A Phase 2b Open-Label Study of 200 mg or 400 mg Sofosbuvir+RBV for 24 Weeks in Genotype 1 or 3 HCV-Infected Subjects with Renal Insufficiency

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(Protocol Am2 dd. 20-Feb-2014, p17/93)The primary objectives of this study are:- To evaluate the safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks as assessed by review of the accumulated safety data in each treatment arm-...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON40565

Source
ToetsingOnline

Brief title
GS-US-334-0154

Condition

- Hepatic and hepatobiliary disorders

Synonym
Chronic Hepatitis C Virus Infection, Hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences

Source(s) of monetary or material Support: By Gilead Sciences;Inc.

Intervention

Keyword: GS-US-334-0154, HCV, Sofosbuvir

Outcome measures

Primary outcome

(Protocol Am2 dd. 20-Feb-2014, p51/93)

The primary safety endpoints include incidences of AEs, laboratory, 12-lead

ECG, and vital sign abnormalities.

The primary PK endpoints are parameters AUCtau, Cmax, and Ctau for analytes

SOF, its metabolites, and RBV as applicable.

The primary efficacy endpoint is SVR12 (HCV RNA
discontinuation of therapy).

Secondary outcome

(Protocol Am2 dd. 20-Feb-2014, p52/93)

Secondary PK endpoints are parameters AUClast, Clast, Tmax, Tlast, *z, and t1/2

for analytes SOF, its metabolites, and RBV as applicable.

Secondary efficacy endpoints include the proportion of subjects with SVR4 and

SVR24, the proportion of subjects with virologic failure including viral

breakthrough and relapse.

Study description

Background summary

(Protocol Am2 dd. 20-Feb-2014, p13/93)

Hepatitis C virus (HCV) is responsible for a large proportion of chronic liver disease worldwide and accounts for 70% of cases of chronic hepatitis in industrialized countries. The global prevalence of chronic hepatitis C is estimated to average 3% {19705}. The most common genotype worldwide is genotype 1 followed by genotypes 2 and 3 {19705}. Although there is evidence that the incidence of viral infection may be decreasing, the prevalence of liver disease caused by HCV is on the rise, primarily due to the lag between the onset of infection and the clinical manifestation of liver disease {19705}. The prevalence of chronic HCV is significantly higher among patients with chronic renal failure, and HCV itself is associated with impaired renal function. Treatment of these individuals is therefore recommended but is often complicated by the substantial increase in hematologic toxicities associated with the use of ribavirin in the setting of low creatinine clearance {23275}. Standard of care for genotype 1 HCV infection involves 24-48 weeks of an HCV protease inhibitor in combination with pegylated interferon-alfa (PEG)+ribavirin (RBV). The recommended first-line treatment for subjects with genotype 2 or genotype 3 chronic hepatitis C is PEG+ RBV for 24 weeks {13693}, {17940}. There are minimal data regarding the optimal regimen for patients with severe renal disease (e.g., Cr clearance<30 mL/min) or end stage renal disease on maintenance hemodialysis. Interferon monotherapy for 48 weeks which provides an SVR rate of approximately 40% in clinical trials is often deemed the treatment of choice. Due to the side effects and lengthy duration of current treatment, there is substantial need for a short, simple, interferon-free regimen, particularly in patients who are more susceptible to drug toxicities, such as those with renal insufficiency.

Study objective

(Protocol Am2 dd. 20-Feb-2014, p17/93)

The primary objectives of this study are:
- To evaluate the safety of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks as assessed by review of the accumulated safety data in each treatment arm
- To evaluate the efficacy of sofosbuvir (SOF) 200 mg or 400 mg + ribavirin (RBV) for 24 weeks measured by the proportion of subjects with renal insufficiency who have achieved a sustained viral response 12 weeks after treatment discontinuation (SVR12) in each treatment arm
- To evaluate the steady state pharmacokinetics of SOF and its metabolites upon dosing SOF 200 mg or 400 mg in subjects with renal insufficiency

The secondary objectives of this study are:
- To evaluate the proportion of subjects with renal insufficiency who attain SVR at 4 and 24 weeks after discontinuation of treatment (SVR4 and SVR24)
- To evaluate the kinetics of plasma HCV RNA during and after treatment

discontinuation
- To evaluate the emergence of viral resistance to SOF during and after treatment discontinuation

The exploratory objective of this study is:
- To identify or validate genetic markers that may be predictive of the natural history of disease, response to therapy and/or tolerability of medical therapies through genetic discovery research (e.g., pharmacogenomics), in subjects who provide their separate and specific consent

Study design

(Protocol Am2 dd. 20-Feb-2014, p18/93)

This is a multicenter, open label study that will evaluate the safety, tolerability and antiviral efficacy of SOF with RBV in chronic renal insufficiency and HCV infection subjects with genotype 1 or genotype 3 HCV infection, including those with compensated cirrhosis.

This study will have 2 parts.

Part 1 will enroll approximately 20 subjects with severe renal insufficiency.
- 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 1 SOF 200 mg group, 10 additional subjects will receive SOF 400 mg QD + RBV 200 mg QD for 24 weeks.

Part 2 will enroll approximately 20 subjects on dialysis following review of safety, efficacy and PK data through post-treatment Week 4 of Part 1 SOF 400 mg group.
- 10 subjects will receive SOF 200 mg QD + RBV 200 mg QD for 24 weeks.
- Following review of safety, efficacy and PK data through post-treatment Week 4 of the Part 2 SOF 200 mg group, 10

Intervention

(Protocol Am2 dd. 20-Feb-2014, p18/93)

In Part 1, following screening procedures and Day 1 assessments, eligible subjects will receive either SOF 200 mg or 400 mg QD + RBV 200 mg QD for 24 weeks.

In Part 2, following screening procedures and Day 1 assessments, eligible subjects receive either SOF 200 mg or 400 mg QD + RBV 200 mg QD for 24 weeks.

Study burden and risks

RISK:
Adverse events of the study medication (Also, see E9.)

BURDEN: (As in E4)
Maximum study duration: ca. 1 year, 16 visits, duration: 0.5-3h
15x physical examn (Vital Signs, blood pressure, pulse, temperature. Height and weight at screening only
11x 12-lead ECG
11x serum pregnancy tests (if applicable)
3x Echocardiogram
33x blood tests for a total of 546ml of blood

BENEFIT: (As in E1a)
The potential benefit of successful treatment of HCV in these subjects is substantial. Few patients with severe renal insufficiency can tolerate combination therapy with PEG+RBV due to profound anemia. SVR rates to interferon monotherapy administered for 48 weeks are less than 50%. Interferon-free treatment for 24 weeks could provide substantial improvements in safety, tolerability and efficacy for individuals with chronic HCV infection and end stage renal disease.

Also: (Protocol Am2 dd. 20-Feb-2014, p16/93, Risk/benefit ration)
To date there has been no safety signal identified that is attributable to SOF when administered as part of a combination regimen. Furthermore, SOF does not exacerbate the toxicities associated with RBV, most notably hemolytic anemia. Clinical data with SOF in severe renal insufficiency and in subjects requiring hemodialysis is limited to a single dose study in non-HCV infected subjects. No specific safety signals were identified. The current study is designed to assess the safety and efficacy of therapeutic treatment with SOF+RBV in a small number of subjects with severe renal insufficiency. The 2-part stepwise design will allow a full review of the risk/benefit of both doses and treatment arms in patients with Cr clearance <30 mL/min before proceeding to the cohort of patients on dialysis who are predicted to have higher SOF and GS-331007 exposures.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

(Protocol Am2 dd. 20-Feb-14, p21/93)
1) Willing and able to provide written informed consent
2) Male or female, age greater or equal to 18 years
3) Chronic HCV infection
4) Infection with HCV GT 1 or 3 as determined at Screening
5) Subjects must have the following laboratory parameters at screening:
HCV RNA * 104 IU/mL; ALT*10 the upper limit of normal (ULN); AST * 10x ULN; Hemoglobin * 9 g/dL; Albumin * 3.0 g/dL; Direct bilirubin * 1.5 x ULN; HbA1c * 10%; Creatinine clearance (CLcr) * 30 mL/min* (see protocol p22/93)
6) INR less than or equal to 1.5 x ULN unless subject has known hemophilia or is stable on an anticoagulant regimen affecting INR.
7) A negative serum pregnancy test for female subjects of childbearing potential
8) Male subjects and female subjects of childbearing potential must agree to use protocol specified method(s) of contraception
9) Lactating females must agree to discontinue nursing before administration of study drug
10) Subject must be of generally good health as determined by the Investigator
11) Subject must be ableto comply with the dosing instructions for study drug administration and able to complete the study schedule of assessments.

Exclusion criteria

(Protocol Am2 dd. 20-Feb-13, p23/93)
1) BMI < 18
2) Prior exposure to an direct-acting antiviral targeting the HCV NS5B polymerase
3) Prior null response to PEG+RBV therapy
4) Male with pregnant female partner
5) Chronic liver disease of a non-HCV etiology
6) Infection with hepatitis B virus (HBV) or human immunodeficiency virus (HIV)
7) Unstable psychiatric condition
8) Significant cardiac disease including or resulting in:
a) Cardiomyopathy
b) Left ventricular ejection fraction * 50%
c) Hospital admission for myocardial infarction, heart failure within 1 year of Screening
d) Pulmonary hypertension within 1 year of Screening
9) Clinically significant abnormality on ECG at Screening, including a QTcF >500 msec, or >450 msec in patients who concomitantly use methadone.
10) History of clinically significant hemoglobinopathy
11) History of porphyria
12) Malignancy within the 5 years prior to screening
13) Chronic use of systemically administered immunosuppressive agents
14) Clinically-relevant drug or alcohol abuse within 12 months of Screening.
15) Current or prior history of clinical hepatic decompensation

Study design

Design

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	3
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Ribavirin
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sofosbuvir
Generic name:	Sofosbuvir

Ethics review

Approved WMO Date:	20-01-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-04-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	EUCTR2013-002897-30-NL
ClinicalTrials.gov	NCT01958281
CCMO	NL46963.018.13