A Phase II/III Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172 and MK-8742 in Subjects with Chronic Hepatitis C Virus Infection with Advanced Cirrhosis and Child-Pugh (CP)-B Hepatic Insufficiency.

Published: 01-12-2014
Last updated: 21-04-2024

The Primary Objectives are:(1) 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

Ethical review	Approved WMO
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON41892

Source
ToetsingOnline

Brief title
MK5172-059

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: industrie

Intervention

Keyword: cirrhosis, hepatic insufficiency, Hepatitis C

Outcome measures

Primary outcome

The primary measurement for efficacy in this study is the plasma HCV RNA level

based on SVR12 (Sustained Virologic Response 12 weeks after the end of all

study therapy)

Secondary outcome

Secondary evaluations of efficacy are based on SVR4 (Sustained Virologic

Response 4 weeks after the end of all study therapy), HCV RNA measurements at

Week 2, Week 4, and end of treatment (Week 12)

Study description

Background summary

Every year, 3-4 million people worldwide are newly infected with HCV [1], and approximately 80% of these will progress to chronic infection [2]. It is estimated that 130-170 million people, or 2-3% of the world*s population, are chronically infected with HCV [3]. Long-term complications of chronic HCV infection develop in chronically infected individuals over the course of several years to decades; these complications include cirrhosis, end-stage liver disease and hepatocellular carcinoma (HCC) [4]. More than 350,000 people die from HCV-related liver diseases every year [1].

The goal of therapy for chronic HCV infection is eradication of the virus, which is typically measured as a sustained virologic response (SVR). 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 leads to SVR rates of 40%-50% in those with GT1 and of 80% or more in those with GT2 and 3 infections [7].

Cirrhotic CHC subjects are a high-priority group for treatment, since they have a greater risk for liver-related complications than non-cirrhotics. Successful eradication of HCV in cirrhotic patients is associated with improved outcomes. In the large HALT-C trial, subjects with advanced fibrosis who achieved SVR with antiviral therapy had reduced rates of hepatic decompensation and liver-related mortality and improved survival [22]. The current SOC for patients with HCV G1 infection is a direct acting antiviral + PR. However, interferon-based regimens are not recommended for use in patients with decompensated cirrhosis (typically defined by Child-Pugh score >7), due to poor tolerability, unacceptably high levels of complications, and low efficacy. Thus, there is a clear medical need for improved, interferon-free antiviral therapies in CHC patients with moderate hepatic insufficiency (HI), most of whom have decompensated cirrhosis. This trial will examine the safety and efficacy of an all-oral combination of MK-5172 + MK-8742 in such subjects.

Study objective

The Primary Objectives are:

(1) 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.

(2) To evaluate the safety and tolerability of MK-5172 in combination with MK-8742.

The secondary Objectives are:

(1) To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the mean improvement in MELD score from baseline (Day 1) to follow-up week 12 in subjects who receive the dose of MK-5172 used in Part C.

(2) To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of subjects who receive the dose of MK-5172 used in Part C achieving:
• SVR4 (Sustained Virologic Response 4 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 4 weeks after the end of all study therapy.
• SVR24 (Sustained Virologic Response 24 weeks after the end of all study therapy), defined as HCV RNA <25 IU/mL (either TD(u) or TND) 24 weeks after the

end of all study therapy.

(3) To evaluate the efficacy of MK-5172 in combination with MK-8742 as assessed by the proportion of CP-B subjects who receive the dose of MK-5172 used in Part C achieving undetectable (TND) HCV RNA and HCV RNA < LLoQ at Week 2, 4 and 12.

Study design

This is a nonrandomized, historical-controlled, multi-site, open-label Phase 2/3 study

Intervention

All patients will recieve a dose of MK5172 (50mg) / MK8742(50mg) OF MK5172 (100mg) / MK8742(50mg) once daily. The amount of MK5172 is dependent on the outcome of part A and B of this study.

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. have HCV RNA (>= 10,000 IU/mL in peripheral blood) at the time of screening.;3. have documented chronic HCV GT1 infection (Part C subjects may have GT4 or GT6 infection), with no evidence of non-typeable or mixed genotype) infection:;• Positive for anti-HCV antibody, HCV RNA, or any of the above HCV genotypes at least 6 months before screening, or;• Positive for anti-HCV antibody or HCV RNA at the time of screening with a liver biopsy consistent with chronic HCV infection (or a liver biopsy performed before enrollment with evidence of CHC disease, such as the presence of fibrosis);4. have evidence of hepatic cirrhosis with a score on the Child-Pugh scale from 7 to 9 (moderate hepatic insufficiency) at the time of screening and not anticipated to receive a liver transplant within the next 36 weeks (for Arm 1 in Part A, Arm 3 in Part B and Arm 4 in Part C);5. agree (if subject is of reproductive potential) to remain truly abstinent or use (or have their partner use) 2 acceptable methods of birth control from at least 2 weeks prior to Day 1 and continue until at least 6 months after last dose of study drug, or longer if dictated by local regulations.;6. understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.;7. provide written informed consent for the trial. The subject may also provide consent for Future Biomedical Research. However, the subject may participate in the main trial without participating in Future Biomedical Research.

Exclusion criteria

1. is under the age of legal consent, is mentally or legally incapacitated, has significant emotional problems at the time of pre-study screening visit or expected during the conduct of the study or has a history of a clinically significant psychiatric disorder which, in the opinion of the investigator, would interfere with the study procedures. ;2. is co-infected with hepatitis B virus (e.g. HBs Ag positive) or HIV.;3. has previously received direct-acting antiviral therapy for HCV.;4. has a history of malignancy <=5 years prior to signing informed consent except for adequately treated basal cell or squamous cell skin cancer or in situ cervical cancer or carcinoma in situ; or is under evaluation for other active or suspected malignancy. ;5. has cirrhosis and liver imaging within 4 weeks prior to screening showing evidence of hepatocellular carcinoma (HCC), or is under evaluation for HCC.;Note: If liver imaging within 4 weeks of screening is not available, imaging is required during screening.;6. is taking or plans to take any of the prohibited medications listed in Section 5 of this protocol or taking herbal supplements, including but not limited, to St. John*s Wort (Hypericum perforatum) within 2 weeks of Day 1. Only silymarin (Milk Thistle, Silybum marianum) is permitted during the trial.;7. is currently participating or has participated in a study with an investigational compound within 30 days of signing informed consent and is not willing to refrain from participating in another such study during the course of this study. ;8. has a clinically-relevant drug or alcohol abuse within 12 months of screening.;9. is a female and is pregnant or breast-feeding, or expecting to conceive or donate eggs from at least 2 weeks prior to Day 1 and continue throughout treatment and follow up, or longer if dictated by local regulations, or male subject who is expecting to donate sperm from at least 2 weeks prior to Day 1 and continue throughout treatment and follow up, or longer if dictated by local regulations.;10. has any of the following conditions:;• Organ transplants (including hematopoietic stem cell transplants) other than cornea and hair.;• Poor venous access that precludes routine peripheral blood sampling required for this trial.;• Subject with a history of gastric surgery (e.g., stapling, bypass) or subject with a history of malabsorption disorders (e.g., celiac sprue disease).;• Any medical condition requiring, or likely to require, chronic systemic administration of corticosteroids during the course of the trial.;11. has any condition or prestudy laboratory abnormality, or history of any illness, which, in the opinion of the investigator, might confound the results of the study or pose additional risk in administering the study drugs to the subject.;12. has a life-threatening SAE during the screening period.;13. has evidence or history of chronic hepatitis not caused by HCV, including but not limited to nonalcoholic steatohepatitis (NASH), drug-induced hepatitis, and autoimmune hepatitis.

Study design

Design

Study phase:	2
Study type:	Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	4
Type:	Anticipated

Ethics review

Approved WMO Date:	01-12-2014
Application type:	First submission
Review commission:	METC Brabant (Tilburg)
Approved WMO Date:	25-02-2015
Application type:	First submission
Review commission:	METC Brabant (Tilburg)

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	EUCTR2014-000672-25-NL

Register	ID
CCMO	NL51355.028.14