A Randomized Clinical Trial Using Fine Needle Aspiration For Evaluation of Hepatic Pharmacokinetics of MK-7009 in Chronic Hepatitis C Patients

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Primary:To evaluate the probability that FNA successfully obtains liver tissue specimens from which to evaluate liver drug concentrationsSecondary:1. To characterize the steady-state hepatic pharmacokinetics of MK-7009 (e.g., area under the liver...

Ethical review	Not approved
Status	Will not start
Health condition type	Viral infectious disorders
Study type	Interventional

Summary

ID

NL-OMON37067

Source
ToetsingOnline

Brief title
MK-7009-048

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 Corp.

Intervention

Keyword: Fine Needle Aspiration, Hepatitis C, Pharmacokinetics

Outcome measures

Primary outcome

MK-7009 Hepatic and Plasma PK Measurements:

Hepatic tissue samples from FNA will be obtained at 3, 12 and 24-hours post-dose to assess hepatic concentrations of MK-7009 (CH,3hr, CH,12hr and CH,24hr, respectively), to calculate an apparent terminal half life (tH,1/2) in the liver for MK-7009, and an area under the liver concentration versus time curve (population AUCH,0-12hr), as appropriate.

Samples will also be obtained (48 and 72 hours post-dose) to characterize the elimination phase in the liver.

Plasma samples will be obtained throughout the dosing period (refer to the study flow chart for time-points) to assess the plasma PK of MK-7009 (e.g., population area under the plasma concentration versus time curve over 12 hours [AUC0-12hr], maximum concentration of drug in the plasma [Cmax], trough concentration of drug in the plasma [Ctrough], time to reach Cmax [Tmax], and apparent terminal half life [t1/2], as appropriate).

Plasma sample may be analyzed for protein binding for MK-7009. The actual date and time of all PK samples, the actual date and time for the dose prior to each

PK sample, and the actual date and time of the first MK-7009, Peg-IFN and RBV dose should be collected and recorded.

Viral Resistance Measurements:

Blood will be drawn from each patient prior to and after dosing on Day 7 to assess viral resistance mutations at the time-points as indicated in the Study Flow Chart.

Efficacy Measurements:

Blood will be drawn from patients to assess plasma HCV RNA levels at the time points as outlined in the study flow chart. Results from screening visit blood draws will be used to determine eligibility. Blood draws from time 0 through dosing and post-dosing will be used for efficacy analyses.

RNA Profiling:

RNA levels will be measured from blood samples for validation of blood specific gene expression for estimation of liver and blood content in the FNA samples. Refer to the study flow chart for collection times.

Secondary outcome

N/A

Study description

Background summary

MK-7009, along with other direct-acting antivirals (DAA) for chronic hepatitis C virus (HCV) infection, exhibits nonlinear disposition kinetics, characterized by greater than dose-proportional increases in plasma exposure that may be due in part to saturable hepatic uptake of the compound from plasma. Tools for predicting human liver drug concentration are limited.

Core needle biopsy, the gold standard for obtaining liver tissue to evaluate drug concentrations, is associated with risk of bleeding and patient discomfort, which minimizes its ability to be performed frequently over a short period of time in a single patient. Fine needle aspirate (FNA), an ultrasound-guided procedure to acquire small amounts of liver tissue, has been demonstrated to be safe and well-tolerated by patients in a number of studies, amendable to frequent sampling and has been qualified previously in Experimental Medicine study, MK0000-123 as a platform for qualifying RNA expression analysis of liver tissue. In MK0000-123, multiple FNA samples were safely obtained at each of two sessions within 7 days in that study.

This study proposes to qualify FNA as a platform to evaluate hepatic pharmacokinetics in genotype 1, non-cirrhotic, chronic HCV-infected patients under conditions of both low and high oral doses of MK-7009. Plasma drug concentrations will also be obtained. The clinical study is planned based on successful completion of preclinical studies that quantitatively measure drug concentrations in liver tissue obtained by FNA, and successfully determine the amount of liver tissue versus blood present in the retrieved samples. The study will answer the following questions:
1) Can FNA procure sufficient tissue to evaluate liver drug concentrations with available methods?
2) Do liver PK results derived from FNA generally agree with results from core needle biopsy (CNB)?
3) Can the data contribute to a multicompartmental pharmacokinetic model of drug disposition?
4) Is the technique of FNA transferable across clinical sites (i.e., can it be performed reliably at typical phase I study sites)?

Ways in which this platform might benefit the HCV program include:
1) Understanding drug kinetics in the liver may allow better choice amongst compounds.
2) Understanding drug kinetics in liver may allow more rational exploration of dose and regimen in early phase 2 studies.
3) Data would facilitate interpretation of intrinsic and extrinsic differences in plasma exposure.
4) Access to liver tissue could provide mechanistic understanding of liver drug levels permitting more rational drug design. For instance, if the levels of key transporters are hypothesized to influence liver drug levels, this can be explicitly tested. One can measure mRNA or protein levels of the transporter proteins as a covariate and ask whether they explain liver drug levels.

The platform may also be utilized in evaluating DAA combinations, in bridging PK studies, in drug-drug interaction (DDI) studies, in evaluating potential for fixed-dose combinations (FDC), and in lifecycle management or special population studies.

The criteria that will be utilized to decide whether the platform is useful include:
1) Liver FNA needs to be executable in phase 1 environment, and enrollment needs to be rapid (e.g., < ~6 months)
2) The accuracy of drug level by FNA has to be within a reasonable range of that obtained from core needle biopsy. Since these drugs are highly concentrated in the liver relative to blood, a geometric mean ratio within 3 fold of CNB appears plausible.
3) To make the method useful for liver compartment modeling it should be feasible to be able to sample liver within patient with a frequency sufficient to detect changes between clearance from the blood and clearance from the liver.

Study objective

Primary:
To evaluate the probability that FNA successfully obtains liver tissue specimens from which to evaluate liver drug concentrations

Secondary:
1. To characterize the steady-state hepatic pharmacokinetics of MK-7009 (e.g., area under the liver concentration versus time curve, concentration of drug in the liver at 3, 12, 24, 48, and 72 hours post-dose, apparent terminal half life in the liver and liver-to-plasma ratio) derived from fine needle aspirate.
2. To compare FNA-derived liver PK to CNB-derived liver PK

Exploratory Objective
(1) To assess hepatic PK/plasma PD (viral titer) relationship
(2) To compare liver and plasma exposures at different doses of MK-7009
(3) To evaluate variability of liver drug concentration in samples from different liver regions or in portions of the same CNB sample
(4) To determine differences in uptake transporter gene expression in the liver that may contribute to different liver drug concentrations in FNA samples and core biopsy samples
(5) To determine the impact of FNA sample quality (as determined by % liver tissue and RIN score) on drug concentration measurements
(6) To evaluate immune responses (such as intrahepatic T cell populations via flow cytometry methods) after treatment derived from FNA and/or CNB liver samples and PBMC

Study design

The study will be performed using an adaptive design approach, in two study parts. In Study Part 1, patients meeting the study entry criteria will be randomized on Day 1 to 1 of 5 FNA/CNB time-point collection sequences (outlined in Protocol Section 2.4.2, Treatment Plan). The FNA/CNB time-point collection sequence identifies the timing of the FNA/CNB relative to the time of the last dose of treatment. There will be 10 patients receiving Treatment A, which will consist of 600 mg of MK-7009 administration twice a day (BID) Days 1-6, and a single dose on Day 7.
Each FNA time-point will consist of 4 FNA passes obtained under Doppler ultrasound guidance. The quality of each FNA pass (reflecting amount of blood contamination) will be recorded, along with the total number of FNA passes collected at each time-point.
Each FNA pass will be scored according to a color scale of 1-4 (1= clear, 2, light pink, 3= dark pink and 4= red). Should a FNA pass be scored a 4, this sample will be discarded and replaced with another FNA pass. The maximum number for FNA passes allowed at each time-point will be 5 passes, but that decision will be based on the judgment of the investigator as patient safety is of primary importance. CNB samples will also be scored for color, and can be replaced at the judgment of the investigator with a second CNB sample if the first sample is scored a 4.

At select sites based on operational feasibility, the 4th FNA pass collected at each timepoint will be placed in a separate tube for flow cytometric and functional analysis.

Blood samples will be collected for plasma PK pre-dose on Day 1 (before 1st dose of MK-7009), pre-dose Day 2 (~24 hrs after 1st dose), pre-dose Day 3, pre-dose Day 5, predose Day 7, at hours 0.5, 1.5, 2, 3, 4, 6, 8, 12, 16 and 24 post-day 7 dose, and at subsequent time-points coincident with those at which FNA are obtained. Plasma protein binding samples will also be obtained at pre-dose on Day 1 (before 1st dose of MK-7009).
Assessment for HCV viral load, viral resistance, and RNA profiling will also be performed.

An interim analysis for futility of the technical feasibility of FNA sample analysis will be performed prior to enrolling additional patients in Study Part 2. If futility is not declared, the study will proceed to Study Part 2, where patients will be randomized to 1:1 ratio of MK 7009 at 300 mg or 600 mg, and assigned to 1 of 5 FNA/CNB time-point collection sequences (outlined in Protocol Section 2.4.2, Treatment Plan) on Day 1.

MK-7009 will be administered twice a day on Days 1-6, then a single dose on Day 7. (For part 2 only) Randomized patients will be given Peg-IFN/RBV therapy throughout the whole study.

All study procedures and collections for liver tissues (via FNA and CNB), plasma PK and protein binding, and assessments for HCV viral load, viral

resistance and RNA profiling will be conducted the same as in Study Part 1.

As strongly recommended by US and European regulatory agencies, following completion of the study, patients will complete a post-study evaluation by the Investigator and will subsequently be eligible to receive a full treatment course of standard-of-care treatment as per local guidelines.

Intervention

MK-7009 (Study Parts 1 and 2):
All doses of MK-7009 will be administered orally in an open-label fashion using the Phase II formulation, which is a liquid filled capsule formulation (known as nLFC3), to be delivered using soft gelatin capsules (SGC) in 150 mg potencies.
On Days 1-6, the morning dose of MK7009 will be administered in the clinic. The evening dose will be taken at home, approximately 12 hours after the morning dose. A dosing diary card will be provided for at home dosing. MK-7009 will be taken without food restrictions.

On Day 7 only, MK-7009 will be administered in the clinic as a single dose after an 8 hour overnight fast to allow for collection of pharmacokinetic sampling. Water will be restricted 1 hour prior to and 1 hour after the dose of study drug. Fasting will continue for up to 3 hours post dose and/or after the FNA procedure.
Dosing at the clinic and at home will be done at approximately the same times each day (±30 minutes).

Study Part 1:
Treatment A: 600 mg MK-7009 (4 x 150 mg capsules) administered BID on Days 1 through 6 and single dose of 600 mg MK-7009 (4 x 150 mg capsules) on Day 7

Study Part 2:
Treatment B: 300 mg MK-7009 (2 x 150 mg capsules) administered BID on Days 1 through 6 and single dose of 300 mg MK-7009 (2 x 150 mg capsules) on Day 7

Treatment C: 600 mg MK-7009 (4 x 150 mg capsules) administered BID on Days 1 through 6 and single dose of 600 mg MK-7009 (4 x 150 mg capsules) on Day 7

Background Therapy (Study Part 2 only):
Pegylated Interferon (Peg-IFN) and Ribavirin (RBV) will be provided (per respective product labels - refer to Attachments 7) to randomized patients in combination with MK7009, and will continue for the entire duration of the study. Peg-IFN alfa-2b (PegIntron*), at a dose of 1.5 µg/kg/week, will be administered as weekly subcutaneous injections in the clinic during the course of the study. Each Peg-IFN alfa-2b dose must be administered approximately 7 days apart.

RBV (Rebetol*), at a total daily dose of 600 mg to 1400 mg based on patient

weight on Day 1, will be administered as twice-daily oral doses (see Table 1-1) with food per product label. During scheduled outpatient visits, one dose will be administered in the clinic, and one will be taken at home. On Day 7, the morning dose of RBV will be administered after the completion of 3 hour fasting postdose of MK-7009 administration and/or FNA procedure, whichever comes earlier. During other days, patients will take medication at home twice daily at approximately same times as they would during schedule visit days. If a patient misses a dose of RBV, then they should take the missed dose as soon as possible with food during the same day. If an entire day has gone by, then these missed doses should be skipped, and the normal dosing schedule should be resumed. Patients should not double the next dose in order to "make up" what has been missed. A study medication diary will be provided to patients to complete during the study for RBV at home dosing.

Study burden and risks

Risks:
- Possible side effects of MK-7009
- Fine Needle Aspiration
- Core Needle Biopsy

Burden:
- Physical exams
- Blood draws
- Administration of MK-7009
- Completion of medication diary
- (Only in study part 2): background therapy with Peg-IFN and RBV

Contacts

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US
Scientific
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One Merck Drive 1
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US

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

• Patient is a male or female between 18 to 65 years of age.
• Patient has a Body Mass Index (BMI) >=18.5 kg/m2 and <=32.0 kg/m2.
• Patient has chronic compensated, genotype 1 HCV infection as defined by positive serology for HCV and detectable HCV RNA (>levels >= 10,000 IU/mL) in peripheral blood.
• The patient does not have cirrhosis as confirmed by FibroSure*/FibroTest® and/or local country procedure (e.g. transient elastography/Fibroscan).
• Patient is treatment-naive, or treatment-experienced, with regard to prior treatment for chronic HCV infection, defined as:
Patient has previously been treated with and has tolerated at least 12 weeks of continuous licensed interferon (including pegylated interferon) and ribavirin combination therapy for HCV (patients previously treated with licensed NS3/4A protease inhibitors are not eligible for inclusion) with at least a partial response (>=2-log10 drop in HCV RNA at week 12) and/or patient has previously been treated with investigational products and/or vaccines for chronic HCV infection, other than NS3/4A protease inhibitors, either alone or in combination with other licensed therapies for chronic HCV infection.
• Patient is able to avoid use of anticoagulants, nonsteroidal anti-inflammatory agents and aspirin for at least seven (7) days preceding the initial liver biopsy and continuing throughout the entire study.

Exclusion criteria

• Patient is under the age of legal consent, is mentally or legally incapacitated
• Patient has a history of stroke, chronic seizures, or major neurological disorder.
• Patient did not achieve a viral response to prior treatment with licensed interferon-based therapy (i.e., is a *null responder*). Viral response is defined by a >=2-log10 decline in HCV viral RNA within the first 12 weeks of therapy.
• Patient has previously been treated with an NS3/4A protease inhibitor (investigational or

licensed) for chronic HCV infection.
• Evidence of high grade bridging fibrosis (e.g., METAVIR score >3, Ishak score >4 or Scheuer score >3) from prior liver biopsy within 3 years of study entry and/or non biopsy procedure (e.g. Fibroscan) as per local guidelines.
• Patient has evidence or history of chronic hepatitis not caused by HCV infection including but not limited to non-HCV viral hepatitis, nonalcoholic steatohepatitis (NASH), drug-induced hepatitis or autoimmune hepatitis.
• Patient has clinical or laboratory evidence of cirrhosis or other advanced liver disease.
• Patient has a history of clinically significant uncontrolled endocrine, gastrointestinal, cardiovascular, hematological, immunological, renal, respiratory, or genitourinary abnormalities or diseases.
• Patient has a history of clinically significant neoplastic disease (including leukemia, lymphoma, malignant melanoma), or myeloproliferative disease, regardless of the time since treatment.

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	9
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Nog niet beschikbaar
Generic name:	vaniprevir
Product type:	Medicine
Brand name:	PegIntron
Generic name:	peginterferon-alfa-2b

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

Ethics review

Approved WMO Date:	11-09-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)
Not approved Date:	12-10-2012
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	EUCTR2012-003284-21-NL
CCMO	NL41782.078.12
Other	Nog niet bekend