Grazoprevir (MK-5172) + Elbasvir (MK-8742) for the treatment of *ACUTE* hepatitis C genotype 1 or 4. The Dutch Acute HCV in HIV Study (DAHHS-2)

RESEARCH PROTOCOL

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PROTOCOL TITLE

Grazoprevir (MK-5172) + Elbasvir (MK-8742) for the treatment of *ACUTE* hepatitis C genotype 1 or 4. The Dutch Acute HCV in HIV Study (DAHHS-2)

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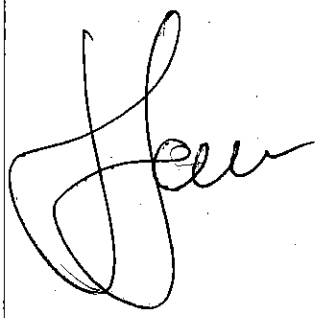
Sponsor or legal representative: **Head of Department** **Professor J.L.C.M. van Saase, MD, PhD** Erasmus MC, Room D-423 Postbox 2040 3000 CA Rotterdam, the Netherlands Phone No. +31107037549 **j.vansaase@erasmusmc.nl**		4/X/17
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LIST OF ABBREVIATIONS AND RELEVANT DEFINITIONS

ABR	ABR form, General Assessment and Registration form, is the application form that is required for submission to the accredited Ethics Committee (In Dutch, ABR = Algemene Beoordeling en Registratie)
AE	Adverse Event
AR	Adverse Reaction
BID	Twice daily
CA	Competent Authority
CCMO	Central Committee on Research Involving Human Subjects; in Dutch: Centrale Commissie Mensgebonden Onderzoek
CV	Curriculum Vitae
D	Day
DSMB	Data Safety Monitoring Board
DDI	Drug-drug interaction
EU	European Union
EudraCT	European drug regulatory affairs Clinical Trials
GCP	Good Clinical Practice
HAART	Highly active retroviral therapy
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IB	Investigator's Brochure
IC	Informed Consent
IL-28	Interleukin 28
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
METC	Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)
MSM	Men who have sex with men
PO	Per os (oral intake)
RVR	Rapid viral response
(S)AE	(Serious) Adverse Event
SOC	Standard of care
Sponsor	The sponsor is the party that commissions the organisation or performance of the research, for example a pharmaceutical company, academic hospital, scientific organisation or investigator. A party that provides funding for a

	study but does not commission it is not regarded as the sponsor, but referred to as a subsidising party.
SUSAR	Suspected Unexpected Serious Adverse Reaction
SVR	Sustained viral response
Wbp	Personal Data Protection Act (in Dutch: Wet Bescherming Persoonsgevens)
WMO	Medical Research Involving Human Subjects Act (in Dutch: Wet Medisch-wetenschappelijk Onderzoek met Mensen
PREP	Pre exposure profylaxis

SUMMARY

Rationale:

Over the last 2 years, the treatment of chronic HCV underwent an enormous change in a positive way. New and recently EMA approved direct acting antiviral (DAA) combination therapies cure as many as 95% of the patients *chronically* infected with HCV genotype 1 and 4. Grazoprevir (MK-5172) and elbasvir (MK-8742) combination therapy is such a combination DAA therapy. Two recent phase II and 1 phase III clinical trial showed that chronic HCV genotype 1 can be cured with 12 weeks of combination therapy with grazoprevir and elabsvir in 95% of HCV mono-infected and 87% (without ribavirin) to 97% (with ribavirin) of HIV-HCV co-infected patients. Furthermore, all 18 patients with genotype 4 infection that were treated for 12 weeks in the C-EDGE study were cured.

However, none of these new HCV therapies have been well studied for the treatment of *acute* HCV and are therefore not registered for this indication. The only treatment approved for acute HCV is interferon. Interferon based therapy for the treatment of HCV has been shown to be much more effective when given during the acute phase of the HCV infection than at a time when the infection has become chronic. A likely explanation for this difference in success for acute versus chronic HCV therapy is a substantial immune response that is present during the acute phase of HCV infection, but becomes exhausted during chronic infection. This potent immune response is broadly targeted against various HCV epitopes and eradicates approximately 20% of HCV infections within the first 12 to 18 months of infection. However, spontaneous cure of HCV becomes very rare after the first 12 to 18 months of infection due to immune exhaustion. It is likely that the synergistic effect of the host's immune response and antiviral therapy when given during the first 6 months of HCV infection makes antiviral therapy during acute HCV infection more effective.

Objectives:

To document that treatment of *acute* HCV with grazoprevir (MK-5172), elbasvir (MK-8742) is effective. To show that, due to the host's immune response at the time of an acute HCV infection, the duration of therapy with grazoprevir (MK-5172) and elbasvir (MK-8742) for *acute* HCV genotype 1 and 4 infections can be shortened from 12 to 8 weeks without substantial loss in efficacy.

Study design and intervention: Prospective open label interventional clinical trial in which 80 *acute* HCV genotype 1 or 4 monoinfected patients or co-infected patients with HIV will receive 8 weeks of grazoprevir and elbasvir (a once-daily combination tablet). Therapy will be initiated no later than 26 weeks after the presumed day of HCV infection.

Study population: 80 Adult HIV-positive or HIV-negative patients with an acute HCV genotype 1 or 4 infection from 12 HIV and/or HIV treatment centers in the Netherlands and Belgium will be included.

Primary endpoint:

Sustained viral response (SVR) 12 weeks after the end of therapy in ITT study population *(=genotype 1 and 4).*

Secondary endpoints:

SVR12 in all genotype 1 infected patients in the mITT.

SVR12 in genotype 1a infected patients with no NS5a polymorphisms at positions 28/30/31 or 93 versus SVR12 in patients with 1 or more of these polymorphisms

SVR12 in genotype 4 infected patients (ITT and mITT)

SVR12 in all patients included (=genotype 1 and 4, mITT)

SVR12 in RVR2 and RVR4 (mITT)

SVR12 in all patients (=genotype 1+4) according to IL28 genotype

SVR24 (mITT and ITT)

Cost-effectivity of acute HCV therapy in comparison with treatment 12 months after infection or treatment only at a certain level of liver fibrosis.

Alterations of biomarkers by therapy induced viral eradication: Viral sequencing, mutation analysis, gene expression analysis, RNA analysis in body fluids and for Erasmus MC patients only: functional assays at the cell level.

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The side effects of grazoprevir and elbasvir observed in the phase II and III clinical trials when given to patients with chronic HCV are summarized on page 11 of appendix D. In general, therapy was very well tolerated with a side effect profile comparable to placebo and treatment discontinuation for adverse events occurring in only 1%. As acute HCV is mainly asymptomatic, the side effect profile of for the treatment of *acute* HCV is expected to be the same. The only currently available treatment for acute hepatitis C consists of peginterferon with ribavirin without or without a direct acting antiviral and is associated with significantly more side effects than a interferon sparing treatment like grazoprevir and elbasvir.

The burden associated with participation in the study consists of 1 additional visits on top of the 5 visits that are needed when the current standard of care treatment is given. During these 8 visits additional blood samples are taken for a total of approximately 90 millilitres of blood for all study patients and approximately 200 millilitres blood for Erasmus MC patients. The study will be beneficial for those patients that reach a SVR as they will be cured of HCV without the need for interferon-based therapy. For those patients that do not achieve a SVR,

another therapy for HCV may have to be administered at a later point in time. With the current SOC this is the case for approximately 25%. It is possible that, against expectations, fewer patients will reach a SVR with the 8-week 2 DAA regimen that will be studied here.

1. INTRODUCTION AND RATIONALE

A newly acquired HCV infection is mostly asymptomatic. Therefore, if liver enzymes are not measured in the context of medical care for another disease, the new HCV infection remains undiagnosed for years or decades in most patients. Since 2000, a new epidemic of sexually transmitted HCV infections among HIV positive men who have sex with men (HIV+MSM) emerged[1]. This new epidemic was rapidly identified because regular liver enzyme testing is a standard procedure to look for liver injury induced by combination antiretroviral therapy (cART). In 2014, a prospective observational study in 18 Dutch HIV treatment centers showed that this HCV epidemic is now well established throughout the Netherlands. During the 12 months of the study, 99 acute HCV infections were diagnosed among 8849HIV positive MSM in care in these centers. The incidence of acute HCV was therefore 11/1000 patient years, which means that 1.1% of Dutch HIV+MSM acquired a new HCV infection in 2014 alone. This is 100-1000 fold higher than what can be expected in the general Dutch population. Of these acute HCV infections, 79% were genotype 1 (n=78) and 18% genotype 4 (n=18). Other genotypes were rarely seen (genotype 2 in 2 and genotype 3 in 0 patients respectively)[2]. Until recently, acute hepatitis C infections were almost exclusively seen in HIV-positive patients because only this risk was screened several times a year for hepatitis during their HIV control. London was the first increase of acute hepatitis C in HIV-negative gay men seen[3]. In the Netherlands last year, however, was rolled out PrEP (pre exposure prophylaxis) implementation program in Amsterdam. In this program HIV negative gay men at risk for HIV take drug that protects them against HIV. In this context, they are tested for HIV several times a year but also hepatitis. As a result, it is now also possible to detect acute HCV infections in HIV-negative patients, because it can be proved in this setting that it is a recent infection (on the basis of a preliminary negative hepatitis test). In this PREP implementation program already five acute hepatitis C infections have been identified[4].

Recently 2 interferon-free single tablet HCV therapies, sofosbuvir/ledipasvir and dasabuvir/ombitasvir/ paritaprevir/ritonavir received European Medicines Agency approval for the treatment of genotype 1 and 4. In patients with chronic HCV but without cirrhosis, both regimens cure >95% of the patients. Previously, sofosbuvir, simeprevir and daclatasvir received EMA approval for the treatment of chronic HCV. The current medication costs for a 12-week treatment with e.g. sofosbuvir/ledipasvir is 94500 USD (approximately 81000 euro). This very high cost per treatment and therefore major impact on national health-care budgets has resulted in a restrictive reimbursement policy in most European countries. In the Netherlands, only patients with chronic HCV and documented severe liver fibrosis or cirrhosis get their treatment reimbursed by the health insurance.

None of these new HCV therapies have been well studied for the treatment of *acute* HCV and are therefore not registered for this indication. The only treatment for acute HCV that is currently reimbursed in most countries is pegylated or unpegylated interferon. Interferon based therapy for the treatment of HCV has been shown to be much more effective when given during the acute phase of the HCV infection than at a time when the infection has become chronic. Based on our own review of studies published as a full paper or a conference report, acute HCV infections can be cured with interferon-based therapy in 542 of 711 (76%) HIV negative patients with an acute HCV. In HIV+ patients the cure rates were somewhat lower at 310/467 or 66%. These responses of 66-76% are in sharp contrast with cure rates of only +- 35-45% for chronic HCV genotype 1/4 with pegylated interferon and ribavirin. A likely explanation for this difference in success for acute versus chronic HCV therapy is a substantial immune response that is present during the acute phase of HCV infection, but becomes exhausted during chronic infection[5]. This potent immune response is broadly targeted against various HCV epitopes and eradicates approximately 20% of HCV infections within the first 12 to 18 months of infection. However, spontaneous cure of HCV becomes very rare after the first 12 to 18 months of infection due to immune exhaustion. It is likely that the synergistic effect of the host's immune response and antiviral therapy when given during the first 6 months of HCV infection makes antiviral therapy during acute HCV infection more effective.

A the end of 2013, the investigator initiated Dutch Acute HCV in HIV Study (DAHHS) started to recruit acute HCV genotype 1 infected patients in 10 Dutch HIV treatment centers. In 14 months, 65 patients were included (out of the >100 acute genotype 1 and 4 infections that were diagnosed in these 14 months). After spontaneous clearance was observed in 8 patients, the 57 remaining patients started treatment with 12 weeks of boceprevir peginterferon and ribavirin. We observed that the vigorous immune response during the acute phase of HCV, together with the addition of a single first-generation DAA to the peginterferon ribavirin therapy, cured 86% of the patients with only 12 weeks of treatment. We were therefore able to shorten peginterferon therapy with 50% without loss of efficacy[6]. In the subset of patients with a rapid viral response at week 4, 100% reached SVR12. It became clear that the DAHHS network is able to recruit a very significant number of acute HCV infected patients in a short time without any patients being lost-to-follow up. Another relevant observation in the DAHH-study was that, with all patients being on cART, their median CD4 count was very high at 660/mm3. This is substantially higher than the median CD4 count seen in patients with HIV and chronic HCV. Therefore, from an immunological

point of view HIV+MSM diagnosed with an acute HCV are comparable to HIV negative patients.

Two recent phase II and 1 phase III clinical trial showed that chronic HCV genotype 1 can be cured with 12 weeks of combination therapy with grazoprevir (MK-5172) and elbasvir (MK-8742) in 95% of HCV mono-infected and 87% (without ribavirin) to 97% (with ribavirin) of HIV-HCV co-infected patients. Furthermore, all 18 patients with genotype 4 infection that were treated for 12 weeks in the C-EDGE study were cured[7]. Larger clinical trials for the treatment of chronic HCV genotype 4 are ongoing but the *in vitro* potency of MK-8742 and MK-5172 against HCV genotype 4 is very high with an EC50 of 0.003-0.0003 nM and 0.062 nM respectively.

The long-term goal of policy makers, healthcare providers and the pharmaceutical industry should be to reduce the number of new HCV infections in a substantial way. Ultimately, the eradication of HCV may be possible in certain countries and patient populations. The first patient population for which HCV eradication may become a realistic future perspective is the easy to reach population of HIV-positive MSM and HIV-negative MSM. To make this happen, health care providers should be able to treat newly diagnosed acute HCV infections as soon as they are diagnosed to prevent ongoing sexual HCV transmission. If patients are only treated years later, at a time when fibrosis has been documented they will remain a significant source of new sexually transmitted HCV infections for years. Treatment as prevention as soon as an acute HCV infection is diagnoses could therefore be an important measure to halt the spread of HCV among HIV+MSM just as treatment as prevention works to prevent HIV transmission.

HCV treatment as prevention, is currently not possible because DAA are not registered for the treatment of acute HCV because their effectivity in the context of acute HCV has not been shown.

The goal of this study is to document the efficacy of a shortened 8-week therapy with grazoprevir and elbasvir in patients with acute HCV genotype 1 or 4 infection.

2. OBJECTIVES

Primary objectives

1. To document that treatment of *acute* HCV with grazoprevir (MK-5172), elbasvir (MK-8742) is effective

2. To show that, due to the host's immune response at the time of an acute HCV infection, the duration of therapy with grazoprevir (MK-5172) and elbasvir (MK-8742) for *acute* HCV genotype 1 and 4 infections can be shortened from 12 to 8 weeks without substantial loss in efficacy

Secondary objectives

1. To determine the cost-effectivity of acute HCV therapy in comparison with treatment 12 months after infection or treatment only at a certain level of liver fibrosis.

3. STUDY DESIGN

Single arm open label multicenter study
Treatment duration of 8 weeks
Treatment: grazoprevir (MK-5172) 100mg QD + elbasvir (MK-8742) 50mg QD given as a fixed drug combination tablet

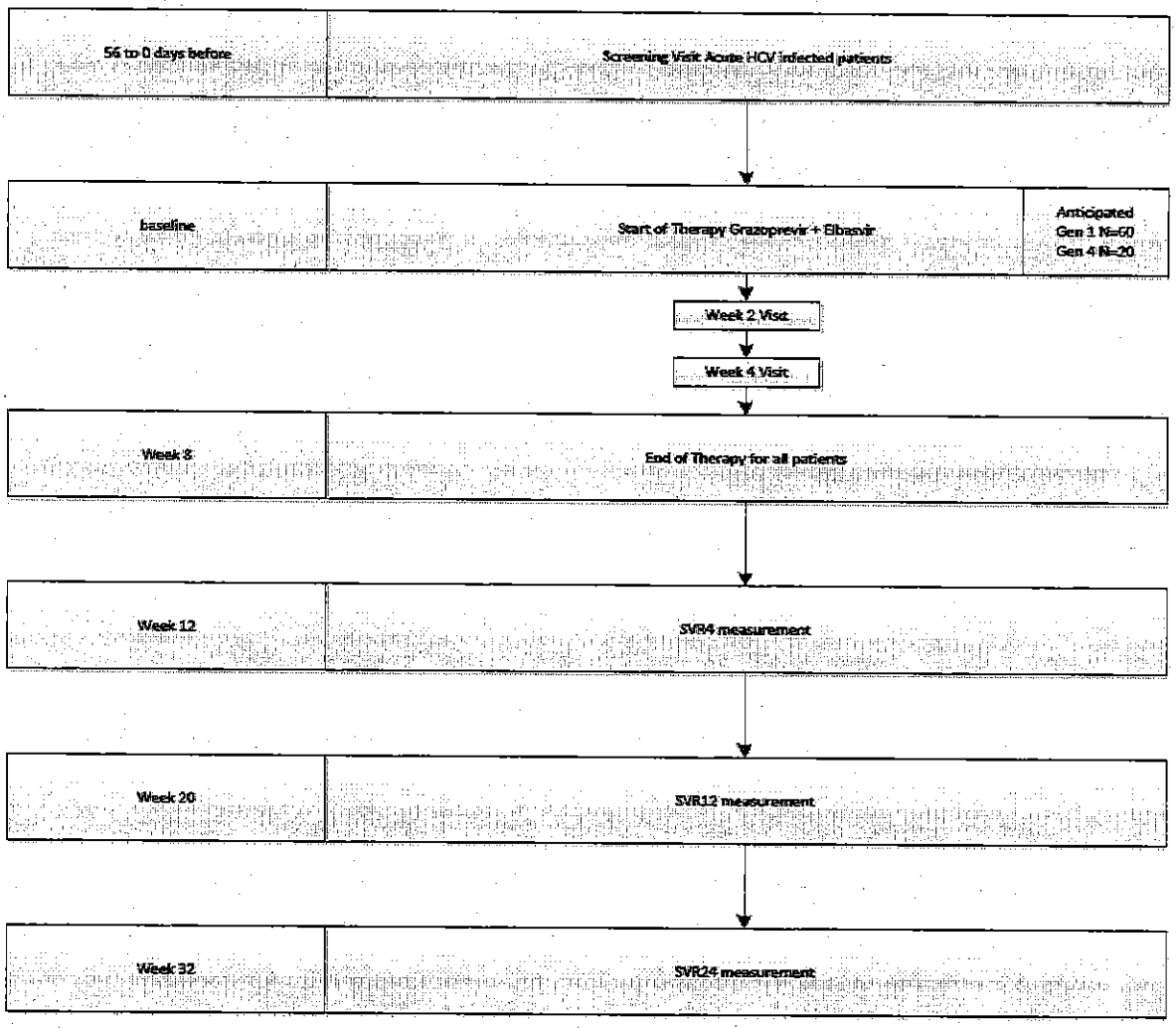
Sample size: n=80 patients, genotype 1 or 4

The study inclusion will end when in total 80 patients are included.

HCV relapse definition:
HCV relapse is defined as HCV RNA detectable after a previously undetectable HCV RNA level within 24 weeks after treatment discontinuation.

Reinfection is relatively frequent in HIV+MSM. It is therefore important to differentiate reinfection from relapse, as reinfection will not be counted as therapy failure. Therefore, all strains of presumed HCV relapses will be send to the department of virology at Erasmus MC together with the baseline plasma sample for sequencing to exclude reinfection.

Diagram of patient flow through the DAHHS study protocol



4. STUDY POPULATION

4.1 Population (base)

80 Adult HIV positive and HIV negative patients (minimum age 18 years) with an acute HCV genotype 1 or 4 infection from HCV and/or HIV treatment centers in the Netherlands and Belgium will be included. Based on historical data on the incidence of acute HCV infection in the Netherlands and the participating centers, recruitment will take 12-18 months after all centers have been initiated.

HIV-infected patients in care are tested for liver disease with ALAT twice a year on the HIV-outpatient clinic. A rise in ALAT (often the first sign of HCV infection) will be followed by HCV diagnostic tests.

Furthermore, detection of cases of acute HCV in HIV negative MSM will be performed in centers were HIV pre-exposure prophylaxis is prescribed to MSM at risk for HIV in particular in Antwerp, Belgium. These HIV-negative MSM will be tested twice a year for HCV to allow for a prompt HCV diagnosis at the time when the infection is still acute and therefore inclusion in the DAHHS2 study possible.

4.2 Inclusion criteria

1. Acute HCV genotype 1 or 4 infection (≤26 weeks old at the baseline visit) according to definition mentioned below.

4.3 Exclusion criteria

1. If HIV positive: Not on cART and a CD4 <500 at the time of screening
2. If HIV positive: Patients on cART for >6 months with a HIV viral load >400 copies
3. Disallowed co-medication that cannot be stopped or replaced: Therefore ALL co-medication, including over-the-counter drugs should be checked for potential drug-drug interactions using the investigators brochure (appendix A en B). In particular, care should be taken for patients that are taking >10mg atorvastatin or >5mg rosuvastatin per day and the dose should be reduced to the lowest dose available (10mg for atorvastatin and 5 for rosuvastatin). Alternatively a switch to pravastatin may be preferred. When in doubt about drug-drug interactions, contact the coordinating investigator.
4. History of liver cirrhosis of any etiology. Inclusion of patients with a chronic well-controlled HBV (HBV-DNA <below the limit of detection) is allowed if fibroscan excludes >F1 fibrosis. Fibroscan reports <5 years old can be used for screening.
5. If HIV positive: Protease inhibitor based and NNRTI based cART regimens are not allowed. Therefore, the inability to switch to a HAART regimen consisting of 2 nucleoside/tide reverse transcriptase inhibitors and an allowed third agent which can be raltegravir (Isentress®) 400mg BID, dolutegravir (Tivicay) 50mg QD or rilpivirine 25mg QD.

5. TREATMENT OF SUBJECTS

5.1 Investigational product/treatment

Grazoprevir (MK-5172) is a HCV protease inhibitor that is currently under review by the EMA for chronic HCV genotype 1 and 4 infection when given in combination with elbasvir.

Elbasvir (MK-8742) is a NS5A inhibitor HCV inhibitor that that is currently under review by the EMA for chronic HCV genotype 1 and 4 infection when given in combination with grazoprevir.

Grazoprevir 100mg and elbasvir 50mg are given for 8 weeks as a fixed drug combination tablet that needs to be taken once daily. We refer to the IB for further information (appendix A and B).

5.2 Use of co-intervention (if applicable)

Co-medication

Patients will be informed about the use of co-medication by the patient information form and by the treating physician. Co-medication that affects the efficacy of the study drugs must be avoided (see IB, appendix A p197-204 and appendix B p 120-123). Therefore, participating patients may have to stop certain medications they use. If needed, an appropriate alternative will be prescribed by the treating physician.

Additional rules that apply concerning cART during the study

Due to drug-drug interactions, some cART regimens cannot be combined with grazoprevir and elbasvir, as they are known to result in drug concentrations outside the therapeutic window of either grazoprevir/elbasvir or 1 of the components of the cART regimen (see IB for further information (appendix A p197-204 and appendix B p120-123). Therefore, all patients should be on a cART regimen that can be combined with grazoprevir and elbasvir. Allowed cART regimens are 2 nucleoside/tide reverse transcriptase inhibitors (taken as 1 tablet Truvada® or Kivexa®) plus either raltegravir (Isentress®) 400mg BID or dolutegravir 50mg QD or rilpivirine (Edurant®) 25mg QD.

Patients not on such a regimen will have to switch to this regimen. For patients on a cART regimen containing efavirenz or nevirapine this switch should take place at least 2 weeks

before the baseline visit to be sure for the CYP induction by these drugs has disappeared at the baseline visit.

For patients with a CD4 <500/mm3 and not on cART at the time of screening cART should be started immediately after the screening visit as the patient has to be on cART for at least 4 weeks at the baseline visit. As a integrase inhibitor based regimen leads to the fastest HIV RNA decline, the preferred regimen to start with in these patients is with raltegravir (Isentress®) 400mg BID or with dolutegravir 50mg QD both given with Truvada® or Kivexa®.

Guidelines on acute HCV management in HIV infected patients recommend that HCV therapy has started within 12 weeks of diagnosis and within 26 weeks after the presumed day of infection because SVR rates go down seem to decrease after 26 weeks. Therefore, we do not require patients to have a documented HIV plasma viral load below 50 copies/ml after they switch to 1 of the allowed HAART regimens as this would lead to an unacceptable delay in HCV treatment initiation. New cART may have new side-effects, while side-effects from the old HAART will likely resolve. All patients will be informed on the possible side effects of the new cART regimen.

Adequate contraception for women and men

Women are not allowed to get pregnant or breastfeed during, or for 14 days after the study. Men are not allowed to reproduce during, or 14 days after the study.

Prevention of drug-drug interactions

The patient's regular pharmacy will be informed on the participation in this study to prevent unwanted drug-drug interactions (DDI). However, all patients will be instructed to contact the local investigator before any new medication is started, whether over the counter or on-prescription.

5.3 Escape medication (if applicable)

Not applicable

6. INVESTIGATIONAL PRODUCTS

6.1 Grazoprevir and Elbasvir

Elbasvir (MK-8742) is a NS5A inhibitor HCV inhibitor that that is currently under review by the EMA for chronic HCV genotype 1 and 4 infection when given in combination with grazoprevir.

Grazoprevir 100mg and elbasvir 50mg are given for 8 weeks as a fixed drug combination tablet that needs to be taken once daily.

6.2 Summary of findings from non-clinical studies concerning grazoprevir and elbasvir

Findings from non-clinical studies concerning the investigational products can be found in the IB (IB, appendix A p31-73 and appendix B p23-58).

6.3 Summary of findings from clinical studies

Findings from clinical studies concerning the investigational products can be found in the IB (IB, appendix A p79-219 and appendix B p59-149).

Most importantly, in the phase III C-EDGE study (of which the data are not yet included in the latest IB), 273 of the 288 patients or 95% of the patients chronically infected with genotype 1 were cured of their disease (SVR12) and all 18 patients with genotype 4 had a SVR12. Furthermore, the number of AE and SAE in the placebo group was identical than in the patients treated with grazoprevir and elbasvir. 3 of the 316 patients or 1% discontinued therapy for an AE.

6.4 Summary of known and potential risks and benefits

Peginterferon with or without ribavirin is currently the only approved therapy for acute HCV. The experimental therapy of grazoprevir and elbasvir is better tolerated and associated with significantly less adverse events than peginterferon with or without ribavirin. As mentioned in 6.3 the number of AE and SAE in patients on grazoprevir and elbasvir was comparable to patients treated with placebo. Adverse events that were associated with grazoprevir and elbasvir are described in the IB (appendix A en B) and on page 11 of the informed consent form (appendix D).

The expectation is that the large majority of the patients in this study will be cured without the use of peginterferon. This is clearly a benefit for those patients reaching a SVR. If no SVR is reached, retreatment with peginterferon-based therapy can still be given.

6.5 Description and justification of route of administration and dosage

The dose of 100mg grazoprevir and 50mg elbasvir as a fixed dose combination tablet is the dose that was studied in the phase II and III studies and is the dose that is under review by the EMA. The same dose will be given in this study.

6.6 Dosages, dosage modifications and method of administration

Day 1-56: All patients will receive grazoprevir/elbasvir fixed dose combination oral tablet consisting of 100/50mg per tablet.

An ~1.6-fold increase in MK-5172 PK exposures was seen in patients with grade 3-5 renal insufficiency. For MK-8742 a ~2-fold increase in PK exposure was observed in these patients (see IB appendix A p136). Therefore, no dose modifications are required for patients with chronic stage 3-5 renal insufficiency because modeling of the phase II data predicted that for MK-5272 there is a 5% risk of experiencing a late ALT/AST elevation >5X ULN only when the patients population mean of GM C2hr or GM Ctrough levels are above 2020 nM or 115 nM, respectively. These levels were not observed in patients with grade 3-5 renal insufficiency. For MK-8742 no exposure-toxicy relation was observed in the phase I-II studies and therefore no dose modications are required in grade 3-5 renal insufficiency.

6.7 Preparation and labelling of Investigational Medicinal Product

The investigational product will be labeled according to the relevant good manufacturing practice (GMP) guidelines. The investigational product will be delivered by MSD to the clinical trial pharmacy unit at Erasmus MC. Upon approval of a study patient by the coordinating investigator, study drugs will be ordered by the local investigator and sent to the local pharmacy of the participating site. Charge numbers will be registered in the patient's files when bottles are given to the patient as well as when (empty) bottles are returned. Pill counts will be done when bottles are returned.

6.8 Drug accountability

The pharmacy and investigators will carry out the drug accountability. Batch numbers of medication dispensed to and returned by the patients will be recorded in the patient files and CRF. Pill counts of returned medication will be done. The central pharmacy at Erasmus MC will be responsible for the destruction of medication that is returned pursuant to the ICH/GCP Guidelines, local regulations and the investigator's institutional policies. Clinical supplies will be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator, a pharmacist or its designated assistant have access. Clinical supplies are dispensed in accordance with the protocol. The investigator is responsible for keeping accurate records of the clinical supplies, the amount dispensed to and returned by the patients, and the disposition at the end of the study.

7. METHODS

Primary hypothesis

For the treatment of *acute* HCV, 8 weeks of therapy with grazoprevir (MK-5172) and elbasvir (MK-8742) leads to a comparable percentage of cures than the 12 weeks that is needed to cure *chronic* HCV.

7.1 Study parameters/endpoints

7.1.1 Main study endpoint

SVR 12 weeks after the end of all therapy in the entire ITT population (=genotype 1 and 4)

7.1.2 Secondary study endpoints

1. SVR12 in all genotype 1 infected patients (ITT and mITT)
2. SVR12 in genotype 1a infected patients with no NS5a polymorphisms at positions 28/30/31 or 93 versus SVR12 in patients with 1 or more of these polymorphisms [($)]
3. SVR12 in genotype 4 infected patients (ITT and mITT)
4. SVR12 in all patients included mITT
5. SVR12 in RVR2 and RVR4 subpopulation mITT
6. SVR12 in all patients (=genotype 1+4) according to IL28 genotype [(*)]
7. SVR24 (mITT and ITT)[(%)]
8. Cost-effectivity of treatment during the acute phase of HCV in comparison with treatment 12 months later for chronic HCV or treatment only at a certain level of liver fibrosis.

9. Alterations of biomarkers by therapy induced viral eradication: Viral sequencing, mutation analysis, gene expression analysis, RNA analysis in body fluids and for Erasmus MC patients only: functional assays at the cell level.

(*) The reason to include this analysis as a secondary endpoint is that despite the fact that no interferon is used, IL28 genotype may impact the SVR rates because it determines the spontaneous cure rates of acute HCV. Therefore, a favorable IL28 genotype may work synergistically with DAA and increase SVR rates.

(%) The SVR12 endpoint was only thoroughly validated for the treatment of *chronic* HCV. Therefore, we prefer to include SVR24 as a secondary endpoint, to confirm that SVR12 is also a reliable predictor of SVR24 in acute HCV therapy

($) Very recently, an analysis of all patients included in the phase II and III program of grazoprevir and elbasvir showed that in patients with a chronic HCV genotype 1a infection (not in genotype 1b or 4), certain polymorphisms is the NS5a gene are associated with a lower response rate (ref.7). More specifically, polymorphisms at positions 28 30 31 and 93 were associated with a lower response rate of 71% in comparison with 98% in those patients without any polymorphisms. The clinical relevance of these polymorphisms for patients with acute HCV genotype 1a remains to be shown. To look into this, we have included the SVR12 rate in patients with a HCV genotype 1a virus without any of these NS5a polymorphisms versus those with 1 or more polymorphisms present as a secondary endpoint.

Definitions of the patient populations:

ITT population

All patients that initiated study drugs

mITT population

Same as ITT population but excluding patients that are lost to follow-up or discontinued treatment for other reasons than virological failure

Presumed day of HCV infection

Therapy will be initiated no later than 26 weeks after the presumed day of HCV infection. The presumed day of HCV infection is calculated as the day in between the most recent day without laboratory signs of HCV infection and the first day in which laboratory signs of HCV infection were documented.

Acute HCV infection

The definition of acute HCV infection is adapted from the Dutch HCV guideline[8]:

a. Positive anti-HCV IgG or positive HCV-RNA in the presence of documented negative antibody or RNA test in the previous 12 months

or

Patients without a documented negative HCV antibody or RNA test within the last 12 months that fulfill all of the following 4 criteria:

1. A positive HCV-RNA in association with an acute rise in ALAT >5xULN and a documented normal ALAT within the last 12 months.
2. No change in antiretroviral therapy and no introduction of any other medication that may explain the ALAT elevation within the last 12 months.

3. Documented negative HCV IgG antibody test at any time in the past

4. No other likely explanation for the ALAT elevation. In particular, acute HEV, EBV and CMV should be excluded.

The above-mentioned definitions are straightforward because in all HIV treatment centers in the Netherlands, HCV antibody testing is mandatory at the time of HIV diagnosis or Prep implementation. Therefore, a historical HCV test is available in >95% of the HIV patients in care in the Netherlands. Furthermore, all HIV centers store plasma of every patient visit for at least 12 months to allow for retrospective HCV-RNA or antibody testing at the time of a suspected acute HCV infection.

SVR12

SVR is defined as HCV RNA below the limit of detection 12 weeks or more after the end of therapy. HCV RNA will be determined with the local standard of care HCV RNA test (TaqMan 2.0 assay (Roche Diagnostics) or Abbott Realtime M2000)

NS5a polymorphisms:

NS5a polymorphisms are those NS5a polymorphisms that have been shown to decrease the in vitro susceptibility of HCV genotype 1a to NS5a in inhibitors and are situated at position 28 30 31 and 93. The presence of these polymorphisms will be determined with population sequencing where the limit of minority variant detection in the population is approximately 25% of the viral population but also with next generation sequencing, where the sensitivity for variant detection of 1% will be used.

7.2 Randomisation, blinding and treatment allocation

There is no randomisation, blinding or variation of treatment allocation in this single arm open label intervention study.

7.3 Study procedures

Please refer to appendix C for standard and additional procedures that subjects will undergo in the course of the research.

7.4 Withdrawal of individual subjects

Subjects can leave the study at any time for any reason if they wish to do so without any consequences. The investigator can decide to withdraw a subject from the study for urgent medical reasons.

7.5 Replacement of individual subjects after withdrawal

Based on the experience of the first DAHH-Study, which was conducted in the same patient population, we do not anticipate withdrawals of subjects. Subjects will not be replaced after withdrawal.

7.6 Follow-up of subjects withdrawn from treatment

Patients withdrawn from treatment will be followed-up according to the current international good clinical practice guidelines.

7.7 Premature termination of the study

Interim analysis

A single interim efficacy analysis will be performed after 30 patients have reached SVR12. If at this time the upper 95% C.I. of the SVR12 in these 30 patients is <85%, the study will be discontinued as a SVR < 85% is considered unacceptable. This means that at least 21 of the 30 patients should have HCV RNA levels below the limit of detection 12 weeks after the end of therapy (as the upper 95% C.I. limit of 21/30 is 83%).

8. SAFETY REPORTING

8.1 Section 10 WMO event

In accordance to section 10, subsection 1, of the WMO, the investigator will inform the subjects and the reviewing accredited METC if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited METC, except insofar as suspension would jeopardise the subjects' health. The investigator will take care that all subjects are kept informed.

8.2 AEs, SAEs and SUSARs

8.2.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study, whether or not considered related to study drugs. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded.

8.2.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that at any dose:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients' hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

Handling of adverse events

Individual investigators in the participating centers are responsible for the handling of SAEs that occur in the patients that receive the experimental therapy in their center. In addition, individual investigators in the participating centers are responsible for the written documentation of SAEs and communication of SAEs to the coordinating investigator ultimately within 2 working days after the SAE has been presented to the investigator. The coordinating investigator is responsible for the handling of SAEs that occur in the patients that are receiving the experimental therapy in his center, and is responsible for the central documentation of all SAEs.

The sponsor will report the SAEs through the web portal *ToetsingOnline* to the accredited METC that approved the protocol, within 15 days after the sponsor has first knowledge of the serious adverse reactions.

SAEs that result in death or are life threatening should be reported expedited. The expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse reaction. This is for a preliminary report with another 8 days for completion of the report.

8.2.3 Suspected unexpected serious adverse reactions (SUSARs)

Adverse reactions are all untoward and unintended responses to an investigational product related to any dose administered.

Unexpected adverse reactions are SUSARs if the following three conditions are met:

1. the event must be serious (see chapter 9.2.2);
2. there must be a certain degree of probability that the event is a harmful and an undesirable reaction to the medicinal product under investigation, regardless of the administered dose;
3. the adverse reaction must be unexpected, that is to say, the nature and severity of the adverse reaction are not in agreement with the product information as recorded in IB of the study drugs

The sponsor will report expedited the following SUSARs through the web portal *ToetsingOnline* to the METC:

- SUSARs that have arisen in the clinical trial that was assessed by the METC;
- SUSARs that have arisen in other clinical trials of the same sponsor and with the same medicinal product, and that could have consequences for the safety of the subjects involved in the clinical trial that was assessed by the METC.

The remaining SUSARs are recorded in an overview list (line-listing) that will be submitted once every half year to the METC. This line-listing provides an overview of all SUSARs from the study medicine, accompanied by a brief report highlighting the main points of concern.

The expedited reporting of SUSARs through the web portal ToetsingOnline is sufficient as notification to the competent authority.

The sponsor will report expedited all SUSARs to the competent authorities in other Member States, according to the requirements of the Member States.

The expedited reporting will occur not later than 15 days after the sponsor has first knowledge of the adverse reactions. For fatal or life threatening cases the term will be maximal 7 days for a preliminary report with another 8 days for completion of the report.

Handling of SUSARs

Individual investigators in the participating centers are responsible for the handling of SUSARs that occur in the patients that receive the experimental therapy in their centre. In addition, individual investigators in the participating centers are responsible for the written documentation of SUSARs and communication of SUSARs to the coordinating investigator ultimately within 2 working days after the SUSAR has been presented to the investigator. The coordinating investigator is responsible for the handling of SUSARs that occur in the patients that are receive the experimental therapy in his centre, and is responsible for the central documentation of all SUSARs.

8.3 Annual safety report

The annual safety report will be combined with the annual progress report (see chapter 12.4).

In addition to the expedited reporting of SUSARs, the sponsor will submit, once a year throughout the clinical trial, a safety report to the accredited METC, competent authority, and competent authorities of the concerned Member States.
This safety report consists of:

- a list of all suspected (unexpected or expected) serious adverse reactions, along with an aggregated summary table of all reported serious adverse reactions, ordered by organ system, per study;
- a report concerning the safety of the subjects, consisting of a complete safety analysis and an evaluation of the balance between the efficacy and the harmfulness of the medicine under investigation.

8.4 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.
SAEs need to be reported till end of study within the Netherlands, as defined in the protocol

8.5 Data Safety Monitoring

A data safety monitoring board (DSMB) is not necessary, as the investigational product has been very well tolerated in the phase II and III studies.

9. STATISTICAL ANALYSIS

9.1 Statistical methods

A single arm prospective clinical trial was chosen as the design for the following reasons:

1. The current standard of care is associated with significant side effects. Therefore a substantial part of the patients with acute HCV prefer not to be treated with the current standard of care. This proportion of patients has increased substantially over the last 2 years because the HIV positive patient population and their HIV negative partners with acute HCV are very well informed about peginterferon-free treatment options for chronic HCV that will be available in the future. They therefore increasingly prefer to wait until they can be treated for their HCV infection somewhere in the future. We have observed this change in the DAHH-study that preceded this study. Therefore, more and more patients with acute HCV will therefore not agree to participate in a randomized trial in which 1 of the study arms will be peginterferon therapy. Furthermore, because new treatment options will become available in the future, patients that will experience side effects of peginterferon (which the majority do) can be expected to discontinue treatment prematurely much more often than in an era when no other treatment options were expected soon.

2. The number of patients diagnosed with acute HCV in the entire HIV+ patient cohort in the Netherlands was recently measured by Hullegie et al. Approximately 1.1% of the HIV+ patients acquire a new HCV infection annually which equals 100 to 150 acute HCV infections annually in the Netherlands. Of course only a subset of them will fulfill in and exclusion criteria and agree to participate in the study. Therefore, we consider a well-powered superiority randomized clinical trial in which the current standard of care is given to half of the patients not feasible because such a study would take many years, as 2 groups of 75-100 patients would be needed.

9.2 Primary endpoint analysis

The primary endpoint is the proportion of patients that have a SVR12 and can therefore be considered as being cured of their HCV infection. As defined above, a patient with an

SVR12 is a patient with plasma HCV RNA below the limit of detection measured at least 12 weeks after the end of therapy. The proportion of patients with an SVR12 will be calculated with a 2-sided C.I. using the Wilson score method without continuity correction.

9.3 Secondary endpoints analyses

For secondary endpoints 1 to 6 the proportion of patients will be calculated with a 2-sided C.I. using the Wilson score method without continuity correction.

For secondary endpoint 2, the SVR12 rate will be compared between the patients with and those without NS5a polymorphisms. The 1-tailed Fisher-Exact test for proportions will be used for this purpose. A one-tailed approach is considered appropriate because NS5a polymorphisms that lead to an in vitro decrease in elbasvir susceptibility can only lead to a decrease in SVR12.

For secondary endpoint 7 a HCV transmission model will be build that includes (among other variables) the costs of ongoing HCV transmission among HIV+MSM, the costs of untreated chronic HCV infection (liver cirrhosis, liver cancer) and the costs of HCV therapy. Incremental cost-effectivity ratios will be calculated (costs per QALY) for different treatment policies (treat all acute HCV infections with peginterferon, treat all acute HCV infections with grazoprevir/elbasvir, do not treat acute HCV infections but treat these infections with peginterferon-free regimens when they have become chronic and evolved into grade 3 liver fibrosis on liver ultrasound (which is the current reimbursement criterium in the Netherlands).

9.4 Multiplicity

Not applicable (as no direct comparison against a control group will be performed and only 1 primary endpoint will be analyzed. No multiplicity correction will be performed for the secondary endpoints.

9.5 Missing data

Patients that are lost to follow-up after the start of study drugs will be considered treatment failures in the ITT analysis but will be excluded from the mITT analysis (see definitions above).

9.6 Sample size calculation

We hope to show that a treatment of 8 weeks given to patients with an acute HCV leads to a comparable cure rate than the cure rate observed with a 12-week therapy when given to

patients with *chronic* HCV (overall response in genotype 1a and 4 together was 162/175 or 93% in the C-edge phase III study). Although the current study is a non-randomized single arm study and therefore not a formal non-inferiority randomized clinical trial, we tried to estimate an appropriate sample size by calculating the sample size under the assumption that the cure rate with 8 weeks of therapy for acute HCV will also be 93%.

Our hypothesis therefore is that we can shorten therapy duration to 8 weeks without a substantial loss of effectivity. If we assume an identical 93% effectivity when 8 weeks therapy is given during acute HCV infection, then a sample size of 80 patients gives the study a 89% power (one-sided with alfa error of 5%) to exclude that this 8-week treatment is more than 10% worse than a 93% SVR and therefore cures <83% of the patients with acute HCV (nquery advisor 7, using one group Chi-square test that proportions equals user specifed value (normal approximation).

9.7 Responsibility for data analysis

The coordinating investigator will be responsible for analyzing the study data.

9.8 Monitoring

At least 20% of patient data will be monitored on site.

9.9 Interim efficacy analysis

A single interim efficacy analysis will be performed after 30 patients have reached SVR12. If at this time the upper 95% C.I. of the SVR12 in these 30 patients is <85%, the study will be discontinued as a SVR < 85% is considered unacceptable. This means that at least 21 of the 30 patients should have HCV RNA levels below the limit of detection 12 weeks after the end of therapy (as the upper 95% C.I. limit of 21/30 is 83%).

ETHICAL CONSIDERATIONS

9.10 Regulation statement

The study will be performed in accordance with the protocol, the guidelines of Good Clinical Practice/ICH, which underwrites the principles of the Declaration of Helsinki, as most recently revised by the 59th WMA General Assembly in Edinburgh, Scotland, October 2008.

9.11 Ethical committee approval

The study protocol will be formally submitted to the ethical committee of the Erasmus MC. The study will start after approval from the ethical committee has been obtained. The nature of the study and an outline of those investigative procedures, which might be in excess of their usual care, will be explained to the patients. They will be required to give their written informed consent before entering the study (informed consent form, appendix C).

9.12 Recruitment and consent

Patients will be recruited at the study sites mentinoned on page 2-3. It is the responsibility of the investigators or the co-investigators to obtain written informed consent from each subject participating in this study, after adequate explanation of the aims, methods, anticipated, and potential hazards of the study (patient information form, appendix D).

Besides the specific information regarding the study, the following standard items are covered in the patient information form (Dutch: patiënten informatie formulier, appendix D):

- Patient's right to withdraw from the clinical study anytime without giving reasons and without any consequences for further medical treatment.
- The information that all study findings will be stored in a computer database and handled confidentially
- Patient names will be kept separate from research data and patients will be identifiable by subject number only.
- Information about the possibility of inspection of relevant parts of the hospital records by regulatory authorities. Inspection will only take place if a confidentiality agreement has been signed.
- The existence of patient insurance policy in case the patient will be harmed by participating in the study (using the study drug)
- All novel clinically relevant information that will become available during the study and is possibly important for the patient will be communicated to him/her by one of the investigators.

The signature of an investigator or co-investigator on the form will attest that the information in the consent form was accurately explained and understood. Thereafter the patient will sign after a period of reflection. If new safety information results in

significant changes in the risk/benefit assessment, the consent form will be reviewed and updated after approval by the ethical committee. Then, all subjects (including those already being treated) will be informed of the new information, will be given a copy of the revised form and will be asked to give their consent to continue the study.

9.13 Benefits and risks assessment

The side effects of grazoprevir and elbasvir observed in the phase II and III clinical trials when given in patients with chronic HCV are summarized on page 11 of appendix D. In general, therapy with these drugs was very well tolerated as the number as type of observed adverse events in the placebo and grazoprevir/elbasvir group were identical. Also only 1% of the patients discontinued therapy for an AE. As acute HCV is mainly asymptomatic, the side effect profile of for the treatment of *acute* HCV can be expected to be the same. The currently available treatment for acute hepatitis C consists of peginterferon with ribavirin without or without a direct acting antiviral and are associated with significantly more side effects than a interferon sparing treatment like grazoprevir and elbasvir.

The burden associated with participation in the study consists of 1 additional visit on top of the 7 visits that are needed when the current standard of care treatment is given. During these 8 visits additional blood samples are taken for a total of approximately 90 millilitres of blood for all study patients and approximately 200 millilitres blood for Erasmus MC patients. The study will be beneficial for those patients that reach a SVR as they will be cured of HCV without the need for interferon-based therapy. For those patients that do not achieve a SVR, another therapy for HCV may have to be administered at a later point in time. With the current SOC this is the case for approximately 25%. It is possible that, against expectations, fewer patients will reach a SVR with the 8-week regimen that will be studied here.

9.14 Compensation for injury

Liability insurance sponsor/investigator

The sponsor/investigator has a liability insurance which is in accordance with article 7, subsection 6 of the WMO.

Insurance for study participants

The Erasmus MC WMO insurance applies for all patients included in this study. The certificate can be found in appendix E.

9.15 Incentives

No incentive will be given.

10. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

10.1 Handling and storage of data and documents

Data will be handled confidential and if possible anonymously. Where it is necessary to be able to trace data to an individual subject, a subject identification code list will be used to link the data to the subject. The code will not be based on the patient initials and birth-date. The key to the code will be safeguarded by the investigator. as the data and human material will be kept for a longer period of time. The handling of personal data will comply with the Dutch Personal Data Protection Act (in Dutch: De Wet Bescherming Persoonsgegevens, Wbp).

Case record form (CRF)

All data of patients, including results from standard procedures during treatment, collected during the study will be recorded in Case Record Forms. The CRF must be completed fully and legibly. Corrections of possibly erroneous entries must be carried out in such a manner that the initial entry is not rendered illegible. Corrections should be written alongside or above the pertinent place with the date and initials. Correction fluid must not be used.

The investigators are responsible for the quality of the data recorded in the Case Record Forms (CRF). Where the investigators have not been responsible for completing the CRF, an additional signature from the co-investigator overseeing the data entry of the study must be obtained.

In the event that the investigators need to deviate from the protocol, the nature of and reasons for protocol deviation must be recorded in the hospital patient record and in the CRF. In nearly all cases it is desirable that the patient continues the study to allow the most informative intention-to-treat analysis; however, the patient may be excluded from the per-protocol analysis.

Privacy rules

Patients will be identified in the CRF by their identification code. The investigators will keep a patient identification log, including sufficient information to link the hospital record and CRFs.

The subjects will be informed that the data will be stored on paper and electronically, that local regulations for the handling of computerized data will be followed as described in the written patient information / consent form and that identification of individual patient data will only be possible for the investigators. Furthermore, the subjects will be informed about the possibility of inspections of relevant parts of the hospital records by health authorities. These officials will be identified and have signed a confidentiality agreement. The data are stored and processed using a database program for personal computers. From this database the data will be transferred to a statistical program for further analysis. Only data, with coded patient identity will be transferred to the statistician for analysis.

Data processing

After a visual plausibility check the CRF data will be entered in the computer and processed using a database program. Data base print outs will be produced and checked by one of the principle investigators or his co-investigators. When approved, the data will be transferred from the database to a statistical data file, with conversion in uniform data and formation of a master database for further analysis. The data transfer to the statistician can take place during the study

Data achieving

Patient identification log, hospital records, informed consent forms, case record forms and databases must be kept for at least 5 years after completing the study (EU-directive 2005/28/EG). If the investigators move or retire, they must nominate someone in writing to be responsible for record keeping. Archived data may be held on microfiche or electronic record, provided that a backup exists and a hard copy can be obtained from it if required.

10.2 Monitoring and Quality Assurance

Please refer to our monitoring plan.

10.3 Amendments

Amendments are changes made to the research after a favourable opinion by the accredited METC has been given. All amendments will be notified to the METC that gave a favourable opinion.

A 'substantial amendment' is defined as an amendment to the terms of the METC application, or to the protocol or any other supporting documentation, that is likely to affect to a significant degree:

- the safety or physical or mental integrity of the subjects of the trial;
- the scientific value of the trial;
- the conduct or management of the trial; or
- the quality or safety of any intervention used in the trial.

All substantial amendments will be notified to the METC and to the competent authority.

Non-substantial amendments will not be notified to the accredited METC and the competent authority, but will be recorded and filed by the sponsor. Examples of non-substantial amendments are typing errors and administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation.

10.4 Annual progress report

The sponsor/investigator will submit a summary of the progress of the trial to the accredited METC once a year. Information will be provided on the date of inclusion of the first subject, numbers of subjects included and numbers of subjects that have completed the trial, serious adverse events/ serious adverse reactions, other problems, and amendments.

10.5 End of study report

The sponsor will notify the accredited METC and the competent authority of the end of the study within a period of 90 days. The end of the study is defined as the last patient's last visit.

In case the study is ended prematurely, the sponsor will notify the accredited METC and the competent authority within 15 days, including the reasons for the premature termination.

Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited METC and the Competent Authority.

10.6 Public disclosure and publication policy

The sponsor is free to publically disclose and publish all research data. Please refer to the contract between de sponsor and the subsidising party for arrangements made concerning public disclose and publication of research data.

11. STRUCTURED RISK ANALYSIS

11.1 Potential issues of concern

a. Level of knowledge about mechanism of action

There is adequate pre-clinical and clinical knowledge on the mechanism of action of grazoprevir and elbasvir. Please refer to chapter 6 of this protocol and the IB (appendix A and B) for more information on the investigational products.

b. Previous exposure of human beings with the test product(s) and/or products with a similar biological mechanism

984 patients have been treated with grazoprevir in phase II clinical trials. Several phase III studies are ongoing. Data on phase III studies that included a total of 454 patients have been presented at EASL 2015.

c. Can the primary or secondary mechanism be induced in animals and/or in *ex-vivo* human cell material?

The purpose of this study is showing efficacy in patients with acute HCV. This cannot be reproduced in animal models.

d. Selectivity of the mechanism to target tissue in animals and/or human beings

Grazoprevir and elbasivir do not selectively target certain tissue. However, it is widely distributed throughout the body, including the liver, where hepatocytes (liver cells) are the reservoir for the hepatitis C virus.

e. Analysis of potential effect

The investigational products have been shown to be safe and well tolerated in phase II and III trials In the phase III C-edge study 95% of the patients were cured of their HCV infection after 12 weeks of therapy. No additional side effects are expected when these drugs are used for the treatment of acute HCV.

f. Pharmacokinetic considerations

Pharmacokinetics of grazoprevir and elbasvir are well known. Please refer to the IB of both drugs (appendices A and B) for further information. There are no special pharmacokinetic considerations for this study except for potential drug-drug interactions with comedication as described under 5.2.

g. Study population

80 Adult HIV positive patients (minimum age 18 years) with an acute HCV genotype 1 or 4 infection from HIV treatment centers in the Netherlands and Belgium will be included. These patients are outpatients that are never critically ill as acute HCV infection is rarely accompanied by serious complaints.

h. Interaction with other products

There is special attention for potential unwanted drug-drug interactions. Please refer to chapters 4.3, 5.2 and the informed consent form for more information.

i. Predictability of effect

The effect of the intervention is quite predictable. We have made statements on this topic in the introduction of this protocol (chapter 1), the methods section (chapter 7)

j. Can effects be managed?

The side-effects of grazoprevir and elbasvir can be managed, as potential side effects are limited and well known.

11.2 Synthesis

The only registered treatment for acute HCV in the Netherlands is (peg)interferon with cure rates of 60-80%. This treatment of 24 weeks is associated with side effects that significantly interfere with daily live. Given the very high cure rate observed in the phase III C-edge study of grazoprevir and elbasvir in which 95% of the 316 patients were cured with side effects comparable to placebo treatment, the possible advantages for the patient are obvious: a cure of their acute HCV infection without the side effects of peginterferon and ribavirin. Because we will study a treatment duration of 8 instead of 12 weeks is it possible that the treatment will be less effective than the 95% cure seen in the phase III C-edge study. A possible disadvantage for the patient is therefore that, when the study treatment fails, he or she may have to be treated a second time (which may or may not include peginterferon and ribavirin). Great care will be taken to avoid drug-drug interactions between the study drugs and the cART regimen that all patients take as well.

In conclusion, we think that in this study the benefits outweigh the risk

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Appendix A: See IB pdf document called MK-5172 ib-edition-10

Appendix B: See IB pdf document called MK-8742 ib-edition-8

Appendix C: patient visit schedule

	Remarks	Screening	Baseline	wk2	wk4	wk8	wk12	wk20	wk32
Eligibility check		x							
Informed consent		x							
Medical history		x							
Anticonception counselling	A	x							
Patiënt details	B	x							
Co-medication		x	x	x	x	x	x	x	x
HAART switch if necessary	C	x							
Physical examination	D	x	x		x	x		x	x
Quality of life			x		x	x		x	x
(S)AE	E		x	x	x	x	x	x	x
Study drug dispensing			x						
Drug accountability				x	x	x			
Fibroscan	F	x	x						
Laboratory measurements									
Virology	G	x							
Pregnancy	H	x							
Liver	I	x						x	
HIV RNA if HIV+		x*	x			x		x	
Safety	J	x	x	x	x	x	x	x	x
CD4 if HIV+	K	x						x	
HCV RNA		x**	x		x	x		x	
Biomarkers	L	x	x	x		x		x	
HCV Seq	M						x	x	x
HCV genotyping	N	x							
PBMC + Tempus	O		x	x				x	
IL28B	P	x	x						
Oral fluid sample	Q		x						

A For female AND bi- or heterosexual male patients

B Year of Birth, gender ,etnicity, M-number

C Allowed cART regimens are 2 NRTI's plus either raltegravir (Isentress®) 400mg BID or dolutegravir 50mg QD (Tivicay®) or rilpivirine (Edurant®) 25mg QD.

D Height, complete physical examination at screening only. Blood pressure, pulse, weight and directed physical examination at all other visits.

E Detection and handling of (serious) adverse events

F	Optional (at discretion of the local investigator) at screening or baseline for AHCV infected patients, obliged for chronic HBV carriers
G	See acute HCV definition in the protocol under 7.1.2
H	If patiënt is female
I	Alk.fosfatase, AST, gamma-GT, Albumin, INR
J	Hb, Ht, MCV, WBC, Platelets, Bilirubin, ALT, Creatinin, Estimated GFR (Cockroft-Gault or MDRD).
K	Historical CD4 count <12 months old can be used for screening.
L	Extra: other biomarkers (one 8 mL tube for serum, one 6 mL tube for plasma).
M	For the purpose of HCV RNA sequencing to enable differentiation of reinfection from relapse
N	On site, if not already performed previously
O	Extra: for Erasmus MC only, 40 mL extra blood,
P	4.0 mL edta, has to be taken only once
Q	Erasmus MC only
*	If already performed <8 weeks before screening, this measument doesn't need to be repeated
**	If already performed <4 weeks before screening, this measument doesn't need to be repeated

Appendix D: informed consent form (See E1/E2 of submission approval METC ErasmusMC)

Appendix E: Certificaat van verzekering voor patienten in Nederland

CNA / HARDY

VERZEKERINGSCERTIFICAAT

PROEFPERSONENVERZEKERING – NEDERLAND

Nota : Deze verzekering voldoet aan het bepaalde in de WMO en het daarop gebaseerde verzekeringsbesluit en Besluit verplichte verzekering bij medisch-wetenschappelijk onderzoek met mensen 2015.

Verzekeraar:

CNA Insurance Company Limited (handelsregisternummer 950) Erkend door de Prudential Regulation Authority en gereguleerd door de Financial Conduct Authority en de Prudential Regulation Authority (statutair referentienummer 202777)

Uitgevend kantoor:

CNA Insurance Company Limited, Strawinskylaan 703, 1077 XX Amsterdam

Contactpersoon bij agenda: mw. Esther van Herk, T +31 (0)20 573 72 74, Esther.vanherk@cnahardy.com

Polisvoorwaarden:

CT CNA-2015 HCCD0418C – Netherlands Clinical Trials Liability Policy NLNL

Ondergenaamde verklaart verzekerd te hebben:

Verzekeringnemer:

ERASMUS UNIVERSITAIR MEDISCH CENTRUM

Verzekeringstermijn:

Van: 01/01/2017

Tot: 01/01/2018, verder voor twaalf maanden doorlopend, met stilzwijgende verlenging

Verzekerd onderzoek:

Alle aangemelde wetenschappelijk onderzoeken verricht, gefaciliteerd of uitgevoerd door Erasmus Universitair Medisch Centrum Rotterdam of Stichting voor Lever en Maag-Darm Onderzoek

Dekkingsgebied:

In Nederland uitgevoerde wetenschappelijke onderzoeken of verrichtingen

Verzekerd bedrag:

1. EUR 650.000,- per proefpersoon, maximaal
2. EUR 5.000.000,- per onderzoek, en maximaal
3. EUR 7.500.000,- per jaar voor alle onderzoeken tezamen

Voorts onderworpen aan alle voorwaarden en verplichtingen als beschreven op het Polisblad met polisnummer 10220935

CNA Insurance Company Ltd

Mark Gepfert

Amsterdam, 28 december 2016