COVER PAGE

TITLE: A randomised, multicentre, double-blind, placebo-controlled study on the efficacy and safety of a therapeutic strategy of post-partum haemorrhage comparing early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins following vaginal delivery.

NCT Number: NCT02155725

DOCUMENT: Informed consent form (v 7.0)

VERSION & DATE OF DOCUMENT: Version 7.0; March 06, 2018

INFORMATION SHEET IN EMERGENCY SITUATION

FIDEL STUDY

This information document is intended for the patient. However, in the case of an emergency situation, if the patient cannot receive this information, then it must be delivered to a family member or trusted person designated by the patient.

Dr ……..……..…….. is proposing that you participate in a biomedical study entitled:

"A multicentre, controlled, randomised, double-blind study to evaluate the benefits and tolerance of a treatment strategy for postpartum haemorrhage associating early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins after vaginal delivery – FIDEL"

This study is conducted by the Laboratoire français du Fractionnement et des Biotechnologies [French Laboratory for Fractionation and Biotechnologies] (LFB BIOMEDICAMENTS, 3 avenue des Tropiques, BP50052, Les Ulis, 91942 Courtaboeuf Cedex).

The Lille Ethics Committee gave its favourable opinion on 10/12/2013. The French National Agency for Medicines and Health Products Safety (ANSM) also gave its authorisation on 25/11/2013.

You have just given birth and persistent bleeding, also called Postpartum Haemorrhage (PPH), has been observed. Therefore, you may be able to participate in the study.

PPH is excessive bleeding that occurs after childbirth.

The haemorrhage is associated with loss of blood proteins, including fibrinogen, which plays an important role in clotting. The administration of a fibrinogen concentrate could therefore compensate for the loss of this protein and help stop the bleeding.

Fibrinogen has been available in France as a medicine called Clottafact® since May 2009. Its use is authorised in the management of postpartum haemorrhages.

The aim of the study is to evaluate whether the early administration of Clottafact could help control the bleeding.

The study will take place in France, in around twenty hospitals and, if you accept, you will be one of the 470 patients who will participate.

1. *BIOMEDICAL STUDY PROCEDURES*

Allocation of the study treatment:
In this study you will receive by drawing lots either 3g of fibrinogen, that is to say Clottafact®, or a placebo which contains no active substance.
However, the doctor can find out the treatment if he/she deems this necessary.

Your follow-up during the study:
Before the study treatment is administered, you will have a blood sample taken from your arm (24 ml or about 1.5 tablespoons) to perform blood tests including the assay of fibrinogen.

Your treatment (Clottafact® or placebo) will then be administered to you all at once by an infusion into a vein, which will last about twenty minutes.

You will then be examined by the study doctor and a blood sample will be 3 more times: 2 hours, 6 hours, then the second day after administration of the study treatment.
If the study doctor deems it necessary, he/she may administer fibrinogen even if you are in the group of patients who received placebo.

Throughout your stay in the hospital, your treatment will be identical to that which you would have received if you had not participated in the study.

2. *POSSIBLE BENEFITS*

Early administration of Clottafact may help to control the bleeding, for example by reducing the need for blood transfusions and more invasive treatments.

You may not derive any particular benefit from this study if you receive the placebo.

But, in any case, your participation will be useful, in the future, to other patients who will be in the same situation as you, by helping us to better understand PPH and better manage it.

3. *RISKS AND POSSIBLE INCONVENIENCES*

Like all medicines, Clottafact can cause adverse effects, although not everybody gets them.

- Headache, dizziness, ringing in the ears, difficulty breathing (asthma), vomiting associated with headaches, redness, itching, skin rash, night sweats, feeling hot,
- Blood circulation disorders (deep vein thrombosis, superficial thrombophlebitis, pulmonary embolism) from the formation of a blood clot in an artery or vein. However, it is known that the risk of having this type of event is increased after childbirth, even in the absence of treatment with Clottafact®,
- Allergic reaction (including anaphylactic shock, paleness, vomiting, cough, low blood pressure, chills, hives) as with medicine containing proteins that is administered intravenously.

4. *CONFIDENTIALITY*

Your file will be viewed by LFB BIOMEDICAMENTS, or its representatives, in order to verify the validity of the clinical data collected.

All personal information about you collected and processed by computer for the purposes of the study (age, sex, height, weight, medical history) will be kept strictly confidential.

5. *INSURANCE*

LFB BIOMEDICAMENTS has taken out civil liability insurance covering any health problem related to your participation in the study (company: HDI-GERLING - Contract no.: 01010260-14023).

Your participation in the study is completely free and voluntary and you can refuse if you wish.
If you authorise your doctor to include you in the study, he/she will get back to you as soon as your state of health allows it to give you more detailed information. You will then have time to ask him/her any questions you want. He/she will then ask you to confirm that you agree to your data being used.

If you refuse to participate or if, at any time, you decide to withdraw, your decision will in no way affect the quality of the care you will receive or the relationship with your doctor

PATIENT CONSENT IN EMERGENCY SITUATION

FIDEL STUDY

"A multicentre, controlled, randomised, double-blind study to evaluate the benefits and tolerance of a treatment strategy for postpartum haemorrhage associating early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins after vaginal delivery – FIDEL"

I the undersigned (LAST NAME, First name) …… agree to participate in the study.

It was clearly explained to me that I am free to accept or refuse to participate in this study.
I was given a written information sheet describing what the study entails.
My data will be processed by computer to allow for analysis of the study results. As soon as my condition allows, I will be able, if I wish, to oppose the computer processing of my medical data collected previously.

THE PATIENT

Date (dd/mm/vvvv)	|___|___| / |___|___| / |___|___|___|___|	Time (24 hour format)	|___|___| / |___|___|
(Signature)			

THE INVESTIGATOR

I the undersigned (LAST NAME, First name)	……		
Date (dd/mm/yyyy)	|___|___| / |___|___| / |___|___|___|___|	Time (24 hour format)	|___|___| / |___|___|
(Signature)			

RELATIVE/TRUSTED PERSON CONSENT IN EMERGENCY SITUATION

FIDEL STUDY

"A multicentre, controlled, randomised, double-blind study to evaluate the benefits and tolerance of a treatment strategy for postpartum haemorrhage associating early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins after vaginal delivery – FIDEL"

I the undersigned (LAST NAME, First name) ……, confirm

that I was given a written information sheet describing what the study entails.

❑ **The patient has given her oral consent to participate but is physically unable to sign her consent**	❑ **The patient is unable to give her oral consent to participate in the study**
I certify as a relative or a trusted person, that Ms …… has received minimal oral information on the nature of the study and has given her oral agreement to participate in the study but is physically unable to sign the emergency consent herself.	I accept as a relative or trusted person that Ms …… is participating in the study. It was clearly explained to me that I am free to accept or refuse her participation in this study.

Her data will be used to allow for analysis of the results of the study. As soon as her condition allows, she can, if she wishes, oppose the computer processing of her medical data collected previously.

THE RELATIVE / TRUSTED PERSON

Date (dd/mm/yyyy)	|___|___| / |___|___| / |___|___|___|___|	Time (24-hour format)	|___|___| / |___|___|
(Signature)			

THE INVESTIGATOR

I the undersigned (LAST NAME, First name)	……		
Date (dd/mm/yyyy)	|___|___| / |___|___| / |___|___|___|___|	Time (24-hour format)	|___|___| / |___|___|
(Signature)			

POST-INCLUSION INFORMATION SHEET

FIDEL STUDY

❑ On [date] ……., after your initial consent was signed, you were included by Dr ……..…….. in the biomedical study entitled:

OR

❑ On [date] ……., after the written declaration of your relative (or trusted person) confirming your oral consent was signed, you were included by Dr ……..…….. in the biomedical study entitled:

OR

❑ On [date] ……..……., after the initial authorisation signed by your relative (or trusted person) Mr/Ms ……..……., you were included in the biomedical study entitled:

"A multicentre, randomised, double-blind study to evaluate the benefits and tolerance of a treatment strategy for postpartum haemorrhage associating early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins after vaginal delivery – FIDEL"

You were included in this biomedical study in an emergency situation and the purpose of this second information sheet is to allow you to decide whether to continue or stop participating in it.

This biomedical study (also called a "clinical study") is conducted by the Laboratoire français du Fractionnement et des Biotechnologies [French Laboratory for Fractionation and Biotechnologies] (LFB BIOMEDICAMENTS, 3 avenue des Tropiques, BP50052, Les Ulis, 91942 Courtaboeuf Cedex, FRANCE).

Please take your time to read this information sheet carefully. It will give you the necessary information on why this study is carried out and what it will imply for you if you decide to continue participating. If you would like further information or clarifications, do not hesitate to ask the study doctor (called "investigator") any questions you may have.

Your participation in the study is completely free and voluntary and you can refuse if you wish. If you agree to continue participating, you will need to sign a new informed consent form. By signing this document, you do not waive any of your legal rights, you certify that you have received and understood the information relating to the FIDEL biomedical study.

A copy of this information sheet and signed consent will be given to you, as well as a copy of the first information sheet and initial consent.
If you refuse to continue participating or if you decide to withdraw at any time, your decision will not affect the quality of the care you receive or the relationship with your doctor.

The Independent Ethics Committee (Lille Ethics Committee) gave its favourable opinion on 10/12/2013. The French National Agency for Medicines and Health Products Safety (ANSM) also gave its authorisation on 25/11/2013.

POST-INCLUSION INFORMATION SHEET

FIDEL STUDY

1. *AIM OF THE BIOMEDICAL STUDY*

You were included in the study in an emergency situation, when significant and persistent bleeding, also called Postpartum Haemorrhage (PPH), was observed after your childbirth.

PPH is excessive bleeding that occurs after childbirth. It is one of the main causes of maternal mortality in the world and a very widespread cause of serious maternal pathologies in developed countries. PPH is first managed with treatments called uterotonics, such as oxytocin, which help the uterus to contract and eventually stop the bleeding. If this treatment fails, another uterotonic is given, called prostaglandin. If this second treatment still does not stop the bleeding, other more invasive procedures must then be considered, such as vascular ligation (certain blood vessels which bring blood to the uterus are tied with absorbable thread), arterial embolisation (injection of a resorbable biological substance that temporarily blocks blood supply to the uterus) or hysterectomy (removal of the uterus) in the most severe cases.

The blood loss is also known to be associated with the loss of a blood protein called fibrinogen. This protein is involved in blood clotting. Too little fibrinogen in the blood has been shown to help maintain haemorrhaging. Fibrinogen is therefore used commonly in many hospitals in France to treat women in your situation when the bleeding does not stop despite proper care.

Fibrinogen has been available in France as an antihaemorrhagic drug under the name Clottafact® since May 2009. It is manufactured by LFB BIOMEDICAMENTS. Approximately 46,000 units of Clottafact were administered to patients between May 2009 and December 2012.
It is authorised for use in the management of severe haemorrhages such as PPH, but the time of its administration after the start of bleeding needs to be better specified.

LFB BIOMEDICAMENTS' fibrinogen concentrate, Clottafact, is therefore already used in women with PPH, but generally after the decreased fibrinogen level has been demonstrated by a blood test.
The aim of the study is to evaluate whether early administration of Clottafact, with the start of a prostaglandin infusion, could help control the haemorrhage and its consequences, such as by reducing the need for blood transfusions or the need for more invasive treatments. The study will also assess the safety of early administration of Clottafact.

The study takes place in France, in around twenty hospitals. A total of 470 patients are planned to be included.

2. *BIOMEDICAL STUDY PROCEDURES*

Allocation of the study treatment:
You have already received the study treatment because it was to be given as soon as possible after the start of the prostaglandin infusion.
This study is called a "double-blind" study, which means that neither you nor the study doctor will know which treatment you were given. This procedure is used to be sure that the doctor's assessment will be completely objective.

You therefore received one of the following 2 treatments :
1. Active treatment: Clottafact (3g of fibrinogen),
2. Placebo: this is a treatment that contains no active substance.

The study is also "randomised" (the treatments were allocated by drawing lots), which means that half of the patients included in the study receive Clottafact and the other half receive placebo. You therefore have a 50% chance of having received Clottafact.

Your follow-up during the study:

Before administering the study treatment, the study doctor examined you (measured your blood pressure and heart rate) and checked your medical history, the medicines you usually take and the ones you took before you came to the hospital.

Then you gave a blood sample from the arm (24 ml or about 1.5 tablespoons) for biological tests: haematological tests (blood count, haemoglobin, haematocrit, platelets), biochemical tests (urea, creatinine) and tests of certain coagulation parameters including fibrinogen. This blood sample would have been taken in the same way even if you were not participating in the study.

Your treatment (3g of Clottafact or placebo) was then administered all at once by an infusion which lasted about twenty minutes.

As part of the study, your doctor will then perform a new examination (blood pressure and heart rate) and take 3 blood samples: 2 hours (15 ml or 1 tablespoon of blood), 6 hours (15 ml or 1 tablespoon of blood) and then the morning of the second day (24 ml or approximately 1.5 tablespoons of blood) after administration of the study treatment.

The same tests as for the first blood sample will be carried out: haematological, biochemical tests (except at hours 2 and 6) and coagulation parameters including fibrinogen.
Throughout the duration of the study, a total volume of 78 ml or approximately 5 tablespoons of blood will be taken from you. For information, when donating blood, the volume collected is around 450 ml.

Throughout your stay in the hospital, your treatment will be identical to that which you would have received if you had not participated in the study, apart from the administration of the study treatment and the blood sample at 6 hours.

Whichever treatment you are given, if the study doctor deemed it necessary and based on the level of fibrinogen in your blood, he/she may have administered fibrinogen to you, provided that 2 units of blood cells were administered to you or one hour had elapsed since the study treatment was administered.
This administration of fibrinogen can be done provided that you have received Clottafact or placebo. Furthermore, since this was not blinded, your doctor will be able to tell you if you received more fibrinogen, when and at what dose.

End-of-study visit/call:
You will be followed as part of the study from the time the informed consent was signed in an emergency situation until your discharge from the hospital.
Then, 4 to 8 weeks after giving birth, your doctor will see you during an obstetrical follow-up visit or he/she will call you (if no visit is scheduled) to collect information on the medicines you have taken and any complications that have occurred since your discharge from the hospital. No other examination or collection of additional information will be carried out during this last contact with the study doctor.

Your doctor may decide to withdraw you from the study if he/she considers it in your interest, in case of non-compliance with the study procedures or on the decision of LFB BIOMEDICAMENTS or the health authorities.

Your doctor may have to inform your treating doctor about your participation in the study, after having obtained your agreement.

Your participation in the study is completely free and voluntary and you can refuse if you wish. If you refuse to continue participating or if, at any time, you decide to withdraw, your decision will in no way affect the quality of the care you will receive or the relationship with your doctor.
In this case, your doctor will ask you to confirm that you agree to the use of your data collected during the study.

3. *CONSTRAINTS*

You will be asked to comply with all of the steps taken by the study doctor throughout your follow-up:
- that you answer as precisely as possible about your medical history, your allergies to certain medicines, the medicines that you usually take or that you took before your arrival at the hospital,
- that you accept the blood samples,
- that you report immediately to your doctor any adverse events which you note, even if you think that they are not related to the study treatment,
- that you make yourself available for the telephone call or the end-of-study visit.

4. *POSSIBLE BENEFITS*

Postpartum Haemorrhage (PPH) is characterised by bleeding which can be severe and therefore life-threatening for the patient.

Early administration of Clottafact®, as soon as possible after the start of administration of prostaglandins, may help to control the bleeding, for example by reducing the need for blood transfusions and more invasive treatments.

However, you may not derive any particular benefit from this study, especially if you received the placebo.
However, in any case, your participation will be useful, in the future, to other patients who will be in the same situation as you, by helping us to better understand PPH and better manage it.

5. *RISKS AND POSSIBLE INCONVENIENCES*

Since it was launched on the market in France in 2009, Clottafact® has been administered not only to many patients with PPH but also to patients with other pathologies. As an indication: around 6000 patients received it in 2010 and around 9000 received it in 2011. The data for 2012 and 2013 are yet not available at this time.

In addition, as part of the study, an expert committee will regularly review any adverse events that occur and ensure that the benefits for patients outweigh the risks.

5.1 Potential adverse events and inconveniences connected with the study treatment

In any clinical study, the study drug and other therapeutic measures may involve risks, some of which are already known and others that are not yet described.

You should be aware that Clottafact may present the risks and disadvantages described below:

- Common: headaches,
- Uncommon:
  - An allergic reaction (including anaphylactic shock (severe allergic reaction), paleness, vomiting, cough, low blood pressure, chills, itching (hives)), as with any medicine containing proteins that is administered intravenously,
  - Dizziness,
  - Ringing in the ears,
  - Blood circulation disorders (deep vein thrombosis, superficial thrombophlebitis, pulmonary embolism) from the formation of a blood clot in an artery or vein. However, it is known that the risk of having this type of event is increased after childbirth, even in the absence of treatment with Clottafact®,
  - Difficulty breathing (asthma),
  - Vomiting associated with headaches,
  - Redness, itching, skin rash, and night sweats,
  - Feeling hot

Clottafact is purified from the blood of selected donors and according to a manufacturing process that includes three steps to remove/inactive viruses and infectious agents (solvent-detergent, dry heating, nanofiltration). Despite these highly secure measures, the risk of infectious disease due to the transmission of infectious agents, including those whose nature is still unknown, cannot be definitively excluded.

To date, no drug-drug interaction has been described with other treatments that may be administered to you to manage your PPH.
However, you must inform the study doctor of any modification of the medicines that you take between your discharge from the hospital and the last visit or telephone call at the end of the study.

5.2 Potential adverse events and inconveniences connected with the study-specific procedures

Administration of the study treatment requires the use of a needle inserted into a vein. This needle was also used to take the blood samples. These procedures may involve the following inconveniences:

- Mild pain at the injection site,
- Feeling dizzy,
- Bruise,
- Exceptionally, an infection (risk present each time the skin is injured) or bleeding at the puncture site.

However, as with any delivery, whether or not the patient participates in the study, an intravenous line is installed for any blood samples and infusions required. This means that there are no additional disadvantages associated with the study-specific procedures.

6. *PREGNANCY AND BREAST-FEEDING*

The safety of Clottafact during pregnancy and breast-feeding has not been evaluated in controlled clinical trials.
However, clinical experience in the treatment of obstetrical complications does not suggest that any adverse effects should be expected on the outcome of pregnancy or on the development of the foetus or newborn.

Clottafact was administered to you after you gave birth. It therefore poses no risk to your pregnancy and will not prevent you from breast-feeding if you wish.

7. *FINANCIAL ASPECTS*

Your participation in the study is completely free: all examinations and other medical costs specific to the study as well as the study treatment will be covered by LFB BIOMEDICAMENTS.

The study doctor and the hospital are receiving financial compensation from LFB BIOMEDICAMENTS for this study.

8. *CONFIDENTIALITY*

All personal information about you collected for the purposes of the study (age, sex, height, weight, medical history) will be kept strictly confidential.

In order to respect your privacy and guarantee professional secrecy, you will only be identified by an identification number and your initials (1st letter of your last name and 1st letter of your first name) for all the data collected and in the database in which the information will be stored. The confidentiality of your data will be ensured in accordance with what is permitted by the laws in force at this time.

Your medical file will be viewed by LFB BIOMEDICAMENTS, or its representatives, in order to verify the validity of the clinical data collected. This will be done in total respect for your privacy.
The Ethics Committee as well as the Health Authorities could also request to have direct access to your file if necessary.

If information relating to this study is published or presented at scientific conferences, neither your identification number nor other personal information will be used and all data will remain confidential.

By signing the informed consent, you authorise access to and use of your data under the conditions described above, to allow for analysis of the results of the biomedical study in accordance with its aim as it was presented to you.

To that end, medical data concerning you will be transmitted to LFB or to persons or companies acting on its behalf, in France or abroad. These data may also, under conditions ensuring their confidentiality, be transmitted for regulatory submission purposes and/or monitoring of the medicinal product to French or foreign health authorities and/or to LFB BIOMEDICAMENTS subsidiaries as well as to companies acting on its behalf that may be located outside the European Union.

In accordance with the French Data Protection Law (CNIL): Law no. 2004-801 of 6 August 2004 on the protection of individuals with regard to the processing of personal data and amending Law no. 78-17 of 6 January 1978 on data processing, files and freedoms, you have a right of access and rectification. You also have a right of opposition to the transmission of data covered by professional secrecy likely to be used within the framework of this study and analysed, it being specified that you cannot exercise this right of opposition on data falling under a legal obligation of LFB BIOMEDICAMENTS, in particular with regard to monitoring of the medicinal product.
You can exercise these rights at any time through the study doctor.
If you withdraw your consent during the study, LFB BIOMEDICAMENTS will ensure that no additional data concerning you are collected from that time forward.

9. *INSURANCE*

LFB BIOMEDICAMENTS has taken out civil liability insurance covering any health problem related to your participation in the study (company: HDI-GERLING - Contract no.: 01010260-14023).

If you are harmed by the study, tell your doctor.

10. *NEW INFORMATION*

Your doctor will inform you of any new information or changes to the study that may have an impact on your health or on your wish to continue the study.

If the study is stopped for any reason, you will be notified.

If you wish, your doctor will inform you of the general results of the study approximately one year after the last patient has completed her end-of-study visit.

11. *CONTACTS*

If you have any further questions about the study, before, during or after your participation, you can always ask your doctor.

STUDY DOCTOR
Name: ……
Address: ……
Telephone number: ……

Thank you for having taken the time to read this information sheet. If you agree to continue the study, please date and sign the 2 copies of the attached consent and initial each page of this document.

PATIENT POST-INCLUSION CONSENT

FIDEL STUDY

"A multicentre, randomised, double-blind study to evaluate the benefits and tolerance of a treatment strategy for postpartum haemorrhage associating early administration of human fibrinogen versus placebo in patients treated with intravenous prostaglandins after vaginal delivery – FIDEL"

I the undersigned, (last name, first name) ……. , confirm:

☐ In the case of a written declaration from my relative (or trusted person), to have given my oral agreement to participate in the study but was physically unable to sign the emergency consent myself

I certify in the context of this post-inclusion consent that I:

- have read the attached information sheet and understand the nature and aim of the study,
- was able to ask any questions I had regarding the study and received satisfactory answers from the study doctor,
- had enough time to decide whether to continue participating in the study,
- have understood that my participation in the study is completely free and voluntary as well as the implications of my participation. I can withdraw from the study at any time without affecting my medical care or my rights,
- have understood that I can exercise my rights of access, rectification and opposition regarding my data at any time by contacting the study doctor,
- know that I can access the personal data concerning my health that are kept by the investigator at any time during the study or after it, in accordance with article L. 1111-7 of the French Public Health Code,
- accept the transmission for regulatory submission purposes and/or monitoring of the medicinal product of my personal data to the health authorities of foreign countries and to any company or companies including their subsidiaries mandated by LFB BIOMEDICAMENTS, which may be located outside the European Union,
- accept that representatives of LFB BIOMEDICAMENTS, the Ethics Committee or the Health Authorities may access my personal data,
- have understood that a specific insurance policy has been taken out by LFB BIOMEDICAMENTS to cover my participation in the study,
- have noted that, if I wish, I can be informed of the results of the study by the study doctor,
- have understood that a copy of the information sheet and consent will be given to me,

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☐ agree to continue participating in the study and authorise computer processing by the Sponsor or on its behalf of my anonymised data already collected and that will be collected,

☐ **OR** refuse to continue the study, but authorise computer processing by the Sponsor or on its behalf of my anonymised data already collected,

☐ **OR** refuse to continue the study and opposes computer processing by the Sponsor or on its behalf of my anonymised data already collected.

THE PATIENT (to be completed personally by the patient)

Date (dd/mm/yyyy)	|___|___| / |___|___| / |___|___|___|___|	Time (24 hour format)	|___|___| / |___|___|
(Signature)			

THE INVESTIGATOR

I the undersigned (LAST NAME, First name) .....

certify that the patient who signed this consent has received and understood the required information about the nature of the study as well as the risks and benefits that her participation may entail.

Date (dd/mm/yyyy)	|___|___| / |___|___| / |___|___|___|___|	Time (24 hour format)	|___|___| / |___|___|

(Signature)