A Phase 2, Randomized, Double-Blind, Placebo-Controlled, Multi-center Study to Evaluate the Safety ad Efficacy of GS-9620 for the Treatment of Virally-Suppressed Subjects with Chronic Hepatitis B

Published: 07-10-2014
Last updated: 22-04-2024

The primary objectives of this study are:• To evaluate the safety and tolerability of GS-9620 in subjects with chronic hepatitis B (CHB) infection currently being treated with oral antivirals (OAV)• To evaluate the efficacy of GS-9620 at Week 24...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON41916

Source
ToetsingOnline

Brief title
GS-US-283-1059

Condition

- Viral infectious disorders

Synonym
Liver inflammation and jaundice

Research involving

Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: Gilead Sciences

Intervention

Keyword: Chronic Hepatitis B, Double-Blind, Placebo-Controlled

Outcome measures

Primary outcome

The primary efficacy endpoint is the mean change in serum HBsAg (log10 IU/ml)

from Baseline to Week 24.

Secondary outcome

• The proportion of subjects with HBeAg loss and seroconversion at Weeks 24 and

48

• The proportion of subjects with HBsAg loss and seroconversion at Weeks 24 and

48

• The mean change in log10 IU/ml serum HBsAg at Weeks 4, 8, 12 and 48

• The proportion of subjects with >= 1 log10 decline in serum HBsAg titers from

Baseline at Weeks 4, 8, 12, 24 and 48

• The proportion of subjects with breakthrough (defined as HBV DNA > 69 IU/ml

with confirmation > 2 weeks after the initial test in the setting of

satisfactory adherence to treatment with OAV) through Week 48

• The proportion of subjects with drug resistance mutations at Week 48

Study description

Background summary

See page 22 of the protocol, section 1.1 Background

Study objective

The primary objectives of this study are:
• To evaluate the safety and tolerability of GS-9620 in subjects with chronic hepatitis B (CHB) infection currently being treated with oral antivirals (OAV)
• To evaluate the efficacy of GS-9620 at Week 24 measured by the change from Baseline (BL) in serum hepatitis B s antigen (HBsAg log10 IU/ml) levels

Study design

Approximately 150 virally suppressed subjects, currently being treated with OAV for chronic hepatitis B, will be randomized in 3 sequential cohorts. Each cohort will dose for a different treatment period (4, 8 or 12 weeks). Cohorts will be explored in a sequential manner: 8 weeks of treatment will only be explored after completion and safety review of the 4 week treatment cohort; 12 weeks of treatment duration will only be explored upon complete evaluation of the 8 week treatment cohort. Within each cohort 50 subjects will be randomized in a 1:3:3:3 ratio to placebo or one of the following doses of GS-9620: 1, 2 or 4 mg.

After treatment completion (Week 4, Week 8, or Week 12), dosing of study drug will be discontinued. All subjects will continue on OAV and will be followed up to Week 48. The total study duration for each subject will be 48 weeks inclusive of the treatment period.

Liver Substudy
Approximately ten additional subjects (in addition to the 150 initially planned) will participate in the Liver Substudy. The ten subjects will be randomized in a 1:3:3:3 ratio to placebo on one of the following doses of GS-9620: 1, 2 or 4 mg for 8 weekly doses. Upon consent, fine needle aspirate liver biopsy samples will be collected at Baseline and Study Visit Week 7 + 24 hours, to determine effect of GS-9620 on the liver cell populations. Additionally whole blood samples for lymphophenotyping and RNA evaluation will be obtained at Baseline and at Study Visit Week 7 + 24 Hours.
The visit schedule includes ten study visits: screening, three visits during the 8 week treatment period (Baseline, Week 4 and Week 7 + 24 hours) and six Follow Up visits (Study Weeks 8, 12, 16, 24, 36 & 48).

Intervention

GS-9620 or placebo will be administered once a week (every 7 days), with the last dose at Week 3 (Cohort A), Week 7 (Cohort B) or Week 11 (Cohort C). All subjects will remain on OAV for the entire 48-week duration of study.

In the Liver Substudy, one tablet of GS-9620 or placebo must be taken once every 7 days for 8 weeks duration.

Study burden and risks

GS-9620 Possible Adverse Events
The study drug GS-9620 has been administered to 181 patients: healthy volunteers, patients with chronic hepatitis C, and patients with chronic hepatitis B.

• Study GS-US-243-0101 - A Phase 1 study in which 55 healthy patients were given a single dose of GS-9620 ranging from 0.3 mg to 12 mg
• Study GS-US-243-0102 - A Phase 1b study in which 42 patients with chronic HCV infection were given one or two weekly doses of GS-9620 ranging from 0.3 mg to 4 mg.
• Studies GS-US-283-0102 and 283-0106 - Two Phase 1b studies in which 84 patients with chronic HBV infection were given one or two weekly doses of GS-9620 ranging from 0.3 mg to 4 mg. 43 HBV patients were on treatment with oral antiviral drugs (Study GS-US-283-0102) and 41 HBV patients were not on treatment with any other oral antiviral drug (Study GS-US-283-0106).

Flu-Like Symptoms
GS-9620 stimulates the immune system, so it may cause immune system-related side effects. These effects may be similar to those you get when fighting off the common cold or flu (such as fever, aches, chills, etc.) and may include changes in white blood cell and platelet counts. Often, a fever is accompanied by a higher pulse rate.
Among the 55 healthy volunteers who received GS-9620, ten patients had flu-like symptoms following doses of GS 9620 at 8 mg or 12 mg. These are higher doses than you will receive in this study where the maximum dose will be 4 mg. Among the 84 patients with chronic HBV given GS-9620, 4 patients had temporary mild flu-like symptoms, including fever and chills.
Your white blood cells and/or platelets may become lower than normal. For this reason your blood cell count will be closely monitored during this study.

Hepatic Flare
GS-9620 is an immune-modulator. This means that it works by activating your own immune system to fight the HBV infection. Since HBV infects the cells of the liver (called hepatocytes), and GS-9620 is designed to attack the cells in the liver infected with HBV, GS-9620 may cause increased liver inflammation called a hepatic flare. This may be severe and require close monitoring by your doctor, medication, or even hospitalization.
General Adverse Events (AEs)

GS-9620 was well tolerated in healthy subjects dosed up to 8 mg. The most common side effects were headache, muscle pain, back pain, chills, fever, and loss of appetite.
GS- 9620 was also well tolerated in chronic HBV infected patients treated with lower doses ranging from 0.3 mg to 4 mg. The most common side effects observed in the 84 HBV patients treated with GS-9620 were mild to moderate headache and muscle pain. Other side effects noted in more than two HBV patients were mild to moderate fatigue, bruising (considered to be related to the drawing of the blood), diarrhea, nausea, dizziness, cough, mouth/throat pain, back pain and drowsiness. Among the 84 patients treated with GS-9620, 1 patient experienced a Serious Adverse Event of an arm fracture. This event was considered not related to the study drug. No patient had to discontinue taking GS-9620 for an adverse reaction.

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Burden and risks have been further updated based on the preliminary data of Cohort A, B and C (see Informed Consent Form, topic 3).

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. Must have the ability to understand and sign a written informed consent form; consent must be obtained prior to initiation of study procedures
2. Adult male and non-pregnant, non-lactating female subjects, (lactating females must agree to discontinue nursing before the study drug is administered), 18-65 years of age inclusive based on the date of the screening visit
3. A negative serum pregnancy test is required for female subjects (unless surgically sterile or greater than two years post-menopausal)
4. Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception
5. Documented evidence of chronic HBV infection (e.g. HBsAg positive for more than 6 months) with detectable HBsAg levels at screening
6. Have been on approved HBV OAV treatment for >= 1 year prior to screening, with HBV DNA below LLOQ (measured at least once) 6 or more months prior to screening, and HBV DNA < 20 IU/ml at screening
7. Subjects currently taking an approved HBV OAV (tenofovir, entecavir, adefovir, lamivudine or telbivudine, either as single agents or in combination) with no change in regimen for 3 months prior to screening
8. Willing to provide blood sample for TLR-7 and IL28B SNP assessment
9. Must be willing and able to comply with all study requirements

Exclusion criteria

1. Extensive bridging fibrosis or cirrhosis as defined clinically, by imaging or by the following:
a) Metavir >= 3 or Ishak fibrosis score >= 4 by a liver biopsy within 5 years of screening, or, in the absence of an appropriate liver biopsy, either
b) Screening FibroTest score of > 0.48 and APRI > 1, or
c) Historic FibroScan with a result > 9 kPa within <= 6 months of screening (if available)

If liver biopsy is available, the liver biopsy result supersedes (b) and/or (c, if available).
If an appropriate liver biopsy is not available, fibrosis will be evaluated by (b) and/or (c, if available). In the event of discordance between (b) and (c), the FibroScan results will take precedence.
2. Subjects meeting any of the following laboratory parameters at screening:
• White Blood cell count < 2500 IU/ml
• Neutrophil count < 1500 cell/mm3 (or < 1000 cell/mm3 if considered a physiological variant in a subject of African descent)
• ALT > 3x ULN
• INR > ULN unless the subject is stable on an anticoagulant regimen affecting INR
• Albumin < 3.9 g/dL
• Total bilirubin > 2 mg/dl
• Platelet Count < 125,000 /ml
• Estimate creatinine clearance (CLcr) < 50 ml/min (using the Cockcroft-Gault method) based on serum creatinine and actual body weight as measured at the screening evaluation
3. Co-infection with HIV, hepatitis C virus (HCV) or hepatitis D virus (HDV)
4. Evidence of hepatocellular carcinoma (e.g. as evidenced by recent imaging)
5. Malignancy within 5 years prior to screening, with the exception of specific cancers that are cured by surgical resection (e.g. basal cell skin cancer). Subjects under evaluation for possible malignancy are not eligible
6. Significant cardiovascular, pulmonary, or neurological disease
7. Any of the following conditions that may worsen in response to IFN :
• Autoimmune disease (e.g. lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, sarcoidosis, moderate or severe psoriasis)
• Poorly controlled diabetes mellitus
• Significant psychiatric disorders
• Thyroid disorder (unless controlled under treatment)
• Significant pulmonary diseases (e.g. chronic obstructive pulmonary disease)
• Retinal disease
• Immunodeficiency disorders
8. Chronic liver disease of a non-HBV etiology (e.g. hemochromatosis, Wilson*s disease, alpha-1 antitrypsin deficiency, cholangitis)
9. Received solid organ or bone marrow transplant
10. Received prolonged therapy with immunomodulators (e.g. corticosteroids) or biologics (e.g. monoclonal antibody, interferon) within 3 months of screening
11. Use of another investigational agents within 3 months of screening, unless allowed by the Sponsor
12. Current alcohol or substance abuse judged by the investigator to potentially interfere with subject compliance
13. Known hypersensitivity to study drug, metabolites or formulation excipients
14. Screening electrocardiogram (ECG) with clinically significant abnormalities and with QTcF interval (QT corrected using Fridericia*s formula) >= 450 msec for males and >= 470 msec for females
15. Women who may wish to become pregnant during the course of the study
16. Male subjects unwilling to refrain from sperm donation for at least 90 days after the last dose of study drug
17. Use of any prohibited con-medications

18. Believed by the Study Investigator to be inappropriate for study participation for any reason not otherwise listed

Study design

Design

Study phase:	2
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):	29-09-2015
Enrollment:	10
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	4-Amino-2-butoxy-8-[3-(pyrrolidin-1-ylmethyl)benzyl]-7,8-dihydropteridin-6(5H)

Ethics review

Approved WMO

Date:	07-10-2014
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	15-01-2015
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-03-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-04-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	14-09-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	25-11-2015
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	07-01-2016
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	EUCTR2014-001400-22-NL
ClinicalTrials.gov	NCT02166047
CCMO	NL50274.078.14