A Phase III Randomized Clinical Trial to Study the Efficacy and Safety of the Combination Regimen of MK-5172/MK-8742 in Treatment-Naïve Subjects with Chronic HCV GT1, GT4, and GT6 Infection who are on Opiate Substitution Therapy.

Published: 17-04-2014
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3.1 Primary Objective(s): 1) 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...

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

Summary

ID

NL-OMON42051

Source
ToetsingOnline

Brief title
MK-5172-062

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: HCV, Opiate Substition Therapy, Treatment naieve

Outcome measures

Primary outcome

Efficacy outcome: plasma HCV RNA level following SVR12

Safety outcome: 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 param eters including vital signs, physical examinations, etc.

PK outcome: C(2hr) en C(through)

Secondary outcome

Part A: Efficacy outcome: plasma HCV RNA level following SVR4 and SVR24

Part B: primary measurement is plasma HCV RNA, collected every 6 months to evaluate long term durability of SVR and incidence of reinfection in subjects with detectable HCV RNA.

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 decade s, 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 spe cific 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 -44% 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.

Study objective

3.1 Primary Objective(s):
1) 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.

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

3.2 Secondary Objective(s):
Part A
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), defined as HCV R NA

Part B
1) To evaluate the durability of SVR and the incidence of detectable HCV RNA, classified as either relapse or reinfection, over a three year followup period following the treatment/follow-up as defined in Part A .
2) To characterize the HCV virus detected during the Part A treatment and follow-up periods and as well as in the Part B 3-year follow-up period including:
a. To describe the presence of baseline viral resistance-associated variants (RAVs)
b. To describe treatment emergent RAVs
c. To determine reinfection versus relapse

Study design

This is a randomized, parallel-group, placebo-controlled, multi-site, double blind trial of 100 mg of MK-5172 in combination with 50 mg of MK-8742 (MK-5172A) in subjects with chronic Hepatitis C Virus (HCV), genotype (GT) 1, 4, or 6 infection who are on opiate
substitution therapy, to be conducted in conformance with Good Clinical Practices. A total of 300, GT 1, 4, or 6 HCV subjects on opiate substitution therapy will be enrolled. Approximately 20% of the enrolled subjects may have evidence of cirrhosis at screening. Enrolled subjects may be co-infected with HIV. All subjects must be treatment-naïve. Subjects in the immediate treatment group will receive MK-5172A 100mg/50mg (100 mg MK-5172/50 mg MK-8742) for 12 weeks with 24 weeks of follow-up after dosing is completed. Subjects in the deferred treatment group will receive Placebo for 12 weeks followed by 4 weeks of follow-up and then 12 weeks of open-label treatment with MK-5172A 100mg/50mg (100 mg MK-5172/50 mg MK-8742) with 24 weeks of follow-up after dosing is completed.
All subjects who received at least one dose of MK-5172 in combination with MK-8742 in Part A will be asked to participate in Part B (3-year followup).
Safety and tolerability will be carefully monitored throughout the study by the SPONSOR (or designee) in accordance with standard procedures.

Intervention

Part A:
Immediate Blinded Treatment:
Arm 1: MK-5172A 100mg/50mg (100 mg MK-5172/50mg MK- 8742) for 12 weeks

Deferred Treatment Blinded for first 12 weeks Followed by 12 Weeks of Open-Label Therapy:

Arm 2: Placebo for 12 weeks followed by open-label treatment for 12 weeks

Part B: no intervention

Study burden and risks

Part A and B:
*Blood samples: drawing blood from your arm may cause pain, bruising, lightheadedness, and rarely, infection.

Part A only:
* 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: Generally there is no pain or discomfort associated with the procedure.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Part A:
*You are greater than or equal to 18 years of age.;*You have chronic genotype 1, 4, or 6 Hepatitis C virus. ;*You must be on opiate substitution therapy (OST), have kept at least 80% of scheduled appointments while on OST, and not missed any scheduled appointments between screening and study entry;*You have had a liver biopsy, Fibroscan, or Fibrotest to check for cirrhosis or no cirrhosis. ;*You are treatment naïve to all HCV treatment ;*You may be co-infected with HIV;Part B:
- have received at least one dose of MK-5172 in combination with MK-8742 as detailed in Part A.
- understand the study procedures, alternative treatments available, risks involved with the study, and voluntarily agrees to participate by giving written informed consent.

Exclusion criteria

Deel A:
*You have signs of decompensated liver disease.;*You are coinfected with Hepatitis B virus.;*You have signs of hepatocellular carcinoma or history of malignancy.;*You are taking or plan to take any medication not allowed for this study. ;*You have a history of, or signs of, chronic hepatitis not caused by hepatitis C virus.;*You have an exclusionary laboratory

value;*If you have HIV, you use HIV drugs other than a dual NNRTI backbone of tenofovir or abacavir and either emtricitabine or lamivudine PLUS raltegravir [or dolutegravir or rilpivine];*You have a history of opportunistic infection in the preceding 6 months prior to screening.;Part B:
- 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.
- The subject has a medical condition or personal circumstance which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk through continued participation in the trial or does not allow the subject to adhere to the requirements of the protocol.

Study design

Design

Study phase:	3
Study type:	Interventional
Masking:	Double blinded (masking used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-09-2014
Enrollment:	4
Type:	Actual

Ethics review

Approved WMO

Date:	17-04-2014
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:	21-08-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	09-10-2014
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
Approved WMO Date:	06-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-07-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date:	18-09-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	02-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-01-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-02-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	21-07-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-08-2017
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2017
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	EUCTR2014-000343-32-NL
CCMO	NL48768.018.14