A Randomized Study of Stopping Treatment at 24 Weeks or Continuing Treatment to 48 Weeks in Treatment-NaÃ¯ve Subjects with Genotype 1 Chronic Hepatitis C who Achieve an Extended Rapid Viral Response (eRVR) While Receiving Telaprevir, Peginterferon Alfa2a (PegasysÂ®) and Ribavirin (CopegusÂ®)

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Primary:To estimate the difference in SVR rates between T12/PR24 and T12/PR48 treatment regimens in subjects who achieve eRVR.Secondary:To evaluate the safety of telaprevir in combination with Peg-IFN-alfa-2a and RBV in treatment-naïve subjects with...

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

Summary

ID

NL-OMON33525

Source
ToetsingOnline

Brief title
VX08-950-111 542/008

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Liver disease

Research involving
Human

Sponsors and support

Primary sponsor: Vertex Pharmaceuticals
Source(s) of monetary or material Support: Farmaceutisch bedrijf

Intervention

Keyword: Chronic Hepatitis C, Peginterferon □-2a, Ribavirin, Telaprevir

Outcome measures

Primary outcome

Proportion of randomized subjects achieving sustained viral response (SVR), demonstrated by achieving undetectable HCV RNA 24 weeks after last dose of study treatment

Secondary outcome

* Proportion of subjects enrolled in the study achieving an SVR

* Proportion of subjects who have undetectable HCV RNA at Week 72

* Proportion of enrolled subjects achieving eRVR (extended RVR), demonstrated by achieving undetectable HCV RNA at Week 4 and at Week 12

* Proportion of randomized subjects who have undetectable HCV RNA 12 weeks after last dose of study treatment

* Proportion of randomized subjects who relapse, defined as those who complete treatment, have undetectable HCV RNA at end of treatment (EOT; Week 24 or Week

48 respectively), and become HCV RNA detectable during antiviral follow-up

* Proportion of enrolled subjects who relapse, defined as those who have

undetectable HCV RNA at the EOT, and become HCV RNA detectable during antiviral

follow-up

* Proportion of subjects who have undetectable HCV RNA at the end of treatment

(Week 24 or Week 48 respectively)

* Adverse events, physical examination findings, and clinical laboratory, vital

sign, and electrocardiogram (ECG) assessments

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).1,2 The majority of these patients are above the age of 50 and have been infected for at least 30 years, putting them at risk for severe liver disease. The current standard of care for patients with chronic hepatitis C, a 48-week regimen of pegylated interferon (Peg-IFN) combined with ribavirin (RBV), results in sustained clearance of HCV RNA in 40% or less for patients with genotype 1 chronic hepatitis C.3 This combination therapy has numerous adverse effects, including flu-like symptoms (fatigue, fever, malaise, nausea, myalgia, and arthralgia) and neuropsychiatric effects (anxiety, increased irritability, and depression).4,5 As a result of the low efficacy and poor tolerability, the treatment rates of diagnosed patients with HCV are suboptimal.

Telaprevir is being developed to meet the unmet medical need for more effective therapies to treat patients with chronic, genotype 1 hepatitis C. Telaprevir (VX-950), being developed by Vertex Pharmaceuticals Incorporated (Vertex) in collaboration with Tibotec BVBA, is a member of a new class of drugs being developed for chronic hepatitis C: specifically-targeted antiviral treatments for hepatitis C (STAT-C). Unlike Peg-IFN and RBV, STAT-C compounds act directly on HCV. Telaprevir is a specific, reversible, covalent, tight- and slow-binding NS3*4A inhibitor that was derived through structure-based drug design. Telaprevir prevents HCV replication by inhibiting the HCV NS3*4A protease, an enzyme that is essential for HCV replication.

The nonclinical and clinical data available to date support further clinical development of telaprevir as a treatment for chronic hepatitis C. The results of nonclinical, Phase 1, and Phase 2a studies are summarized in the Investigator*s Brochure.6 Interim results from two complementary Phase 2 studies (104 and 104EU) are summarized below, and additional details are provided in the Investigator*s Brochure.6

Studies 104 and 104EU, conducted in treatment-naïve subjects with chronic, genotype 1 hepatitis C, evaluated the safety and efficacy of 12 weeks of telaprevir treatment (750 mg every 8 hours [q8h]) in combination with 12, 24, or 48 weeks of peginterferon alfa-2a (Peg-IFN-alfa-2a), with and without RBV. Final data from Study 104 and interim data from Study 104EU show a benefit for telaprevir-treated subjects. The treatment arms receiving 12 weeks of telaprevir in combination with 24 weeks of Peg-IFN-alfa-2a and RBV, had a sustained viral response (SVR) rate of 61% (Study 104) and an SVR rate of 68% (Study 104EU). Among all subjects who completed 12 weeks of telaprevir in combination with 24 weeks of Peg-IFN-alfa-2a and RBV in these studies, who had undetectable hepatitis C virus at 12 weeks of follow-up and have had 24 weeks of follow-up data, no relapses have been seen past 12 weeks.

The SVR rate for subjects who received 12 weeks of telaprevir in combination with 48 weeks of Peg-IFN-alfa-2a and RBV in was 67%, similar to the SVR rate for the 24-week telaprevir treatment regiment (61%). The difference in SVR rate between these 2 treatment regimens may be attributed to a lower discontinuation rate in the 48-week treatment arm compared to the 24-week arm during the initial 12 weeks of the study (10% versus 19%); however, as the treatment regimen was identical during the 12-week period (telaprevir, Peg-IFN-alfa-2a, and RBV), this difference was apparently by chance. The response to the 24-week treatment regimen is being confirmed in an ongoing clinical study, which will evaluate a 24-week regimen in subjects who achieve an eRVR (extended rapid viral response) and a 48-week regimen in subjects who do not achieve eRVR.

Relapse rates in subjects who completed 12 weeks of telaprevir in combination with 24 weeks of Peg-IFN-alfa-2a and RBV and were undetectable at the time of completion were 2% in Study 104 and 14% in Study 104EU. In these subjects in Study 104EU who had an eRVR, the relapse rate was 7%. In study 104, the relapse rate in subjects who completed the 48-week treatment regimen and had undetectable HCV RNA at the end-of-treatment was 6%.

Viral breakthrough (defined as increase of >1 log in HCV RNA levels during treatment) occurred in 5% of subjects treated with telaprevir, Peg-IFN-alfa-2a, and RBV in the first 12 weeks in Studies 104 and 104EU. Breakthroughs were associated with telaprevir resistant variants, and the majority of breakthroughs occurred early (in the first 4 weeks) in the dosing period, suggesting that breakthrough is the result of selection of pre-existing variants. The duration of telaprevir treatment did not affect the incidence of viral breakthrough and is not associated with increasing levels of phenotypic

resistance in the majority of subjects.

In Phase 2 Studies 104 and 104EU, the safety profile of telaprevir administered for 12 weeks in combination with Peg-IFN alfa-2a has been well characterized. Based on combined interim safety analyses of Study 104 and 104EU, the treatment discontinuation rate due to adverse events through 12 weeks was 13% for the telaprevir, Peg-IFN-alfa-2a, and RBV regimen compared to 3% for the control. The adverse event profile of the telaprevir, Peg-IFN-alfa-2a, and RBV regimen was similar to that observed with control, with the exception of rash and anemia that occurred at a higher incidence and with greater severity in subjects receiving the telaprevir-containing regimens. The data suggest that telaprevir and RBV have overlapping effects on rash and anemia, resulting in some events of greater severity when telaprevir and RBV are administered in combination. Rash and anemia appeared to be reversible after the discontinuation of telaprevir dosing.7 The current protocol includes a Rash Management Plan to guide investigators on the grading, reporting and management of rash events reported in this study (See Section 13.1.2).

In conclusion, the efficacy and virology data demonstrate the potential of a regimen of 12 weeks of telaprevir, in combination with 24 or 48 weeks of Peg-IFN-alfa-2a and RBV, to be a substantial improvement over current therapy. Similar SVR rates were observed between two different telaprevir treatment regimens, 12 weeks of telaprevir in combination with 24 weeks of Peg-IFN-alfa-2a and RBV or with 48 weeks of Peg-IFN-alfa-2a and RBV. The difference in relapse rates reported between these groups was minimal, supporting the further investigation of the 24week telaprevir-based treatment regimen.

However, the PROVE1 study, which included both of these arms, included an *RVR criterion* such that only subjects who had an RVR, and then remained HCV RNA undetectable through the rest of their treatment period, could stop treatment at Week 24 (if they did not have an RVR, they were to continue dosing through Week 48), and the SVR rates are based only on those subjects treated for a 24-week duration. The 48-week treatment arm had no similar criterion, so all subjects randomized to this arm are included in the efficacy analysis, and it is difficult to compare the arms. This current investigation will allow evaluation of the efficacy and safety of the 24-week and 48-week total treatment durations in the same population (subjects who achieve an eRVR).

Study objective

Primary:
To estimate the difference in SVR rates between T12/PR24 and T12/PR48 treatment regimens in subjects who achieve eRVR.

Secondary:
To evaluate the safety of telaprevir in combination with Peg-IFN-alfa-2a and

RBV in treatment-naïve subjects with genotype 1 chronic hepatitis C.

Study design

This is a randomized, open-label, multicenter study to be conducted in treatment-naïve subjects with genotype 1, chronic hepatitis C infection.
Enrollment is planned for a total of 470-500 subjects.
Subjects who achieve an extended rapid viral response will be randomized 1:1 to stop all study treatment at Week 24 (randomized withdrawal) (eRVR T12/PR24 group), or to continue Peg-IFN-alfa-2a and RBV treatment through 48 weeks (eRVR T12/PR48 group). Subjects who do not achieve eRVR will be assigned Peg IFN alfa 2a and RBV dosing for 48 weeks (non-eRVR T12/PR48 group). Randomization will be blocked and stratified to optimize balance among the treatment groups with regard to genotype subtype (1a, 1b, and other) and race (Black or non-Black, self-identified).
HCV RNA results will be double-blinded up to Week 24. Even after the Week 24 time point, the HCV RNA values prior to Week 24 will not be revealed to the investigator or subject until the end of the study. Individual viral response monitoring will be conducted by an unblinded independent reviewer while the site, subject, and sponsor remain blinded to HCV RNA data, and then by the site investigator following HCV RNA data unblinding.
HCV RNA results will be monitored at specific time points throughout the treatment period starting at Week 4 to determine if treatment and procedural modifications should be made for individual subjects based on the prespecified viral response criteria shown in Table 8-1 of the main protocol.

Intervention

Starting on Day 1, all participants will receive initial treatment with telaprevir in combination with PEG-IFN and RBV for 12 weeks followed by 12 weeks of PEG-IFN + RBV.

Peginterferon *-2a (PEG-IFN):
PEG-IFN is an injection. PEG-IFN will be injected under your skin (subcutaneously) once a week for 24 or 48 weeks. The dose will be 180 micrograms.

Ribavirin (RBV):
RBV are tablets (200 mg each). RBV will be taken twice a day for 24 or 48 weeks. The dose will be 1000 mg per day (5 tablets) if you weigh less than 75 kg (160 pounds) and 1200 mg (6 tablets) if you weigh more than 75 kg (160 pounds). RBV can be taken with the morning and evening doses of telaprevir.

Telaprevir:
Telaprevir are tablets which will be taken every 8 hours, for a total 12 weeks. The dose of telaprevir will be 750 mg (2 tablets of 375 mg each).

Telaprevir should be taken with a glass of water and with food.

Study burden and risks

The most common side effects (generally reported by more than 50% of participants) are:
* Fatigue
* Nausea
* Itching skin (sometimes with a rash, sometimes without a rash)

Other common side effects (reported by 25% - 50% of participants) are:
* Flu-like symptoms (may include aches, headache, fevers, chills, feeling ill in general)
* Headache
* Mild skin rash
* Insomnia (inability to sleep)
* Diarrhea
* Skin redness or irritation at the site of the interferon injection
* Low red blood cell counts (anemia), which can cause fatigue, weakness, and sometimes fainting

Less common side effects (5- 25%) are:
* Dizziness
* Vomiting
* Moderate skin rash
* Fever, and chills
* Aching joints and/or muscles
* Dry skin
* Coughing
* Shortness of breath, or trouble catching your breath
* Depression
* Hair loss or hair thinning
* Hemorrhoids, or itching/irritation around the anus
* Low white blood cell counts (neutropenia), so your body may not be able to fight infections as well
* Low platelet cell counts, so your blood may not be able to form clots as well
* Loss of appetite
* Blurred vision

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. May not have received any previous treatment with any approved or investigational drug or drug regimen for the treatment of hepatitis C
2. Male and female subjects, 18 to 70 years of age, inclusive
3. Genotype 1, chronic hepatitis C with detectable HCV RNA. Genotype must be confirmed during screening. Confirmation that the disease is chronic (as opposed to acute disease of less than 6 months duration) must be by at least 1 of the following criteria:
* Diagnosis of HCV >6 months before the screening visit
* Abnormal alanine aminotransferase (ALT) levels for >6 months before the screening period (Note: ALT does not have to be elevated to be eligible for the study, but history of elevated ALT can indicate duration of the infection).
4. Screening laboratory values within the following acceptable ranges:
Hepatitis B surface antigen (HBsAg): Seronegative
Human Immunodeficiency Virus (HIV) 1 and 2 antibodies (Ab): Seronegative
Absolute neutrophil count: * 1,500/cmm
Platelet count: * 90,000/cmm
Hemoglobin: * 12 g/dL for females * 13 g/dL for males
Uric acid: Within normal range
TSH and T4 Within normal range, or adequately controlled thyroid function on treatment

All other hematology and clinical chemistry results: Within normal limits or showing no clinically significant abnormalities
5. Subject must have documentation of a liver biopsy within 1 year before the screening visit, or the subject must agree to have a biopsy performed within the screening period. Liver biopsy must show evidence of hepatitis (demonstrated by inflammation and/or fibrosis). If a biopsy more than 1 year prior to screening has already demonstrated histological cirrhosis, the biopsy does not need to be repeated if this biopsy report can be provided.
6. Subjects (or their female partners) must not be pregnant, or planning to become pregnant throughout the study dosing period and through 6 months post-dosing for female study subjects, 7 months post-dosing for female partners of male study subjects; or they must be permanently sterile or otherwise of non-childbearing potential. They must also not be breastfeeding. If of child-bearing potential, female subjects must agree to use 2 effective methods of contraception from screening through 6 months after the last dose of RBV. Male subjects who have a female partner of childbearing potential must agree to use 2 effective methods of contraception from Screening through 7 months after the last dose of RBV unless vasectomized. (For additional information on pregnancy and contraception requirements, please see Section 11.7.)
7. Willing and able to refrain from the concomitant use of any medications, substances, or foods noted in Section 10.12, from 14 days prior to the first day of dosing through the end of treatment.
8. Able to read and understand, and willing to sign the informed consent form and abide by the study restrictions.

Exclusion criteria

1. Subject has any contraindications to Peg-IFN-alfa-2a or RBV therapy, including but not limited to any of the following:
* Hypersensitivity to any component of Peg-IFN *alfa-2a or RBV
* Hemoglobinopathies (including thalassemia major, sickle-cell disease)
* History or other clinical evidence of significant or unstable cardiac disease (e.g. angina, congestive heart failure, recent myocardial infarction, significant arrhythmia) and/or clinically significant ECG abnormalities
* Abnormal thyroid function that cannot be controlled effectively by medication
* Poorly controlled diabetes mellitus as evidenced by HbA1C * 8.5% at screening
* Creatinine clearance * 50mL/min at screening
* Antinuclear antibody (ANA) titer *1:640 at screening and/or evidence of autoimmune hepatitis on liver biopsy
2. Evidence of hepatic decompensation in cirrhotic subjects: history of ascites, hepatic encephalopathy, or bleeding esophageal varices, and/or screening laboratory results of any of the following:
* International Normalized Ratio (INR) of *1.5
* Serum albumin <3.3 g/dL
* Serum total bilirubin >1.8 times the upper limit of normal (ULN), unless history of Gilbert*s disease
3. Any other cause of significant liver disease in addition to hepatitis C, which may include,

but is not limited to malignancy with hepatic involvement, hepatitis B, drug or alcohol-related cirrhosis, autoimmune hepatitis, hemochromatosis, Wilson*s disease, nonalcoholic steatohepatitis (NASH), or primary biliary cirrhosis
4. Diagnosed or suspected hepatocellular carcinoma as evidenced by screening alfa-fetoprotein (AFP) of * 50 ng/mL. If AFP is * 50 ng/mL, absence of a mass must be demonstrated by ultrasound within two months prior to the screening period
5. Active malignant disease or history of malignant disease within 5 previous years (with the exception of treated basal cell carcinoma)
6. Pre-existing psychiatric condition that could interfere with the subject*s participation in and completion of the study, including but not limited to:
* severe depression or hospitalization for depression,
* schizophrenia, bipolar illness, severe anxiety or personality disorder,
* a period of disability or impairment due to a psychiatric disease within the past 5 years.
7. History of significant craniocerebral trauma or active seizure disorders requiring medication
8. History of organ transplant, with the exception of corneal transplants and skin grafts
9. Medical condition that requires frequent or prolonged use of systemic corticosteroids (e.g., severe asthma, severe arthritis or autoimmune conditions, organ transplantation, adrenal insufficiency, etc.)
10. Autoimmune-mediated disease (e.g., Crohn*s disease, ulcerative colitis, idiopathic thrombocytopenic purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma, severe psoriasis)
11. History of acute pancreatitis within 5 years prior to the screening visit
12. History or other evidence of severe retinopathy or clinically significant ophthalmological disorder due to diabetes mellitus or hypertension. For subjects with a history of hypertension or diabetes, written clearance from an ophthalmologist has to be obtained before the start of treatment
13. History or other clinical evidence of chronic pulmonary disease associated with functional impairment
14. History of hemophilia
15. Evidence of serious or severe bacterial or fungal infection(s), including active tuberculosis
16. Currently abusing illicit drugs (narcotics or other controlled substances) or alcohol, or has a history of illicit substance or alcohol abuse within 2 years prior to the screening visit. Subjects who have a history of abuse of illicit drugs or alcohol should have had no incidents of abuse within the 2 years prior to the screening visit. Patients with a history of abuse of narcotics or other controlled substances should be known by the investigative site and considered to be a good candidate for this clinical research study. Patients treated with methadone should be on a stable methadone program for at least 6 months prior to screening.
17. Participation in any investigational drug study within 90 days before study drug dosing, or participation in more than 2 drug studies in the 12 months before study drug dosing, or participation in any concurrent research study including non-drug studies from screening until the end of the subject*s participation in this study
18. Hypersensitivity to tartrazine (yellow dye #5)

Study design

Design

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

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-09-2008
Enrollment:	27
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:	Onbekend
Generic name:	Telaprevir
Product type:	Medicine
Brand name:	Pegasys
Generic name:	Peginterferon □-2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	12-09-2008
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2009
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-07-2009
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	EUCTR2008-003836-39-NL
CCMO	NL24713.018.08