An Open-Label Study to Evaluate the Safety, Antiviral Activity and Pharmacokinetics of Direct-Acting Antiviral Agent (DAA) Treatment in Combination with Peginterferon *-2a and Ribavirin (pegIFN/RBV) in Chronic Hepatitis C Virus (HCV) Infected Subjects Who Have Experienced Virologic Failure in a Previous AbbVie or Abbott DAA Combination Study

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

Summary

ID

NL-OMON39209

Source
ToetsingOnline

Brief title
M13-101

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: Antiviral activity, Hepatitus C virus infection, Open-label

Outcome measures

Primary outcome

Efficacy:

The primary efficacy endpoint is the percentage of subjects with sustained

virologic response 12 weeks after the last actual dose of study drug (including

DAA, pegIFN, and RBV) (SVR12actual).

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 are the percentage of subjects with sustained

virologic response 24 weeks after the last actual dose of study drug (including

DAA, pegIFN, and RBV) (SVR24actual) and the percentage of subjects with eRVR

(HCV RNA < LLOQ at Weeks 4 through 12 in Substudy 1).

Study description

Background summary

Hepatitis C viral (HCV) infection is a global health problem, with over 170 million individuals infected worldwide. While therapy for this condition has improved considerably, the currently available treatment regimens are not optimal. Until recently, the standard of care (SOC) for treatment of HCV genotypes 1a and 1b (the most common genotypes in North America and Europe) consisted of weekly injections of pegylated interferon-alpha (pegIFN) and daily oral doses of ribavirin (RBV) for up to 48 weeks. Approximately 50% of patients with genotype 1 HCV infection treated with pegIFN and RBV fail to achieve a sustained virologic response (SVR). Thus, there is a clear unmet need for effective anti-HCV compounds which can increase the likelihood of successful treatment for this population.
To meet this need, a number of small molecules with direct antiviral activity (direct-acting antiviral agent [DAA]) against specific stages of the HCV life cycle have been developed. Clinical studies to date with these DAA HCV inhibitors, such as the NS3/4A protease inhibitors telaprevir and boceprevir, used in combination with pegIFN plus RBV, have demonstrated improved SVR rates in treatment-naïve and pegIFN-experienced patients, with shorter treatment durations for a subset of naïve subjects. As a result, these regimens are now considered the standard of care for chronic genotype 1 HCV infection.
Abbott/AbbVie currently has a number of DAA compounds in clinical development: ABT-450 is an NS3/NS4A protease inhibitor and ABT-267 is an NS5A inhibitor, and ABT-333 is a non-nucleoside NS5B polymerase inhibitor.
The current study is intended to offer subjects who experience virologic failure in a previous pegIFN-free Abbott DAA combination study an optional intensified treatment regimen. This study will assess the safety, antiviral activity and resistance profile of ABT-450/r 200/100 mg QD and ABT-267 25 mg QD combined with pegIFN and RBV in subjects who met a virologic failure criterion in a previous study.

Study objective

The primary objective of this study is to evaluate the safety and antiviral efficacy, defined as the percentage of subjects with sustained virologic response 12 weeks post-dosing (SVR12; HCV RNA < LLOQ 12 weeks after the last dose of study drug).

The secondary objectives of this study are to evaluate the percentage of

subjects with sustained virologic response 24 weeks post-dosing (SVR24; HCV RNA < LLOQ 24 weeks after the last dose of study drug) and the percentage of subjects with extended rapid virologic response (eRVR) (HCV RNA < LLOQ at TI Weeks 4 through 12).

Study design

This is an open label, multiple-dose, rollover study exploring the safety, antiviral activity and pharmacokinetics of ABT-450 with ritonavir (ABT-450/r) + ABT-267 in combination with pegIFN and RBV in HCV-infected subjects who have experienced virologic failure in a previous AbbVie/Abbott DAA combination study.

Intervention

This protocol consists of three substudies. In Substudy 1, subjects who have met virologic stopping criteria in a previous Abbott DAA combination study may choose to enter this study and receive intensified treatment with ABT-450/r, ABT-267, pegIFN and RBV for 24 weeks. Subjects who complete or discontinue DAA treatment in Substudy 1 will enter Substudy 2. In Substudy 2, subjects receive pegIFN and RBV for an additional 24 weeks for a total treatment of up to 48 weeks across Substudies 1 and 2. In Substudy 3, subjects will be monitored for resistance and viral response for 48 weeks after discontinuation of study drug treatment.

Study burden and risks

The risks associated with this study are linked together with the possible side effects of the investigational products, ritonavir, 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. Subject must have experienced virologic failure as defined in a previous AbbVie/Abbott DAA
combination trial.
2. Female who is:
* not of childbearing potential, defined as:
* postmenopausal for at least 2 years prior to screening (defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone [FSH] level indicating a postmenopausal state), or
* surgically sterile (defined as bilateral tubal ligation, bilateral oophorectomy or hysterectomy) or has a vasectomized partner(s), or
* practicing total abstinence from sexual intercourse (minimum 1 complete menstrual cycle), or
* sexually active with female partners only
* of childbearing potential and sexually active with male partner(s):
* currently using at least one effective method of birth control at the time of screening and agree to practice two effective methods of birth control while receiving study drugs (as outlined in the subject information and consent form or other subject information documents), starting with Study
Day 1 and for 7 months after stopping study drug as directed by the local ribavirin label (Note: Hormonal contraceptives, including oral, topical, injectable or implantable varieties, may not be used during Substudy 1 or for 2 weeks after the last dose of DAA therapy) study drug treatment.
3. Females must have negative results for pregnancy tests performed:
* at Screening by urine specimen within 42 days prior to initial study drug administration, and

* at Baseline (prior to dosing) by urine specimen.
Female subjects with a borderline hCG result at Day 1 may enroll into the study if they either:
* have a documented history of bilateral tubal ligation, hysterectomy, bilateral oophorectomy; or
* are confirmed to be postmenopausal defined as amenorrheic for longer than 2 years, age appropriate, and confirmed by a follicle-stimulating hormone (FSH) level indicating a postmenopausal state at Screening.
4. Sexually active males must be surgically sterile or have male partners only or if sexually active with female partner(s) of childbearing potential must agree to practice two effective forms of birth control (as outlined in the subject information and consent form or other subject information documents) throughout the course of the study, starting with Study Day 1 and for 7 months after stopping study drug or as directed by the local ribavirin label. (Note: Contraceptives containing ethinyl estradiol or depo-progesterone are considered effective if used by the female
partners of male subjects.)
5. For cirrhotic subjects, compensated cirrhosis defined as Child-Pugh score of * 6 at Screening.
6. Subject is infected with HCV genotype 1 at Screening Visit.

Exclusion criteria

1. In subjects with a prior null or partial response to pegIFN/RBV treatment at any time prior to
pre-screening for this study or any prior failure with pegIFN/RBV plus telaprevir, the presence of
variants relative to the appropriate prototypic reference sequence (H77 for 1a or Con1 for 1b) at any of the following amino acid positions: NS3 protease 155, 156, or 168; NS5A 28, 29, 30, 31, 32, 58, or 93.
2. Females who are pregnant or plan to become pregnant, or breastfeeding, or males whose partners are pregnant or planning to become pregnant within 7 months (or per local RBV label) after their last dose of RBV.
3. Use of known strong inhibitors (e.g., ketoconazole) or inducers (e.g., phenobarbital, rifampin,
carbamazepine, St. John's Wort) of CYP3A within 2 weeks prior to study drug administration.
4. Use of any medications contraindicated for use with ABT 450, ABT 267, pegIFN, RBV or ritonavir
within 2 weeks prior to study drug administration.
5. Discontinuation of antiviral therapy due to intolerance or a DAA or RBV associated adverse event in a previous AbbVie/Abbott DAA combination study (excluding intolerance or AEs associated with telaprevir).

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-07-2014
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	ABT-267
Generic name:	ABT-267
Product type:	Medicine
Brand name:	ABT-450
Generic name:	ABT-450
Product type:	Medicine
Brand name:	Copegus
Generic name:	Ribavirin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Norvir
Generic name:	Ritonavir
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	Pegasys
Generic name:	Peg-interferon alpha-2a
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	21-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-04-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-01-2014
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	EUCTR2011-005393-32-NL
ClinicalTrials.gov	NCT01609933
CCMO	NL40079.018.12