A Phase IIa randomized, open-label study of telaprevir (VX-950) administered every 12 or every 8 hours in combination with either Peg-IFN alfa2a (Pegasys®) and ribavirin (Copegus®) or Peg-IFN alfa2b (PegIntron®) and ribavirin (Rebetol®) in treatment naive subjects with chronic genotype 1 hepatitis C infection.

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

Summary

ID

NL-OMON30970

Source
ToetsingOnline

Brief title
Telaprevir study in subjects with chronic genotype 1 HCV infection

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Hepatitis C infection

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: sponsor van dit onderzoek (Tibotec BVBA)

Intervention

Keyword: chronic hepatitis Cinfection, genotype 1, protease inhibitor, treatment naive patients

Outcome measures

Primary outcome

The following efficacy parameters will be explored:

- The proportion of subjects with undetectable HCV RNA at all assessment time

points and after the completion of all anti-HCV therapy (EOT);

- Time to first undetectable HCV RNA level;

- The proportion of subjects with viral breakthrough (defined as an increase >

1 log in HCV RNA level from the lowest level reached, or a value of HCV RNA >

100 IU/mL in subjects whose HCV RNA had previously become undetectable at all

assessment time points;

- The proportion of subjects with partial response (at least 2 log drop from

baseline, but not undetectable) at all assessment time points;

- HCV RNA values and changes from baseline over time;

- Early viral kinetics (antiviral effectiveness - epsilon) and changes in HCV RNA from baseline over time during the first week of treatment and thereafter until EOT;

- The proportion of subjects in each treatment arm with sustained viral response 24 weeks after the end of treatment (SVR24).

Pharmacokinetics and Pharmacodynamics; the following will be explored: the pharmacokinetics of telaprevir and VRT-127394, Peg-IFNs, and RBV; the possible drug-drug interaction of RBV, telaprevir, and each type of Peg-IFN.

Secondary outcome

NAP

Study description

Background summary

One hundred and seventy million people in the world (approximately 3% of the global population), are infected with hepatitis C virus (HCV) of which 8 million persons in EU, where the average prevalence is 1%. About 70% of acute HCV infections become persistent.
Chronic HCV infection is often associated with serious liver disease. HCV is recognized as the most common infection causing chronic liver disease and is a leading cause of death worldwide. The prevalence of the disease is approximately 3-fold higher among persons aged 30 to 49 years of age, and death from HCV usually occurs 20 or more years after the initial infection. Consequently, the death rate due to HCV infection is expected to increase substantially between 2009 and 20199.
The current standard of care (SOC) for patients with hepatitis C, pegylated interferon (Peg-IFN) combined with ribavirin (RBV), results in sustained clearance of HCV ribonucleic acid (RNA) in approximately 50% of patients with genotype 1 hepatitis C. SOC therapy has numerous adverse effects, such as flu-like symptoms and neuropsychiatric effects (Peg-IFN), nausea, weight loss, and hemolytic anemia (RBV), which often requires dose reduction or dose interruptions. Patients not eligible for current therapy include many with co-morbid conditions that often accompany hepatitis C, including decompensated liver disease and renal failure. There is an unmet need for hepatitis C

therapies that are more effective and better tolerated than what is available at present. An antiviral drug, such as telaprevir, that could be effective in combination with direct or indirect-acting antivirals and could provide a better safety profile, a higher rate of sustained viral response, and a shorter duration of treatment, is highly desirable.
Telaprevir is an inhibitor of the NS3-4A protease, currently under development at a dose of 750 mg q8h in co-administration with standard therapy (Peg-IFN alfa2a [Pegasys] and RBV [Copegus]) for chronic genotype 1 hepatitis C. This dosage was selected based on the results of a 14-day trial21 showing that telaprevir monotherapy at doses of 750 mg q8h was associated with continued decreases of the HCV RNA level throughout the dosing period in most subjects. It can be hypothesized that co-administration of telaprevir with standard therapy may allow sustained antiviral efficacy with less frequent dosing than every 8 hours when using the same total daily dose.

Study objective

The objective of this trial is to explore the efficacy, safety, tolerability, pharmacokinetics, and pharmacokinetic-pharmacodynamic relationships of telaprevir when administered as 750 mg q8h or 1125 mg q12h in combination with Peg IFN alfa2a (Pegasys®) and RBV (Copegus®) or Peg IFN alfa2b (PegIntron®) and RBV (Rebetol®).

Study design

This is an open-label, randomized, multicenter trial in subjects with chronic genotype 1 HCV infection who will be randomized to receive 1 of 2 different dose regimens of telaprevir in combination with standard therapy (Peg-IFN alfa2a [Pegasys®] and RBV [Copegus®] or Peg-IFN alfa2b [PegIntron®] and RBV [Rebetol®] at the standard doses). A total of 160 subjects (40 per treatment group) are planned to be enrolled.
The trial consists of a screening phase of approximately 4 weeks, a treatment phase of up to 48 weeks, and a follow-up phase of at least 24 weeks.
Subjects will be randomized to 1 of 4 treatment groups:
A. telaprevir 750 mg q8h with Pegasys/Copegus
B. telaprevir 750 mg q8h with PegIntron/Rebetol
C. telaprevir 1125 mg q12h with Pegasys/Copegus
D. telaprevir 1125 mg q12h with PegIntron/Rebetol
All subjects will receive 12 weeks of telaprevir treatment in combination with standard therapy (i.e., pegylated interferon [Peg IFN] and ribavirin [RBV]). At Week 12, telaprevir dosing ends and subjects continue on standard therapy only. The duration of treatment will depend on subjects' individual virologic response, with a maximum duration of 48 weeks.

For the substudy, at the first visit, visit 'week 8' and visit 'week 20', 4, 9, and 9 additional bloodsamples are taken, respectively; until 12 hours after

injection/ intake of studymedication.

Intervention

Telaprevir: white to off-white oval tablets containing 375 mg of telaprevir for oral administration (Phase III formulation).
Peg-IFN alfa2a (Pegasys®): a solution for subcutaneous injection in a pre-filled syringe.
Peg-IFN alfa2b (PegIntron®): a powder and solvent for solution for subcutaneous injection in a pre-filled pen.
RBV (Copegus®): a 200-mg tablet for oral administration.
RBV (Rebetol®): a 200-mg capsule for oral administration.
Commercially available supplies will be used.

Study burden and risks

The following assessment are included in this trial (see also flow-chart protocol):
- Electrocardiogram (ECG); At the baseline visit, two ECGs will be performed.
- Assessment of the liver; At the beginning of the study, the effect of the Hepatitis C virus on the liver is assessed. This is usually done as part of the normal clinical practice before starting anti-HCV treatment. Depending on the hospital, either a liver biopsy or a Fibroscan will be performed.
- Physical examination; A full examination of all body parts.
- Vital signs; Temperature, pulse (heart rate) and blood pressure will be measured.
- Blood draws; At all visits during this study, blood will be taken. for determination of safety and efficacy of the treatment. Blood will be drawn 6 times at the Baseline visit and 2 times on Day 2. The total amount of blood that will be collected over the entire study period will be about 850 mL at most.
- Urine tests; At most visits during the study, for safety tests.
- Pregnancy test; Bloodtest at the screening; at other visits, a urine pregnancy test. If no monthly visit is planned, a pregnancy test will be performed at home until 24 weeks after last dose of ribavirin.
- Fasting before the visit; At some visits it is required not to eat nor drink within 8 hours before the visit.
- Diary; subjects fill out time of studymedication intake in a diary.

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. Male and female subjects 18-65 years of age.
2. Chronic genotype 1 hepatitis C infection. Chronic disease status must be confirmed by at least 1 of the following standard criteria:
- history of a remote risk factor (e.g., intravenous drug abuse or blood transfusion), or
- abnormal alanine aminotransferase (ALT) levels for > 6 months prior to screening (note: elevated ALT is not an inclusion criterion if one of the other criteria for chronic hepatitis C is met), or
- diagnosis of hepatitis C > 6 months before the screening period.
3. Naïve of therapy for HCV (including investigational products).
4. Screening laboratory values of the following variables must meet the acceptable values defined below:
Laboratory variable Acceptable values
Absolute neutrophil count >= 1,500/mm^3
Platelet count >= 100,000/mm^3
Bilirubin Within normal range (except for subjects with Gilbert*s Syndrome)
Hemoglobin Within normal range
All other hematology and clinical chemistry must show no clinically significant abnormalities, as judged by the investigator.

5. Detectable plasma HCV RNA > 10,000 IU/mL at entry.
6. Liver biopsy (preferred) or Fibroscan (alternative) within three years of the screening to assess the degree of liver fibrosis. If no biopsy or Fibroscan results are available at screening, such procedure should be performed as part of the screening procedures.
7. Judged to be in otherwise good health, in the opinion of the investigator.
8. Agree to the use of two effective methods of contraception (as outlined in section 5.2.4 of the protocol) if heterosexually active, unless the male partner has undergone a vasectomy or if the female sexual partner has had a bilateral oophorectomy, or a total hysterectomy, or if she is post-menopausal for at least two years.
9. Willing to refrain from the concomitant use of any medications, substances or foods prohibited in this trial.
10. Informed Consent Form (ICF) signed voluntarily before first trial-related activity.
11. Agree not to participate in other clinical studies (with the exception of observational studies) for the duration of his/her participation in this trial.

Exclusion criteria

1. Presence of a concomitant medical condition that in the opinion of the investigator could influence the results of the trial or that could represent an additional risk for the administration of the study medication to the subject.
2. Any medical contraindications to Peg-IFN alfa2a, Peg-IFN alfa2b, or RBV therapy including but not limited to the following:
- abnormal thyroid stimulating hormone (TSH) levels (except if well-controlled on medication) or poorly controlled thyroid function;
- evidence of clinically significant cardiac dysfunction;
- history of psychiatric disorders determined by the investigator to contra-indicate the use of IFN-based therapy;
- antinuclear antibody (ANA) titer >= 1:320;
- history of hemoglobinopathies.
3. History or evidence of cirrhosis or decompensated liver disease defined as a prior or current
history of ascites, hepatic encephalopathy, bleeding esophageal or gastric varices.
4. Any other cause of significant liver disease in addition to hepatitis C; this may include but is not limited to, hepatitis B, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson*s disease, nonalcoholic steatohepatitis, or primary biliary cirrhosis.
5. Diagnosed or suspected hepatocellular carcinoma. Alfa-fetoprotein at screening must be less than 50 ng/mL, or if higher, absence of a mass on an ultrasound must have been documented.
6. History or suspicion of alcohol, barbiturate, or amphetamine recreational or narcotic drug use, which in the investigator*s opinion would compromise the subject*s safety and/or compliance with trial procedures.
7. Human immunodeficiency virus (HIV) or hepatitis B virus (HBV) co-infection.
8. Women who are pregnant, planning on becoming pregnant, or breast feeding, and partners of women who are pregnant or breast feeding.

9. Hypersensitivity to tartrazine.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-10-2007
Enrollment:	16
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Copegus®
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Pegasys®
Generic name:	Peginterferon alfa-2a
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	PegIntron®
Generic name:	Peginterferon alfa-2b
Registration:	Yes - NL intended use
Product type:	Medicine

Brand name:	Rebetol®
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Telaprevir
Generic name:	Telaprevir

Ethics review

Approved WMO Date:	24-10-2007
Application type:	First submission
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	16-11-2007
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	08-08-2008
Application type:	Amendment
Review commission:	METC Leids Universitair Medisch Centrum (Leiden)
Approved WMO Date:	07-07-2009
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	EUCTR2007-001044-44-NL
CCMO	NL19209.058.07