CONSENT DOCUMENT

STREAGER : A Phase 3, Global, Multicenter, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis.

Protocol N° : 2016-001363-37

- **Promotor :**

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You are invited to participate in a research study. You will find in this document the information which will be useful for you to decide if you wish to participate or not in this research. Your participation is entirely free and voluntary. You have time to reflect before making your decision; therefore, take the time to read this information document carefully and to ask the study doctor and his team members any questions you wish. You should not sign this consent form before you have understood all of the information presented in the following pages, or before you have obtained a satisfactory answer to all of the questions you have about this research.

If you agree to participate in this biomedical research, you and your doctor must date and sign this document which includes the consent form in two copies before any procedure intended for research. You will keep one copy and your doctor will keep the second in your medical file.

About This Study

Hepatitis C is a disease caused by a virus (known as HCV) that has infected your liver. A virus is a very small organism that attaches itself to your healthy cells and causes them to make more viruses. This leads to inflammation of healthy cells. Over time, this can generate scar tissue (fibrosis) and cirrhosis in the liver, which will impair liver function. Over time, if the virus is left untreated, people with a chronic hepatitis C virus infection may develop liver cancer and / or need a liver transplant.

Your body is trying to fight viruses, but the hepatitis C virus is very strong. In some people, the virus will transform to cope with your body's defenses. It can also change and become resistant to drugs used to kill the virus (this is called "resistance").

The objective of this study is to evaluate the effectiveness of the Elbasvir / Grazoprevir (EBV / GZR) combination, for 8 weeks in treatment-naïve patients, genotype 1b, with non severe fibrosis. This combination has been approved for marketing in Europe for a treatment period of 12 weeks and in the United States and Canada for a treatment period of 8 weeks.
120 patients will participate in this study in 14 centers in France.

Your participation in this research will last approximately 36 weeks.

There may be several reasons why you could not participate in this study. Your doctor or a member of their team will discuss this with you.
In fact, there are treatments that are contraindicated in the present study. These will be provided to you on a patient identification card indicating that you are participating in a clinical trial. This card will include information on taking the study treatment, contraindicated medications and contact details for the study doctor. You will need to keep this card with you throughout the study. If you need to take any treatment or medication during the study, you should consult your doctor with your patient card. In general, this identification card should be shown to any healthcare professional if necessary.

7 TRIAL FLOW CHART

Visit No.	1	2	3	4	5	6	7	8		
Study Period		Treatment Weeks				Follow-Up Wks			Unscheduled	
STUDY PROCEDURES	Scr	Day 1[4]	2	4	8	FU4	FU 12	FU 24	Unsched/ Viral Fail Conf Visit	Early Discon Visit
ADMINISTRATIVE PROCEDURES										
Informed Consent	x									
Inclusion/Exclusion Criteria	x									
Medical History	x									
Prior and Con-med Review	x	x	x	x	x	x	X	X	x	x
DRUG ADMINISTRATION										
EBV/GZR dispensation[5]		x								
EBV/GZR compliance[5]			x	x	x					
CLINICAL SAFETY EVALUATIONS										
Physical Examination[1]	x	x			x					x
Weight	x	x	x	x	x	x	x	x	x	x
Height	x									
Fibroscan®	x									
Vital Signs	x	x	x	x	x	x	x	x	x	x
Confirmation of Birth Control	x	x	x	x	x	x	x	x	x	x
Review (Serious) Adverse Events[2]	x	x	x	x	x	x	x	x	x	x
LABORATORY SAFETY EVALUATIONS										
Coagulation	x	x			x				x	x
Fibrotest®	x									
Chemistry & Hematology	x	x	x	x	x	x			x	x
HCV, HIV, HBV testing	x									
HCV Genotyping	x									
HCV RNA Level	x	x	x	x	x	x	x	x	x	X[6]
Urine Analysis	x									
Urine Pregnancy Test (females of child bearing potential only)[3]	x	x		x	x	x	x	x	x	x

A comprehensive PE will be done at screening and baseline (Day 1). For all other visits focused PE will be conducted if necessary

[2] Review of Adverse Events should include collecting serious adverse events and Events of Clinical Interest throughout the study, and collecting all adverse events Day 1(post-dose) through 14 days following the last dose of study drug. Adverse events occurring prior to study drug administration or after study drug discontinuation, as a result of a protocol-specified procedure or intervention, should also be reported.

[3] When study visits are spaced more than one month apart in the follow-up period, urine pregnancy test kits will be dispensed to female subjects of childbearing potential so that **monthly** pregnancy testing can continue for 6 months post dosing. The test results must be provided to the investigator and/or site personnel. Subjects should be instructed to contact the investigator and/or site personnel immediately if the result of the self-pregnancy test is positive.

[4] Procedures on Day 1 should be performed prior to the first morning dose unless specified otherwise.

[5] EBV/GZR will be provided at the baseline visit.

[6] If HCV RNA is collected during viral failure confirmation visit and the subject is confirmed viral failure during therapy (i.e. breakthrough/rebound), then the sample collection for HCV RNA is not needed for the early discontinuation visit

What will you be asked to do?

If you participate in this biomedical research, you will need to:

• Go to the study doctor about 8 times.

• You will receive a patient identification card indicating that you are participating in a clinical trial. This card will carry the coordinates of the study center so that you can use them in an emergency.

• Keep a record of the date, time and number of tablets of the study medication you take each day.

• If you are a woman of childbearing potential, you must agree to use two authorized methods of contraception at least 2 weeks before the start of the study, to continue for the duration of the study, and then for at least 6 months after administration of the last dose of study drug. The doctor or study staff will tell you what contraceptive methods are acceptable.

• If you are a man whose partner is of childbearing age, you must agree to use two authorized methods of contraception at least 2 weeks before the start of the study, to continue for the duration of the study, and then for at least 6 months after the last dose of study drug is administered. The doctor or study staff will tell you what contraceptive methods are acceptable.

• To determine your fibrosis rate, you must do a FibroScan at the selection visit.

• Do not eat grapefruit and do not drink grapefruit juice during the treatment period. The doctor or study staff will discuss this with you in more detail.

• Take the study medication (s) as directed: Elbasvir and Grazoprevir, oral, once a day, in the morning, with or without food.

When you start the study, you will be asked to take the study medications for 8 weeks. At the end of the study treatment, you will be asked to go to the center for a follow-up of up to 24 weeks.

What will happen during study visits?

During the study visits, the investigator or a member of his team may perform some or all of the following acts to assess the effect of the study drug and / or to monitor your health.

• Deliver study drug and recommendations.
• Review your medical history.
• Review the medications you have taken in the past or are currently taking.
• Perform a clinical examination.
• Check your vital signs (including: blood pressure, heart rate, temperature).
• Measure your height and weight.

• Review the study treatment and count pill.
  Review the adverse event you may have had.
• Confirm that you are using acceptable contraceptive methods.
• Perform a blood and urine sample.
    - o For routine laboratory analyzes.
    - o Assess the levels of HCV in the blood.
    - o Perform an HIV test and a hepatitis B test.

o Perform a pregnancy test if you are a woman of childbearing potential.

What effects can these analyzes or examinations have?

The analyzes or examinations listed below may possibly cause discomfort or risks which may include:

• Blood samples: drawing blood from your arm can cause pain, bruising, dizziness and rarely, infection.

• FibroTest: A FibroTest is a blood test, and therefore requires a blood sample to be taken by a healthcare professional, who will then send it to a laboratory for analysis. The main risks associated with blood tests are bruising and pain around the point where the needle enters.

• FibroScan: Ultrasonic pulse elastography (also known by its brand name, FibroScan) is a form of ultrasound. The procedure is therefore very similar to an ultrasound procedure and allows healthcare professionals to measure fibrosis in the liver non-invasively. An ultrasound probe is placed on the surface of the skin of the rib cage. The probe emits a sound wave that travels through the liver and returns an echo to the probe. A computer calculates the speed and strength of the echo to measure the elasticity or stiffness of the liver. There is usually no pain or discomfort associated with the procedure.

ABOUT THE STUDY DRUG

EBV / GZR is a combination of two direct acting antiviral agents with distinct mechanisms of action and non-overlapping resistance profiles thus allowing direct targeting of hepatitis C virus at different life cycle and multiplication stages of the virus.

The Elbasvir molecule is an inhibitor of the HCV NS5A protein, which is essential for viral RNA replication and virion assembly.Grazoprevir is an inhibitor of NS3 / 4A proteases which are necessary and essential for virus replication.

Drug	Dose/Potency	Dose Frequency	Route of Administration	Regimen/ Treatment Period	Use
Grazoprevir(GZR)°	100 mg	QD	Oral	8 Weeks	Experimental
Elbasvir (EBV)	50 mg	QD	Oral	8 Weeks	Experimental

The EBV / GZR combination is a new drug that has been tested by Merck & Co., Inc. for the possible treatment of hepatitis C virus (HCV) infection.

In the United States, Canada and Europe, this combination has marketing authorization for the treatment of hepatitis C virus genotype 1, 3 or 4:

Without Ribavirin:

• For genotypes 1 or 4 naïve to any treatment or already treated with a bitherapy based on interferon and relapsing, the EBV / GZR combination is then prescribed for 12 weeks.

• For genotypes 1 already treated by a protease inhibitor with an interferon-based dual therapy, with relapse to treatment. EBV / GZR is then prescribed for a period of 12 weeks.

For genotypes 1b, naive of any treatment and not cirrhotic. The duration of treatment with EBV / GZR is then 8 weeks (according to AMM United States and Canada) and 12 weeks (according to European AMM).

• For genotypes 1b, relapsing to dual interferon therapy or triple therapy including a protease inhibitor and interferon therapy. The EBV / GZR treatment is then prescribed for 12 weeks.

With Ribavirin:

• For genotypes 1a having received dual or triple interferon therapy plus or minus a protease inhibitor and having no response to this treatment. Prescription of EBV / GZR takes 16 weeks.

• For genotypes 4 which have already undergone dual therapy with interferon with no response. The duration of treatment with EBV / GZR is also 16 weeks.

With Sofosbuvir:

• For genotypes 3 naïve to any treatment. EBV / GZR is then specified for 12 weeks.

Adverse events of EBV / GZR treatment

Adverse events occurring between 1 and 5% in subjects with chronic hepatitis C and treated with EBV / GZR for 12 weeks in phase II and III clinical studies.

Adverse events
Abdominal pain (2%), constipation (2%), diahrea (3%), dry skin (1%), nausea (1%)
Asthenia
Decreased appetite (2%)
Muscular pain (2%)
Dizziness (2%)
Anxiety (1%), depressive syndrome (1%), insomnia (3%), irritability (2%)
Hair loss (1%), itchy skin (1%)

Most of these effects were mild to moderate in intensity and short.
During treatment with EBV / GZR, serum total bilirubin (a substance in your blood that is produced by the body and excreted by the liver) and / or transaminases has increased in some patients and has generally decreased over time.
There may be other adverse event which are not yet known. These can include serious adverse event, or life threatening. It is important that you tell the study staff about any side effects you may have, even if you think they are not associated with the study medicine.
We will provide you with important information in a timely manner that may affect your decision to continue participating in the study.
If you are a patient infected with HCV, it is possible that your virus may develop resistance to treatment with EBV / GZR. Resistance means the treatment may not be effective in treating your virus; a change in the effectiveness of other drugs currently used to treat hepatitis C is not expected, however, no one knows if this resistance will cause your virus to respond less well to new treatments in the future.

Are there other risks?

There are other less common adverse events reported with using this study drugs that your doctor or a member of their team can discuss with you.
There may be other adverse events still unknown to date. You will be notified as soon as possible of any new event occurring during the study which could influence your willingness to participate in it. A new information document and a new consent form will then be given to you as soon as possible.

Are there any risks in the event of pregnancy?

It is not known whether the study drug can affect the development of the embryo, fetus or infant.
<u>Risks if you are a woman</u>
If you are pregnant or wish to become pregnant or plan to donate eggs or if you are breast-feeding, you should not be included in the study. A urine or blood pregnancy test will be done at the start and during the study if you are likely to be pregnant.

If you are likely to be pregnant and do not want to be abstinent (no sex), you must use two effective methods of contraception for at least two weeks before the start of the study, during the study and for a duration 6 months or more after your last dose of study medication. The following contraceptive methods are allowed during the study:

• Intrauterine device (IUD)
• Diaphragm with spermicide
• Contraceptive sponge
• Female condom
• Male condom with spermicide
• Male partner having had a vasectomy
• Hormonal contraceptives (such as birth control pills, patches, injectables).

If you are pregnant during the study or within 14 days after completing the study, you must immediately notify the study doctor. The study drug will be stopped and you will be released from the study.

Risks for your partner if you are a man

There may be risks if you are a man and your partner is pregnant or wants to be pregnant. If you are a man and your partner can have a baby and you do not want to be abstinent (no sex), you and your partner must use two effective methods of contraception for at least two weeks before the start of treatment. study, during the study and for a minimum of 6 months after your last dose of the study medication (or 7 months if you are taking ribavirin). The following contraceptive methods are allowed during the study:

• Intrauterine device (IUD)
• Diaphragm with spermicide
• Contraceptive sponge
• Female condom
• Male condom with spermicide
• Vasectomy
• Hormonal contraceptives (such as birth control pills, patches, injectable contraceptives)

If your partner is pregnant during the study or within 14 days of completing the study, you should tell the study doctor immediately. You must also agree not to donate sperm during the study and for 6 months after your last dose of study medicine.

OTHER INFORMATION YOU SHOULD KNOW

If you are harmed by the study drug, who will pay the doctor and hospital costs?

In the event of damage to your health resulting directly from taking the study drug, or from the implementation of a procedure in accordance with the study protocol, the Sponsor will bear all the costs related to medical treatment, unless he can prove that the damage is not attributable to his fault or that of any party involved; for this purpose, he has taken out an insurance policy intended to cover these costs, in accordance with article L.1121-10 of the Public Health Code (SHAM contract 147161). You will not be asked to assign or waive your legal rights to the institution, investigator or sponsor for any liability for negligence.

What benefits can you expect from your participation in this study?

If the study drug is effective, you may benefit. The study drug may not work and you may not benefit from it. However, the information from this study may help others in the future.

Will you receive financial compensation per visit to cover any costs related to the study?

You will not receive any financial compensation for your participation in this study.
Your transport costs to get to the consultations provided for in the protocol or the expenses incurred by your participation in the study will be covered on presentation of supporting documents.

Will you have any costs associated with your participation in the study?

Some tests or treatments used in this study may be part of your standard treatment. You would have them even if you did not participate in this study.
The cost of this standard treatment will be covered by your health insurance plan.

If you agree to participate in this study, the study drugs will be provided to you free of charge. Consultations and examinations carried out as part of the study will also be free.

Are there other options if you decide not to participate in this study?

If you decide not to participate in this study, or if you leave the study, the investigator can advise you of other treatments.
Alternative therapies for treating your hepatitis C genotype 1b (GT-1b) with non severe fibrosis include bitherapy with interferon and ribavirin or bitherapy with direct antivirals as recommended.

If you have any questions about these alternative treatments and their potential benefits and risks, ask the study doctor for more information. You do not have to participate in this study for your hepatitis C to be treated.

What will happen if you choose to stop your participation to the study?

Your decision to participate in this study is entirely voluntary. You can choose to withdraw from the study at any time by informing the study doctor without any penalty or loss of the benefits to which you are entitled.
If you choose to stop taking the study treatment, please tell the study doctor or a member of their team so that it can be done safely.
If at some point you plan to withdraw from the study, you can decide whether you are willing to continue providing information or not. They would be useful for the study. To help you make a decision, the study doctor or a member of their team can tell you what procedures and information should still be done or obtained if you stop taking the study medicine but choose to continue the follow-up.

How will the confidentiality of your health data be protected?

If you decide to participate in this study, the study physician and the research team will use your health data to conduct this study, as described in this document. These may include your first and last name, address, telephone number, medical history, medical imaging, date of birth, and information obtained

during your study visits. This health data can come from your family doctor or any other healthcare professional.

As part of the biomedical research in which the promotor proposes to you to participate, a processing of your personal data will be implemented to allow the analysis of the study with regard to the objective.
To this end, medical data concerning you and data relating to your lifestyle, as well as, to the extent that these data are necessary for research, your ethnic origins, data relating to your sex life, will be transmitted to the Promotor or to persons or companies acting on its behalf, in France or abroad. These data will be identified by a code number.
This data may, under conditions ensuring their confidentiality, be transmitted to French or foreign health authorities, and also to other entities of the promoter.

By signing this document, you authorize the research team to share your health data with:
- Health authorities around the world,
- The study promotor and persons working on behalf of or with it, which may be subsidiaries of Merck & Co., Inc.
Health authorities and those working on behalf of or with the sponsor to ensure that study procedures are followed will be able to access all health data about you at the study center.
Your name will not appear on the health data transmitted to the promotor and to persons working on behalf of the promotor. Instead, this data may include your initials, date of birth and the dates of your study visits. Your name will not appear in any report published as part of this study or in any other scientific publication or presentation.
The promotor and people working on his behalf or with him, his subsidiaries where applicable, can use the health data sent to them:

• To see if the study drug is effective and well tolerated;
• To compare the study drug with other drugs;
• For other activities (such as development or regulatory activities) related to the study drug.

For these reasons, the Sponsor may share this health data with others involved in these activities, provided they agree to use this health data only as described herein. The sponsor and those working on or with it, which may include its subsidiaries, may transfer health data about you to other countries where the laws on the protection of personal data are not as strict.

Your permission to use and share your health data is given without time limit.

You can object to the processing of health data concerning you at any time by writing to the study

doctor. If you do, you will no longer be able to participate in this study. No new health data you concerning will be collected after this date. However, the health data you concerning already collected may still be used and communicated to others as described in this document.

In accordance with the provisions of the computing law, files and freedoms, you have the right to access and rectify. You also have the right to oppose the transmission of data covered by professional secrecy that may be used in the context of this research and be processed.
You can also access all of your medical data directly or through a doctor of your choice in accordance with the provisions of Article L. 1111-7 of the Public Health Code. These rights are exercised with the doctor who follows you as part of the research and who knows your identity. Unless you object, your general practitioner (attending physician) may be informed of your participation in this study.

You will be able throughout the duration of the study, upon written request to your doctor, to access your personal data collected during the study and to modify them if necessary. However, to ensure the scientific integrity of the study, some of your personal data related to the study will only be communicated to you at the end of it.

At the end of the study, you have the right to be informed of the overall results of the study by the study doctor when these results are available.

Will the information concerning this study be recorded in a database?

A description of this clinical study will also be notably available on the site http://www.ansm.sante.fr as required by French regulations.

Who should you contact if you have any questions related to the study?

The study doctor or a member of their team will answer your questions. If you have any questions regarding the study or any medical problem related to this study or your rights as a participant, you will find the contact details of the study doctor on the first page of this information document.

Regulatory aspects

This biomedical research will be carried out in accordance with the legislative and regulatory provisions relating to biomedical research (law of August 9, 2004 relating to public health policy), and in particular

the Public Health Code, Book 1, Title II relating to biomedical research.

In accordance with the law,

- The Clermont-Ferrand University Hospital, which organizes this biomedical research as a promotor, has taken out insurance in accordance with the legislative provisions, guaranteeing its civil liability and that of any intervening with the Société Hospitalière d'Assurances Mutuelles (SHAM, contract no. ° 147161). In the event that your state of health is altered as a result of your participation in the study, in accordance with Public Health Law n ° 2004-806 of August 9, 2004, you would be entitled to receive compensation within the framework of this specific insurance contract ..
- This research received the favorable opinion of the South East VI People Protection Committee on 09/26/2016 as well as the prior authorization of the competent health authority.
- The National Agency for the Safety of Medicines and Health Products gave its authorization for the implementation of this biomedical research on 11/18/2016

This research may be interrupted, if circumstances so require, by the sponsor or at the request of the health authority.

You can also access all of your medical data directly or through a doctor of your choice in accordance with the provisions of Article L. 1111-7 of the Public Health Code. These rights are exercised with the doctor who follows you as part of the research and who knows your identity.

Conditions of participation

You will only be able to participate in this biomedical research if you are affiliated to the social security or beneficiary of such a scheme.

Your participation in this study is free and voluntary. You can refuse to participate or withdraw from the study at any time. This will not result in any subsequent damage to the quality of the care you receive and your relationship with your doctor.

If you decide to withdraw from the study, you may receive the treatment conventionally used to treat your condition. This will not prevent you from participating in studies in the future.

By signing the Informed Consent Collection Form, you retain all of your legal rights. You do not waive any of your legal rights in the event of negligence or professional misconduct by anyone involved in the study.

Adults protected by law, persons deprived of their liberty by a judicial or administrative decision, persons hospitalized without consent under Articles L. 3212-1 and L. 3213-1 which do not fall under the provisions of Article L 1121-8 and people admitted to a health or social establishment for purposes other than research cannot participate in the study.
Only patients without a relationship of dependency with the site staff in charge of the research, or with the sponsor, can participate in this study.

You should also be aware that you cannot participate in other biomedical research in parallel.
Before any participation in this biomedical research, you must not have participated in another biomedical research in the 30 days before signing of the consent collection form and you must not participate in another biomedical research until the last visit of this study.

Date : ……/……/……

Signature of patient
(Preceded by the words "Read and understood")

Initials of Investigator

CONSENT FORM TO PARTICIPATE IN BIOMEDICAL RESEARCH

STREAGER : A Phase 3, Global, Multicenter, Open-Label Study to Investigate the Efficacy of Elbasvir/Grazoprevir Fixed-Dose Combination for 8 Weeks in Treatment-Naïve, HCV GT1b-Infected Patients, with non-severe fibrosis.

Principal Investigator:

Professor Armando ABERGEL
Adresse : Consultation Digestive et Hépatobiliaire CHU ESTAING
1 place Lucie et Raymond Aubrac 63003 CLERMONT-FERRAND
Phone: 04 73 75 05 23

I, the undersigned)

Mrs., Miss, Mr. (cross out unnecessary) (name, first name) ……

Born ……..

Adress ……

Declares:

- that the Doctor (last name, first name, phone) …… .. …… .. Suggested that I participate in the mentioned study,

- that he explained me the protocol in detail,

- which he made me known in particular:

• the objective, method and duration of the study

• the constraints and potential risks incurred

• my right to refuse to participate and in case of disagreement to withdraw my consent at any time

• my obligation to register for a social security system

• that, if I so wish, at the end of it, I would be informed by the investigating doctor of his overall results

• that I would not be allowed to participate in other clinical studies for a period of 36 weeks

• that the South East People Protection Committee issued a favorable opinion on 09/26/2016

• that the ANSM issued an authorization for this study.

• that as part of this study, the promotor, the Clermont-Ferrand University Hospital, took out insurance covering this research.

- that I have answered in good faith questions concerning my state of health and my participation in other studies,

- that I am not placed under judicial protection.

Informations about the study collected by the investigator are treated confidentially. I accept that the data recorded during this research may be the subject of anonymous computer processing. I have noted that the right of access provided for by the law of August 6, 2004 relating to computers, files and freedoms is exercised at any time with the doctor who follows me in the context of research and who know my identity. I can exercise my right of rectification and opposition with this same doctor, who will contact the research sponsor.

After having freely discussed and obtained answers to all my questions, I freely and voluntarily agree to participate in this biomedical research under the conditions specified in the information and consent form.

I will receive a copy of this signed and dated consent document.

This document must be produced in 2 original copies, the first of which must be kept for 15 years by the investigator, another given to the person giving his consent.

Printed Name of Subject	Signature of Subject	Date (MM/DD/YYYY)
Printed Name of Person Conducting Consent Discussion	Signature of Person Conducting Consent Discussion	Date (MM/DD/YYYY)