A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Efficacy and Safety of ABT-450/Ritonavir/ABT-267 (ABT-450/r/ABT-267) and ABT-333 Co-administered with Ribavirin (RBV) in Treatment-Experienced Adults with Genotype 1 Chronic Hepatitis C Virus (HCV) Infection (SAPPHIRE-II)

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

Summary

ID

NL-OMON39734

Source
ToetsingOnline

Brief title
M13-098

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: Abbott

Intervention

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

Outcome measures

Primary outcome

Efficacy:

1. SVR12: Non-inferiority of Arm A to the historical rate for telaprevir plus

pegIFN and RBV; lower bound of 95% confidence interval (LCB) must exceed 60% to

achieve noninferiority.

2. SVR12: Superiority of Arm A to the historical rate for telaprevir plus

pegIFN and RBV; LCB must exceed 70% to achieve superiority.

Safety:

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

examinations, clinical

laboratory tests, 12-Lead ECGs and vital signs.

Secondary outcome

Efficacy:

The secondary endpoints are:

1. ALT normalization rate in Arm A compared to Arm B in the DB Treatment Period.

2. SVR12: In GT1a subjects, superiority of Arm A to the historical rate for

telaprevir plus pegIFN and RBV; to demonstrate superiority, the LCB must exceed

65%.

3. SVR12: In GT1b subjects, superiority of Arm A to the historical rate for

telaprevir plus pegIFN and RBV; to demonstrate superiority, the LCB must exceed

77%.

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 efficacy and safety of combination therapy of ABT-450/ritonavir/ABT-267 (ABT-450/r/ABT-267), ABT-333 with and without RBV in the absence of pegIFN in pegIFN/RBV treatment-experienced, HCV genotype 1-infected subjects compared to a placebo-arm.

Study objective

The primary objectives of this study are to compare the percentage of subjects achieving SVR12 (HCV RNA < lower limit of quantification [LLOQ] 12 weeks following treatment) of 12 weeks of treatment with ABT-450/r/ABT-267 and

ABT-333 co-administered with RBV (the DAA combination regimen) to the historical SVR rate of telaprevir plus pegIFN and RBV therapy and to assess the safety of the DAA combination regimen versus
placebo for 12 weeks in pegIFN/RBV treatment-experienced HCV genotype 1-infected adults without cirrhosis.

The secondary objectives of this study are to measure the effect of the DAA combination regimen compared to placebo for 12 weeks on normalizing alanine aminotransferase (ALT) levels and demonstrate the effect of the DAA combination regimen on SVR12 in subjects with HCV genotype 1a and genotype 1b infection, and on HCV RNA levels during and after treatment as measured by on-treatment virologic failure and
post-treatment relapse, respectively.

Study design

This is a Phase 3, randomized, double-blind, placebo-controlled, multicenter study evaluating ABT-450/r/ABT-267 and ABT-333 co-administered with RBV in pegIFN/RBV treatment-experienced non-cirrhotic HCV genotype 1-infected adults Approximately 400 HCV genotype 1-infected, treatment-experienced adults will be randomized to Arms A and B in a 3:1 ratio in the Double-Blind Treatment Period.

Arm A: ABT-450/r /ABT-267 150 mg/100 mg/25 mg once daily (QD) + ABT-333 250 mg twice daily (BID) weight-based RBV BID for 12 weeks.
Arm B: Placebo for ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + Placebo for ABT-333 250 mg BID with weight-based Placebo for RBV BID for 12 weeks followed by ABT-450/r/ABT-267 150 mg/100 mg/25 mg QD + ABT-333 250 mg BID with weight-based RBV BID for 12 weeks

Intervention

The study will include a screening period of up to 35 days, a treatment period 12 weeks (arm A) or 24 weeks (arm B) and a 48-week follow-up
period. All subjects receive study medication and ribavirin. After the first 12, double-blinded weeks, de subjects are unblinded. Subjects that received placebo in arm B, will now be treated with study medication and ribavirin for 12 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, ritonavir and ribavirin. The patients treated with placebo for 12 weeks can show signs of worsening of the disease. 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 and age is between 18 and 70 years, inclusive, at time of screening.
2. Subject must have documentation that they were adherent to prior pegIFN/RBV combination therapy and meet one of the following categories:
- Null-responder: received at least 12 weeks of pegIFN/RBV for the treatment of HCV and failed
to achieve a 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 * 16); or received less than 12 weeks of pegIFN/RBV for the treatment of HCV and achieved a <1 log10 IU/mL reduction in HCV RNA at Week 4 (* 25 days); or
- Partial responder: received at least 20 weeks of pegIFN/RBV for the treatment of HCV and

achieved * 2 log10 IU/mL reduction in HCV RNA at Week 12 (Weeks 10 * 16), but failed to achieve HCV RNA undetectable at the end of treatment; or
- Relapser: received at least 36 weeks of pegIFN/RBV for the treatment of HCV and was undetectable at or after 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 related to the previous
pegIFN/RBV treatment. PegIFN/RBV therapy must have been completed no less than 2 months prior to the Screening Visit.
3. Chronic HCV infection is defined as one of the following:
- Positive for anti-HCV antibody (Ab) or HCV RNA at least 6 months before Screening, and positive for HCV RNA and anti-HCVAb at the time of Screening; or
- Positive for anti-HCV Ab and HCV RNA at the time of Screening with a liver biopsy consistent with chronic HCV infection.
4. Screening laboratory result indicating HCV genotype 1-infection.
5. Per local standard practice, documented results of one of the following:
- A liver biopsy within 24 months prior to or during screening demonstrating the absence of cirrhosis, e.g., a METAVIR Score of 3 or less, Ishak score of 4 or less; or
- A screening FibroTest score of * 0.72 and Aspartate Aminotransferase to Platelet Ratio Index (APRI) * 2; or
- A screening FibroScan result of < 9.6 kPa.
Subjects with a non-qualifying Fibrotest/APRI or Fibroscan result may only be enrolled if they have
a qualifying liver biopsy preformed within 24 months prior to or during screening.
6. Subject has plasma HCV RNA level > 10,000 IU/mL at Screening.

Exclusion criteria

1. Recent (within 6 months prior to study drug administration) history of drug or alcohol abuse that
could preclude adherence to the protocol.
2. Positive test result for Hepatitis B surface antigen (HBsAg) or anti-Human Immunodeficiency virus antibody (HIV Ab).
3. History of uncontrolled seizures, uncontrolled diabetes as defined by a glycated hemoglobin
(hemoglobin A1C) level > 8.5%, at the Screening Visit, active or suspected malignancy or history of
malignancy (other than basal cell skin cancer or cervical carcinoma in situ) in the past 5 years.
4. Any current or past clinical evidence of cirrhosis such as ascites or esophageal varices, or prior
biopsy showing cirrhosis, e.g., a Metavir Score of >3 or Ishak score of > 4.
5. Screening laboratory analyses showing any of the following abnormal laboratory results:
- Alanine aminotransferase (ALT) > 5 × upper limit of normal (ULN)

- Aspartate aminotransferase (AST) > 5 × ULN
- Calculated creatinine clearance (using Cockcroft-Gault method) < 60 mL/min
- Albumin < Lower limit of normal (LLN)
- Prothrombin time/International normalized ratio (INR) > 1.5. Subjects with a known inherited
blood disorder and INR > 1.5 may be enrolled with permission of the AbbVie Study Designated
Physician
- Hemoglobin < LLN
- Platelets < 120,000 cells per mm3
- Absolute neutrophil count (ANC) < 1500 cells/*L (< 1200 cells/*L for subjects of African descent who are black)
- Indirect bilirubin > 1.5 × ULN and direct bilirubin > ULN

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-04-2013
Enrollment:	15
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
Product type:	Medicine
Brand name:	Placebo
Generic name:	Placebo

Ethics review

Approved WMO Date:	05-12-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-03-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-04-2013
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:	11-07-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2013
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	EUCTR2012-002035-29-NL
CCMO	NL42305.018.12