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BIOMEDICAL RESEARCH PROTOCOL

SAHIV pilot trial

Short duration therapy of acute hepatitis C genotypes 1 or 4: efficacy and tolerability of grazoprevir 100mg/elbasvir 50mg during 8 weeks

Etude pilote SAHIV

Essai thérapeutique de traitement court de l'infection aiguë par le virus de l'hépatite C de génotype 1 ou 4 : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines

Version n°5.0 – 19/01/2018

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TABLE OF PROTOCOL VERSIONS

Version n°	Date	Amendment n°	Main modifications
2.0	30/05/2016		
3.0	30/01/2017	1	<ol style="list-style-type: none"> 1. Adding name and address of the coordinating pharmacy in charge of labeling and management of study treatments. 2. Addition of a new secondary objective: evaluating the sensitivity of Rapid Tests (TROD) for the detection of anti-Hepatitis C virus antibodies during fist acute infection. HCV serology will be done at Day 0 using a rapid antibody test and standard ELISA. In case of a negative result, these tests will be repeated at Week 4. The TROD selected for this study is Oraquick® (the most commonly used rapid test with CE certification). 3. New anticipated study timelines 4. Change visit names W12, W20 and W56 to identify post-treatment visits (PT4, PT12, PT48) 5. Lengthening of the time window for visits W4, W8, W12 and W20. 6. Modification of treatment dispensation: treatments will be dispensed once at day 0. 7. Adding stopping rules of premature study discontinuation (and deleting last sentence of section 11.2.3 which is already used 8. Adding the method used to calculate creatinine clearance: CKD-EPI 9. Remove of measurement of HCV drugs concentrations (error in page 40). 10. Modification patient anonymous code (3 characters instead of 5). <p>The study timetable and the informed consent have been modified accordingly.</p>
4.0	31/03/2017	New version of the protocol requested by ANSM	<ol style="list-style-type: none"> 1. Adding that serious and non serious adverse events will be collected from the time the patient signed the study-specific informed consent and until 30 days following the end of study treatment. 2. Adding that all concomitant treatments will be collected from the time the patient signed the study-specific informed consent and until 30 days following the end of study treatment. Thereafter, only medications associate with HCV and HIV treatment will be recorded. 3. Adding HCV virologic failure criteria. <p>The study timetable has been modified accordingly. The informed consent form has not been modified.</p>

Version n°	Date	Amendment n°	Main modifications
5.0	19/01/2018	2	<p>1- In order to accelerate patient recruitment, it was decided to modify the protocol as follows:</p> <ul style="list-style-type: none"> - Including mono-infected patients with acute HCV infection (genotypes 1 or 4), - Allowing to include patients having reported a risk factor for HCV contamination (traumatic sexual intercourse, intranasal, rectal or intravenous drug use) inferior or equal to 6 months, - Reducing the sample size to 30 patients, - Extending inclusion period by three months, <p>2- Dr Jessica Krause, infectious disease physician at Saint-Antoine hospital will replace Dr Julie Bottero and will perform the following tasks:</p> <ul style="list-style-type: none"> - Principal investigator of Saint Antoine hospital study center - Scientific committee member - Study pharmacovigilance management <p>3- Dr Karine Lacombe, the study coordinating investigator, has been named as Professor.</p> <p>4- These modifications resulted in a revised study title, informed consent form and study timetable.</p>

LIST OF ABBREVIATIONS AND DEFINITION TERMS

AE	Adverse Event
AIDS	Acquired Immune Deficiency Syndrom
ALP	Alkaline Phosphatase
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ALT	Alanine aminotransferase (SGPT)
ART	Anti Retroviral Treatment
AST	Aspartate aminotransferase (SGOT)
CI	Confidence Interval
CPP	Comité de Protection des Personnes
CRA	Clinical Research Associate
DSMB	Data and Safety Monitoring Board
EC	Ethic Committee
eCRF	Electronic Case Report Form
FBC	Full blood count
GCP	Good Clinical Practice
GGT	Gammaglutamyl-transpeptidases
HCV	Hepatitis C Virus
HIV	Human Deficiency Virus
ITT	Intent-to-treat
IU	International Unit
LLOQ	Lower limit of quantification
PP	Per Protocole
RNA	RiboNucleic Acid
SAB	Scientific Advisory Board
SAE	Serious Adverse Event
SmPC	Summary of the Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Event
SVR	Sustained Virologic Response
TSH	ThyreoStimuline Hormon

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SAHIV pilot trial

Short duration therapy of acute hepatitis C genotypes 1 or 4: efficacy and tolerability of grazoprevir 100mg/elbasvir 50mg during 8 weeks

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Essai thérapeutique de traitement court de l'infection aiguë par le virus de l'hépatite C de génotype 1 ou 4 : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines

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Version n°5.0 – 19/01/2018

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1 SYNOPSIS

N°EudraCT / ClinicalTrials ID : 2016-001125-13

Title of the study

Pilot study - Short duration therapy of acute hepatitis C genotypes 1 or 4: efficacy and tolerability of grazoprevir 100mg/elbasvir 50mg during 8 weeks

Short title SAHIV

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Participating country **France (See list of investigator sites in Appendix B3)**

Objectives/ Endpoints

Objectives	Endpoints
Primary	
To assess the rate of sustained virological response (SVR) 12 weeks after 8 weeks of oral treatment with grazoprevir 100mg/elbasvir 50mg (MRK-combo) in patients with acute hepatitis C genotype 1 or 4.	SVR rate defined by an undetectable plasma HCV RNA (<12 IU/mL) 12 weeks post-treatment (SVR12).
Secondary	
HCV virological assessment	
To describe the HCV virological response (W4, W8, PT4 and PT12) as a whole and according to genotypes.	- Median (+IQR) of log HCV RNA at W4, W8, PT4 and PT12, globally and according to genotypes. - Rate of HCV RNA (<12 IU/mL) at W4, W8, PT4 and PT12, globally and according to genotypes.
To study the prognostic factors associated with SVR12 (PT12).	Odds ratio of risk factors associated with SVR12 (PT12).
To assess the emergence of resistance in case of virological failure (HCV RNA ≥12 IU/mL).	Number and description of HCV (NS5A and NS3/4) resistance mutations in patients with virological failure.
To describe treatment adherence and quality of life during the course of the study	Rate of adherence and quality of life measured by specific scales using self questionnaires.
To evaluate the incidence of HCV reinfection at 1 year (PT48).	Number of patients with positive HCV RNA per hundred months follow-up.
To evaluate the sensitivity of HCV rapid testing (using the Oraquick HCV rapid antibody test) in patients with first acute Hepatitis C.	To evaluate the proportion of positive rapid tests

HIV virological assessment (only for HIV co-infected patients)	
To describe the evolution of HIV parameter during treatment (CD4 count and HIV-RNA)	- Median (+IQR) of log HIV RNA at D0 and PT12 - Median (+IQR) of CD4 and CD8 cell counts (absolute count, percentage and CD4/CD8 ratio) at D0 and PT12. - Number of AIDS-defining clinical or biological events using CDC classification (95% CI).
Safety assessment	
To describe all the clinical and biological events occurring during the study course	Number of adverse clinical and biological events that occur during the treatment and up to 48 weeks after the end of the treatment (95% CI).

Methodology

Non-randomized, single arm, multicenter, open-label, Phase IIb pilot study conducted in France

Estimated enrolment 30 patients

Study population

Inclusion criteria

1. Adult ≥ 18 years.
2. A recent acute HCV infection or reinfection (see definition below) occurred within 6 months prior screening:

An acute HCV infection is defined by:

- a. HCV RNA was detectable within 6 months after a negative HCV RNA or HCV serology test.

OR

- b. Detectable HCV RNA and an acute clinical hepatitis occurred within 5 months prior to the screening visit.

Clinical Hepatitis is defined by:

- ALT ≥ 250 IU/L with normal ALT within the preceding 8 months,

or

- ALT ≥ 500 IU/L with either no measured ALT or with abnormal ALT within the preceding 8 months.

OR

- Patients having reported a risk factor for HCV contamination (traumatic sexual intercourse, intranasal, rectal or intravenous drug use) inferior or equal to 6 months.

HCV reinfection is defined by:

- a. Documented *de novo* infection after prior clearance after treatment or spontaneously,
 - After-treatment clearance is defined by one negative HCV RNA ≥ 6 months after end of treatment.
 - Spontaneous clearance is defined by two negative HCV RNA a minimum of 6 months apart.

OR

- b. Documented infection with a new viral strain, confirmed by phylogenetic or genotypic analysis.

3. Infection with HCV genotype 1 or 4 (confirmed at screening visit or by using a previous biological test performed 1 to 4 weeks before D0).
4. Plasma HCV-RNA ≥ 1000 IU/mL (confirmed at screening visit or by using a previous biological test performed 1 to 4 weeks before D0).
5. Confirmed HIV infection (only for HIV co-infected patients).
6. Without HIV treatment or with an authorized stable HIV treatment for at least two weeks (See section 8.3 of the protocol, only for HIV co-infected patients).
7. Body weight ≥ 40 kg and ≤ 125 kg.

8. Female patients with child-bearing potential and their heterosexual partners must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug. Male participants must agree to consistently and correctly use a condom, while their female partner must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug.
9. Informed and signed consent.
10. Patients with Health insurance (*Sécurité Sociale* or *Couverture Médicale Universelle*).

Non-inclusion criteria

Current condition

1. Opportunistic infections (stage C), active or occurred within 6 months prior to baseline.
2. Primary HIV infection.
3. Co-infection with Hepatitis B virus (AgHBs +) without appropriate treatment (TDF or TAF) for at least 2 weeks.
4. Confirmed cirrhosis (before acute HCV diagnosis).
5. Any other causes of acute hepatitis.
6. Pregnant or breast-feeding women.
7. Liver transplant recipients.
8. Evolutive malignancy.
9. Patients with a history of non-adherence, who will be at risk of being unable to respect the study follow-up timetable.
10. Patients participating in another clinical trial (with an experimental treatment) or within an exclusion period of a previous clinical trial at screening.
11. Patients under legal guardianship or incarcerated.

Biological criteria

12. Hb < 10 g/dL (female) or < 11g/dL (male).
13. Platelets < 50 000/mm³.
14. Neutrophil count < 750/mm³.

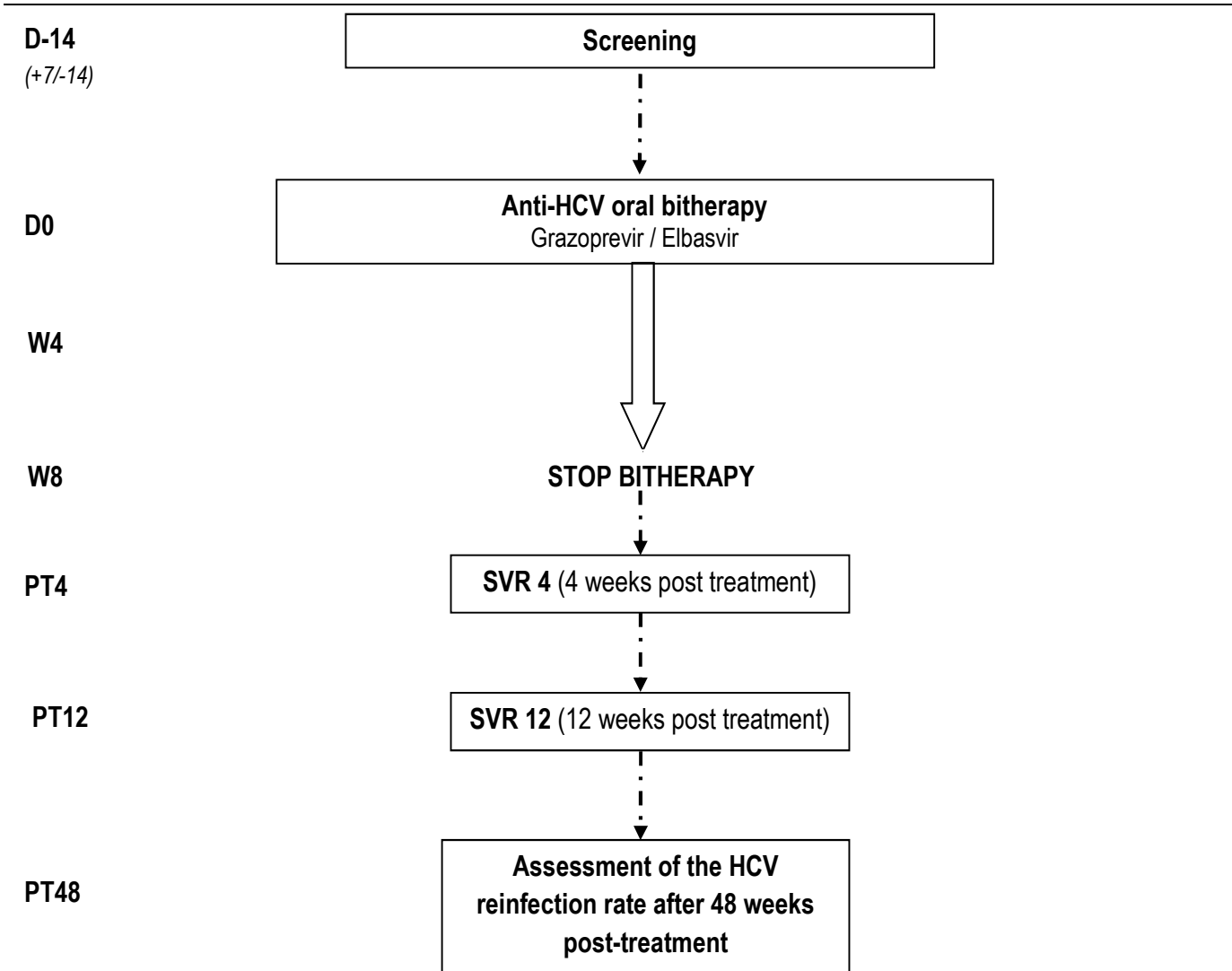
Criteria related to study drugs

15. Other antiretroviral drugs than those allowed in the study (list provided in section 8.3 of the protocol).
16. Contra-indications to Grazoprevir and/or Elbasvir or to any of the excipients listed in the summary of the product characteristics.
17. Contra-indicated treatment likely to interfere with the study drugs as listed in the summary of the product characteristics.

Study design

Non-randomized, single arm, multicentre open-labeled phase IIb study.

Patients will receive 8 weeks of bitherapy – **Grazoprevir / Elbasvir fixed dose combination 100mg/ 50mg** (MRK-combo), 1 tablet once a day (in the morning)



Statistical methods

• Statistical hypotheses

The main end-point in statistical analysis is defined as SVR12 and its precision, calculated as the 95% Clopper-Pearson confidence interval (CI). In order to maintain an absolute difference between lower and upper bounds of the 95%CI <30% with an SVR12 \geq 80%, 30 patients need to be included.

• Population analyzed

All patients included in the study, apart from patients who present at least one of the following conditions:

- patients who have never taken treatment,
 - patients who have withdrawn their consent,
 - patients included erroneously with contra-indications to the treatment of the study or without indication to be treated,
- constitute the modified intent-to-treat (ITT) population and will be analyzed.

• Evaluation of the primary endpoint

The main endpoint of the trial is the Sustained Virological Response defined by undetectable plasma HCV RNA (< 12 IU/mL) 12 weeks after cessation of treatment with Grazoprevir / Elbasvir.

- Patients who will be lost to follow-up at PT12 visit and patients who will meet the criteria for interruption of treatment for virological failure will be considered as failures in the analysis of the main endpoint.
- Patients who undergo the treatment up to W8 and with undetectable HCV-RNA at PT12 will be considered as successful
- Patients who stop treatment prematurely for intolerance and with undetectable HCV-RNA at PT12 will be considered as successful.

- Patients who cannot undergo the PT12 visit and with undetectable HCV-RNA at W48 will be considered as successful.

Study timetable

- Trial start date: **May-June 2017**
 - Enrolment period: **12 months**
 - Subject participation duration: screening (1 to 4 weeks before D0), then 56 weeks of follow-up → **approximately 60 weeks maximum**
 - Total trial duration: **24 months**
 - Estimated study completion date: Mid **2019**
-

Schedule of assessments

- Evaluation of inclusion criteria: 1 to 4 weeks
- Anti-HCV treatment: 8 weeks
- Follow up: 48 weeks following the end of the treatment

2 FOLLOW-UP TIMETABLE

	Screening ^a D-14	D0	W4	W8	PT4 SVR4	PT12 SVR12	PT48 SVR48
Time windows (days)	+7 or -14 (from D-28 to D-7 before D0)	/	+/-7	+/-7	+/-7	+/-7	+/-7
Patient instructions	/	No medication intake before coming		/	/	/	/
Eligibility criteria / Informed Consent	X						
Clinical examination (including sitting blood pressure, weight, drugs*, tobacco* and alcohol consumption*) <i>*Only at screening</i>	X	X	X	X	X	X	X
Concomitant treatments (After 30 days post-study treatment, only medications associate with HCV and HIV treatment)	X	X	X	X	X		
Serious or not serious adverse events (until 30 days after the end of study treatment)	X	X	X	X	X		
HCV Genotype	X						
HCV RNA	X	X	X	X	X	X	X ^b
HCV antibodies (ELISA and Rapid test) ^d		X ^d	X ^{d,e}				
HIV antibodies (only for HCV mono-infected patients)	X						
HBs Ag ^c	X						
AST, ALT, total and conjugated bilirubin, GGT, ALP	X	X	X	X	X	X	X
CD4, CD8 (only for HIV co-infected patients)		X				X	
HIV RNA (only for HIV co-infected patients)		X				X	
FBC, platelets	X	X	X	X	X	X	
Blood creatinine and creatine clearance (CKD-EPI)		X	X	X	X	X	
Beta-HCG (Screen) or urinary pregnancy test (if applicable)	X	X	X	X	X	X	
QUESTIONNAIRES							
Adherence self-questionnaire			X	X			
“Quality of life” Questionnaire		X				X	
SAMPLES FOR BIOBANK							
Blood for serum collection (7/8 mL in dry tubes)		X	X	X	X	X	X
Blood for plasma collection (7/8 mL in EDTA tubes)		X	X	X	X	X	X
PHARMACY							
Treatment Dispensation/Return (Grazoprevir / Elbasvir)		X		X			

^a Screening visit will be only performed if the biological results needed to check the eligibility criteria are not available in the patient medical file and dated between 1 to 4 weeks before D0 (≤ 3 months for Ag HBs). In this case, the clinical examination and the signature of informed consent could be done at D0.

^b In case of positivity, a phylogenetic analysis will be performed in order to differentiate a late relapse from reinfection.

^c Only done, if there is no result ≤ 3 months before D0 in the medical file.

^d Only for patients with first acute infection

^e Only done if HCV antibodies results are negative at Day 0.

3 STUDY RATIONALE AND JUSTIFICATION

WILL BE MODIFIED LATER

3.1 Study rationale

Increasing rates of acquisition of HCV in men who have sex with men (MSM), in particular in HIV-infected patients, have been reported since 2001 in Western European countries and particularly in France (1). Observational studies have recently reported that HIV-infected gay and bisexual men with sexually transmitted hepatitis C have shown unexpectedly rapid liver disease progression in a relatively short period of time (2,3).

It is therefore admitted that, in the absence of a spontaneous HCV clearance within 3 months of acute HCV infection, treatment should be initiated (4). Pegylated interferon in combination with weight-adapted ribavirin is still recommended as the treatment of choice for all HCV genotypes in an acute setting (5). For patients developing a rapid virologic response, treatment duration of 24 weeks is recommended (4). If antiviral therapy was initiated within 24 weeks after diagnosis, sustained virologic response rates of 60 to 80% have been observed at the price of a high side effects burden.

However, short course therapies with new direct acting antivirals are likely to be safer and more efficient. But their efficacy in acute hepatitis C has still to be established. To date, US- and Europe- based trials are ongoing in this setting with the association of sofosbuvir and ribavirin, sofosbuvir / ledipasvir or sofosbuvir / simeprevir, for a duration of 4, 6, 8 or 12 weeks. Preliminary results are very diverse, with SVR12 ranging from 56% to 95%. The MSD company has been evaluating the efficacy and safety of a double drug combination (grazoprevir + elbasvir) in HIV-infected patients which exhibits paramount efficacy and excellent tolerance in a diverse range of genotypes (6), including 1 and 4 HCV strains, which are those mainly encountered in the French acute HCV epidemics in MSM. This association has the potential to be used for short treatment duration especially with regards to the fact that patients will have no fibrosis at the time of treatment initiation. This MRK-combo would therefore be an ideal candidate for treating acute hep C due to GT1 or 4 in a “test and treat” approach in high-risk population such as MSM.

3.2 Brief background

3.2.1- Incidence of acute hepatitis C in France

France, and especially Paris, has been since 2004 at the epicenter of the epidemic of acute hepatitis C in HIV infected patients, alongside with other European countries such as Germany, the Netherlands and the UK (1). Mainly transmitted through unprotected sex and now what is called “chemical sex” (7), acute hepatitis C has remained a challenge for French clinicians because of the high rate of HCV reinfection after treatment or spontaneous clearance. Recent data from the Probe-C observational cohort indeed suggest that France holds the highest rank of reinfection in HIV-infected men having sex with men after cure (8), with as many as 21% of them getting reinfected within 3 years of HCV eradication (9,10).

3.2.2- Current standard of treatment for acute hepatitis C

As for now, the only recommended treatment in acute hepatitis C worldwide still relies on the use of Peg-Interferon ± Ribavirin for 3, 6 or 12 months depending on the HIV status and the rapid virological response after 1 month of treatment initiation. In HIV infected patients, guidelines from the NEAT network are usually followed (4) and consider the bitherapy with Peg-Interferon and weight-based ribavirin for 6 or 12 months as the gold standard, at the price of a high side effects burden. The current gold standard of treatment according to the EACS and EASL guidelines is also a combination of pegIFN at standard doses (alpha-2b, 1.5µg/kg/week and alpha- 2a, 180µg/week) and weight-adapted RBV (<75kg: 1000mg/d; ≥75kg: 1200mg/d) leading to SVR rates of 60–80%, regardless of HCV genotype (11).

Currently, there are additional data from 3 studies using 1st generation protease inhibitors (PI) in combination with pegIFN and RBV in the setting of acute hepatitis C. Nineteen HIV positive MSM from New York with acute HCV infection were treated with pegIFN, RBV and telaprevir (12). Overall SVR24 rate was 84% (16/19) in contrast to 63% (30/48) in a comparator group (treated prior to the availability of, or ineligible for, telaprevir) from the same clinic. Overall SVR24 rate was 84% (16/19) in contrast to 63% (30/48) in a comparator group (treated prior to the availability of, or ineligible for, telaprevir) from the same clinic.

However retrospective comparison of the two cohorts, which were not matched by baseline characteristics, demonstrated a difference in the distribution of the IL28B CC genotype which limits the conclusions from this trial. The results of additional trial based on boceprevir with peg-Interferon and ribavirin for 3 months have been recently published that report an overall rate of response close to 86% in 57 patients (13).

However, given the high rate of side effects associated with the use of 1st generation PI and the trend towards the use of peg-interferon free regimen, national and international guidelines have not included the option of using such DAA in the context of acute HCV infection so far.

3.2.3- The rationale for a “test and treat” approach regarding acute hepatitis C

As highly effective IFN and RBV free therapeutic options are rolled out amongst the HIV/HCV coinfecting population there is likely to be an impact on the current epidemic of acute hepatitis C in HIV positive MSM. It is possible that increased treatment uptake will lead to a reduction in the infective pool and reduced rates of transmission. There has been a lot of modeling work done to examine the impact of DAA on the prevalence of HCV. Much of this work focuses on the epidemic in people who inject drugs (PWID), but the general conclusions may well be transferrable to the MSM population. Martin et al assessed the current PWID treatment rates in seven UK settings and projected the potential impact of current and scaled-up treatment with IFN free regimens on HCV chronic prevalence (14). Switching to IFN free DAA therapy alone is unlikely to impact on the chronic prevalence of HCV, but scale up with the newer therapies to 26/1000 PWID demonstrated a reduction in the chronic prevalence of at least 15% within a decade. Thus scale up of IFN-free therapy is likely to result in a generalised reduction in the prevalence of chronic HCV over time. However as has been demonstrated in HIV and gonorrhoea epidemics in the 70', the HCV epidemic cannot be controlled without also controlling the core transmission group and it has been confirmed by another modeling study from Martin et al who demonstrated that associating scaling up in HCV treatment to an increased rate of screening in high risk groups and a change in sexual behaviors will significantly curve the HCV epidemics in MSM (15).

3.2.4- Overview of DAA-based strategies in acute hepatitis C

The following table reports the clinical trials that investigate the efficacy and safety of a short duration of various combinations of DAA as of the 1st January 2016.

Study name	Coordinator	DAAs	HCV genotype	Duration (weeks)	HIV status
DAHHS	UMC Utrecht	BOC + pegIFN + RBV	1	12	pos
CHAT	UKB	TPV + pegIFN + RBV	1	12	pos
SWIFT-C	ACTG	SOF + RBV	all	8 versus 12	pos
DARE C III	Kirby Institute	SOF + RBV	all	6	neg + pos
GS-US-337-1612	Gilead	SOF + LDV	1, 4	6	pos
Hep-Net Acute HCV	MHH	SOF + LDV	1	6	neg

Results of three of those trials have been released at AASLD 2015 [SWIFT-C (16) , DARE-C II (17) and SLAM-C (18)] and one at CROI 2016 (GS-US-337-1612) (19). The main characteristics and SVR12 of those trials are reported in the table below.

NAME	DAA COMBINATION	NUMBER OF PATIENTS	DURATION	SRV12
DARE-C II	SOF-RBV	19	6 weeks	26%
SWIFT-C (ACTG5327)	SOF-RBV (1 st arm)*	17	12 weeks	59%
SLAM-C	SOF-LDV	14	4 weeks	100%
	SOF-SMV	15	8 weeks	93,3%
GS-US-337-1612	SOF-LDV	26	6 weeks	77%

- The 2nd arm w/OF+LDV for 8 weeks is still recruiting (27 patients)

It should be noted that all trials included a rather small number of patients with no previous power calculation that precludes any strong conclusion on the efficacy of DAA in the setting of acute infection. Besides, in some trials, the definition of acute hepatitis C has been rather large, which may have led to the inclusion of early chronic infections. This may partly explain why short strategies based on the use of SOF and ribavirin have failed to cure more than 60% of the patients.

3.3 Research hypothesis

The first hypothesis supporting the conduction of the SAHIV trial is that acute hepatitis C in HIV-infected patients is not only an individual concern, but also and above all a public health concern. Indeed, HIV-infected patients and especially those men having sex with men represent a group where the risk of HCV transmission remains at a very high level, the HCV community viral load being so high that the epidemic cannot be self-contained. This means that treating only patients with chronic hepatitis C will not be enough to put an end to the chain of transmission.

The second hypothesis addresses the duration of treatment. Based on previous trials in acute hepatitis C in the context of HIV, we hypothesise that a short course of treatment (8 weeks) will allow an overall SVR rate of at least 80%. A shorter course of treatment may not be enough to reach at least 80% of treatment (as suggested by trials such as DARE-C trial with Sofosbuvir + ribavirin for 6 weeks or the Germany-UK trial with Sofosbuvir + Ledipasvir for 6 weeks). A longer duration of treatment will not make the option of treating at the acute stage interesting enough with regards to the duration of treatment in chronic hepatitis C (usually 12 weeks in non cirrhotic patients).

The third hypothesis is based on the choice of study drugs. Grazoprevir and Elbasvir for 12 weeks have demonstrated SVR12 rates above 95% in non cirrhotic, genotype 1 or 4 patients co-infected with HIV (C-EDGE clinical trial). No safety signal has been reported during the 12 weeks of treatment.

The fourth hypothesis pertains to the characteristics of the patients' HIV status. In the C-EDGE trial, patients had access to study drugs regardless of being HIV-treated, provided that their level of CD4 was above 200/mm³ and HIV-RNA was below 50 000 copies/mL. Their ARV status did not influence the overall SVR12 rate.

4 **OBJECTIVES**

4.1 **Principal objective**

The principal objective of this study is to assess the rate of sustained virological response (SVR) 12 weeks after 8 weeks of oral treatment with grazoprevir 100mg/elbasvir 50mg (MRK-combo) in patients with acute hepatitis C genotype 1 or 4.

4.2 **Secondary objectives**

HCV virological assessment

- To describe the HCV virological response (W4, W8, PT4 and PT12) as a whole and according to genotypes.
- To study the prognostic factors associated with SVR12.
- To assess the emergence of resistance in case of virological failure (HCV RNA \geq 12 IU/mL).
- To describe treatment adherence and quality of life during the course of the study.
- To evaluate the incidence of HCV reinfection at 1 year (PT48).
- To evaluate the sensitivity of HCV rapid testing (using the Oraquick HCV rapid antibody test) in patients with first acute Hepatitis C.

HIV virological assessment (only for HIV co-infected patients)

- To describe the evolution of HIV parameter during treatment (CD4 count and HIV-RNA).

Safety assessment

- To describe all the clinical events occurred during the study course

5 **METHODOLOGY**

5.1 **General design of the research**

Non-randomized, single arm, multicenter, open-label, Phase IIb pilot study conducted in France.

5.2 **Research milestones**

- Trial start date: Beginning 2017
- Enrolment period: 9 months
- Subject participation duration: screening (1 to 3 weeks before D0), then 56 weeks of follow-up → approximately 60 weeks maximum
- Total trial duration: 24 months
- Estimated study completion date: Beginning 2019

The end of the trial corresponds to the date of the last visit of the last patient.

6 STUDY ENDPOINTS

6.1 Primary endpoint

The primary endpoint will be the SVR rate defined by an undetectable plasma HCV RNA (<12 IU/mL) 12 weeks post-treatment (SVR12).

6.2 Secondary endpoints

HCV virological assessment

- Median (+IQR) of log HCV RNA at W4, W8, PT4 and PT12, globally and according to genotypes.
- Rate of HCV RNA (<12 IU/mL) at W4, W8, PT4 and PT12, globally and according to genotypes.
- Odds ratio of factors associated with SVR12.
- Number of HCV (NS5A and NS3/4) resistance mutations in patients with virological failure.
- Rate of adherence and quality of life measured by specific scales using self questionnaires.
- Number of patients with positive HCV RNA per hundred months follow-up.
- To evaluate the proportion of positive rapid tests.

HIV virological assessment

- Median (+IQR) of log HIV RNA at D0 and PT12
- Median (+IQR) of CD4 and CD8 cell counts (absolute count, percentage and CD4/CD8 ratio) at D0 and PT12.
- Number of AIDS-defining clinical or biological events using CDC classification (95% CI).

Safety assessment

- Number of adverse clinical and biological events that occur during the treatment and up to 48 weeks after the end of the treatment (95% CI).

7 ELIGIBILITY CRITERIA

The patient's written informed consent will be collected at the screen visit at the latest and before any examination required by the research. Eligibility criteria will be checked during the pre-inclusion phase and the following criteria must be met:

7.1 Inclusion criteria

1. Adult ≥ 18 years
2. A recent acute HCV infection or reinfection (see definition below) occurred within 6 months prior screening:

An acute HCV infection is defined by:

- a. HCV RNA was detectable within 6 months after a negative HCV RNA or HCV serology test.

OR

- b. Detectable HCV RNA and an acute clinical hepatitis occurred within 5 months prior to the screening visit.

Clinical Hepatitis is defined by:

- ALT ≥ 250 IU/L with normal ALT within the preceding 8 months,

or

- ALT ≥ 500 IU/L with either no measured ALT or with abnormal ALT within the preceding 8 months.

OR

Patients having reported a risk factor for HCV contamination (traumatic sexual intercourse, intranasal, rectal or intravenous drug use) inferior or equal to 6 months. HCV reinfection is defined by:

- a. Documented *de novo* infection after prior clearance after treatment or spontaneously,
 - After-treatment clearance is defined by one negative HCV RNA ≥ 6 months after end of treatment.
 - Spontaneous clearance is defined by two negative HCV RNA a minimum of 6 months apart.

OR

- b. Documented infection with a new viral strain, confirmed by phylogenetic or genotypic analysis.
3. Infection with HCV genotype 1 or 4 (confirmed at screening visit or by using a previous biological test performed 1 to 4 weeks before D0)
4. Plasma HCV-RNA ≥ 1000 UI/mL (confirmed at screening visit or by using a previous biological test performed 1 to 4 weeks before D0)
5. Confirmed HIV infection (only for HIV co-infected patients)
6. Without HIV treatment or with an acceptable stable HIV treatment for at least two weeks (See section 8.3 of the protocol, only for HIV co-infected patients)
7. Body weight ≥ 40 kg and ≤ 125 kg
8. Female patients with child-bearing potential and their heterosexual partners must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug. Male participants must agree to consistently and correctly use a condom, while their female partner must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug
9. Informed and signed consent
10. Patients with Health insurance (Sécurité Sociale or Couverture Médicale Universelle)

7.2 Non-inclusion criteria

Current condition

1. Opportunistic infections (stage C), active or occurred within 6 months prior to baseline.
2. Primary HIV infection.
3. Co-infection with Hepatitis B virus (AgHBs +) without appropriate treatment (TDF or TAF) for at least 2 weeks.
4. Confirmed cirrhosis (before acute HCV diagnosis).
5. Any other causes of acute hepatitis.
6. Pregnant or breast-feeding women.
7. Transplant recipients.
8. Evolutive malignancy.
9. Patients with a history of non-adherence, who will be at risk of being unable to respect the study follow-up timetable.
10. Patients participating in another clinical trial (with an experimental treatment) or within an exclusion period of a previous clinical trial at screening.
11. Patients under legal guardianship or incarcerated.

Biological criteria

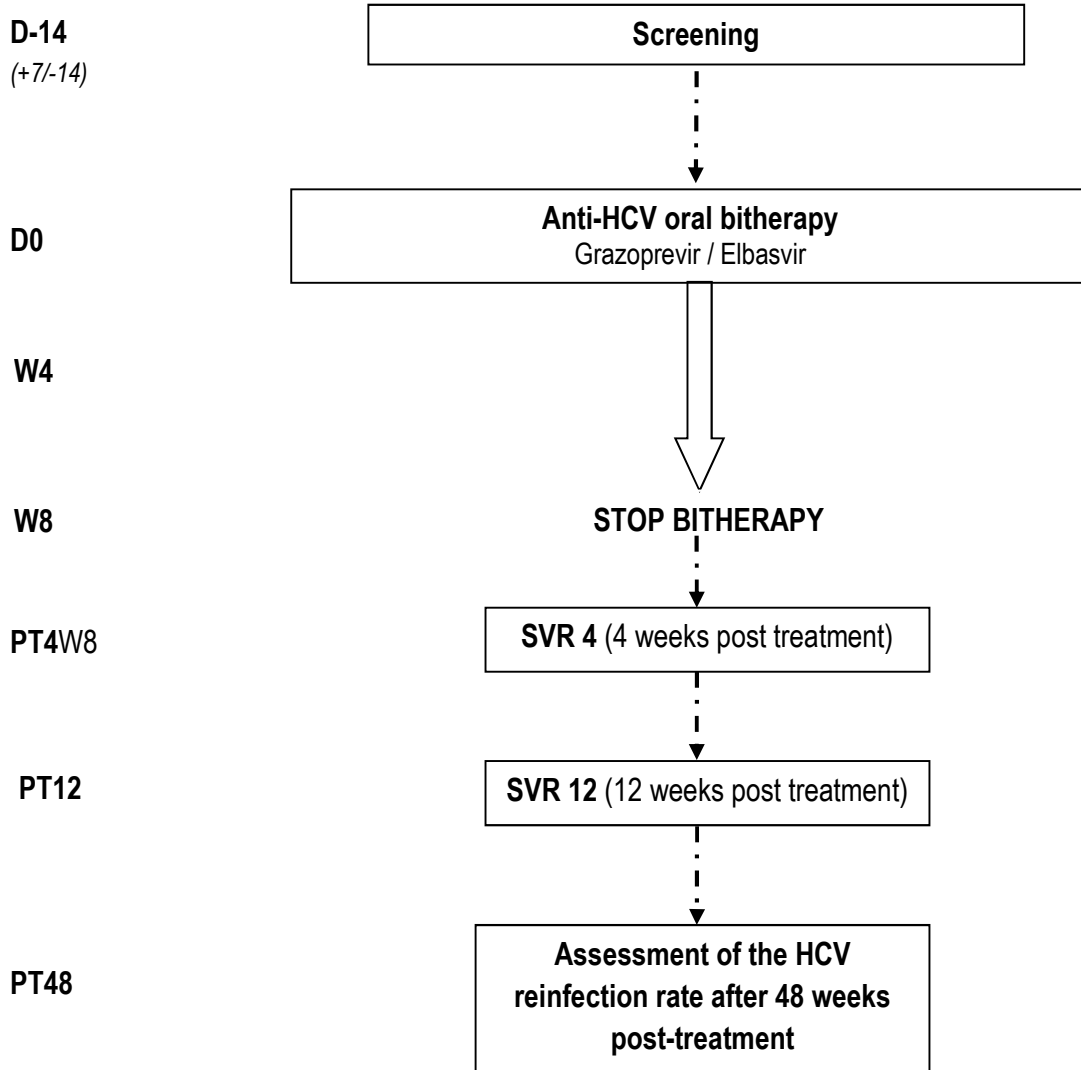
12. Hb < 10 g/dL (female) or < 11 g/dL (male).
13. Platelets $< 50\ 000$ /mm³.
14. Neutrophil count < 750 /mm³.

Criteria related to study drugs

15. Other antiretroviral drugs than those allowed in the study (please refer to section 8.3 of the protocol).
16. Contra-indications to Grazoprevir and/or Elbasvir or to any of the excipients listed in the summary of the product characteristics.
17. Contra-indicated treatment likely to interfere with the study drugs as listed in the summary of the product characteristics.

8 TREATMENTS

8.1 Study treatment strategy



8.2 Study Treatment: Grazoprevir / Elbasvir

Patients will receive 8 weeks of oral bitherapy – **Grazoprevir / Elbasvir fixed dose combination 100mg/ 50mg (MRK-combo)**, 1 tablet once a day (in the morning).

8.2.1 Reference documents

The reference documents for this study will be the summary of product characteristics.

8.2.2 Major expected side effects

The major adverse reactions (frequency $\geq 10\%$) occurring in subjects receiving the study treatment alone for 12 weeks were the following:

- Fatigue (11%)
- Headache (10 %)

The common adverse reactions (frequency $<10\%$) occurring in subjects receiving the study treatment alone for 12 weeks are listed below by body system:

Body System	Adverse Drug Reactions (%)
Gastrointestinal disorders:	Nausea (5%), abdominal pain (2%), abdominal pain upper (2%), constipation (2%), diarrhea (3%), dry mouth (1%), vomiting (1%)
General disorders and administration site conditions:	Asthenia (4%)
Metabolism and nutrition disorders:	Decreased appetite (2%)
Musculoskeletal and connective tissue disorders:	Arthralgia (2%), myalgia (2%)
Nervous system disorders:	Dizziness (2%)
Psychiatric disorders:	Anxiety (1%), depression (1%), insomnia (3%), irritability (2%)
Skin and subcutaneous tissue disorders:	Alopecia (1%)
Skin and subcutaneous tissue disorders:	Pruritus (1%)

The type and severity of adverse reactions in subjects with HCV/HIV-1 co-infection were comparable to subjects without HCV/HIV-1 co-infection and among subjects treated with 8, 12 or 16 weeks.

8.2.3 Description of selected adverse reactions

Laboratory abnormalities

- *Serum ALT elevations*

During clinical trials with the study treatment (with or without ribavirin), regardless of treatment duration, $< 1\%$ (13/1690) of subjects experienced elevations of ALT from normal levels to greater than 5 times the ULN, generally at or after treatment week 8 (mean onset time 10 weeks, range 6-12 weeks). Most ALT elevations resolved with ongoing therapy with the study treatment or after completion of therapy. The frequency of ALT elevations was higher in subjects with higher grazoprevir plasma concentration. The incidence of late ALT elevations was not affected by treatment duration. Cirrhosis was not a risk factor for ALT elevations.

- *Serum Bilirubin Elevations*

During clinical trials with the study treatment (with or without ribavirin), regardless of treatment duration, elevations in bilirubin at greater than 2.5 times ULN were observed in 6% of subjects receiving the study treatment with ribavirin compared to $< 1\%$ in those receiving the study treatment alone. These bilirubin increases were predominantly indirect bilirubin and were generally observed in association with ribavirin co-administration. Bilirubin elevations were typically not associated with serum ALT elevations.

- *Decreased Hemoglobin*

During clinical trials with the study treatment (with or without ribavirin), the mean change from baseline in hemoglobin levels in subjects treated with the study treatment for 12 weeks was -0.19 mmol/L (-0.3 g/dL) and with the study treatment with ribavirin for 16 weeks was approximately -1.37 mmol/L (-2.2 g/dL). Hemoglobin declined during the first 8 weeks of treatment, remained low during the remainder of treatment, and normalized to baseline levels during follow-up. Less than 1% of subjects treated with the study treatment with ribavirin had hemoglobin levels decrease to less than 5.28 mmol/L (8.5 g/dL) during treatment. No subjects treated with the study treatment alone had a hemoglobin level less than 5.28 mmol/L (8.5 g/dL)

Adverse reactions in subjects with HCV/HIV-1 co-infection

The type and severity of adverse reactions in subjects with HCV/HIV-1 co-infection (n=298) were comparable to subjects without HCV/HIV-1 co-infection.

8.1 Prior and concomitant treatments

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins and/or herbal supplements) that the patient is receiving from the time of signing the consent through the Treatment Period and 30 days after study drugs are stopped, must be recorded in the electronic case report form (eCRF) along with the reason for use and date(s) of administration including start and end dates. The investigator should review all concomitant medications for any potential interactions (see paragraph 8.2).

During the Post-Treatment Period, all medications taken will be recorded until 30 days following the last dose of study drugs. Only medications associate with HCV and HIV treatment will be recorded thereafter.

8.2 Treatments contraindicated / not recommended

8.2.1 Contraindicated treatments

HIV medications:

- Atazanavir
- Darunavir
- Lopinavir
- Saquinavir
- Tipranavir
- Efavirenz
- Etravirine
- Elvitegravir/cobicistat/emtricitabine/tenofovir

OATP1B1 inhibitors:

- Antimycobacterial: rifampicin
- Immunosupressant: cyclosporine

Strong CYP3A/P-gp inducers:

- Anticonvulsants: carbamazepine and phenytoin
- Endothelin antagonist: bosentan
- Herbal supplements: St. John's Wort

HMG-CoA reductase inhibitors:

- Atorvastatin (if daily dose exceed 20 mg)
- Rosuvastatin (if daily dose exceed 10 mg)
- Fluvastatin (if daily dose exceed 20 mg)
- Lovastatin (if daily dose exceed 20 mg)
- Simvastatin (if daily dose exceed 20 mg)

Diverse:

- Antifungals: ketoconazole
- Antibacterial: nafcillin
- Endothelin antagonist: bosentan
- Immunosuppressants: tacrolimus
- Wakefulness-promoting agent: modafinil

8.2.2 HIV Antiretroviral treatment modification

The antiretroviral treatment may be modified within the context of the study in two situations:

- Before study entry: at least two weeks prior to initiating HCV treatment,
- During the study: because of toxicity, intolerance, for virological reasons, patient or physician's decision.

Regardless of the reason, the modified treatment will be chosen according to the discretion of the investigator and must be compatible with the study (see section 8.3.1).

8.2.3 Contraception

Female patients with child-bearing potential, and their heterosexual partners must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug. Male participants must agree to consistently and correctly use a condom, while their female partner must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug.

8.3 Treatment circuits

Supply of products

Grazoprevir / Elbasvir tablets will be supplied by the sponsor in the context of a partnership with MSD.

Packaging and labeling

The Grazoprevir / Elbasvir will be packaged and labeled by coordinating pharmacy, in accordance with the current French law which establishes the content of labels for experimental drugs, and delivery to the investigating sites pharmacies.

Dispatch and Management of products

To ensure the traceability of these products, the items below must be reported in specific pharmacy forms by the trial site pharmacist: the treatment number, batch number and expiration date.

The pharmacist is responsible for maintaining the accounts for the products, for verifying the use-by date and storage in the recommended conditions.

The pharmacist will keep up to date the products dispensed and returned in the pharmacy record provided by the sponsor.

Return and destruction of unused products

After the visit of the CRA in the pharmacies to count used and unused treatments, the unused treatments will be destroyed by each pharmacy on the written request of the sponsor.

8.4 Monitoring of adherence

- All of the treatments and associated procedures during the study must be reported on specific forms in the case report file.
- Non-adherence of the anti-HCV treatment is likely to have a negative impact on the virological response to the treatment.
- An evaluation of **adherence** (self-questionnaire, appendix A6) will be done at W4 and W8. This questionnaire will specifically include information on both the antiretroviral treatment and the treatment for hepatitis C. The evaluation of adherence will be completed by the data reported in the dispensation record by the pharmacy of the investigating centre (pharmacy refill), which will make it possible to estimate, with the patient, the number of units dispensed and the number of units not used by the patient and better estimate treatment interruptions.

9 RESEARCH SCHEDULE

9.1 Research timetable

	Screening ^a D-14	D0	W4	W8	PT4 SVR4	PT12 SVR12	PT48 SVR48
<i>Time windows (days)</i>	+7 or -14 (from D-28 to D-7 before D0)	/	+/-7	+/-7	+/-7	+/-7	+/-7
<i>Patient instructions</i>	/	No medication intake before coming		/	/	/	/
Eligibility criteria / Informed Consent	X						
Clinical examination (including sitting blood pressure, weight, drugs*, tobacco* and alcohol consumption*) <i>*Only at screening</i>	X	X	X	X	X	X	X
Concomitant treatments (After 30 days post-study treatment, only medications associate with HCV and HIV treatment will be collected)	X	X	X	X	X		
Serious or not serious adverse events (until 30 days after the end of study treatment)	X	X	X	X	X		
HCV Genotype	X						
HCV RNA	X	X	X	X	X	X	X ^b
HCV antibodies (ELISA and Rapid test) ^d		X ^d	X ^{d,e}				
HIV antibodies (only for HCV mono-infected patients)	X						
HBs Ag ^c	X						
AST, ALT, Total and cinjugated bilirubin, GGT, ALP	X	X	X	X	X	X	X
CD4, CD8 (only for HIV co-infected patients)		X				X	
HIV RNA (only for HIV co-infected patients)		X				X	
FBC, platelets	X	X	X	X	X	X	
Blood creatinine and creatine clearance (CKD-EPI)		X	X	X	X	X	
Beta-HCG (Screen) or urinary pregnancy test (if applicable)	X	X	X	X	X	X	
QUESTIONNAIRES							
Adherence self-questionnaire			X	X			
"Quality of life" Questionnaire		X				X	
SAMPLES FOR BIOBANK							
Blood for serum collection (7/8 mL in dry tubes)		X	X	X	X	X	X
Blood for plasma collection (7/8 mL in EDTA tubes)		X	X	X	X	X	X
PHARMACY							
Treatment Dispensation/Return Grazoprevir / Elbasvir		X	X	X			

^a Screening visit will be only performed if the biological results needed to check the eligibility criteria are not available in the patient medical file and dated between 1 to 4 weeks before D0 (≤ 3 months for Ag HBs). In this case, the clinical examination and the signature of informed consent could be done at D0.

^b In case of positivity, a phylogenetic analysis will be performed in order to differentiate a late relapse from reinfection.

^c Only done, if there is no result ≤ 3 months before D0 in the medical file.

^d Only for patients with first acute infection

^e Only done if HCV antibodies results are negative at Day 0.

9.2 Inviting patients to take part in the research

The protocol could be presented to the patient by the investigating physician during a routine follow-up consultation. During this visit, the investigator will:

- Present the research i.e objectives, benefits and constraints for the patient, and answer any questions raised by the patient
- Check the eligibility criteria against available patient biological and clinical data
- Provide the patient with adequate information

9.3 Collection of consent

During the presentation visit, there are two possibilities:

- Either the patient is certain that he/she wishes to take part and requires no further time to consider participation: in this case, the physician can collect the patient's written informed consent during the visit. The procedures and prescription intended for the pre-inclusion visit can be done immediately, after that the investigator has filled in his/her part of the written informed consent form.
- Or the patient agrees to participate in the research, but needs more time to think about his/her participation. In this case an appointment is made with the patient for a pre-inclusion visit.

9.4 Screening visit (D- 28 to D-7)

9.4.1 Clinical examination

After confirmation with the patient of his/her wish to take part in the research, the pre-inclusion visit is conducted by the investigating physician. This visit will take place from D-28 to D-7 before the inclusion visit (D0).

N.B.: It will be allowed to use previous biological results which have been done 1 to 4 weeks before D0 (≤ 3 months for Ag HBs). In this case, it will not be necessary to do it again and all the items mentioned below will be done at D0.

During this visit, the investigator will:

- Collect the patient's signed written informed consent
 - for participation in the study
- Assign an anonymisation code (**See § 14.4**)
- Check the eligibility criteria
- Question the patient to collect:
 - date of birth (only the year), gender and demographic data,
 - history and ongoing consumption: drugs, alcohol, tobacco,
 - therapeutic, medical and surgical history (considered clinically significant for the study according to the investigator's discretion),
 - intercurrent diseases and ongoing treatments
 - History of HIV (if applicable) and HCV
- Perform a clinical examination with notably measurements of weight, height and sitting blood pressure.

- Perform the following biological tests (**do not need** to be done in a fasting state):
 - HCV Genotype
 - HCV RNA
 - HIV antibodies (only for HCV mono-infected patients)
 - HBs Ag
 - AST, ALT, total and conjugated bilirubin, GGT, ALP
 - FBC, platelets
 - Beta-HCG (Screen) or urinary pregnancy test (if applicable)

Female patients with child-bearing potential, and their heterosexual partners must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug. Male participants must agree to consistently and correctly use a condom, while their female partner must use adequate contraception from the date of screening until 30 days after administration of the last dose of study drug.
- Plan the following appointment (D0) **and inform the patient not to take any medication before coming** (do not need to be in a fasting state except for medication).
- At the end of the pre-inclusion visit, the investigator will send by fax or email to the Methodology and Management Centre the pre-inclusion notification document together with a copy blacked-out of the consent form.

9.4.2 Procedure for notification of inclusion (before D0)

When an investigating physician has at his/her disposal all of the necessary results for inclusion of a patient in the study and he/she wishes to enroll this patient, he/she will:

- Fill in the eligibility criteria section of the e-CRF,
- Send by Fax or by email to the Methodology and Management Centre the anonymised documents showing the results of all necessary examinations at inclusion.

9.5 Inclusion visit D0

This visit corresponds to the start of the treatment.

For all patients, the inclusion visit takes place with the investigator. During this visit, the investigator will:

- Interview the patient for intercurrent diseases and ongoing treatments
- Perform a clinical examination with notably measurements of weight and sitting blood pressure.
- Carry out the following biological tests (**do not need** to be in a fasting state except for medication):
 - HCV RNA
 - HCV antibodies using Rapid Testing (Oraquick®) and ELISA
 - AST, ALT, total and conjugated bilirubin, GGT, ALP
 - CD4, CD8 (only for HIV co-infected patients)
 - HIV RNA (only for HIV co-infected patients)
 - FBC, platelets
 - Blood creatinine and creatinine clearance
 - Beta-HCG (Screen) or urinary pregnancy test (if applicable)
 - 7/8 mL of blood for serum collection (in dry tube)
 - 7/8 mL of blood for plasma collection (in EDTA tube)

- Provide the following **questionnaire** to be self-administered by the patient:
 - “Quality of life” questionnaire
- Give the **prescription** for 8 weeks of trial treatment to the patient: 1 tablet per day of Grazoprevir / Elbasvir fixed-dose (100/50 mg)
- Plan the following visit (W4) and tell the patient **not to take any medication before coming** (do not need to be in a fasting state except for medication). The patient will bring his/her antiretroviral treatment and the tablets of Grazoprevir / Elbasvir.

9.6 Visits W4 and W8

During these visits, the investigator will:

- Interview the patient for intercurrent diseases and ongoing treatments
- Perform a clinical examination with notably measurements of weight and sitting blood pressure.
- Carry out the following biological tests (**these examinations need to be done in a fasting state i.e neither food nor beverages except water during the previous 12 hours**):
 - HCV RNA
 - HCV antibodies using Rapid Testing (Oraquick®) and ELISA, only done at W4 if negative at D0)
 - AST, ALT, total and conjugated bilirubin, GGT, ALP
 - FBC, platelets
 - Blood creatinine and creatinine clearance
 - Beta-HCG (Screen) or urinary pregnancy test (if applicable)
 - 7/8 mL of blood for serum collection (in dry tube)
 - 7/8 mL of blood for plasma collection (in EDTA tube)
- Provide the following **questionnaire** to be self-administered by the patient:
 - “Self-adherence questionnaire
- Plan the following appointment (do not need to be in a fasting state). The patient will bring his/her antiretroviral treatment and the tablets of Grazoprevir / Elbasvir.
- Following each visit, the investigator will fax to the Methodology and Management Center the anonymised result of the HCV viral load.

9.7 Visits PT4 (SVR12), PT12 (SVR12) and PT48 (SVR48)

These visits will make it possible to validate the sustained virological response respectively 4, 12 weeks and 48 after cessation of the anti-HCV bitherapy and to reassess hepatic impairment.

During these visits, the investigator will:

- Interview the patient for intercurrent diseases and ongoing treatments (until 30 days after the end of study treatment. Thereafter, only medications associate with HCV and HIV treatment will be collected)
- Perform a clinical examination with notably measurements of weight and sitting blood pressure.

- Carry out the following biological tests (do not need to be in a fasting state):
 - HCV RNA
In case of positivity, a phylogenetic analysis will be performed in order to differentiate a late relapse from reinfection.
 - AST, ALT, total and conjugated bilirubin, GGT, ALP
 - CD4, CD8 (**only at PT12** and for HIV co-infected patients)
 - HIV RNA (**only at PT12** and for HIV co-infected patients)
 - FBC, platelets (**except at PT48**)
 - Blood creatinine and creatinine clearance (**except at PT48**)
 - Beta-HCG (Screen) or urinary pregnancy test (if applicable, **only at PT4 and PT12**)
 - 7/8 mL of blood for serum collection (in dry tube)
 - 7/8 mL of blood for plasma collection (in EDTA tube)
- Provide the following **questionnaire** to be self-administered by the patient:
 - “Quality of life” questionnaire (**only at and PT12**)
- **Only at PT4 and PT12:** plan the following appointment (do not need to be in a fasting state).
- Following each visit, the investigator will fax to the Methodology and Management Center the anonymised result of the HCV viral load.

9.8 Time windows of each visit

For each visit, a time window of plus or minus is allowed as follows:

- +7/-14 days for screening visit,
- +/-7 days for visits W4, W8, PT4, PT12, and PT48.

9.9 HCV virologic failure criteria

The following criteria will be considered evidence of HCV virologic failure for the purposes of patient management:

- Confirmed increase from nadir in HCV RNA (defined as 2 consecutive HCV RNA measurement of > 1 log₁₀ IU/mL above nadir) at any time point during study drug treatment.
- Confirmed HCV RNA ≥ 100 IU/mL (defined as 2 consecutive HCV RNA measurements ≥ 100 IU/mL) after HCV RNA < LLOQ during study drug treatment.

When confirmatory testing is required, it should be completed as soon as possible and the subject should remain on study drug treatment until the virologic failure criteria has been confirmed. Subjects meeting the virologic failure criteria will be discontinued from study drug and will continue to be followed in the Post-Treatment Period for the emergence and persistence of resistant viral variants until 48 weeks post-treatment (PT48).

9.10 End of patient follow-up

The theoretical date of end of patient follow-up in the study is PT48.

Following participation in the study, there are two possibilities:

- **undetectable HCV RNA at 12 and 48 weeks post-treatment: cure of hepatitis C.**

The patient should continue his antiretroviral treatment according to the current guidelines.

- **detectable HCV RNA at 12 and/or 48 weeks post-treatment: virological failure.**

The patient should continue his antiretroviral treatment according to the current guidelines. Hepatitis C may be retreated according to reasons of virologic failure (toxicity, safety, compliance, virologic reasons) and virologic response profile during the study (non response, incomplete virologic response, breakthrough and relapse). The mode of this potential retreatment will depend on the current available molecules at the time and on the safety/toxicity/resistance profile. A long-run monitoring of any cirrhosis involution and a hepatocarcinoma screening are necessary in these patients.

9.11 Premature treatment discontinuation

If a patient stops the trial treatment (Grazoprevir / Elbasvir) prematurely, he has to continue the follow-up provided for in the context of the protocol (visits, samples, complementary examinations, etc) to permit Intention To Treat (ITT) analysis.

Reasons of anticipated treatment discontinuation may include:

- Subject's wish
- A major protocol violation
- Any medical event requiring or leading to interruption of the treatment (the onset of intolerance or an SAE, the appearance or worsening of an intercurrent disease, disease progression, death), life-threatening event
- Pregnancy onset (cf. § 10.4)
- Non compliance with the treatment
- The need for the patient to be treated with a not allowed treatment in the context of the protocol

Apart from these reasons, anticipated treatment discontinuation is considered as a protocol deviation. Anticipated treatment discontinuation must be reported rapidly and as soon as it is known to the MMC by fax or by email then by filling in the e-CRF. The reasons for as well as the date of this discontinuation must be recorded.

Treatment discontinuation for virological reasons deserves particular attention.

The patient who stops the treatment must receive the best possible care given his/her state of health and the state of current knowledge.

9.12 Loss to follow-up

The Methodology and Management Centre must be informed if a patient is lost to follow-up using the 'End of participation in the trial' form. The patient will be considered lost to follow-up at the date of the end of the trial.

A patient who comes back/or gives news to the investigating site will no longer be considered lost to follow-up. At this renewed contact, as much information as possible concerning his/her follow-up must be obtained.

9.13 Withdrawal of consent

Patients who wish to withdraw their consent to participate in the research, as they have the right to do at any time, will not be followed in the context of the protocol, but will benefit from the best care possible given their state of health and the state of current knowledge. The date and the reasons for withdrawal (if the patient agrees to inform the investigator) **must be reported in the medical record.**

When a patient withdraws his/her consent to take part in the research, the investigator must contact the Methodology and Management Centre as soon as possible. Withdrawal of consent implies the immediate interruption of any biological testing and any act specific to the consent from the date of withdrawal of consent (date of withdrawal included).

Any data collected until this date has to be deleted in accordance with the current French law (loi relative à l'informatique et aux libertés n°78-17 du 6 janvier 1978 modifiée, article 38). The biological samples collected until this date also have to be destroyed.

This applies unless the patient gives authorisation to continue to collect, to check and to analyse the data in question (if the patient agrees to inform the investigator) **must be reported in the medical record.**

9.14 Violations of the protocol and derogations

Deviations from protocol must be reported in the patient's case report form.

Apart from deviations that have been authorised in writing by the Methodology and Management Centre and the coordinating investigator, the following are considered major violations deviations as regards:

- legal aspects
- eligibility criteria
- the principal endpoint
- the treatment strategy of the trial

Any major deviation from the protocol will be submitted to the Scientific Advisory Board.

9.15 Guidelines for the collection of data

Data will be collected in an electronic Case Report File under the responsibility of the principal investigator of each centre. Every patient will be assigned an e-CRF.

Guidelines to facilitate e-CRF filling will be available at every study site.

All the forms must be filled in from the medical record jointly with the study physician or his designated representative at every visit (in any case, the data collected remain under the responsibility of the principal investigating physician of the site).

An anonymised copy of the HCV-RNA results will be faxed to the MMC after the relevant visits.

10 ADVERSE EVENTS AND PREGNANCY

10.1 Definitions

10.1.1 Adverse Event (AE)

An adverse event refers to any untoward medical occurrence in a patient or a clinical trial subject to whom a medicinal product has been administered including occurrences which are not necessarily caused by or related to that product.

10.1.2 Adverse Reaction (AR)

An adverse reaction refers to all untoward and unintended responses to an investigational medicinal product related to any dose administered.

10.1.3 Serious Adverse Event/Reaction (SAE/SAR)

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

- results in death,
- is life-threatening,
- results in persistent or significant disability or incapacity,
- requires hospitalization or prolongation of existing hospitalization,
- is a congenital anomaly or birth defect,
- is a grade 4 clinical adverse event,
- is a grade 4 biological adverse event,
- is an "important medical event" (medical events, based upon appropriate medical judgment, which may jeopardize the subject or may require medical or surgical intervention to prevent one of the above characteristics/consequences).

Examples: allergic bronchospasm requiring intensive treatment at an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, suspected transmission of an infectious agent via a medicinal product...

EXCEPTIONS:

- medical or surgical procedures (e.g. : *surgery, endoscopy, tooth extraction, transfusion*); only the condition that leads to the procedure should be notified if the condition is referring to a seriousness criteria described above.
- pre-existing diseases or present conditions or detected prior to start of study drug administration, that do not worsen.
- situations where an untoward medical occurrence has not occurred (e.g. : *hospitalization for elective surgery if known prior to start study, social and/or convenience admissions, pre-specified study hospitalizations for observation*).
- grade 4 biological adverse events detected at the screening visit and proven to be pre-existing events (e.g. previous biological results) and those detected prior to start of study drug administration: those must be solely reported in the CRF AE form.
- outpatient care; the patient has been formally admitted to a hospital for medical reasons with no seriousness criteria (described above) and does not require overnight hospitalization.

10.1.4 Suspected Unexpected Adverse Reaction (SUSAR)

An adverse reaction, the nature, the outcome or severity of which is not consistent with the applicable Reference Safety Information: Investigator's Brochure for Grazoprevir / Elbasvir.

10.1.5 New fact

A new fact is defined as any safety data that could modify significantly the evaluation of the benefit/risk ratio of the clinical trial. Examples: a serious adverse event which could be associated with the trial procedures and which could modify the conduct of the trial, a significant hazard to the subject population such as lack of efficacy of an investigational medicinal product used for the treatment of a life-threatening disease, recommendations of the DSMB, if any, where relevant for the safety of subjects.

10.2 Responsibilities of the Investigator**10.2.1 Timelines**

The investigator has to notify to the sponsor all Serious Adverse Events (SAE) occurring in the trial, **as soon as he becomes aware of it**, except those that the protocol identifies as not requiring immediate reporting (see section 10.1.3).

The immediate report must include the minimum information following: the identifiable coded subject, the identifiable reporter, one suspect medicinal product and one AE.

The immediate report shall be followed, if needed, by complementary detailed reports. The investigator ensures that all relevant information is forwarded to the sponsor within 8 days after the initial notification.

The investigator must follow the subject until clinical recovery is complete and laboratory results have returned to normal or baseline, or until the event has stabilized. Follow-up should continue after completion of protocol treatment if requested.

10.2.2 Notification period

All serious or not serious adverse events must be reported if they occur:

- From the time the subject signed the study-specific informed consent,
- Until 30 days following the end of study treatment.

Serious adverse events occurring to a subject after the treatment of that subject has ended should be reported to the sponsor if the investigator becomes aware of them. The investigator does not need to actively monitor subjects for adverse events once the trial has ended.

10.2.3 Assessment of severity, seriousness, causality and expectedness

Severity

The severity (i.e. intensity) of all AEs/ARs (serious and non-serious) should be graded using the French table “Echelle cotation de la gravité des Evénements Indésirables chez l’adulte” (see appendix A4) and reported by the investigator in the corresponding form of the CRF.

Seriousness

The judgment as to whether the event is serious is usually made by the reporting investigator (see section 10.1.3 for serious criteria).

Deaths must be reported for subjects as the outcome of an adverse event and not as an adverse event itself if the cause is known. If the cause is unknown, the death should be reported as “unknown cause of death”.

Causality

The investigator must assess the causality of all SAE in relation to the trial therapy, concomitant medication and the research.

In the absence of information on causality from the reporting investigator, the sponsor should consult the reporting investigator and encourage him to express an opinion on this aspect.

All SAE for which the investigator or the sponsor considers that a causal relationship is a reasonable possibility are considered as suspected SAR. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator’s causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

Expectedness

Assessment on expectedness is usually done by the sponsor.

The expectedness of a SAR is assessed in the light of the Reference Safety Information (see section 7)

If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

10.2.4 Notification procedure

AE notification

Grade 1, 2 and 3 biological events and all other AE/AR have to be reported in the proper CRF AE form, except those detected prior to start of study drug administration. If a clinical or biological event is present at inclusion, only its aggravation will be notified.

SAE notification

All SAE/SAR has to be notified by the investigator to the sponsor, immediately as soon as he becomes aware of it, using SAE notification forms, (initial and complementary forms), dated and signed, with due care being paid to the grading, causality and expectedness of the event.

All SAE/SAR should be recorded by the investigator, in corresponding form of the CRF.

When the SAE notification form is filled in, the investigator sends it to the MMC, by fax: +33 1 49 28 25 95 or by email: karine.lacombe2@aphp.fr and jessica.krause@aphp.fr

Concerning SAE notification forms filling:*The serious adverse event:*

The investigator should assess, if possible, the **diagnosis** of all SAE/SAR.

Diagnosis, or if not available, syndrome should be reported whenever possible.

When several symptoms are linked together (to one pathology), they will not be reported as additional adverse events (e.g. pancreatitis and abdominal pain) but they will be reported on one SAE notification form.

Event onset date :

Date of “event onset” on SAE notification form should be earlier (or the same day) than date of seriousness, and should correspond to the “start date” of the event on the corresponding AE form.

Event outcome:

SAE outcome (which actually corresponds to event outcome) at the time of reporting should be provided on the initial SAE notification form.

Any change in the initial outcome (e.g. resolved, back to previous status, worsening...) should be reported using complementary reporting form(s), outcome on the initial reporting form should not be modified. As long as the adverse event is not resolved, any new worsening will be reported using complementary forms of the corresponding initial SAE.

If the outcome of the event is “resolved”: the date of resolution corresponds to the date of the AE resolution and not of the end of seriousness. “Stop date of seriousness” can be reported on AE form, when the event is no longer considered as serious.

If the outcome of the event is “back to previous status” or “improvement”, the date of event outcome corresponds to the end of seriousness.

The investigational medicinal product:

“Occurring at any dose” does not imply that the subject is receiving study drug at the time of the event. Dosing may have been given as treatment cycles or interrupted temporarily prior to the onset of the SAE, but may have contributed to the event.

Relevant documentation related to SAE notification

The investigator should collect all relevant information related to the SAE/SAR.

All relevant documentation related to the SAE/SAR (e.g. hospitalization report, laboratories results...) must be sent to the MMC, immediately and no later than 24 hours after being made aware of it, by fax: +33 1 49 28 25 95 or by email: karine.lacombe2@aphp.fr and jessica.krause@aphp.fr.

The subject's name should not be used on any correspondence, instead the trial number and the subject code should be written down.

10.3 Responsibilities of the sponsor**10.3.1 Recording and assessment of SAE**

The sponsor is responsible for ensuring that all SAE are reported.

The sponsor shall keep detailed records of all SAE which are reported to him by investigators.

The sponsor is also responsible for the assessment of the causality of the SAE in relation to the trial therapy, concomitant medication (e.g. drug-drug interaction) and the research. The causality assessment given by the investigator should not be downgraded by the sponsor. If the sponsor disagrees with the investigator’s causality assessment, the opinion of both the investigator and the sponsor should be provided with the report.

The expectedness of the SAR shall be determined by the sponsor.

The sponsor assesses if the SAE is expected or not using the applicable Reference Safety Information (RSI): Summary of the Product Characteristics (SmPC) for an authorized product and Investigator’s Brochure (IB) for an unauthorized investigational product.

If information on expectedness has been made available by the reporting investigator, this should be taken into consideration by the sponsor.

10.3.2 Reporting of safety data to the national competent authority and the Ethics Committee

10.3.2.1 SUSAR reporting

All Suspected Unexpected Adverse Reactions (SUSARs) have to be reported, within the legal timeframe, by the MSD Pharmacovigilance unit to the national competent authority of the Member State concerned, directly or indirectly through EudraVigilance Clinical Trial Module (EVCTM):

- direct reporting: the sponsor reports the SUSAR directly as an individual case safety report (ICSR) to the national competent authority of the relevant Member State;
- indirect reporting: the sponsor reports the SUSAR as an ICSR through EVCTM to the national competent authority of the relevant Member State.

MSD Pharmacovigilance unit should also report to the concerned Ethics Committee, all SUSAR occurred in the territory of that Member State.

The timelines for expedited initial reporting (day 0) starts as soon as the information containing the minimum reporting criteria has been received by the sponsor.

For fatal and life-threatening SUSAR, the sponsor should report at least the minimum information as soon as possible and in any case no later than 7 calendar days after being made aware of the case. Relevant complementary information should be collected and notified within 8 extra-days.

SUSAR which are not fatal and not life-threatening are to be reported within 15 calendar days. Relevant complementary information should be collected and notified within 8 extra-days.

10.3.2.2 New fact reporting

The sponsor should inform the national competent authority and the Ethics Committee of safety data that may be relevant in terms of subject safety, or safety issues which might alter the current benefit-risk assessment of the trial.

10.3.2.3 Annual safety reporting

At the anniversary date of the protocol approval by the first Competent Authority + 60 days, the sponsor submits, once a year throughout the clinical study, an Annual Safety Report (ASR) to the concerned national competent authorities and the concerned Ethics Committee.

The ASR is prepared in collaboration between the MSD safety department and the coordinating investigator and includes:

- a line listing of all suspected serious adverse reactions, including unexpected and expected SAR;
- a cumulative summary tabulation of all SAE and SAR by SOC;
- a concise and critical analysis of patient safety suitable for research.

If no new safety information occurs in the concerned period, the sponsor addresses to the national competent authority a letter in which he informed the absence of safety data, instead of the annual safety report.

10.3.2.4 Six-months line-listing SUSAR

According to the applicable regulation, all SUSARs occurred with Grazoprevir and/or Elbasvir provided by MSD are reported every 6 months as a line listing accompanied by brief report by the MSD Pharmacovigilance unit to the concerned Ethic Committee with copy to the national competent authority.

10.4 Pregnancies

10.4.1 Pregnancy notification

Any pregnancy occurring during the trial and its outcome, concerning either the enrolled woman or the wife of an enrolled man, should be systematically reported to the sponsor.

If pregnancy concerns the wife of enrolled man, the investigator must obtain her consent for information on pregnancy.

The investigator has to notify each pregnancy to the sponsor, as soon as he becomes aware of it, using the "initial pregnancy notification form" and specifying estimated date of delivery, obstetrician contact and name of maternity hospital.

The investigator has to follow the subject until the end of the pregnancy or its interruption and to notify the outcome to the sponsor using the "final pregnancy notification form".

Follow-up of pregnant participant continues until the end of the trial. Any exceptions, related to the indication of maternal treatment, should be discussed between the investigator, the coordinating investigator, the sponsor and if necessary a specialist in terato-vigilance.

Warning:

- The medical surveillance of the women and their children should be reinforced: a particular attention must be given on serious pathology occurring during pregnancy abnormalities. A SAE initial report form should be filled if any **anomaly or birth defect** is detected.
- All **voluntary interruption of pregnancy, therapeutic interruption of pregnancy or miscarriage needing a hospitalization** is considered as a SAE/SAR and should be notified as mentioned in section 10.2.4. SAE notification.

All pregnancies should be recorded in corresponding notification form.

When the pregnancy notification form is completed, the investigator sends it to the MMC, by fax: +33 1 49 28 25 95 or by email: karine.lacombe2@aphp.fr and jessica.krause@aphp.fr.

10.4.2 Pregnancy management

If a female participant becomes pregnant, all study and concomitant treatments that should not be administered during pregnancy must be discontinued.

11 MANAGEMENT OF THE TRIAL

11.1 Scientific Advisory Board (SAB)

The Scientific Advisory Board has the mission to ensure the good scientific, ethical and logistical conduct of the research project and as such, it engages its liability, in particular to the Sponsor.

The Scientific Advisory Board of a research project is appointed by the coordinating investigator.

11.1.1 Composition

The Scientific Advisory Board (SAB) must include at least the following members:

→ Voting members:

- the coordinating Investigator who is most often the chairperson,
- the methodologist and/or the statistician of the research,
- the project manager of the MMC,
- at least one investigator from clinical sites participating in the research,
- virologist(s) and scientific advisor(s).

→ Non-voting members:

- a member of the pharmacovigilance department of MSD, if specified in the meeting agenda,
- a representative of each pharmaceutical partner supplying the research products
- possibly a representative of a patients' association: his presence will be decided at the first SAB meeting.

Other individuals, in addition to permanent members, may occasionally participate in the SAB meetings when invited by the chairperson or the Sponsor. Their presence shall be recorded in the minutes of the meeting.

It is composed of the following members:

- Karine Lacombe (principal investigator),
- Anders Boyd (methodologist and biostatistician),
- Hayette Rougier (project manager),
- Jessica Krause (investigator),
- Julie Chas (investigator),
- Eric Rosenthal (investigator),
- Marc-Antoine Valantin (investigator),
- Yasdan Yazdanpanah (investigator),
- Patrick Miailhes (investigator),
- Stéphane Chevaliez (virologist),
- Lionel Piroth (scientific advisor),
- Amir Guidoum (medical advisor hepatitis, representing MSD),
- if necessary, a representative of a patients association.

11.1.2 Meetings periodicity

The first meeting of the Scientific Advisory Board should be organized prior to the start of the research, and if possible before initiating regulatory procedures to validate all scientific, ethical and logistical aspects of the study.

The subsequent meetings are scheduled every three months after the first inclusion and until the end of the research according to the specificities and the progress of each research project.

Extraordinary meetings may be decided by the chairperson of the Scientific Advisory Board of the research upon request from the Sponsor, or from one or several members.

11.1.3 Missions

The Scientific Advisory Board's missions are:

- to approve the composition of the Data Safety and Monitoring Board proposed by the Coordinating Investigator in agreement with the representative of the department concerned by the research,
- to ask the MMC for information regarding the progress of the research project, any potential issue and available results,
- to ensure compliance with ethics requirements,
- to perform the scientific follow-up of the research: maintain the relevance of the research objectives and the permanent validity of the methods implemented to meet them,
- to make all important decisions at the demand of the Coordinating Investigator or the DSMB regarding the good conduct of the research in compliance with the protocol, any procedure specific to the research and Good Clinical Practices,
- to decide on all relevant modifications of the protocol required to achieve the research project,
- to provide information to all investigators and other participants in the research,
- to ensure that rules related to data and biological samples access are followed,
- to ensure that rules related to communication and publication of research results are abided by.

After each meeting, a report is written by the MMC in collaboration with the chairperson and diffused to each member of the Board and to the invited persons.

11.2 The Data Safety Monitoring Board (DSMB)

The Data Safety and Monitoring Board (DSMB) is a consultative committee appointed to ensure the good conduct of the research, particularly by advising the Scientific Advisory Board and the Sponsor.

11.2.1 Composition

The Data Safety and Monitoring Board must include three to five clinicians or even more (odd number) according to the nature of the research project, with expertise fields specifically adapted to the research project:

- a methodologist,
- a clinician,
- a virologist,
- a member with expertise in ethics in research,
- if necessary, a representative of a patients association.

Appointed members cannot be directly involved in the research project. The members participate in the board as designed experts independently of the organizations they already belong to.

11.2.2 Meetings periodicity

A first meeting to present the research project to the Data Safety and Monitoring Board shall be organized at the start of the research if possible, at the initiative of the chairperson of the Scientific Advisory Board. The next meetings are scheduled in an agenda established at the beginning of the inclusions.

Extraordinary meetings may be requested by the chairperson of the Scientific Advisory Board of the research or the Sponsor in case of unexpected or serious issues.

11.2.3 Missions

The mission of the Data Safety and Monitoring Board is to ensure the safety of the participants and to maintain the scientific and ethics integrity of the research project during the whole conduct of the research. This Board has a consultative role for the Scientific Advisory Board and the Sponsor.

The DSMB may help to make, during the conduct of the research, decisions for which an independent judgment is needed. It may give advice in the following circumstances:

- Recommendation on an early trial termination (for toxicity reason or because the trial is not anymore feasible, or because all the elements of conclusion are achieved)
- Recommendation on major protocol modification, regarding enrollment or study follow-up or new scientific data
- Interim analysis: analysis results interpretation, asks for analysis or additional study data.

The written Independent Committee opinion is sent to the sponsor and the Scientific Committee Director. The sponsor shall send the opinion to the Ethics Committee and to the Competent Authorities as part of the safety annual report. A duplicata is sent to the MMC for filing.

The DSMB will review the progress, efficacy, and safety data of this study after the first fifteen patients have completed the treatment period (W8) or prematurely discontinued the study drug.

No formal stopping rules will be used by the DSMB for safety outcomes. Rather, a clinical assessment will be made to determine if the nature, frequency, and severity of adverse events associated with the treatment under investigation warrants the early termination of the study in the best interest of the participants.

11.3 Methodology and Management Centre (MMC)

The sponsor mandates the team of the MMC to manage the study

The project team of the MMC is constituted of a coordinating investigator, a methodologist/biostatistician, a project manager, a data manager and Clinical Research Associates.

The MMC is in charge of the study:

- Performs study set up, the procedure of subjects' enrollment, study data collection and monitoring, the constitution and management of the data base and statistical analysis,
- Coordinates the functioning of the investigation sites (clinical units, hospital pharmacy, virology laboratory),
- Informs the sponsor and the Scientific Committee of the study progression,
- Organises the Scientific Advisory board and general assembly of investigators,
- Actively participates in the communication and the publication of the results.

12 CIRCUIT OF SAMPLES

12.1 Samples for the biological analyses planned by the protocol

Blood samples are constituted at the various study visits to allow the realization of the biological check-up. Biological analyses are performed in real time at recruitment site local laboratories, with respect to the site procedures.

12.2 Biobank

At some study visits (cf. timetable §2), blood samples are drawn to establish biobank constituted of serum and plasma samples.

Samples will be prepared, labelled, anonymised (study patient number) and stored at -80°C according to biobank procedure. This procedure will mention details of the sampling in terms of volume, numbers of drawn tubes as well as the modalities of preparation of each type of sample.

Samples will be collected and stored on each investigator's site.

Biobank samples may be used to verify biological data of the protocol and to perform further researches authorised by the Scientific Advisory Board of the study. This may allow to understand best or to prevent clinical, biological, therapeutic evolution of hepatitis C in co-infected patients.

➤ **The samples of serum and plasma bank will be used to perform the following analyses:**

- Genotypic resistance test if HIV virological failure
- Measure of HCV viral load and genotypic resistance test if HCV virological failure
- Assessment if necessary of ART concentrations

Several complementary virologic studies are considered. They would be performed with stored biobank samples following acceptance by the Scientific Advisory board, and depending on their interest and pertinence based on the evolution of knowledge.

13 STATISTICAL CONSIDERATIONS

13.1 Statistical hypotheses

The main end-point during statistical analysis is defined as SVR12 and its precision, calculated as the 95% Clopper-Pearson confidence interval (CI), with a type I error of 5%.

13.2 Sample size determination

Since the study is single-arm, non-comparative in design, the sample size will be based on statistical precision and not a comparative statistical test. The sample size should allow a precision of <30% absolute difference between lower and upper bounds of the Clopper-Pearson 95%CI. The expected SVR12 rate is 80% from previous studies, hence bounds are calculated from point estimates of SVR12 $\geq 80\%$. A total 30 patients are necessary to fulfill the statistical criteria above.

13.3 Statistical methods

- **Qualitative variables**

Qualitative variables will be described in terms of numbers of patients, percentages and confidence intervals.

- **Quantitative variables**

Quantitative variables will be described in terms of populations, medians, range and interquartile range or means, standard deviations and confidence intervals of the mean.

- **Variables of the type 'Time to onset of an event'**

The risk of the first onset of events of interest will be described in terms of probability of onset and confidence intervals with the Kaplan-Meier method. The date of origin is the date of inclusion in the research and the time to onset is the difference between the date of diagnosis of the event and the date of inclusion.

A graphic representation will be associated with the results of the analyses whenever possible.

- **Software used for the statistical analysis**

The analyses will be done using STATA® software for usual statistical analyses.

13.4 Population analysed

All patients included in the study, apart from patients who present at least one of the following conditions:

- patients who have never taken treatment,
- patients who have withdrawn their consent,
- patients included erroneously with contra-indications to the treatment of the study or without indication to be treated,

constitute the modified intent-to-treat (ITT) population and will be analysed.

Deceased patients and patients lost to follow-up will be included in the analysis until the time of their death/last news.

The decision to exclude a patient from the analysis is made jointly with the Scientific Advisory Board following the recommendations of the independent committee after the collection of the data by the Methodology and Management Centre, without knowing the evolution of the patient after inclusion.

13.5 Description of inclusions and follow-up

Patients pre-included and non-included in the research will be described and compared with included patients. The following will be presented :

- flow chart of the study
- the number of patients included, the inclusions curve (evolution of the number of patients included between the first and last inclusion)

- the theoretical number of visits corresponding to the number of patients included, the real number of visits and the relationship between the two (true number of visits/ theoretical number of visits) are presented for each group.
- the accumulated duration of follow-up is calculated (sum of the time each included patient participates (time between the inclusion date and the date of last news in the research) and the ratio of the accumulated duration of follow-up/expected accumulated duration is presented.

13.6 Characteristics of patients before the start of treatment

Respect of the inclusion criteria and the characteristics of patients pre-included and included in the analysis will be presented:

- respect, non respect, reasons of non-respect of the eligibility criteria (separating minor from major violations / with regard to the inclusion criteria)
- demographic characteristics
- clinical characteristics
- biological/immunological/virological characteristics
- treatment characteristics.

13.7 Study treatments

- number, duration, reasons for stopping treatment/ trial treatment strategy
- duration of follow-up under trial treatment / trial treatment strategy

13.8 Primary endpoint

The main endpoint of the trial is the Sustained Virological Response defined by undetectable plasma HCV RNA (< 12 IU/mL) 12 weeks after cessation of treatment with Grazoprevir / Elbasvir.

- Patients who will be lost to follow-up at PT12 visit and patients who will meet the criteria for interruption of treatment for virological failure will be considered as failures in the analysis of the main endpoint.
- Patients who undergo the treatment up to W8 and with undetectable HCV-RNA at PT12 will be considered as successful
- Patients who stop treatment prematurely for intolerance and with undetectable HCV-RNA at PT12 will be considered as successful.
- Patients who cannot undergo the PT12 visit and with undetectable HCV-RNA at W48 will be considered as successful.

13.9 Secondary endpoints

HCV virological assessment

- Median (+IQR) of log HCV RNA at W4, W8, PT4 and PT12, globally and according to genotypes.
- Rate of HCV RNA (<12 IU/mL) at W4, W8, PT4 and PT12, globally and according to genotypes.
- Odds ratio of factors associated with SVR12.
- Number of HCV (NS5A and NS3/4) resistance mutations in patients with virological failure.
- Rate of adherence and quality of life measured by specific scales using self questionnaires.
- Number of patients with positive HCV RNA per hundred months follow-up.

HIV virological assessment

- Median (+IQR) of log HIV RNA at D0 and PT12
- Median (+IQR) of CD4 and CD8 cell counts (absolute count, percentage and CD4/CD8 ratio) at D0 and PT12.
- Number of AIDS-defining clinical or biological events using CDC classification (95% CI).

Safety assessment

- Number of adverse clinical and biological events that occur during the treatment and up to 48 weeks after the end of the treatment (95% CI).

14 ETHICAL AND REGULATORY CONSIDERATIONS

14.1 Ethical considerations

This trial is performed in compliance with the ethical rules of the Helsinki declaration (64th General Meeting of the World Medical Association, Fortaleza, Bresil, October 2013).

14.2 Legal and regulatory considerations

This trial is also being conducted in conformity with the Public Health Code, as modified, notably, by Public Health Law no. 2004-806 of August 9, 2004 and its subsequent texts, for which the Decision of November 24, 2006 established the guidelines for Good Clinical Practice for biomedical research on drugs for human use, OR ICH Good Clinical Practice E6 – Step 5 (May 1996), as well as European Directive no. 2005/28/EC establishing the principles and detailed guidelines concerning the application of good clinical practice with regard to investigational drugs for human use, as well as the requirements for granting authorization to manufacture or import these drugs.

This trial is recorded in the Eudract database according to the article L1121.15 of the Public Health Code.

This trial/study is recorded in the website <http://clinicaltrials.gov/>.

The protocol, information sheet and consent form (Appendix B1) of this trial are approved by the CPP (Appendix B1).

The trial data will be recorded and be managed informatically by the sponsor. The sponsor has sent to the National Commission of Informatic and Liberty (CNIL) the commitment of compliance with the Reference Methodology MR-001 attesting that data management is compliant with the Reference Methodology requirements.

This trial is performed according to this present protocol. Except emergency situations needing the implementation of particular therapeutic evaluations, investigators or their representatives commit to respect the whole protocol, especially regarding the informed consent form collection and adverse events reporting and follow-up.

14.3 Information and consent

The consent of the person participating in the research must be signed before ANY clinical or paraclinical exams specific to the study are performed, and after the investigator has explained the objective, nature, constraints, and expected risks of the research. The information sheet and consent form will then be provided to the subject (see Appendix B1). The patient will have a period to reflect before making a decision. Each subject must be informed that his/her participation is voluntary and that he/she will be free, without needing to justify himself/herself, to withdraw at any time without any consequences on the quality of the care that his/her treating physician will continue to provide him/her with.

These provisions have been taken in conformity with article L. 1122-1 of the Public Health Code.

If the subject gives his/her consent to participate, the subject and the investigator will clearly write their first and last names and sign and date the consent form.

The different copies of the information and consent form are then divided as follows:

- The 1st sheet is kept by the study physician, even in the event that the patient withdraws during the research, in a safe place not accessible to third parties, for a duration of 15 years after the end of the research,
- The 2nd sheet of the signed consent form is given to the patient.

A copy of the consent form (on which the subject's identity has been blinded) is faxed to the MMC on the pre-enrollment day, accompanied by the pre-enrollment report (sheet in the investigator's file).

At the end of the enrollments or, at the latest, at the end of the research, a copy of the original sheet kept by the investigator will be made and returned to the CRA in charge of monitoring, in a tamper-proof envelope.

All amendments that modify patient treatment will be the subject of another information sheet and consent form, which will be collected in the same way as that cited above.

14.4 Data anonymisation/identification

All the collected patient data will be strictly confidential and anonymous. Only persons mandated by the sponsor and involved in the trial management and Health Authorities are able to access to medical files of patients, in order to check the accuracy of the collected data.

The patients will be identified as follows:

/ /
/ / / /
 Site n° Patient rank n° in the study

In order to respect patient anonymity, each subject will be allocated an anonymous code with 3 characters (n°investigation site and enrolment n° by site according to the chronological admission). Only the anonymous code of the subject will be reported in the CRF.

14.5 Protocol amendment

All substantial modifications to the protocol, i.e. those with a significant impact on all aspects of the research, notably on the protection of subjects, including with regard to their safety, the validity conditions of the research, and if applicable, the quality and safety of the investigational products, on the interpretation of scientific documents that support the course of the research or the procedures for conducting it, are the subject of a written amendment that will be submitted to the Scientific Advisory Board of the study, the sponsor, then the Ethics Committee (CPP), and to the competent authority (ANSM), according to national law.

After the favorable opinion of the Ethics Committee and the authorization of the ANSM, the amendment is signed by the coordinating investigator and the sponsor, and similarly for the protocol version approved by the ethics committee and the competent authority.

Non-substantial amendments are sent to the Ethics Committee and to the competent authority for informational purpose.

All protocol amendments must be notified to all investigators participating in the study. The investigators will respect their content.

14.6 Insurance

The sponsor of this study, has taken out a civil liability insurance policy with Biomedic insure compagny according to article L1121-10 of the Public Health Code. A copy of the insurance policy is attached in Appendix A3.

14.7 Archiving and storage of documents at the end of study

The documents and data regarding the research constitute essential documents that make up the permanent file during the research. These documents are to demonstrate that all of the stakeholders in the research respect the guidelines on good clinical practice, as well as the legislative and regulatory texts in force.

The following documents are under the investigator's responsibility during the regulatory duration of archiving:

- Within 15 years following the end of the study:

- The protocol and potential amendments
- A paper or electronic version of the CRFs
- Essential documents of subjects who signed an informed consent form
- Any other documents or posts relative to the study
- The copy of the informed consent forms signed by the subjects.

The following documents are under the responsibility of the MMC (mandated by the sponsor) or the sponsor:

- Within 15 years following the end of the study:

- The protocol and potential amendments
- A paper or electronic version of the CRFs
- Any other documents or posts relative to the study

15 MONITORING AND GOOD CLINICAL PRACTICE

15.1 General organisation

The monitoring is performed by the Clinical Research Associates (CRA) of the MMC mandated by the sponsor according to the applicable regulation and Good Clinical Practices recommendations.

At any time, the principal investigator and the MMC in charge of the trial may be contacted for any question related to the protocol, the conduct of the protocol, and procedures.

15.2 Monitoring of the investigational centres

The CRA mandated by the MMC support the investigator in the conduct of the trial. A general meeting with at least one representative of each participant site takes place before the beginning of the trial. Then several visits are planned during the trial and a last visit takes place at the end of trial.

Interim visits are performed to check that:

- The trial/study is conducted according the protocol and Good Clinical Practices, especially:
 - Informed consent forms are dated and signed by the investigator and by the subject, prior to any evaluations required by the protocol.
 - All the adverse events are reported.
- Data collected in the e-CRF is in compliance with the essential documents.

Patient data shall be collected according to confidentiality respect and professional secret.

The monitoring is performed on:

- 100% of the regulatory data: informed consent forms and adverse events
- 100% of the data reported in the CRF forms.

15.3 Audit - Inspection

An audit may be performed at any time by sponsor mandated and trial independent persons. The objective is to ensure trial quality, results availability and compliance with applicable laws and regulations.

An inspection may be performed for the same objectives, by competent authorities' representatives.

15.4 Scientific communication

Any written or oral communication of the trial must first receive the approval of the coordinating investigator and the Scientific Advisory Board, according to the contract between the sponsor and the pharmaceutical firm partner, especially informations procedures (time frame...) of transmission for information of abstracts and full-text articles.

Therefore, all the abstracts and full-text articles must be systematically sent to the sponsor, prior to any submission, for approval of compliance with publication rules, sponsor and MMC visibility, and for information to the pharmaceutical partner firm in the time frame defined in the contract.

The data analysis provided by the investigation sites is performed by the MMC. Therefore, a results report is submitted to the Scientific Advisory Board for approval and is used for the preparation of one or several publication(s). The final version must receive the approval of the Scientific Advisory Board.

Publication rules are as follows:

- The acronym of the study (SAHIV) must be mentioned in the study title and at the end of the authors.

The publication of the main results shall mention the name of the sponsor, all the investigators who perform enrollment or follow-up of subjects in the trial, the constitution of the Scientific Advisory Board and the pharmaceutical partner firm.

The Scientific Advisory Board alone is competent to decide whether to mention the name of any other person in publications relative to the study.

- Signature of the coordinating investigator, the methodologist, scientific experts according to the publication objective, involved investigation sites (one investigator by site) at prorata of the number of enrolled subjects and in the limit of the number of required authors by the daynal, then by those who significantly contributed to the conduct of the trial (to be detailed by the Scientific Committee at the redaction of abstracts and full-text).

- Study-group description:

Each participants of the trial shall be mentioned, especially investigation sites with investigator(s) who were especially involved, biologists, the MMC, IMEA as sponsor and MSD as financial partner ("Trial conduct with the support of MSD)...

16 CESSION OF DATA

Data collection and management are performed by the MMC.

Procedures for cession of all or a part of the study data base must be decided by the study sponsor and a written contract must be signed by both parties.

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18 APPENDICES

APPENDICES A

- 18.1 Appendix A1: Ethics Committee approval**
- 18.2 Appendix A2: ANSM authorization**
- 18.3 Appendix A3: Insurance form**
- 18.4 Appendix A4: Scale for cotation of adverse events seriousness**
- 18.5 Appendix A5: AIDS Classification (CDC 1993)**
- 18.6 Appendix A6: Self-adherence questionnaire**
- 18.7 Appendix A7: Quality of life Questionnaire**

APPENDICES B (LOOSE APPENDICES)

- 18.8 Appendix B1: Letter of information and consent form**
- 18.9 Appendix B2: Procedure of biobank constitution**
- 18.10 Appendix B3: Investigating sites**

18.1 APPENDIX A1: ETHICS COMMITTEE APPROVAL

CPP - Ile-de-France VI Groupe Hospitalier Pitié-Salpêtrière

CPP n° 23-16
EudraCT : 2016-001125-13

A Paris, le 7 juin 2016

Le comité a été saisi le : 14 mars 2016

d'une demande d'avis pour le projet de recherche intitulé :

« Essai thérapeutique de traitement court de l'infection aiguë par le virus de l'hépatite C de génotype 1 ou 4 chez les patients infectés par le VIH : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines » Etude pilote SAHIV

- . Protocole SAHIV du 30/5/16
- . Note d'information et formulaire de consentement du 30/5/16
- . Liste des investigateurs du 12/3/16

dont le promoteur est : **IMEA (Institut de Médecine et d'épidémiologie Appliquée - Fondation Léon M'Ba)**

dont le coordinateur est : **Docteur K. LACOMBE**

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

1^{er} juin 2016

Ont participé à la délibération :

Nathalie BRION - Thérapeute (T)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFAUCON - Représentant des associations agréées de malades (T)
Micheline DENANCE - Représentante des associations agréées d'usagers du système de santé (S)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
Marie GICQUEL-BENADE - Travailleur social (T)
Nathalie JOUNIAUX-DELBEZ - Psychologue hospitalier (S)
Christiane LOOTENS - Représentante des associations agréées de malades (S)
Marie-Cécile MASURE - Psychologue hospitalier (T)
Michèle MEUNIER-ROTIVAL - Chercheur en génétique (T)
Anne-Laure MORIN - Qualifiée en matière juridique (T)
Thang NGUYEN - Médecin généraliste (T)
Marie-Pascale SCHULLER - Pneumologue (S)
Sophie TEZENAS DU MONTCEL - Biostatisticien (T)

LE COMITÉ A ADOPTÉ LA DÉLIBÉRATION SUIVANTE : AVIS FAVORABLE

Motivation : Le comité a estimé que le rapport bénéfice/risque est acceptable pour les sujets participant à la recherche.

. Conformément à l'article R. 1123-28 du code de la santé publique, le présent avis devient caduque si la recherche n'a pas débuté dans un délai d'un an.



Le Président du CPP
Professeur Nathalie BRION

CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tél: 01 42 16 16 83 Fax: 01 42 16 27 15

CPP - Ile-de-France VI Groupe Hospitalier Pitié-Salpêtrière

Projet de recherche enregistré
Sous le n° 23-16
EudraCT : 2016-001125-13

A Paris, le 13 mars 2017

Documents soumis à l'approbation du comité :

- . **Amendement du 30/1/17**
- . **Note d'information et formulaire de consentement du 30/1/17**

Le comité a été saisi le : 10 février 2017

d'une demande d'avis pour les documents ci-dessus référencés relatifs au protocole intitulé :

« Essai thérapeutique de traitement court de l'infection aiguë par le virus de l'hépatite C de génotype 1 ou 4 chez les patients infectés par le VIH : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines » Etude pilote SAHIV

dont le promoteur est : **IMEA (Institut de Médecine et d'épidémiologie Appliquée
Fondation Léon M^{Ba})**

dont le coordinateur est : **Docteur K. LACOMBE**

Le comité a examiné les informations relatives à ce projet lors de sa séance du :

8 mars 2017

Ont participé à la délibération :

Kevin BIHAN - Pharmacien hospitalier (S)
Nathalie BRION - Thérapeute (T)
Laurent CAPELLE - Neurochirurgien (T)
Christophe DEMONFAUCON - Représentant des associations agréées de malades (T)
Marie-Hélène FIEVET - Pharmacien hospitalier (T)
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Marie-Pascale SCHULLER - Pneumologue (S)
Sophie TEZENAS DU MONTCEL - Biostatisticien (T)

LE COMITE A ADOPTE LA DELIBERATION SUIVANTE : AVIS FAVORABLE



Le Président du CPP
Professeur Nathalie BRION

**CPP IDF VI 47, Boulevard de l'Hôpital 75013 PARIS
Tél: 01 42 16 16 83 Fax: 01 42 16 27 15**

18.2 APPENDIX A2: ANSM AUTHORIZATION

07/04/2017 10:32

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ANSM/INFHEP

PAGE 01/01



AUTORISATION D'ESSAI CLINIQUE DE MEDICAMENT A USAGE HUMAIN

Nombre de pages : **1**
(incluant la page de garde)

Envoi par Télécopie

Date : **07 AVR. 2017**

Identifiants de l'essai clinique			
Titre	Etude pilote SAHIV - Essai thérapeutique de traitement court de l'infection aiguë par le virus de l'hépatite C de génotypes 1 ou 4 chez les patients infectés par le VIH : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines.		
Promoteur	IMEA (Institut de Médecine et d'Epidémiologie Appliquée)- Fondation Léon M'Ba	Réf. CPP	Non disponible
Réf. Promoteur	SAHIV-IMEA50 (SAHIV)	N° EudraCT	2016-001125-13
		Réf. ANSM	170061A-41
Expéditeur		Destinataire (demandeur ; nom / société / tél.)	
ANSM / Direction Produit INFHEP / Equipe Virologie- Thérapie génique		Hayette Rougier IMEA (Institut de Médecine et d'Epidémiologie Appliquée - Fondation Léon M'Ba) +331 49282405	
Dossier suivi par : Pauline Hologne Tél : 33 (0) 1 55 87 38 09 / Fax : 33 (0) 1 55 87 36 26 Mel : pauline.hologne@ansm.sante.fr		Fax	+331 49282595
CPP destinataire en copie	Ile-de-France VI (Paris-La-Pitié)	Fax	01.42.16.27.15
		Code	30

AEC

Vu le code de la santé publique et notamment l'article L. 1123-8, et les dispositions réglementaires prises pour son application, et vu le dossier de demande d'autorisation d'essai clinique adressé à l'Agence nationale de sécurité du médicament et des produits de santé (ANSM) ;

L'autorisation mentionnée à l'article L. 1123-8 du code de la santé publique est accordée pour l'essai clinique cité en objet.

Si vous ne recevez pas toutes les pages de cette télécopie, veuillez contacter le secrétariat de la Direction Produit INFHEP / Equipe Virologie-Thérapie génique au :
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Virologie et thérapie génique
Direction des vaccins, des médicaments anti-infectieux,
en hépato-gastro-entérologie, en dermatologie,
de thérapie génique et des maladies métaboliques rares

Nathalie MORGENSZTEJN

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18.3 APPENDIX A3: INSURANCE CERTIFICATE



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IMEA
FONDATION LEON M'BA
HOPITAL BICHAT CLAUDE BERNARD
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75018 PARIS

Le 10/04/2017

Objet : Assurance recherche impliquant la personne humaine

Police n° 05882401 160001 - Protocole SAHIV
Etude pilote SAHIV - Essai thérapeutique de traitement court de l'infection aigue par le virus de l'hépatite C de génotypes 1 ou 4 chez les patients infectés par le VIH : efficacité et tolérance de l'association combinée grazoprevir 100mg/elbasvir 50mg pendant 8 semaines

LETTRE DONT ACTE

Madame, Monsieur,

Nous accusons réception de votre demande concernant l'affaire citée en référence.

Par la présente, nous en prenons bonne note et vous donnons acte que :

- L'étude doit se dérouler du 18/04/2017 au 18/04/2019

Veuillez agréer, Madame, Monsieur, l'expression de nos sentiments distingués.

Maryvonne Sevestre

18.4 APPENDIX A4: INSERM-ANRS SCALE TO GRADE THE SEVERITY OF ADVERSE EVENTS

Version n° 1.0 4 November 2008

This severity scale is a working guide intended to harmonise evaluation and grading practices for symptomatology in ANRS biomedical research protocols.

In practice, the items evaluated are grouped according to the system taking the form of a non-exhaustive symptomatic table (and not a classification of pathologies). Our choices focus on the most frequently observed clinical and biological signs or those whose monitoring is essential to ensure the protection of the subjects participating in the research.

For abnormalities NOT found elsewhere on the Table, refer to the scale below to estimate grade of severity:

GRADE 1	Mild	Mild or transient discomfort, without limitation of normal daily activities; no medical intervention or corrective treatment required.
GRADE 2	Moderate	Mild to moderate limitation of normal daily activities; minimal medical intervention or corrective treatment required.
GRADE 3	Severe	Marked limitation of normal daily activities; medical intervention and corrective treatment required, possible hospitalisation.
GRADE 4	Life-threatening	Severe limitation of normal daily activities; medical intervention and corrective treatment required, almost always in a hospital setting.

Abbreviations used in the table:

ULN	: Upper Limit of Normal
RBC	: Red Blood Cells
FEV1	: Forced Expiratory Volume in one second
EMG	: Electromyogram
Prothrombin Time (%)	: Corresponds to Quick time (sec)
aPTT	: activated Partial Thromboplastin Time

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Please note that this scale was devised for use in HIV, HCV or HBV related pathologies.

ANRS scale to grade the severity of adverse events in adults (version no 1.0 4 November 2008)

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
HAEMATOLOGY					
1	Haemoglobin (g/dl)	8.0 – 9.4	7.0 – 7.99	6.5 – 6.99	< 6.5
2	Leucocytes (/mm ³)	3 000 – 3 900	2 000 – 2 999	1 000 – 1 999	< 1 000
3	Neutrophils (/mm ³)	1 000 – 1 500	750 – 999	500 – 749	< 500
4	Platelets (/mm ³)	75 000 – 99 000	50 000 – 74 999	20 000 – 49 999	<20 000 or generalized petechiae
5	Prothrombin Time (%)	/	45 – ≤ 70	20 – < 45	< 20
6	aPTT	1.0 – 1.66 x ULN	> 1.66 – 2.33 x ULN	> 2.33 – 3.0 x ULN	> 3.0 x ULN
BIOCHEMISTRY					
<i>Hepatic and pancreatic biochemistry</i>					
7	AST (SGOT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
8	ALT (SGPT) (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
➤ 9	GAMMA GT (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
10	Alkaline phosphatase (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
11	Hyperbilirubinaemia (µmol/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0x ULN
- 2	Amylaseaemia (UI/l) / Lipasaemia (UI/l)/ Pancreatitis	≥1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 3.0 x ULN with acute abdominal pain and/or imaging indicating acute pancreatitis.	> 3.0 x ULN with abdominal pain and signs of shock.
- 3	CPK (UI/l)	1.25 – 2.50 x ULN	> 2.50 – 5.0 x ULN	> 5.00 – 10.0 x ULN	> 10.0 x ULN
Lipid status					
14	Hypertriglyceridaemia (mmol/l)	/	4.50 – 8.59	8.60 – 13.70	> 13.70
15	Hypercholesterolaemia (mmol/l)	>ULN –7.75	>7.75 – 10.34	>10.34 – 12.92	>12.92

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Electrolytes / Evaluation of renal function / Metabolism					
16	Hyponatraemia (mEq/l)	130 – 135	123 – 129	116 – 122	<116
17	Hypernatraemia (mEq/l)	146 – 150	151 – 157	158 – 165	>165
18	Hypokalaemia (mEq/l)	3.2 – 3.4	2.8 – 3.1	2.5 – 2.7	<2.5
19	Hyperkalaemia (mEq/l)	5.6 – 6.0	6.1 – 6.5	6.6 – 7.0	>7.0
20	Bicarbonate (mEq/l or mmol/l)	20.0 – 24.0	15.0 – 19.99	10.0 – 14.99	< 10.0
21	Creatininaemia (µmol/l)	1.0 – 1.50 x ULN	> 1.50 – 3.0 x ULN	> 3.0 – 6.0 x ULN	6.0 x ULN or dialysis required
22	Blood Urea Nitrogen (UI/l)	1.25 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	> 10 x ULN
23	Hypocalcaemia (mmol/l)	1.95 – 2.10	1.75 – 1.94	1.50 – 1.74	< 1.50
24	Hypercalcaemia (mmol/l)	2.65 – 2.87	2.88 – 3.13	3.14 – 3.38	> 3.38
25	Hypophosphataemia (mg/dl)	2.0 – 2.4	1.5 – 1.9	1.0 – 1.4	<1.0
26	Hyperuricaemia (µmol/l)	1.25 – 2.0 x ULN	> 2.0 – 5.0 x ULN	> 5.0 – 10.0 x ULN	> 10.0 x ULN
27	Hypoglycaemia (mmol/l)	3.1 – 3.6	2.2 – 3.0	1.7 – 2.1	< 1.7
28	Hyperglycaemia (mmol/l)	6.1 – 7.0	> 7.0 – 16.5	> 16.5 without ketosis.	See diabetes Item no. 52 (grade 4)
29	Hyperlactataemia (mmol/l) (venous blood sample)	2.0 – 2.99*	3.0 – 3.99**	4.0 – 4.99**	≥ 5.0***
Urinalysis					
30	Proteinuria (dipstick)	+	++	≥ +++	Nephrotic syndrome
31	Haematuria.	≥ 80 RBC/µl (dipstick).	≥ 200 RBC/µl (dipstick).	Macroscopic with or without clots.	Obstructive or requiring a blood transfusion.

* Lactataemia – GRADE 1: a confirmatory test is necessary within 8 to 10 days ** Lactataemia – GRADE 2, 3: a confirmatory test is necessary within 24 hours. *** Lactataemia – GRADE 4: a confirmation test is necessary immediately.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
<i>Gastro-intestinal/hepatic/pancreatic abnormalities</i>					
32	Nausea.	Transient, normal diet.	Restricted diet for less than 3 days.	Restricted diet for more than 3 days.	Liquid only diet. Hospitalization required.
33	Vomiting.	Transient: 2 – 3 episodes / day or duration ≤ 1 week.	Repeated: 4 – 5 episodes / day or duration > 1 week.	Solid/liquid vomiting for 24 h. Orthostatic hypotension. Perfusion required.	Hospitalization for hypovolemic shock.
34	Diarrhoea.	Transient, 3 – 4 stools / day, diarrhoea ≤ 1 week.	Persistent, 5-7 stools / day, diarrhoea > 1 week.	> 7 stools/day or requiring perfusion. Bloody stools.	Hospitalization, Hypovolemic shock, perfusion.
35	Constipation.	/	Moderate abdominal pain, 78 h without stools. Treatment required.	Meteorism. Requiring disimpaction or hospital treatment.	Meteorism with vomiting or occlusion.
36	Dysphagia.	Mild discomfort when swallowing.	Difficulty in swallowing but food intake possible.	Inability to swallow solids.	Inability to swallow liquids, perfusion required.
37	Oesophagitis.	Pyrosis occurring less than once a week	Pyrosis occurring at least once a week but relieved by PPIs*	Pyrosis occurring at least once a week but not relieved by PPIs*	Food intolerance and vomiting

*PPIs: proton pump inhibitors

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Respiratory abnormalities					
38	Bronchospasm.	Transient, no treatment, FEV1 70 % - < 80 %.	Permanent, Improvement under bronchodilation FEV1 50 % - < 70 %.	Persistent under bronchodilation. FEV1 25 % - < 50 %.	Cyanosis, FEV1 < 25 % intubation.
39	Dyspnoea	Dyspnoea upon exertion.	Dyspnoea during normal daily activities.	Dyspnoea at rest.	Dyspnoea requiring respiratory assistance.
Muscular abnormalities					
40	Myalgia (excluding injection site).	Mild myalgia for less than 4 weeks. Not requiring analgesic treatment.	Presence of one of the following symptoms: 1 – Mild to moderate myalgia for more than 4 weeks and/or which may require treatment with level 1* analgesics. 2 – Predominance of difficulties upon exertion (difficulty in climbing stairs or rising from a sitting position). Can walk without assistance. Optional confirmation through the identification of biological (CPK), electromyographical (EMG) or histological (muscular biopsy) abnormalities.	Presence of one of the following symptoms: 1 – Moderate to severe myalgia for more than 4 weeks requiring treatment with level I/II* analgesics. 2 – Assistance required for walking and normal daily activities. Paraclinical confirmation recommended (CPK, EMG and/or muscular biopsy).	Presence of one of the following symptoms: 1 – Severe myalgia not related to exertion requiring treatment with level II/III* analgesics. 2 – Muscular weakness making walking impossible without assistance. 3 – Acute rhabdomyolysis with muscular necrosis and oedema. 4 – Acute rhabdomyolysis with electrolytic disturbances and renal insufficiency. Paraclinical confirmation required (biology, EMG and/or muscular biopsy).

* Level I analgesics

: Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs) ;

* Level II analgesics

: Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine) ;

* Level III analgesics

: Morphine.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Cardiovascular abnormalities					
41	Arterial hypertension.	Transient or permanent. Increased blood pressure \leq 20 mmHg and systolic BP 140-159 or diastolic BP 90-99.	Permanent. Increased blood pressure $>$ 20 mmHg and systolic BP 160-179 or diastolic BP 100-109.	Permanent. Systolic BP \geq 180 or diastolic BP $>$ 110	Malignant or accelerated arterial hypertension.
42	Orthostatic hypotension.	Decreased systolic blood pressure \leq 20 mmHg in orthostatic position. No treatment.	Decreased systolic blood pressure $>$ 20 mmHg, durable but corrected with liquid intake per os.	Perfusion required.	Hypovolemic shock requiring hospitalization.
43	Ventricular cardiac rhythm disorders.	/	Isolated ventricular extrasystoles, no treatment, symptomatic or asymptomatic.	Recurrent, persistent or symptomatic cardiac rhythm disorders. Treatment required.	Dysrhythmia requiring hospitalization.
44	Prolongation of the QT interval.	/	Man: $>$ 450 and $<$ 500 ms Woman: $>$ 470 and $<$ 500 ms	$>$ 500ms	$>$ 500 ms with clinical symptoms (ventricular rhythm disorders, syncope, torsade de pointes)
45	Cardiac ischaemia.	/	Atypical pain under exploration.	Appearance of angina upon exertion, controlled with treatment.	Myocardial infarction, unstable angina, preinfarction syndrome.
46	Pericarditis.	Chance discovery of a small effusion during ultrasound scan	Moderate effusion with few symptoms. No treatment or intervention deemed necessary for the time being.	Moderate or significant symptomatic effusion but without tamponade. Treatment required and hospitalization to be considered.	Tamponade. Hospitalization and intervention required.
47	Stroke.	/	/	Transient Ischemic Attack (regressive focal neurological syndrome within 24 h).	Cerebrovascular accident non-regressive within 24 h.
48	Peripheral arterial embolism.	/	/	/	Peripheral arterial embolism. Hospitalization. Adapted treatment.
49	Deep vein thrombosis and/or pulmonary	/	/	Deep vein thrombosis. Anticoagulant treatment. Hospitalization to be considered.	Pulmonary embolism. Adequate hospitalization and treatment.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
<i>Endocrine abnormalities</i>					
50	Hyperthyroidism.	Infraclinical hyperthyroidism. Low TSH. Normal free T3 and T4.	Moderate, non-complicated thyrotoxicosis. Treatment required.	Malignant exophthalmia. Cardiac arrhythmia. Myopathy.	Thyrotoxic crisis and/or cardiac insufficiency.
51	Hypothyroidism.	Infraclinical hypothyroidism. Increased TSH but <12 mU/l. Normal free T4.	Simple hypothyroidism without complications. Treatment required.	Severe hypothyroidism with multiple clinical symptoms. Urgent treatment. Hospitalization to be considered.	Myxoedematous coma.
52	Diabetes/hyperglycaemia.	Moderate fasting hyperglycaemia between 6.1 and 7 mmol/l. No immediate treatment required.	Fasting glycaemia: > 7 mmol/l. Special diet required, possibly supplemented with oral antidiabetics.	Fasting glycaemia: >16.5 mmol/l on an empty stomach, with or without clinical symptoms. Insulin therapy required.	Ketoacidosis or hyperosmolarity (>27.8 mmol/l without acidosis).
<i>Cutaneous abnormalities</i>					
53	Cutaneous and/or mucosal eruptions.	Erythema, Moderate pruritis.	Extended maculopapular eruption, with or without pruritis.	Extended papulovesicular or oozing eruption. Palpable purpura (suggestive of vasculitis). Polymorphous erythema. Small-size cutaneous or mucous ulcerations.	Any blistering cutaneous and/or mucosal lesions (Lyell or Stevens-Johnson). Febrile erythrodermia, whether or not associated with other signs indicative of hypersensitivity. Cutaneous necrosis requiring surgical excision.
54	Symptoms of immediate hypersensitivity, with or without cutaneous symptoms.	/	Acute localised urticaria.	Giant urticaria, Quincke's oedema.	Anaphylactic shock.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Neurological abnormalities					
55	Wakefulness / sleep disorders.	Minor attention and concentration impairment.	Diurnal somnolence and/or difficulty falling asleep and/or night time awakening, mental activity decreased, obtundation.	Sleep-wake cycle modification or insomnia requiring treatment or change in dream content. Obvious confusional syndrome with temporal disorientation.	Sleep-wake cycle disorganisation not responding to treatment. Dreamlike confusional syndrome, coma and/or convulsion.
56	Psychiatric disorders.	Minor anxiety.	Anxiety requiring treatment or moderate depression.	Major anxiety or confirmed depressive episode requiring treatment.	Acute psychosis requiring hospitalization, including suicidal ideation, manic state, hallucinatory delusion.
57	Cephalalgia.	Intermittent, no treatment.	Requiring level I* analgesics.	Requiring at least level II* analgesics.	Not responsive to level III* analgesics.
58	Paraesthesia.	Paraesthesia, mild pain, no treatment.	Paresthesia, permanent pain of moderate intensity, requiring level I* analgesics.	Paraesthesia, permanent pain of severe intensity, requiring at least level II* analgesics.	Unbearable pain resulting in disability, restricted activity despite administration of level III* analgesics.
59	Motor deficiency.	Subjective feeling of weakness without objective impairment, no reflex changes.	Distal motor deficiency, moderate functional impairment or reflex changes.	Marked motor deficiency interfering with normal daily activities.	Confined to bed or a wheelchair because of motor deficiency.
60	Difficulty controlling movement.	Occasional clumsiness, mild coordination difficulties.	Tremor or dyskinesia or dysmetria, or dysarthria, moderate limitation of normal daily activities.	Upper or lower limbs ataxia or abnormal movements, limitation of normal daily activities.	Inability to stand up. Total dependence.
61	Sensory loss.	Mild sensory loss, regardless of mode and distribution (focal or symmetric).	Moderate sensory loss.	Severe sensory loss.	Extensive sensory loss involving the trunk and four limbs.

* Level I analgesics : Peripheral analgesics (paracetamol and/or salicylics or non-steroid anti-inflammatory drugs) ;

* Level II analgesics : Weak opiates (codeine, dextropropoxyphene), morphinic agonists-antagonists (buprenorphine, nalbuphine) ;

* Level III analgesics : Morphine.

GRADES		GRADE 1 Mild	GRADE 2 Moderate	GRADE 3 Severe	GRADE 4 Life-threatening
Miscellaneous					
62	Fever (oral temperature, °C) for more than 12 h.	37.7 – 38.9	39 – 39.5	39.6 – 40.5	> 40.5
63	Renal colic.	Spontaneous regression of symptoms. Pain not requiring treatment.	Colic requiring medical treatment.	Obstructive syndrome, does not disappear spontaneously.	/
64	Fatigue.	Normal daily activities reduced by less than 25% for less than 48 h.	Normal daily activities reduced by 25 – 50 % for more than 48 h.	Normal daily activities reduced by more than 50%, cannot work for more than 48 h.	Unable to care for self. Assistance required for normal daily activities.
65	Arthritis / Arthralgia.	Arthralgia.	Arthralgia, with or without articular effusion or with moderate functional impairment.	Marked arthritis with or without effusion or with severe functional impairment.	/
66	Ocular disorders.	Conjunctival hyperaemia.	Moderate pain. Conjunctivitis.	Decreased visual acuity. Uveitis. Severe pain. Glaucoma.	/

18.5 APPENDIX A5: AIDS CLASSIFICATION (CDC 1993)

Catégorie A :

Un ou plusieurs des critères listés ci-dessous chez un adulte ou un adolescent infecté par le VIH, s'il n'existe aucun des critères des catégories B ou C :

- infection VIH asymptomatique
- lymphadénopathie persistante généralisée
- primo-infection symptomatique

Catégorie B :

Manifestations cliniques chez un adulte ou un adolescent infecté par le VIH, ne faisant pas partie de la catégorie C et qui répondent au moins à l'une des conditions suivantes :

- Elles sont liées au VIH ou indicatives d'un déficit immunitaire.
- Elles ont une évolution clinique ou une prise en charge thérapeutique compliquée par l'infection VIH.

Les pathologies suivantes font partie de la catégorie B, la liste n'est pas limitative.

- angiomatose bacillaire
- candidose oro-pharyngée récidivante
- candidose vaginale, persistante, fréquente, ou répondant mal au traitement
- dysplasie du col (modérée ou grave), carcinome in situ
- syndrome constitutionnel : fièvre (= 38,5°C) ou diarrhée supérieure à 1 mois
- leucoplasie chevelue de la langue
- zona récurrent ou envahissant plus d'un dermatome
- purpura thrombocytopénique idiopathique
- salpingite, en particulier lors de complications par abcès tubo-ovariens
- neuropathie périphérique

Catégorie C :

Cette catégorie correspond à la définition du stade SIDA chez l'adulte. Lorsqu'un sujet a présenté une des pathologies de cette liste, il est classé définitivement dans la catégorie C :

- candidose bronchique, trachéale ou pulmonaire
- candidose de l'œsophage
- cancer invasif du col
- coccidioïdomycose, disséminée ou extra-pulmonaire
- cryptococcose extra-pulmonaire
- cryptosporidiose intestinale supérieure à 1 mois
- infection à CMV (autre que foie, rate, ganglions)
- rétinite à CMV (avec altération de la vision)
- encéphalopathie due au VIH
- infection herpétique, ulcères chroniques supérieurs à 1 mois, ou bronchique, pulmonaire ou œsophagienne
- histoplasiose disséminée ou extra-pulmonaire
- isosporidiose intestinale chronique (>1 mois)
- sarcome de Kaposi
- lymphome de Burkitt
- lymphome immunoblastique
- lymphome cérébral primitif
- infection à Mycobacterium avium ou kansasii, disséminée ou extra-pulmonaire
- infection à Mycobacterium tuberculosis, quel que soit le site (pulmonaire ou extra-pulmonaire)

- infection à mycobactérie, identifiée ou non, disséminée ou extrapulmonaire
- pneumonie à Pneumocystis carinii
- pneumopathie bactérienne récidivante
- leuco-encéphalopathie multifocale progressive
- septicémie à salmonelle non typhi récurrente
- syndrome cachectique dû au VIH
- toxoplasmose cérébrale

18.6 APPENDIX A6: SELF-ADHERENCE QUESTIONNAIRE**AUTO-QUESTIONNAIRE D'OBSERVANCE**

Madame, Monsieur,

Vous participez à l'essai **SAHIV** et nous tenons à vous en remercier.

Afin de mieux connaître les difficultés auxquelles vous êtes confronté(e) pour vos médicaments antirétroviraux contre le VIH/sida et vos médicaments contre l'hépatite C, nous vous demandons de nous indiquer comment vous avez **réellement pris ces médicaments**.

Les questions concernent 3 périodes :

les 4 derniers jours,
le week-end dernier (qui peut être inclus dans les 4 derniers jours),
les 4 dernières semaines.

Vos réponses à ce questionnaire seront directement transmises au centre qui les analysera et ne seront pas communiquées à l'équipe qui vous suit à l'hôpital.

VOTRE TRAITEMENT CONTRE LE VIH

A. Au cours des 4 derniers jours, vous est-il arrivé de manquer la prise de tout (ou d'une partie) de vos médicaments antirétroviraux ?

Cochez la réponse exacte :

- Oui, 1 jour
- Oui, 2 jours
- Oui, 3 jours
- Oui, 4 jours
- Non, jamais

B. Au cours des 4 derniers jours, vous est-il arrivé de prendre la dose journalière d'un (ou de plusieurs) des médicaments de votre traitement antirétroviral en une seule fois ?

Cochez la réponse exacte :

- Non, jamais
- Oui, une fois
- Oui, plusieurs fois
- Oui, toujours car mon traitement se prend en une seule fois

C. Dans le tableau ci-dessous, cochez chacun des médicaments antirétroviraux qui vous sont prescrits, le nombre de prises et le nombre de comprimés (ou de gélules, cuillères, verres) prescrits par jour, ainsi que le nombre de comprimés (ou de gélules, cuillères, verres) NON pris durant les 4 derniers jours :

Nom du médicament antirétroviral Précisez (EN MAJUSCULES)	Nombres de prises journalières	Nombre de comprimés (gélules, etc.) prescrits par jour	Combien de comprimés (gélules, etc.) avez-vous manqué ?			
			<i>Ecrivez "0" si vous avez tout pris</i>			
			HIER	AVANT-HIER	IL Y A 3 JOURS	IL Y A 4 JOURS
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					
	1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/>					

D. Avez-vous oublié de prendre l'un de vos médicaments antirétroviraux le week-end dernier (samedi ou dimanche dernier) ?

Cochez la réponse exacte :

- Oui
 Non
 Je ne sais pas

E. Au cours des 4 dernières semaines, vous avez : (cochez une seule case) :

- Respecté strictement toutes les prises (rythme et quantités)
 Respecté globalement les prises hormis quelques écarts
 Souvent modifié les prises
 Rarement respecté les prises
 Arrêté tout traitement à la demande du médecin
 Arrêté tout traitement de votre propre initiative
 Arrêté tout traitement pour d'autres raisons

Ne pas répondre à la question suivante

Précisez,

F. Au cours des 4 dernières semaines, si vous avez arrêté vos médicaments antirétroviraux, à quand remonte la dernière prise ?

Cochez la réponse exacte :

- À moins d'une semaine (1 à 7 jours)
 Entre 1 et 2 semaines (8 à 14 jours)
 Entre 2 et 4 semaines (15 à 28 jours)

VOTRE TRAITEMENT CONTRE L'HEPATITE C

A. Au cours des 4 derniers jours, vous est-il arrivé de manquer la prise de tout (ou d'une partie) de votre traitement par Grazoprevir / Elbasvir ?

Cochez la réponse exacte :

- Oui, 1 jour
- Oui, 2 jours
- Oui, 3 jours
- Oui, 4 jours
- Non, jamais

B. Dans le tableau ci-dessous, cochez pour votre traitement par Grazoprevir / Elbasvir le nombre de comprimés NON pris durant les 4 derniers jours :

Nombre de comprimés <u>NON</u> pris			
<i>Ecrivez "0" si vous avez pris tous vos comprimés.</i>			
Hier	Avant-hier	Il y a 3 jours	Il y a 4 jours

C. Avez-vous oublié de prendre votre traitement par Grazoprevir / Elbasvir le week-end dernier (samedi ou dimanche dernier) ?

Cochez la réponse exacte :

- Oui
- Non
- Je ne sais pas

D. Au cours des 4 dernières semaines, pour votre traitement par Grazoprevir / Elbasvir, vous avez :
(cochez une seule case) :

- Respecté strictement toutes les prises (rythme et quantités)
- Respecté globalement les prises hormis quelques écarts
- Souvent modifié les prises
- Rarement respecté les prises
- Arrêté tout traitement à la demande du médecin
- Arrêté tout traitement de votre propre initiative
- Arrêté tout traitement pour d'autres raisons

Ne pas répondre à la question suivante

Précisez, _____

E. Au cours des 4 dernières semaines, si vous avez arrêté votre traitement par Grazoprevir / Elbasvir, à quand remonte la dernière prise ?

Cochez la réponse exacte :

- À moins d'une semaine (1 à 7 jours)
- Entre 1 et 2 semaines (8 à 14 jours)
- Entre 2 et 4 semaines (15 à 28 jours)

Merci d'avoir rempli ce questionnaire.

18.7 APPENDIX A7: QUALITY OF LIFE QUESTIONNAIRE

QUESTIONNAIRE DE QUALITE DE VIE			
1	Dans l'ensemble, pensez-vous que votre santé est :		
	<input type="checkbox"/> 1	Excellente	
	<input type="checkbox"/> 2	Très bonne	
	<input type="checkbox"/> 3	Bonne	
	<input type="checkbox"/> 4	Médiocre	
	<input type="checkbox"/> 5	Mauvaise	
2	Voici une liste d'activités que vous pouvez avoir à faire dans votre vie de tous les jours : (Pour chacune d'entre elles indiquez si vous êtes gêné(e) en raison de votre état de santé actuel)		
	- Efforts physiques modérés tels que déplacer une table, passer l'aspirateur, jouer aux boules	<input type="checkbox"/> 1	Oui, beaucoup
		<input type="checkbox"/> 2	Oui, un peu
		<input type="checkbox"/> 3	Non, pas du tout
	- Monter plusieurs étages par l'escalier	<input type="checkbox"/> 1	Oui, beaucoup
		<input type="checkbox"/> 2	Oui, un peu
<input type="checkbox"/> 3		Non, pas du tout	
3	Au cours des 4 dernières semaines, et en raison de votre état physique :		
	- Avez-vous fait moins de choses que ce que vous auriez souhaité ?	<input type="checkbox"/> 1	En permanence
		<input type="checkbox"/> 2	Très souvent
		<input type="checkbox"/> 3	Quelquefois
		<input type="checkbox"/> 4	Rarement
		<input type="checkbox"/> 5	Jamais
	- Avez-vous dû arrêter de faire certaines choses ?	<input type="checkbox"/> 1	En permanence
		<input type="checkbox"/> 2	Très souvent
		<input type="checkbox"/> 3	Quelquefois
		<input type="checkbox"/> 4	Rarement
<input type="checkbox"/> 5		Jamais	
4	Au cours des 4 dernières semaines, et en raison de votre état émotionnel (vous sentir triste, nerveux(se) ou déprimé(e)) :		
	- Avez-vous fait moins de choses que ce que vous auriez souhaité ?	<input type="checkbox"/> 1	En permanence
		<input type="checkbox"/> 2	Très souvent
		<input type="checkbox"/> 3	Quelquefois
		<input type="checkbox"/> 4	Rarement
		<input type="checkbox"/> 5	Jamais
	- Avez-vous eu des difficultés à faire ce que vous aviez à faire avec autant de soin et d'attention ?	<input type="checkbox"/> 1	En permanence
		<input type="checkbox"/> 2	Très souvent
		<input type="checkbox"/> 3	Quelquefois
		<input type="checkbox"/> 4	Rarement
<input type="checkbox"/> 5		Jamais	
5	Au cours des 4 dernières semaines, dans quelle mesure vos douleurs physiques vous ont-elles gêné(e) dans votre travail ou vos activités domestiques ?		
	<input type="checkbox"/> 1	Pas du tout	
	<input type="checkbox"/> 2	Un petit peu	
	<input type="checkbox"/> 3	Moyennement	
	<input type="checkbox"/> 4	Beaucoup	
	<input type="checkbox"/> 5	Enormément	

6	Au cours des 4 dernières semaines, y a-t-il eu des moments où votre état de santé, physique ou émotionnel, vous a gêné(e) dans votre vie et vos relations avec les autres, votre famille, vos amis, vos connaissances ?					
					<input type="checkbox"/> 1	En permanence
					<input type="checkbox"/> 2	Très souvent
					<input type="checkbox"/> 3	Quelquefois
					<input type="checkbox"/> 4	Rarement
				<input type="checkbox"/> 5	Jamais	
7	Les questions qui suivent portent sur comment vous vous êtes senti(e) au cours des 4 dernières semaines.					
	Pour chaque question merci d'indiquer la réponse qui vous semble la plus appropriée.					
	Au cours des 4 dernières semaines, y a-t-il eu des moments où :					
		1. En permanence	2. Très souvent	3. Quelquefois	4. Rarement	5. Jamais
	Vous vous êtes senti(e) calme et détendu(e)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Vous vous êtes senti(e) débordant(e) d'énergie ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Vous vous êtes senti(e) triste et abattu(e) ?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

Merci d'avoir rempli ce questionnaire.

18.8 APPENDIX B1 (LOOSE): LETTER OF INFORMATION AND CONSENT FORM

⇒ *See investigator's file*

18.9 APPENDIX B2 (LOOSE): PROCEDURE FOR BIOBANK CONSTITUTION

⇒ *See investigator's file*

18.10 APPENDIX B3 (LOOSE): INVESTIGATOR SITES

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