A Phase III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Subjects who have Failed Prior Treatment with Pegylated Interferon and Ribavirin (P/R) with Chronic HCV GT1, GT4, and GT6 Infection

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Primary Objective(s) & HypothesisObjective: To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving SVR12 (Sustained Virologic Response 12 weeks after the end of all study therapy),...

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

Summary

ID

NL-OMON40780

Source
ToetsingOnline

Brief title
MK5172-068

Condition

- Viral infectious disorders

Synonym
chronic hepatitis C

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Merck Sharp & Dohme BV

Intervention

Keyword: Chronic Hepatitis C, pegylated interferon, Ribavirin

Outcome measures

Primary outcome

efficacy: Plasma HCV RNA levels according to SVR12

Secondary outcome

efficacy: Plasma HCV RNA levels according to SVR4

safety: The safety and tolerability of MK-5172 in combination with MK-8742 are assessed by a clinical evaluation of adverse events and inspection of other study parameters including vital signs, physical examinations, etc.

PK: C2hr for MK-5172 and MK-8742, and Ctrough for MK-5172, MK-8742 and ribavirin.

Study description

Background summary

Every year, 3*4 million people worldwide are newly infected with HCV, and approximately 80% of these will progress to chronic infection. It is estimated that 130*170 million people, or 2*3% of the world*s population, are chronically infected with HCV. Long-term complications of chronic HCV infection develop in

chronically infected individuals over the course of several years to decades, including cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC). More than 350,000 people die from HCV-related liver diseases every year. HCV has six major genotypes (GT), which can each be split into multiple subtypes. The global distribution of HCV genotypes is diverse, which reflects differences in epidemiology, modes of transmission and ethnic variability. HCV GT 1, 2 and 3 have a fairly broad geographical distribution, whereas HCV GT 4, 5 and 6 are generally confined to specific geographical regions.

The goal of therapy for chronic HCV infection is eradication of the virus, which is typically measured as a sustained virologic response (SVR). Until recently, SVR at 24 weeks post treatment (SVR24) has been considered the gold standard for treatment success; this end point is predictive of long term eradication of the virus and correlates with a reduction in symptoms and in the rate of negative clinical outcomes. However, there is evidence that most patients who have an SVR at earlier time points (such as SVR12) maintain it until week 24; therefore, the US FDA has concluded that SVR12 is suitable as a primary end point for regulatory approval.
Until 2011, the standard of care (SOC) treatment for chronic HCV infection with all genotypes was pegylated-interferon (peg-IFN) plus ribavirin (RBV) (PR) administered for either 48 weeks (HCV GT 1, 4, 5, and 6) or for 24 weeks (HCV GT 2 and 3). PR therapy led to SVR rates of 40%-50% in those with GT1 and of 80% or more in those with GT 2 and 3 infections.
Subjects co-infected with HCV and HIV have SVR rates of 27-38% when treated with peginterferon plus ribavirin (PR) for 48 weeks. In HCV co-infected patients, the addition of boceprevir and telaprevir to PR has been shown to increase the efficacy of therapy substantially. Furthermore the safety profile in co-infected subjects was similar to that in monoinfected persons.

Subjects who have a failed a prior regimen of peg-IFN and RBV are defined in the Inclusion Criteria Section of the protocol. This population is among one of the most in need of new therapies since a proportion also have cirrhosis of the liver. Therefore, this study will enroll both non-cirrhotic and cirrhotic subjects. Also, this patient population is more likely to be IL28 non-CC and be infected with HCV GT1a. Studying such a group will provide insight into the effectiveness of MK-5172/MK-8742 under challenging circumstances.
Among subjects who have failed a prior regimen of peg-IFN and RBV, the null responders to peg-IFN and RBV may be the most difficult to cure with alternative regimens, HCV GT1-infected subjects who were null-responders to peg-IFN and RBV have been effectively treated with several investigational DAA regimens.

Study objective

Primary Objective(s) & Hypothesis

Objective:

To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects achieving SVR12 (Sustained Virologic Response 12 weeks after the end of all study therapy), defined as HCV RNA TD(u) or TND) 12 weeks after the end of all study therapy.

Hypothesis:
In at least one of the arms, the proportion of subjects receiving MK-5172 in combination with MK-8742 achieving SVR12 will be superior to 58%.

Objective:
To evaluate the safety and tolerability of MK-5172 in combination with MK-8742.

Secondary Objective

Objective:
To evaluate the efficacy of MK-5172 in combination with MK-8742 (+/- ribavirin) as assessed by the proportion of subjects achieving SVR24 (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA (either TD(u) or TND) 24 weeks after the end of all study therapy.

Study design

This is a randomized, parallel-group, multi-site, open-label trial of MK-5172 and MK-8742 in subjects with hepatitis C, with and without compensated cirrhosis who have failed prior treatment with pegylated interferon (peg-IFN) and ribavirin (RBV) to be conducted in conformance with Good Clinical Practices.
A total of 400 GT 1, 4, 5, or 6 HCV infected subjects will be enrolled. All subjects will have failed prior therapy with peg-IFN and RBV. Approximately 30% of the enrolled subjects will have evidence of compensated cirrhosis at screening and approximately 20% of the subjects can be HIV co-infected. The number of prior peg-IFN and RBV relapsers will be capped to approximately 20%.
Study subjects will receive MK-5172A (Fixed Dose Combination of 100 mg MK-5172 + 50 mg MK-8742) QD for 12 or 16 weeks, with or without RBV with 24 weeks of follow-up after dosing is completed.
Safety and tolerability will be carefully monitored throughout the study by the SPONSOR (or designee) in accordance with standard.

Intervention

Treatment Groups:
* MK-5172 + MK-8742 (FDC) for 12 weeks
* MK-5172 + MK-8742 (FDC) + ribavirin for 12 weeks
* MK-5172 + MK-8742 (FDC) for 16 weeks
* MK-5172 + MK-8742 (FDC) + ribavirin for 16 weeks

Study burden and risks

Blood samples: drawing blood from the arm may cause pain, bruising, lightheadedness, and rarely, infection.
ECG: The electrocardiogram (ECG) procedure may cause minimal discomforts during the attachment and removal of the ECG leads to and from the skin.
Liver Biopsy: Pain at the biopsy site is the most frequent risk of percutaneous liver biopsy, occurring in about 20 percent of patients. The risk of excessive bleeding, called hemorrhage, is about 1 in 500 to 1 in 1,000. Risk of death is about 1 in 10,000 to 1 in 12,000. If hemorrhage occurs, a procedure called embolization, assisted by an x-ray procedure used to visualize blood vessels called angiography, can be used to stop the bleeding. In some cases, a blood transfusion is necessary. Surgery can also be used to stop a hemorrhage. Other risks include puncture of other internal organs, infection, and spread of cancer cells, called cancer seeding.
FibroTest/FibroSure®:. The main risks associated with blood tests are bruising and some pain around the needle*s entry point.
FibroScan (if applicable for your country): Generally there is no pain or discomfort associated with the procedure.

Contacts

Public
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL
Scientific
Merck Sharp & Dohme (MSD)

Waarderweg 39
Haarlem 2031 BN
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1. Be *18 years of age on day of signing informed consent.;2. HCV RNA (* 10,000 IU/mL in peripheral blood) at the time of screening.;3. Have documented chronic HCV GT1, GT4, or GT6;4. Have had a liver biopsy, Fibroscan, or Fibrotest to check for cirrhosis;5. Have a previous HCV treatment status that is of non-response, partial response or treatment relapse;6. For HIV-1 co-infection, documented by any licensed rapid HIV test or HIV enzyme or chemiluminescence immunoassay (E/CIA) test kit;7. For HIV-1 co-infection CD4+ T-cell count > 200 cells/mm3 at screening

Exclusion criteria

1. Has evidence of decompensated liver disease;2. Is coinfected with hepatitis B virus (e.g. HBsAg positive).;3. Has previous direct acting antiviral treatment.;4. Has signs of hepatocellular carcinoma or history of malignancy;5. Is taking or plans to take (a) any HIV therapy, or other medication not allowed for the study;6. Have an exclusionary laboratory value

Study design

Design

Study phase:	3
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):	12-06-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Rebetol
Generic name:	ribavirin
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	06-05-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-06-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	15-07-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	12-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-11-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-11-2014
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	EUCTR2014-000824-12-NL
CCMO	NL48769.018.14