An Open-Label, Multicenter Study to Evaluate Long-Term Outcomes With ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With or Without Ribavirin (RBV) in Adults With Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (TOPAZ-I).

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Objectives: The primary objective of this study is to evaluate the effect of response to treatment (assessed by SVR12 status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ABT-450/...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON55830

Source
ToetsingOnline

Brief title
AbbVie M14-423

Condition

- Other condition
- Viral infectious disorders

Synonym

Chronic Hepatitis C Virus Infection, infectious disease affecting primarily the liver

Health condition

chronische hepatitis C-virusinfectie

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie Ltd.
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Chronic Hepatitis C, direct-acting antiviral agents

Outcome measures

Primary outcome

Primary efficacy endpoint is the effect of response to treatment (assessed by

SVR12) on clinical outcomes, based on subjects in this study and companion

study TOPAZ II. The endpoint will be assessed by comparing the incidence of the

following events between subjects who achieve SVR12 and those who do not using

the Cox regression model:

* All-cause death

* Liver-related death

* Liver decompensation

* Liver transplantation

* Hepatocellular carcinoma

* Composite of any of the above outcomes

Secondary outcome

Secondary endpoint analyses:

* The long-term change from baseline in liver stiffness (as assessed by

transient elastography

[Fibroscan®]), when available, will be assessed by baseline fibrosis stage and

sustained virologic

response.

* The percentage of subjects achieving SVR12 and 2-sided 95% confidence

interval will be

presented by baseline fibrosis score (F0-F1, F2, F3 and F4).

Study description

Background summary

Treatment of HCV-infected patients could reduce the risk of cirrhosis, decompensation,
cancer and liver-related deaths.
AbbVie's IFN-free regimen for the treatment of chronic HCV genotype 1 infection includes a combination of 3 direct-acting antiviral agents (DAAs) targeting different steps in HCV replication. ABT-450 is a nonstructural protein 3/nonstructural protein 4A (NS3/NS4A) protease inhibitor co-administered with the pharmacokinetic enhancer, ritonavir (ABT-450/r); ABT-267 (ombitasvir) is a NS5A inhibitor, and ABT-333 (dasabuvir) is a NS5B non-nucleosidepolymerase inhibitor. Ribavirin is a guanosine (ribonucleic) analog used to stop viral RNA synthesis and viral mRNA capping, thus, it is a nucleoside inhibitor. Its brand names include Moderyba, Copegus, Rebetol, Ribasphere, Vilona, and Virazole, and it is an anti-viral drug.

The 3-DAA regimen has been studied with and without ribavirin in over 2,300 patients in
Phase 3 trials across a variety of patient populations including those with compensated
cirrhosis. Based on Phase 3 data, the regimen with or without RBV appears to be safe,
well tolerated and efficacious in treatment-naïve and treatment-experienced HCV genotype 1-infected subjects including those with compensated cirrhosis.

The current study is a phase 3b study and will be the first study to evaluate

long term outcomes with ABT-450/r/ABT-267 and ABT-333 with or without RBV for 12 or 24 weeks in subjects with chronic HCV GT1 infection outside of the US. The study population comprises HCV GT1 infected subjects who are treatment-naïve or treatment-experienced, including subjects with and without cirrhosis. The study will include up to 25% of subjects with compensated cirrhosis which approximates the projected prevalence among chronic HCV-infected subjects.

Study objective

Objectives:
The primary objective of this study is to evaluate the effect of response to treatment (assessed by SVR12 status) on the long-term progression of liver disease in adults with chronic HCV GT1 infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin, as measured by allcause death, liver-related death, liver decompensation, liver transplantation, and hepatocellular carcinoma.

Secondary Objectives:
To evaluate the long-term progression of fibrosis by baseline fibrosis stage and sustained virologic response, as measured by change from baseline in liver stiffness measured by transient elastography (FibroScan®) when available, in adults with genotype 1 (GT1) chronic HCV infection who received treatment with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin.
To evaluate the percentage of subjects achieving SVR12 with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin in adults with GT1 chronic HCV infection.

Study design

The TOPAZ studies are composed of 2 studies (TOPAZ-I [M14-423; to be conducted in non-US regions] and TOPAZ-II [Study M14-222; to be conducted in the US]) due to administrative reasons. This study (TOPAZ-I) is a Phase 3b, open-label, multi-center study designed together with companion study TOPAZ-II, which shares the primary objective of evaluating the effect of SVR12 status on the long-term clinical outcomes in adults with GT1 chronic HCV infection with or without compensated cirrhosis, who are either treatment-naïve or IFN-based therapy (IFN or pegIFN monotherapy, IFN/RBV, or pegIFN/RBV) treatment-experienced. In both studies, subjects will be treated with ABT-450/r/ABT-267 and ABT-333 with or without ribavirin (RBV).
Subjects meeting the eligibility criteria will be enrolled until approximately 1650 subjects have been enrolled at approximately 200 sites.
The study will consist of a Screening Period, Treatment Period and a Post-Treatment Period.
Treatment Period: HCV GT1-infected subjects who are either treatment-naïve or IFN-based therapy treatment experienced will receive ABT-450/r/ABT-267 and ABT-333. Subjects with HCV GT1a infection and all GT1-infected subjects with

compensated cirrhosis will also receive RBV.
The treatment duration will be 12 weeks for all subjects except HCV GT1a-infected subjects with compensated cirrhosis; these subjects will receive treatment for 24 weeks. Treatment duration of 12 weeks for HCV GT1a-infected subjects with compensated cirrhosis may be selected by the investigator where consistent with the local approved label, in countries where marketing authorization has been granted for the regimen included in this study.
HCV GT1a-infected subjects with compensated cirrhosis who were originally assigned to 12 weeks of treatment under a previous version of this protocol will be assigned to 24 weeks of treatment unless 1) the investigator determines that a 12-week duration of therapy is appropriate based on the approved local label; or 2) the subject has already completed the original study drug treatment and additional treatment cannot be initiated within 15 days of the date that the original treatment was completed.
Post-Treatment Period: subjects who receive at least one dose of study drug will be followed for up to 260 weeks. At these visits subjects will be assessed for antiviral response, progression of liver fibrosis, and clinical outcomes, including all-cause death, liver-related death, occurrence of hepatocellular carcinoma, liver decompensation and liver transplantation.
The number of cirrhotic subjects (an equivalent Metavir score of F4) will be limited to less than or approximately equal to 400 subjects; the number of subjects enrolled without fibrosis or with portal fibrosis without septa (an equivalent Metavir score of F0 or F1 respectively) will be limited to 1000 subjects. In the absence of a qualifying liver biopsy, the equivalent Metavir score corresponding to the results of a screening FibroScan or FibroTest will be used to determine the fibrosis stage.

Intervention

Investigational Products:
ABT-450/r/ABT-267: 75 mg/50 mg/12.5 mg tablet
ABT-333: 250 mg tablet
Ribavirin: 200 mg tablet

Doses:
ABT-450/r/ABT-267: 150/100/25 mg QD
ABT-333: 250 mg BID
Ribavirin: weight-based dosing 1000 or 1200 mg divided twice daily or adjusted for renal impairment subjects

Mode of Administration: Oral

Study burden and risks

Study Drug Risks (ABT-450/r/ABT-267, ABT-333)
Over 5,000 HCV-infected patients have been treated with paritaprevir/r-based

interferon free, combination DAA (direct acting antiviral) HCV treatment regimen during Phase 2/3 and currently ongoing clinical trials.
Side effects which were considered related to the 3-DAA + ribavirin (RBV) medications are listed below:

Very common (* 10%)
* itching (15.7%),
* tiredness (34.2%),
* nausea (22.3%),
* weakness (13.5%),
* trouble sleeping (14%),

Common (* 1% and < 10%):
* low blood count (5,3%).

These events occurred at least 5% more often in patients receiving 3-DAA + RBV medications than with patients who received a sugar pill (placebo) in placebo-controlled Phase 3 studies.
The side effect that was considered related to the 3-DAA medications alone (without RBV) was
* itching (6%)

About 1 % of subjects permanently stopped treatment with 3-DAA + when taken alone or in combination with RBV due to side effects.
Approximately 1.2% and 0.3% of patients receiving 3-DAA + RBV and 3-DAA (without RBV), respectively, permanently stopped treatment due to side effects.
Additional risks are increased levels in the blood of alanine aminotransferase (ALT) and bilirubin, decrease of hemoglobin, allergic reactions, potential reproductive risks, drug interaction risks, development of resistance to the study drugs and risks associated with the study procedures. See addendum V for more information.
Ribavirin Study Drug Risks
In this study the patient may or may not receive RBV depending on the treatment assignment as discussed above.
Ribavirin has been marketed for the treatment of HCV infection administered in combination with other HCV drugs (ribavirin is not effective against HCV infection when given by itself). Side effects which may be experienced with RBV include:
* Nausea, anorexia, vomiting, diarrhea, dyspepsia, abdominal pain, insomnia and rash.
* Hemolytic anemia (decrease in red blood cells caused by breakdown of red blood cells). The breakdown of red cells may lead to increased levels of bilirubin, and uric acid (these will show up in lab results). The hemolytic anemia may cause worsening of heart disease which may lead to heart attacks and, sometimes, death.
* Significant birth defects if pregnancy occurs while taking the drug or pregnancy occurs up to 7 months after taking the drug.

The patient should not use ribavirin if he/she has been diagnosed with blood disorders such as sickle cell anemia or certain other genetic blood disorders which affect the red blood cells.
The information provided here only describes some of the side effects reported with RBV. Therefore, refer to the RBV label for additional risks.
The patient might have side effects or discomforts that are not listed in this form. Some side effects may not be known yet which include HCV getting worse or even death. .
The patient should get medical help and contact the study doctor or study staff if the patient has any of these or any other side effects during the study whether or not the patient thinks these are related to the study drug.
The study doctor may give the patient other drugs to help with side effects.
If the patient or the study doctor thinks that the patient cannot tolerate the side effects, the study drug may be stopped altogether and the patient will be withdrawn from the study.
The patient should ask the study doctor if he/she has questions about the signs or symptoms of any side effects the patient reads about in the consent form.

What are the possible advantages and disadvantages of participation in the study?
The information that is obtained during this study may be useful scientifically and thus be helpful to others with the same condition in the future.
De patient may or may not receive any direct medical benefit from being in this study. The condition of the patient may get better, it may get worse, or it may stay the same.
Disadvantages of participation are that the patient has to make additional visits to the clinic , follow the instructions for participation in the trial and may experience side-effects.

Contacts

Public
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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 and females at least 18 years old at screening
2. Females must be post-menopausal for more than 2 years or surgically sterile or practicing acceptable forms of birth control
3. Chronic hepatitis C, genotype 1 infection
4. Males must be surgically sterile or agree to practice acceptable forms of birth control
5. Screening laboratory result indicating HCV genotype 1 infection.

Exclusion criteria

1. Use of contraindicated medication within 2 weeks of dosing
2. Abnormal laboratory tests
3. Current or past clinical evidence of Child-Pugh B or C classification or history of liver decompensation
4. Confirmed presence of hepatocellular carcinoma
5. History of solid organ transplant

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):	26-03-2015
Enrollment:	21
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Exviera
Generic name:	ABT-333
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Moderyba
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Viekirax
Generic name:	ABT-450/r/ABT-267
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-11-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-03-2015
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-04-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-08-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-09-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2017
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-07-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	01-02-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-03-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-05-2019
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-06-2021
Application type:	Amendment

Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-06-2021
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	EUCTR2014□001022□14-NL
ClinicalTrials.gov	NCT02219490
CCMO	NL50039.018.14