A Phase III, Randomised, Partially Double-Blind and Placebo-Controlled Study of BI 207127 in Combination with Faldaprevir and Ribavirin in Treatment-Naïve Patients with Chronic Genotype 1 HCV Infection

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The aim of the study is to confirm efficacy and safety of treatment with 600 mg of BID BI207127 in combination with 120 mg QD Faldaprevir and RBV for 16 and 24 weeks in target chronically infected HCV GT1b treatment naïve patients, including a...

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

Summary

ID

NL-OMON40119

Source
ToetsingOnline

Brief title
Oral treatment for hepatitis C patients

Condition

- Hepatic and hepatobiliary disorders

Synonym
hepatitis, liver inflammation

Research involving

Human

Sponsors and support

Primary sponsor: Boehringer Ingelheim
Source(s) of monetary or material Support: boehringer-ingelheim

Intervention

Keyword: Deleobuvir (BI207127), Faldaprevir (BI201335), Hepatitis C

Outcome measures

Primary outcome

The primary objective is to determine if there is a clinically meaningful

difference between 16- and 24-week treatment durations.

Secondary outcome

The secondary objective is to determine if the minimum historical target SVR12

(Sustained Viralogic Response, 12 weeks after end of treatment) rates of 71%

can be achieved by the triple therapy of BI 207127, Faldaprevir and RBV,

including patients with compensated cirrhosis.

Study description

Background summary

Despite the improved virologic response rates in patients with HCV GT1 infection following the recent approvals of new medications, the increasing aging population with contraindications to PegIFN and the limiting side effects of the current standard of care indicate that there remains an urgent need for more effective, less toxic, shorter, more convenient and less invasive therapy for these patients. Effective antiviral therapy without PegIFN would constitute a major breakthrough in HCV treatment.This will be particularly important for populations of patients
with progressive liver cirrhosis or with HCV re-infection after liver transplantation. Therefore, BI is investigating the safety and efficacy of BI 207127, an oral, specific and reversible non-nucleoside HCV specific

RNA-dependent RNA polymerase inhibitor, in
combination with Faldaprevir (FDV, also known as BI 201335), a potent, oral HCV NS3/4a protease inhibitor, and RBV.

Study objective

The aim of the study is to confirm efficacy and safety of treatment with 600 mg of BID BI207127 in combination with 120 mg QD Faldaprevir and RBV for 16 and 24 weeks in target chronically infected HCV GT1b treatment naïve patients, including a separate group of patients with compensated cirrhosis to be treated open-label for 24 weeks.

The primary objective is to determine if there is a clinically meaningful difference between 16- and 24-week treatment durations.

The secondary objective is to determine if the minimum historical target SVR12 rates of 71% can be achieved by the triple therapy of BI 207127, Faldaprevir and RBV, including patients with compensated cirrhosis. For further details on defining the minimum historical target
SVR12 rates cf. Section 7.3.2.

Study design

The trial is multi-centre, randomised, double-blind and placebo-controlled for comparison of the 16 weeks (Group 1) versus 24 weeks (Group 2) treatment duration. Matching placebo is used for the last 8 weeks in Group 1 to secure blinding. In addition, an open label arm (Group
3) of 24 weeks treatment duration is included for patients with compensated cirrhosis.

There are three treatment arms:

- Group 1:16 weeks of 600 mg BID BI 207127 and 120mg QD Faldaprevir in combination
with standard weight-based dose of RBV, followed by additional 8 weeks of placebo BID
BI 207127+ placebo QD Faldaprevir in combination with placebo RBV (n= 195 patients)

- Group 2: 24 weeks of 600 mg BID BI 207127 and 120mg QD Faldaprevir in combination
with standard weight-based dose of RBV (n= 195 patients)

- Group 3: Patients with compensated cirrhosis 24-week arm: BI 207127 in combination

with Faldaprevir and RBV for 24 weeks (n= 40 - 70). This arm will be open-label.

After the treatment phase of 24 weeks is a follow-uip phase of 12, 24 or 48 weeks (depending on the treatment group and the reaction to the study medication SVR12).. The patient will not be further treated for hepatitis C. The patient will be asked to return frequently to the site to check the medical condition and to review if patient is completely cured of the hepatitis C infection.

Intervention

At Visit 2 patients will be start with oral triple treament of BI207127, faldaprevir and ribavirine for 16 to 24 weeks. If the treatment is not succesfull, patients may participate in a rescue medication program, in which they will be treated for maximal 48 weeks with a combination of faldaprevir, PEG-interferon and ribavirin.

Study burden and risks

If patient will complete maximal study duration of about 1.5 years (screening, 24 weeks treatment, depending on treatment group and response to medication (SVR12) 12, 24 or 48 weeks follow-up - in total 17 visits) this means:

- physical examination (completed or targeted): 17 times
- Urine sample: 17 times
- blood sampling: 17 times
- pregnancy testing (if applicable): 12 times and monthly at home (also partner)
- vital sigs: 17 times
- ECG: 12 times
- Questionnaires: 9 times
- Hepatitis B and HIV testing (1 time)
- Drugs screening (1 time)
- Possible adverse events

Contacts

Public
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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. Chronic hepatitis C infection diagnosed by by positive anti-HCV antibodies and;detected HCV RNA at screening in addition to at least one of the following:;a. positive anti-HCV antibodies or detected HCV RNA at least 6 months prior to;screening, OR;b. liver biopsy indicating chronic HCV infection, OR;c. history of elevated alanine aminotransferase (ALT) levels at least 6 months prior;to screening.;2. HCV infection of sub-GT1b confirmed by genotypic testing at screening.;3. Treatment naïve defined as:;a. no prior treatment with any interferon, pegylated interferon, and /or ribavirin;AND;b. no prior treatment with at least one dose of any other licensed or investigational;antiviral agent of for acute or chronic hepatitis C infection;4. Plasma HCV RNA * 1,000 IU/mL at screening;5. Liver biopsy within three years or fibroscan within 6 months prior to randomisation.;Note: patients with a liver biopsy performed 3 or more years or fibroscan performed 6;months or more prior to randomisation demonstrating cirrhosis do not need to repeat a;liver biopsy or fibroscan. Patients with a liver biopsy performed 3 or more years (or;fibroscan performed 6 months or more) prior to randomisation, negative for the presence;of cirrhosis need to repeat the liver biopsy or fibroscan, with the result available before;randomisation visit.;6. Age 18 * 75 years (inclusive);7. Female patients;a. with documented hysterectomy, OR;b. who have had both ovaries removed, OR;c. with documented tubal ligation, OR;d. who are post-menopausal with last menstrual period at least 12 months prior to;screening, OR;e. of childbearing potential with a negative pregnancy test at screening and on Day 1;(Visit 2), that agree to use two non-hormonal methods of birth control from the date;of screening until 7 months after the last dose of ribavirin. They must not breast-feed;at any time from the date of screening until 7 months after the last dose of ribavirin.;Accepted methods of contraception for females in this trial are diaphragm with;spermicide substances, intrauterine devices, cervical caps and condoms.;Note: Systemic hormonal contraceptives may not be as effective in women taking

BI;207127/FDV combination therapy and are not accepted methods of contraception in the;study.;OR;Male patients;a.who are documented to be sterile, OR;b. who consistently and correctly use a condom while their female partners (if of;child-bearing potential) agree to use one of the appropriate medically accepted;methods of birth control from the date of screening until 7 months after the last dose;of ribavirin, AND;c. without pregnant female partners. It is in the responsibility of the male patient to;ensure that his partner (or partners) is not pregnant prior to enrolment into the study;or becomes pregnant during the treatment and follow-up phase. Female partners of;childbearing potential must perform monthly pregnancy tests from the date of;screening until 7 months after the last dose of ribavirin (tests will be provided by the;sponsor).;8. Signed informed consent form prior to trial participation

Exclusion criteria

1. HCV infection of mixed genotype (1/2, 1/3, and 1/4) diagnosed by genotypic testing;at screening;2. HCV subtype 1a, GT1 undefined or mixed 1a/1b.;3. Evidence of liver disease mainly due to causes other than chronic HCV infection;such as autoimmune hepatitis, primary biliary cirrhosis, hemochromatosis or;Wilson*s disease.;Note: patients with steatosis as part of the histologic findings on liver biopsy are not;excluded.;4. HIV-1 or HIV-2 infection;5. Hepatitis B virus (HBV) infection based on presence of HBs-Ag;6. Evidence of decompensated liver disease, or history of decompensated liver disease,;defined as history of ascites, hepatic encephalopathy, bleeding esophageal varices or;any other evidence of previous decompensation;7. International Normalized Ratio (INR) of *1.7;8. Serum albumin <3.3 g/dL;9. Serum total bilirubin >2.0 times the upper limit of normal (ULN), unless history of;Gilbert*s disease;10. Active or suspected malignancy or history of malignancy within the last 5 years;(with the exception of appropriately treated basal cell carcinoma of the skin or in situ;carcinoma of the uterine cervix);11. Patients with ongoing or historical photosensitivity or recurrent rash;12. Alcohol or drug abuse (except cannabis) within the past 12 months;13. Body mass index <18 or > 35 kg/m2;14. Usage of any investigational drugs within 28 days prior to randomisation, or the;planned usage of an investigational drug during the course of the current study;15. Known hypersensitivity to any ingredient of the study drugs;16. A condition that is insufficiently diagnosed, treated or clinically unstable which in;the opinion of investigator may put the patient at risk because of participation in this;study, influence the results of this study, or limit the patient*s ability to participate in;this study;17. Alpha fetoprotein value >100ng/mL at screening; if > 20ng/mL and * 100ng/mL,;patients can be included if there is no evidence of liver cancer in an appropriate;imaging study within 6 months prior to randomisation;18. A history of severe pre-existing cardiac disease, including unstable or uncontrolled;cardiac disease (e.g. congestive heart failure, myocardial infarction, unstable angina;and arrhythmic disorders) current or within the previous 12 months before;randomisation;19. Received concomitant hematopoietic growth factor, or immunomodulatory treatment;within 28 days prior to randomisation;20. Received silymarin (milk thistle), glycyrrhizin, Sho-saiko-to (SST) or any;medication listed in a restricted medication list provided in ISF within 28 days prior;to randomisation, with the exception of parenteral analgesics used during liver biopsy;procedure.;The following exclusion criteria are potential contraindications for the use of PegIFN;+/- RBV (for rationale please cf. Section

3.2);21. Pre-existing psychiatric conditions including but not limited to severe depression or;hospitalization for depression, suicidal ideation and attempted suicide, schizophrenia,;bipolar illness, severe anxiety or personality disorder, a period of disability or;impairment due to a psychiatric disease current or within the previous 3 years before;randomisation;22. Abnormal thyroid function that cannot be controlled effectively by medication;23. Active autoimmune-mediated disease known to be exacerbated by peginterferon;therapy (e.g., Crohn*s disease, ulcerative colitis, idiopathic thrombocytopenic;purpura, systemic lupus erythematosus, autoimmune hemolytic anemia, scleroderma,;severe psoriasis);24. Requirement for chronic systemic corticosteroids (nasal or pulmonary steroids will;be allowed);25. History or other evidence of severe retinopathy or clinically significant;ophthalmological disorder due to diabetes mellitus or hypertension (but not limited to;these conditions). For subjects with a history of hypertension or diabetes, written;clearance from an ophthalmologist has to be obtained before the start of treatment;26. Hemoglobin <11.0g/dL for women and <12.0g/dL for men;27. Absolute neutrophil count < 1,500 cells/mm3;28. Platelet count < 90,000 /mm3;29. Creatinine clearance *50 ml/min;30. Diabetes mellitus with HbA1c > 8.5%;31. Clinically evident red blood cell disorders which include but are not limited to;thalassemia major, sickle cell anemia or glucose-6-phosphate dehydrogenase;deficiency or glucose-6-phosphate dehydrogenase deficiency

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):	06-02-2013
Enrollment:	15
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:	not applicable
Generic name:	deleobuvir
Product type:	Medicine
Brand name:	not applicable
Generic name:	Faldaprevir
Product type:	Medicine
Brand name:	Pegasys
Generic name:	pegylated interferon
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-11-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	15-02-2013
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:	17-04-2013
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:	30-07-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	17-12-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-05-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-05-2014
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	EUCTR2012-003533-41-NL
CCMO	NL42391.018.12