A Phase 3, Multicenter, Randomized, Active-Controlled Study to Investigate the Safety and Efficacy of PSI-7977 and Ribavirin for 12 Weeks Compared to Pegylated Interferon and Ribavirin for 24 Weeks in Treatment-Naïve Patients with Chronic Genotype 2 or 3 HCV Infection

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Primary:* To determine the efficacy of PSI-7977 in combination with RBV administered for 12 weeks compared with PEG/RBV administered for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3 as assessed by the rate of SVR12 (HCV RNA

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON37539

Source
ToetsingOnline

Brief title
FISSION

Condition

- Viral infectious disorders

Synonym
Chronic HCV infection, Hepatitus C viral infection

Research involving
Human

Sponsors and support

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

Intervention

Keyword: chronic hepatitis C, liver disease, PSI-7977

Outcome measures

Primary outcome

The primary efficacy endpoint is SVR12 (HCV RNA
weeks after cessation of therapy) in the randomized and dosed population

Secondary outcome

Additional efficacy evaluations will include breakthrough on therapy, relapse,

serum HCV RNA

change from baseline, and proportion of subjects with HCV RNA

Study description

Background summary

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% [1]. The most common genotype in the USA and in Europe is Genotype 1 (GT-1) followed by Genotype 2 (GT-2) and Genotype 3 (GT-3). 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. At present, the recommended first-line treatment for patients with GT-2 or GT-3 (GT-2/3) chronic hepatitis C is pegylated interferon-alfa (PEG) in combination with ribavirin (RBV) for 24 weeks.
This regimen is associated with significant and well characterized toxicities.

Pegylated interferon alfa may cause or aggravate serious neuropsychiatric, autoimmune, ischemic, and infectious disorders. This study may lead to a new treatment or GT-2 of GT-3 (GT-2/3) chronic hepatitis C without pegylated interferon and these side effects.

GS-7977 in combination with ribavirin (RBV) administered for 12 weeks is safe and superior to PEG/RBV administered for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3 (GT-2 or GT-3) as assessed by the rate of sustained viral response (SVR) 12 weeks after the discontinuation of therapy (SVR12).

Study objective

Primary:
* To determine the efficacy of PSI-7977 in combination with RBV administered for 12 weeks compared with PEG/RBV administered for 24 weeks in treatment-naïve patients with HCV genotype 2 or 3 as assessed by the rate of SVR12 (HCV RNA of therapy)

Secondary:
* To assess the safety and tolerability of GS-7977/RBV administered for 12 weeks as measured by the frequency of deaths, serious adverse events (SAEs), discontinuations due to AEs, and Grade 3 or 4 laboratory abnormalities
* To determine the SVR at Week 24 (SVR24) following completion of treatment for each investigational arm (HCV RNA * To evaluate the change in circulating HCV RNA in patients over 12 or 24 weeks
of dosing
* To determine the proportion of patients with HCV RNA below the lower limit of quantitation (LOQ) and lower limit of detection (LOD) at various time points throughout the study
* To determine the proportion of patients whose ALT normalizes during therapy
* To describe rates of virologic failure
* To characterize HCV drug resistance substitutions at baseline, during, and after therapy with GS-7977

Study design

This is a phase III, Multicenter, randomized, active-controlled interventional study

Intervention

- PSI-7977will be taken twice a day by mouth

- Ribavirintablets will be taken by mouth and dosage is dependent on the weight of the patient. Ribavirin should be taken togheter with food.
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- pegylated interferon will be taken at home once a week given by an injection under the skin in the fatty tissue.

Study burden and risks

In total, the patient will have to perform 7-10 visits plus 8 Followup visits, during which blood will be taken 13 times. Other procedures are physical exmination, 3 times a ECG and a liver scan or biopsy.

In a previous research where GS-7977 where given in combination with Ribavirin or pegylated interferon, the side effects were similar to those previously reported with pegylated interferon and ribavirin alone. The most frequently reported side effects in subjects receiving GS-7977 with interferon and ribavirin were headache, fatigue, nausea, chills, and joint and muscle aches. In shorter studies with GS-7977 and a related drug, PSI-7851, subjects also reported headaches, dizziness, and abdominal cramping.

There may or may not be direct benefits for the patient in taking part in this study. However, taking part may help patients
get better care in the future.

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

1) Males or females at least 18 years old, or the legal age of consent, whichever is older, at Screening. Subjects or their heterosexual partner(s) must either be of non-childbearing potential or they must use effective contraception from 2 weeks before the initiation of therapy until 6 months (or the duration recommended locally for ribavirin if longer) after the last dose of study medication.;2) Chronic Genotype 2 or 3 HCV-infection documented by at least one measurement of serum HCV RNA * 10,000 IU/mL;3) Patients with Childs A cirrhosis may be included (up to 20% of patients randomized);4) Subjects must be naïve to all HCV antiviral treatment(s), including but not limited to immunomodulatory and nucleoside/tide treatments for chronic HCV infection.;5) A body mass index (BMI) of *18kg/m2;6) Otherwise suitable for participation as determined by the medical history, physical examination, ECG, and clinical laboratory measurements performed at Screening;7) Able to effectively communicate with the Investigator and other center personnel. Willing to give written informed consent and comply with the study restrictions and requirements

Exclusion criteria

1) Positive test at Screening for HBsAg, anti-HBc IgM Ab, or anti-HIV Ab.;2) History of any other clinically significant chronic liver disease.;3) A history of consistent with decompensated liver disease including ascites, variceal hemorrhage, hepatic encephalopathy, hepatorenal syndrome and hepatopulmonary syndrome, among others.;4) History or current evidence of psychiatric illness, immunologic disorder, hemoglobinopathy, pulmonary disease (including pneumonia or pneumonitis), cardiac disease, seizure disorder or anticonvulsant use, poorly controlled diabetes, cancer, or a history of malignancy that in the opinion of the investigator makes the patient unsuitable for the study. Chronic medical conditions, especially if treated with medications (such as hypertension), must be stable at the time of screening. No new therapies should be started prior to the study that may confound the assessment of study drug safety.;5) Clinical signs and symptoms of acute pancreatitis with elevated lipase;6) Clinically significant ECG findings at screening, screening QTc * 450 ms (non-cirrhotic) or * 500 ms (cirrhotic), or a personal or family history of Torsades de pointes.;7) History of major organ transplantation with an existing functional graft.;8) Active substance abuse which, in the opinion of the investigator, would make the candidate inappropriate for participation in this study.;9) History of uncontrolled thyroid disease or abnormal TSH levels as defined <0.8 x LLN or >1.2 x ULN at Screening (subjects will be eligible with an abnormal TSH if the T3 and T4 are within normal limits).;10) Abnormal haematological and biochemical parameters.;11) Donation or loss of more than 400 mL blood

within 2 months prior to first dose administration.;12) History of clinically significant drug allergy to nucleoside/nucleotide analogs.;13) History of having received any systemic antineoplastic or radiation therapy within 6 months prior to the first dose of study drug or the expectation that such treatment will be needed at any time during the study.;14) Subjects receiving oral or intravenous strong p-glycoprotein inhibitors (including cyclosporine, quinidine, dronedarone, itraconazole, verapamil or ritonavir) within 28 days of dosing. Additional concomitant medications disallowed in this study are outlined in Section 7.7. of the protocol.;15) Participation in a clinical study with an investigational drug, biologic, or device within 3 months prior to first dose administration.;16) Pregnant/Breastfeeding women or males whose partners are currently pregnant.;17) Poor venous access making the patient unable to complete the required laboratory testing
schedule.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	26-03-2012
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pegasys
Generic name:	peginterferon alfa-2a
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Rebetol, Copegus
Generic name:	Ribavirin Mylan
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Sofosbuvir
Generic name:	GS-7977

Ethics review

Approved WMO Date:	22-03-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-05-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-12-2012
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	EUCTR2011-005055-14-NL
ClinicalTrials.gov	NCT01497366
CCMO	NL39467.018.12