A Phase II/III Randomized 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 and Chronic Kidney Disease

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Advances in the treatment of patients with hepatitis C infection have contributed to improved efficacy in several populations. However, for patients with CKD, particularly those with stages 3-5, treatment options remain limited and suboptimal. Given…

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

Summary

ID

NL-OMON40914

Source
ToetsingOnline

Brief title
MK5172-052

Condition

- Viral infectious disorders
- Renal disorders (excl nephropathies)

Synonym

Chronic Hepatitis C and Chronic Renal Insufficiency, Liver inflammation and Kidney Disease

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: CKD, HCV, MK-5172, MK-8742

Outcome measures

Primary outcome

Primary Objective(s) & Hypothesis(es)

In subjects who have chronic kidney disease (CKD Stages 4-5) and chronic HCV

GT1 infection with pre-treatment HCV RNA of at least 10,000 IU/mL:

The Primary Objective(s) are:

(1) Objective: To evaluate the efficacy of MK-5172 + MK-8742 in HCV GT1

subjects with chronic kidney disease (CKD) within the immediate treatment and

the intensive PK groups.

Hypothesis: The proportion of HCV GT1 infected CKD 4-5 subjects achieving SVR

(defined as HCV RNA
study therapy will be superior to 45% (see Section 4.2.1- Rationale for Study).

(2) Objective: To evaluate the safety and tolerability of MK -5172 in

combination with MK-8742 in the immediate treatment group relative to the

placebo treatment of the deferred treatment group.

Secondary outcome

Secondary Objective(s) & Hypothesis(es)

(1) Objective: To evaluate the efficacy of MK-5172 in combination with

MK-8742 as assessed by the proportion of subjects achieving:

• SVR24 (Sustained Virologic Response 24 weeks after the end of all study

therapy) within the immediate treatment and the intensive PK groups, defined

as HCV RNA < LLoQ (either TD(u) or TND) 24 weeks after the end of all study

therapy.

• SVR4 (Sustained Virologic Response 4 weeks after the end of all study ther

apy), defined as HCV RNA
all study therapy.

• SVR12 (Sustained Virologic Response 12 weeks after the end of

all study therapy), defined as HCV RNA
after the end of all study therapy on active period of deferred treatment arm,

• SVR12 (Sustained Virologic Response 12 weeks after the end of

all study therapy), defined as HCV RNA
after the end of all study therapy for all active treatment arms combined.

(2) Objective: To evaluate the safety and tolerability of MK -5172 in

combination with

MK-8742 for all treatment arms.

(3) Objective: To evaluate the emergence of viral resistance-associated

variants (RAVs) resistant to MK-5172 and MK-8742 when administered as part of a

c ombination regimen.

Study description

Background summary

MK-5172 is an inhibitor of the HCV NS3/4 protease and MK-8742 is a small molecule inhibitor of Hepatitis C Virus (HCV) non-structural protein 5A (NS5A) protein which is a pleiotropic protein with important roles in both HCV RNA replication and modulation of cell physiology of the host cell. HCV infection is a global health challenge affecting an approximately (~) 170 million people [1]. After initial infection, 55 to 85% of subjects progress to chronic hepatitis C virus (CHC) infection, leading to chronic liver disease and eventually, cirrhosis or hepatocellular cancer.
HCV has become the most common indication for liver transplantation in developed nations. The prevalence of subjects diagnosed with HCV will peak over the next 2 decades [2]. The current standard of care (SOC) for HCV G1 infection (excluding CKD patients) is a first
generation HCV NS3/4A protease inhibitor (boceprevir or telaprevir) + Pegylated Interferon (PegIFN) + Ribavirin (RBV). A 24 to 48 week course of therapy results in sustained viral clearance of HCV RNA (Sustained Virologic Response, or SVR) 24 weeks after completion
of therapy (SVR24) in 66-79% of treatment-naïve (TN), non-cirrhotic G1-infected patients [3,4]. Further improvements in HCV therapies are anticipated. In particular, better -tolerated, more effective, and more convenient regimens, consisting of orally administered, novel direct
acting antivirals (DAAs) are in development or approved. This trial will examine the safety and efficacy of such a regimen (an all-oral combination of MK-5172 and MK-8742) which is being evaluated in trials of HCV patients with and without CKD.

Study objective

Advances in the treatment of patients with hepatitis C infection have

contributed to improved efficacy in several populations. However, for patients with CKD, particularly those with stages 3-5, treatment options remain limited and suboptimal. Given the limitations of currently available therapies, it is clear that better therapies for HCV are urgently needed. The ideal HCV regimen for the CKD Class 3-5 patient should be
ribavirin-free, non-nephrotoxic and include agents whose primary mode of elimination is not renal. Further improvements in HCV therapies are anticipated. In particular, better -tolerated, more effective, and more convenient regimens, consisting of orally administered, novel direct acting antivirals (DAAs) are in development or approved. This trial will examine the safety and efficacy of such a regimen (an all-oral combination of MK-5172 and MK-8742) which is being evaluated in trials of HCV patients with and without CKD.

Study design

This is a randomized, parallel-group, multi-site, placebo controlled trial of MK-5172 and MK-8742 in subjects with Hepatitis C and Chronic Kidney disease (CKD) to be conducted in conformance with Good Clinical Practices. The trial will enroll approximately 220 cirrhotic and non-cirrhotic, Genotype 1 (GT1), HCV patients who have chronic kidney disease (CKD). A definition of the HCV and CKD disease status for targeted subjects in this study is included in Table 1. Patients on maintenance hemodialysis (including subjects awaiting renal transplant and subjects with a previous failed kidney transplant no longer on immunosuppressant therapy) and patients with CKD stages 4-5 who are not on hemodialysis will be enrolled with a minimum of 20% of patients in the latter category. Subjects must be either treatment naïve to all HCV treatments including any direct acting antivirals (DAA) or are intolerant or who have relapsed or were null-responders to a prior IFN-based treatment regimen. Subjects are required to undergo liver biopsy or non-invasive test to determine the presence or absence of cirrhosis.

Study subjects (210) will be randomized in a 1:1 ratio to receive MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed (immediate treatment group) or 12 weeks of placebo to MK-5172 and MK-8742 followed by
unblinding (after a 4 week unblinding period) and then 12 weeks of MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed (deferred treatment group).

In addition, 10 subjects (5 on hemodialysis and 5 non-dialysis CKD) will be assigned to receive open-label MK-5172 100 mg QD and MK-8742 50 mg QD for 12 weeks with 24 weeks of follow-up after dosing is completed. These 10 subjects will constitute the Intensive PK arm.
In the Netherlands no subjects will participate in the Intensive PK arm.

Intervention

The first dose of trial treatment will be administered at the trial site at Visit 2, or the Day 1 visit. Subsequent dosing will be performed once daily by the subject (i.e., unsupervised at his/her home) at approximately the same time each day.
Treatment Groups:

Immediate Treatment: MK-5172 100 mg + MK-8742 50 mg for 12 weeks

Deferred Treatment: MK-5172 placebo+ MK-8742 placebo for 12 weeks + 4 weeks unblinding period follow-up followed by MK-5172 100 mg + MK-8742 50 mg for 12 weeks

Intensive PK: MK-5172 100 mg + MK-8742 50 mg for 12 weeks (open-label)
In the Netherlands no subjects will participate in the Intensive PK arm.

Study burden and risks

Subjects may feel discomfort during some of these tests or may experience some inconveniences. Some may also have risks, which may include:
• The electrocardiogram (ECG): procedure may cause minimal discomforts during the attachment and removal of the ECG leads to and from the skin.
• Blood samples: drawing blood from the arm may cause pain, bruising, lightheadedness, and rarely, infection.
• Liver Biopsy: A liver biopsy is a procedure to remove a small piece of the liver so it can be examined with a microscope for signs of disease. All main types of biopsy remove liver tissue with a needle; however, each takes a different approach to needle insertion. A liver biopsy may be performed at a hospital or outpatient center. The most commonly used technique for collecting a liver sample is percutaneous liver biopsy. For this method, a needle is inserted through the abdomen into the liver to remove a small piece of tissue. 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: A Fibrotest is a blood test, and hence requires a blood sample to be taken by a healthcare provider, which he or she then sends to a lab for analysis. The main risks associated with blood tests are bruising and some pain around the needle*s entry point.

• FibroScan: Transient elastography (also known by its brand name, Fibroscan) is a form of ultrasound. The procedure is therefore very similar to an ultrasound procedure and allows a healthcare provider to measure fibrosis in the liver in a non-invasive way. An ultrasound probe is placed on top of the skin over the ribcage. The probe sends out a sound wave that travels through the liver and echoes back to the probe. A computer calculates the speed and strength of the echo to measure the elasticity or stiffness of the liver. Generally there is no pain or discomfort associated with the procedure.

Information about the side effects of the investigational drugs can also be found in the patient information form.

Contacts

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NL
Scientific
Merck Sharp & Dohme (MSD)

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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 documented chronic (at least 6 months) HCV GT1 infection (with no evidence of non typable or mixed genotypes) :
• Positive for anti-HCV antibody, HCV RNA, or an HCV genotype
• HCV RNA (>= 10,000 IU/mL in peripheral blood)
3.Subjects with or without cirrhosis may be enrolled into this study. All subjects must have one of the below liver disease staging assessments as follows:
• Liver biopsy performed within 24 months of Day 1 (if subject is cirrhotic then there is no time restriction on biopsy)
• Fibroscan performed within 12 months of Day 1
• A FibroSure® (Fibrotest®) and Aspartate Aminotransferase to Platelet
Ratio Index (APRI) (APRI is automatically calculated by central laboratory) during Screening
In the absence of a definitive diagnosis of presence or absence of cirrhosis by the above critieria, a liver biopsy is required. Liver biopsy results supersede the results obtained by Fibroscan or FibroSure®.
4. Have an HCV treatment status that is one of the following:
Treatment naïve: Naive to all anti-HCV treatment
Prior IFN or PEG-IFN + Ribavirin Treatment failures: Null responders, Partial responders, Relapsers. P/R Intolerant: Subjects were intolerant to a prior IFN or PEG-IFN ± Ribavirin regimen, Subjects discontinued treatment prematurely and were therefore unable to complete a full course of therapy because of drug-related toxicity.
5. Have Chronic Kidney Disease defined as:
Subjects with GFR <=29 who are non-dialysis dependent (NDD) or have been on hemodialysis (HD) for at least 3 months (including subjects awaiting kidney transplant and subjects with failed kidney transplants no longer on immunosuppressant therapy).
6. 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 through 14 days after the last dose of study drugs, or longer if dictated by local regulations.
If acceptable by local regulatory agencies, methods of birth control allowed in the study are: intrauterine device (IUD), diaphragm with spermicide, hormonal contraceptives (e.g., birth control pills, transdermal patch, or injectables), contraceptive sponge, female condom, male condom with spermicide or vasectomy.
7. A female subject who is not of reproductive potential is eligible without requiring the use of contraception. A female subjects who is not of reproductive potentials is defined as one who has either 1) reached natural menopause (defined as 12 months with no menses without an alternative medical cause), 2) 6 weeks post surgical bilateral oophorectomy with or without hysterectomy, or 3) bilateral tubal ligation.
8. A male subject who is not of reproductive potential is eligible without requiring the use of contraception. A male subject who is not of reproductive potential is defined as: one who has undergone a successful vasectomy. A successful vasectomy is defined as: (1) microscopic documentation of azoospermia, or (2) a vasectomy more than 2 years ago with no resultant pregnancy despite sexual activity post vasectomy.
9. understand the study procedures, alternative treatments available, risks involved with the

study, and voluntarily agrees to participate by giving written informed consent.
10. 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. Evidence of decompensated liver disease manifested by the presence of or history of ascites, gastric or variceal bleeding, hepatic encephalopathy or other signs or symptoms of advanced liver disease.
3. Is on peritoneal dialysis for management of Kidney disease
4. In the opinion of the investigator the subject has a high likelihood of receiv ing a renal transplant during the study treatment period (up to 24 weeks from Day 1).
5. Is coinfected with hepatitis B virus (e.g. HBsAg positive) or HIV.
6. 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 has evidence of hepatocellular carcinoma (HCC) or is under evaluation for other active or suspected malignancy.
7. Is taking or plans to take any of the prohibited medications listed in Section 5 of this protocol within 2 weeks of Day 1.
8. 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.
9. has a clinical diagnosis of substance abuse of the following specified drugs within specified timeframes:
• alcohol, intravenous drugs, inhalational (not including marijuana), psychotropics, narcotics, cocaine use, prescription or over -the-counter drugs: within 1 year of the screening visit or, if shorter is judged by the investigator to be capable of complying with study procedures, OR
• history of marijuana use is deemed excessive by a physician investigator or is interfering with the subject's daily function. If subject's marijuana use is not deemed excessive and does not interfere with daily function, subject must be instructed to discontinue any current use of recreational marijuana prior to entry into trial and throughout the trial period.
10. Female subject who is pregnant or breast-feeding, or expecting to conceive or donate eggs from Day 1 and through 14 days after the last dose of study drugs, or longer if dictated by local regulations or male subject who is expecting to donate sperm from Day 1 and through 14 days after the last dose of study drugs, or longer if dictated by local regulations.
11. Has any of the following conditions:
• Organ transplants (including hematopoietic stem cell transplants) other than kidney, cornea and hair.
• Poor venous access in non-dialysis patients 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.
• Has uncontrolled or poorly controlled hypertension including but not limited to hypertensive emergency or hospitalization for hypertension in preceding 3 months.
• Diagnosed with a significant cardiovascular disorder (e.g. MI or unstable angina) or has had a cardiovascular procedure (e.g. CABG or PTCA) within 3 months prior to signing informed consent.
• Has new or worsening signs or symptoms of congestive heart failure within 3 months of signing informed consent.
• Has severe active peripheral vascular disease, (e.g., manifested by claudication with minimal activity, a non-healing ischemic ulcer, or disease which is likely to require intervention such as with bypass or angioplasty).
• Has a recent (within 3 months prior to signing informed consent) diagnosis, episode or recurrence of stroke, TIA or neurological disorder, including but not limited to seizures, blackouts, or a recent (within 3 months prior to signing informed consent) change in the dose or class of medications used to treat these conditions.
12. Subject has any condition prestudy laboratory abnormality or ECG 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.
13. Had a life-threatening SAE during the screening period.
14. 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.
NOTE: Subjects with history of acute non-HCV-related hepatitis, which resolved > 6 months before study entry, can be enrolled.
15. For subjects diagnosed with diabetes mellitus, chart documented HbA1c >8.5 % to exclude uncontrolled diabetics
16. Has exclusionary laboratory values as listed in table 4 of the protocol.
17. Is or has an immediate family member (spouse or children) who is investigational site or sponsor staff directly involved with this trial.

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):	12-06-2014
Enrollment:	6
Type:	Actual

Ethics review

Approved WMO Date:	25-02-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-05-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	27-05-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	12-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	30-06-2014
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2013-003858-25-NL
ClinicalTrials.gov	NCT02092350
CCMO	NL47686.056.14