A Randomized, Open-Label, Multicenter Study to Evaluate the Safety and Antiviral Activity of the Combination of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 With and Without Ribavirin in Treatment-Experienced Subjects with Genotype 1b Chronic Hepatitis C Virus (HCV) Infection (PEARL*II)

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The primary objectives of this study are to evaluate the safety of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with and without RBV, and to show the non-inferiority in SVR12 rates (the percentage of subjects achieving a 12-week...

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

Summary

ID

NL-OMON39091

Source
ToetsingOnline

Brief title
M13-389

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
hepatitis C, viral liver infection

Research involving
Human

Sponsors and support

Primary sponsor: AbbVie B.V.
Source(s) of monetary or material Support: AbbVie B.V.

Intervention

Keyword: 12 week treatment, Antiviral activity, Hepatitis C virus infection

Outcome measures

Primary outcome

Efficay:

- SVR12: non-inferiority of Arm 2 to the historical rate for telaprevir plus

pegIFN/RBV

- SVR12: non-inferiority of Arm 1 to the historical rate for telaprevir plus

pegIFN/RBV

Safety:

Safety and tolerability will be assessed by monitoring adverse events, physical

examinations, clinical laboratory tests, 12-lead ECGs and vital signs.

Secondary outcome

The secondary efficacy endpoints:

- Comparison of the percentage of subjects with a decrease in hemoglobin to

below the lower limit of normal (LLN) at the end of treatment with

ABT-450/r/ABT-267 and ABT-333 with RBV vs. without RBV;

- SVR12: Superiority of Arm 1 to the historical rate for telaprevir plus pegIFN

and RBV

- SVR12: Superiority of Arm 2 to the historical rate for telaprevir plus pegIFN

and RBV

- SVR12: Non-inferiority of Arm 2 to Arm 1

Study description

Background summary

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals chronically infected worldwide. While therapy for this condition has improved considerably with approval of the protease inhibitors telaprevir and boceprevir, these direct-acting antiviral agents (DAA) must be used in combination with pegylated interferon (pegIFN) and ribavirin (RBV) for up to 48 weeks. Both pegIFN and RBV are associated with considerable, often treatment-limiting toxicity. Thus, the currently available treatment regimens are not optimal and there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment and/or decrease the need for pegIFN and RBV as components of HCV therapy.
AbbVie currently has a number of DAA compounds in clinical development: ABT-267 is a novel NS5A inhibitor, ABT 450 is a nonstructural protein 3/nonstructural protein 4A (NS3/4A) protease inhibitor and ABT-333 is a non-nucleoside nonstructural protein 5B (NS5B) polymerase inhibitor.
This study will explore the antiviral activity, pharmacokinetics, safety and tolerability of combination therapy of ABT-450/r/ABT-267, ABT-333 with and without RBV in the absence of pegIFN in pegIFN/RBV treatment-experienced, HCV genotype 1b-infected subjects.
If a treatment arm or subgenotype of a treatment arm is terminated from further enrollment, those subjects currently enrolled and active in the Treatment Period will be offered either the option to continue their assigned DAA regimen or the option to add on a 48 week course of pegIFN and RBV therapy.

Study objective

The primary objectives of this study are to evaluate the safety of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with and without RBV, and to show the non-inferiority in SVR12 rates (the percentage of subjects achieving a 12-week sustained virologic response, SVR12, [HCV RNA < LLOQ 12 weeks following therapy]) of both arms to the historical SVR rate of telaprevir plus pegIFN and RBV.

The secondary objectives of this study are:
- To compare the percentage of subjects with a decrease in hemoglobin to below the lower limit of normal (LLN) by the end of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV and without RBV;
- To show the superiority in SVR12 rates of 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with and without RBV to the historical SVR rate of telaprevir plus pegIFN and RBV therapy;
- To show the non-inferiority in SVR12 rates of 12 weeks of treatment with ABT-450/r/ABT-267, and ABT-333 without RBV (3 DAA/12) to 12 weeks of treatment with ABT-450/r/ABT-267 and ABT-333 with RBV (3 DAA/RBV/12);
- To summarize the percentage of subjects with virologic failure during treatment and the percentage of subjects with relapse post-treatment in each of the treatment groups.

Study design

This is a Phase 3, open-label, randomized, combination treatment study of ABT-450/r/ABT-267, and ABT-333 with or without RBV enrolling up to 210 pegIFN/RBV treatment-experienced, HCV genotype 1b-infected subjects at approximately 45 sites globally .

Intervention

The study will include a screening period of up to 35 days, a treatment period 12 weeks and a 48-week follow-up period. All subjects receive study medication. Subjects in arm 1 also receive ribavirin.
Subjects have the possibility to add pegIFN (arm 1) and pegIFN and RBV (arm 2) for a maximum treatment period of 48 weeks. This is followed by a follow-up period of 48 weeks.

Study burden and risks

The risks associated with this study are linked together with the possible side effects of the investigational products, ribavirin and pegIFN.
The burden for the subject will continue to work with the study procedures, visits and venapunctions. All subjects will be closely monitored and supervised by experienced physicians and study staff for possible side effects.

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 or female between the age of 18 and 70 years, inclusive, at time of enrollment.
2. Subject must have documentation that they were adherent to prior pegIFN/RBV combination
therapy and meet one of the following categories:
* Null-responders: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed to achieve a 2 log10 reduction in HCV RNA at Week 12. Subjects will be considered to meet this definition if the lack of treatment response was documented following 10 to 16 weeks of treatment;
* Non-responders/partial responders: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and achieved * 2 log10 reduction in HCV RNA at Week 12, but failed to achieve HCV RNA undetectable at the end of treatment. Subjects will be considered to meet this definition if the lack of treatment response was documented following 10 to 16 weeks of

treatment; or
* Relapsers: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at the end of treatment, but HCV RNA was detectable within 52 weeks of treatment follow-up.
Viral loads documenting the type of prior non-response should be obtained during the previous
pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months
prior to the Screening Visit.
3. Body mass index (BMI) is * 18 to < 38 kg/m2. Body mass index is calculated as weight measured in kilograms (kg) divided by the square of height measured in meters (m).
4. Chronic HCV genotype 1b-infection for at least 6 months prior to study Screening. Chronic HCV infection is defined as one of the following:
* Positive for anti-HCV antibody or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCV antibody at the time of Screening; or
* Positive for anti-HCV antibody and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection.
5. Subject has a plasma HCV RNA level > 10,000 International Units (IU)/mL at Screening.
6. Subject's HCV genotype is subgenotype 1b at Screening without co-infection with any other
genotype/subgenotype.

Exclusion criteria

1. History of severe, life-threatening sensitivity to any drug.
2. Females who are pregnant or plan to become pregnant, or breastfeeding or males whose partner(s) are pregnant or planning to become pregnant within 6 months (or 7 months if required by the local ribavirin label) after their last dose of study drug/RBV.
3. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that, in the opinion of the investigator, could preclude adherence to the protocol.
4. Positive test result for hepatitis B surface antigen (HBsAg) or anti-HIV antibodies (anti-HIV Ab).
5. Any current or past clinical evidence of ascites or esophageal varices or prior biopsy showing cirrhosis e.g., a Metavir Score of > 3 or an Ishak score > 4.
6. Any cause of liver disease other than chronic HCV infection.

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):	23-05-2013
Enrollment:	8
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	01-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	26-10-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-11-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-02-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-05-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2014
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	EUCTR2011-005740-95-NL
CCMO	NL39903.018.12