A Phase 3, Global, Multicenter, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis.

Tittle : STREAGER

(Short TREAtment course Grazoprevir ElbasviR)

Code Promoteur	N° EudraCT ou n° d'enregistrement ANSM
«RBHP 2016 ABERGEL»	«2016-001363-37»

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LIST OF ABBREVIATION

Term	Definition
AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine aminotransferase (SGPT)
ANSM	French National Agency for Medicines and Health Products Safety
AST	Aspartate aminotransferase (SGOT)
cEVR	Complete Early Viral Response, defined as undetectable (TND) HCV RNA at Week 12
CPP	Institutional Review Board
CRF	Case Report Form
CRO	Clinical Research Organization
CSR	Clinical Study Report
CTC	Clinical Trial Coordinator
CTD	Clinical Trial Directive
DSMB	Data and Safety Monitoring Board
ECI	Events of Clinical Interest
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EU	European Union
FDA	Food and Drug Administration, USA
FW	Follow-up Week
GCP	Good Clinical Practice
HCV	Hepatitis C visrus
hCG	Human Chorionic Gonadotropin
IATA	International Air Transport Association
IB	Investigator's Brochure
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IND	Investigational New Drug Application; legal instrument in the USA that allows trial of unapproved, investigational new drugs in human subjects
Investigational Product	The drug, biologic, and/or device being investigated in the current trial
IRB	Institutional Review Board
LDH	Lactate Dehydrogenase
LLoQ	lower limit of quantification

PROTOCOL SYNOPSIS

Study Title :	STREAGER : A Phase 3, Global, Multicenter, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis
EudraCT Number :	**2016-001363-37**
Clinical Trials.gov Identifier :	**160789A-41**
Promotor Code :	**RBHP 2016 ABERGEL**
Study Centers Planned :	14 centers in France

Objectives :

The primary objectives of this study are as follows:

- To evaluate the efficacy of of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR 12).
- To evaluate the safety and tolerability of EBV/GZR treatment

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment.
- To evaluate the emergence of viral resistance to EBV/GZR during treatment and after cessation of treatment

Study Design :	Approximately one hundred and twenty treatment-naïve subjects with chronic HCV GT1b infection without cirrhosis will be enrolled. There will be one treatment group with EBV/GZR (50/100 mg) once daily without regards to food for 8 weeks.
Target Population :	Adults with chronic hepatitis C genotype 1b virus (HCV GT1b) infection who have not been previously treated.
Duration of treatment :	Subjects will be treated for 8 weeks.
Diagnosis and Main Eligibility Criteria :	Treatment-naïve chronic HCV GT1b-infected male and nonpregnant female subjects aged 18 years or older.
Inclusion Criteria:	Subjects must meet all of the following inclusion criteria to be eligible for participation in this study: 1 - Willing and able to provide written informed consent 2 - Male or female, age ≥ 18 years 3 - Body Mass Index (BMI) ≥ 18 kg/m2 4 - HCV RNA ≥ 10^4 IU/mL at Screening 5- Chronic HCV infection (≥ 6 months) documented by prior medical history or liver biopsy. Only patients infected by genotype 1b virus will be included. 6 - Treatment-naïve with no prior exposure to any IFN, RBV, or approved or experimental HCV-specific DAA 7 – Non severe fibrosis (F ≤ 2) according to combination of theses two tests: Fibroscan® lower than 9.5 kPa **AND** Fibrotest lower than 0.59. 8 - Females of childbearing potential (as defined in protocol Appendix 4) must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1 prior to enrollment

9 - Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use effective method(s) of contraception

10 - Lactating females must agree to discontinue nursing before starting study drug

11 - Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator

12 - Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments

Exclusion Criteria: Subjects who meet **any** of the following exclusion criteria are **not** to be enrolled in this study.

1 - Current or prior history of any of the following:

a) Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded

b) Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug

c) Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy

d) History of decompensation (e.g., clinical ascites, encephalopathy, and/or variceal hemorrhage)

e) Solid organ transplantation

f) Significant cardiac disease

g) Unstable psychiatric condition including hospitalization, suicidal attempt, and/or a period of disability as a result of their psychiatric illness within 2 years prior to Screening

h) Malignancy within the 5 years prior to Screening, with the exception of specific cancers that have been cured by surgical resection (e.g., basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are not eligible

I) Significant drug allergy (e.g., hepatotoxicity)

2 - Subject has the following laboratory parameters at Screening:

a) ALT > 10 x the upper limit of normal (ULN)

b) AST > 10 x ULN

c) Direct bilirubin > 1.5 x ULN

d) Platelets < 75,000/µL

e) HbA1c > 8.5%

f) Creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation

g) Hemoglobin < 10 g/dL

h) Albumin < 3 g/dL

i) INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regime affecting INR

3 - Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis)

4 - Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)

5 - Clinically-relevant alcohol or drug abuse within 12 months of Screening. A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator

6 - Use of any prohibited concomitant medication

7 - Known hypersensitivity to the study drug, the metabolites, or formulation excipient

Study Procedures/ Frequency :

Screening assessments will be completed within 28 days of the Day 1 visit. The screening window can be extended to 42 days for subjects requiring a liver biopsy, or extenuating circumstances.

All subjects will complete the following study visits: Screening, Day 1, and on-treatment visits at the end of week 2, week 4 and week 8.

Posttreatment visits will occur at Weeks 4, 12, and 24 after last dose of study drug. All subjects will complete the posttreatment Week 4 and 12 visits. Subjects who achieve SVR12 (HCV RNA < LLOQ at posttreatment Week12) will complete the posttreatment Week 24 visit.

Screening assessments will include physical examination, medical history, height, weight, vital signs, adverse events related to screening procedures, concomitant medications, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, serology (HCV, HBV), serology and/or antigen testing for HIV, HCV genotyping, hemoglobin A1c (HbA1c), assessment of the absence of cirrhosis or severe fibrosis (including Fibrotest® and Fibroscan®), serum β-human chorionic gonadotropin (β-hCG) (females of child-bearing potential only), urinalysis.

On-treatment assessments include adverse events (AEs), concomitant medications, study medication dispensation and pill count, physical examination, weight, vital signs, safety laboratory tests, HCV RNA, and urine pregnancy tests (females of child bearing potential only).

Posttreatment assessments include Aes, concomitant medications, vital signs, safety laboratory tests (including hematology, chemistry, and coagulation), HCV RNA, and urine pregnancy tests (females of child-bearing potential only).

Test Product, Dose, And Mode of Administration :	EBV/GZR is manufactured as a 50/100 mg tablet for oral administration. Subjects will take 1 tablet daily without regards to food.

Criteria for Evaluation :

Safety : AEs and laboratory tests will be collected throughout the study.

Efficacy : Efficacy will be evaluated using scheduled assessments of HCV RNA performed using ROCHE COBAS® AmpliPrep / COBAS® TaqMan® HCV Quantitative Test, v2.0 or ABBOTT Amplification Reagent Real Time kit HCV

Statistical Methods :

The sample size estimation was performed according to the precision of 95% confidence interval of the primary outcome measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment. Considering an efficacy at 96%, n=120 patients will be included in this study and will be able to obtain an exact 95% confidence interval with a lower bound greater than 91.5%, which could be considered as the minimal efficacy obtained in several works presented recently in literature.

The primary efficacy endpoint for the study is the proportion of subjects with SVR12 in all enrolled and treated subjects.

Secondary efficacy endpoints include SVR4 and SVR24, and the proportion of subjects with virologic failure.

Safety endpoints will be analyzed by the number and percent of subjects with events or abnormalities for categorical values or 8-number summary (n, mean, standart deviation, median, Q1, Q3, minimum, maximum) for continuous data.

1.INTRODUCTION

1.1 Study Tittle

A Phase 3, Global, Multicenter, Randomized, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis

Abbreviated tittle : STREAGER (Short TREAtment course Grazoprevir ElbasviR)

EudraCT Number : 2016-001363-37

ANSM Number : 160789A-41

1.2 Promotion Code

RBHP 2016 ABERGEL

1.3 Promotion

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1.7 Committee for the protection of persons

Comité de Protection des Personnes Sud Est

1.8 Provisional Timelines for the study

CPP Soumission : September 2016
ANSM Autorisation : November 2016
Beginning of Study : December 2016
Inclusions : Starting January 2017
End of Study : November 2018
Final Report : December 2018/January2019

2 BACKGROUND

2.1 General Background

Hepatitis C (HCV) viral infection is a global health challenge affecting an estimated 170 million people (1), but seroprevalence and incidence rates vary significantly by risk group, even within world regions or nations. The majority (55 to 85%) of subjects progress to chronic hepatitis C virus (CHC) infection. Attendant consequences include chronic liver disease (~70%), with annual rates of progression to cirrhosis and hepatocellular carcinoma of ~20% and ~1 to 5%, respectively. HCV has become the most common indication for liver transplantation in developed nations. Given the asymptomatic nature of early infection and slow progression to severe chronic liver disease, it is expected that the prevalence of subjects diagnosed with HCV will peak over the next 2 decades (2).

Six major genotypes (GT) have been identified for HCV. While genotype 1 is by far the most common, accounting for about 60% of global infections, the public health burden of other genotypes is also significant. In particular, GT2 the next most prevalent genotype worldwide accounts for 10-15% of infections in the United States. In Europe the frequency varies from a relatively low prevalence of 0.9% in Turkey to a very significant proportion of HCV infections in France and Italy (10.4% and 27%, respectively). Other genotypes are also responsible for a large number of CHC infections, particularly in certain geographic locations. For example, GT3 is endemic in south-east Asia; GT4 is principally found in the Middle East, Egypt, and central Africa; and GT 5 and 6 are found almost exclusively in South Africa, and in Asia, respectively (3).

Previously, the standard of care (SOC) treatment for CHC infection with all genotypes was pegylated-interferon (peg-IFN) plus RBV (P/R) (4,5) a poorly tolerated drug with moderate efficacy. For GT1 infection, a major landmark was the approval of the first two direct-acting antiviral (DAA) agents, HCV NS3/4A protease inhibitors (PI), boceprevir or telaprevir. Addition of these DAAs to the P/R backbone significantly increased SVR_{24} rates in GT1 subjects but these regimens are no longer recommended (6–9).

Recent drug development has focused on all-oral, interferon (IFN) free regimens that include agents that directly and specifically inhibit viral structural proteins (direct-acting antivirals, or DAAs). Four DAA classes have been developed: NS3/4A Protease Inhibitors (PIs), NS5A Inhibitors (NS5AIs), Nucleoside-Mimetic NS5B Polymerase Inhibitors (NIs), and Non- Nucleoside NS5B Polymerase Inhibitors (NNIs). Candidate medicines within each of these categories can vary substantially in terms of potency across genotypes and against resistance associated- variants (RAVs) within each genotype and subgenotype (10–16).

The most effective regimens are for genotype 1 HCV which accounts for approximately 46% of infections worldwide (3). Genotypes 2 and 3 HCV, the next most common genotypes, were historically grouped together in treatment guidelines, but recent studies have shown that infection with genotype 3, especially in patients with cirrhosis, is more difficult to treat (17,18). Many interferon-free combinations are now available for these and the other 3 HCV genotypes (19,20),

but clinicians must take into account the genotype and even the subtype as well as patterns of antiviral resistance in the choice of a regimen.

Shorter durations of therapy using novel combinations of DAAs may offer benefits such as increased compliance, lower cost and broader usage and acceptance by treating providers.

2.2 Pharmaceutical and Therapeutic Background

Refer to the Investigator's Brochure (IB)/approved labeling for detailed background information on EBV and GZR.

2.2.1 In vitro studies EBV/GZR

EBV is a potent inhibitor of the viral protease, NS3/4A, with broad i*n vitro* genotypic activity. It has low nanomolar activity (< 1nM) against all 6 (GT 1-6) genotypes as assessed by enzymatic assays. In such assays the Ki values were lowest for GT1b virus, highest for GT3 virus, with values in the intermediate range for GT2 and GT4-6 HCV.
Similar trends are seen in replicons studies with EBV. These data suggests that EBV will be a potent anchor drug with broad genotypic coverage for the treatment of CHC infection.

GZR is an inhibitor of the HCV non-structural protein, 5A (NS5A), a pleiotropic protein with important roles in both HCV RNA replication and viral assembly. Using a panel of sub- genomic replicon cell lines, GZR has been shown to be highly potent against most HCV genotypes with EC_{50} values in the low picomolar range.

2.2.2 Clinical pharmacology EBV/GZR

Grazoprevir is a substrate of CYP3A/P-gp. Co-administration of moderate or strong inducers of CYP3A/P-gp with GZR may decrease grazoprevir plasma concentrations, leading to reduced therapeutic effect of GZR. Co-administration of GZR/EBR with moderate or strong CYP3A/P-gp inducers is not recommended. Co-administration of GZR with strong CYP3A4/P-gp inhibitors increases grazoprevir and elbasvir plasma concentrations, but the increases are not clinically relevant. Therefore, CYP3A/P-gp inhibitors may be coadministered with GZR/EBR.
Grazoprevir is a substrate of organic anion transporting polypeptide 1B (OATP1B) drug transporters. Co-administration of GZR with drugs that inhibit OATP1B transporters may result in a significant increase in the plasma concentration of grazoprevir. As such, coadministration of GZR/EBR with OATP1B inhibitors (such as rifampin and cyclosporine) is not recommended.
Grazoprevir and elbasvir are inhibitors of the drug transporter breast cancer resistance protein (BCRP) at the intestinal level in humans and may increase plasma concentrations of coadministered BCRP substrates. Grazoprevir is a weak, but not clinically relevant, CYP3A inhibitor in humans. Therefore, no dose adjustment is required for CYP3A substrates when co-administered with GZR/EBR. Grazoprevir is not a P-gp or OATP1B inhibitor. Clinically significant drug interactions with

GZR as an inhibitor of other CYP enzymes, UGT1A1, and esterases (CES1, CES2, and CatA), are not expected, and multiple-dose administration of GZR is unlikely to induce the metabolism of drugs metabolized by CYP isoforms based on in vitro data.

The GZR/EBR FDC may be coadministered with sofosbuvir and ribavirin (HCV medications). Methadone and buprenorphine/naloxone opioid substitution therapies may be coadministered with the GZR/EBR FDC without dose adjustment. The following immunosuppressants may be coadministered with the GZR/EBR FDC without dose adjustment: mycophenolate mofetil, prednisone, and tacrolimus. Coadministration of cyclosporine with the GZR/EBR FDC is not recommended. Acid-reducing agents, oral contraceptives, and phosphate binders may be coadministered with the GZR/EBR FDC without restriction.
The GZR/EBR FDC may be coadministered with the following HIV antiretroviral medications: lamivudine, emtricitabine, abacavir, tenofovir disoproxil fumarate, raltegravir, dolutegravir, and rilpivirine. Coadministration of GZR/EBR FDC with efavirenz, etravirine, atazanavir, and ritonavir-boosted HIV protease inhibitors is not recommended.
Pravastatin and pitavastatin HMA-CoA reductase inhibitors may be coadministered with the GZR/EBR FDC without dose adjustment. Atorvastatin, rosuvastatin, fluvastatin, lovastatin, or simvastatin may be coadministered with GZR/EBR, but may result in increases in exposures of these statins. As such, the dose of atorvastatin, fluvastatin, lovastatin, or simvastatin should not exceed a daily dose of 20 mg and the dose of rosuvastatin should not exceed a daily dose of 10 mg when coadministered with GZR/EBR.
Relative to fasting conditions, the administration of a single dose of GZR/EBR with a highfat (900 kcal, 500 kcal from fat) meal to healthy subjects resulted in increases in grazoprevir AUC0-inf and Cmax of approximately 1.5-fold and 2.8-fold, respectively. These differences in grazoprevir exposure are not clinically relevant; therefore, GZR/EBR may be taken without regard to food.

2.3 Clinical trials studies with EBV/GZR combination

The core clinical development program includes 4 Phase 2 studies (Protocols 035, 047, 048,074), and 4 pivotal Phase 3 registration trials (Protocols 052, 060, 061, 068) in which 2704 HCV-infected subjects received GZR without EBR, GZR with EBR (either in the form of two separate tablets, termed GZR + EBR, or in the form of a fixed-dose combination tablet, termed GZR/EBR, or MK-5172A), or placebo for GZR/EBR followed by GZR/EBR. No HCV-infected subject received EBR without GZR in Phase 2 or 3. Studies evaluated these regimens alone or in combination with RBV. Also, GZR/EBR was evaluated with sofosbuvir in one study. Of the 2704 subjects in these studies, 1969 received GZR 100 mg with EBR 50 mg and support the key efficacy conclusions summarized below and an overview of these trials is provided in Table 1

Table 1 : Trials Conducted with GZR with EBV

Trial	Population	Study Arms and Duration (Number of Subjects Treated)
PN060/C-EDGE TN (double-blind)	GT 1, 4, 6 TN with or without cirrhosis	• GZR/EBR for 12 weeks (N=316) • Placebo for 12 weeks (N=105)
PN061/C-EDGE COINFECTION (open-label)	GT 1, 4, 6 TN with or without cirrhosis HCV/HIV-1 co-infection	• GZR/EBR for 12 weeks (N=218)
PN052/C-SURFER (double-blind)	GT 1 TN or TE with or without cirrhosis Chronic Kidney Disease	• GZR* + EBR* for 12 weeks (N=122) • Placebo for 12 weeks (N=113)
PN035/C-WORTHY (open-label)	**GT 1, 3 TN with or without cirrhosis TE Null Responder with or without cirrhosis TN HCV/HIV-1 co-infection without cirrhosis**	**• GZR* + EBR* for 8, 12, or 18 weeks (N=31, 136, and 63, respectively) • GZR* + EBR* + RBV† for 8, 12, or 18 weeks (N=60, 152, and 65, respectively)**
PN047/C-SCAPE (open-label)	GT 4, 6 TN without cirrhosis	• GZR* + EBR* for 12 weeks (N=14) • GZR* + EBR* + RBV† for 12 weeks (N=14)
PN068/C-EDGE TE (open-label)	GT 1, 4, 6 TE with or without cirrhosis HCV/HIV-1 co-infection	• GZR/EBR for 12 or 16 weeks (N=105, and 105, respectively) • GZR/EBR + RBV † for 12 or 16 weeks (N=104 and 106, respectively)
PN048/ C-SALVAGE (open-label)	GT 1 TE with HCV protease inhibitor regimen ‡ with or without cirrhosis	• GZR* + EBR* + RBV† for 12 weeks (N=79)
PN074/C-SWIFT (open-label)	GT 1, 3 TN with or without cirrhosis	• GZR/EBR + sofosbuvir§ for 8 or 12 weeks in GT 3 (N= 15 and N=26, respectively) • GZR/EBR + sofosbuvir§ for 4, 6 or 8 weeks in GT 1 (N=31, 50, and 21, respectively)

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

2.4 Efficacy measurement

Sustained virologic response was the primary endpoint in all trials and was defined as HCV RNA less than the lower limit of quantification (LLOQ) at 12 weeks after the cessation oftreatment (SVR). Serum HCV RNA values were measured during these clinical trials using the COBAS AmpliPrep/COBAS Taqman HCV test (version 2.0) with an LLOQ of 15 HCV RNA IU/mL, with the exception of Protocol 035/C-WORTHY and Protocol 047/C-SCAPE where the assay had an LLOQ of 25 HCV RNA IU/mL.

2.5 Adverse events

GZR/EBR combination was evaluated in safety pharmacology studies (in vitro and in vivo) consistent with ICH S7A and S7B guidances to determine the potential cardiovascular, respiratory, and neurobehavioral effects. GZR/EBR was devoid of any effects of concern in these studies.

Adverse reactions occurring in a pooled analysis of Phase 2 and 3 clinical trials at ≥5% frequency in subjects treated with GZR with EBR for 12 weeks are presented below. The majority of the adverse reactions were mild in severity. No subjects treated with GZR with EBR had serious adverse reactions. The proportion of subjects who permanently discontinued treatment due to adverse reactions was <1%. The type and severity of adverse reactions in subjects with cirrhosis were comparable to those seen in subjects without cirrhosis.
Adverse Reactions Occurring at ≥5% Frequency in Subjects with Chronic Hepatitis C
Infection Treated with GZR with EBR for 12 Weeks in Protocol 060/C-EDGE TN or with GZR with EBR for 12 weeks in the Pooled Phase 2 and 3 Clinical Trials are presented below :

Table 2 : Adverse Reactions Occuring at ≥5% Frequency in Subjects with Chronic Hepatitis C Infection Treated with GZR with EBR for 12 Weeks in Protocol 060/C-EDGE TN or with GZR with EBR for 12 weeks in the Pooled Phase 2 and 3 Clinical Trials

	PN060/C-EDGE TN		**Pooled***
	GZR with EBR N=316 %(n) 12 weeks	**Placebo N=105 % (n) 12 weeks**	**GZR with EBR N=834 % (n) 12 weeksh**
Nervous system disorders			
Headache	10% (31)	9% (9)	10% (86)
Gastrointestinal disorders			
Nausea	4% (14)	5% (5)	5% (43)
General disorders and administration site conditions			
Fatigue	11% (35)	10% (10)	11% (94)

*Includes C-WORTHY, C-SCAPE, C-SALT, C-EDGE TN, C-EDGE COINFECTION, C-EDGE TE and P058
The type and severity of adverse reactions were comparable among subjects treated with 8, 12 or 16 weeks of GZR with EBR.

During clinical trials of GZR with EBR with or without ribavirin, regardless of treatment duration, <1% of subjects experienced elevations of ALT from normal levels to greater than 5 times the upper limit of normal (ULN), generally at or after treatment week 8. ALT elevations were typically asymptomatic and most resolved with ongoing or completion of therapy. Hepatic laboratory testing should be performed prior to therapy and periodically thereafter. Patients should be instructed to consult their healthcare professional without delay if they have onset of fatigue, weakness, lack of appetite, nausea and vomiting, jaundice or discolored feces. Consider discontinuing GZR with EBR if ALT levels remain persistently greater than 10 times the ULN. Discontinue GZR with EBR if ALT elevation is accompanied by signs or symptoms of liver inflammation or increasing conjugated

bilirubin, alkaline phosphatase, or INR. The frequency of ALT elevations was higher in subjects with higher grazoprevir plasma concentration. The incidence of late ALT elevations was not affected by treatment duration.
Cirrhosis was not a risk factor for ALT elevations.

No dose adjustments are recommended for GZR for most intrinsic factors, such as age, gender, body weight/BMI, renal impairment, and mild hepatic impairment. No dosage adjustment of GZR/EBR is required in patients who are on dialysis. However, the GZR/EBR FDC is not recommended for HCV-infected patients with moderate hepatic impairment (Child Pugh B) and is contraindicated for HCV-infected patients with severe hepatic impairment (Child Pugh C).

2.6 Clinical Data

Based on the efficacy and safety data from the key clinical, Table below (Table 3) provides the recommended GZR/EBR treatment regimen and duration based on the patient population and genotype in hepatitis C virus (HCV) mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis.

Table 3 : Recommended Dosage Regimens and Durations for EBR/GZR for Treatment of Chronic Hepatitis C Infection in Patients with or without Cirrhosis

HCV genotype	Treatment and duration
1a	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/ml and/or the presence of specific NS5A polymorphisms causing at least a 5-fold reduction in activity of elbasvir to minimise the risk of treatment failure (see section 5.1).
1b	ZEPATIER for 12 weeks
4	ZEPATIER for 12 weeks ZEPATIER for 16 weeks plus ribavirin[A] should be considered in patients with baseline HCV RNA level >800,000 IU/ml to minimise the risk of treatment failure (see section 5.1).

[A] In the clinical studies, the dose of ribavirin was weight-based (< 66 kg = 800 mg/day, 66 to 80 kg = 1,000 mg/day, 81 to 105 kg = 1,200 mg/day, > 105 kg = 1,400 mg/day) administered in two divided doses with food.

In case a dose is missed and it is within 16 hours of the time GZR/EBR is usually taken, the patient should be instructed to take GZR/EBR as soon as possible and then take the next dose of GZR/EBR at the usual time. If more than 16 hours have passed since GZR/EBR is usually taken, then the patient should be instructed that the missed dose should NOT be taken and to take the next dose per the usual dosing schedule. Patients should be instructed not to take a double dose.
If GZR/EBR is co-administered with ribavirin or sofosbuvir, the information for ribavirin or sofosbuvir with regard to contraception, pregnancy testing, pregnancy, breastfeeding, and fertility also applies to this combination regimen (refer to the prescribing information of the co-administered medicinal product for additional information).

2.7 Recent clinical trials with 8 weeks of treatment containing DAAs

The protease inhibitor ABT-450 with ritonavir (ABT-450/r), the nonnucleoside polymerase inhibitor ABT-333, and ribavirin showed efficacy against the hepatitis C virus (HCV) in a pilot study involving patients with HCV genotype 1 infection. The addition of another potent agent, the NS5A inhibitor ABT-267, may improve efficacy, especially in difficult-to-treat patients. This study was designed to evaluate multiple regimens of direct-acting antiviral agents and ribavirin in patients with HCV genotype 1 infection without cirrhosis who had not received therapy previously or who had no response to prior therapy with pegylated interferon and ribavirin.
In this phase 2b study of interferon-free antiviral regimens, the treatment regimens were associated with rates of sustained virologic response at 24 weeks after treatment that ranged from 83 to 100%. Among previously untreated patients, the rate of treatment failure was lower among those receiving three direct acting agents plus ribavirin for 12 weeks than among those who received the same regimen for only 8 weeks and among those who received fewer agents; extending the treatment to 24 weeks offered no further benefit. The rate of sustained virologic response at 24 weeks after treatment was 88% in the subgroup that received 8 weeks of therapy and 95% in the subgroup that received 12 weeks of therapy (difference between 8-week and 12-week subgroups, −7 percentage points; 95% confidence interval, −19 to 5; P = 0.24). The higher number of relapses among patients in the 8-week treatment group (in 10 of 80 patients, vs. in 1 of 79 patients in the 12-week treatment group) and the absence of resistance-associated variants in most patients who had a relapse in the 8-week treatment group suggest that 8 weeks of treatment might not be sufficient to eradicate the susceptible HCV population in these patients.
Treatment durations longer than 8 weeks were not associated with a less favorable safety profile (21).

In a phase 3 trial involving previously untreated patients with HCV genotype 1 infection without cirrhosis to explore the feasibility of shortening the treatment duration. It was assessed the single-tablet regimen of ledipasvir– sofosbuvir administered for 8 weeks, with or without ribavirin (Ribasphere, Kadmon Pharmaceuticals), as compared with ledipasvir–sofosbuvir alone administered for 12 weeks.

In conclusion of this phase 3 trial, 8 weeks of treatment with a single-tablet regimen of ledipasvir–sofosbuvir resulted in a high rate of sustained virologic response among previously untreated patients with HCV genotype 1 infection without cirrhosis. Indeed, the SVR was 94 % (95% confidence interval [CI], 90 to 97). This results show that ribavirin worsens the treatment burden without enhancing efficacy. A 12 weeks duration of treatment with ledipasvir–sofosbuvir was not more effective than 8 weeks of treatment. The uniformly high rates of response in all the patient subgroups suggest the efficacy of this regimen across a broad range of previously untreated patients with HCV genotype 1 infection without cirrhosis. The 8-week regimen of ledipasvir–sofosbuvir has not been evaluated in patients with cirrhosis (12).

In a phase 2 study of treatment-naive noncirrhotic patients treated by Sofosbuvir With Velpatasvir in Genotype 1 to 6 Hepatitis C Virus Infection, Rates of SVR were lower with 8 weeks versus 12 weeks of treatment in patients with HCV genotype 1 or 2 infection. More particularly for genotype 1, SVR was 85% (95% CI). The small sample size and limited number of virologic failures in each treatment group precluded analysis of the association between viral load and virologic failure. The high SVR rates achieved with 12 weeks of treatment, even in patients with pretreatment RAVs, may indicate that the 12-week regimen is more efficacious for patients with negative predictors, such as baseline resistance (22).

High efficacy was also demonstrated in treatment-naive, non-cirrhotic (F0-F3) GT1b infected patients in 8 weeks of treatment by EBR/GZR.

Indeed, in the Protocol 035/C-WORTHY trial (Cf ANNEXE n°1), treatment-naïve subjects with genotype 1b CHC without cirrhosis were treated with GZR + EBR with or without RBV for 8 weeks. In subjects treated with GZR + EBR without RBV, the subjects had a median age of 56 years (range: 28 to 71); 42% of the subjects were male; 81% were White; 19% were Black or African American; 3% were Hispanic or Latino; mean body mass index was 28 kg/m2; 87% had baseline HCV RNA levels greater than 800,000 IU/mL; and 90% had non-C/C IL28B alleles (CT or TT). By liver biopsy or non-invasive tests, all were non-cirrhotic and 94% (29/31) had METAVIR scores of F0-F2 and the other 2 subjects had a METAVIR score of F3.

Overall SVR was achieved in 94% (29/31) in treatment-naïve subjects with genotype 1b without cirrhosis who received GZR + EBR for 8 weeks. Two of the thirty-one subjects did not achieve SVR due to relapse. SVR was achieved in 97% (28/29) of subjects with METAVIR scores of F0-F2 and 50% (1/2) subjects with METAVIR score of F3. The addition of RBV was not shown to improve the treatment outcomes observed with GZR + EBR (23,24).

A summary of this studies are presented in the table 4 :

Table 4 : Summary of treatment studies of genotype 1 patients during 8 weeks and without cirrhosis

Treatment combination	SVR Genotype 1b	SVR Genotype 1	Comments
Elbasvir + Grazoprevir	97% (29/31)	NA	F0-F2 patients
3D Abbvie +/- RBV	NA	88% (70/80)	F2- F3 patients
Sofosbuvir + Ledipasvir	98% (42/43)	94% (202/215) *	F0-F3 patients * F3 (19%); Genotype 1a : 80%; Genotype 1b : 20%
Sofosbuvir + Velpatasvir(100mg)	NA	84% (51/60)	F0-F3 patients

Results of these studies suggest that 8 weeks of treatment with EBR/GZR combination might be sufficient to eradicate the susceptible HCV population in treatment-naive, non-severe fibrosis (F0-F2) GT1b infected patients (12,21–25).

2.8 Rationale for the Trial

Details regarding specific benefits and risks for subjects participating in this clinical trial may be found in the accompanying Investigators Brochure (IB) and Informed Consent documents.

2.8.1 Overview of Efficacy Endpoints

The primary measurement for efficacy in this study is the plasma HCV RNA level. Long term suppression of HCV RNA, typically reported as Sustained Virologic Response (SVR), has been associated with improved outcomes in subjects with chronic hepatitis C infection as measured by biochemical and histological remission of liver disease. Though long term outcome data are limited, most available data suggest that SVR following antiviral therapy reduces the risk of progression to cirrhosis and may prevent the development of severe liver complications and improve survival (26).

The primary evaluation of efficacy in this trial is based on SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy). The primary endpoint used in Phase III trials for all currently approved anti-HCV therapy has been based on SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy). However, a high degree of concordance has been observed between SVR_{12} and SVR_{24} (27) , and SVR_{12} is increasingly being used as the primary endpoint in more recent Phase III trials. Therefore, it is appropriate to use SVR_{12} as the primary efficacy endpoint in this trial; SVR_{24} will be a key secondary efficacy endpoint.

Other secondary evaluations of efficacy are based on SVR_4 (Sustained Virologic Response 4 weeks after the end of all study therapy), HCV RNA measurements at Week 2, Week 4, and end of treatment visit (Week 8).

2.8.2 Measurements of HCV RNA

HCV-RNA levels in plasma will be measured using the Roche COBAS™ Taqman™ HCV Test, v2.0 for use with the High Pure system or ABBOTT Amplification Reagent Real Time kit HCV on blood samples drawn from each subject at various time points, prior to, during, and after dosing, as indicated in the Study Flow Chart (Section 7). Samples will be collected and processed as per provided instructions.

Results from samples collected at the screening visit are used to determine eligibility. Samples collected at other time points are used for efficacy analyses. They are also used to identify subjects who meet virologic failure criteria.

The Roche COBAS™ Taqman™ HCV Test, v2.0 ® for use with the High Pure system assay has a lower limit of detection and quantitation (LLoQ) of 15 IU/mL.
The ABBOTT Amplification Reagent Real Time kit HCV has a lower limit of quantitation and detection of 12 IU/mL.

2.8.3 Definition of Efficacy Endpoints

Efficacy will be defined at different timepoints during the trial. Specific endpoints are:
a) SVR_4 (Sustained Virologic Response 4 weeks after the end of all study therapy). The subject has HCV RNA <LLoQ [either TD(u) or TND] 4 weeks after the end of all study therapy

b) SVR_{12} (Sustained Virologic Response 12 weeks after the end of all study therapy): The subject has HCV RNA <LLoQ [either TD(u) or TND] 12 weeks after the end of all study therapy.

c) SVR_{24} (Sustained Virologic Response 24 weeks after the end of all study therapy). The subject has HCV RNA <LLoQ [either TD(u) or TND] 24 weeks after the end of all study therapy.

2.8.4 Definition of Virologic Failure: Futility, Virologic Breakthrough, Rebound, and Relapse

Lack of efficacy at different timepoints in the trial will be categorized as:

- Futility:

Subject has HCV RNA LLoQ [TD(q)] at treatment Week 4 with confirmation. The results of the next available blood draw will be used as the confirmatory test. This confirmatory test must be obtained within 2 weeks. Futility is defined as HCV RNA ≥25 IU/mL from the confirmatory test.

- Rebound

Subject has a rebound defined as >1 $\log_{10}$ increase in HCV RNA from nadir while on treatment and confirmed from a separate blood draw within 2 weeks.

- Virologic breakthrough:

Subject has a confirmed HCV RNA ≥ LLOQ [TD(q)] after being < 25 IU/mL previously [TD(u) or TND]. Confirmation is defined as an HCV RNA ≥ LLoQ from a separate blood draw repeated within 2 weeks.

- Relapse:

Subject has a confirmed HCV RNA ≥ LLoQ [TD(q)] following end of all study therapy, after becoming undetectable (TND) at end of treatment. Confirmation is defined as an HCV RNA ≥ LLoQ from a separate blood draw repeated within 2 weeks.

2.8.5 Safety Endpoints

The safety and tolerability of EBR/GZR combination will be assessed by a clinical evaluation of adverse experiences and other study parameters including vital signs, physical examinations, and standard laboratory safety tests at appropriate time points as specified in the Study Flow Chart (Table 7). Adverse experiences are graded and recorded according to Section 8.2.4/Table 9. Subjects may be asked to return for unscheduled visits in order to perform additional safety monitoring.

3. OBJECTIVES

3.1 Primary objective

The primary objectives of this study are as follows:

- To evaluate the efficacy of of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non- severe fibrosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR 12).
- To evaluate the safety and tolerability of EBV/GZR treatment

3.2 Secondary objective

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure
- To evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment.
- To evaluate the emergence of viral resistance to EBR/GZR during treatment and after cessation of treatment

4. STUDY DESIGN

4.1 Trial Design

This is a multi-site, open-label evaluating the efficacy of GRAZOPREVIR (100 mg - second-generation protease inhibitor) in combination with ELBASVIR (50 mg - NS54A inhibitor), in treating non-cirrhotic, treatment-naïve (TN) subjects with chronic hepatitis C (CHC) infection with genotypes 1b to be conducted in conformance with Good Clinical Practice.

Approximately 120 subjects will be enrolled in this study.
There will be one treatment group with EBR/GZR (50/100 mg) once daily without regards to food for 8 weeks.

Several measures have been included in order to limit risk to the study subject.

- Subjects will be discontinued from all study therapy (where applicable) if they meet any of the criteria for discontinuation (details in Section 5.4).

- Study therapy will also be discontinued for subjects who meet criteria for virologic failure (defined in section 2.8.4).

- In the event there is an unacceptable rate of virologic failure (details in section 2.8.4) or discontinuation of study medications due to safety concerns, the treatment or the entire study may be terminated.

Specific procedures to be performed during the trial, as well as their prescribed times and associated visit windows, are outlined in the Trial Flow Chart - Table 7 Details of each procedure are provided in Section 8.1 – Trial Procedures.

4.2 Study category

This is a Clinical trial of investigational medicinal products.

5. STUDY POPULATION

5.1. Subject Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible for participation in this study:

1 - Willing and able to provide written informed consent

2 - Male or female, age ≥ 18 years

3 - Body Mass Index (BMI) ≥ 18 kg/m2

4 - HCV RNA ≥ 10^4 IU/mL at Screening

5- Chronic HCV infection (≥ 6 months) documented by prior medical history or liver biopsy, only genotype 1b virus. (Positive for anti HCV antibody, HCV RNA, or an HCV genotype)

6 - Treatment-naïve with no prior exposure to any IFN, RBV, or approved or experimental HCV-specific DAA

7- Non severe fibrosis (F < 2) according to combination of this two tests :

- **Fibroscan® lower than 9.5 kPa AND Fibrotest lower than 0.59**

8 - Females of childbearing potential (as defined in protocol Appendix 4) must have a negative serum pregnancy test at screening and a negative urine pregnancy test on Day 1 prior to enrollment

9 - Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use 2 effective method(s) of contraception from at least two weeks prior to Day 1 through 14 days after the last dose of study drugs.
If acceptable by local regulatory agencies, methods of birth control allowed in the study are: intrauterine device (IUD), diaphragm with spermicide, hormonal contraceptives (e.g., birth control pills, transdermal patch, or injectables), contraceptive sponge, female condom, male condom with spermicide or vasectomy.
Note: Periodic abstinence (e.g., abstinence only on certain calendar days, abstinence only during ovulation period, use of symptothermal methods, use of post-ovulation methods and withdrawal) are not acceptable methods of contraception.

10 - A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subjects who is not of reproductive potentials is defined as one who has either 1) reached natural menopause (defined as 12 months with no menses without an alternative medical cause), 2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.

11 - A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.

12 - Lactating females must agree to discontinue nursing before starting study drug

13 - Subject must be of generally good health, with the exception of chronic HCV infection, as determined by the Investigator

14 - Subject must be able to comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments

5.2 Subject Exclusion Criteria

Subjects who meet **any** of the following exclusion criteria are **not** to be enrolled in this study.

1 - Is under the age of legal consent, is mentally or legally incapacitated, has significant emotional problems at the time of pre-study screening visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder which, in the opinion of the investigator, would interfere with the study procedures.

2 - Current or prior history of any of the following:

a) Clinically significant illness (other than HCV) or any other major medical disorder that may interfere with subject treatment, assessment or compliance with the protocol; subjects currently under evaluation for a potentially clinically significant illness (other than HCV) are also excluded

b) Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug

c) Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy

d) History of decompensation (e.g., clinical ascites, encephalopathy, and/or variceal hemorrhage)

e) Solid organ transplantation (including hematopoietic stem cell transplants) other than cornea and hair.

f) Significant cardiac disease

g) Unstable psychiatric condition including hospitalization, suicidal attempt, and/or a period of disability as a result of their psychiatric illness within 2 years prior to Screening

h) Malignancy within the 5 years prior to Screening, with the exception of specific cancers that have been cured by surgical resection (e.g., basal cell skin cancer, etc.). Subjects under evaluation for possible malignancy are not eligible

I) Significant drug allergy (e.g., hepatotoxicity)

3 - Subject has the following laboratory parameters at Screening:

a) ALT > 10 x the upper limit of normal (ULN)

b) AST > 10 x ULN

c) Direct bilirubin > 1.5 x ULN

d) Platelets < 75,000/µL

e) HbA1c > 8.5%

f) Creatinine clearance < 50 mL/min as calculated by the Cockcroft-Gault equation

g) Hemoglobin < 10 g/dL

h) Albumin < 3 g/dL

i) INR > 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regime affecting INR

4 - Chronic liver disease of a non-HCV etiology (e.g., hemochromatosis, Wilson's disease, alfa-1 antitrypsin deficiency, cholangitis)

5 - Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)

6 - Clinically-relevant alcohol or drug abuse within 12 months of Screening.

a. Alcohol, intravenous drugs, inhalational (not including marijuana), psychotropic, narcotics, cocaine use, prescription or over-the-counter drugs: within 1 year of the screening visit, or if shorter, is judged by investigator to be capable of complying with study procedures
b. receiving opiate agonist substitution therapy within 1 year of screening visit, or if shorter, is judged by investigator to be capable of complying with study procedures
c. history of marijuana use if deemed excessive by a physician investigator or interferes with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must agree to discontinue any current use of recreational marijuana prior to entry into trial and throughout the trial period

   A positive drug screen will exclude subjects unless it can be explained by a prescribed medication; the diagnosis and prescription must be approved by the investigator

7 - Use of any prohibited concomitant medication listed in Section 9.8 of this protocol within 2 weeks prior to day 1.

8 - Known hypersensitivity to the study drug, the metabolites, or formulation excipient

9 - Is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent and is not willing to refrain from participating in another study. Collection of additional blood, urine, or tissue samples or additional data,

beyond that specified in this protocol, is prohibited (other than that related to subject's medical care).

10 - (female) is pregnant, lactating, expecting to conceive or donate eggs, or is of childbearing potential and unwilling to commit to two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criteria); or male subject is planning to impregnate or provide sperm donation or has a female sexual partner of childbearing potential and is unwilling to commit to using a two methods of birth control throughout treatment and after the completion of all treatment (see Inclusion Criteria).

11 - Had a life-threatening SAE during the screening period.

12 - Is a member or a family member of the investigational study staff or sponsor staff directly involved with this study.

13 - Has evidence or history of chronic hepatitis not caused by HCV, including but not limited to nonalcoholic steatohepatitis (NASH), drug-induced hepatitis, and autoimmune hepatitis.

NOTE: Subjects with history of acute non-HCV-related hepatitis, which resolved > 6 months before study entry, may be enrolled.

14 - For subjects diagnosed with diabetes mellitus, documented HbA1c >8.5% (to exclude uncontrolled diabetes).

15 - Has any of the following conditions:.

- Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).
- Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the trial.

16 - Has exclusionary laboratory values as listed below (see Table 5 for unit conversions of some laboratory values specified below):

Note: If any of the laboratory exclusion criteria below are met, the site may have the abnormal value retested one time.

Table 5 : Exclusionary laboratory values

Laboratory Assessment	
hemoglobin	< LLN (lower limit of normal) of labora=tory reference range
neutrophils	$<1.5 \times 10^3/\mu L$ ($<1.2 \times 10^3/\mu L$ for Blacks)
platelets	$<75 \times 10^5/\mu L$
direct bilirubin	>1.5 x ULN
Total Bilirubin	>1.6 mg/dL unless history of Gilbert's disease. (If Gilbert's disease is the proposed etiology, this must be documented in the subject's chart)

Serum Albumin	< 3.0 g/dL (lower limit of normal) of laboratory reference range
creatinine clearance	<50 mL/min
INR	>1.5
ALT	>350
AST	>350

5.3 Considerations for study visits

Procedures visits should be scheduled as close to the indicated study days and study weeks as possible. See the Study Flow Chart in Section 7 for a complete listing of study procedures required at each visit.

5.4 Subject Withdrawal/Discontinuation Criteria

Subjects may withdraw consent at any time for any reason or be dropped from the trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrollment into the trial is inappropriate, the trial plan is violated, or for administrative and/or other safety reasons.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent. Discontinuation from treatment is permanent. Once a subject has discontinued treatment, even though he/she continues to be monitored in the trial, he/she shall not be allowed to begin treatment again.

A subject must be discontinued from the trial for any of the following reasons:

- The subject or legal representative (such as a parent or legal guardian) withdraws consent.
- Request of the subject (subjects have the right to discontinue treatment at any time for any reason).

A subject must be discontinued from treatment (but may continue to be monitored in the trial) for any of the following reasons:

- Subject meets any virologic failure criteria (see section 2.8.4 for definitions of virologic failure)
- Suicidal or homicidal ideation or attempt.
- Severe depression.

- Subject has a positive test for nonprescription opiates, methamphetamines, or cocaine.
- Subject becomes pregnant during the trial.
- A physician investigator feels it is in best interest of the subject to discontinue.
- The subject's ALT or AST increases to >500 IU/L.
- The subject's ALT or AST increases to >3x baseline, is >100 IU/L, and there is a simultaneous increase in total bilirubin >2x ULN and/or INR >1.5.
- The subject's ALT or AST increases to >3x the nadir value, is >100 IU/L, and there is a simultaneous increase in total bilirubin > 2x ULN and/or INR >1.5.
- The subject's ALT or AST increases to >3x baseline, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following adverse experiences that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to EBV/GZR (50/100 mg): nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).
- The subject's ALT or AST increases to >3x the nadir value, is >100 IU/L, and is temporally associated with the new onset or worsening of any of the following adverse experiences that are of moderate or severe intensity and deemed by the investigator to be at least possibly related to EBV/GZR (50/100 mg): nausea, vomiting, right upper quadrant pain or tenderness, and/or eosinophilia (>5%).
- The subject's alkaline phosphatase increases to >3x ULN, there is a simultaneous increase in total bilirubin > 2x ULN and other causes of elevated alkaline phosphatase are excluded.
- The subject's alkaline phosphatase increases to >5x ULN and other causes of elevated alkaline phosphatase are excluded.
- A subject **may** be discontinued from treatment for any of the following reasons:

  SAE assessed by the physician investigator as possibly or probably related to study medication. Investigator may continue the subject in the trial, if it is deemed to be in the best interest of the subject to stay on the study treatment.

  Failure to comply with the dosing, evaluations, or other requirements of the trial.

5.4.1 Subject Replacement Strategy

A subject that discontinues from the trial will not be replaced except if the subject is a screen fail or wrongly included. The screen fail rate is estimated at around 20%, so we plan to include about

145 patients in the study (patient who signed the informed consent form).

5.4.2 Beginning and End of the Trial

The overall trial begins when the first subject signs the informed consent form. The overall trial ends when the last subject completes the last trial visit, discontinues from the trial or is lost to follow-up (i.e. the subject is unable to be contacted by the investigator).

6. STUDY METHODOLOGY

6.1 Entry Criteria

6.1.1 Primary endpoint

The primary efficacy endpoint is the proportion of subjects with SVR12 (HCV RNA < LLOQ 12 weeks after cessation of treatment) in the full analysis set

6.1.2 Secondary Endpoint

The secondary objectives of this study are as follows:

- To determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24)
- To evaluate the proportion of subjects with virologic failure

6.2 Trial Treatment(s)

The treatments to be used in this trial are outlined below in Table 6

Table 6 : Trial Treatment

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Grazoprevir(GZR)°	100 mg	QD	Oral	8 Weeks	Experimental
Elbasvir (EBV)	50 mg	QD	Oral	8 Weeks	Experimental

Elbasvir/Grazoprevir

Subjects will receive treatment with EBV/GZR (50/100 mg) fixed dose combination once-daily (QD) orally. Study therapy will be supplied once during the treatment period at Day 1. Subjects will be instructed to take their daily medications as instructed on the bottle labels.

6.2.1 Dose Selection/Modification

6.2.1.1 Dose Selection

The rationale for selection of doses to be used in this trial is provided in Section 2 - Background.

6.2.1.2 Dose Modification

Dose modification of EBR/GZR is not permitted.

If for any reason EBR/GZR need to be interrupted, the medication may be interrupted for up to 3 days. If the drugs are interrupted for more than 3 days, all treatment should be discontinued.

6.2.2 Timing of Dose Administration

EBV/GZR 50/100 mg fixed dose

Subjects will be instructed to take EBR/GZR 50/100 mg fixed dose orally, once daily without regards to food for 8 weeks

If a subject misses a dose of EBR/GZR 50/100 mg fixed dose and if less than 8 hours remain before the next dose is to be taken, the missed dose should be skipped, and the normal dosing schedule should be resumed. Subjects should not double the next dose to compensate for the missed dose.

6.2.3 Trial Blinding/Masking

This is an open-label trial; therefore, the Sponsor, investigator and subject will know the treatment administered.

6.3 Rescue Medications & Supportive Care

No rescue or supportive medications are specified to be used in this trial.

7 TRIAL FLOW CHART

Visit No.	1	2	3	4	5	6	7	8		
Study Period		Treatment Weeks				Follow-Up Wks			Unscheduled	
STUDY PROCEDURES	Scr	Day 1[4]	2	4	8	FU4	FU 12	FU 24	Unsched/ Viral Fail Conf Visit	Early Discon Visit
ADMINISTRATIVE PROCEDURES										
Informed Consent	x									
Inclusion/Exclusion Criteria	x									
Medical History	x									
Prior and Con-med Review	x	x	x	x	x	x	X	X	x	x
DRUG ADMINISTRATION										
EBV/GZR dispensation[5]		x								
EBV/GZR compliance[5]			x	x	x					
CLINICAL SAFETY EVALUATIONS										
Physical Examination[1]	x	x			x					x
Weight	x	x	x	x	x	x	x	x	x	x
Height	x									
Fibroscan®	x									
Vital Signs	x	x	x	x	x	x	x	x	x	x
Confirmation of Birth Control	x	x	x	x	x	x	x	x	x	x
Review (Serious) Adverse Events[2]	x	x	x	x	x	x	x	x	x	x
LABORATORY SAFETY EVALUATIONS										
Coagulation	x	x			x				x	x
Fibrotest®	x									
Chemistry & Hematology	x	x	x	x	x	x			x	x
HCV, HIV, HBV testing	x									
HCV Genotyping	x									
HCV RNA Level	x	x	x	x	x	x	x	x	x	X[6]
Urine Analysis	x									
Urine Pregnancy Test (females of child bearing potential only)[3]	x	x		x	x	x	x	x	x	x

[1] A comprehensive PE will be done at screening and baseline (Day 1). For all other visits focused PE will be conducted if necessary

[2] Review of Adverse Events should include collecting serious adverse events and Events of Clinical Interest throughout the study, and collecting all adverse events Day 1(post-dose) through 14 days following the last dose of study drug. Adverse events occurring prior to study drug administration or after study drug discontinuation, as a result of a protocol-specified procedure or intervention, should also be reported.

[3] When study visits are spaced more than one month apart in the follow-up period, urine pregnancy test kits will be dispensed to female subjects of childbearing potential so that **monthly** pregnancy testing can continue for 6 months post dosing. The test results must be provided to the investigator and/or site personnel. Subjects should be instructed to contact the investigator and/or site personnel immediately if the result of the self-pregnancy test is positive.

[4] Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.

[5] EBV/GZR will be provided at the baseline visit.

[6] If HCV RNA is collected during viral failure confirmation visit and the subject is confirmed viral failure during therapy (i.e. breakthrough/rebound), then the sample collection for HCV RNA is not needed for the early discontinuation visit

8. STUDY PROCEDURES

8.1 Trial Procedure

The Trial Flow Chart - Section 7 summarizes the trial procedures to be performed at each visit. Individual trial procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator.

Furthermore, additional evaluations/testing may be deemed necessary by the investigator and or the Sponsor for reasons related to subject safety. In some cases, such evaluation/testing may be potentially sensitive in nature (e.g., HIV, Hepatitis C, etc.), and thus local regulations may require that additional informed consent be obtained from the subject. In these cases, such evaluations/testing will be performed in accordance with those regulations.

8.1.1 Administrative Procedure

8.1.1.1 Informed Consent

The investigator must obtain documented consent from each potential subject prior to participating in a clinical trial.

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the trial.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the trial. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a trial and the trial population will be added to the consent form template at the protocol level.

The informed consent will adhere to CPP/ANSM requirements, applicable laws and

regulations and Sponsor requirements.

8.1.1.2 Inclusion/Exclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the trial.

8.1.1.3 Subject Identification Card

All subjects will be given a Subject Identification Card identifying them as participants in a research trial. The card will contain trial site contact information (including direct telephone numbers) to be utilized in the event of an emergency. The investigator or qualified designee will provide the subject with a Subject Identification Card after the subject provides written informed consent.

8.1.1.4 Medical History

A medical history will be obtained by the investigator or qualified designee.
Medical history, including details regarding illnesses and allergies (including sulfa-containing drug allergy), date(s) of onset, and whether condition(s) is currently ongoing, and medication history will be collected on all subjects during screening.

8.1.1.5 Prior and Concomitant Medications Review

8.1.1.5.1 Prior Medications

The investigator or qualified designee will review prior medication use, including any protocol-specified washout requirement, and record prior medication taken by the subject within 30 days before starting the trial.

8.1.1.5.2 Concomitant Medications

The investigator or qualified designee will record medication(s), if any, taken by the subject during the trial.

8.1.1.6 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject for all procedures that occur prior allocation. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit.

All eligible subjects will be allocated and will receive a study number. This number identifies

the subject for all procedures occurring after treatment allocation. One number is assigned to a subject; it can never be re-assigned to another subject. A single subject cannot be assigned more than 1 number.

8.1.1.7 Trial Compliance

The investigator/study coordinator will be responsible for entering the subject's identification, visit number. The subject will be instructed to record dates/times and the number of tablets of study drug doses (EBR/GZR 50/100mg) on the diary card for the entire time period. At visits when used/unused study medications are returned, site personnel must verify the accuracy of the dosing diary by comparing entries with amounts of returned study medication. If a discrepancy is noted, investigator/study coordinator must discuss the discrepancy with the subject, and the explanation must be documented. Only the subject shall make any changes to the entries on the diary card. The subject will initial the diary card to confirm that the information is accurate. The investigator/study coordinator will be responsible for transferring the appropriate information from the diary card onto the appropriate case report form.

8.1.2 Clinical Procedures/Assessments

8.1.2.1 Physical Examination

All physical examinations must be performed by the principal investigator or sub-investigator (physician, physician assistant or nurse practitioner).

A complete physical examination performed at screening, Day 1 and Week 8 (end of treatment), includes the following assessments: general appearance, head, eyes ears/nose/ throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. For all other visits a focused exam will be performed when clinically indicated. Any significant changes between the screening visit and Day 1 should be noted in the Medical History eCRF. Any significant changes after receiving study therapy at Day 1 must be reported as adverse events and entered on the adverse event eCRF.
If the subject is discontinued for any reason (Early Discontinuation Visit) during the treatment phase, every attempt should be made to perform a final physical examination.

8.1.2.2 Weight and Height Assessment

The subject's weight should be assessed as noted in the flow chart (screening, day 1, Week 8 and post treatment week 4, 12 and 24). The subject height should be measured at screening only. Clinically significant changes from Day 1 should also be captured as AEs in the CRF.

8.1.2.3 Fibroscan ®

The subject eslastography was realized as noted in the flow chart, at the screening Day only. It is a non-invasive method to determine presence or absence of cirrhosis. Fibroscan® uses elastography, which is a technique similar to ultrasound that measures the stiffness of your liver. The absence of cirrhosis is a result of FibroScan ≤ 12.5 kPa. For this study, subject must have Fibroscan® lower than 9.5 kPa to be randomized.

During the procedure the Fibroscan® uses an ultrasound probe which emits a mechanical pulse at the surface of the skin, measuring the condition of the liver through sound waves. The data is analyzed by a computer which displays a two-dimensional picture of the liver. The level of the fibrosis can be measured in relation to the stiffness of the liver – so the harder the liver is, the more serious the fibrosis is likely to be.

8.1.2.4 Vital Signs

Vital signs will include heart rate (sitting), blood pressure (sitting), and oral temperature. Subjects should be resting in a semi-recumbent position for at least 10 minutes prior to having vital sign measurements obtained.
Note: Oral temperatures should be taken, but if oral is not possible, tympanic, rectal, and axillary temps may be taken.
After the screening visit, the site should indicate whether or not the results are clinically significant. Any subsequent changes constitute an adverse experience.

8.1.2.5 Birth Control Confirmation

Extreme care must be taken to avoid pregnancy in female subjects of childbearing potential and female partners of male subjects of childbearing potential.
Site personnel should confirm that subjects and their partner(s) are using acceptable methods of contraception. This assessment must be documented in the subject's study chart at each specified visit.

8.1.2.6 Adverse Events

During the screening period only SAEs should be recorded.

The principal investigator or sub-investigator (physician, physician assistant or nurse practitioner) must determine the severity and relationship to study medication(s) of all adverse events. A physician investigator must review, initial and date the severity of all adverse events and their relationship to study medications when initial assessment of an adverse event is made by a physician assistant or nurse practitioner. Designated medical practitioners must be licensed and the responsibilities transferred to them must be documented in the site file. For details please refer to Table 9.

8.1.3 Laboratory Safety Evaluations

Details regarding specific laboratory procedures/assessments to be performed in this trial are provided below. The total amount of blood to be collected by visits is between 45 to 75 mL over the course of the trial (from pre-trial to post-trial visits).

Coagulation: INR, Prothrombin time (PT) Activated partial thromboplastin time (APTT)

Hematology : Hematocrit, Hemoglobin (Hb), Platelet Count, Red blood celle count (RBC), White blood cell count (WBC) with differential (absolute and percentage) including Lymphocytes, Monocytes, Neutrophils, Eosinophils, Basophils, Reticulocytes count and MCV.

Chemistry : Alanine aminotransferase (ALT/SGPT), Aspartate aminotransferase (AST/SGOT), Albumin, Alkaline Phosphatase, Creatine Kinase, Creatinine, Total Bilirubin (reflex to Direct Bilirubin), Glucose, Lipase, Potassium, Sodium, Direct Bilirubin at screening only, Hemoglobin A1c (HbA1c), Fibrotest®, Urea, Hyaluronic Acid.

Virological Tests : Serologies for HCV, HBV and HIV. HCV RNA will measured using the Cobas® Taqman® HCV Test, v2.0 for use with Ampliprep. HCV genotype and subtype will be determined using classic local process. Samples for HCV genotype evaluation must be obtained as part of the main consent for inclusion in the study in each local laboratory

Blood must be drawn from each subject as part of the main consent to assess HCV RNA plasma levels at various time points as shown in the flow chart. HCV-RNA in plasma will be measured using a COBAS™ Taqman™ HCV Test, v2.0 ® assay for use with the High Pure System with a lower limit of detection and quantification of 15 IU/mL or using ABBOTT Amplification Reagent Real Time HCV with limit of detection and quantification of 12 IU/mL.

Urinalysis : Appearance, Blood, Color, Glucose, Leukocyte esterase, pH, Protein, Urobilinogen, Reflex to microscopic urinalysis if dipstick result is abnormal.

Urine Pregnancy Test : Serum beta-hCG ou urine beta-hCG (if positive, requires immediate confirmation with Serum β-hCG). All females of childbearing potential will have a serum pregnancy test at Screening. Urine pregnancy testing will occur at Day 1 and every 4 weeks during the dosing period and for 30 days following the last dose of study drug. If required by local regulations, additional pregnancy tests beyond 4 weeks may be added. In the event of a positive urine pregnancy result, subjects will be instructed to stop study drug immediately (if applicable) and return to the clinic as soon as possible for a serum pregnancy test.

Laboratory tests for hematology, chemistry and additional testing are specified in Table 8.

Table 8 : Laboratory Tests during trial

Hematology	*Chemistry*	*Other*
Hematocrit	*Albumin*	
Hemoglobin	*Alkaline phosphatase*	*HBsAg*
Platelet count	*Alanine aminotransferase (ALT)*	*Hepatitis C Virus Genotype*
WBC (total and differential)	*Aspartate aminotransferase (AST)*	*Prothrombin time (PT)*
Erythrocytes (RBC count)	*Glucose*	*APTT*
	Urea	*Hyaluronic Acid*
Reticulocytes	*Creatinine*	*International normalized Ratio (INR)*
	Creatinine clearance (screening only)	*Choriogonadotropin Beta (Urine pregnancy test kits to sites)*
	Creatine Kinase	*HCV RNA assay*
	Potassium	*Fibrosure® (Fibrotest) as requested by site for entry critiera (may be performed locally)*
	Sodium	*Plasma HIV RNA*
	Total Bilirubin	*HbA1c*
	Direct Bilirubin	
	Glycemia	
	Lipase	

8.1.4 Other Procedures

8.1.4.1 Rescreening

Subjects who have previously completed the screening visit (Visit 1) and were deemed eligible for randomization into this study, but failed to be randomized within the 28-days window, may be rescreened to re-evaluate study eligibility. To reconfirm the subject eligibility, all pre-study evaluations should be repeated, after approval from the SPONSOR.

The screening window can be extended to 42 days for subjects requiring a liver biopsy, or for extenuating circumstances, with sponsor approval.

Note: Subjects may be retested once within the 28-days screening window if their laboratory results are outside the specified criteria. If any of the laboratory exclusion criteria are met, the site may have the abnormal value retested one time only.

8.1.4.2 Withdrawal/Discontinuation

When a subject discontinues/withdraws from participation in the trial, all applicable activities scheduled for the early discontinuation visit should be performed at the time of discontinuation. Any adverse events which are present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 8.2 - Assessing and Recording Adverse Events.

8.1.4.3 Blinding/Unblinding

This is an open label trial; there is no blinding for this trial.

8.1.5 Visit Requirements

Visit requirements are outlined in Section 7 - Trial Flow Chart. Specific procedure-related details are provided above in Section 8.1 - Trial Procedures.

8.1.5.1 Screening (Visit 1)

During a 28 days period prior to administration of the initial dose of study drug, potential subjects will be evaluated to determine if they fulfill the Inclusion/Exclusion entry requirements as described in Section 5.1 and 5.2

Subjects will be instructed that they are required to use two acceptable methods of birth control from at least 2 weeks prior to Day 1, throughout treatment, and for at least 6 months (or longer if dictated by local regulations) after the last dose of study medication.

All subjects will be given a card, at the time of screening, identifying them as participants in a research study. The card will contain contact information (including direct telephone numbers) to be utilized in the event of an emergency.

The following procedures will be performed and documented

- Obtain informed consent
- Determine inclusion/exclusion criteria
- Obtain medical history
- Obtain details of Prior and Concomitant medications
- Perform complete physical examination
- Obtain body height and weight
- Fibroscan®
- Obtain vital signs (resting blood pressure, pulse, respiratory rate and temperature)
- Confirmation of Birth Control
- Obtain details of adverse events related to screening procedures
- Obtain blood sample for test
  Coagulation tests

Fibrotest®
Hematology and chemistry
HCV antibody, HIV antibody, and HBs antigen
Determination of genotype and subtype of HCV
HVC RNA
Serum beta-hCG pregnancy test for females of childbearing potential only

- Obtain urine sample for urinalysis
- Urine pregnancy test for females of childbearing potential only

Subject meeting all the inclusion criteria and none of the exclusion criteria will return to the clinic fort the Baseline/Day 1 visit assessments and randomization.

8.1.5.2 Study/Treatment Visits

8.1.5.2.1 Baseline/ Day 1 (Visit 2)

Day 1 procedures listed on the Study Flow Chart should be performed prior to dosing unless specified otherwise.

The following baseline tests and procedures must be completed prior to the first dose of study drugs :

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for :
  Hematology and chemistry
  Coagulation
  HCV RNA
- Confirmation of birth control
- For female subjects, a urine pregnancy test will be performed at the site prior to study drug initiation. If the urine pregnancy test result is negative, the subject will be eligible for randomization and the remainder of the pretreatment (Day 1) testing/procedures will be performed. If the urine pregnancy test result is positive, the subject must not be randomized.
- Confirm eligibility
- Drug administration (refer section 8.1.5.4):
- Dispense study drugs as directed by the Promotor Pharmacist
  Instruct the subject on the packaging, storage and administration of study drugs
  Observe the subject taking the first dose of study drugs and record the time of first dose

8.1.5.2.2 Week 2 (visit 3 + 3 days)

The following procedures must be completed at the end of Week 2

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for :
  Hematology and chemistry
  HCV RNA
- Review study drug compliance and drug administration instruction with subject

8.1.5.2.3Week 4 (visit 4 + 3 days)

The following procedures must be completed at the end of Week 4

- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for :
  Hematology and chemistry
  HCV RNA
- Obtain urine sample for :
  Beta-HCG pregnancy test for females of childbearing potential only
- Review study drug compliance and drug administration instruction with subject
- Drug administration (refer section 8.1.5.4):

8.1.5.2.4 Week 8 (visit 5 + 3 days)

The following procedures must be completed at the end of Week 8:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood for :
  Hematology and chemistry
  Coagulation
  HCV RNA
- Confirmation of birth control
- Obtain urine sample for :
  Beta-HCG pregnancy test for females of childbearing potential only
- Review study drug compliance and drug administration instruction with subject
- Complete medication pill count

8.1.5.2.5Early termination (ET)/Unscheduled Visit (UV)

A subject should attend an unscheduled visit if requested by the sponsor or the investigator. The assessments are at the investigator's discretion. At all unscheduled visits initiated for the purpose of confirming virologic failure.

The Sponsor and Promotor must be informed as soon as possible, when a subject comes off treatment due to an AE.

If a subject discontinues treatment early for any reason then the following assessments for the Early Termination (ET) Visit must be performed:

- Perform complete physical examination
- Obtain body weight
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for :
  Hematology and chemistry
  Coagulation
  HCV RNA
- Confirmation of birth control
- Obtain urine sample for :
  Beta-HCG pregnancy test for females of childbearing potential only
- Complete medication pill count

8.1.5.3 Post Treatment Assessments

The post treatment Week 4, 12 and 24 visits should be timed from the date of last administration of study drugs. All subjects must be complete the post treatment Week 4 and 12 visits. Subject with HCV RNA < LLOQ at the post treatment week 12 will complete the post treatment Week 24 visit, unless viral relapse is determined.

Female subjects of childbearing potential should be provided with Urine Pregnancy Test Kits, instructed on their use and requested to continue to self-monitor for pregnancy between scheduled study visits, every 4 weeks, for 6 months after their last dose of study drugs. If required by regulations, additional pregnancy test beyond 6 months may be added. The subject will be contracted every 4 weeks and asked to report results of the urine pregnancy tests.

8.1.5.3.1 Post treatment Week 4 (± 5 days)

The following procedures are to be completed for all subjects, 4 weeks after taking the last dose of study drugs :

- Obtain body weight
- Obtain vital signs
- Assessment of AEs and concomitant medications
- Obtain blood samples for :
  Hematology and chemistry

HCV RNA
- Confirmation of birth control
- Obtain urine sample for :
  Beta-HCG pregnancy test for females of childbearing potential only

8.1.5.3.2Post Treatment Week 12 and 24 (+ 5 days)

The following procedures are to be completed 12 and 24 weeks after taking the last dose of study drugs :
- Obtain body weight
- Obtain vital signs
- Assessment of AEs only related to study procedure
- Concomitant medications
- Obtain blood samples for :
  HCV RNA
- Confirmation of birth control
- Obtain urine sample for :
  Beta-HCG pregnancy test for females of childbearing potential only

Subjects with HCV RNA < LLOQ at the post treatment Week 12 Visit will return for the Post treatment Week 24 Visit

8.1.5.4 Drug Administration

Following completion of the Day 1 procedures and confirmation of eligibility, the site pharmacist or study coordinator will contact the Promotor for assignment of the drug to be administered.
Sites should not call the Promotor for drug administration until the subject has met all criteria for the study and is ready to receive the first dose of study medication on Day 1.
The first dose of prescribed study medications should be administered at the Day 1 visit. Subjects who discontinue therapy in the trial prior to the last scheduled treatment visit should have an Early Discontinuation visit and then continue with the follow-up visits.

At a minimum, collect the following information when a subject discontinues from the trial:

1. The reason the subject discontinued.

2. The date of the last dose of study medications from the trial.

3. The date of the last assessment and/or contact. A follow-up contact (telephone or visit) will be arranged as appropriate.

4. (Serious) Adverse events.

5. Final Assessments: Every effort should be made to ensure that all procedures and evaluations scheduled for the Early Discontinuation Visit are performed.

6. Retrieve all study medications from the subject.

8.1.6 Evaluations of Laboratory Safety Signals

Laboratory safety measurements will be evaluated weekly during the first 2 weeks, followed by monthly for the entire treatment period, and during the follow up period to assess potential liver safety signals as outlined in the flow chart.

If a subject has one or more of the laboratory ECI criteria (Refer section 8.1.3) at the last dosing visit then the subject should return to the site weekly for additional monitoring until the values normalize.

8.2 Assessing and Recording Adverse Events

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with *the* use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator medication) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in clinical trials or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

Adverse events may also occur in screened subjects during any pre-allocation baseline period as a result of a protocol-specified intervention, including washout or discontinuation of usual therapy, diet, placebo treatment or a procedure.

All adverse events will be recorded from the time the consent form is signed through 14 days following cessation of treatment and at each examination on the Adverse Event case report forms/worksheets.

8.2.1 Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor

In this trial, an overdose is any dose higher than any intake in excess of prescribed dose per calendar day.

If an adverse event(s) is associated with ("results from") the overdose of Sponsor's product the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

If a dose of Sponsor's product meeting the protocol definition of overdose is taken without any associated clinical symptoms or abnormal laboratory results, the overdose is reported as a non-serious Event of Clinical Interest (ECI), using the terminology "accidental or intentional overdose without adverse effect."

All reports of overdose with and without an adverse event must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

8.2.2 Reporting of Pregnancy and Lactation to the Sponsor

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them), including the pregnancy of a male subject's female partner that occurs during the trial or within 14 days of completing the trial. All subjects and female partners of male subjects who become pregnant must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.

Such events must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

8.2.3 Immediate Reporting of Adverse Events to the Sponsor

8.2.3.1 Serious Adverse Events

A serious adverse event is any adverse event occurring at any dose or during any use of Sponsor's product that:

- Results in death;
- Is life threatening;
- Results in persistent or significant disability/incapacity;
- Results in or prolongs an existing inpatient hospitalization;
- Is a congenital anomaly/birth defect;
- Is a cancer;
- Is associated with an overdose;
- Is an other important medical event

Refer to Table 11 for additional details regarding each of the above criteria

Any serious adverse event, or follow up to a serious adverse event, including death due to any cause that occurs to any subject from the time the consent is signed through 14 days following cessation of treatment or within the established off therapy follow -up period for safety described in the protocol, whether or not related to the Sponsor's product, must be reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binder.

Additionally, any serious adverse event, considered by an investigator who is a qualified physician to be related to the Sponsor's product that is brought to the attention of the investigator at any time outside of the time period specified in the previous paragraph also must be reported immediately to the Sponsor.

All subjects with serious adverse events must be followed up for outcome.

8.2.3.2 Events of Clinical Interest

Selected non-serious and serious adverse events are also known as Events of Clinical Interest (ECI) and must be recorded as such on the Adverse Event case report forms/worksheets and reported within 24 hours to the Sponsor either by electronic media or paper. Sponsor Contact information can be found in the Investigator Trial File Binde.

Events of clinical interest for this trial include:

- an overdose of Sponsor's product, as defined in Section 7.2.1 - Definition of an Overdose for This Protocol and Reporting of Overdose to the Sponsor, that is not associated with clinical symptoms or abnormal laboratory results.

- first instance of ALT or AST >500 IU/L
- first instance of ALT or AST >3x baseline AND >100 IU/L
- first instance of alkaline phosphatase >3x ULN

8.2.4 Evaluating Adverse Events

An investigator who is a qualified physician will evaluate all adverse events with respect to the elements outlined in Table 9. The investigator's assessment of causality is required for each adverse event. Refer to Table 9 for instructions in evaluating adverse events.

Table 9: Evaluating Adverse Events

Maximum Intensity	***Mild***	*awareness of sign or symptom, but easily tolerated (for pediatric trials, awareness of symptom, but easily tolerated)*
	Moderate	*discomfort enough to cause interference with usual activity (for pediatric trials, definitely acting like something is wrong)*
	Severe	*incapacitating with inability to work or do usual activity (for pediatric trials, extremely distressed or unable to do usual activities)*
Seriousness	*A serious adverse event (AE) is any adverse event occurring at any dose or during any use of Sponsor's product that:*	
	*†**Results in death**; or*	
	*†**Is life threatening; or** places the subject, in the view of the investigator, at immediate risk of death from the event as it occurred [Note: This does not include an adverse event that, had it occurred in a more severe form, might have caused death.]; or*	
	*†**Results in a persistent or significant disability/incapacity** (substantial disruption of one's ability to conduct normal life functions); or*	
	*†**Results in or prolongs an existing inpatient hospitalization** (hospitalization is defined as an inpatient admission, regardless of length of stay, even if the hospitalization is a precautionary measure for continued observation. (Note: Hospitalization [including hospitalization for an elective procedure] for a preexisting condition which has not worsened does not constitute a serious adverse event.); or*	
	*†**Is a congenital anomaly/birth defect (**in offspring of subject taking the product regardless of time to diagnosis); or*	
	Is a cancer; or	
	***Is associated with an overdose** (whether accidental or intentional). Any adverse event associated with an overdose is considered a serious adverse event. An overdose that is not associated with an adverse event is considered a non-serious event of clinical interest and must be reported within 24 hours.*	
	***Other important medical events** that may not result in death, not be life threatening, or not require hospitalization may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed previously (designated above by a †).*	
Duration	*Record the start and stop dates of the adverse event. If less than 1 day, indicate the appropriate length of time and units*	
Action taken	*Did the adverse event cause the Sponsor's product to be discontinued?*	
Relationship to Sponsor's Product	*Did the Sponsor's product cause the adverse event? The determination of the likelihood that the Sponsor's product caused the adverse event will be provided by an investigator who is a qualified physician. The investigator's signed/dated initials on the source document or worksheet that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. This initialed document must be retained for the required regulatory time frame. The criteria below are intended as reference guidelines to assist the investigator in assessing the likelihood of a relationship between the test drug and the adverse event based upon the available information.* ***The following components are to be used to assess the relationship between the Sponsor's product and the AE**; the greater the correlation with the components and their respective elements (in number and/or intensity), the more likely the Sponsor's product caused the adverse event:*	
	Exposure	*Is there evidence that the subject was actually exposed to the Sponsor's product such as: reliable history, acceptable compliance assessment (pill count, diary, etc.), expected pharmacologic effect, or measurement of drug/metabolite in bodily specimen?*
	Time Course	*Did the AE follow in a reasonable temporal sequence from administration of the Sponsor's product?* *Is the time of onset of the AE compatible with a drug-induced effect (applies to trials with investigational medicinal product)?*
	Likely Cause	*Is the AE not reasonably explained by another etiology such as underlying disease, other drug(s)/vaccine(s), or other host or environmental factors*

Relationship To Sponsor's Product (continued)	***The following components are to be used to assess the relationship between the Sponsor's product and the AE: (continued)***	
	Dechallenge	*Was the Sponsor's product discontinued or dose/exposure/frequency reduced?* *If yes, did the AE resolve or improve?* *If yes, this is a positive dechallenge. If no, this is a negative dechallenge.* *(Note: This criterion is not applicable if: (1) the AE resulted in death or permanent disability; (2) the AE resolved/improved despite continuation of the Sponsor's product; (3) the trial is a single-dose drug trial); or (4) Sponsor's product(s) is/are only used one time.)*
	Rechallenge	*Was the subject re-exposed to the Sponsor's product in this trial?* *If yes, did the AE recur or worsen?* *If yes, this is a positive rechallenge. If no, this is a negative rechallenge.* *(Note: This criterion is not applicable if: (1) the initial AE resulted in death or permanent disability, or (2) the trial is a single-dose drug trial); or (3) Sponsor's product(s) is/are used only one time.)* *NOTE: IF A RECHALLENGE IS PLANNED FOR AN ADVERSE EVENT WHICH WAS SERIOUS AND WHICH MAY HAVE BEEN CAUSED BY THE SPONSOR'S PRODUCT, OR IF RE-EXPOSURE TO THE SPONSOR'S PRODUCT POSES ADDITIONAL POTENTIAL SIGNIFICANT RISK TO THE SUBJECT THEN THE RECHALLENGE MUST BE APPROVED IN ADVANCE BY THE U.S. CLINICAL MONITOR AND THE INSTITUTIONAL REVIEW BOARD/INDEPENDENT ETHICS COMMITTEE.*
	Consistency With Trial Treatment Profile	*Is the clinical/pathological presentation of the AE consistent with previous knowledge regarding the Sponsor's product or drug class pharmacology or toxicology?*
The assessment of relationship will be reported on the case report forms /worksheets by an investigator who is a qualified physician according to his/her best clinical judgment, including consideration of the above elements.		
Record one of the following*:*	***Use the following scale of criteria as guidance (not all criteria must be present to be indicative of a Sponsor's product relationship).***	
Yes, there is a reasonable possibility of Sponsor's product relationship.	*There is evidence of exposure to the Sponsor's product. The temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable. The AE is more likely explained by the Sponsor's product than by another cause.*	
No, there is not a reasonable possibility of Sponsor's product relationship	*Subject did not receive the Sponsor's product OR temporal sequence of the AE onset relative to administration of the Sponsor's product is not reasonable OR there is another obvious cause of the AE. (Also entered for a subject with overdose without an associated AE.)*	

8.2.5 Sponsor Responsibility for Reporting Adverse Events

All Adverse Events will be reported to regulatory authorities, CPP/ANSM and investigators in accordance with all applicable global laws and regulations.

9. LABELING, PACKAGING, STORAGE AND RETURN OF CLINICAL SUPPLIES

9.1 Investigational Product

EBR is an HCV NS5A inhibitor and GZR is an HCV NS3/4A protease inhibitor which is direct-acting antiviral agents against the hepatitis C virus.
The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution and usage of investigational product in accordance with the protocol and any applicable laws and regulations.

Clinical Supplies will be provided by the Sponsor as summarized in Table 10

Table 10 : Summary product information

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
oral	Tablet 50 mg elbasvir and 100 mg grazoprevir	Lactose monohydrate *For a complete listing see Dosage Forms, Composition and Packaging section.*

9.2 Dosage and Administration

EBR/GZR is a two-drug, fixed-dose combination product containing 50 mg of elbasvir and 100 mg of grazoprevir in a single tablet. The recommended dosage of EBR/GZR is one tablet taken orally once daily with or without food [see Clinical Pharmacology (section 2.2.2)]. EBR/GZR is used in combination with ribavirin in certain patient populations (see Table 1). When administered with EBR/GZR, the recommended dosage of ribavirin in patients without renal impairment is weight-based administered in two divided doses with food. For further information on ribavirin dosing and dosage modifications, refer to the ribavirin prescribing information.

Treatment Regimen and Duration of Therapy Relapse rates are affected by baseline host and viral factors and differ between treatment regimens and durations for certain subgroups [see Clinical Studies (section 2.3)]. Table below provides the recommended EBR/GZR treatment regimen and duration based on the patient population and genotype in HCV mono-infected and HCV/HIV-1 co-infected patients with or without cirrhosis and with or without renal impairment including patients receiving hemodialysis.

Table 11 : Recommended Dosage Regimens and Durations for EBV/GZR for treatment of HCV genotype 1 or 4 in Patients with or without Cirrhosis

PATIENT POPULATION	TREATMENT	DURATION
Genotype 1a : treatment-naïve or PegIFN/RBV-experienced without baseline NS5A polymorphisms	**EBR/GZR**	**12 weeks**
Genotype 1a : treatment-naïve or PegIFN/RBV-experienced with baseline NS5A polymorphisms	**EBR/GZR + RBV**	**16 weeks**
Genotype 1b : treatment-naïve or PegIFN/RBV-experienced	**EBR/GZR**	**12 weeks**
Genotype 1a or 1b : PegIFN/RBV/Protease inhibitor experienced	**EBR/GZR + RBV**	**12 weeks**
Génotype 4 : Treatment naïve	**EBR/GZR**	**12 weeks**
Génotype 4 : PegIFN/RBV-experienced	**EBR/GZR + RBV**	**16 weeks**

9.3 Packaging and Labeling Information

ZEPATIER® (elbasvir and grazoprevir) is a fixed-dose combination tablet for oral administration containing 50 mg of elbasvir and 100 mg of grazoprevir. The beige and oval shaped film-coated tablets bear the inscription "770" on one side and are smooth on the other. ZEPATIER® is available in two blister packs of 28 tablets.

Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

Subjects will receive Open Label EBR(50mg)/GZR(100mg) at the baseline visit.

9.4 Clinical Supplies Disclosure

This trial is open-label; therefore, the subject, the trial site personnel, the Sponsor and/or designee are not blinded. Drug (name, strength) is included in the label text; random code/disclosure envelopes or lists are not provided.

9.5 Storage and Handling Requirements

Clinical supplies must be stored in a secure, limited-access location under the storage conditions specified on the label. EBR/GZR bottle should be stored at controlled room temperature until required for administration. Controlled room temperature is defined as 25 °C, excursions are permitted between 15°C and 30°C.

Receipt and dispensing of trial medication must be recorded by an authorized person at the trial site.

Clinical supplies may not be used for any purpose other than that stated in the protocol.

9.6 Returns and Reconciliation

The investigator is responsible for keeping accurate records of the clinical supplies received from the Sponsor or designee, the amount dispensed to and returned by the subjects and the amount remaining at the conclusion of the trial.

For all trial sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return.

9.7 Study drug adherence and drug Accountability

Subjects must be instructed to bring back all bottles of study medications in the original container at every study visit after Day 1 through the end of treatment.
Study medications will be reconciled using medication pill count at every study visit after Day 1 by the investigator or designee in order to monitor the subject's adherence with the medication regimen.

9.8 Drug Interactions

Co-administration of EBR/GZR and OATP1B inhibitors may significantly increase grazoprevir plasma concentrations and is contraindicated.
The concomitant use of EBR/GZR and strong CYP3A inducers or efavirenz may significantly decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced

therapeutic effect of study drug. Therefore, the use of EBR/GZR with strong CYP3A inducers or efavirenz is contraindicated.
The concomitant use of EBR/GZR and moderate CYP3A inducers may decrease elbasvir and grazoprevir plasma concentrations and may lead to a reduced therapeutic effect of study drug. Therefore, the use of EBV/GZR with moderate CYP3A inducers is not recommended.
The concomitant use of EBR/GZR and strong CYP3A inhibitors increases elbasvir and grazoprevir concentrations. Co-administration of EBR/GZR with certain strong CYP3A inhibitors is not recommended.
The plasma concentration of grazoprevir is increased if EBR/GZR is co-administered with cyclosporine. Co-administration with cyclosporine is contraindicated.

Co-administration of EBR/GZR with P-gp inhibitors is expected to have a minimal effect on the plasma concentrations of EBR/GZR.
Grazoprevir is a substrate of OATP1B drug transporters. Co-administration of EBR/GZR with drugs that inhibit OATP1B transporters may result in a significant increase in the plasma EBR/GZR concentration of grazoprevir. As such, co-administration of EBR/GZR with OATP1B inhibitors is contraindicated.
Investigational agents are not permitted.

The following medications/therapies are contraindicated in this study

Strong CYP3A/P-gp inhibitors, including but not limited to

- Antibiotics: clarithromycin, erythromycin, telithromycin
- Antifungals: itraconazole, ketoconazole, voriconazole
- Antihypertensives: nifedipine
- nefazodone

Strong and moderate CYP3A/P-gp inducers,including but not limited to

- Anti-infectives: nafcillin, rifampin
- Anticonvulsants: carbamazepine, phenytoin, phenobarbital
- bosentan
- modafinil
- St. John's Wort

OATP inhibitors, including but not limited to

- Immunosuppressants: cyclosporine
- Anti-infectives: rifampin
- Diabetes agents: glibeclamide, glyburide
- Lipid lowering agents: gemfibrozil
- eltrombopag
- lapatinib
- grapefruit/grapefruit juice

All HMG-CoA reductase inhibitors (statins)

In general, CYP3A4 substrates with narrow therapeutic ranges (e.g. warfarin, amiodarone, flecainide, propafenone, quinidine, fentanyl, sildenafil or tadalafil when used for the treatment of pulmonary arterial hypertension) are not prohibited but their levels can potentially be increased by approximately 30% when co-administered with study drugs.

Diet Consideration

EBV/GZR can be taken without regard to food. Intake of grapefruit or grapefruit juice is contraindicated during the treatment period of the trial.

10.STATISTICAL ANALYSIS PLAN

10.1 Sample size estimation

To evaluate the efficacy of of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve for HCV GT1b-Infected Patients, with non-severe fibrosis, the sample size estimation was performed according to the precision of 95% confidence interval of the primary outcome measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment. Considering an efficacy at 96%, n=120 patients will be able to obtain an exact 95% confidence interval with a lower bound greater than 91.5%, which could be considered as the minimal efficacy obtained in several works presented recently in literature.

An exploratory interim analysis will be conducted. More precisely, we want to evaluate whether after the inclusion of the first 50 patients, the expected SVR12 rate of 96% always seems a robust and possible assumption. In order to better estimate the rate of responders treated and to ensure that with 120 patients the lower limit of the 95% confidence interval is well above 91.5%, it seems reasonable and relevant to consider early intermediate analysis, without inflation of type I error.

10.2 Statistical Analysis Plan Summary

The analysis set for antiviral activity analyses will be the Full Analysis Set which includes subjects who were enrolled and received at least one dose of study drug and have naïve chronic genotype 1b HCV infection with non severe fibrosis.
Statistical analysis will be performed using Stata software (version 13; Stata-Corp, College Station, Tex., USA). All statistical tests will be two-sided and $p<0.05$ will be considered significant.

Qualitative variables will be described in terms of numbers and proportions.
Quantitative variables will be described in terms of numbers, mean ± standard deviation or median [inter-quartile range] according to statistical distribution (normality studied using Shapiro-Wilk test).
Graphic representations will be complete presentations of results.
Sensitivity analyses will be considered to measure the possible impact of missing data on results and the more appropriate imputation method. For the analysis of post-baseline categorical efficacy endpoints, if a data point is missing and is immediately preceded and followed in time by values that are deemed successes, then the missing data point will be termed a success; otherwise the data point will be termed a failure. For example if a data point is missing and is preceded and followed in time by values that are <LLOQ target not detected (TND), then the missing data point will be set to < LLOQ TND.
Demographic and baseline measurements will be summarized using standard descriptive methods by treatment group and overall.
Exploratory analyses may be performed to assess the relationship between demographic, baseline characteristics, (including baseline viral load, age, sex, baseline ALT level, bodyweight, fibrosis score and additional endpoints as necessary) and antiviral activity (HCV RNA reduction, proportion of subjects with HCV RNA below the limit of quantification and target not detected at various time points during and following discontinuation of study drugs). Predictive factors of antiviral activities may be examined using regression type of analysis.

An interim SVR 12 Clinical Study Report (CSR) will be done because SVR12 is suitable as a primary end point for regulatory approval. SVR12 and SVR24 measurements were concordant in a large population of subjects with HCV infection who participated in clinical trials with various treatment regimens and durations (28). Since the protocol continues to Post Treatment Week 24 visit, then we provide a SVR 24 CSR wich will be the final CSR.

10.3 Analyses for the primary outcome

To evaluate the efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve for HCV GT1b-Infected Patients, with non-severe fibrosis as measured by the proportion of subjects with sustained viral response 12 weeks after cessation of treatment (SVR 12), the proportion of patients presenting a sustained viral response 12 weeks after cessation of treatment (HCV RNA < LLOQ 12 weeks after cessation of treatment) will be presented with the associated 95% confidence interval estimated using binomial exact distribution (exact confidence interval). The lower-bound of the confidence intervals will be studied and analyzed regardless assumptions proposed for sample size estimation.
A detailed description of patients not assume SVR12 will be proposed according to clinical relevance using age, gender, BMI, fibrosis score, viral charge and additional endpoints as necessary

10.4 Analyses for the secondary objectives

Most of secondary analyses will be exploratory and will be performed as described previously (i) to evaluate the safety and tolerability of EBR/GZR treatment, (ii) to determine the proportion of subjects who attain SVR at 4 and 24 weeks after cessation of treatment (SVR4 and SVR24), (iii) to evaluate the proportion of subjects with virological failure and (iv) to evaluate the emergence of viral resistance to EBR/GZR during treatment and after cessation of treatment. Finally, to evaluate the kinetics of circulating HCV RNA during treatment and after cessation of treatment, a descriptive statistical analysis will be proposed. This analysis will be completed using random-effects models useful to evaluate kinetics taking into account between and within patient variability.

To better understand the potential for Resistance Associated Variants (RAVs) with EBR and/or GZR, samples will be retained from Day 1 and viral failure visits and RAVs will be assessed for any subject who has detectable virus above 1000 UI/mL and has met a virologic failure criteria. Subjects who discontinue the treatment will continue to participate in the scheduled follow-up activities including monitoring for resistance.

Exploratory IL28B genotyping may also be conducted to detect genetic variations associated with response to treatment of hepatitis C. A separate siganture will be required to document a subject's agreement to provide additional samples for optional genetic research.

11. DIRECT ACCESS TO SOURCE DATA/DOCUMENTS

11.1 Access to source data

The sponsor shall be permitted to inspect the investigator center prior to commencement and during the course of the study to satisfy itself that the center is suitable and has the necessary facilities, staff and capacity to conduct the study. The investigator will ensure that his center has the necessary facilities, time and staff for conducting the study, and that these will be maintained for the duration of the study. The investigator will co-operate with the sponsor and any affiliated person to monitor or supervise the conduct of the study.

The study may be subjected to auditing by representatives of the sponsor and/or to inspection(s) by authorized representatives of local and/or foreign health authorities. In case of an audit or inspection, the investigator will be informed in advance.

The CRFs are to be made available for review by the clinical monitor or auditor or national regulatory inspectors. The investigators are required to give access to all source documents and study data in accordance with laws and regulations (articles L.1121-3 and R.5121-13 of the code of public health). The sponsor will not require the investigator or any member of their staff to take any action or be a party to any action which is contrary to the laws of the country in which the study is being carried out or to medical ethics.

11.2 Source documents

The investigator agrees to allow direct access to source data of the study during monitoring visits, audits or inspections by authorized representatives of local and/or foreign health authorities. Source documents (medical records, the original results of laboratory test …) are defined as any document proving the existence or the accuracy of a data or a registered event during the clinical study. It will be archived for 15 years by the investigator.

11.3 Confidentiality

In accordance with GCP and with the national data protection laws, all information concerning the subjects in the study must be treated as strictly confidential by all persons involved in the study including the clinical, medical and statistical monitor.
The investigator acknowledge that any information acquired from the sponsor or developed or acquired in connection with the study are strictly confidential and that they will not be disclosed to any third party nor use them for any purpose without first obtaining the written consent of the sponsor.
People involved in the study and investigators themselves are subject to professional secrecy (under the conditions defined by Articles 226-13 and 226-14 of the Penal Code).
Such consent shall be deemed to have been given for disclosure to any person for whom the investigator is responsible at his centre, but only so far as required for the purposes of the study, and, in the case of disclosures to staff, only if such staff are bound by obligations of confidentiality no less strict than those set out herein.

11.4 Archiving

The investigator must retain the subject identification codes for at least 15 years after completion or discontinuation of the study. Subject files and other source data must be kept for the maximum period of time permitted by the hospital, institution or private practice, but not less than 10 years, to meet international registration requirements. The investigator must produce them or supply copies thereof to the sponsor or to the regulatory authorities upon demand, whilst ensuring subject confidentiality at all times.

12. QUALITY CONTROL AND QUALITY ASSURANCE

The CRFs, containing all the clinical information, will be carefully checked both by the Investigators and the Monitors against the source documents according to the Good Clinical Practices Guideline (CPMP/ICH/135/95).

12.1 Commitment of the investigators and the sponsor

The investigators agrees that the study is conducted in accordance with the Public Health law N° 2004-806 - 9 August 2004 on biomedical research, the implementing decree N° 2006-477 from 26/04/2006 amending chapter I of title II of book I of the first part of the code of Public Health relating to biomedical research and the applicable orders.

The Good Clinical Practice (GCP) for biomedical research involving human drugs, referred to the Article L.1121-3 of the Code of public Health and the order of November 24, 2006 will also apply.

The study will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki (Tokyo 2004, reviewed).

12.2 Quality assurance

The Clinical research assistant commissioned by the sponsor is responsible for inspection of the case report form at regular intervals, according to the monitoring plan of the study, throughout the study to ensure adherence to the protocol, compliance with the source documents, data consistency, and adherence to regulations on the conduct of clinical research.

The Clinical research assistant commissioned must have access to subject's medical file and other records related to the study required to verify the case report forms of the study.

Controls of consistency will be made by computer according to predefined rules. Requests for information or queries will be generated when possible errors have been detected.

12.3 Quality control

The investigator is responsible for the authenticity of collected data as part of the study and accepts the legal provisions allowing the sponsor of the study to develop a quality control.

The investigator and coordinator agree to make themselves available for the monitoring visits. During this visits, the following documents will be reviewed:

- Informed consent
- Compliance with the protocol and procedures defined therein
- Quality of collected data in the case report forms : accuracy, missing data, data consistency with the source documents
- Product management

12.4 Case Report Form

In order to meet regulatory requirements (Guidance for Computerized systems Used in Clinical Trials, International Conference on Harmonisation, Good clinical Practice 2001/20/CE), e-Case Report Formdesign, data monitoring and database extractions will be performed with Clinsight® software package.
CLINSIGHT meet the FDA recommendations regarding the Computerized systems for clinical trial management ("Guidance for computerized systems used in clinical trials") and electronic signature ("21 CFR Part 11") and international standards for the health.

13. ETHICS

13.1 Independent ethics committee

The protocol and the Subject informed form and consent and case report form will be submitted to The Independent Ethics Committee (CPP Sud-Est) and written approval from the Chair of the Ethics Committee is required before the initiation of the study.

The notification of the approval will be forwarded to the French authority ANSM and Promotor. A request for authorization will be sent by the Promotor to ANSM before the start of the study.

13.2 Subject information and consent

Subjects will be informed fully and fairly, in understandable terms, about the objectives, the constraints of the study, the potentials risks involved, and monitoring measures, security, their rights to refuse to participate in the study and the possibility to withdraw at any time.

The investigator must also inform the subjects of the approval of the ethic committee.

All these informations must be listed on the informed consent given to the subjects.

The informed and written consent of the subjects will be collected by the investigator. These documents are approved by the competent ethic committee and no other version shall be used.

Three original consents will be co-signed by the investigator and the subject. One will be given to the subject, the second retained by the investigator and the third retained by the sponsor in a sealed envelope maintaining the confidentiality. This envelope will be archived during the legal period of 15 years.

13.3 Amendments to the protocol

There will be no alterations or changes to the protocol without agreement of all investigators and sponsor. If such an agreement, the planned changes will constitute an amendment that will be attached to the protocol. Any amendment must be notified to the ethic committee if the planned changes affect the ethical or medical-scientific study (evaluation criteria, addition of a new center ….). Minor modifications do not require a review of the ethic committee.

13.4 Reimbursement of travel costs

Reimbursement of travel costs will be provided for each protocol visit on presentation of supporting documents

14. DATA HANDLING AND RECORD KEEPING

14.1 Electronic Case Report Forms (e-CRFs): entry and data processing

For each subject consented, an eCRF will be completed by an authorized study staff member whose training for this function is documented according to study procedures. eCRFs should be completed on the day of the subject visit to enable the sponsor to perform central monitoring of safety data.

The Eligibility Criteria eCRF should be completed only after all data related to eligibility have been received. Subsequent to data entry, a study monitor will perform source data verification within the EDC system. Original entries as well as any changes to data fields will

be stored in the audit trail of the system. Prior to database lock (or any interim time points as described in the clinical data management plan), the investigator will use his/her log in credentials to confirm that the forms have been reviewed, and that the entries accurately reflect the information in the source documents. The eCRF capture the data required per the protocol schedule of events and procedures. System-generated or manual queries will be issued to the investigative site staff as data discrepancies are identified by the monitor, who routinely review the data for completeness, correctness, and consistency. The site coordinator is responsible for responding to the queries in a timely manner, within the system, either by confirming the data as correct or updating the original entry, and providing the reason for the update (e.g. data entry error). At the conclusion of the trial, Promotor will provide the site with a read-only archive copy of the data entered by that site. This archive must be stored in accordance with the records retention requirements.

14.2 CNIL

The data will be processed in accordance with the provisions of the Act of 6 august 2004 about protection of individual data with regard to the processing of personal data and amending Act of 6 January 1978 relating to computers, files and liberties.
This change was approved by decision of 5 January 2006. The CHU Clermont-Ferrand, study sponsor, signed a commitment to comply with the "Reference Methodology", dated 15/03/2007.

14.3 Archiving

The following documents will be archived by the name of the study in the CIC of Clermont-Ferrand to the end of the period of practical use (15 years).
These documents are:

- Protocol and annexes, any amendments,
- Information and consent forms signed (originals)
- Individual data (authenticated copies of raw data)
- Follow-up documents
- Statistical analysis
- Final report of the study

At the end of the period of practical use, all documents to be archived, as defined in the procedure PG.06.005 “Managing the documentation of protocols” of the University Hospital of Clermont-Ferrand will be transferred to central archives and will be under the responsibility of the Hospital for 15 years after the end of the study according to institutional practices.

No destruction can be performed without the consent of the sponsor; at the end of the 15 years, the sponsor will be consulted for destruction. All data, all documents and reports may be subject to audit or inspection.

15. FINANCING AND INSURANCE

15.1 Budget

Cf ANNEXE n°2

15.2 Insurance

The study will be covered under a liability insurance policy n°147161 in accordance with the Article L209-7 of the French Code of public health subscribed by the sponsor to Societé Hopitalière d'Assurances Mutelles (SHAM) in the case of an adverse event in relation to the study.

The sponsor will support the additional costs of any supplies or tests specifically required by the protocol.

16. PUBLICATION POLICY

Investigator will have full and unrestricted access to the database with all anonymized data.

It is intended to publish the results of the clinical trial collectively (no individual report or publication will be allowed).

Neither the Investigator nor his agents, consultants, associates or employees shall, directly or indirectly, originate, issue or disclose news releases or any type of announcements, whether written or oral, or organize any presentation or issue any publications regarding the study, and/or any information, data, results, inventions or discoveries made or obtained during the study, without the prior written consent of sponsor, which consent shall not be unreasonably withheld.

In order to protect possible intellectual property rights and commercial confidentiality in the interest of the sponsor, a waiting period of up to few months after the end of the trial and until publication may be agreed between the investigators and the sponsor.

Sponsor’s representative(s) have the option to be a named co-author(s) of any such publications, presentations or news releases. Sponsor retains the exclusive rights over the data resulting from the study for any purpose, including data from other participating institutions.

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ANNEXE n°1 : Etude C-WORTHY, partie C.

Conference Reports for NaTaP

EASL - The International Liver Congress 2015
50th annual Meeting of the European
association for the Study of the Liver
Vienna, austria april 22-26

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EFFICACY OF AN 8-WEEK REGIMEN OF GRAZOPREVIR PLUS ELBASVIR WITH AND WITHOUT RIBAVIRIN IN TREATMENT-NAIVE, NONCIRRHOTIC HCV GENOTYPE 1B INFECTION

Reported by Jules Levin
EASL 2015 April 22-26 Vienna Austria

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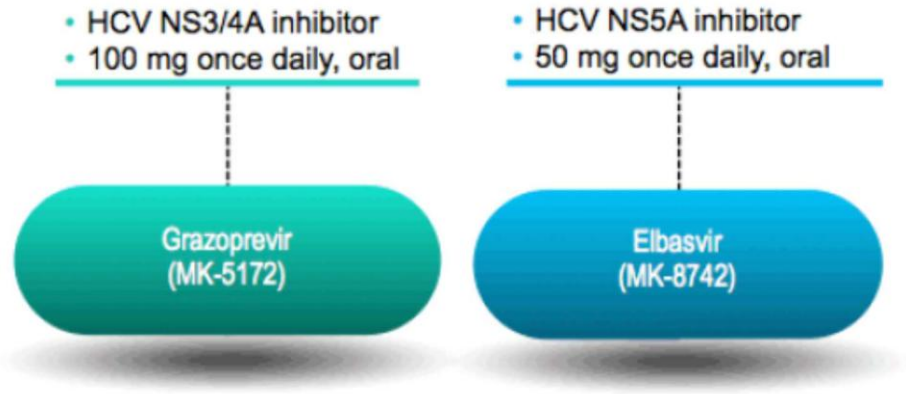
C-WORTHY

CONCLUSIONS

- GZR/EBR ± RBV for 8 weeks in treatment-naive, noncirrhotic patients with HCV GT1b infection was
  - Highly efficacious
  - Safe and well tolerated
  - Rarely associated with RAVs at the time of failure

BACKGROUND



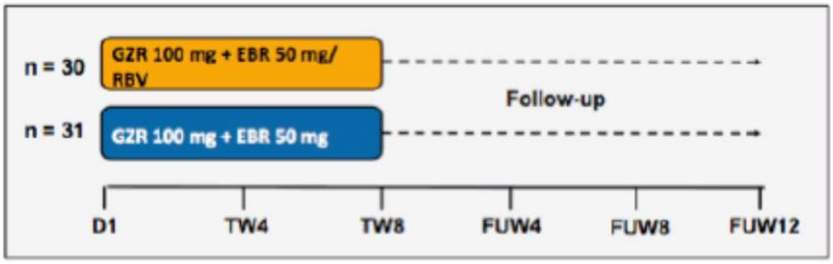
- All-oral, once-daily regimen
- Broad activity against most hepatitis C virus (HCV) genotypes (GT)[1-3]
- Retains activity against many clinically relevant resistance-associated variants (RAVs)[1-3]

BACKGROUND AND AIM

- In C-WORTHy parts A and B, grazoprevir (GZR) plus elbasvir (EBR) for 12 weeks demonstrated high efficacy in treatment-naive, noncirrhotic subjects[1,2]
  - A 12-week regimen of GZR + EBR without ribavirin (RBV) in treatment-naive, noncirrhotic, GT1a- and GT1b-infected patients, achieved a 98% sustained virologic response (HCV RNA <25 IU/mL) at follow-up week 12 (SVR12)
  - An 8-week regimen of GZR + EBR + RBV in 30 patients with HCV GT1a infection yielded a suboptimal SVR12 of 83% in part B
  - C-WORTHy part C, therefore, was developed to evaluate an 8-week regimen of GZR + EBR further in patients with HCV GT1b infection
- The aim of C-WORTHy part C was to assess the safety and efficacy of an 8-week regimen of GZR + EBR ± RBV in treatment-naive, noncirrhotic patients with HCV GT1b infection

METHODS

Figure 1. Study design.



EBR = elbasvir; FW = follow-up week; GZR = grazoprevir; RBV = ribavirin; TW = treatment week.

- Phase 2, randomized, open-label study
  - Randomized treatment with GZR/EBR, with or without RBV
- Treatment-naive patients with GT1b infection
  - Cirrhotic and HIV-coinfected patients excluded
- Primary end point
  - SVR12 (HCV RNA <25 IU/mL)* at follow-up week 12

*COBAS TaqMan v2.0 (limit of quantitation [LOQ] = 25 IU/mL)

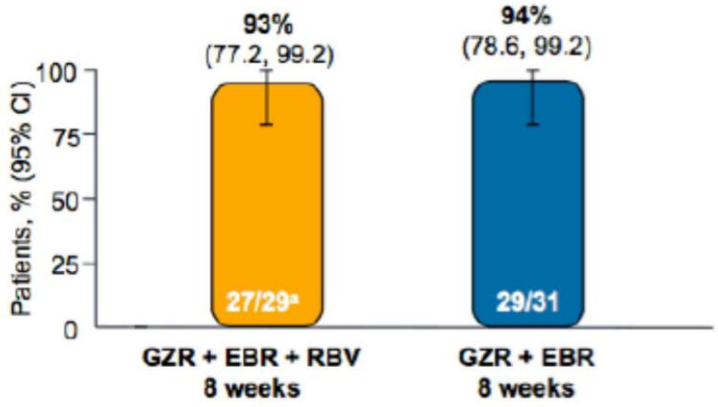
RESULTS

Table 1. Demographics

	GZR + EBR + RBV 8 weeks (n = 30)	GZR + EBR 8 weeks (n = 31)
Sex, n (%)		
Male	16 (53.3)	13 (41.9)
Female	14 (46.7)	18 (58.1)
Race, n (%)		
White	25 (83.3)	25 (80.6)
Black/African American	5 (16.7)	6 (19.4)
Other	0 (0)	0 (0)
Mean baseline viral load, IU/mL	4,954,362	8,220,775
***IL28B* CC, n (%)**	11 (36.7)	3 (9.7)
Fibrosis, n (%)		
METAVIR F0-F2	27 (90)	29 (93.5)
METAVIR F3	3 (10)	2 (6.5)

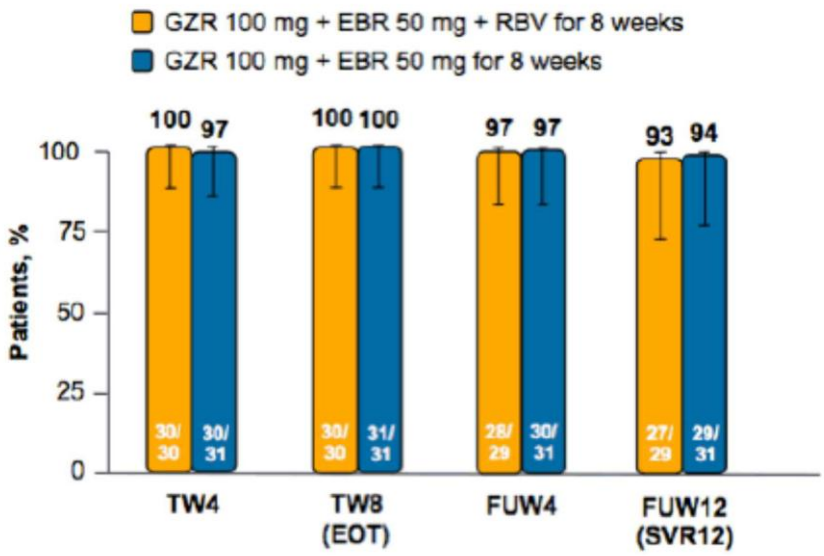
EBR = elbasvir; GZR = grazoprevir; RBV = ribavirin.

Figure 2. SVR12: modified intention to treat.



AE = adverse event; CI = confidence interval; EBR = elbasvir; FW = follow-up week; GZR = grazoprevir; RBV = ribavirin; SVR12 = sustained virologic response (HCV RNA <25 IU/mL) at follow-up week 12.
[a]Excludes 1 patient who discontinued early unrelated to AE or virologic failure.
Values are % (95% CI).

Figure 3. Virologic response.[a]



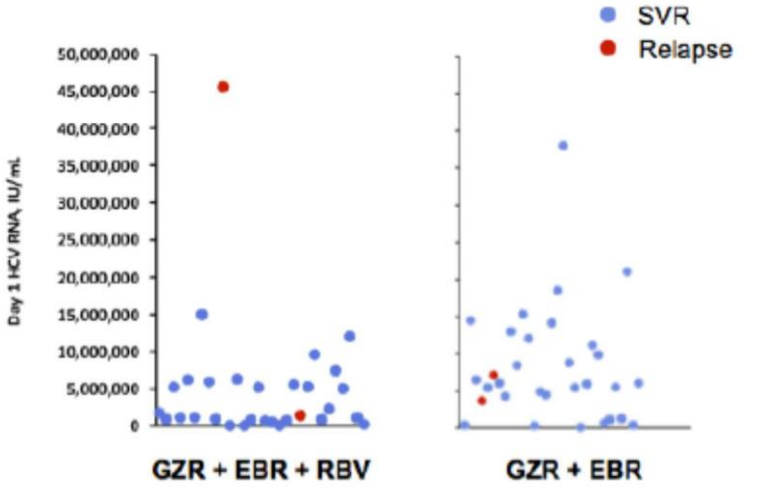
EBR = elbasvir; EOT = end of treatment; FUW = follow-up week; GZR = grazoprevir; RBV = ribavirin; SVR12 = (HCV RNA <25 IU/mL) at FUW12; TW = treatment week.
[a]HCV RNA <25 IU/mL.

Table 2. Virologic Failure

	GZR + EBR + RBV 8 weeks (n = 30)	GZR + EBR 8 weeks (n = 31)
Virologic failure		
Breakthrough/rebound	0	0
Relapse	2	2
At FUW4	1	1
At FUW12	1	1

EBR = elbasvir; FUW = follow-up week; GZR = grazoprevir; RBV = ribavirin.

Figure 4. Baseline viral load and SVR.



EBR = elbasvir; GZR = grazoprevir; HCV = hepatitis C virus; RBV = ribavirin; SVR = sustained virologic response.

- In 4 patients who relapsed:
  - At baseline, no patient had an NS3 RAV; 1/4 had NS5A RAV at baseline
  - At failure, no patient had an NS3 RAV; 1/4 failed with a preexisting Y93H NS5A RAV at failure

Table 3. RAVs in Patients With Virologic Failure

Pt	RBV	Day 1		At Time of Viral Failure		FUW4		FUW8		FUW12		FUW24	
		NS3	NS5A	NS3	NS5A	NS3	NS5A	NS3	NS5A	NS3	NS5A	NS3	NS5A
1	Yes	WT	WT	WT	WT			WT	WT	WT	WT	WT	WT
2	Yes	WT	WT	WT	WT			WT	WT	WT	WT	WT	WT
3	No	WT	WT	WT	Y93H/Y			WT	Y93H/Y	WT		WT	Y93H
4	No	WT	WT	WT	WT					WT	WT	WT	WT

FUW = follow-up week; RBV = ribavirin; WT = wild type.

Table 4. Characteristics of Patients With Relapse

Pt	RBV	Baseline Viral Load	BMI	Fibrosis Stage	*IL28B*	Baseline NS5A RAV
White, male	Yes	3,706,721	31.1	F0-F2	TC	WT
White, male	Yes	7,195,429	29.5	F3	TC	Y93H
White, male	No	45,636,595	26.9	F0-F2	TC	WT
White, male	No	1,409,481	29.1	F0-F2	TC	WT

BMI = body mass index; RAV = resistance-associated variant; RBV = ribavirin; WT = wild-type.

Table 5. Adverse Events	GZR + EBR + RBV 8 weeks (n = 30)	GZR + EBR 8 weeks (n = 31)
AEs, n (%)		
Fatigue	10 (33.3)	3 (9.7)
Headache	6 (20)	5 (16.1)
Asthenia	1 (3.3)	2 (6.5)
Serious AE, n (%)	1[a] (3.3)	0 (0)
Serious drug-related AE, n (%)	0 (0)	0 (0)
Discontinuation due to AE, n (%)	0 (0)	0 (0)
Deaths, n (%)	0 (0)	0 (0)

AE = adverse event; EBR = elbasvir; GZR = grazoprevir; RBV = ribavirin.
[a]One patient experienced non–drug-related cholangitis, which led to the temporary interruption of study medication, and a serious AE of bacteremia, which occurred during follow-up.

Table 6. Laboratory Values

	GZR + EBR + RBV 8 weeks (n = 30)	GZR + EBR 8 weeks (n = 31)
Lowest Hgb on treatment, n (%)		
≥8.5 to <10 g/dL	1 (3.3)	1 (3.2)
<8.5 g/dL	1 (3.3)	0 (0)
ALT, n (%)		
1.1-2.5 × baseline	1 (3.3)	0 (0)
>2.5 × baseline	2 (6.7)	0 (0)
AST, n (%)		
1.1-2.5 × baseline	3 (10)	0 (0)
>2.5 × baseline	1 (3.3)	0 (0)
Late elevation of ALT or AST,[a] n (%)		
>5.0 × ULN	1 (3.3)	0 (0)
Total bilirubin, mg/dL, n (%)		
>2.5-5.0 × baseline	5 (16.7)	0 (0)
>5.0-10.0 × baseline	1 (3.3)	0 (0)
>10.0 × baseline	0 (0)	0 (0)

ALT = alanine aminotransferase; AST = aspartate aminotransferase; EBR = elbasvir; GZR = grazoprevir; RBV = ribavirin; TW = treatment week; ULN = upper limit of normal; Hgb=hemoglobin.
[a]Occurrence on treatment after TW4, with ALT/AST ≤ ULN between TW2 and TW4 (direct bilirubin in this patient was 0.19 mg/dL).

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ANNEXE n°2

BUDGET (amended on 03 march 2017)

Impact Logistics Score	14
Risk	C
Monitoring	Medium Level

120 Patients
9 Sites

PROMOTION COSTS (1)		TOTAL
Méthodologist time		2 150
Biostatistician time	*36 days*	10 908
CRA Scientific Project Coordination time	*24 days*	7 488
Physician Scientific Project Coordination time	*11 days*	6 809
Data Manager time	*40 days*	11 480
e-CRF		5 900
Pharmacovigilance		8 944
Pharmacist time		1 881
Pharmacy Costs		2 850
Monitoring CRA time	*155 days*	39 215
Monitoring Travel Expenses		53 734
Set-up and Close-out CRA time	*68 days*	17 204
Set-up and Close-out Travel Expenses		11 560
Office Supplies		1 900
Assurances		2 000
Administrative Fees		2 303
Results Presentation Travel Expenses		2 600
Poster and Publication		500
SUBTOTAL 1		189 426
ADDITIONAL HOSPITAL COSTS (2)		
Fixed Costs (Clinical Research and Innovation Head Unit)	*400* site*	3 600
Investigator (1h/screening)	*120 hours*	8 400
Investigator (0,5h/visit)	*3,5 h*pt*	29 400
Study Coordinator (visit - eCRF - monitoring)	*16 h*pt*	65 280
Nurse (0,25h/visit)	*2 h*pt*	8 160
Reimbursement of travel costs for patients	*167€xpt*	20 040
Clinical and Biological Investigations		144 180
Site Pharmacy Costs		6 994
Archiving	*100*site*	900
SUBTOTAL 2		286 954
INVESTIGATOR FEES (SUBTOTAL 3)	*756*pt*inv*	90 720
Overhead Costs 10%		56 710
TOTAL (1+2+3) + Management Fees		623 810

ANNEXE n°3

SIGNATURES

Sponsor's Representative

NAME	SIGNATURE	DATE

Investigator

I agree to conduct this clinical trial in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol). I agree to conduct the trial in accordance with generally accepted standards of Good Clinical Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse events as defined in Section 7.0 – Assessing and Recording Adverse Events. I also agree to handle all clinical supplies provided by the Sponsor and collect and handle all clinical specimens in accordance with the protocol. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's Brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the trial is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure or access by third parties.

NAME	SIGNATURE	DATE