A blinded, randomized, placebo-controlled trial in genotype 1 hepatitis C-infected subjects to evaluate the efficacy, safety, tolerability and pharmacokinetics of repeated doses of TMC435350, with or without peginterferon alpha-2a and ribavirin.

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The primary objectives of this trial are the following:- to determine the dose dependency of the antiviral effect of TMC435350 during 1 week ofmonotherapy in treatment-naïve HCV-infected subjects;- to determine the dose dependency of the antiviral...

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

Summary

ID

NL-OMON32015

Source
ToetsingOnline

Brief title
TMC435350 study in genotype 1 hepatitis C-infected subjects

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: Industrie ;met name de sponsor van de studie

Intervention

Keyword: chronic hepatitis C infection, Copegus, Pegasys, viral protease inhibitor

Outcome measures

Primary outcome

The primary efficacy parameter is the viral load drop at the end of the 4-week

treatment regimen.

Secondary outcome

Secondary parameters include:

- the proportion of subjects with viral load below the limit of quantification

and limit of detection respectively.

- Also the proportion of subjects per treatment regimen with viral breakthrough

will be assessed.

- The results of the viral genotype will be evaluated by the Sponsor

Virologist. Relevant changes

in the viral sequence, detected by the viral genome sequencing will be

tabulated and described.

Study description

Background summary

Hepatitis C virus (HCV) is a leading cause of liver disease worldwide and has become a focus of considerable medical research. An estimated 170 million people (i.e., 3% of the global population) are infected with HCV. More than 50% of HCV infections become chronic in nature.
This may lead to the development of liver fibrosis, cirrhosis, and occasionally hepatocellular carcinoma. Chronic HCV infection is the leading cause of liver failure requiring liver transplantation.
Current HCV therapies are based on peginterferon alpha-2a (PegIFN-*) in combination with ribavirin (RBV). This combination therapy yields a sustained virologic response in approximately 80% of subjects infected with genotypes 2 and 3 HCV, and in approximately 45% of subjects infected with genotype 1 HCV. In addition to the limited efficacy on genotype 1 HCV, this combination therapy has significant side effects and is poorly tolerated in some subjects. Major side effects include influenza-like symptoms, hematologic abnormalities, and neuropsychiatric symptoms.
In recent clinical trials, new investigational drugs acting directly on the virally encoded protease target have demonstrated that significant reductions in HCV viral load can be achieved during short courses of monotherapy, or when administered in addition to PegIFN + RBV combination therapy. There is a need for HCV inhibitors that may overcome the disadvantages of current HCV therapy such as side effects, limited efficacy, the emerging resistance, and compliance failures.
Lead optimization has led to new compounds with a low EC50, including the compound TMC435350. TMC435350 was shown to be an inhibitor of HCV NS3/NS4A protease activity in enzymatic assays in vitro and of HCV replication using the cellular replicon model. In vitro, TMC435350 has an EC50 on HCV replication of 8nM (6 ng/mL) in the human hepatoma cell line (Huh7)-Luc cell line engineered with a genotype 1 HCV replicon sequence3

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Study objective

The primary objectives of this trial are the following:
- to determine the dose dependency of the antiviral effect of TMC435350 during 1 week of
monotherapy in treatment-naïve HCV-infected subjects;
- to determine the dose dependency of the antiviral effect of TMC435350 during combined
tritherapy with PegIFN*-2a and RBV in treatment-naïve HCV-infected subjects.

The secondary objectives of this trial are the following:
- to determine the safety, tolerability and pharmacokinetic profile of TMC435350 during
1 week of monotherapy, and during combined tritherapy with PegIFN*-2a and RBV, in
treatment-naïve HCV-infected subjects;
- to determine the 4-week efficacy and safety of 2 selected doses of TMC435350 given in
combination with PegIFN*-2a and RBV in treatment-experienced (prior non-responders
to IFN-based therapy/relapsers, who did not discontinue anti-HCV therapy due to AEs)
HCV-infected subjects;
- to determine the frequency, kinetics, and genetics of viral breakthrough of HCV during
monotherapy and combination therapy; genetics of viral breakthrough will also be determined during SoC treatment;
to follow-up rapid virologic response (RVR) in subjects at Week 4 until Week 24 (after
20 weeks of SoC treatment) or Week 48 (after 44 weeks of SoC treatment), to determine
the incidence of sustained virologic response (SVR) at these time points and during a
24-week treatment-free observation period;
- to study the potential drug-drug interaction by TMC435350 on RBV.

Study design

This trial is randomized and blinded (during the course of the investigational treatment phase, the
Sponsor, Investigator, and the patient will remain blinded for treatment) to allow for an objective
comparison of efficacy, tolerability, and safety between active TMC435350 treatment and

placebo. When the previous dose cohort was found safe and efficacious (data review meeting,
see Section 6.2.6), the next dose level will be tested in a new dose cohort. After completion of
each of the individual cohorts* the Sponsor will require access to the treatment codes. The
Investigator will be provided access to the individual treatment code at Week 20.
Current HCV therapies are based on PegIFN-* in combination with RBV. This combination
therapy yields a sustained virologic response in approximately 45% of subjects chronically
infected with genotype-1 HCV, and is considered SoC.

Intervention

A first cohort of 48 treatment-naïve subjects will be randomized to low-dose treatment or
placebo. This cohort will be equally distributed over Panels A and B. In this first cohort, each
panel will consist of 2 dose groups of TMC435350 (25 or 75 mg; n = 9 subjects each) and one
placebo group (n = 6 subjects). Subjects in Panel A will receive TMC435350 or placebo in
monotherapy for 7 days. This 7-day monotherapy period will be followed by a 21-day combined
tritherapy period in which TMC435350 or placebo is coadministered with PegIFN*-2a
(Pegasys®) and RBV (Copegus®). Subjects in Panel B will receive 4 weeks of
combinedtritherapy. Stopping rules for dose limiting toxicity and definitions for determination of a
possible Maximum Tolerated Dose (MTD) have been defined. Data Review Meetings will be
organized by the Sponsor with the Principal Investigator before dose escalation as follows:
After a careful blinded review of the first-week safety, tolerability and, to the available extent,
pharmacokinetic data of the low-dose cohort, a next cohort of 24 treatment-naïve subjects will be
randomized to middle dose treatment (200 mg) or placebo. This cohort will also be equally
distributed over Panels A and B. In this second cohort, each panel will consist of one
TMC435350 dose group (200 mg, n = 9 subjects) and one placebo group (n = 3 subjects).
Combined treatment with PegIFN*-2a and RBV in Panels A and B will happen as described for

the first cohort.
After a careful blinded review of the safety, tolerability, and pharmacokinetic data after
completion of the middle dose cohort, a third cohort of 24 treatment-naïve subjects will be
randomized to high dose treatment (400 mg) or placebo. This cohort will again be equally
distributed over Panels A and B. In this third cohort, each panel will consist of one TMC435350
dose group (400 mg, or the final selected dose based on safety and PK data, not exceeding
400mg; n = 9 subjects) and one placebo group (n = 3 subjects). Combined treatment with
PegIFN*-2a and RBV in Panels A and B will happen as described for the first cohort.
After a first-week blinded safety and PK review in the highest dose cohort of treatment-naïve
subjects, the 24 treatment-experienced subjects (non-responders/relapsers) will be randomized
over 2 TMC435350 dose groups (200 mg or 400 mg, or the final selected dose based on safety,
tolerability, and pharmacokinetic data, not exceeding 400 mg; n = 9 subjects each) or placebo
(n = 6 subjects) in Panel C. These subjects will receive 28-day combined tritherapy.
Randomization in this cohort will be stratified for previous relapsers and non-responders.
In addition, 10 HCV-infected non-responding/relapsing subjects having participated in trial
TMC435350-TiDP16-C101 will be included in the last cohort. These subjects will all receive
28-day combined tritherapy including active TMC435350 treatment at a dose of 400 mg (or the
final selected dose based on safety, tolerability and pharmacokinetic data, not exceeding
400 mg), in combination with RBV and PegIFN*-2a after safe completion of the 400 mg dose in
Panel B.
After each 28-day treatment period, subjects will be offered free of charge standard of care (SoC)
treatment containing PegIFN*-2a (Pegasys®) and RBV (Copegus®) until Week 48 (or Week 24)
depending on the virologic response during the initial 20 weeks of treatment.

Study burden and risks

- Number of bloodsamples:

Panel A: 199 - 3.9 ml per sample
Panel B-C-D: 198 - 3.9 ml per sample
In case of drop out: 20 blood samples; 4,4ml per sample.
- Number of visits to the site: 46
- Physical examination: 14
- Risks: In healthy volunteers the following adverse events were reported (they received either placebo or TMC435350): loose stool, diarrhea, flatulence, heavy headedness, frequent defecation, light headedness, somnolence. Furthermore a mild and transient readness of the skin after direct exposure of the skin to the sun was reported by 3 people who received either placebo, either TMC435350. Other risks: skin sensitivity to the sun; rash; known adverse events of the Standard of Care treatment; possible blood draw risks.
- Justification of the study: The patient's health will be monitored closely. After the 28 days 'experimental' phase (including 21 days in combination with the Standard of Care), the Standard of Care treatment for HCV is provided for 24 or 48 weeks (depending on the response).

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. Aged between 18 and 70 years, extremes included;
2. Documented chronic (diagnosis of hepatitis C > 6 months before the screening period) genotype 1a or 1b HCV infection (as assessed by line probe assay); treatment-naïve subjects or prior non-responding subjects/relapsers to previous treatment regimens (IFN/RBV or pegylated IFN/RBV), who did not discontinue anti-HVC therapy due to AEs; genotype 1 HCV patients with hemophilia or with stable methadone use may be enrolled; (subtyping in genotype 1a and 1b patients will also be done);
3. ICF signed voluntarily before the first trial related activity;
4. Able to comply with the protocol requirements and having good accessible veins;
5. HCV plasma viral load * 10,000 IU/mL at screening (as assessed by the Taqman assay);
6. Bodyweight as defined by a Quetelet Index (Body Mass Index [BMI], weight in kg divided by the square of height in meters) between 18 and 32 kg/m², extremes included.

Exclusion criteria

1. Evidence of Child Pugh B or C liver disease or Metavir score 4 at screening with a history or evidence of decompensated cirrhosis defined as prior or current history of ascites, hepatic encephalopathy, bleeding esophageal or gastric varices. 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, non-alcoholic steatohepatitis, or primary biliary cirrhosis. Subjects with diagnosed or suspected hepatocellular carcinoma;
2. Subjects receiving or having received polymerase inhibitor or protease inhibitor treatment for HCV during the 6 months before screening;
3. Male subjects with female partners of childbearing potential not agreeing to use a reliable birth control method for 90 days after the last dosing of TMC435350 in the trial or as prescribed in the leaflet of the medication as administered in the SoC treatment period (when taking PegIFN*-2a in combination with RBV, all subjects must use effective birth control methods during treatment and for 7 months afterwards);
4. Female, except if postmenopausal for over 2 years, or posthysterectomy, or post-tubal ligation (without reversal operation);
5. History or evidence of current use of alcohol, barbiturate, amphetamine, recreational or narcotic drug use, which in the Investigator*s opinion would compromise the subject*s safety and/or compliance with the trial procedures (period of non-drug/alcoholic misuse must at least be 1 month before the first administration of study medication).
6. A positive urine drug test at screening. Urine will be tested to check the current use of amphetamines, cocaine, and opioids (with the exclusion of methadone).
7. Subjects with at least one of the following laboratory abnormalities as defined by the

Division of Microbiology and Infectious Diseases (DMID) Adult Toxicity Table at screening:
- Bilirubin * 1.5x upper limit of laboratory normal range (ULN);
- Platelet count < 80,000/mm3;
- White blood cell (WBC) count < 2,000 cells/mm3;
- Any other lab toxicity found to be clinically significant by the Investigator.
8. Subjects coinfected with HIV-1 or HIV-2, or hepatitis A or B virus infection (confirmed by hepatitis A antibody immunoglobulin [IgM], or hepatitis B surface antigen [HBsAg]) at screening;
9. Subjects with a pathologically prolonged QTc value (> 500 ms) at screening, or any active clinically significant disease (e.g., tuberculosis, cardiac dysfunction), or medical history or physical examination findings during screening that, in the Investigator*s opinion, would compromise the outcome of the trial;
10. Subjects having uncontrolled/unstable diabetes, epilepsy, a manifest psychiatric disease;
11. Non-stable methadone use or subjects having any other unstable disease;
12. Subjects enrolled in another clinical trial within 90 days prior to screening;

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	15-12-2007
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 alpha-2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	25-10-2007
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-01-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-04-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-08-2008
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	27-01-2009
Application type:	Amendment
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
Approved WMO Date:	17-06-2010
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

ID: 22664
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2007-003289-16-NL
CCMO	NL20160.018.07
OMON	NL-OMON22664
OMON	NL-OMON29020