MAGNITUDE-A Phase 3 Evaluation of the Safety and Efficacy of Lambda/RBV/DCV in Treatment Naïve Subjects with Chronic HCV Infection, who have Underlying Mild or Moderate Hemophilia or Patients who are Prior Relapsers to Pegylated interferon alfa/RBV;Revised Protocol 01 Incorporates Amendment 02 and Administrative Letter 01 and 02;+ Pharmacogenetics Blood Sample Amendment Number 01 - Site Specific (version 1.0, dated 11-Sep-12)

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Primary Objectives:The primary objective for this study is to evaluate the proportion of subjects who achieve SVR12 (HCV RNA < LLOQ (target not detected) at post-treatment follow-up Week 12 in subjects with GT-1b, -4 and GT-2, -3.Secondary...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Interventional

Summary

ID

NL-OMON39678

Source
ToetsingOnline

Brief title
AI452-030

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Chronic Hepatitis, Hemophilia

Research involving
Human

Sponsors and support

Primary sponsor: Bristol-Myers Squibb
Source(s) of monetary or material Support: Bristol-Myers Squibb

Intervention

Keyword: Chronic HCV Infection, Daclatasvir, Hepatitis C Virus, Lambda

Outcome measures

Primary outcome

The primary objective for this study is to evaluate the proportion of subjects

who achieve SVR12 (HCV RNA < LLOQ (target not detected) at post-treatment

follow-up Week 12 in subjects with GT-1b, -4 and GT-2, -3.

Secondary outcome

Secondary Objectives:

The secondary objectives for this study are:

Evaluate rates of on treatment viral suppression at Weeks 4, 12, and 24 (only

for GT-1b, -4) by treatment group

Evaluate the safety of treatment with Lambda/RBV/DCV in reducing treatment emergent cytopenic abnormalities (anemia as defined by Hb < 10 g/dL, and/or neutropenia as defined by ANC < 750 mm3 and/or thrombocytopenia as defined by platelets < 50,000 mm3) through Week 12 for GT-2, -3 and through Week 24 for GT-1b, -4.

Evaluate the following on-treatment IFN-associated symptoms during treatment with Lambda/RBV/DCV through Week 12:
Flu-like symptoms (as defined by pyrexia or chills or pain)
Musculoskeletal symptoms (as defined by arthralgia or myalgia or back pain)

Evaluate SVR24 by treatment group

Evaluate, safety as measured by the frequency of dose reductions, discontinuations due to adverse events (AEs), and serious adverse events (SAEs) through the end of follow-up (maximum of 60 weeks for GT-2, -3 and 72 weeks for GT-1b, -4)

Study description

Background summary

HCV infection is a major cause of morbidity and mortality in hemophilic patients. The majority of hemophiliacs became infected with HCV as a result of clotting factor concentrates infusions prior to the introduction of viral inactivation techniques in the mid-1980s. Most of these individuals also were infected with the human immunodeficiency virus (HIV). However, many coinfected hemophiliacs died in the 80s and early 90s secondary to AIDS. Of all infected

patients, approximately 10% to 20% spontaneously clear the virus, as documented by the persistence of serum anti-HCV antibodies with negative serum HCV-RNA, whereas the majority (approximately 80%) develop a chronic HCV infection which in approximately 20% of cases progresses to the end stages (cirrhosis, liver failure and HCC) after 20 years of infection. HCV GT-1, duration of HCV infection and co-infection with HIV has been identified as important predictors of disease progression. As highly active antiretroviral therapy has revolutionized the prognosis of HIV infection, HCV infection in this population, has assumed much greater importance, particularly as liver disease has become the most common cause of death in patients with HIV/HCV co-infection.

The American Association for the Study of the Liver Disease (citation) guidelines do not make any specific recommendations for the pharmacological treatment of Chronic HCV infection in patients with bleeding disorders. Furthermore, Telapravir and Boceprevir are not recommended for use in hemophiliac patients due to insufficient data. The United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO) guidelines suggest IFN/RBV as the standard of care for the treatment of chronic HCV infection in patients with hemophelia.

In patients infected with chronic HCV GT-1, despite the improvement in SVR rates and the option of short treatment duration, when a DAA is used in combination with alfa and RBV, the use of these DAA, TVR and BOC, results in unique DAA related adverse events (AEs). The most common AEs associated with the use of TVR are rash, anemia, pruritus, nausea and diarrhea while treatment with BOC is commonly associated with anemia and dysgeusia. Furthermore, the use of alfa/RBV in itself is also associated with AEs that prevent initiation of therapy for a number of HCV infected subjects. The AEs commonly associated with the use of alfa are flu-like symptoms, hematological and hepatic abnormalities and, neuropsychiatric disorders. Other AEs include gastrointestinal, dermatological, autoimmune, cardiac as well as pulmonary and ophthalmologic. The use of RBV most notably leads to hemolytic anemia, which in combination with the myelosuppressive effects of alfa can be a significant clinical problem. The toxicities associated with the use of TVR, BOC, alfa and RBV may lead to avoidance of therapy, delays in starting therapy or discontinuation of treatment. Furthermore, the toxicities associated with the use of alfa or RBV may lead to dose reductions and early discontinuation of treatment. These factors, including poor adherence to treatment, may decrease the likelihood of achieving SVR. Adherence to therapy (defined as receiving 80% of the prescribed alfa dose and**80% of the RBV dose for the duration of therapy) has been associated with higher SVR rates in chronic HCV GT-1 infected patients.

Despite the advantages of alfa/RBV based DAA treatment regimens, using the currently approved DAAs, TVR or BOC, are not without their toxicities and concerns about resistance. These regimens also do not address many of the safety and tolerability issues associated with the use of alfa and RBV and not

all patients are eligible for a shortened duration of treatment. Furthermore, while access to TVR and BOC gradually increases, they are only approved for use in patients with GT-1 chronic HCV infection. Presently, there are no approved DAAs for patients infected with GT-2 or -3 chronic HCV infection. As such, there remains a need for the development of other similarly efficacious treatment regimens that have the potential to offer a safer or more tolerable treatment option while providing broader HCV genotypic coverage.

An alternative approach to improving treatment outcomes in subjects with chronic HCV infection is to develop newer IFN molecules that maybe combined with newer DAAs, to improve the tolerability and adherence to IFN-based treatments regimens. This approach may limit IFN related dose reductions and treatment discontinuations and, may potentially enable the development of efficacious treatment regimens that may shorten treatment durations.

Therefore the rationale for conducting this study is to be able to offer hemophiliac subjects infected with GT-1b, -2, -3, and -4 chronic HCV infection the opportunity to be treated and cured with a potentially more tolerable interferon, peginterferon lambda-1a (BMS-914143, hereafter referred to as Lambda) in combination with the Direct-acting Antiviral (DAA), Daclatasvir (DCV) and RBV over a shorter treatment duration.

Study objective

Primary Objectives:
The primary objective for this study is to evaluate the proportion of subjects who achieve SVR12 (HCV RNA < LLOQ (target not detected) at post-treatment follow-up Week 12 in subjects with GT-1b, -4 and GT-2, -3.

Secondary Objectives:
The secondary objectives for this study are:
Evaluate rates of on treatment viral suppression at Weeks 4, 12, and 24 (only for GT-1b, -4) by treatment group

Evaluate the safety of treatment with Lambda/RBV/DCV in reducing treatment emergent cytopenic abnormalities (anemia as defined by Hb < 10 g/dL, and/or neutropenia as defined by ANC < 750 mm3 and/or thrombocytopenia as defined by platelets < 50,000 mm3) through Week 12 for GT-2, -3 and through Week 24 for GT-1b, -4.

Evaluate the following on-treatment IFN-associated symptoms during treatment with Lambda/RBV/DCV through Week 12:
Flu-like symptoms (as defined by pyrexia or chills or pain)
Musculoskeletal symptoms (as defined by arthralgia or myalgia or back pain)

Evaluate SVR24 by treatment group

Evaluate, safety as measured by the frequency of dose reductions, discontinuations due to adverse events (AEs), and serious adverse events (SAEs) through the end of follow-up (maximum of 60 weeks for GT-2, -3 and 72 weeks for GT-1b, -4)

Exploratory Objectives:
Rates of laboratory abnormalities

Evaluate in subjects with chronic HCV infection the association of host IL28B and ENT 1 single nucleotide polymorphism (SNP) GT (including IL28B rs12979860) with clinical responses to treatment with Lambda/RBV/DCV

Compare, by treatment group, the association between baseline IP-10 and clinical responses to Lambda/RBV/DCV

Evaluate, by treatment group, subjects with eRVR (HCV RNA < LLOQ target not detected at
Weeks 4 and 12 of treatment), undetectable HCV RNA at end of treatment (EOT) and relapse following EOT

Evaluate, by treatment group, the association between isoAsp concentration and, efficacy and safety events
Describe immunogenicity of Lambda and its association with isoAsp concentration and, efficacy and safety events

Describe population pharmacokinetics (PK) of Lambda, and the association between Lambda exposure, safety, and anti-viral effect

Evaluate, by treatment group, the association between biomarkers of host immune response (serum protein markers) and clinical responses to Lambda

Evaluate, by treatment group, the association between Lambda/RBV/DCV and the development of autoimmune hypothyroidism (Hashimotos) and transient hyperthyroidism(Painless Thyroiditis)

Evaluate on-treatment IFN-associated constitutional symptoms (fatigue or asthenia)
Depression evaluated using the Patient Health Questionnaire (PHQ-9)

Study design

This study will run as an open label, non randomized study, without a control arm. The reason for not including a control treatment group that consists of an arm of alfa/RBV is because of recent regulatory guidance that suggests that all subjects with GT-1b, -4 infection should be treated with a combination of telaprevir or boceprevir with alfa/RBV. These regimens have not been studied in hemophiliacs and hence their safety in this population is uncertain. Historical

data from studies that have used alfa/RBV to treat HCV among hemophiliacs will be used to benchmark safety and efficacy measures in this study.

This study will evaluate the safety and efficacy of a regimen of Lambda/DCV/RBV in hemophiliacs with chronic HCV GT-1b, -2, -3 and -4 infection. Duration of treatment will be 12 weeks for HCV GT-2, -3 infection and 24 weeks for GT-1b, -4 infection. Duration of dosing of DCV in both regimens will be for 12 weeks. Subject with GT-1b, -4 infection will receive an additional 12 weeks of Lambda/RBV after the initial 12 weeks of the triple regimen. This study will allow inclusion of subjects who have mild or moderate hemophilia. This study will also allow inclusion of a small number (capped at 10%) of subjects who have compensated cirrhosis or subjects who have relapsed after prior treatment with alfa/RBV (capped at 20%).

A total of 100 subjects infected with HCV GT-1b, -2, -3 or -4 will be treated. Subjects with GT-1b, -4 will be treated with Lambda/RBV/DCV for 12 weeks followed by Lambda/RBV treatment for an additional 12 weeks. Subjects with GT-2, -3 will be treated with Lambda/RBV/DCV for 12 weeks.

Intervention

The screening period for this study is 42 days. At screening - patients will be allocated into a treatment arm depending on their HCV genotype and their prior treatment history (Relapsers to previous HCV therapy are allowed up to 20% of the total number of patients recruited) and also their liver status (Cirrhotic patients are allowed up to 10% of the total patients recruited)

Eligible subjects must be dosed within 42 days of the day they were screened. On Day 1, after all Day 1 procedures have been performed, eligible subjects will start study drugs.

The first dose (Day 1) of Lambda must occur in the office/clinic under medical supervision. Selection and timing of dose for each subject are as follows (with the exceptions described below):

Lambda: All subjects will self-administer 180 *g Lambda injection subcutaneously once weekly throughout the entire dosing period.

DCV: DCV tablets should be taken once daily for the duration of assigned treatment. DCV may be taken with or without a meal, and may be taken with RBV. All subjects, regardless of which treatment regimen they are randomized to will take 60 mg (1 tablet) daily.

RBV: GT-2, -3 subjects will be treated with 800 mg of RBV per day divided into a morning and evening dose and taken with food for a maximum of 12 weeks. GT-1b, -4 subjects weighing < 75 kg, will be treated with 1000 mg of RBV per day and for those weighing >75 kg, 1200 mg per day divided into a morning and

evening dose and taken with food for a maximum of 24 weeks.

Treatment duration could last between 12 to 24 weeks, depending on the patients genotype. Following treatment, they will be followed up for 24 weeks and depending on whether they are determined to have failed on this therapy (if HCV RNA > LLOQ at Week 24), could continue for an additional 24 weeks for extended follow up assessments.

Study burden and risks

With regards to specific burdens that the subject may have:
Subjects are required to attend visits to the clinic for treatment and assessments, for a maximum of 60 to 72 weeks depending on the cohort to which they are assigned.

Subjects in Cohort A with GT-2, -3 infection will be treated with a 12 week duration of study drugs and will then be followed up for 24 weeks.
Subjects found to have detectable HCV virus during the follow-up period (Protocol figure 3.1.3 - defined as HCV >= LLOQ) will be evaluated for a further 24 weeks (total of 48 weeks follow-up) to assess the presence of HCV sequence variants over time.

Subjects in Cohort B with GT-1, -4 infection will receive study drugs for 12 weeks, followed by an additional 12 weeks of Lambda/RBV (therefore 24 weeks of treatment) and will be evaluated for 24 weeks in the post-treatment follow-up period.
Subjects found to have detectable HCV virus during the follow-up period (Protocol figure 3.1.3 - defined as HCV >= LLOQ) will be evaluated for an additional 24 weeks (total of 48 weeks follow-up) to assess the presence of HCV sequence variants over time.
These visits are however vital to monitor the subjects safety and wellbeing, and patients often appreciate the additional and more detailed attention provided by medical staff as part of the study visits, compared to what would be received in normal care. Also subjects will receive reasonable reimbursement for the cost of their travel whilst taking part in the study.

During the treatment period, subjects will attend a Screening, Baseline (day 1) and then week 1, followed by week 2, 4, 6, 8, 12, 16, 20 and week 24 which marks the end of treatment visit. During which the subjects will undergo assessments and procedures associated with the clinical testing of HepC infection - including;
Physical examinations, ECG tests, Questionnaires on patient health, completion of patient diaries to document their treatment, retinal eye exam and a review of their other medications taken other than study drugs provided.

In addition to the above, subjects will undergo blood sampling at each visit (averaging a total of 28.5ml blood per visit via venipuncture). Blood sampling

is necessary to confirm the subject*s eligibility, but more importantly to monitor their continued safety on the trial through measuring HCV viral load, resistance to therapy and any drug toxicities that may occur. Side effects of blood sampling can include infection, bruising and bleeding at the needle puncture site, so to limit the discomfort to the patient; only one venipuncture will be performed at each visit for the necessary volume of blood to be collected. Also these samples will be collected by a hospital doctor, an experienced research nurse or a phlebotomist to further limit the possibility of any discomfort or complication to the patient.

Other than study specific procedures, patients will also be informed of their responsibility not to use any contraindicated medications and to comply with the requirements relating to contraception and consumption of study medications during meal times.

Any subject who receives Lambda and has undetectable HCV (Protocol figure 3.1.3 - defined as RNA < LLOQ) at the completion of the required post-treatment follow-up period will be offered enrollment into the BMS long-term follow-up (LTFU) study AI452016 which will assess long-term durability of response.

However specifically with regards to direct risks for the patient;
As for any relatively new drug or new drug combination - there may be unknown side effects. Based on what we have learned up to this point, the following study drug associated risks are known;

Regarding risks associated with Lambda treatment:
The key safety risks associated with the use of 180µg dose of Lambda as observed in previous BMS studies, EMERGE and D-LITE, in treatment naive subjects with chronic HCV are Liver AST/ALT elevations and direct bilirubin elevations. These risks have been described in the protocol Section 1.1.1.1 and Section 1.1.1.2.

Regarding risks associated with Daclatasvir treatment:
Because DCV is concentrated in the liver, there is potential for drug-induced hepatic inflammation or other hepatotoxicity. In the Phase 2a AI444014 study, the majority of subjects randomized to DCV (N = 36; 3, 10, or 60 mg) demonstrated stable or improved ALT levels after 48 weeks of therapy, and there were no significant trends or discontinuations in this study related to liver laboratory abnormalities or hepatic AEs. No significant hematologic findings secondary to bone marrow suppression were reported other than what might be expected from the use of peg-alfa Inteferon and RBV alone. Week 12 antiviral data demonstrated that when DCV is combined with alfa/RBV, early treatment emergent resistant variants, such as those observed in AI444004, can be partially or fully suppressed, and high rates of SVR are attainable relative to subjects treated with alfa/RBV alone.

Another ongoing Phase 2b study *COMMAND-1* in treatment-naive GT-1 HCV infected subjects has safety data available through 24 weeks of therapy (DCV: 20 mg N = 159; DCV 60 mg N = 158; Placebo N = 78). Serious adverse events, discontinuations due to AEs, and the most common AEs reported on study were consistent with the AE profile of alfa/RBV. No apparent differences in safety outcomes were observed for subjects who discontinued DCV at Week 12 compared to those who continued DCV through Week 24. One case of aplastic anemia was reported, which was considered by BMS as probably related to alfa, based on previous cases reported in the literature. Otherwise, there were no safety signals unique to DCV, and, in particular, there were no hepatic, hematologic, dermatologic, or gastrointestinal safety signals which are events of interest for other classes of DAAs.

The details of the above studies and their findings are found in Section 1.5.3 of the protocol.

It should be noted that potential adverse effects from the DAA, Lambda and RBV combination described above are monitored closely through liver function testing during the patient*s study visits. Predetermined AST, ALT, bilirubin and creatinine clearance levels are detailed in the protocol to flag the occurrence of any potential drug induced liver injury and in the event of such a case, a dose modification could be applied or the patient may be withdrawn.

Contacts

Public
Bristol-Myers Squibb

Vijzelmolenlaan 9
Woerden 3447 GX
NL
Scientific
Bristol-Myers Squibb

Vijzelmolenlaan 9
Woerden 3447 GX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Infection with the hepatitis C virus (HCV) with underlying mild or moderate hemophilia;• Males 18 years of age and above ;• Have not been previously treated with an interferon

Exclusion criteria

• Not infected with the hepatitis C virus (HCV), hepatitis D virus (HDV) or human immunodeficiency virus (HIV);• Do not have a serious liver, psychiatric, blood, thyroid, lung, heart or eye disease;• Presence of Bethesda inhibitor

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	25-03-2013

Enrollment:	10
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:	Daclatasvir
Generic name:	Daclatasvir
Product type:	Medicine
Brand name:	Lambda
Generic name:	peginterferon lambda-1a

Ethics review

Approved WMO Date:	17-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-04-2013
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:	19-06-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-06-2013
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:	23-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-02-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2015
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	EUCTR2012-003463-22-NL
ClinicalTrials.gov	NCT01741545
CCMO	NL42230.018.12