weeks of GRZ/EBR treatment with or without RBV in 420 Treatment Experienced subjects with prior failure (Prior Treatment Failure) on peginterferon (PEG) infected with HCV GT1, 4 or 6.

  *Core Phase II studies:*

  – P048 'C-SALVAGE' is a Phase II open-label, single-arm clinical study evaluating 12 weeks of treatment with GRZ + EBR + RBV in 79 Treatment Experienced Prior Treatment

Failures with Direct Acting Antivirals (boceprevir, telaprivir, simeprevir or sofosbuvir + PEG + RBV) infected with HCV GT1.

- P074 'C-SWIFT' is a Phase II randomised open-label clinical study investigational shorter regimens of 4, 6, 8 or 12 weeks treatment with GRZ/EBR + sofosbuvir in 143 subjects infected with HCV GT1 or 3 who received.
- P059 is a Phase II/III nonrandomised open-label study evaluated 12 weeks of GRZ+EBR treatment without RBV in 130 subjects with Child Pugh B cirrhosis and HCV GT1 infection.
- P047 'C-SCAPE' is a Phase II open-label study evaluating 12 weeks of GZR therapy with or without EBR and/or RBV in 98 non-cirrhotic subjects infected with HCV GT2, 4, 5 or 6.
- P035C 'C-WORTHY' is a randomised Phase II study evaluated GRZ+EBR for 8, 12 or 18 weeks with or without RBV in 468 cirrhotic subjects infected with GT1b.

- Six supportive studies including three dose-finding Phase II studies (P003, P038, P035) and three other supportive studies (P058, P039 and P047).

**Comment**: P035 was the main Phase II study for determining the dose of EBR, the treatment duration and the patient population to be evaluated in the core Phase II/III studies and this study has been discussed below.

- Two ongoing studies: *Study P062* in HCV infected subjects on opiate substitution treatment and *Study P065* in HCV-infected subjects with inherited blood disease (IBD). Another ongoing, long-term follow-up study *(P017*) to evaluate the durability of virologic response and/or viral resistance patterns among subjects with chronic Hepatitis C who have been previously treated with GZR in a prior clinical trials (P035 and P047).
- Pooled analyses, meta-analyses, Integrated Summary of Efficacy, Integrated Summary of Safety, etc.

### 3.1.1. Paediatric data

The submission did not include paediatric data.

An agreed-upon Paediatric Study Plan (PSP) was submitted on January 21, 2015 to the FDA, and included a deferral of paediatric assessments until after approval of the NDA in adults, and a waiver for paediatric assessments in patients less than 3 years of age.

On December 12, 2014, the Paediatric Committee of the European Medicines Agency granted a positive opinion for the Paediatric Investigation Plan for MK-5172/MK-8742, including a waiver for subjects less than 3 years of age and deferral of proposed studies.

### 3.1.2. Good clinical practice

All the clinical studies were conducted in conformance with GCP standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. The only exception was the ongoing Phase II Study P059 in which some minor GCP non-compliance issues were observed (discussed in Efficacy section of the report).

# 4. Pharmacokinetics

Table 2 (below) shows the studies relating to each pharmacokinetic topic.

**Table 2: Submitted pharmacokinetic studies**

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| PK in healthy adults | General PK | 5172-P069 | Effect of a high fat meal on the GZR and EBR PKs following a single dose of the FDC tablet |
| | | 5172-P055 | GZR and EBR PKs following a single dose of $FDC_2$ cf. free combination |
| | | 5172-P040 | GZR F following $^{14}C$-micro-dosing |
| | | 8742-P020 | F of a single dose of EBR relative to [$^{13}C10$, $^{15}N2$] EBR administered as an IV micro-dose. |
| | | 5172-P045 | PKs of GZR PMF1 cf. PKs of capsule formulation |
| | | 5172-P002v1 | PKs of 3 candidate PMFs of GZR relative to the FFP tablet |
| | | 5172-P008 | PKs of GZR from two different PMF versus the Phase I FFP |
| | | 5172-P027 | PK profile of 100 mg GZR with and without famotidine |
| | | 5172-P001v01 | PKs following single-rising oral doses of GZR and food effect. In addition, DDIs b/w single dose ketonazole and single dose of 200 mg GZR |
| | | 8742-P005 | PK profiles of 100 mg EBR with and without famotidine |
| | | 8742-P001v01 | PKs of EBR after single and multi-oral dose administrations |
| | | 8742-P0018 | Effect of a high-fat meal on the PKs of EBR PMF2 |
| | | 8742-P006v01 | PKs following 50 mg EBR for 28 consecutive days |
| | | 5172-P050 | PKs of multiple daily doses of GZR and EBR co-administered to subjects with ESRD on HD days to those obtained on non HD days and in healthy subjects |
| | | 5172-P007 | Elimination and mass balance of GZR following a single oral dose of [$^{14}C$]GZR |
| | | 8742-P014 | Elimination and mass balance of EBR following a single oral dose of [$^{14}C$]EBR |
| | | 045496 | popPK model of GZR PKs in healthy subjects and HCV infected patients |

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| | | 044ZSQ | popPK model of EBR PKs in healthy subjects and HCV infected patients |
| Target population§ | HCV patients | 5172-P004v02 | PKs and anti-viral activity of GZR administered for 7 consecutive days to HCV-infected male patients |
| | | 8742-P002v02 | PKs and anti-viral activity of GZR administered for 5 consecutive days to HCV-infected male patients |
| Special populations | Hepatic impairment | 5172-P013 | PKs of GZR following 10 days dosing to patients with mild-, moderate- and severe-hepatic insufficiency without hepatitis C and healthy subjects |
| | | 8742-P009 | PKs of EBR following a single dose to patients with mild-, moderate- and severe-hepatic insufficiency and healthy subjects |
| | Age | 5172-P014 | PKs of multi-dose GZR in healthy elderly male and female subjects |
| | | 8742-P004 | PKs of a single oral dose of EBR in healthy elderly male, healthy elderly female and healthy young male subjects |
| | Race | 5172-P009 | PKs of GZR following single and multiple QD oral doses to healthy young Japanese subjects |
| | | 7009-P050 | PKs of EBR following a single oral dose to healthy Japanese subjects |
| | | 5172-P042 | PKs of GZR following multiple doses of GZR in healthy Chinese subjects |
| Interaction Studies | Active components | 8742-P008 | DDIs between single and multiple doses of GZR and EBR |
| | CYP3A substrates and strong CYP3A inhibitors | 5172-P053 | DDI b/w free-combination of GZR FFP and EBR FFP (200 mg/50 mg QD) and rilpivirine |
| | | 5172-P029 | DDI b/w 200 mg GZR QD and either LPV/RTV (400/100 mg BD), ATV/RTV (300/100 mg BD) or DRV/RTV (600/100 mg BD) |
| | | 8742-P017 | DDI b/w 50 mg EBR QD and either LPV/RTV (400/100 mg BD), ATV/RTV (300/100 mg BD) or DRV/RTV (600/100 mg BD) |
| | CYP3A4 | 5172-P073 | DDIs b/w a single-dose of 400 mg cyclosporine, tacrolimus, MMF and prednisone, and multiple |

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| | substrates | | doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg QD) |
| | | 5172-P076 | DDIs b/w a single-dose of 10 mg atorvastatin and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg QD) |
| | | 5172-P030 | DDIs b/w multiple doses of 200 mg GZR QD and either methadone or buprenorphine/naloxone |
| | | 5172-P032 | DDIs b/w multiple doses of 200 mg GZR QD and midazolam (2 mg) or atorvastatin (20 mg) or pitavastatin (1 mg) |
| | | 5172-P046 | DDIs b/w multiple doses of 200 mg GZR QD and a single-dose of OC (EE 0.03 mg/LNG 0.15 mg) |
| | | 5172-P070 | DDIs b/w multiple oral doses of 200 mg GZR QD and montelukast (10 mg) |
| | | 8742-P010 | DDIs b/w multiple doses of 50 mg EBR QD and methadone |
| | | 8742-P021 | DDIs b/w a single dose buprenorphine/naloxone (8 mg/2 mg) and single oral dose of 50 mg EBR. |
| | | 8742-P013 | DDIs b/w multiple doses of 50 mg EBR QD and a single dose of OC (0.03 mg EE/0.15 mg LNG) |
| | Strong CYP3A4 inhibitors | 5172-P006v01 | DDIs b/w multiple doses of 100 mg RTV BD and a single-dose of 200 mg GZR |
| | | 8742-P003 | DDIs b/w multiple doses of 400 mg ketoconazole and a single-dose of 50 mg EBR |
| | CYP3A4 - inducers | 5172-P031 | DDIs b/w GZR (200 mg QD) and rifampin (600 mg QD or SD) or efavirenz (600 mg QD) |
| | | 8742-P011 | DDIs b/w a single IV or oral dose of rifampin (600 mg) and a single oral dose of EBR (50 mg) |
| | | 8742-P016 | DDIs b/w multiple oral doses of EBR (50 mg QD) and multiple doses of efavirenz (600 mg QD) |
| | HMG CoA reductase inhibitors. | 5172-P054 | DDIs b/w a single 10 mg dose of rosuvastatin or a single dose of pravastatin and multiple doses of GZR (200 mg QD) alone or with multiple doses of GZR/EBR (200 mg/50 mg QD) |
| | CYP2C19 – substrate | 5172-P072 | DDIs b/w multiple oral doses of pantoprazole (40 mg QD) or famotidine (20 mg) and multiple oral doses of a 100 mg GZR/50 mg EBR FDC |

| PK topic | Subtopic | Study ID | * |
|---|---|---|---|
| | | | tablet |
| | UGT1A1 – substrates | 5172-P057 | DDIs b/w a single oral 50 mg dose of dolutegravir and multiple oral doses of GZR and EBR (200 mg/50 mg QD). |
| | BCRP- and P-gp-substrates | 5172-P063 | DDIs b/w multiple oral doses of GZR and EBR (200 mg/50 mg QD) and a single oral 400 mg dose sofosbuvir |
| | | 8742-P023 | DDIs b/w multiple oral doses of EBR (50 mg QD) and a single dose of 0.25 mg digoxin |
| | HIV nucleoside reverse transcriptase inhibitor | 5172-P026 | DDIs b/w multiple oral doses of GZR (200 mg QD) and tenofovir (300 mg QD) |
| | Inhibitors of NS5A | 5172-P023 | DDIs b/w multiple oral doses of GZR (400 mg QD) and GS-5885 (90 mg QD). |
| | | 5172-P036 | DDIs b/w multiple oral doses of GZR (200 mg QD) and 60 mg daclatasvir |
| | | 8408-P004 | DDIs b/w multiple oral doses of GZR (200 mg QD) and MK8408 (60 mg QD) |
| | Inhibitor of NS3/4A | 2748-P004 | DDIs b/w multiple oral doses of EBR (50 mg QD) and MK-2748 (400 mg QD) |
| | Inhibitors of NS5B | 3682-P007 | DDIs following multiple oral doses of GZR/EBR (200 mg QD/50 mg QD) and MK-3682 (300 mg QD) |
| | | 3682-P008 | DDIS b/w steady state levels of MK-3682 (300 mg QD) and steady state levels of GZR (200 mg QD) and MK-8408 (60 mg QD) |
| | Phosphate–binder drugs | 5172-P056 | DDIs b/w a single oral dose of 100 mg GZR and 50 mg EBR and either calcium acetate or sevelamer carbonate |

cf. - compared with; b/w – between
* Indicates the primary aim of the study.
§ Subjects who would be eligible to receive the drug if approved for the proposed indication.

None of the pharmacokinetic studies had deficiencies that excluded their results from consideration.

## 4.1. Summary of pharmacokinetics

The information in the following summary is derived from conventional pharmacokinetic studies unless otherwise stated.

**Comment**: It should be noted that relatively few studies undertaken as part of this submission have examined the PKs of the FDC. Where this data exists it will be preferentially reported in this evaluation. In its absence, studies examining the PMF formulations of the individual active components will take preference over studies examining the FFP formulations.

### 4.1.1. Analytical methods

Plasma GZR concentrations were determined using either liquid chromatography-tandem mass spectrometric (LC/MS/MS) or ultra-performance chromatographic-tandem mass spectrometric detection (UPLC/MS/MS) methods. The lower limit of quantitation (LLOQ) for GZR was 1.00 ng/mL (1.30 nM).

EBR levels in plasma were determined using either validated LC/MS/MS or UPLC/MS/MS methods. The LLOQ for both assays was 0.25 ng/mL (0.28 nM).

### 4.1.2. Pharmacokinetics in healthy subjects

#### *4.1.2.1. Absorption*

*Sites and mechanisms of absorption*

Zepatier FDC tablets containing 100 mg GZR and 50 mg EBR are intended for oral dosing.

Two studies examined the PKs of GZR and EBR following administration of a single, oral dose of the $FDC_2$ (GZR/EBR 100 mg/50 mg) to healthy subjects in the fasted state (Studies 5172-P069 and 5172-P055). Under these conditions the GZR median $T_{max}$ values ranged from 2.0 h to 3.0 h whereas, EBR median $T_{max}$ occurred at 3.5 h in both studies.

#### *4.1.2.2. Bioavailability*

*Absolute bioavailability*

No studies examined the absolute bioavailability (F) of the FDC. However, Study 5172-P040 examined the F of GZR following a single oral 200 mg dose of GZR FFP relative to a 100 µg IV bolus micro-dose in six healthy subjects. In this study a number of different forms of analysis were undertaken but the results of the co-primary analyses, in which individual GZR F (%) values were calculated as the individual dose-normalised AUC ratios between the oral and IV doses, for each period separately, indicated that the mean F values for GZR were 27.3 % and 14.9% for co-primary analysis 1 and co-primary analysis 2, respectively. Similarly Study 8742-P020 examined the F of EBR following a single oral dose of 50 mg EBR in a fasted state, followed by a single IV bolus micro-dose of 100 µg [$^{13}$C10, $^{15}$N2] EBR administered at 3.5 h after oral dosing in six healthy subjects. The results indicate that the EBR F (%) GM (90% CI) was 32.4 (27.0, 38.8).

*Bioavailability relative to an oral solution or micronised suspension*

Not applicable.

*Bioequivalence of clinical trial and market formulations*

*FDC and free-combination*

Study 5172-P055 examined the bioequivalence of the $FDC_2$ (GBZ/EBR 100 mg/50 mg) and a free-combination of 100 mg GZR FFP tablet and 50 mg EBR PMF2 tablet following a single oral dose in fasted healthy subjects. The results indicated that although the $FDC_2$ and the free-combination were bioequivalent (that is, the 90% CI for the GMR fell between 0.80 and 1.25) in regards to GZR $AUC_{0\text{-inf}}$ (GMR: 0.94; 90%CI: 0.84, 1.07), the two treatments were not

bioequivalent in regards to GZR $C_{max}$ (0.94; 0.78, 1.12), EBR $C_{max}$ (1.18; 1.05, 1.33) or EBR $AUC_{0\text{-}inf}$ (1.15; 1.04, 1.26).

**Comment**: Although not strictly bioequivalent, the differences in exposure between the fixed-dose and free-combinations were relatively small (max difference of 18%); therefore, these differences are unlikely to be clinically significant.

*Different forms of EBR in the presence of GZR*

Study 5172-P045 compared the PKs of different forms of EBR (50 mg of PMF1, PMF2 and the FFP formulation) when administered with GZR (100 mg, FFP) in healthy subjects aged 20 to 54 years. In addition, the PKs of EBR were also examined following administration of a test FDC (FDC1) and EBR PMF2 or EBR FFP in the presence of famotidine. The results indicated that although not strictly bioequivalent, when EBR PMF2 was co-administered with GZR FFP the $C_{max}$ and $AUC_{0\text{-}inf}$ values for EBR were similar to those seen when EBR FFP was co-administered with GZR FFP with GMRs (90% CIs) of 0.93 (0.74, 1.18) and 0.92 (0.70, 1.19) for the two PK parameters, respectively. By contrast, following administration of EBR PMF1 in the presence of GZR or FDC1, EBR exposures were significantly lower than when EBR FFP was co-administered with GZR FFP and these formulations were not evaluated further.

*GZR PMF and FFP*

Study 5172-P002v1 assessed PKs of 3 candidate PMFs of GZR (formulations 002, 003 and 004) relative to the FFP tablet formulation following single doses in healthy subjects. Following a 600 mg dose of each formulation, all 3 candidate PMF formulations demonstrated reduced GZR exposure compared to the FFP tablet with the GMR $C_{max}$ values ranging from 0.05 to 0.42 and the GMR $AUC_{0\text{-}inf}$ values ranging from 0.15 to 0.56.

A second study, Study 5172-P008 compared the GZR PKs of a further two PPF formulations (005 and 006) to the FFP tablet following a single 600 mg dose to healthy subjects. The GMRs (PMF 005/FFP 001) and 90% CIs for the statistical comparison of GZR were 1.21 (0.97, 1.51) for $AUC_{0\text{-}inf}$, 1.35 (1.00, 1.83) for $C_{max}$, and 0.98 (0.90, 1.08) for $C_{24}h$. By contrast, the GMRs (PMF 006/FFP 001) for the statistical comparison of GZR were 0.56 (0.45, 0.70) for $AUC_{0\text{-}inf}$, 0.52 (0.39, 0.70) for $C_{max}$ and 0.85 (0.76, 0.94) for $C_{24}h$. Speed of absorption was similar for all three GZR formulations (median $T_{max}$ range of 3.00 to 3.50 h) and $t_{1/2}$ ranged from 23.39 h to 26.25 h. The results of the study indicated that PKs of formulation 05 were similar enough to those of the FFP.

*Bioequivalence of different dosage forms and strengths*

Not applicable.

*Bioequivalence to relevant registered products*

Not applicable.

*Influence of food*

*FDC*

Study 5172-P069 assessed the effect of a high fat meal on the GZR and EBR PKs following the administration of a single dose of the FDC tablet of GZR/EBR (100 mg GZR/50 mg EBR) to healthy subjects. For the GZR component, the GMRs and 90% CIs of the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $C_{max}$ and $C_{24}h$ of the fed state versus the fasted state for the FDC tablets were 1.54 (1.34, 1.76), 1.91 (1.67, 2.18), 2.83 (2.16, 3.72) and 1.65 (1.47, 1.85), respectively. Median $T_{max}$ and mean $t_{1/2}$ values for GZR were 2.0 h after a high fat breakfast and 3.0 h in a fasted state and 30.98 h after a high fat breakfast and 35.80 h in a fasted state, respectively. For EBR, the GMRs of the $AUC_{0\text{-}inf}$, $AUC_{0\text{-}t}$, $C_{max}$ and $C_{24}h$ of the fed state versus the fasted state for the FDC tablets were 0.891 (0.817, 0.971), 0.885 (0.812, 0.964), 0.852 (0.772, 0.941) and 0.926 (0.850, 1.01), respectively. Median

$T_{max}$ was 3.5 h after a high fat breakfast and 3.0 h in a fasted state, whereas, the $t_{1/2}$ was similar in both states (approximately 17.75 h).

*Other studies*

A number of other studies examined the effects of a high fat meal on the various developmental forms of GZR and EBR. These included *Studies 5172-P027* and *5172-P001v01* for GZR FFP formulation and *Studies 8742-P005* and *8742-P001v01* for EBR FFP and *Study 8742-P0018* for the EBR PMF2 formulation. As the current application is for the FDC tablet only these studies will not be discussed further at this time.

#### *4.1.2.3. Dose proportionality*

*FDC*

No dedicated PK studies examined the dose proportionality of the FDC tablet in healthy subjects.

*GZR FFP*

Study 5172-P001v01 assessed the PKs of GZR following single-rising oral doses of GZR FFP (2 to 1600 mg) in fasted, healthy young males. At doses between 2 - 10 mg, GZR could not be detected in plasma and therefore no PK parameters could be determined. Following a 25 mg dose of GZR approximately 50% of the plasma concentrations were below the limit of quantitation (BLQ). At all other doses, GZR was rapidly absorbed with median $T_{max}$ ranging from 2.0 to 4.0 h and $t_{1/2}$ ranging from 16.6 to 42.9 h over the 50 mg to 1600 mg dose range. An exploratory analysis of dose proportionality suggests that $AUC_{0-24}$ and $C_{max}$ increased in a greater than dose proportional fashion over the dose range studied. For example, between doses of 400 and 800 mg GZR, GM $C_{max}$ and $AUC_{0-inf}$ increased by factors of approximately 10- and 6-fold, respectively.

*EBR FFP*

Study 8742-P001v01 examined the PKs of EBR following single doses ranging from 5 to 400 mg EBR in healthy males under fasted conditions. Following single-dose administration, EBR was rapidly absorbed with median $T_{max}$ ranging from 3.5 to 4.0 h and $t_{1/2}$ ranged from 14.5 to 19.9 h over the 5 mg to 400 mg dose range. An exploratory analysis of dose proportionality, conducted over the studied 5 mg to 100 mg dose range, suggested that AUC and $C_{max}$ increased in an approximately dose proportional fashion.

#### *4.1.2.4. Bioavailability during multiple-dosing*

*FDC*

No dedicated PK studies examined bioavailability following multiple doses of the FDC tablet in healthy subjects.

*GZR FFP*

Study 5172-P001v01 also assessed the PKs of GZR following single- and multiple doses of GZR FFP ranging from 100 mg to 1g. Following multiple-dose administration for 10 days, GZR median $T_{max}$ ranged from 2 to 4 h and the $t_{1/2}$ ranged from 16.9 to 24.7 h. Exploratory analysis of dose proportionality on Day 10 suggested that $AUC_{0-24}$ and $C_{max}$ increased in a greater than dose proportional fashion. The linearity ratios (steady-state Day 10 $AUC_{0-24}$/single-dose $AUC_{0-inf}$) were 1.17, 1.66 and 2.46 for doses of 100, 200, and 400 mg, respectively. Therefore, GZR PKs appear to be non-linear (time-dependent) with single-dose exposure not being predictive of multiple-dose exposure for the 200 - 400 mg doses.

Study 5172-P040 evaluated the absolute bioavailability (F) of GZR following seven once daily oral 200 mg dose of GZR FFP relative to a single 100 □g IV bolus micro dose administered on Day 7 in six healthy subjects. The geometric mean F of GZR after multiple dosing was 38.3% for co-primary analysis 1 and 21.4% for co-primary analysis 2.

*EBR FFP*

Study 8742-P001v01 examined the PKs of EBR FFP following single- and multiple doses of EBR FFP at doses ranging from 10 to 200 mg in healthy males. Following multiple-dose administration for 10 days, EBR had a median $T_{max}$ ranging from 2.5 to 4.0 h and $t_{1/2}$ of approximately 20 h over the 10 mg to 200 mg dose range. The linearity ratios (steady-state Day 10 $AUC_{0-24}$/single-dose $AUC_{0-inf}$) were 1.01, 0.86, 0.78, and 0.66 for doses of 10, 50, 100, and 200 mg, respectively. In contrast to GZR FFP, EBR PKs appears to be approximately linear (time-independent), with single-dose exposure predictive of multiple-dose exposure for 10 and 50 mg QD GM accumulation ratios for $AUC_{0-24}$ ranged from 0.981 at 100 mg to 2.05 at the 10 mg dose. Exploratory analysis of dose proportionality on Day 10 suggests that AUC and $C_{max}$ increased in an approximately dose proportional to slightly less than dose proportional fashion over the 10 mg to 100 mg dose range studied.

Study 8742-P006v01 examined EBR PKs following single and multiple-doses of 50 mg to healthy males. In this study, the accumulation ratios (steady-state Day 28/single-dose) for $AUC_{0\ 24}$ , $C_{max}$ and $C_{24}$ were 1.39 (1.13, 1.76), 1.20 (0.96, 1.50) and 1.46 (1.21, 1.77), respectively, whereas, the median $T_{max}$ was 4 h on both days.

#### *4.1.2.5. Effect of administration timing*

Not examined.

### 4.1.3. Distribution

#### *4.1.3.1. Volume of distribution*

No studies specifically examined the volume of distribution of GZR and EBR following dosing with the FDC. However, *Study 5172-P050* examined the apparent volume of distribution (Vz/F) following administration of 100 mg GZR and 50 mg EBR QD for 10 days in 8 healthy subjects as part of an investigation into the effects of end-stage renal disease (ESRD) on the PKs of the two active components. The results indicated that for the GZR and the EBR components the geometric mean Vz/F values (90% CIs) were 5760 L (4180, 7930) and 901 L (699, 1160), respectively.

#### *4.1.3.2. Plasma protein binding*

In vitro studies indicated that GZR has a plasma unbound fraction of 0.012 and binds to both human serum albumin and α1-acid glycoprotein; however, the binding of [$^3$H]GZR to human plasma proteins was low and was concentration independent over concentrations up to 10 μM. The mean blood/plasma concentration ratio was 0.7. By contrast, EBR is extensively bound to human plasma proteins, binding to both serum albumin and α1-acid glycoprotein, with an unbound fraction of <0.001. In the concentration range of 1-10 μM there was no evidence of saturation of plasma protein binding within the analytical limits of the assay (ranging from an unbound fraction of <0.001 to <0.005). The mean blood/plasma concentration ratio of EBR was determined in fresh human blood to be 0.62.

#### *4.1.3.3. Erythrocyte distribution*

The mean blood/plasma concentration ratios for GZR (0.7) and EBR (0.62) indicate that neither drug binds preferentially to red blood cells.

#### *4.1.3.4. Tissue distribution*

The relatively high Vz/F values for both GZR (5760 L) and EBR (901 L) indicate that both drugs are highly distributed within the tissues.

### 4.1.4. Metabolism

#### *4.1.4.1. Interconversion between enantiomers*

Not applicable.

#### *4.1.4.2. Sites of metabolism and mechanisms / enzyme systems involved*

Based on the results of the mass balance study, *5172-P007*, it is proposed that GZR elimination in man is likely mediated by both oxidative metabolism and biliary secretion. A second mass balance study, *8742-P014*, indicated that EBR elimination is mediated in part by oxidative metabolism as two mono-oxidative metabolites, M2 and M3, were identified in the faeces as well as unchanged drug.

#### *4.1.4.3. Non-renal clearance*

Clearance of both GZR and EBR was primarily via non-renal pathways as there was little of either drug excreted in the urine (<0.3% of total radioactivity in mass balance studies).

#### *4.1.4.4. Metabolites identified in humans*

No circulating metabolites of GZR or EBR were detected in Studies 5172-P0007 and 8742-P014, respectively.

*Active metabolites*

Not applicable.

*Other metabolites*

*GZR*

A gut bacterial reductive metabolite M10 and 6 oxidative metabolites (M4a, M4b, M7a, M11a, M11b, and M14) were identified in the faeces of healthy males following administration of a 200 mg (approximately 200 μCi) dose of [$^{14}$C] GZR.

*EBR*

Two mono-oxidative metabolites (M2 and M3) were identified in the faeces of healthy males following the administration of a 50 mg (approximately 200 μCi) dose of [$^{14}$C] EBR.

#### *4.1.4.5. Pharmacokinetics of metabolites*

Not applicable.

#### *4.1.4.6. Consequences of genetic polymorphism*

Not applicable.

### 4.1.5. Excretion

#### *4.1.5.1. Routes and mechanisms of excretion*

As stated previously both GZR and EBR were primarily excreted via the faeces, whereas, there was little to no excretion via the urine (<0.3%).

#### *4.1.5.2. Mass balance studies*

*GZR*

Following administration of approximately 200 mg [$^{14}$C]GZR (approximately 200 μCi) to 6 healthy males (Study 5172-P007), total radioactivity in plasma fell to below the lower limit of quantitation (LLOQ) within 24 h, whereas, plasma GZR concentrations were detected up to 168 h post-dose. In urine, radioactivity fell below the LLOQ in all subjects by 216 h post-dose, whereas, radioactivity in faeces were quantifiable up to at least 288 h post-dose in all subjects, and even up to the last collection interval, from 552 – 576 h post-dose, in 2 subjects. On average, by 168 h post-dose, the majority of the radioactive dose appeared to have been excreted in faeces (102%), with less than 0.3% being excreted in urine. Overall, 110.30% (95% CI: 93.61% - 126.99%) of the radioactive dose was recovered, with 109.77% in faeces (95% CI: 93.26% - 126.27%) and 0.29% in urine (95% CI: 0.22% - 0.36%).

*EBR*

Following administration of approximately 50 mg [$^{14}$C] EBR (approximately 200 µCi) to 6 healthy males (Study 8742-P014), total radioactivity in plasma fell below the LLOQ in all subjects by 36 h post-dose. By contrast, plasma EBR concentrations were quantifiable in all subjects throughout the entire 96 h post-dose sampling interval. Radioactivity in urine fell below the LLOQ in all subjects by 48 h post-dose, whereas, levels of radioactivity in faeces were detected from 24 h post-dose to at least 96 h post-dose in all subjects, and as far as 240 h post-dose in 1 subject (LLOQ was 11.73 ng equivalent/g). Overall, 94.3% (95% CI: 88.3% - 100%) of the radioactive dose was recovered, with 94.1% in faeces (95% CI: 88.1% - 100%) and 0.175% in urine (95% CI: 0.118% - 0.232%).

#### *4.1.5.3. Renal clearance*

There was little to no renal clearance of either GZR or EBR following administration of radioactively labelled forms of either drug.

### 4.1.6. Intra- and inter-individual variability of pharmacokinetics

#### *4.1.6.1. GZR*

The estimated inter-subject variability on CL/F and V/F, derived from a PopPK analysis, Study 045496 were 42.1% and 68.8%, whereas the residual variability was 0.51.

#### *4.1.6.2. EBR*

The estimated inter-subject variability on CL/F and Vc/F, derived from a PopPK analysis, Study 044ZSQ were 13.4% and 26.3%, whereas the residual variability was 0.35.

## 4.2. Pharmacokinetics in the target population

#### *4.2.1.1. GZR*

Study 5172-P004v02 examined the plasma PK profiles of GZR following QD doses of 10 to 800 mg GZR for 7 consecutive days in GT1 HCV-infected males and at QD doses of 100 to 800 mg in GT3 HCV-infected males. The results indicated that GZR is absorbed with a Tmax of approximately 2 - 4 h, and is eliminated with a biphasic decline (initiating at approximately 16 - 24 h post-dose) with an apparent elimination $t_{1/2}$ of approximately 25 - 45 h. A secondary peak was observed at approximately 24 h post-dose at lower doses of 10 - 50 mg, which may have resulted in the longer $t_{1/2}$ at the lower doses. Accumulation of GZR was apparent following multiple dosing for both $C_{max}$ and $AUC_{0-24}$ for all dose strengths tested. For example following dosing with 100 mg GZR the Day7/Day1 GMR for $C_{max}$ and $AUC_{0-24}$ were 1.68 and 2.36, respectively. Dose proportionality was also assessed and the resulting estimates (95% CIs) of the slope for the regression line fitted on log-transformed $AUC_{0-24}$, $C_{max}$, and $C_{24}$ were 1.71 (1.58, 1.84), 1.92 (1.78, 2.05), and 0.95 (0.82, 1.08), respectively, indicating that dose related increases in GZR plasma concentrations in subjects with HCV occurred in a greater than dose-proportional manner. Time to steady state was achieved on average within 5 days across all dose levels. Compared to multiple 100 mg QD doses in healthy subjects (values taken from Study 5172-P001v01,), following multiple 100 mg QD doses in patients with HCV the $C_{max}$, $AUC_{0-24}$ and $C_{24}$ values were approximately 1.91-, 1.63- and 1.46 fold higher, respectively.

#### *4.2.1.2. EBR*

Study 8742-P002v02 evaluated the plasma PK profile of EBR following multiple oral QD doses of 5 mg to 100 mg EBR to 48 HCV-infected male patients. Results indicated that EBR was rapidly absorbed, with a median $T_{max}$ of 2.13 - 3.00 h on Day 5 in HCV-patients infected with GT1, GT1a and GT3. The mean $t_{1/2}$ ranged between 20 to 24 h. The GM $AUC_{0-24}$ and $C_{24}$ ranged from 0.155 to 2.08 µM.h and from 3.89 to 56.2 nM, respectively. The accumulation ratios (Day 5/Day 1) for $AUC_{0-24}$ ranged from approximately 1.5 to 1.9 across all dose levels. EBR PKs increased in an

approximately dose-proportional fashion over the 5 to 50 mg range and the resulting estimates (95% CIs) of the slopes for the regression line fitted on ln-transformed $AUC_{0-24}$, $C_{max}$, and $C_{24}$ were 1.15 (0.95, 1.35), 1.16 (0.94, 1.39), and 1.13 (0.94, 1.32), respectively. Steady state of EBR seemed to be attained by Day 2 following administration of 5 mg and 50 mg EBR QD and by Day 3 following the administration of 10 mg and 100 mg EBR QD. Compared to multiple 50 mg QD doses in healthy subjects (values taken from **Study 8742-P001v01**), following multiple 50 mg QD doses in patients with HCV the $C_{max}$, $AUC_{0-24}$ and $C_{24}$ values were approximately 1.02-, 1.11- and 1.11 fold lower, respectively.

## 4.3. Pharmacokinetics in other special populations

### 4.3.1. Pharmacokinetics in subjects with impaired hepatic function

#### *4.3.1.1. GZR*

Study 5172-P013 compared the PKs after multiple dose administration of GZR for 10 days to patients with mild, moderate and severe hepatic insufficiency without hepatitis C with that of healthy matched control subjects. The QD GZR doses administered to the mild-, moderate and severe-groups were 200 mg, 100 mg and 50 mg, respectively. The results indicated that compared to matched healthy subjects the GZR $C_{max}$ [90% CIs], $AUC_{0-24}$ and $C_{24}$ values were 1.37 fold [0.83. 2.27], 1.66 fold [1.05. 2.61] and 1.92 fold [1.40. 2.63] higher, respectively, in subjects with mild hepatic insufficiency. In subjects with moderate hepatic insufficiency, GZR $C_{max}$ [90% CIs], $AUC_{0-24}$ and $C_{24}$ values were 5.98 fold [2.84, 12.57], 4.82 fold [2.60, 8.93] and 3.59 fold [1.81, 7.11] higher, respectively, than in healthy subjects. In subjects with severe hepatic insufficiency GZR $C_{max}$ [90% CIs], $AUC_{0-24}$ and $C_{24}$ values were 13.01 fold [6.00, 28.21], 11.68 fold [6.10, 22.35] and 9.34 [4.98, 17.51] higher respectively, than in healthy subjects. Following multiple doses, GZR $T_{max}$ ranged from 1.75 to 3.00 h in subjects with varying degrees of hepatic insufficiency, whereas in healthy subjects $T_{max}$ ranged from 1.00 to 3.01 h. Overall, GZR $t_{1/2}$ was prolonged in subjects with hepatic insufficiency ($t_{1/2}$ ranged from 39.59 to 54.24 h) compared to healthy subjects (31.02 to 39.80 h).

#### *4.3.1.2. EBR*

Study 8742-P009 compared the plasma EBR PKs following a single 50 mg administration of EBR to patients with mild, moderate and severe hepatic insufficiency with that of healthy matched control subjects. The results indicated that the EBR $C_{max}$ GMRs [90% CIs] for mild, moderate, and severe hepatic insufficiency/healthy matched control comparisons were 0.58 [0.32, 1.05] (mild), 0.69 [0.38, 1.24] (moderate), and 0.58 [0.32, 1.08] (severe).

The corresponding values for EBR $AUC_{0-inf}$ GMRs [90%CIs] were 0.61 [0.34, 1.08] (mild), 0.72 [0.40, 1.31] (moderate) and 0.88 [0.48, 1.61] (severe), respectively, and for EBR $C_{24}$ GMRs were 0.61 [0.34, 1.08] (mild), 0.69 [0.38, 1.25] (moderate) and 0.78 [0.43, 1.43] (severe), respectively. The median EBR $T_{max}$ values were similar in patients with varying degrees of hepatic insufficiency and healthy matched control subjects (3.50 - 4.00 h). The observed mean apparent terminal $t_{1/2}$ values were comparable in patients with mild and moderate hepatic insufficiency (24.80 and 25.39 h, respectively) and prolonged in patients with severe hepatic insufficiency (33.72 h) compared to healthy matched control subjects (20.74 h).

### 4.3.2. Pharmacokinetics in subjects with impaired renal function

Study 5172-P050 examined the effects of ESRD and haemodialysis (HD) on the PKs of GZR and EBR following administration of 100 mg GZR and 50 mg EBR QD for 10 days. GZR PK parameters were similar between subjects with ESRD on HD days and non-HD days. GMRs for exposure parameters ($AUC_{0-24}$, $C_{max}$, $C_{24}$, $C_2$), as well as CL/F, were all close to unity, with CIs which all contained 1.0, indicating no statistically significant differences. Subjects with ESRD on HD Day 10 had slightly lower exposures relative to healthy matched control subjects, with GZR GMRs ranging from 0.78 – 0.93, but with 90% CIs all containing 1.0, indicating non-statistically

significant differences. CL/F and Vz/F were also comparable between ESRD subjects on HD compared to healthy matched control subjects. $T_{max}$ values were similar; however, apparent terminal $t_{1/2}$ values were shorter in subjects with ESRD on HD (28.38 h) relative to healthy matched control subjects (35.18 h). Subjects with ESRD on non-HD Day 9 had GZR exposure parameter GMRs ranging from 0.79 – 1.15 with 90% CIs all containing 1.0.

EBR PK parameters ($AUC_{0-24}$, $C_{max}$, and $C_{24}$) were slightly increased (approximately 12 to 24%) in subjects with ESRD on the HD day compared with non-HD day. Median $T_{max}$ was 5 h on the HD day and 4 h on the non-HD day. EBR PK parameters were similar when compared between subjects with ESRD on HD Day 10 relative to healthy matched control subjects, with GMRs close to 1.0. Larger decreases were observed for subjects with ESRD on non-HD Day 9 relative to healthy subjects, with EBR exposure parameter GMRs ranging from 0.77 - 0.97; however, the 90% CIs all included 1.0.

### 4.3.3. Pharmacokinetics according to age

#### *4.3.3.1. GZR*

Study 5172-P014 compared GZR PKs following administration of multiple QD oral doses of 400 mg GZR to healthy elderly female subjects and healthy elderly male subjects. This study also compared the results from the healthy elderly males to results for healthy young males previously described in Study 5172-P001v01. Initially this second comparison was to be performed using the data from both elderly males and females but due to intrinsic differences in GZR PKs between the two groups this comparison could not be undertaken as planned (see below). The results indicated that the GZR $AUC_{0-24}$ was 118% greater in elderly males than in young males [GMR of 2.18 (90% CI: 1.01 – 4.71)] and $C_{max}$ was 68% greater in elderly males than in young males [GMR of 1.68 (90% CI: 0.73 - 3.90)].

#### *4.3.3.2. EBR*

Study 8742-P004 compared EBR PKs following administration of single oral doses of EBR to healthy elderly female subjects and healthy elderly male subjects. This study also compared the results from the healthy elderly males to results for healthy young males previously described in Study 8742-P001v01. Initially this second comparison was to be performed using the data from both elderly males and females but due to intrinsic differences in EBR PKs between the two groups this comparison could not be undertaken as planned (see below). The results indicated that the EBR $AUC_{0-inf}$ GMR [90% CI] for the comparison of a single dose of 100 mg EBR administered to healthy elderly males versus healthy young males was 1.02 [0.69, 1.53]. Similar results were observed for $C_{max}$, $AUC_{0-24}$, and $C_{24}$. In general, peak EBR concentrations occurred between 2 and 4 h with a median $T_{max}$ slightly delayed (30 mins) in young male subjects. The apparent $t_{1/2}$ values ranged from 15 to 25 h and were similar between treatments.

### 4.3.4. Pharmacokinetics related to genetic factors

Not applicable.

### 4.3.5. Pharmacokinetics {in other special population/according to other population characteristic}

#### *4.3.5.1. Gender*

*GZR*

Study 5172-P014 indicated that GZR $AUC_{0-24}$ was 76% greater in elderly females than in elderly males [GMR of 1.76 (90% CI: 0.82 - 3.81)] and $C_{max}$ was 90% greater in elderly females than in elderly males [GMR of 1.90 (90% CI: 0.82 - 4.41)].

*EBR*

Study 8742-P004 indicated that EBR $AUC_{0-inf}$ GMR [90% CI] for the comparison of a single dose of 100 mg EBR administered to healthy elderly females versus healthy elderly male subjects

was 1.67 [1.12, 2.48]. The upper limit of the 90% CI was not within the pre-specified interval [0.05. 2.00]. Similar results were observed for $C_{max}$, $AUC_{0-24}$, and $C_{24}$. Therefore, administration of EBR resulted in higher EBR exposure (by approximately 70%) in elderly female subjects as compared to elderly male subjects.

#### *4.3.5.2. Japanese subjects*

*GZR*

Study 5172-P009 examined the PKs of GZR after administration of single oral doses of 100 to 1200 mg and multiple QD oral doses of 400 mg and 800 mg for 10 days to healthy young Japanese subjects. The results indicated that following single doses of GZR ranging from 100 to 1200 mg, median $T_{max}$ of GZR was in the range from 3.00 to 5.00 h and was not dependent on dose and the GM $t_{1/2}$ for GZR ranged from 20.0 to 37.6 h and appeared to decrease with increasing dose. Systemic exposure, as reflected by $AUC_{0-inf}$ and $C_{max}$, were estimated to increase in a greater than dose-proportional manner and GZR exposure ($AUC_{0-inf}$ and $C_{max}$) was higher in Japanese subjects than in non-Japanese subjects (data taken from Study 5172-P001v01) across the all dose levels. The GMRs [Japanese/non-Japanese] (90% CIs) at the dose of 100, 400, 800 and 1200 mg were 1.38 (0.86, 2.22), 2.07 (1.47, 2.90), 2.53 (1.75, 3.66) and 2.84 (1.87, 4.32) for $AUC_{0-inf}$, and 1.21 (0.73, 2.03), 2.28 (1.66, 3.12), 3.12 (2.15, 4.52) and 3.74 (2.40, 5.85) for $C_{max}$, respectively. Following QD GZR doses for 10 days of 400 and 800 mg, median $T_{max}$ of GZR was 3.50 h on Day 1 and 3.00 and 4.00 h on Day 10, respectively, and the GM $t_{1/2}$ values for GZR were 26.4 and 20.7 h for the 400 and 800 mg doses, respectively. The geometric means of the accumulation ratio (Day 10/Day 1) and 90% CIs for $AUC_{0-24h}$ of GZR at 400 and 800 mg were 1.91 (1.18, 3.09) and 2.76 (1.70, 4.47), respectively. Systemic exposure ($AUC_{0-24h}$ and $C_{max}$) was higher in Japanese subjects compared to non-Japanese subjects. The GMRs [Japanese/non-Japanese] (90% CIs) for $AUC_{0-24h}$ and $C_{max}$ across the dose ranges from 100 to 1000 mg QD were 2.88 (2.01, 4.12) and 2.31 (1.57, 3.39), respectively.

*EBR*

Study 7009-P050 examined the PKs of EBR after administration of single oral doses of 10, 50 and 100 mg EBR to healthy Japanese subjects. The results indicated that EBR plasma concentration reached $C_{max}$ at the median $T_{max}$ of 2.5 – 4.0 h after dose, and subsequently decreased with the GM $t_{1/2}$ of approximately 17 – 18 h. $T_{max}$ and apparent terminal $t_{1/2}$ were similar between the 3 EBR single doses (10, 50 and 100 mg). EBR plasma exposure ($AUC_{0-inf}$, $AUC_{0-24h}$, $C_{max}$ and $C_{24}$) increased approximately dose-proportionally over the range of the doses studied. The EBR plasma exposure was greater in Japanese than in non-Japanese over 5- to 100-mg dose, with the GMRs (Japanese/non-Japanese) and corresponding 90% CIs of 1.69 (1.30, 2.21) for $AUC_{0-inf}$, 1.68 (1.32, 2.14) for $AUC_{0-24h}$, 1.77 (1.38, 2.28) for $C_{max}$, and 1.59 (1.22, 2.07) for $C_{24}$h. $T_{max}$ and apparent terminal $t_{1/2}$ were generally consistent between Japanese and non-Japanese.

#### *4.3.5.3. Chinese subjects*

*GZR*

Study 5172-P042 assessed GZR PK parameters following administration of multiple, oral, QD doses of 100 mg or 200 mg GZR to healthy Chinese subjects. Results indicated that healthy Chinese subjects had higher GZR exposure (approximately 1.4 to 2.8 fold increase in $C_{max}$ and $AUC_{0-24h}$) when compared with non-Asian subjects administered multiple doses of 100 mg or 200 mg GZR. However, healthy Chinese subjects had similar GZR exposure ($C_{max}$ and $AUC_{0-24}$h) when compared with Japanese subjects following a 100 mg single dose.

## 4.4. Pharmacokinetic interactions

### 4.4.1. Pharmacokinetic interactions demonstrated in human studies

**Comment**: Due to the extremely comprehensive nature of the DDI studies undertaken by the sponsor, in most cases where little to no interaction has been identified then the summaries will be kept as brief as possible. In addition, please note that many of the interaction studies have been conducted using a 200 mg QD dose of GZR and not the proposed marketing dose of 100 mg QD.

#### *4.4.1.1. Interaction between GZR and EBR*

Study 8742-P008 compared the plasma PK profiles of EBR (20 mg QD) with and without 200 mg GZR QD and the plasma PKs of GZR (200 mg QD) ) with and without 20 mg EBR QD in healthy subjects. The results indicated that GZR had little to no effect on the PKs of EBR. For instance, EBR $AUC_{0\text{-}24}$, $C_{max}$ and $C_{24}$ GMR values (90% CI) following the multiple-dose administration of EBR co-administered with multiple-doses of GZR for 8 days as compared to EBR administered alone for 7 days were 1.01 (0.83, 1.24), 0.93 (0.76, 1.13) and 1.02 (0.83, 1.24), respectively. For GZR, exposure was slightly lower following co-administration with EBR compared to when GZR was administered alone. For instance, the $AUC_{0\text{-}24}$, $C_{max}$ and $C_{24}$ GMR values (90% CI) following the multiple-dose administration of EBR co-administered with multiple doses of GZR for 8 days as compared to GZR administered alone for 7 days were 0.90 (0.63, 1.28), 0.87 (0.50, 1.52) and 0.94 (0.77, 1.15), respectively.

**Comment**: In Study 8742-P008 the sponsor has examined the direct interaction between GZR and ERB using doses that do not correspond (that is, 200 mg/20 mg QD) with the proposed dose for marketing (that is, 100 mg/50 mg QD).

#### *4.4.1.2. Interaction with CYP3A substrates and OATP1B inhibitors*

*GZR and EBR*

Study 5172-P053 examined the interaction between a free-combination of GZR FFP and EBR FFP (200 mg/50 mg QD) and rilpivirine (25 mg QD), a non-nucleoside reverse transcriptase inhibitor for the treatment of HIV-1 and CYP3A substrate, in healthy subjects. The results indicated that rilpivirine had little to no effect on the $C_{max}$, $AUC_{0\text{-}24}$ or $C_{24}$ values for either GZR or EBR when administered as the free-combination. Similarly, the free-combination had little to no effect on the PKs of rilpivirine.

Two further studies examined the effects of 200 mg GZR QD (Study 5172-P029) and 50 mg EBR QD (Study 8742-P017) on the steady-state PKs of the protease-inhibitor, CYP3A substrate, CYP2C9- and CYP2C19-inducer and OATP1B and BCRP inhibitor, lopinavir (LPV) following dosing with 400/100 mg LPV/ritonavir BD in healthy subjects. Under these conditions, GZR and EBR had no effect on the PKs of LPV when LPV was co-administered with ritonavir (RTV).

#### *4.4.1.3. Interaction with strong CYP3A inhibitors*

*GZR*

Study 5172-P029 also examined the PKs of GZR in the presence and absence of the CYP3A-, CYP2C8-, UGT1A1-, OATP1B-, P-gp- and BCRP-inhibitor atazanavir (ATV) and the strong CYP3A4- and CYP2D6-inhibitor ritonavir (RTV). When administered under these conditions. GZR exposure (AUC, $C_{max}$, and $C_{24}$) was markedly increased with administration of ATV/RTV + GZR and the $AUC_{0\text{-}24}$ GMR (90% CI) for the ATV/RTV + GZR / GZR alone comparison was 10.58 (7.78, 14.39). For comparison, the GZR AUC GMR following co-administration with darunavir (DRV), a CYP3A4 substrate and P-gp inhibitor and RTV was 7.50 (5.92, 9.51).

*EBR*

Similarly, Study 8742-P017 examined the PKs of EBR in the presence and absence of ATV/RTV. Under these conditions, the EBR $AUC_{0\text{-}24}$ GMR (90% CI) for the comparison of multiple doses of

50 mg EBR co-administered with multiple doses of 300/100 mg ATV/RTV versus multiple doses of 50 mg EBR alone was 4.76 (4.07, 5.56). For comparison, the EBR AUC GMR following co-administration with DRV/RTV was 1.66 (1.35, 2.05).

#### *4.4.1.4. CYP3A4 substrates and/or substrates for multiple enzymes/transporters*

*GZR and EBR*

Part 1 of Study 5172-P073 examined plasma PKs following a single-dose of 400 mg cyclosporine (a CYP3A4 substrate, CYP3A-, P-gp-, BCRP- and OATP1B-inhibitor) and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg). For cyclosporine, the $AUC_{0\text{-}inf}$ GMR (90% CI) for the GZR + EBR + cyclosporine/cyclosporine alone comparison was 0.96 (0.90, 1.02). By contrast for GZR, the $AUC_{0\text{-}24}$ GMR (90% CI) for the GZR + EBR + cyclosporine/GZR + EBR alone comparison was 15.21 (12.83, 18.04) and the EBR $AUC_{0\text{-}24}$ GMR (90% CI) for the GZR + EBR + cyclosporine/GZR + EBR alone comparison was 1.98 (1.84, 2.13).

Study 5172-P076 examined plasma PKs of atorvastatin and its metabolites following a single-dose of 10 mg atorvastatin (a CYP3A4-, OATP1B-, BRCP-, P-gp-substrate) and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg). The results indicated that co-administration of atorvastatin + GZR/EBR resulted in a 1.94 fold (1.63, 2.33) increase in atorvastatin $AUC_{0\text{-}inf}$ and 4.34 fold (3.10, 6.07) increase in atorvastatin $C_{max}$. Orthohydroxyatorvastatin exposure was also increased; whereas, the effect of GZR/EBR on parahydroxyatorvastatin exposure was difficult to quantify as concentrations were mostly BLOQ in 8 of 16 subjects tested.

*GZR*

Study 5172-P030 examined the effect of multiple doses of 200 mg GZR QD on the PK profiles of CYP3A4 substrates methadone (total, S-, and R-enantiomers) or buprenorphine (including norbuprenorphine metabolite) (administered as buprenorphine/naloxone), respectively. In addition, methadone is a CYP2B6 substrate and that buprenorphine and naloxone are metabolised through glucuronidation and CYP3A-, CYP2D6-, and UGT- substrates. Subjects remained on their maintenance therapy of oral methadone 20 - 150 mg QD (QD; Panel A) or oral buprenorphine/naloxone 8/2 - 24/6 mg QD (Panel B) during the course of the study. Results indicated that GZR co-administration had little effect on plasma levels of R-methadone, whereas, it induced a small increase in exposure to S-methadone (for example, $AUC_{0\text{-}24}$/D GMR [90% CI] for S-methadone was 1.23 [1.12, 1.35]. Similarly, there was little to no effect of GZR co-administration on plasma levels of buprenorphine, norbuprenorphine or naloxone. Co-administration of methadone had little to no effect on GZR PKs, whereas, buprenorphine/naloxone induced a small decrease (approximately 25%) in GZR exposure.

Study 5172-P032 determined the effect of steady-state GZR (200 mg QD) on the PKs of a single dose of the CYP3A4 substrates midazolam (2 mg) or atorvastatin (20 mg). The $AUC_{0\text{-}inf}$ GMR (90% CI) for the midazolam + GZR/midazolam alone comparison was 1.34 (1.29, 1.39). For atorvastatin, the co-administration of GZR resulted in a 200% [GMR (90% CIs) of 3.00 (2.42, 3.72)] increase in atorvastatin $AUC_{0\text{-}inf}$. By contrast, GZR exposure was only slightly increased (approximately 25%) in the presence of atorvastatin.

**Comment**: It should be noted that in *Study 5172-P032* the effect of the co-administration of GZR on the exposure of the CYP3A4 substrates atorvastatin and midazolam was not consistent.

Study 5172-P046 assessed the effect of multiple doses of GZR (200 mg QD) on the single-dose PK profile of oral contraceptive (OC) components, ethinyl estradiol (EE) and levonorgestrel (LNG) after a single dose of Nordette-28 or generic equivalent (EE 0.03 mg/LNG 0.15 mg). The results indicated that the EE $AUC_{0\text{-}inf}$ and $C_{max}$ GMRs [90% CI] for the GZR + Nordette-28/Nordette-28 comparison were 1.10 [1.05, 1.14] and 1.05 [0.98, 1.12], respectively and the

LNG $AUC_{0\text{-}inf}$ and $C_{max}$ GMRs [90% CI] for the GZR + Nordette-28/Nordette-28 comparison were 1.23 [1.15, 1.32] and 0.93 [0.84, 1.03], respectively.

Study 5172-P070 assessed the effect of multiple oral doses of GZR (200 mg QD) on the PKs of a single oral dose of the CYP3A4-, CYP2C9- and CYP2C8-substrate montelukast (10 mg). Co-administration with GZR resulted in 10% and 39% increases in plasma montelukast $AUC_{0\text{-}last}$ (GMR [90% CI] of 1.10 [1.01, 1.20]) and $C_{24}$ (GMR [90% CI] of 1.39 [1.25, 1.56]), respectively.

*EBR*

Study 8742-P010 examined the effect of multiple doses of EBR (50 mg) on the respective PK profiles of co-administered methadone (total, S- and R-enantiomers) in subjects receiving maintenance therapy of oral methadone 20 – 150 mg (20 – 120 mg actual). The results indicated that EBR had little to no effect on exposure to R-, S-or total methadone. By contrast, EBR exposure was higher in the subjects receiving co-administered methadone versus historical control subjects receiving EBR alone. For instance, EBR $AUC_{0\text{-}24}$, $C_{24}$, and $C_{max}$ GMRs (90% CIs) were 1.71 (1.16, 2.51), 1.86 (1.22, 2.83), and 1.93 (1.30, 2.86), respectively. Study 8742-P021 examined the effect of a single sublingual dose of buprenorphine/naloxone (8 mg/2 mg) on the PK profile of a co-administered single oral dose of 50 mg EBR. The results indicated that the EBR $AUC_{0\text{-}inf}$ and $C_{max}$ were 1.22 fold (0.98, 1.52) and 1.13 fold (0.87, 1.46) higher, respectively following co-administration. By contrast exposure to buprenorphine and naloxone was unaffected by co-administration with EBR.

**Comment**: The DDI between buprenorphine/naloxone and EBR (**Study 8742-P021**) was only examined following a single dose of EBR and DDIs at steady state levels of EBR were not examined.

Study 8742-P013 assessed the effect of multiple doses of EBR (50 mg QD) on the single dose PK profile of OC components, EE and LNG after a single dose of Nordette-28 or generic equivalent (0.03 mg EE/0.15 mg LNG). EBR had little to no effect on either EE or LNG exposure.

#### *4.4.1.5. Strong CYP3A4 inhibitors*

*GZR*

Study 5172-P006v01 assessed the effect of multiple doses of RTV (100 mg BD), a strong CYP3A4 inhibitor, on the single-dose PK profile of GZR (200 mg). In this study, co-administered RTV induced a 1.91 fold (1.31, 2.79) and 1.88 fold (1.65, 2.14) increase in GZR $AUC_{0\text{-}24}$ and $C_{24}$, respectively.

**Comment**: The DDI between RTV and GZR (*Study 5172-P006*) was only examined following a single dose of GZR and not following multiple doses of GZR.

Part 3 of Study 5172-P001v01 assessed the effect of multiple doses of ketoconazole (400 mg QD), a strong CYP3A4 inhibitor, on the single-dose PK profile of 100 mg GZR. For GZR, the GM $C_{max}$ and $AUC_{0\text{-}inf}$ ratios (GZR + Ketoconazole/GZR Alone) and corresponding 90% CIs were 1.13 and (0.77, 1.67) and 3.02 and (2.42, 3.76), respectively.

**Comment**: The DDI between ketoconazole and GZR (*Study 5172-P001*) was only examined following a single dose of GZR and not at steady-state levels of GZR.

*EBR*

Study 8742-P003 assessed the effect of multiple doses of ketoconazole (400 mg) on the single-dose PK profile of EBR (50 mg). Under these conditions, EBR $C_{max}$ and $AUC_{0\text{-}24}$ GMRs (90% CI) were 0.88 (0.44, 1.77) and 1.02 (0.53, 1.96), respectively. By contrast, EBR $C_{24}$ was elevated (1.38-fold) following co-administration. The EBR median $T_{max}$ was approximately 3.50 h post-dose with and without co-administration with ketoconazole, whereas, the mean $t_{1/2}$ was delayed by approximately 5 h when EBR was co-administered with ketoconazole.

**Comment**: The DDI between ketoconazole and EBR (*Study 8742-P003*) was only examined following a single dose of EBR and not at steady-state levels of EBR.

#### *4.4.1.6. CYP3A4 – inducers*

*GZR*

Study 5172-P031 examined the DDIs between GZR (200 mg QD) and the potent CYP3A4 inducer rifampin (600 mg QD), which is also an OATP1B-inhibitor, glucuronidation and intestinal P-gp, and the CYP3A4 inducer efavirenz (600 mg). Under these conditions, a single IV dose of 600 mg rifampin substantially increased single dose GZR exposure (AUC and $C_{max}$) by approximately 10 to 13 fold over GZR alone, whereas, a single oral dose of 600 mg rifampin administered after 7 days of 200 mg GZR QD increased GZR exposure (AUC and $C_{max}$) by approximately 7 to 8 fold over GZR alone. By contrast, the GMRs for GZR exposures at steady-state following multiple oral doses of GZR + PO rifampin relative to GZR alone were near 1.0, with the $AUC_{0-24}$ GMR (90% CI) being 0.93 (0.75, 1.17).

Following co-administration GZR with efavirenz QD for 7 days, the $AUC_{0-24}$, $C_{max}$, and $C_{24}$ values for GZR were reduced by 83%, 87%, and 69%, respectively, whereas, GZR had little to no effect on efavirenz exposure.

**Comment**: Given that in vitro studies have identified that GZR is primarily metabolised by CYP3A and that rifampin is a potent CYP3A inducer, it might be expected that GZR co-administration with rifampin would result in significant decreases in GZR exposure, similar to those seen following co-administration of GZR and efavirenz. It is interesting to note, however, that in **Study 5172-P031** following a single dose co-administration of either IV or PO rifampin and GZR there is a significant increase in GZR exposure (approximately 7- to 13-fold) and that steady-state levels of rifampin had little effect on GZR exposure.

*EBR*

Study 8742-P011 assessed the effect of a single IV or oral dose of rifampin (600 mg) on the PKs of a single oral dose of EBR (50 mg). Following IV rifampin, the EBR $AUC_{0-inf}$, $C_{max}$, and $C_{24}$h values (90% CIs) were 1.22 fold [1.06, 1.40] 1.41 fold [1.18, 1.68], and 1.31 fold [1.12, 1.53] higher, respectively, than when EBR was administered alone. Similarly, following oral rifampin, the EBR $AUC_{0-inf}$, $C_{max}$, and $C_{24}$h values were 1.17 [0.98, 1.39], 1.29 [1.06, 1.58] and 1.21 [1.03, 1.43] higher, respectively, than when EBR was administered alone.

**Comment**: The DDI between rifampin and EBR (*Study 8742-P011*) was only examined following a single dose of EBR and not at steady-state levels of EBR.

Part 3 of Study 8742-P016 assessed DDIs following multiple oral doses of EBR (50 mg QD) and multiple doses of efavirenz (600 mg QD). Following multiple doses of EBR and efavirenz, EBR exposure was decreased, as the EBR $AUC_{0-24}$ GMR (90% CI) for the comparison of EBR + efavirenz/EBR was 0.46 (0.36, 0.59), whereas, the efavirenz $AUC_{0-24}$ GMR (90% CI) for EBR + efavirenz/efavirenz was 0.82 (0.78, 0.86).

#### *4.4.1.7. CYP2C9 – substrates*

*GZR and EBR*

Part 1 of Study 5172-P054 examined DDIs following a single 10 mg dose of the CYP2C9 substrate rosuvastatin and multiple doses of GZR (200 mg QD) alone or with multiple doses of GZR (200 mg QD) in combination with EBR (50 mg QD). Rosuvastatin exposure ($AUC_{0-inf}$, $AUC_{0-24}$, and $C_{max}$) was increased when co-administered with either GZR or GZR and EBR. Larger increases in rosuvastatin $AUC_{0-inf}$, $AUC_{0-24}$, and $C_{max}$ were observed when rosuvastatin was co-administered with both GZR and EBR (GMRs of 2.26 [1.89, 2.69], 2.68 [2.26, 3.17], and 5.49 [4.29, 7.04], respectively) relative to when rosuvastatin was co-administered with GZR only

(GMRs of 1.59 [1.33, 1.89], 1.85 [1.56, 2.19], and 4.25 [3.25, 5.56], respectively). By contrast, GZR plasma PKs were not affected following co-administration with rosuvastatin.

*GZR*

Part 3 of Study 5172-P032 examined DDIs following the administration of a single 1 mg dose of another CYP2C9 substrate pitavastatin and multiple QD doses of 200 mg GZR. The results indicate that there was a small increase in pitavastatin exposure following co-administration with GZR and the $C_{max}$ and $AUC_{0\text{-}inf}$ GMR values (90% CI) for the pitavastatin + GZR/pitavastatin alone comparison were1.27 (1.07, 1.52) and 1.11 (0.91, 1.34), respectively.

#### *4.4.1.8. CYP2C19 – substrates*

*GZR and EBR*

Study 5172-P072 examined DDIs following administration of multiple oral doses of the proton pump inhibitor and CYP2C19–substrate pantoprazole (40 mg QD) and multiple oral doses of a 100 mg GZR/50 mg EBR FDC tablet (GZRA). For the GZR component, the $C_{max}$ and $AUC_{0\text{-}inf}$ GMR values (90% CIs) for GZRA + pantoprazole/GZRA were 1.10 (0.89, 1.37) and 1.12 (0.96, 1.30), respectively. For the EBR component, the $C_{max}$ and $AUC_{0\text{-}inf}$ GMR values for GZRA + pantoprazole/GZRA were 1.02 (0.92, 1.14) and 1.05 (0.93, 1.18), respectively.

#### *4.4.1.9. UGT1A1 – substrates (metabolised by glucuronidation)*

*GZR and EBR*

Study 5172-P057 assessed DDIs following administration of a single oral 50 mg dose of the integrase inhibitor dolutegravir and multiple oral doses of GZR and EBR (200 mg/50 mg QD). Co-administration of dolutegravir with GZR and EBR did not have a clinically meaningful effect on the PKs of dolutegravir. The dolutegravir $AUC_{0\text{-}inf}$ and $C_{24}$ GMRs (90% CIs) were 1.16 (1.00, 1.34) and 1.14 (0.95, 1.36), respectively. Similarly, co-administration of dolutegravir had no effect on the multiple-dose PKs of EBR and the EBR $AUC_{0\text{-}24}$, $C_{max}$, $C_2$, and $C_{24}$ GMRs (90% CIs) were 0.98 (0.93, 1.04), 0.97 (0.89, 1.05), 0.98 (0.86, 1.11), and 0.98 (0.93, 1.03), respectively. By contrast, decreases were observed in GZR PKs following co-administration with dolutegravir and the GZR $AUC_{0\text{-}24}$, $C_{max}$, $C_2$, and $C_{24}$ GMRs (90% CIs) were 0.81 (0.67, 0.97), 0.64 (0.44, 0.93), 0.52 (0.28, 0.97), and 0.86 (0.79, 0.93), respectively.

#### *4.4.1.10. P-gp-substrates*

*GZR and EBR*

Study 5172-P063 assessed the effect of multiple oral doses of GZR and EBR (200 mg/50 mg QD) on the PKs of a single oral 400 mg dose of the P-gp substrate sofosbuvir. Co-administration with multiple doses of GZR + EBR increased the PKs of sofosbuvir. Sofosbuvir $AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$, and $C_{max}$ GMRs (90% CIs) for sofosbuvir + GZR + EBR/sofosbuvir alone comparisons were 2.43 (2.12, 2.79), 2.59 (2.28, 2.94) and 2.27 (1.72, 2.99), respectively, whereas, the plasma AUCs ($AUC_{0\text{-}inf}$, $AUC_{0\text{-}last}$) of the sofosbuvir metabolite GS-331007 following a single-dose administration of sofosbuvir with GZR + EBR were slightly increased compared to those after a single dose of sofosbuvir alone, with GMRs (90% CIs) of 1.13 (1.05, 1.21) and 1.13 (1.04, 1.22), respectively.

*EBR*

Study 8742-P023 examined the effect of multiple oral doses of EBR (50 mg QD) on the PK profile of digoxin following co-administration of a single 0.25 mg dose of digoxin. For digoxin, the $AUC_{0\text{-}inf}$ and $C_{max}$ GMR values [90% CI] were 1.11 [1.02, 1.22] and 1.47 [1.25, 1.73], respectively. The GM $t_{1/2}$ of digoxin was similar when digoxin was co-administered with EBR (41.96 h) compared to when digoxin was administered alone (45.10 h).

#### *4.4.1.11. Organic anion transporting polypeptide –substrate*

*GZR/ERB*

Part II of Study 5172-P054 examined the effect of steady-state GZR and EBR (200 mg/50 mg EBR QD) on the PKs of single-dose of 40 mg pravastatin. Co-administration of pravastatin with GZR + EBR resulted in approximately 30% higher exposure relative to the administration of pravastatin alone. The pravastatin $AUC_{0\text{-}inf}$ and $C_{max}$ GMRs (90% CI) were 1.33 (1.09, 1.64) and 1.28 (1.05, 1.55), respectively.

#### *4.4.1.12. HIV nucleoside reverse transcriptase inhibitor*

*GZR*

Part I of Study 5172-P026 assessed DDIs following multiple oral doses of GZR (200 mg QD) on the steady-state PKs of the HIV nucleoside reverse transcriptase inhibitor tenofovir (300 mg QD). For GZR, the $C_{max}$, $AUC_{0\text{-}24}$ and $C_{24}$ GMR values (90% CI) for the tenofovir + GZR/GZR comparison were 0.78 (0.51, 1.18), 0.86 (0.65, 1.12) and 0.89 (0.78, 1.01), respectively. For tenofovir, the $C_{max}$, $AUC_{0\text{-}24}$ and $C_{24}$ GMR values were 1.14 (1.04, 1.25), 1.18 (1.09, 1.28) and 1.24 (1.10, 1.39), respectively.

*EBR*

Part I of Study 8742-P016 assessed DDIs following multiple oral doses of EBR (50 mg QD) on the multi-dose PKs of tenofovir (300 mg QD). For EBR, the $C_{max}$, $AUC_{0\text{-}24}$ and $C_{24}$ GMR values (90% CI) for the tenofovir + EBR/EBR comparison were 0.88 (0.77, 1.00), 0.93 (0.82, 1.05) and 0.92 (0.81, 1.05), respectively. For tenofovir, the $C_{max}$, $AUC_{0\text{-}24}$ and $C_{24}$ GMR values were 1.47 (1.32, 1.63), 1.34 (1.23, 1.47) and 1.29 (1.18, 1.41), respectively.

#### *4.4.1.13. HIV integrase inhibitor*

*GZR*

Part 2 of Study 5172-P026 assessed DDIs following multiple oral doses of GZR (200 mg QD) and raltegravir (400 mg BD). Co-administration of raltegravir induced a small decrease in exposure to GZR as the $C_{max}$, $AUC_{0\text{-}24}$ and $C_{24}$ GMR values (90% CI) for the raltegravir + GZR/GZR comparison 0.85 (0.62, 1.16), 0.89 (0.72, 1.09) and 0.90 (0.82, 0.99), respectively. By contrast, the $C_{max}$, $AUC_{0\text{-}12}$ and C12 GMR values (90% CI) for raltegravir for the raltegravir +GZR/raltegravir comparison were 1.46 (0.78, 2.73), 1.43 (0.89, 2.30) and 1.47 (1.085, 1.998), respectively.

*EBR*

Part 2 of Study 8742-P016 assessed DDIs following single oral doses of 50 mg EBR and 400 mg raltegravir. Raltegravir co-administration induced a small decrease in exposure to EBR as the EBR $C_{max}$, $AUC_{0\text{-}inf}$ and $C_{24}$ GMR values (90% CI) for the comparison of a single dose of 50 mg raltegravir co-administered with a single dose of 400 mg raltegravir versus a single dose of 50 mg EBR alone were 0.89 (0.61, 1.29), 0.81 (0.57, 1.17) and 0.80 (0.55, 1.16), respectively. The raltegravir C12 GMR (90% CI) for the comparison of a single dose of 400 mg raltegravir co-administered with a single dose of 50 mg EBR versus a single dose of 400 mg raltegravir alone was 0.99 (0.80, 1.22).

**Comment**: The DDI between raltegravir and EBR (Part 2 of *Study 8742-P016*) was only examined following a single dose of EBR and not at steady-state levels of EBR.

#### *4.4.1.14. Inhibitors of non-structural protein 5A (NS5A)*

*GZR*

Study 5172-P023 assessed DDIs following multiple oral doses of GZR (400 mg QD) and the novel NS5A inhibitor GS-5885 (90 mg QD). The results indicated that the Day 7 $AUC_{0\text{-}24h}$ and $C_{24}$ GMR values (90% CI) for GZR for the GZR + GS-5885/GZR comparison were 1.48 (1.34, 1.65)

and 1.77 (1.59, 1.98), respectively. For GS-5885, the Day 7 $AUC_{0\text{-}24h}$ and $C_{24}$ GMR values for the GZR + GS-5885/GS-5885 comparison were 1.87 (1.63, 2.15) and 1.97 (1.70, 2.28), respectively.

Study 5172-P036 examined DDIs following multiple oral doses of GZR (200 mg QD) and 60 mg BMS-790052 (daclatasvir). Co-administration of daclatasvir with GZR had little to no effect on daclatasvir exposure as the daclatasvir $AUC_{0\text{-}\tau}$ GMR (90% CI) for the BMS-790052 + GZR/BMS-790052 alone comparison was 1.02 (0.93, 1.11). Similarly daclatasvir co-administration had little effect on GZR exposure and the GZR $AUC_{0\text{-}\tau}$ GMR (90% CI) for the BMS-790052 + GZR/GZR alone comparison was 1.12 (0.87, 1.44).

Study 8408-P004 examined DDIs following multiple oral doses of GZR (200 mg QD) and the novel NS5A inhibitor MK8408 (60 mg QD). The results indicate that there was little PK interaction between the two drugs.

*EBR*

Study 2748-P004 assessed DDIs following multiple oral doses of EBR (50 mg QD) and MK-2748 (400 mg QD). The results indicate that there was little PK interaction between the two drugs.

#### *4.4.1.15. Inhibitors of non-structural protein 5B (NS5B)*

*GZR and EBR*

Study 3682-P007 assessed DDIs following multiple oral doses of GZR/EBR (200 mg QD/50 mg QD) and the novel NS5B inhibitor MK-3682 (300 mg QD). Co-administered MK-3682 had no meaningful effect on the plasma exposures of GZR and EBR as the GMR values were close to 1. By contrast, co-administration of MK-3682 with GZR and EBR increased the $C_{max}$ and $AUC_{0\text{-}t}$ of MK-3682 by 28% and 20%, respectively, and decreased the $C_{max}$ and $AUC_{0\text{-}24}$,ss of IDX20664 (MK-3682 metabolite) by 22% and 10%, respectively, while having no meaningful impact on Ctrough of IDX20664.

*GZR*

Study 3682-P008 examined the effect of steady state levels of MK-3682 (300 mg QD) on the steady state plasma PK of GZR (200 mg QD) and MK-8408 (60 mg QD). The steady state $AUC_{0\text{-}24,ss}$ and $C_{max}$ of GZR were 36% and 56% higher, respectively, following co-administration of GZR, MK-8408 and MK-3682 compared to co-administration of GZR and MK-8408 alone. By contrast, MK-3682 did not affect the plasma exposure to MK-8408 as the GMR values were very close to 1.0. For MK-3682, $AUC_{0\text{-}t}$ and $C_{max}$ values were 26% and 21% higher, respectively, after multiple-dose administration of MK-3682 co-administered with multiple doses of GZR/MK-8408 than after multiple-dose administration of MK-3682 alone.

#### *4.4.1.16. Phosphate–binder drugs*

Patients with end stage renal disease and patients with severe renal insufficiency requiring dialysis often receive phosphate binder drugs.

*GZR and EBR*

Study 5172-P056 examined the effect of phosphate binder drugs on GZR/EBR PKs following co-administration of a single oral dose of 100 mg GZR and 50 mg EBR with either calcium acetate or sevelamer carbonate. Co-administration of calcium acetate appeared to cause a small decrease in plasma exposure to GZR/EBR as the GZR and EBR $AUC_{0\text{-}inf}$ GMRs (90% CIs) for GZR + EBR + calcium acetate/GZR + EBR alone were 0.79 (0.68, 0.91) and 0.92 (0.75, 1.14), respectively. Co-administration of sevelamer carbonate also decreased plasma exposure to GZR ($AUC_{0\text{-}inf}$ GMR = 0.82 [0.68, 0.99]), whereas, EBR exposure was slightly higher ($AUC_{0\text{-}inf}$ GMR = 1.13 [0.94, 1.37]).

#### *4.4.1.17. pH modifying agents*

*GZR and EBR*

Study 5172-P045 evaluated the effects of pre-treatment with famotidine, an H2-receptor antagonist that inhibits gastric acid secretion, on the PKs of a GZR/EBR tablet (FDC1, one tablet containing 100 mg GZR and 50 mg EBR). For the EBR component, the observed EBR $C_{24}$h, $C_{max}$, and $AUC_{0\text{-}inf}$ GM values were approximately 35 - 50% higher following administration of FDC + famotidine tablets when compared to values following administration of the FDC tablet alone. For the GZR component, the GZR $C_{24}$h, $C_{max}$, and $AUC_{0\text{-}inf}$ GM values were approximately 15 - 21% higher following administration of the FDC + famotidine tablets when compared to values following FDC tablet given alone.

**Comment**: The DDI between famotidine and FDC tablet (Study 5172-P045) was only examined following a single dose of the FDC and not at steady-state levels of GZR/EBR.

A second study, 5172-P072 also examined the effect of pre-treatment with famotidine on the PKs of a single dose of the GZR/EBR FDC tablet. The results of this study in contrast to Study 5172-P045 indicated there was little to no interaction between the FDC and famotidine as the GZR and EBR $AUC_{0\text{-}inf}$ GMRs (90% CIs) for GZRA + famotidine/GZRA were 1.10 (0.95, 1.28) and 1.05 (0.92, 1.18), respectively.

**Comment**: Results of Study 5172-P072 indicated a lack of interaction between the FDC and famotidine, whereas the results of Study 5172-P045 indicate that EBR exposure is increased (35%) in the presence of famotidine. There is no clarification provided to explain these inconsistent results.

#### *4.4.1.18. Clinical implications of in vitro findings*

*GZR*

The in vitro data indicates that GZR is a substrate of CYP3A, P-gp, OATP1B1, and OATP1B3. The data also suggests that GZR has some potential to inhibit CYP3A at the intestinal but not systemic level. In addition, GZR did not inhibit any other major CYP isoforms, UGT1A1, CES1, CES2, or CatA and at clinical doses it is also unlikely to inhibit most transporters (P-gp, OATP1B1, OATP1B3, MRP2, MRP3, and MRP4) but has some potential to inhibit BCRP at the intestinal level and BSEP. GZR does not exhibit an induction potential for CYP3A4, 1A2, or 2B6.

*EBR*

The in vitro data demonstrate that EBR is substrate for CYP3A and P-gp. At the proposed clinical dose of 50 mg, EBR is not anticipated to inhibit any of the major CYP isoforms, UGT1A1, CES1, CES2 or CatA, whereas, it has some potential to inhibit intestinal P-gp and BCRP and hepatic OATP1B3. EBR does not exhibit an induction potential for CYP3A4, CYP1A2, or CYP2B6 in human hepatocyte incubations.

#### *4.4.1.19. PopPK studies*

*GZR*

Study 045496 identified that GZR PKs could be best described by a two compartment open model with first order elimination. Oral absorption was described by two parallel first order pathways:

1. a pathway handling the majority of absorption that has a food-dependent absorption rate that, for HCV-infected patients, is faster compared to the other pathway, and
2. a secondary pathway with an absorption rate that is slower than the majority pathway, especially for lower doses (doses less than or equal to 100 mg).

In the Step 4 working full model, approximately 63% of the dose was absorbed through the first pathway, with the remaining 37% of the dose absorbed through the second pathway.

Simulations were conducted to explore the covariate effects on GZR steady state $AUC_{0-24}$, $C_{max,ss}$ and $C_{min,ss}$. Overall, these simulations suggest that moderate hepatic insufficiency (HCV-infected, with cirrhosis, Child-Pugh B) leads to the largest increase in all three summary PK measures, with an approximately 4 fold increase in AUC relative to non-cirrhotic HCV-infected patients. Other factors that led to increased AUC of MK-5172 (all by less than 2-fold) include Asian race, Hispanic ethnicity, female gender, compensated cirrhosis (Child-Pugh A), low body weight and increased age. Combinations of these factors (for example, low body weight Asian female) may lead to larger than 2 fold increases in AUC of MK-5172, but less than a 5 fold increase. Factors that decrease AUC of MK-5172 include Black race, decreased age, and high body weight, but all effects are small (less than 20% decrease), though combinations may lead to larger decreases.

*EBR*

Study 044ZSQ identified that a 2-compartment disposition model with lagged first order absorption adequately described the pooled PK data. The Stage-2 final covariate model included a number of categorical and continuous covariates on select PK parameters including age on Ka; body weight, gender and health status on V2/F; and age, EGFR, gender, race (Black and Asian races), ethnicity (Hispanic), treatment status (treatment experienced with Peg-IFN/RBV), RBV co-administration, moderate CYP/P-gp inhibitors co-administration and methadone co-administration on CL/F. The impact of these covariate effects on the population PK parameter values, along with the corresponding percent change relative to the parameter estimates at their respective reference levels were summarised. Overall, the results suggested that the female covariate resulted in the largest decrease of 31.8% and 29.8% on CL/F and V2/F, respectively. Other covariates with > 20% changes are age (32 year) on Ka, HCV infection on V2/F and methadone co-administration on CL/F.

## 4.5. Evaluator's overall conclusions on pharmacokinetics

Zepatier FDC tablets containing 100 mg GZR and 50 mg EBR are intended for oral dosing.

### 4.5.1. ADME

- Following administration of a single, oral dose of the $FDC_2$ (GZR/EBR 100 mg/50 mg) to healthy subjects in the fasted state the GZR median $T_{max}$ values ranged from 2.0 h to 3.0 h, whereas, EBR median $T_{max}$ occurred at 3.5 h. GZR and EBR bioavailability (F) were 27.3% and 32.4%, respectively.
- $FDC_2$ and the free-combination were bioequivalent in regards to GZR $AUC_{0-inf}$ (GMR: 0.94; 90%CI: 0.84, 1.07); however, the two treatments were not bioequivalent in regards to GZR $C_{max}$ (0.94; 0.78, 1.12), EBR $C_{max}$ (1.18; 1.05, 1.33) or EBR $AUC_{0-inf}$ (1.15; 1.04, 1.26).
- Following administration of a single dose of the FDC tablet, GZR exposure was approximately 1.5 fold to 2.8 fold higher (based on $AUC_{0-inf}$, $C_{max}$ and $C_{24}$h) in the fed state than in the fasted state. By contrast, food appeared to slightly decrease or have no effect on EBR exposure.
- GZR $AUC_{0-24}$ and $C_{max}$ increased in a greater than dose proportional fashion over the dose range of 100 to 1000 mg. For example, between doses of 400 and 800 mg GZR, GM $C_{max}$ and $AUC_{0-inf}$ increased by factors of approximately 10- and 6-fold, respectively. Following 10 days dosing with GZR, $AUC_{0-24}$ and $C_{max}$ increased in a greater than dose proportional fashion. The linearity ratios (steady-state Day 10 $AUC_{0-24}$/single-dose $AUC_{0-inf}$) were 1.17, 1.66 and 2.46 for doses of 100, 200 and 400 mg, respectively.
- Over the dose range 5 mg to 100 mg, EBR AUC and $C_{max}$ increased in an approximately dose proportional fashion. Following 10 days dosing with EBR, the linearity ratios were 1.01,

0.86, 0.78 and 0.66 for doses of 10, 50, 100 and 200 mg, respectively. Accumulation ratios for EBR $AUC_{0-24}$ ranged from 0.981 at 100 mg to 2.05 at the 10 mg dose. Following multiple doses, EBR AUC and $C_{max}$ increased in an approximately dose proportional to slightly less than dose proportional fashion over the 10 mg to 100 mg dose range studied.

- Following administration of GZR and EBR (100 mg QD/50 mg QD) for 10 days, the GM Vz/F values (90% CIs) were 5760 L (4180, 7930) and 901 L (699, 1160) for GZR and EBR, respectively.
- GZR binds to both human serum albumin and α1-acid glycoprotein; however, the binding of [$^3$H]GZR to human plasma proteins was low and was concentration independent over concentrations up to 10 μM.
- EBR is extensively bound to human plasma proteins, binding to both serum albumin and α1-acid glycoprotein, with an unbound fraction of <0.001.
- The mean blood/plasma concentration ratios for GZR (0.7) and EBR (0.62) indicate that neither drug binds preferentially to red blood cells.
- The relatively high Vz/F values for both GZR (5760 L) and EBR (901 L) indicate that both drugs are highly distributed within the tissues.
- GZR elimination in man is likely mediated by both oxidative metabolism and biliary secretion. * EBR elimination is mediated in part by oxidative metabolism as two mono-oxidative metabolites, M2 and M3, were identified in the faeces as well as unchanged drug.
- Clearance of both GZR and EBR was primarily via non-renal pathways. No circulating metabolites of GZR or EBR have been detected. * GZR and EBR were primarily excreted via the faeces, whereas, there was little to no excretion via the urine (<0.3%). There was little to no renal clearance of either GZR or EBR following administration of radioactively labelled forms of either drug.
- The estimated inter-subject variability on GZR CL/F and V/F were 42.1% and 68.8%, whereas the residual variability was 0.51. For EBR, the estimated inter-subject variability on CL/F and Vc/F were 13.4% and 26.3%, whereas, the residual variability was 0.35.

*Target population*

- Following QD doses of 10 to 800 mg GZR in GT1 HCV-infected males and at QD doses of 100 to 800 mg in GT3 HCV-infected males the GZR median Tmax occurred at approximately 2 - 4 h, and it was eliminated with a biphasic decline (initiating at approximately 16 - 24 h post-dose) with a mean t1/2 of approximately 25 - 45 h. GZR exposure increased in a greater than dose proportional manner, as the estimates (95% CIs) of the slope for the regression line fitted on log-transformed AUC0-24, Cmax, and C24 were 1.71 (1.58, 1.84), 1.92 (1.78, 2.05), and 0.95 (0.82, 1.08), respectively. Time to steady state was achieved on average within 5 days across all dose levels. Compared to healthy subjects GZR Cmax, $AUC_{0-24}$ and $C_{24}$ values were approximately 1.91-, 1.63- and 1.46 fold higher, respectively, in patients with HCV.
- Following multiple oral QD doses of 5 mg to 100 mg EBR to HCV-infected male patients, EBR was rapidly absorbed, with a median $T_{max}$ of 2.13 - 3.00 h in HCV-patients infected with GT1, GT1a and GT3. Mean $t_{1/2}$ ranged between 20 to 24 h and the accumulation ratios for $AUC_{0-24}$ ranged from approximately 1.5 to 1.9. EBR exposure increased in an approximately dose-proportional fashion over the 5 to 50 mg range and the resulting estimates (95% CIs) of the slopes for the regression line fitted on ln-transformed $AUC_{0-24}$, $C_{max}$, and $C_{24}$ were 1.15 (0.95, 1.35), 1.16 (0.94, 1.39), and 1.13 (0.94, 1.32), respectively. Steady state of EBR seemed to be attained by Day 2 following administration of 5 mg and 50 mg EBR QD and by Day 3 following the administration of 10 mg and 100 mg EBR QD. EBR exposure was similar in healthy subjects and patients with HCV.

*Impaired hepatic function*

- Compared to matched healthy subjects the GZR $C_{max}$ [90% CIs], $AUC_{0-24}$ and $C_{24}$ values were 1.37 fold [0.83. 2.27], 1.66 fold [1.05. 2.61] and 1.92 fold [1.40. 2.63] higher, respectively, in subjects with mild hepatic insufficiency. In subjects with moderate hepatic insufficiency, GZR $C_{max}$, $AUC_{0-24}$ and $C_{24}$ values were 5.98 fold [2.84, 12.57], 4.82 fold [2.60, 8.93] and 3.59 fold [1.81, 7.11] higher, respectively, than in healthy subjects and in subjects with severe hepatic insufficiency GZR $C_{max}$ [90% CIs], $AUC_{0-24}$ and $C_{24}$ values were 13.01 fold [6.00, 28.21], 11.68 fold [6.10, 22.35] and 9.34 [4.98, 17.51] higher, respectively, than in healthy subjects.
- EBR $C_{max}$ GMRs [90% CIs] for mild, moderate, and severe hepatic insufficiency/healthy matched control comparisons were 0.58 [0.32, 1.05] (mild), 0.69 [0.38, 1.24] (moderate), and 0.58 [0.32, 1.08] (severe). The corresponding values for EBR $AUC_{0-inf}$ GMRs [90%CIs] were 0.61 [0.34, 1.08] (mild), 0.72 [0.40, 1.31] (moderate), and 0.88 [0.48, 1.61] (severe), respectively, and for EBR $C_{24}$ GMRs were 0.61 [0.34, 1.08] (mild), 0.69 [0.38, 1.25] (moderate), and 0.78 [0.43, 1.43] (severe), respectively.

*Age and gender*

- Following administration of multiple QD oral doses of 400 mg, GZR $AUC_{0-24}$ was 118% greater in elderly males than in young males [GMR of 2.18 (90% CI: 1.01 – 4.71)] and $C_{max}$ was 68% greater in elderly males than in young males [GMR of 1.68 (90% CI: 0.73 - 3.90)], whereas, age had no effect on the PKs of a single dose of EBR.
- GZR $AUC_{0-24}$ was 76% greater in elderly females than in elderly males [GMR of 1.76 (90% CI: 0.82 - 3.81)] and $C_{max}$ was 90% greater in elderly females than in elderly males [GMR of 1.90 (90% CI: 0.82 - 4.41)]. Similarly for GBR, EBR $AUC_{0-inf}$ GMR [90% CI] for the comparison of a single dose of 100 mg EBR administered to healthy elderly females versus healthy elderly male subjects was 1.67 [1.12, 2.48].

*Race*

- GZR exposure ($AUC_{0-inf}$ and $C_{max}$) was higher in Japanese subjects than in non-Japanese subjects as the GMR values [Japanese/non-Japanese] (90% CIs) following single doses of 100, 400, 800 or 1200 mg were 1.38 (0.86, 2.22), 2.07 (1.47, 2.90), 2.53 (1.75, 3.66) and 2.84 (1.87, 4.32) for $AUC_{0-inf}$, respectively. Following multiple doses from 100 to 1000 mg GZR QD, the GMR values [Japanese/non-Japanese] (90% CIs) for $AUC_{0-24h}$ and $C_{max}$ were 2.88 (2.01, 4.12) and 2.31 (1.57, 3.39), respectively.
- Following single doses of 5- to 100- mg dose EBR, plasma exposure was greater in Japanese than in non-Japanese over, with the GMRs (Japanese /non-Japanese) and corresponding 90% CIs of 1.69 (1.30, 2.21) for $AUC_{0-inf}$, 1.68 (1.32, 2.14) for $AUC_{0-24h}$, 1.77 (1.38, 2.28) for $C_{max}$, and 1.59 (1.22, 2.07) for $C_{24}$h.
- Chinese subjects had higher GZR exposure (approximately 1.4 to 2.8 fold increase in $C_{max}$ and $AUC_{0-24h}$) when compared with non-Asian subjects administered multiple doses of 100 mg or 200 mg GZR, whereas, there was little difference in GZR exposure following a 100 mg single dose in healthy Chinese and Japanese subjects.

*DDI studies – GZR and EBR*

- There was little to no difference in EBR exposure following co-administration of EBR (20 mg QD) with GZR (200 mg QD) compared to EBR alone, whereas, GZR exposure was slightly lower following co-administration; however, this decrease was unlikely to be clinically significant.

*DDIs with CYP3A substrates*

- Co-administration of rilpivirine (25 mg QD) had little to no effect on GZR or EBR exposure (200 mg/50 mg QD). Similarly, GZR/EBR had little to no effect on the PKs of rilpivirine or LPV when LPV was co-administered with RTV.

*DDIs with strong CYP3A inhibitors*

- GZR exposure was markedly increased following administration of ATV/RTV + GZR as the GZR $AUC_{0-24}$ GMR (90% CI) for the ATV/RTV + GZR / GZR alone comparison was 10.58 (7.78, 14.39).
- EBR $AUC_{0-24}$ GMR (90% CI) for the comparison of multiple doses of 50 mg EBR co-administered with multiple doses of 300/100 mg ATV/RTV versus multiple doses of 50 mg EBR alone was 4.76 (4.07, 5.56).

*DDIs with CYP3A4 substrates*

- Following a single-dose of 400 mg cyclosporine and multiple doses of the free-combination of GZR FFP and EBR PMF2 (200 mg/50 mg) the cyclosporine $AUC_{0-inf}$ GMR (90% CI) for the GZR + EBR + cyclosporine/cyclosporine alone comparison was 0.96 (0.90, 1.02), whereas for GZR, the $AUC_{0-24}$ GMR for the GZR + EBR + cyclosporine/GZR + EBR alone comparison was 15.21 (12.83, 18.04) and for EBR was 1.98 (1.84, 2.13).
- Following a single-dose of 10 mg atorvastatin and multiple doses of GZR FFP and EBR PMF2 (200 mg/50 mg), atorvastatin $AUC_{0-inf}$ increased 4.34 fold (3.10, 6.07) compared to when atorvastatin was administered alone. The $AUC_{0-inf}$ GMR (90% CI) for the midazolam + GZR/midazolam alone comparison was 1.34 (1.29, 1.39). For atorvastatin, the co-administration of GZR resulted in a 200% increase in atorvastatin $AUC_{0-inf}$, whereas, GZR exposure was only slightly increased (approximately 25%) in the presence of atorvastatin.
- Co-administration of GZR or EBR with methadone is unlikely to affect exposure of S-or R-methadone to clinically significant levels. GZR or EBR co-administration also had little to no effect on plasma levels of buprenorphine, norbuprenorphine or naloxone.
- Although methadone co-administration had no effect on GZR exposure, EBR exposure was higher in the subjects receiving co-administered methadone versus historical control subjects receiving EBR alone (EBR $AUC_{0-24}$ GMR [90% CIs] was 1.71 [1.16, 2.51]).
- Buprenorphine/naloxone co-administration induced a small decrease (approximately 25%) in GZR exposure, whereas, it induced a 1.22 fold (0.98, 1.52) increase in EBR $AUC_{0-inf}$.
- Co-administration of GZR (200 mg OD) or EBR (50 mg QD) had little to no effect on the plasma levels of EE or LNG following a single dose of OC.
- Co-administration with GZR resulted in 10% to 39% increases in plasma montelukast exposure.

*DDIs with strong CYP3A4 inhibitors*

- Co-administration of RTV (100 mg BD) with a single dose of 200 mg GZR, induced a 1.91 fold (1.31, 2.79) and 1.88 fold (1.65, 2.14) increase in GZR $AUC_{0-24}$ and $C_{24}$, respectively.
- Co-administration of ketoconazole (400 mg QD) with either a single dose of 100 mg GZR or 50 mg EBR induced a 2 fold increase in GZR $AUC_{0-inf}$, whereas it had little to no effect on EBR $AUC_{0-inf}$.

*DDIs with CYP3A4 – inducers*

- Following co-administration of a single dose of IV rifampin (600 mg) with GZR (200 mg), GZR exposure increased substantially (that is, approximately 10 fold increase GZR AUC), whereas, following multiple oral doses of GZR + PO rifampin, the GZR $AUC_{0-24}$ GMR (90% CI)

was 0.93 (0.75, 1.17). By contrast, following IV rifampin, EBR $AUC_{0\text{-}inf}$ was increased by 1.22 fold [1.06, 1.40] compared to when EBR was administered alone and following oral rifampin, EBR $AUC_{0\text{-}inf}$ was 1.17 [0.98, 1.39] higher.

- Following co-administration of GZR with efavirenz QD for 7 days, the $AUC_{0\text{-}24}$, $C_{max}$, and $C_{24}$ values for GZR were reduced by 83%, 87%, and 69%, respectively. Similarly, the EBR $AUC_{0\text{-}24}$ GMR (90% CI) for the comparison of multiple doses of 50 mg EBR co-administered with multiple doses of 600 mg efavirenz versus multiple doses of 50 mg EBR alone was 0.46 (0.36, 0.59). By contrast, co-administration of either GZR or EBR with efavirenz was unlikely to affect efavirenz exposure to clinically significant levels.

*DDIs with CYP2C9 – substrates*

- Rosuvastatin exposure was increased when co-administered with GZR. Larger increases in rosuvastatin $AUC_{0\text{-}inf}$, $AUC_{0\text{-}24}$, and $C_{max}$ were observed when rosuvastatin was co-administered with both GZR and EBR (GMRs of 2.26 [1.89, 2.69], 2.68 [2.26, 3.17], and 5.49 [4.29, 7.04], respectively) relative to when rosuvastatin was co-administered with GZR only (GMRs of 1.59 [1.33, 1.89], 1.85 [1.56, 2.19], and 4.25 [3.25, 5.56], respectively). By contrast, GZR plasma PKs was not affected following co-administration with rosuvastatin.
- There was a small increase in pitavastatin exposure following co-administration with GZR as the $C_{max}$ and $AUC_{0\text{-}inf}$ GMR values (90% CI) for the pitavastatin + GZR/pitavastatin alone comparison were1.27 (1.07, 1.52) and 1.11 (0.91, 1.34), respectively.

*DDIs with CYP2C19 – substrate*

- Co-administration of pantoprazole (40 mg QD) had little to no effect on the PKs of GZR and EBR following multiple oral doses of a 100 mg GZR/50 mg EBR FDC tablet.

*DDIs with UGT1A1 – substrate*

- There were no clinically significant DDIs following administration of a single oral 50 mg dose of dolutegravir and multiple oral doses of GZR and EBR (200 mg/50 mg QD).

*DDIs with P-gp-substrate*

- Exposure to sofosbuvir was increased following co-administration with GZR/EBR; sofosbuvir $AUC_{0\text{-}inf}$ and $C_{max}$ GMRs (90% CIs) for sofosbuvir + GZR + EBR/sofosbuvir alone comparisons were 2.43 (2.12, 2.79) and 2.27 (1.72, 2.99), respectively.
- Following co-administration of multiple doses of EBR (50 mg QD) with a single 0.25 mg dose of digoxin, the digoxin $AUC_{0\text{-}inf}$ and $C_{max}$ GMR values [90% CI] were 1.11 [1.02, 1.22] and 1.47 [1.25, 1.73], respectively.

*DDIs with Organic anion transporting polypeptide –substrate*

- Co-administration of multiple doses of GZR and EBR (200 mg/50 mg EBR QD) with single-dose of 40 mg pravastatin resulted in approximately 30% higher exposure of pravastatin relative to when pravastatin was given alone.

*DDIs with HIV nucleoside reverse transcriptase inhibitor*

- Tenofovir induced small (clinically insignificant) changes in GZR or EBR exposure when co-administered with either GZR or EBR. GZR co-administration with tenofovir had little to no effect on tenofovir exposure, whereas, EBR induced a moderate increase in tenofovir exposure (approximately 29 to 47%).

*DDIs with HIV integrase inhibitor*

- Raltegravir (400 mg BD or a single dose) induced small (clinically insignificant) changes in GZR or EBR exposure when co-administered with either GZR (200 mg QD) or a single 50 mg dose of EBR. By contrast, the $C_{max}$, $AUC_{0\text{-}12}$ and C12 GMR values (90% CI) for raltegravir for

the raltegravir +GZR/raltegravir comparison were 1.46 (0.78, 2.73), 1.43 (0.89, 2.30) and 1.47 (1.085, 1.998), respectively, whereas, EBR had little to no effect on raltegravir exposure.

*DDIs with inhibitors of NS5A*

- Following multiple doses, $AUC_{0\text{-}24h}$ and $C_{24}$ GMR values (90% CI) for GZR for the GZR + GS-5885(a novel NS5A inhibitor)/GZR comparison were 1.48 (1.34, 1.65) and 1.77 (1.59, 1.98), respectively. For GS-5885, the Day 7 $AUC_{0\text{-}24h}$ and $C_{24}$ GMR values for the GZR + GS-5885/GS-5885 comparison were 1.87 (1.63, 2.15) and 1.97 (1.70, 2.28), respectively. By contrast, daclatasvir had no effect on GZR exposure and GZR co-administration had little to no effect on daclatasvir exposure.
- There was little evidence of a DDI between EBR (50 mg QD) and the novel NS5A inhibitor) MK-2748 (400 mg QD).

*Inhibitors of non-structural protein 5B (NS5B)*

- Co-administration of MK-3682 had no meaningful effect on the plasma exposures of GZR and EBR as the GMR values were close to 1. By contrast, co-administration of MK-3682 with GZR and EBR increased the $C_{max}$ and $AUC_{0\text{-}t}$ of MK-3682 by 28% and 20%, respectively, and decreased the $C_{max}$ and $AUC_{0\text{-}24}$,ss of IDX20664 (MK-3682 metabolite) by 22% and 10%, respectively.
- The $AUC_{0\text{-}24,ss}$ and $C_{max}$ values for GZR were 36% and 56% higher, respectively, following co-administration of GZR, MK-8408 and MK-3682 compared to co-administration of GZR and MK-8408 alone. By contrast, MK-3682 did not affect the plasma exposure to MK-8408 as the GMR values were very close to 1.0. For MK-3682, $AUC_{0\text{-}t}$ and $C_{max}$ values were 26% and 21% higher, respectively, after multiple-dose administration of MK-3682 co-administered with multiple doses of GZR/MK-8408 than after multiple-dose administration of MK-3682 alone.

*Phosphate–binder drugs*

- Co-administration of calcium acetate appeared to cause a small decrease in plasma exposure to GZR/EBR as the GZR and EBR $AUC_{0\text{-}inf}$ GMRs (90% CIs) for GZR + EBR + calcium acetate/GZR + EBR alone were 0.79 (0.68, 0.91) and 0.92 (0.75, 1.14), respectively. Co-administration of sevelamer carbonate also decreased plasma exposure to GZR ($AUC_{0\text{-}inf}$ GMR = 0.82 [0.68, 0.99]), whereas, EBR exposure was slightly higher ($AUC_{0\text{-}inf}$ GMR = 1.13 [0.94, 1.37]).

*pH modifying agents*

- Following administration of a single FDC tablet (100 mg GZR/50 mg EBR) in subjects who had been pre-treated with famotidine the EBR $C_{24}$h, $C_{max}$, and $AUC_{0\text{-}inf}$ GM values were approximately 35 - 50% higher following administration of FDC + famotidine tablets compared to when given the FDC tablet alone. For the GZR component, the GZR $C_{24}$h, $C_{max}$, and $AUC_{0\text{-}inf}$ GM values were approximately 15 - 21% higher following administration of the FDC + famotidine tablets when compared to values following FDC tablet given alone.

*Clinical implications of in vitro findings*

- GZR is a substrate of CYP3A, P-gp, OATP1B1, and OATP1B3 and has some potential to inhibit CYP3A at the intestinal but not systemic level. In addition, GZR did not inhibit any other major CYP isoforms, UGT1A1, CES1, CES2, or CatA and is also unlikely to inhibit most transporters. GZR does not exhibit an induction potential for CYP3A4, 1A2, or 2B6.
- EBR is substrate for CYP3A and P-gp. It is not anticipated to inhibit any of the major CYP isoforms, UGT1A1, CES1, CES2 or CatA, whereas, it has some potential to inhibit intestinal P-gp and BCRP and hepatic OATP1B3. EBR does not exhibit an induction potential for CYP3A4, CYP1A2, or CYP2B6 in human hepatocyte incubations.

*PopPK*

- GZR PKs could be best described by a two compartment open model with first order elimination. The analysis indicated that moderate hepatic insufficiency (HCV-infected, with cirrhosis, Child-Pugh B) leads to the largest increase in all three summary PK measures, with an approximately 4 fold increase in AUC relative to non-cirrhotic HCV-infected patients. Other factors that led to increased AUC of MK-5172 (all by less than 2-fold) include Asian race, Hispanic ethnicity, female gender, compensated cirrhosis (Child-Pugh A), low body weight and increased age. Combinations of these factors (for example, low body weight Asian female) may lead to larger than 2 fold increases in AUC of MK-5172, but less than a 5 fold increase. Factors that decrease AUC of MK-5172 include Black race, decreased age, and high body weight, but all effects are small (less than 20% decrease), though combinations may lead to larger decreases.
- A 2-compartment disposition model with lagged first order absorption adequately described the EBR data. The final covariate model included a number of covariates on select PK parameters including age on Ka; body weight, gender and health status on V2/F; and age, EGFR, gender, race (black and Asian races), ethnicity (Hispanic), treatment status (treatment experienced with Peg-IFN/RBV), RBV co-administration, moderate CYP/P-gp inhibitors co-administration and methadone co-administration on CL/F.

*Limitations of the PK studies*

- No dedicated PK studies examined bioavailability following multiple doses of the FDC tablet.
- No dedicated PK studies examined the dose proportionality of the FDC tablet.
- No studies specifically examined the volume of distribution following dosing with the FDC.
- The drug-drug interactions studies primarily examined GZR or EBR when given alone or as a free combination. Therefore, in most cases the DDIs with the FDC tablet are unknown.
- A number of DDI studies examined the interaction following only single doses of GZR and/or EBR rather than at steady-state levels.
- Many of the studies which examined the DDIs interaction between GZR and other drugs used a higher dose of GZR (200 mg) than the dose proposed for marketing (100 mg).
- The direct interaction between GZR and ERB was examined using doses that do not correspond (that is, 200 mg/20 mg QD) with the proposed dose for marketing (that is, 100 mg/50 mg QD).

# 5. Pharmacodynamics

## 5.1. Studies providing pharmacodynamic data

Table 3 shows the studies relating to each pharmacodynamic.

**Comment**: Two studies (**5172-P004v02** and **8742-P002v02**), which provided PK as well as primary and secondary PD data in the target population have been summarised in this report.

**Table 3: Submitted pharmacodynamic studies**

| PD Topic | Subtopic | Study ID | * |
|---|---|---|---|
| Secondary Pharmacology | Effect on QTc | 5172-P049 | To evaluate effects of a single supratherapeutic oral dose of GZR on QTc interval in healthy subjects |
| | | 8742-P015 | To evaluate effects of a supra-therapeutic dose of EBR on the QTc interval in healthy subjects |

* Indicates the primary aim of the study.

None of the pharmacodynamic studies had deficiencies that excluded their results from consideration.

## 5.2. Summary of pharmacodynamics

The information in the following summary is derived from conventional pharmacodynamic studies in humans unless otherwise stated.

### 5.2.1. Mechanism of action

Zepatier is a combination of two direct-acting antiviral agents, which have distinct mechanisms of action and non-overlapping resistance profiles that target HCV at multiple steps in the viral lifecycle.

GZR inhibits 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.

EBR is a second generation HCV NS5A inhibitor. NS5A is phosphoprotein that 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.

### 5.2.2. Pharmacodynamic effects

#### *5.2.2.1. Primary pharmacodynamic effects*

No dedicated PD studies examined the PD effects of the FDC tablet proposed for marketing.

*Antiviral activity*

Antiviral-activity was assessed by measuring HCV RNA levels pre-dose and at pre-specified time points post-dose. For each patient, the baseline measurement was defined as the measurement obtained pre-dose on the first day of dosing.

*GZR*

A secondary objective of **Study 5172-P004v02** was to establish a generally safe and well-tolerated QD dose of GZR in GT1 and GT3 HCV-infected patients that mediated a viral load reduction that was significantly greater in the GZR treatment group than in a placebo group following doses of 10 mg to 800 mg to GT1 HCV-infected and 100 mg to 800 mg in GT3 HCV-infected patients. Administration of GZR for 7 days resulted in dose-dependent reduction of HCV RNA in GT3 patients, whereas, viral load reduction appeared to plateau between 50 - 800 mg in

GT1 infected patients. The largest mean differences (GZR – placebo) and corresponding 90% CIs in maximum log10 HCV RNA reduction (IU/mL) was 5.34 (4.93, 5.74) in GT1 HCV-infected male patients (achieved at the 800 mg dose) and 4.98 (4.42, 5.53) in GT3 HCV-infected male patients (achieved at the 600 mg dose).

*EBR*

One of the primary objectives of Study 8742-P002v02 was to establish a generally safe dose of EBR that mediated a viral load reduction, which was greater following multiple dose oral administration of EBR (5 mg to 100 mg QD) than following administration of placebo, in GT1a and GT1b HCV-infected patients. The results indicated that administration of EBR to HCV-infected patients resulted in dose-dependent reductions in HCV RNA. The largest mean differences (EBR – placebo) and corresponding 90% CI in log10 HCV RNA reductions identified were 4.41 (3.92, 4.90) in GT1 HCV-infected male patients (achieved at the 50 mg dose), 3.95 (3.44, 4.47) in GT1a HCV-infected male patients (achieved at the 50 mg dose), and 2.72 (2.05, 3.39) in GT3 HCV-infected male patients (achieved at the 100 mg dose), respectively.

#### *5.2.2.2. Secondary pharmacodynamic effects*

*Cardiac conduction*

Studies 5172-P049 and 8742-P015 examined the effects of supratherapeutic doses of GZR (1600 mg) and EBR (700 mg), respectively on QTc in healthy subjects. For GZR, the maximum mean difference from placebo (GZR-placebo) in QTcF change from baseline occurred at 8 h post-dose [-0.48 msec, 90% CI (-2.54, 1.58)]. Similarly for EBR, the largest mean difference (90% CI) was 0.856 (-1.06, 2.78), occurring at 1.5 h post-dose. In contrast to moxifloxacin, the upper limits of the 90% CIs for both GZR and EBR did not exceed 10 msec at any time point post-dose; therefore, indicating that neither GZR nor EBR prolongs the QTc to a clinically significant degree.

*Viral resistance*

*GZR*

Study 5172-P004v02 also investigated the HCV NS3/4A gene in patient plasma samples with viral loads in excess of 1000 IU/mL for the existence of treatment-emergent, post-baseline variations in amino acid structure (that is, virus variants that were detected during and/or after treatment but not at baseline). Post-baseline variants that were present in > 10% of the samples were noted and variants with more than 5 fold reduced susceptibility to GRZ in the in vitro assays were considered as resistance associated variants (RAVs).

Among all of the polymorphisms examined, substitutions at amino acids 168, 156, 56 and 155 were observed in > 10% of the patients treated with GZR. Amino acid variants were also observed at other positions within the NS3/4A sequence; however, examination of HCV isolate sequences in Genbank database showed that most of these positions are highly polymorphic and it is not clear the role of these polymorphisms on antiviral resistance. Post-baseline RAVs observed in GT1a, GT1b and GT3a patients receiving different doses of grazoprevir were summarised. Overall, there was no notable difference in terms of the types of RAVs and the prevalence of RAVs selected by different dose levels within each genotype.

*EBR*

A similar analysis was undertaken as a part of Study 8742-P002v02 to determine whether treatment with EBR induced changes in the amino acid structure of the NS5A protein. Among the polymorphisms identified, substitutions at amino acids 28, 30, 31, and 93 were observed in greater than 10% of subjects (or >4 out of 35 subjects). Polymorphisms were also observed in other amino acids especially in Domain III; however, examination of the HCV isolate sequences in the Genbank database showed that most of these positions are highly polymorphic and it is not clear if these polymorphisms have any impact on EBR or play any role in the viral

replication. Post-baseline RAVs selected by different doses of MK-8742 in GT1a, GT1b and GT3 were summarised. Overall, there was no notable difference in terms of the types of RAVs and the prevalence of RAVs selected by different dose levels within each genotype subtype.

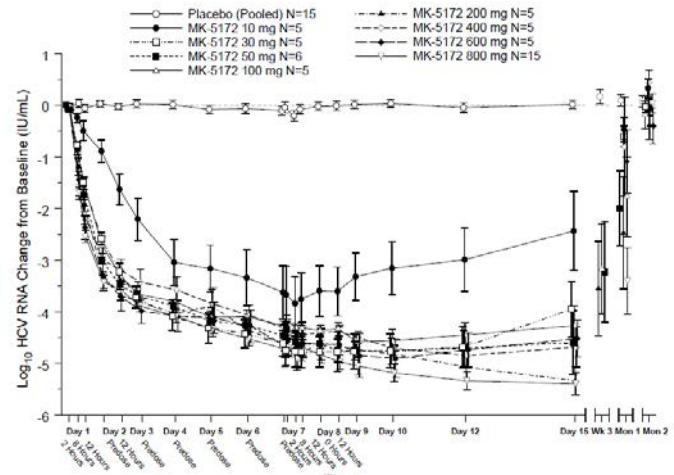
### 5.2.3. Time course of pharmacodynamic effects

*GZR*

The time course for GZR induced reductions in viral load for GT1 and GT3 HCV-infected patients are summarised in Figures 1 and 2, respectively. Following the first QD dose of 100 mg in GT1 HCV infected patients there was rapid decline in viral load (approximately 2.5 log units) by 12 h post-dose. With each following dose viral load continued to decline up until the final dose on Day 7 and then remained fairly stable up until Day 15 (day 8 post final dose) (Figure 1). For GT3 HCV-infected patients, although viral load decreased following the first 100 mg QD dose, the reduction was considerably smaller (approximately 0.75 log units at 12 h post-dose). As for GT1 infected patients, GT3 viral load continued to decrease during the 7 days of dosing but by Day 15 viral load had almost retained pre-dose/baseline levels (Figure 2).

**Figure 1: Study 5172-P004v02**

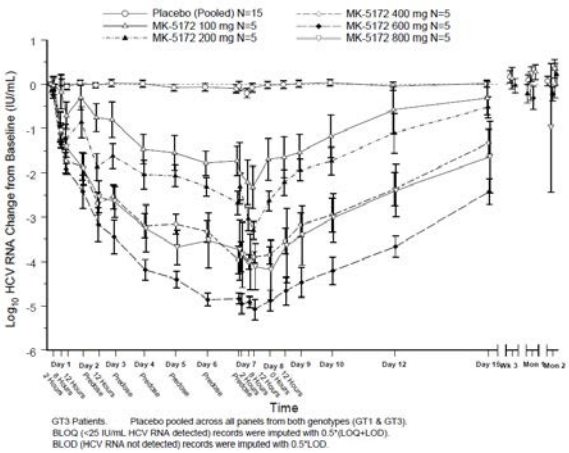
Arithmetic Mean (± SE) of $\log_{10}$ HCV RNA Change From Baseline (IU/mL) Following the Administration of Multiple Oral Doses of 10 to 800 mg Grazoprevir (MK-5172) QD in GT1 HCV-Infected or Placebo QD in GT1 and GT3 HCV-Infected Male Patients on Days 1 - 7




GT1 Patients. Placebo pooled across all panels from both genotypes (GT1 & GT3).
BLOQ (<25 IU/mL HCV RNA detected) records were imputed with 0.5*(LOQ+LOD).
BLOD (HCV RNA not detected) records were imputed with 0.5*LOD.

**Figure 2: Study 5172-P004v02**

Arithmetic Mean (± SE) of $\log_{10}$ HCV RNA Change From Baseline (IU/mL) Following the Administration of Multiple Oral Doses of 100 to 800 mg Grazoprevir (MK-5172) QD in GT3 HCV-Infected or Placebo QD in GT1 and GT3 HCV-Infected Male Patients on Days 1 - 7

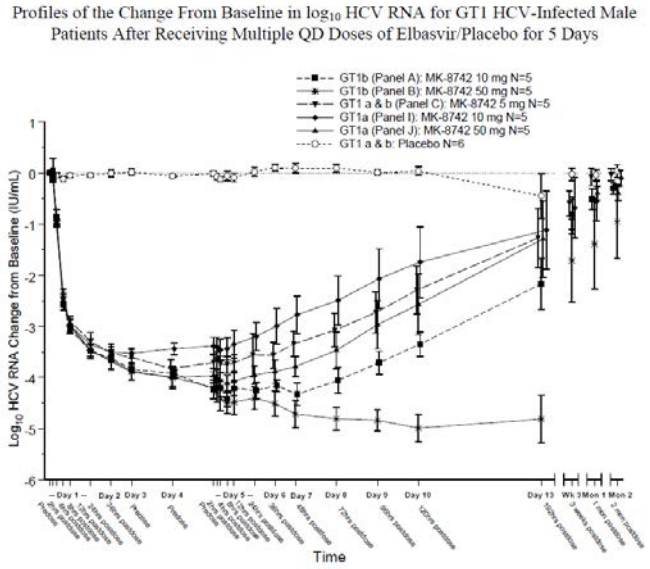



GT3 Patients. Placebo pooled across all panels from both genotypes (GT1 & GT3).
BLOQ (<25 IU/mL HCV RNA detected) records were imputed with 0.5*(LOQ+LOD).
BLOD (HCV RNA not detected) records were imputed with 0.5*LOD.

*EBR*

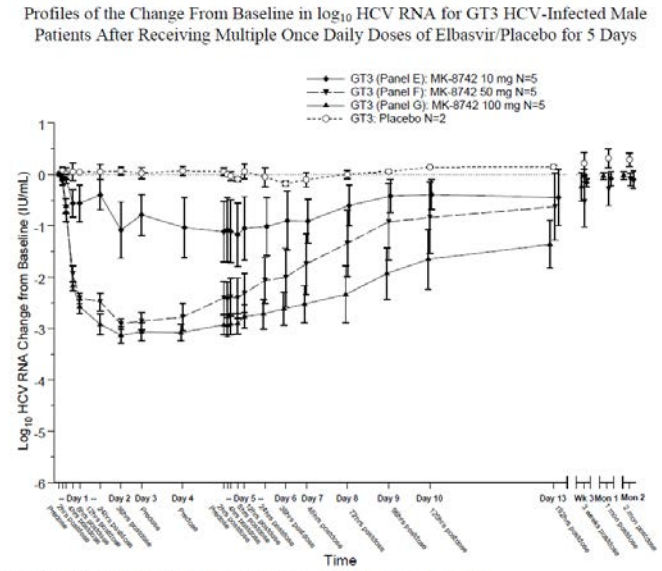
The time course for EBR induced reductions in viral load for GT1 and GT3 HCV-infected patients are summarised in Figures 3 and 4, respectively. Following the first QD dose of 50 mg EBR, there was a rapid decline in GT1 viral load (approximately 3 log units by 12 h post-dose) and viral load continued to decrease with every following dose (Figure 3). Following 5 days QD dosing with 100 mg EBR, viral load in GT1b HCV-infected subjects remained relatively stable up until Day 13 (that is, 8 days post the final dose), whereas, viral load commenced returning to baseline by Day 6 in GT1a HCV-infected subjects. As seen for GZR, viral load in GT3 HCV-infected patients appeared to be more resistant to treatment with EBR than GT1 infected patients (Figure 4).

**Figure 3: Study 8742-P002v02**




* BLOQ (< 25 IU/ml HCV RNA detected) records were imputed with 0.5*(LOQ + LOD).
* BLOD (HCV RNA not detected) records were imputed with 0.5*LOD.
* LOQ = 25 IU/ml, LOD = 3.8 IU/ml.

**Figure 4: Study 8742-P002v02**




* BLOQ (<25 IU/ml HCV RNA detected) records were imputed with 0.5*(LOQ + LOD).
* BLOD (HCV RNA not detected) records were imputed with 0.5*LOD.
* LOQ = 25 IU/ml, LOD = 3.8 IU/ml.

**Comment**: GT3 HCV-infected patients appear to be more resistant to treatment with either GZR or EBR than GT1 HCV-infected subjects.

#### 5.2.4. Relationship between drug concentration and pharmacodynamic effects

A stated previously, administration of GZR for 7 days resulted in a dose-dependent reduction of HCV RNA in GT3 patients, whereas, viral load reduction appeared to plateau between 50 - 800 mg in GT1 infected patients. For EBR (5 mg – 100 mg), reductions in HCV RNA were dose dependent in GT1, GT1A- and GT3 HCV-infected male patients.

#### 5.2.5. Genetic-, gender- and age-related differences in pharmacodynamic response

Not examined as both dedicated PD studies (Studies 5172-P004v02 and 8742-P002v02) were undertaken in predominantly White males.

#### 5.2.6. Pharmacodynamic interactions

Not examined.

### 5.3. Evaluator's overall conclusions on pharmacodynamics

#### 5.3.1. Mechanism of action

- Zepatier is a combination of two direct-acting antiviral agents: GZR, which inhibits HCV NS3/4A protease and EBR, which is a HCV NS5A inhibitor.

#### 5.3.2. Antiviral activity

- For GZR, the largest mean differences (GZR – placebo) and corresponding 90% CIs in maximum log10 HCV RNA reduction (IU/mL) was 5.34 (4.93, 5.74) in GT1 HCV-infected male patients (achieved at the 800 mg dose) and 4.98 (4.42, 5.53) in GT3 HCV-infected male patients (achieved at the 600 mg dose).
- For EBR, the largest mean differences (EBR – placebo) and corresponding 90% CI in log10 HCV RNA reductions identified were 4.41 (3.92, 4.90) in GT1 HCV-infected male patients (achieved at the 50 mg dose), 3.95 (3.44, 4.47) in GT1a HCV-infected male patients (achieved at the 50 mg dose), and 2.72 (2.05, 3.39) in GT3 HCV-infected male patients (achieved at the 100 mg dose), respectively.

#### 5.3.3. Cardiac conduction

- Supratherapeutic doses of GZR or EBR had no effect on QTc.

#### 5.3.4. Viral resistance

- Following administration of GZR, treatment-emergent substitutions in the NS3/4A sequence at amino acids 168, 156, 56 and 155 were observed in > 10% of the patients. Overall, there was no notable difference in terms of the types of RAVs and the prevalence of RAVs selected by different dose levels within each genotype.
- Following administration of EBR, treatment-emergent substitutions in the NS5A sequence at amino acids 28, 30, 31, and 93 were observed in greater than 10% of subjects (or >4 out of 35 subjects). Overall, there was no notable difference in terms of the types of RAVs and the prevalence of RAVs selected by different dose levels within each genotype subtype.

#### 5.3.5. Time course of pharmacodynamic effects

- Following the first QD dose of 100 mg in GT1 HCV infected patients there was rapid decline in viral load (approximately 2.5 log units) by 12 h post-dose. With each following dose viral load continued to decline up until the final dose on Day 7 and then remained fairly stable up until Day 15. For GT3 HCV-infected patients, although viral load decreased following the first 100 mg QD dose, the reduction was considerably smaller (approximately 0.75 log units at 12 h post-dose). As for GT1 infected patients, GT3 viral load continued to decrease during the 7 days of dosing but by Day 15 viral load had almost retained pre-dose/baseline levels.

- Following the first QD dose of 50 mg EBR, there was a rapid decline in GT1 viral load (approximately 3 log units by 12 h post-dose) and viral load continued to decrease with every following dose. Following 5 days QD dosing with 100 mg EBR, viral load in GT1b HCV-infected subjects remained relatively stable up until Day 13, whereas, viral load commenced returning to baseline by Day 6 in GT1a HCV-infected subjects. As seen for GZR, viral load in GT3 HCV-infected patients appeared to be more resistant to treatment with EBR than GT1 infected patients. GT3 HCV-infected patients appear to be more resistant to treatment with either GZR or EBR than GT1 HCV-infected subjects.
- Administration of GZR for 7 days resulted in a dose-dependent reduction of HCV RNA in GT3 patients, whereas, viral load reduction appeared to plateau between 50 - 800 mg in GT1 infected patients. For EBR (5 mg – 100 mg), reductions in HCV RNA were dose dependent in GT1 , GT1A- and GT3 HCV-infected male patients.

#### 5.3.6. Limitations of the PD studies

- No dedicated PD studies examined the PD effects of the FDC tablet proposed for marketing.
- No dedicated PD studies examined PD interactions with the FDC tablet or GZR or EBR when administered alone.

# 6. Dosage selection for the pivotal studies

The initial Phase II studies provided information that determined the doses of GZR and EBR, the duration of treatment, regimen, that is, with or without RBV and the patient populations for the pivotal or core studies which are discussed in section 7.

## 6.1. Phase II studies which provided data for dosage selection for the pivotal studies

### 6.1.1. Study P003

P003 was a Phase II, randomised, multicentre, boceprevir (BOC)-controlled, dose-ranging study to evaluate the safety, tolerability and efficacy of different regimens of MK-5172 (grazoprevir or GZR) when administered concomitantly with Peginterferon alfa-2b and Ribavirin (PR) in Treatment-Naïve (TN) patients with chronic Genotype 1 HCV infection. The study was initiated in June 2011 and is still ongoing. It was conducted at 70 trial centres: 2 in Argentina, 4 in Canada, 4 in France, 4 in Germany, 2 in Israel 2 in Italy and 52 in the United States.

Non-cirrhotic subjects were randomised in a 1:1:1:1:1 ratio to one of four arms treated with GZR or a BOC control arm. The protocol enrolled two cohorts sequentially: a Vanguard Cohort (n = 136) and a Second Cohort (n = 196). The GZR arms were treated with GZR 100, 200, 400, or 800 mg once daily (QD) + placebo for BOC + PR for 12 weeks and PR for an additional 12 or 36 weeks per response-guided therapy (RGT). Non-cirrhotic subjects in the control arm received 4 weeks of PR followed by BOC 800 mg three times daily (TID) + placebo for GZR + PR for 24 or 32 weeks + a 12 week PR tail per RGT. After an interim analysis of the Vanguard Cohort identified dose-dependent increases in alanine and aspartate aminotransferases (ALT and AST), particularly among subjects in the 400 mg and 800 mg dose groups, 79 subjects in the Second Cohort who were receiving GZR 400 or 800 mg QD were down-dosed to GZR 100 mg QD. Subjects in the 100 and 200 mg GZR arms remained blinded and continued dosing as per protocol. A subsequently added cohort of cirrhotic subjects received open label GZR 100 mg QD + PR for 12 weeks and PR for an additional 12 or 36 weeks per RGT. Subjects were followed for 24-48 weeks after end of treatment. Subjects who relapsed were followed for 48 weeks beyond the time of failure.

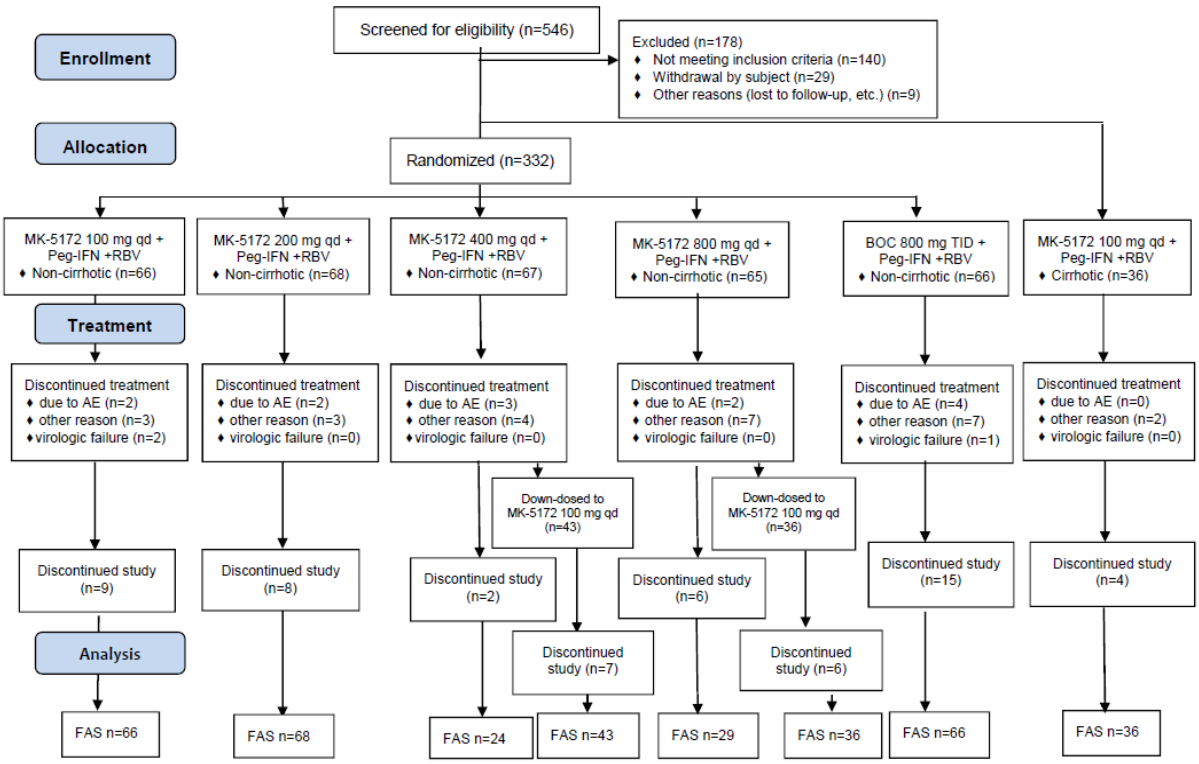
The primary efficacy endpoint was the proportion of subjects achieving complete Early Viral Response (cEVR), defined as undetectable HCV RNA at Week 12 in the GZR treatment arms. The secondary efficacy endpoints were:

1. time to first achievement of undetectable HCV RNA,
2. proportion of subjects achieving RVR, SVR12 and SVR24 and the proportion of subjects with undetectable HCV RNA at Week 72.

For the cirrhotic cohort, the following endpoints were evaluated as exploratory efficacy analyses: RVR, cEVR, SVR4, SVR12 and SVR24, and proportion of subjects achieving undetectable HCV RNA at Weeks 2 and 72. An assumption of an underlying cEVR rate of approximately 75% was made based on the results of earlier teleprevir studies (McHutchinson, 2009; Hezode, 2009).[1]

Overall, 278/332 (83.7%) of subjects completed study; the rate of study completion was lower for the BOC treatment arm (77.3%) than the GZR treatment arms, in which the completion rate declined with increasing GZR dose level from 86.4% on the 100 mg regimen to 79.3% on the 800 mg regimen; 43 subjects in the GZR 400-mg arm and 36 subjects in the GZR 800-mg arm were down-dosed to 100 mg QD after an interim analysis identified late dose-related increases in transaminases (Figure 5). Adverse events (AEs) were the primary reason for study drug discontinuation (3-3.4% in GZR arms and 6.1% in BOC arm) (Figure 5).

**Figure 5: Flow diagram of subject disposition**




Majority of the subjects were male, White and had the non-CC *IL28B* genotype with median age was 51 (18 to 72) years; Reported compliance with GZR/matching placebo treatment was very high among non-cirrhotic (97-99.5%) and cirrhotic (99%) subjects.

[1] In a study of a different protease inhibitor (telaprevir), 175 TN subjects across three treatment arms had cEVR rates ranging from 68% to 80% (McHutchinson, 2009) . In a separate study with telaprevir (Hezode, 2009), 163 TN subjects in two treatment arms had cEVR rates of 73% to 80%.

The percentage of subjects with undetectable HCV RNA at TW12 (cEVR) was 80.3% (95% CI: 68.7% - 89.1%) in the non-cirrhotic GZR 100 mg + PR arm and 75.9% or higher in treatment arms dosed with GZR 200, 400 or 800 mg QD, including subsets of subjects in the two highest dose groups who were down-dosed to 100 mg QD. Response rates in all GZR arms were numerically higher than in the BOC + PR control arm (69.7%). The cEVR for cirrhotic subjects was numerically higher than the cEVR in non-cirrhotic subjects also treated with the GZR 100-mg regimen (94.4% and 80.3%, respectively). Overall, 43 of the 67 subjects randomised to receive 400 mg of GZR QD were still on therapy and were therefore eligible to be down-dosed to a regimen with GZR 100 mg QD. Of these 43 subjects, 37 re-initiated theraphy with GZR 100 mg; the duration of 100 mg QD therapy ranged from 1 day to 9 weeks and 6 days. The cEVR rate in the down-dosed subjects was 86.0% (37/43), compared with 87.5% (21/24) among subjects who received the entire 12 week treatment with GZR 400 mg QD. Thirty-six (36) of the 65 subjects randomised to receive 800 mg of GZR QD were still on therapy and were therefore eligible to be down-dosed to a regimen with GZR 100 mg QD. Of these 36 subjects, 31 re-initiated theraphy with GZR 100 mg; the duration of 100 mg QD therapy ranged from 2 days to 8 weeks and 3 days. The cEVR rate in the subjects who were down-dosed was 86.1% (31/36) compared with 75.9% (22/29) among subjects who were not down-dosed.

Overall, cEVR rates in the 288 of 332 (86.7%) subjects in the FAS population were included in the PP population for the supportive analysis of the cEVR. The major reasons for excluding subjects from the PP population included: subjects in the non-cirrhotic cohort were judged to be cirrhotic (and vice-versa) by the central pathologist, subjects were treated for only 24 weeks but should have been treated for 48 weeks per the response-guided therapy rules, and subjects were non-compliant with study medication before Week 4. For all randomised non-cirrhotic treatment arms in the PP population, response rates were slightly higher than rates observed in the FAS population. The proportions of subjects who achieved cEVR were generally numerically higher in the GZR + PR arms compared with the BOC + PR arm (Table 4). The cEVR rate in cirrhotic subjects (100%) in the PP population was numerically higher than that among cirrhotic subjects in the FAS population (94.4%) (Table 4). Across the GZR treatment arms, cEVR rates were not consistently affected by the subject's gender, HCV genotype (GT1a, GT1b and other GT1), *IL28B* genotype (CC or non-CC); HCV RNA at Screening (low or high); or METAVIR fibrosis grade (F0-F2, F3, and F4) (Table 5). The small numbers of cirrhotic subjects precluded an analysis of efficacy by subgroup.

**Table 4: Analysis of the proportion of subjects with complete early viral response (cERV) in MK-5172 treatment regiments and undetectable (TND) HCV RNA at treatment Week 16 in control regimen Per protocol cEVR Analysis population**

| Treatment | N | n (%) | 95% Confidence Interval[†] |
|---|---|---|---|
| TN Cirr: MK-5172 100 mg qd + Peg-IFN + RBV | 25 | 25 (100.0) | (86.3, 100.0) |
| TN Non-cirr: MK-5172 100 mg qd + Peg-IFN + RBV | 60 | 50 (83.3) | (71.5, 91.7) |
| TN Non-cirr: MK-5172 200 mg qd + Peg-IFN + RBV | 59 | 55 (93.2) | (83.5, 98.1) |
| TN Non-cirr: MK-5172 400 mg qd + Peg-IFN + RBV | 21 | 20 (95.2) | (76.2, 99.9) |
| TN Non-cirr: MK-5172 800 mg qd + Peg-IFN + RBV | 24 | 22 (91.7) | (73.0, 99.0) |
| TN Non-cirr: MK-5172 400 mg Down-Dosed to 100 mg qd + Peg-IF | 38 | 35 (92.1) | (78.6, 98.3) |
| TN Non-cirr: MK-5172 800 mg Down-Dosed to 100 mg qd + Peg-IF | 32 | 31 (96.9) | (83.8, 99.9) |
| TN Non-cirr: Boceprevir 800 mg tid + Peg-IFN + RBV | 54 | 45 (83.3) | (70.7, 92.1) |

[†]Based on Clopper-Pearson method.
N = Number of subjects included in the analysis.
n (%) = Number of subjects with undetectable (TND) HCV RNA at the MK-5172 Treatment Week 12 or Control Treatment Week 16 visit and the percentage calculated as (n/N)*100.

**Table 5: Analysis of the proportion of subjects with complete early viral response (cERV) and undetectable (TND) HCV RNA at treatment Week 16 in control regimen by various subgroups Full Analysis Population**

| | TN Cirr: MK-5172 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 200 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 400 mg qd + Peg-IFN + RBV | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* |
| Gender | | | | | | | | | | | | |
| Male | 22 | 21 (95.5) | (77.2, 99.9) | 41 | 36 (87.8) | (73.8, 95.9) | 36 | 31 (86.1) | (70.5, 95.3) | 12 | 12 (100.0) | (73.5, 100.0) |
| Female | 14 | 13 (92.9) | (66.1, 99.8) | 25 | 17 (68.0) | (46.5, 85.1) | 32 | 27 (84.4) | (67.2, 94.7) | 12 | 9 (75.0) | (42.8, 94.5) |
| IL28B Genotype | | | | | | | | | | | | |
| CC | 9 | 9 (100.0) | (66.4, 100.0) | 17 | 15 (88.2) | (63.6, 98.5) | 19 | 18 (94.7) | (74.0, 99.9) | 4 | 3 (75.0) | (19.4, 99.4) |
| Non-CC | 27 | 25 (92.6) | (75.7, 99.1) | 49 | 38 (77.6) | (63.4, 88.2) | 49 | 40 (81.6) | (68.0, 91.2) | 20 | 18 (90.0) | (68.3, 98.8) |
| Screening HCV RNA | | | | | | | | | | | | |
| <=800,000 IU/mL | 7 | 7 (100.0) | (59.0, 100.0) | 17 | 14 (82.4) | (56.6, 96.2) | 18 | 14 (77.8) | (52.4, 93.6) | 6 | 5 (83.3) | (35.9, 99.6) |
| >800,000 IU/mL | 29 | 27 (93.1) | (77.2, 99.2) | 49 | 39 (79.6) | (65.7, 89.8) | 50 | 44 (88.0) | (75.7, 95.5) | 18 | 16 (88.9) | (65.3, 98.6) |
| HCV Genotype | | | | | | | | | | | | |
| 1a | 32 | 31 (96.9) | (83.8, 99.9) | 43 | 31 (72.1) | (56.3, 84.7) | 41 | 35 (85.4) | (70.8, 94.4) | 10 | 8 (80.0) | (44.4, 97.5) |
| 1b | 4 | 3 (75.0) | (19.4, 99.4) | 23 | 22 (95.7) | (78.1, 99.9) | 27 | 23 (85.2) | (66.3, 95.8) | 13 | 12 (92.3) | (64.0, 99.8) |
| 1-Other | 0 | 0 ( ) | | 0 | 0 ( ) | | 0 | 0 ( ) | | 1 | 1 (100.0) | (2.5, 100.0) |
| Metavir Hepatic Fibrosis Score | | | | | | | | | | | | |
| 0 | 0 | 0 ( ) | | 6 | 6 (100.0) | (54.1, 100.0) | 4 | 4 (100.0) | (39.8, 100.0) | 1 | 0 (0.0) | (0.0, 97.5) |
| 1 | 0 | 0 ( ) | | 45 | 35 (77.8) | (62.9, 88.8) | 52 | 43 (82.7) | (69.7, 91.8) | 21 | 20 (95.2) | (76.2, 99.9) |
| 2 | 5 | 5 (100.0) | (47.8, 100.0) | 10 | 9 (90.0) | (55.5, 99.7) | 9 | 9 (100.0) | (66.4, 100.0) | 1 | 1 (100.0) | (2.5, 100.0) |
| 3 | 4 | 4 (100.0) | (39.8, 100.0) | 2 | 1 (50.0) | (1.3, 98.7) | 1 | 0 (0.0) | (0.0, 97.5) | 0 | 0 ( ) | |
| 4 | 27 | 25 (92.6) | (75.7, 99.1) | 3 | 2 (66.7) | (9.4, 99.2) | 2 | 2 (100.0) | (15.8, 100.0) | 0 | 0 ( ) | |

| | TN Non-cirr: MK-5172 800 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 400 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 800 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: Boceprevir 800 mg tid + Peg-IFN + RBV | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* |
| Gender | | | | | | | | | | | | |
| Male | 14 | 9 (64.3) | (35.1, 87.2) | 28 | 25 (89.3) | (71.8, 97.7) | 23 | 20 (87.0) | (66.4, 97.2) | 37 | 24 (64.9) | (47.5, 79.8) |
| Female | 15 | 13 (86.7) | (59.5, 98.3) | 15 | 12 (80.0) | (51.9, 95.7) | 13 | 11 (84.6) | (54.6, 98.1) | 29 | 22 (75.9) | (56.5, 89.7) |
| IL28B Genotype | | | | | | | | | | | | |
| CC | 9 | 6 (66.7) | (29.9, 92.5) | 13 | 12 (92.3) | (64.0, 99.8) | 9 | 7 (77.8) | (40.0, 97.2) | 19 | 12 (63.2) | (38.4, 83.7) |
| Non-CC | 20 | 16 (80.0) | (56.3, 94.3) | 30 | 25 (83.3) | (65.3, 94.4) | 27 | 24 (88.9) | (70.8, 97.6) | 47 | 34 (72.3) | (57.4, 84.4) |
| Screening HCV RNA | | | | | | | | | | | | |
| <=800,000 IU/mL | 5 | 4 (80.0) | (28.4, 99.5) | 11 | 10 (90.9) | (58.7, 99.8) | 9 | 9 (100.0) | (66.4, 100.0) | 17 | 13 (76.5) | (50.1, 93.2) |
| >800,000 IU/mL | 24 | 18 (75.0) | (53.3, 90.2) | 32 | 27 (84.4) | (67.2, 94.7) | 27 | 22 (81.5) | (61.9, 93.7) | 49 | 33 (67.3) | (52.5, 80.1) |
| HCV Genotype | | | | | | | | | | | | |
| 1a | 15 | 11 (73.3) | (44.9, 92.2) | 27 | 21 (77.8) | (57.7, 91.4) | 22 | 20 (90.9) | (70.8, 98.9) | 43 | 32 (74.4) | (58.8, 86.5) |
| 1b | 14 | 11 (78.6) | (49.2, 95.3) | 15 | 15 (100.0) | (78.2, 100.0) | 14 | 11 (78.6) | (49.2, 95.3) | 23 | 14 (60.9) | (38.5, 80.3) |
| 1-Other | 0 | 0 ( ) | | 1 | 1 (100.0) | (2.5, 100.0) | 0 | 0 ( ) | | 0 | 0 ( ) | |
| Metavir Hepatic Fibrosis Score | | | | | | | | | | | | |
| 0 | 1 | 1 (100.0) | (2.5, 100.0) | 3 | 2 (66.7) | (9.4, 99.2) | 2 | 2 (100.0) | (15.8, 100.0) | 2 | 1 (50.0) | (1.3, 98.7) |
| 1 | 19 | 14 (73.7) | (48.8, 90.9) | 28 | 25 (89.3) | (71.8, 97.7) | 23 | 21 (91.3) | (72.0, 98.9) | 50 | 36 (72.0) | (57.5, 83.8) |
| 2 | 6 | 5 (83.3) | (35.9, 99.6) | 9 | 8 (88.9) | (51.8, 99.7) | 10 | 7 (70.0) | (34.8, 93.3) | 10 | 6 (60.0) | (26.2, 87.8) |
| 3 | 2 | 1 (50.0) | (1.3, 98.7) | 1 | 1 (100.0) | (2.5, 100.0) | 1 | 1 (100.0) | (2.5, 100.0) | 4 | 3 (75.0) | (19.4, 99.4) |
| 4 | 0 | 0 ( ) | | 0 | 0 ( ) | | 0 | 0 ( ) | | 0 | 0 ( ) | |

| | TN Cirr: MK-5172 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 200 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 400 mg qd + Peg-IFN + RBV | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* |
| Metavir Hepatic Fibrosis Score | | | | | | | | | | | | |
| Unknown | 0 | 0 ( ) | | 0 | 0 ( ) | | 0 | 0 ( ) | | 1 | 0 (0.0) | (0.0, 97.5) |

| | TN Non-cirr: MK-5172 800 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 400 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: MK-5172 800 mg Down-Dosed to 100 mg qd + Peg-IFN + RBV | | | TN Non-cirr: Boceprevir 800 mg tid + Peg-IFN + RBV | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* | N | n (%) | 95% CI* |
| Metavir Hepatic Fibrosis Score | | | | | | | | | | | | |
| Unknown | 1 | 1 (100.0) | (2.5, 100.0) | 2 | 1 (50.0) | (1.3, 98.7) | 0 | 0 ( ) | | 0 | 0 ( ) | |

*Confidence Interval based on Clopper-Pearson method.
N = Number of subjects included in the subgroup analysis.
n (%) = Number of subjects with undetectable (TND) HCV RNA at the MK-5172 Treatment Week 12 or Control Treatment Week 16 visit and the percentage calculated as (n/N)*100.

All GZR dose levels led to rapid achievement of undetectable (TND) HCV RNA; median time to first TND ranged from 15 to 29 days across GZR dose groups, without an apparent dose relationship. Cirrhotic subjects on the GZR 100-mg achieved TND HCV RNA more slowly (median time of 22 days) compared with non-cirrhotic subjects on the GZR 100-mg (median time of 15 days) regimen. Approximately, 87.6% (233 of 266) of subjects in the GZR arms had a rapid virologic response (defined as undetectable HCV-RNA level at TW4) and did not show a consistent pattern of increase with GZR dose level. In contrast, a markedly lower percentage of subjects in the BOC control group achieved TND HCV RNA at TW8 (59.1%). The mean RVR rate at TW4 was lower in cirrhotic subjects (72.2%) than in non-cirrhotic subjects (90.9%) in the GZR 100-mg treatment arm. Higher proportions of subjects in the GZR + PR arms achieved SVR12 and SVR24 (89.4% and 86.4%, respectively) compared with subjects in the BOC + PR (60.6% and 57.6%, respectively). Among subjects in the GZR treatment arms, 28 and 29 subjects did not achieve SVR12 and SVR24, respectively. Of these, 22 (79%) for SVR12 and 23

(79%) for SVR24 failed for non-virologic reasons.[2] Excluding the 22 subjects who failed for non-virology reasons, SVR12 and SVR24 was achieved in 97.5% (238/244) and 97.5% (237/243) of subjects, respectively. In the GZR 100 mg arm, 92.2% (59/64) and 91.9% (57/62) of subjects achieved SVR12 and SVR24, respectively. The rate of virologic failure was notably higher in the BOC control arm (19.7% [13/66]) than in the GZR 100-mg dose group (7.6% [5/66]) for both SVR12 and SVR24. In the open-label, cirrhotic subjects, both SVR12 and SVR24 were achieved in 72.2% of subjects.

**Comment**: P003 was the first Phase II study to evaluate a curative treatment regimen based on GZR, a novel HCV NS3/4A protease inhibitor. Initially, treatment-naïve, non-cirrhotic HCV GT1 infected subjects were randomised to receive blinded therapy with GZR doses of 100, 200, 400, or 800 mg or BOC, each in combination with PR. Because elevations of ALT and/or AST levels were observed late in the course of therapy (that is, after Treatment Week 4) among a proportion of subjects who received GZR 200 mg, 400 mg, or 800 mg, the protocol was amended so that subjects who were receiving GZR 400 or 800 mg QD were down-dosed to 100 mg QD, which was also the dose evaluated in all the Phase III studies. This study demonstrated the potent efficacy of a 12 week regimen of GZR given with 24 to 48 weeks of PR. The primary efficacy endpoint was the proportion of subjects achieving cEVR, defined as undetectable HCV RNA at TW12 in the GZR non-cirrhotic treatment arms. These endpoint definitions are more stringent than the current definitions of SVR12 and SVR24, in which achievement of SVR is defined as HCV RNA below limit of quantitation (that is, including TND and Target detected but unquantifiable, or TDu). It was an acceptable primary endpoint for the initial evaluation of a novel regimen; SVR12, an endpoint typically used in registration studies for HCV therapy, was a pre-specified secondary endpoint in this study and correlated well with cEVR.

A high proportion (>86%) of non-cirrhotic subjects in each of the GZR + PR arms (89.4%, 91.2%, 91.0% and 86.2% in the 100, 200, 400 and 800 mg arms respectively) achieved SVR12 compared with the BOC + PR arm (62.1%). In the cirrhotic cohort, 26/36 (72.2%) of subjects achieved SVR12. GT1b infected subjects and those with *IL28B* CC genotype were associated with higher SVR12 rates, although the sample sizes were relatively small. Presence of baseline NS3/4A variants or Q80K/R did not impact efficacy, distinguishing GZR from earlier protease inhibitors (PIs). This initial Phase II study provided preliminary evidence that GZR maintains potency against many of the signature RAVs associated with failure to first generation PIs.

### 6.1.2. Study P038

This was a Phase II, randomised, dose-ranging, parallel group, multicentre, double-blind trial to evaluate the safety, tolerability and efficacy of different doses of MK-5172 (GZR) when administered concomitantly with Peginterferon alfa-2b and Ribavarin (PR) in treatment-naïve (TN) subjects with chronic HCV infection. Ninety subjects aged >18 years with pre-treatment HCV RNA of at least 10,000 IU/ml and compensated HCV GT1 infection were randomised in a 1:1:1 ratio into 3 arms of the study for 12 weeks of treatment with GZR doses of 25, 50 and 100 mg in combination with peg-IFN and RBV. The primary endpoint was Sustained virologic

[2] 19 and 21 failed due to administrative reasons (loss to follow-up or withdrawal of consent) for SVR12 and SVR24, respectively; 2 failed due to early discontinuation for adverse experiences (irritability, gingival erosion) for both SVR12 and SVR24; 1 subject failed to achieve SVR12 due to inconsistent HCV RNA results ( had one quantifiable HCV RNA result of 35 IU/mL and two undetectable results at the Follow-Up Week 12 visit). This subject achieved both SVR4 and SVR24.

response 12 weeks after the end of all study therapy (SVR12)[3] in each treatment arm of GZR. The secondary endpoints were:

1. the time to first achievement of undetectable (TND) HCV RNA;
2. proportion of subjects achieving undetectable (TND) HCV RNA and by the proportion of subjects achieving HCV RNA <25 IU/mL at Week 2, Week 4, Week 12 and End of Treatment visit;
3. proportion of subjects achieving SVR4 and SVR24 ;
4. emergence of antiviral resistance to MK-5172;
5. the proportion of patients who receive 24 weeks of therapy based on RGT.

The exploratory endpoints included:

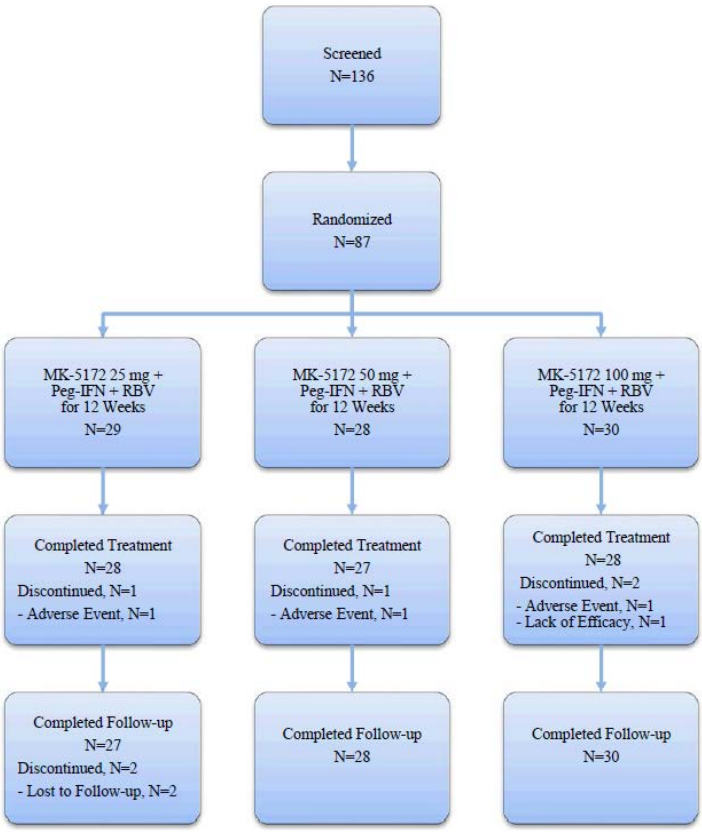
1. effect of genetic variation in the human *IL28B* gene as a predictor of virologic response,
2. effect of biomarkers (proteins, RNA expression, and metabolite production) that may be predictive of the tolerability of study drugs and virologic response,
3. the PK of MK-5172, peg-IFN, and RBV,
4. the PK/PD relationship which may include MK-5172, peg-IFN, or RBV,
5. Change from baseline in health-related quality of life for each of the SF- 36v2 eight health domain scores and the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores.

The Per-Protocol (PP) population was the primary analysis population for efficacy analyses. The Full Analysis Set (FAS) population was used for supportive analyses of primary and key secondary efficacy endpoints.

All 87 randomised subjects received at least one dose of study therapy, and 85 (97.7%) completed the protocol-specified study visits during treatment and follow-up (Figure 6).

[3] SVR12 defined as subjects who had HCV RNA <25 IU/mL, either target detected and unquantifiable (TD[u]) or undetectable (TND).

**Figure 6: Study P038 Flow diagram of subject disposition**




Twelve subjects were excluded from the PP analyses subsequent to their protocol deviations (5, 3 and 4 subjects in the 25, 50 and 100 mg treatment groups, respectively). Median age was 51 years (range, 20 to 70). Majority were males, White (75.9%), had the non-CC *IL28B* genotype (80.5%), had HCV genotype 1a (81.6%) and had plasma HCV-RNA above 800,000 IU/mL (69%). Compared with the MK-5172 25-mg and 50-mg treatment groups, the 100-mg treatment group had slightly lower proportions of subjects with HCV genotype 1a and with HCV-RNA above 800,000 IU/mL. No subject had evidence of cirrhosis at screening and only 8 subjects (9.2%) had a METAVIR fibrosis score of F3. Reported compliance with MK-5172 treatment was very high (mean, 99.4%; range 92.8% -100%) and mean rates of reported compliance with peg-IFN and RBV treatment were also above 95% with similar compliance rates across treatment groups.

In the PP analysis, the GZR 25 mg arm had the numerically lowest SVR12 rate (54.2%), while the SVR12 rate was similar in the 50 mg (84%) and 100 mg (88.5%) arms. There were 19 virologic failures (11, 4 and 4 in the GZR 25 mg, 50 mg and 100 mg arms, respectively). All but two of the failures were due to Relapse. The two other failures were due to end-of-treatment failure, and were both in the GZR 25 mg arm. The results of the FAS analysis were similar to those of the PP population with lowest SVR12 rate in the GZR 25 mg arm (48.3%, 75% and 86.7% in the 25, 50 and 100 mg GZR groups, respectively).

Subgroup analysis showed that the SVR12 rates were higher in subjects with *IL28B* CC genotype, lower HCV RNA levels at screening and Metavir stage F0-F2.

**Comments**: Though some patterns or trends were observed in the subgroup analyses, results must be interpreted with caution due to the relatively small number of subjects sizes per treatment arm in these subgroup analyses, especially for the few subjects in the GT1 non-a/*IL28B* CC genotype/Metavir stage F3 category.

### 6.1.3. Secondary efficacy results:

Overall, all GZR doses led to rapid achievement of undetectable (TND) HCV RNA with subjects in the GZR 100 mg arm achieved undetectable (TND) HCV RNA at a slightly earlier time compared to the other treatment groups (median time to first achievement of TND was 16, 22 and 22 days in the 25, 50 and 100 mg GZR groups, respectively). The presence of baseline RAVs did not affect treatment outcomes; SVR12 was 65% (25/38) and 71% (35/49) in patients with and without baseline RAVs, respectively. There was no difference in the type of baseline variants detected in SVR versus Non-SVR subjects. Q80K was detected in 24/71 (34%) GT1a subjects but not in GT1b infected subjects. Baseline Q80K has been reported to be associated with poor treatment outcomes in patients treated with simeprevir. However, there was no association of baseline Q80K with treatment response in the current study (SVR12 was 71% and 68% of patients with and without baseline Q80K, respectively). Among the 23 non-SVR subjects for whom sequence information was available, >70% of the non-SVR subjects had detectable RAVs at the time of virologic failure. The prevalence and pattern of RAVs were similar among different dose groups. Mutations at D168, in particular D168A/E, were by far the most prevalent substitutions which were observed in 14/23 non-SVR subjects. Overall, the mean scores for the PCS, MCS and the 8 health domains of SF36v2 were higher at baseline than during treatment and rebounded to or above mean baseline scores during follow-up. The mean change from baseline scores at the FW 12 and 24 visits for PCS and MCS were not significantly different from 0 for all subjects, subjects who achieved SVR12 and subjects who did not achieve SVR12.

**Comments**: Administration of a 12 week regimen of GZR 100 mg + peg-IFN + RBV is highly efficacious in clearing HCV genotype 1 infection among treatment-naïve, non-cirrhotic, HCV genotype 1 subjects in this well-conducted Phase II study. Dose of 25 mg GZR demonstrated sub-optimal efficacy. The SVR12 rates observed in the GZR 100 mg+PR dose group in this study was generally comparable to SVR12 of 90% following a 12- week regimen of sofosbuvir with PR (Lawitz E, 2013). Although the prevalence of baseline protease inhibitor RAVs was high (44%), there was no clear association between virologic failure and the presence of baseline RAVs, including the Q80K variant, which has been associated with failure to simeprevir. In subjects who failed GZR treatment, >70% had RAVs detectable by population sequencing at the time of virologic failure, with mutations of D168A/E and A156T most commonly noted. This is consistent with the known in vitro resistance profile of GZR.

## 6.2. Study P035

### 6.2.1. Study design

This is a multicentre, randomised, parallel-group trial conducted in 4 parts (A, B, C, and D) to evaluate MK-5172 (GZR) 100 mg QD in combination with MK-8742 (EBR) ± ribavirin (RBV) for treatment of chronic hepatitis C. The CSR in the current submission presents data through Follow-up Week 24 for Parts A, B and C and through Follow-up Week 12 for Part D (Table 6).

**Table 6: Treatment groups**

| Treatment groups | | |
|---|---|---|
| | Arm A1 | Treatment-naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 20 mg + RBV for 12 weeks (n=25) |
| Part A | Arm A2 | Treatment-naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=27) |
| | Arm A3 | Treatment-naïve (non-cirrhotic/GT1b only): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=13) |
| Part B | Arm B1 | Treatment-naïve (non-cirrhotic/GT1a only): MK-5172 100 mg + MK-8742 50 mg + RBV for 8 weeks (n=30) |
| | Arm B2 | Treatment-naïve (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=33) |
| | Arm B3 | Treatment-naïve (non-cirrhotic/GT1a only): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=31) |
| | Arm B4 | Treatment-naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=31) |
| | Arm B5 | Treatment-naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=29) |
| | Arm B6 | Treatment-naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=32) |
| | Arm B7 | Treatment-naïve (cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=31) |
| Part B | Arm B8 | Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=32) |
| | Arm B9 | Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=33) |
| | Arm B10 | Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=33) |
| | Arm B11 | Null Responders (cirrhotic and non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 18 weeks (n=32) |
| | Arm B12 | Treatment-naïve Co-Infected with HIV (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=29) |
| | Arm B13 | Treatment-naïve Co-Infected with HIV (non-cirrhotic): MK-5172 100 mg + MK-8742 50 mg for 12 weeks (n=30) |
| Part C | Arm C1 | Treatment-naïve (non-cirrhotic), GT1b, Mono-Infected: MK-5172 100 mg + MK-8742 50 mg +RBV for 8 weeks (n= 30). |
| | Arm C2 | Treatment-naïve (non-cirrhotic), GT1b, Mono-Infected: MK-5172 100 mg + MK-8742 50 mg for 8 weeks (n=31) |
| Part D | Arm D1 | Treatment-naïve (non-cirrhotic), GT3, Mono-Infected: MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks (n=20) |
| | Arm D2 | Treatment-naïve (non-cirrhotic), GT3, Mono-Infected: MK-5172 100 mg + MK-8742 50 mg + RBV for 18 weeks (n=21) |

**Comments**: This is the main, core Phase II study which determined the dose for EBR, treatment duration and patient populations to be evaluated in the Phase II/III studies.

**Part A** included a double-blind, dose-response evaluation of MK-8742 (EBR), without active control in 60 TN, non-cirrhotic subjects with genotype (GT) 1 were to be randomised in an 1:1:1 ratio to one of 3 treatment arms for GT 1b, and in a 1:1 ratio to the first two treatment arms for GT1a (at least 50% of total subjects):

- MK-5172 100 mg + MK-8742 20 mg + RBV for 12 weeks
- MK-5172 100 mg + MK-8742 50 mg + RBV for 12 weeks
- MK-5172 100 mg + MK-8742 50 mg for 12 weeks

Subjects in Part A could be discontinued due to futility at Treatment Week (TW) 4.

**Part B** was an open label evaluation of MK-5172 100 mg QD in combination with MK-8742 50 mg QD ± RBV for 8, 12, or 18 weeks without active control in diverse study populations. A total of 390 subjects, who were cirrhotic or non-cirrhotic, mono-infected or HCV/HIV-co-infected, and TN or prior null treatment responders, were to be randomised to one of 13 treatment arms. The investigator and subjects were to be blinded to treatment duration from randomisation through TW8 or TW12 (except for Arms B12 and B13), depending on the treatment arm.

**Part C** was an open label evaluation of MK-5172 100 mg QD plus MK-8742 50 mg QD ± RBV for 8 weeks without active control in approximately 60 treatment-naïve non-cirrhotic subjects with HCV GT1b.

**Part D** is an ongoing open label evaluation of MK-5172 100 mg QD + MK-8742 50 mg QD + RBV for 12 or 18 weeks without active control (2 arms) in approximately 40 treatment-naïve, non-cirrhotic subjects infected with HCV GT3 who were to be randomised to one of two treatment arms. The study treatments in each of the treatment arms in Part A, B, C and D of the study is summarised in Table 6.

The study was initiated in February 2013 and is still ongoing with data cut-off date of 19 February 2015. It was conducted at 76 trial centres: 5 in Australia; 6 in Canada; 5 in Denmark; 12 in France; 5 in Hungary; 5 in Israel; 1 in New Zealand; 1 in Puerto Rico; 4 in Spain; 4 in Sweden; 3 in Turkey; and 25 in the United States.

### 6.2.2. Inclusion/ exclusion criteria

Study P035 was designed to define the efficacy of a once daily regimen combining GZR and EBR in a diverse population of HCV infected subjects. The study focused primarily on subjects infected with HCV GT1, although Part D explored the efficacy of the GZR+ EBR regimen among GT3 subjects.

**Comments**: The evaluation of a diverse population of GT1 subjects is important because the efficacy and tolerability of HCV regimens have been shown to vary by demographic and HCV disease factors. At the time the protocol was developed, factors that had been associated with relatively higher efficacy and tolerability among patients considered 'easy to cure' included lack of prior treatment, absence of cirrhosis, and HCV GT1b infection. In contrast, prior failure following PR-based regimens, presence of advanced fibrosis or cirrhosis, and GT1a are markers of lower treatment response and/or lower efficacy, and these 'hard to cure' patients typically require longer treatment duration and/or the inclusion of RBV in the treatment regimen. Hence, the patient population evaluated in this Phase II study included subjects with GT1a or GT1b infection; subjects who were treatment-naïve and subjects who had a null response to PR-based therapy (Null response represents a particularly negative predictive factor for treatment success, even within the spectrum of subjects who fail PR-based therapy); subjects with or without compensated cirrhosis and subjects with or without HIV co-infection.

Overall, this important Phase II study attempted to address all issues related to dose, duration and target patient population by dividing the study in to a pilot phase (Part A) among GT1 infected subjects, an evaluation of efficacy among several HCV GT1 subpopulations (Parts B and C), and finally, an evaluation of efficacy among GT3-infected subjects (Part D).

### 6.2.3. Efficacy endpoints, statistical considerations

The primary efficacy endpoint was the proportion of subjects achieving SVR12 in each of the treatment arms. The secondary efficacy endpoints and exploratory efficacy endpoints were similar to those described for Study P038 above.

The Per-Protocol (PP) population was the primary population for the analysis of efficacy data in this study. As the primary Phase II study upon which Phase III decisions would be made, it was determined that the primary population would be PP which excluded subjects due to important deviations from the protocol that could substantially affect the results of the primary and key secondary efficacy endpoints.

Across Parts A, B, and C, Protocol 035 tested different durations and use of RBV in a diverse population. For the most meaningful presentation of data, treatment arms for GT1 infected subjects were divided into two groupings-'Easy to Cure' and 'Hard to Cure'.

Populations and arms considered *'Easy to Cure'* included:

- TN, non-cirrhotic, mono-infected subjects: 8 weeks: Arms B1, C1, $C_2$; 12 weeks: Arms A1, A2, A3, B2, B3;
- TN, non-cirrhotic, HIV co-infected subjects: 12 weeks: Arms B12, B13.

Among the *'Hard to Cure'* subpopulations, P035 evaluated:

- TN cirrhotic, mono-infected subjects: 12 weeks: Arms B4, B5; 18 weeks: Arms B6, B7
- Prior treatment failure ± cirrhosis, mono-infected subjects: 12 weeks: Arms B8, B9; 18 weeks Arms B10, B11.

In addition, Part D of this study evaluated two arms of TN, non-cirrhotic, GT3-infected subjects. - 12 weeks: Arm D1; - 18 weeks: Arm D2.

### 6.2.4. Patient disposition

A total of 532 subjects infected with HCV GT1 were randomised to treatment in Parts A, B and C. All subjects received at least one dose of study therapy, and 514 (96.6%) completed the protocol-specified study visits during treatment and follow-up. Overall, 97.2% of GT1 infected subjects completed study therapy with MK-5172 + MK- 8742 ± RBV. Study therapy completion rates were similar for subjects on regimens with and without RBV, for subjects on 8 week, 12 week and 18 week regimens, for cirrhotic and non-cirrhotic subjects, for HIV co-infected and mono-infected subjects, and for treatment-naïve and prior null responder subjects. Two subjects (0.4%), both on regimens with RBV, discontinued study medication due to AEs. Lack of efficacy resulted in discontinuation of study medication in 5 subjects, including 2 with HIV co-infection, one prior null responder, one TN cirrhotic subject, and one TN non-cirrhotic subject.

Refer to Figures 8-10 for details of subject disposition in various arms of Part A, B and C.

**Figure 8: Flow diagram of subject disposition: Part A treatment-naïve non-cirrhotic subjects**

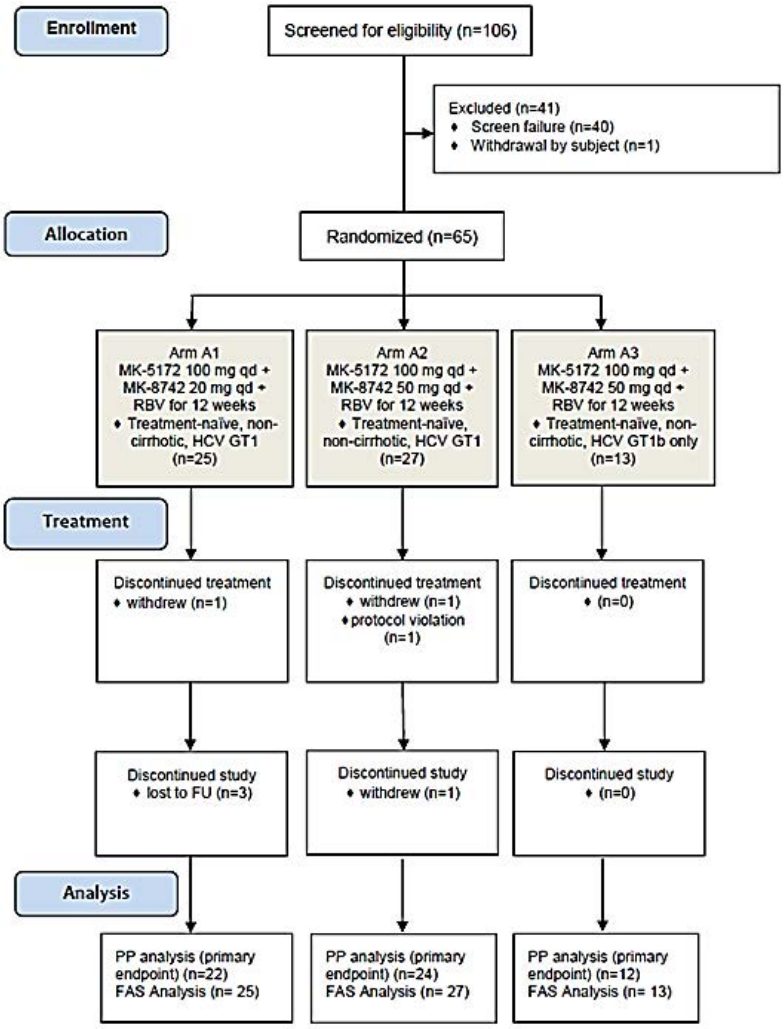


**Figure 9: Flow diagram of subject disposition: Part B treatment-naïve HIV/HCV co-infected subject**

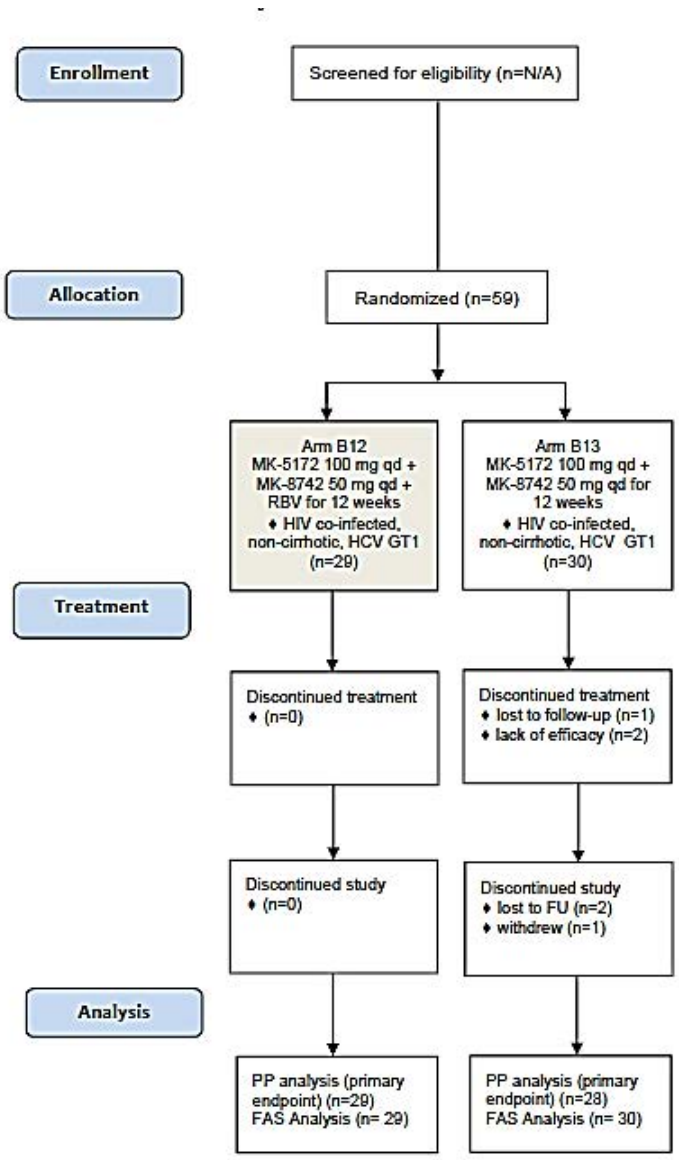
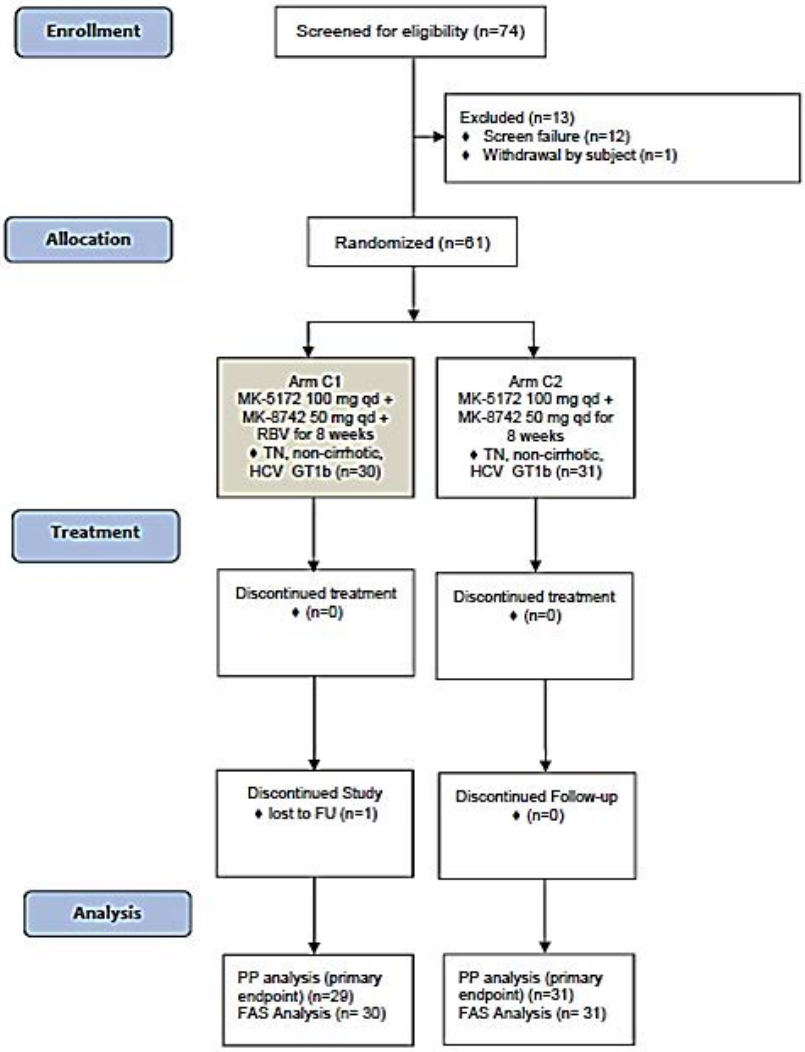
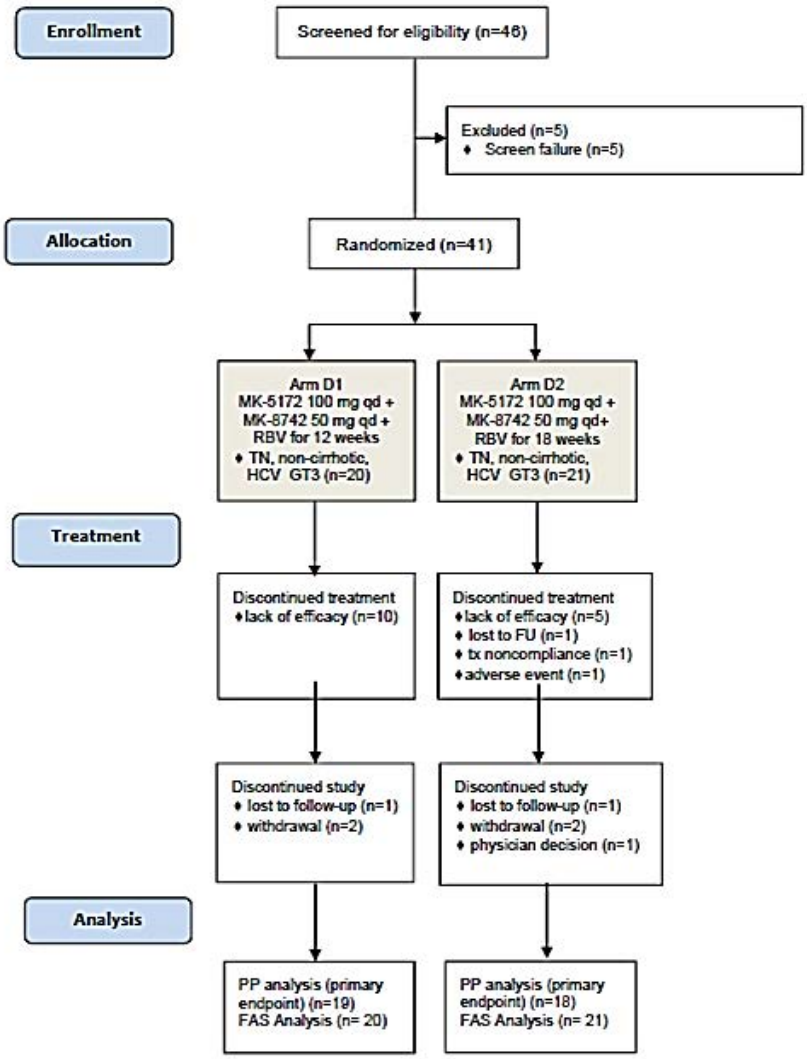


**Figure 10: Flow diagram of subject disposition: Part C treatment-naïve non-cirrhotic, HCV genotype 1b infected subject**




A total of 41 subjects infected with HCV GT3 were randomised to treatment in Part D. All subjects received at least one dose of study therapy, and 80.5% (33/41) of subjects in these ongoing treatment arms completed the protocol-specified study visits through Follow-up Week 12. Overall, 56.1% (23/41) of GT3-infected subjects completed study therapy with GZR+EBR+RBV (Figure 11). Study therapy completion rates were higher for subjects on the 18 week regimen compared with the 12 week regimen (61.9% and 50.0%, respectively) and reflect a difference in the proportion of subjects who discontinued study medication due to lack of efficacy (23.8% and 50.0%, respectively); only 1 subject on the 18 week regimen discontinued therapy due to an AE.

**Figure 11: Flow diagram of subject disposition: Part D treatment-naïve non-cirrhotic, HCV genotype 3 infected subject**




### 6.2.5. Baseline data

#### *6.2.5.1. Subjects with HCV genotype 1*

*'Easy to cure', TN, non-cirrhotic, monoinfected subjects (Arms A1, A2, A3, B2, B3, B1, C1 and C2):*
Approximately half of TN non-cirrhotic monoinfected subjects were male and most were White (non-Hispanic), but the distribution of subjects with these demographics varied across treatment arms. Median age was 52 years (range, 20 to 73). At screening, similar percentages of TN non-cirrhotic subjects had HCV genotype 1a or 1b; Subjects in Arms A1 and A2 were stratified by HCV genotype (GT1a versus GT1b), and at least 50% of subjects were to have GT1a. The majority of subjects (76.8%) had screening HCV-RNA above 800,000 IU/mL (25.8% had HCV-RNA levels above 10 million IU/mL at baseline) and had a non-CC IL28B genotype (76.4 %). Nearly all subjects (92.3%) in the TN non-cirrhotic arms had mild or moderate liver fibrosis (METAVIR scores of F0- F2) and the remainder were fibrosis stage F3. These non-cirrhotic subjects all had mildly elevated mean transaminase levels but albumin levels and platelet counts were within normal range.

*'Easy to cure', TN, non-cirrhotic, HIV co-infected subjects (Arms B12 and B13):*

Majority of subjects were male (79.7%), White (non-Hispanic) with median age of 47 years (range 23-63) and had HCV genotype 1a (78%) with similar demographics between treatment

arms. Approximately 80% of subjects had screening HCV-RNA above 800,000 IU/mL (27.1% had HCV-RNA levels above 10 million IU/L at baseline), Most subjects (67.8%) had a non-CC *IL28B* genotype and nearly all subjects (91.5%) in the HIV co-infected arms had mild or moderate liver fibrosis (METAVIR scores of F0-F2) with albumin levels and platelet counts within normal range and mildly elevated mean transaminase levels at baseline.

*'Hard to Cure' Treatment-naive, Cirrhotic, Monoinfected Subjects (Arms B4 to B7):*

Majority of subjects were male (60.2%), White (non-Hispanic) with median age of 58 years (range 41-82) and had HCV genotype 1a (70.7%); subject demographics varied across treatment arms. Majority of subjects (83.7%) had Screening HCV-RNA above 800,000 IU/mL, and 14.6% had HCVRNA levels above 10 million IU/mL at Baseline. Most subjects (69.1%) had a non-CC *IL28B* genotype. At Screening, all but one subject (99.2%) in the TN cirrhotic treatment arms had METAVIR scores of F4 based on results of either liver biopsy or a non-invasive test. consistent with cirrhosis, 3.3% had elevated albumin levels, 17.1% had low platelet counts and mean transaminase levels were moderately elevated.

*'Hard to Cure': Prior Null Responder, Monoinfected Subjects (Arms B8 to B11):*

Majority of subjects were male (56.9%), White (non-Hispanic) with median age of 56 years (range 18-77) and had HCV genotype 1a (58.5%); subject demographics varied across treatment arms**.** Most subjects (96.9%) had plasma HCV-RNA above 800,000 IU/mL, and 27.7% had levels above 10 million IU/mL. Nearly all prior null responder subjects (98.5%) had a non-CC *IL28B* genotype. Approximately half (48.5%) of prior null responders had mild or moderate liver fibrosis (METAVIR scores of F0- F2) at screening based on results of either liver biopsy or a non-invasive test. Forty-nine subjects (37.7%) were cirrhotic (F4), and 18 subjects (13.8%) had a METAVIR fibrosis score of F3.

#### *6.2.5.2. Subjects with HCV genotype 3*

Less than half of GT3-infected subjects (39.0%) were male, none were black/African American or Hispanic with median age of 49 (range, 22 to 61) years. Majority (61.0%) had a non-CC *IL28B* genotype; 61% had plasma HCV-RNA above 800,000 IU/mL and 24.4% had levels above 10 million IU/mL. Nearly all (95.1%) GT3-infected subjects had mild or moderate liver fibrosis (METAVIR scores of F0-F2) at screening and the remainder had a METAVIR fibrosis score of F3. There were no clinically meaningful differences between treatment arms in the incidence of prior common medical illness or use of concomitant medications across both HCV genotype 1 and 3 subjects. Reported average compliance with the treatment regimens was very high (98.1%) in the Easy to Cure: TN, non-cirrhotic, monoinfected subjects, irrespective of treatment duration (8 or 12 weeks) or the inclusion of RBV. In the TN, non-cirrhotic, HIV co-infected subjects, reported mean compliance was lower on the RBV-containing regimen than on the RBV-free regimen (89.7% and 100%, respectively). In the TN, cirrhotic, monoinfected subjects, the overall compliance with treatment regimens (MK-5172 + MK- 8742 ± RBV) was very high (mean, (97.6%). In the Hard to Cure: Prior Null Responder, monoinfected subjects, reported compliance with the treatment regimens (MK-5172 + MK-8742 ± RBV) was very high (mean, 99.2%, regardless of duration (12 or 18 weeks) or the inclusion of RBV. GT3-infected subjects also had high reported overall compliance (mean, 92.7%) with two RBV containing regimens of different duration. However, 3 subjects took between 75% and 90% of doses on the 18 week regimen, whereas compliance with the 12 week regimen was 100%.

### 6.2.6. Primary efficacy results

#### *6.2.6.1. In HCV genotype 1 infected subjects*

Study Part A was a pilot phase to assess the dose-response of elbasvir (EBR) and a RBV-free regiment following 12 weeks treatment in TN non-cirrhotic GT1 infected subjects and failed to show a dose-response for EBR; SVR12 was achieved in 100.0% (22/22) of subjects in Arm A1 (EBR 20 mg) and 95.8% (23/24) of subjects in Arm A2 (EBR 50 mg); A RBV-free regimen of GZR

100 mg + EBR 50 mg resulted in SVR12 among 100.0% [12/12]) of TN, non-cirrhotic subjects with HCV GT1b infection (Arm 3). The high efficacy seen in Part A supported expansion of P035 to Parts B and C.

*SVR12 in 'Easy to cure' TN, non-cirrhotic subjects*

Administration of MK-5172 + MK-8742 ± RBV resulted in SVR12 in 95.8% to 100.0% of subjects in the PP populations of the relevant arms. Similar SVR12 rates were observed in the RBV-free (97.7%) and RBV containing (98.7%) regiments. Efficacy was also comparable between GT1a infected (97.9%) and GT1 (non-a) infected subjects (100%). Following 12 weeks of treatment in TN, HIV/HCV co-infected non-cirrhotic subjects, SVR12 was achieved in 92.9% (26/28) of subjects in RBV-free arm and 96.6% (28/29) of subjects in the RBV-treated arm. Following 8 weeks of treatment in TN, non-cirrhotic, mono-infected subjects administration of a RBV-containing regimen to GT1a infected subjects (Arm B1) resulted in SVR12 in 82.8% (24/29) while among GT1b infected subjects, administration of GZR+EBR±RBV resulted in SVR12 in 93.3% (56/60). Among TN, non-cirrhotic, mono-infected subjects, only, 2/118 (1.7%) of subjects had virologic failure; all were relapses among GT1a infected subjects. Among the HIV co-infected population, virologic failure occurred in 5.3% (3/57) of subjects, 1 of which was due to relapse (in the B12 arm), and 2 of which were due to breakthrough. Following 8 weeks of therapy in TN mono-infected subjects (Arms B1, C1, and $C_2$), among the GT1a infected TN, non-cirrhotic subjects, 5 (17.2%) of the 29 subjects experienced virologic failure by FW12; all 5 subjects had relapse by Follow-up Week 12.

*SVR12 in 'Hard to cure' TN cirrhotic subjects and prior null responders with or without cirrhosis:*

Treatment with MK-5172/MK-8742 to TN subjects with cirrhosis showed high sVR12 rates irrespective of RBV use; SVR12 was achieved in 95.0% (57/60) and 95.1% (58/61) of subjects in the RBV-free and RBV-treated arms, respectively.. Extension of treatment to 18 weeks did not result in a meaningful improvement to SVR12 on the basis of 95% CIs (see Arms B6 and B7).

Prior null responders to peg-IFN/RBV, 38% of whom were cirrhotic, were evaluated in Arms B8, B9, B10, and B11. Following 12 weeks of treatment with the proposed GZR+EBV combination, SVR12 was achieved in 100.0% (11/11) and 92.9% (13/14) in RBV-free and RBV-treated arms, respectively. However, the SVR12 rates increased to 100% following 18 weeks of treatment in both RBV-free and RBV-treated arms (Arms B10 and B11). Data in prior null responder, non-cirrhotic subjects showed similar results; subjects treated for 12 weeks with and without RBV achieved SVR12 in 100.0% (19/19) and 89.5% (17/19), respectively. Subjects treated for 18 weeks with and without RBV achieved SVR12 in 100.0% (21/21) and 95.2% (20/21), respectively.

Virologic failure occurred in 5.0% (6/121) of subjects, 5 of these failures were due to relapse among GT1a infected subjects and the other failure was due to breakthrough in a GT1 (non-a) subject. The frequency of virologic failure was comparable among subjects in the RBV-containing or RBV-free arms (3/61, or 4.9% of subject in RBV-containing arms; 3/60 or 5.0% of subjects in RBV-free arms), but failure was slightly lower in the 18 week arms (2/62, or 3.2% of subjects) compared with the 12 week arms (4/59, or 6.8% of subjects). In prior null responders to PR therapy, the rate of virologic failure was 3.1% (4/128)[4] and the 12 week, RBV-free regimen resulted in low rates of virologic failure among prior null responders, with or without cirrhosis [4.0%(1/25), and 5.3% (2/38), respectively],who were infected with HCV GT1a or 1b. A slight reduction in the rate of virologic failures was seen in both cirrhotic and non-cirrhotic prior null responder subjects when GZR+EBR treatment was extended from 12 to 18 weeks, but

[4] 2 of which were due to relapse in GT1a subjects in the B9 arm (1 was cirrhotic and 1 was noncirrhotic), 1 of which was due to relapse in a noncirrhotic GT1b infected subject in the B9 arm and 1 of which was due to virologic breakthrough in a noncirrhotic GT1a infected subject in the B11 arm

interpretation was limited by small numbers. Virologic failure occurred in 0% (0/16) and 9.1% (2/22), of GT1a infected prior null responders treated for 12 weeks with and without RBV, respectively. Similar results were observed among GT1b infected subjects.

#### *6.2.6.2. In HCV Genotype 3 infected subjects*

P035 was the first study to evaluate the efficacy of GZR 100 mg + EBR 50 mg among GT3-infected subjects. Although EBR was shown to be highly potent against GT3 in vitro and in Phase Ib studies, similar studies had shown that GZR 100 mg was less potent against GT3 infection compared with GT1 infection. Hence, this study limited enrolment to include only TN, non-cirrhotic GT3-infected subjects, tested only RBV-containing regimens and included an evaluation of an18 week duration of therapy.

SVR12 was achieved in 47.4% (9/19) of subjects treated for 12 weeks and 61.1% (11/18) of subjects treated for 18 weeks. All of the failures were on-treatment (breakthrough, futility or rebound); no post-treatment relapses were observed. Although the efficacy was slightly higher in the 18 week arm, the difference may not be meaningful as all on-treatment failures occurred by Treatment Week 12. Virologic failure occurred in 10 (52.6%) of 19 subjects treated for 12 weeks and 7 (38.9%) of 18 subjects treated for 18 weeks. All but 1 of the failures (futility in a subject in the D1 arm) was due to either breakthrough or rebound. All subjects in whom on-therapy virologic control was maintained achieved SVR12 and there were no cases of relapse.

#### *6.2.6.3. Secondary and other efficacy results*

In subjects with GT1 HCV infection, all treatment regimens led to rapid achievement of TND HCV RNA. The median time to first TND ranged from 16.0 days to 30.5 days across GZR dose groups, without an apparent relationship to RBV. Treatment-naïve, cirrhotic subjects and null responders first achieved TND HCV RNA at a marginally later time than TN, non-cirrhotic subjects after treatment initiation. There was no apparent difference in the median times to TND in GT3 versus GT1 subjects or in subjects with or without HIV co-infection.

Although the sample sizes were small, all subjects who achieved TND HCV RNA within 8 days also achieved SVR12. However, the numerical difference in SVR12 rates between subjects who achieved TND HCV RNA within 8 days and those who did not was large only for GT1a subjects treated for 8 weeks. For this subgroup, results suggested that SVR12 may be higher than in subjects who achieved TND HCV RNA within 15 days than in subjects who did not have TND within 15 days.

Subjects achieved undetectable HCV-RNA levels rapidly on treatment regimens with and without RBV. At TW4, undetectable HCV RNA was achieved in 298 (76.4%) of 390 TN subjects and 87 (68.5%) of 127 subjects with prior PR null response which included 44 (77.2%) of 57 HIV co-infected subjects and 341 (74.1%) of 460 monoinfected subjects. At TW12, undetectable HCV RNA was achieved in 289 (97.6%) of 296 treatment-naïve subjects and 124 (97.6%) of 127 subjects with prior PR null response; and includes 53 (93.0%) of 57 HIV-co-infected subjects and 360 (98.4%) of 366 monoinfected subjects. Similarly, subjects achieved HCV RNA levels <25 IU/mL rapidly on treatment regimens with and without RBV with at least 90% or more of subjects in each treatment arm achieved HCV RNA <25 IU/mL by TW4. At TW12, HCV RNA levels <25 IU/mL was achieved in 292 (98.6%) of 296 treatment-naïve subjects and 126 (99.2%) of 127 subjects with prior PR null response; and includes 55 (96.5%) of 57 HIV-co-infected subjects and 363 (99.2%) of 366 mono-infected subjects.

SVR24 in GT1 HCV subjects was summarised: Among subjects in the 'Easy to cure' TN, non-cirrhotic subjects 12 week arms, SVR24 was achieved by 166/172 (96.5%) of subjects [100/102 (98.0%) with RBV and 66/70 (94.3%) without RBV]. The difference in efficacy between the pooled RBV-containing and RBV-free arms was due to lower efficacy in Arm B13 (GZR + EBR among HIV co-infected, TN, non-cirrhotic GT1 infected subjects). SVR24 rate was lower (22/28, 78.6%) in non-cirrhotic, GT1a infected subjects on the 8 week regimen of GZR+EBR+ RBV). The proportions of TN, non-cirrhotic, GT1b infected subjects (8 week regimen of GZR+EBR with or

without RBV, respectively) that achieved SVR24 were comparable to those who achieved SVR12 and no relapses were observed between FW12 and FW24. Overall, 113/119 (95.0%) of TN cirrhotic subjects achieved SVR24 and the highest efficacy was observed in the 18 week/RBV and 12 week/no RBV arms. Overall, 122/126 (96.8%) of null responders to prior peg-IFN/RBV achieved SVR24 and the highest efficacy was observed in the 18 week/RBV and 12 week/RBV arms.

Overall, GZR+EBR had a small impact on subjects' HRQOL during therapy. However, as expected, the addition of RBV to MK-5172+MK-8742 did contribute to a worsening in HRQOL during the treatment period. Differences in HRQOL occurring during treatment did not persist during the follow-up period, where HRQOL rebounded near to or above baseline levels. Among subjects achieving SVR12 and SVR24, improvements were noted in the General Health, Vitality or Social Functioning domains.

**Comments**: A 20 mg dose of EBR provided relatively similar response to 50 mg in combination with GZR in Part A of this study. Because the safety profile was similar for both dose levels of EBR, and in vitro studies suggested that the EBR exposures associated with the 50 mg dose are likely to cover more common NS5A RAVs compared with the 20 mg dose of EBR, the 50 mg dose was selected for subsequent studies. Furthermore, efficacy of the proposed 50 mg EBR dose was confirmed in Part B of this study when a 12 week regimen of GZR 100 mg+EBR 50 mg (without RBV) resulted in high efficacy and correspondingly low rates of virologic failure.

Among TN, non-cirrhotic GT1a or GT1 (non-a) infected subjects with or without HIV co-infection:- 12 weeks of GZR 100 mg+EBR 50 mg (without RBV) resulted in high efficacy and correspondingly low rates of virologic failure; Eight weeks of therapy was highly effective in clearing HCV GT1b infection, but an 8 week regimen was not adequate for treatment of GT1a infection.

Among traditionally Hard to Cure subjects, virologic failures remained infrequent and were primarily due to relapse. Among TN cirrhotic subjects with GT1a or GT1 (non-a) infection, neither duration nor use of RBV appeared to impact efficacy rates. The highest SVR12 rates were observed in the 18 week/RBV arm (100%, 31/31 subjects), but comparable efficacy was observed in the 12 week/no RBV arm (96.6%, 28/29 subjects). Among prior PR null responders (± cirrhosis), there did not appear to be an impact of RBV or duration on efficacy among GT1b infected subjects. Among GT1a infected subjects, use of RBV, or extension to 18 weeks was associated with numerically higher response rates and corresponding lower proportion of subjects that relapsed, but these differences were based on small subgroups, with large swings in failure rates on the basis of 1-2 subjects. Accordingly, the Phase III Study P068 among prior PR treatment failures included an evaluation of the impact of adding RBV and/or increasing the duration of therapy on efficacy.

Furthermore, efficacy of the GZR 100 mg +EBR 50 mg +RBV treatment regimen was also shown in 41 TN, non-cirrhotic subjects with HCV GT3 infection with SVR12 rates of 47.4% (9/19) and 61.1% (11/18) following treatment for 12 and 18 weeks, respectively.

Overall, detailed evaluation of the proposed dosing regimens and target population in this well-conducted Phase II study supported the selection of the proposed FDC dose of GZR 100 mg and EBR 50 mg in the Phase III and other core Phase II studies.

## 6.3. Study P039

This was a Phase IIa, randomised, parallel-group, multi-site, open label, proof-of-concept trial evaluating treatment durations of 12 weeks and 24 weeks with GZR 100 mg once daily plus RBV in 26 treatment-naïve subjects with chronic genotype 1 HCV infection. The study was conducted

from 21 January 2013 to 12 March 2014 at 6 centres: 4 in Israel; 1 in New Zealand; and 1 in Australia.

Twenty-six subjects were randomised in a 1:1 ratio into two parallel treatment arms that differed with respect to assigned treatment duration. Randomisation of subjects was stratified by HCV genotype (GT1a versus GT1 non[a]), and at least 50% were to have been infected with GT1a. Subjects received GZR 100 mg once daily (QD) and twice daily (BD) ribavirin (RBV) at a total daily dose based on the subject's weight on Day 1. After completing either 12 weeks or 24 weeks of therapy, each subject was followed up for 24 weeks within the trial. Response-guided therapy (RGT) was applied to subjects in the 12- week arm. Subjects were to receive an additional 12 weeks of study therapy if they had HCV RNA detected but <25 IU/mL at Treatment Week (TW) 4. If HCV RNA was ≥25 IU/mL at TW4 and was subsequently confirmed, the subject was discontinued due to futility and offered rescue therapy with peg-IFN alfa-2b + RBV.

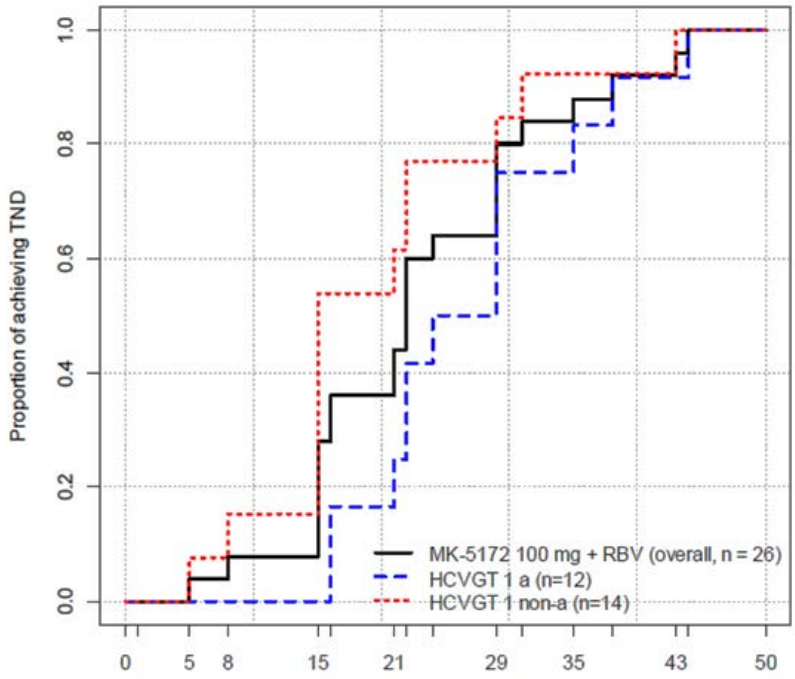
Majority of the subjects were male (65.4%), White (100%) with mean age of 43 years. Almost all patients had IL28B-CC genotype with screening HCV RNA >800,000IU/ml and Metavir F0-F2; study included 12 and 14 subjects with HCV genotype 1a and 1b, respectively.

In the PP analysis, the 12 week RGT arm had an SVR12 rate of 58.3% (95% CI: 27.7, 84.8), whereas the SVR12 rate of the 24 week arm was 90% (95% CI: 55.5, 99.7). Within the 12 week RGT arm, the SVR12 rate for the 8 subjects who had TND at TW4 and received 12 weeks of therapy was 62.5% (95% CI: 24.5, 91.5); the other 4 subjects, who had TD(u) at TW4 and had their treatment duration extended to 24 weeks, had SVR12 of 50% (95% CI: 6.8, 93.2).

**Comments**: Interpretation of these results was limited by the wide confidence intervals and small number of subjects in this study.

In the FAS analysis, SVR12 rates of the 12 week RGT arm and the 24 week treatment arm were reduced to 53.8% and 69.2%, respectively, due to inclusion of additional subjects with missing HCV RNA evaluations at FW12 (treatment withdrawal, protocol violators) imputed as treatment failures. The SVR12 rates by HCV genotype suggest that GT 1a subjects tended to have lower response rates compared to GT 1 non-a subjects, for a given treatment duration. Overall, the time to first achievement of TND ranged from 5 to 44 days with longer times to TND in the HCV GT1a subjects compared to the GT1(non-a) subjects (Figure 12).

**Figure 12: Kaplan-Meier plot for time to first achievement of undetectable HCV RNA (TND) Full Analysis Set Population**




The odds ratio (95% CI) of achieving SVR12 for a one-day increment in the time to first TND was estimated to be 0.909 (0.818, 1.009), with p-value of 0.0732. In general, the 24 week arm had higher SVR4 and SVR24 rates than the subjects who received 12 weeks of treatment or the subjects whose treatment duration was extended to 24 weeks. Among the 11 non-SVR subjects, 8 met the criteria of virologic failure. One or more resistance-associated variants (RAVs), including Y56H, A156T, S122T and D168A/N, were detected in 5 of the 8 subjects (63%) who met the criteria of virologic failure. There was no difference in RAVs between GT1a and 1b, or between the 12- and 24 week treatment groups. Either wild type (WT) or single RAVs were detected in subjects with viral relapse, whereas dual and triple linked mutations were observed in subjects with viral breakthrough.

## 6.4. Study P047

This was a Phase II, multi-site, open-label, parallel group trial evaluating the safety and efficacy of 100 mg of GZR in combination with or without 50 mg of EBR and/or RBV in treating 98 non-cirrhotic, treatment-naïve (TN) subjects with chronic hepatitis C (CHC) infection with genotypes 2, 4, 5 and 6. The study was conducted from 2 Oct 2013 to 4 Dec 2014 at 30 centres: 10 in the USA; 5 in Australia; 5 in Israel; 4 in France; 3 in the UK; 2 in Spain; and 1 in Belgium.

In the first part of the study (Part A), 30 GT2 infected subjects received GZR+EBR+ RBV for 12 weeks (Arm A1). Enrolment was controlled on the basis of the amino acid at Position 31 of the NS5A Protein. HCV GT2 virions encoding a methionine (31M) at this position are resistant to EBR; to determine the impact of this variant on the efficacy of GZR+EBR + RBV, at least 8 subjects with 31M GT2 infection were enrolled. The second part of the study (Part B) consisted of 3 arms: Arm B1: 30 subjects with GT2 infection were enrolled and received GZR + RBV (no EBR).

Arms B2, B3: 40 subjects with GT4, GT5 or GT6 HCV infection were randomised in a 1:1 ratio to receive 12 weeks of therapy with GZR+EBR+ RBV or GZR+EBV without RBV. Enrolment was stratified by genotype: a minimum of 4 subjects each with GT4 or GT6 infections were to be

enrolled in each of the 2 arms (there was no minimum enrolment of GT5). All subjects were followed for 24 weeks post-treatment in the study.

Overall, 93.3% (28/30) and 100% (19/19) of subjects completed study therapy with GZR + EBR+ RBV in Arms A1 and B2 respectively, compared with 83.3% (25/30) who completed therapy with GZR+ RBV (Arm B1), and 89.5% (17/19) who completed therapy with GZR + EBV (Arm B3). Majority of subjects in the study were male (57.1%), had IL28B Non-CC (58.2%), baseline HCV RNA of >2 million IU/mL (59.2%) and mild or moderate liver fibrosis (METAVIR score F0 to F2) at screening (91.8%). Median age was 49.6 (range, 20 to 80) years, and the majority were White (84.7%) and non-Hispanic (90.8%). Average baseline ALT/AST laboratory values were generally similar across treatment arms, with Arm B2 having lower average results than other treatment arms. Most demographic characteristics were similar across treatment groups.

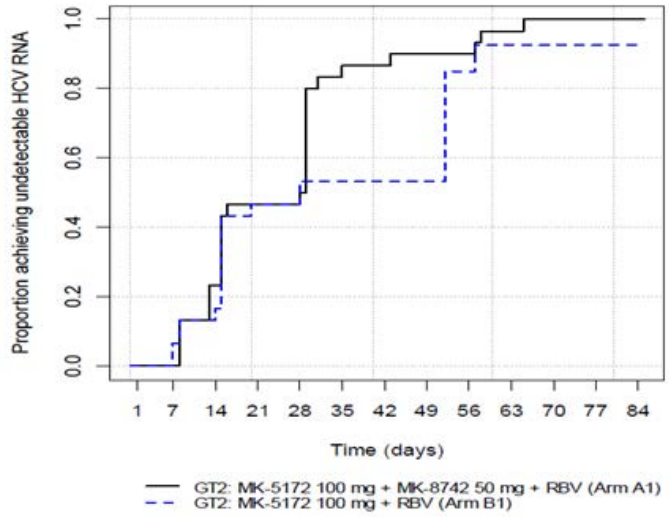
Among GT2 infected, treatment-naïve (TN), non-cirrhotic (NC) subjects, therapy with GZR+EBR+ RBV (Arm A1) resulted in higher SVR12 (85.2%) compared with GZR + RBV (Arm B1) (75.0%). In Arm A1, efficacy was higher among GT2 (31L)-infected subjects (100% SVR12) compared with GT2 (31 M)-infected subjects (71.4% SVR12). The most common type of virologic failure was relapse (Arm A1) or breakthrough (Arm B1). Administration of GZR+EBR + RBV for 12 weeks resulted in SVR12 in 16/17(94.1%) subjects GT4, 5, 6 subjects in the PP population of Arm B2. Administration of GZR+EBV for 12 weeks (Arm B3) resulted in a lower SVR12: 76.9% (10/13 subjects) achieved SVR12.

Among GT4 infected subjects, administration of GZR+EBR ± RBV (Arms B2 and B3) for 12 weeks resulted in 100% SVR12. No cases of virological failure were observed in either arm.

Among GT5-infected subjects, administration of GZR+EBR + RBV (Arm B2) resulted in 100% SVR12; administration of GZR+EBR without RBV (Arm B3) resulted in lower efficacy (33.3%). Among GT6 infected subjects, administration of GZR+EBR + RBV (Arm B2) resulted in 75.0% (3/4) SVR12; administration of GZR+EBR without RBV (Arm B3) resulted in similar SVR12 of 66.7% (2/3). Addition of RBV did not appear to impact the efficacy of GZR+EBR in GT6 patients.

In all arms, regardless of GT, the majority of failures were relapses, occurring between end of study therapy and 4 weeks after the end of study therapy. There were few failures reported between 4 and 12 weeks after the end of study therapy. No additional failures were reported between 12 weeks after the end of therapy and 24 weeks after the end of therapy. All treatment regimens led to rapid achievement of undetectable (TND) HCV RNA. The mean time to first TND ranged from 19.2 to 29.6 days across treatment arms. No clear relationship to treatment arm or genotype was apparent in the mean-time to first achievement of TND majority, 66.7% to 100%, of GT2, GT4, GT5 (treated with or without RBV) and GT6 subjects (treated with RBV) achieved TND HCV RNA at TW 4. In GT2 subjects in Arms A1 and B1, the proportion of subjects remaining TND at TW12 was sustained. For Genotypes 4, 5 and 6, the proportion of subjects remaining TND was sustained for all genotypes in Arm B2. In Arm B3 in the GT6 population with a RBV-free regimen, on treatment failure was associated with a decline in the proportion of subjects who were TND at TW 12 due to breakthrough (Figure 13).

**Figure 13: Kaplan-Meier plot for time to first achievement of undetectable (TND) HCV RNA for GT2 subjects Full Analysis Set Population**




## 6.5. Summary of dosage selection for pivotal studies

Doses of GZR 30 to 800 mg, administered once daily, were anticipated to be efficacious based on the in vitro activity of GZR and the in vivo efficacy of GZR in earlier Phase I and II trials in HCV-infected subjects. Across this dose-range, a 7-day course of GZR monotherapy given once daily (QD) to HCV GT1 infected subjects resulted in approximately 5-log10 mean maximal reduction in HCV RNA levels.

Two Phase II studies evaluated GZR doses ranging from 25 to 800 mg QD (P003 and P038).

In Study P003, 266 TN, non-cirrhotic, HCV GT1 infected subjects were given 12 weeks of therapy with GZR 100 mg, 200 mg, 400 mg, or 800 mg QD, combined with 2 or 48 weeks of PR. In Study P038, 87 TN, non-cirrhotic, HCV GT1 infected subjects were given 12 weeks of therapy with GZR 25 mg, 50 mg, or 100 mg QD, combined with 12 or 24 weeks of PR. Combining both studies, the optimal efficacy and safety profile was observed with the GZR 100 mg dose as summarised below:

- approximately 88% of treatment naïve subjects achieved SVR12 following administration of GZR 100 mg QD x 12 weeks with varying durations of PR;
- the proportion of subjects who achieved SVR12 was lower among subjects who received daily GZR doses of 25 mg or 50 mg in combination with PR; and
- the proportion of subjects who achieved SVR12 did not increase among subjects who received daily GZR doses of 200 mg, 400 mg, or 800 mg in combination with PR; however, the administration of GZR 400 and 800 mg resulted in greater than dose proportional steady state GZR pharmacokinetics (PK), along with a low, but dose dependent frequency of late elevations of ALT and/or AST, which were in some cases associated with changes in liver function. The frequency of ALT and/or ALT elevations was increased in the 200 mg arm, but no changes to hepatic function were noted.

The efficacy of the 100 mg dose of GZR was confirmed in two more Phase II studies: P035, a study of GZR 100 mg + EBR 20-50 mg ± RBV administered for 8, 12, or 18 weeks in a diverse population of GT1 infected subjects; and P047, a study of GZR 100 mg ± EBR 50 mg ± RBV, administered for 12 weeks in TN, non-cirrhotic GT2, GT4, GT5, or GT6 infected subjects. Administration of these regimens resulted in high efficacy and a favourable safety profile among GT1, GT4, and GT6 infected subjects. Among GT1 infected subjects, efficacy remained high

across a diverse population that included cirrhotic subjects, subjects who failed prior PR therapy, and HIV-infected subjects.

The potency of EBR was evaluated in vitro against wild-type and RAV-containing replicons. These studies, along with Phase I PK studies, suggested that a regimen of EBR 10 mg or higher, administered QD would result in substantial efficacy against HCV GT1a, GT1b, GT2a, and GT4 infections. The ability of EBR to suppress RAVs was predicted to be dose-dependent, with increasing coverage predicted over the range of 10 to 50 mg. Phase Ib monotherapy studies among GT1a, GT1b, and GT3 patients evaluated doses ranging from 10 to 100 mg (GT1) and 50 to 100 mg (GT3). In these studies, administration of EBR 50 mg resulted in a mean maximal reduction in HCV RNA of 4.1-, 5.1, and 3.1-log10 IU/mL compared with baseline. The 100 mg dose was associated with minimal improvements in HCV RNA suppression compared with the 50 mg dose. The choice of EBR 50 mg for evaluation in Phase III trials was made in important Phase II P035. In the pilot Phase of the study (P035, Part A), a regimen of GZR 100 mg + EBR 20 mg + RBV was compared to a regimen of GZR 100 mg + EBR 50 mg + RBV among TN, non-cirrhotic, HCV GT1a/b infected patients. Efficacy and safety profiles were comparable between the two treatment groups. Given these results, and the prediction from in vitro studies that administration of EBR 50 mg QD would result in substantial increase in coverage against common NS5A RAVs, the 50 mg QD dose was chosen for further evaluation. This choice was confirmed in Part B of P035, in which a regimen of GZR 100 mg + EBR 50 mg, without ribavirin, administered for 12 weeks, resulted in high efficacy (97% and 98% SVR12 rates in cirrhotic and non-cirrhotic, treatment-naïve, HCV GT1 infected subjects, respectively) as well as a favourable safety profile in a diverse population of GT1 infected patients The choice of 50 mg also offered an advantage in that factors which might result in decreases in EBR levels, such as drug-drug interactions, would be less likely to result in lower efficacy.

P035/C-WORTHY was the main Phase II study in the GZR/EBR clinical development program that evaluated both treatment duration (12 and 18 weeks) and need for RBV in diverse patient populations. In an 'easier to cure' population (GT1 TN, non-cirrhotic mono- and HIV/HCV co-infected subjects), a 12-wk RBV-free regimen of GZR 100 mg + EBR 50 mg was highly effective, with SVR12 86.7– 100%; addition of RBV did not result in a substantially higher response rate.

- An 8 week regimen of GZR 100 mg + EBR 50 mg, administered once daily with RBV, was suboptimal in HCV GT1a infected subjects (80% SVR12). Therefore, this duration was not pursued further in GT1a subjects. In GT1b subjects, a regimen of GZR 100 mg + EBR 50 mg ± RBV was shown to be highly effective (SVR12 91.8%).
  - In a 'harder to cure' population (GT1, TN with cirrhosis or PR null responders with or without cirrhosis), a 12 week RBV-free regimen was highly effective in some populations including GT1a and GT1b infected subjects, subjects with baseline high or low viral load, and subjects with or without cirrhosis. Increasing the treatment duration, adding RBV, or both, may have contributed to achieving higher SVR12 rates in GT1a infected subjects who were prior PR null responders. Because these differences were accompanied by large confidence intervals, it was not clear whether these differences were meaningful; therefore, the effect of a longer treatment duration and the contribution of RBV to efficacy in PR treatment-experienced subjects was further explored in Phase III in Protocol 068/C-EDGE TE.

P035 also evaluated the impact of duration on the efficacy and safety profiles of GZR + EBR. Administration of GZR + EBR for 12 weeks resulted in high efficacy among subjects who were treatment-naïve or had prior treatment failure, and in subjects with and without cirrhosis. Efficacy in TN subjects was not increased by prolonging therapy to 18 weeks and 12 week duration of therapy was chosen for pivotal Phase III Study P060.

The contribution of RBV to the efficacy of GZR with EBR was further evaluated in Part B of the Phase II Study 047, that evaluated a 12 week regimen GZR and EBR, with or without RBV, among TN, non-cirrhotic subjects infected with HCV GT 2, 4, 5 or 6.

In subjects with HCV GT2 infection, administration of a 12 week regimen of GZR+EBR + RBV is more efficacious than a regimen of GZR+ RBV due to the added benefit of EBR in treating subjects with 31 L variant (100% SVR12). Administration of a 12 week regimen of GZR+ RBV is inadequate in clearing HCV infection among non-cirrhotic, treatment-naïve, HCV GT2 infected subjects.

Administration of a 12 week regimen of GZR+EBV with or without RBV is highly efficacious in clearing HCV infection among non-cirrhotic, TN, HCV GT4 infected subjects.

Among a total of 8 GT5- infected subjects, a 12 week regimen of GZR + EBR + RBV appeared to be more efficacious (SVR in 4/4 subjects) than a regimen of GZR + EBR (SVR in 1/4 subjects). Based on these results, the Phase III trials were amended to exclude HCV GT5 infected subjects.

Administration of a 12 week regimen of GZR+EBV ±RBV was effective in clearing HCV infection in the 7 non-cirrhotic treatment-naïve HCV GT6 infected subjects (SVR rates of 66% to 75%).

These results formed the basis for the selection of the GZR100 mg and the EBR 50 mg doses and the 12 week treatment duration in the pivotal Phase III studies.

Results from the studies described above also determined the HCV genotypes which were evaluated further in the Phase II/III clinical trials. The Phase III program focused primarily on evaluation of a 12 week regimen of FDC of GZR/EBR, generally administered without RBV. Results of the Phase II studies described above supported inclusion of GT1, GT4 and GT6 infected subjects in these Phase III studies as follows:

- GT1. In Study 035, 127/136 (93.4%) GT1 infected subjects (including mono-infected and HIV co-infected, treatment-naïve or prior PR failures, cirrhotics and non-cirrhotics) achieved SVR12. These results provided the rationale for including GT1 infected subjects in Phase III studies.
- GT2. In Study 047, efficacy of GZR + EBR + RBV was high among subjects whose GT2 infection consists of virions with NS5A L31 variant; efficacy was insufficient among subjects whose GT2 infection consists of virions with NS5A M31 variant. As pre-screening of HCV GT2 infected subjects is impractical, a decision was made not to include evaluations of efficacy of GZR/EBR among GT2 infected subjects in the core Phase III studies.
- GT3. In Study 035D, 9/20 (45.0%) non-cirrhotic, treatment naïve subjects achieved SVR12 following administration of GZR + EBR + RBV for 12 weeks. Thus, GT3-infected subjects were not included in Phase III studies; however, Protocol 074, a study of GZR/EBR with sofosbuvir (which is active against GT3 infection), was conducted.
- GT4. In Study 047, 9/10 (90.0%) of treatment-naïve non-cirrhotic, GT4 infected subjects (primarily 4a, 4d, and 4-other) achieved SVR12 following administration of GZR + EBR for 12 weeks; no virologic failures were observed. These results provided the rationale for including GT4 infected subjects in Phase III studies.
- GT5. In Study 047, 1/4 (25.0%) of non-cirrhotic, treatment-naïve GT5-infected subjects achieved SVR12 following administration of GZR + EBR for 12 weeks. Although 4/4 subjects who received GZR + EBR + RBV achieved SVR12, as Phase III studies were focused on GZR/EBR (no RBV), GT5-infected subjects were not included in the Phase III studies.
- GT6. In Study 047, 3/4 (75.0%) of non-cirrhotic, treatment-naïve GT6 infected subjects achieved SVR12 following administration of GZR + EBR for 12 weeks. Hence, GT6 infected subjects were included in the Phase III studies.

# 7. Clinical efficacy

## 7.1. Indication 1: Treatment of chronic hepatitis C infection in adults

### 7.1.1. Pivotal efficacy studies

#### *7.1.1.1. Study P060 (C-EDGE)*

*Study design, objectives, locations and dates*

This was a Phase III, randomised, parallel-group, multi-site, double-blinded trial to evaluate the fixed-dose combination regimen of GZR/EBR among treatment-naïve (TN), cirrhotic and non-cirrhotic subjects with chronic Hepatitis C. (HCV) genotype (GT) 1, 4 or 6 infection. The study was designed to enrol approximately 400 subjects. All subjects were to be TN to all anti-HCV treatment including any DAAs. Enrolment was managed to ensure that at least 20% of the subjects had compensated cirrhosis and that approximately 15% of enrolled subjects had GT4 or GT6 infection. Subjects were randomised in a 3:1 ratio to an immediate treatment arm or a deferred treatment arm. Subjects in the immediate treatment group received GZR/EBR 100 mg/50 mg for 12 weeks with planned 24 weeks of follow-up after dosing was completed. Subjects in the deferred treatment group received placebo for 12 weeks followed by 4 weeks of follow-up and then 12 weeks of open-label treatment with GZR/EBR 100 mg/50 mg with planned 24 weeks of follow-up after dosing was completed.

The primary objective was to evaluate the efficacy of GZR in combination with EBR as assessed by the proportion of subjects in the immediate treatment arm achieving SVR12[5] and to evaluate the safety and tolerability of GZR in combination with EBR. The secondary objectives were to evaluate efficacy of the proposed FDC by proportion of patients in the immediate treatment arm achieving SVR24[6] . The study was initiated on 11 June 2014 and is still ongoing (report date was 14 August 2015). It was conducted at 60 trial centres: 4 in Australia, 4 in the Czech Republic, 5 in France, 5 in Germany, 5 in Israel, 3 in Puerto Rico, 3 in South Korea, 4 in Sweden, 3 in Taiwan and 24 in the US.

**Comment**: This study design allowed for a blinded evaluation of safety parameters between subjects on GZR/EBR and those on placebo during the first treatment period. In addition, this design enabled a comparison of patient-related outcomes (PRO) between subjects on GZR/EBR and placebo. As SVR12 is achieved only with active antiviral therapy, a comparison of efficacy between GZR/EBR and placebo was unnecessary. Accordingly, placebo-treated subjects were crossed-over to active therapy 4 weeks after completing the placebo treatment phase.

The study report provided in the current submission summarises the efficacy data for subjects in the immediate treatment arm through 12 weeks after the end of all study therapy; the CSR mentions that the secondary endpoint SVR24 will be summarised in a future study report.

#### *7.1.1.2. Inclusion and exclusion criteria*

The main inclusion criteria were:

- Male and female subjects with documented chronic HCV GT1, GT4 or GT6 (with no evidence of non-typeable or mixed genotype); aged ≥ 18 years;
- HCV RNA (≥ 10,000 IU/mL in peripheral blood) at the time of screening;

[5] Sustained Virologic Response 12 weeks after the end of all study therapy, defined as HCV RNA < LLOQ (either TD[u] or TND) 12 weeks after the end of all study therapy.
[6] Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA < LLOQ (either TD(u) or TND)24 weeks after the end of all study therapy

- Positive for anti-HCV antibody, HCV RNA, or any of the above HCV genotypes at least 6 months before screening (HCV RNA and HCV genotype must be confirmed by screening lab results), or Positive for anti-HCV antibody or HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrolment with evidence of CHC disease, such as the presence of fibrosis.
- Have liver disease staging assessment as follows:
  - Cirrhosis is defined as any one of the following: A liver biopsy performed prior to Day 1 of this study showing cirrhosis (F4); Fibroscan performed within 12 calendar months of Day 1 of this study showing cirrhosis with result >12.5 kPa; or FibroSure® (Fibrotest®) performed during Screening with a score of >0.75 and an AST: platelet ratio index ([APRI[7]) of >2.
  - Absence of cirrhosis is defined as any one of the following: Liver biopsy performed within 24 months of Day 1 of this study showing absence of cirrhosis; Fibroscan[8] performed within 12 months of Day 1 of this study with a result of ≤12.5 kPa or a Fibrosure® (Fibrotest®) score of ≤0.48 and APRI of ≤1 during Screening. In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy was required and the liver biopsy results supersede the results obtained by Fibroscan® or Fibrosure.
  - Treatment naïve: Naïve to all anti-HCV treatment;
  - Females not of reproductive potential or if so then agrees to avoid becoming pregnant (by using at least 2 contraceptive measures) while receiving study drug and for 14 days after last dose of study drug.
  - Written informed consent.

The main exclusion criteria were:

- evidence of decompensated liver disease manifested by the presence of or history of ascites, oesophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver disease. For cirrhotics, subjects that are Child-Pugh Class B or C or who have a Pugh-Turcotte (CPT) score > 6.
- co-infected with hepatitis B virus (for example, Hepatitis B surface antigen [HBsAg] positive) or HIV.
- history of malignancy ≤ 5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or carcinoma in situ; or is under evaluation for other active or suspected malignancy.
- has cirrhosis and liver imaging within 6 months of Day 1 showing evidence of hepatocellular carcinoma (HCC) or is under evaluation for HCC.
- taking or plans to take any of the prohibited medications or taking herbal supplements, including but not limited to St. John's Wort (Hypericum perforatum) within 2 weeks of Day 1.
- currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent.

[7] APRI formula: AST÷lab upper limit of normal (ULN) for AST x 100÷ {platelet count÷100} (APRI calculation to be provided by the central laboratory).
[8] Fibroscan cut-off of 12.5 kPa has a positive predictive value of 90% and a sensitivity of 95% for ≥F3. Based on box and whisker plot of interquartile distribution >12.5 kPa will exclude the majority of subjects with Metavir F3 fibrosis.

- has a clinically-relevant drug or alcohol abuse within 12 months of screening.
- pregnant or breast-feeding female, or expecting to conceive or donate eggs from Day 1 throughout treatment, and 14 days after the last dose of study medication.
- has any of the following conditions: Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair; Poor venous access that precludes routine peripheral blood sampling required for this trial; Subject with a history of gastric surgery (for example, stapling, bypass) or subject with a history of malabsorption disorders (for example, celiac sprue disease); History of a medical/surgical condition that resulted in hospitalisation within the 3 months prior to enrolment, other than for minor elective procedures; Medical/surgical conditions that may result in a need for hospitalisation during the period of the study; or any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids, TNF antagonists, or other immunosuppressant drugs during the course of the trial.
- has any condition or pre-study laboratory abnormality, ECG abnormality, or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.
- had a life-threatening SAE during the screening period.
- has evidence of history of chronic hepatitis not caused by HCV, including but not limited to non-alcoholic steatohepatitis (NASH), drug-induced hepatitis, and autoimmune hepatitis.
- abnormal laboratory values meeting exclusion criteria[9]
- has an immediate family member (for example, spouse, parent/legal guardian, sibling or child) who is investigational site or sponsor staff directly involved with this trial.

#### *7.1.1.3. Study treatments*

Subjects were randomised in 3:1 ratio to the following treatment arms:

- Arm 1: Immediate Blinded Treatment (Immediate Treatment Group, or ITG): GZR 100 mg QD/EBR 50 mg QD for 12 weeks and 24 weeks of post-treatment follow-up.
- Arm 2: Deferred Treatment Blinded for first 12 weeks Followed by 12 Weeks of Open-Label Therapy (Deferred Treatment Group, or DTG): Placebo QD for 12 weeks, plus 4 weeks follow-up, then open-label treatment of GZR 100 mg QD / EBR 50 mg QD for 12 weeks plus and 24 weeks of post-treatment follow-up.

Dose modification of GZR/EBR was not permitted. Subjects were allowed to take GZR/EBR without regard to food. If a dose was missed, and it was less than 8 hours before the next dose, the subject was allowed to skip the missed dose and then resume the normal dosing schedule. Subjects were instructed not to double the next dose in order to compensate for what had been missed. If GZR/EBR had to be interrupted for any reason, interruption could occur for up to 3 days. If the duration of interruption was for more than 3 days, the sponsor had to be consulted. Subjects were allowed to take GZR/EBR without regard to food.

#### *7.1.1.4. Efficacy variables and outcomes*

*Virologic response*

The main efficacy variables for the study included SVR12 and SVR24. Sustained Virologic Response 12 and 24 weeks after the end of all study therapy was defined as HCV RNA < LLOQ (either TD[u] or TND) occurring 12 or 24 weeks after the end of all study therapy. HCV RNA

[9] Laboratory Exclusion Criteria: Creatinine Clearance <50 mL/min; Haemoglobin <9.5 g/dL for both male and female subjects; Platelets <50 x 103/µL; Serum Albumin < 3.0 g/dL; INR >1.7 unless subject has a stable INR on an anticoagulant regimen; HbA1c >10%; ALT >10XULN; AST >10XULN; 15.

levels were measured using the Roche COBAS® AmpliPrep/COBAS® TaqMan® HCV Test, v2.0, which has a lower limit of quantification of 15 IU/mL and a lower limit of detection of 15 IU/mL.

Lack of efficacy at different time-points in the trial was categorised as:

- Non-response: Subject had HCV RNA detected at end of treatment without HCV RNA < LLOQ on treatment.
- Rebound: subject had a rebound defined as >1 log10 IU/mL increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.
- Virologic breakthrough: Subject had a confirmed HCV RNA ≥ LLOQ [TD (q)] after being < LLOQ previously while on treatment. Confirmation was defined as an HCV RNA ≥ LLOQ from a separate blood draw repeated within 2 weeks.
- Relapse: Subject had a confirmed HCV RNA ≥ LLOQ [TD (q)] following end of all study therapy, after becoming undetectable (TND) at end of treatment. Confirmation was defined as an HCV RNA ≥ LLOQ from a separate blood draw repeated within 2 weeks.

*Viral resistance measurements*

Hepatitis C virus RAVs are an important consideration in treatment with DAAs. RAVs present prior to therapy may impact efficacy. In addition, virologic failure (VF) may be accompanied by the emergence of RAVs. To better understand the impact of pre-therapy RAVs on the efficacy of GZR/EBR, and to determine whether VF is accompanied by the emergence of RAVs, blood samples were obtained for HCV viral resistance testing at baseline, at Week 16 for subjects in the deferred treatment arm (open label phase), viral failure confirmation visit, and Follow-up Week (FW) 4, FW8, FW12, and FW24 visits. Baseline samples were assayed for presence of RAVs for all subjects. In addition, RAVs were assessed for any subject with VF and detectable virus above 1000 IU/mL after failure was observed. These subjects were also offered participation in a 3 year long-term follow-up P017, to determine the persistence of RAVs and to determine time course of reversion to wild-type. Viral resistance testing, using population sequencing methodology, focused on the entire NS3/4A and NS5A regions for all subjects at baseline and for those who met the subject virologic failure criteria.

*Genomic exploratory measurements*

The impact of IL-28B genotypic variation on the efficacy of GZR/EBR was evaluated as IL- 28B SNP polymorphisms were shown to be important determiners of efficacy of interferon based HCV therapies. In addition, samples were collected to allow evaluation of whether genetic variation within a clinical trial population correlated with response to the treatment under evaluation. If genetic variation was found to predict efficacy or AEs, the data may inform optimal use of therapies in the patient population.

**Comments**: Genetic studies on collected samples have not yet been performed and the CSR states that any future studies will be reported in a future CSR.

*Patient reported outcomes/health-related quality of life measurements*

There were five self-administered questionnaires to assess various aspects of health-related quality of life in P060 including: Short Form Health Survey, Version 2 (SF- 36v2® Health Survey Acute[10]); EuroQol 5 Dimensions health questionnaire, with 5 levels (EQ-5D-5L[11]); Functional

[10]The SF-36v2® Health Survey, Acute (1 week recall) Form, is a generic health survey, which includes 36 questions to measure functional health and well-being from the subject's perspective. It measures each of the following 8 health domains: Physical Functioning, Role Limitations-Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Limitations-Emotional, and Mental Health; these health domain scores contribute to the Physical Component Summary (PCS) and Mental Component Summary (MCS) scores

Assessment of Chronic Illness Therapy-Fatigue Scale, Version 4 (FACIT Fatigue Scale[12]);- Work Productivity and Activity Impairment Questionnaire, Hepatitis C , 2.0 (WPAI: Hepatitis C[13]); and the HCV-specific version of the Chronic Liver Disease Questionnaire (CLDQ-HCV[14]). An electronic device, TrialMax Slate™, was used to administer the patient-reported outcomes (PROs). The development and programming of the electronic device which was initiated prior to the final selection of countries required language translations to be available for each PRO. Due to lack of broad language availability of the CLDQ-HCV, as compared to the other PROs, the use of the CLDQ-HCV was limited to subjects in the United States (US) only.

The primary efficacy endpoint was SVR12 rate for the subjects in the immediate treatment arm.

The secondary efficacy endpoint was SVR24 rate for the subjects in the immediate treatment arm.

The exploratory efficacy endpoints included:

1. The proportion of subjects achieving undetectable HCV RNA (TND) and HCV RNA < LLOQ (TD(u)) at Week 2, Week 4 and Week 12, and the proportion of subjects achieving SVR4 in the immediate treatment arm.
2. Longitudinal HRQOL scores and change in HRQOL scores from baseline HRQOL score: SF-36v2® (8 health domain scores, PCS and MCS); EQ-5D-5L Health State and VAS scores; FACIT-Fatigue Scale score; Total CLDQ-HCV score and CLDQ-HCV Domain (Activity/Energy, Emotion, Worry, System) scores; Work Productivity and Activity Impairment scores.
3. The emergence of viral resistance to GZR or EBR among subjects who fail to achieve SVR.
4. The relationship between genetic variations (eg IL28 gene polymorphisms) and subject.

**Comments**: The efficacy endpoints used in this pivotal Phase III study were appropriate and complied with CHMP guidelines for 'evaluation of antiviral agents for treatment of chronic HCV infection.' The endpoints were also similar to those used for the recently approved DAAs such as simeprevir and sofosbuvir.

#### *7.1.1.5. Randomisation and blinding methods*

Randomisation was performed centrally using an interactive voice response system (IVRS)/integrated web response system (IWRS). There were 2 treatment arms. Subjects were to have been assigned randomly in a 3:1 ratio to: GZR/EBR FDC (active) – 'immediate' treatment arm; or Placebo to GZR/EBR FDC followed by GZR/EBR FDC (active) – 'deferred 'treatment arm.

[11]The EuroQol EQ-5D-5L is a validated, standardised 5-item health-state questionnaire, applicable to a wide range of health conditions and treatments and used to assess health outcomes ; the 5 health state dimensions include: mobility, self-care, usual activities, pain/ discomfort, and anxiety/ depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The recall period is today. It also includes a graded (0 to 100) 20 cms vertical visual analog scale (EQ VAS) on which subjects rate their current general state of health, from 'the worst health you can imagine' to 'the best health you can imagine.

[12]The Functional Assessment of Chronic Illness Therapy-Fatigue Scale (FACIT-Fatigue Scale), Version 4, is a 13-item questionnaire, that assesses self-reported fatigue, including feelings of tiredness, listlessness, energy as well as fatigue's impact on daily activities and function (e.g., trouble doing things, need to sleep, and social limitations). It uses a 5-point Likert-type response scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very Much) with a recall period of 'during the past 7 days.

[13]The Work Productivity and Activity Impairment Questionnaire, Hepatitis C,V2.0 (WPAI: Hepatitis) is a self-administered questionnaire consisting of 6 items which evaluates the effect of hepatitis C on the subject's ability to work and perform regular activities; the recall period for this questionnaire is 7 days.

[14]The CLDQ-HCV consists of 29 questions divided into 4 domains: activity and energy, emotional, worry, and systemic. The CLDQ-HCV has a 7- point Likert-type response scale ranging from 1 (most impairment) to 7 (least impairment) and a recall period of 'during the last two weeks'.

Randomisation was stratified according to the following factors: Fibrosis stage (Non-cirrhotic versus Cirrhotic); HCV genotype/sub-type (GT1a versus GT1 non-a versus GT4/GT6).

The first 12 weeks of the treatment period plus first 4 weeks of follow-up were conducted as a double-blind study under in-house blinding procedures. GZR /EBR and placebo were packaged identically so that blind/masking was maintained. The subject, the investigator and sponsor personnel or delegate(s) who were involved in the treatment or clinical evaluation of the subjects were unaware of the group assignments. The subject, the investigator and the sponsor did not know the treatment they were administered or the HCV RNA results through Week 16 of the study, including the in-house team responsible for medical monitoring. However, a separate, in-house unblinded medical monitoring team[15] from outside the Hepatology area consisting of a Physician and a Clinical Development Scientist had access to the treatment group assignments and HCV RNA results.

#### *7.1.1.6. Analysis populations*

The immediate treatment arm of the Full Analysis Set (FAS) population served as the primary population for the analysis of efficacy data in this study. The FAS population consisted of all randomised subjects who had received at least one dose of study treatment. A supportive analysis that used the immediate treatment arm of the Per Protocol (PP)[16] population was performed for the primary (SVR12) and key secondary efficacy endpoints. Resistance Analysis Population (RAP) included all subjects from the FAS population who either achieved SVR12 or met criteria for virologic failure. The RAP did not include any subject who discontinued the study for reasons other than virologic failure. Samples were collected at baseline and population sequencing was performed and analysed for the presence of variants that are known to confer resistance to either NS3 or NS5A inhibitors.

#### *7.1.1.7. Sample size*

The study was to have randomised approximately 400 subjects with 300 subjects in the immediate treatment arm and 100 in the deferred arm. The deferred arm served as placebo control for the first 12 weeks, then received open-label active treatment after unblinding at Week 16, four weeks after the end of the placebo treatment period. Assuming a response rate of at least 85% in the immediate treatment arm, the study had over 99% power to demonstrate that the SVR12 rate was superior to the reference rate of 73% at an overall one-sided 2.5% alpha-level.

The historical reference rate of 73% was derived from the Phase III trials of simeprevir/PR in TN, HCV mono-infected subjects (QUEST 1 and 2 studies, Manns et al, 2014; Jacobson et al, 2014) after adjusting for the expected proportion of subjects with cirrhosis in this study and an expected improved safety profile related to an interferon (IFN) free regimen. The SVR12 in QUEST 1 and 2 studies was approximately 80%; however, in these studies only 9% of the patients had compensated cirrhosis. The SVR rate was 60% in patients with compensated cirrhosis and 82% in the non-cirrhotic patients. Accounting for a higher percentage of patients with compensated cirrhosis in this protocol (20%), a historical SVR rate of approximately 78% is calculated. A 5% decrease is applied to this response rate because of an expected improved safety profile related to an IFN-free regimen. This approximation was used as the historical reference rate in assessing the primary hypothesis of the study that includes patients with HCV GT4 and GT6, in addition to patients with HCV GT1.

[15] They were responsible for the following activities: - Reviewing unblinded HCV RNA results to monitor for virologic failures; and - During the blinded phase of the study and on an 'as needed' basis, review SAEs in the Immediate and Deferred Treatment arms, if treatment information was needed as part of the review.

[16] The PP population is a subset of the FAS population and excluded subjects due to important deviations from the protocol that could have substantially affected the results of the primary and key secondary efficacy endpoints.

#### *7.1.1.8. Statistical methods*

The primary hypothesis was that subjects in the immediate treatment arm would achieve an SVR12 rate superior to the reference rate of 73%, tested at a 1-sided significance level (type-I error) of 0.025. A two-sided 95% confidence interval (CI) was also constructed for the SVR12 rate. The SVR12 rate was estimated by the proportion of subjects with SVR12 in the immediate treatment arm of the FAS population. A two-sided 95% asymptotic (Wald) confidence interval was planned to be calculated. However, due to the small number of subjects who did not achieve SVR12, the Clopper-Pearson method was actually used to construct the 95% confidence intervals for the SVR12 rate. The Missing=Failure (M=F) approach was used to handle missing values. The SVR4 rate was estimated using the approaches described for the SVR12 rate. The HCV RNA values at TW2, TW4, TW12, and FW4 visits for the immediate treatment arm were summarised as the proportion of subjects achieving TND and <LLOQ for the FAS and PP populations. For FAS, the M=F approach was used to handle the type 3 missing data, and for the PP population, the Treatment-Related Discontinuation (TRD) = F approach was used to handle the type 3 missing data. Summary statistics were provided to describe the rates of occurrence of subject virologic non-response, rebound, breakthrough, and relapse.

#### *7.1.1.9. Participant flow*

Of the 469 subjects screened for inclusion in the study, 48 were excluded during screening and not randomised. The most common inclusion criteria not met were: documented chronic HCV GT1, GT4, or GT6 (with no evidence of non-typeable or mixed genotype) infection (15 subjects [35.7%]); and HCV RNA levels ≥10,000 IU/mL (7 subjects [16.7%]). The most common exclusion criteria met were:- exclusionary laboratory values (7 subjects [16.7%]); and evidence of decompensated liver disease manifested by the presence of or history of ascites, oesophageal or gastric variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver disease (4 subjects [9.5%]). A total of 421 subjects were randomised to treatment (all subjects received at least one dose of study therapy) and 415 (98.6%) completed the protocol-specified study visits during the initial treatment period. For those 316 subjects randomised to the immediate treatment arm, a total of 3 (0.9%) have completed the study through FW24 by the cut-off date for this report of 26 February 2015, and 310 (98.1%) completed the FW12 visit and are still in follow-up. Overall 311/316 (98.4%) of the subjects completed their study therapy with GZR/EBR for the immediate treatment arm. Of the 5 subjects (1.6%) in the immediate treatment arm that discontinued study medication, 3 (0.9%) discontinued study medication due to AEs[17]; one (0.3%) due to death and one (0.3%) was lost to follow-up. A total of 104/105 (99.1%) subjects completed study therapy with placebo in the deferred treatment arm for the initial treatment period and 102 subjects[18] in the deferred arm remain in the ongoing study.

#### *7.1.1.10. Major protocol violations/deviations*

There were 59 major protocol deviations which required action of which 36 were related to Informed Consent[19]; upon identification of these deviations, all subjects were re-consented and

[17] The 3 (0.9%) subjects in the immediate treatment arm that discontinued study medication due to adverse events included 1 subject with anxiety and palpitations, and 2 subjects with increased AST/ALT.
[18] One subject (0.9%) in the immediate treatment arm discontinued study medication due to an AE of rash; this subject remained in the study for follow-up and has completed the study through FW24 by the cut-off date for this report of 26-Feb-2015. Two subjects withdrew after the initial treatment period, one prior to starting deferred active treatment and one during the deferred active treatment period (withdrew consent).
[19] In 34 of these cases, a routine urinalysis was collected prior to the subject signing the most recent version of the Informed Consent form. In one case, the subject did not sign the most recently approved consent form (for Amendment 1) and 4 visits occurred prior to the site identifying this deviation. In one case a subject signed the Future Biomedical Research consent for the wrong study.

none of these deviations led to exclusion of subject data from the analyses in this report. Four protocol deviations were related to Entry Criteria[20]. Two protocol deviations were related to Prohibited Medications: one subject was taking carbamazepine and another subject was simvastatin for a past history of hyperlipidaemia; both prohibited medications were discontinued and these deviations did not exclude the subject from the analyses. Seven protocol deviations were related to safety assessments although only 1 of these subjects was excluded from the PP analysis. Eight protocol deviations were related to clinical supplies but none of the 8 subjects were excluded from the efficacy analysis. Overall, only 3 subjects were excluded from the PP analysis: two deaths due to unrelated causes (strangulated hiatal hernia following a laparoscopic appendectomy between the TW2 and TW4 visits and presumed arrhythmia with autopsy-documented coronary disease); another subject was incarcerated and missed the TW8 visit and was discontinued from study medication and the study.

#### *7.1.1.11. Baseline data*

The FAS population consisted of majority of males (53.9%), White (62.7%) with the non-CC *IL28B* genotype (65.3%), had plasma HCV-RNA above 800,000 IU/mL (68.4%) and had mild or moderate liver fibrosis (21.9% had compensated cirrhosis). The median age was 54 years. At screening, TN subjects had either HCV GT1 (382 [90.7%]), GT4 (26 [6.2%]) or GT6 (13 [3.1%]). Of the GT1 subjects, 211 (55.2%) had GT1a, 171 (44.8%) had GT1b; 412 (97.9%) subjects were IFN treatment eligible. Demographic characteristics were generally similar across treatment groups. The conditions that were most often (> 10 or more subjects) reported in medical histories were drug abuse (3-4%), large intestine polyp (3.3%), alcohol abuse (2.9%) and depression (2.9%). Overall, 317 of the 421 randomised subjects had used prior non-HCV therapies (that is, took at least 1 medication from 30 days prior to the screening visit up until the day before randomisation) and the most common prior medications included agents acting on the renin-angiotensin system (21.1%), analgesics (21.1%), vitamins (20.7%), drugs used for acid related disorders (15.4%), anti-inflammatory and anti-rheumatic products (13.3%), psychoanaleptics (13.1%), psycholeptics (12.8%), beta blocking agents (10.9%), drugs used in diabetes (10.7%), lipid modifying agents (10.2%), and calcium channel blockers (10%). There were no clinically meaningful differences among treatment groups in the use of prior medications. Overall, 346 (82.2%) subjects took concomitant medications during the period of Day 1 through Follow-up Day 14 and medication usage was generally similar during the study treatment period compared with the prior history. The following classes of medications increased usage during study treatment compared to the 30- day period prior to randomisation: analgesics (30.4% versus 21.1%); antiinflammatory/ antirheumatic products (22.6% versus 13.3%); antibacterials for systemic use (13.1% versus 4.3%); and drugs for obstructive airway diseases (10.2% versus 9.0%). However, lipid modifying agents decreased slightly from 10.2% usage prior to randomisation to 8.3% during study treatment. Other drug therapeutic categories commonly used (>10%) during study treatment included: renin-angiotensin system (21.9%), vitamins (21.4%), drugs used for acid-related disorders (17.1%), psycholeptics (15.9%), psychoanaleptics (15.0%), beta blocking agents (11.2%), drugs used in diabetes (11.2%) and calcium channel blockers (10.2%). There were no clinically meaningful differences among treatment groups in the use of concomitant medications post randomisation. Reported

[20] In 2 of the cases, subjects were randomised into the IVRS system as non-cirrhotic, however per their fibrosis/liver biopsy results, the subjects were cirrhotic. In one case, the subject was randomised into the IVRS system as cirrhotic, but per their fibrosis/liver biopsy results was non-cirrhotic. These subjects were analysed according to their actual cirrhotic status in the assessments in this report. The third subject initially reported an SAE of prostate cancer approximately 2 months after study entry, however upon further questioning, the subject disclosed that he had been evaluated for prostate cancer prior to study entry. This subject's SAE report was updated to reflect a start day for the SAE of prostate cancer prior to study randomisation.

treatment compliance[21] with GZR/EBR treatment was high (mean, 99.8%; range 84.3% to 100%), and rates were similar across treatment groups.

**Comments**: The patients enrolled in this pivotal Phase III study were representative of the target patient population for GZR/EBR 100/50 mg. However, the number of GT4 and GT6 infected patients was only 9.3% which is less than the proposed 15% mentioned in the study protocol.

#### *7.1.1.12. Results for the primary efficacy outcome*

Overall, 299 of the 316 subjects achieved SVR12 (94.6% with a two-sided 95% Clopper-Pearson CI of 91.5, 96.8%); the one-sided one-sample exact test established the superiority of the SVR12 rate following GZR 100 mg /EBR 50 mg administered for 12 as compared to the historical response rate of 73% ($p<0.001$). Across all genotypes, SVR12 was achieved in 94.6% (299/316) of study subjects. The SVR12 rate was numerically lower in the GT1a infected subjects (144/157, 91.7%, 95% CI: 86.3, 95.5) compared to the GT1b (129/131, 98.5%, 95% CI: 94.6, 99.8] and GT4 infected subjects (18/18, 100%, 95% CI: 81.5, 100), but the confidence intervals overlapped. A total of 80% (8/10, 95% CI: 44.4, 97.5) of GT6 infected subjects achieved SVR12.

A total of 17 subjects (5.4%) failed to achieve SVR12. Of these 4 subjects, or 1.3% of the FAS population of the immediate treatment arm, experienced non-virologic failure. Of these 4, 3 were GT1a infected subjects and 1 was a GT1b infected subject. The causes for non-virologic failure were 2 deaths (incarcerated hernia and cardiac arrhythmia), 1 loss to follow-up and 1 discontinuation due to drug related AE (palpitations/anxiety). Thirteen subjects, or 4.1% of the FAS population of the immediate treatment arm, experienced virologic failure. Of these, 1 subject experienced a breakthrough (GT1a infected subject, at TW8) and 12 relapses (9 GT1a infected subjects, 1 GT1b infected subject, and 2 GT6 infected subjects).

SVR12 was achieved in 95.5% (95% CI 92.6 to 97.5%) of the per-protocol population excluding 3 subjects with missing SVR12 results due to reasons unrelated to study medication. In the PP analysis, 144/155 (92.9%) of GT1a infected subjects and 129/130 (99.2%) of GT1b infected subjects achieved SVR12.

Subgroup analysis did not identify meaningful differences in the proportions of subjects who achieved SVR12 within the subgroups of gender, age, race or ethnicity; African-Americans constituted 18.7% of the FAS population of the immediate treatment arm and 96.6% of subjects in this important subpopulation achieved SVR12. The impact of HCV sub-genotype, *IL28B* genotype, cirrhosis, baseline viral load, and IFN eligibility on efficacy (SVR12) was also evaluated. The highest SVR12 rate was achieved among GT4 (100%) and GT1b (98.5%) infected subjects, followed by GT1a infected subjects (91.7%) then GT6 infected subjects (80%). Presence of cirrhosis did not impact the efficacy of GZR/EBR as 68 of 70 (97.1%) cirrhotic subjects achieved SVR12, compared to 231/246 (93.9%) non-cirrhotics. SVR12 was achieved in 32/34 (94.1%) of the GT1a infected cirrhotic subjects and all 34 GT1b cirrhotic subjects (100%). Only 2 GT4 infected cirrhotics were enrolled and both achieved SVR12. No GT6 infected cirrhotics were enrolled. Neither *IL28* genotype nor interferon-eligibility had a meaningful impact on efficacy. SVR12 was achieved in 94/94 (100%, 95% CI 96.2, 100.0) of subjects whose HCV RNA levels were ≤ 800,000 IU/mL at baseline compared with 205/222 (92.3%, 95% CI 88.0, 95.5) of subjects whose HCV RNA levels were > 800,000 IU/mL at baseline. Comparable findings were observed at the 2,000,000 IU/mL and 10,000,000 IU/mL baseline viral load cut-points. The effect of the presence of baseline NS5A RAVs on efficacy was only observed for subjects with higher (> 800,000 IU/mL) baseline viral loads. SVR12 was achieved in 183/189

[21] Each subject received a Study Medication Diary in which the subject was to record dates/times study drug doses (GZR/EBR) during the study period. The subject was to return the completed diary card at each scheduled visit.

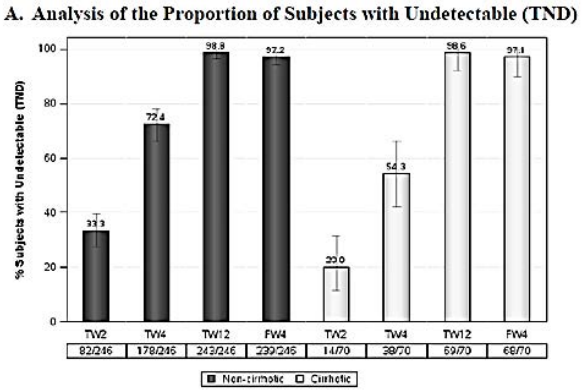
(96.8%; 95% CI 93.2, 98.8) of subjects in the FAS population who had viral loads above 800,000 IU/mL but did not have NS5A RAVs at baseline. In contrast, SVR12 was achieved in 22/33 (66.7%; 95% CI 48.2, 82.0) of subjects who had viral loads above 800,000 IU/mL and did have NS5A RAVs at baseline.

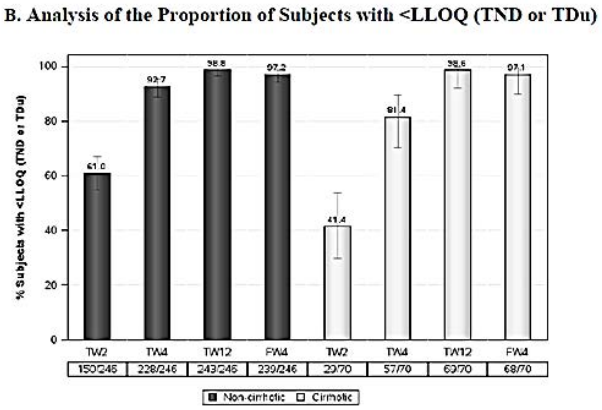
#### *7.1.1.13. Results for other efficacy outcomes*

The secondary endpoint (SVR24) will be summarised in a future study report.

The proportion of subjects achieving undetectable HCV RNA (TND) and HCV RNA < LLOQ (TND or TDu) at TW2, TW4 and TW12 as well as FW4 visits for the immediate treatment arm of the FAS population was summarised. There was a trend towards slightly faster viral clearance in non-cirrhotic compared to cirrhotic subjects through TW4, with comparable responses by TW12 (Figure 14).

**Figure 14: treatment response at TW2, TW4, TW12 and FW4 visits by cirrhotic status for FAS population. A (top): Analysis of the proportion of subjects with undetectable (TND). B (bottom): Analysis of the proportion of subjects with< LLOQ (TND or TDu).**




*Antiviral resistance to grazoprevir and elbasvir*

Impact of baseline NS3 RAVs on efficacy by genotype subtype

There was no evident association between baseline GT1 NS3 RAVs and virologic failure. SVR12 was achieved in 107/111 (96.4%) and 162/169 (95.9%) of subjects with GT1 infection with or without NS3 RAVs, respectively. All of the GT1 infected subjects (N = 3) who harboured RAVs associated with >5 fold reduced susceptibility to GZR at baseline achieved SVR12. SVR12 was achieved in all GT4 infected subjects (18/18; 100%): 7/7 and 11/11 GT4 infected subjects with and without baseline NS3 RAVs achieved SVR12. All GT6 subjects had baseline NS3 RAVs and SVR12 was achieved in 7/9 (77.8%) subjects. NS3 RAVs were detected at baseline in 86/151 (57%) and 25/129 (19%) of subjects with GT1a and GT1b infection, respectively. SVR12 was achieved in 83/86 (96.5%) and 58/65 (89.2%) of subjects with GT1a infection with or without NS3 RAVs, respectively. The corresponding SVR12 rates among subjects with GT1b infection

were 24/25 (96%) and 104/104 (100%). The Q80K mutation, which has been associated with decreased efficacy among GT1a infected subjects treated with simeprevir/PR, was detected in 61/151 (40.4%) GT1a infected subjects and was rare in GT1b infected subjects (2/129; 1.6%). In vitro, Q80K or Q80R substitutions do not cause any potency shift to GZR and no association was observed between the presence of baseline Q80K and treatment response. Among the GT1a infected subjects, SVR12 rate was 96.7% (59/61) and 91.1% (82/90) in subjects who did and did not harbour viruses with Q80K at baseline, respectively. The impact of baseline GT1a NS3 RAVs on treatment outcome was not affected by cirrhosis status: SVR12 was 95.8% (23/24) and 60/62 (96.8%) in cirrhotic and non-cirrhotic GT1a infected subjects, respectively with baseline NS3 RAVs. There was no difference in SVR12 for GT1b subjects with baseline NS3 RAVs that confer >5 fold shift in potency (3/3; 100%) or ≤ 5 fold shift in potency (21/22; 95.5%) to GZR. The impact of baseline GT1b NS3 RAVs on treatment outcome was also not affected by cirrhosis status: 100% (10/10) and 93.3% (14/15) of the GT1b subjects with baseline NS3 RAVs with and without cirrhosis, respectively. All 18 GT4 subjects achieved SVR12. The majority of these subjects (16/18, 88.9%) were non-cirrhotic. Of the non-cirrhotic subjects, 5/16 (31.3%) had NS3 RAVs at baseline while of the cirrhotic subjects 2/2 (100%) had NS3 RAVs at baseline. The majority of GT6 subjects in the RAP (7/9; 77.8%) achieved SVR12, and all 9 were non-cirrhotic.

*Impact of baseline NS5A RAVs on efficacy by genotype subtype*

The association of baseline NS5A RAVs with efficacy outcomes differed by sub-genotype. NS5A RAVs were identified at baseline in 19/154 (12.3%) GT1a infected subjects; SVR12 was achieved in 11/19 (57.9%) of these subjects compared with 133/135 (98.5%) among subjects without baseline NS5A RAVs. SVR12 in subjects with baseline GT1a RAVs that cause ≤ 5 fold potency shift of EBR in vitro was 90% (9/10) versus 22.2% (2/9) in subjects with baseline GT1a RAVs that shift the potency of EBR > 5 fold in vitro. In contrast, among GT1b infected subjects, SVR12 rates were achieved among 94.4% (17/18) of subjects with detectable baseline NS5A RAVs versus 100% (112/112) in those without baseline RAVs. SVR12 in subjects with baseline GT1b RAVs with ≤5 fold shift versus > 5 fold shift was 100% (1/1) versus 94.1% (16/17).

Subjects were evaluated for the presence of both NS3 and NS5A baseline RAVs. 5.7% (16/280) of GT1 infected subjects in the RAP had both NS3 and NS5A RAVs at baseline, and SVR12 was achieved in 12/16 (75%).

**Comment**: The presence of baseline NS5A RAVs that cause a >5 fold shift in the potency of EBR in vitro among GT1a infected subjects was associated with a substantial reduction in efficacy, from an SVR12 of 98.5% in subjects without baseline GT1a RAVs to 90.0% in subjects with baseline GT1a RAVs that cause ≤ 5 fold shifts, and to 22.2% in subjects with > 5 fold baseline shifts. Subjects with > 5 fold shifts at baseline accounted for only 5.8% (9/154) of GT1a infected subjects, but comprised 70% (7/10) of all GT1a virologic failures.

Overall efficacy among GT1a infected cirrhotics was higher than among non-cirrhotics. The impact of baseline NS5A RAVs on efficacy was less apparent as interpretation was limited by the small sample sizes. Presence of NS5A RAVs at baseline did not impact the efficacy of GZR/EBR among GT1b infected subjects and although the sample size was small, the impact of baseline GT1b NS5A RAVs on treatment outcome was not affected by cirrhosis status; Of the GT1b subjects with baseline NS5A RAVs with cirrhosis, 3/3 (100%) achieved SVR12, compared to 14/15 (93.3%) GT1b subjects with baseline NS5A RAVs without cirrhosis.

All GT4 subjects in the RAP achieved SVR12 (18/18); therefore the presence or absence of baseline NS5A RAVs did not affect the rate of SVR12. Overall, 7 of 9 (77.8%) of GT6 infected subjects achieved SVR12. NS5A RAVs were present at baseline in 3/9 (33.3%) subjects; of those without baseline NS5A RAVs, 5/6 (83%) achieved SVR12, compared with 2/3 (66.7%) subjects with baseline NS5A RAVs. However, interpretation was limited by small sample sizes.

SVR12 was achieved in 94/94 (100%, 95% CI 96.2, 100.0) of subjects whose HCV RNA levels were ≤ 800,000 IU/mL at baseline compared with 205/222 (92.3%, 95% CI 88.0, 95.5) of subjects whose HCV RNA levels were >800,000 IU/mL at baseline. In the FAS population, SVR12 was achieved in 183/189 (96.8%; 95% CI 93.2, 98.8) of subjects who had viral loads above 800,000 IU/mL but did not have NS5A RAVs at baseline. In contrast, SVR12 was achieved in 22/33 (66.7%; 95% CI 48.2, 82.0) of subjects who had viral loads above 800,000 IU/mL and had NS5A RAVs at baseline. The impact of baseline viral load of efficacy was also evaluated by sub genotype and the effect of NS5A RAVs on efficacy was most striking with respect to GT1a.

*Post-baseline resistance analysis*

In the RAP, the virologic failure rate for GT1a was 6.5% (10/154). Of the 10 GT1a virologic failures, 4 (40%) subjects did not have treatment emergent NS3 RAVs. Of the 6 subjects (60%) with treatment-emergent NS3 RAVs, all had RAVs that cause a >5 fold decrease in GZR potency in vitro, including Y56H and D168A/G/V. Of these 6 subjects, 3 had baseline RAVs that were also detected at failure, in addition to the treatment-emergent RAVs. No virologic failure subject had baseline RAVs that were not also detected at failure. There was only one GT1b virologic failure in the RAP (1/130; 0.8%), and treatment emergent NS3 RAVs were not detected in this subject, who failed due to relapse. There were no GT4 virologic failures. The two GT6 subjects who failed therapy by relapse were non-cirrhotic and were found to have treatment emergent RAVs at amino acid positions 56 (56H) and 168 (168E, 168Y) NS5A RAVs.

Among the 10 GT1a infected subjects who experienced virologic failure, 9 (90%) had treatment-emergent NS5A RAVs at failure. Seven of the 9 subjects with treatment-emergent RAVs also had baseline RAVs that cause a >5 fold decrease in EBR potency in vitro; in all 7 subjects, the baseline RAVs were also detected at failure along with one additional treatment emergent RAV In the single GT1b infected subject who experienced virologic failure, a treatment-emergent NS5A RAV was detected at failure. All treatment-emergent RAVs detected among GT1 infected subjects who failed to achieve SVR cause a >5 fold decrease in EBR potency in vitro (M28A/G, Q30R, L31M/V, Y93H/N). Only two GT6 subjects could be assessed in this RAP analysis and 1 subject was found to have a 31M variant in NS5A this non-cirrhotic failed with relapse.

Treatment with GZR/EBR had a positive, but small, impact on subjects' general (SF-36), and disease-specific (EQ-VAS) HRQOL, fatigue levels, impairment while working (presenteeism) and activity impairment due to Hepatitis C during treatment and/or the follow-up period. In the placebo group, there was a mean decline in general HRQOL, but a mean improvement in disease-related HRQOL. Among employed subjects in both the GZR/EBR and placebo groups, Absenteeism (% work time missed due to Hepatitis C) increased over the study period. The Absenteeism findings were inconsistent with subjects' improvement in HRQOL, fatigue levels, and impairment while working and during usual activities. Increasing reports of absenteeism may be due to the subjects' participation in the clinical trial. Across the different PROs, the mean change from baseline in PRO scores during treatment and follow-up did not appreciably differ between GZR/EBR and placebo. The impact of achieving SVR on PROs was not assessed due to the small number of non-responders in this study.

### 7.1.2. Study P052 (C-SURFER)

#### *7.1.2.1. Study design, objectives, locations and dates*

P052 (C-SURFER) was a Phase II/III randomised, placebo-controlled, parallel group, multicentre study to evaluate the efficacy and safety of the combination regimen of grazoprevir and elbasvir in HCV Genotype 1 (GT1)-infected subjects with Chronic Kidney Disease (CKD) Stages 4 or 5 ± cirrhosis. This study was to enrol approximately 220 subjects, of which a minimum of 20% were to be non-haemodialysis-dependent. Eligible subjects included those who were HCV treatment-naïve, those who were intolerant to interferon (IFN), and those who relapsed or had a null response or partial response to a prior IFN-based treatment regimen Subjects received either GZR 100 mg plus EBR 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing

completed (immediate treatment group) or 12 weeks of placebo (to GZR/EBR) followed by unblinding (after a 4 week unblinding period) and then 12 weeks treatment with GZR 100 mg plus EBR 50 mg QD and 24 weeks of follow-up after dosing was completed (deferred treatment group). In addition, 10 subjects (5 on haemodialysis and 5 non-dialysis CKD) were assigned to receive open-label GZR 100 mg plus EBR 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed (Intensive PK arm).

The primary objectives were to evaluate the efficacy of GZR + EBR in HCV GT1 subjects with CKD within the immediate treatment and the intensive PK groups and to evaluate the safety and tolerability of GZR in combination with EBR in the immediate treatment group relative to the placebo treatment of the deferred treatment group. The secondary objectives were to evaluate the efficacy of GZR + EBR in terms of SV24, SVR12, SVR4 and also to evaluate safety and tolerability GZR in combination with EBR for all treatment arms including emergence of viral resistance-associated variants (RAVs) resistant to GZR and EBR when administered as part of a combination regimen.

This study was initiated on 18 March 2014 and still ongoing with data cut-off till 6 March 2015. It was conducted at (79) study centres: USA (48); Argentina (1); Australia (2); Canada (5); Estonia (2); France (4), Israel (5); Korea (2); Lithuania (3); Netherlands (2); Spain (3); Sweden (2).

#### *7.1.2.2. Inclusion and exclusion criteria*

The main inclusion criteria were:

- Age >18 years;
- have documented chronic (at least 6 months) HCV GT1 infection (with no evidence of non-type able or mixed genotypes);
- Positive for anti-HCV antibody, HCV RNA, or an HCV genotype and HCV RNA (≥ 10,000 IU/mL in peripheral blood);
- subjects with or without cirrhosis (liver staging assessments similar to those discussed in above);
- have one of the following HCV treatment status: (1) Treatment naïve: Naive to all anti-HCV treatment, (2) Prior IFN or PEG-IFN + Ribavirin Treatment failures: Null responders, Partial responders, Relapsers, (3) P/R Intolerant: Subjects were intolerant to a prior IFN or Peg-IFN ± ribavirin regimen. Subjects discontinued treatment prematurely and were therefore unable to complete a full course of therapy because of drug-related toxicity.
- have Chronic Kidney Disease defined as: Subjects with GFR ≤ 29 who are non-dialysis dependent (NDD) or have been on haemodialysis (HD) for at least 3 months (including subjects awaiting kidney transplant and subjects with failed kidney transplants no longer on immunosuppressant therapy).
- adequate birth control to be practiced by patients of reproductive potential and all subjects should be able to provide written informed consent.

The exclusion criteria were similar to those described for Study P060. The only additional exclusion criteria specific to this study was that patient on peritoneal dialysis and patients with high likelihood of receiving a renal transplant during the study treatment period (up to 24 weeks from Day 1) were excluded.

**Comments**: The study inclusion/exclusion criteria reflected the target patient population of HCV infected patients with CKD (80% on haemodialysis and <20% were not dialysis dependent) most likely to benefit from clearance of HCV infection especially due to high morbidity associated with the pegylated interferon and ribavirin based therapy.

#### *7.1.2.3. Study treatments*

Subjects were randomised to the following treatment arms:

1. GZR 100 mg QD + EBR 50 mg QD for 12 weeks and 24 weeks of post-treatment follow-up. (Immediate).
2. Placebo QD for 12 weeks, plus 4 weeks unblinding period, then open-label treatment of GZR 100 mg QD / EBR 50 mg QD for 12 weeks plus and 24 weeks of post treatment follow-up (Deferred).
3. GZR 100 mg QD + EBR 50 mg QD for 12 weeks and 24 weeks of post-treatment follow-up (Intensive PK).

Subjects were instructed to take GZR and EBR together at bedtime. Phosphate binders were to be taken at least 3 hours before or at least 3 hours after taking the investigational study medications. For the TW 12 and 28 (for deferred treatment arm) visits, all subjects withheld their last evening dose of study medications. Subjects had a predose PK sample taken the next morning at their study visit, then subjects took their study medications and had a 2 hour post dose sample taken. If a subject missed a dose of GZR and/or EBR and it was less than 8 hours before the next dose, the missed dose was to be skipped and the normal dosing schedule resumed. Subjects were instructed not to double the next dose in order to compensate for what had been missed.

#### *7.1.2.4. Efficacy variables and outcomes*

The primary efficacy endpoint was SVR12 in the combined population of the ITG and the intensive PK group. Subjects had HCV RNA < 15 IU/mL, either target detected but unquantifiable (TD[u]) or target not detected (TND).

The secondary efficacy endpoints were: (1) The SVR4 and SVR24 rates of the subjects within the immediate treatment and the intensive PK arms (2) The SVR4, SVR12, and SVR24 rates in the deferred treatment arm following the end of all active study therapy, (3) The SVR4, SVR12, and SVR24 rates following the end of all active study therapy for all treatment arms combined. (4) The emergence of viral resistance to GZR and EBR when administered as a combination regimen. (5) Proportion of patients achieving Target Not Detected (TND), Target Detected, unquantifiable [TD(u)], and Target Detected, quantifiable [TD(q)] at End Of Treatment (EOT).

The exploratory endpoints were: level of biomarkers (for example, proteins and metabolite production), that may be predictive of tolerability of study drugs and virologic response to GZR in combination with EBR; Change from baseline in health-related quality of life for each of the SF-36v2 (8 health domain scores, PCS and MCS); Change from baseline in serum cryoglobulin level, rheumatoid factor, and C4 Complement in subjects with cryoglobulinemia.

**Comments:** At the time of this report, subjects in the immediate treatment and intensive PK arms had reached the follow-up Week 12 (FW12) visit, but not the FW24 visit. Subjects in the deferred treatment arm are undergoing therapy and most, but not all, subjects have achieved the Follow-up Week 4 (FW4) visit. The CSR mentions that the following results will be summarised in a later report: SVR24 for the immediate treatment group SVR4, SVR12 and SVR24 for the deferred treatment arm, and for the combined population of the immediate treatment group, the deferred treatment group, and the intensive PK group. Biomarkers for safety signals and impact of HCV treatment on cryoglobulinemia will also be summarised in a later report.

#### *7.1.2.5. Randomisation and blinding methods*

Initially subjects were randomised to the Immediate or Deferred treatment groups. Subjects were stratified at baseline by diabetes status (yes/no) and haemodialysis status (HD/non-HD). Later, the intensive PK arm was to enrol 10 subjects: 5 on haemodialysis (HD) and 5 not on

haemodialysis (non-HD). The investigators and subjects were blinded to the assigned treatment regimen in the randomised arms from randomisation through Week 16.

#### *7.1.2.6. Analysis populations*

The primary analysis population was the Modified Full Analysis Set (mFAS). The mFAS population is a subset of the Full Analysis Set (FAS)[22] population in the immediate treatment and the intensive PK arms and includes all subjects who were enrolled and received at least 1 dose of GZR + EBR. It excludes subjects with missing HCV RNA results due to premature study discontinuation unrelated to study medication or progression of liver disease. Supportive analyses that used the immediate treatment and intensive PK arms of the FAS and Per Protocol (PP)[23] populations were also performed for the primary efficacy endpoint (SVR12). The Resistance Analysis Population (RAP) includes all subjects who (1) have baseline sequencing data available and (2) who either achieved SVR12 or met criteria for virologic failure. The RAP does not include any subject for whom baseline sequencing data was not available or any subject who discontinued the study for reasons other than virologic failure. For subjects who met a virologic failure criterion, RAVs were assessed for any subject who had detectable virus above 1000 IU/mL.

*mFAS population:* Overall, 6 subjects discontinued the study prematurely due to reasons unrelated to their responses to study medication or progression of their liver disease and were excluded from the mFAS population after their discontinuation visit or last visit on record.

*PP population:* In addition to the 6 subjects excluded from the mFAS population subsequent to their premature study discontinuation, one more subject (ITG) who discontinued study medication due to a kidney transplant at TW4 was also excluded from the PP population after the TW4 visit. Although the subject discontinued the study medication early, the subject did not discontinue participation in the study and was in follow-up throughout the study. Therefore the subject was included in the mFAS population but not the PP population. The subject was TND at the TW4, FW4 and FW12 visits.

#### *7.1.2.7. Sample size*

This study was to allocate 105 subjects into the immediate treatment arm and 105 subjects into the deferred treatment group. In addition, 10 subjects were to be enrolled as an intensive PK cohort. The primary hypothesis was to be evaluated within the subjects of the immediate treatment and the intensive PK arms (n=115). It would have at least 95% power to demonstrate that the SVR12 rate of GZR + EBR was higher than the reference SVR12 rate of 45% at an overall one-sided 0.025 α-level, if the true SVR12 rate of GZR + EBR is about 65%. The power and sample size were based on the assumption that approximately 10% of the randomised subjects would have a missing SVR12 rate due to death or early discontinuation from study with reasons unrelated to their responses to the HCV treatment and would be excluded from the mFAS population (that is, assuming the mFAS population size of 103 subjects). The calculation is based on SAS PROC POWER based on a z-test using the normal approximation to the binomial distribution. Table 7 summarises such power calculations for the primary efficacy analysis under various assumptions about the true SVR12 rate of GZR + EBR.

[22] The FAS population for efficacy analysis includes subjects randomised to the immediate treatment arm or assigned to the intensive PK arm who received at least one dose of study treatment.
[23] The PP population is a subset of the mFAS population and excluded subjects due to important deviations from the protocol that could have substantially affected the results of the primary and key secondary efficacy endpoints.

**Table 7: Power calculations for the primary hypothesis test based on subjects in the combined immediate treatment and intensive PK arms**

| True $SVR_{12}$ rate | Power to reject $H_0$ |
|---|---|
| 60% | 86% |
| 62% | 93% |
| 65% | 98% |
| 70% | >99% |

#### *7.1.2.8. Statistical methods*

The hypothesis was that the proportion of HCV GT1 infected CKD 4-5 subjects achieving SVR (defined as HCV RNA <LLoQ (either TD(u) or TND) 12 weeks after the end of all study therapy will be superior to 45% in the immediate treatment and Intensive PK groups (LLoQ is defined as <15 IU/mL). The choice of a reference SVR of 45% for this study was based on the following:

1. IFN mono-therapy is recommended in the KDIGO guidelines for HCV-infected subjects with CKD Stages 3-5 who are on or not yet on maintenance dialysis therapy (Gordon, 2008). The meta-analyses, conducted by Fabrizi et al (2007) produced a summary SVR24 of 39% (CI 32%-46%).
2. Given the substantial variation in the proportion of subjects with GT1 across the studies (ranging from 0 to 1) in the Fabrizi meta-analyses, a Bayesian logistic regression model for SVR was used to account for the variation in the proportion of subjects with GT1. Twenty studies with GT1 proportion were identified from the Fabrizi paper and included in the re-analysis conducted by Merck. Non-informative priors were used for the Bayesian random-effect model containing a random intercept and a fixed-effect of GT1 proportion. The model predicts that, if the studies had enrolled 100% GT1, the posterior probability/confidence that the true overall population mean for SVR rate would have been at most 45% is about 0.90.
3. A SVR of approximately 40% was observed in a large study of peg-IFN/RBV in 3,070 HCV GT1 subjects without CKD conducted in the United States (McHutchinson JG, 2009). The SVR response of subjects with CKD 4/5 was not expected to be higher than that of the general HCV population without CKD.

**Comment**: The hypothesis and the choice of a reference SVR of 45% for this study were justified.

As there was only a single primary efficacy hypothesis conducted at the one-sided $\alpha$=0.025 level, no multiplicity adjustment was needed for the primary efficacy analysis. The secondary efficacy objectives were estimation objectives, and were supportive in nature and had no associated hypotheses. Therefore, no multiplicity adjustment was necessary for the secondary efficacy analyses. There was no multiplicity adjustments applied to the safety summaries or PRO variables.

#### *7.1.2.9. Participant flow*

Overall, 91 of 328 subjects screened for inclusion in the study were not randomised, including 88 subjects (97%) who were screening failures. A total of 237 subjects were assigned or randomised to treatment (11, 112, and 114 in the intensive PK, immediate treatment and deferred treatment arms, respectively) at 68 sites worldwide of which 235 subjects received at least one dose of study therapy. Similar percentages of subjects in each treatment arm completed 12 weeks of treatment, (100%, 96% and 95%, respectively). Five subjects in the immediate treatment arm discontinued treatment early due to death, kidney transplant, lost to follow-up, non-compliance and withdrawal for other reasons (n=1 in each category). In the

deferred treatment arm, 6 subjects discontinued treatment early due to AE (n=5) and 1 was lost to follow-up. Eleven (11) out of 11 and 105 out of 111 completed FW 12 in the Intensive PK and Immediate treatment arms, respectively (Table 8).

**Table 8: Disposition of subjects; All subjects randomised/enrolled**

| | Intensive PK arm: GZR 100mg + EBR 50mg for 12 Weeks<br>n (%) | Immediate treatment arm: GZR 100mg + EBR 50mg for 12 Weeks<br>n (%) | Deferred treatment arm: GZR Placebo + EBR Placebo for 12 Weeks<br>n (%) | Total<br>n (%) |
|---|---|---|---|---|
| Not randomized/enrolled | | | | 91 |
| Subjects randomized/enrolled | 11 | 112 | 114 | 237 |
| **Status for Trial** | | | | |
| Completed Study[†] | 9 (81.8) | 40 (35.7) | 2 (1.8) | 51 (21.5) |
| Completed Follow-up Week 12 Visit and Still in Follow-up | 2 (18.2) | 65 (58.0) | 12 (10.5) | 79 (33.3) |
| Did Not Yet Reach Follow-up Week 12 Visit | 0 (0.0) | 0 (0.0) | 89 (78.1) | 89 (37.6) |
| Discontinued | 0 (0.0) | 7 (6.3) | 11 (9.6) | 18 (7.6) |
| Adverse Event | 0 (0.0) | 0 (0.0) | 4 (3.5) | 4 (1.7) |
| Death | 0 (0.0) | 1 (0.9) | 4 (3.5) | 5 (2.1) |
| Lost To Follow-Up | 0 (0.0) | 2 (1.8) | 1 (0.9) | 3 (1.3) |
| Non-Compliance With Study Drug | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Physician Decision | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Screen Failure | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Withdrawal By Subject | 0 (0.0) | 1 (0.9) | 2 (1.8) | 3 (1.3) |
| **Subject Study Medication Disposition for Initial Treatment Period** | | | | |
| Started | 11 | 111 | 113 | 235 |
| Completed | 11 (100.0) | 106 (95.5) | 107 (94.7) | 224 (95.3) |
| Discontinued | 0 (0.0) | 5 (4.5) | 6 (5.3) | 11 (4.7) |
| Adverse Event | 0 (0.0) | 0 (0.0) | 5 (4.4) | 5 (2.1) |
| Death | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Kidney Transplant | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Lost To Follow-Up | 0 (0.0) | 1 (0.9) | 1 (0.9) | 2 (0.9) |
| Non-Compliance With Study Drug | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |
| Withdrawal By Subject | 0 (0.0) | 1 (0.9) | 0 (0.0) | 1 (0.4) |

[†]Completed study means the subject completed the Follow-up Week 24 visit

#### *7.1.2.10. Major protocol violations/deviations*

Overall, 7 subjects were excluded from the PP population due to major protocol deviations, 6 subjects excluded from mFAS due to reasons unrelated to liver disease or study medication and another subject discontinued study medication due to kidney transplant.

#### *7.1.2.11. Baseline data*

A majority of subjects were male (73.2%) either White (46.4%) or African American (46%) and had the non-CC *IL28B* genotype (72.8%). The median age was 57 years (range: 28 to 80). At baseline, about half the subjects had GT1a and a similar proportion had plasma HCV-RNA above 800,000 IU/mL. Plasma HCV-RNA ranged from about 10,000 to over 10 million IU/mL. Overall, 14 (6.0%) of subjects had cirrhosis. The majority of subjects were treatment-naïve (80.4%) and were on haemodialysis (76.2%).; 81.3% of subjects were CKD Stage 5 and 19.1% had prior renal transplant failures. There was a higher percentage of prior renal transplant failures in the deferred treatment arm (24.8%) compared with the immediate treatment arm (13.5%). Hypertension (39.1%) and Type 2 Diabetes Mellitis (19.6%) were the 2 most commonly reported underlying aetiologies for renal disease. Baseline renal laboratory assessments were generally similar across treatment arms. The mean eGFR was 11.2 (range 3 to 43), BUN was 42.6 (range 12 to 97), and creatinine was 6.9 (range 1.4 to 16.6); 118 subjects (50.2%) were missing baseline urine protein and 100 subjects (42.6%) had urine protein of 2+ and higher at

baseline. Baseline laboratory assessments (ALP, ALT, AST, total bilirubin, Hg, serum albumin, and platelet count) were generally similar across treatment arms.

The conditions that were most often reported in medical histories were hypertension (86.0%), diabetes mellitus (29.7%) and anaemia[24] (28.9%). There were no clinically meaningful differences among treatment groups. All of the 235 treated subjects had used prior non-HCV therapies and the most common prior medications were vitamins (63.8%), beta blocking agents (52.8%), calcium channel blockers (51.9%), analgesics (50.6%), drugs for acid related disorders (48.5%), other therapeutic products (including herbal supplements) (49.8%), anti-anaemic preparations (37.4%), agents acting on the renin-angiotensin system (36.2%), calcium homeostatis (32.8%), drugs used in diabetes (30.6%), and lipid modifying agents (30.6%). There were no clinically meaningful differences among treatment groups in the use of prior therapies, except that a higher percentage of subjects in the deferred treatment arm used vitamins, anti-anaemic preparations, and lipid modifying agents (70.8%, 44.2% and 40.7%) compared to the immediate treatment arm (55.9%, 28.8% and 21.6%). Overall, use of analgesics increased during treatment compared to prior to starting study treatment (60.4% versus 50.6%). Use of anti-hypertensives increased slightly during treatment from 29.4% to 33.2% whereas use of lipid modifying agents decreased slightly from 30.6% to 24.3% There were no clinically meaningful differences among treatment groups in the use of concomitant medications during the treatment period, except that similar to prior medications used, there was a higher percentage of subjects in the deferred treatment arm who used vitamins, anti-anaemic preparations and lipid modifying agents. Reported compliance with GZR + EBR treatment was high (mean 99.1, range 78.6 to 100%), and rates were similar across all treatment groups.

#### *7.1.2.12. Results for the primary efficacy outcome*

Overall, 115 of the 116 subjects in the mFAS population of the combined immediate treatment and intensive PK arms achieved SVR12. The observed SVR12 rate was 99.1% (95% CI: 95.3, 100.0) and the two-sided one-sample exact test established the superiority of GZR 100 mg + EBR 50 mg administered for 12 weeks with respect to %SVR12 to the historical response rate of 45% (P-value <0.001). Across genotype 1 subtypes, SVR12 was achieved in 99.1% (115/116) of study subjects. Efficacy was comparable for GT1a and GT1b infected subgroups. The single subject who failed to achieve SVR12 due to virologic failure was a haemodialysis-dependent, non-cirrhotic, White, GT1b infected 59-year-old man who had previously failed to achieve SVR following a prior regimen of IFN-based treatment. His viral load was $7.27\times10^6$ at baseline. The subject first achieved TND after 20 days of study medication, completed 12 weeks treatment with 99% compliance and remained TND through FW4. He relapsed at the FW 12 visit. These results were consistent in the FAS and the PP analysis.

No meaningful differences in the proportions of subjects who achieved SVR12 were observed within the subgroups of gender, age, race, ethnicity, *IL28B*-genotype, dialysis, baseline HCV RNA, genotype, dialysis status, diabetes status and CKD Stage due to the high overall response rate (only 1 virologic failure), The proportions of cirrhotic and non-cirrhotic subjects who achieved SVR12 were comparable, although this finding should be interpreted with caution due to the small size of the cirrhotic subgroup (n=6). Higher proportion of treatment naïve subjects achieved SVR12 compared with treatment experienced subjects, although confidence intervals overlapped and the difference was a function of a single virologic failure.

#### *7.1.2.13. Results for other efficacy outcomes*

*Secondary endpoints*

Subjects had a rapid response to treatment with GZR 100 mg + EBR 50 mg. Among the 121 subjects in the mFAS population for the combined immediate and PK intensive arms at the TW4

[24] Including terms anaemia, macrocytic anaemia, anaemia of chronic disease, iron deficiency anaemia, nephrogenic anaemia

visit, 94 subjects (77.7%) achieved undetectable HCV-RNA levels and 109 subjects (90.1%) achieved HCV RNA < LLoQ (that is, <15 IU/ml). At the TW12 visit, 100% of the subjects achieved TND; 99.2% of the subjects remained TND at FW4 visit with only one subject TD(u) at that time. This subject was TND at FW12. Among subjects who have reached FW 24 time-point, 2 subjects[25] experienced relapse.

*Antiviral resistance to grazoprevir and elbasvir*

The presence of baseline NS3 RAVs had no impact on SVR12 for either GT1a or GT1b subjects; SVR12 was achieved in 100% (36/36) of subjects with baseline RAVs and in 98.6% (75/76) of subjects without baseline RAVs. The presence of baseline NS5A RAVs had no impact on SVR12 for either GT1a or GT1b subjects. SVR12 was achieved in 16/17 (94.1%) of subjects compared with 98/98 (100%) of subjects without baseline NS5A RAVs. Due to the high SVR rate in this trial (only 1 GT1b subject failed, with presence of NS5A RAVs at baseline causing a >5 fold decrease in EBR potency) it is not possible to draw conclusions about the impact of RAVs in GT1a relative to GT1b in this trial.

#### *7.1.2.14. Patient-reported outcome: health-related quality of life*

Subjects completed the HRQOL questionnaire, SF-36v2®, at baseline (Day 1) and TW12 for both the immediate and deferred treatment arms. Subjects in the ITG also completed the SF- 36v2® at FW12. Treatment with GZR + EBR (ITG) had a small, mostly positive, impact on HRQOL. In contrast, treatment with placebo (DTG) had a small negative impact on HRQOL. However, the mean changes from baseline in SF-36 scores during treatment did not differ between the GZR + EBR (ITG) and placebo (DTG) groups.

## 7.2. Other efficacy studies

### 7.2.1. Study P061

This was a Phase III, open-label, multi-centre, single-arm study in treatment-naïve cirrhotic and non-cirrhotic adult subjects with chronic Hepatitis C (HCV) genotype (GT) 1, 4, or 6 infection co-infected with HIV. All subjects received a fixed-dose combination regimen of GZR/EBR 100 mg/50 mg QD for 12 weeks with 24 weeks of follow-up once dosing had been completed.

The study was conducted from 11 June 2014 and is ongoing (with database lock at 2 March 2015). It was conducted at 37 centres; 18 USA; 2 in Australia; 2 in Canada; 3 in Denmark; 3 in France; 3 in Germany; 3 in Israel; 3 in Spain and 2 in UK. The main inclusion and exclusion criteria were summarised and were representative of a patient population co-infected with HIV and HCV. The primary efficacy endpoint was SVR12; secondary endpoint was SVR24[26] and exploratory endpoints included proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA<LLOQ at Week 2, 4 and 12 and proportion of subjects achieving SVR4; change in HRQOL scores from baseline (included SF-36v2, EQ-5D, FACIT, WPAI; emergence of viral resistance and proportion of subjects who develop HIV-1 virologic failure. The hypothesis for

[25] (1) A [information redacted] treatment-naïve, non-cirrhotic, white male with GT1a infection who has been on haemodialysis since 2012. At the Day 1 visit, the subject's viral load was 2,272,577 IU/mL. At TW 3, the HCV RNA was TND and remained TND at each subsequent visit until the FW 24 visit, when HCV RNA was reported as 1,050,609 IU/mL. Repeat viral load testing confirmed virologic relapse with HCV RNA 621,410 IU/mL. At baseline, he had WT NS3 virus and NS5A L31L/M, M28M/V, and Q30Q/R RAVs; at failure NS5A Q30R, L31M were detected. (2) A 60 year old treatment-naïve, non-cirrhotic, Black or African American female with GT1a infection who has been on haemodialysis since 2012. At the Day 1 visit, the subject's viral load was 1,104,634 IU/mL. At TW 2, the HCV RNA was TND and remained TND at each subsequent visit until the FW 24 visit, when HCV RNA was reported as 742,048 IU/mL. At baseline, she had NS3 Q80K RAV and NS5A L31M; post-baseline sequencing has not been completed yet.

[26] SVR24 has not been reached by any subject; therefore these data are not included in this CSR but will be provided in a future report.

this study was that the proportion of subjects receiving GZR in combination with EBR achieving SVR12 will be superior to 70%. Assuming a true SVR12 of 85%, this study had >99.9% power to demonstrate that the true rate is >70%; however, if the true SVR12 is 80%, the study had 93.1% power to demonstrate that the true rate is >70%.

All subjects received at least one dose of study medication and 217 completed treatment period. There were 54 major protocol violations (majority related to informed consent), but only 4 of these led to exclusion from the Per Protocol analysis. Majority of subjects were male (83.9%), Caucasian (76.6%), had HCV genotype 1a (66.1%) had non-CC IL28B genotype (64.7%) and had mild moderate liver fibrosis (Metavir score F0 to F2 in 73.4%) and were on ART with an NRTI (21.6% on an abacavir-containing regimen, and 73.4% on a tenofovir-containing regimen). The third agent in the antiretroviral regimen included raltegravir (51.8%), dolutegravir (27.1%) and rilpivirine (17.4%). Median age was 49 years (range: 21-71 years); 91 subjects 41.7%) had HCV RNA (IU/mL) of ≤ 800,000; 135 subjects (61.9%) had HCV RNA ≤ 2,000,000 IU/ml and 214 (98.2%) had HCV RNA ≤ 10,000,000. Reported compliance with GZR/EBR treatment was high, with 99.5% of patients reporting >90% treatment compliance over 12 weeks.

Overall, 95% (207/218) of the subjects achieved SVR12 with a 95% confidence interval (CI) of (91.2, 97.5) and the primary efficacy hypothesis was met and a conclusion that the true SVR12 is >70% was supported as the one-sided p-value was of <0.001. The overall efficacy in the PP population (96.7%; 95% CI: 93.4, 98.7) was slightly higher than that seen in the FAS population. Of the 11 subjects that did not achieve SVR12: 7 met criteria for virologic failure; 1 discontinued due to prohibited concomitant medication; 3 subjects were categorised as 'Other' and were missing HCV RNA data[27] at the SVR12 time-point. All 7 subjects that met virologic failure criteria were categorised as relapses. Of the relapses, 5 subjects were GT1a, 1 GT1b and 1 GT4; all relapsers were non-cirrhotic. Subgroup analysis of the primary efficacy endpoint (SVR12) showed that age, gender, race, HCV genotype, IL28BB genotype and baseline HCV RNA levels did not have any relevant effect on efficacy of GZR+EBV treatment regimen. However, the proportion of cirrhotic subjects who achieved SVR12 (35/35 subjects, or 100%) was slightly higher than that observed in subjects without cirrhosis (172/183 subjects, or 94%). Out of the 218 treatment naïve subjects, 11 subjects were classified as interferon ineligible and 13 subjects specified they were interferon unwilling in the study. All 24 of these subjects achieved SVR12. There were no meaningful differences in SVR12 when comparing subjects who were taking an abacavir containing regimen for HIV infection to subjects who were taking a tenofovir containing regimen. Similarly, SVR12 rates were comparable regardless of whether the third agent in the subjects' regimen was raltegravir, dolutegravir or rilpivirine.

Of the 218 subjects in the FAS population, 207 subjects (95%) achieved HCV RNA <LLoQ by TW4. All but 1 subject achieved HCV <LLoQ at TW12; this subject discontinued at TW2 due to a protocol deviation. Although the prevalence of baseline NS3 RAVs was high (44%), there was no clear association between virologic failure and the presence of baseline RAVs, including the Q80K variant, which has been associated with failure to simeprevir. The prevalence of baseline NS5A RAVs was 15/183 (8%) and subjects with baseline NS5A RAVs had a lower SVR12 than those who did not (13/15 or 86.7% versus 164/168 or 97.6%, respectively). This effect was observed solely in GT1a infected subjects, in which subjects with baseline NS5A RAVs had a lower SVR12 (80%, or 8/10 subjects) compared to GT1a infected subjects without baseline NS5A RAVs (97.7% or 127/130 subjects). Treatment with GZR/EBR had a positive, but small, impact on the subjects' general and disease-specific HRQOL, fatigue levels, and activity impairment due to Hepatitis C during treatment and/or the follow-up period.

[27] 1 subject lost-to-follow-up (last visit at FW4 on 28-Oct-14 with HCV RNA TND); - 1 subject lost to follow-up (last visit at FW4 on 28-Nov-14 with HCV RNA TND); - 1 subject's Follow-up Week 12 visit occurred too early per the protocol-specified visit windows; per protocol the FW12 visit must be between 70 and 146 days after Day1. This subject's last visit was 65 days after Day1 on 22-Dec-14 with HCV RNA TND

**Comments**: Overall, results from this Phase III, open-label, uncontrolled study demonstrated the efficacy of proposed FDC of GZR/EBR 100 mg/50 mg once daily in HIV co-infected, HCV GT1 or GT4 infected subjects ± cirrhosis with very high SVR12 rates (95% in the FAS primary analysis and 96.7% in the PP analysis).

### 7.2.2. Study P068

This is an ongoing, Phase III, randomised, parallel-group, multicentre, open label trial of GZR/ EBR 100/50 mg fixed-dose combination (FDC) tablets administered once daily with or without RBV for 12 or 16 weeks to 420 subjects with hepatitis C virus genotype (GT) 1, 4, or 6 infection, with and without compensated cirrhosis, who failed prior treatment with pegylated interferon and RBV. Subjects were to be randomised in a 1:1:1:1 ratio to receive 12 weeks of treatment with GZR/EBR QD, 12 weeks of treatment with GZR/EBR QD + RBV, 16 weeks of treatment with GZR/EBR QD, or 16 weeks of treatment with GZR/EBR QD + RBV. Randomisation was stratified by the presence or absence of cirrhosis and by prior PR treatment response (relapser, partial responder or null responder). The investigators and subjects were to be blinded to the assigned treatment duration during the period from randomisation through Treatment Week 12 (TW12). After dosing was completed, subjects were to be followed for 24 weeks.

The study was conducted from 11 June 2014 to 13 March 2015 at 65 study centres in Australia (3), Canada (5), Demark (2), Finland (1), France (3), Israel (5), Korean (3), Malaysia (3), Netherlands (3), New Zealand (3), Poland (3), Puerto Rico (2), Spain (3), Taiwan (1) and USA (25). It is important to note that the CSR provided in the submitted dossier only summarises the study's primary efficacy and safety results from enrolment through 12 weeks following the end of therapy.

The study included adult (aged >18 years) patients with HCV GT1, GT4 and GT6 subjects although majority of subjects were GT1 infected to reflect fact that GT1 is the predominant genotype world-wide. Subjects with and without compensated cirrhosis were included in the study. Furthermore, subjects who were relapsers, partial responders and null responders to prior PR treatment were all enrolled in the study. However, the percentage of subject who were prior treatment relapsers was limited to 20% to allow for a sufficient evaluation of efficacy across categories of PR failure (actual relapser enrolment for this study is 36%).

The primary endpoint was SVR12 (HCV RNA <LLOQ either TD(u) or TND at 12 weeks after end of therapy). The secondary endpoint was SVR24 but this will be reported in a later SCR with final results of the study as many subjects have not yet reached the Week 24 follow-up visit. Exploratory endpoints included the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA<LLOQ at Week 2, 4 and 12 and proportion of subjects achieving SVR4; Longitudinal HRQOL scores and change in HRQOL scores from baseline HRQOL scores; emergence of viral resistance. In HIV-co-infected patients only proportion of patients who develop HIV-1 virologic failure and changes in CD4+ T-cell counts from baseline were also evaluated. The hypothesis was that in at least one of the arms, the proportion of subjects receiving GZR in combination with EBR (+/- RBV) achieving SVR12 will be superior to 58%. The historical reference rate of 58% was derived from a Phase IIb registration trial of simeprevir (100 mg or 150 mg once daily) for 12, 24, or 48 weeks in combination with PR for 48 weeks in treatment-experienced subjects. Adjustments were made for the expected proportion of subjects that are null and partial responders in this trial and an expected improved safety profile related to an IFN-free regimen. The approximate response rate from the Phase IIb simeprevir treatment experienced study is 70%; however, in the simeprevir study, 40% of the patients were prior relapsers while the percentage of relapsers was limited to 20% in this protocol. The SVR rate for simeprevir was 70% in prior partial responders and 45% in prior null responders who accounted for 35% and 25% of patients enrolled, respectively. Assuming 40% prior null responders and 40% prior partial responders in this protocol, the estimated response is adjusted to 63%. A 5% decrease is applied to this response rate because of an expected improved safety profile related to an IFN-free regimen.

**Comments**: It is important to note that although the proportion of relapsers was supposed to be limited to 20%, the actual enrolment of relapsers was 36%.

A total of 420 subjects were randomised to treatment with GZR/EBR +/- RBV and 408 subjects (97.1%) completed study therapy. The overall trial discontinuation rate was low. AEs were the most common reason for study medication discontinuation. There were 90 major protocol violations (67 related to informed consent, 10 to study entry criteria, 8 to safety assessments, 3 to study drug administration and 2 were related to prohibited medications). Overall, only 12 subjects were excluded from the PP analysis due to major protocol violations.

Majority of the subjects in the study were White (68.1%) and male (64.5%) with median age of 56 (range from 19 to 77 years). Most subjects were infected with HCV GT1; 54.0% had HCV GT1a and 35.0% had GT1b. However, the 16 week RBV-free treatment arm had a somewhat lower proportion of GT1a infected subjects and a somewhat higher proportion of GT1b infected (46%) subjects relative to the other treatment arms (28-36%). The majority of subjects had plasma HCV-RNA above 800,000 IU/mL (75.2%), and a small proportion (4.3%) had plasma HCV-RNA above 10 million IU/mL. As expected in a prior PR-treatment failure population, the majority of subjects had a non- CC IL28B genotype (79.0%). Compared with the other treatment arms, however, the 16 week RBV-free treatment arm had a slightly higher proportion of subjects with IL28B CC. Overall, 43.3% of subjects were null responders to prior treatment. The proportions of subjects in the various categories of prior treatment response were similar across treatment groups. The demographic and other baseline characteristics were generally similar across the treatment arms. All subjects (100%) in the RBV-free treatment arms took >90% of their prescribed study medication but only 84.6% and 73.6% of subjects took > 90% of their medication in the arms that received GZR/EBR with RBV for 12 and 16 weeks, respectively**.**

#### *7.2.2.1. Primary efficacy results*

The proportions of subjects who achieved SVR12 (in the FAS analysis) treated with GZR/EBR with or without RBV for 12 or 16 weeks (92.4%, 94.2%, 92.4%, and 97.2% of subjects achieved SVR12 in the 12 week GZR/EBR arm, 12 week GZR/EBR + RBV arm, 16 week GZR/EBR arm, and 16 week GZR/EBV + RBV arm, respectively) were statistically superior to the historical reference rate of 0.58 for each of the four treatment arms in the study ($p<0.001$). These results were confirmed in the PP analysis. Pooling across treatment durations, the difference in SVR12 rates between the subjects who received RBV and the subjects who did not was 3.3% (95% CI: -1.3%, 8.2%) suggesting that the addition of RBV to the treatment regimen does not substantially increase SVR12 rates.

**Comments**: Interpretation may have been confounded by fact that the 16 week RBV-free treatment arm had a somewhat higher proportion of GT1b infected (46%) subjects relative to the other treatment arms (28-34%); this is important as GT1b infected subjects have a better response rate to GZR/EBR compared to GT1a infected subjects.

However, the subjects who received RBV for the longer treatment duration of 16 weeks had numerically higher SVR12 rates than subjects who did not receive RBV. Pooling regimens with and without RBV for a given treatment duration, the difference in SVR12 rates between the subjects who received 16 weeks of treatment and the subjects who received 12 weeks of treatment was 1.5% (95% CI: -3.2%, 6.3%) suggesting that treatment duration did not appear to substantially increase SVR12 rates. However, as noted above, subjects who received 16 weeks of GZR/EBR in combination with RBV had numerically higher SVR12 rate than subjects in the other treatment arms. Overall, 25 subjects did not achieve SVR12 of which 19 subjects had virologic failure and 6 discontinued the study before FW12. Incidence of virologic failure was evenly distributed among the two 12 week treatment arms and the 16 week RBV-free treatment arm.

Relapse occurred most often by FW4 (in 9 subjects [56%]); 3 subjects (19%) relapsed between FW4 and FW8 and 4 subjects (25%) relapsed between FW8 and FW12. The timing of relapses was comparable across the 3 treatment arms with virologic failure. GT1a infected subjects comprised 75% (12/16) of the subjects with relapse in the study (yet they comprise only 54% of the overall study population), while GT1b infected subjects account for 12.5% (2/16) of relapsers (compared with 35% of the overall population), and GT4 infected subjects account for the remaining 12.5% (2/16) of relapsers (compared with 8.8% of the overall population). Among the 16 relapsers, 10 (63%) were null responders to prior IFN-based therapy, 4 (25%) were partial responders to prior therapy and 2 (13%) had relapsed after completing prior therapy Half of the subjects with relapse had cirrhosis, and nearly all of the relapsers with cirrhosis (7 of the 8) were null responders to prior therapy. Three subjects (18% of the subjects with virologic failure) experienced virologic breakthrough or rebound in the study.

#### *7.2.2.2. Subgroup analysis*

There was no consistent impact of gender, age (< versus ≥ 65 years), race or ethnicity on the virologic response rates among the treatment arms. The analysis of SVR12 rates by HCV genotype showed that subjects infected with HCV GT1a, GT4 and GT6 have lower response rates than subjects infected with HCV GT1b. Subjects with GT1b had observed SVR12 rates > 95% in all treatment arms. Subjects with GT4 and GT6 have the lowest response rates overall, but the results for these genotypes should be interpreted with caution because subjects with HCV GT4 and GT6 comprise only 8.8% and 1.4% of the randomised subjects, respectively. In the limited pool of GT4 subjects, the response rates tended to be higher in the treatment arms that received RBV. Most GT6 infected subjects (5/6) responded to treatment. SVR12 rates in subjects with IL28B CC were generally similar to those in subjects with IL28B non-CC genotype. There was no consistent trend toward higher response rates in subjects who received RBV or had longer treatment duration within the categories of IL28B genotype. The analyses of SVR12 rates in subjects with and without cirrhosis suggest that non-cirrhotic subjects (Metavir F0-F3) have response rates that are similar to subjects with cirrhosis (Metavir F4) overall. However, non-cirrhotic subjects tended to have better responses than cirrhotic subjects in the 12 week treatment arms. While RBV and treatment duration did not appear to consistently impact response rates for either cirrhotic or non-cirrhotic subjects, cirrhotic subjects in the 16 week treatment arm that received RBV had higher response rates than cirrhotic subjects in the other treatment arms.

#### *7.2.2.3. Other efficacy results*

By treatment Week 4, 64.5% of the study subjects had undetectable HCV RNA with similar proportions of subjects with undetectable HCV RNA by Week 4 across treatment regimens, between regimens with and without RBV and between regimens with 12 and 16 weeks of treatment durations. Nearly all subjects had HCV RNA TND or TD (u) at the end of treatment (98.6%), but 10 subjects (2.4%) relapsed or discontinued the study by FW4. In general, RBV does not seem to substantially accelerate the rate of clearance of HCV RNA.

None of the 21 HIV-1 co-infected subjects in the study experienced HIV virologic failure[28] while on treatment.

The presence of baseline RAVs with a > 5 fold decrease in potency to either GZR or EBR was assessed in order to determine the impact on SVR12. In GT1 infected subjects, the presence of baseline NS5A RAVs associated with a > 5 fold reduction in potency to EBR was noted in a small percentage of subjects (10.8%) and was associated with a reduced SVR12. Overall, 12 of the 14 GT1 infected subjects had baseline NS5A RAVs with a > 5 fold decrease in potency to EBR. The impact of baseline NS5A RAVs on SVR12 was greater in GT1a infected subjects than in GT1b

[28] HIV-1 virologic failure was defined as HIV-1 RNA ≥ 200 copies/mL, confirmed on two consecutive tests at least 2 weeks apart, in subjects compliant with their HIV antiretroviral therapy.

infected subjects**.** The presence of baseline NS3 RAVs did not impact SVR12. At the time of virologic failure (13 with sequence), treatment emergent NS5A or NS3 RAVs were noted in 11 and 9 GT1 infected subjects, respectively; 8 of these subjects had treatment-emergent RAVs to both NS5A and NS3. In GT4 subjects NS3 baseline RAVs had no impact on SVR12 as all 7/7 subjects with baseline NS3 RAVs achieved SVR12. The small numbers of subjects with baseline NS5A RAVs made it difficult to assess the impact of baseline RAVs on SVR12 in GT4 subjects. The small numbers of subjects as well as lack of sequence for the 1 subject who failed made it difficult to assess the impact of baseline RAVs on SVR12 in GT6 subjects.

Of the subjects for who sequence information was available, post-baseline NS3 and NS5A RAVs were not detected in 4 and 2 subjects, respectively, by population sequencing. Nine (9) out of 13 (69.2%) subjects had treatment-emergent NS3 RAVs and 11/13 (84.6%) had treatment-emergent NS5A RAVs based on population sequencing. 8/13 (61.5%) of subjects had both NS3 and NS5A RAVs at failure or follow-up visits; all 8 were GT1a infected subjects. No subjects were WT for both NS3 and NS5A at failure.

Treatment with GZR/EBR, for 12 or 16 weeks duration, had a positive, but small, impact on subjects' general and disease-specific HRQOL, fatigue levels, and work productivity and activity impairment due to Hepatitis C during treatment and/or the follow-up period. However, as expected, the addition of RBV to GZR/EBR did contribute to a worsening of HRQOL, fatigue levels, work productivity and activity impairment during treatment. Treatment differences were detected suggesting better HRQOL, less fatigue and less work productivity and activity impairment for GZR/EBR groups compared with the GZR/EBR + RBV groups during the treatment period. At FW12, HRQOL, fatigue and work productivity and activity impairment scores were near or better than the baseline scores. Treatment differences at FW12 were only detected in the 16 week treatment duration arms. GZR/EBR group had better overall physical health and less fatigue than the GZR/EBR + RBV group.

**Comment**: Results of this open-label Phase III study indicated that administration of a 12 week regimen of GZR/EBR 100/ 50 mg ±RBV is effective in treating chronic HCV GT 1, 4 and 6 infections among subjects who did not achieve SVR with prior PR treatment. Specifically, administration of a 12 week regimen of GZR/EBR 100/ 50 mg without RBV is highly effective in treating:

- chronic HCV GT1b infection among subjects who did not achieve SVR with prior PR treatment.
- chronic HCV GT1a, 4 and 6 infection in subjects who had reported relapse following prior PR treatment.

However, administration of a 12 week regimen of GZR100 mg + EBV 50 mg without RBV has lower efficacy among HCV GT1a , 4- and 6-infected subjects with a null or partial response to prior PR treatment. Administration of a 16 week regimen of GZR/EBR 100/ 50 mg + RBV is highly effective in achieving SVR12 among subjects who are GT1a, 4- and 6-infected and had a null or partial response to prior PR treatment.

### 7.2.3. Study P048

This is an ongoing, Phase II, multicentre, open label, single-arm study of GZR/EBR 100/50 mg QD + RBV (weight-based, twice daily dosing) administered for 12 weeks to subjects with chronic hepatitis C virus genotype 1 infection who failed a prior approved direct-acting antiviral (DAA) regimen of boceprevir, telaprevir, simeprevir, or sofosbuvir taken concomitantly with peginterferon alfa and ribavirin. The study was conducted from 23 May 2014 to 28 January 2015 at 14 trial centres: 4 in the United States; 2 in Austria, 5 in Israel, and 3 in Spain.

A total of 80 subjects with HCV genotype 1 (GT1) were to receive open label GZR/EBR 100/ 50 mg and weight-based twice daily (BID) dosing of RBV for 12 weeks and to be followed up for an

additional 24 weeks. All subjects were required to have received at least 4 weeks of treatment with a DAA on the prior regimen, and approximately 80% of subjects were required to have met criteria for virologic failure (with or without resistance associated variants [RAVs]). Other subjects may have failed a prior regimen for reasons such as AEs or administrative reasons. The proportion of cirrhotic patients in the study was to be limited to a maximum of 40%. The specific inclusion and exclusion criteria with respect to failure of prior DAA +PR treatment regimen were summarised**.** Other inclusion and exclusion criteria were general and similar to those used in the other Phase III and 2 clinical trials.

The primary endpoint was the proportion of subjects achieving SVR 12 weeks after the end of all study therapy. Subjects had HCV RNA <LLoQ, either target detected and unquantifiable (TD[u]) or undetectable (TND) 12 weeks after the end of all study therapy.

The secondary endpoints were: the proportion of subjects achieving SVR12 by prior DAA (boceprevir, telaprevir, simeprevir, sofosbuvir) and by prior DAA class; the emergence of antiviral resistance to GZR and EBR when administered as a combination regimen with RBV; the proportion of subjects achieving SVR24 and SVR4; the time to first achievement of undetectable (TND) HCV RNA; the proportion of subjects achieving undetectable (TND) HCV RNA and HCV RNA < LLoQ at Week 2, Week 4 and Week 12.

The exploratory endpoints were: the proportion of subjects achieving SVR12 who met criteria for virologic failure in prior therapy; the proportion of subjects achieving SVR12 who met criteria for virologic failure in prior therapy and have baseline RAVs in this study; the proportion of subjects achieving SVR12 by mode of virologic failure in prior regimen.

All 79 subjects received at least one dose of study therapy, and 78 (98.7%) completed the 12 week regimen with GZR + EBR +RBV. A total of 78 subjects (98.7%) completed the protocol-specified study visits through Follow-up Week 12 and only 1 subject (1.3%) discontinued all study therapy after receiving 80 of the planned 84 days of therapy due to AEs. The PP population served as the primary population for the analysis of efficacy data in the study and 9 patients from the FAS were excluded from the PP analysis due to major protocol violations. Majority of subjects were male (58.2%), White (97.5%), had HCV genotype 1b (62%), had the non-CC *IL28B* genotype (97.5%) and had plasma HCV-RNA above 800,000 IU/mL (63.3%) but below 2 million IU/mL at screening. Median age was 54.4 (range: 23-75 years). Although proportion of cirrhotic (METAVIR F4) subjects in the study was to be limited to a maximum of 40%, the actual proportion of cirrhotic[29] patients was 43% after enrolment was completed. Consistent with the large proportion of cirrhotic subjects, approximately 15% were thrombocytopenic at baseline and 3.8% had hypoalbuminemia. Mildly elevated ALT or AST was common. Over half (54.4%) of subjects failed prior therapy with telapravir (PR), approximately one-third (35.4%) failed a boceprevir/PR regimen, and the other 10.1%% failed simeprevir/PR therapy. Virologic failure was the primary reason (83.5%) for prior treatment failure. various odes of failure included relapse (32.9%), nonresponse (20.3%), viral breakthrough during PR tailing therapy (20.3%), and breakthrough during DAA/PR therapy (10.1%). Signature RAVs were present in 45.6% of subjects at baseline.. Twenty-nine subjects (36.7%) had received the last dose of their prior DAA + PR regimen less than 1.1 years before receiving their first dose in this study. Baseline characteristics for the 70 subjects in the Per Protocol population, which was used for the primary efficacy analysis, were similar to those for the 79 subjects in the FAS. Reported compliance with the study treatment regimen was very high (mean, 99.2%; range 90.5% - 100%).

[29] These 34 subjects had evidence of cirrhosis at screening from results of either liver biopsy or a non-invasive test. Eight subjects (10.1%) had a METAVIR fibrosis score of F3, and the remainder had mild to moderate fibrosis at screening.

**Comments**: It is important to note that patients who had prior DAA treatment with sofosbuvir were not actually enrolled in the study although it was mentioned in the study protocol.

*Primary efficacy results*

Following 12 weeks treatment with GZR + EBR + RBV, 97.1% (68/70) of subjects in the PP population who previously failed a DAA regimen achieved SVR12. The FAS30 analysis showed consistent results. Treatment with GZR + EBR + RBV for 12 weeks resulted in comparable high rates of SVR12 regardless of the protease inhibitor (boceprevir, telaprevir, or simeprevir) used in the previous failed regimen. The presence of signature RAVs at baseline was associated with a slightly lower %SVR12 compared with the absence of baseline RAVs, but there was wide overlap in the 95% confidence intervals for these subgroups Subjects with prior virologic failure had a slightly lower SVR12 rate compared with subjects who failed previous treatment for other reasons (that is, lack of tolerability), but interpretation was limited by wide overlap in the 95% confidence intervals for these subgroups. SVR12 was achieved in nearly 90% or higher of subjects regardless of age, gender, racial/ethnic background, submgenotype, IL 28 status, fibrosis stage, and baseline viral load. Numerically lower %SVR12 (but with broadly overlapping confidence intervals) were observed among GT1a infected subjects, cirrhotics and in subjects whose previous course of HCV therapy was completed within one year of enrolment.

*Other efficacy results*

Overall, the regimen of GZR + EBR +RBV led to rapid achievement of undetectable (TND) HCV RNA. The response to study therapy was rapid; 90% of subjects had unquantifiable HCV RNA by Treatment Week 4, all subjects had HCV RNA TND at Week 12 and only 1 subject in the PP population relapsed at the Follow-up Week 4 visit. In this study of subjects who had failed prior therapy with a first generation protease inhibitor, the overall prevalence of baseline NS3/4A variants at the specified loci was high; 34/78 (43.6%) of subjects had one or more baseline polymorphisms at these loci prior to treatment. However, only 4 subjects had baseline NS3/4A variants associated with a > 5 fold shift in potency to GZR. High rates of SVR12 were achieved regardless of the presence of NS3/4A variants at baseline; 100% (44/44) of the subjects without detectable NS3 variants at baseline achieved SVR12, compared to 91% (31/34) of the subjects who had NS3 variants detected at baseline. There was no association between presence of baseline Q80K and treatment response. The overall prevalence of baseline NS5A variants at the specified loci was low; only 8/79 (10.1%) of subjects had any NS5A baseline polymorphisms at these loci prior to treatment, and only 5 had variants with >5 fold resistance to EBR. Though conclusions regarding these data are limited by the small number of failures in this study and the small number of subjects (8) with NS5A variants detected at baseline, 98.6% (70/71) of the subjects who had no NS5A variants detected at baseline achieved SVR12, compared to 75% (6/8) of the subjects who had NS5A variants detected at baseline. Only 3 subjects experienced virologic failure in this study and all 3 subjects had treatment emergent A156T RAVs detected at the time of failure, and 2 of 3 subjects had other treatment emergent NS3/4A RAVs. All 3 subjects had treatment emergent NS5A RAVs, including Q30H, Q30R and Y93H. The persistence of specific RAVs remains to be determined as follow-up is limited at this time.

**Comments**: This study demonstrated the efficacy of a 12 week regimen of GZR 100 mg + EBR 50 mg + RBV in subjects who failed a prior regimen of boceprevir, telaprevir or simeprevir in combination with PR. This regimen was highly efficacious in this

[30] Of the 9 subjects who were excluded from the Per-Protocol population, 8 achieved SVR12. The remaining subject (AN480048) relapsed at FUW4. This subject was excluded from the PP population because he had received two prior DAA containing regimens, one with telaprevir, and another with faldaprevir, which represents a violation of the inclusion criterion wherein only subjects who received prior therapy with boceprevir, telaprevir, simeprevir or sofosbuvir, each in combination with PR, were to be enrolled

population; of the 79 subjects enrolled in the trial, only 3 failed to achieve SVR12, all due to relapse after the completion of study therapy. Thus, SVR12 was achieved in 96.2% of subjects. Comparable high rates of SVR12 were achieved regardless of the protease inhibitor (boceprevir, telaprevir, or simeprevir) used in the previous failed regimen. High rates of SVR12 were also achieved regardless of the presence of signature RAVs at baseline overall or among the subjects who had previous virologic failure high proportion of subjects had characteristics associated with an unfavourable response to treatment with a first generation PI + PR; 43% of the subjects were cirrhotic and 98% had a non-CC IL28B genotype. However, neither of these factors had an impact on efficacy in this trial. Efficacy was also similar in subjects infected with HCV GT1a and GT1b. These findings suggest that a 12 week regimen of GZR 100 mg + EBR 50 mg + RBV is highly efficacious in clearing HCV genotype 1 infection among subjects with chronic HCV GT 1 infection who have failed prior treatment with a PI + PR regimen.

### 7.2.4. Study P074

This is an ongoing, Phase II, randomised, parallel group, open-label, single-centre, multiple-arm trial of, a fixed dose combination of GZR/EBR (100 mg/50 mg) and 400 mg of sofosbuvir (SOF), both administered once daily in treatment naïve subjects with chronic HCV Genotype 1 (GT1) or Genotype 3 (GT3) with compensated cirrhosis or without cirrhosis. The study was conducted from 16 June 2014 to 23 April 2015 at a single centre in USA.

This study included four cohorts of subjects defined by HCV genotype (GT1 or GT3) and disease characteristic (cirrhotic or non-cirrhotic). Within the first three cohorts, a separate randomisation assigned subjects into one of two groups defined by duration of therapy (4 or 6 weeks, 6 or 8 weeks, and 8 or 12 weeks) according to a computer generated allocation schedule. Within the fourth cohort, patients were assigned to the 12 week duration group (no randomisation). Randomisation of subjects within the GT1 cohorts (treatment arms 1-4) was stratified based on Genotype Sub-type (1a versus non-1a) (see Table 9 below).

**Table 9: Treatment arms by cohort and duration**

| | | Cohort | | | |
|---|---|---|---|---|---|
| | Duration | GT1 non-cirrhotic (N=60) | GT1 cirrhotic (N=40) | GT3 non-cirrhotic (N=30) | GT3 cirrhotic (N=10) |
| Randomized Group | 4 weeks (n=30) | Arm 1 (n=30) | | | |
| | 6 weeks (n=50) | Arm 2 (n=30) | Arm 3 (n=20) | | |
| | 8 weeks (n=35) | | Arm 4 (n=20) | Arm 5 (n=15) | |
| | 12 weeks (n=25) | | | Arm 6 (n=15) | Arm 7 (n=10) |

The primary efficacy endpoint was SVR12 in the PP population. The secondary endpoints were SVR4 and PK assessments. Exploratory endpoints included: viral kinetics for first 32 hours in some cohorts; emergence of viral resistance associated variants (RAVs) to GZR, EBR or SOF when administered as part of combination regimen; proportion of subjects with HCV RNA <LLOQ (either TD(u) or TND) at treatment week 4, end of treatment, FU Week 8 or FU Week 24.

A total of 143 subjects (102 subjects were GT1 and 41 subjects were GT3) were enrolled to treatment, and all subjects received at least one dose of study therapy. Of these, 100 (98.0%) GT1 subjects and 40 (98.0%) GT3 subjects completed study therapy with GZR/EBR and SOF, and 99 (97.1%) GT1 subjects and 40 (97.6%) GT3 subjects completed the protocol specified study visits during treatment and follow-up). At the time of data cut-off for this CSR, all subjects in the 12 week treatment arms had completed study treatment or had discontinued treatment. A total of 4 subjects discontinued the study, 3 GT1 subjects and 1 GT3 subject. There were 7 major protocol violations and 3 of these led to exclusion from the PP analysis. Majority of the subjects were male (64-71%), White and had non-CC IL28B genotype. Majority of GT1 subjects

73/102 (71.6%) and GT3 subjects 21/41 (51.2%) had plasma HCV-RNA above 800,000 IU/mL; 4/102 (3.9%) GT1 subjects and 2/41 (4.9%) GT3 subjects had plasma HCV-RNA above 10 million IU/mL. The distribution among treatment arms was comparable. Baseline laboratory assessments (ALT, AST and total bilirubin), were generally similar across treatment arms and within cirrhotic versus non-cirrhotic groups. Compliance with the GZR/EBR + SOF treatment regimens was very high in both GT1 and GT3 serotype subjects (mean: 97%, range: 88% to 100%; mean: 98%; range: 78% to 100%) and compliance rates were similar across treatment groups. No subjects took less than 75% of the prescribed doses of study medication.

*Primary efficacy results*

Primary efficacy analysis of the GT1 subjects showed that SVR12 rates after proposed treatment with FDC+sofosbuvir were only 33%, but increased to 90% following 6 weeks of treatment. In all arms HCV GT1b infected subjects had higher efficacy compared to GT1a infected subjects. Notably as the duration increased the gap in efficacy between GT1b and GT1a narrowed. At durations of 4, 6, and 8 weeks comparing GT1b and GT1a, efficacy was 60% versus 28% (4 wk Arm 1), 100% versus 87.5% (6 wk Arm 2), 75% versus 81.3% (6 wk Arm 3) and 100% versus 93.3% (8 wk Arm 4 – excluding subject failing with GT2). No other factor demonstrated substantial differences in the subgroup analyses at any duration. There were small differences with trends toward higher efficacy for females, IL-28 CC genotype, and subjects with low viral load (that is, <800,000 IU/mL). the analyses of SVR12 in the PP population suggest that a 6 week duration of therapy may be sufficient to treat non-cirrhotic, treatment-naïve HCV GT1 infected subjects, whereas an 8 week duration of therapy may be sufficient to treat cirrhotic, treatment-naïve, GT1 infected subjects.

Results of primary efficacy analysis in GT3 patients showed that the 12 week duration of therapy was highly effective in clearing HCV GT3 infection in both cirrhotic and non-cirrhotic subjects. An 8 week regimen may be sufficient to clear HCV GT3 infection in non-cirrhotic subjects. Results in the FAS analysis were consistent with results of the PP analysis for both GT1 and GT3 HCV patients.

*Other efficacy results*

The secondary efficacy endpoint (SVR4) analysis showed that following 4 week treatment duration, SVR4 was achieved by 71.0% of non-cirrhotic GT1 subjects, but SVR12 was achieved by only 33% of subjects due to relapse between FUW4 and FUW12. In contrast, similar proportions of subjects achieved SVR4 and SVR12 in the PP population of the 6 week arm confirming that the 4 week duration of therapy with GZR/EBR + SOF is insufficient to clear HCV GT1 infection in non-cirrhotic patients. In cirrhotic patients, the proportions of subjects who achieved SVR4 were higher than the proportions who achieved SVR12 in both the 6 week and 8 week treatment duration arms with relapses occurring between 4 week and 12 week follow-up visits. In HCV GT3 non-cirrhotic patients, all subjects achieved SVR4 with only relapse between FUW4 and FUW12. In cirrhotic GT3 patients, the proportions of subjects who achieved SVR4 and SVR12 were identical.

AT TW4, the proportions of GT1 HCV subjects in the PP population of each arm who achieved HCV RNA <15 IU/mL were comparable across study arms, regardless of the presence of cirrhosis. At EOT, the proportion of subjects in the PP population of the 4 week (non-cirrhotic) who achieved HCV RNA <15 IU/mL was lower than in other arms. With an additional 2 to 4 weeks of therapy, 96.4 to 100% of subjects achieved HCV RNA <15 IU/mL. The 6 week duration of therapy was evaluated in both cirrhotic and non-cirrhotic subjects. The proportions of subjects who achieved HCV RNA <15 IU/mL were comparable across these two arms.

AT TW4 in the GT3 HCV subjects, combining the two non-cirrhotic arms, 26/29 (89.7%) subjects achieved HCV RNA <15 IU/mL. A lower proportion of cirrhotic subjects achieved HCV RNA <15 IU/mL at this time-point. At *EOT, a*ll subjects in the PP population of each arm

achieved HCV RNA <15 IU/mL. These results support the high efficacy of the regimen in both cirrhotic and non-cirrhotic subjects.

The presence of baseline NS3 RAVs in GT1a infected subjects was associated with a numerically lower SVR12 rate compared to subjects who did not have baseline RAVs (63.6% (28/44) versus 75.5% (28/37). There was only 1 GT1b subject who had baseline RAV; this subject achieved SVR. Overall, subjects who had baseline NS5A RAVs had lower SVR12 (6/13, 46.2%) as compared to those who did not (62/85, 72.9%). Differences in the relative overall impact of NS5A RAVS were observed in subjects treated with different durations with no impact following 4 week treatment duration, but impact of NS5A RAVs was more apparent in the 6 and 8 week treatment arms. After viral relapse, 3% (1/29) of the virologic failures harboured NS3 variants and 40% (12/30) of the virologic failures had NS5A variants conferring a ≥ 5 fold change in susceptibility to GZR or EBR, respectively. No NS5B RAVs were observed. Of the 29 virologic failures with sequence information for all 3 target genes, 1/29 (3%) had both NS3 and NS5A RAVs.

Overall, 97.3% (37/38) of the GT3 subjects who had baseline NS3 variants achieved SVR12 All GT3 subjects who had baseline NS5A RAVs achieved SVR12. Of the 40 GT3 subjects that participated in this study, NS5B baseline sequences were obtained from only 33 subjects and none of them reported any NS5B variants. Of the 40 GT3 subjects in the RAP, there were only 2 virologic failures[31]:

**Comments**: Results of this exploratory Phase II study supported the efficacy of the proposed FDC (GZR+EBR 100/50 mg) +Sofosbuvir 400 mg as follows:

treatment with above combination for 4 weeks was insufficient to clear HCV GT1 infection in most patients;

treatment for 6 weeks was effective in clearing HCV infection among non-cirrhotic, treatment-naïve, GT1 infected patients;

treatment for 8 weeks was highly efficacious in clearing HCV infection among cirrhotic, treatment-naïve, GT1 infected patients;

treatment for 8 to 12 weeks was highly efficacious in clearing HCV infection among non-cirrhotic, treatment-naïve, GT3-infected patients (SVR12 was 93% and 100% following 8 and 12 weeks treatment regimens, respectively);

treatment for 12 weeks was highly efficacious in clearing HCV infection among cirrhotic, treatment-naïve, GT3-infected patients with SVR12 of around 91%.

Relapse was the primary mechanism of failure to clear HCV GT1 or GT3 infection following administration of GZR/EBR 100 mg/50 mg FDC). + sofosbuvir (400 mg).

### 7.2.5. Study P059

This is an ongoing, Phase II/III, nonrandomised, multi-site, open-label Phase II/III study of GZR 50 mg in combination with EBR 50 mg in subjects with chronic HCV infection who have cirrhosis and a Child- Pugh (CP) score between 7-9 (CP-B). The study is to be conducted in three Parts:

Part A evaluated GZR 50 mg QD + EBR 50 mg QD for 12 weeks among 30 HCV genotype 1 (GT1)-infected CP-B subjects (Arm 1). Ten (10) HCV GT1 non-cirrhotic subjects received GZR 100 mg QD + EBR 50 mg QD for 12 weeks (Arm 2). These non-cirrhotic subjects were enrolled for the purpose of collecting GZR and EBR plasma pharmacokinetics (PK) in non-cirrhotic subjects. As

[31] One relapsed after 8 weeks of treatment with GZR/EBR/SOF and had WT viruses at baseline as well as at relapse. YT= The other subject relapsed after 12 weeks of treatment with GZR/EBR/SOF; this subject had NS3 Q168Q/R, WT NS5A and WT NS5B at baseline. At relapse, this subject had variants at NS3 Q168R, NS5A Y93H and WT NS5B.

of the cut-off date of 29-Jan-2015, dosing was complete in Part A, and all subjects have reached follow-up week 4 (FU4). The protocol stated that if GZR 50 mg QD + EBR 50 mg QD for 12 weeks was well-tolerated and adequately efficacious among CP-B subjects, then the study was to proceed directly to evaluate GZR 50 mg + EBR 50 mg QD among 100 GT1, GT4, or GT6 infected CP-B subjects in Part C (the Phase III portion) If the combination studied in Part A was well-tolerated, but did not have adequate efficacy, the study would progress to Part B, in which a regimen of GZR 100 mg + EBR 50 mg QD, administered for 12 weeks, was to be evaluated in 30 GT1 HCV infected CP-B subjects. In Part B, if the safety and efficacy findings of the regimen containing 100 mg of GZR were acceptable, the study would expand to Part C using the GZR 100 mg + EBR 50 mg QD for 12 weeks. In all three Parts, subjects will be in follow-up (FU) for 24 weeks. The treatment groups are summarised in Table 10.

**Table 10: Study P059 Treatment groups**

| | | |
|---|---|---|
| Treatments groups | Part A: Arm 1 | GZR 50 mg + EBR 50 mg for 12 wks (CP-B subjects); 30 Subjects |
| | Part A: Arm 2 | GZR 100 mg + EBR 50 mg for 12 wks (non-cirrhotic subjects): 10 Subjects |
| | Part B: Arm 3 | GZR 100 mg + EBR 50 mg for 12 wks (CP-B subjects) *Not conducted yet* |
| | Part C: Arm 4 | GZR 50 mg + EBR 50 mg for 12 wks (CP-B subjects); OR GZR 100 mg + EBR 50 mg for 12 wks (CP-B subjects) *Not conducted yet* |

The CSR in the submitted dossier summarises Part A (conducted at 9 centres in USA) results as of the cut-off date of 29 January 2015. This trial was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. However, issues of non-compliance associated with some requirements of Good Clinical Practice were identified as follows: The following materials were not submitted to the central IRB for approval prior to their distribution or use in the study: request to provide patients with a (1) Patient Carry-all bag; (2) Part A Medication Diary; and Request for approval of the Document titled 'Event of Clinical Interest (ECI) Guidance for Potential DILI (Drug-Induced Liver Injury) in Clinical Trials - Site Guidance Document for Assessment and Follow-up.'

The omission of these items for review by the central IRB was not considered to have had a significant impact on study conduct or safety considerations for patients or investigators.

The submitted dossier only contains Part A data: efficacy data through 4 weeks after the end of study therapy, safety and PK data. The trial's primary endpoint (the portion of subjects achieving SVR12), the secondary endpoints and the exploratory endpoints will be summarised in a future study report.

In the FAS analysis, 28 of 30 CP-B subjects (93.3%; 95% CI 84.4% to 100.0%) in Part A who received a 12 week regimen of GZR 50 mg + EBR 50 mg QD achieved SVR4. Among the two subjects who failed to achieve SVR4, one GT1a infected subject experienced a relapse at FU4, and one subject died at FU4 after achieving TND HCV RNA at end of treatment (EOT). The subject who died was excluded from the per-protocol population. In the PP population, 28 of 29 CP-B subjects (96.6%; 95% CI 89.9% to 100.0%) in Part A who received a 12 week regimen of GZR 50 mg + EBR 50 mg QD achieved SVR4. One subject experienced virologic relapse at FU4. Among CP-B subjects who received GZR 50 mg in combination with EBR 50 mg QD for 12 weeks, the rate of virologic failure at FU4 was 3.4% (1/29). In the FAS analysis, CP-B subjects in Part A who received GZR 50 mg in combination with EBR 50 mg QD for 12 weeks had a mean changes of CP score from baseline to EOT of -0.41 with 95% CI of (-0.71, -0.12). As of database lock, 29/30 subjects had CP scores available at screening and at TW12. Of these, 15/29 subjects

had a decrease in CP score between screening and TW12; 1 subject and 14 subjects, respectively, had a decrease in CP score by 2 points and 1 point. Ten (10)/29 subjects had no change in CP score between screening and TW12. Overall, 4 of the 29 subjects showed an increase in CP score between screening and TW12; in all 4 subjects, CP score increased by 1 point.

### 7.2.6. Study P058

This is an ongoing, Phase II, randomised, dose-ranging, parallel-group, multisite (at 19 centres in Japan), double-blinded trial of GZR and EBR in Japanese subjects with chronic HCV genotype 1 infection. The study consists of two parts: Part 1 is the study to evaluate the safety and tolerability of two doses of GZR (50 or 100 mg) in combination with EBR (50 mg) administered for 12 weeks (with 24 weeks of follow-up); and Part 2 is placebo-controlled, double-blind study of the safety and efficacy of GZR at the dose selected in Part 1 in combination with EBR (50 mg) for 12 weeks. Part 1 of the study was initiated in Aug 2014 and Part 2 has not yet started. The CSR included in the submitted dossier only reports preliminary interim results for Part 1 only and includes data from the start of the treatment period through 4 weeks of post-treatment follow-up. The treatment groups are summarised in Table 11.

**Table 11: Study P058 Treatment groups**

| | | |
|---|---|---|
| Treatments groups | Part1:<br>MK-5172 50 mg Arm | Non-cirrhotic subjects: MK-5172 50 mg + MK-8742 50 mg for 12 weeks (N=31) |
| | Part1:<br>MK-5172 100 mg Arm | Non-cirrhotic subjects: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (N=32) |
| | Part2: Arm 1 | Non-cirrhotic subjects: the selected dose of MK-5172 + MK-8742 50 mg for 12 weeks (N will be ~180) |
| | Part2: Arm 2 | Non-cirrhotic subjects: Placebo for 12 weeks followed by the selected dose of MK-5172 + MK-8742 50 mg for 12 weeks (N will be ~60) |
| | Part2: Arm 3 | Cirrhotic subjects: the selected dose of MK-5172 + MK-8742 50 mg for 12 weeks (N will be ~30) |

A total of 63 subjects were randomised with 62 subjects receiving and completing study medication; 1 subject in GZR 100 mg arm was randomised but did not receive study medication due to an AE during the screening period. All subjects who received treatment were continuing in the study at the time of this report. Approximately 60% of the randomised subjects in Part 1 were female. The median age of the subjects was approximately 60 years, and approximately 38% of subjects were 65 year of age or older. All patients had GT1b CHC. Approximately 52% of the randomised patients were treatment-naïve, approximately 10% were PR intolerant, and approximately 38% had failed prior treatment with PR (approximately 6% were non-responders). The baseline characteristics were generally balanced between the treatment arms.

The SVR4 rates for the GZR 50 mg and 100 mg arms were 100% (31/31) and 100% (31/31), respectively. In addition, the percentages of subjects with viral response defined as TND in the GZR 50 mg and 100 mg arms, respectively, were 22.6% (7/31) and 35.5% (11/31) at Week 2 (very early RVR), 77.4% (24/31) and 83.9% (26/31) at Week 4 (RVR), and 100% (31/31) and 100% (31/31) at the end of all study therapy (EOT). The safety results demonstrated that administration of GZR at both 50 mg and 100 mg in combination with EBR at 50 mg was generally well tolerated among non-cirrhotic, GT1, HCV infected Japanese subjects.

### 7.2.7. Other ongoing studies

**P062** is an ongoing, randomised, parallel-group, placebo-controlled, multi-site, double-blind trial of GZR/EBR 100/50 mg in subjects with chronic HCV, genotype (GT) 1, 4, or 6 infections who are on opiate substitution therapy. The submitted dossier only contains interim safety results (until the time of database lock on 28-Feb-2015). At the time of database lock, 301

subjects had been randomised in a 2:1manner to receive either immediate treatment (GZR/EBR for 12 weeks), or deferred treatment (placebo for 12 weeks followed by GZR/EBR for 12 weeks). Both groups are to be followed for 24 weeks after completing study medication. Treatment assignment remains blinded in this study. Each subject is unblinded as they complete the Week16 visit. At the time of this ongoing study report, 195 subjects had completed the Week16 visit and were unblended**.** Majority of the 310 subjects in the study were male (76.4%), with genotype (GT) 1a (76.1%), of the non-CC genotype (67.8%) with hepatic fibrosis stage Metavir score F0 to F22 (49.5%) or F4 (21%)**.**

**Comment**: Despite the public health importance of treating HCV infection in people who inject drugs (PWID), participation of PWID in clinical trials of all-oral HCV treatment, as well as access to licensed HCV medicines has been severely limited. The above study has enrolled subjects who stop injecting drugs and use opiate substitution therapy (OST) which represents a small subgroup of the PWID population and clinical trials among a broader, and more representative, range of PWID may still be needed to determine if current all-oral HCV medicines are safe and effective in this population and to determine whether this population can be adherent with these regimens. Efficacy results from this study were not provided in the current dossier and only safety results were provided which have been summarised under Safety below.

**P065** is an ongoing, randomised, double blind, placebo-controlled, multi-site study evaluating the fixed dose combination single tablet regimen of GZR/EBR 100/50 mg in subjects with chronic HCV genotype (GT) 1, GT4 and GT6 infection with inherited blood disorders with and without HIV co-infection. The current dossier only contains safety data until the time of a database lock on 01-Mar-2015. At the time of database lock, 92 subjects had been randomised in a 2:1 manner to receive either immediate treatment (GZR/EBR for 12 weeks) or deferred treatment (placebo for 12 weeks followed by GZR/EBR for 12 weeks). Majority of 92 randomised subjects were male (83.7%), and White (82.6%) and about half had GT1a (43.5%). The mean age of subjects was 44.4 years; the IBD diagnosis was haemophilia or Von Willebrand's disease in 62 subjects, beta thalassemia for 23 subjects and sickle cell disease for 7 subjects. Chronic HCV infection remains a significant clinical burden for individuals with inherited blood disorders (IBD) who have a life-long dependence on blood and blood product transfusions. As patients with haemoglobinopathies such as sickle cell (SS) disease and beta thalassemia and those with blood clotting factor deficiencies such as haemophilia and Von Willebrand are living longer due to improved specialised medical care, complications from chronic HCV infection have emerged as a major cause of morbidity and mortality. HCV infection is the second leading cause of death among individuals with IBD. Although the standard of care treatment has evolved to tolerable and efficacious interferon-free combinations of direct acting antivirals (DAA) for a majority of individuals with chronic HCV infection, these therapies have not been studied exclusively in patients with IBD. Accordingly, monotherapy with interferon or pegylated interferon (Peg-IFN), which are both fraught with treatment limiting side effects and toxicities remains the standard of care for treatment of HCV in patients with IBD

**Comment**: Hence, this study should help to provide important data in this patient population with an unmet medical need. Efficacy results from this study were not provided in the current dossier and only safety results were provided which have been summarised under Safety below.

**P017** is a long-term follow-up study to evaluate the durability of virologic response and/or viral resistance patterns among subjects with chronic Hepatitis C who have been previously treated with GZR in a prior clinical trial. No treatments are administered in Study P017. Monitoring includes assessment of durability of virologic response in subjects who achieved SVR24 and to characterise reversion of RAVs to wild type virus in patients who failed with RAVs. Subjects are evaluated every 6 months for up to 5 years (depending on the parent study from which they enrolled). For the purpose of this application, only subjects enrolled into P017 from studies of

GZR with EBR ±RBV were considered. A total of 388 subjects from Studies P035 and P047 were enrolled: 372 subjects who achieved SVR24 and 16 subjects who had experienced virologic failure in the parent study. Of these, 208 have reached the 6 month visit and 27 have reached the 1 year visit. As of 04 February 2015, no subjects from Phase III studies were eligible for enrolment into P017. Of the 372 subjects who achieved SVR24 in the parent study and entered P017, recurrent HCV detection was observed in only 1 (0.27%) subject (testing is under way to evaluate whether this case represents true late relapse or re-infection). Overall, SVR achieved following administration of GZR/EBR ±RBV is durable through at least 30 weeks following the end of therapy. NS3 resistance data was available on 7 of 16 subjects who entered P017 who had experienced virologic failure in the parent study; 6 with GT1 infection and 1 with GT3 infection at baseline in the parent protocol. Treatment emergent NS3 RAVs from the parent protocol were present in a single subject sample at FW24/ Day 1 in P017. NS5 RAV data was not available at the time of this summary. Overall, it is not possible to determine the persistence of NS3 and NS5A RAVs that emerge among subjects who fail to achieve SVR following GZR+EBR treatment due to the small number of failures to date and the short follow-up duration.

## 7.3. Analyses performed across trials (pooled analyses and meta-analyses)

### 7.3.1. Efficacy in special patient populations:

#### *7.3.1.1. Comparison of efficacy in treatment-naïve subjects treated for 12 weeks with GZR and EBR without RBV*

This comparison includes TN subjects from Studies P035, P047, P052, P060 and P061. Of the 752 subjects randomised to receive a 12 week regimen of GZR with EBR (no RBV), 738 (98.1%) completed study therapy**.** Majority of subjects were male (67.0%), White (67.2%) and were infected with HCV GT1 (681/752, 90.5%); 57%, 7.4% and 2% with GT1a, GT4 and GT6, respectively. The median age was 53 (from 20 to 82) years, mean baseline HCV RNA was approximately 2.8 million IU/mL and 248/752 subjects (33.0%) were HIV co-infected. A total of 79/752 (10.5%) subjects and 138/752 (18.4%) subjects had a METAVIR fibrosis score of F3 and F4, respectively.

Integrating all studies, 711/752 (94.5%) of subjects in the FAS population achieved SVR12 with comparable SVR12 rates across studies (Table 12).

**Table 12: Comparison of results across studies-Treatment naïve subjects treated for 12 weeks without RBV**

| Trial | PN060 | | | PN061 | | | PN052 | | | PN035 | | | PN047 | | | All Studies | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | GZR and EBR 12 Weeks N=316 | | | GZR and EBR 12 Weeks N=218 | | | GZR and EBR 12 Weeks N=101 | | | GZR and EBR 12 Weeks N=103 | | | GZR and EBR 12 Weeks N=14 | | | GZR + EBR 12 Weeks N=752 | | |
| | % | n | N | % | n | N | % | n | N | % | n | N | % | n | N | % | n | N |
| Overall SVR | 94.6% | 299 | 316 | 95.0% | 207 | 218 | 95.0% | 96 | 101 | 94.2% | 97 | 103 | 85.7% | 12 | 14 | 94.5% | 711 | 752 |
| Outcome for subjects without SVR | | | | | | | | | | | | | | | | | | |
| On-treatment VF | 0.3% | 1 | 316 | 0.0% | 0 | 218 | 0.0% | 0 | 101 | 1.9% | 2 | 103 | 7.1% | 1 | 14 | 0.5% | 4 | 752 |
| Relapse | 3.8% | 12 | 316 | 3.2% | 7 | 218 | 0.0% | 0 | 101 | 1.9% | 2 | 103 | 0.0% | 0 | 14 | 2.8% | 21 | 752 |
| Other | 1.3% | 4 | 316 | 1.8% | 4 | 218 | 5.0% | 5 | 101 | 1.9% | 2 | 103 | 7.1% | 1 | 14 | 2.1% | 16 | 752 |
| SVR by Genotype | | | | | | | | | | | | | | | | | | |
| GT1a | 91.7% | 144 | 157 | 94.4% | 136 | 144 | 98.1% | 52 | 53 | 93.1% | 67 | 72 | - | - | - | 93.7% | 399 | 426 |
| GT1b† | 98.5% | 129 | 131 | 95.6% | 43 | 45 | 91.7% | 44 | 48 | 96.8% | 30 | 31 | - | - | - | 96.5% | 246 | 255 |
| GT4 | 100.0% | 18 | 18 | 96.4% | 27 | 28 | - | - | - | - | - | - | 90.0% | 9 | 10 | 96.4% | 54 | 56 |
| GT6 | 80.0% | 8 | 10 | 100.0% | 1 | 1 | - | - | - | - | - | - | 75.0% | 3 | 4 | 80.0% | 12 | 15 |
| SVR by Cirrhosis status | | | | | | | | | | | | | | | | | | |
| No‡ | 93.9% | 231 | 246 | 94.0% | 172 | 183 | 94.8% | 92 | 97 | 93.2% | 69 | 74 | 85.7% | 12 | 14 | 93.8% | 576 | 614 |
| Yes | 97.1% | 68 | 70 | 100.0% | 35 | 35 | 100.0% | 4 | 4 | 96.6% | 28 | 29 | - | - | - | 97.8% | 135 | 138 |
| SVR by HIV status | | | | | | | | | | | | | | | | | | |
| HCV mono-infected | 94.6% | 299 | 316 | - | - | - | 95.0% | 96 | 101 | 97.3% | 71 | 73 | 85.7% | 12 | 14 | 94.8% | 478 | 504 |
| HCV/HIV co-infected | - | - | - | 95.0% | 207 | 218 | - | - | - | 86.7% | 26 | 30 | - | - | - | 94.0% | 233 | 248 |

VF = virologic failure
†Includes genotype 1 subtypes other than 1a and 1b.
‡ Includes one subject with cirrhosis status of "Unknown" in Protocol 047.

Excluding the 'Other' category, which describes administrative, non-virologic failures (for example, losses to follow-up, subject withdrawal from study and so on), SVR12 was achieved in 711/736 (97%) of subjects. Relapse was the predominant form of virologic failure. Efficacy varied by genotype: high efficacy was observed among GT1a , GT1b and GT4 infected subjects, whereas efficacy was lower among GT6 infected subjects, though the number of GT6 infected subjects was small. Efficacy was not affected by presence of cirrhosis or HIV co-infection status (Table 12).

#### *7.3.1.2. Comparison of efficacy in treatment experienced subjects:*

This comparison includes efficacy results from treatment experienced subjects in Studies P035, P048, P052 and P068. Of the 650 subjects in this group, 159 subjects were treated for 12 weeks and did not receive RBV, 215 were treated for 12 weeks and received RBV, 137 subjects were treated for either 16/18 weeks and did not receive RBV and 139 subjects were treated for either 16/18 weeks and received RBV. Overall, 97.4% of subjects completed study therapy. The completion rates for regimens that included RBV (98.1 and 96.4% for the 12 week and 16/18 week RBV-containing arms, respectively) were similar to the completion rates for RBV-free regimens (98.7 and 95.6% for the 12 week and 16/18 week RBV-free arms, respectively). A total of 16 subjects (2.5%) discontinued study therapy. The most common reason for discontinuing study drug was due to non-fatal adverse events, which was reported by 8 subjects (1.2%); 7 of these 8 subjects were in RBV containing arms. The next most common reason for discontinuing study drug was lack of efficacy, which was reported by 4 subjects (0.6%), all of whom were in the 16/18 week RBV-free arm. Majority of subjects were male (62.9%), White (76%), non-cirrhotic (13.2% and 35.8% had METAVIR fibrosis score of F3 and F4, respectively) and infected with GT1 (93.4%) with 5.2.8%, 5.7% and 0.6% infected with GT1a, GT4 and GT6, respectively. The median age was 56 (18-77) years; the mean baseline HCV RNA was approximately 4 million IU/mL and 54% had plasma HCV-RNA above 2 million IU/mL. Only 21/650 (3%) of subjects were HIV co-infected.

A total of 159 subjects received regimen of GZR with EBR (no RBV) for 12 weeks in 3 trials (P035, P052 and P068). Overall, 91.8% of subjects achieved SVR12 and efficacy was generally comparable across studies. Excluding non-virologic failures ('Other' line in the table, including losses to follow-up, subject withdrawal from the study, etc.), 146/156 (93.6%) of subjects achieved SVR12. Virologic failure was observed in 6.3% of subjects; all failures were relapses.

Efficacy varied by genotype. The highest efficacy was observed among GT1b infected subjects. Efficacy was lower in GT4 infected subjects, although the sample size was small. No GT6 infected subjects received this regimen. Efficacy was slightly lower among cirrhotics compared with non-cirrhotics. There was a difference in observed efficacy by prior treatment response. Efficacy was highest among subjects who had experienced a relapse after completion of prior therapy. Subjects who experienced on-treatment failure were less likely to achieve SVR12 (Table 13A).

A total of 215 subjects received regimen of GZR with EBR and RBV for 12 weeks in 3 studies (P035, P048 and P068). Overall, 94.9% of subjects achieved SVR12 and efficacy was generally comparable across studies. Excluding non-virologic failures, 204/213 (95.8%) of subjects achieved SVR12. Virologic failure was observed in 4.2% of subjects; all failures were relapses. High efficacy was observed the GT1 and GT4 infected subjects. No GT6 infected subjects received this regimen. Efficacy was slightly lower among cirrhotics compared with non-cirrhotics. Efficacy appeared to be generally slightly higher in prior relapsers (Table 13B).

**Table 13A: Comparison of results across studies-Treatment experienced subjects- for 12 weeks without RBV**

| Trial | PN068 | | | PN052 | | | PN035 | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Regimen | GZR and EBR 12 weeks N=105 | | | GZR and EBR 12 weeks N=21 | | | GZR and EBR 12 weeks N=33 | | | GZR and EBR 12 weeks N=159 | | |
| | % | n | N | % | n | N | % | n | N | % | n | N |
| Overall SVR | 92.4% | 97 | 105 | 90.5% | 19 | 21 | 90.9% | 30 | 33 | 91.8% | 146 | 159 |
| Outcome for subjects without SVR | | | | | | | | | | | | |
| On-treatment VF | 0.0% | 0 | 105 | 0.0% | 0 | 21 | 0.0% | 0 | 33 | 0.0% | 0 | 159 |
| Relapse | 5.7% | 6 | 105 | 4.8% | 1 | 21 | 9.1% | 3 | 33 | 6.3% | 10 | 159 |
| Other | 1.9% | 2 | 105 | 4.8% | 1 | 21 | 0.0% | 0 | 33 | 1.9% | 3 | 159 |
| SVR by Genotype | | | | | | | | | | | | |
| GT1a | 90.2% | 55 | 61 | 90.0% | 9 | 10 | 90.9% | 20 | 22 | 90.3% | 84 | 93 |
| GT1b[†] | 100% | 35 | 35 | 90.9% | 10 | 11 | 90.9% | 10 | 11 | 96.5% | 55 | 57 |
| GT4 | 77.8% | 7 | 9 | - | 0 | 0 | - | 0 | 0 | 77.8% | 7 | 9 |
| GT6 | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 |
| SVR by Cirrhosis status | | | | | | | | | | | | |
| No | 94.1% | 64 | 68 | 94.4% | 17 | 18 | 89.5% | 17 | 19 | 93.3% | 98 | 105 |
| Yes | 89.2% | 33 | 37 | 66.7% | 2 | 3 | 92.9% | 13 | 14 | 88.9% | 48 | 54 |
| Response to Prior HCV Therapy | | | | | | | | | | | | |
| Prior On-Treatment VF[‡] | 88.6% | 62 | 70 | 100% | 7 | 7 | 90.9% | 30 | 33 | 90.0% | 99 | 110 |
| Prior Treatment Relapser | 100.0% | 35 | 35 | 91.7% | 11 | 12 | - | 0 | 0 | 97.9% | 46 | 47 |
| Other[§] | - | 0 | 0 | 50.0% | 1 | 2 | - | 0 | 0 | 50.0% | 1 | 2 |
| SVR by HIV status | | | | | | | | | | | | |
| HCV mono-infected | 91.9% | 91 | 99 | 90.5% | 19 | 21 | 90.9% | 30 | 33 | 91.5% | 140 | 153 |
| HCV/HIV co-infected | 100% | 6 | 6 | - | 0 | 0 | - | 0 | 0 | 100% | 6 | 6 |

VF = virologic failure
[†]Includes genotype 1 subtypes other than 1a and 1b
[‡]Includes PR null responders, PR partial responders,
[§]Includes intolerance to or non-compliance with prior therapy

**Table 13B: Comparison of results across studies-Treatment experienced subjects- 12 weeks with RBV**

| Trial<br>Regimen | PN068<br>GZR and EBR + RBV<br>12 weeks<br>N=104 | | | PN035<br>GZR and EBR + RBV<br>12 weeks<br>N=32 | | | PN048<br>GZR and EBR + RBV<br>12 weeks<br>N=79 | | | Combined<br>GZR and EBR + RBV<br>12 weeks<br>N=215 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | n | N | % | n | N | % | n | N | % | n | N |
| Overall SVR | 94.2% | 98 | 104 | 93.8% | 30 | 32 | 96.2% | 76 | 79 | 94.9% | 204 | 215 |
| Outcome for subjects without SVR | | | | | | | | | | | | |
| On-treatment VF | 0.0% | 0 | 104 | 0.0% | 0 | 32 | 0.0% | 0 | 79 | 0.0% | 0 | 215 |
| Relapse | 5.8% | 6 | 104 | 0.0% | 0 | 32 | 3.8% | 3 | 79 | 4.2% | 9 | 215 |
| Other | 0.0% | 0 | 104 | 6.3% | 2 | 32 | 0.0% | 0 | 79 | 0.9% | 2 | 215 |
| SVR by Genotype | | | | | | | | | | | | |
| GT1a | 93.3% | 56 | 60 | 88.9% | 16 | 18 | 93.3% | 28 | 30 | 92.6% | 100 | 108 |
| GT1b[†] | 96.6% | 28 | 29 | 100% | 14 | 14 | 98.0% | 48 | 49 | 97.8% | 90 | 92 |
| GT4 | 93.3% | 14 | 15 | - | 0 | 0 | - | 0 | 0 | 93.3% | 14 | 15 |
| GT6 | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 |
| SVR by Cirrhosis status | | | | | | | | | | | | |
| No | 97.1% | 67 | 69 | 95.0% | 19 | 20 | 97.8% | 44 | 45 | 97.0% | 130 | 134 |
| Yes | 88.6% | 31 | 35 | 91.7% | 11 | 12 | 94.1% | 32 | 34 | 91.4% | 74 | 81 |
| Response to Prior HCV Therapy | | | | | | | | | | | | |
| Prior On-Treatment VF[‡] | 90.9% | 60 | 66 | 93.8% | 30 | 32 | 95.0% | 38 | 40 | 92.8% | 128 | 138 |
| Prior Treatment Relapser | 100% | 38 | 38 | - | 0 | 0 | 96.2% | 25 | 26 | 98.4% | 63 | 64 |
| Other[§] | - | 0 | 0 | - | 0 | 0 | 100% | 13 | 13 | 100% | 13 | 13 |
| SVR by HIV status | | | | | | | | | | | | |
| HCV mono-infected | 93.9% | 93 | 99 | 93.8% | 30 | 32 | 96.2% | 76 | 79 | 94.8% | 199 | 210 |
| HCV/HIV co-infected | 100.0% | 5 | 5 | - | 0 | 0 | - | 0 | 0 | 100.0% | 5 | 5 |

VF = virologic failure
[†]Includes genotype 1 subtypes other than 1a and 1b
[‡]Includes PR null responders, PR partial responders, PR+DAA non-responders, virologic breakthrough and virologic rebound
[§]Includes intolerance to or non-compliance with prior therapy

A total of 137 subjects who failed prior PR-based therapies received regimen of GZR with EBR (no RBV) for 16/18 weeks in 2 studies (PN035, PN068). Overall, 93.4% of subjects achieved SVR12 and efficacy was generally comparable between the two studies. Excluding non-virologic failures, 128/136 (94.1%) of subjects achieved SVR12. Virologic failure was observed in 5.8% of subjects; on-treatment failures and relapses were observed. High efficacy was observed in GT1a and GT1b infected subjects. Combining subtypes, SVR12 was achieved in 122/128 (95.3%) of subjects. Efficacy was lower among GT4 and GT6 infected subjects (of note, both breakthroughs occurred in these subjects). Efficacy was comparable among cirrhotics and non-cirrhotics. Efficacy was numerically lower among the HIV co-infected subjects (83.3% compared to 93.9% among the mono-infected subjects), although interpretation was limited as only 6 of the 137 subjects were co-infected in this regimen. Efficacy appeared to be generally comparable regardless of the reason for failure to achieve SVR12 in the context of the previous PR-based regimen (Table 14).

**Table 14: Comparison of results across studies-Treatment experienced subjects- 16/18 weeks without RBV**

| Trial<br>Regimen | PN068<br>GZR and EBR<br>16 weeks<br>N=105 | | | PN035<br>GZR and EBR<br>18 weeks<br>N=32 | | | Combined<br>GZR and EBR<br>16/18 weeks<br>N=137 | | |
|---|---|---|---|---|---|---|---|---|---|
| | % | n | N | % | n | N | % | n | N |
| Overall SVR | 92.4% | 97 | 105 | 96.9% | 31 | 32 | 93.4% | 128 | 137 |
| Outcome for subjects without SVR | | | | | | | | | |
| On-treatment VF | 2.9% | 3 | 105 | 3.1% | 1 | 32 | 2.9% | 4 | 137 |
| Relapse | 3.8% | 4 | 105 | 0.0% | 0 | 32 | 2.9% | 4 | 137 |
| Other | 1.0% | 1 | 105 | 0.0% | 0 | 32 | 0.7% | 1 | 137 |
| SVR by Genotype | | | | | | | | | |
| GT1a | 93.8% | 45 | 48 | 94.1% | 16 | 17 | 93.8% | 61 | 65 |
| GT1b[1] | 95.8% | 46 | 48 | 100% | 15 | 15 | 96.8% | 61 | 63 |
| GT4 | 60.0% | 3 | 5 | - | 0 | 0 | 60.0% | 3 | 5 |
| GT6 | 75.0% | 3 | 4 | - | 0 | 0 | 75.0% | 3 | 4 |
| SVR by Cirrhosis status | | | | | | | | | |
| No | 92.5% | 62 | 67 | 95.2% | 20 | 21 | 93.2% | 82 | 88 |
| Yes | 92.1% | 35 | 38 | 100% | 11 | 11 | 93.9% | 46 | 49 |
| Response to Prior HCV Therapy | | | | | | | | | |
| Prior On-Treatment VF[2] | 92.5% | 62 | 67 | 96.9% | 31 | 32 | 93.9% | 93 | 99 |
| Prior Treatment Relapser | 92.1% | 35 | 38 | - | 0 | 0 | 92.1% | 35 | 38 |
| Other[3] | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 |
| SVR by HIV status | | | | | | | | | |
| HCV mono-infected | 92.9% | 92 | 99 | 96.9% | 31 | 32 | 93.9% | 123 | 131 |
| HCV/HIV co-infected | 83.3% | 5 | 6 | - | 0 | 0 | 83.3% | 5 | 6 |

VF = virologic failure
[1]Includes genotype 1 subtypes other than 1a and 1b
[2]Includes PR null responders, PR partial responders, [3]Includes intolerance to or non-compliance with prior therapy

A total of 139 subjects who failed prior PR-based therapies received GZR with EBR and RBV for 16/18 weeks in 2 studies (P035, P068). Overall, 97.8% of subjects achieved SVR12 and efficacy was generally comparable between the two studies. Excluding non-virologic failures, 136/136 (100%) of subjects achieved SVR12. No subject experienced virologic failure. Efficacy was comparable among cirrhotics and non-cirrhotics. Efficacy appeared to be generally comparable regardless of the reason for failure to achieve SVR12 in the context of the previous PR-based regimen (Table 15).

**Table 15: Comparison of results across studies-Treatment experienced subjects- 16/18 weeks with RBV**

| Trial | PN068 | | | PN035 | | | Combined | | |
|---|---|---|---|---|---|---|---|---|---|
| Regimen | GZR and EBR + RBV 16 weeks N=106 | | | GZR and EBR + RBV 18 weeks N=33 | | | GZR and EBR + RBV 16/18 weeks N=139 | | |
| | % | n | N | % | n | N | % | n | N |
| Overall SVR | 97.2% | 103 | 106 | 100% | 33 | 33 | 97.8% | 136 | 139 |
| Outcome for subjects without SVR | | | | | | | | | |
| On-treatment VF | 0.0% | 0 | 106 | 0.0% | 0 | 33 | 0.0% | 0 | 139 |
| Relapse | 0.0% | 0 | 106 | 0.0% | 0 | 33 | 0.0% | 0 | 139 |
| Other | 2.8% | 3 | 106 | 0.0% | 0 | 33 | 2.2% | 3 | 139 |
| SVR by Genotype | | | | | | | | | |
| GT1a | 94.8% | 55 | 58 | 100% | 19 | 19 | 96.1% | 74 | 77 |
| GT1b[†] | 100% | 38 | 38 | 100% | 14 | 14 | 100% | 52 | 52 |
| GT4 | 100% | 8 | 8 | - | 0 | 0 | 100% | 8 | 8 |
| GT6 | 100% | 2 | 2 | - | 0 | 0 | 100% | 2 | 2 |
| SVR by Cirrhosis status | | | | | | | | | |
| No | 95.7% | 66 | 69 | 100% | 21 | 21 | 96.7% | 87 | 90 |
| Yes | 100.0% | 37 | 37 | 100% | 12 | 12 | 100% | 49 | 49 |
| Response to Prior HCV Therapy | | | | | | | | | |
| Prior On-Treatment VF[‡] | 95.5% | 63 | 66 | 100% | 33 | 33 | 97.0% | 96 | 99 |
| Prior Treatment Relapser | 100% | 40 | 40 | - | 0 | 0 | 100% | 40 | 40 |
| Other[§] | - | 0 | 0 | - | 0 | 0 | - | 0 | 0 |
| SVR by HIV status | | | | | | | | | |
| HCV mono-infected | 97.1% | 99 | 102 | 100% | 33 | 33 | 97.8% | 132 | 135 |
| HCV/HIV co-infected | 100% | 4 | 4 | - | 0 | 0 | 100% | 4 | 4 |

VF = virologic failure
[†]Includes genotype 1 subtypes other than 1a and 1b
[‡]Includes PR null responders, PR partial responders,
[§]Includes intolerance to or non-compliance with prior therapy

Overall, in treatment-experienced HCV patients, each of the above GZR+EBR regimens resulted in high efficacy with SVR12 was achieved in 91.8% to 97.8% of subjects. Excluding administrative ('Other') failures, SVR12 was achieved by 146/156 (93.6%), 204/213 (95.8%), 128/136 (94.1%), and 136/136 (100%) of subjects in the 12 week (no RBV), 12 week (+ RBV), 16 week (no RBV) and 16 week (+ RBV) arms, respectively. The corresponding virologic failure rates were 6.3%, 4.2%, 5.8%, and 0%. Taking these results together, efficacy was highest in the 16 week (+ RBV) arm. However, high efficacy was observed in important subgroups of subjects receiving the 12 week (no RBV). In particular, GT1b infected subjects and subjects of any genotype who experienced a relapse following completion of a prior PR achieved high SVR12 rates (Table 16).

**Table 16: Comparison of results across studies-Treatment experienced subjects treated for 12 or 16/18 weeks with or without RBV**

| Trial<br>Regimen | Combined GZR and EBR 12 weeks N=159 | | | Combined GZR and EBR + RBV 12 weeks N=215 | | | Combined GZR and EBR 16/18 weeks N=137 | | | Combined GZR and EBR + RBV 16/18 weeks N=139 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | % | n | N | % | n | N | % | n | N | % | n | N |
| Overall SVR | 91.8% | 146 | 159 | 94.9% | 204 | 215 | 93.4% | 128 | 137 | 97.8% | 136 | 139 |
| Outcome for subjects without SVR | | | | | | | | | | | | |
| On-treatment VF | 0.0% | 0 | 159 | 0.0% | 0 | 215 | 2.9% | 4 | 137 | 0.0% | 0 | 139 |
| Relapse | 6.3% | 10 | 159 | 4.2% | 9 | 215 | 2.9% | 4 | 137 | 0.0% | 0 | 139 |
| Other | 1.9% | 3 | 159 | 0.9% | 2 | 215 | 0.7% | 1 | 137 | 2.2% | 3 | 139 |
| SVR by Genotype | | | | | | | | | | | | |
| GT1a | 90.3% | 84 | 93 | 92.6% | 100 | 108 | 93.8% | 61 | 65 | 96.1% | 74 | 77 |
| GT1b[†] | 96.5% | 55 | 57 | 97.8% | 90 | 92 | 96.8% | 61 | 63 | 100.0% | 52 | 52 |
| GT4 | 77.8% | 7 | 9 | 93.3% | 14 | 15 | 60.0% | 3 | 5 | 100.0% | 8 | 8 |
| GT6 | - | 0 | 0 | - | 0 | 0 | 75.0% | 3 | 4 | 100.0% | 2 | 2 |
| SVR by Cirrhosis status | | | | | | | | | | | | |
| No | 93.3% | 98 | 105 | 97.0% | 130 | 134 | 93.2% | 82 | 88 | 96.7% | 87 | 90 |
| Yes | 88.9% | 48 | 54 | 91.4% | 74 | 81 | 93.9% | 46 | 49 | 100.0% | 49 | 49 |
| Response to Prior HCV Therapy | | | | | | | | | | | | |
| Prior On-Treatment VF[‡] | 90.0% | 99 | 110 | 92.8% | 128 | 138 | 93.9% | 93 | 99 | 97.0% | 96 | 99 |
| Prior Treatment Relapser | 97.9% | 46 | 47 | 98.4% | 63 | 64 | 92.1% | 35 | 38 | 100.0% | 40 | 40 |
| Other§ | 50.0% | 1 | 2 | 100.0% | 13 | 13 | - | 0 | 0 | - | 0 | 0 |
| SVR by HIV status | | | | | | | | | | | | |
| HCV mono-infected | 91.5% | 140 | 153 | 94.8% | 199 | 210 | 93.9% | 123 | 131 | 97.8% | 132 | 135 |
| HCV/HIV co-infected | 100.0% | 6 | 6 | 100.0% | 5 | 5 | 83.3% | 5 | 6 | 100.0% | 4 | 4 |

VF = virologic failure
[†]Includes genotype 1 subtypes other than 1a and 1b
[‡]Includes PR null responders, PR partial responders, PR+DAA non-responders, virologic breakthrough and virologic rebound
[§]Includes intolerance to or non-compliance with prior therapy

#### *7.3.1.3. Comparison of efficacy in treatment-naïve, non-cirrhotic HCV GT1b infected subjects treated for 8 or 12 weeks with GZR and EBR without RBV:*

Overall, 141 treatment-naïve, non-cirrhotic subjects with HCV GT1b infection were evaluated in Studies P060, P035 (8 and 12 week arms) and 100% of subjects completed study. Across the groups, 42- 54% were males, the mean age was 43-55years, 54-81% were White and 38-77% had baseline viral load >2,000,000 IU/mL. Among the 110 subjects who received GZR with EBR, 108 subjects, or 98.2%, achieved SVR12. Excluding a single administrative failure, SVR12 was achieved in 108/109 (99.1%) of subjects. Among the 31 subjects who received the 8 week regimen, 93.5% of subjects achieved SVR12. Both virologic failures had high viral loads (3,708,721 and 7,195,429 IU/mL), compared with the overall mean of 3,090,205 IU/mL among the overall 8 week cohort. In the 8 week arm, 1/2 (50%) of subjects with F3 Metavir score achieved SVR12 compared to 17/18 (94.4%) of subjects with an F3 Metavir score treated with the 12 week regimen.

**Comments**: Both 8 and 12 treatment regimens with GZR+EBR (100/50 mg) were highly effective (SVR12 of 93-100%) in treatment of TN, Non-Cirrhotic HCV GT1b infected subjects although SVR12 rates were slightly better following 12 weeks of treatment.

### 7.3.2. Efficacy in subgroups

For the comparison of results in subpopulations, efficacy data from Phase II and Phase III studies have been pooled. Two different pooled datasets were used, one for treatment-naïve subjects (the TN-PEP), and one for treatment experienced subjects (the TE-PEP).

#### *7.3.2.1. Subgroup analysis in the treatment-naïve pooled efficacy population (TN-PEP):*

The treatment arms and studies included and excluded from the TN PEP is summarised in Table 17. Of the total of 886 patients in this group, 752 did not receive RBV and 134 received RBV along with GZR+EBR**.** Majority of the subjects were male, White and infected with HCV GT1 (801/886, 90.4% and 57% with GT1a). A total of 66/886 (7.4%) and 19/886 (2.1%) subjects were infected with HCV GT4 and GT6, respectively and 277/886 subjects (31.3%) were HIV co-

infected. The mean baseline HCV RNA was approximately 3 million IU/mL, and 384/886 (43.3%) had plasma HCV-RNA above 2 million IU/mL; the mean baseline HCV RNA was slightly higher in the RBV-containing group (approximately 5 million IU/mL) compared to the RBV free group (approximately 2.8 million IU/mL).

**Table 17: Arms and studies included (top) and excluded (bottom) in the treatment naïve pooled efficacy population**

| Trial | Treatment Groups | Population | GT | N | Comments |
|---|---|---|---|---|---|
| Phase 2 | | | | | |
| 035A | GZR 100 mg + EBR 50 mg | TN NC | 1 | 13 | |
| 035A | GZR 100 mg + EBR 50 mg + RBV | TN NC | 1 | 27 | |
| 035B | GZR 100 mg + EBR 50 mg | TN NC, TN C, HIV Co-infected | 1 | 90 | 12 week arms only |
| 035B | GZR 100 mg + EBR 50 mg + RBV | TN NC, TN C, HIV Co-infected | 1 | 93 | 12 week arms only |
| 047B | GZR 100 mg + EBR 50 mg | TN NC | 4, 6 | 14 | GT4 and GT6 infected subjects only |
| 047B | GZR 100 mg + EBR 50 mg + RBV | TN NC | 4, 6 | 14 | |
| Phase 3 | | | | | |
| 052 | GZR 100 mg + EBR 50 mg | TN (NC and C) with CKD | 1 | 101 | Immediate and Intensive PK arms, treatment-naïve subjects only |
| 060 | GZR/EBR | TN (NC and C) | 1, 4, 6 | 316 | Immediate treatment arm only |
| 061 | GZR/EBR | HIV Co-infected, TN (NC and C) | 1, 4, 6 | 218 | |

GZR/EBR: Fixed dose combination. TN: Treatment Naive. NR: Null Responder. NC: Non-Cirrhotic. C: Cirrhotic. CKD: Chronic kidney disease

Arms and Studies Excluded from the Treatment-Naïve Pooled Efficacy Population

| Trial | Treatment Groups | Population | GT | N | Comments |
|---|---|---|---|---|---|
| Phase 2 | | | | | |
| 035A | GZR 100 mg + EBR 20 mg + RBV | TN NC | 1 | 25 | 20 mg dose of EBR |
| 035B/C | GZR 100 mg + EBR 50 mg | TN NC, TN C, NR NC, NR C, HIV Co-infected | 1 | 127 | Exclude 8-week and 18-week arms and all treatment experienced arms |
| 035B/C | GZR 100 mg + EBR 50 mg + RBV | TN NC, TN C, NR NC, NR C, HIV Co-infected | 1 | 157 | Exclude 8-week and 18-week arms and all treatment experienced arms |
| 035D | GZR 100 mg + EBR 50 mg + RBV | TN NC | 3 | 41 | GT3 indication not being sought |
| 047A | GZR 100 mg + EBR 50 mg + RBV | TN NC | 2 | 30 | GT2 indication not being sought |
| 047B | GZR 100 mg + RBV | TN NC | 2 | 30 | GT2 indication not being sought |
| 047B | GZR 100 mg + EBR 50 mg | TN NC | 5 | 4 | GT5 indication not being sought |
| 047B | GZR 100 mg + EBR 50 mg + RBV | TN NC | 5 | 4 | GT5 indication not being sought |
| 048 | GZR 100 mg + EBR 50 mg + RBV | Prior DAA failure (NC and C) | 1 | 79 | Treatment experienced |
| 074 | GZR 100 mg + EBR 50 mg + SOF | TN (NC and C) | 1, 3 | 143 | Includes SOF in regimen |
| Phase 3 | | | | | |
| 052 | GZR 100 mg + EBR 50 mg | TN (NC and C) with CKD | 1 | 113 | Deferred treatment arm-- FU12 not complete |
| 052 | GZR 100 mg + EBR 50 mg | TE (NC and C) with CKD | 1 | 21 | Exclude treatment experienced subjects only |
| 060 | GZR/EBR | TN (NC and C) | 1, 4, 6 | 105 | Deferred treatment arm-- FU12 not complete |
| 068 | GZR/EBR or GZR/EBV + RBV for 12 or 16 weeks | Prior PR failures (NC and C) | 1, 4, 6 | 420 | Treatment experienced |

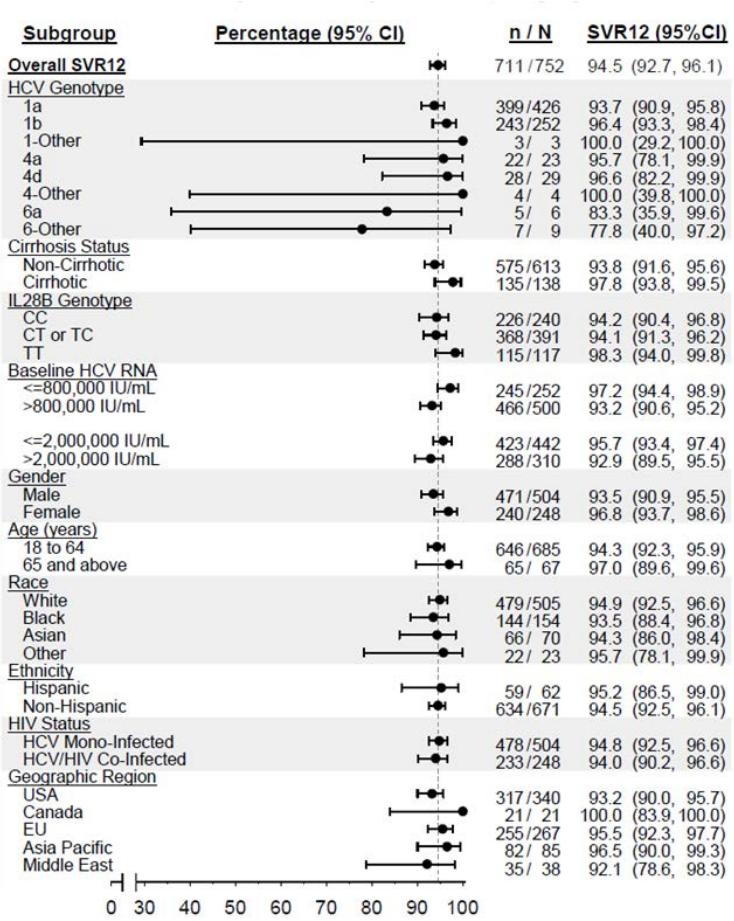
TN: Treatment Naïve. TE: Treatment Experienced. NC: Non-Cirrhotic. C: Cirrhotic. CKD: Chronic kidney disease.

A total of 834 of the 886 subjects in the TN-PEP achieved SVR12 with an estimated SVR12 rate is 94.1% (95% CI: 92.4, 95.6). The SVR12 rate (95% CI) was 94.5% (92.7, 96.1) and 91.8% (85.8, 95.8) in subjects treated for 12 weeks with GZR/EBR 100/50 mg without and with RBV, respectively. Across both arms, 19 subjects (2.1% of the overall TN-PEP) failed to achieve SVR12 for reasons other than virologic failure (primarily due to administrative matters, such as loss to follow-up or non-AE-related discontinuation). Excluding these subjects, SVR12 was achieved in 711/736 (96.6%) of subjects who received 12 weeks of therapy with GZR/EBR (no RBV) and 123/131 (93.8%) of subjects who received 12 weeks of therapy with GZR, EBR (+RBV). Virologic failure occurred in 25/752 (3.3%) of subjects who received 12 weeks of therapy with GZR with EBR (no RBV). Relapse was the predominant type of virologic failure, accounting for 84% of all virologic failures. Virologic failure occurred in 8/134 (5.9%) of subjects who received 12 weeks of therapy with GZR, EBR, and RBV. Relapse was the predominant type of virologic failure, accounting for 75% of all virologic failures. Overall, these results suggested that, addition of RBV to the proposed GZR/EBR treatment regimen provided no additional benefit for treatment-naïve subjects.

Additional analyses have been performed to assess the consistency of the response across various subgroups within the TN-PEP based on both virus and disease related characteristics (HCV genotype and sub-genotype, stage of liver fibrosis and baseline viral load), demographic

factors (gender, age, race/ethnicity, HIV co-infection) and geographic region. Overall, high efficacy was observed in each of the subgroups evaluated, including subgroups traditionally associated with lower response rates to HCV therapy such as cirrhosis, HIV-co-infection, older patients and high HCV viral loads at baseline. Efficacy was comparable, or in many instances higher, in the RBV-free group compared to the RBV-containing group, demonstrating that there is no additional benefit to including RBV in the regimen for treatment-naïve subjects. Small differences in the proportion of subjects achieving SVR12 between various subgroups were observed, but for each comparison, the 95% confidence intervals for the various groups overlapped (Figure 15).

**Figure 15: Forest plot summarising SVR12 rates by subgroup**




In addition, differences observed within a given subgroup may be confounded by other baseline factors. Specific differences that were observed include:

- SVR12 was achieved in a slightly lower proportion of GT1a compared to GT1b infected subjects (93.4% versus 95.9%) driven by slightly higher rate of virologic failure (predominantly relapse) in GT1a infected compared with GT1b infected subjects (4.6% versus 1.3%).
- SVR12 was achieved in a slightly higher proportion of cirrhotic subjects compared to non-cirrhotic subjects (96.4% versus 93.6%).
- In contrast to results from studies using interferon-based regimens, SVR12 was achieved in a slightly higher proportion of subjects with the *IL28B* TT genotype (97.8%) compared to subjects with the *IL28B* CC genotype (93.9%) or CT genotype (93.6%).

- SVR12 was achieved in a higher proportion of subjects with low baseline HCV RNA (≤ 800,000 IU/mL) compared to subjects with high baseline HCV RNA (> 800,000 IU/mL) (97.2% versus 92.7%), but confidence intervals were broadly overlapping. The impact was most notable in GT1a infected subjects.
- SVR12 was achieved in a slightly higher proportion of older subjects (>= 65 years of age) compared to younger subjects (< 65 years of age) (97.4 versus 93.8%).

Subgroup analysis in the Treatment-Experienced Pooled Efficacy Population (TE-PEP):

The Treatment Experienced Pooled Efficacy Population (TE-PEP) includes data from each of the Phase II and Phase III studies, or arms of such studies and included 650 subjects who had failed prior HCV therapy; the treatment arms and studies included in the TE-PEP are summarised in Table 18.

**Table 18: Treatment arms and studies included (top) and excluded (bottom) in the treatment experienced pooled efficacy population**

| Trial | Treatment Groups | Population | GT | N | Comments |
|---|---|---|---|---|---|
| Phase 2 | | | | | |
| 035B | GZR 100 mg + EBR 50 mg | NR NC, NR C | 1 | 65 | |
| 035B | GZR 100 mg + EBR 50 mg + RBV | NR NC, NR C | 1 | 65 | |
| 048 | GZR 100 mg + EBR 50 mg + RBV | Prior DAA failure (NC and C) | 1 | 79 | |
| Phase 3 | | | | | |
| 052 | GZR 100 mg + EBR 50 mg | TN/TE (NC and C) with CKD | 1, 4, 6 | 21 | Treatment experienced subjects only |
| 068 | GZR/EBR for 12 or 16 weeks | Prior PR failures (NC and C) | 1, 4, 6 | 210 | |
| 068 | GZR/EBR + RBV for 12 or 16 weeks | Prior PR failures (NC and C) | 1, 4, 6 | 210 | |

GZR/EBR: Fixed dose combination. TN: Treatment Naïve. NR: Null Responder. NC: Non-Cirrhotic. C: Cirrhotic. CKD: Chronic kidney disease

Arms and Studies Excluded from the Pooled Efficacy Population

| Trial | Treatment Groups | Population | GT | N | Comments |
|---|---|---|---|---|---|
| Phase 2 | | | | | |
| 035A | GZR 100 mg + EBR 20 mg + RBV | TN NC | 1 | 25 | Treatment-naive |
| 035A | GZR 100 mg + EBR 50 mg | TN NC | 1 | 13 | Treatment-naive |
| 035A | GZR 100 mg + EBR 50 mg + RBV | TN NC | 1 | 27 | Treatment-naive |
| 035B | GZR 100 mg + EBR 50 mg | TN NC, TN C, HIV Co-infected | 1 | 121 | Treatment-naive |
| 035B | GZR 100 mg + EBR 50 mg + RBV | TN NC, TN C, HIV Co-infected | 1 | 155 | Treatment-naive |
| 035C | GZR 100 mg + EBR 50 mg | TN NC, TN C, HIV Co-infected | 1 | 31 | Treatment-naive |
| 035C | GZR 100 mg + EBR 50 mg + RBV | TN NC, TN C, HIV Co-infected | 1 | 30 | Treatment-naive |
| 035D | GZR 100 mg + EBR 50 mg + RBV | TN NC, TN C, HIV Co-infected | 3 | 41 | Treatment-naive, GT3 |
| 047A | GZR 100 mg + EBR 50 mg + RBV | TN NC | 2 | 30 | Treatment-naive, GT2 |
| 047B | GZR 100 mg + RBV | TN NC | 2 | 30 | Treatment-naive, GT2 |
| 047B | GZR 100 mg + EBR 50 mg | TN NC | 4, 5, 6 | 19 | Treatment-naive |
| 047B | GZR 100 mg + EBR 50 mg + RBV | TN NC | 4, 5, 6 | 19 | Treatment-naive |
| 074 | GZR 100 mg + EBR 50 mg + SOF | TN (NC and C) | 1, 3 | 143 | Treatment-naive |
| Phase 3 | | | | | |
| 052 | GZR 100 mg + EBR 50 mg | TN/TE (NC and C) with CKD | 1, 4, 6 | 101 | Exclude only treatment-naive subjects |
| 060 | GZR/EBR | TN (NC and C) | 1, 4, 6 | 421 | Treatment-naive (immediate and deferred treatment arms) |
| 061 | GZR/EBR | HIV Co-infected, TN (NC and C) | 1, 4, 6 | 218 | Treatment-naive |

TN: Treatment Naïve. TE: Treatment Experienced. NC: Non-Cirrhotic. C: Cirrhotic. CKD: Chronic kidney disease

Of the 650 subjects in the TE-PEP, 607 (93.4%) were infected with HCV GT1; of these, 343 (52.7%) were infected with GT1a, 261 (40.1%) were infected with GT1b and 3 (0.5%) were infected with other GT1 subtypes. The majority of GT1 infected subjects were male, white and non-Hispanic, and the mean age was between 55 and 58 years old. More than a half of subjects had baseline HCV RNA >2,000,000 IU/mL, more than two-thirds had non-CC *IL28B* genotypes, and approximately 35% had compensated cirrhosis. The baseline demographic and disease characteristics of GT1a and GT1b infected subjects were generally similar, although GT1a infected subjects were slightly more likely to be male (70% versus 53.3%), black (17.8% versus 8.8%) and HCV/HIV co-infected (4% versus 2%). Asian race was more common in GT1b (14.6%) than GT1a (5.0%) infected subjects. The baseline demographics and disease

characteristics of GT4 infected subjects were generally similar to GT1 infected subjects. All HCV GT6 infected subjects were Asian and included 3 males and 3 females.

Overall, 215, 159, 139 and 137 were included in the 12 week GZR+EBR (no RBV), 12 week GZR+EBR+RBV, 16 week GZR+EBR (no RBV) and 16 week GZR+EBR + RBV treatment arms, respectively. Baseline demographics in these patients were similar across the 4 groups. Overall, each of the above GZR+EBR regimens resulted in high efficacy in treatment-experienced HCV patients with SVR12 achieved in 91.8% to 97.8% of subjects, but the highest SVR12 (100%) in treatment-experienced HCV patients was observed following 16 weeks treatment with GZR+EBR+RBV. Administration of GZR+EBR ± RBV for 12/16 weeks was effective in all subgroups irrespective of genotype, cirrhosis, and baseline viral load and HIV co-infection. Although there were minor numerical differences between subgroups, the 95% confidence intervals were overlapping and efficacy was generally maintained in all subgroups (Figures 16-17).

**Figure 16: Forest plot summarising SVR12 rates by subgroup: GZR and EBR+RBV for 12 weeks**

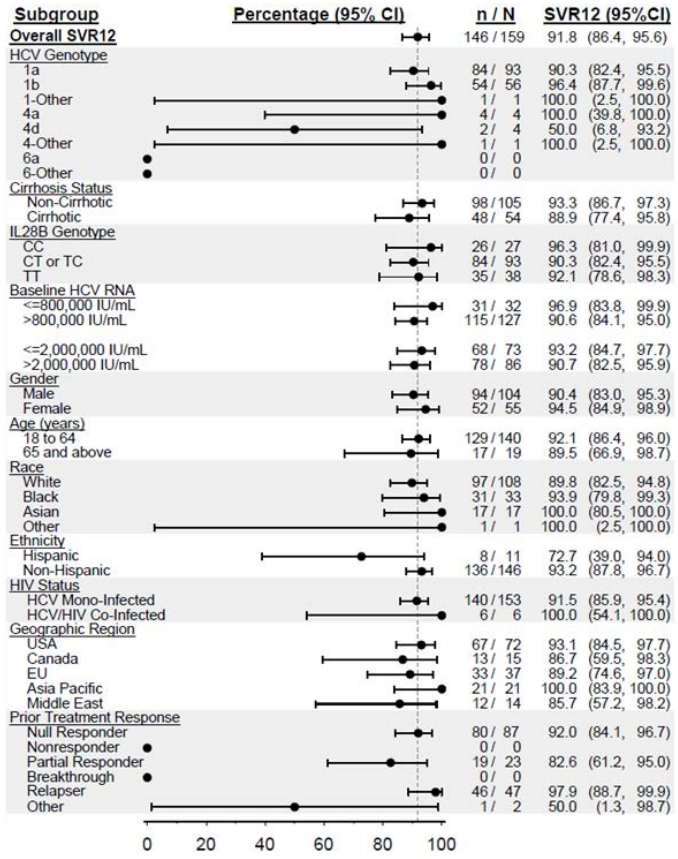
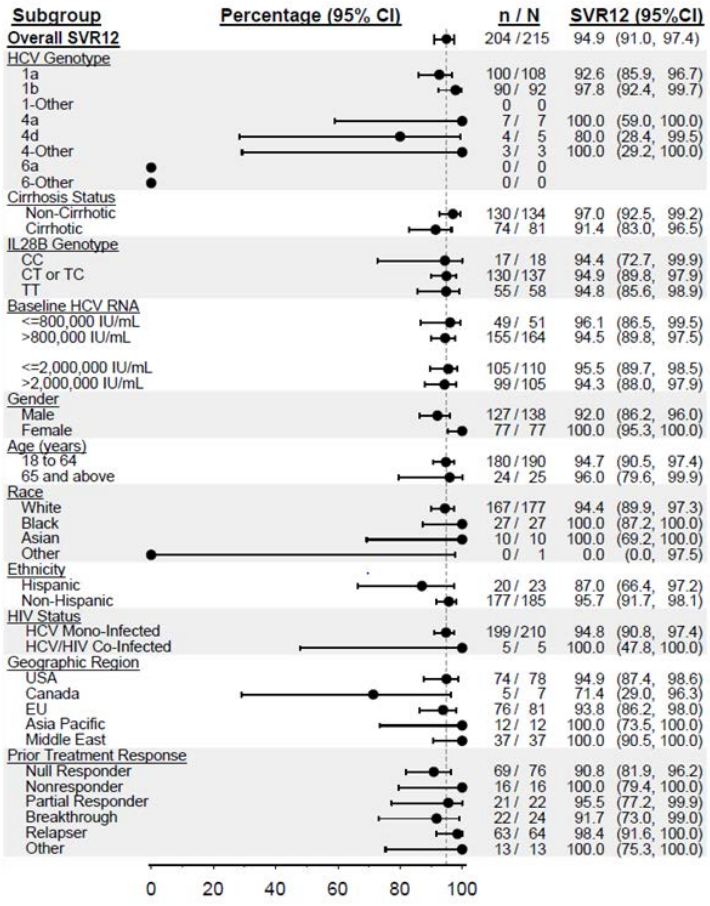


**Figure 17: Forest plot summarising SVR12 rates by subgroup: GZR and EBR+RBV for 16/18 weeks**




### 7.3.3. Overall assessment of predictors of SVR12

As supportive exploratory analyses, logistic regression models were used to evaluate potential predictors of SVR12. Separate logistic regression models were used for the TN-PEP and TE-PEP.

*Predictors for SVR12 in TN subjects:* Univariate logistic regression models were fitted with one variable at time in assessing the potential association with SVR12 in the TN cohort. The majority of subjects in the TN cohort had either genotype 1a (57%) or genotype 1b (33%). Given the cumulative knowledge from the Phase II and Phase III studies of GZR with EBR and data from other DAA drugs, the treatment regimen and factors affecting SVR12 tend to be different for TN subjects infected with GT1a and those infected with GT1b. Thus, separate analyses were performed for the GT1a and GT1b cohorts. This approach was considered both feasible, because of the relatively large number of TN GT1a subjects available and appropriate, because it inherently accounts for possible interactions between GT1a and GT1b subjects.

*SVR12 predictors in GT1a TN subjects*

After univariate logistic regression models were fitted, the variables that appeared to be associated with SVR12, as assessed by either the p-value or the magnitude of the estimated odds ratio include: baseline HCV RNA (≤ 800,000 IU/mL versus > 800,000 IU/mL) and presence of baseline NS5A RAVs (with a larger association seen for presence of baseline NS5A RAVs with >5 fold resistance).

Multi-variable logistic regression models with forward selection (with p-values of 0.05 and 0.10 as selection criteria)[32] were applied to identify significant independent predictors of SVR12.

Using a significance level of 0.05, only presence of any baseline NS5A RAVs was found to be an independent significant predictor of SVR12. Using a significance level of 0.10, presence of any baseline NS5A RAVs, baseline HCV load and presence of baseline NS3 RAVs were found to be significant predictors of SVR12. When controlling for baseline NS5A RAVs, subjects with baseline NS3 RAVs have higher SVR12 rates than subjects with no baseline NS3 RAVs. Thus, the level of baseline NS5A RAVs has a substantial impact on SVR12, but the presence of baseline NS3 RAVs does not negatively impact the SVR12 rate. In particular, when no baseline NS5A RAVs have been detected, the sample sizes are large, and SVR12 rates are very high and similar in subjects with (216/217 = 99.5%) and without (211/217 = 97.2%) baseline NS3 RAVs. Thus, the only consistently identified potential prognostic factors for SVR12 were baseline HCV RNA (> 800,000 IU/mL versus ≤ 800,000 IU/mL) and presence of baseline NS5A RAVs.

**Comments**: Overall, the lowest SVR12 rate was observed among patients with higher baseline HCV RNA load (>800,000 IU/mL) and presence of baseline NS5A RAVs that confer > 5 fold reductions in the potency to EBR in vitro but this represents only 5.3% of the total cohort of treatment naïve subjects with HCV GT1a infection.

*SVR12 predictors in GT1a TN subjects*

The SVR12 rate was slightly higher in subjects infected with GT1b (95.9%, 280/292) than in subjects infected with GT1a (93.4%, 470/503). Given the relatively few non-responders (12 out of 292) , majority of whom were not virologic failures, and the smaller sample size in the TN GT1b cohort, the ability to fit multi-variable models was more limited than for the TN GT1a cohort, nevertheless, similar approaches to those used for the GT1a cohort were applied to TN GT1b subjects. Only RBV use was identified as a potential predictor of SVR12 by the forward selection method using both 0.05 and 0.10 significance levels. The estimated ORs for RBV use was 0.15 (95% CI: 0.02 – 1.09, p = 0.06), suggesting a negative impact of adding RBV to GZR with EBR.

Overall conclusions for the TN-PEP subjects with HCV Genotype 1

- The use of RBV in addition to GZR with EBR does not increase SVR12 in treatment naïve subjects with HCV Genotype 1a or Genotype 1b.
- The commonly used design factors for stratification, cirrhosis status and HIV co-infection, do not substantially impact SVR12 rates in GT1a or GT1b subjects. There is no suggestion of a negative impact of cirrhosis on SVR12, but there is a numerical trend for slightly lower rates in HIV co-infected subjects.
- Demographic factors of age and gender do not substantially impact SVR12 rates in GT1a subjects, although subjects > 65 years of age have very high SVR12 rates and females have slightly higher rates than males.
- After controlling for NS5A RAVs, there is no suggestion of a negative impact of baseline NS3 RAVs on SVR12 in GT1a subjects. In GT1b subjects, even the presence of NS5A baseline RAVs has only a modest numerical effect.

Only baseline HCV RNA (> 800,000 versus ≤ 800,000) and presence of baseline NS5A RAVs were identified as significant predictors of SVR12 in GT1a subjects. However, baseline HCV RNA >

[32] Because the forward selection procedure starts with no variable in the model, this method is more likely to avoid the very small sample sizes and/or 100% SVR12 rates within the individual cells of the multiple variables included in the model at a given step/

800,000 has a substantial impact on SVR12 only in the presence of baseline NS5A RAVs (with > 5 fold resistance). No clear significant predictors for SVR12 were identified for GT1b subjects.

Efficacy (SVR12) by On-Treatment Response was conducted in the TN pooled efficacy population only. Although subjects who became undetectable relatively early (by Day 7 or by Day 13) had slightly higher SVR12 rates than subjects who became undetectable later, the relationship between time to first negative HCV RNA and SVR12 is not strong. These results suggest that 12 week treatment duration is sufficient to ensure that response rates are high even for subjects who do not achieve undetectable HCV RNA relatively early.

*Multi-variable logistic regression analysis of SVR12 in TE-PEP*

Overall, conclusions for the TE GT1 cohort were:

- For the overall TE GT1 cohort, using a significance level of 0.10, the use of RBV in addition to GZR with EBR, longer treatment duration, being female, and having genotype 1b were independently significantly associated with a higher SVR12 rate (all odds ratios were at least 2.5), compared to the corresponding reference group. The presence of baseline NS5A RAVs had a very strong (OR = 0.02), highly significant ($p < 0.0001$) negative impact on SVR12, compared to the absence of baseline NS5A RAVs.
- The OR for RBV use was numerically larger in GT1a subjects with prior on treatment failure (2.85) than in GT1a subjects with prior relapse (1.64), suggesting that RBV use has more impact on SVR12 in GT1a subjects with prior on-treatment failure than in GT1a subjects with prior relapse, where the effect is modest. Little impact of RBV use was seen in GT1b subjects.
- Longer treatment duration (16/18 weeks) has a (numerically) positive impact on SVR12 in GT1a subjects with prior on-treatment failure (OR = 2.72), but does not impact SVR12 in GT1a subjects with prior relapse (OR = 0.86). For GT1b TE subjects overall, the OR for longer treatment duration (2.08) was lower than for GT1a TE subjects overall (2.48), suggesting less impact of duration on GT1b TE subjects. The odds ratios for longer treatment duration could not be estimated for GT1b prior on-treatment failures or GT1b prior relapsers due to the very high response rates.
- SVR12 rates ranged from 96% to 100% across the four subgroups defined by prior treatment response (on-treatment failure versus relapse) and treatment duration (12 weeks versus 16/18 weeks).
- Presence of cirrhosis has a (numerically) negative impact on SVR12 in GT1a TE subjects overall (OR = 0.53), and this impact appears larger in GT1a subjects with prior on-treatment failure (OR = 0.40). Presence of cirrhosis did not have a negative impact in GT1b TE subjects overall.
- For GT1a subjects with prior on-treatment failure and cirrhosis, the OR for RBV use (2.26) was similar to the OR for all GT1a subjects with prior on-treatment failure, but the OR for longer treatment duration (9.56) was substantially higher, although it was not statistically significant ($p = 0.16$) due to the small sample size.
- There is no clear impact of HIV co-infection on SVR12.

### 7.3.4. Analysis of resistance-associated variants (RAVs)

To examine the potential impact of baseline RAVs within the NS3 or NS5A proteins on the efficacy of GZR and EBR, respectively, and to evaluate whether virologic failure is associated with the development of RAVs, the following analyses were conducted: (1) NS3 and NS5A RAVs present prior to therapy were assessed for their impact on the efficacy of GZR and EBR, as measured by SVR12. (2) The frequency, types of mutations, and persistence of treatment-emergent NS3 and NS5A RAVs were evaluated in subjects with virologic failure.

Plasma samples from all subjects who participated in the studies were collected prior to dosing to generate baseline sequence information. Additional samples were collected from subjects who met the criteria for virologic failure and follow-up visits whenever available. Due to assay limitations, only samples with viral titters above 1000 IU/mL were sequenced. The HCV NS3/4A and NS5A genes from subject plasma samples were amplified using reverse transcription polymerase chain reaction (RT-PCR) followed by population sequencing. The limit of minority variant detection in the population was >25% of the viral population.

Post-baseline variant analysis was conducted by comparing the amino acid sequences at virologic failure time points to those at baseline (Day 1, pre-dose). A treatment-emergent RAV was defined as an amino acid substitution at a specific locus within HCV NS3 or NS5A that was present at virologic failure and/or follow-up visits but not at baseline. Therefore, treatment-emergent RAV analysis was conducted in subjects for whom both baseline and follow up visit sequences were available for NS3 and/or NS5A.

#### *7.3.4.1. Analysis of RAVs in the treatment naïve pooled efficacy population (TN-PEP):*

Pooled Resistance Analysis Population (RAP) included all subjects from the Treatment-Naïve Pooled Efficacy Population (TN-PEP), who either achieved SVR12 or met criteria for virologic failure. The RAP does not include any subject who discontinued the study for reasons other than virologic failure (Table 19).

**Table 19: Resistance analysis population**

| | GT1a | GT1b | GT1-other | GT4 | GT6 |
|---|---|---|---|---|---|
| **Subjects in FAS** | 503 | 292 | 6 | 66 | 19 |
| **Subjects Excluded from the RAP** | 10 | 8 | 0 | 1 | 0 |
| D/C due to an adverse event | 1 | 0 | 0 | 0 | 0 |
| D/C due to admin reason | 6 | 8 | 0 | 1 | 0 |
| Outside visit window | 3 | 0 | 0 | 0 | 0 |
| **Subjects in the RAP** | 493 | 284 | 6 | 65 | 19 |
| **Analysis of BL RAVs** | | | | | |
| Subjects with Sequences for NS3 Available | 487 | 280 | 3 | 64 | 18 |
| Subjects with Sequences for NS3 Not Available | 6 | 4 | 3 | 1 | 1 |
| Subjects with Sequences for NS5A Available | 491 | 281 | 3 | 64 | 18 |
| Subjects With Sequences for NS5A Not Available | 2 | 3 | 3 | 1 | 1 |
| **Analysis of RAVs at VF** | | | | | |
| Subjects Achieved $SVR_{12}$ | 470 | 280 | 5 | 64 | 15 |
| Subjects with Virologic Failure | 23 | 4 | 1 | 1 | 4 |
| Subjects with VF; Post-baseline Sequences Available | 21 | 3 | 0 | 1 | 4 |
| NS3 Sequences Available | 21 | 3 | 0 | 1 | 4 |
| NS5A Sequences Available | 21 | 3 | 0 | 1 | 4 |
| Subjects with VF; Post-baseline Sequences Not Available | 2 | 1 | 1 | 0 | 0 |
| NS3 Sequences Not Available | 2 | 1 | 1 | 0 | 0 |
| NS5A Sequences Not Available | 2 | 1 | 1 | 0 | 0 |

NS3 variants commonly associated with resistance to first generation protease inhibitors were detected at baseline among 287/770 (37.3%) GT1 infected subjects; the most common baseline NS3 RAVs (present in >5% of subjects) were Q80K (175/770, 22.7%) and S122G (54/770, 7.0%). The prevalence of RAVs causing a >5 fold decrease in GZR potency was very low (4/770, 0.5%) and all were GT1b infected subjects with the D168E RAV. At baseline, NS3 RAVs were most commonly observed among GT1a infected subjects (249/487, or 51.1%) compared with GT1b infected subjects (37/280 subjects, or 13.2%). Among GT1a infected subjects, the most common baseline NS3 RAVs were nearly the same as in the overall GT1 RAP; Q80K and S122G

occurred in 35.5% (173/487) and 7.0% (34/487), respectively. The only NS3 RAV that occurred at a frequency of >5% in subjects with GT1b infection was S122G, present in 7.1% (20/280). No NS3 RAV causing a >5 fold decrease in GZR potency was detected at baseline in GT1a infected subjects. In GT1b infected subjects, only 1 NS3 RAV causing a >5 fold decrease in GZR potency, D168E, was detected in 4 subjects at baseline. The Q80K RAV, which has been associated with decreased efficacy in GT1a infected subjects treated with simeprevir/PR was detected in 173/487 (35.5%) GT1a infected subjects and in 2/280 (0.7%) of GT1b infected subjects. Q80K causes a ≤ 5 fold decrease in GZR potency in vitro. There was a >10% higher prevalence of baseline NS3 RAVs among cirrhotics (73/160 [45.6%]) compared to non-cirrhotic subjects (214/610 [35.1%]). There was also a >10% higher prevalence of baseline NS3 RAVs in subjects with the *IL28B CC* genotype (113/236 [47.9%]) compared to subjects with non-CC *IL28B* genotypes (173/532 [32.5%]). Overall, 12/52 (23.1%) GT4 infected subjects had one or more baseline NS3 RAVs prior to treatment. All 18 GT6 infected subjects in the TN-PEP RAP had one or more baseline RAVs prior to treatment.

There was no evident association between baseline GT1 NS3 RAVs and virologic failure. SVR12 was achieved in 277/287 (96.5%) and 466/483 (96.5%) of subjects with GT1 infection with or without NS3 RAVs, respectively. All of the GT1 infected subjects (N = 4) who harboured RAVs associated with >5 fold reduced susceptibility to GZR at baseline achieved SVR12. There were no notable differences in the impact of baseline NS3 RAVs among HCV GT1a subjects compared with HCV GT1b infected subjects; the SVR12 rate was slightly higher in GT1a infected subjects with baseline NS3 RAVs (96.4%) compared to those without RAVs (94.1%). There was no notable impact of baseline NS3 RAVs in any of the other key subgroups of GT1 infected subjects. There was no association between the presence of baseline Q80K and treatment response; SVR12 rates were 96% (166/173) and 94.9% (298/314) in subjects with and without baseline Q80K. The impact of baseline GT1a or GT1b NS3 RAVs on treatment outcome was not affected by cirrhosis status. Overall, 12/64 (18.8%) of the GT4 infected subjects in the TN-PEP RAP had baseline NS3 RAVs, and 63/64 (98.4%) achieved SVR12. All GT6 infected subjects in the TN-PEP RAP had baseline NS3 RAVs, but the majority (14/18; 77.8%) achieved SVR12 (Table 20).

**Table 20: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment naïve subjects NS3/4 resistance analysis population with HCV genotypes 4 or 6**

| | Did Not Have Baseline NS3 RAVs | | Had Baseline NS3 RAVs | | Total | |
|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) |
| Total | 52 | 51 (98.1) | 30 | 26 (86.7) | 82 | 77 (93.9) |
| **HCV Genotype** | | | | | | |
| 4a | 22 | 22 (100.0) | 6 | 6 (100.0) | 28 | 28 (100.0) |
| 4d | 28 | 27 (96.4) | 4 | 4 (100.0) | 32 | 31 (96.9) |
| 4-Other | 2 | 2 (100.0) | 2 | 2 (100.0) | 4 | 4 (100.0) |
| 6a | 0 | 0 ( ) | 7 | 6 (85.7) | 7 | 6 (85.7) |
| 6-Other | 0 | 0 ( ) | 11 | 8 (72.7) | 11 | 8 (72.7) |
| **Cirrhosis Status** | | | | | | |
| Non-Cirrhotic | 49 | 48 (98.0) | 26 | 22 (84.6) | 75 | 70 (93.3) |
| Cirrhotic | 3 | 3 (100.0) | 3 | 3 (100.0) | 6 | 6 (100.0) |
| Unknown | 0 | 0 ( ) | 1 | 1 (100.0) | 1 | 1 (100.0) |
| **IL28B Genotype** | | | | | | |
| CC | 13 | 13 (100.0) | 15 | 14 (93.3) | 28 | 27 (96.4) |
| Non-CC | 39 | 38 (97.4) | 15 | 12 (80.0) | 54 | 50 (92.6) |
| **Baseline HCV RNA** | | | | | | |
| <=2,000,000 IU/mL | 36 | 36 (100.0) | 17 | 17 (100.0) | 53 | 53 (100.0) |
| >2,000,000 IU/mL | 16 | 15 (93.8) | 13 | 9 (69.2) | 29 | 24 (82.8) |
| **HIV Status** | | | | | | |
| HCV Mono-Infected | 27 | 27 (100.0) | 26 | 22 (84.6) | 53 | 49 (92.5) |
| HCV/HIV Co-Infected | 25 | 24 (96.0) | 4 | 4 (100.0) | 29 | 28 (96.6) |
| **Treatment Regimen** | | | | | | |
| GZR with EBR | 43 | 42 (97.7) | 26 | 23 (88.5) | 69 | 65 (94.2) |
| GZR with EBR + RBV | 9 | 9 (100.0) | 4 | 3 (75.0) | 13 | 12 (92.3) |

N = Number of subjects in RAP with HCV genotype 4 or 6 with baseline NS3 sequencing.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

The overall prevalence of baseline GT1 variants commonly associated with resistance to NS5A inhibitors was low (91/775, 11.7%) with >5 fold resistance to EBR at baseline was 67/775 (8.6%). The prevalence of baseline NS5A RAVs was generally comparable in subjects in the RBV-free compared to RBV-containing treatment regimens the most common baseline NS5A RAVs (present in >1% of subjects) were M28V (27/775, 3.5%), L31M (27/775, 3.5%) and Y93H (25/775 3.2%). With the exception of M28V, each of these RAVs, are associated with a >5- fold shift in potency to EBR. The overall prevalence of baseline GT1 NS5A RAVs was slightly lower among GT1ainfected subjects (52/491, 10.6%) versus GT1b infected subjects (39/281, 13.9%). The prevalence of baseline NS5A RAVs was generally comparable in cirrhotic compared to non-cirrhotic subjects, in subjects with the *IL28B CC* genotype compared to subjects with non-CC *IL28B* genotypes, subjects with high or low baseline HCV RNA, and HCV monoinfected subjects compared to HCV/HIV co-infected subjects (Table 21). The overall prevalence of baseline NS5A variants was high for GT4 infected subjects; 25/64 (39.1%) subjects had one or more baseline NS5A RAVs prior to treatment 6/18 (33.3%) of GT6 infected subjects in the TN-PEP RAP had one or more baseline NS5A RAVs prior to treatment (Table 22).

**Table 21: Prevalence and types of baseline NS5A variants pooled efficacy population Treatment naïve subjects NS5A resistance analysis population with HCV genotype 1**

| Population | Subjects | Sequences Available | Did Not Have Baseline NS5A RAVs | | Had Baseline NS5A RAVs But None That Conferred >5-Fold Resistance to EBR | | Had Baseline NS5A RAVs That Conferred >5-Fold Resistance to EBR | |
|---|---|---|---|---|---|---|---|---|
| | N | m | x | x/m (%) | y | y/m (%) | z | z/m (%) |
| Overall GT1 in RAP | 783 | 775 | 684 | 88.3 | 24 | 3.1 | 67 | 8.6 |
| HCV Genotype | | | | | | | | |
| 1a | 493 | 491 | 439 | 89.4 | 23 | 4.7 | 29 | 5.9 |
| 1b | 284 | 281 | 242 | 86.1 | 1 | 0.4 | 38 | 13.5 |
| 1-Other | 6 | 3 | 3 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Cirrhosis Status | | | | | | | | |
| Non-Cirrhotic | 621 | 616 | 543 | 88.1 | 19 | 3.1 | 54 | 8.8 |
| Cirrhotic | 162 | 159 | 141 | 88.7 | 5 | 3.1 | 13 | 8.2 |
| IL28B Genotype | | | | | | | | |
| CC | 242 | 238 | 209 | 87.8 | 9 | 3.8 | 20 | 8.4 |
| Non-CC | 539 | 535 | 473 | 88.4 | 15 | 2.8 | 47 | 8.8 |
| Unknown | 2 | 2 | 2 | 100.0 | 0 | 0.0 | 0 | 0.0 |
| Baseline HCV RNA | | | | | | | | |
| <=2,000,000 IU/mL | 438 | 435 | 387 | 89.0 | 14 | 3.2 | 34 | 7.8 |
| >2,000,000 IU/mL | 345 | 340 | 297 | 87.4 | 10 | 2.9 | 33 | 9.7 |
| HIV Status | | | | | | | | |
| HCV Mono-Infected | 541 | 536 | 464 | 86.6 | 16 | 3.0 | 56 | 10.4 |
| HCV/HIV Co-Infected | 242 | 239 | 220 | 92.1 | 8 | 3.3 | 11 | 4.6 |
| Treatment Regimen | | | | | | | | |
| GZR with EBR | 666 | 660 | 584 | 88.5 | 22 | 3.3 | 54 | 8.2 |
| GZR with EBR + RBV | 117 | 115 | 100 | 87.0 | 2 | 1.7 | 13 | 11.3 |

N = Number of subjects in RAP with HC V genotype 1
m = Number of subjects in RAP with HCV genotype 1 with baseline NS5A sequencing

**Table 22: Prevalence and types of baseline NS5A variants pooled efficacy population Treatment naïve subjects NS5A resistance analysis population with HCV genotype 4 or 6**

| Population | Subjects | Sequences Available | Did Not Have Baseline NS5A RAVs | | Had Baseline NS5A RAVs | |
|---|---|---|---|---|---|---|
| | N | m | x | x/m (%) | y | y/m (%) |
| Overall GT4 or 6 in RAP | 84 | 82 | 51 | 62.2 | 31 | 37.8 |
| HCV Genotype | | | | | | |
| 4a | 28 | 28 | 18 | 64.3 | 10 | 35.7 |
| 4d | 32 | 32 | 18 | 56.3 | 14 | 43.8 |
| 4-Other | 5 | 4 | 3 | 75.0 | 1 | 25.0 |
| 6a | 7 | 7 | 3 | 42.9 | 4 | 57.1 |
| 6-Other | 12 | 11 | 9 | 81.8 | 2 | 18.2 |
| Cirrhosis Status | | | | | | |
| Non-Cirrhotic | 77 | 75 | 46 | 61.3 | 29 | 38.7 |
| Cirrhotic | 6 | 6 | 4 | 66.7 | 2 | 33.3 |
| Unknown | 1 | 1 | 1 | 100.0 | 0 | 0.0 |
| IL28B Genotype | | | | | | |
| CC | 29 | 28 | 18 | 64.3 | 10 | 35.7 |
| Non-CC | 55 | 54 | 33 | 61.1 | 21 | 38.9 |
| Baseline HCV RNA | | | | | | |
| <=2,000,000 IU/mL | 54 | 53 | 34 | 64.2 | 19 | 35.8 |
| >2,000,000 IU/mL | 30 | 29 | 17 | 58.6 | 12 | 41.4 |
| HIV Status | | | | | | |
| HCV Mono-Infected | 55 | 53 | 33 | 62.3 | 20 | 37.7 |
| HCV/HIV Co-Infected | 29 | 29 | 18 | 62.1 | 11 | 37.9 |
| Treatment Regimen | | | | | | |
| GZR with EBR | 70 | 69 | 41 | 59.4 | 28 | 40.6 |
| GZR with EBR + RBV | 14 | 13 | 10 | 76.9 | 3 | 23.1 |

N = Number of subjects in RAP with HC V genotype 4 or 6
m = Number of subjects in RAP with HCV genotype 4 or 6 with baseline NS5A sequencing

SVR12 was achieved in 74/91 (81.3%) of these subjects, compared with 674/684 (98.5%) for subjects in whom baseline NS5A RAVs were not detected. NS5A RAVs were categorised by their effect on the potency of EBR in vitro. Among GT1 infected subjects whose baseline RAVs cause a ≤5 fold shift in the potency of EBR in vitro, SVR12 was achieved in 21/24 (87.5%) subjects. Among GT1 infected subjects whose baseline RAVs cause a >5 fold shift in the potency of EBR in vitro, SVR12 was achieved in 53/67 (79.1%) subjects. The association of baseline NS5A RAVs with efficacy outcomes differed by sub-genotype. NS5A RAVs were identified at baseline in 52/491 (10.5%) GT1a infected subjects; SVR12 was achieved in 36/52 (69.2%) of these subjects compared with 432/439 (98.4%) among subjects without baseline NS5A RAVs. In contrast, among GT1b infected subjects, SVR12 rates were achieved among 97.4% (38/39) of subjects with detectable baseline NS5A RAVs versus 98.8% (239/242) in those without baseline RAVs. The impact of baseline NS5A RAVs, particularly those with >5 fold shift in potency, was higher in subjects with the *IL28B* CC genotype compared with non-CC genotypes. There was no clear difference in the impact of baseline NS5A RAVs in any of the other key subgroups in GT1 infected subjects. There was little apparent difference in responses between subjects with and without cirrhosis. All of the 25 GT4 infected subjects with baseline NS5A RAVs achieved SVR12. Baseline NS5A RAVs were observed in 6/18 (33.3%) of GT6 infected subjects, and 4/6 (66.7%) of subjects with baseline NS5A RAVs achieved SVR12. The 2 GT6 infected patients who did not achieve SVR12 were non-cirrhotic, had non-CC *IL-28B* genotype, were HCV mono-infected, had baseline HCV viral loads >2,000,000 IU/ml, and received therapy with GZR and EBR without ribavirin.

Of the 21 GT1a virologic failures with both baseline and post-baseline sequences available, 6 (28.6%) subjects did not have treatment emergent NS3 RAVs. Of the 15 subjects (71.4%) with treatment-emergent NS3 RAVs, all had RAVs that cause a >5 fold decrease in GZR potency in vitro, including Y56H, A156SG/T, and D168A/G/V/Y. None of these 15 subjects had baseline NS3 RAVs There were 3 GT1b virologic failures in the RAP (3/284; 1.1%). Treatment emergent NS3 RAVs were detected in only 1 subject, who failed with 2 RAVs (Y56F and V107I) that each confer <5 fold loss of GZR potency. Among key subgroups, cirrhotics had a higher proportion of patients than non-cirrhotics (4/4 [100%] versus 11/20 [55%], though the number of patients in these subgroups was small. No treatment-emergent NS3 RAVs were observed in the lone GT4 failure, whereas treatment-emergent NS3 RAVs were detected in all 4 of the GT6 failures. The GT4 infected subject had no baseline NS3 RAVs, but all 4 of the GT6 infected virologic failures had baseline RAVs that were also detected at failure, in addition to the treatment-emergent RAVs. No virologic failure subject had baseline RAVs that were not also detected at failure. Five of the 21 GT1a virologic failures in the RAP (23.8%) did not have treatment emergent NS5A RAVs. Of the 16 subjects (76.2%) with treatment-emergent NS5A RAVs, 14 had RAVs that cause a >5 fold decrease in EBR potency in vitro, including M28A/T, Q30H/K/R, L31M/V, H58D, and Y93H/N. Treatment-emergent RAVs conferring ≤ 5 fold loss of potency were observed in 2 GT1a subjects. Of the 14 subjects with treatment-emergent NS5A RAVs conferring >5 fold potency shift to EBR, 9 had baseline NS5A RAVs that were also detected at failure, in addition to the treatment-emergent RAVs. No virologic failure subject had baseline RAVs that were not also detected at failure. There were 3 GT1b virologic failures in the RAP (3/284; 1.1%). Treatment emergent NS5A RAVs were detected in 2 subjects, both of whom failed with RAVs that confer >5 fold loss of GZR potency (L31F/V, Y93H). Treatment-emergent NS5A RAVs were observed in the lone GT4 failure (L28S) and in 1/4 GT6 failure (L31M). Neither of these 2 subjects with treatment-emergent NS5A RAVs had baseline NS5A RAVs.

#### *7.3.4.2. Analysis of RAVs in the treatment experienced pooled efficacy population (TE-PEP)*

Details of subjects included in the RAP for the TE-PEP are summarised in Table 23.

**Table 23: Resistance analysis population**

| | GT1a | GT1b | GT1-other | GT4 | GT6 |
|---|---|---|---|---|---|
| **Subjects in FAS** | 343 | 261 | 3 | 37 | 6 |
| **Subjects Excluded from the RAP** | | | | | |
| D/C due to an adverse event | 2 | 0 | 0 | 1 | 0 |
| D/C due to admin reason | 5 | 1 | 0 | 0 | 0 |
| **Subjects in the RAP** | 336 | 260 | 3 | 36 | 6 |
| **Analysis of BL RAVs** | | | | | |
| Subjects with Sequences for NS3 Available | 335 | 258 | 1 | 36 | 4 |
| Subjects with Sequences for NS3 Not Available | 1 | 2 | 2 | 0 | 2 |
| Subjects with Sequences for NS5A Available | 334 | 259 | 1 | 36 | 4 |
| Subjects With Sequences for NS5A Not Available | 2 | 1 | 2 | 0 | 2 |
| **Analysis of RAVs at VF** | | | | | |
| Subjects Achieved $SVR_{12}$ | 319 | 255 | 3 | 32 | 5 |
| Subjects with Virologic Failure | 17 | 5 | 0 | 4 | 1 |
| Subjects with VF; Post-baseline Sequences Available | 16 | 5 | 0 | 4 | 0 |
| NS3 Sequences Available | 16 | 5 | 0 | 4 | 0 |
| NS5A Sequences Available | 16 | 5 | 0 | 4 | 0 |
| **Subjects with VF; Post-baseline Sequences Not Available** | 1 | 0 | 0 | 0 | 1 |
| NS3 Sequences Not Available | 1 | 0 | 0 | 0 | 1 |
| NS5A Sequences Not Available | 1 | 0 | 0 | 0 | 1 |

Overall, 192/594 (32.3%) GT1 infected subjects were found to have NS3 variants commonly associated with resistance to first generation protease inhibitors at baseline. The most common baseline NS3 RAVs (present in >5% of subjects) were Q80K (110/594, 18.5%) and S122G (30/594, 5.1%). However, the prevalence of RAVs causing a >5 fold decrease in GZR potency was low (only 7/594, 1.2%). The prevalence of NS3 RAVs was higher among GT1a infected subjects compared with GT1b infected subjects (164/335 [49.0%] *versus* 27/258 [10.5%]). The types of baseline NS3 RAVs were similar for these 2 subtypes. The prevalence of baseline NS3 RAVs was higher among cirrhotic (78/210 [37.1%]) compared to non-cirrhotic subjects (114/384 [29.7%]). The prevalence of baseline NS3 RAVs was similar in subjects with CC versus non-CC *IL28B* genotype, subjects with high or low baseline HCV RNA, and for HCV mono-infected subjects compared to HCV/HIV co-infected subjects. Subjects who had previously failed therapy with PR + an NS3 Protease Inhibitor had a higher prevalence of baseline NS3 RAVs (34/78, 43.6%) compared with subjects who had previously failed PR alone (158/515, 30.1%). Subjects who were either non-responders or breakthroughs during previous therapy had a higher prevalence of baseline NS3 RAVs than null or partial responders, but the significance of this observation is unclear given the small number of subjects in these subgroups.

Overall, 11/40 (27.5%) GT4 infected subjects had one or more baseline RAVs prior to treatment. The prevalence was higher in GT4a-infected subjects (4/18 [22.2%]) compared to GT4d-infected subjects (1/14 [7.1%]). All 4 evaluable GT6 infected subjects in the TE-PEP RAP had one or more baseline RAVs prior to treatment.

A slightly lower proportion of GT1 infected subjects with baseline NS3 RAVs achieved SVR12 compared with subjects lacking baseline NS3 RAVs (181/192 [94.3%] and 391/402 [97.3%], respectively). Six (6) of the 7 (85.7%) GT1 infected subjects who harboured baseline NS3 RAVs associated with >5 fold reduced susceptibility to GZR achieved SVR12. Although there was a higher prevalence of baseline RAVs in GT1a infected subjects compared to GT1b infected subjects, there was no major difference in the impact of baseline NS3 RAVs in HCV GT1a subjects compared to HCV GT1b subjects; the SVR12 rate in GT1a infected subjects with baseline NS3 RAVs was slightly lower (154/164, 93.9%) compared to those without baseline NS3 RAVs (164/171, 95.9%). Notably, 9/11 (82%) of GT1 patients with baseline NS3 RAVs who

did not achieve SVR12 also had NS5A baseline RAVs, making it difficult to determine the relative contributions of NS3 and NS5A baseline RAVs to different SVR12 rates (Table 24). Among the 109 GT1a infected subjects who harboured viruses with Q80K at baseline, 102 (93.6%) achieved SVR12. Among subjects who did not harbor viruses with Q80K at baseline, 216/226 (95.6%) achieved SVR12. Five (5) of 6 GT1a infected patients with baseline Q80K who failed to achieve SVR12 also had NS5A RAVs detected at baseline. Thus there was no obvious association between the presence of baseline Q80K and treatment response. The impact of baseline GT1a and GT1b NS3 RAVs on treatment outcome was not affected by cirrhosis status. Seven GT4 infected subjects had baseline NS3 RAVs, and all 7 of them achieved SVR12.All 4 GT6 infected subjects in the TE-PEP RAP had baseline NS3 RAVs, and all of these patients achieved SVR12. In the pooled GT4 and GT6 population, all 11 patients with baseline NS3 RAVs achieved SVR12; this group included 5 cirrhotics.

**Table 24: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment experienced subjects NS3/4 resistance analysis population with HCV genotype 1**

| | Did Not Have Baseline NS3 RAVs | | Had Baseline NS3 RAVs But None That Conferred >5-Fold Resistance to GZR | | Had Baseline NS3 RAVs That Conferred >5-Fold Resistance to GZR | | Total | |
|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Total | 402 | 391 (97.3) | 185 | 175 (94.6) | 7 | 6 (85.7) | 594 | 572 (96.3) |
| **HCV Genotype** | | | | | | | | |
| 1a | 171 | 164 (95.9) | 162 | 153 (94.4) | 2 | 1 (50.0) | 335 | 318 (94.9) |
| 1b | 231 | 227 (98.3) | 22 | 21 (95.5) | 5 | 5 (100.0) | 258 | 253 (98.1) |
| 1-Other | 0 | 0 ( ) | 1 | 1 (100.0) | 0 | 0 ( ) | 1 | 1 (100.0) |
| **Cirrhosis Status** | | | | | | | | |
| Non-Cirrhotic | 270 | 263 (97.4) | 111 | 106 (95.5) | 3 | 2 (66.7) | 384 | 371 (96.6) |
| Cirrhotic | 132 | 128 (97.0) | 74 | 69 (93.2) | 4 | 4 (100.0) | 210 | 201 (95.7) |
| **IL28B Genotype** | | | | | | | | |
| CC | 58 | 56 (96.6) | 26 | 26 (100.0) | 1 | 1 (100.0) | 85 | 83 (97.6) |
| Non-CC | 343 | 334 (97.4) | 157 | 147 (93.6) | 6 | 5 (83.3) | 506 | 486 (96.0) |
| Unknown | 1 | 1 (100.0) | 2 | 2 (100.0) | 0 | 0 ( ) | 3 | 3 (100.0) |
| **Baseline HCV RNA** | | | | | | | | |
| <=2,000,000 IU/mL | 177 | 175 (98.9) | 83 | 79 (95.2) | 5 | 4 (80.0) | 265 | 258 (97.4) |
| >2,000,000 IU/mL | 225 | 216 (96.0) | 102 | 96 (94.1) | 2 | 2 (100.0) | 329 | 314 (95.4) |
| **HIV Status** | | | | | | | | |
| HCV Mono-Infected | 391 | 380 (97.2) | 179 | 170 (95.0) | 7 | 6 (85.7) | 577 | 556 (96.4) |
| HCV/HIV Co-Infected | 11 | 11 (100.0) | 6 | 5 (83.3) | 0 | 0 ( ) | 17 | 16 (94.1) |
| **Prior Treatment Failure Status** | | | | | | | | |
| Prior PR Failure | 357 | 347 (97.2) | 155 | 147 (94.8) | 3 | 3 (100.0) | 515 | 497 (96.5) |
| Prior DAA Failure | 44 | 44 (100.0) | 30 | 28 (93.3) | 4 | 3 (75.0) | 78 | 75 (96.2) |
| Other | 1 | 0 (0.0) | 0 | 0 ( ) | 0 | 0 ( ) | 1 | 0 (0.0) |
| **Prior Treatment Response** | | | | | | | | |
| Null Responder | 207 | 200 (96.6) | 79 | 74 (93.7) | 2 | 2 (100.0) | 288 | 276 (95.8) |
| Nonresponder | 7 | 7 (100.0) | 8 | 8 (100.0) | 1 | 1 (100.0) | 16 | 16 (100.0) |
| Partial Responder | 57 | 55 (96.5) | 22 | 20 (90.9) | 0 | 0 ( ) | 79 | 75 (94.9) |
| Breakthrough | 9 | 9 (100.0) | 13 | 11 (84.6) | 2 | 2 (100.0) | 24 | 22 (91.7) |
| Relapser | 110 | 109 (99.1) | 61 | 60 (98.4) | 2 | 1 (50.0) | 173 | 170 (98.3) |
| Other | 12 | 11 (91.7) | 2 | 2 (100.0) | 0 | 0 ( ) | 14 | 13 (92.9) |

**Table 24 continued: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment experienced subjects NS3/4 resistance analysis population with HCV genotype 1**

| | Did Not Have Baseline NS3 RAVs | | Had Baseline NS3 RAVs But None That Conferred >5-Fold Resistance to GZR | | Had Baseline NS3 RAVs That Conferred >5-Fold Resistance to GZR | | Total | |
|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| **Treatment Regimen** | | | | | | | | |
| GZR 100 mg with EBR 50 mg for 12 Weeks | 99 | 94 (94.9) | 46 | 42 (91.3) | 1 | 1 (100.0) | 146 | 137 (93.8) |
| GZR 100 mg with EBR 50 mg + RBV for 12 Weeks | 129 | 125 (96.9) | 62 | 59 (95.2) | 6 | 5 (83.3) | 197 | 189 (95.9) |
| GZR 100 mg with EBR 50 mg for 16/18 Weeks | 94 | 92 (97.9) | 33 | 30 (90.9) | 0 | 0 ( ) | 127 | 122 (96.1) |
| GZR 100 mg with EBR 50 mg + RBV for 16/18 Weeks | 80 | 80 (100.0) | 44 | 44 (100.0) | 0 | 0 ( ) | 124 | 124 (100.0) |

N = Number of subjects in RAP with HCV genotype 1 with baseline NS3 sequencing.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

The overall prevalence of baseline GT1 NS5A RAVs was comparable in GT1a infected (39/334, 11.7%) and GT1b infected subjects (36/259, 13.9%). However, the frequency of RAVs that confer > 5x reductions in the potency of EBR were less frequent among GT1a infected subjects than GT1b infected subjects. Of the most common NS5A RAVs, M28V was only detected in GT1a infected subjects, whereas Y93H and L31M were both more common in GT1b infected subjects The prevalence of baseline NS5A RAVs was generally comparable in cirrhotic compared to non-cirrhotic subjects, in subjects with the *IL28B CC* genotype compared to subjects with non-CC *IL28B* genotypes, subjects with high or low baseline HCV RNA, HCV mono infected subjects compared to HCV/HIV co-infected subjects, and subjects with different prior treatment histories and prior treatment responses. The overall prevalence of baseline NS5A variants in GT4 infected was high; 18/40 (45.0%) subjects had one or more baseline NS5A RAVs prior to treatment. The prevalence was higher in GT4d-infected subjects (10/14 [71.4%]) compared to GT4a-infected subjects (5/18 [27.8%]); 2/4 (50.0%) of evaluable GT6 infected subjects in the TE-PEP RAP had one or more baseline NS5A RAVs prior to treatment.

SVR12 was achieved in only 58/76 (76.3%) of GT1 subjects with NS5A RAVs at baseline, compared with 514/518 (99.2%) subjects in whom NS5A RAVs were not detected at baseline; SVR12 was achieved in 13/13 (100%) subjects whose baseline RAVs cause a ≤5 fold shift in the potency of EBR in vitro, while SVR12 was achieved in 45/63 (71.4%) of subjects whose baseline RAVs cause a >5 fold shift in the potency of EBR in vitro, SVR12 was achieved in 26/39 (66.7%) of these subjects compared with 291/295 (98.6%) among subjects without baseline NS5A RAVs. SVR12 in subjects with baseline GT1a RAVs that cause ≤5 fold potency shift of EBR in vitro was 100% (13/13) versus 50.0% (13/26) in subjects with baseline GT1a RAVs that shift the potency of EBR > 5 fold in vitro Among GT1b infected subjects, SVR12 rates were achieved among 86.1% (31/36) of subjects with detectable baseline NS5A RAVs versus 100% (223/223) in those without baseline RAVs. All 36 GT1b subjects with baseline NS5A RAVs had RAVs conferring >5 fold shift to EBR in vitro. The impact of baseline NS5A RAVs, particularly those with >5 fold shift in potency, was higher in the following categories: on-treatment failure (null-responder, non-responder, partial responder, breakthrough) versus prior relapsers (63.4% versus 90.5%; higher baseline HCV viral load especially for those with > 800.000 IU/ml and cirrhosis (68.4% versus 80.4% in non-cirrhotics) (Table 25).

**Table 25: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment experienced subjects NS5Aresistance analysis population with HCV genotype 1**

| | Did Not Have Baseline NS5A RAVs | | Had Baseline NS5A RAVs But None That Conferred >5-Fold Resistance to EBR | | Had Baseline NS5A RAVs That Conferred >5-Fold Resistance to EBR | | Total | |
|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Total | 518 | 514 (99.2) | 13 | 13 (100.0) | 63 | 45 (71.4) | 594 | 572 (96.3) |
| **HCV Genotype** | | | | | | | | |
| 1a | 295 | 291 (98.6) | 13 | 13 (100.0) | 26 | 13 (50.0) | 334 | 317 (94.9) |
| 1b | 223 | 223 (100.0) | 0 | 0 ( ) | 36 | 31 (86.1) | 259 | 254 (98.1) |
| 1-Other | 0 | 0 ( ) | 0 | 0 ( ) | 1 | 1 (100.0) | 1 | 1 (100.0) |
| **Cirrhosis Status** | | | | | | | | |
| Non-Cirrhotic | 334 | 331 (99.1) | 11 | 11 (100.0) | 40 | 30 (75.0) | 385 | 372 (96.6) |
| Cirrhotic | 184 | 183 (99.5) | 2 | 2 (100.0) | 23 | 15 (65.2) | 209 | 200 (95.7) |
| **IL28B Genotype** | | | | | | | | |
| CC | 73 | 73 (100.0) | 0 | 0 ( ) | 13 | 11 (84.6) | 86 | 84 (97.7) |
| Non-CC | 444 | 440 (99.1) | 13 | 13 (100.0) | 48 | 32 (66.7) | 505 | 485 (96.0) |
| Unknown | 1 | 1 (100.0) | 0 | 0 ( ) | 2 | 2 (100.0) | 3 | 3 (100.0) |
| **Baseline HCV RNA** | | | | | | | | |
| <=2,000,000 IU/mL | 236 | 235 (99.6) | 4 | 4 (100.0) | 25 | 19 (76.0) | 265 | 258 (97.4) |
| >2,000,000 IU/mL | 282 | 279 (98.9) | 9 | 9 (100.0) | 38 | 26 (68.4) | 329 | 314 (95.4) |
| **HIV Status** | | | | | | | | |
| HCV Mono-Infected | 504 | 500 (99.2) | 12 | 12 (100.0) | 61 | 44 (72.1) | 577 | 556 (96.4) |
| HCV/HIV Co-Infected | 14 | 14 (100.0) | 1 | 1 (100.0) | 2 | 1 (50.0) | 17 | 16 (94.1) |
| **Prior Treatment Failure Status** | | | | | | | | |
| Prior PR Failure | 446 | 443 (99.3) | 10 | 10 (100.0) | 57 | 42 (73.7) | 513 | 495 (96.5) |
| Prior DAA Failure | 71 | 70 (98.6) | 3 | 3 (100.0) | 5 | 3 (60.0) | 79 | 76 (96.2) |
| Other | 1 | 1 (100.0) | 0 | 0 ( ) | 1 | 0 (0.0) | 2 | 1 (50.0) |
| **Prior Treatment Response** | | | | | | | | |
| Null Responder | 254 | 251 (98.8) | 5 | 5 (100.0) | 27 | 18 (66.7) | 286 | 274 (95.8) |
| Nonresponder | 14 | 14 (100.0) | 2 | 2 (100.0) | 0 | 0 ( ) | 16 | 16 (100.0) |
| Partial Responder | 66 | 66 (100.0) | 2 | 2 (100.0) | 11 | 7 (63.6) | 79 | 75 (94.9) |
| Breakthrough | 20 | 20 (100.0) | 1 | 1 (100.0) | 3 | 1 (33.3) | 24 | 22 (91.7) |
| Relapser | 150 | 149 (99.3) | 3 | 3 (100.0) | 21 | 19 (90.5) | 174 | 171 (98.3) |
| Other | 14 | 14 (100.0) | 0 | 0 ( ) | 1 | 0 (0.0) | 15 | 14 (93.3) |
| GZR 100 mg with EBR 50 mg for 12 Weeks | 127 | 125 (98.4) | 4 | 4 (100.0) | 15 | 8 (53.3) | 146 | 137 (93.8) |
| GZR 100 mg with EBR 50 mg + RBV for 12 Weeks | 174 | 172 (98.9) | 6 | 6 (100.0) | 18 | 12 (66.7) | 198 | 190 (96.0) |
| GZR 100 mg with EBR 50 mg for 16/18 Weeks | 108 | 108 (100.0) | 1 | 1 (100.0) | 17 | 12 (70.6) | 126 | 121 (96.0) |
| GZR 100 mg with EBR 50 mg + RBV for 16/18 Weeks | 109 | 109 (100.0) | 2 | 2 (100.0) | 13 | 13 (100.0) | 124 | 124 (100.0) |

N = Number of subjects in RAP with HCV genotype 1 with baseline NS5A sequencing
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

**Table 25 continued: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment experienced subjects NS5Aresistance analysis population with HCV genotype 1a**

| | Did Not Have Baseline NS5A RAVs | | Had Baseline NS5A RAVs But None That Conferred >5-Fold Resistance to EBR | | Had Baseline NS5A RAVs That Conferred >5-Fold Resistance to EBR | | Total | |
|---|---|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) | N | n (%) |
| Total | 295 | 291 (98.6) | 13 | 13 (100.0) | 26 | 13 (50.0) | 334 | 317 (94.9) |
| **Cirrhosis Status** | | | | | | | | |
| Non-Cirrhotic | 187 | 184 (98.4) | 11 | 11 (100.0) | 16 | 9 (56.3) | 214 | 204 (95.3) |
| Cirrhotic | 108 | 107 (99.1) | 2 | 2 (100.0) | 10 | 4 (40.0) | 120 | 113 (94.2) |

N = Number of subjects in RAP with HCV genotype 1a with baseline NS5A sequencing
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

**Table 25 continued: Analysis of proportion of subjects with sustained viral response (HCV RNA <LOQ) 12 weeks after end of all study therapy (SVR12) by various subgroups and baseline NS3 RAV status. Pooled efficacy population-treatment experienced subjects NS5Aresistance analysis population with HCV genotype 1b**

| | Did Not Have Baseline NS5A RAVs | | Had Baseline NS5A RAVs That Conferred >5-Fold Resistance to EBR | | Total | |
|---|---|---|---|---|---|---|
| Subgroup | N | n (%) | N | n (%) | N | n (%) |
| Total | 223 | 223 (100.0) | 36 | 31 (86.1) | 259 | 254 (98.1) |
| **Cirrhosis Status** | | | | | | |
| Non-Cirrhotic | 147 | 147 (100.0) | 24 | 21 (87.5) | 171 | 168 (98.2) |
| Cirrhotic | 76 | 76 (100.0) | 12 | 10 (83.3) | 88 | 86 (97.7) |

N = Number of subjects with HCV genotype 1b with baseline NS5A sequencing.
n (%) = Number of subjects with undetectable (TND) or unquantifiable (TD(u)) HCV RNA at the Follow-Up Week 12 visit and the percentage calculated as (n/N)*100. A missing HCV RNA result is imputed to TND or TD(u) if TND or TD(u) at both preceding and subsequent visits.

In the combined GT4+GT6 population, 15/18 (83.3%) subjects with baseline NS5A RAVs achieved SVR12 compared with 21/22 (95.5%) of subjects with no detectable baseline NS5A RAVs. In general there were no substantial differences among the various subgroups shown; however, the small size of the various subgroups prohibits definitive conclusions.

Of the 16 GT1a virologic failures with both baseline and post-baseline sequences available, 2 (12.5%) subjects did not have treatment emergent NS3 RAVs. Of the 14 subjects (87.5%) with treatment-emergent NS3 RAVs, 12 had RAVs that cause a >5 fold decrease in GZR potency in vitro, including Y56H, A156G/T/V, and D168A/G/V, while 2 displayed only RAVs that confer ≤ 5-decrease in potency. Of the 12 subjects with treatment emergent RAVs conferring >5 fold shift in GZR potency, none had detectable baseline RAVs There were 5 GT1b virologic failures in the RAP (5/260; 1.9%). Treatment emergent NS3 RAVs were detected in only 1 subject, who failed with a RAV that confers >5 fold loss of GZR potency, A156T. Treatment-emergent NS3 RAVs were observed in 2 of the 4 GT4 failures (156M/T/V, 168A/G, 170I). No sequence data were available for the GT6 failure due to inability to the PCR to amplify the HCV NS3/4A gene from this subject. Overall, 14 of the 16 GT1a subjects (87.5%) with treatment-emergent NS5A RAVs, all had RAVs that cause a >5 fold decrease in EBR potency in vitro, includingM28T, Q30H/R, H58D, and Y93H/S There were 5 GT1b virologic failures in the RAP (5/260, 1.9%). Treatment emergent NS5A RAVs were detected in all 5 subjects: 1 subject had a RAV conferring <5 fold shift in EBR potency, and 4 subjects failed with the NS5A RAV Y93H, which confers >5 fold loss of EBR potency. All 5 GT1b virologic failures had baseline NS5A RAVs conferring > 5 fold potency shift to EBR, and all of these BL RAVs were also observed after virologic failure in addition to any treatment-emergent RAV. Treatment-emergent NS5A RAVs, including L28S/T, M31I/V, P58D, and Y93H, were observed in all of the GT4 failures. No sequence data were available for the GT6 subject due to failure of PCR amplification.

#### *7.3.4.3. Persistence of RAVs*

In general, treatment-emergent NS3 RAVs had low persistence and in many cases became undetectable over time based on population sequencing. Based on the limited data and monitoring duration in GT1a infected subjects, RAVs at NS3 156 declined in abundance the fastest with a median time of returning to WT in approximately 17 days. Variants at 56 and 168 also waned over time: treatment-emergent RAVs at these positions were no longer detectable by population sequencing at FW24 in 3/3 and 4/6 subjects. A similar trend for NS3 RAVs was also observed in GT1b, GT2 and GT3-infected virologic failures. The number of GT4 to 6-infected subjects who had treatment-emergent NS3 RAVs was too few to provide an accurate characterisation. Treatment-emergent NS5A RAVs were generally more persistent than treatment-emergent NS3 RAVs in subjects who failed GZR and EBR treatment. Among the GT1a

infected subjects who had one or more of the treatment-emergent NS5A RAVs at amino acids 28, 30, 31, 58 or 93, these RAVs became undetectable at FUW12 in only 5% of subjects. Persistence of RAVs was also observed in GT1b and GT3-infected virologic failures. In addition, all GT3 virologic failures were infected with viruses harbouring pre-existing NS5A baseline RAVs which persisted during therapy and after failure. The longevity of NS5A RAVs in in GT4 6 could not be determined due to limited number of virologic failures in these genotypes.

## 7.4. Evaluator's conclusions on clinical efficacy

***For treatment of chronic hepatitis C infection in adults***

All the clinical studies in this submission were well-conducted in compliance with the TGA adopted EU guidelines on the Clinical Evaluation of DAA Intended for Treatment of Chronic HCV (EMEA/CHMP/EWP/30039/2008, published in 2009).

Results of initial Phase II trials supported selection of a broad population for later Phase II and Phase III studies: GT1, 4 and 6; TN and TE (subjects who failed a prior PR or DAA+ PR regimen); mono and HIV/HCV co-infected subjects; cirrhotics and non-cirrhotics; and subjects with CKD Stages 4-5. Phase II studies were conducted to select the dose of each medicine for Phase III (P003 and P038 for GZR, and P035 for EBR), to evaluate the effect of treatment duration on efficacy (P035), and to evaluate the need for ribavirin (RBV) in the regimen (P035 and P047). The effect of treatment duration and the need for RBV were further evaluated in subjects that had failed prior therapy with PR in Phase III (P068). Additional Phase II trials evaluated the efficacy and safety of GZR and EBR in a broader variety of patient populations, including those infected with HCV genotypes other than GT1 (GT3 in P035, and GT2, 4, 5 and 6 in P047), in subjects who had failed prior DAA therapy (P048) and in cirrhotic subjects with moderate hepatic insufficiency (Child-Pugh class B) (P059). In addition, P074 evaluated the triple combination of DAA (Sofosbuvir + GZR/EBR) in GT1 and GT3 HCV infected subjects with and without cirrhosis, with different durations of treatment.

Phase II/III and Phase III studies were designed to confirm the safety and efficacy of GZR with EBR in key populations, including both treatment-naïve (Studies P060, P061 and P052) and PR treatment-experienced (Study P068) subjects, HCV/HIV co-infected subjects (P061 and P068), and HCV-infected subjects with advanced chronic kidney disease (P052). Each of the Phase III studies included subjects with or without compensated cirrhosis. At the time the clinical program for Zepatier commenced, there were no approved interferon-free regimens for treatment of HCV, so an immediate versus deferred treatment (placebo-controlled) study design was adopted in the Phase II/III controlled studies (P060, P052) to overcome the tolerability and feasibility challenges of treating the control arm with peginterferon (administered via injection).

Overall, the comprehensive clinical Phase II and III program for GZR with EBR enrolled and treated 1715 HCV GT1, GT4, and GT6 infected subjects, along with 82 HCV GT3 infected subjects. These studies enrolled a diverse population of subjects and efficacy was evaluated across the spectrum of HCV infected individuals including approximately:

- 54% GT1a, 35% GT1b, 5% GT3 5%, GT4 and 1% GT6 infected
- 64% treatment-naïve and 36% treatment-experienced subjects (including 79 subjects that had failed prior therapy with a first generation HCV protease inhibitor + PR);
- 28% subjects with compensated cirrhosis;
- 122 subjects with CKD Stages 4/5, including those on haemodialysis;
- 296 HIV/HCV co-infected subjects;
- Diverse racial/ethnic backgrounds: 15% Black, 8% Asian and 9% were Hispanic.

Each of the Phase II and Phase III efficacy studies of GZR with EBR achieved their primary efficacy endpoint with high and consistent efficacy observed across the populations evaluated.

### 7.4.1. Efficacy of a 12 week regimen of GZR/EBR ±RBV among GT1 , GT4 and GT6 infected treatment naïve subjects

The 12 week (no RBV) regimen was highly efficacious among GT1a , GT4 , and GT6 infected subjects. Overall, 711/752 subjects (94.5%, 95% CI: 92.7 to 96.1%) achieved SVR12 and only 25/752 (3.3% of subjects) experienced virologic failure. Addition of RBV to the regimen did not improve efficacy overall or in any sub-population. Efficacy was high among GT1a , GT1b , and GT4 infected subjects. Activity was also observed among GT6 infected subjects. The main efficacy results in this pool of TN HCV subjects were:

- 399/426 (93.7%; 95% CI: 90.9 to 95.8%) of GT1a infected subjects achieved SVR12; virologic failure occurred among 19/426 (4.5%) of subjects.
- 243/252 (96.4%; 95% CI: 93.3 to 98.4%) of GT1b infected subjects achieved SVR12; virologic failure occurred among 2/252 (0.8%) of subjects.
- All 3 subjects infected with GT1 subtypes other than GT1a or GT1b achieved SVR12.
- 22/23 (95.7%: 95% CI: 78.1, 99.9%) of GT4a-infected, 28/29 (96.6%, 95% CI: 82.2, 99.9%) of GT4d and 4/4 (100%; 95% CI: 39.8, 100.0%) of GT4 Other-infected subjects achieved SVR12. Overall, 54/56 (96.4%) of treatment naïve GT4 infected subjects achieved SVR12; virologic failure occurred in only 1/56 (1.8%) of GT4 infected subjects.
- 5/6 (83.3%; 95% CI: 35.9, 99.6%) of GT6a-infected, 7/9 (77.8%; 95% CI: 40.0, 97.2%) of GT6 Other-infected subjects achieved SVR12. Overall, 12/15 (80%) of GT6 infected subjects achieved SVR12; virologic failure occurred among 3/15 (20.0%) subjects.

Baseline demographics (age, gender, race/ethnicity), presence of HIV co-infection, and geographic region did not substantially impact the efficacy of the 12 week (no RBV) regimen. Efficacy was also comparable among cirrhotics and non-cirrhotics. In particular, SVR12 was achieved in 135/139 (97.8%; 95 CI: 93.8 to 99.4%) of GT1 GT4 and GT6 infected cirrhotics, a population in immediate need for clearance of HCV infection. Only 2/138 (1.4%) of the cirrhotic subjects experienced a virologic failure. Efficacy among GT1a cirrhotics, a traditionally harder-to-cure population was also high: SVR12 was achieved in 73/76 (96.1%) of GT1a cirrhotics; only 2/76 (2.6%) experienced a virologic failure.

Two factors were identified that impacted efficacy of the 12 week (no RBV) among GT1a infected subjects but not among GT1b or GT4 infected subjects: (1) Baseline viral load (VL) with slightly lesser efficacy in GT1a subjects with baseline VL >800,000 IU/mL compared to < 800,000 IU/ml [SVR12: 92.1% (278/302) versus 97.6% (121/124)]; (2) the presence of baseline NS5A RAVs that cause a >5 fold shift in the potency of EBR in vitro among GT1a infected subjects was associated with a substantial reduction in efficacy, from an SVR12 of 98.4% to 55.2% in subjects without and with baseline GT1a RAVs, respectively. Overall, a small subpopulation of subjects with baseline NS5A RAVs with > 5 fold potency shift to EBR and baseline HCV RNA >800,000 IU/mL, representing 26/491 or 5.3% of the population, was the source of 56.5% (13/23) of all GT1a virologic failures. In the remaining GT1a population, 455/465 (97.8%) subjects achieved SVR12. Hence, a 12 week regimen of GZR/EBR (no RBV) may be appropriate for majority of TN GT1a infected subjects.

Among TN, non-cirrhotic GT1b infected subjects, a 12 week regimen of GZR and EBR (no RBV), SVR12 was achieved in 13/13 (100%) subjects (95% CI 75.3, 100%). Given this high degree of efficacy a shorter duration of therapy was also evaluated. With an 8 week regimen of GZR and EBR, 29/31 (93.5%) subjects (95% CI 78.6, 99.2) achieved SVR12. Virologic failure rates for TN, non-cirrhotic GT1b subjects treated for 8 weeks was comparable to that achieved with 12 weeks of treatment. There was no apparent association of baseline factors that predicted

failure. Of note, 3 of the 4 subjects who relapsed in the 8 week treatment arms had no detectable NS3 or NS5A RAVs at the time of failure, suggesting that subjects that fail a shorter regimen may still have multiple options for retreatment. As these results are based on data in very few subjects, it still seems prudent to use the same 12 week treatment regimen in GT1b infected patients.

The observed efficacy of GZR/EBR (no RBV) was lower among GT6 infected subjects compared with GT1 or GT4 infected subjects. However, the GZR/EBR regimen was still active in this population. As no all-oral regimen is currently indicated in this population, the availability of a regimen with higher efficacy and better tolerability compared to PR against GT6 infection provides an important option for this population. It is important to note that a relatively small population of GT6 infected subjects enrolled in the program was likely due to the low prevalence of GT6 infection in the North American and European HCV population.

#### 7.4.2. Efficacy of GZR/EBR (±RBV) among GT1, GT4, GT6 infected subjects who failed prior PR-containing regimens

High efficacy was also observed in treatment experienced (TE) subjects, including those that had failed prior treatment with PR and also those who had failed a first generation HCV protease inhibitor + PR (PI+PR) regimen. In TE subjects, the effects of adding RBV to the regimen and extending treatment duration were also evaluated. Overall, efficacy was highest in the 16/18 week (+ RBV) arm. However, high efficacy was observed in the following subgroups of TE subjects receiving the 12 week (no RBV) regimen:

1. 12 week regimen of GZR/EBR 100 mg/50 mg (no RBV) resulted in SVR12 among 96.5% (55/57) of GT1b/other-infected subjects in the TE-PEP, regardless of the prior response category. Virologic failures occurred among 3.5% of subject,
2. 12 week regimen of GZR/EBR 100 mg/50 mg (no RBV) resulted in SVR12 among 46/47 (97.9%) of prior-relapser subjects, regardless of genotype. The only failure was a subject who discontinued for administrative reasons. Hence, no prior-relapsers experienced virologic failure with this regimen.

Of note, both of these populations included cirrhotics and non-cirrhotics, subjects with high viral load, subjects with CKD Stages 4/5, subjects with IL-28 TT genotype and HIV co-infected subjects. Thus, this population included subjects with demographic and disease features previously associated with low responsiveness to therapy. Furthermore, presence of baseline NS5A RAVs conferring >5 fold shift in the potency of EBR did not impact the efficacy of 12 week regimen in this population.

GT1a, GT4 or GT6 infected subjects who experienced on-treatment failure during their prior treatment regimen (PR null responders, PR partial responders, PR+DAA non-responders, virologic breakthrough and virologic rebound) were less likely to achieve SVR12 following administration of a 12 week regimen of GZR/EBR (no RBV); however, in these subjects, no virologic failures occurred in the 16/18 week (+ RBV) arm, including subjects with high baseline viral load and/or cirrhosis. These results support a dosing regimen of 16 weeks of GZR/EBR (+ RBV) in GT1a, GT4 or GT6 infected subjects who experienced on-treatment failure during their prior treatment regimen.

Treatment with GZR and EBR had a positive impact on HRQOL, fatigue levels, and impairment while working and performing other daily activities, when assessing mean change from baseline in PRO scores within the GZR and EBR (without RBV) groups. Differences in mean change from baseline in PRO scores between GZR and EBR and placebo groups were not apparent (P052 and P060), except with improvements in mental components of general health and overall health among treatment-naïve subjects (P060). As expected, the addition of RBV to GZR and EBR had a negative impact on PROs (P035 and P068). Treatment-experienced subjects treated with GZR/EBR (P068) had better physical and mental components of general health, less fatigue, and less impairment while working and performing other daily activities than subjects treated with

GZR/EBR with RBV. However, interpretation of the PROs results in the open-label studies (P035, P068) was limited due to inherent bias of the open-label nature of these studies.

P048/C-Salvage demonstrated the high efficacy of GZR and EBR in subjects who had failed a first generation HCV protease inhibitor + PR (PI+PR) regimen. High rates of SVR12 were achieved regardless of the presence of signature RAVs at baseline overall or among the subjects who had previous virologic failure. Variants in the NS3/4A gene at amino acid loci prone to resistance selection by HCV protease inhibitors were common (44%) but efficacy remained high. This observation is explained by the substantial differences between GZR and earlier PIs with respect to in vitro potency; in particular GZR maintains potency against many of the signature RAVs associated with failure to first generation PIs. Baseline NS3/4A variants associated with a >5 fold shift in potency to GZR were present in only 4/78 (5.1%) subjects, and 3 of these 4 subjects achieved SVR12. Among GT1a infected subjects, presence of Q80K/R variants did not impact efficacy, again distinguishing GZR from earlier PIs. These results demonstrate that subjects who have failed a prior PI+PR regimen respond similar to those who have failed PR alone, supporting similar dosing recommendations for these subjects.

#### *7.4.2.1. Efficacy of GZR/EBR (no RBV) among patients with CKD Stage 4/5*

Study P052/C-SURFER demonstrated high efficacy of a 12 week regimen of GZR + EBR in CKD 4-5 HCV-infected patients, a population for which there is an unmet medical need for safe and effective anti- HCV therapy. High response rates were observed across several subgroups, including subjects on haemodialysis and not on haemodialysis, GT1a and GT1b infected subjects, treatment-naïve subjects and those who prior interferon treatment failures and, notably, those with characteristics historically associated with poor response to HCV therapy. In particular, SVR12 was achieved in 100% of GT1a infected subjects, 100% of African American subjects, 98.9% of subjects with the *IL28B* non-CC genotype, 97.6% of subjects with diabetes and all 6 subjects with cirrhosis. Efficacy was similar in TN and TE subjects.

The sponsors claim that due to the consistency of efficacy of GZR and EBR in GT1, GT4 and GT6 infected subjects observed in various subgroups throughout the clinical development program, it is anticipated that efficacy in GT4 and GT6 infected subjects with advanced CKD would be similar to that in subjects with normal renal function infected with these genotypes. Based on these considerations the recommended RBV-free dosing regimen in patients with advanced CKD, including those on dialysis, would be 12 weeks of GZR/EBR (100/50 mg QD) in treatment-naive GT1, GT4 or GT6 infected subjects, all GT1b infected subjects and GT1a , GT4 and GT6 infected subject who relapsed after a prior interferon-based regimen. Due to lack of an oral, RBV-free treatment option in these patients, the above justification provided by the sponsor is acceptable, although efficacy/ safety of GZR+EBR has not actually been evaluated in CKD patients with HCV GT4 or GT6.

#### *7.4.2.2. Impact of baseline RAVs in TN subjects*

There was no evident association between baseline NS3 RAVs and virologic failure in either GT1a or GT1b infected subjects overall or in key subgroups. The Q80K mutation, which has been associated with decreased efficacy among GT1a infected subjects treated with simeprevir/PR, was detected more than a third GT1a infected TN subjects, but there was no association between the presence of baseline Q80K and treatment response. NS5A RAVs were less prevalent than NS3 RAVs among GT1 infected subjects: approximately 9% of GT1 infected subjects had NS5A RAVs, and approximately 3% of GT1 infected subjects had NS5A RAVs which conferred >5 fold resistance to EBR. This impact was most apparent in GT1a infected subjects with baseline viral loads >800,000 IU/mL, though it should be noted that this subgroup represents only 5.3% of the total cohort of TN subjects with HCV GT1a infection. There was a very modest (and not statistically significant) negative impact of baseline NS5A RAVs on SVR12 in TN GT1b subjects. The impact of NS3 and NS5A RAVs in GT4 and GT6 infected subjects was similar to that observed in GT1 infected subjects.

#### *7.4.2.3. Impact of baseline RAVs in TE subjects*

There was a higher prevalence of baseline NS3 RAVs in GT1a infected subjects than in subjects infected with GT1b and a slightly lower proportion of GT1a infected subjects who had baseline NS3 RAVs achieved SVR12 compared with GT1b infected subjects. However, since 9/11 (82%) of GT1 infected patients with baseline NS3 RAVs who experienced virologic failure also had baseline NS5A RAVs, it is not clear that the baseline NS3 RAVs were a critical driver of virologic failure. As in TN subjects, the presence of baseline NS5A RAVs that cause a >5 fold shift in the potency of EBR in vitro among TE GT1a infected subjects was associated with a substantial reduction in efficacy. Subjects with baseline RAVs that confer > 5 fold shift in potency to EBR accounted for only 7.8% (26/334) of GT1a infected subjects, but comprised 76.5% (13/17) of all GT1a virologic failures. The impact of NS3 and NS5A RAVs in GT4 and GT6 infected subjects was similar to that observed in GT1a infected subjects.

#### *7.4.2.4. Post-baseline RAVs*

In both TN and TE subjects, treatment-emergent RAVs in the NS3 and/or NS5A genes were commonly observed in subjects experiencing virologic failure, although there were differences according to genotype. NS3 RAVs conferring > 5 fold shift in GZR potency were more commonly observed in GT1a subjects than in GT1b infected subjects, although the small number of GT1b failures precludes definitive conclusions. NS5A RAVs conferring > 5 fold shift in EBR potency were observed in equal proportions in GT1a failures and GT1b failures. Treatment-emergent RAVs were also noted in the GT4 and GT6 infected subjects that experienced virologic failure, though the small number of failures with these genotypes also precludes definitive conclusions.

#### *7.4.2.5. Durability of efficacy, and long-term impact of virologic failure*

At the time of this submission, only limited data are available on the durability of efficacy as SVR24 (secondary efficacy endpoints for many studies) data was not available for studies P060, P052 and P068. Furthermore, primary efficacy (SVR12) results for Study P058 in Japanese HCV subjects and Study P059 in HCV patients with cirrhosis (CP score 7-9) were also not available and will only be provided in future study reports. The ongoing, long-term follow-up Study P017 was designed to evaluate long term development of resistance, etc. in over 300 subjects treated with GZR/EBR±RBV with follow-up for 5 years. Overall, it is not possible to determine the persistence of NS3 and NS5A RAVs that emerge among subjects who fail to achieve SVR following GZR+EBR treatment due to the small number of failures to date and the short follow-up duration.

#### *7.4.2.6. GZR/EBR + Sofosbuvir among treatment-naïve GT3 infected subjects with and without cirrhosis*

With other DAA regimens, efficacy for the HCV GT3 infected populations has been less robust than the GT1 infected population and a longer duration of treatment may be necessary for some regimens. Patients with HCV GT3 infection have been well studied in SOF containing regimens. For SOF + RBV high efficacy requires extending duration from 12 to 24 weeks. P074/C-SWIFT was conducted to evaluate a regimen combining 3 different direct acting antiviral with different mechanisms of actions (GZR+EBR+SOF) in GT3-infected subjects. The results of this trial demonstrated that high efficacy was obtained in GT3 TN subjects with and without cirrhosis treated for 8 or 12 weeks; SVR12 was achieved in 14/15 (93.3%) and 14/14 (100%) non-cirrhotic subjects treated for 8 or 12 weeks, respectively, and in 10/12 (83.3%) of cirrhotic subjects treated for 12 weeks. The efficacy was comparable to that observed with the approved regimen of SOF + PR administered for 24 weeks.

There are 3 ongoing trials hoping to provide evidence for efficacy and safety of proposed FDC GZR/EBR 100/ 50 mg in certain patient populations prone to chronic HCV: The Phase II trial (P059) is being conducted in HCV patients with cirrhosis, the Phase III Study P062 is being conducted in HCV patients receiving opiate substitution therapy while Study P065 is being conducted in HCV patients with Inherited blood disorders (IBD). These studies hope to provide

important data in these patient subgroups with an unmet medical need who continue to be treated with older HCV PR based regimens despite availability of more effective and tolerable DAA based treatment regimens. However, these trials were ongoing at the time of the submission and efficacy data from these trials are not yet available.

Overall, the comprehensive clinical program provided adequate evidence of efficacy of the FDC GZR/EBR (100/50 mg) for the proposed indication.

# 8. Clinical safety

## 8.1. Studies providing evaluable safety data

The following studies provided evaluable safety data:

### 8.1.1. Pivotal Efficacy studies

Six Phase III studies evaluated combined therapy with GZR and EBR among 1687 subjects. Of the six Phase III studies, 1 study (P052) administered the study drug as two separate tablets (GZR + EBR in the immediate treatment group) and 5 studies (P060, P061, P062, P065 and P068) administered the study drug as a fixed-dose combination (GZB/EBR). However, studies P062 and P065 are ongoing with limited safety data provided in the current submission which has been summarised separately below. AEs, treatment-related AEs, deaths/SAEs, discontinuations due to AEs have been evaluated individually for the other 4 Phase III studies and summarised below.

### 8.1.2. Pivotal studies that assessed safety as a primary outcome

None.

### 8.1.3. Dose-response and non-pivotal efficacy studies

The Phase II program characterised the efficacy and safety profiles of GZR-containing regimens. Two sets of studies were conducted: an evaluation of GZR without EBR (but in combination with other agents), and an evaluation of proposed FDC of GZR with EBR. No Phase II studies evaluating EBR without GZR were conducted. Four Phase II studies evaluated GZR, without EBR, among 579 subjects (P003, P038, P039 and P047). Six (6) Phase II studies evaluated combined therapy with GZR and EBR among 917 subjects. Of the six Phase II studies, 5 studies (P035, P047, P048, P058 and P059) administered the study drug as two separate tablets (GZR + EBR) and 1 study (P074) administered the study drug as a FDC (GZB/EBR). The safety results related to AEs, treatment-related AEs, deaths/ SAEs, discontinuations due to AEs important Phase II studies have also been summarised individually below.

**Comments**: Four pools of studies were also used for safety evaluations. These 4 have been briefly described below and their safety results are summarised in separate sections throughout section 8 of this evaluation report.

#### *8.1.3.1. Protocol 060/ Protocol 061/ Protocol 068 12-week safety pool*

This pool allowed presentation of the 12 week safety summary from the pivotal Phase III Studies P060 (treatment-naïve), P061 (HIV/HCV co-infected) and P068 (PR treatment-experienced). This pool includes P060 (immediate treatment group and placebo portion of the deferred treatment group), P061, and the 12 week arms of P068. This pool does not include the Phase III study, P052, since subjects with CKD Stage 4-5 have a substantially higher rate of CKD-associated AEs than subjects without advanced CKD. The pool was evaluated for AEs (including common AEs, deaths, other SAEs, ECIs, and discontinuations due to AEs) and laboratory evaluations. The above were also evaluated for each of the following subgroups: RBV-free versus RBV-containing arms, subjects with and without cirrhosis, HCV mono-infected versus

HCV/HIV co-infected subjects, and active treatment groups versus placebo deferred treatment group.

#### *8.1.3.2. Integrated safety pool (ISP)*

This was the primary pool used for evaluation of AEs (including common AEs, deaths, other SAEs, ECIs, and discontinuations due to AEs) and laboratory evaluations. The ISP includes a total of 1690 subjects from 8 treatment groups receiving:

1. GZR/EBR + No RBV with the following treatment durations: 8 weeks (n=31); 12 weeks (n= 834); 16 weeks (n=105); 18 weeks (n= 63).
2. GZR/EBR + RBV with the following treatment durations: 8 weeks (n=60); 12 weeks (n= 405); 16 weeks (n=106); 18 weeks (n= 86).

The P060 placebo deferred treatment group x 12 weeks (n= 105) was included for comparisons within the ISP.

Safety for the above groups was also evaluated in each of the following subgroups: RBV-free versus RBV-containing arms, treatment duration (8 weeks, 12 weeks, 16 weeks and 18 weeks), subjects with and without cirrhosis, HCV mono-infected versus HCV/HIV co-infected subjects, and active treatment groups versus placebo deferred treatment group. As the proposed treatment regimen contains GZR 100 mg and EBR 50 mg, this pool focuses on Phase II and Phase III studies, or arms of such studies, in which these doses of GZR and EBR were administered. Studies and arms with different HCV genotypes were combined, as safety is expected to be comparable across genotypes.

### 8.1.4. Hepatic safety pool (HSP)

In the Phase II Study P003, elevations of ALT and/or AST levels above the upper limits of normal (ULN) were observed late in the course of therapy among a proportion of subjects who received GZR 200 mg, 400 mg or 800 mg, and who had ALT levels within normal limits at baseline. The rate and severity of these events were dose-dependent. In particular, the frequencies of ALT and/or AST levels >5x ULN occurring late in the course of therapy (>TW4) among subjects in whom ALT and AST levels were within normal limits at TW2 and TW4 (termed 'Late ALT/AST Elevation Events'), were 0.7%, 1.5%, 6.0% and 9.2% among subjects in the GZR 100 mg, 200 mg, 400 mg, and 800 mg dose arms, respectively. To further characterise this phenomenon and to understand its clinical significance, subsequent protocols included careful, frequent (ranging from weekly to monthly) monitoring of liver-related laboratory tests (including liver transaminases) to detect Late ALT/AST Elevation Events. Furthermore, non-specific hepatic events of clinical interest (ECI) criteria were defined to create a sensitive screen for the presence of potential liver abnormalities in study subjects. Hepatic laboratory ECIs were defined as the following:

- ALT or AST >500 IU/mL regardless of baseline ALT/AST (not associated with virologic failure); or
- ALT or AST >3x baseline and >100 IU/mL (not associated with virologic failure); or
- Alkaline phosphatase >3x ULN (not associated with virologic failure).

Hence, the Hepatic Safety Pool (HSP) allows for a comprehensive evaluation of hepatic safety findings, focused on Late ALT/AST Elevation Events as well as hepatic laboratory ECIs, and discontinuations due to hepatic laboratory abnormalities. This pool includes data among 2405 subjects from all completed Phase II and III studies or study arms that evaluated a regimen of GZR of at least 8 weeks' duration as of the cut-off dates, regardless of GZR dose, regimen, or subject population. The pool includes the following studies: P003, P035, P038, P039, P047, P048, P052, P058, P059A, P060, P061, P068, and P074.

**Comments**: As the rate of Late ALT/AST Elevation Events has been shown to be related to GZR levels, an integrated analysis of these events in the HSP required inclusion of all Phase II and III studies evaluating GZR, regardless of the dose of GZR evaluated in these studies and regardless of whether EBR was co-administered.

### 8.1.5. PK/'Late ALT/AST elevation event' pool (PKP)

This pool is used to provide data for a PK/'Late ALT/AST Elevation Event' analysis, which correlates plasma GZR exposure (according to population PK) with Late ALT/AST Elevation Events. Of note, PK sampling was conducted over the entire study for each subject and was not necessarily conducted at the time of the Late ALT/AST Elevation Event; thus this data set informs the relationship between the typical PK exposure in a subject and the subject's risk for a Late ALT/AST Elevation Event.

This pool is identical to the Hepatic Safety Pool, except for the following:

- The cut-off date for data availability is 28 January 2015 in order to enable analysis of PK samples and completion of modelling the pool is limited to subjects with available PK. Of note, the PK/'Late ALT/AST Elevation Event' analysis model included the subset of PKP subjects who had laboratory evaluations of ALT/AST between TW2 and TW4 (inclusive), as well as between TW4 and until the end of treatment (inclusive).
- The pool includes a total of 2279 subjects from the same studies which contributed to the HSP. Of these 2279 subjects, 2236 subjects had both PK and safety lab data for the evaluation of Late ALT/AST Elevation Events and so the PK/'Late ALT/AST Elevation Event' analysis was performed on these 2236 Subjects.

The following safety data were collected for the individually summarised studies/study arms and the 4 main study pools:

- General AEs: For each Phase I, Phase II, and Phase III protocol, monitoring of safety was done by the investigator(s) at each study visit. AEs were coded by the Medical Dictionary for Regulatory Activities (MedDRA) 17.1. All AEs were recorded from the time the consent form was signed through 14 days following cessation of treatment. Subjects who discontinued early were requested to complete an end of treatment visit, and AEs were reported through this visit. Subjects were asked about any AEs during their study visits and the information was recorded on case report forms. The investigator assessed if there was or was not a reasonable possibility that the AE was related to study therapy. Drug-related AEs were those the investigator assessed to be possibly, probably, or definitely related to study therapy. AEs were graded by the investigator as mild, moderate, or severe intensity.
- Deaths, other SAEs (non-fatal SAEs), other significant AEs (discontinuations of study medication due to AEs): Any SAE was to be reported within 24 hours to the Merck Clinical Monitor. Each SAE was fully investigated and, if considered drug-related by the investigator, a decision was made as to whether the risk/benefit warranted the subject's continuation in the study. Decisions to temporarily withhold or reinitiate therapy because of an AE were reviewed on a case-by-case basis by the investigator.
- Laboratory evaluations: Throughout the Phase II and III studies, clinical laboratory evaluations included chemistry (including liver function tests), haematology and coagulation tests that were performed at a minimum frequency of at least every two weeks during the treatment period. Urinalysis was performed at Baseline and at the end of treatment; in the Phase III studies, urinalysis was additionally performed at TW4 and TW8. For the Phase II and Phase III studies, following each visit, investigators received laboratory test results from the central laboratory. Guidelines for grading the severity of laboratory abnormalities are based on the Division of AIDs Common Toxicity Criteria (DAIDS CTC). Investigators assessed whether laboratory values outside the normal

range were adverse events. Clinical laboratory values that were protocol-specified events of clinical interest (ECIs) and/or resulted in discontinuation of study drug were recorded as AEs.

– Events of clinical interest (ECIs), Late ALT/AST Elevation Events' (ALT or AST >5 x ULN developing after TW4, in subjects with ALT or AST < ULN between TW2 and TW4.

### 8.1.6. Other studies evaluable for safety only

None.

### 8.1.7. Pivotal studies that assessed safety as a primary outcome

None.

## 8.2. Patient exposure

Safety data was available from 2806 HCV-infected subjects in the Phase II and III studies, as well as from 1234 healthy volunteers, 66 non-HCV-infected patients with liver or kidney dysfunction, and 139 HCV-infected patients in 58 Phase I clinical pharmacology studies.

**Phase II and III studies:** The extent of GZR[33] exposure for all 1389 subjects who were treated with GZR single entity (SE) in the arms of Studies P003, P035, P038, P039, P047, P048, P052, P058 and P059 which had completed exposure is summarised in Table 26. The extent of GZR and EBR exposure for all 1097 subjects who were treated with GZR/EBR in the arms of P060, P061, P068 and P074 which had completed exposure is summarised in Table 27. The extent of EBR exposure for all 944 subjects who were treated with EBR SE in the arms of studies P035, P047, P048, P052, P058 and P059 which had completed exposure is summarised in Table 28.

**Table 26: Extent of exposure in GZR single entity (SE) tablets by dose All Study arms with completed exposure.**

| Grazoprevir (GZR) Single Entity (SE) Tablets | <4 weeks | 4 weeks to <6 weeks | 6 weeks to <8 weeks | 8 weeks to <12 weeks | 12 weeks to <16 weeks | 16 weeks to <18 weeks | 18 weeks to <24 weeks | ≥24 weeks | Total Subjects | Duration Range | Mean Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Any Dose | 18 | 14 | 18 | 286 | 901 | 20 | 123 | 9 | 1,389 | 1 to 171 days | 85.8 days |
| 25 mg | 4 | 0 | 0 | 3 | 25 | 0 | 0 | 0 | 32 | 1 to 91 days | 74.9 days |
| 50 mg | 6 | 0 | 0 | 15 | 73 | 0 | 0 | 0 | 94 | 1 to 88 days | 79.0 days |
| 100 mg | 57 | 27 | 30 | 229 | 658 | 21 | 122 | 9 | 1,153 | 1 to 171 days | 82.7 days |
| 200 mg | 43 | 1 | 2 | 27 | 38 | 0 | 0 | 0 | 111 | 1 to 88 days | 50.2 days |
| >200 mg to <400 mg | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 to 1 days | 1.0 days |
| 400 mg | 8 | 6 | 10 | 32 | 15 | 0 | 0 | 0 | 71 | 1 to 89 days | 60.2 days |
| >400 mg to <800 mg | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 7 | 1 to 1 days | 1.0 days |
| 800 mg | 7 | 6 | 11 | 23 | 19 | 0 | 0 | 0 | 66 | 1 to 87 days | 61.9 days |
| >800 mg | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 6 | 1 to 12 days | 3.5 days |

Each subject who received Grazoprevir (GZR) Single Entity (SE) Tablets is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Grazoprevir (GZR) Single Entity (SE) Tablets.
Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.
Includes all subjects in study arms with completed exposure to GZR SE from the following studies: P003, P035, P038, P039, P047, P048, P052 (immediate treatment arm), P058 and P059.

[33] The total number of subjects in studies/arms with completed exposure who received any dose of GZR in the Phase II and III studies as of 27-Mar-2015 is 2486 (1389 SE + 1097 FDC). This number includes subjects originally reassigned to GZR, GZR and EBR or GZR/EBR as well as those originally assigned to placebo who later received GZR and EBR or GZR/EBR. This number does not include the active portions of the deferred treatment groups of Protocol 060 and Protocol 052 as these arms had ongoing exposure nor does it include studies P062 and P065, as both studies remained blinded as of 18-Feb-2015.

**Table 27: Extent of exposure in GZR/EBR fixed dose (FDC) tablets by dose All Study arms with completed exposure.**

| Grazoprevir/Elbasvir (GZR/EBR) Fixed Dose Combination (FDC) Tablets | <4 weeks | 4 weeks to <6 weeks | 6 weeks to <8 weeks | 8 weeks to <12 weeks | 12 weeks to <16 weeks | 16 weeks to <18 weeks | ≥18 weeks | Total Subjects | Duration Range | Mean Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| Any Dose | 8 | 38 | 51 | 99 | 724 | 177 | 0 | 1,097 | 1 to 120 days | 85.0 days |
| 100 mg/50 mg | 8 | 38 | 51 | 108 | 719 | 173 | 0 | 1,097 | 1 to 120 days | 84.9 days |
| >100 mg/50 mg | 41 | 0 | 0 | 0 | 0 | 0 | 0 | 41 | 1 to 7 days | 1.8 days |

Each subject who received Grazoprevir/Elbasvir (GZR/EBR) Fixed Dose Combination (FDC) Tablets is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Grazoprevir/Elbasvir (GZR/EBR) Fixed Dose Combination (FDC) Tablets.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Includes all subjects in study arms with completed exposure to GZR/EBR FDC from the following studies: P060 (immediate treatment arm only), P061, P068 and P074.

**Table 28: Extent of exposure in EBR single entity (SE) tablets by dose All Study arms with completed exposure.**

| Elbasvir (EBR) Single Entity (SE) Tablets | <4 weeks | 4 weeks to <6 weeks | 6 weeks to <8 weeks | 8 weeks to <12 weeks | 12 weeks to <16 weeks | 16 weeks to <18 weeks | ≥18 weeks | Total Subjects | Duration Range | Mean Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| Any Dose | 7 | 6 | 9 | 200 | 585 | 20 | 117 | 944 | 1 to 138 days | 87.1 days |
| <20 mg | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 4 | 2 to 57 days | 30.5 days |
| 20 mg | 0 | 1 | 0 | 0 | 24 | 0 | 0 | 25 | 35 to 91 days | 83.4 days |
| >20 mg to <50 mg | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 to 10 days | 5.5 days |
| 50 mg | 8 | 7 | 11 | 207 | 550 | 21 | 116 | 920 | 1 to 136 days | 86.8 days |
| >50 mg | 39 | 0 | 0 | 0 | 0 | 0 | 0 | 39 | 1 to 19 days | 2.8 days |

Each subject who received Elbasvir (EBR) Single Entity (SE) Tablets is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Elbasvir (EBR) Single Entity (SE) Tablets.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Includes all subjects in study arms with completed exposure to EBR SE from the following studies: P035, P047, P048, P052 (immediate treatment arm), P058 and P059.

The total number of subjects in studies/arms receiving GZR 100 mg with EBR 50 mg in the Phase II and III studies is 1955 (858 SE + 1097 FDC). **Table 29** summarises the extent of GZR 100 mg and EBR 50 mg exposure for all 858 subjects who were assigned to treatment with GZR 100 mg and EBR 50 mg SE in the arms of P035, P047, P048, P052, P058 and P059 which had completed exposure. The mean (range) number of days exposed to study drug for subjects treated with GZR 100 mg + EBR 50 mg was 87.3 days for GZR SE and 87.4 days for EBR SE. The mean (range) number of days for subjects on FDC GZR/EBR was 85.0 days.

**Table 29: Extent of exposure in EBR (top) and GZR (bottom) single entity (SE) tablets by dose Subjects who received GZR 100 mg + EBR 50 mg in All Study arms with completed exposure**

Extent of Exposure to Grazoprevir (GZR) Single Entity (SE) Tablets by Dose
Subjects Who Received GZR 100 mg + EBR 50 mg in All Study Arms with Completed Exposure

| Grazoprevir (GZR) Single Entity (SE) Tablets | <4 weeks | 4 weeks to <6 weeks | 6 weeks to <8 weeks | 8 weeks to <12 weeks | 12 weeks to <16 weeks | 16 weeks to <18 weeks | 18 weeks to <24 weeks | ≥24 weeks | Total Subjects | Duration Range | Mean Duration |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Any Dose | 7 | 5 | 11 | 191 | 507 | 19 | 118 | 0 | 858 | 1 to 139 days | 87.3 days |
| 100 mg | 7 | 5 | 14 | 193 | 502 | 20 | 117 | 0 | 858 | 1 to 138 days | 87.2 days |
| 200 mg | 31 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 31 | 1 to 19 days | 2.5 days |

Each subject who received Grazoprevir (GZR) Single Entity (SE) Tablets is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Grazoprevir (GZR) Single Entity (SE) Tablets.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Includes all subjects in study arms with completed exposure to GZR 100 mg + EBR 50 mg from the following studies: P035, P047, P048, P052 (immediate treatment arm only), P058 and P059.

Data Source: [Ref. 5.3.5.2: P035V01] [Ref. 5.3.5.2: P047] [Ref. 5.3.5.2: P048V01] [Ref. 5.3.5.1: P052V01] [Ref. 5.3.5.2: P058V01] [Ref. 5.3.5.2: P059V01]

Extent of Exposure to Elbasvir (EBR) Single Entity (SE) Tablets by Dose
Subjects Who Received GZR 100 mg + EBR 50 mg in All Study Arms with Completed Exposure

| Elbasvir (EBR) Single Entity (SE) Tablets | <4 weeks | 4 weeks to <6 weeks | 6 weeks to <8 weeks | 8 weeks to <12 weeks | 12 weeks to <16 weeks | 16 weeks to <18 weeks | ≥18 weeks | Total Subjects | Duration Range | Mean Duration |
|---|---|---|---|---|---|---|---|---|---|---|
| Any Dose | 7 | 5 | 9 | 190 | 510 | 20 | 117 | 858 | 1 to 138 days | 87.4 days |
| <20 mg | 2 | 0 | 0 | 2 | 0 | 0 | 0 | 4 | 2 to 57 days | 30.5 days |
| >20 mg to <50 mg | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 2 | 1 to 10 days | 5.5 days |
| 50 mg | 7 | 7 | 11 | 197 | 499 | 21 | 116 | 858 | 1 to 136 days | 87.1 days |
| >50 mg | 39 | 0 | 0 | 0 | 0 | 0 | 0 | 39 | 1 to 19 days | 2.8 days |

Each subject who received Elbasvir (EBR) Single Entity (SE) Tablets is counted once on the "Any Dose" row in the column that reflects the total duration of exposure to Elbasvir (EBR) Single Entity (SE) Tablets.

Each subject is counted again on one or more specific dose category rows that correspond to the actual dose(s) received. On each applicable specific dose row, the subject is counted once in the column that reflects the duration of exposure to that specific dose.

Includes all subjects in study arms with completed exposure to GZR 100 mg + EBR 50 mg from the following studies: P035, P047, P048, P052 (immediate treatment arm only), P058 and P059.

**Exposure in the 060, 061 and 068 studies 12 week safety population pool:** The mean (range) number of days for the 743 subjects on GZR/EBR in this population was 84.6 (4 to 106); 639 subjects were exposed to GZR/EBR without RBV exposure and the remaining 104 subjects

in this pool were exposed to RBV in addition to exposure to GZR/EBR. Of the 743 subjects in the P060/ P061/ P068 12-Week Safety Population Pool, 98.9% of subjects completed study medication, and 98.9% completed the trial up to follow-up Week 12. Majority of the 743 treated with GZR/EBR+RBV in this safety pool were male, aged 18-64 years, White with HCV genotype 1a or 1b, baseline HCV RNA > 800,000IU/ml, non-cirrhotic and treatment naïve (all 104 subjects who received GZR/EBR +RBV were treatment experienced).

**Integrated safety pool (ISP):** The total number of subjects in the ISP was 1690 (736 SE + 954 FDC). Table 29 summarises the extent of GZR and EBR exposure for all 736 subjects in the ISP who were assigned to treatment with GZR and EBR SE. The mean duration of any dose was 88.1 days; of the 736 subjects exposed to GZR SE in the ISP, 289 subjects were exposed to GZR and EBR SE without RBV exposure, while the remaining 447 subjects in this pool exposed to GZR SE were also exposed to RBV. The extent of GZR/EBR exposure for all 954 subjects in the ISP who were assigned to treatment with GZR/EBR: The mean duration of any dose of GZR/EBR FDC was 90.3 days; of the 954 subjects exposed to GZR/EBR in the ISP, 744 subjects were exposed to GZR/EBR without RBV exposure, while the remaining 210 subjects in this pool exposed to GZR/EBR were also exposed to RBV.

The rates of completion of study treatment and follow-up at week 12 was slightly higher among subjects who received GZR/EBR without RBV (95-100%) compared to those who received GZR/EBR with RBV (88-100%). Although the overall frequency of discontinuations due to AE was low, there were numerically more discontinuations observed in the 16 and 18 week arms with RBV with 3.8% (4/106) and 2.3% (2/86), respectively, compared to 0.6% (5/834) in the 12 week no RBV and 0% in both 16- and 18-wk with no RBV arms.

Majority of the subjects in the ISP were male (61.4%), White (75.5%) with median age of 54 years (range 18-82 years) and 11.1% of subjects were >65 years of age. The majority of subjects had GT1 HCV (87.2%), whereas smaller proportions had GT2 (1.8%), GT3 (2.4%), GT4 (6.1%), GT5 (0.5%), and GT6 (1.5%) HCV. 51.2% of subjects had GT1a, and 36.0% had GT1b, and 0.5% had non subtypeable GT1 infection. 25.3% of subjects had baseline HCV RNA ≤800,000 IU/mL and approximately half of subjects (49.7%) had baseline HCV RNA ≤2,000,000 IU/mL; 27.0% of all subjects had cirrhosis, 38.2% were HCV treatment-experienced and 17.6% of all subjects were co-infected with HIV and HCV. The group of subjects that received placebo for 12 weeks was similar to the group of subjects in the ISP who received GZR with EBR. A slightly lower proportion (53.3%) was male, and a higher proportion (17.1%) was Black. No subjects had GT 2 or GT3 infection. A lower proportion of subjects (37.1%) had HCV RNA <800,000 IU/mL at Baseline. A slightly lower proportion (21.0%) subjects had cirrhosis, no subjects were HCV treatment experienced, and no subjects were co-infected with HIV and HCV.

**Hepatic safety pool (HSP):** The total number of subjects who received any dose of GZR in the Hepatic Safety Pool was 2405 (1389 SE+ 1016 FDC). This number includes subjects originally assigned to treatment with GZR without EBR, GZR+EBR, or GZR/EBR as well as those originally randomised to placebo who then received GZR/EBR. The mean (range) number of days for subjects on GZR 100 mg and EBR 50 mg was 82.7 and 86.8, respectively. The mean (range) number of days for subjects on FDC GZR/EBR was 88.8. Demographic and baseline disease characteristics were representative of subjects with chronic HCV and were comparable to those of the subjects in the Integrated Safety Population Pool.

**PK/'Late ALT/AST elevation event' pool (PKP):** The mean duration of exposure to GZR/EBR for the 1101 subjects in this safety pool was 89.1 days. Similar to the HSP, the demographic and baseline characteristics of the PKP were comparable to the characteristics of the subjects in the ISP.

## 8.3. Adverse events

### 8.3.1. All adverse events (irrespective of relationship to study treatment)

#### *8.3.1.1. Pivotal studies*

In Study P060**,** AEs occurred in 213 (67.4%) and 72 (68.6%) of patients in the immediate treatment and placebo-controlled deferred treatment groups, respectively. The incidence of AEs by SOC was generally similar between the two arms. The most common AEs reported in more than 10% of all subjects in any arm were headache (16.5% in active arm versus 18.1% in placebo arm) and fatigue (15.5% versus 17.1%) with similar rates across treatment groups and across non-cirrhotic and cirrhotic subjects.

In Study P0**52**, the incidence of AEs, drug-related AEs, SAEs, and drug-related SAEs was markedly higher in this study's placebo deferred group, compared to that in Study P060, reflecting the underlying comorbidities of the CKD population. However, within Study P052, there were no clear differences between the GZR+EBR immediate treatment and placebo-controlled deferred treatment groups in the incidence of AEs, drug-related AEs, SAEs, drug-related SAEs, deaths and study drug discontinuations due to AEs. Overall, 75.7% versus 84.1% had one or more AEs in the immediate GZR+EBR and placebo deferred treatment arms, respectively. The most frequently reported (incidence ≥10%) AEs by subjects in the GZR+EBR and PBO arms, respectively were: headache (17.1% versus16.8%), nausea (15.3% versus 15.9%) and fatigue (9.9% versus 15.0%); the most frequently reported laboratory AE was blood alkaline phosphatase increased 1.8% and 4.4%, respectively in the immediate treatment group compared to the placebo-controlled deferred treatment group). It is important to note that alkaline phosphatase elevations are common in the CKD population. These events were also reported as ECIs.

In the open-label Study P061 of GZR/EBR 100/50 mg for 12 weeks in 218 HCV/HIV co-infected subjects, 161(73.9%) of subjects reported one or more AEs. The most common AEs (in >10% of subjects) were fatigue (13.3%) and headache (12.4%). Other common AEs were nausea (9.2%), upper respiratory tract infections (7.8%), diarrhoea (7.8%), insomnia (6.9%) and nasopharyngitis (5%). The majority of AEs reported were of mild or moderate severity, and only 1.4% was considered severe.

The Phase III, 4-arm Study P068 evaluated 12- or 16 week regimens of GZR/EBR with or without RBV in 420 non-cirrhotic or cirrhotic GT1, GT4, or GT6 infected subjects who previously failed PR therapy. Overall, 331/420 (78.8%) of subjects experienced AEs; 74/105 (70.5%), 85/104 (81.7%), 77/105 (73.3%), and 95/106 (89.6%) of subjects experienced AEs, respectively for the GZR/EBR 12 week, GZR/EBR + RBV 12 week, GZR/EBR 16 week and GZR/EBR + RBV 16 week treatment groups. The most frequent (≥10% in one or more groups) AEs were fatigue (23.1%), headache (19.8%) and nausea (11.0%).

**Comments**: An increase in the proportion of subjects with non-serious AEs and drug-related AEs was observed in treatment arms that received RBV relative to the arms that did not receive RBV.

#### *8.3.1.2. Other studies*

In Study 059**,** 86.7% of CP-B subjects and 80.0% of non-cirrhotic subjects experienced one or more AE. In CP-B subjects, the most frequent (>10%) AEs were: fatigue, arthralgia, nausea, pyrexia, influenza, and headache. In non-cirrhotic subjects, the most frequent (>10%) AEs were: headache, fatigue, nausea and arthralgia.

In Phase II open-label Study P074, incidence of AEs was 23.1% following treatment with GZR/EBR 100/50 mg with sofosbuvir 400 mg for 4, 6, 8, or 12 weeks among 143 TN non-cirrhotic or cirrhotic GT1 and GT3-infected subjects; the most frequent AEs were: headache (6/143 [4.2%]), nausea (4/143 [2.8%]) and fatigue.

In Study P058 which compared two doses of GZR (50 mg and 100 mg) in combination with EBR 50 mg for 12 weeks in 62 non-cirrhotic, GT1, HCV infected Japanese subjects, the overall incidence of AEs was slightly higher in the 100 mg GZR group (24/31, 77.4%) compared to the GZR 50 mg ((21/31, 67.7% ) group; the most common AEs were nasopharyngitis (GZR 50 mg versus 100 mg: 22.6% versus 32.3%)and headache (12.9% versus 9.7%).

In the dose-finding Studies P038, P003 and P035A, the incidence of AEs was generally similar across the 25-800 mg GZR dose range. Nearly all subjects at each dose reported AEs, including one or more events that the investigators considered to be drug-related. There tended to be an association of increased incidence of SAEs with increasing GZR dose.

In Study P003 in non-cirrhotic subjects, the incidence of AEs by SOC was generally similar across the GZR treatment arms. Overall, the most common AEs reported in the non-cirrhotic GZR arms were fatigue, headache, nausea, pyrexia, chills, influenza like illness, alopecia, decreased appetite, anaemia and rash; each of which was reported in 20% or more of all subjects, with similar rates across treatment groups. There was no clear pattern of increase in AEs of anaemia, neutropenia, rash, or vomiting with GZR dose level; however, the incidence of diarrhoea and of nausea was highest among subjects treated with the GZR 800- mg regimen. Other common AEs with a higher incidence in the GZR 800-mg arm were fatigue, pain, injection site erythema, and alopecia. The cirrhotic subjects in this study showed a similar AE profile.

In Study P038 the most common AEs were fatigue, headache, chills, nausea, decreased appetite, anaemia and pyrexia, each of which was reported in more than 30% of all subjects. There was no clear pattern of increase in AEs of anaemia, neutropenia, rash, nausea, vomiting, or diarrhoea with GZR dose level. Four AEs of increased ALT were reported and two of these were considered drug related by the investigators.

In Study P035A Arms A1 and A2, GT1a and GT1b infected subjects received GZR 100 mg with either EBR 20 mg + RBV (A1, n=25) or EBR 50 mg + RBV (A2, n=28) for 12 weeks. Other arms of this study (Arms B1, B2, B3, C1 and $C_2$) included subjects who received GZR 100 mg with EBR 50 mg with or without RBV for 8, or 12 weeks. There were no clear differences in the rates of AEs between subjects who received GZR 100 mg with either EBR 20 mg + RBV (Arm A1) or EBR 50 mg + RBV (Arm A2). In subjects who received GZR 100 mg with EBR 20 mg + RBV (A1), the most common AEs (incidence >10%) were: fatigue (36.0%), nausea (20.0%), dyspnoea (20.0%), abdominal pain upper (16%), dizziness (16.0%), headache (16.0%), anaemia (12.0%), diarrhoea (12.0%), dyspepsia (12.0%), INR increased (12.0%) and insomnia (12.0%). In subjects who received GZR 100 mg with EBR 50 mg + RBV (A2), the most common AEs (incidence >10%) were: nausea (25.0%), headache (21.4%), diarrhoea (17.9%), rash (17.9 %), fatigue (17.9%), vomiting (14.3%) and sinusitis (10.7%).

Study P047 Arm B1 was a study of GZR 100 mg + RBV for 12 weeks in 30 GT2 HCV subjects and the most common AEs (>10%) in Arm B1 (GZR 100 mg with RBV) were accidental overdose, nausea, headache, asthenia and fatigue.

### 8.3.2. Treatment-related adverse events (adverse drug reactions)

#### *8.3.2.1. Pivotal studies*

In Study P060, drug-related AEs occurred in 114 (36.1%) and 41 (39.0%) subjects in the immediate treatment group and placebo-controlled deferred treatment group, respectively. All drug-related AEs had comparable rates in both arms. The most common drug-related AEs overall were fatigue (immediate treatment group versus placebo-controlled deferred arm: 11.1% versus 9.5%), headache (9.8% versus 8.6%) and nausea (4.4% versus 4.8%)**.** The majority of the 155 subjects who reported drug-related AEs reported on treatment or within the first 14 days of follow-up experienced mild (113/155, or 72.9% of subjects who reported drug-related AEs) or moderate (38/155, or 24.5% of subjects who reported drug-related AEs) intensity. The overall frequencies of mild or moderate drug-related AEs were comparable across treatment arms Overall, severe AEs were infrequent, and there were no clear differences in

incidence in the GZR/EBR immediate treatment group compared to the placebo deferred treatment group. Across arms, 4 subjects reported severe intensity drug-related AEs while on treatment or within the first 14 days of follow-up. Drug-related AEs of severe intensity occurred in 3/316 (0.9%) subjects in the GZR/EBR immediate treatment group (ALT increased [2 subjects], CPK increased [1 subject]) and in 1/105 (1.0%) subject in the placebo-controlled deferred treatment group (hepatic enzymes increased).

In Study P052**,** the incidence of drug-related AEs was 34.2% versus 34.5% in the immediate GZR+EBR and placebo deferred treatment arms, respectively. The following drug-related AEs were more frequent in the GZR+EBR immediate treatment group, compared to the placebo-controlled deferred treatment group: nausea (12.6% versus 8.0%), headache (11.7% versus 5.3%), and dyspepsia (1.8% versus 0.9%). The incidence of drug-related AEs of mild, moderate and severe intensity was 26.1%, 8.1% and 0.0%, respectively, In the immediate treatment group (compared with 25.7%, 7.1% and 1.8%, respectively in the placebo deferred treatment group). there was a low rate of drug-related AEs of moderate to severe intensity with no clear difference in the incidence of moderate and severe drug-related AEs between the GZR+EBR immediate treatment group and the placebo deferred treatment group.

In the open-label Study P061, drug-related AEs were reported by 75 subjects (34.4%) with fatigue (7.3%) and headache (6.9%) most common.

In Study P068, the incidence of drug-related AEs varied among treatment groups with the lowest rates in the groups that did not receive RBV. Among RBV-treated subjects, those who received treatment for 16 weeks had a higher incidence of drug-related AEs than those who received 12 weeks of treatment. Although more subjects in the 16 week treatment arms reported drug-related AEs than in the 12 week arms, the incidence of the common drug-related AEs did not appear to increase with treatment duration. Most subjects (56.0%) reported AEs that the investigators considered to be drug-related. The AEs most often reported as drug-related were fatigue (19.3%), headache (14.8%), nausea (8.6%), asthenia (7.4%) and anaemia (6.9%) were also among the most common AEs overall.

#### *8.3.2.2. Other studies*

In Study 059, 14 subjects (35.0%) reported AEs that the investigators considered to be drug-related.

In Study P074, 8.4% of all subjects reported drug-related AEs with headache (5.3%) and nausea (2.1) most common.

In Study P058, drug-related AEs were reported in 29.0% (18/62) of the subjects; 32.3% (10/31) and 25.8% (8/31) of the subjects in the GZR 50 mg and 100 mg arms, respectively.

In Study P038, 95.4% of the subjects reported drug-related AEs; the most common AEs overall (fatigue, headache, chills, nausea, decreased appetite, anaemia, and pyrexia) were also the AEs most often reported as drug related and all of these are well recognised as AEs associated with peg-IFN + RBV therapy. The incidence of common drug-related AEs did not appear to increase consistently with GZR dose level.

In Study P003, non-cirrhotic subjects, most treated with GZR (97.0%) reported one or more drug-related AEs. The AEs most often reported as drug-related (fatigue, headache, and nausea) were also the most common AEs overall and all of these are well recognised as side effects associated with peg-IFN + RBV therapy. The incidence of most common drug-related AEs did not appear to increase consistently with GZR dose level, with the exception of drug-related diarrhoea and nausea, which were reported more often among subjects treated with the GZR 800 mg regimen, and resulted in treatment discontinuation in one subject. Common drug-related AEs that were reported more often in the BOC control arm were neutropenia, and dysgeusia, none of which were treatment limiting in these subjects. Other common drug-related

AEs in the BOC arm occurred with an incidence similar to that observed in the GZR treatment arms.

In Study P003 cirrhotic subjects, the profiles of drug-related AEs were generally similar between these cirrhotic subjects and non-cirrhotic subjects in the GZR 100 mg QD + PR treatment arms. Cirrhotic subjects had a higher incidence of anaemia, neutropenia, and anaemia-associated AEs (for example, dyspnoea) than non-cirrhotic subjects on the GZR regimen, but these events were not treatment limiting except in one cirrhotic subject with neutropenia. Anaemia was managed with RBV dose reduction in 10/36 (27.8%) cirrhotic subjects.

In Study P035, the incidence for drug-related AEs was 72% and 78.6% in the A1 (GZR 100 mg with EBR 20 mg + RBV) and A2 (GZR 100 mg with EBR 50 mg + RBV) treatment arms, respectively. The most common drug-related AEs (incidence >5%) in A1 were fatigue (36.0%), nausea (20.0%), headache (16.0%), dyspnoea (16.0%), anaemia (12.0%), diarrhoea (12.0%), INR increased (12.0%), dizziness (12.0%), dyspepsia (8.0%), flatulence (8.0%), vomiting (8.0%), malaise (8.0%), myalgia (8.0%), agitation (8.0%), insomnia (8.0%), irritability (8.0%) and alopecia (8.0%); most common drug-related AEs in A2 were: nausea (21.4%), headache (17.9%), rash (17.9%), diarrhoea (10.7%), fatigue (10.7%), anaemia (7.1%), vomiting (7.1%), dizziness (7.1%), insomnia (7.1%) and pruritus (7.1%).

In Study P047 (Arm B1), 19/30 (63.3%) of the subjects reported drug-related AEs with asthenia and fatigue reported most commonly (>15%). Anaemia was reported as an AE in a greater rate in Arm B1 (which contained RBV [6.7%]) compared to the RBV free arm (Arm B3 [0.0%]).

### 8.3.3. Deaths and other serious adverse events

#### *8.3.3.1. Pivotal studies*

In Study P060, there were 2 deaths both in the GZR/EBR immediate treatment group, both were considered by the investigators to be unlikely related to study drug (due to the incarcerated hiatal hernia which occurred in the follow-up phase after treatment was completed; other death was due to arrhythmia from autopsy documented coronary disease). Twelve (2.9%) subjects experienced SAEs during the treatment period through the first 14 days of follow-up, 9 (2.8%) in the immediate treatment group and 3 (2.9%) in the deferred treatment group, none of which were considered drug-related. Four additional patients (1.3%) in the immediate treatment group had SAEs with onset after the first 14 follow-up days up to the cut-off date, none of which were considered to be drug-related.

In Study P052, there were 4 deaths (1 in the GZR+EBR immediate treatment group and 3 were in the placebo deferred treatment group). Of the AEs that resulted in death, 3 occurred in the follow-up phase after treatment was completed. Of the AEs that resulted in death, all were considered by the investigators to be unlikely related to study drug (cardiopulmonary death, unknown cause; thoracic artery aneurysm and septic shock). Overall, 35 subjects had SAEs in P052: 16 (14.4%) and 19 (16.8%) in the GZR+EBR immediate treatment and placebo deferred treatment groups, respectively. There were no SAEs in the intensive PK arm. None of the SAEs in GZR+EBR immediate treatment group, and 1 (0.9%) of the SAEs in the placebo deferred treatment were considered by the investigator to be drug-related.

In the Phase III open-label Study P061**,** there were no deaths and only 6 subjects experienced SAEs (2.8%); 2 SAEs occurred during treatment and the other 4 events occurred during the follow-up period, after more than 1 month of completing treatment and none of the SAEs were drug-related.

In Phase III Study P068, no deaths occurred during treatment or the first 14 days of post-treatment follow up and only 4 subjects reported non-fatal SAEs.

#### *8.3.3.2. Other studies*

In Study P059, there was one death in the follow-up period after treatment (due to hepatic failure) and there were 4 non-fatal SAEs (2 on treatment and 2 during follow-up), none of which were considered drug-related.

In Study P074, there were no deaths and 2 subjects reported SAEs that occurred on treatment or with 14 days of follow-up: both were cirrhotic; one received 6 weeks of therapy, the other received 8 weeks of therapy.

In Study P058, there were no deaths and 3 subjects experienced SAEs, including 2 subjects on treatment (one who received GZR 50 mg and one who received GZR 100 mg) and 1 subject (who received GZR 100 mg) in follow-up. None of these subjects had SAEs that were considered drug-related.

No subjects died in dose-finding studies P003, P038 and P035A. In Study P035 (Arms A1 and A2), there were no deaths and only 1 subject who received GZR 100 mg with EBR 20 mg + RBV (A1) had an SAE (drug-related nausea).

In Study P047 (Arm B1), there were no deaths and only 1 SAE.

### 8.3.4. Discontinuation due to adverse events

#### *8.3.4.1. Pivotal studies*

In Study P060, 4 subjects (1.0%) discontinued study medication as a result of AEs , 3 (0.9%) in the immediate treatment group(2 subjects reported increased ALT/AST which resolved with study medication discontinuation); 1 subject reported anxiety/ palpitations) and 1 (1.0%) in the deferred treatment group (moderate pruritic rash).

In Study P052, incidence of discontinuations due to AEs was 0 (0%) and 5 (4.4%) in the GZR/EBR immediate treatment group and the placebo deferred treatment groups, respectively.

In Study P061, there were no discontinuations due to AEs.

In Study P068, 6/420 (1.4%) subjects discontinued study medication due to an AE during treatment or the first 14 follow-up days.

#### *8.3.4.2. Other studies*

In Study P059 and P058 there were no discontinuations due to AEs.

In Study P074, there was only 1 discontinuation due to AE (non-drug related pneumonia).

In dose finding Studies P003 and P038, discontinuations due to AEs were infrequent, but they tended to increase with increasing GZR dose. Three (3) subjects discontinued due to an SAE; one each of these subjects received GZR 100 mg, GZR 400 mg, and GZR 400 mg that was down-dosed to 100 mg. In Study P035 (Arms A1 and A2) and in Study P047, there were no discontinuations due to AEs.

## 8.4. Laboratory tests

### 8.4.1. Liver function

#### *8.4.1.1. Pivotal studies*

In Study P060, ALT/AST increases were infrequent at baseline and during treatment, and occurred at a slightly lower in rate in the GZR/EBR immediate treatment group than in the placebo deferred treatment group.. These increases were transient, not associated with clinical AEs and did not limit study therapy. Grade 3 and Grade 4 ALT/AST elevations were uncommon; among subjects in the GZR/EBR immediate treatment group, 4/316 (1.3%) and 3/316 (0.9%), respectively, had Grade 3/4 ALT or AST increases. Among subjects in the placebo deferred

treatment group, 13/105 (12.4%) and 3/105 (2.9%), respectively, had Grade 3/4 ALT or AST increases. Total bilirubin increases were infrequent at Baseline and during treatment, and were similar in rate in the GZR/EBR immediate treatment group compared to the placebo deferred treatment group.

In Study P052, worsening (increased) ALT and/or AST Grade from baseline occurred less frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group [(3/111,2.7%) and (25/113, 22.1%), respectively]; 2/111 (1.8%) and 18/113 (15.9%), respectively, developed worsened AST Grade while on treatment. No subject (0/111, 0.0%) in the GZR+EBR immediate treatment group had worsening of ALT/AST by >2 Grades while on treatment. In the placebo deferred treatment group, 2/113 (1.8%) and 1/113 (0.9%), respectively, had worsening of ALT and AST by >2 Grades while on treatment. Overall, 3/111 (2.7%), 1/111 (0.9%), 0/111 (0.0%), and 0/111 (0.0%), respectively, of GZR+EBR immediate treatment group subjects developed new Grade 1, Grade 2, Grade 3, or Grade 4 ALT increases. 2/111 (1.8%), 0/111 (0.0%), 0/111 (0.0%), and 0/111 (0.0%), respectively, of immediate treatment group subjects developed new Grade 1, Grade 2, Grade 3, or Grade 4 AST increases. Total bilirubin increases were infrequent at Baseline and during treatment, although they were of a slightly higher rate in the placebo deferred treatment group than in the GZR+EBR immediate treatment group.

In open-label, Phase III Study P061, 3 subjects had a hepatic laboratory ECIs; 1 of these 3 subjects also had a Late ALT/AST Elevation Event.

In Study P068, 4 subjects had ECIs due to hepatic laboratory abnormalities; 3 of these subjects also had Late ALT/AST Elevation Events. Overall, 4 subjects had elevation of ALT or AST >5x ULN. Of these, 1 was in the GZR/EBR (+ RBV) 12 week arm, and 3 subjects were in the GZR/EBR (no RBV) 16- week arm. Increases in total bilirubin were common among subjects who received RBV. Altogether, 14 subjects (6.7%) in the GZR/EBR (+ RBV) arms had a Grade 3 or 4 total bilirubin increase (5 treated for 12 weeks, 9 treated for 16 weeks); the majority were associated with decreases in haemoglobin.

#### *8.4.1.2. Other studies*

In Study P074, no subjects had elevations of ALT or AST >5x ULN that were either new or worsened from baseline.

In Study P059, no subject had an ECI due to a hepatic laboratory abnormality or a Late ALT/AST Elevation Event; 1/30 (3.3%) CP-B subject had a Grade 1 ALT increase during treatment and 2/30 (6.7%) CP-B subjects had a Grade 1 AST increase during treatment. No subject (either CP-B or non-cirrhotic) developed Grade 3 or 4 ALT or AST increases while on treatment. No non-cirrhotic subject had a Grade 1, 2, 3, or 4 total bilirubin increase during treatment. Thirteen (13)/30 (43.3%), 4/30 (1.3%), 0/30 (0.0%), and 0/30 (0.0%), respectively, of CP-B subjects had Grade 1, 2, 3, or 4 total bilirubin increases at Baseline. 14/30 (46.6%)of CP-B subjects developed worsened total bilirubin by ≥ 1 Grade while on treatment; 2/30 (6.7%) of CP-B subjects developed worsened total bilirubin by ≥ 2 Grades while on treatment. No non-cirrhotic subject developed worsened total bilirubin by ≥ 1 Grade while on treatment.

In Study P058, 1 subject experienced a drug-related hepatic ECI (68 year old female being treated with GZR/EBR 50/50 mg) and no subjects experienced a Late ALT/AST Elevation Event.

In Study P039, no subject (0/30 (0.0%) had elevation of ALT or AST >5x ULN. In Study P047 (Arm B1 GZR 100 mg +RBV), 2% (2/98) subjects had elevation of ALT or AST >5x ULN.

### 8.4.2. Kidney function

#### *8.4.2.1. Pivotal studies*

In Study P060, in the majority of subjects, clinical laboratory values remained within normal ranges throughout the treatment period with no significant changes in serum creatinine or urine protein.

In Study P052, mean creatinine decreased during the treatment period in both the GZR+EBR immediate treatment group and the placebo deferred treatment groups, although there were no meaningful differences between the two arms. Worsening creatinine from baseline occurred less frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group. 7/111 (6.3%) and 15/113 (13.3%), respectively, of subjects in the GZR+EBR and placebo groups developed worsened (increased) creatinine by >1 Grade while on treatment. No subjects in either treatment group had worsening of serum creatinine by ≥2 Grades. Worsening urine protein from baseline occurred at similar frequencies in the GZR+EBR immediate treatment group and the placebo deferred treatment group. Overall, 23/49 (47.0%) and 20/50 (40.0%), respectively, of subjects in the GZR+EBR and placebo groups developed worsened (increased) urine protein by ≥ 1 Grade while on treatment, and 4/49 (8.2%) and 8/50 (16.0%) of subjects, respectively, in the GZR+EBR immediate treatment group and in the placebo deferred treatment group, had worsening of urine protein by ≥ 2 Grades.

### 8.4.3. Other clinical chemistry

#### *8.4.3.1. Pivotal studies*

In Study P060, majority of subjects entered the study with CK below ULN. Worsening CK Grade from baseline occurred at <similar> frequencies in the GZR/EBR immediate treatment group and the placebo deferred treatment group; 20/316 (6.3%) and 5/105 (4.8%), respectively, of subjects in the GZR/EBR and placebo groups developed worsened CK Grade (by >1 Grade) while on treatment; 7/316 (2.2%) and 2/105 (1.9%), respectively, of subjects in the GZR/EBR and placebo groups developed worsened CK by >2 Grade while on treatment. In the GZR/EBR immediate treatment group, 15/316 (4.7%), 6/316 (1.9%), 0/316 (0.0%), and 2/316 (0.6%), respectively, of subjects developed new Grade 1, Grade 2, Grade 3, or Grade 4 CK elevations. 4/105 (3.8%), 1/105 (1.0%), 0 (0.0%), and 1/105 (1.0%), respectively, of subjects in the placebo deferred treatment group developed new Grade 1, Grade 2, Grade 3, or Grade 4 CK elevations.

In Study P052, majority (219/224 [97.8%]) of subjects entered the study with CK below ULN. Worsening (increased) of CK Grade from baseline occurred at similar frequencies in the GZR+EBR immediate treatment group and the placebo deferred treatment group. Worsening of CK levels by >1 Grade while on treatment occurred in 6/111 (5.4%) and 5/113 (4.4%) of subjects in the GZR+EBR and placebo groups, respectively; worsening by >2 Grade was observed in 0/111 (0.0%) and 2/113 (1.8%), respectively. In the majority of subjects, clinical laboratory values remained within normal ranges throughout the treatment period. Grade 3 and Grade 4 lipase elevations were observed in 19/111 (17.1%) of subjects in the immediate treatment group, and in 19/113 (16.8%) of subjects in the placebo (deferred treatment) group.

#### *8.4.3.2. Other studies*

In Study P059, 12/30 (40.0%) of CP-B subjects entered the study with serum albumin below ULN. 14/30 46.7%), 4/30 (13.3%), 0/30 (0.0%), and 0/30 (0.0%), respectively, of CP-B subjects had Grade 1, 2, 3, or 4 serum albumin decrease at baseline. 8/30 (26.7%) of CP-B subjects developed worsened serum albumin by ≥1 Grade while on treatment; 2/30 (6.7%) of CP-B subjects developed worsened serum albumin by ≥2 Grades while on treatment.

### 8.4.4. Laboratory parameters in the studies 061/060/068, 12 week safety population pool

The majority of subjects had elevated ALT or AST at baseline. Following initiation of GZR with EBR, ALT or AST levels usually declined, in parallel with the decrease in HCV RNA. Grade 3 or 4 ALT or AST elevations were rare, were generally transient, and they were infrequently associated with other hepatic laboratory evaluations or abdominal symptoms. Overall, 55.2% (58/105) subjects in the placebo group had worsening ALT grade (1 to < 2.5 times baseline) compared to only 3.4% (22/639) in the GZR/EBR 100/50 mg group and 0% in the GZR+EBR+RBV group; similar results were observed for AST. Among subjects who received GZR with EBR (combined RBV-free and RBV-containing treatment groups) the majority of subjects with an elevation >2x ULN and <5x ULN in ALT ((42/55) or AST (18/35) had the initial ALT/AST elevation >2x ULN and <5x ULN at TW1. Mean ALT and AST Baseline and TW4 values decreased slightly (approximately 50 IU/mL) from 73.9 and 62.3 to 22.8 and 25.4, respectively for the GZR/EBR 12 week regimen. In the GZR/EBR + RBV 12 week regimen, the decrease was from 78.7 and 64.3 to 22.4 and 24.0, respectively; mean ALT and AST values did not substantially change fromTW4 to FW4. However, the placebo group did not show any meaningful change in ALT/AST during the treatment period until FW4. Overall, there were no clear differences in worsening of ALT/AST Grade according to cirrhosis status or HCV/HIV co-infection status, regardless of RBV co-administration. The incidence of elevation in total bilirubin levels > 2xULN and < 5ULN was highest in the GZR/EBR+ RBV (9/104, 8.6%) compared to GZR/EBR (9/639, 1.4%) and placebo (4/105, 3.8%) groups. There was no meaningful change in mean total bilirubin from baseline during the course of therapy and through follow-up Week 4 in the GZR/EBR (RBV-free) and placebo groups compared to an increase observed in the GZR/EBR (+ RBV) group with the increase, peaking at TW1. Grade 1 and Grade 2 elevations in bilirubin were more frequent among cirrhotics versus non-cirrhotics treated with GZR/EBR (+ RBV). There was no clear relationship between the rate of total bilirubin elevation and HIV co-infection status, regardless of RBV co-administration. Direct bilirubin remained within normal range for most subjects. Elevations above baseline were infrequent, but occurred more often among subjects who received RBV.

GGT remained within normal range for most subjects; elevations above baseline were infrequent, and they were similar among subjects in the RBV-free and RBV-containing groups with no clear differences in elevations of GGT according to cirrhosis status or HCV/HIV co-infection status.

Alkaline phosphatase remained within normal range for most subjects; elevations above baseline were infrequent, and they were similar among subjects who received either GZR with EBR (no RBV) or GZR with EBR (+RBV). No subject in either group had a Grade 3 or Grade 4 elevation worse from baseline. Although Grade 1 elevations were more frequent in cirrhotics, compared to non-cirrhotics, similar differences were also seen among subjects who received placebo.

Subjects with baseline serum albumin <3.0 g/dL were excluded from Studies P060, P061 and P068. Serum albumin remained within normal range for most subjects. Decreases below baseline were infrequent, and they were similar among subjects in the RBV-free and RBV-containing groups with no meaningful differences were seen in non-cirrhotics versus cirrhotics.

Serum amylase and lipase remained within normal range for most subjects during treatment with GZR/EBR. Elevations above baseline were infrequent, and they were similar among subjects in the RBV-free and RBV-containing groups. No subject had an AE of pancreatitis during the treatment period. Two subjects (both in Study P060) had SAEs of pancreatic mass reported after FW12. There were no clear differences in elevations of amylase or lipase according to treatment duration, cirrhosis status, or HCV/HIV co-infection status.

Creatine kinase remained within normal range for most subjects treated with GZR/EBR. Elevations above baseline were infrequent, and they were similar among subjects in the RBV-free and RBV-containing groups; Grade 3 or 4 elevations in CK were observed in 0.6%, 1% and 1% of subjects in GZR/EBR (no RBV), GZR/EBR (+RBV) and placebo groups, respectively.

Serum creatinine remained within normal range for most subjects treated with GZR/EBR; elevations above baseline were infrequent and they were similar among subjects in the RBV-free and RBV-containing groups; Grade 2 or 4 elevations were observed in 0.2% and 0% of subjects in GZR/EBR (no RBV) and GZR/EBR (+RBV) groups, respectively. There were no clear differences in elevations in CK or serum creatinine according to treatment duration, cirrhosis status, or HCV/HIV co-infection status.

Subjects with baseline haemoglobin <9.5 g/dL were excluded from studies P060, P061 and P068. Worsening haemoglobin from baseline was infrequent, but was more common in the RBV-containing group [20/104 (19.2%), 4/104 (3.8%), 5/104 (4.8%) and 0/104 (0.0%) had Grade 1, Grade 2, Grade 3 and Grade 4 decreases worse than baseline, respectively]compared to the RBV-free group [12/639 (1.9%), 3/639 (0.5%), 0/639 (0%) and 0/639 (0.0%), respectively].

Leukocyte, lymphocyte and neutrophil counts remained within the normal range for most subjects treated with GZR/EBR. Decreases were infrequent, and they were similar among subjects in the RBV-free and RBV containing groups with no clear differences according to treatment duration, cirrhosis status, or HCV/HIV co-infection status. No subject had a Grade 3 or Grade 4 leukocyte decrease.

There were no meaningful changes for serum potassium, sodium, total protein and blood urea nitrogen (BUN) in subjects who received GZR/EBR, either with or without RBV. Among subjects who received GZR with EBR (no RBV), mean CD4 counts generally did not decrease during treatment; however, among the few subjects who received GZR with EBR (+ RBV), mean CD4 counts decreased during treatment, but there was no clear difference in mean CD4 counts according to treatment duration. Furthermore, no subjects had persistent loss of HIV suppression or antiretroviral failure during treatment with GZR with EBR.

### 8.4.5. Laboratory parameters in the Integrated safety population pool (ISP)

The majority of subjects had elevated ALT and ALT at baseline. Following initiation of GZR with EBR (+/- RBV), ALT/AST levels usually declined, in parallel with the decrease in HCV RNA. Grade 3 or 4 ALT/AST elevations were rare, were generally transient, and they were very infrequently associated with other hepatic laboratory evaluations or abdominal symptoms. Overall incidence of ALT/AST elevations were much higher in the placebo group compared to the GZR/EBR (+RBV) groups with the exception of Grade 4 ALT/AST elevations which were higher GZR/EBR group (6/1033, 0.6%) compared to GZR/EBR+RBV (1/656, 0.2%) or placebo (0%) groups. Majority of subjects with an ALT/AST elevation > 2x ULN and < 5x ULN had the initial ALT (125/158) and AST (45/70) elevation at TW1.

For both RBV-free and RBV containing groups, mean ALT/AST decreased to <ULN by TW2, in parallel with a rapid decline in HCV RNA and this decreases was maintained through follow-up Week 4. However, the placebo group showed no meaningful change in mean ALT/AST levels from baseline during the treatment period. In subjects treated with GZR with EBR (no RBV), worsening ALT/AST Grade from baseline was infrequent, but mild elevations were slightly more frequent in subjects treated with longer durations however, for subjects in the GZR/EBR + RBV group, worsening ALT Grade from baseline was infrequent and there was no clear association with treatment duration. Overall, there were no clear differences in worsening of ALT/ AST Grade according to cirrhosis status, regardless of RBV co-administration. Overall, there were no clear differences in worsening of ALT Grade according to HIV co-infection status, regardless of RBV co-administration. In particular, Grade 3 and 4 elevations were similar in

HCV/HIV co-infected subjects, compared to HCV mono-infected subjects. The majority of subjects had total bilirubin levels within normal limits during treatment.

Total bilirubin elevations were infrequent with GZR with EBR (no RBV), but were more frequent with GZR with EBR (+RBV). When they occurred, total bilirubin elevations usually occurred in the first two weeks of therapy and spontaneously resolved. Total bilirubin elevations were very infrequently associated with abdominal symptoms or abnormalities in other hepatic laboratory evaluations. In the GZR+EBR+RBV group, treatment duration, presence of cirrhosis or HCV/HIV co-infection did not affect the elevations in total bilirubin.

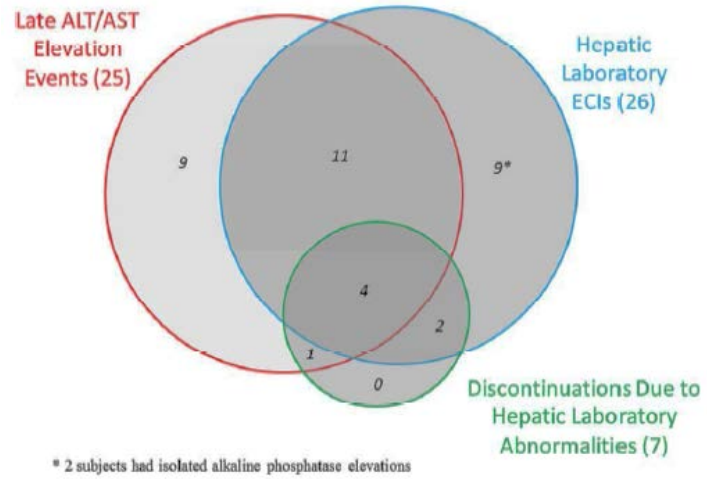
Changes in other laboratory parameters such as GGT, alkaline phosphatase, CK, serum creatinine, amylase and lipase were similar to those described in the 12 week safety pool above. Similar changes were also observed in haemoglobin. While the rate of Hb decline was higher in subjects receiving RBV versus no RBV, there was not a clear relationship between the rate of Hb decline and treatment duration, regardless of RBV co-administration. Of note, in the GZR with EBR (+ RBV) regimen, the rate of Grade 2 Hb declines was higher in the 16 week group, compared to the 12 week group; however this increased rate was not observed in the 18 week group. Cirrhosis and HIV co-infection did not affect the haemoglobin changes. Leukocyte, lymphocyte, neutrophil and eosinophil counts remained within the normal range for most subjects. Decreases were infrequent, and they were similar among subjects in the GZR with EBR (no RBV) and GZR with EBR (+RBV) regimens. Subjects with baseline platelet counts <50 x $10^3$/ml were excluded from studies included in the ISP. Platelet counts remained within the normal range for most subjects. Decreases were infrequent and they were similar among subjects in the GZR with EBR (no RBV) and GZR with EBR (+ RBV) regimens.

### 8.4.6. Hepatic safety pool analysis

The HSP contains a total of 2405 subjects from all unblinded Phase II and III studies with a regimen of at least 8 weeks of GZR as of the last database lock date of 27 March 2015, regardless of GZR dose, regimen, or subject population. Regimens of less than 8 weeks (the 4 and 6 week arms of P074) are not included, since the majority of hepatic safety events occur after 8 weeks of therapy; this restriction allows a more accurate assessment of the rate of hepatic safety events with a regimen of GZR and EBR that is 8 weeks or longer in duration, reflecting the proposed duration of treatment.

In the HSP, 36/2405 (1.5%) subjects had a Late ALT/AST Elevation Event, hepatic laboratory ECI, and/or discontinued study medication due to protocol-specified hepatic laboratory discontinuation criteria. Of these 36 subjects, 25/2405 (1.0%) had a Late ALT/AST Elevation Event, 26/2405 (1.1%) had a hepatic laboratory ECI, and 7 (0.3%) discontinued study medication due to protocol-specified hepatic laboratory abnormality discontinuation criteria. There was an increase in the rate of Late ALT/AST Elevation Events and hepatic laboratory ECIs in subjects who received doses of GZR greater than 100 mg administered with PR. Overall, the most frequent hepatic laboratory criterion fulfilled was 'ALT or AST >3x baseline and >100 IU/L', which occurred in 19/26 subjects who met ECI Criteria. There was considerable overlap among subjects who had a Late ALT/AST Elevation Event, hepatic laboratory ECI, and/or discontinued study drug due to a hepatic laboratory or eosinophil count abnormality (Figure 18).

**Figure 18: Venn diagram of subjects with late ALT/AST elevation events, any hepatic laboratory ECI or discontinuations due to hepatic laboratory abnormalities Hepatic safety pool**




### *Late ALT/AST elevation events*

Overall, 25/2405 (1.0%) subjects in the HSP had Late ALT/AST Elevation Events. No subjects who were initially assigned to doses of GZR <100 mg or to GZR 100 mg with PR had a Late ALT/AST Elevation Event. Of the 25 subjects in the HSP with Late ALT/AST Elevation Events: ☐ The rate and severity of Late ALT/AST Elevation Events was increased among subjects who received GZR doses >100 mg with PR. 14/2087 (0.7%), 1/68 (1.5%), 4/67 (6.0%) and 6/65 (9.2%) of subjects who received 100, 200, 400, and 800 mg, respectively, of GZR with PR had a Late ALT/AST Elevation Event. Only one subject had concomitant elevation in total bilirubin >2x ULN; this subject received GZR 800 mg + PR. Only 2 subjects had abdominal symptoms; both of these subjects received GZR 800 mg + PR; 5 subjects discontinued study medication. Of these 5 subjects, 3 received GZR 100 mg without PR, 1 received 400 mg GZR + PR, and 1 received GZR 800 mg + PR. All 25 subjects had resolution[34] of the Late ALT/AST Elevation Event); 12 subjects had resolution before EOT, 2 had resolution at EOT, and 11 had resolution after EOT. Among the 14 subjects who received GZR 100 mg, 6 subjects had resolution before EOT, 2 had resolution at EOT, and 6 had resolution after EOT with GZR. Seven subjects had concomitant eosinophil counts >5%[35] and 6 of these 7 subjects received GZR 100 mg without PR, and one received GZR 800 mg with PR. In 4 of these subjects, the peak eosinophil counts were below (the laboratory ULN (7.0) while 1 subject (with a peak eosinophil count of 18.2%) had chronic clonorchiasis and a Baseline eosinophil count of 15.8%.

Of the total 25 subjects with Late ALT/AST Elevation Events, 2 (8.0%) had the initial detection at TW6, 10 (40.0%) had the initial detection at TW8, 7 (28.0%) had the initial detection at TW10, 5 (20.0%) had the initial detection at TW12, and only 1 (4.0%) subject had the initial detection after TW12. Of the 25 subjects with a Late ALT/AST Elevation Event, 11 (44.0%) experienced resolution within 2 weeks, 11 (44.0%) experienced resolution after 2 weeks or more but before 4 weeks, 1 (4.0%) experienced resolution after 4 weeks or more but before 6 weeks and 2 (8.05%) experienced resolution after 6 weeks. For all 25 subjects, the duration mean, median, and range of ALT/AST >5x ULN was 14.8 days, 14 days, and 3-44 days, respectively. There was no clear difference in the duration until resolution among subjects who did not discontinue study medication, compared to subjects who discontinued study medication.

[34] Resolution is defined as a decrease of ALT/AST to ≤5x ULN
[35] The peak eosinophil counts were 5.3%, 5.8%, 6.0%, 6.0% 8.8%, 8.8%, and 18.2%, respectively

Of the 25 subjects in the HSP with Late ALT/AST Elevation Events, 5 subjects discontinued the study medication; 3 of these subjects received GZR 100 mg. Of the 5 subjects who discontinued, 1 subject had associated liver-related abnormalities (elevated total bilirubin and INR) and abdominal symptoms (nausea, vomiting, and abdominal pain), 2 subjects had eosinophil counts >5% without abdominal symptoms, and 2 subjects did not have any associated liver-related abnormalities, eosinophil counts >5%, or abdominal symptoms. Of the 25 subjects in the HSP with Late ALT/AST Elevation Events, 7 subjects had concomitant liver-related laboratory or eosinophil count abnormalities (total bilirubin >2x ULN, INR >2x ULN, and/or eosinophil count >5%): 1 subject had a total bilirubin >2x ULN (2.2 mg/dL) and an eosinophil count >5% (6%), and 7 subjects had a simultaneous eosinophil count >5%, without elevation of total bilirubin >2x ULN or INR >2x ULN; one of these subjects had an elevated eosinophil count at Baseline, and in 3 of these subjects, the peak eosinophil count was below the laboratory ULN (7.0%). None of the subjects with eosinophil counts >5% had a concomitant fever or rash. The majority of subjects with Late ALT/AST Elevation Events were asymptomatic as only 2/25 subjects had concomitant AEs of nausea, vomiting, and/or abdominal pain (one received GZR 800 mg, and the other received GZR 100 mg). An additional subject (GZR 800 mg) had abdominal symptoms that were not reported as AEs.

Among the 25 subjects with Late ALT/AST Elevation Events, 4 subjects had potential alternative (non-study drug related) aetiologies that either solely explained the Late ALT/AST Elevation Event or contributed to the development of the Late ALT/AST Elevation Event. Distribution of Late ALT/AST Elevation Events in various subject subpopulations showed that these events occurred at a higher rate among female subjects (15/936 [1.6%]), compared to male subjects (10/1469 [0.7 %]) and also in Asian females (3/103, 2.9%) compared to 1/109 (0.9%) in Asian males with similar rates observed in Black females, 2/120 (1.7%), compared to 1/210 (0.5%) in black males; incidence was slightly lower among subjects of Hispanic ethnicity (1/220[0.5%]), compared to non-Hispanic subjects (23/2143 [1.1 %]). Late ALT/AST Elevation Events occurred at a higher rate among subjects who received IFN (11/389 [2.8%]), compared with subjects who did not receive IFN (14/2103 [0.7%]). This may reflect confounding as a large number of subjects received higher doses of GZR in P003 in which subjects received GZR + PR. The rate of Late ALT/AST Elevation Events did not clearly differ (that is, less than a 2- fold difference) with race, age, BMI, cirrhosis status (21/1842 [1.1%] for non-cirrhotics versus 4/562 [0.7%] for cirrhotics), HIV co-infection, prior PR treatment status or among subjects who did or did not receive concomitant RBV, sofosbuvir, or strong /moderate CYP3A4/5 inhibitors.

**Comments**: Interpretation of analysis of late ALT/AST Elevation events in various subpopulations was limited by different sample sizes of the subgroups and other confounding factors (for example, relationships between gender, ethnicity, age and/or BMI).

### *Hepatic laboratory ECI*

Among subjects in the HSP, 26/2405 (1.1%) had hepatic laboratory ECIs. The rate of hepatic laboratory ECIs was slightly higher among subjects who received >100 mg GZR + PR, compared to those who received ≤100 mg GZR without PR (frequencies were 1.5%, 1.5% and 3.1%, respectively, among subjects who received 200 mg, 400 mg, or 800 mg of GZR + PR, compared to 1.0% among those who received GZR 100 mg without PR). Of the 26 subjects with hepatic laboratory ECIs, 15 subjects had Late ALT/AST Elevation Events, while 11 subjects had hepatic laboratory ECIs without experiencing Late ALT/AST Elevation Events. Overall, the hepatic laboratory ECIs were infrequent; 10/2087 (0.5%) subjects who received GZR 100 mg had hepatic laboratory ECIs in the absence Late ALT/ AST Elevation Events. Furthermore, the rate did not clearly differ according to GZR dose and was infrequently associated with abnormalities of other tests of hepatic function, or liver-related symptoms. In most (8/11) of these subjects, the initial detection of the hepatic laboratory ECI occurred at or before TW8: 5 (45%), 2 (18%), 1 (9%), 1 (9%) and 2 (18%) had the initial detection of a hepatic laboratory ECI at or before

TW4, at TW6, at TW8, at TW10 and at TW12, respectively; no subject had a hepatic ECI after TW12. Of the total 11 subjects who had a hepatic laboratory ECI and who did not experience a Late ALT/AST Elevation Event, 5 (45.5%) experienced resolution within less than 2 weeks. Four (4) (36.4%) experienced resolution at or after 2 weeks but before 4 weeks. Two (2) (18%) experienced resolution at ≥ 6 weeks; both of these were haemodialysis-dependent subjects from P052 (CKD), and elevated alkaline phosphatase >3x ULN was the sole reason for ECI in these subjects. In both of these subjects, alkaline phosphatase was persistently elevated throughout the treatment period and the subjects did not have concomitant ALT/AST elevations or abdominal AEs. Majority of the 11 subjects in the HSP who had hepatic laboratory ECIs and who did not experience Late ALT/AST Elevation Events were asymptomatic as only 2 subjects had abdominal symptoms. Furthermore, 7 of these 11 subjects had the identification of potential alternative (non-study drug-related) aetiologies. Potential alternative aetiologies were identified in 1/1 and 6/9, respectively of subjects who received GZR 100 mg with PR and GZR 100 mg without PR.

***Discontinuations***

In the HSP, only 7/2405 (0.29%) subjects discontinued study medication for any of the pre-defined discontinuation criteria[36]. Of these, 5 experienced a Late ALT/AST Elevation Event, 6 subjects experienced a hepatic laboratory ECI, and 4 subjects experienced both a Late ALT/AST Elevation Event and a hepatic laboratory ECI. There were no subjects who discontinued study medication due to the above criteria and who did not have a Late ALT/AST Elevation Event or a hepatic laboratory ECI.

***Subjects with concomitant ALT/AST >3x ULN and total bilirubin >2x ULN***

Overall, 9/2405 (0.4%) subjects were identified as having ALT or AST >3x ULN and total bilirubin >2x ULN which included 1 placebo-treated subject (from placebo-controlled studies P060 and P052) and remaining 8/2405 (0.3%) subjects who received GZR with EBR. Of the 8 subjects who received GZR/EBR and had ALT/AST >3x ULN concomitant with total bilirubin >2x ULN, 8 subjects received RBV, and 7 subjects received peg-IFN. The rate of ALT/AST >3x ULN concomitant with total bilirubin >2x ULN was increased among subjects who received GZR doses >100 mg with PR: 2/2087 (0.1%), subjects who received GZR 100 mg had ALT/AST >3x ULN concomitant with total bilirubin >2x ULN, whereas 1/68 (1.5%), 1/67 (1.5%), and 4/65 (6.2%) respectively, of subjects who received 200, 400 mg, and 800 mg of GZR had ALT/AST >3x ULN concomitant with total bilirubin >2x ULN. Only one subject received the proposed dose of GZR 100 mg with EBR 50 mg and the temporal pattern of elevation in this subject was not consistent with hepatocellular injury. Of the 8 subjects who received GZR with EBR and had ALT/AST >3x ULN concomitant with total bilirubin >2x ULN, 2 subjects (receiving GZR 800 mg + PR; GZR 100 mg +PR) discontinued study medication due to protocol-specified stopping rules. In all 8 subjects, the elevations resolved while continuing treatment or following completion of treatment.

[36] Discontinuation criteria included: (1) ALT/AST increased to >3x baseline, was >100, with simultaneous increase in total bilirubin >2x ULN and/or INR > 1.5;(2)ALT/AST increased to >3x nadir, was >100, with simultaneous increase in total bilirubin >2x ULN and/or INR > 1.5; (3) ALT/AST increased to >3x baseline, was >100, and was temporally associated with the new onset or worsening of any of the following adverse events that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to GZR and/or EBR: nausea, vomiting, right upper quadrant pain/tenderness, and/or eosinophils >5%;(4)ALT/AST increased to >3x nadir, was >100, and was temporally associated with the new onset or worsening of any of the following adverse events that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to GZR and/or EBR: nausea, vomiting, right upper quadrant pain/tenderness, and/or eosinophils >5%;(5) Alkaline phosphatase increased to >3x ULN, with simultaneous increase in total bilirubin >2x ULN, with no other causes of elevated alkaline phosphatase.

### 8.4.7. PK/'Late ALT/AST elevation event' analysis

Of subjects in the PKP, 22/2235 (1.0%) were observed to have Late ALT/AST Elevation Events. Of these 22 subjects, 14 (out of 2004, 0.7%) received GZR 100 mg, 0 (out of 38, 0%) received GZR 200 mg, 4 (out of 41, 9.8%) received GZR 400 mg, and 4 (out of 36, 11.1%) received GZR 800 mg. Late ALT/AST Elevation Events were observed in none of the 104 and 111 subjects who received placebo in the deferred treatment group of studies P060 and P052, respectively. The analyses of the relationship between GZR PK parameters and Late ALT/AST Elevation Events showed that all three GZR PK parameters evaluated (steady state $AUC_{0-24}$, $C_{max}$, and $C_2$) were well correlated with Late ALT/AST Elevation Events; $AUC_{0-24}$ appeared to be slightly more predictive based on the values of area under the receiver operating characteristic curves (AUC of ROC). The observed and predicted event rates of Late ALT/AST Elevation Events at each dose/population are summarised in Table 30.

**Table 30: Observed and predicted event rates of Late ALT/AST Elevation Events at various GZR dose levels $AUC_{0-24}$ based results**

| Dose / Population | GZR AUC0-24hr Values in Patients with PK Data | | | Observed Rate in Patients with Safety Data | | | Predicted Rate (%, 95% CI) |
|---|---|---|---|---|---|---|---|
| | N (PK)† | GM AUC0-24 (nM·hr) | GMR‡ | N (Event)§ | N (Safety)‖ | Rate (%, 95% CI) | |
| 25 mg | 29 | 242 | 0.14 | 0 | 28 | 0.0 (0.0, 12.3) | 0.1 (0.0, 0.2) |
| 50 mg | 89 | 1303 | 0.76 | 0 | 88 | 0.0 (0.0, 4.1) | 0.4 (0.2, 0.7) |
| 100 mg Reference | 1270 | 1721 | 1.00 | 7 | 1273 | 0.5 (0.2, 1.1) | 0.5 (0.3, 0.8) |
| 100 mg Other | 770 | 2818 | 1.64 | 7 | 769 | 0.9 (0.4, 1.9) | 0.8 (0.5, 1.2) |
| 200 mg | 39 | 8498 | 4.94 | 1 | 65 | 1.5 (0.0, 8.3) | 2.1 (1.2, 3.1) |
| 400 mg | 42 | 31062 | 18.05 | 4 | 64 | 6.3 (1.7, 15.2) | 6.2 (3.4, 9.9) |
| 800 mg | 40 | 113645 | 66.05 | 6 | 58 | 10.3 (3.9, 21.2) | 16.6 (8.3, 27.8) |

† N (PK): Number of patients with available PK data.

‡ GMR = geometric mean ratio of PK relative to the reference population at 100 mg.

§ N (Event): Number of patients with occurrence of the Late ALT/AST Elevation Event.

‖ N (Safety): Number of patients with available safety information for the evaluation of Late ALT/AST Elevation Event.

The reference population included non-cirrhotic, non-severe CKD, non-Asian HCV-infected patients in the 100 mg dosing arms of the Phase 2 and 3 studies/arms included in this analysis.

These exposure-response analyses suggest that a 5 fold increase in GZR $AUC_{0-24}$ relative to the reference population corresponds to a predicted population Late ALT/AST Elevation Event rate of approximately 2%; the reference population is predicted to have a Late ALT/AST Elevation rate of 0.5%, and the expanded population (including subjects at 100 mg with cirrhosis, CKD, and are of Asian race) is predicted to have a Late ALT/AST Elevation rate of 0.8%. In addition, there is a predicted population Late ALT/AST Elevation Event rate of 5% when the population geometric mean of GZR $AUC_{0-24}$ reaches approximately 23.7 μM·hr, which represents a GZR exposure margin of approximately 14 fold above the geometric mean (GM) $AUC_{0-24}$ observed with 100 mg GZR in the reference population. GZR $AUC_{0-24}$ increases in a greater than dose proportional manner, and so a 5 fold increase in GZR $AUC_{0-24}$ over that observed with a 100 mg dose in the reference population results in AUC values similar to those observed with a 200 mg GZR dose, and a 14 fold increase in GZR $AUC_{0-24}$ results in AUC values between those observed at 200 and 400 mg doses. These analyses demonstrate that the risk of Late ALT/AST Elevation Events is associated with GZR exposure. In a population of HCV-infected subjects, including non-cirrhotics, as well as subjects with CP-A/compensated cirrhosis, the risk of Late ALT/AST Elevation Events associated with GZR 100 mg is low (0.5 – 0.9%). Using the exposure-safety model, it is possible to predict the increase in the risk of Late ALT/AST Elevation Events associated with factors that increase GZR exposure. Increases in GZR exposure of 5 fold and 14 fold relative to the exposure at a 100 mg GZR dose in the reference population correspond to an estimated event rate of Late ALT/AST Elevation Events of 2% and 5%, respectively. Based on a population PK analysis using a dataset including the same studies included in the PK/Late ALT/AST Elevation Event analysis, the following intrinsic factors were found to increase steady

state GZR $AUC_{0\text{-}24}$hr: female gender, age, Asian race, Hispanic ethnicity, cirrhosis, severe CKD, and low body weight.

**Comments**: Increases in GZR exposure of 5 fold and 14 fold relative to the exposure at a 100 mg GZR dose in the reference population correspond to an estimated event rate of Late ALT/AST Elevation Events of 2% and 5%, respectively. A 5% incidence rate of Late ALT/AST Elevation Events is considered acceptable from a safety perspective, because these events are monitorable, consistent in terms of timing of initial detection, generally reversible with continued therapy and rarely associated with clinical abnormalities associated with liver dysfunction.

#### 8.4.8. Electrocardiograph

All the Phase II and III studies provided summary of changes from baseline in ECG parameters of PR interval and QTc interval with Bazett's and Fridericia's corrections. There were no meaningful changes from baseline for the ECG parameters in the individual Phase II/III studies.

#### 8.4.9. Vital signs

Vital signs (blood pressure, pulse, and temperature) were measured at scheduled intervals, and weight was measured at baseline and at the end of treatment. Clinically significant changes were recorded as AEs. There were no meaningful changes in vital signs from baseline in the individual Phase II/III studies.

## 8.5. Post-marketing experience

Zepatier has not received marketing approval to date and no post marketing data is available.

## 8.6. Safety issues with the potential for major regulatory impact

#### 8.6.1. Liver toxicity

Based on the investigation of safety signals observed in Study P003, a program of hepatic safety monitoring was instituted in all subsequent studies that evaluated GZR. This program, developed in consultation with the FDA, included frequent, comprehensive laboratory testing, and defined 3 types of hepatic safety events: Late ALT/AST Elevation Events: the typical GZR-related hepatic safety signal; Hepatic Events of Clinical Interest (ECI)[37]; and Hepatic Discontinuation Criteria: if a subject met one of these criteria, study therapy would be stopped. This has been discussed in detail above.

An increased rate of Late ALT/AST Elevation Events was associated with doses of GZR above 100 mg administered with PR. The majority of subjects who discontinued study medication for protocol-defined hepatic laboratory discontinuation criteria had Late ALT/AST Elevation Events. No subjects without Late ALT/AST Elevation Events and/or hepatic laboratory ECIs discontinued study medication for protocol-defined hepatic laboratory discontinuation criteria. Overall, Late ALT/AST Elevation Events were not clinically significant and were not accompanied by abnormalities of other tests of hepatic function or by liver-related symptoms. The risk of Late ALT/AST Elevation Events was increased moderately by intrinsic and extrinsic factors which were evaluated using a PK/'Late ALT/AST Elevation Event' analysis, and rates of late ALT/AST elevation events were observed to be higher in females, Asians, the elderly, and those with low BMI; however, the rates in each of these subgroups was <2.5%. In a limited number of settings (CP-C cirrhosis, concomitant cyclosporine use) where GZR exposure is increased by >14-fold, the risk of Late ALT/AST Elevation Events is increased to >5%. Of the 25 subjects with Late ALT/AST Elevation Events, 23 subjects had ALT elevations >5x ULN, and 2

[37] Detection of an ECI in a given subject would prompt further monitoring and testing.

subjects just had an AST elevation >5x ULN. The 2 subjects with just an AST elevation >5x ULN likely had increased AST due to skeletal muscle breakdown, rather than hepatic injury.

Hepatic laboratory ECIs, a less-specific measure of GZR-related hepatotoxicity, were infrequent, majority of these were transient and not associated with symptoms or other liver-related laboratory abnormalities; these resolved in all subjects, except for 2 CKD subjects with persistent alkaline phosphatase elevations which were likely caused by underlying renal disease. No subject who did not have a Late ALT/AST Elevation Event or a hepatic laboratory ECI discontinued study medication due to hepatic laboratory abnormalities.

Only 1 subject who received GZR 100 mg had concomitant ALT/AST >3x ULN and total bilirubin >2x ULN; this subject was asymptomatic, and the temporal pattern of ALT/AST and total bilirubin elevations was not consistent with hepatocellular injury.

Populations at increased risk of Late ALT/AST Elevation Events have been identified based upon PK data, PK/PD modelling and also analysis of the clinical data. The risk of Late ALT/AST Elevation Events is increased in the presence of intrinsic factors known to increase GZR exposure. Modest increases in GZR exposure are expected in some populations, including females, Asians, cirrhotics, and CKD patients who are not on dialysis. The population pharmacokinetic model predicts that GZR steady-state exposures (AUC) are approximately 1.7 fold higher for elderly (67 years old) versus young (31 years old) patients, 1.15 fold higher for low weight (53 kg) versus medium weight (77 kg) patients, 1.4 fold higher for females versus males, 1.6 fold higher for Asians versus Whites, 1.6 fold for CP-A/compensated cirrhotics versus non-cirrhotics, and 1. 4 fold higher in non-dialysis-dependent CKD patients compared to patients without CKD. The highest GZR exposures are likely to occur in Asian, female patients with cirrhosis; the population pharmacokinetic model predicts GZR exposures to be approximately 3 fold higher in this patient population. Adding in additional effects of low weight (for example, 53 kg) and increased age (for example, 67 years) predicts a 4.4 fold increase in GZR for an elderly, low-weight, cirrhotic, Asian, female patient, compared to a young, medium weight, non-cirrhotic white male patient.

**Comments**: The proposed PI contains adequate information regarding hepatic laboratory testing which should be performed prior to therapy and periodically thereafter.

### 8.6.2. Haematological toxicity

Haemoglobin decreases were infrequent in the GZR with EBR (no RBV) regimen, but were more frequent in the GZR with EBR (+ RBV) regimen, consistent with the well-known side effects of RBV. In the GZR with EBR (no RBV) regimen, no subjects had a Grade 3 or 4 Hb decrease; 0.2% (2/1033) had worsening by ≥ 2 grades. In the GZR with EBR (+ RBV) regimen, 2.7% (19/656) had a Grade 3 decrease, and no subjects had a Grade 4 decrease and 11.7% (77/656) had worsening by ≥ 2 grades. The majority of decreases occurred during the first 4 weeks of treatment which overlapped with the time course of bilirubin elevations. Mean haemoglobin levels did not change in the GZR with EBR (no RBV) regimen but they decreased in the GZR with EBR (+ RBV) regimen. Haemoglobin levels declined approximately 2.4 gm/dL during the first 8 weeks of study treatment in the GZR with EBR (+RBV) 16 week regimen. The magnitude and timing of haemoglobin decrease are consistent with what has been observed with other anti-HCV regimens that utilise RBV.

### 8.6.3. Serious skin reactions

None.

### 8.6.4. Cardiovascular safety

None.

### 8.6.5. Unwanted immunological events

None.

## 8.7. Other safety issues

### 8.7.1. Safety in special populations

#### *8.7.1.1. Twelve week safety pool, which includes subjects from protocol 060, 061, and 068 who were treated with GZR/EBR for 12 weeks:*

This pool provides safety information for the 12 week (no RBV) regimen, which is the regimen that is recommended for the largest proportion of subjects for which licensure is being sought, using the fixed dose combination tablet, which is the final marketed image; the placebo group presented for comparison is the P060 placebo deferred treatment group, which consists of treatment naïve, HCV mono-infected subjects who received placebo without RBV for 12 weeks.

The overall AE profile of GZR/EBR (no RBV) was comparable to that of placebo and was similar in non-cirrhotics and cirrhotics. For both the GZR/EBR (no RBV) regimen and in the GZR/EBR (+ RBV) regimen, the overall AE profile was similar in HCV mono-infected subjects and HCV/HIV co-infected subjects. AEs and drug-related AEs were slightly less frequent in HCV mono-infected subjects compared with HCV/HIV co-infected subjects.

*AEs*

The incidence of AEs was 68.6%, 70.1% and 81.7% in the placebo, GZR+EBR and GZR+EBR+RBV groups, respectively. Overall, the most frequently reported (incidence >10%) AEs among subjects who received GZR/EBR (with or without RBV) were fatigue (17.0%) and headache (16.4%). The most common AEs in the GZR/EBR (no RBV) and placebo groups were headache (15-18%) and fatigue (15-17%). Fatigue (26.9%), headache (20.2%), nausea (14.4%), accidental overdose (14.4%), anaemia (11.5%), insomnia (10.6%) and pruritus (10.6%) were most common in the GZR/EBR (+ RBV) group. In the GZR/EBR (no RBV) regimen, the incidences of AEs overall, and by SOC, were comparable between cirrhotics and non-cirrhotics. Similarly, the incidences of AEs overall, and by SOC, were comparable between cirrhotics who received GZR/EBR and cirrhotics who received placebo. Among subjects who received GZR/EBR (+ RBV), the rate of AEs overall was higher in cirrhotics compared with non-cirrhotics, although there was not a clear difference in the distributions of particular AEs by SOC. Overall, the incidences of AEs and by SOC were generally comparable among HIV/HCV co-infected and HCV mono-infected subjects in both the GZR/EBR (no RBV) and GZR/EBR (+ RBV) regimens, although only a small number of HIV/HCV co-infected subjects received GZR/EBR (+ RBV) in these studies.

*Drug-related AEs*

The incidences of drug-related AEs overall (39%, 36% and 64.4% in the placebo, GZR+EBR and GZR+EBR+RBV groups, respectively) and by SOC were comparable between subjects who received GZR/EBR (no RBV) and placebo. More subjects in the GZR/EBR (+RBV) group experienced drug-related AEs overall and the largest differences were in AEs commonly associated with RBV, including anaemia, nausea, fatigue, dyspnoea, and pruritus. The incidences of drug-related AEs overall, and by SOC were comparable among cirrhotics and non-cirrhotics who received GZR/EBR (no RBV). The incidences of drug-related AEs overall, and by SOC were comparable among cirrhotics who received GZR/EBR (no RBV) and cirrhotics who received placebo. The incidence of drug-related AEs overall was higher among cirrhotics compared with non-cirrhotics. The largest differences were in asthenia, fatigue, and pruritus. However, there were no clear differences in the incidence of overall or particular drug-related AEs according to HCV/HIV co-infection status in the GZR+EBR and placebo groups; interpretation in the GZR+EBR+RBV group was limited due to small number (n=5) of HIV co-infected subjects.

*Deaths, SAEs, discontinuations due to AEs*

Only two deaths were observed in this pooled data set. Both events occurred in the GZR/EBR (no RBV) regimen and both occurred in the follow-up phase after treatment was completed and did not reflect an AE that had begun while on treatment. One case was a strangulated hiatal

hernia, and the second case was an unwitnessed death, likely due to atherosclerotic cardiovascular disease, that occurred after completion of study therapy.

SAEs were rare, and the frequencies of such events were comparable between the GZR/EBR (no RBV), GZR/EBR (+ RBV) and the placebo regimen (2.3%, 2.9% and 2.9%, respectively). There was no apparent clustering of cases in any of the arms and SAE terms were not reported in more than one subject. Only a single subject[38] with two drug-related SAEs was reported in the pool. Cirrhosis or HIV-co-infection status did not affect the incidence or pattern of SAEs.

Among all subjects in the 12-Week Safety Population Pool who received GZR with EBR (with or without RBV), 5/743 (0.7%) discontinued due to an AE: 4/639 (0.6%) of subjects in GZR/EBR (no RBV) discontinued due to an AE (2 subjects discontinued due to protocol-specified criteria-ALT or AST increased; the remaining 2 subjects discontinued due to AEs of anxiety and palpitations (1 subject) and ascites (1 subject who died of peritonitis, sepsis and progressive renal failure 22 days after study drug discontinuation) 1/104 (1.0%) subject in GZR/EBR (+ RBV): discontinued due to an AE (affect lability). One subject who received placebo (1/105, 1.0%) and discontinued due to drug-related pruritic rash. The incidence of ECIs was higher in the GZR+EBR+RBV group compared with the GZR+EBR group (15.4% versus 3.4%); accidental overdose, ALT and AST increased were most common in both groups.

### 8.7.2. Integrated safety pool (ISP)

The overall AE profile of GZR/EBR (no RBV) was comparable to that of placebo. The incidence of overall AEs was slightly higher in the 16 week compared to the 12 week (12 week versus 16 week: 71% versus 73.3%) regimens with similar results for drug-related AEs (37.4% versus 43.8%). The incidences of both overall AEs (82.5%) and drug-related AEs (65.1%) were higher in the 18 week regimen. It is important to note that the higher observed AE rates in the 18 week regimen may be reflective of the overall higher AE rates observed in P035, which was the sole contributor to the subjects in the ISP's 18 week regimen; AE rates were also higher for the 12 week (no RBV) regimen in P035, compared to the 12 week (no RBV) regimen in the ISP. SAEs, drug-related SAEs, deaths, and discontinuations due to AEs were infrequent across groups, and there were no clear increases with longer treatment durations. The rates of AEs, drug-related AEs, SAEs, deaths, and discontinuations were comparable among cirrhotics and non-cirrhotics who received GZR/EBR (no RBV) and GZR+EBR+RBV; the rates of AEs, drug-related AEs, SAEs, deaths, and discontinuations were comparable among cirrhotics and non-cirrhotics who received GZR/EBR (+ RBV). In the GZR with EBR (no RBV) group, the rates of AEs, drug-related AEs, SAEs, deaths, and discontinuations were comparable among HCV mono-infected subjects and HCV/HIV co-infected subjects. In the GZR with EBR (+RBV) group, the rates of AEs were higher in HCV mono-infected subjects (84.3%), compared to HCV/HIV co-infected subjects (71.1%). Similarly, rates of drug-related AEs were higher in HCV mono-infected subjects (68.7%), compared to HCV/HIV co-infected subjects (50.0%). SAEs, deaths, and discontinuations were comparable among HCV mono-infected subjects and HCV/HIV co-infected subjects.

*AEs*

The incidence of AEs was 68.6%, 71.4% and 83.6% in the placebo, GZR+EBR and GZR+EBR+RBV groups, respectively. Overall, the most frequently reported (incidence >10%) AEs among subjects who received GZR/EBR (with or without RBV) were fatigue (20.90%), headache (19.1%) and nausea (10.8%). The most common AEs in the GZR/EBR (no RBV) and placebo groups were headache (18%) and fatigue (16-17%). Fatigue (28.5%), headache (20.9%), nausea (15.2%), asthenia (11.3%), insomnia (10.8%) and pruritus (10.7%) were most common in the GZR/EBR (+ RBV) group. In the GZR with EBR (no RBV) group, the rates of the most common

[38] This was a subject who received GZR/EBR (+ RBV) and had severe abdominal pain requiring hospitalisation and a transient ischemic attack (TIA) requiring hospitalisation.

AEs did not meaningfully differ between subjects in 12 week or 16 week regimens; however, AEs were slightly increased in subjects who received 18 weeks of therapy and the following AEs were increased in rate by >5% between the 16 week and the 18 week regimens: headache, fatigue, diarrhoea, and back pain. In the GZR with EBR (+ RBV) group, the rates of the most common AEs did not meaningfully differ between subjects in 12 week or 16 week regimens (with no increase in common AEs between 12 and 16 weeks), but AEs were slightly increased in subjects who received 18 weeks of therapy and the following AEs were increased in rate by >5% between the 16 week and the 18 week regimens: headache, fatigue, asthenia, insomnia, cough, dyspnoea, dry skin, pruritus, and rash. The incidence of AEs was similar between the cirrhotics and non-cirrhotics. The frequencies of the most common AEs by SOC generally were lower in HCV/HIV co-infected subjects, compared to HCV mono-infected subjects in both the GZR with EBR (± RBV) groups. No subject with HCV/HIV co-infection had an AIDS-related opportunistic infection or AIDS-defining condition[39].

*Drug-related AEs*

The incidence of drug-related AEs was also higher in the GZR with EBR (+RBV) group (39%, 40.1% and 67.6% in the placebo, GZR+EBR and GZR+EBR+RBV groups, respectively). Among the subjects who received (GZR with EBR no RBV), the most frequently reported (incidence ≥ 5%) AEs were fatigue (12.0%) and headache (11.5%); the most frequently reported drug-related AEs in the placebo group were fatigue (9.5%), headache (8.6%), and pruritus (6.7%) and the most frequently reported drug-related AEs in the GZR with EBR (+RBV) group were fatigue (24.7%), headache (16.3%), nausea (12.6%), asthenia (9.3%), anaemia (9.1%), insomnia (8.8%), pruritus (8.8%), rash (6.8%) and dyspnoea (6.4%). Overall, the majority of drug-related AEs were of mild severity. The incidence of moderate drug-related AEs was 9.5%, 10.1% and 20.1% in the placebo, GZR+EBR+RBV and GZR+EBR+RBV groups, respectively; headache, anaemia, asthenia and nausea were the common drug-related AEs of moderate intensity. Severe drug-related AEs were rare overall (1%, 0.8% and 1.7% in the placebo, GZR+EBR+RBV and GZR+EBR+RBV groups, respectively) with no clear differences in the incidence of severe drug-related AEs by SOC. Rates of the most common drug-related AEs did not meaningfully differ between subjects in 12 week or 16 week regimens Drug-related AEs were slightly increased in subjects who received 18 weeks of therapy; headache, fatigue, nausea, and asthenia were increased in rate by >5% between the 16 week and the 18 week regimens. The frequencies of drug-related AEs by SOC generally were similar in the cirrhotic and non-cirrhotic subjects and also similar in the HCV/HIV co-infected subjects, compared to HCV mono-infected subjects.

*Deaths, SAEs, discontinuations due to AEs*

Only three deaths[40] were observed in this pooled data set. Two events occurred in the GZR with EBR (no RBV) regimen, and one occurred in the GZR with EBR (+ RBV) regimen; none of these 3 deaths were judged to be related to GZR with EBR. SAEs were rarely observed in the ISP and the overall incidences of SAEs were comparable among subject who received placebo, GZR with EBR (no RBV) and GZR with EBR (+ RBV) (2.9%, 2.2% and 2.4%, respectively). Four (4) subjects with drug-related SAEs were reported in the ISP: one had severe abdominal pain, one had severe asthenia, one had an accidental overdose associated with an AE of anaemia, and one

[39] That is, Candidiasis, invasive cervical cancer, coccidioidomycosis,cryptococcosis, cryptosporidiosis, cytomegalovirus disease, encephalopathy, herpes simplex (chronic ulcer(s) [greater than 1 month's duration]; or bronchitis, pneumonitis, or esophagitis), histoplasmosis, isosporiasis, Kaposi's sarcoma, lymphoma, mycobacterial infection, *Pneumocystis jirovecii* pneumonia, recurrent pneumonia, progressive multifocal leukoencephalopathy, salmonella septicemia, toxoplasmosis of brain, or wasting syndrome due to HIV.

[40] One case was a strangulated hiatal hernia, one case was an unwitnessed death, likely due to atherosclerotic cardiovascular disease that occurred after completion of study therapy, and the other case was due to a motor vehicle accident.

subject had SAEs of severe abdominal pain and a TIA. The incidence of non-fatal SAEs was not affected by treatment duration, cirrhosis or HIV co-infection.

Across regimens, few subjects discontinued therapy for an AE. Among all subjects who received GZR with EBR, 16/1690 (0.9%) discontinued due to an AE. Of these subjects, 3 subjects discontinued due to protocol-specified criteria (ALT or AST increased) and other 13 subjects discontinued due to investigator discretion.[41] Three (3) subjects discontinued due to SAEs (ascites, atrial fibrillation and gastrointestinal inflammation); none of these SAEs were considered related to treatment.[42] The incidence of discontinuations due to AEs was not affected by treatment duration, cirrhosis or HIV co-infection.

Overall (combined RBV-free and RBV-containing treatment groups), 97/1690 (5.7%) of subjects had ECIs; of these subjects, 81/1690 (4.8%), had an ECI of accidental overdose. The overall incidence of ECI was highest in the GZR with EBR (+RBV) group (1.9%, 3% and 10% in the placebo, GZR+EBR+RBV and GZR+EBR+RBV groups, respectively). The incidence of ECIs was not affected by treatment duration, cirrhosis or HIV co-infection.

### 8.7.3. Safety in ongoing studies

As of the cut-off dates, no GZR/EBR-treated subjects in the deferred treatment groups in the ongoing studies P052 and P060 have died; 1 subject and 26 subjects, in the deferred treatment (GZR/EBR) arms of P060 and P052 respectively, had non-fatal SAEs during the initial treatment period and first 14 follow-up days; 0 subjects and 3 subjects, respectively, have discontinued due to AEs; 0 subjects and 1 subject, respectively, experienced ECIs, excluding study medication overdoses (with no Late ALT/AST Elevation Events).

In the ongoing Study P062 in 301 subjects with chronic HCV, genotype (GT) 1, 4, or 6 infection who are on opiate substitution therapy, there was 1 death (due to pneumonia); 10 subjects experienced a SAE; 2 of which were assessed to be drug-related (auditory hallucination and pneumonia). Two hepatic events of clinical interest (ECI) were observed. Both were asymptomatic elevations of ALT and AST, and both resolved without interruption of study therapy.

In the ongoing Study P065 in 92 subjects with chronic HCV genotype (GT) 1, GT4 and GT6 infection with inherited blood disorders with and without HIV co-infection, GZR/EBR was generally well tolerated with no deaths or discontinuations due to AEs. The safety events of note were as follows:

- One hepatic event of clinical interest (ECI)- a transient increase in alanine aminotransferase (ALT) > 3x baseline and > 100 at treatment week 8, not considered drug-related
- 3 SAEs in 2 subjects: erosive gastritis and hypophosphatemia, both considered drug related (active or placebo); rectal haemorrhage, considered not drug-related. Late ALT/AST Elevation Events are not summarised for the ongoing blinded studies P062 and P065.

### 8.7.4. Safety in clinical pharmacology studies

Four studies examined the effect on safety of a range of multiple-dose regimens of GZR and ERB QD given alone in healthy (Studies 5172-P001v01 and 8742-P001v01) and HCV-infected (Studies 5172-P004v02 and 8742-P002v02) males. The results indicated that there was no

[41] In these subjects, the most frequent reasons for discontinuation of study drug were: anxiety (2 subjects), palpitations (2 subjects), and dyspnoea (2 subjects).

[42] Due to an SAE (all 3 were not drug-related); one was a cirrhotic subject in the GZR with EBR (no RBV) regimen who was hospitalised for new-onset, rapidly progressing ascites. He discontinued study medication and developed renal failure, sepsis and peritonitis that led to death 22 days after discontinuation of study medication; the other subject had atrial fibrillation, and the other subject had gastrointestinal inflammation.

relationship observed between AE incidence and GZR or EBR exposure at doses up to 8 fold higher than the proposed dose of GZR and 2 fold higher than the proposed dose of EBR.

Overall, there were no major safety concerns in these studies with similar safety profile to that observed in most of the Phase II/III studies.

### 8.7.5. Effect of intrinsic factors on safety of GZR/EBR

The effect of intrinsic factors such as gender, race, age, BMI, hepatic and renal Impairment on the safety of GZR/EBR was evaluated by comparing AEs and laboratory parameters in various subgroups within the ISP. In the GZR and EBR population PK models, gender was a significant covariate that translated into an approximately 30% and 50% increase in GZR and EBR AUC, respectively, for females versus males.

Overall, among subjects who received GZR with EBR (with or without RBV), a greater rate of females had one or more AEs, compared to males (82.7% versus 72.1%) although a similar difference was also present in the placebo group (75.5% versus 62.5%). The incidence of drug-related AEs was also higher in females (56.0% versus 47.5%); a smaller difference was observed in subjects treated with placebo (40.8% versus 37.5%). There was a slight increase in the incidence of Late ALT/AST Elevation Events in females compared to males (1.7% versus 0.2%). There were no clear differences in SAEs, deaths, or discontinuations due to AEs, according to gender.

In the GZR and EBR population PK models, Asian, Black and Hispanic race was identified as significant covariates. This translated into GZR and EBR AUC estimates that were approximately 50% and 15% higher, respectively, for Asian subjects compared with Whites; 10% lower and 9% higher, respectively, in Black subjects compared with Whites; 20% and 10% higher, respectively, in Hispanics compared with Non-Hispanics. Overall, among subjects who received GZR with EBR (with or without RBV), the incidence of one or more AEs was slightly lower in Asians (71.5%), compared to Whites (76.8%) or Blacks (75.2%); however, in the placebo group, Asians also had a lower incidence of one or more AEs. Headache, nausea, fatigue, asthenia and insomnia were more common in Whites compared to both Asians and Blacks. Although the rate of Late ALT/AST Elevation Events was low, regardless of race/ethnicity category, it was higher in Asians (2.4%) and Blacks (0.9%), compared to Whites (0.5%).There were no clear differences in the rate of AE according to ethnicity (Hispanic versus non-Hispanic). Drug-related AEs were more frequent among Whites (54.2%), compared to Blacks (40.4%) or Asians (39.4); this difference was not seen in the placebo group. There were no clear differences in the rate of drug-related AEs, according to ethnicity (Hispanic versus non- Hispanic) with no clear differences in SAEs, deaths, or discontinuations, according to race and ethnicity.

Age was also identified as a covariate that translated into GZR and EBR AUC estimates that were approximately 72% and 14% higher, respectively, for subjects ≥ 65 years old compared to subjects < 65 years old. Among subjects who received GZR with EBR, subjects ≥ 65 years old and subjects < 65 years old had comparable frequencies of AEs and drug-related AEs, regardless of RBV co-administration. Among subjects who received GZR with EBR (+ RBV), a slightly greater rate of subjects ≥ 65 years old had SAEs, compared to subjects < 65 years old (4.3% versus 2.4%). However, higher rates of SAEs were also reported in placebo subjects ≥ 65 years old compared to subjects < 65 years old (11.1% versus 1.1%). The rate of Late ALT/AST Elevation Events was low, regardless of age category, but it was higher in subjects ≥ 65 years old compared to subjects < 65 years old (1.6% versus 0.7%). There were no clear differences in drug-related SAEs, deaths, or discontinuations, according to age.

Among subjects who received GZR with EBR, subjects with BMI < 30 kg/m$^2$ and subjects with BMI ≥ 30 kg/m$^2$ had comparable frequencies of AEs, drug-related AEs, SAEs, deaths and discontinuations due to AEs. The rate of Late ALT/AST Elevation Events was low, but it was higher in subjects with BMI < 25 kg/m$^2$ compared to subjects with BMI ≥ 25 kg/m$^2$ (1.1% versus 0.5%).

For the Phase II/III Program (except for P059, which studied GZR 50 mg with EBR100 mg in CP-B cirrhotics), only Child-Pugh A/compensated cirrhotics were enrolled. Analyses of AEs and clinical laboratory evaluations were performed for subjects without cirrhosis (Metavir F0-F3 equivalent) and with compensated cirrhosis (Metavir F4 equivalent) in the P060/P061/P068 12-Week Safety Population Pool and in the Integrated Safety Population Pool. A total of 124 subjects with cirrhosis were included in the Integrated Safety Population Pool. Among all subjects who received GZR with EBR (with or without RBV), there was a comparable incidence of overall AEs in cirrhotics (75.8%), compared to non-cirrhotics (77.9%). Drug-related AEs were comparable in cirrhotics (51.6%), compared to non-cirrhotics (54.4%). SAEs were infrequent, but they were slightly more frequent in cirrhotics (4.0%) versus non-cirrhotics (2.5%). Deaths and discontinuations due to AEs were infrequent, and they did not appear to differ in cirrhotics, compared to non-cirrhotics. The safety and pharmacokinetics data outlined above demonstrate that mild hepatic impairment, including compensated cirrhosis, does not meaningfully affect the safety profile of GZR with EBR. Therefore, no dosage adjustment of 100 mg GZR/50 mg EBR is warranted in HCV-infected patients with Child-Pugh A, including those with compensated cirrhosis.

Among subjects in the ISP, AEs, drug-related AEs, SAEs and drug-related SAEs were less frequent in HCV/HIV co-infected subjects, compared to HCV mono-infected subjects; differences in frequency of AEs and drug-related AEs were more apparent in subjects who received GZR with EBR (+ RBV). Deaths were infrequent, and they were similar in HCV mono-infected and HCV/HIV co-infected subjects. Discontinuations due to AEs were infrequent; moreover, they occurred less often in HCV/HIV co-infected subjects, compared to HCV mono-infected subjects. Discontinuations due to SAEs were very infrequent; however, they did not appear to differ based upon HIV co-infection status. There were no clear differences in AEs by SOC between HCV mono-infected versus HCV/HIV co-infected subjects. No subject had an opportunistic infection.

Overall, among subjects who received GZR with EBR (with or without RBV), slightly higher frequencies of treatment-experienced subjects had one or more AEs, compared to treatment-naïve subjects (80.2% versus 73.7%, respectively). Similarly, higher frequencies of treatment-experienced subjects had drug-related AEs, compared to treatment-naïve subjects (58.4% versus46.1%, respectively). SAEs, drug-related SAEs, deaths, and discontinuations were infrequent, with no clear differences between the two groups. The following AEs were observed to be >5% greater in treatment-experienced, compared to treatment-naive subjects: asthenia (11.3% versus 5.7%) and fatigue (24.8% versus 18.6%). However, the frequencies of Late ALT/AST Elevation Events were similar in both groups (0.8% versus 0.8%). Overall, the data suggest that prior PR treatment status does not meaningfully affect the safety profile of GZR with EBR.

For studies included in the Integrated Safety Population Pool, subjects with an eGFR < 50mL/min/1.73 $m^2$ were excluded. During treatment with GZR with EBR, serum creatinine remained within normal range for most subjects. Elevations worse than Baseline were infrequent, and they were similar among subjects in the RBV-free and RBV-containing groups. Worsening of serum creatinine by 2 or more Grades was infrequent; among all subjects who received GZR with EBR, 3/1690 (0.2%) had a worsening by >2 Grades.

Study P052 had a higher overall rate of AEs; however, this increased rate was most likely due to underlying renal disease, since there were very similar rates between subjects who received GZR+EBR and placebo. When subjects in the GZR+EBR active treatment regimen were compared to subjects in the placebo deferred treatment group, there were no meaningful differences in the incidence of AEs, deaths, other SAEs, discontinuations due to AEs, or the most common AEs. Moreover, there did not appear to be any meaningful differences in clinical laboratory evaluations, including evaluations of renal function (that is, serum creatinine and urine protein). Compared to subjects in the ISP (RBV-free treatment group), CKD 4-5 subjects in Protocol 052 had higher overall frequencies of Grade 1 and Grade 2 abnormalities of most

laboratory parameters, particularly of haemoglobin; however, these increased frequencies were most likely due to underlying renal disease, since the frequencies were generally not increased in subjects who received GZR+EBR, compared to subjects who received placebo. The presence of severe CKD does not appear to affect the hepatic safety of GZR with EBR. Overall, the above data suggest that treatment with GZR with EBR does not meaningfully affect the safety profile in subjects with CKD as the rates of AEs, deaths, SAEs, and discontinuations did not meaningfully differ based on renal function. As such, no dosage adjustment of GZR/EBR is warranted in HCV-infected patients with renal impairment regardless of dialysis status.

In addition to examining safety in subpopulations outlined above, safety was also examined in patients with GZR or EBR exposure in the highest quartile (4th quartile) of the pooled Phase II and III dataset. Patients whose exposures were in the highest quartile had an approximately 2.6-fold increase in GZR AUC over the overall geometric mean value for 100 mg for the GZR analysis and an approximately 1.6 fold increase in EBR AUC over the geometric value for 50 mg for the EBR analysis. The incidence of AEs, drug-related AEs, SAEs, drug-related SAEs, deaths, discontinuations due to AEs, discontinuations due to drug-related AEs, discontinuations due to SAEs, and discontinuations due to drug-related SAEs did not appear to differ according to GZR or EBR AUC quartile.

### 8.7.6. Safety related to drug-drug interactions and other interactions

The clinical drug interaction results demonstrate clinically relevant decreases in exposure of GZR and EBR with moderate and strong CYP3A/P-gp inducers, but no clinically relevant increases in exposure with CYP3A/P-gp inhibitors. Therefore, concomitant use of GZR/EBR is not recommended in patients taking moderate or strong CYP3A/P-gp inducers; however, no dose adjustment is required when GZR/EBR is co-administered with CYP3A/P-gp inhibitors. A clinically relevant increase in GZR (but not EBR) exposure was observed when GZR was coadministered with OATP1B inhibitors; therefore concomitant use of GZR with OATP1B inhibitors is not recommended.

Clinical data also support the in vitro predictions that GZR is a weak inhibitor of CYP3A, intestinal BCRP, and not an inhibitor of OATP1B. Elbasvir is an inhibitor of intestinal BCRP, not an inhibitor of OATP1B, and has minimal intestinal P-gp inhibition that does not result in a clinically meaningfully increase in the exposure of digoxin (a P-gp substrate). Additionally, GZR and EBR are unlikely to alter the pharmacokinetics of renally cleared drugs since the renal elimination for GZR and EBR are minimal (< 1%). Overall, in vitro and clinical data support a conclusion that no dose adjustment is required when GZR/EBR is co-administered with substrates of CYP3A, other common CYP isoforms, UGT1A1, CES1, CES2, CatA, OATP1B, or P-gp.

Grazoprevir/EBR may be co-administered with sofosbuvir, ribavirin, pravastatin, pitavastatin, lamivudine, emtricitabine, abacavir, raltegravir, dolutegravir, tenofovir disoproxil fumarate (TDF), methadone, buprenorphine/naloxone, mycophenolate, tacrolimus, prednisone, digoxin, oral contraceptives, phosphate binders, and acid reducing agents without dose adjustments. Co-administration with GZR/EBR may increase plasma exposures of atorvastatin, rosuvastatin, fluvastatin, lovastatin, and simvastatin, which can increase the risk of myopathy; thus, a maximum daily dose of 20 mg of atorvastatin, fluvastatin, lovastatin, or simvastatin or 10 mg of rosuvastatin may be co-administered with GZR/EBR. Concomitant use of GZR/EBR is not recommended in patients taking atazanavir or ritonavir-boosted HIV protease inhibitors because co-administration with GZR/EBR may result in clinically relevant increases in GZR and/or EBR concentrations.

A clinical pharmacology study in healthy volunteers (Study P063) showed that multiple-dose co-administration of GZR+EBR and sofosbuvir resulted in increased pharmacokinetics of sofosbuvir but not GS-33107 (a metabolite formed by dephosphorylation of sofosbuvir). PK data from Phase II Study P074 confirmed the findings in Study P063, namely that sofosbuvir and GZR/ EBR did not have any meaningful PK interactions. P074 was a study of GZR/EBR with

sofosbuvir 400 mg for 4, 6, 8 or 12 weeks among TN non-cirrhotic or cirrhotic GT1 and GT3-infected subjects. Co-administration of sofosbuvir did not appear to affect the incidence of the most common AEs, deaths, SAEs or discontinuations due to AEs, The percentage of subjects with abnormal laboratory values at baseline was low and was comparable to the Integrated Safety Pool. No subjects had elevations of ALT or AST >5x ULN that were either new or worsened from baseline. Hence, the overall safety profile of GZR/EBR with sofosbuvir was comparable to that of GZR with EBR in subjects in the Integrated Safety Pool.

Co-administration of strong CYP3A/P-gp inhibitors (studies 5172-P001 and 8742-P003) resulted in approximately 3.3 and approximately 1.8 fold increase in GZR and EBR, respectively. Since these changes in GZR and EBR are not clinically relevant, the concomitant use of weak, moderate, and strong CYP3A inhibitors was permitted in the Phase II and III studies. In the ISP, 35 of 1690 subjects took concomitant moderate CYP3A4 inhibitors with GZR with EBR (with or without RBV). There were no clear differences in the frequencies of AEs or drug-related AEs between subjects who took and did not take moderate CYP3A4 inhibitors with GZR with EBR although the small number of subjects who took moderate CYP3A4 inhibitors limits interpretation of the data. However, there was an increased rate of SAEs in subjects who took moderate CYP3A4 inhibitors 6/35 (17.1%), compared to subjects who did not take moderate CYP3A4 inhibitors (36/1655 [2.2%]); [2/35 (5.7%) subjects who took moderate CYP3A4 inhibitors, and 1/1655 (0.1%) subjects who did not take moderate CYP3A4 inhibitors, discontinued due to an SAE. These differences were not present in the RBV-free group; in the RBV free group, SAEs occurred in 1/20 (0.5%) and 24/1013 (2.4%) of subjects who did and did not take, respectively, moderate CYP3A4 inhibitors. Of the 6 subjects who took moderate CYP3A4 inhibitors and had SAEs, the SAEs (skin ulcer, atrial fibrillation, gastrointestinal inflammation, colitis, infectious colitis, and tibia fracture) were not liver related.

In the ISP, 9 of 1690 subjects took concomitant strong CYP3A4 inhibitors with GZR with EBR (with or without RBV). However, there were no clear differences in the frequencies of AEs, drug-related AEs, SAEs, or discontinuations between the two groups.

Co-administration of TDF with GZR or EBR showed increases in tenofovir pharmacokinetics when co-administered with GZR (approximately 1.2 fold increase in TDF AUC) or EBR (approximately 1.3 fold increase in TDF AUC), while TDF had no effect on GZR or EBR pharmacokinetics. The concomitant use of GZR with EBR and TDF was permitted in the Phase II and III program. In the Integrated Safety Population Pool, 232 of 1690 subjects took TDF for at least 7 consecutive days with GZR with EBR (with or without RBV). Overall, AEs and drug-related AEs were slightly less frequent in subjects who took TDF, whereas there were no clear differences in the frequencies of SAEs or discontinuations. Co-administration of GZR with EBR with TDF did not appear to increase the incidence of AEs or renal dysfunction as measured by serum creatinine, suggesting that co-administration of TDF and GZR with EBR was well-tolerated in HCV/HIV co-infected subjects.

Phase I studies in healthy volunteers demonstrated no clinically meaningful DDI between GZR+EBR and pitavastatin and pravastatin. However, the rosuvastatin AUC and $C_{max}$ were increased by 2.3- and 5.5-fold, when co-administered with GZR+EBR respectively. Similarly, the atorvastatin AUC and $C_{max}$ were increased by 2- and 4-fold, respectively when co-administered with GZR+EBR. In the Integrated Safety Population Pool, 34 of 1690 subjects took statins (rosuvastatin, atorvastatin, pravastatin, fluvastatin, lovastatin, simvastatin and pitavastatin) for at least 7 consecutive days with GZR with EBR (with or without RBV). The small number of subjects who took statins limits interpretation of the data. However, there were no clear differences in frequencies of AEs, drug-related AEs, SAEs, or discontinuations between subjects taking statins versus subjects not taking statins with GZR with EBR There was no clear meaningful increase in myalgia, a symptom of myopathy or rhabdomyolysis, in subjects who took statins while receiving GZR with EBR These result support the conclusions that 1) GZR/EBR may be co-administered with pravastatin and pitavastatin without a dose adjustment,

and 2) co-administration with GZR/EBR may result in increases in exposures of atorvastatin, rosuvastatin, fluvastatin, lovastatin, and simvastatin; thus, a maximum daily dose of 20 mg of atorvastatin, fluvastatin, lovastatin, or simvastatin or 10 mg of rosuvastatin may be co-administered with GZR/EBR.

Phase I studies failed to show any PK interactions following concomitant administration of GZR/ EBR with methadone or buprenorphine/ naloxone. In the Integrated Safety Population Pool, 39 of 1690 subjects took methadone with GZR with EBR (with or without RBV) and 13 of 1690 subjects took buprenorphine with GZR with EBR. The small numbers of subjects on methadone or buprenorphine limit interpretation of the data. However, there were no clear meaningful differences in frequencies of AEs, drug related AEs, SAEs, or discontinuations between subjects taking methadone or buprenorphine versus subjects not taking methadone or buprenorphine with GZR with EBR . In particular, there was no clear increase in symptoms of opiate withdrawal (*that is,* irritability, insomnia, nausea, vomiting, or diarrhoea) in subjects who received methadone or buprenorphine. Overall, the incidence of AEs known to be associated with GZR/EBR or opioid substitution therapies did not increase following co-administration of GZR with EBR with methadone or buprenorphine/naloxone.

The effect of multiple-dose administration of GZR or EBR on Nordette® (ethinyl estradiol [EE] 003 mg/levonorgestrel [LNG] 0.15 mg) was evaluated in separate studies (5172-P046 and 8742-P013, respectively) and failed to demonstrate clinically relevant effects on the pharmacokinetics of the oral contraceptive components, EE and LNG, with less than a 1.25 fold increase in both AUC and $C_{max}$. Hence, OCPs were allowed in the Phase II and III studies. In the Integrated Safety Population Pool, 35 of 652 female subjects took concomitant oral contraceptive pills (OCPs) with GZR with EBR (with or without RBV) and there were no clear differences in frequencies of AEs, drug-related AEs, SAEs, or discontinuations due to AEs in females taking OCPs versus females not taking OCPs with GZR with EBR. Furthermore, there were no clear differences in any of the laboratory parameters evaluated, including ALT, AST, total bilirubin, alkaline phosphatase, or INR. Of note, none of the 35 subjects who took OCPs had a Grade 2, 3 or 4 elevation in ALT, AST, total bilirubin, or alkaline phosphatase. However, interpretation was limited by the small number of subjects who took OCPs.

**Comments**: Medications which may be used by chronic HCV-infected patients to treat co-morbidities which occur with HCV infection (such as HIV, HBV, depression, opiate substitution therapy for persons whom inject drugs (PWID), renal insufficiency, liver or kidney transplants, hepatocellular carcinoma) or are commonly associated with an aging population (such as gastric reflux, diabetes, hypertension, high cholesterol, cancers) were all evaluated in the extensive DDI clinical trials in healthy subjects and the safety data from the clinical trials in HCV patients. The results of the clinical pharmacology DDI studies and the clinical experience with concomitant medications in the Phase II and III studies were accurately represented in the proposed PI regarding guidance around DDIs for GZR/EBR.

### 8.7.7. Use in pregnancy/lactation

There were 3 pregnancies reported for female subjects and 2 pregnancies reported in a female partner of a male subject in the Phase II and III studies. One pregnancy was detected during the screening before starting study medication (screen failure); one pregnancy led to delivery of healthy baby and the outcome of the pregnancy was not known in the 3 remaining cases.

No reproductive studies have been done to date for GZR with EBR. The use of GZR/EBR in pregnancy and lactation is not recommended.

### 8.7.8. Overdose; drug abuse; withdrawal and rebound; effect on ability to drive or operate machinery or impairment of mental ability:

An overdose of GZR or EBR was defined as any intake in excess of the prescribed dose of GZR or EBR per calendar day. An overdose was to have been reported as an AE (if associated with

clinical symptoms or abnormal laboratory results) or an event of clinical interest. In the ISP there were 19/1033 (1.8%), 62/657 (9.4%) and 81/1690 (4.8%) cases, respectively, of GZR with EBR (no RBV), GZR with EBR (+ RBV), and GZR with EBR (with or without RBV) overdose during the conduct of the clinical studies. In the majority of these subjects, the overdose consisted of double the protocol-specified dose of GZR and/or EBR or RBV. The duration ranged from 1-15 days. The majority of subjects with overdose were asymptomatic and only 1 subject with an overdose of RBV resulted in an AE of anaemia.

No reports of abuse of study drug occurred in any patients participating in the studies. Based upon the activity profile of GZR/EBR and the relative lack of CNS toxicity, the abuse potential of GZR/EBR is considered low.

In the development program for GZR/EBR, no specific studies have been conducted to assess the response to withdrawal and rebound. No withdrawal or rebound was observed in clinical trials to date. GZR and EBR are not targeted to elicit a change in human physiology or biochemistry, but rather are anti-infectives with activities against HCV. Therefore, the terms withdrawal and rebound are not applicable to GZR/EBR. Although no studies on the effects on the ability to drive and use machines have been performed, there is no information to suggest that GZR/EBR affects a subject's ability to drive and use machines.

## 8.8. Evaluator's overall conclusions on clinical safety

The safety profile of GZR/EBR has been well defined in an extensive clinical development program. In Phase I-3 studies, 1234 healthy volunteers, 66 non-HCV-infected persons with liver or kidney impairment and 2704 HCV-infected subjects have been treated with any dose or regimen of GZR and/or EBR.

The Integrated safety population (ISP) pool is the primary pool used for evaluation of AEs and laboratory evaluations and consists of subjects in Phase II/III studies who received at least 8 weeks of therapy with GZR 100 mg with EBR 50 mg. The pool does not include CKD subjects from P052, since these subjects have a distinct safety profile, and the pool does not contain subjects from P074, in which sofosbuvir was co-administered. The ISP includes 1690 HCV-infected subjects who received the doses proposed for marketing (100 mg GZR and 50 mg EBR) for 8 weeks (91 subjects), 12 weeks (939 subjects), 16 weeks (214 subjects), or 18 weeks (149 subjects), and it is therefore the most relevant population for overall safety. Slightly more than one-third (657/1690 [38.9%]) of subjects in the ISP received RBV. The ISP is representative of the overall HCV-infected population, and it included important subsets of HCV-infected individuals. In the ISP, 457/1690 (27.0%) of subjects were cirrhotic and 298/1690 (17.6%) subjects had HCV/HIV co-infection. Additionally, diverse ethnic groups were included in the ISP; the population consisted predominantly of Whites (75.5%), Blacks (12.9%) and Asians (9.8%). This pool provides the most relevant profile for FDC of GZR/EBR at doses and durations proposed for marketing.

The general safety profile of the ISP demonstrated good tolerability of GZR 100 mg with EBR 50 mg. There were few deaths, non-fatal SAEs, or AEs leading to discontinuation; very few of these events were assessed as related to treatment. Few AEs occurred at a rate >10%; the majority were mild, and very few were severe. The most common AEs overall were headache (18.0%) and fatigue (16.2%). The most common drug-related AEs were headache (11.5%) and fatigue (12.0%). Safety profiles were similar in important subpopulations: Cirrhotics and non-cirrhotics had similar AE profiles. HCV/HIV co-infected and HCV mono-infected subjects had similar profiles; HCV mono-infected subjects had a slightly higher incidence of AEs. A RBV-free regimen has a safety advantage, compared to a RBV-containing regimen. The incidence of well-known RBV-related AEs (anaemia, fatigue, dyspnoea, rash, and pruritus) was increased in subjects who received RBV-containing regimens. Despite this, GZR with EBR (+ RBV) was generally well-tolerated with few discontinuations. Safety profiles did not meaningfully differ according to the

duration of the treatment regimen GZR 100 mg with EBR 50 mg is safe and well-tolerated, with and without RBV co-administration, for durations of 8, 12, 16, or 18 weeks. GZR 100 mg with EBR 50 mg is safe and well-tolerated, with and without RBV co-administration regardless of the presence of cirrhosis or HCV/HIV co-infection.

AEs were similar in important subpopulations with no differences in AE profiles based on age, gender, or race/ethnicity. Compared to subjects in the ISP (RBV-free treatment regimens), CKD 4-5 subjects in P052 had a higher overall rate of AEs. However, this increased rate was most likely due to underlying renal disease, since AE rates were similar between subjects who received GZR+EBR and placebo; furthermore, compared to subjects in the ISP, CKD subjects had a similar profile of individual AEs. Compared to non-cirrhotics, cirrhotics had a slightly higher, although comparable, incidence of AEs noted in the P060/P061/P068 12-Week Pool, but rates of AEs were similar in the larger ISP. This slightly higher incidence of AEs in the smaller pool was likely reflective of underlying comorbidities related to cirrhosis, rather than due to GZR with EBR. In the Phase III, pivotal, placebo-controlled Study P060, once daily fixed-dose oral regimen of GZR/ EBR 100/50 mg for 12 weeks was generally well-tolerated in 421 TN cirrhotic and non-cirrhotic subjects with HCV GT1, GT4, or GT6 infection. Drug-related SAEs and discontinuations for AEs were uncommon. Importantly in P060, no relevant differences were observed between GZR/EBR and placebo (deferred treatment) groups.

Treatment with GZR with EBR does not meaningfully affect the safety profile in subjects with CKD as the rates of AEs, deaths, SAEs, and discontinuations did not meaningfully differ based on renal function. As such, no dosage adjustment of GZR/EBR is warranted in HCV-infected patients with renal impairment regardless of dialysis status.

The safety advantages of a RBV-free regimen were clearly shown in terms of a reduced rate of RBV-related AEs and haemoglobin abnormalities. The rates of common AEs and drug-related AEs were more common with RBV co-administration.

The hepatic safety profile of GZR/EBR has been thoroughly evaluated in the clinical development program. In the GZR development program, dose/exposure-related elevations in ALT/AST were first noted in Study P003, predominantly at doses of 400 – 800 mg/day. The Hepatic Safety Pool (HSP) pool consists of 2405 subjects in Phase II/III who received at least 8 weeks of therapy with GZR, regardless of GZR dose and provides the most comprehensive picture of hepatic safety and defines hepatic safety risks associated with higher doses of GZR. In the HSP, 36/2405 (1.5%) subjects had a Late ALT/AST Elevation Event, hepatic laboratory ECI, and/or discontinued study medication due to protocol-specified hepatic laboratory discontinuation criteria. Of these 36 subjects, 25/2405 (1.0%) had a Late ALT/AST Elevation Event, 26/2405 (1.1%) had a hepatic laboratory ECI, and 7 (0.3%) discontinued study medication due to protocol-specified hepatic laboratory abnormality discontinuation criteria. There was an increase in the rate of Late ALT/AST Elevation Events and hepatic laboratory ECIs in subjects who received doses of GZR greater than 100 mg administered with PR. Overall, the most frequent hepatic laboratory criterion fulfilled was 'ALT or AST >3x baseline and >100 IU/L', which occurred in 19/26 subjects who met ECI criteria.

PK/'Late ALT/AST Elevation Event' Pool (PKP), was similar to the HSP and consisted of 2236 subjects. The PKP describes the correlation between GZR exposure and risk of late ALT/AST Elevation Events. Late ALT/AST Elevation Events, a specific measure of GZR-related hepatic safety, occurred in a dose-related manner, and they occurred in <1% of subjects who received the proposed dose of GZR 100 mg. These events generally occurred at or after TW8, and were transient, with most resolving while continuing treatment and the remaining events resolving after discontinuation of treatment. These events were not of clinical concern as they were not accompanied by abnormalities of other tests of hepatic function or by liver-related symptoms. The risk of Late ALT/AST Elevation Events was increased moderately by intrinsic and extrinsic factors; GZR exposure is expected to be increased by >12 fold (with geometric mean ratio [90% CIs] of 11.68 [6.10, 22.35] in patients with Child-Pugh C cirrhosis. The risk of Late ALT/AST

Elevation Events is predicted to be >5% in this population, especially in the context of the underlying advanced liver disease. Labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events. Increase in ALT is the most specific hepatic laboratory parameter for assessing hepatic safety of GZR with EBR. Periodic monitoring of ALT is recommended in the proposed label.

Among the 2704 subjects in the Phase II/III program, no other obvious laboratory safety concern associated with GZR or GZR with EBR was identified. Moreover, among the 1690 subjects in the Integrated Safety Population Pool (which represents a subset of the protocols and subjects in the from those included in the Phase II/III program, no obvious laboratory safety concern associated with GZR 100 mg with EBR 50 mg was identified. Laboratory abnormalities (in particular, the incidence of ALT/AST, total bilirubin, and haemoglobin abnormalities) were generally similar among subjects treated for 8, 12, 16 or 18 weeks.

Overall, safety of proposed FDC of SZR/EBR (100/50 mg QD) was adequately evaluated with no major safety concerns with the exception of a pattern of ALT/AST elevations associated with GZR administration occurring late in the course of therapy. The rate and severity of these events are dose-dependent. Among subjects who received GZR 100 mg, these late ALT/AST elevation events were infrequent (occurring in <1% of subjects), monitorable (with a consistent timing of initial detection), generally reversible with continued therapy and very infrequently associated with abnormalities associated with liver dysfunction. Other concerns are lack of safety data in HCV patients with severe hepatic insufficiency, liver transplant, HBV/HCV co-infection.

# 9. First round benefit-risk assessment

## 9.1. First round assessment of benefits

The benefits of Zepatier in the proposed usage are:

- offers a single tablet, once-daily oral regimen
- provides a simple, well tolerated ribavirin and interferon-free regimen for patients infected with HCV GT 1, 3, 4 and 6.
- treats HCV infected patients including hard-to-treat populations such as those with HIV co-infection, Chronic Kidney Disease, and HCV genotype 3, 4 and 6 infection.
- provides a 12 week dosing regimen - without ribavirin - for most patients (GT 1, 4 and 6 Treatment Naïve and Treatment-Experienced Relapsers, and GT1b Treatment-Experienced On-Treatment-Virologic-Failures (OTVF)).
- 8 week regimen may be considered for Treatment Naïve GT1b patients.
- 12 week regimen with concomitant administration of sofosbuvir was effective in treating HCV GT3 infected TN patients.
- 16 week regimen with concomitant administration of ribavirin is recommended for GT1a, 4 and 6 Treatment-Experienced OTVF.
- in GT4 infected (treatment-naïve / treatment experienced, ± HIV co-infection, ± cirrhosis) HCV patients, treatment with GZR+EBR (100/50 mg) for 12 weeks was highly effective (SVR12 up to 96%) and well tolerated. Although only small number of GT6 subjects were evaluated in the Phase II/III studies, there was strong data to support use for GT6 (SVR12 of 80%).
- the well-conducted Study P052 demonstrated that 12 weeks of treatment with GZR+EBR (100/50 mg) was well tolerated and highly efficacious (SVR12 of 94%) in 225 advanced

CKD patients, including patients on haemodialysis, thus avoiding the need for peginterferon, ribavirin or sofosbuvir in treating these patients and addressing this urgent unmet need.

## 9.2. First round assessment of risks

The risks of Zepatier in the proposed usage are:

- Lack of adequate data to demonstrate durability/maintenance of efficacy; SVR24 results for core Studies P060, P052 and P068 were not available for evaluation in the current submission. Furthermore, the current dossier also does not provide adequate efficacy results from ongoing Studies P058, P059, P017, P062 and P065.
- Development of NS3 and/or NS5A RAVs in subjects with virologic failure has been characterised. NS3 RAVs are likely to revert to wild-type virus and have limited impact on retreatment options. NS5A RAVs are likely to persist for a longer period of time, based on experience with other NS5A inhibitors. The implications on re-treatment have not yet been determined. However, the incidence of virologic failure was generally <4%.
- Increased risk of Late ALT/AST Elevation Events, especially in patients with Child-Pugh C cirrhosis. However, periodic monitoring of ALT is recommended in the proposed label.
- Risk of drug interactions although labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events.
- Hyperbilirubinemia has been observed in regimens of GZR with EBR (+ RBV) and reflects the well-known haemolytic effects of RBV.
- Lack of efficacy/ safety data in patients with severe hepatic impairment (CP-C cirrhosis), liver transplant patients and HBV/HCV co-infection.
- Lack of efficacy/ safety data in pregnancy/ lactation and paediatric patients.

## 9.3. First round assessment of benefit-risk balance

Chronic hepatitis C virus (HCV) infection is a global public health challenge, affecting up to 170 million people worldwide. Globally, up to 4 million people worldwide, annually, are estimated to have incident HCV infection. Approximately, 55-85% of newly infected persons progress to develop chronic infection. Since 2013, other DAAs have become available, and there is now clear evidence that interferon-free regimens, consisting of combinations of DAAs targeting different targets in the HCV life cycle, can be highly effective in clearing chronic HCV infection. While these regimens represent substantial improvements in the therapeutic options for HCV-infected patients, they continue to have important deficits:

- Some regimens require use of RBV, a medicine that is associated with substantial adverse experiences (even in an interferon-free setting), that is taken twice-daily, with food, and that requires close monitoring and strong pregnancy precautions;
- Some regimens have suboptimal efficacy (for example, SVR12 below 90%) or require prolonged therapy among important subpopulations, including those at urgent need for therapy (for example, prior PR-null responders with cirrhosis, GT3-infected patients);
- Regimens that include RBV or NIs are not optimal for use in patients with advanced CKD; such patients are particularly impacted by HCV infection, in that HCV infection increases all-cause mortality in patients with advanced CKD relative to absence of HCV infection, and HCV-infection substantially worsens outcomes following renal transplant.

The selection of the appropriate regimen and duration of therapy depends on several patient factors including genotype, sub-genotype, mono-infection versus HCV/HIV co-infection, prior

treatment experience (for example, PR null-responders), advanced liver disease (for example, compensated cirrhosis, decompensated cirrhosis), advanced chronic kidney disease (CKD) and presence of liver or kidney transplant. Table 9 in AusPAR lists all oral regimens which are available for treating HCV infection.

Grazoprevir (MK-5172 or GZR) is a once-daily PI with a high potency against GT1, GT2, GT4 GT6, with somewhat less potency against GT3; in vitro, it retains high potency against resistance associated variants (RAVs) that are commonly detected among individuals who fail therapies with first generation PIs such as boceprevir, telaprevir and simeprevir. Elbasvir (MK-8742 or EBR) is a once-daily NS5AI with high potency against GT1, GT2a, GT3, GT4, GT5, and GT6; in vitro, it retains potency in the presence of RAVs associated with failure of other NS5A inhibitors such as daclatasvir and ledipasvir. Pre-clinical data suggested that co-administration of GZR with EBR would create a highly potent regimen for HCV GT1 patients, as well as potential utility in GT3 patients. A fixed-dose combination (FDC) of GZR/EBR has been developed, to improve compliance and convenience with a simple daily dosing regimen, low pill burden of one tablet, low potential for medication error, and no potential for off-label use of individual components. The efficacy and safety was extensively evaluated in Phase II, Phase II/III and Phase III clinical trials including a diverse population of GT1 to GT6 infected subjects, including treatment-naïve and treatment-experienced, HCV mono- and HCV/HIV co-infected, and non-cirrhotic and cirrhotic subjects were enrolled in these studies. A distinctive feature of the program was the evaluation of HCV-infected patients with end-stage renal disease on haemodialysis, a population for which interferon-free treatment options are not available.

The pivotal efficacy studies have consistently demonstrated that Zepatier is efficacious with high SVR 12. Key results include:

- 94-96% SVR12 rates in GT1 and GT4 Treatment Naïve subjects
- 80% SVR12 rates in GT6 Treatment Naïve subjects
- Potential to reduce treatment duration to 8 weeks in Treatment Naïve GT1b infected subjects who do not have significant fibrosis or cirrhosis.
- 100% SVR12 rates in GT1, 4 and 6 Treatment Experienced relapsers following 12 weeks of treatment with a ribavirin free regimen.
- 96% SVR in GT1a, 4 or 6 Treatment Experienced on-treatment virologic failures when treated for 16 weeks with ribavirin. When infected with GT1b, only 12 weeks of treatment without ribavirin resulted in 100% SVR12 for Treatment Experienced on-treatment virologic failures.
- 93% SVR12 in GT3 Treatment Naïve cirrhotic and non-cirrhotic patients when treated for 12 weeks with sofosbuvir and Zepatier.
- Treatment responses are comparable across subgroups, including cirrhotics, HIV/HCV co-infected and subjects with advance CKD.
- 94% SVR in patients with advanced CKD (including those on haemodialysis), addressed unmet clinical need. The dosing recommendations are comparable to non-CKD subjects (with the exclusion of ribavirin).
- High rates of efficacy persist for at least 24 weeks (94% of Treatment Experienced and 92% of Treatment Naïve subjects achieved SVR 24). At time of submission, longer-term follow up is ongoing.

The safety and tolerability profile of Zepatier has been well defined and found to be generally favourable in an extensive clinical development program. Comparable safety was observed in all subpopulations for example, cirrhotics, HIV coinfection, CKD. Importantly, in the placebo controlled studies no relevant differences were observed between the active treatment and

placebo (deferred treatment) groups. Also, the safety profiles did not meaningfully differ according to the duration of treatment (12 versus 16 weeks). The most frequent AEs reported (>10%) were headache, asthenia, fatigue and nausea. Notably these AEs occurred at a similar frequency in the active and placebo treatments. There were no deaths assessed as being related to the study drug or were there any CNS or cardiovascular events associated with therapy. Non-fatal serious AEs related to study drug occurred at 0-0.5% frequency. These were reported as abdominal pain or overdose (per protocol, overdose for example, taking two tablets daily, was classed as a serious AE regardless of severity).

The safety of GZR/EBR, with or without RBV, has been evaluated in a large and diverse population. GZR/EBR, with or without RBV, has a generally favourable safety profile There were very few deaths, SAEs or discontinuations; in particular, treatment-related events of significance were infrequent and demonstrated no consistent pattern. Common AEs were fatigue, headache and nausea which occurred at a similar frequency on active and placebo treatments. RBV-containing regimens were associated with an expected increase in frequency of drug-related AEs of asthenia, anaemia, pruritus, rash and dyspnoea. Tolerability did not differ substantially according to baseline factors such as age, gender, race/ethnicity, presence of cirrhosis, presence of HCV/HIV co-infection, or the presence of advanced CKD (Stage 4-5). Tolerability was not affected by treatment duration (12 versus 16 weeks).

Late ALT/AST Elevation Events, a specific measure of GZR-related hepatic safety, occurred in a dose-related manner, and they occurred in <1% of subjects who received the proposed dose of GZR 100 mg. These events generally occurred at or after TW8, and were transient, not accompanied by abnormalities of other tests of hepatic function, or by liver-related symptoms and most of these events resolved while continuing treatment or after discontinuation of treatment. Among the 2704 subjects in the Phase II/III program, no obvious laboratory safety concern associated with GZR or GZR with EBR was identified. Moreover, among the 1690 subjects in the ISP, no other obvious laboratory safety concerns associated with GZR 100 mg and EBR 50 mg was identified. Laboratory abnormalities (in particular, the incidence of ALT/AST, total bilirubin, and haemoglobin abnormalities) were generally similar among subjects treated for 8-, 12, 16- or 18 weeks.

In Australia, there is currently no approved therapeutic regimen for treatment of HCV GT4 or GT6 infection that does not require concomitant administration of ribavirin or pegylated interferon. These drugs have poor tolerability and the treatment burden is well documented, resulting in AEs, discontinuation of treatment and failure to achieve 'cure'. Zepatier would address this unmet medical need as it offers peginterferon and ribavirin-free dosing in these patients. This application presents adequate clinical data to support use in HCV GT4 and GT6 infected patients, although number of patients evaluated was small which was likely related to low incidence of these HCV genotypes. .

HCV has a significant adverse effect on the progression of renal disease and outcomes of renal transplants. HCV infection and Chronic Kidney Disease (CKD) results in a burden of mortality that is greater than the sum of morbidity and mortality caused by each condition alone. There is currently no registered treatment for patients with chronic HCV infection with severe renal impairment receiving haemodialysis. The DAAs currently approved for treatment of HCV infection in Australia are not suitable for use in patients with severe renal disease as these agents are either excreted primarily through the renal pathway (sofosbuvir-based regimens or require co-administration of pegylated interferon and/or ribavirin. In addition to their tolerability limitations, ribavirin exacerbates renal-failure related anaemia. The efficacy and safety of GZR/EBR FDC (Zepatier) has been evaluated in a study (P052) in 225 HCV patients with CKD Stage 4 or 5 of whom 76% were receiving haemodialysis.

The proposed Indication is as follows:

> *Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity.)*

The sponsor contends a non-genotype specific Indication '*for treatment of Hepatitis C*' is justified based on the available data against the background of a rapidly evolving HCV therapeutic landscape.

- This would allow GZR/EBR to be used in combination with emerging therapies and thus not limit treatment options for current and future patients with the greatest unmet need.
- Furthermore a non-genotype specific Indication would ensure patients with HCV GT 2 and 5 infection who may have other co-morbidities preventing them receiving existing treatments, have access to a peginterferon/ ribavirin free regimen.

The above justification provided by the sponsor seems appropriate considering the proposed Indication clearly cross references other sections of the PI where detailed information on studied combinations, HCV patient subgroups (genotypes, disease state characteristics, prior treatment history) and recommended treatment durations are located. The long term consequences of CHC infection if left untreated include cirrhosis, liver disease, hepatocellular carcinoma and may result in liver transplantation. To date, there has been resistance to treatment in some patients due to the poor tolerability of existing interferon and ribavirin based regimens. The advent of interferon-free regimens offers patients simple, all-oral therapies, with the potential to halt liver disease progression in less than three or four months of treatment.

The benefit-risk profile of Zepatier given the proposed use is favourable.

### 9.4. First round recommendation regarding authorisation

It is recommended that the application for marketing approval of Zepatier be approved for the proposed indication:

> *Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity).*

However, the approval is subject to incorporation of suggested changes to the proposed draft PI document and a satisfactory response to clinical questions below.

## 10. Clinical questions

### 10.1. Pharmacokinetics

1. Why were the following drug-drug interactions only examined following a single dose of EBR when it would it have not been more meaningful to examine the interaction with EBR at steady-state:
    - buprenorphine/naloxone (Study 8742-P021);
    - ketoconazole (Study 8742-P003);
    - rifampin (Study 8742-P011); and
    - raltegravir (Study 8742-P016).
2. Why were the following drug-drug interactions only examined following a single dose of GZR when it would it have not been more meaningful to examine the interaction with GZR at steady-state:

- RTV (Study 5172-P006); and
- ketoconazole (Study 5172-P001).

3. Why was Study 5172-P045 conducted as a single dose study as the interaction with famotidine should have at least been examined following multiple doses of the FDC?
4. Why do the results of Study 5172-P072 indicating a lack of interaction between the FDC and famotidine differ from the results of Study 5172-P045 which indicate that for EBR at least exposure is increased (35%) in the presence of famotidine?
5. Why was the direct interaction between GZR and ERB examined using doses of 200 mg and 20 mg, respectively, rather than with the proposed dose for marketing (that is, 100 mg/50 mg QD).
6. In Study 5172-P032, why does GZR co-administration have such divergent effects on the exposure of the two CYP3A4 substrates atorvastatin and midazolam?
7. Given that in vitro studies have identified that GZR is primarily metabolised by CYP3A and that rifampin is a potent CYP3A inducer, can the sponsor please clarify the single dose results (Study 5172-P031) in which rifampin co-administration resulted in an increase in GZR exposure? In addition can the sponsor clarify why at steady-state levels of rifampin and GZR co-administration with rifampin is having little effect on GZR exposure, whereas, co-administration of efavirenz (another CYP3A4 inducer) results in a significant decrease in GZR exposure?

## 10.2. Pharmacodynamics

None.

## 10.3. Efficacy

1. The CSR for pivotal Phase III Study P060 mentions that the secondary endpoint (SVR24) will be provided later. The CSR for pivotal Phase II/III Study P052 mentions that the following results will be summarised in a later report: SVR24 for the immediate treatment group SVR4, SVR12 and SVR24 for the deferred treatment arm, and for the combined population of the immediate treatment group, the deferred treatment group, and the intensive PK group. Biomarkers for safety signals and impact of HCV treatment on cryoglobulinemia will also be summarised in a later report. In Phase III Study P068, the secondary efficacy endpoint of SVR24 will be reported later when final results of study are available as many subjects have not yet reached the Week 24 follow-up visit. In Phase II/III Study P059 in 30 patients with cirrhosis (CP score 7-9), only 4 week data was submitted in current dossier. The primary (SVR12), secondary and exploratory endpoints will be summarised in a future study report. For the ongoing Phase II Study P058 in 62 Japanese subjects, only SVR4 rates available (100% results with 50 mg and 100 mg GZR doses in combination with EBR 50 mg).

   Other ongoing studies include the open-label Study P017 with follow-up periods of up to 5 years; Study P062 in HCV infected subjects on opiate substitution therapy and Study P065 in HCV infected subjects with inherited blood disease (IBD).

   There is not much evidence on durability/maintenance of efficacy following treatment with Zepatier. On completion of the above-mentioned ongoing studies, the final CSRs should be provided for evaluation.
2. The CSR of Study P052 in HCV subjects with CKD did not mention if the study treatments were given without regard to food intake as proposed in the PI. Could the sponsor please clarify this?

3. The CSR of pivotal Phase III Study P060 mentions that RAVs were assessed for any subject with VF and detectable virus above 1000 IU/mL after failure was observed. And these subjects were also offered participation in a 3 year long-term follow-up P017, to determine the persistence of RAVs and to determine time course of reversion to wild-type. Viral resistance testing, using population sequencing methodology, focused on the entire NS3/4A and NS5A regions for all subjects at baseline and for those who met the subject virologic failure criteria. However, the CSR for P017 only mentions data on 388 subjects enrolled from Study P035 and P047. Could the sponsors clarify if any of the subjects from Study P060 were actually enrolled in the long-term Study P017?

### 10.4. Safety

1. 'Worsening (increased) ALT and/or AST Grade from baseline occurred more frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group. 3/111 (2.7%) and 25/113 (22.1%), respectively, of subjects in the GZR+EBR immediate treatment and placebo deferred treatment groups developed worsened ALT Grade while on treatment; 2/111 (1.8%) and 18/113 (15.9%), respectively, of subjects in the GZR+EBR immediate treatment and placebo deferred treatment groups developed worsened AST Grade while on treatment.'

**Comments**: The above statement should read that worsening (increased) ALT and/or AST Grade from baseline occurred ~~more~~ **less** frequently in the GZR+EBR immediate treatment group compared to the placebo deferred treatment group based on the values provided in the subsequent sentences. Could the sponsors please provide clarification?

2-6. Typographical errors noted.

**Comments**: There were a few typographical errors in the SCS in Module 2.7.4. Some of them have been pointed out.

7. For the Phase II/III Program (except for Protocol 059, which studied GZR 50 mg with EBR 100 mg in CP-B cirrhotics), only Child-Pugh A/compensated cirrhotics were enrolled.

**Comments**: Study P059 evaluated GZR 50 mg with EBR 50 mg (not 100 mg as mentioned in the SCS. Could the sponsors provide clarification?

# 11. Second round evaluation of clinical data submitted in response to questions

The sponsors have provided responsex to clinical questions raised by evaluators in section 10. The sponsors have also provided additional long term efficacy data in terms of SVR24 data from different clinical trials (for which only interim data was available at time of initial submission). The proposed PI has been considerably modified to address all the concerns raised by the evaluators. Furthermore, Zepatier (elbasvir/grazoprevir) has been approved for use by Health Canada (approval dated 19 January 2016) and by the US FDA (approval dated 28 January 2016).

Review of the sponsor's response followed by evaluator's comments on their response is presented below.

## 11.1. Pharmacokinetics

### 11.1.1. Question 1

#### *11.1.1.1. Sponsor's response:*

EBR pharmacokinetics are linear and time-independent up to an 100 mg dose. Therefore, the steady-state pharmacokinetics of EBR can be predicted based on single-dose pharmacokinetics of EBR at the clinical dose of 50 mg. At the clinical dose, EBR AUC at steady state was slightly higher than on Day 1 (accumulation ratio of 1.24). EBR has no known enzyme induction or time-dependent enzyme inhibition properties.

a. Study 8742-P021 was conducted to assess the drug interaction potential between EBR and the opiate substitution therapy buprenorphine/naloxone. Buprenorphine is metabolised by CYP3A and glucuronidation; naloxone is metabolised through glucuronidation. As in vitro data demonstrated that EBR is not an inhibitor of CYP3A or UGT1A1, no significant interaction between EBR and buprenorphine/naloxone was expected. Based on this information and the pharmacokinetic properties of EBR, a single-dose design is considered adequate to assess both the victim (dose-proportional and time-independent EBR pharmacokinetics) and the perpetrator (no known induction or time-dependent enzyme inhibition activities, and a marginal accumulation at steady state compared to a single dose for EBR) potential of EBR.

b. Study 8742-P003 was conducted to assess the effect of strong CYP3A inhibition on the pharmacokinetics of EBR, a CYP3A substrate. As ketoconazole does not have time-dependent (mechanism-based) inhibitory activities, and based on the PK properties of EBR (dose-proportional and time-independent pharmacokinetics), the victim potential of EBR does not need to be assessed at steady state, and a single-dose design is considered adequate.

c. Study 8742-P011 was conducted to assess the effect of inhibiting intestinal and/or liver and systemic transporters (for example, BCRP, OATP1B, P-gp) on the pharmacokinetic of EBR. The probe inhibitor used in this study was a single-dose rifampin. As the inhibition activity is not known to be time-dependent, and based on the PK properties of EBR (dose-proportional and time-independent pharmacokinetics), the victim potential of EBR does not need to be assessed at steady state, and a single-dose design is considered sufficient. It is noted that repeated rifampin administration induces CYP3A and P-gp, a time-dependent activity. As EBR is a CYP3A and P-gp substrate, the effect of CYP3A induction was not assessed in 8742-P011. The effect of CYP3A and P-gp induction on EBR pharmacokinetics was assessed with efavirenz as the CYP3A inducer (Study 8742-P016) with a multiple-dose design.

d. Part 2 of Study 8742-P016 was conducted to assess the drug interaction potential between EBR and raltegravir. Raltegravir is a UGT1A1 substrate, whereas in vitro data demonstrated that EBR is not a UGT1A1 inhibitor. Therefore, no significant interaction between EBR and raltegravir was expected. Based on this information and the pharmacokinetic properties of EBR, a single-dose design (50 mg EBR) is considered adequate to assess both the victim (dose-proportional and time-independent EBR pharmacokinetics) and the perpetrator (no known induction or time-dependent enzyme inhibition activities, and a marginal accumulation at steady state compared to a single dose for EBR) potential of EBR.

#### *11.1.1.2. Evaluator's response:*

The PK/PD Evaluator is satisfied with the sponsor's response regarding the drug-drug interaction studies.

### 11.1.2. Question 2

#### *11.1.2.1. Sponsor's response:*

In vitro data demonstrated that GZR is a CYP3A substrate. The potential for strong CYP3A inhibitors to affect single-dose GZR plasma concentrations was assessed in two studies, Protocol 5172-P001 (ketoconazole) and 5172-P006 (ritonavir). Population PK modelling was used to assess the potential effect of these strong CYP3A4 inhibitors on multiple-doses of GZR, and compared to the observed results with a single dose of GZR. The modelling results suggest that the design in which a single-dose of GZR was administered in these studies is adequate to determine the clinical relevance of strong CYP3A4 inhibition on GZR, and the same conclusions would be anticipated if the DDI studies were conducted with GZR administered as multiple doses.

The potential effect of multiple doses of ketoconazole on steady state GZR pharmacokinetics following 200 mg of GZR administered once-daily has been evaluated using population PK modelling. The population PK model was first used to estimate (by fitting the model to the Phase I data) the reduction in GZR clearance (CL/F) (approximately 75%) and elimination rate constant (kel) (approximately 80%) and increase in volume of distribution (Vd/F) (approximately 30%) that results from co-administration of ketoconazole. These changes in the model GZR PK parameters (kel, CL/F, and Vd/F) were applied to the model in order to simulate the steady-state 200 mg GZR PK profile following co-administration with multiple-doses of ketoconazole. The population PK model-estimated increase in steady-state GZR AUC when multiple doses of GZR are co-administered with multiple doses of ketoconazole (approximately 3.75-fold) is slightly higher than that observed with a single dose of GZR co-administered with multiple doses of ketoconazole (3.02-fold). Assuming similar uncertainty in the geometric mean ratio (GMR) estimate as that for the 3.02 GMR, the upper bound of the 90% confidence interval for the GMR of 3.75 for the effect of multiple-dose co-administration of ketoconazole on steady-state GZR PK is anticipated to be approximately 4.7, within the proposed [0.4, 5.0] therapeutic bounds for GZR PK. Hence, the anticipated increase in steady-state GZR exposures when co-administered with multiple doses of ketoconazole, a strong CYP3A and P-gp inhibitor, is not considered clinically relevant.

Ritonavir is a strong inhibitor and an inducer of CYP3A and P-gp. At steady-state, the net inhibition is predominant. Co-administration of GZR with ritonavir, increases single-dose GZR AUC by 2-fold, with an upper bound of the 90% confidence interval of 2.56. Similar to what has been demonstrated with ketoconazole, the magnitude of increase of GZR exposure following the administration of ritonavir with multiple-dose GZR is anticipated to be only modestly higher than that observed with single-dose GZR (2-fold), which is supported by the results from the PBPK modelling (Table 31). Thus, the magnitude of increase in GZR, when administered as a SD or MD, would be well within the proposed GZR clinical bounds. Based on these drug interaction study results with ketoconazole and ritonavir, the anticipated increase in GZR exposures with strong CYP3A inhibitors is not considered clinically relevant and most strong CYP3A inhibitors may be co-administered with GZR/EBR.

**Table 31: Observed and SimCYP-predicted pharmacokinetic parameters[a] of GZR following oral administration of GZR[c] in the presence and absence of 100 mg ritonavir (RTV) once daily for 21 days**

| | Observed | Predicted | |
|---|---|---|---|
| Study Population | Healthy Subject | Healthy Subject | |
| MK-5172 Dosing Regimens | 200 mg single dose | 200 mg single dose | 200 mg q.d. for 8 days |
| $AUC_{0\text{-}inf}$ GM (95%CI)[b] GZR alone (μM*h) | 1.51 (1.03, 2.20) | 1.3 (1.1, 1.6) | 1.4 (1.1, 1.8) |
| $AUC_{0\text{-}inf}$ GM (95%CI)[b] GZR w/RTV (μM*h) | 3.03 (2.08, 4.43) | 2.9 (2.4, 3.5) | 3.9 (3.1, 5.0) |
| $C_{max}$ GM (95%CI) GZR alone (μM) | 0.20 (0.12, 0.35) | 0.1 (0.1, 0.2) | 0.2 (0.1, 0.2) |
| $C_{max}$ GM (95%CI) GZR w/ RTV (μM) | 0.23 (0.13, 0.41) | 0.19 (0.15, 0.23) | 0.3 (0.3, 0.4) |
| $AUC_{0\text{-}inf}$ GMR (90% CI) | 2.01 (1.59, 2.55) | 2.2 (2.1, 2.3) | 2.8 (2.7, 2.9) |
| $C_{max}$ GMR (90% CI) | 1.15 (0.60, 2.18) | 1.3 (1.3, 1.4) | 2.0 (1.9, 2.0) |

[a] GMR = geometric mean ratio (RTV+GZR /GZR alone), GM = geometric mean; [b] $AUC_{0\text{-}24h}$ for multiple dose studies;
[c] GZR dosing was started with the 15th dose of ritonavir.

#### *11.1.2.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response regarding the effects of multiple dose ketoconazole and RTV on the PKs of GZR and although the proposed PI currently includes the following information concerning the interactions between ketoconazole/RTV and GZR:

- it identifies the interactions between ketoconazole/RTV and GZR in Table 2 [in PI];
- it alludes to these interactions in the section entitled '*Risk of Adverse Reactions or Reduced Therapeutic Effect Due to Drug Interactions*'; and
- the interaction between ketoconazole and GZR is included in Table 9, the interaction between RTV and GZR is not currently included in Table 9 of the revised PI.

However, due to the magnitude of the potential increase in GZR exposure following multiple dose co-administration with RTV (that is, predicted approximately 2.8 fold increase in GZR $AUC_{inf}$, see Table 31 above); the potential for an increased risk of ALT elevations; the possibility that RTV may be co-administered with other drugs that effect GZR exposure; and the possibility that Zepatier + RTV may be administered to patients with mild hepatic impairment, which in itself increases GZR $AUC_{0\text{-}24}$ by approximately 1.66-fold, the PK/PD evaluator believes that Table 9 of the proposed PI should also include the following information regarding the interaction between RTV and GZR.

Therefore, the evaluator proposes the following changes for Table 9 of the revised PI:

| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| HIV Medications: ritonavir | ↑ GZR | Concomitant use of systemic ritonavir and Zepatier increases grazoprevir exposure and may increase the overall risk of hepatotoxicity, particularly in |

| Concomitant Drug Class: Drug Name | Effect on Concentration | Clinical Comment |
|---|---|---|
| | | patients with mild hepatic impairment or in combination with other drugs that induce increases in grazoprevir exposure; co-administration of ritonavir is not recommended. |

### 11.1.3. Question 3

#### *11.1.3.1. Sponsor's response:*

Administration of famotidine increases gastric pH, which has the potential to affect the solubility of both grazoprevir and elbasvir drug substances, and therefore potentially affect absorption.

As the effect on solubility is pre-absorption, repeated administration is not expected to influence the outcome and a single-dose design to evaluate the potential drug interaction between famotidine and grazoprevir or elbasvir is considered sufficient.

#### *11.1.3.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response.

### 11.1.4. Question 4

#### *11.1.4.1. Sponsor's response:*

The FDC formulation evaluated in 5172-P072 is the same as that used in the core Phase III studies (5172-P060, 5172-P061 and 5172-P068) and is very similar to the proposed marketing image, except for colour in the film coat and debossing. The elbasvir component of the FDC tablet evaluated in 5172-P072 is identical to the elbasvir PMF2 single-entity formulation, and is different from the elbasvir component of the FDC tablet evaluated in 5172-P045. Specifically, the spray dried intermediate (SDI) for elbasvir for the FDC tablet evaluated in 5172-P072 is hypromellose 2910 and TPGS (vitamin E polyethylene glycol succinate) based, with pH-independent solubility, whereas the SDI for elbasvir for the FDC tablet evaluated in 5172-P045 is hypromellose acetate succinate based with pH-dependent solubility. The differences in the SDI could contribute to the different effects of famotidine on elbasvir between the two studies. The FDC tablets used in 5172-P045 and 5172-P072 and the compositions are provided. The results from 5172-P072 indicate that co-administration of acid-reducing agents with the proposed market image of EBR/GZR FDC has no clinically meaningful effect on the pharmacokinetics of EBR or GZR.

#### *11.1.4.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response regarding the differences between the two studies.

### 11.1.5. Question 5

#### *11.1.5.1. Sponsor's response:*

As the plasma exposure of GZR in HCV-infected patients is approximately 2 fold higher than in healthy subjects at steady state, a 200 mg dose of GZR was chosen for the drug-drug interaction (DDI) study between GZR and EBR (and most GZR DDI studies) in healthy subjects to match the exposure of the proposed 100 mg dose for use in HCV-infected patients.

The GZR/EBR DDI study was conducted early during program development in healthy subjects with the planned clinical dose of EBR at that time (20 mg) in order to assess the safety of co-

administering GZR and EBR prior to Phase II and III studies using the combination treatment in HCV patients. Given that the PK of EBR is linear and time-independent in the clinical dose range (up to 100 mg), the lack of a clinically-relevant change in EBR exposure observed following co-administration of EBR 20 mg with GZR is also expected to be observed following co-administration of EBR 50 mg and GZR. The GZR population PK model, including pooled Phase I, Phase II, and III data, was used to assess the potential for co-administration of EBR to impact GZR PK in HCV-infected patients. The population PK model included data from GZR co-administration with 20 mg and 50 mg of EBR in HCV patients. The GZR population PK model results demonstrate that co-administration with EBR does not impact the exposure (AUC) of GZR. Together, the results confirm that the co-administration of GZR and EBR does not impact the PK of either compound.

#### *11.1.5.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response regarding the doses used in the GZR/EBR interaction study.

### 11.1.6. Question 6

#### *11.1.6.1. Sponsor's response:*

Although both atorvastatin and midazolam are both CYP3A substrates, differences in their susceptibility to interactions mediated by transporter pathways are the likely reasons for the differing results. In vitro data demonstrated that GZR is an inhibitor of CYP3A and an inhibitor of BCRP. In vitro data indicated that, at the 100 mg clinical dose, GZR does not have the potential to inhibit OATP1B in vivo. Grazoprevir is not an inhibitor of P-gp. Midazolam is primarily eliminated by metabolism via CYP3A, and midazolam plasma exposure is sensitive to CYP3A inhibition. The small increase in midazolam plasma exposure (1.34-fold) following co-administration with GZR was due to the weak CYP3A inhibitor activity of GZR. Atorvastatin is a substrate of CYP3A, P-gp, BCRP and OATP1B. As discussed, the larger increase in atorvastatin plasma exposure (3-fold) following co-administration with GZR compared to midazolam was due to a combination of CYP3A and BCRP inhibition.

#### *11.1.6.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response regarding effects of GZR on the PKs of atorvastatin and midazolam.

### 11.1.7. Question 7

#### *11.1.7.1. Sponsor's response:*

Grazoprevir is a substrate for CYP3A and OATP1B. The increase in GZR plasma exposure when co-administered with a single oral or IV rifampin compared to GZR alone is due to OATP1B inhibition of rifampin. The lack of a change in exposures of GZR following multiple dose GZR co-administration with multiple doses of oral rifampin likely represents the net effect of OATP1B inhibition and strong induction of CYP3A4/Pgp by rifampin, although the possibility of rifampin also inducing OATP1B cannot be excluded.

Efavirenz is not an OATP1B inhibitor, and the significant decrease in GZR exposure following co-administration of GZR with multiple doses of efavirenz represent the effect of CYP3A induction on the plasma exposure of GZR.

#### *11.1.7.2. Evaluator's response:*

The PK/PD evaluator is satisfied with the sponsor's response.

## 11.2. Efficacy

### 11.2.1. Question 1

The CSR for pivotal Phase III Study P060 mentions that the secondary endpoint (SVR24) will be provided later. The CSR for pivotal Phase II/III Study P052 mentions that the following results will be summarised in a later report: SVR24 for the immediate treatment group SVR4, SVR12 and SVR24 for the deferred treatment arm, and for the combined population of the immediate treatment group, the deferred treatment group, and the intensive PK group. Biomarkers for safety signals and impact of HCV treatment on cryoglobulinemia will also be summarised in a later report. In Phase III Study P0**68**, the secondary efficacy endpoint of SVR24 will be reported later when final results of study are available as many subjects have not yet reached the Week 24 follow-up visit. In Phase II/III Study P0**59** in 30 patients with cirrhosis (CP score 7-9), only 4 week data was submitted in current dossier. The primary (SVR12), secondary and exploratory endpoints will be summarised in a future study report. For the ongoing Phase II Study P0**58** in 62 Japanese subjects, only SVR4 rates available (100% results with 50 mg and 100 mg GZR doses in combination with EBR 50 mg).

Other ongoing studies include the open-label Study P0**17** with follow-up periods of up to 5 years; Study P0**62** in HCV infected subjects on opiate substitution therapy and Study P0**65** in HCV infected subjects with inherited blood disease (IBD).

There is not much evidence on durability/maintenance of efficacy following treatment with Zepatier. On completion of the above-mentioned ongoing studies, the final CSRs should be provided for evaluation.

#### *11.2.1.1. Sponsor's response*

A summary of the status of each pivotal Phase III study formerly listed as ongoing for which additional efficacy data are available is provided.

The final CSR for P059, P061, and P068 are included with this response and contain complete SVR24 data which were not included in the interim CSR. These studies are completed and no further activities are planned. An interim CSR for P058 is also provided with this response. It includes s SVR24 data from Part A of the study. This study is still ongoing and SVR24 data from Part B will be reported in a final CSR in second quarter of 2016. Final CSRs for P052 and P060 will be available in late May 2016. The final study visits including all time-points for both the Immediate Treatment Group (ITG) and Deferred Treatment Group (DTG) for both studies have been achieved and SVR24 data were provided in this response although final reports are not yet available. For P052 the final reports will also include impact of HCV treatment on cryoglobulinemia. Interim CSRs for these studies were included in the original application and included data through SVR12 time-point for the ITG.

A summary of the SVR24 data which are currently available was provided. Overall, SVR24 rates were high, with very few relapses observed between SVR12 and SVR24.

In Study P052, were two subjects in the Immediate + Intensive PK arms that relapsed between Follow-up Week 12 and Follow-up Week 24. Efficacy remains high with SVR24 in the Immediate Treatment group >97% (SVR12 was 99%).

In Study P058, SVR24 data for Part 1 was provided and no relapses were observed after follow-up week 12. Efficacy remains high with SVR24 at >96% in both treatment groups.

In Study P059, no relapses were observed after follow-up week 12 and efficacy remains high with SVR24 at 90% in CP-B subjects.

In Study P060, there were breakthroughs and 'administrative failures' in both arms prior to SVR12, but in terms of durability between SVR12 and SVR24, there was one subject in the Immediate treatment arm that relapsed. Thus, efficacy remains high with SVR24 in the Immediate Treatment group 94.3% (SVR12 was 94.6%).

In Study P061, no relapses were observed after follow-up week 12 and efficacy remained high with SVR24 at >93%.

In Study P068, one subject in the GZR/EBR for 16 weeks arm relapsed between Follow-up Week 12 and Follow-up Week 24. Efficacy of GZR/EBR with or without RBV for 12 or 16 weeks remained high with SVR24 ranging from >89% to >95% in all treatment groups (SVR12 was >90% in all treatment arms).

The final CSRs from other ongoing studies, including the open-label Study P017, Study P062 in HCV infected subjects on opiate substitution therapy and Study P0**65** in HCV infected subjects with inherited blood disease (IBD) will be provided upon completion.

#### *11.2.1.2. Evaluator's response:*

The response is satisfactory.

### 11.2.2. Question 2

#### *11.2.2.1. Sponsor's response*

In P052, study treatments were given without regard to food. This was specified in Section 5.7 of the protocol which is copied below:

*'**5.7 Diet/Activity/Other Considerations Dietary Considerations:** MK-5172 and MK-8742 can be taken without regard to food; however, intake of grapefruit or grapefruit juice is prohibited during the dosing period of the trial.'*

#### *11.2.2.2. Evaluator's response:*

The response is satisfactory.

#### *11.2.2.3. Question 3*

#### *11.2.2.4. Sponsor's response*

Subjects enrolled in P017 after completing follow-up (through SVR24) in a GZR treatment trial. The P017 report submitted with the Marketing Application did not include subjects from P060 because, at that time, those subjects had not completed follow-up in P060 which continues for 24 weeks after the end of study drug. As of March 10, 2016, 339 subjects from P060 have completed the 24 week follow up time-point in P060 and have consented to enrol in P017.

#### *11.2.2.5. Evaluator's response:*

The response is satisfactory.

## 11.3. Safety

### 11.3.1. Question 1

#### *11.3.1.1. Sponsor's response*

The sponsor agrees there was an error in the statement regarding the frequency of worsening (increased) ALT and/or AST Grade from baseline. Worsening (increased) ALT and/or AST Grade from baseline occurred less frequently in the GZR+EBR immediate treatment group compared to the placebo deferred group. In addition, the rate of the placebo deferred treatment group was incorrectly listed as 25/113 (22.1%); it should have been listed as 23/113 (20.4%).

#### *11.3.1.2. Evaluator's response:*

The response is satisfactory.

### 11.3.2. Questions 2-6

#### *11.3.2.1. Sponsor's response*

The sponsor agrees there were typographical errors and these have been corrected.

#### *11.3.2.2. Evaluator's response:*

The response is satisfactory.

### 11.3.3. Question 7

#### *11.3.3.1. Sponsor's response*

The sponsor agrees there was an error in the notation of the Protocol 059 treatment regimen for CP-B cirrhotics. The statement should read:

*'For the Phase II/III Program (except for Protocol 059, which studied GZR 50 mg with EBR 50 mg in CP-B cirrhotics), only Child-Pugh A/compensated cirrhotics were enrolled.'*

#### *11.3.3.2. Evaluator's response:*

The response is satisfactory.

## 11.4. Evaluator's response to the sponsor

### 11.4.1. Evaluator's response to the sponsor's document entitled 'Errors of Fact & Omission Identified in the Clinical Evaluation Report'

All of the corrections to the first round CER proposed by the sponsor have been made, except for Error Number 3:

> *'There are many errors and omission in this table. The errors and omission are marked as red text in a copy of Table 2 in the Clinical Evaluation Report, with references to correct information in the submission dossier provided as an extra column. P 56-57 of M272 in the dossier and in [Ref. 5.3.3.4: P031]'.*

Where appropriate these errors in Table 2[43] have been corrected; however, some of these errors should be considered misunderstandings between the evaluator and the company. For instance, the following error:

| | | | | | |
|---|---|---|---|---|---|
| Error: The primary objective of the study is PK in renal impairment patients.<br><br>PK in non-HCV subjects with renal insufficiency | | 5172-P050 | PKs of multiple daily doses of GZR and EBR co-administered to subjects with ESRD on HD days to those obtained on non HD days and in healthy subjects | Table 4.14 | Pg. 52 of M272 in the dossier |

The evaluator is well aware of the primary objective of this study as can be determined from the stated objective. However, it understood that in Table 2[43] the relevant summary should be brief and should appear numbered in the order in which it appears in the report. As this study is first discussed in the CER report in relation to the volume of distribution in healthy subjects it appears under the healthy subjects section of Table 2[43]. In addition, many of the omissions identified by the sponsor occur as a result of the need for brevity in Table 2[43], especially considering the number of studies submitted and that the studies are described in considerably more detail [elsewhere] in the CER.

[43] See Table 2 of this document

# 12. Second round benefit-risk assessment

## 12.1. Second round assessment of benefits

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefits of Zepatier in the proposed indication are modified as follows:

The benefits of Zepatier in the proposed usage are:

- offers a single tablet, once-daily oral regimen.
- provides a simple, well tolerated ribavirin and interferon-free regimen for patients infected with HCV GT 1, 3, 4 and 6.
- treats HCV infected patients including hard-to-treat populations such as those with HIV co-infection, Chronic Kidney Disease, and HCV genotype 3, 4 and 6 infection.
- Provides a 12 week dosing regimen, without ribavirin, for most patients (GT 1, 4 and 6 Treatment Naïve and Treatment-Experienced Relapsers, and GT1b Treatment-Experienced On-Treatment-Virologic-Failures (OTVF)).
- 8 week regimen may be considered for Treatment Naïve GT1b patients.
- 12 week regimen with concomitant administration of sofosbuvir was effective in treating HCV GT3 infected TN patients.
- 16 week regimen with concomitant administration of ribavirin is recommended for GT1a, 4 and 6 Treatment-Experienced OTVF.
- In GT4 infected (treatment-naïve / treatment experienced, ± HIV co-infection, ± cirrhosis) HCV patients, treatment with GZR+EBR (100/50 mg) for 12 weeks was highly effective (SVR12 up to 96%) and well tolerated. Although only small number of GT6 subjects was evaluated in the Phase2/3 studies, there was strong data to support use for GT6 (SVR12 of 80%).
- The well-conducted Study P052 demonstrated that 12 weeks of treatment with GZR+EBR (100/50 mg) was well tolerated and highly efficacious (SVR12 of 94%) in 225 advanced CKD patients, including patients on haemodialysis, thus avoiding the need for peginterferon, ribavirin or sofosbuvir in treating these patients and addressing this urgent unmet need.
- A summary of the SVR24 data from studies P052, P058, P059, P060, P061 and P068, were provided in the sponsor's response. Overall, maintenance of efficacy of Zepatier was demonstrated as SVR24 rates were high, with very few relapses observed between SVR12 and SVR24.

## 12.2. Second round assessment of risks

After consideration of responses to clinical questions and other information submitted by the sponsors, the risks of Zepatier in the proposed indication are modified as follows:

The risks of Zepatier in the proposed usage are:

- Development of NS3 and/or NS5A RAVs in subjects with virologic failure has been characterised. NS3 RAVs are likely to revert to wild-type virus and have limited impact on retreatment options. NS5A RAVs are likely to persist for a longer period of time, based on experience with other NS5A inhibitors. The implications on re-treatment have not yet been determined. However, the incidence of virologic failure was generally <4%.

- Increased risk of Late ALT/AST Elevation Events, especially in patients with Child-Pugh C cirrhosis. However, periodic monitoring of ALT is recommended in the proposed label.
- Risk of drug interactions although labelling will address specific patient populations and DDIs that are pertinent to the risk of Late ALT/AST Elevation Events.
- Hyperbilirubinemia has been observed in regimens of GZR with EBR (+ RBV) and reflects the well-known haemolytic effects of RBV.
- Lack of efficacy/ safety data in patients with severe hepatic impairment (CP-C cirrhosis), liver transplant patients and HBV/HCV co-infection.
- Lack of efficacy/ safety data in pregnancy/ lactation and paediatric patients.

### 12.3. Second round assessment of benefit-risk balance

After consideration of responses to clinical questions and other information submitted by the sponsors, the benefit-risk profile of Zepatier in the proposed indication remains favourable.

# 13. Second round recommendation regarding authorisation

It is recommended that Zepatier be approved for the proposed indication of:

> *Zepatier is indicated for the treatment of Chronic Hepatitis C infection in adults (see Dosage and Administration and Clinical Trials). (See Clinical Trials for information on HCV genotype-specific activity.)*

Approval is subject to incorporation of some minor changes to the proposed PI.

# 14. References

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