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.

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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

Short title: FIbrinogen in haemorrhage of DELivery: FIDEL

CLINICAL STUDY PROTOCOL

EudraCT no. 2013-002484-26

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List of abbreviations and definition of terms

aPTT	Activated Partial Thromboplastin Time
AE	Adverse Event
ANOVA	ANalysis Of VAriance
ATC	Anatomical Therapeutic Chemical
CRF	Case Report Form
CRO	Contract Research Organisation
CSP	Code de la Santé Publique
CV	Curriculum Vitae
D	Day
DSMB	Data and Safety Monitoring Board
EC	Ethics Committee
FAS	Full Analysis Set
FFP	Fresh Frozen Plasma
FIGO	International Federation of Gynecology and Obstetrics
FU	Follow-up
GCP	Good Clinical Practice
h	Hour
HAS	Haute Autorité de Santé
Hb	Haemoglobin
HES	Hydroxyethylstarch
Ht	Haematocrit
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICM	International Confederation of Midwives
IEC/IRB	Independent Ethics Committee (IEC) or International Review Board (IRB)
IMP	Investigational Medicinal Product
IV	IntraVenous
LDH	Lactate DeHydrogenase
LFB	Laboratoire français du Fractionnement et des Biotechnologies
LLT	Lowest Level Term
LMWH	Low-Molecular-Weight Heparin
LOCF	Last Observation Carried Forward
MedDRA	Medicinal Dictionary for Regulatory Activities
min	Minute
NA	Not Applicable
NCR	No Carbon Required
ND	Not Done
PCC	Prothrombin Complex Concentrates
PICU	Post Interventional Care Unit
PPH	Post-Partum Hemorrhage
PT	Preferred Terms
PT	Prothrombin Time
QT	Quick's Test
RBC	Red Blood Cells

rFVIIa	Recombinant activated Factor VII
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SPC	Summary of Product Characteristics
SOFA	Sequential Organ Failure Assessment
TRALI	Transfusion-Related Acute Lung Injury
UNK	UNKnown
VBL	Volume of Blood Loss
WHO	World Health Organization

SYNOPSIS

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. Short title: FIbrinogen in haemorrhage of DELivery: FIDEL
SPONSOR	LFB BIOMEDICAMENTS ZA de COURTABOEUF 3, avenue des Tropiques - 91940 LES ULIS (France)
COORDINATING INVESTIGATOR / SCIENTIFIC COMMITTEE	Coordinating Investigator: [redacted] Scientific Committee: [redacted]
INVESTIGATIONAL MEDICINAL PRODUCT (IMP) AND ASSOCIATED TREATMENTS	Investigational medicinal products (IMP): The participants are assigned to either: o Fibrinogen (Clottafact®): 3g (2 vials of 1.5g/100 ml) or, o Placebo: 2 vials of 100 ml Route of administration: o As soon as possible during the 30 minutes following the start of prostaglandin infusion o Intravenous (IV) administration with a flow rate ≤ 20 ml/min Treatment allocation: o The treatment will be double-blind. o Randomisation will be stratified on the centre. o Each treatment unit contains 2 vials of powder and 2 solvent vials of 100 ml. o Treatment units will be numbered and will be allocated in chronological order of inclusion by ascending number.

	Associated treatments: o IMP is administered as soon as possible after start of prostaglandin infusion. The dose of prostaglandin will be administered according to the 2004-recommendations provided by the French National Authority for Health (Haute Autorité de Santé, or HAS). o Following the administration of IMP, the therapeutic management will be totally left to the discretion of the investigator. o However, some concomitant treatments will be administered in accordance with the following recommendations: o Fibrinogen concentrate as rescue therapy: if administered, it will not be administered: ▪ within 60 minutes following the start of IMP administration, **OR** ▪ before at least 2 units of packed RBCs have been administered to the patient. o Tranexamic acid: ▪ The administration of tranexamic acid will be allowed only after prostaglandin infusion has been decided. ▪ Recommended dose: 1 g IV to be renewed once after 30 min. o Transfusional strategy: in accordance with the following objectives: - Hemoglobin (Hb) ≥ 8 g /100 ml, - PT ≥ 40%, - Platelets count ≥ 50 000/mm^3, Transfusions of red blood cells (RBC), fresh frozen plasma (FFP) and platelets units can be performed before availability of laboratory results, when indicated. o Hydroxyethylstarch (HES): maximum dose of 1.5 L during the first 24 hours.
STUDY DESIGN	Phase IV multicentre, randomised, double-blind, placebo-controlled, parallel-group study
OBJECTIVES	Primary: • To assess the benefits of a therapeutic strategy that associates an early administration of human fibrinogen concentrate in the management of PPH on the reduction of bleeding after the initiation of prostaglandins intravenous infusion. Secondary: • To assess the evolution of haemorrhage • To assess the need for haemostatic intervention • To assess the need for intrauterine balloon

	• To assess the maternal morbi-mortality • To assess the biological effects of fibrinogen concentrate administration • To assess the tolerance of fibrinogen concentrate administration
NUMBER OF PATIENTS	It is estimated that, in the control group, 42% of patients will fulfill the primary endpoint. With an expected percentage of patients in the Clottafact®-treated group of 27%, the difference between the two groups will be 15%. With a power (1-ß) = 90%, an α risk-error = 5% and a two-sided test (Z test, unpooled variance), a sample size of 412= 2x206 evaluable patients is needed per group of treatment. Assuming a 5% rate of dropouts, about 434 patients are planned to be randomized in the study. As there is some uncertainty about the test Z variance depending itself on the expected rates, the variance will be re-estimated in a blind way at 80% of the initially planned sample size and the sample size will be increased according to the new estimated variance so as to maintain the power to 90% while still considering the same originally planned difference in failure rates, i.e. 15%. It can be shown that the possible increase in sample size (after adjusting for drop-outs) cannot exceed 50 additionnal patients. Hence the restimated sample size will not exceed 484 patients.
STUDY POPULATION (ELIGIBILITY CRITERIA)	<u>Inclusion criteria</u>: • Signed and dated informed consent form • Vaginal delivery • PPH requiring IV administration of prostaglandins • At least one available result of Hb level during the third trimester of pregnancy • 18-year-old female patients and older • Covered by healthcare insurance in accordance with local requirements <u>Non-inclusion criteria</u>: • Caesarean section • Haemostatic intervention (as ligation, embolization or hysterectomy) already decided at the time of inclusion • Known placenta praevia or accreta • Hb level < 10g/dl during the third trimester of pregnancy • History of venous or arterial thromboembolic event • Known inherited bleeding or thrombotic disorders • Treatment with low-molecular-weight heparin (LMWH) within 24 hours prior to the inclusion • Treatment with acetylsalicylic acid within 5 days prior to the inclusion • Treatment with vitamin K antagonists within 7 days prior to the inclusion • Administration of fibrinogen concentrate within 48 hours prior to the

	inclusion • Administration of FFP, platelets units or prohaemostatic drugs, tranexamic acid and rFVIIa or prothrombin complex concentrates (PCC) within 48 hours prior to the inclusion • Administration of RBCs within 3 months prior to the inclusion • Participation in another interventional clinical study using an investigational medicinal product within 30 days prior to the inclusion • Previous inclusion/enrolment in the present clinical study • Known history of hypersensitivity or other severe reaction to any component of Clottafact® or placebo • Minors, majors under guardianship, persons staying in health or social institutes and people deprived of their freedom • Known drug or alcohol abuse • Patients whose use of concomitant medication may interfere with the interpretation of data • Any other current significant medical condition that might interfere with treatment evaluation according to the investigator's judgement • Patients who are unlikely to survive through the treatment period and evaluation • Patients transferred from another service after the delivery
DURATION OF PATIENT PARTICIPATION	6 ± 2 weeks after the delivery
DATES OF BEGINNING AND END OF STUDY	• Planned date of inclusion of first patient: December 2013 • Planned date of last patient out: August 2018 at the latest
STUDY DESCRIPTION	Consent: Informed consent will be obtained through an emergency procedure. Inclusion: • Will take place after signing the emergency informed consent and checking the eligibility criteria. • Blood sampling n° 1 for biological data at inclusion. Randomisation: • Will be stratified on the centre. • The start of IMP administration corresponds to H0 (D0). • Recording of the time (start, end) of IMP infusion, H2 (120 ± 30 min): Blood sampling n° 2. H6 (360 ± 30 min): • Blood sampling n° 3.

	Morning of D2: • Blood sampling n° 4. Hospital discharge: • Parameters of therapeutic management and events that occurred during the admission in an ICU, including maximum SOFA score (if applicable), • PPH management summary At 6 ± 2 weeks following delivery: Collection of tolerance data on the IMP during an obstetrical follow-up visit or a phone contact.
DESCRIPTION OF AND JUSTIFICATION FOR DATA COLLECTED	Anamnestic parameters: • Demographic parameters: height, weight prior to pregnancy and last known weight, • History of thromboembolic, obstetrical events and any clinically relevant medical conditions. • Obstetrical parameters of the pregnancy, mainly: o Date of last menstrual period, gestational age, levels of Hb of the third trimester of pregnancy, o Ht and platelets will be collected if available. Delivery parameters: • Times of the start and the end of delivery and number of live births and/or stillbirths, • Start and end hours of haemorrhage, • Initial obstetrical management of the haemorrhage : artificial delivery, uterine or genital examination, • Any haemostatic intervention (intrauterine balloon, uterine ligation, embolization, vascular ligation, hysterectomy), • Vascular filling (if any): volumes and types of filling solutes since the start of delivery until D2, • Transfusions: types and number of transfused blood products since the start of delivery. Clinical events until hospital discharge: • Duration of stay in the obstetrics room (arrival and discharge hours), • Number of days of hospital stay following delivery, • Number of days in resuscitation and/or intensive care and/or PICU and/or continuous care units, • Number of days with assisted ventilation, • Maximum SOFA score for patients transferred in resuscitation and/or intensive care and/or PICU and/or continuous care units,

	• Renal failure requiring dialysis, • Hypotension episodes that required continuous vasopressor therapy, • Acute pulmonary oedema, acute respiratory distress syndrome, transfusion-related acute lung injury (TRALI), • Measured and/or estimated volumes of total blood loss, • Blood-collecting containers (if any): date, time and duration of setting and removal, <u>Adverse events during the study</u> • From the signature of the informed consent form to the end of study visit (6 ± 2 weeks after delivery): serious and non-serious AEs whether or not considered to be causally related to the investigational medicinal product (IMP). <u>Laboratory parameters</u> (at inclusion, H2, H6, D2): • Complete blood count, Hb, Ht and platelets • Plasma fibrinogen • Haemostatic profile: PT, QT, aPTT, D-dimers • Plasma creatinine and urea at inclusion and D2 <u>Prior/Concomitant treatments (total dose, modalities, start and end of administration)</u>: • Prior treatment: all relevant prior medication taken within 7 days before inclusion, including all medication administered since the beginning of the delivery • Concomitant treatments including intravenous fluids, blood products, tranexamic acid and fibrinogen concentrate as rescue therapy
ENDPOINTS AND EVALUATION PARAMETERS	<u>Primary endpoint</u>: Percentage of patients losing at least 4 g/dl of Hb, and/or requiring the transfusion of at least 2 units of packed RBCs within the 48 hours following the administration of IMP. The reference for Hb level is the most recent value recorded during the third trimester of pregnancy. <u>Secondary endpoints</u>: • Evolution of haemorrhage o Percentage of patients losing at least 4 g/dl of Hb, 48 hours following the IMP administration, with regards to the Hb reference level. o Percentage of patients losing at least 3 g/dl of Hb, 48 hours following the IMP administration, with regards to the Hb reference level. o Percentage of patients requiring transfusion of at least 2 units of packed RBCs, 48 hours following the IMP administration. o Percentage of patients losing at least 4 g/dl of Hb, 48 hours

	following the IMP administration, with regards to the level of Hb measured at inclusion. o Percentage of patients with an occurrence of Hb level < 9 g/dl within the 48 hours period following inclusion. o Number of units of transfused blood products within the 48 hours period following IMP administration. o Calculated volume of total blood loss, 48 hours following the IMP administration. • Need for haemostatic intervention o Percentage of patients requiring at least one of the following interventions within 48 hours following the IMP administration: uterine ligation (B Lynch or other techniques), pelvic arteries embolization, surgical vascular ligation, administration of rFVIIa and hysterectomy. • Need for intrauterine balloon o Percentage of patients requiring the use of intrauterine balloon within 48 hours following the administration of IMP. o Time of intrauterine balloon placement. • Maternal morbi-mortality o Length of stay in resuscitation and/or intensive care and/or post interventional care units (PICU) and/or continuous care. o Duration of admission in obstetrics unit. o Single or multi-organ failure (SOFA score) in case of transfer to resuscitation and/or intensive care and/or PICU and/or continuous care units. o Death during the study. • Biological effects of fibrinogen concentrate administration o Evolution of blood fibrinogen level and hemoconcentration between H0 (start of IMP infusion) and D2. • Tolerance of fibrinogen concentrate administration o Serious and non-serious adverse events (AE).
STATISTICS	The distribution of parameters will be summarised using descriptive statistics according to the study variable: • Quantitative variables will be presented by their mean, standard deviation, standard error, median, quartiles and range, minimum and maximum values. The number of documented values will also be mentioned. • Categorical variables (binary, nominal and ordinal) will be presented by contingency tables (frequencies and percents). Number and percentages of missing data will also be mentioned. All statistical tests will be two-sided with a threshold of statistical significance of 0.05. The statistical analysis will be carried out according to the Intent-to-Treat (ITT) principle, depending on the group of randomisation regardless of the received treatment. A per-protocol analysis will be carried out on the subgroup of patients with

	no major protocol deviation if the per-protocol set represents less than 80% of the ITT set. Unless otherwise specified, the following statistical tests will be used: • Categorical data will be compared using chi-square test or Fisher exact test if a theoretical number of one category or more is below 5. • Continuous quantitative data will be compared by t test or, if normality of distribution is rejected, by Wilcoxon non parametric test. No subgroup analysis is planned. The primary analysis will be conducted in the ITT set. Missing data will not be replaced in the primary analysis. The primary model of analysis will be an exact logistic regression adjusting for treatment, centre, and baseline fibrinogen (categorized into three classes, ≤ 2 g L^{-1} ,] 2 g L^{-1} 4 - g L^{-1}] , > 4 g L^{-1}). The treatment effect (odds ratio of failure) with its 95% confidence interval will be estimated in this model. The same analysis proposed will be performed in the ITT and PP sets. Sensitivity analyses replacing missing data with failures regardless of the treated group will be implemented. Analysis of tolerance will be carried out on women at least one dose of IMP. No interim analysis is planned.

STUDY FLOW-CHART (Table 1)

ETUDE FIDEL	CONSENT FORM	INCLUSION	TREATMENT	FOLLOW-UP				END OF STUDY
	Visit 1 Inclusion Blood sampling 1		Visit 2 Randomisation IMP infusion	Visit 3 Blood sampling 2	Visit 4 Blood sampling 3	Visit 5 Morning of D2 Blood sampling 4	Visit 6 Hospital discharge	Visit 7
	Before H0		H0 = start of IMP infusion*	H2 (120 ± 30 min)	H6 (360 ± 30 min)			6 ± 2 weeks after delivery
Informed consent	x							
Inclusion/exclusion criteria	x	x						
Demographics		x						
Medical history (including thromboembolic and obstetrical events and any clinically relevant medical condition)		x						
Pregnancy parameters		x						
Delivery parameters		x						
Clinical exams								
PPH parameters		x	x	x	x		x	
Physical examination		x					x	
Vital signs (arterial pressure, heart rate)		x		x	x	x	x	
Stay in ICU data (if applicable)								
SOFA score maximum**							x**	
Laboratory tests								
Biochemical tests (plasmatic creatinine and urea)		x				x		
Coagulation tests (fibrinogen, PT, QT, aPTT, D-dimers)		x		x	x	x		
Haematological tests (CBC, Hb, Ht, Plt)		x		x	x	x		

ETUDE FIDEL	CONSENT FORM	INCLUSION	TREATMENT	FOLLOW-UP				END OF STUDY
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
Treatments								
Prior treatments		x						
Concomitant treatments		x	x	x	x	x	x	x
Resuscitation fluids		x	x	x	x	x		
Transfusions of blood products		x	x	x	x	x	x	x
IMP								
Reconstitution			By a third party					
Administration			H0*					
Adverse event collection			x	x	x	x	x	x

* Start of IMP infusion should be within the 30 min following the start of prostaglandin infusion and at a flow rate ≤ 20 ml/min

** SOFA score will be assessed only for patients transferred in an Intensive Care Unit

1. INTRODUCTION AND BACKGROUND INFORMATION

1.1. Disease and context

1.1.1. Physiopathology of post-partum haemorrhage

Pregnancy induces changes in coagulation towards a more procoagulant state with mild thrombocytopenia, increased procoagulant factors and diminished fibrinolysis (1), ultimately serving as physiological protection against postpartum bleeding. However, postpartum haemorrhage (PPH), which was defined by the World Health Organization (WHO) as 'blood loss greater than or equal to 500ml (vaginal delivery) or 1000ml (caesarean section) within 24 hours after birth', is the leading cause of maternal mortality (2).

Published data have shown the difficulty of an exact blood loss measurement in clinical obstetrics (3). Severe then massive haemorrhages are also defined by a volume of blood loss greater than 1000 ml and 1500 ml that represent respectively around 1% and 0.5% of vaginal deliveries. For caesarean section, volume of blood loss defining a severe haemorrhage is greater than 1500 ml.
However, this definition cannot be used in clinical practice because blood loss assessment is inaccurate in such emergency situations (4).

The most common causes of PPH are uterine atony, retained placental products, genital-tract trauma. Pre-existing coagulation abnormalities can also be the cause, but more frequently the important aggravating factor is the acquired coagulopathy.
Uterine atony is the main cause of PPH and is observed as a single cause in 50-60% of cases (5), a uterine massage followed by the infusion of uterotonic drugs is the first step of the medical management. The different uterotonics are used in different algorithms, 3 main kinds of uterotonic drugs – oxytocin, prostaglandins and methylergometrine are used to stimulate uterine contraction. The European and American practices tend to remain with just 2 drugs i.e. i.v. oxytocin as the 1st line uterotonic and i.v. sulprotone (prostaglandin E2) – as the 2nd line uterotonic treatment. The administration schemes of oxytocin vary, the sulprostone is dosed more uniformly according to its SPC. The current protocol is based on the standard of care algorithm, which is derived from the American and French guidelines (5).

Except the incision in the caesarean delivery that itself causes additional blood loss, there is no other underlying difference in mechanisms between the 2 types of delivery. There are differences in the management of the PPH during Caesarean section – some centres tend to implement the ultimate measures – uterine artery ligations or haemostatic hysterectomy earlier, compared to the PPH after vaginal delivery (the guidelines permit at least 30 min after the start of the 2nd line uterotonic for the evaluation of the effect and before deciding for intervention) (5).

1.1.2. Epidemiology of PPH

PPH is a major cause of maternal death worldwide and an important cause of severe maternal morbidity in high income countries (6,7,8):

- The incidence of PPH is estimated to be around 5% of deliveries (9).
- This accounts for about 100 000 deaths every year, nearly 25% of all maternal deaths throughout the world (10).
- In Europe, 1.75% of births are complicated by severe PPH (blood loss > 1000 mL) (11) with the risk of death in western countries at 1:100 000 births (12).

Moreover, it can kill a healthy woman within 2 hours and is the quickest maternal killer (8).

1.1.3. Types of PPH

There are two clinical types of PPH (2):

- Primary PPH: bleeding that occurs in the first 24 hours following delivery. Most cases of morbidity and mortality are due to primary PPH. Primary PPH is also divided into two types:
    - Third stage haemorrhage: primary haemorrhage that occurs after the delivery of the baby but before the expulsion of the placenta.
    - True primary PPH: haemorrhage that occurs after the delivery of the placenta at any time within 24 hours of the birth of the baby.
- Secondary PPH: any abnormal or excessive bleeding from the birth canal occurring between 24 hours and 12 weeks postnatally.

The present protocol will focus only on primary PPH.

To be sure of the mechanism involved in the development of the acquired PPH related coagulopathy, caesarean section and abnormal placental insertion will not be included to avoid surgical and placental bleeding.

1.1.4. Management / Treatment of PPH

According to French guidelines issued in 2004 (13) and the International Confederation of Midwives (ICM), the International Federation of Gynecology and Obstetrics (FIGO) (14) and the WHO's Integrated Management of Pregnancy and Childbirth guidelines (2), the PPH management is a step by step approach including:

1. Step 1: The obstetric team needs to focus on the search and basic treatment of the most commun causes of PPH such as utrine atony (IV oxytocin ± uterine massage).

   While the anesthetic one provides basic rescucitation and adequate analgesia

2. Step 2: If uterine atony is resistant and oxytocin ineffective, prostaglandins must be used within a maximum delay of 15 to 30 mn.

   More advanced rescucitation and monitoring are also usually needed.

3. Step 3: When medical treatment fails, arterial embolization, intrauterine balloon (e.g : Bakri or Belfort-Dildy balloon) or surgical ligation is applied.

4. The last step is hysterectomy; meanwhile, the use of recombinant activated factor VII (rFVIIa) can be considered.

1.1.5. PPH associated coagulopathy

Fibrinogen is essential in the development of a strong and functional blood clot. It is produced in the liver and the average plasma level is 2.0 to 4.5 g/L. In relation with pregnancy (especially the third trimester) the level of fibrinogen rises to an average of 5 g/L (15,16,17).

Upon activation by thrombin, factor XIII is activated into FXIIIa. FXIIIa is a transglutaminase, which acts on fibrin to form cross links between fibrin molecules. Consequently, polymerized fibrin is held together and forms an insoluble clot. Fibrin can therefore be seen as the end product of the coagulation cascade.

Besides its central position in the coagulation process, fibrinogen is also involved in primary haemostasis through its platelet receptor. This receptor is a heterodimer consisting of the plasma-membrane glycoproteins GPIIb/IIIa (also known as αIIbβ3). GPIIb/IIIa belongs to the integrin family, which not only bind adhesive ligands, but also act as signalling receptors for platelet aggregation.

In summary, fibrinogen is a major component of both coagulation and primary haemostasis, which explain the bleeding phenotype in case of acquired or inherited fibrinogen deficiencies.

During progressive blood loss, fibrinogen appears to represent the coagulation factor first reaching a critical low threshold level at around 1 g/L (18). This state of impaired haemostasis also develops in relation to PPH (15,19). The decrease of fibrinogen is the sole independent factor that predicts the severity of PPH as shown by Charbit and al (19) 2 hours after the beginning of PPH and more recently, by Cortet and al (16) 45 minutes after the beginning of PPH.

It has been previously shown that treatment with fibrinogen concentrates was highly useful for controlling massive PPH (15,20,21). Such beneficial effect would be of high interest in the control of massive or oxytocin-resistant PPH.

The threshold at which fibrinogen concentrate should be administered and its therapeutic target have not been studied in PPH but determined in polytrauma and surgery. The restoration of a plasma fibrinogen level between 1.5 g/L to 2 g/L is one of the treatment objectives (22,23). In trauma and surgery massive bleedings, the earlier coaguloapthy is corrected, the better outcome is (24).

1.2. Non-Clinical and Clinical Information

Clottafact® is a human fibrinogen concentrate that had a marketing authorization in France since May 2009 and in Lebanon since January 2013. Clottafact® is labellized in France as a complementary treatment for the management of severe uncontrolled bleeding resulting in acquired hypofibrinogenaemia (25,26) which can be due to an increased consumption of fibrinogen that is

associated with a life-threatening uncontrolled haemorrhage encountered in obstetrical, surgical, or traumatic conditions and also to impaired hepatic synthesis.

Clottafact is also labellized in France for constitutional hypo-, dys- or afibrinogenaemia in patients with spontaneous or posttraumatic haemorrhage.

Clottafact® has been developed in accordance with European "Note for guidance on plasma-derived medicinal products" (CPMP/BWP/269/95 rev.3) (27), which specifies that all plasma derived products must incorporate effective steps for inactivation/ removal of viruses. The manufacturing process of Clottafact® includes two viral inactivation steps, i.e. solvent and detergent treatment and dry heating, and one viral removal step, i.e. 35 nm filtration.

1.3. Rationale of the study

1.3.1. Clinical study rationale

As plasma fibrinogen level is essential for the formation of the fibrin clot, it could be considered as a relevant predictor of severity in massive bleeding and PPH (16,19). Although physicians acknowledged that it was unclear whether low fibrinogen contributed to PPH or reflected its severity, it was demonstrated that fibrinogen levels obtained at the time of PPH were more predictive than other coagulation studies such as Prothrombin Time, Partial Thromboplastin Time, and platelet counts in determining the severity of PPH (19,28).

An early treatment with a transfusion of fresh frozen plasma (in association with packed RBCs in a ratio of 1:2 to 1:1 has been recommended for the control of severe post-traumatic haemorrhage (1,29). Two retrospective publications give some information on this strategy in severe PPH (30,31).

In view of the above data, the correction of hypofibrinogenaemia has been suggested in large cohorts of polytrauma or surgery to be useful in the control of massive bleeding. Historical comparison showed that fibrinogen concentrate administration was more effective than fresh frozen plasma in the treatment of PPH (32,33).

Coagulopathy contributes to the persistence and severity of bleeding. Fibrinogen is the first coagulation factor to fall below physiological levels during haemorrhage, contributing further to excessive bleeding (19).

In current practice fibrinogen concentrate is administered after the determination of fibrinogen level in order to correct hypofibrinogenaemia (20,32). Time between blood sampling and results delays the time of administration of fibrinogen concentrate when it has been shown that the sharp fall of fibrinogenaemia is time dependent (16,19)

Therefore, a randomised, double-blind, placebo-controlled study is highly required to evaluate the benefit of a therapeutic strategy with an early bolus dose of human fibrinogen concentrate in PPH.

1.3.2. CLOTTAFACT® dose regimen and infusion rationale

Clottafact is a human fibrinogen concentrate. According to the current SPC of Clottafact® (26), the dose of Clottafact® depends on the severity of haemorrhage and the patient's clinical condition.

Clottafact® is for intravenous route only and available as vials of 1.5g. An initial dose of 1 to 2 g is usually administered and could eventually be repeated. In case of severe acute obstetrical haemorrhage, larger doses of fibrinogen concentrate (4 to 8 g) may be necessary.

In this study, Clottafact® will be administered at a bolus dose of 3 g. This dose was chosen according to the anticipated amount of blood loss and corresponding loss of fibrinogen. As the main objective of the study is to assess the benefit of a therapeutic strategy that associates an early administration of fibrinogen, the 3-g dose of the protocol is lower than the 4 to 8 g mentioned in the SPC. In both group, additional open-label administrations of fibrinogen concentrate will be allowed as a rescue therapy if the severity of the clinical situation required such additional fibrinogen administration according to the investigator.(cf 7.2.)

1.3.3. Rationale of the population studied

As a general preventive approach, the use of oxytocin for active management of the third stage of labour is strongly recommended, because it reduces PPH by more than 60% (34). However, as previously mentioned, in case of oxytocin-resistant PPH, prostaglandins are the second-line treatment that should be associated with transfusion (33,35). Therefore, in the present study, only patients with oxytocin-resistant PPH will be included. To make sure only oxytocin-resistant PPH patients will be selected, inclusion will be performed after the decision of administration of prostaglandins has been taken.

Bleeding related to caesarean section may be due to surgical injury therefore only patients with PPH occurring after vaginal delivery will be included in the present study to select a more homogeneous population of patients.

2. STUDY OBJECTIVES

2.1. Primary objective

The primary objective of this study is to assess the benefits of a therapeutic strategy that associates an early administration of human fibrinogen concentrate in the management of PPH on the reduction of bleeding after the initiation of prostaglandins intravenous infusion.

2.2. Secondary objectives

The secondary objectives of the study are:

- To assess the evolution of haemorrhage,
- To assess the need for haemostatic intervention,
- To assess the need for intrauterine balloon,

- To assess the maternal morbi-mortality,
- To assess the biological effects of fibrinogen concentrate administration,
- To assess the tolerance of fibrinogen concentrate administration.

3. STUDY DESIGN

3.1. Design

A study flow-chart is available in the protocol synopsis section.

The present study is a phase IV, multicentre, randomised, double-blind, placebo-controlled, parallel-group study.

The patients will be randomly allocated to one of the two groups of treatment:

1. Active treatment: fibrinogen concentrate (Clottafact®) 3g, or,
2. Placebo treatment.

The investigational medicinal product (IMP) is administered as a single-dose as soon as possible during the 30 minutes after the start of prostaglandin infusion.

The duration of participation of each patient is 6 ± 2 weeks after randomisation.

No interim analysis is planned.

3.2. Endpoints

3.2.1. Primary endpoint

The primary endpoint is a composite endpoint defined as the percentage of patients:

- Losing at least 4 g/dl of Hb, within the 48 hours following IMP administration

and/or

- Requiring the transfusion of at least 2 units of packed RBCs within the 48 hours following the administration of IMP.

The reference of Hb level is the most recent Hb value recorded within the third trimester of pregnancy.

The 4-g/l threshold has been used to define the severity of PPH in several studies (16,19). The determination of Hb level during the third trimester is mandatory in France and is independent of delivery, PPH and vascular loading. It is the reason why it was chosen preferably to Hb at the time of the inclusion.

The Hb might be modified by transfusion therefore transfusion is also included in the composite endpoint. The amount of transfusion is physician dependent and it is the reason why it has been decided not to use this sole criterion, and in addition, a minimum of 2 packs of RBCs has been defined. The 48-hour follow-up duration is chosen according to Ozier et al (36) because of the stabilisation of the hemoconcentration after PPH. In order to determine the time point evaluation at 48 hours after delivery (H48), a 20-hour time interval (from H32 to H52) will be allowed to show more flexibility towards the variability of the time of delivery and the hour of IMP administration (H0).

3.2.2. Secondary endpoints

3.2.2. 1. Evolution of haemorrhage

- Percentage of patients losing at least 4 g/dl of Hb, 48 hours following IMP administration with regards to the Hb reference level.
- Percentage of patients losing at least 3 g/dl of Hb, 48 hours following IMP administration with regards to the Hb reference level.
- Percentage of patients requiring the transfusion of at least 2 units of RBCs, 48 hours following IMP administration.
- Percentage of patients losing at least 4 g/dl of Hb, 48 hours following IMP administration with regards to the level of Hb measured at inclusion.
- Percentage of patients with an occurrence of Hb level < 9 g/dl within the 48 hours period following inclusion.
- Number of units of transfused blood products within the 48 hours period following IMP administration.
- Calculated volume of total blood loss, 48 hours following IMP administration.

3.2.2. 2. Need for haemostatic intervention

- Percentage of patients requiring at least one of the following interventions within 48 hours following the administration of IMP: pelvic arteries embolization, surgical vascular ligation, uterine ligation (B Lynch or other techniques), administration of recombinant activated Factor VII (rFVIIa) and hysterectomy.

3.2.2. 3. Need for intrauterine balloon

- Percentage of patients requiring the use of intrauterine balloon within 48 hours following the administration of IMP.
- Time of intrauterine balloon placement

3.2.2. 4. Maternal morbi-mortality

- Length of stay in resuscitation and/or intensive care and/or post interventional care units (PICU) and/or continuous care.
- Length of stay in obstetrics units.
- Single or multi-organ failure (SOFA score) in women transferred to resuscitation and/or intensive care and/or PICU and/or continuous care units.
- Death during the study.

3.2.2. 5. Biological effects of fibrinogen concentrate administration

- Evolution of blood fibrinogen level between inclusion (blood sampling 1) and D2 (blood sampling 4).
- Evolution of haemoconcentration between H0 and D2.

3.2.2. 6. Tolerance of fibrinogen concentrate administration

- Serious and non-serious adverse events (AE).

3.3. Measures to avoid/minimise bias

All patients will be randomly assigned to one of two groups of treatment, at a ratio of 1:1. Full information about the randomisation procedure is provided in Section 8.2.2.

To avoid any bias in assessing the efficacy and safety of Clottafact®, the use of placebo as a control group should ensure objective assessment of the clinical endpoints.

Furthermore the primary endpoint has been defined independently of the clinical practices in order to limit the influence of centre effect.

Rules for the use of concomitant medication that has an effect on coagulation status and for the transfusion of blood products will be proposed to the investigators in order to limit the differences in PPH management among centres. The global algorithm of the PPH treatment (derived from French guidelines) (37,38) will be provided at the end of protocol (See Appendix 20.3). Adherence to this algorithm will be checked for each centre during the feasibility/selection process. In case of none or partial acceptance of the algorithm the final selection of the centre will be discussed with the scientific committee.

3.4. Study Investigational Centres

The study will be conducted in approximately 25 French investigational centres.

Each centre is expected to enrol a mean of 29 eligible patients.

Investigators will be the physicians who usually treat the patient with haemostatic drugs (including fibrinogen concentrate) in the centre according to the local established practice.

Midwives can also shoulder investigator's responsibilities except for haemostatic treatments prescription which is made by the physician.

The investigational centres should have immediate access to equipment and staff for resuscitation.

The participating centre should have an organisation allowing a third-party, not involved in patient care, to reconstitute the IMP before its administration by the medical team. The procedure describing such process and the persons involved will be established for each centre (see Section 6.4.2).

3.5. Data and Safety Monitoring Board/Scientific Committee

3.5.1 Scientific Committee

A Scientific Committee has been set-up for the study. Its main responsibilities are:

- To define the study global methodology and design,
- To propose a study synopsis,
- To participate to the study protocol writing and to validate the final version of the protocol and of the amendments if any,
- To validate the final selection of each centre,
- To maintain a continuous communication with the investigators during the study,
- To review the data before the database lock,
- To validate the clinical study report before writing all reports and publications.

3.5.2 Data and Safety Monitoring Board

A Data and Safety Monitoring Board (DSMB) will be set up to ensure patient's safety.

The DSMB is an expert committee, independent of the Investigators and the Sponsor of the clinical study. This committee will periodically examine data accumulated during the study and ensures that the benefit/risk ratio remains acceptable for participating patients.

The Sponsor will timely provide the members of the DSMB with the safety data of patients.

The DSMB will be asked to regularly review safety data and especially all reported serious adverse events (SAE) in order to decide if it would be necessary to generate an amendment or even to discontinue the study for security reasons.

Quality of the DSMB members, the board organisation and its mode of operation will be described in an ad-hoc document before the start of the study.

The DSMB will include a board steering experts who are not involved in the study (apart from the Sponsor, subsidiaries or study team):

- A specialist in anaesthesia and resuscitation (MD, PhD),

- A specialist in Obstetrics and Gynaecology (MD, PhD),
- An expert in biostatistics (MD, PhD).

4. DURATION AND DATES OF THE STUDY

The duration of this study is expected to be approximately 4 years. The first patient's first visit took place on April 10th, 2014, and the last patient's last visit is expected in August 2018 at the latest.

5. STUDY POPULATION

5.1. Number of patients

Sample size calculation is determined as a total of 412 evaluable patients (206 in each group) completing the study. Since the primary endpoint is measured shortly after the inclusion, the rate of drop-out is assumed to be approximately 5%. Then 434 patients will be included in this study (see Section 12.3).

As there is some uncertainty about the variance of the test statistics, the variance will be re-estimated in a blind way so as to maintain the power to 90% while still considering the same originally planned difference in failure rates, i.e. 15%. It can be shown that the possible increase in sample size (after adjusting for drop-outs) cannot exceed 50 additionnal patients. Hence the restimated sample size will not exceed 484 patients (see Section 12.3).

In this multicentre study, a mean number of 29 patients is expected to be enrolled by each centre.

The enrolment objectives for each centre will take into consideration the enrolment period, i.e. approximately 1 patient per month.

5.2. Eligibility Criteria

Before any study-related procedure is undertaken, a written informed consent must be obtained (see Section 8.1.1).

For a patient to be eligible, all of the inclusion criteria and none of the exclusion criteria must be met.

5.2.1. Inclusion criteria

For patient inclusion, all of the following criteria must be met:

a. Signed and dated informed consent form,

b. Vaginal delivery,

c. PPH requiring IV administration of prostaglandin,

d. At least one available result of Hb level during the third trimester of pregnancy,

e. 18-year-old female patients and older,

f. Covered by healthcare insurance in accordance with local requirements.

5.2.2. Non-inclusion criteria

Patients will not be eligible for inclusion in this study if any of the following criteria is met:

a. Caesarean section,

b. Haemostatic intervention (as ligation, embolization or hysterectomy) already decided at the time of inclusion,

c. Known placenta praevia or accreta,

d. Hb level < 10g/dL during the third trimester of pregnancy,

e. History of venous or arterial thromboembolic event,

f. Known inherited bleeding or thrombotic disorders,

g. Treatment with low-molecular-weight heparin (LMWH) within 24 hours prior to the inclusion,

h. Treatment with acetylsalicylic acid within 5 days prior to the inclusion,

i. Treatment with vitamin K antagonists within 7 days prior to the inclusion,

j. Administration of fibrinogen concentrate within 48 hours prior to the inclusion,

k. Administration of FFP, platelets units or prohaemostatic drugs, tranexamic acid and rFVIIa or PCC within 48 hours prior to the inclusion,

l. Administration of RBCs within 3 months prior to the inclusion,

m. Participation in another interventional clinical study using an investigational medicinal product within 30 days prior to the inclusion,

n. Previous inclusion in the present clinical study,

o. Known history of hypersensitivity or other severe reaction to any component of Clottafact® or placebo,

p. Minors, majors under guardianship, persons staying in health or social institutes and people deprived of their freedom,

q. Known drug or alcohol abuse,

r. Patients whose use of concomitant medication may interfere with the interpretation of data,

s. Any other current significant medical condition that might interfere with treatment evaluation according to the investigator's judgement,

t. Patients who are unlikely to survive through the treatment period and evaluation,

u. Patients transferred from another service after the delivery

5.3. Duration of Patient participation

For each patient, the participation will last for 6 ± 2 weeks after the delivery.

The exclusion period defined for this study is 1 month. During this period the patient can not participate to another biomedical research after the end of the study or its early termination.

5.4. Discontinuation criteria

The Investigator must document the date and the reason of any patient withdrawal or discontinuation by a narrative description in the patient's medical records.

A patient may be discontinued from the study at any time for one or more of the following reasons:

a. Non randomised patient,

b. Worsening of the patient's condition requiring emergency measures that do not allow the administration of IMP,

c. Withdrawal of consent for any reason, at any time,

d. Lost to follow-up.

Data to be collected are detailed in Section 8.

If at the time of withdrawal, the patient has received the IMP (partially or totally), she must be advised to agree to follow up safety investigations.

If a patient withdraws from the study, the investigator will make every effort to complete the final evaluation by performing an "end of study visit". All evaluation results, the date and a narrative description of the reason(s) for discontinuation must be recorded in the source documents and in the Case Report Form (CRF).

5.5. Lost to Follow-up

Investigators should make every effort to minimise the number of patients lost to follow-up and to obtain a maximum of information on patients lost to follow-up. All attempts will be documented in the patient's medical record.

6. INVESTIGATIONAL MEDICINAL PRODUCTS (IMPS)

6.1. Description of IMPs

The active investigational product Clottafact® and placebo will be supplied, free of charge, by the sponsor. Their management at the investigational centre will be under the responsibility of the investigator.

6.1.1. Fibrinogen

Clottafact® is an anti-haemorrhagic drug (B02BB01) composed of a fibrinogen concentrate derived from human plasma.

Clottafact® is manufactured by LFB BIOMEDICAMENTS and has obtained a marketing authorization in France in May 2009 for congenital and acquired fibrinogen deficiencies.

The manufacturing process of Clottatact® includes three viral inactivation/removal steps:

- A solvent-detergent treatment which has been shown to be effective in the inactivation of enveloped viruses such as Human Immunodeficiency Virus, hepatitis B and C viruses,
- A dry heating which inactivates small non-enveloped viruses, especially parvovirus B19 and hepatitis A virus,
- A 35 nm filtration which eliminates both enveloped and non-enveloped viruses that are larger than 35 nm, and thus, contributes to the reduction of the theoretical risk of transmission of unconventional agents such as prions.

Clottafact® is available in the form of a glass vial containing a freeze-dried powder, along with a solvent for reconstitution in the form of 100 mL of sterile water ready for injection. Each vial contains approximately 1.5 g of fibrinogen.

Clottafact® also contains relative amounts of other co-purified plasma proteins: fibronectin (5.3%), IgM (1.2%), C4 (0.57%), FXIII (0.40%) and plasminogen (0.40%).

The principal excipients are:
- Arginine hydrochloride (4.0 g)
- Isoleucine (1.0 g)
- Sodium citrate (0.25 g)
- Lysine hydrochloride (0.2 g)
- Glycine (0.1 g)

The reconstituted solution contains approximately 15 mg/mL of human fibrinogen.

For more information, see the Summary Product Characteristics (SPC).

6.1.2. Placebo

The placebo will be supplied in identical glass vial containing a freeze-dried powder, along with a solvent for reconstitution in the form of 100 mL of sterile water ready for injection.

In order to offer appearance, consistency and observable properties as close as possible to Clottafact® that contains proteins, the vial of placebo is composed of the following excipients:

- Mannitol (3.5 g)
- Saccharose (4.4 g)
- Sodium chloride (0.18 g)
- Polysorbate 80 (5 mg)

6.2. IMP packaging and labelling

6.2.1. Packaging

Clottafact® and placebo will be packaged in the same type of vials and boxes to guarantee the blinding.

The IMP (Clottafact® or placebo) is composed with:

- 1 vial of IMP (Clottafact® 1,5g or placebo),
- 1 vial of 100 ml sterile water,
- 1 transfer system.

Then, two IMPs will be packed as a set which will contain the treatment needed for one patient/injection so two boxes of IMP. Each set will also contain:

- 1 tinted tubing for the infusion in order to ensure blinding during the administration of the reconstituted IMPs,
- Adhesive film (blinding label) to mask the 2 vials of reconstituted IMPs.

IMP sets will be packaged and sent to the investigational centres in dispatch boxes containing the treatment for 4 patients.

6.2.2. Labelling

The labels will carry required regulatory texts. Each vial and external packaging will be labelled at least with the following information:

- FIDEL Study
- Number of treatment unit
- Batch No:
- Expiry date: MM/AAAA
- Patient N°|__|__|-|__|__| (to be filled in)
- Investigator's name (to be filled in)
- Read the package leaflet before use
- For intravenous use only
- Powder and solvent for solution for injection
- Storage requirements: do not store above +25°C, protect from light, do not freeze
- To be used within 6 hours following reconstitution

- Medicinal product derived from human plasma
- For clinical use only
- For use under medical supervision

- LFB BIOMEDICAMENTS contact details :
  3, avenue des Tropiques - BP 40305
  91958 COURTABŒUF Cedex - France
  Phone number: (+33) (0)1 69 82 70 10

The IMP vials will bear two tear-off labels as well as the external packaging, a label for plasma-derived product traceability with two stickers. Traceability label will be stuck on CRF, patient's medical record and pharmacy site file.

6.3. Management of IMP

Clottafact® and placebo will be supplied by the Sponsor in blind packages to the Hospital Pharmacist in investigational sites, free of charge for the hospital and the patient.

6.3.1. Shipment and receipt

The IMP will be shipped to the Hospital Pharmacist by a Drug Distributor (under the Sponsor responsibility) in accordance with local requirements. Shipment of IMP will be done at refrigerated temperature (+2°C/+8°C), these conditions being ensured by the use of a temperature monitoring device.

A first shipment of 2 dispatch boxes (each box containing the IMPs for 4 patients) will be performed to each centre as soon as the initiation of the centre is validated by the Sponsor.

Upon receipt of the IMPs at site, the Pharmacist will inventory the study treatment and complete the acknowledgment of receipt form. Should any abnormality of the supplied boxes be observed, the Pharmacist must immediately inform the Monitor/Sponsor. The acknowledgment of receipt form must be returned to the Sponsor or representative as instructed.

6.3.2. Storage requirements

The IMP must be protected from light, stored in a secured limited-access area and maintained at a temperature below +25°C without being frozen. They must be kept in their original dispatch boxes.

If the reconstituted IMP is not administered immediately, storage must not exceed 6 hours. Reconstituted IMP must be stored below +25°C and must not be frozen (for additional information, see SPC).

The Investigator and/or the Hospital Pharmacist are responsible for the appropriate storage of the IMP at the investigational centre.

If the required storage conditions are not respected, the Investigator and/or the Hospital Pharmacist must immediately inform the Monitor/Sponsor.

For any temperature deviation, a written approval from the Sponsor must be obtained prior to any dispensation/administration. During the evaluation of the temperature deviation, the concerned IMP must be placed under quarantine. If the decision is not to use the quarantined IMP, the vials will remain under quarantine until shipment back to the Drug Distributor.

6.3.3. IMP re-supplying

The investigational centres will be re-supplied with IMPs according to their respective enrolment rates.
One, or more, dispatch box will be sent accordingly.

The IMPs will be sent to the centre within 5 working days from the request.

6.3.4. IMP return, destruction and recall

6.3.4. 1. Return and destruction

Used and unused IMPs will be returned back to the Sponsor's Drug Distributor at the close-out visit at the latest. IMPs return will be organised by the Hospital Pharmacist and the Monitor. The Hospital Pharmacist or a delegate should be available at the predetermined date and time when the boxes will be collected from the investigational centre.

The used/unused IMPs (vials, tubings and original containers) must NOT be destroyed at the Hospital Pharmacy without a written authorisation from the Sponsor. If an on-site destruction is required, the site must have a written authorisation from the Sponsor for destruction which will be filed along with the certificate of destruction in the IMP section of the Pharmacy site file.

At the end of the study, a final reconciliation between delivered, dispensed, used/unused and returned IMPs will be conducted by the Monitor.

6.3.4. 2. Recall

If an IMP batch is suspected to be defective, the Investigator and the Hospital Pharmacist will be immediately informed by the Sponsor.

The Monitor will organise with the Hospital Pharmacist the return of the concerned batch(es) as per the return procedure. Depending on the study stage, new batch(es) may be sent to the investigational centre.

6.4. Treatment of patients

6.4.1. Methods for Assigning Patients to Treatment Groups

IMP will be numbered and treatment will be assigned to eligible patients according to the ascending order of their randomisation.

The steps for assigning patients to treatment groups are described in Section 8.1.3.

6.4.2. Dispensing

Under no circumstances will the Investigator allow the IMP to be used other than as directed in the protocol.

- **IMP reconstitution**

  To prevent any risk of unblinding of the investigating study team which may occur during IMP preparation, a third party not involved in patient care will be in charge of this task.

  - IMP is to be reconstituted before infusion: 2 vials of powder (Clottafact® or placebo) will be reconstituted each with 100 mL of sterile water for injection, in order to administer 200 mL of reconstituted IMP to the patient.

  - Participants, outcome assessors, trials investigators, statisticians and monitors are blinded, as well as care providers such as midwives, obstetricians, anaesthesiologists and anaesthetist nurses.
    - Use current guidelines for aseptic procedure.
    - If necessary, bring the two vials (powder and solvent) to ambient temperature.
    - Remove the protective cap from the solvent vial (water for injection) and from the powder vial.
    - Disinfect the surface of each stopper.
    - Remove the translucent protective sheath from the transfer system, and completely insert the exposed needle through the centre of the stopper of the solvent vial while simultaneously twisting the needle.
    - Remove the second protective sheath from the other end of the transfer system.
    - Keeping both vials horizontal (vented spike pointing upwards), quickly push the free end of the needle in the centre of the stopper of the powder vial.
    - Ensure that the needle always remains immersed in the solvent to avoid releasing the vacuum prematurely.
    - Immediately place the system upright in a vertical position, keeping the solvent vial directly above the powder vial, to allow the solvent to transfer into the powder.
    - During transfer, direct the jet of solvent over the whole surface of the powder. Ensure that all of the solvent is transferred.
    - The vacuum is automatically released at the end of the transfer procedure (sterile air).
    - Remove the empty vial (solvent) with the transfer system.
    - Lightly swirl with a rotating movement to avoid the formation of foam until the powder has completely dissolved.

- The reconstituted product should be examined visually in order to ensure that it does not contain particulate matter. The reconstituted solution should be slightly or more markedly opalescent. Do not use solutions which are cloudy or contains deposits.

- Note that in light of its stability after reconstitution, the injection may be performed within a period of six hours.

    - The IMP must not be administered if it does not conform to the description. The Investigator/Hospital Pharmacist should immediately alert the Monitor/Sponsor.

- The 2 vials of IMP should be masked with an adhesive film (blinding label):

    - While wrapping the blinding label around the vial, the third party pushes the small flaps on the upper edge of the label against the vial carefully. He/she will then write the patient number on the blinded vial.

- For additional information on IMP reconstitution, see SPC of Clottafact® (26) and the study document entitled "Guidelines for IMP reconstitution".

▪ **Treatment dose and schedule**

- IMP is administered at a fixed dose: a total volume of 200 mL of IMP (2 vials of 100 mL of reconstituted IMP) are injected to every patient.

- Only one injection of IMP will be performed to the patient throughout the study.

- Injection of IMP must start as soon as possible and within 30 minutes following the start of prostaglandin infusion.

▪ **Method and route of administration**

- Only intravenous route is allowed for the administration of the reconstituted solution of IMP.

- The administration will be performed using the tinted tubing provided with the IMP.

- The reconstituted solution of each IMP should be warmed up to room or body temperature before administration, and then infused at a flow rate ≤ 20 mL/min.

- Date and time of administration (start/end) are to be reported in the CRF and patient's medical records.

- IMP label (tear-off part on the masking system) has to be stuck on corresponding visit page in CRF.

- Following the administration of IMP, the therapeutic management of PPH will be left to the discretion of the Investigator.

6.4.3. Misuse /Overdose

Any IMP misuse/or overdose associated or not with any adverse event should be reported on an Adverse Event form and faxed to the Sponsor immediately and no later than 24 hours (see Section 9.5.6).

6.4.4. Compliance

Compliance with treatment is defined as the administration of IMP to the patient performed entirely (2 vials) according to the investigator's judgement.

The compliance will be considered as non-optimal if, for any reason, the infusion of at least 1 of the 2 IMP vials has been stopped before the total volume has been administered.

6.5. IMP accountability

The Sponsor will provide specific forms for drug accountability, which will be kept up-to-date by the Investigator and/or Hospital Pharmacist throughout the study.

All reasons for non-compliance must be carefully monitored, recorded and tracked.

The accountability forms should be filed in the investigator site file. The Monitor will verify the drug accountability forms for completeness and accuracy at each site visit.

At the end of the study, it must be possible to reconcile delivery records with dispensing and used/unused records. Any discrepancy must be accounted for.

Used/unused IMP should be kept in a secured place at the centre until the verification of records by the Monitor and organisation of return to Drug Distributor.

6.6. Randomisation Codes and Procedures for Unblinding

The Sponsor will provide the Investigator or Pharmacist with decoding devices in sealed envelopes with an acknowledgement of receipt at the same time as the IMP. These codes should be kept in a secured place with restricted access and returned to the Sponsor at the end of the study.

The Investigator is entitled to unblind the treatment in case of medical emergency when the identity of the administered treatment may determine the strategy of patient management.

The Sponsor should preferably be consulted prior to the blind being broken, but in any case, unblinding must be reported to the Sponsor immediately.

In the case of premature unblinding, the following items must be recorded on the decoding device: the date and time of unblinding, the name of the person responsible and the reason for unblinding.

The Investigator must sign and date the decoding envelop just before opening it, and document the unblinding in the patient's file.

The circumstances under which the code for a given patient has been broken should be fully documented in the Investigator's file.

7. PRIOR AND CONCOMITANT MEDICATION

7.1. Prior Medication

The term 'prior medication' refers to any medication given before inclusion, i.e. before the informed consent form was signed.

All prior medication relevant with regard to the patient's baseline description, taken within 7 days before inclusion, including all medication administered since the beginning of the delivery, must be recorded in the patient's medical records and documented on the appropriate pages of the CRF. Non-inclusion criteria related to prior medication are:

- Treatment with Low Molecular Weight Heparin (LMWH) within 24 hours prior to the inclusion,
- Treatment with acetylsalicylic acid within 5 days prior to the inclusion,
- Treatment with vitamin K antagonists within 7 days prior to the inclusion,
- Administration of fibrinogen concentrate within 48 hours prior to the inclusion,
- Administration of RBCs, FFP, platelets units or prohaemostatic drugs, tranexamic acid and rFVIIa or PCC within 48 hours prior to the inclusion.

All authorised medications taken regularly at baseline will be continued and documented as a concomitant medication throughout the study protocol.

7.2. Concomitant Medication

The term 'concomitant medication' refers to any medication that the patient receives at any time during the study, i.e. from inclusion to the end of study visit/phone call.

The concomitant treatments below will be administered in accordance with the following recommendations:

- The dose of prostaglandins will be administered according to the 2004-recommendations provided by the French National Authority for Health (Haute Autorité de Santé, or HAS) (13).

- Fibrinogen concentrate as rescue therapy will not be administered :

    - within 60 minutes following the start of IMP

      or

    - before the administration of at least 2 units of packed RBCs.

- In clinical situation where severe uncontrolled haemorrhage require immediate coagulopathy management including blood product transfusion and fibrinogen concentrate, RBC would be administrated within a short period of time after the start of IMP infusion. Therefore in such cases, the fibrinogen concentrates as rescue therapy would be administrated after the RBC infusion and before the 60 minutes period. Then, this administration will not interfere with the assessment of the primary criteria.

- Tranexamic acid:
  - The administration of tranexamic acid will be allowed only after prostaglandin infusion has been decided.
  - Recommended dose: 1 g IV to be renewed once after 30 min.

- Blood transfusion in accordance with the following objectives:
  - Hb ≥ 8 g/100 ml,
  - PT ≥ 40%,
  - Platelets count ≥ 50 000/mm^3,
  - Transfusions of RBC, FFP and platelets units can be performed before the availability of laboratory results, when indicated (29, appendix 20.4).

- Hydroxyethylstarch (HES): maximum dose of 1.5 litres during the first 24 hours.

All concomitant medication, including intravenous fluids and blood products, must be recorded in the patient's medical records and documented on the appropriate pages of the CRF.

8. STUDY PLAN

The method for assessing each study parameters is described in Section 10.

Investigators may also refer to the study flow-chart (Table 1).

8.1. Patient recruitment

8.1.1. Informed Consent

Patients with significant blood loss may have impaired consciousness and may be unable to give properly informed consent. In this emergency situation it may not be medically appropriate to delay the start of treatment. In this study, informed consent will be obtained from either the patient or a member of her family or the reliable person depending of the patient's level of consciousness.

The EU Directive (2001/20/EC) requires that, prior to participation in a trial, written informed consent from a legal representative of any person unable to consent for herself has to be obtained. The requirements of the relevant ethics committee will be adhered to at all times. An informed

consent form for legal representative will be available in addition to an inform consent form for patients.

Under certain circumstances, PPH may represent a critical condition for both the patient and her family (her husband the most often) or any other person in a position of trust. In such an emergency, it would be impossible to ask them to read a complete and very detailed information sheet at the moment of inclusion. Therefore, concise information on the study will be given as soon as PPH is diagnosed. Depending on the patient's physical condition, the concise information will be given to the patient or a family member or the person of trust.

The initial information may be given to the patient during the last prenatal consultation (with the obstetrician or the anaesthetist) by the sites which would prefer to anticipate this procedure.

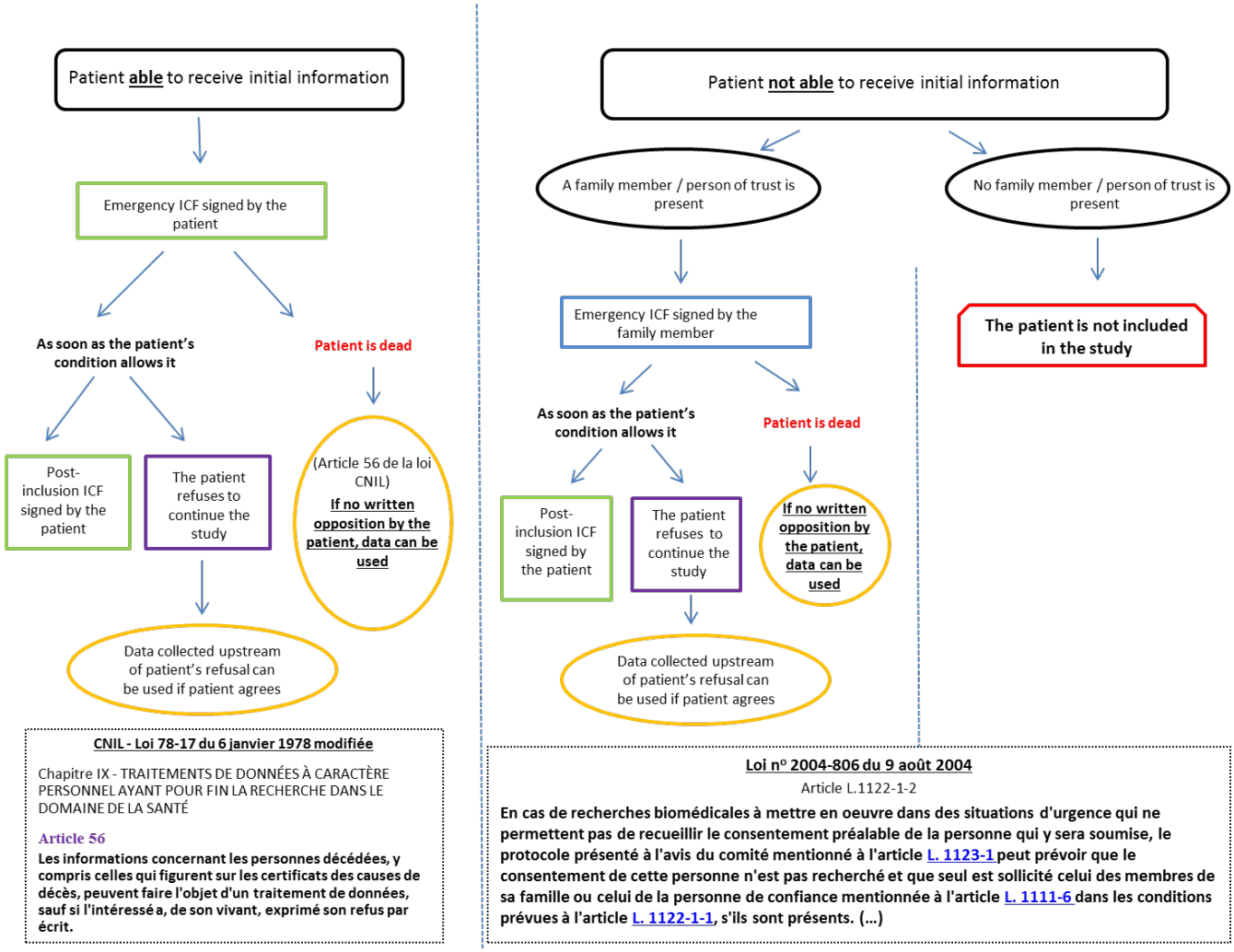
The procedures for collecting written informed consent in emergency situation are described on the next page.

In all cases, as soon as the patient regains competence, she will receive full required information about the study. **Her post-inclusion consent to continue the study must be requested**.

She should have enough time and opportunity to inquire about study details. All her questions should be answered with complete satisfaction. The patient must be informed about her right to withdraw from the study at any time.

She may also decide to reject the use of her data in the context of the study.

An NCR (No Carbon Required) copy of the informed consent form (emergency and post-inclusion), signed and dated by both the patient (or the designated person as described above) and the Investigator should be given to the patient (or the designated person as described above). The process for obtaining consent will be documented in the patient's file and in the CRF.



8.1.2. Patient Inclusion

The patient is considered as included when emergency informed consent form has been signed by the patient or a member of her family or the person of trust (see Section 8.1.1).

8.1.3. Patient Randomisation

Randomisation corresponds to the attribution of a study treatment unit to the patient.

As soon as prostaglandin infusion has been decided, the patient will be randomly allocated to one of the two groups of treatment:

1. Active treatment group: fibrinogen (Clottafact®) 3g or,
2. Placebo group.

The treatment will be double-blind.

Given that the inclusion will be realised in emergency situation, the randomisation will be done in the centre. Each centre will receive pre-numbered treatments in dispatch boxes. According to the time of inclusion, study treatment units will be allocated sequentially in chronological order of randomisation in ascending manner.

An inclusion fax will be sent to the Monitor within the 24 hours after inclusion.

Randomisation will be stratified on the centre.

8.1.4. Replacement of early withdrawals

No patient will be replaced.

8.2. Schedule of visits

The duration of patient participation is 6 ± 2 weeks starting from randomisation. After enrolment, all patients will be treated with IMP. The start of IMP administration corresponds to H0.

8.2.1. Visit 1: Inclusion / Blood sampling 1

Information on the study will be given at the moment of the diagnosis of haemorrhage (see Section 8.1.1).

- Informed consent must be obtained before any study procedure;
- Eligibility criteria check (inclusion and non-inclusion criteria);
- Date and start time of prostaglandin infusion;
- Demographics (height, weight prior to pregnancy and last known weight);
- Thromboembolic and obstetrical events and any clinically relevant medical conditions;
- Pregnancy parameters:
    - Hb level during the third trimester,
    - Hb level at the sixth month,
    - Ht and platelets will be collected if available
    - Date of last menstrual period, gestational age,
- Delivery parameters
    - Times of the start and the end of delivery;
    - Number of live births and/or stillbirths;
    - Procedures: artificial delivery, uterine or genital examination
- Prior and concomitant treatment (see Section 7) including intravenous fluids and blood products since the start of delivery;
- Haemorrhage parameters :
    - Haemorrhage start time;
    - Measured or estimated volume of blood loss at the start of prostaglandin infusion;
- Physical examination will include a comprehensive standard evaluation of all systems: cardiovascular system, respiratory system, skin and appendices, gastrointestinal system, ear-

nose-throat, lymphatic nodes, spleen, central nervous system, eyes, musculoskeletal system, endocrine system, argental system, psychiatric state. Signs for possible thrombosis will be checked.

- Vital signs:
  - Measurement of arterial blood pressure (systolic and diastolic),
  - Heart rate.

- Blood sampling for laboratory parameters at inclusion:
  - Complete blood count, Hb, Ht, platelets,
  - Haemostatic profile: fibrinogen, PT, QT, aPTT, D-dimers,
  - Blood urea and serum creatinine.

8.2.2. Visit 2: Randomisation and IMP infusion

- Randomisation will be performed as soon as possible after inclusion and after the start of prostaglandins infusion (see Section 8.1.3).
- IMP administration
  - A third party reconstitutes the IMP (see Section 6.4.2).
  - The start of IMP infusion corresponds to H0 and should be within the 30 minutes following the start of prostaglandins infusion.
  - The start and the end times and the administered volume will be collected in the CRF.
- Concomitant treatments including intravenous fluids and blood products;
- Local tolerance which occurred during IMP infusion and AEs if any.

8.2.3. Visit 3: H2 (120 ± 30 min) / Blood sampling 2

The following data will be collected in the CRF:

- Blood sampling:
  - Complete blood count, Hb, Ht, platelets,
  - Haemostatic profile: fibrinogen, PT, QT, aPTT, D-dimers,

- Vital signs
  - Measurement of arterial blood pressure (systolic and diastolic),
  - Heart rate;
- Haemorrhage parameters:
  - Measured or estimated volume of blood loss from the start of bleeding;
- Concomitant treatments including intravenous fluids, blood products, tranexamic acid and fibrinogen concentrate as rescue therapy: any modification or institution of a new treatment;
- AEs if any.

8.2.4. Visit 4: H6 (360 ± 30 mn) / Blood sampling 3

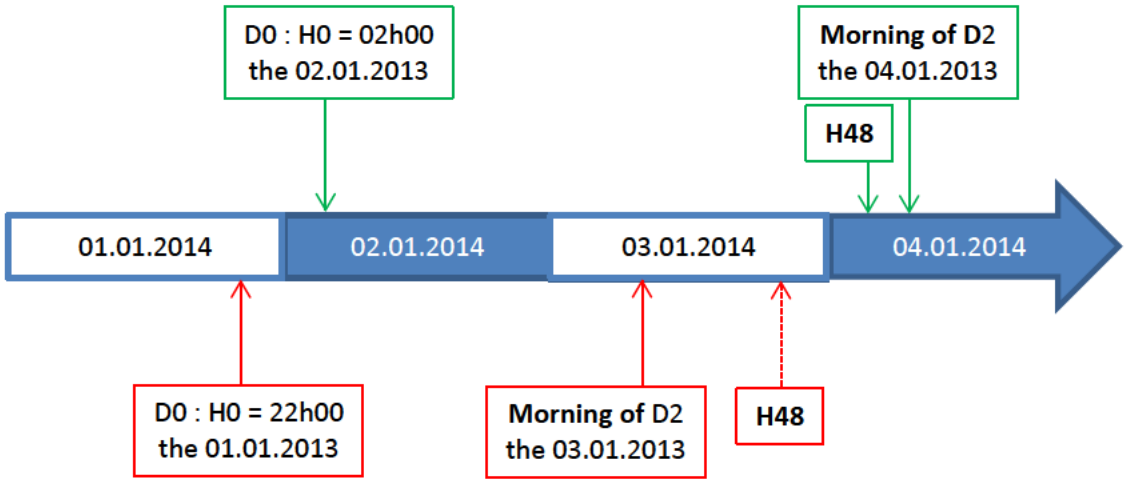
The following data will be collected in the CRF:

- Blood sampling:
  - Complete blood count, Hb, Ht, platelets,
  - Haemostatic profile: fibrinogen, PT, QT, aPTT, D-dimers,
- Vital signs
  - Measurement of arterial blood pressure (systolic and diastolic);
  - Heart rate;
- Haemorrhage parameters:
  - Measured or estimated volume of blood loss from the start of bleeding;
- Concomitant treatments including intravenous fluids, blood products, tranexamic acid and fibrinogen concentrate as rescue therapy: any modification or institution of a new treatment;
- AEs if any.

8.2.5. Visit 5: morning of D2 / Blood sampling 4

Depending on the time of delivery, the assessment in the morning of D2 may differ from H48 (considering that the first blood sampling in hospital is performed around 7h00 in the morning).

H0 = start of IMP administration



Even if the patient has been transferred to another hospital or department within the same hospital, the investigator must ensure that all laboratory analyses will be performed, and the following parameters will be recorded in the CRF:

- Blood sampling:
  - Complete blood count, Hb, Ht, platelets,
  - Haemostatic profile: fibrinogen, PT, QT, aPTT, D-dimers,
  - Blood urea and serum creatinine
- Vital signs:
  - Measurement of arterial blood pressure (systolic and diastolic);
  - Heart rate;

- Concomitant treatments including intravenous fluids, blood products, tranexamic acid and fibrinogen concentrate as rescue therapy: any modification or institution of a new treatment;
- AEs if any.

8.2.6. Visit 6: Hospital discharge

Visit 6 corresponds to the final hospital discharge regardless the site of the patient's last admission after delivery and 6 weeks after delivery at the latest.

The data for this visit will also be collected if the patient is prematurely withdrawn after randomisation.

- Date of discharge;
- Date and time of obstetric room discharge;
- Stay in resuscitation and/or intensive care and/or PICU and/or continuous care units during hospitalisation (yes/no); if yes:
    - Length of stay in the unit;
    - Maximum SOFA score during the stay in the unit;
    - Number of days with assisted ventilation;
    - Renal failure that required dialysis;
    - Hypotension episodes that required continuous vasopressor therapy;
    - Acute pulmonary oedema, acute respiratory distress syndrome, transfusion-related acute lung injury (TRALI);
- Haemorrhage parameters:
    - Haemorrhage end date and time;
    - Total volume of blood loss: measured or estimated;
    - Blood-draining containers (if any): date and time of setting and removal and the total volume collected;
    - Possible haemostatic intervention needed: uterine tamponade by compression balloon (Bakri or Belfort-Dildy balloon), uterine compression sutures (B-Lynch suture, multiple squares/rectangles technique of Cho), arterial embolization or ligature, hysterectomy.
- Physical examination;
- Vital signs:
    - Measurement of arterial blood pressure (systolic and diastolic);
    - Heart rate;
- Concomitant treatments including intravenous fluids, blood products, tranexamic acid and fibrinogen concentrate as rescue therapy: any modification or institution of a new treatment;
- AEs if any.

8.2.7. Visit 7: End of Study Visit/Contact

The following tolerance data will be collected by the Investigator during an obstetrical follow-up visit or a phone contact at 6 ± 2 weeks after delivery, and reported in the CRF:

- Administration of any antithrombotic treatment since hospital discharge;
- Administration of iron (IV or oral) including the dose and the date of last administration, since hospital discharge;
- Serious and non-serious AEs.

8.3. Assessments

1) Clinical assessments

Clinical assessment	Time of assessment
Physical examination: It will include a comprehensive standard evaluation of all systems, like: cardiovascular system, respiratory system, skin and appendices, gastrointestinal system, ear-nose-throat, lymphatic nodes, spleen, central nervous system, eyes, musculoskeletal system, endocrine system, argental system, psychiatric state. Signs for possible thrombosis will be checked.	Inclusion Discharge of the hospital
Vital signs (arterial blood pressure and heart rate)	Inclusion H2, H6 Morning of D2 Hospital discharge
Maximum SOFA score	Upon discharge of resuscitation and/or intensive care and/or PICU and/or continuous care units (if any)

2) Laboratory assessments

Plasmatic assessments	Volume of blood sample	Type of tube	Time of assessment
Complete blood count, platelets, Hb, Ht	10 ml	EDTA	Inclusion, H2, H6 and D2
Fibrinogen, PT, QT, aPTT, D-dimers	5 ml	Sodium citrate	
Creatinine	5 ml	EDTA	Inclusion and D2

Urea	4 ml	Lithium heparinate	

A total of 78 mL of blood will be collected throughout the study according to the protocol. All biological parameters will be determined locally.

Any abnormal laboratory finding judged clinically significant by the investigator will be considered as an adverse event.

8.4. Compliance with the Study Plan

The Investigator should make every effort to comply with the study plan. If the Investigator encounters difficulties in complying with the study plan, e.g. with regard to the schedule of visits or the required procedures, he/she must alert the Sponsor or his/her designee. The Sponsor may consider it relevant to generate an amendment.

The Investigator should make every effort to avoid the occurrence of deviations from the study plan. If deviations occur or if the Investigator knows that a deviation will occur, he/she must promptly inform the Sponsor to determine how to manage the deviation.

9. SAFETY

9.1. Safety Reference Document

In this study, the Clottafact® current SPC, applicable at the time of an adverse event occurrence, will be considered as the Safety Reference Document, based on which evaluation of the adverse event will be performed, in particular regarding expectedness.

9.2. Benefit/Risk Information

The safety information received during the period covered by the PSUR (from 05/May/2009 to 31/Oct/2012), did not modify the safety profile of CLOTTAFACT as described in the SPC.During that period, no case with a fatal outcome related to CLOTTAFACT administration has been reported.

During the period covered by the PSUR (from 05/May/2009 to 31/Oct/2012), approximately 119 739 g of CLOTTAFACT were sold (among which more than 98 % in France).
An estimate of the number of treatments potentially administered has been calculated based on volume of CLOTTAFACT, sold in France and outside France, during the period and the estimated mean dose per treatment of 3.4 g. The estimated exposure was around 35,217 treatments.

During the period covered by the PSUR, the reporting rate was estimated to 0.06 %. There was no evidence of any significant increase in the frequency of ICSRs (Individual Case Safety Reports) with ADRs (Adverse Drug Reactions) reported over the time.

The non-interventional Post –Authorization safety Study (PASS) study was initiated at the time of CLOTTAFACT launch on the market and has been completed.

The primary objective was the assessment of CLOTTAFACT safety in current use and the secondary objective was the collection of efficacy data to better document the benefit/risk balance.

The PASS included 2 cohorts :

- ✓ "Acquired fibrinogen deficiency" cohort: 156 patients were included and received CLOTTAFACT.
- ✓ "Congenital fibrinogen deficiency" cohort: 14 patients were included and received CLOTTAFACT.

Concerning the "Acquired fibrinogen deficiency" cohort the report concluded:

- ✓ Concerning the safety, the investigators assessed CLOTTAFACT safety as good for the overall patient treated considering the patients' medical history. Based on this report, CLOTTAFACT safety was assessed as satisfactory.
- ✓ As regards to the efficacy, no new relevant information about CLOTTAFACT benefit has been raised in this study (the efficacy was the secondary endpoint). The investigators considered CLOTTAFACT efficacy with a success for 73.8 % of infusions (124/168 infusions).

The report concerning the "Congenital fibrinogen deficiency" cohort is under preparation.

Based on marketing experience including PASS with Clottafact®, the benefit/risk balance of Clottafact® remains favourable in the granted indications.

9.2.1. Known and potential risk(s) related to the IMPs

- Clottafact®

As specified in the Risk Management Plan of Clottafact®, the potential risks are:

Thromboembolic events:
Venous and arterial thromboembolic events are the main safety concerns associated with the use of fibrinogen concentrate. However, several minimisation actions are taken in order to limit the potential risks, which are detailed thereafter (see Section 9.3).

Anaphylactic reactions:
Immunoallergic events and anaphylactic accidents are potential concerns, which will be minimised by patient monitoring during administration.

Immunogenicity:
The occurrence of antibodies against fibrinogen is a very rare complication of fibrinogen replacement therapy. The risk of antifibrinogen antibodies appearance has been described only once in a patient with congenital afibrinogenaemia and rheumatic valvular heart disease.

Viral safety:
Clottafact® is purified from human blood of selected donors and its manufacturing process includes three viral/non-conventional transmissible agents removal/inactivation steps (solvent-detergent, dry heating and 35 nm filtration). Despite these highly secured procedures, the risk of viral infection or non-conventional transmissible agents cannot be totally ruled out.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include: selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite these safety procedures, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infectious agents cannot be totally excluded. This is also applied to unknown or emerging viruses and other pathogens. The previously mentioned measures are considered to be effective against enveloped viruses such as HIV, HBV, HCV and for the non-enveloped viruses HAV and parvovirus B19. There is reassuring clinical experience regarding the lack of hepatitis A or parvovirus B19 transmission and it is also assumed that the antibody content makes an important contribution to the viral safety.

- Placebo

At the planned conditions of use of Clottafact® placebo, no risk is expected.

9.2.2. Other expected or potential risk(s)

None.

9.2.3. Benefit/Risk balance

Clottafact® is already indicated in France as a complementary treatment for the management of severe uncontrolled bleeding resulting in acquired hypofibrinogenaemia (25,26). The aim of the present study is to show the benefit of an early administration of Clottafact® before hypofibrinogenaemia has been shown. The expected benefit of the proposed therapeutic strategy is to reduce the oxytocin-resistant PPH by the early administration of human fibrinogen concentrate at the time of prostaglandins infusion (see Section 1.3.3.). It is worthy to note that there is still no non invasive treatment that would be totally effective in preventing the morbidity and mortality of intractable PPH (see Section 1.1.4). This protocol will allow the evaluation of the therapeutic relevance of the proposed strategy by reliable and clinically approved endpoints.

Arterial and/or venous thromboembolic complications are the main known risk of the administration of fibrinogen concentrate. This risk is theoretically increased by the fact that women are in general more at risk of thromboembolic complications during pregnancy and after delivery (39). However, the hypothesis of an increased risk of post-partum thromboembolism is not highly plausible in this context. This is due to the fact that fibrinogen is the first coagulation factor to fall below physiological levels during PPH, contributing further to excessive bleeding (19). Nevertheless, this protocol will assess the safety and efficacy of early administration strategy of fibrinogen concentrate over placebo. Moreover, a DSMB, as an expert committee, will be constituted to ensure patient safety.

9.3. Risk Minimisation Actions Throughout the Protocol

Regarding the venous and arterial thromboembolic risk, the following risk mitigation measures will be taken:

- Exclusion of patients with documented history of venous or arterial thromboembolic event or known inherited bleeding or thromboembolic disorders.

- Exclusion of patients who would have received tranexamic acid within 48 hours prior to the inclusion.

- A DSMB will monitor patient data regularly during the study and will make recommendations to the Sponsor.

The risks of immunoallergic events and anaphylactic reactions will be mitigated by the exclusion of patients with known hypersensitivity or other severe reaction to any component of the investigational medicinal products including the placebo.

In order to minimize the immunogenicity risk, the patients with known inherited bleeding disorders (including congenital afibrinogenaemia) will not be included in the study.

Furthermore, physical examination and regular assessment of vital signs will be performed in order to early detect and treat any eventual adverse event.

9.4. Alternative Therapeutic Management - Emergencies Handling

If allergic or anaphylactic/anaphylactoid reactions occur, the infusion should be stopped immediately. In case of anaphylactic shock, standard medical treatment should be implemented.

In case of abnormally persistent bleeding, medical care will be given according to local management strategies.

In case of misuse or overdose, emergency care is left to the discretion of the investigator.

9.5. Definition and Reporting of (Serious) Adverse Events

9.5.1. Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence in a patient or clinical investigation subject administered a medicinal product that does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavourable and unintended sign, any symptom, syndrome, or disease, whether new or exacerbated, temporally associated with the use of a medicinal product, whether or not related to the IMPs.

An adverse event, whether or not considered to be causally related to the IMP, may be:

- The deterioration of a pre-existing chronic disease or aggravation of a symptom or disease that was present at the patient's enrolment in the study,
- A symptom or disease discovered after the start of the study even if it was probably present prior to the patient's enrolment,
- An abnormal laboratory finding when it is considered/judged as clinically significant by the investigator.

9.5.2. Serious Adverse Event (SAE)

A Serious Adverse Event (SAE) is an AE that, at any time, fulfils one or more of the following criteria:

- **results in death,**
- **is life threatening**, i.e. the patient was at immediate risk of death at the time of the event; it does NOT refer to an event which might have caused death if it was more severe,
- **requires in-patient hospitalisation or prolongation of existing hospitalisation**, i.e. hospitalisation signifies that the patient has been detained, usually (but not systematically) involving at least an overnight stay,
- **results in persistent or significant disability/incapacity,** i.e. substantial disruption of a person's ability to carry out normal life functions,
- **is a congenital anomaly/birth defect,**
- **is any important medical event** that may not be immediately life threatening or result in death or hospitalisation, but, based on appropriate medical judgment, may endanger the patient or may require intervention to prevent one of the other outcomes listed above.

Distinction should be made between serious and severe AEs. Severity is a measure of intensity whereas seriousness is based on the outcome or the action criteria described above. For example, nausea that persists for several hours may be considered as "severe", but not as a "SAE". On the contrary, a cardiovascular event that causes limited degree of disability may be considered as "not severe" but would be recorded as a "SAE".

- Surgical intervention is not considered as SAE but the medical condition requiring the surgery is to be reported as such.

- Events initially reported as an AE may become serious. For example, diarrhoea may become debilitating and require hospitalisation or prolongation of hospitalisation and is then reported as SAE.

- Occurence of IMP overdose, abuse/misuse, or drug dependency, whether or not clinical signs or symptoms are present, should be reported as an "AE" to the sponsor but immediately and no later than 24 hours.
If IMP overdose, abuse/misuse, or drug dependency is associated with a SAE, it should be reported in a SAE Form.

9.5.3. Definition of Specific Events in the Study

All PPH including their time course and progression will be appropriately documented on the case report form as part of the efficacy parameters as well as all transfused units and/or procedures required to manage and treat them. They will not be reported as AEs/SAEs.

Patients who suffered from PPH may develop signs and symptoms related directly to that bleeding such as anaemia, thrombocytopenia, hypofibrinogenemia, worsening of haemorrhage. PPH may also lead to occurrence of morbidity (corresponding to any haemostatic intervention: uterine ligation, embolization, intrauterine balloon, vascular ligation, hysterectomy) being considered as disease-

related. All these signs, symptoms and procedures will not be reported as adverse events or as serious adverse events.

Although they may be emergent when treated with IMP, the investigator has to describe them as part of the bleeding (efficacy parameters) and not as AEs/SAEs if they are directly and unequivocally related to the bleeding.

In this trial, the following adverse events should always be considered and reported as serious adverse events:

- Any deep venous or arterial thromboembolic event, whatever the causality assessment.
- Any suspicion of infectious agents transmission by the IMP.

9.5.4. Period of (Serious) Adverse Event Data Collection

In order to ensure complete safety data collection, recording and reporting, all (S)AEs occurring during the study, i.e. after signature of the Informed Consent, including any pre- and post-treatment periods required by the protocol, must be recorded, even if no IMP was taken. These include all AEs occurring, recurring, or worsening after the signature of the Informed Consent.

The period of observation for this study is from Visit 1 (signature of the Informed Consent) to the end of study visit (6 ± 2 weeks after delivery) (see Section 8.2.7).

If the investigator becomes aware, after that period, of any unusual safety information or any safety information that appears to be IMP-related involving a patient who had participated in the study, even after the patient has completed the study, he should contact the sponsor to determine how it should be documented and reported.

9.5.5. Recording and Description of (Serious) Adverse Event

Apart from adverse events clinically observed by the Investigator, the patient will be given the opportunity to report adverse events spontaneously. A general prompt will also be given to detect adverse events, e.g. “Did you notice anything unusual about your health since your last visit ?”

It is the responsibility of the Investigator to record all relevant information regarding the event.

Each individual AE is to be listed as a separate entry on the AE CRF page. The investigator will provide information on dates of onset and resolution, seriousness, severity, frequency, action(s) taken with regard to corrective therapy or to the IMP and outcome.

The Investigator is also requested to assess the relationship between the investigational product and the occurrence of each (S)AE. Alternative causes, such as the underlying diseases, concomitant therapy or the temporal relationship of the event to the investigational product will be considered.

The investigator must report to the Sponsor or its designee all AEs that occur during the study from the time the written informed consent has been given until the final study visit or early termination, regardless of their relationship to the IMP.

9.5.6. Procedures for reporting Serious Adverse Events

At the occurrence of a patient AE that fulfils one or more seriousness criteria, the Investigator must **immediately** forward to the Sponsor's representative a duly completed "SERIOUS ADVERSE EVENT FORM" provided by the Sponsor, even if the data are incomplete or if it is obvious that more data will be needed in order to draw any conclusion, but as soon as the following minimum information is available:

- Identification of the notifying person,
- Identification of the clinical study,
- Identification of a patient (patient number and/or initials),
- Description of the SAE and causality.

Where needed, the Investigator will ensure a follow-up of an initial SAE to elucidate the nature, the outcome or the causality of the SAE. This may include additional lab tests, histo-pathological examinations, and consultations with other healthcare professionals or any post mortem findings. This follow-up information should be provided to the Sponsor immediately as of their availability.

Supporting documentation (discharge summaries, all examinations carried out, etc.) will not be sent systematically as all relevant information must appear and be summarized in the narrative of the SAE report. However, if considered as important, the investigator could send these documents or LFB could request them (all documents must be blinded with respect to the subject's name).

TIMEFRAME

"Initial" SAE notification form	**"Follow-up" SAE** notification form
IMMEDIATELY As of awareness of an SAE occurrence	**IMMEDIATELY** As of availability of essential follow-up information

If a non-serious adverse event becomes serious, this and other relevant follow-up information must also be forwarded to the Sponsor immediately as described above.

TRANSMISSION

The SAE reports should be sent by fax or e-mail:

To: the CRO

Fax number: [redacted]

E-mail: [redacted]

In rare circumstances, when fax or e-mail transmission is not possible, reporting by telephone is acceptable. However, this should be followed with a completed "SERIOUS ADVERSE EVENT FORM" signed and faxed by the investigator as soon as possible.

9.5.7. LFB MEDICAL contact

For urgent medical matters or questions, the investigator may contact:

- [redacted] (Medical Head of Intensive Care Unit – LFB BIOMEDICAMENTS)
  [redacted] [redacted]

9.5.8. Follow-up of Adverse Events

<u>During the study:</u>

All AEs and SAEs must be followed-up during the study period until resolution or stabilisation.

<u>After the end of the study, or at patient's premature discontinuation:</u>

Only AEs or SAEs related to the study IMP that occurred during the study and:

- That are still recorded as "recovering", "not recovered" or "worsening" at the end of the study, must be continuously followed-up as part of the study data, as long as necessary to adequately evaluate the patient's safety, or until they are considered as "resolved", or until the condition is stabilised, or until the Investigator no longer estimates that they are clinically significant. If resolved, a resolution date must be provided.

If a patient is withdrawn from the study due to safety reasons, she should be followed until the event disappears, is otherwise explained or the patient's condition has stabilised.

Any patient who voluntarily withdraws from the study should be carefully questioned for the possible occurrence of an adverse event.

If no follow-up information can be provided, the Investigator must:

- Provide a written justification and

- Document the outcome as "unknown" (except for cases where the outcome is known, such as death for instance)

(Reminder: if the Investigator detects a new (S)AE after the end of the study and considers the event as possibly related to the IMP, he/she has to contact the Sponsor to determine how it should be documented and reported.)

<u>Follow-up documentation</u>

- In case of follow-up of an AE that worsened in nature or in severity, the follow-up will be documented on a new AE column in the CRF, with the box "follow-up" being ticked

- In case of follow-up of an SAE for which additional information/modification is provided, the follow-up will be reported on a new “SERIOUS ADVERSE EVENT FORM", with the box "follow-up" being ticked

9.6. Regulatory Safety Requirements

The decision to notify SAEs to competent Authorities/Ethics Committee is under the responsibility of the Sponsor.

The Sponsor will ensure that the Investigators, and all other appropriate persons, are informed in a timely manner of findings that could adversely affect the safety of patients.

The Sponsor will communicate additional safety information, when available, to the appropriate Health Authorities/Ethics Committee and all Investigators.

10. PARAMETERS AND ASSESSMENT CRITERIA

10.1. Assessment of Efficacy

10.1.1. Primary Variable

The primary efficacy variable is a binary composite endpoint (failure versus success). Failure is defined when a patient loses at least 4 g/dL of Hb, and/or requires the transfusion of at least 2 units of RBCs within 48 hours following the administration of IMP.

The reference Hb level is the most recent Hb value recorded during the third trimester of pregnancy.

10.1.2. Secondary variables

The following efficacy criteria will be assessed by the investigators:

- Evolution of haemorrhage
    - Percentage of patients losing at least 4 g/dL of Hb, 48 hours following IMP administration with regards to the Hb reference level.
    - Percentage of patients losing at least 3 g/dL of Hb, 48 hours following the IMP administration with regards to the Hb reference level.
    - Percentage of patients requiring the transfusion of at least 2 units of packed RBCs, 48 hours following the IMP administration.
    - Percentage of patients losing at least 4 g/dL of Hb, 48 hours following the IMP administration with regards to the Hb level measured at inclusion.
    - Percentage of patients with an occurrence of Hb level < 9 g/dL within the 48 hours period following inclusion.
    - Number of units of transfused blood products within the 48 hours period following the IMP administration.
    - Calculated volume of total blood loss, 48 hours following the IMP administration.

The calculation and adjustment of total blood loss with regards to transfusional needs will be calculated at time of statistical analysis as follows:

- Total blood loss (mL) = blood loss calculated + blood loss compensated by transfusion
- Calculated blood loss: Pregnancy total blood volume x (Ht0 – Htf) x (100/35)
  - Pregnancy total blood volume = (Maternal weight measured before pregnancy x 65 mL/kg) x 1.4 (40,41)
  - Ht0: last available value of haematocrit before delivery
  - Htf: value of haematocrit in the morning of D2
- Blood loss compensated by transfusion (mL): n RBC x 500mL (with n corresponding to the number of transfused units and 500mL = total transfusated blood volume of 300 mL RBC with Ht of 60%) (36)

- Need for haemostatic intervention
  - Percentage of patients requiring at least one of the following interventions within 48 hours following the administration of IMP: uterine ligation (B Lynch or other techniques), pelvic arteries embolization, surgical vascular ligation, administration of recombinant activated Factor VII (rFVIIa) and hysterectomy.

- Need for intrauterine balloon
  - Percentage of patients requiring the use of intrauterine balloon within 48 hours following the administration of IMP.
  - Time of intrauterine balloon placement.

- Maternal morbi-mortality
  - Length of stay in resuscitation and/or intensive care and/or PICU and/or continuous care
  - Length of stay in obstetrics units
  - Single or multi-organ failure (SOFA) score in women transferred to resuscitation and/or intensive care and/or PICU and/or continuous care units
  - Death during the study

- Evolution of blood fibrinogen level after early administration
  - Change in plasma fibrinogen level between H0 (start of IMP infusion) and D2.
- Evolution of hemoconcentration
  - Change in Hb level between each determination and H0
  - Change in Ht level between each determination and H0
  - Change in RBCs count between each determination and H0

10.2. Assessment of Safety

AEs and SAEs from all patients followed throughout the study will be recorded and reported, as described inSection 9.5, whether or not the AE was determined to be related to the administration of IMP.

Safety evaluation will include the monitoring of the following items:

- Physical examination performed at inclusion and hospital discharge;
- Vital signs (blood pressure and heart rate) will be monitored at inclusion visit, randomisation, H2, H6, discharge from the obstetrics room, morning of D2, intensive care unit discharge (if applicable) and hospital discharge.
- Tolerance of fibrinogen concentrate administration
    - Serious and non-serious adverse events (AE)
    - Symptomatic thromboembolic events within the 6 weeks following the administration of IMP.

In this study, all events related to PPH (anaemia, progressing or worsening of haemorrhage) will not be reported as AEs as they are already reported as efficacy criteria.

- Laboratory parameters:
    - Change in creatinine and urea between inclusion and D2
    - Change in TP, aPTT, D-dimers, platelets between inclusion and each determination times.

11. DATA MANAGEMENT

11.1. CRF completion guidelines

11.1.1. Introduction

All of the information required to be reported to the Sponsor as per protocol will be entered in the printed Case Report Forms (CRFs) for each study patient. The CRFs must be completed by the Investigator or any study centre staff designated by the Investigator.
The Investigator is responsible for ensuring that data recorded in the CRFs are complete, accurate and legible. The CRFs should be completed as soon as possible after the patient's visit and before review by the Monitor at the latest.

11.1.2. General instructions

11.1.2. 1. Overview

The CRFs are printed on NCR paper (triplicate). CRFs should be completed in English with a black ballpoint pen.

All data in the CRFs must come from and be consistent with the source documents, i.e. patient's file or medical records.

Any discrepancy between the data in the CRF and those in the source documents should be documented by the Investigator.

No data field will be left blank.

Abbreviations will be avoided since they are often ambiguous.

No data should be written in the margins.

11.1.2. 2.Header information

Header information should include at least:
- The protocol number,
- The name of the visit,
- Patient's identification:

a) Initials by default: the first letter of the last name (surname) and the first letter of the first name (name) are recorded. Example: Robert Smith: | S |-| R

b) Patient identification number according to local requirements: patient number is recorded with the centre number provided by the Monitor at the set-up visit. The patient number is a sequential number incremented with each patient included in the order of signature of informed consent. Example: 3rd patient included in the centre number 10 : | 1 | 0 |-| 0 | 3 |

11.1.2. 3.Recording dates and time

Dates will be recorded in the CRF using two digits for the day and the month and four digits for the year.
- Example: February 28, 2005 must be entered as 28/02/2005.

Time will be recorded using four digits according to the 24-hour clock.
- Example: 3:25 pm must be entered as 15:25.

11.1.2. 4.Recording of missing data

Before the Monitor reviews the data during the monitoring visits, the Investigator should make every effort to provide the information required. Use of the following codes should be kept to a minimum.

The Investigator should enter in the CRF:
- If the requested item is unknown or not available: UNK.
- If the requested item is not applicable: NA
- If the requested item was not done: ND

11.1.2. 5. CRF corrections

If the Investigator makes an error, he/she should cross out the data item, clearly enter the new data item and initial and date the correction. The use of opaque white correction fluid is prohibited. The corrections should be made while the NCR copies are still together on site.

11.1.2. 6. Confidentiality

Patient names must be kept confidential and should not appear on any CRF page or study-specific documents.

11.1.2. 7. CRF Completion in case of screening failure or premature withdrawal

A CRF must be completed for all patients with a signed informed consent up. Screening failure and premature withdrawal must be documented on the end of study form of the CRF with the cause that has led to screening failure/premature withdrawal.

11.1.3. Collection of CRF

The CRF will be checked by the Monitor during monitoring visits.

After the required corrections have been done by the investigator, the Monitor will collect two copies of each page of the CRF (the original which will be sent to the data manager and one copy which will be kept by the Monitor). The third copy will be archived by the Investigator.

The frequency of monitoring visits will depend on the recruitment rate of each centre.

11.1.4. Specific Case Report Form instructions

Specific instructions for completing the case report form will be detailed in a specific document "CRF completion guidelines".

11.2. CRF and Data Handling

Data processing, from data collection to database lock, will be carried out in accordance with GCP (see ICH-E6, Section 5).

The data handling documents, e.g. annotated CRF, database structure, data entry manual, coding rules and computerised validation, are defined in a Data Management Plan.

The database and data entry screens will be created in a software specifically designed for clinical data management, in compliance with ICH-E6 requirements.

All CRFs received in the Data Management Unit will be tracked and reviewed by the Data Manager before double data entry. The consistency of data will be checked by computerised programs and related queries will be generated for resolution by the Investigator. The database will then be updated accordingly.

Medical terms and drug names will be coded. Quality controls will be made to ensure the overall quality and consistency of the database. Reconciliation of SAE reports with the pharmacovigilance database will also be carried out.

At the end of the data handling process, a data review meeting will be held in order to prepare the database lock. After database lock, data will be transferred into SAS and STDM CDISC file formats for performing statistical analyses.

12. STATISTICS

12.1. Trial Objectives and Design

The main objective of this study is to assess the superiority of the early administration of IMP versus placebo in patients suffering from PPH and treated with intravenous infusion of prostaglandin.

The present study is a phase IV, multicentre, randomised, double-blind and placebo-controlled, comparing 2 parallel groups.

12.2. Statistical Analysis Plan

The material of this section is the basis for the Statistical Analysis Plan (SAP) of the study.

The detailed technical aspects of the statistical analyses will be provided in the SAP. The SAP will possibly take protocol amendments into account and adapt to unexpected issues raised by the trial running and/or data that affect planned analyses in the protocol.

Any deviation from the protocol regarding the description of statistical analysis in the SAP will be discussed in the study report.

Prior to locking the database and unblinding the randomisation code, a data review meeting will be planned in order to review individual data and validate the SAP.

The distribution of parameters will be summarised using descriptive statistics according to the study variable:

- Categorical variables (binary, nominal and ordinal) will be presented by contingency tables (frequencies and percents). Number and percentages of missing data will also be mentioned.

- Quantitative variables will be presented by their mean, standard deviation, standard error, median, quartiles and range, minimum and maximum values. The number of documented values will also be mentioned.

Efficacy data will be presented by randomisation group. Safety data will be presented by treated group (IMP that was effectively administered).

Unless otherwise specified, the following statistical tests will be used:

- Categorical data will be compared using chi-square test or Fisher exact test if a theoretical number of one category or more is below 5.

- Continuous quantitative data will be compared by t test or, if normality of distribution is rejected, by Wilcoxon non parametric test.

Thereafter only parametric tests are mentioned.

No subgroup analysis is planned.

All statistical tests will be two-sided with a threshold of statistical significance of 0.05.

12.3. Sample Size Determination

It is estimated that, in the control group, 42% of patients will fulfil the primary endpoint (unpublished data from the Pithagore cohort). With an expected percentage of patients in the Clottafact® treated group of 27%, the difference between the two groups will be of 15%. With a power (1-ß) of 90%, a type I error (α) of 5% and a two-sided test (Z test, unpooled variance), a sample size of 206 patients per treatment group is needed.

The rate of drop-out is assumed to be approximately 5%. Therefore, 434 patients will be included in the study.

As there is some uncertainty about the test Z variance depending itself on the expected rates, the variance will be re-estimated in a blind way at 80% of the initially planned sample size (i.e. 80% of 412=326 evaluable patients or 348 patients with adjustment for a 5% dropout rate) and the sample size will be increased according to the new estimated variance so as to maintain the power to 90% while still considering the same originally planned difference in failure rates, i.e. 15%.

It can be shown that the possible increase in sample size with adjustment for a 5% dropout rate cannot exceed 50 additionnal patients. Therefore, the new sample size will not exceed 484 patients.“

Of note, as the sample size reassessment is performed in a blind way, i.e. based on an overall estimate of the overall failure rate, it is known to not inflate the type I error of the primary analysis. An additional rule for the reassessment of the sample size is as follows: only an increase (i.e. no decrease) in the sample size will be allowed at the blind interim analysis.

12.4. Randomisation

Treatment units will be pre-numbered and allocated by the Investigator sequentially, in ascending number, and in chronological order of inclusion.

Randomisation will be stratified on the centre using fixed block size and a ratio active treatment/placebo of 1:1.

The randomisation list will be generated with validated SAS program by a subcontractor (not involved in the statistical analysis). LFB BIOMEDICAMENTS keeps a paper copy and an electronic format copy together in a confidential place.

The blindness will be maintained throughout the trial and up to the database lock.

For DSMB activity purpose (if needed), the randomisation list may be transmitted to an independent statistician, external to the sponsor, with high confidentiality.

For details about how blindness is maintained throughout the study, see Section 3.3.

12.5. Interim analysis

No interim analysis is planned.

12.6. Protocol Deviations and Analysis Sets

All deviations from the protocol will be listed and defined as major or minor deviations in the SAP.

According to the proposed analysis, the definition of analysis sets is recommended as follows:

- Efficacy sets:

  - ITT set: all randomised patients
  - Per Protocol set: all ITT patients receiving at least one dose of IMP and without any major deviations. These major deviations will be defined in the SAP prior to unblinding.

- Safety set:

  - All patients who received at least one dose of IMP.

12.7. General Rules for Handling of Missing or Inconsistent Data

Every effort should be made to collect the complete CRF and minimise the amount of missing data.

As a general rule, missing data will not be replaced.

However, concerning the primary efficacy endpoint, missing data (including incomplete dates) will be estimated as failures.

When needed to be able to calculate durations, incomplete dates will be estimated according rules specified in the SAP.

All estimated or replaced data will be edited along with a flag in the statistical appendices.

12.8. Demographic and Baseline Characteristics

Demographic and baseline characteristics of patients will be analysed on the ITT set. Data will be presented per randomisation group.

Statistical tests will not be performed to compare randomisation groups at baseline. Possible differences between groups at baseline will be judged from a clinical viewpoint only. If the PP set represents less than 80% of the ITT set, demographic and baseline characteristics will also be presented on the PP set.

12.8.1. Demographic Characteristics, Medicinal History, Diagnoses

All demographic characteristics and all medical history data will be presented per randomisation group. Pregnancy and data related to the delivery up to randomisation will also be presented in this section.

12.8.2. Previous Treatments

All previous treatments will be listed by patient with the associated ATC codes for the WHO drug dictionary.

Descriptive statistics will be produced to analyse the previous treatments by therapeutic class as defined in Section 7.1.

12.8.3. Baseline Efficacy Variables

All efficacy variables will be presented by randomisation group. Baseline data are defined as the last available data before the start of IMP infusion.

Date and time of the last available Hb (g/dL) determination will be presented. The month of last recorded Hb value during pregnancy will be mentioned.

Fibrinogen, Hb, Ht and RBCs count will be displayed in the efficacy analysis section in order to display baseline and follow-up results in the same tables.

Exploratory variables are efficacy laboratory data and will be displayed in the efficacy analysis section.

12.8.4. Baseline Safety Variables

All safety variables will be presented by randomisation group. Baseline data are defined as the last available data before the start of IMP infusion.

All laboratory data except those defined as efficacy variables (in the above section) or as exploratory variables will be defined as safety criteria. All laboratory data will not be displayed in the baseline section but in the analysis of safety in order to display in the same table the baseline and other data.

12.9. Investigational Product (IMP) and Concomitant Treatments

12.9.1. Extent of Exposure

Summary tables will display the number of patients exposed, duration of exposure (in minutes, automatically derived from the start and end times of IMP infusion), in each randomisation group and, if applicable (any error in allocation treatment), in each treatment group.

12.9.2. Treatment Compliance

The delay between the start of prostaglandin infusion and the start of IMP infusion (in minutes), will be presented as a continuous variable.

The same variables will be estimated and presented on the total treated set in each treatment group.

12.9.3. Concomitant Treatment

All concomitant treatments will be listed by patient with their ATC codes.

Descriptive statistics will be produced to analyse the concomitant treatments by therapeutic class as defined in Section 7.2.

12.10. Efficacy Analysis

12.10.1. Primary Efficacy Variable(s)

12.10.1. 1. Description of the primary efficacy variable(s)

The primary efficacy variable is a binary composite endpoint (failure versus success). Failure is defined when a patient loses at least 4 g/dL of Hb, and/or requires the transfusion of at least 2 units of packed RBCs within 48 hours following the administration of IMP.

The reference of Hb level is the most recent Hb value recorded during the third trimester of pregnancy.

Raw percentages of failures will be estimated within each treatment group (placebo or Clottafact®).

Raw percentages of failures will also be provided by centre, by tranexamic acid intake (yes versus no) and by baseline fibrinogen (categorized into three classes ≤ 2 g L^{-1} ,] 2 g L^{-1} 4 - g L^{-1}] , > 4 g L^{-1} , 19).

12.10.1. 2. Primary analysis

12.10.1. 2.1. Handling of dropouts and missing data

See Section 12.7.

12.10.1. 2.2. Prognostic factors and covariates

Stratified centre and baseline fibrinogen are considered as major prognostic factors for the primary outcome. They will be adjusted in the primary model. As the relationship between baseline fibrinogen and the primary binary outcome (on the logit scale) is unknown, baseline fibrinogen will be categorized into three classes (≤ 2 g L^{-1} ,] 2 g L^{-1} 4 - g L^{-1}] , > 4 g L^{-1}) as suggested by Charbit and al (2007).

The influence of possible administration of tranexamic acid defined as a binary covariate, (i.e. yes versus no) on the primary outcome during the trial will be evaluated in a separate model.

12.10.1. 2.3. Primary Analysis of the primary endpoint

The following hypothesis test will be considered:

- Null hypothesis:

H0: the true failure rate in the Clottafact® randomised group = the true failure rate in the placebo group.

- Alternative hypothesis:

H1: the true failure rate in the Clottafact® randomised group ≠ the true failure rate in the placebo group.

The nominal two-sided level of significance is set to 5%.

The primary analysis will be conducted in the ITT set. The primary model of analysis will be an exact logistic regression adjusting for treatment, centre, and baseline fibrinogen (categorized into three classes, ≤ 2 g L^{-1} ,] 2 g L^{-1} 4 - g L^{-1}] , > 4 g L^{-1}).

The treatment effect (odds ratio of failure) with its 95% confidence interval will be estimated in this model.

12.10.1. 2.4. Sensitivity Analyses and secondary analyses of the primary endpoint

The same analysis proposed here above will be performed in the PP set.

As a sensitivity analysis, missing data will not be estimated as failures and will not be replaced.

Treatment by centre and treatment by baseline fibrinogen interactions will be investigated in secondary logistic regression models. Odds ratios with their 95% CIs will be provided by baseline fibrinogen class.

Influence of tranexamic acid administration and the possible treatment by tranexamic acid administration interactions will be assessed in a secondary logistic regression model. Odds ratios with their 95% CIs will be provided by tranexamic acid administration class (yes versus no).

12.10.1. 2.5. Multiple comparisons and interim analyses

No interim analysis is planned.

12.10.1. 3. Secondary efficacy variables

Analyses of secondary efficacy endpoints will be primarily conducted in the ITT set. Sensitivity analyses will be performed in the PP set. Missing data will not be replaced.

12.10.1. 3.1. Description of secondary efficacy variables

Secondary efficacy variable are listed in Section 10.1.2.

The following parameters will also be derived:

1. Change in plasma fibrinogen level (g/L) between H2 and H0
2. Change in plasma fibrinogen level (g/L) between H6 and H0
3. Change in plasma fibrinogen level (g/L) between D2 and H0
4. The same changes will be calculated for Hb, Ht and RBCs
5. Duration of haemorrhage (hours): end time of haemorrhage – start time of haemorrhage
6. Length of stay in the obstetrics room (arrival and discharge hours)
7. Length of stay in obstetrics units (date of delivery and discharge date)
8. Number of days in resuscitation and/or intensive care and/or PICU and/or continuous care units (admission date and discharge date)
9. Number of days with assisted ventilation

12.10.1. 3.2. Analysis of secondary efficacy variables

Otherwise specified thereafter, all secondary efficacy variables will be compared between the 2 groups using chi-square for categorical data and using t test for continuous quantitative data or other appropriate tests.

Raw laboratory variables (including baseline data) will be presented by randomisation group at each determination (H0, H2, H6 and D2) and shift tables will also be displayed at the same periods. No statistical test will be performed on those data. Determinations at other sampling times will be listed except if other specific times are defined in the SAP.

Changes in laboratory parameters will be presented by randomization group and t test will be performed to test the hypothesis H0: no difference between the 2 randomization groups versus H1: any difference between the 2 randomization groups.

Furthermore, will be compared by t test in the subgroup of patients transferred in resuscitation and/or intensive care and/or PICU and/or continuous care units:

1. Number of days in resuscitation and/or intensive care and/or PICU and/or continuous care units,

2. Number of days with assisted ventilation.

12.11. Safety Analysis

Analyses of safety endpoints will be conducted in the safety set. Missing data will not be replaced.

With respect to AEs, all AEs occurring during the treatment period will be classified using the Lowest Level Term (LLT), Preferred Terms (PT) and System Organ Class (SOC). The duration of the AE and the duration between the last dose of IMP and onset of the adverse event will be calculated.

The number of patients with at least one AE will be tabulated by treatment group, SOC, PT and LLT. Patients with SAEs, IMP-related AEs and other significant AEs will be tabulated by treatment group, SOC, PT and LLT.

The number of AEs will be tabulated by treatment group, SOC, PT and LLT.

All SAEs, IMP-related AEs and other significant AEs will be listed by treatment group, SOC, PT and LLT.

The standard dictionary for coding events will be the MedDRA (version 16.0).

AEs reported before the start of IMP infusion will only be listed with individual patient's AE data collected, if applicable.

Raw laboratory variables (including baseline data) will be presented by treatment group at each determination (H0, H6 and D2) and shift tables will also be displayed at the same periods. Determinations at other sampling times will be listed except if other specific times are defined in the SAP.

Arterial and venous thromboembolic events over the study period will be compared between treatment groups by chi-square.

No statistical tests will be performed on other variables except if it is needed to explore any AE with possible clinical significance.

13. STUDY REPORT

In accordance with the ICH-E3 guidelines, a clinical final study report will be prepared by the Sponsor or subcontractor in collaboration with the coordinating Investigator and, if any, with the scientific committee.

Within 1 year after the end of the study, the Sponsor will provide the Health Authorities with the full study report or summary. Only the Sponsor is entitled to make the study report available to the Authorities.

Neither the complete report nor any part of the study report may be used without the approval of the Sponsor.

14. CONFIDENTIALITY AND PUBLICATION

14.1. Patient confidentiality

Patient data will be kept strictly confidential and patient anonymity will be protected by using number codes and/or initials.

The Sponsor or its representative(s) and the Health Authorities have the obligation to respect medical secrecy and to refrain from divulging any personal patient information they might fortuitously be aware of.

14.2. Use of information

The Investigator shall not divulge unpublished data or information related to the study provided by the Sponsor, including but not limited to the study product characteristics, study protocol, case report forms, assay methods and scientific data, to any third party without written approval from the Sponsor.

In addition, any new information that may become available during the course of the study shall be considered as confidential and shall not be used for any purpose other than the performance of the clinical study.

The study data are the property of the Sponsor. The Investigator and any of the research staff shall obtain written approval from the Sponsor prior to the publication/communication of the results of any work carried out during or in relation with the study.

Publication and/or communication of the results of the clinical study will be of a cooperative nature involving authors representing the Sponsor, the Investigators and the scientific committee, if any.

The Sponsor reserves the right to request modification of the content and/or timing of any publication or presentation if a patent application, an existing patent or other proprietary rights may be jeopardized.

Authorship of any publication related to the study and the order of presentation of the author's names shall be approved by the Sponsor. The Sponsor shall not use an Investigator's name in any publication without his/her written permission and vice versa.

15. ARCHIVING

The Investigators should retain all essential study-related documents, i.e. documents which permit evaluation of the conduct of the study and the quality of the data produced, in accordance with the applicable regulatory requirements of his/her country. These essential documents include but are not limited to signed protocol, CRFs, medical records, laboratory reports, informed consent forms, drug disposition records, safety reports, information regarding participants who discontinued, and other relevant documents and data.

The study-related documents should be kept together in the Investigator Site File provided to the Investigator by the Sponsor.

Sufficient information about the identity of all study patients, e.g. name, medical records number, patient number and study number, should be retained by the Investigator so that any Sponsor representatives, auditors or inspectors may have access to this information if required.

The Investigator must retain all records for 40 years.

The Investigator will contact the Sponsor for authorization prior to the destruction of any study records or in case of accidental loss or destruction of any of them.

The Investigator will also notify the Sponsor should he/she relocate or move the study-related files to a location other than that specified in the Sponsor's Study Master File.

All records should be kept in a secured area. However, in case of audit or inspection, they should be rapidly made available.

16. RESPONSIBILITIES OF PARTICIPANTS

Upon a request for proposal issued by LFB (from October 2012 to January 2013), a Contract Research Organisation (CRO) has been selected in order to assume competences delegation under an outsourcing contract that will ensure the performance of the following tasks:

- Preparation of study files and all trial documents (TMF, SMF, ...)
- Monitoring
- Data Management and Biometrics
- Bio-analysis and Statistics
- Clinical reporting of the study including regulatory documents (Clinical study Report, Data listings to be reviewed by DSMB and/or reference centres)

All activities will be performed by the CRO as a subsidiary, under GCP Management structure, plan and procedures under the governance of the Sponsor.

16.1. Responsibilities of the Investigator(s)

The Investigators will conduct the study in accordance with ICH-E6, all applicable laws in the country where the study is conducted and in accordance with this study protocol.

The Investigator's responsibilities, summarised below, include but are not limited to:

16.1.1. Patient information and consent

Prior to undertaking any study-related procedure, it is the Investigator's responsibility, or that of a formal designee, to provide each patient and/or a member of her family or the reliable person (see Section 8.1.1), with relevant, comprehensive, verbal and written information, including the written information which received approval or a favourable opinion from the IEC/IRB and the Health Authorities.

Signed informed consent must be obtained prior to undertaking any study-related procedure.

All data concerning the obtainment of consent must be described and documented in the patient's file.

16.1.2. Information on the overall results of the study

Pursuant to the French law of "Patient's rights" that was adopted on the 9th of August 2004, the Investigator must provide any patient who so requests it with the overall results of the study. The Sponsor will provide the Investigator with the overall results beforehand.

The Investigator should document in the patient's file the fact that the information has been provided.

16.1.3. Information to other practitioners (if relevant)

In agreement with the patient, the Investigator will formally inform other practitioners of the patient's participation in the study, to avoid any interference or bias in the conduct of the study.

16.1.4. Adverse events

The investigator is responsible for ensuring an adequate safety monitoring and follow-up of the study patients.

The Investigator must report and handle any serious adverse event immediately and no later than 24 hours, and non-serious adverse event, whether clinically observed or spontaneously reported by the patient, using concise medical terminology in accordance with Section 9 of the protocol.

16.1.5. Data recording

It is the Investigator's responsibility to ensure, on an on-going basis, the completion and validation of all case report forms as well as the study-related supportive data.

The Investigator can delegate completion of the CRFs to qualified and trained staff, but the signature of CRFs can only be delegated to physicians or midwives, who are also authorized to include and treat patients as mentioned in section 3.4 of this protocol. The aim of CRFs signature is to certify the accuracy and reliability of the data recorded therein.

16.1.6. Record retention

To enable inspections and audits from Health Authorities or the Sponsor, the Investigator has to agree to keep records, including the identity of all participating patients, i.e. sufficient information to link records, all original signed informed consent forms, copies of all CRFs and detailed records of treatment disposition. The Investigator should maintain a site file with all essential documents (for Archiving, also refer to Section 15).

16.1.7. Use of study-related information

The Investigator has the obligation to provide the Sponsor with complete test results and all data derived from the study.

Only the Sponsor may make information available to physicians, Health Authorities and/or patients enrolled in the study, except as required by local regulations.

16.1.8. IMP

The Investigator is responsible for IMP accountability at the study centre.

16.1.9. Quality control

The Investigator and the relevant staff members should be available during monitoring visits and possible audits or inspections and must ensure that sufficient time is devoted to the process.

The Investigator guarantees the Sponsor or its representative and appropriate Health Authorities the direct access to source documents.

16.1.10. Study discontinuation

Should the Health Authorities or the Sponsor decide to discontinue the study prematurely for any reason, the Investigator must promptly, i.e. within 5 days, contact all participating patients so that they can be appropriately followed-up.

All study supplies must be collected and all case report forms must be completed as fully as possible.

16.1.11. Liability and insurance

Liability and insurance provisions for this study are set out in separate agreements.

16.1.12. Delegation of Investigator duties

The Investigator can delegate certain tasks to the research team but he/she remains responsible for coordinating and informing his/her staff about the protocol and the possible amendments made to it.

The Investigator should ensure that all persons assisting with the study are adequately qualified, and are informed about the study protocol, any amendments to the protocol, the study treatments, and their study-related duties and functions.

The Investigator should maintain a list of appropriately qualified persons to whom significant study-related duties will be delegated. The list is to be kept up-to-date.

The Investigator should supply an up-to-date curriculum vitae (CV) in English, dated and signed, together with a list of his/her collaborators responsible for the practical conduct of the study. These collaborators should also provide a recent English version of their CVs, dated and signed.

16.1.13. Study agreement discontinuation

During the study, if events such as retirement, promotion or relocation prevent the Investigator from conducting the study as agreed, the Investigator should appropriately transfer his/her responsibilities, knowledge and documents to another willing individual, with the agreement of the Sponsor. Study specific contracts must be signed between the Sponsor and the newly assigned Investigator.

16.2. Responsibilities of the Monitor

The responsibilities of the study Monitor are defined in ICH-E6, Chapter 5. The Monitor, who is mandated by the Sponsor, must ensure that the study is conducted in accordance with GCP guidelines and all applicable local laws, and that the rights, the security and the well-being of the patients are respected.

During the conduct of the study, the Monitor reports any deviation or persistent poor compliance with the study requirements. In such case, the Sponsor should make decisions about appropriate corrective actions.

16.2.1. Communication

The Monitor is the main line of communication between the Investigator and the Sponsor.

16.2.2. Training

The Monitor must present the protocol and all procedures related to the study during the study set-up visit and provide the Investigator with case report form completion guidelines.

16.2.3. Compliance

During periodic monitoring visits at mutually convenient times, the Monitor is responsible for assessing the progress of the study, checking that the informed consent forms have been signed, ensuring adhesion to and compliance with the study protocol and other study-related documents, and

ensuring the accuracy and completeness of the CRFs. Inconsistencies in the study records are to be resolved.

16.2.4. Source data verification

The Monitor will examine source documents, validate and request clarifications to ensure the accuracy, completeness and reliability of data.

16.2.5. IMP

The Monitor must ensure that IMP handling is properly carried out and documented.

He/she must ensure that the investigator file is up-to-date with regard to essential documents.

16.3. Responsibilities of the Data Manager

The Data Manager is responsible for the management of clinical data from data entry to database lock.

17. ETHICS AND REGULATORY CONSIDERATIONS

The current study is to be conducted in accordance with globally accepted standards of Good Clinical Practice (ICH-E6), European Directive 2001/20/EC, and the revised version of the Declaration of Helsinki set out in the European Directive, as well as with applicable local requirements.

In France, this study will be conducted in accordance with the 'Code de la Santé Publique' (CSP).

The protocol will be submitted to the Health Authorities and a properly constituted Ethics Committee (EC) for formal approval of the study conduct in accordance with local regulations.

The study may not begin until the protocol has received written approval from the Health Authorities and Ethics Committee (EC) in accordance with local requirements.

During the study, the Sponsor should promptly notify the Investigators, Health Authorities and EC of any relevant information that could influence the safety of patients and could have an impact on the conduct of the study.

Personal Data Protection Committee

For biomedical research in France: the Sponsor attests his conformity regarding the Personal Data Protection French requirements ("Méthodologie de Réference MR001" dated the 5th of January 2006).

Insurance

The Sponsor will contract civil liability insurance to provide patients with compensation for any injury, including the consequences of administration of the investigational medicinal product and of the study procedures.

The insurance company is HDI-GERLING.

N° of insurance: 01010260-14023

In case of injury or disability resulting from participation in the study, the patient is requested to promptly inform the Investigator responsible for the study.

Indemnity

Participation in this study will not entail any financial compensation to the patient.

Changes to the protocol

The Sponsor will not assume any responsibility or liability resulting from the implementation of unapproved deviations or changes.

The only condition in which an amendment may be initiated prior to approval by the Health Authorities is when the change is necessary to eliminate apparent immediate hazards to the patients. In such case, the Investigator must notify the Sponsor, and if applicable the Ethics Committee, in writing within 5 working days after implementation.

18. AUDIT AND INSPECTION

An audit/inspection may be carried out by qualified Sponsor staff, subcontracted auditors or representatives of national or foreign Health Authorities. This procedure aims to ensure that the study is conducted as per protocol and in accordance with regulatory requirements, and to ensure the validity of the data.

Participation in this study implies the acceptance to cooperate in any potential audit/inspection.

The audit/inspection may consist of an inspection of the premises and equipment together with verification of the study documents and data.

The investigational team must be available for inspection or audit.

When the Sponsor or the Investigator is informed that an inspection is to be performed, the other party must be informed immediately.

Audits/inspection may take place after the end of the study.

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