An Open-Label Re-treatment Study with Peg-Interferon Alfa-2a, Ribavirin and BMS-790052 With or Without BMS-650032 for Subjects With Chronic Hepatitis C

Published: 16-07-2012
Last updated: 01-05-2024

Primary ObjectiveTo assess the efficacy based on the proportion of subjects with SVR12, defined as HCV RNA

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

Summary

ID

NL-OMON39047

Source
ToetsingOnline

Brief title
AI444026 Open-Label Re-treatment study.

Condition

- Hepatic and hepatobiliary disorders
- Viral infectious disorders

Synonym
Chronic Hepatitis, Hepatitis C Virus

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic Hepatitis, Hepatitis C Virus, Peg-Interferon, Ribavirin

Outcome measures

Primary outcome

Proportion of subjects with SVR12, defined as HCV RNA
for all subjects infected with HCV genotype 1 who are prior non-responders to

pegIFNα-2a/RBV.

Secondary outcome

•Proportion of subjects with SVR12, defined as HCV RNA
12, for each HCV genotype other than genotype 1 prior non-responders to

pegIFNα- 2a/RBV and treatment naive HCV genotype 1b;

• Frequency of SAEs and discontinuations due to AEs;

• Proportion of subjects who achieve HCV RNA < LOQ (detectable or undetectable)

at weeks: 1, 2, 4, 6, 8 and 12; Weeks 4 and 12 [VR (4 & 12)], EOT, or follow-up

Week 24 (SVR24) for each HCV genotype and treatment regimen;

• Proportion of subjects who achieve HCV RNA undetectable at Weeks: 1, 2, 4, 6,

8, and 12, Weeks 4 and 12 (eRVR), EOT, follow-up Week 12 , or follow-up Week 24

for each HCV genotype and treatment regimen;

• Frequency of genotypic substitutions associated with virologic failure for

each HCV genotype and treatment regimen.

Study description

Background summary

The currently recommended treatment for most subjects with chronic HCV infection is a regimen of pegylated-interferon alpha (2a or 2b) and ribavirin (pegIFNα-2a/2b and RBV,respectively).5,6,7 In 2 pivotal clinical trials in treatment-naive subjects receiving pegIFNα-2b or pegIFNα-2a combined with RBV, treatment failure (defined as persistent HCV replication up to 24 weeks after the end of treatment [EOT]) occurred in 18% and 24% of subjects infected by genotype 2 or 3, and in 58% and 54% of subjects infected by genotype 1, respectively.

In addition to the poor response rate in both naive and non-responders genotype 1 infected subjects, current therapies are associated with significant side effects resulting in high rates of noncompliance and apprehension about starting treatment.

BMS-790052 is a potent and selective inhibitor of the HCV non-structural 5a protein (NS5a) with 50% effective concentration (EC50) values of 9 and 50 pM against genotypes 1a and 1b respectively. BMS-790052 has a broad genotype coverage including EC50 values ranging from 28 and 103 pM for Genotype 2a (JFH) infectious virus and replicon (chimera), respectively; 7.6 nM for genotype 2a replicon (HC-J6CH, chimera); 146 pM
for Genotype 3a replicon (chimera) with NS5A coding sequences; and 12 pM for Genotype 4a (chimera). No activity was observed against a panel of 10 RNA and DNA viruses, suggesting BMS-790052 is highly selective for HCV. In vitro studies demonstrated the emergence of variant HCV strains with resistance to BMS-790052.

Depending on the HCV strain and the number of substitutions in the NS5A gene, the resistance varied from 1 to > 8000-fold, although in many cases this was associated with a decreased replicative ability. BMS-650032, an inhibitor of the HCV non-structural NS3 protein, inhibits HCV
replication with EC50 values of 4 nM against genotype 1a and 1.2 to 2.9 nM against genotype 1b in replicon assays. BMS-650032 also inhibits genotype 4a HCV protease replicon chimera with EC50 of 4.0 nM. BMS-650032 selectively binds to the HCV NS3 protease active site preventing polyprotein processing and subsequent viral RNA replication. In resistance studies, selection of HCV genotypes 1a and 1b replicon cells
with BMS-650032 led to the establishment of cells with decreased antiviral susceptibility to BMS-650032.

In combination studies employing the HCV replicon system, BMS-650032 resulted in additive to synergistic interactions with IFNα and 2 clinical candidates targeting HCV NS5A replication co-factor and NS5B replicase. Neither antagonism

of antiviral activity, nor meaningful enhancement of cytotoxicity was observed with any of the combinations.

The combination of both BMS-790052 and BMS-650032 (which target separate proteins encoded by the HCV genome) with pegIFNα/RBV is therefore anticipated to efficiently suppress viral resistance and potentially achieve a higher rate of SVR in the non-responder population than the addition of a single DAA in combination with pegIFNα/RBV.

Study objective

Primary Objective

To assess the efficacy based on the proportion of subjects with SVR12, defined as HCV RNAgenotype 1 who are prior non-responders to pegIFNα-2a/RBV.

Secondary Objectives
• To assess efficacy, as determined by the proportion of subjects with SVR12 for HCV genotype 2, 3, and 4 prior non-responders to pegIFNα-2a/RBV and treatment naive HCV genotype 1b;

• To assess safety, as measured by the frequency of SAEs and discontinuations due to AEs for each treatment regimen;

• To assess efficacy, as determined by the proportion of subjects who achieve HCV RNA < LOQ (detectable or undetectable) at weeks: 1, 2, 4, 6, 8 and 12; Weeks 4 and 12 [VR (4&12)], EOT, or follow-up Week 24 (SVR24) for each HCV genotype and treatment regimen;

• To assess efficacy, as determined by the proportion of subjects who achieve HCV RNA undetectable at weeks: 1, 2, 4, 6, 8 and 12; Weeks 4 and 12 (eRVR), EOT, follow-up Week 12, or follow-up Week 24 for each HCV genotype and treatment regimen;

• To describe drug-resistant variants associated with virologic failure for each HCV genotype and treatment regimen.

Other Objectives

• To explore the relationship between antiviral activity endpoints and single nucleotide polymorphisms (SNPs) in genes encoding proteins of the IFN* family (IL28A, IL28B, IL29)

• To describe changes in immune response during treatment (using serum and/or RNA markers.

Study design

This study includes three periods (Screening, short term and long term) and is an open label Re treatment study. Following the brief screening period, eligible subjects will enter a 24 week short term treatment period. genotype confirmed and will be assigned to a treatment regimen. Approximately 300 subjects will be treated in total. Subjects infected with HCV genotype 1 and 4 will be treated with BMS-790052, BMS-650032 and peg-interferon alfa-2a and ribavirin for 24 weeks. Subjects infected with HCV genotype 2 and 3 will be treated with BMS-790052 and peg-interferon alfa-2a, and ribavirin for 24 weeks. Enrollment of subjects with Genotype 2 and 3 will only occur after the planned Week 16 interim analysis of Study AI444031 that will include SVR4 from the 12-week treatment arm and EOT data from the 16-week treatment arm for subjects meeting the response-guided therapy criteria in study AI444031. There is no randomization in this open label study.

Duration of therapy: All subjects will be followed for 48 weeks after 24 weeks of treatment or early discontinuation. The purpose of longer follow-up is to allow assessment of the durability of SVR for this regimen. Any subject who demonstrates virologic failure, (regardless of length of treatment), will also require a total of 48 weeks of post-treatment follow-up to monitor for drug-resistant HCV variants. Thus the maximum duration of the study for any subject will be 72 weeks. Following completion of the follow-up period, subjects will be asked to enroll into a separate observational study for an additional 3 year follow-up to assess long-term SVR, resistance and HCV-related complications.

Intervention

Treatment: At screening, subjects will have HCV genotype confirmed and will be assigned to a treatment regimen. Approximately 200 subjects who are prior non-responders to pegIFNα-2a/RBV will be treated. Subjects infected with HCV genotype 1 and 4 will be treated with BMS-790052, BMS-650032 and pegIFNα-2a/RBV for 24 weeks. Subjects infected with HCV genotype 2 and 3 will be treated with BMS-790052 and pegIFNα-2a/RBV for 24 weeks. Enrollment of subjects with Genotype 2 and 3 will only occur after the first interim analysis of Study AI444031 that will include SVR4 from the 12-week treatment arm and EOT data from the 16-week treatment arm for subjects meeting the response-guided therapy criteria in study AI44403

Study burden and risks

As for any relativly new drugs there might be unknown side ffects Patients are informed about potential risks of any study procedure and advrse drug reactions in the patient information sheet. Patients will have the inconvience of more frequent and sometimes longer visits to the hospital than would be usual for

routine clinical care.

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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

Inclusion Criteria
1) Signed Written Informed Consent
a) Freely given informed consent must be obtained from subjects prior to clinical trial participation, including informed consent for any screening procedures conducted to establish subject eligibility for the study.
2) Target Population
a) Subjects must have participated in any BMS-650032, BMS-790052, or BMS-791325 clinical trial, and must have been assigned to the control arm during the trial.
b) Subjects chronically infected with HCV Genotype 1, 2, 3, or 4 (mixed genotypes are not permitted);
c) HCV RNA viral load detectable.
3) Age and Reproductive Status
a) Men or women, >= 18 years of age;
b) Contraception requirements: Men and Women of childbearing potential (WOCBP) must be using 2 separate methods of contraception throughout the study and for up to 24 weeks after the last dose of RBV (or time specified by the country-specific RBV label, whichever is longer) in such a manner that the risk of pregnancy is minimized.
i) For subjects with HCV Genotypes 1 and 4: Oral contraceptive pills may be used but cannot be considered one of the two effective forms of contraception required because drug interaction studies verifying the effectiveness of OCPs when used with BMS-650032 have not been completed.
ii) For Subjects with HCV Genotypes 2 and 3: One (1) form of contraception must be effective barrier method (eg. condom, diaphragm, cervical cap). Oral contraceptive pills (OCPs) may be used in this study as one of the two effective forms of contraception.
Examples of highly effective birth control include:

• condom with spermicide;
• diaphragm and spermacide;
• cervical cap and spermacide
• female condom;
• intrauterine devices (IUDs);
This contraception requirement applies in all cases of heterosexual intercourse in which the female partner is a WOCBP, except when the male partner is vasectomized for a minimum of 6 months and with confirmed azoospermia by the investigator;
c) WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of investigational product. Female subjects must agree to the pregnancy testing requirements of this protocol.
d) Women must not be breastfeeding;
e) Requirements for male subjects (based on RBV label):
i) Male subjects (unless vasectomized) with female partners who are WOCBP must agree to inform their female partners of the protocol-specified contraception requirement and pregnancy testing recommendations during treatment and post-treatment and agree to adhere to these recommendations both on-treatment and during the post-dosing follow-up period;
ii) Male subjects must confirm that their female sexual partners are not pregnant at the time of screening.;In addition to the Inclusion Criteria listed above, the following Inclusion Criteria apply to all rescue subjects prior to initiation of QUAD therapy:
f) Genotype 1b subjects receiving ASV+DCV only, AND
g) Subjects meeting the definition of virologic breakthrough or treatment futility,
AND
h) HCV RNA < 400,000 IU/mL at the last assessment prior the initiation of QUAD regimen

Exclusion criteria

Exclusion Criteria
1) Target Disease Exceptions
a) Discontinuation from prior BMS HCV clinical trial due to a pegIFNα/ RBV-related event;
b) Positive for HBsAg, or HIV-1/HIV-2 antibody at screening.
2) Medical History and Concurrent Diseases
a) Liver transplant recipients;
b) Documented or suspected HCC as evidenced by imaging or liver biopsy;
c) Evidence of decompensated cirrhosis based on radiologic criteria or biopsy results and clinical criteria;
d) Evidence of a medical condition associated with chronic liver disease other than HCV (such as but not limited to: hemochromatosis, autoimmune hepatitis, metabolic liver disease, alcoholic liver disease, and toxin exposure);
e) History of chronic hepatitis B virus (HBV) as documented by HBV serology (eg, (HBsAg-seropositive). Subjects with resolved HBV infection may participate (eg, HBsAb-seropositive);
f) Current of known history of cancer (except in situ carcinoma of the cervix or adequately treated basal or squamous cell carcinoma of the skin) within 5 years prior to enrollment;

g) Any gastrointestinal disease or surgical procedure that may impact the absorption of study drug. (Subjects who have had cholecystectomy are permitted enter the study);
h) Any other medical, psychiatric and/or social reason including active substance abuse as defined by DSM-IV, Diagnostic Criteria for Drug and Alcohol abuse (Appendix 1) , which in the opinion of the investigator, would make the candidate inappropriate for participation in this study;
i) Inability to tolerate oral medication;
j) Poor venous access; Note: The following conditions are exclusion criteria for the use of pegIFNα-2a and/or RBV, based on their respective labels:
k) Severe psychiatric disease, especially untreated or unstable depression, that would prohibit use of pegIFNα-2a, as judged by the investigator;
l) History of hemoglobinopathies (eg. thalassemia major or sickle cell anemia), diagnoses associated with an increased baseline risk for anemia (eg, spherocytosis), hemolytic anemia, or diseases in which anemia would be medically problematic;
m) History of chronic pulmonary disease associated with functional limitation;
n) History of cardiopmyopathy, coronary artery disease (including angina), interventional procedure for coronary artery disease (including angioplasty, stent procedure, or cardiac bypass surgery), ventricular arrhythmia, or other clinically significant cardiac disease;
o) Historical or current ECG findings indicative of cardiovascular instability, including but not limited to evidence of myocardial ischemia, unstable re-entry phenomena, other significant dysarrhythmias and/or uncontrolled hypertension;
p) Pre-existing ophthalmologic disorders considered clinically significant on eye, including retinal, examination. Note: all subjects with a history of diabetes or hypertension must have a documented eye exam within 12 months prior to treatment;
q) History of uncontrolled diabetes mellitus;
r) Any known contraindication to pegIFNα-2a or RBV, not otherwise specified.
3) Physical and Laboratory Test Findings
a) Confirmed ANC < 750 cells/µL;
b) Confirmed platelets < 50,000 cells/µL;
c) Confirmed hemoglobin < 10 g/dL;
d) Confirmed INR >= 1.7;
e) Confirmed Albumin < 3.5 g/dL (35 g/L);
f) Confirmed Creatinine Clearance (CrCl) <= 50 mL/min (as estimated by Cockcroft and Gault);
g) Total bilirubin >= 34 µmol/L (or >= 2 mg/dL) unless the subject has documented history of Gilbert*s disease;
h) Alpha fetoprotein (AFP)
i) AFP > 100 ng/mL OR
ii) AFP >= 50 and <= 100 ng/mL requires a liver ultrasound and subjects with findings suspicious for HCC are excluded.
In addition to the Physical and Laboratory Test Findings Exclusion Criteria listed above, the following Exclusion Criteria apply/take precedence for treatment naive genotype 1b subjects prior to initiation of DUAL therapy.
Note: Growth factors must not be used to achieve eligibility criteria.
i) Confirmed ALT >= 5 x ULN;
j) Confirmed ANC < 500 cells/µL;
k) Confirmed hemoglobin < 8.5 g/dL

4) Allergies and Adverse Drug Reaction
a) History of hypersensitivity to drugs with similar biochemical structure to BMS-790052, or BMS-650032, pegIFNα, or RBV.
5) Prohibited Treatments and/or Therapies (Refer to Section 3.4.1 for a complete list of prohibited/restricted therapies in addition to 5a and 5b below)
a) Any anti-HCV therapy following initial treatment with BMS-650032, BMS-790052, or BMS-791325 clinical trial participation;
b) Exposure to any investigational drug or placebo within 4 weeks of study drug administration.
6) Sex and Reproductive Status
a) Those males and females who do not or cannot meet the requirements outlined in Inclusion Criterion #3;
7) Other Exclusion Criteria
a) Prisoners or subjects who are involuntarily incarcerated;
b) Subjects who are compulsorily detained for treatment of either a psychiatric or physical (eg, infectious disease) illness.
Eligibility criteria for this study have been carefully considered to ensure the safety of the study subjects and to ensure that the results of the study can be used. It is imperative that subjects fully meet all eligibility criteria

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):	07-01-2013
Enrollment:	6
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Asunaprevir
Generic name:	Asunaprevir
Product type:	Medicine
Brand name:	Copegus
Generic name:	Ribavarin
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Daclatasvir
Generic name:	Daclatasvir
Product type:	Medicine
Brand name:	Pegasys
Generic name:	Peginterferon Alfa-2a,
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	16-07-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	31-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-03-2013

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-05-2013
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:	10-07-2013
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:	26-09-2013
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:	11-11-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-02-2015

Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	20-02-2015
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	EUCTR2011-0008376-2-NL
CCMO	NL40401.018.12