A Phase III, open-label trial of TMC435 in combination with peginterferon alpha-2a and ribavirin for HCV genotype-1 infected subjects who participated in the placebo group of a Phase II/III TMC435 study (C201, C205, C206, C208, C216 or HPC3007), or who received short-term (up to 14 days) direct-acting antiviral treatment for hepatitis C infection in a selected Tibotec-sponsored Phase I study.

Published: 16-08-2011
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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hepatic and hepatobiliary disorders
Study type	Interventional

Summary

ID

NL-OMON39317

Source
ToetsingOnline

Brief title
NAp

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
hepatitis C- infection of the liver by hepatitis C-virus

Research involving
Human

Sponsors and support

Primary sponsor: Tibotec Pharmaceuticals
Source(s) of monetary or material Support: de sponsor van de studie

Intervention

Keyword: efficacy, Hepatitis C, protease inhibitor, standard of care

Outcome measures

Primary outcome

The primary objective is to evaluate the antiviral efficacy of TMC435 in

combination with PegIFN*-2a and RBV,

with respect to the proportion of subjects with SVR24 (1) in the subjects who

participated in the placebo group of a

Phase II/III TMC435 study, and (2) in the subjects who participated in a

selected Tibotec-sponsored Phase I study.

Secondary outcome

The secondary objectives are:

* To evaluate the antiviral efficacy of TMC435 in combination with PegIFN*-2a

and RBV with respect to the

proportion of subjects with SVR12.

* To evaluate the on-treatment virologic response to TMC435 in combination with

PegIFN* 2a and RBV at all time

points, with focus on Week 4, Week 12, Week 24, and Week 48.

* To evaluate the incidence of virologic failure during treatment.

* To evaluate the viral relapse rate after treatment.

* To determine the proportion of subjects who are able to discontinue all

treatment at Week 24 in the subgroups of

subjects who experienced viral relapse or viral breakthrough in the placebo

group of a Phase II/III TMC435 study.

* To determine the viral NS3/4A sequence in subjects with virologic failure.

* To evaluate the safety and tolerability of TMC435 in combination with PegIFN*

2a and RBV.

Study description

Background summary

HCV is a leading cause of liver disease worldwide and has become a focus of considerable medical research. An
estimated 170 million people (3% of the global population) are infected with HCV2. More than 50% of HCV infections
become chronic and may lead to the development of liver fibrosis, cirrhosis, and hepatocellular carcinoma (HCC).
Complications of liver disease due to HCV are the leading cause of liver failure requiring liver transplantation.
Current HCV therapies are based on peginterferon-alpha (PegIFNa) in combination with ribavirin (RBV). This combination
therapy yields a sustained virologic response (SVR) in approximately 45% of treatment-naIve 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. Side effects include influenza-like symptoms, hematological

abnormalities, and neuropsychiatric symptoms.
There is a need for new compounds that may overcome the disadvantages of current HCV therapy. In recent clinical
studies, new investigational drugs acting directly on the protease target have demonstrated that significant reductions in
HCV RNA levels and improved SVR rates can be achieved when administered in combination with PegIFNa and RBV.
The HCV-encoded NS3/4A protease is essential for viral replication and mUltidisciplinary discovery research has led to
new specific and potent NS3/4A Pis, including TMC435.

Study objective

The primary objective is to evaluate the antiviral efficacy of TMC435 in combination with PegIFN*-2a and RBV.
In addition to this, the study provides access to TMC435 treatment in combination with PegIFN/RBV to (1) subjects who
participated in the placebo group (PegIFN/RBV) of a Phase II/III TMC435 study and who did not achieve sustained
virologic response (SVR), and (2) subjects who received short-term (up to 14 days) DAA treatment for HCV
infection in a selected Tibotec-sponsored Phase I study.
The efficacy and safety of TMC 435 will be evaluated in this population of carefully characterized treatment experienced patients.

Study design

This is an open label study of TMC435 in combination with PegIFN*-2a and RBV for subjects with genotype 1
HCV infection who participated in the placebo group of a Phase II/III TMC435 study, or who received short-term
(up tp 14 days) DAA treatment for HCV infection in a selected Tibotec-sponsored Phase I study. The efficacy of
TMC435 in combination with PegIFN*-2a and RBV in adult subjects will be evaluated separately for the two
groups of subjects (previously Phase II/III or Phase I, respectively). Safety and tolerability will be evaluated in the
overall population.
Approximately 270 HCV genotype-1 infected subjects who participated in the placebo group of a Phase II/III
TMC435 study are expected to be enrolled in this study. In addition, HCV genotype-1 infected subjects who
received short-term (up to 14 days) DAA treatment for HCV infection in a selected Tibotec-sponsored Phase I study
will also be allowed to enter this study.
Subjects who participated in the placebo group of a Phase II/III TMC435 study

will be classified by the sponsor as
(1) subjects with viral relapse, (2) subjects with viral breakthrough, or (3) nonresponders, i.e., null responders,
partial responders, and others, based on their response to the last course of PegIFN*-2a (2b) and RBV therapy.
Subjects can only enter the study after completion of the last study-related visit in the previous study.
This study will include a screening period of up to 6 weeks. Only under exceptional circumstances and after Sponsor
approval, the 6-week period can be exceeded.
All subjects will receive TMC435 150 mg once daily (q.d.) in combination with PegIFN/RBV for 12 weeks. A
response-guided 24- or 48-week total treatment duration with PegIFN/RBV will be used for subjects classified as
prior relapsers or having had a prior viral breakthrough. To determine total treatment duration with PegIFN/RBV
(24 or 48 weeks), HCV RNA plasma levels should be assessed at Week 4 of treatment:
- If HCV RNA <25 IU/mL undetectable at Week 4: Subjects are to receive PegIFN/RBV for a total treatment
duration of 24 weeks (i.e., 12 weeks of treatment with TMC435 + PegIFN/RBV, followed by an additional
12 weeks of treatment with PegIFN/RBV).
- If HCV RNA <25 IU/mL detectable at Week 4: Subjects are to receive PegIFN/RBV for a total treatment
duration of 48 weeks (i.e., 12 weeks of treatment with TMC435 + PegIFN/RBV, followed by an additional
36 weeks of treatment with PegIFN/RBV).
Prior relapsers or subjects with prior viral breakthrough who do not meet criteria for treatment completion after
24 weeks, all prior nonresponder subjects (null responders, partial responders and others), and subjects
having received short term DAA therapy will be required to continue treatment with PegIFN/RBV for a total of 48
weeks unless a virologic stopping rule is met prior to Week 48.
Virologic stopping rules (i.e. HCV RNA *25 IU/mL at Week 4, confirmed detectable at Week 12 or 24 or 36) have
been incorporated for all subjects to ensure that subjects with no or extremely low chance of treatment success due
to suboptimal response discontinue treatment in a timely manner in order to: 1) limit unnecessary exposure to
TMC435, PegIFN*-2a and RBV and 2) limit the risk for evolution of resistant viral variants during continued
therapy with TMC435. In the event virologic stopping rules are met at any given time point, the study treatment will
be discontinued permanently.
For all subjects, there will be a post-therapy follow-up period of 24 weeks

after the planned end of treatment (i.e.,
Week 24 or Week 48). The total study duration (from screening till final study visit) for any given subject will be a
maximum of 78 weeks, including a screening period up to 6 weeks. The study is considered completed with the last
visit of the last subject participating in the study.

Intervention

Approximately 270 HCV genotype-1 infected subjects who participated in the placebo group of a Phase II/III
TMC435 study are expected to be enrolled in this study. In addition, HCV genotype-1 infected subjects who
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variants during continued therapy with TMC435.

Study burden and risks

number of visites: max 14
A. PHYSICAL EXAMINATION:
PTN IN PART 1A: SCREENING, DAY 1, DAY 14, DAY 28, WEEK 12, WEEK 24, WEEK 28, WEEK 36 AND WEEK 48.
PTN IN PART 2B: SCREENING, DAY 1, DAY 14, DAY 28, WEEK 12, WEEK 24, WEEK 36, WEEK 52, WEEK 60 AND WEEK 72
PTN IN PART 3: AT *WITHDRAWAL* VISIT, 4 WEEKS AFTER THE *WITHDRAWAL* VISIT AND THAN EVERY 12 WEEKS UNTIL WEEK 48 (PART 1A) OR WEEK 72 (PART 1B).
AT SCREENING AN EYE EXAMINATION IS PERFORMED
B. VITAL SIGNS AND ECG :
PTN IN PART 1A: SCREENING, DAY 1, DAY 14, DAY 28, WEEK 12, WEEK 24, WEEK 28, WEEK 36 AND WEEK 48.
PTN IN PART 2B: SCREENING, DAY 1, DAY 14, DAY 28, WEEK 12, WEEK 24, WEEK 36, WEEK 52, WEEK 60 AND WEEK 72

PTN IN PART 3: AT *WITHDRAWAL* VISIT, 4 WEEKS AFTER THE *WITHDRAWAL* VISIT AND THAN EVERY 12 WEEKS UNTIL WEEK 48 (PART 1A) OR WEEK 72 (PART 1B).

ECG: 1X (AT SCREENING)

C. BLOOD TESTING :
- Hematology/Biochemistry : max. 15x
- Test Hepatitis A/B/C : 1x
- determination HCV subtype : 1x
- Test HIV-1 en HIV-2 : 1x
- HCV RNA : max. 15x
- viral sequencing : max. 14x
- IL28B genotyping : 1x
- DNA: 1x (optional)
- Biomarkers/mRNA and cytokines :6x
- Serum pregnancytest : 1x (at screening)

E. URINE-ANALYSIS (DIPSTICK) : MAX. 15X
URINEPREGNANCYTEST: MAX. 15X

RISK OF TMC435
In healthy volunteers who received TMC435 either in single doses or in multiple doses up to 14 days, the most frequent adverse events (>10% of patients) was headache.

Long term safety data in chronic hepatitis C patients who received triple combination therapy with TMC435 (given in daily doses of either 75mg, 100mg or 150mg for either 12 weeks, 24 weeks or 48 weeks) or placebo, peginterferon alfa-2a and ribavirin indicated that rates of adverse events were not related to either dose or duration of TMC435 intake. In general, no substantial differences in type or incidence of adverse events between placebo and the TMC435 treatment groups were observed.
There were only 5 types of adverse events which are currently considered adverse drug reactions to TMC435 during the first 12 weeks of treatment:
1. Mild increases of bilirubin in blood seen in 7.4% of patients as compared to 2.8% in placebo treated patients. This is a transient side effect of TMC435 intake which may make your skin and eyes appear yellow. This side effect is quickly reversible once TMC435 intake is completed.
2. Pruritus seen in 21.9% patients as compared to 14.6% placebo treated patients
3. Rash seen in 21.8% patients as compared to 16.6% placebo treated patients
4. Photosensitivity reaction (development of redness, inflammation or itchy eruptions on patches of sun exposed skin) seen in 4.7% patients as compared to 0.8% placebo treated patients. These photosensitivity reactions typically resolve without treatment.
2.5. Constipation seen in 2,.6 % of patients as compared to 2.5% in placebo treated patients.

Most of the adverse events were mild to moderate in severity. Overall, there was no relevant difference in severity between TMC435 and placebo treated groups.
Rash is usually mild to moderate in nature and is similar to that seen with Pegasys® and ribavirin. It can sometimes be serious and therefore needs medical attention.
In both, healthy volunteers and patients, there were no significant changes in pulse rate, blood pressure, heart rhythm or blood test results noted for TMC435 as compared to placebo.
When TMC435 is given along with other drugs, there may be interactions which affect drug levels of either one. Other drugs could lower blood levels of TMC435 to a level where it is no longer efficient. On the other hand, the presence of TMC435 may increase levels of the other drugs up to the toxic range.
Patients of Asian origin, may have higher blood levels of TMC435 in their bodyat the dose being studied in this trial (150 mg once daily) as compared to Caucasians. However, all available data are consistent with equal tolerability of this dose in Asians and Caucasians.
[It is possible for the virus to become resistant to TMC435 and this may affect future treatment options.

Risk of Pegasys® and Ribavirin therapy
The most frequent side effects of Pegasys®/Ribavirin are (Taken from US package insert)
-flu-like symptoms such as tiredness/fatigue (65%), fever (41%), headache (43%), muscle aches (40%), and chills (25%)
-psychiatric problems such as anxiety/irritability (33%), sleeplessness (30%) and depression (20%)
-skin disorders such as alopecia (28%), dermatitis/rash combined (24%), pruritus (19%), and local reactions at the site the Pegasys® injection was given (23%)
-gastrointestinal symptoms such as nausea/vomiting (25%) and diarrhea (11%)
-hematologic abnormalities such as neutropenia (27%) and anemia (11%)
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Liver Biopsy Risks
While liver biopsy is a common procedure most times without complications, some patients may experience pain (30%). Other risks include bleeding (<5%), infection (<5%) of an internal organ such as the lung, gall bladder, or kidney could be punctured (<5%). Care will be taken to prevent these complications.
Blood Draw Risks
Blood drawing may cause some discomfort, bleeding or bruising where the needle enters the body (1%).
Reproductive Risks: These risks are described in detail in the Participant Information and Informed Consent
The patient will use 2 methods of contraception during the study in order to avoid the risk of getting pregnant (the patient or female partner).
UNKNOWN RISKS

Contacts

Public
Tibotec Pharmaceuticals

Eastgate Village, Eastgate Nap
Little Island, CO Cork Nap
IE
Scientific
Tibotec Pharmaceuticals

Eastgate Village, Eastgate Nap
Little Island, CO Cork Nap
IE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

- Subject was previously randomized to the placebo group of a Phase II/III TMC435 study and did not achieve undetectable HCV RNA levels at the end of treatment or relapsed (confirmed detectable HCV RNA) within 1 year after end of treatment.;OR;Subject received short-term (up to 14 days) DAA treatment for HCV infection in a selected Tibotec-sponsored Phase I study on genotype 1;;- Subject must have completed the last study-related assessment in the previous study.;Please refer to the protocol for the complete list of inclusion criteria.

Exclusion criteria

- Subject shows evidence of hepatic decompensation (history or current evidence of ascites, bleeding varices or hepatic encephalopathy);;- Subject has co-infection with nongenotype 1

HCV. Since all subjects have previously participated in a study evaluating subjects with genotype 1 HCV infection, this screening test is at the discretion of the investigator, to rule out nongenotype 1 HCV infection in case of clinical signs of acute hepatitis infection and suspicion of possible re-infection;;- Subject has co-infection with HIV type 1 or type 2 (HIV-1 or HIV-2) (positive HIV-1 or HIV-2 antibodies test at Screening);;- Subject has any of the following laboratory abnormalities at screening: platelet count * 90,000/mm3; absolute neutrophil count < 1500 cells/mm3 (blacks: < 1200 cells/mm3; hemoglobin < 12 g/dL for women and < 13 g/dL for men; creatinine >1.5 mg/dL; alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) > 10 x ULN; total serum bilirubin > 1.5 x ULN. Note: Retesting of an abnormal laboratory or urinalysis result that leads to exclusion will be allowed once using an unscheduled visit during the screening period to assess eligibility;;- Subject received any DAA HCV therapy, other than having received short-term (up to 14 days) DAA in a selected Tibotec-sponsored Phase I study;;- Subject prematurely stopped medication in the previous TMC435 study for noncompliance;;- Subject prematurely stopped medication in the previous TMC435 study for safety reasons, and it would therefore be unsafe to repeat treatment at investigator*s discretion.;Please refer to the protocol for the complete list of exclusion criteria

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-01-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Copegus

Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	not yet known
Generic name:	not yet known
Product type:	Medicine
Brand name:	Pegasys
Generic name:	Peginterferon alpha 2-a
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-08-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-12-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-06-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-06-2012
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2013
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	EUCTR2011-000416-25-NL
CCMO	NL37792.018.11

Study results

Date completed: 31-03-2015

Results posted: 08-06-2016

Actual enrolment: 11

Summary results
Trial is onging in other countries

First publication
26-11-2015