A Prospective, Multi-Centre Study (B-Sure) to Evaluate Long-Term Durability of Sustained Virologic Response in Chronic Hepatitis B Participants With and Without Nucleos(t)ide Therapy Who Have Received and Responded to GSK3228836 in a Previous Treatment Study

Published: 08-12-2021
Last updated: 05-04-2024

Efficacy: To describe long-term durability of sustained virologic response (SVR) as measured by time to loss of SVR in treatment naïve participants who achieved a complete responseEfficacy: To describe long-term durability of sustained virologic...

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

Summary

ID

NL-OMON50532

Source
ToetsingOnline

Brief title
B-Sure

Condition

- Viral infectious disorders

Synonym
Chronic Hepatitis B; Hepatitis B

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Chronic Hepatitis B, GSK3228836, Phase:IIB

Outcome measures

Primary outcome

Time from achieving SVR in the previous GSK3228836 treatment study to the loss of SVR (first occurrence of either HBsAg or HBV DNA reversion, or first use of any rescue medication)

Time from NA cessation to the loss of SVR (first occurrence of either HBsAg or HBV DNA reversion or first use of any rescue medication)

Secondary outcome

* Time from NA cessation to the first occurrence of HBsAg reversion or first use of any rescue medication

* Time from NA cessation to the first occurrence of virologic relapse or first use of any rescue medication

* Time from NA cessation to the first occurrence of clinical relapse or first use of any rescue medication

* Time from NA cessation to NA retreatment

*

Time from achieving SVR in the previous GSK3228836 treatment study to the loss

of SVR (first occurrence of either HBsAg or HBV DNA reversion, or first use of any rescue medication)

Time from end of treatment in the previous GSK2338836 treatment study to delayed SVR in the absence of rescue medication

* In the subset of participants who go on to achieve a delayed SVR: Time to the loss of SVR from time of achieving delayed SVR

* In NA controlled participants who are continuing NA treatment:

* Time from end of treatment in the previous GSK2338836 treatment study to delayed SVR in the absence of any rescue medication

* In the subset of participants who go on to achieve a delayed SVR: Time to the loss of SVR from time of achieving delayed SVR

* In NA controlled participants who have discontinued NA treatment:

* Time from NA cessation to delayed SVR, in the absence of NA retreatment

* In the subset of participants who go on to achieve a delayed SVR after NA cessation: Time to the loss of SVR from time of achieving SVR

* Time from NA cessation to HBsAg loss in the absence of any rescue medication

* Time from NA cessation to the first occurrence of virologic relapse or first use of any rescue medication

* Time from NA cessation to the first occurrence of clinical relapse or first use of any rescue medication

* Time from NA cessation to the first occurrence of NA retreatment

* Occurrence of anti-HBs (antibody to HBsAg)

* Occurrence of anti-HBe (antibody to HBeAg)

* Actual values and changes from Baseline (EoS visit in the parent study) at

each study visit in HBsAg, HBV DNA, HBeAg, HBcrAg, HBV RNA levels

* Occurrence of mutations prior to GSK3228836 in the parent study and at the

time of virologic breakthrough

Study description

Background summary

HBV infection, especially chronic infection, is a significant worldwide medical problem. Globally, in 2015, an estimated 257 million people were living with CHB, with only 9% of patients being treated. Worldwide, it is estimated that around 650 000 people die each year from the complications of CHB.

It has been proposed that the continued production of hepatitis B viral antigens by infected hepatocytes interferes with immune clearance of both the infected cells and circulating virus particles. In vitro studies with human PBMCs have shown HBsAg impairs the functioning of dendritic cells and inhibits the activation of monocytes. Further, data suggest the production of vast excess of HBsAg (so called non infectious *sub-viral particles*) likely functions as a decoy for host antibody responses. Most chronically infected patients produce antibodies to HBsAg, but these can only be detected as immune complexes due to the vast excess of circulating antigen. HBeAg is also thought to have a role in immune response evasion through down regulation of the innate immune system. Since loss of HBsAg expression is rarely achieved while loss of HBeAg expression occurs in a higher proportion of the patient population, HBsAg appears to be the main antagonist of immune clearance.

The goal of therapy for CHB is to improve quality of life and survival by preventing progression of the disease to cirrhosis, decompensated liver disease, HCC, or death. In both HBeAg-positive and HBeAg-negative CHB, the ultimate treatment endpoint is loss of detectable serum HBsAg and serum HBV DNA. Recently, a functional cure of CHB infection has been endorsed as the endpoint for new HBV therapies. Functional cure of CHB infection is defined as sustained suppression of serum HBsAg to seroconversion,) and undetectable HBV DNA in serum, after completion of a
finite course of treatment.

First-line therapy for CHB is treatment with an NA therapy. While these antiviral agents are effective in suppressing HBV replication in both HBeAg-positive and HBeAg-negative CHB, and improve the prognosis of CHB, patients frequently relapse after treatment is discontinued, particularly if HBsAg loss was not achieved. Pegylated interferons (PegIFNs) are also approved

for treatment of CHB and are dosed for a finite treatment duration (usually up to 48 weeks). Because of the frequent and sometimes severe side effects associated with PegIFN and high cost versus a small gain in treatment response, PegIFNs are less frequently used than NAs. Rates of HBsAg loss following 12 months of treatment with either a NA and/or PegIFN generally range from 0 to 3% in most studies with occasional studies reporting higher rates, for example an approximately 10% functional cure after tenofovir disoproxil fumarate (TDF)+PegIFN for 48 weeks (off-label) [Marcellin, 2016]. Thus, most patients on treatment fail to achieve a sustained off-treatment virologic response and require extended and often life-long therapy to suppress HBV DNA.

GSK3228836, an antisense oligonucleotide, was designed to inhibit the synthesis of HBsAg without having a direct effect on cccDNA or integrated HBV DNA. GSK3228836 directly targets all HBV messenger ribonucleic acids (mRNAs) via ribonuclease H (RNAse H)-mediated degradation, resulting in the reduction of viral proteins including HBsAg. GSK3228836 treatment permits examination of whether reduction of HBsAg allows resumption of a host immune response against HBV and infected cells and can suppress serum HBsAg to been designed and selected to minimise risk of proinflammatory response
associated as a class effect by methylating every cytosine in the antisense oligonucleotide (ASO) sequence as well as avoiding the presence of CpG motifs that can be recognised by pattern recognition receptors [Henry, 2008]. However, it is expected that GSK3228836 may trigger marginal immune activation in the local environment of the liver, which may not be readily detectable in periphery. In turn, the intrinsic immunostimulatory activity of GSK3228836 may contribute to the efficacy in addition to direct pharmacodynamic response of HBsAg reduction . Complete and partial responders from previous studies of GSK3228836 will enter this study to be observed for durability of, late development of, and/or relapse from, their responder status, including attempted NA cessation in participants likely to benefit.

Study objective

Efficacy: To describe long-term durability of sustained virologic response (SVR) as measured by time to loss of SVR in treatment naïve participants who achieved a complete response

Efficacy: To describe long-term durability of sustained virologic response (SVR) after NA cessation as measured by time to loss of SVR in NA controlled participants who achieved a complete response and discontinued NA treatment

Study design

This is a global, multi-centre, long term follow-up study designed to assess durability of efficacy, as measured by SVR, in participants who have received prior treatment with GSK3228836 and had achieved a complete or partial

response.

Intervention

No study medication will be administered in this study.

Study burden and risks

Risks associated with study procedures/tests:

Blood sample: patient may feel faint or experience mild pain, bruising, irritation or redness from the needle. In rare cases, may get an infection and/or swelling and redness along a vein.

Questionnaires
There is a risk or discomfort of possible loss of confidentiality and/or the emotional discomfort answering some of the questions.

Contacts

Public
GlaxoSmithKline

Great West Road 980
Brentford, Middlesex TW8 9GS
GB
Scientific
GlaxoSmithKline

Great West Road 980
Brentford, Middlesex TW8 9GS
GB

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Participants who have previously received at least one dose of GSK3228836 AND
a. Achieved SVR (defined as HBsAg the end of previous investigational treatment [GSK3228836 and/or with or
without pegylated interferon] in the absence of rescue medication) and who maintained SVR until the EoS visit in their previous treatment study (defined as complete responders to GSK3228836 from the parent study) OR
b. Participants who have previously received at least 1 dose of GSK3228836 and demonstrated HBsAg reduction of >=1.0 log10 IU/mL from their treatment study Baseline and also with HBsAg levels <100 IU/mL and HBV DNA after the end of previous investigational treatment [GSK3228836] until the EoS
visit in their previous treatment study in the absence of rescue medication (defined as partial responders to GSK3228836 from the parent study).
2. Participants who enter the study on stable NA are willing and able to cease their NA treatment in accordance with the NA cessation schedule.
3. Capable of giving signed informed consent as described in Section 10.1 which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.

Exclusion criteria

1. Participants who have/or are currently participating in another non-GSK interventional clinical study exploring HBV treatment since completing their treatment with GSK3228836.
2. Any condition which, in the opinion of the investigator or Medical Monitor, contraindicates their participant in this study.

Study design

Design

Study type: Interventional
Masking: Open (masking not used)

Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-04-2022
Enrollment:	2
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	GSK3228836
Generic name:	GSK3228836

Ethics review

Approved WMO Date:	08-12-2021
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Approved WMO Date:	19-01-2022
Application type:	First submission
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	EUCTR2021-000554-26-NL
ClinicalTrials.gov	NCT04954859
CCMO	NL79112.078.21