A Phase 4, Randomized, Open-label, Active-Controlled, Superiority Study to Evaluate the Efficacy and Safety of Tenofovir Disoproxil Fumarate (TDF) in Combination with Peginterferon α-2a (Pegasys®) versus Standard of Care Tenofovir Disoproxil Fumarate Monotherapy or Peginterferon α-2a Monotherapy for 48 Weeks in Non-Cirrhotic Subjects with HBeAg-Positive or HBeAg-Negative Chronic Hepatitis B (CHB)

Published: 10-03-2011
Last updated: 27-04-2024

The primary objective of this study is to evaluate the efficacy of TDF plus Peginterferon *-2a (PEG) combination therapy for 48 weeks versus standard of care TDF monotherapy or PEG monotherapy for 48 weeks in non-cirrhotic CHB subjects as determined...

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

Summary

ID

NL-OMON39436

Source
ToetsingOnline

Brief title
Not applicable

Condition

- Viral infectious disorders

Synonym
HBeAg-Positive or HBeAg-Negative Chronic Hepatitis B, infection of the liver

Research involving
Human

Sponsors and support

Primary sponsor: Gilead Sciences
Source(s) of monetary or material Support: De sponsor: Gilead Sciences;Inc.

Intervention

Keyword: Active-Controlled, Chronic Hepatitis B, Superiority Study

Outcome measures

Primary outcome

The primary endpoint is:

• The proportion of subjects with HBsAg loss at Week 72 following treatment

with 48 weeks of TDF plus PEG combination versus PEG alone for 48 weeks or TDF

alone

Secondary outcome

Secondary:

• The proportion of subjects with HBsAg loss at Week 72 following treatment

with TDF (48 weeks) plus PEG (16 weeks) combination versus PEG alone for 48

weeks or TDF alone

• The proportion of subjects who experience HBsAg loss at Week 96 and Week 120

• The proportion of subjects with virological response (HBV DNA level < 117 IU/mL) at Weeks 72, 96, and 120

• The proportion of subjects with serological response (HBeAg loss and seroconversion, and HBsAg seroconversion) at Weeks 72, 96 and 120

• The proportion of subjects who experience biochemical response (ALT < 30 for males and < 19 for females (based on AASLD 2008 guidelines); ALT < 42 for males and < 32 for females (based on central lab ULN for ALT) at Weeks 72, 96, and 120

• The proportion of subjects who require re-initiation or change of therapy while on therapy or post-treatment

Study description

Background summary

See 1.1 Background of the protocol on page 18

Study objective

The primary objective of this study is to evaluate the efficacy of TDF plus Peginterferon *-2a (PEG) combination therapy for 48 weeks versus standard of care TDF monotherapy or PEG monotherapy for 48 weeks in non-cirrhotic CHB subjects as determined by loss of HBsAg.

The secondary objectives of this study are to evaluate:
• efficacy of TDF (48 weeks) plus PEG (16 weeks) combination therapy versus standard of care TDF monotherapy or PEG monotherapy for 48 weeks in non-cirrhotic CHB subjects as determined by loss of HBsAg
• virological response (HBV DNA < 117 IU/mL)
• serological responses (HBeAg loss and seroconversion, and HBsAg seroconversion)
• Biochemical response (ALT < 30 for males and <19 for females (based on AASLD 2008 guidelines); ALT <42 for males and <32 for females (based on central lab ULN for ALT)

Additional objectives of this study are:
• to quantify HBsAg decline

• to evaluate the proportion of subjects requiring re-treatment post cessation of therapy according to protocol-specified algorithm
• to evaluate the proportion of subjects who discontinue treatment
• to evaluate difference in incidence rate of select adverse events
• to evaluate data on biomarkers to explore associations with treatment responses (including adverse events)

Study design

This is a randomized, open-label, active-controlled, superiority study to evaluate safety and the proportion of subjects with HBsAg loss in subjects who were treated with combination of TDF plus PEG versus standard of care TDF or PEG for 48 weeks.
Seven hundred and twenty non-cirrhotic adult subjects with chronic hepatitis B (CHB), either HBeAg+ or HBeAg-, will be randomized in a 1:1:1:1 ratio to one of the 4 treatment arms A, B, C and D. Arms A and B are test arms. Arms C and D are control arms.
Arm A: Subjects (n=180) will be treated with TDF and PEG concomitantly for 48 weeks.
Arm B: Subjects (n=180) will be treated with TDF and PEG concomitantly for 16 weeks followed by TDF alone for another 32 weeks (total 48 weeks).
Arm C: Subjects (n=180) will be treated with TDF continuously through 120 weeks.
Arm D: Subjects (n=180) will be treated with PEG for 48 weeks.

After completing 48 weeks study treatment, subjects in Arms A, B and D will be followed for 24 weeks (between Week 48 and 72) for off-treatment follow-up. Subsequently, there will be an extended follow-up period for 48 weeks (between Week 72 and 120). Subjects in Arm C will receive continuous TDF treatment and will be followed throughout the 120 weeks

Randomization across treatment arms will be stratified by HBeAg status and viral genotype at screening resulting in ten strata, HBeAg + with genotypes A, B, C, D, E-H and HBeAg- with genotypes A, B, C, D, E-H. Enrollment will be monitored to ensure adequate representation of either HBeAg status and across the common genotypes A, B, C, and D.

Subjects who experience loss of HBsAg during the first 48 weeks will continue treatment until Week 48.
Subjects in Arm C who lose HBsAg after 48 weeks will continue on study treatment based on the following criteria:
•If loss of HBsAg occurs during Week 48-72, subject will continue until Week 72.
•If loss of HBsAg occurs after Week 72, subjects will continue treatment until two consecutive visits confirming negative results.
Subjects who do not lose HBsAg will continue on study treatment until Week 120.

For subjects in Arms A, B, and D who lose HBsAg after starting retreatment with TDF during the post-week 48 period, these subjects will continue TDF for an

additional 24 weeks while participating in the trial.

During the immediate 24-week off-treatment follow-up period, subjects in Arms A, B and D will be monitored every 2 weeks for the first 12 weeks (between Week 48 and Week 60) and every 4 weeks for the second 12 weeks (between Week 60 and 72). Subjects meeting one or more of the criteria mentioned in the protocol, at any time while off-treatment during the study duration of 120 weeks, will be recalled for prompt evaluation for flare management and re-treatment with TDF.

Subjects requiring re-treatment with TDF will be expected to continue on TDF until the end of the study (Week 120). Upon completion of 120 weeks of study treatment, subjects may continue on TDF therapy (not provided by the study) or initiate other OAV therapy per local standard of care at the investigator*s discretion.

The proportion of subjects receiving re-treatment according to the protocol defined criteria above and the proportion of subjects who discontinue treatment will be observed among the different treatment arms.

Analyses are planned at the conclusion of the study for the purpose of establishing association between markers of disease activities and treatment response. For subjects who provide a separate consent, a blood samples will be collected for pharmacogenomic analysis in all countries except Indiafor the exploration of genetic markers that may be predictive of virologic response and the tolerability of HBV therapies.

At sites participating in the liver biopsy substudy, subjects who consent to participate in the liver biopsy substudy will undergo a first liver biopsy prior to their first dose and a second liver biopsy at Week 96(±2 weeks).. In consented subjects who require a new biopsy to enter the main study, the screening biopsy may be used both to qualify the subject for the study and for the substudy. Alternatively, qualified subjects may have a biopsy taken between Screening and Baseline Visits as long as the procedure is performed after proper consent for the substudy has been obtained. Liver biopsies will be evaluated for clinical/histological, and, if appropriate and possible, for molecular correlates of treatment outcome. Declining consent for participation in the biopsy substudy will not disqualify the subject from participating in the main part of the study.

Intervention

Tenofovir disoproxil fumarate (TDF) 300 mg PO once daily in combination with Peginterferon α-2a (PEG), 180 µg subcutaneous injection once weekly

Peginterferon α-2a (PEG), 180 *g, will be administered weekly by subcutaneous injection for the specified period of time (see Study Design, Arms A and B). Pegasys® prefilled syringes (Roche Pharmaceuticals) will be supplied by Gilead

Sciences.

Study burden and risks

An overview of the risks are described in the informed consent form: "Appendix 3: Side effects and risks"

Contacts

Public
PRA Belgium BVBA

Lakeside Drive 333
Foster City, California 94404
US
Scientific
PRA Belgium BVBA

Lakeside Drive 333
Foster City, California 94404
US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult subjects (aged 18-75) with CHB (e.g., positive for either serum HBsAg or HBV DNA for at least 6 months) prior to baseline.;Anti-HBV treatment naïve subjects and subjects who have taken oral anti-HBV nucleoside therapy with the last dose greater than or equal to 24

weeks prior to screening are also eligible.;HBV DNA for HBeAg- >= 2000 IU/ml, and HBeAg+ subjects >= 20000 IU/ml.;ALT > 54 U/L and <= 400 U/L for men, and > 36 U/L and <= 300 U/L for women.;Creatinine clearance rate greater than or equal to 80 mL/min

Exclusion criteria

Known bridging fibrosis or cirrhosis and/or decompensated liver disease;Decompensated liver disease;Absolute neutrophil count < 1,500/mm3, platelet < 100,000/mm3, hemoglobin < 10 g/dL (female) or < 11 g/dL (male).;Evidence of hepatocellular carcinoma;Histroy of significant renal, cardiovascular, pulmonary, neurological, autoimmune disease or bone disease (e.g., osteomalacia,chronic osteomyelitis, osteogenesis imperfecta, osteochrondroses, multiple bone fractures);History of severe depression or severe psychiatric disease;Thyroid dysfunction;Co-infection with HIV, HCV or HDV

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-06-2011
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Pegasys®

Generic name:	Peginterferon
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Viread®
Generic name:	tenofovir
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	26-04-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	03-10-2011
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	17-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	24-04-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	02-05-2012

Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	12-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	28-09-2012
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	29-01-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	26-02-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	21-08-2013
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	05-12-2014
Application type:	Amendment
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

Approved WMO Date:	23-02-2015
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	EUCTR2010-024586-45-NL
ClinicalTrials.gov	NCT01277601
CCMO	NL35689.078.11