A Phase 2, Multicenter, Open-Label Study to Investigate the Safety and Efficacy of Sofosbuvir/Ledipasvir Fixed-Dose Combination + Ribavirin Administered in Subjects Infected with Chronic HCV who have Advanced Liver Disease or are Post-Liver Transplant

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The primary objectives of this study are:•To explore the antiviral efficacy of combination therapy with SOF/LDV FDC + RBV for12 or 24 weeks in subjects with advanced liver disease (either pre-liver transplant or notcurrently wait-listed) and post-...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON40319

Source
ToetsingOnline

Brief title
Gilead GS-US-337-0124 SOLAR2

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym

Hepatitis C / Liver transplant

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: pharmaceutical industry

Intervention

Keyword: Hepatitis C, Liver transplant, Phase 2, Sofosbuvir/Ledipasvir

Outcome measures

Primary outcome

The primary efficacy endpoint is SVR12 (HCV RNA < lower limit of quantitation

[LLOQ]

12 weeks after last dose of study drug) for subjects in the Full Analysis Set.

Secondary outcome

The secondary efficacy endpoints include the proportion of subjects who attain

SVR at 2, 4,

8 and 24 weeks after discontinuation of therapy (SVR2, SVR4, SVR8 and SVR24);

proportion of subjects who have HCV RNA < LLOQ by visit while on treatment;

absolute

and change from Day 1 in HCV RNA through Week 8; virologic failure; and change

from

Day 1 in MELD and CPT scores. Subjects who have a liver transplant while on

study will

have data censored at time of transplant for the primary and secondary efficacy

endpoints

listed above.

For those subjects who have a liver transplant while on study, the proportion

of subjects with

post-transplant virologic response (PTVR, defined as HCV RNA < LLOQ at 12 weeks

post-transplant) will be summarized for subjects in the FAS who have HCV RNA <

LLOQ at

their last observed HCV RNA prior to transplant. Subjects who are transplanted

with an

HCV-infected liver will be excluded from analysis.

Study description

Background summary

Hepatitis C Virus (HCV) infection is a global health challenge with an estimated 180 million individuals infected worldwide. The total HCV-infected population in the United States is estimated to be over 3 million people, with the vast majority infected with genotype 1. Up to 85% of individuals infected with HCV fail to clear the virus and progress to chronic infection. Consequences of chronic infection include cirrhosis and hepatocellular carcinoma. The annual rate of progression to cirrhosis in chronic HCV infected patients with advanced fibrosis is ~10 %. Approximately 1 to 4% of patients per year with established cirrhosis will progress to hepatocellular carcinoma (HCC). Given the asymptomatic nature of early infection, the slow progression to chronic liver disease, and the lack of adequate screening in at risk individuals, it is expected that the prevalence of subjects diagnosed with HCV-related complications will peak over the next 2 decades. Complications of chronic hepatitis C account for the majority of liver transplantations in the United States. In 2007 alone, it is estimated that over 15,000 people in the United States died

from
HCV-related complications. HCV now surpasses human immunodeficiency virus (HIV) as a
cause of death in the United States.
The current standard of care for chronic genotype 1 HCV infection is either telaprevir
(Incivek*) two times daily (BID) or boceprevir (Victrelis*) three times daily (TID) with
once weekly subcutaneous injections of pegylated interferon (PEG-IFN) and twice-daily oral
ribavirin (RBV). Although these regimens have demonstrated sustained virologic response (SVR) rates which are superior to PEG-IFN + RBV alone in subjects with
genotype 1 HCV infection, they are associated with additional morbidity and mortality,
above and beyond that which results from PEG-IFN + RBV use.
Hepatitis C virus genotype 4 is responsible for about 20% of hepatitis C infections
worldwide. The current standard of care for chronic genotype 4 HCV infection is PEG-IFN and weight-based oral RBV for 48 weeks. There are, presently, no other options
for these patients. A shorter, more tolerated regimen is needed.

Study objective

The primary objectives of this study are:
•To explore the antiviral efficacy of combination therapy with SOF/LDV FDC + RBV for
12 or 24 weeks in subjects with advanced liver disease (either pre-liver transplant or not
currently wait-listed) and post-liver transplant HCV subjects with cirrhosis as measured
by SVR 12 weeks after discontinuation of therapy (SVR12 defined as HCV RNA < Lower Limit of Quantification [LLOQ] 12 weeks post-treatment)
•To evaluate the safety and tolerability of SOF/LDV FDC + RBV administered for 12 or
24 weeks in each patient population

The secondary objectives of this study are:
•To determine the proportion of subjects who attain SVR at 2, 4, 8, and 24 weeks after
discontinuation of therapy (SVR2, SVR4, SVR8, and SVR24)
•To determine if the administration of SOF/LDV FDC to HCV-infected subjects undergoing liver transplantation can prevent post-transplant recurrence as determined by
a sustained post-transplant virological response (HCV RNA post-transplant (in those subjects

who undergo liver transplants while on study)
•To determine therapeutic efficacy as measured by the change of CPT score and MELD
score
•To evaluate the emergence of viral resistance to SOF/LDV FDC during and after treatment discontinuation
•To evaluate the kinetics of circulating HCV RNA during and after treatment
•To characterize steady-state PK of study drugs
Exploratory objectives of this study are:
•To identify or validate genetic markers that may be predictive of the natural history of
disease, virologic response to therapy and/or the tolerability of medical therapies through
genetic discovery research (e.g., pharmacogenomics), in subjects who provide a separate
and specific consent

Study design

This is a multi-center, open-label study in genotype 1 and 4 HCV-infected adult male and
female subjects. Approximately 400 subjects will be enrolled in the study. Subjects will be
randomized to receive 12 or 24 weeks of dosing with SOF/LDV FDC (given once daily)
+ RBV (given as a divided dose twice daily). Approximately 100 subjects will be enrolled in
Cohort A and 300 subjects in Cohort B.
Each Group below will enroll approximately 50 subjects (25 subjects randomized to
12 weeks of study drug treatment and 25 subjects randomized to 24 weeks of study drug
treatment) with the exception of Cohort B, Group 3 which will enroll approximately
100 subjects (50 subjects randomized to 12 weeks of study drug treatment and 50 subjects
randomized to 24 weeks of study drug treatment).

Cohort A - Advanced Liver Disease
•Group 1: Subjects with cirrhosis and moderate hepatic impairment (Child-Pugh Class B; 7-9)
•Group 2: Subjects with cirrhosis and severe hepatic impairment (Child-Pugh Class C; 10-12)

Cohort B - Post Transplant
•Group 3: Subjects without cirrhosis (fibrosis stage F0-F3) and with no evidence of

hepatic decompensation
•Group 4: Subjects with cirrhosis and mild hepatic impairment (Child-Pugh Class A; 5-6)
•Group 5: Subjects with cirrhosis and moderate hepatic impairment (Child-Pugh Class B; 7-9)
•Group 6: Subjects with cirrhosis and severe hepatic impairment (Child-Pugh Class C; 10-12)
•Group 7: Subjects with aggressive recurrent disease after transplant with evidence of
cholestasis (fibrosing cholestatic hepatitis)
Subjects will be enrolled as they are identified with the exception of CPT C subjects (Groups
2 and 6). Prior to enrolling CPT C subjects in this study, the following data will be reviewed
by the DMC (data review will include safety and HCV RNA data):
1. Data from an ongoing study (ELECTRON; P7977-0523) in at least 20 CPT B subjects
receiving SOF/LDV FDC without RBV who have completed the Week 4 study treatment visit:
or
2. Data from 20 CPT B subjects from an equivalent study conducted in parallel in the United
States receiving SOF/LDV FDC + RBV who have completed the Week 4 study treatment visit.

Intervention

All subjects take:
once daily 1 keer per dag SOF/LDV FDC -> 400 mg SOF and 90 mg LDV
AND
twice daily Ribavirin -> total daily dosis of :
1000 mg for subjects weighing <
75 kg (2x 500mg)
1200 mg for subjects weighing =
or > 75 kg (2x600mg)

for either 12 of 24 weeks.

No Placebo will be used

Study burden and risks

The SOF/LDV FDC product combines a potent HCV nucleotide NS5B inhibitor and a potent
HCV NS5A inhibitor.
The potential benefits of SOF/LDV FDC + RBV for the treatment of chronic HCV

are:
•Greater antiviral efficacy (i.e., rapid and durable eradication of HCV) compared to the
current standard of care (PI+PEG-IFN+RBV) for genotype 1 patients
•A reduction in the AEs currently associated with the use of PEG-IFN and approved
NS3 protease inhibitors (telaprevir, boceprevir) for genotype 1 patients
•A simple, well-tolerated regimen to replace the current complex, response-guided
PI+PEG-IFN+RBV regimens.
•The potential benefit of a shortened SOF/LDV FDC + RBV therapy

The safety profile of SOF includes approximately 3300 chronic HCV-infected subjects that
have been administered over 12 weeks of SOF in combination with a DAA, PEG-IFN, and/or
RBV. No clinical safety issues related to SOF have been identified to date. The safety profile
of LDV includes over 1000 chronic HCV-infected subjects, of whom over 700 have been
administered more than 12 weeks of LDV, which was given in combination with other
DAAs, PEG-IFN, and/or RBV. No clinical safety issues related to LDV have been identified
to date.
Furthermore, there is no expectation of significant overlapping or new, unexpected toxicities
upon administration of SOF/LDV together as an FDC. To date, the SOF/LDV FDC ± RBV
has been administered to over 500 HCV infected subjects in ongoing phase 2/3 trials, with
over 200 subjects having received SOF/LDV FDC ± RBV for 12 weeks or more. No clinical
safety issues related to the SOF/LDV FDC have been identified to date.

Contacts

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Gilead Sciences

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Willing and able to provide written informed consent or for those subjects where hepatic encephalopathy affects their ability to provide initial or ongoing consent, has an appropriate and legally-authorized representative (LAR) willing and able to provide consent on behalf of the subject.;2. Male or female, Age > or = 18 years;3. Chronic genotype 1 and 4;4. HCV RNA infection with quantifiable virus at Screening;5. Confirmation of chronic (non-acute) HCV infection documented by either:;a. A positive anti-HCV antibody test or positive HCV RNA or positive HCV;genotyping test at least 6 months prior to the Day 1 visit, or;b. A liver biopsy performed prior to the Day 1 visit with evidence of chronic HCV;infection.;6. Screening ECG without clinically significant abnormalities.;7. Negative serum pregnancy test for female subjects (unless surgically sterile or greater;than two years post-menopausal; please see Appendix 4).;8. Male subjects and female subjects of childbearing potential who engage in heterosexual;intercourse must agree to use protocol specified method(s) of contraception as described;in Appendix 4.;9. Lactating females must agree to discontinue nursing before the study drugs are;administered ;10. Subject must be able to comply with the dosing instructions for study drug administration;and able to complete the study schedule of assessments, including all required;post-treatment visits.;11. Ability to determine the presence/absence of cirrhosis for all groups except Cohort B,;Group 7 (which may or may not have cirrhosis);a. Cirrhosis is defined as any one of the following:;• Liver biopsy showing cirrhosis;• Fibroscan (in countries where locally approved) showing cirrhosis or results > 12.5 kPa;• A FibroTest® score of >0.75 AND an AST:Platelet Ratio Index (APRI) of;>2 performed during screening;b. Absence of cirrhosis is defined as any one of the following:;• Liver biopsy within 2 years of Screening showing absence of cirrhosis;• Fibroscan (in countries where

locally approved) with a result of <= 12.5 kPa within <= 6 months of Baseline/Day1;• A FibroTest® score of <= 0.48 AND APRI of <= 1 performed during Screening In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above criteria, a liver biopsy is required; liver biopsy results will supersede blood test results and be considered definitive.;Inclusion Criteria Exclusively for Cohort A;12. Has never received a liver transplant, and if listed for transplant, expected to be at least 12 weeks prior to transplant (from anticipated Day 1 of dosing). The subject may be a candidate for a living donor transplant, as long as it is anticipated to be at least 12 weeks before the transplant surgery will occur.;Inclusion Criteria Exclusively for Cohort B, all Groups;13. Post-liver transplant (primary or secondary, cadaveric or living donor), at least 3 months since transplant procedure for all groups except Cohort B, Group 4, which must be at least 2 months since the transplant procedure).;14. Subjects may be on the waiting list for a second or third transplant. Subjects who are on the waiting list for a liver transplant must be waiting to receive an HCV negative organ.;Inclusion Criteria Exclusively for Cohort B, Group 7 (FCH) only;15. Subject must be within 18 months of transplant at screening;16. Histological evidence of fibrosing cholestatic hepatitis on post-transplant liver biopsy performed within 6 months of screening, confirmed by sponsor medical review prior to randomization;17. Bilirubin >= 2.5x ULN;18. Ultrasound of liver and biliary tree with Doppler or other imaging study no finding of hepatic artery thrombosis within 6 months prior to screening

Exclusion criteria

1. Any serious or active medical or psychiatric illness which, in the opinion of the investigator, would interfere with subject treatment, assessment, or compliance;2. HIV infection or chronic hepatitis B virus (HBV) infection (HBsAg positive);3. Difficulty with blood collection and/or poor venous access for the purposes of phlebotomy.;4. Gastrointestinal disorder or post-operative condition that could interfere with the absorption of the study drug.;5. Alpha-fetoprotein (AFP) > 50 unless negative imaging for hepatic masses within the last;6 months or during screening ;6. Current malignancy (with exception of certain resolved skin cancers or other early cancer for which surgical resection is considered to be completely curative), including hepatocellular carcinoma;7. Treatment with IFN, RBV, telaprevir or boceprevir or any other approved or experimental medication with known anti-HCV activity within 1 month prior to screening date;8. Any prior exposure to an HCV NS5a specific inhibitor;9. Use of GM-CSF, epoetin alfa or other therapeutic hematopoietic agents within 2 weeks of Screening;10. History of clinically significant medical condition associated with other chronic liver disease (e.g., hemochromatosis, autoimmune hepatitis, Wilson*s disease, α-1-antitrypsin deficiency, alcoholic liver disease, non-alcoholic steatohepatitis, or toxin exposures) that may affect the ability to respond to HCV therapy.;11. Active spontaneous bacterial peritonitis at screening;12. Hematological and biochemical parameters, including:;a. Hemoglobin (Hb) < 10 g/dL;b. Platelets <= 30,000/ mm3;c. ALT, AST, or alkaline phosphatase >= 10 ULN, sodium <125 mmol/L;d. Total bilirubin > 10mg/dL (except for the FCH cohort);e. Serum creatinine > 2.5x upper limit of normal and/or evidence of renal impairment (CrCl < 40 mL/min).;13. Infection requiring systemic antibiotics at the time of screening;14. Participation in a clinical study with an investigational drug or biologic within 1 month prior to screening visit, unless information on the investigational drug is available to indicate that there is no

potential drug interaction (safety or efficacy);15. Active or recent history (<= 6 months) of drug or alcohol abuse;16. Any contraindication to RBV therapy, per the approved package insert;17. Any history of organ transplant other than liver or kidney;18. Any medications from Section 5.4 prohibited from used within 28 days prior to the Day 1 visit through the end of treatment;19. Known hypersensitivity to RBV, LDV, SOF, or formulation excipients.;Exclusion criteria Exclusively for Cohort A subjects:;20. Medical justification for any MELD exception points (for HCC, current hepatopulmonary syndrome, intractable encephalopathy, or any other reason);21. History of hepatopulmonary syndrome;22. Chronic use of systemic immunosuppressive agents (for autoimmune diseases, etc);Exclusion Criteria Exclusively for Cohort B, all Groups:;23. Current use of corticosteroids at any dose > 10 mg of prednisone/day (or equivalent dose of other corticosteroid);24. Histological evidence of unresolved rejection requiring treatment or expected to require treatment during the study period;25. Use or planned use of T-cell depleting/masking antibodies, systemic antineoplastic agents, or cyclosporine at a dose of > 300 mg/day;26. Subjects with a Child-Pugh Score of 13-15, due to the serious medical condition and poor prognosis for these patients;Exclusion criterion Exclusively for Cohort B, Group 3:;27. Any clinical evidence of portal hypertension [history of ascites, esophageal or gastric;varices, hepatic encephalopathy, or coagulopathy (INR >1.2 at screening)] ;Exclusion criterion Exclusively for Cohort B, Group 7;28. Presence of alternative explanations for cholestatis/hyperbilirubinemia such as biliary or;hepatic artery complications, and drug induced injury

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	30-07-2014
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Ribasphere Tablets
Generic name:	Ribavirin
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Sofosbuvir/GS-5885 FDC
Generic name:	Sofosbuvir/GS-5885 FDC

Ethics review

Approved WMO Date:	03-12-2013
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	15-05-2014
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	06-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	20-06-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	31-07-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Approved WMO Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	23-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	29-07-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	11-08-2015
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2013-002802-30-NL
CCMO	NL46344.058.13