Determine the Efficacy and Safety of Harvoni in Genotype 1 Chronic Hepatitis C Infected People who are Alcoholics.

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A Phase IV, Single Arm, Open-Label Study to determine the Efficacy and Safety of Ledipasvir/Sofosbuvir (LDV/SOF) in Treatment-Naive Alcoholic Subjects with Chronic Genotype 1 HCV Infection

Sponsored by: Gilead Sciences, Inc

Indication: Hepatitis C Virus Infection

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1.0 Introduction

1.1 Background

Because of the potential for harmful effects, alcohol use is strongly discouraged in patients with liver disease. Alcohol abuse is common in patients with hepatitis C infection (1). In addition to the obvious potentiating effects of alcohol on liver injury, fibrosis and cancer in patients with chronic hepatitis C virus (HCV) infection, there is a well-known concurrent decrease of the effectiveness of interferon-based therapy (1 – 3). It has been previously shown that on-going alcohol intake inhibits the antiviral effects of interferon therapy of chronic hepatitis C (3). Even moderate levels of alcohol ingestion, associated with blood alcohol levels of 50 mg/dl, can impair the activity of interferon in HCV therapy. Alcohol abuse may increase liver enzymes but does not cause acute hepatic failure when medications, including LDV/SOF, are taken as prescribed. This study will monitor liver enzymes during LDV/SOF therapy. "Liver function" is poorly correlated with liver enzymes.

The effect of alcohol on the efficacy of direct-acting antivirals (DAAs) in HCV infection is poorly understood. Sofosbuvir is an oral, well-tolerated DAA with remarkable HCV polymerase inhibitor activity. Sofosbuvir-based therapy exhibits excellent inhibition of HCV replication in infected patients, raising the potential rate of a sustained viral response (SVR) to over 90%. Currently, the therapy of genotype 1 HCV infection with ledipasvir plus sofosbuvir in combination (LDV/SOV), results in an SVR in nearly 95% of naïve patients (4).

Ideally, the therapy of HCV-viremic drinkers should be to both cure the infection and cease alcohol use. Hepatitis C infection can be eradicated in the great majority of genotype 1 infected patients in as little as 8 to 12 weeks (4). The acquisition of sobriety is a typically a much more lengthy process that requires significant dedication and is often associated with relapses intermixed with periods of abstinence (5). The goal, therefore, should be to combine the therapies, acknowledging sobriety can take much longer to achieve than the drug cure of HCV. However, since HCV medications like LDV/SOV are very expensive, despite being cost-effective, insurers are delaying or denying alcoholic patients' access to these DAAs at the present time. Currently, insurers may cite the identification of alcohol abuse as the reason to deny access to highly effective DAAs (5).

The goal of this pilot study is to determine the effectiveness of LDV/SOV in genotype 1 HCV infected patients continuing to ingest alcohol.

1.2 Rationale

Approximately one-third of all HCV infected patients are presently or have been alcohol abusers or alcoholics. By eradicating the hepatitis C infection in alcohol abusers or alcoholics, these patients will have a reduced progression to cirrhosis and should reduce the risk of hepatocellular cancer (6).

2.0 Objectives and Endpoints

2.1 Primary Objectives:

- To determine the antiviral efficacy of LDV/SOF (SVR12) in alcoholics.
- To evaluate the safety and tolerability of LDV/SOF as assessed by review of the accumulated safety data.

2.2 Secondary Objectives:

- To assess HCV RNA at EOT, 12 weeks after therapy
- To assess the adherence of the LDV/SOF in subjects using a monthly calendar and monthly nursing assessment
- To assess changes in the QOL of the subjects from baseline to end of study with the CLDQ-HCV, SF-36 questionnaire and WPAI scores.

2.3 Primary Endpoints:

- The primary efficacy endpoint is SVR12 (HCV RNA <LLOQ 12 weeks after discontinuation of study drug).
- The primary safety endpoint is any AE leading to permanent discontinuation of study drug.

2.4 Secondary Endpoints:

- The proportion of subjects with HCV RNA < LLOQ at EOT

- The adherence rates by pill count and attendance at monthly nurse visits changes in QOL scores (CLDQ-HCV, SF-36, WPAI) from baseline to end of study
- The proportion of patients who are able to complete therapy.

3.0 Study Design

3.1 Treatment Plan and Regimen

This is a single armed, open-labeled study to determine the efficacy and safety of LDV/SOF in treatment-naive alcoholic subjects with chronic genotype 1 HCV Infection either receiving 8 or 12 weeks of therapy as indicated by the FDA approved Harvoni label.

Projected Study Design: 52 weeks of screening and enrollment, 12 weeks of treatment, 12 weeks of follow-up.

N=30 patients.

3.2 Dose Modifications

There will be no dose modifications. If the subject has toxicities that are not tolerable it is advised to stop the therapy and the subject will be removed from the protocol.

3.3 Visit Schedule

All subjects will complete screening, on-treatment, and post-treatment assessments.

Screening assessments will be completed within 28 days of day 1 of starting therapy unless otherwise stated. Monthly nursing visits during therapy $\pm$ 3 days, MD visits at screening, EOT, and 12 weeks after the last dose of therapy. See section 6.0 for detailed subject schedule.

4.0 Eligibility Criteria

4.1 Inclusion Criteria

1. The subject must be willingly and able to provide written informed consent

2. Age 19 years of age or older (The age of consent in Nebraska)

3. HCV treatment-naïve, as defined as no prior exposure to any Interferon (IFN), RBV, or other FDA approved or experimental HCV-specific direct-acting antiviral agent

4. HCV RNA level within 6 months prior to the Baseline/Day 1 visit.

5. HCV genotype 1a, 1b, or mixed 1a/1b. Any non-definitive results will exclude the subject from study participation.

6. Alcohol misuse as defined by the Alcohol Use Disorders Identification Test (AUDIT) score subjects must score ≥ 8 (associated with harmful or hazardous drinking)

7. Cirrhosis determination
   a) Cirrhosis is defined as any one of the following:
      i) History of a liver biopsy showing cirrhosis (e.g. Metavir score = 4 or Ishak score ≥ 5)
      ii) Fibroscan showing cirrhosis or results > 12.5 kPa
      iii) FIBRO Spect II Index consistent with F3 or F4 AND an AST: platelet ratio index (APRI) of> 2 during screening)

   b) Absence of cirrhosis is defined as any one of the following:
      i) Liver biopsy within 2 years of Screening showing absence of cirrhosis
      ii) Fibroscan within 6 months of Baseline/Day1 with a result of ≤ 12.5 kPa
      iii) FIBRO Spect II Index consistent with F0- F2 AND APRI of ≤ 1 during Screening

8. Liver imaging (Abdominal Ultrasound) within 6 months of Baseline/Day 1 to exclude hepatocellular carcinoma HCC

9. Subjects must have the following laboratory parameters at screening:
   a) ALT ≤ 10 x the upper limit of normal (ULN)
   b) AST ≤ 10 x ULN
   c) Bilirubin ≤ 2.0 x ULN
   d) Platelets $\geq 50,000$
   e) HbA1c $\leq 8.5\%$
   f) Creatinine clearance (CLcr) ≥ 60 mL /min, as calculated by the Cockcroft-Gault equation
   g) Hemoglobin ≥ 11 g/dL for female subjects; ≥ 12 g/dL for male subjects.
   h) Albumin ≥ 2.5 g/dL
   i) INR ≤ 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.

10. Subject has not been treated with any investigational drug or device within 30 days of the screening visit.

4.2 Exclusion Criteria

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1. Pregnant women and nursing mothers are ineligible due to the possible risk of adverse effects in the newborn. Eligible patients of reproductive potential should use adequate contraception if sexually active.

2. Serious concurrent medical illness which would jeopardize the ability of the subject to receive the therapy as outlined in this protocol with reasonable safety.

3. Malignancy diagnosed or treated within 5 years (recent localized treatment of squamous or non-invasive basal cell skin cancers is permitted; cervical carcinoma in situ is allowed if appropriately treated prior to screening); subjects under evaluation for a malignancy are not eligible.

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

5. Use of any prohibited concomitant medications within 30 days of the Baseline/Day 1 visit.

6. Known hypersensitivity to LDV/SOF

4.3 Subject Recruitment and Registration

All potential subjects who will be considered for this study will be evaluated in the internal medicine clinics at Nebraska Medicine. On initial presentation, a history and physical examination are performed, AUDIT questionnaire is obtained, as well as laboratory data. Additional studies will be obtained as clinically indicated. Patients who meet the eligibility criteria will be offered the opportunity to participate in this trial. The patient can then decide if they wish to participate. Before patients are enrolled into the study, an eligibility checklist must be completed to verify the subject meets the eligibility criteria. This will be signed by the investigator.

5.0 Drug Formulation and Procurement

5.1 Formulation

LDV/SOV is a fixed-dose combination tablet containing ledipasvir and sofosbuvir for oral administration. Ledipasvir is an HCV NS5A inhibitor and sofosbuvir is a nucleotide analog inhibitor of HCV NS5B polymerase.

Product: LDV/SOF fixed dose combination
Dose: 90/400 mg

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Frequency: Once daily

The tablets include the following inactive ingredients: colloidal silicon dioxide, copovidone, croscarmellose sodium, lactose monohydrate, magnesium stearate, and microcrystalline cellulose. The tablets are film-coated with a coating material containing the following inactive ingredients: FD&C yellow #6/sunset yellow FCF aluminum lake, polyethylene glycol, polyvinyl alcohol, talc, and titanium dioxide.
Ledipasvir: The IUPAC name for ledipasvir is Methyl [(2S)-1-{(6S)-6-[5-(9,9-difluoro-7- {2-[(1R,3S,4S)-2-{(2S)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2- Gilead Sciences 10 azabicyclo[2.2.1]hept-3-yl]-1H-benzimidazol-6-yl}-9H-fluoren-2-yl)-1H-imidazol-2-yl]-5-azaspiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl]carbamate.
It has a molecular formula of C49H54F2N8O6 and a molecular weight of 889.00. It has the following structural formula:
Ledipasvir is practically insoluble (<0.1 mg/mL) across the pH range of 3.0–7.5 and is slightly soluble below pH 2.3 (1.1 mg/mL).
Sofosbuvir: The IUPAC name for sofosbuvir is (S)-Isopropyl 2-((S)-(((2R,3R,4R,5R)-5- (2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2- yl)methoxy)-(phenoxy)phosphorylamino)propanoate. It has a molecular formula of C22H29FN3O9P and a molecular weight of 529.45. It has the following structural formula:
Sofosbuvir is a white to off-white crystalline solid with a solubility of ≥2 mg/mL across the pH range of 2–7.7 at 37oC and is slightly soluble in water.

5.2 Packaging and Labeling

HARVONI tablets are orange, diamond-shaped, film-coated, debossed with "GSI" on one side and "7985" on the other side of the tablet. Each bottle contains 28 tablets (NDC 61958-1801-1), a silica gel desiccant, polyester coil, and is closed with a child-resistant closure.

5.3 Storage and Handling

Store at room temperature below 30°C (86°F).

5.4 Dosage and Administration

Each tablet contains 90 mg ledipasvir and 400 mg sofosbuvir. The tablet is to be administered once daily and can we taken with or without food. Subjects should maintain the same daily dosing interval between doses.

When a dose of study medication is missed the subject should be instructed to take the dose as soon as possible during the SAME day. Subjects should NEVER double the next dose.

5.5 Study Drug Adherence and Drug Accountability

Subjects will be instructed to bring back the bottle of study medication in the original container at each monthly visit. The medication will be reconciled using a pill count at each monthly visit. This will serve as the subject's adherence with the study medication.

Subjects must also bring the medication/ alcohol consumption diary data to each visit.

Subject's diary will include subject's record of missed doses during the month and estimated number of daily drinks (the number of drinks per day and the number of grams per day) for the month.

5.6 Concomitant Medications

H2-receptor antagonist must not exceed a dose of 20mg of omeprazole or equivalent. Antacids that directly neutralize stomach pH may not be taken within 4 hours of study drug administration.

The following medications are prohibited from 30 days prior to the Baseline/Day 1 visit Throughout the end of treatment, or otherwise specified:

- amiodarone (Cordarone®, Nexterone® Pacerone®) within 3 months
- carbamazepine (Carbatrol®, Epitol®, Equetro®, Tegretol®)
- digoxin (Lanoxin®)
- efavirenz, emtricitabine, tenofovir disoproxil fumarate (ATRIPLA®)
- elvitegravir, cobicistat, emtricitabine, tenofovir disoproxil fumarate (STRIBILD®)
- oxcarbazepine (Trileptal®, Oxtellar XR®)
- phenytoin (Dilantin®, Phenytek®)
- phenobarbital (Lumina
- phenobarbital (Luminal®)
- rifabutin (Mycobutin®)
- rifampin (Rifadin®, Rifamate®, Rifater®, Rimactane®)
- rifapentine (Priftin®)
- rosuvastatin (Crestor®)
- simeprevir (Olysio®)
- St. John's wort (Hypericum perforatum) or a product that contains St. John's wort
- tipranavir (Aptivus®) used in combination with ritonavir (Norvir®)
- tenofovir disoproxil fumarate (VIREAD®, TRUVADA®) used in combination with atazanavir (Reyataz®) and ritonavir (Norvir®), darunavir (Prezista®) and ritonavir (Norvir®), or used in combination with lopinavir and ritonavir (Kaletra®)

6.0 Procedures

Clinical Assessments	Day -28	monthly	EOT 13	Week 12 post	
	to Day 1	3 days ±	-3 days up to +4 weeks	-3 days up to +4 weeks	
Informed Consent	x				
Audit -questionnaire	x	x	x	x	
WPAI, SF-36	x	x	x	x	
History & Physical	x		x	x	
Height, Weight	x		x	x	
Vital Signs	x		x	x	
Adverse Events	x	x	x	x	
CBC& WBC differential	x		x	x	
PT, INR	x				
Complete metabolic panel	x	x	x	x	
FIBRO Spect II Index PRN	x				
HCV RNA (within 6 months)	x		x	x	
Ultrasound abdomen (within 6 months)	x				
Fibroscan PRN	x				
Serum Pregnancy test PRN	x				
Urine Drug Screen	x				
Hepatis B surface antigen	x				
HIV panel	x				
Urinalysis	x				
Hemoglobin A1C	x				
Nursing/ Coordinator Visit		x	x	x	
Harvoni reconciliation (pill count)		x	x		
Medication ± alcohol consumption diary	x	x	x	x	

6.2 Monthly Nursing/ Coordinator visits

Subjects will have a monthly visit with the nursing coordinator of the study $\pm$ 3 days. This will be to assess drug adherence and accountability as well as to monitor for side effects and obtain alcohol consumption information we will also administer QOL questionnaires (WPAI, SF-36, Audit)

6.3 Post Treatment Assessments

All subjects must complete the Post-Treatment EOT, and 12 week visit. For subjects who have completed an EOT, the post treatment 12 visit will be scheduled 12, after the last dose of therapy dose -3 days up to 4 weeks.

6.4 Removal from Protocol Therapy

- Extraordinary medical circumstances: if at any time the constraints of this protocol are detrimental to the subject's health (unacceptable toxicity), the subject will be removed from protocol therapy.
- Subject chooses to discontinue treatment.

7.0 Adverse Events Management

7.1 Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. ([1]ICH GCP)

7.2 Assessment of Adverse Events

AEs will be collected from the time the subject signed the consent form and ending at the 24week follow up appointment. Severity of the AE will be reported in the AE case report form (CRF) and will be determined by the principal investigator according to the NCI common toxicity Criteria 4.0. The AE entry will indicate whether the AE was serious, onset, resolution, and whether or not the AE was related to the investigational medicinal product and if the actions taken as well as the severity.

The NCI Common Toxicity Criteria Adverse Events version 4.0 will be used to grade AE's.

7.3 Serious Adverse Events

Any adverse drug experience occurring at any dose that results in any of the following out comes:

- Death
- Life-threatening situation (subject is at immediate risk of death)
- In-patient hospitalization or prolongation of existing hospitalization (excluding those for study therapy or placement of an indwelling catheter, unless associated with other SAEs)
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect in the offspring of a subject who received investigational medicinal product
- Other: medically significant events that may not be immediately life-threatening or result in death or hospitalization, but based upon appropriate medical and scientific judgment, may jeopardize the subject or may require medical or surgical intervention to prevent one of the outcomes listed above

7.4 Serious Adverse Event Reporting

- UNMC's IRB
- Unexpected serious adverse drug reaction
- Any death which occurs while the subject is being treated on protocol or occurs within 30 days of completing research related inventions
- The contact information is: Institutional Review Board, UNMC 987830 Nebraska Medical Center, Omaha, NE 68198-7830; telephone: 402-559-6463; email irbora@unmc.edu
- The investigator will utilize the FDA MedWatch form for the reporting of adverse events to Gilead and follow up information to those events. The form can be found at the following URL: http://www.fda.gov/medwatch

- Data Safety Evaluations of adverse events will be monitored via submission to The Non-cancer UNMC DSMB. All adverse events (possibly, probably or definitely) grade 3 or higher will be submitted to the above independent physicians to review for trial safety and statistical considerations every three months.

7.5 Study Stopping Rules

If any of the three criteria below are met, the trial must be paused and evaluated for safety by the DSMB. The trial may continue after the DSMB determines causality is not associated with the study drug.

- ≥ 3 grade 3 NCI CTCAE version 4.0 in the same category
- ≥ 2 grade 4 NCI CTCAE version 4.0 in the same category
- ≥ 1 grade 5 NCI CTCAE version 4.0 in the same category

8.0 Statistical Considerations

8.1 Criteria for Response

Response Assessment: will be the HCV RNA obtained at EOT, weeks 12. The subject's HCV RNA level should be less than LLOQ for eradication.

8.2 Sample size justification

30 patients will be accrued to the study with the goal of estimating the true proportion of patients continuing to ingest alcohol who achieve complete eradication at 12 weeks.

It is anticipated that approximately 92% of patients will achieve eradication at 12 weeks based on previous research of 400 patients who received the study drug. A sample size of 30 produces a two-sided 95% confidence interval with a width equal to 0.23 when the sample proportion is 0.92.

We assume a screen failure or with drawl rate of 15%. We will need to consent 36 patients.

8.3 Statistical analysis

Descriptive statistics (means, standard deviations, medians, interquartile ranges, frequencies, and percentages) will be used to summarize demographic characteristics and clinical measurements of the study population. The incidence of complete eradication at 12 weeks will be estimated with a proportion and

associated 95% confidence interval. Counts and percentages will be used to summarize medication side effects. Compliance, as measured by pill counts over the study period, will be evaluated using descriptive statistics (mean, standard deviation, median, and interquartile range).

9.0 Publication Plan

Conference/Year:	DDW or AASLD 2017
Publication/Year:	Hepatology 2017 or 2018

10.0 References

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