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

Phase IV study

STATISTICAL ANALYSIS PLAN

Product: Clottafact®

Study No: FIDEL (**F**Ibrinogen in **DEL**ivery)

Date: December 20th, 2018

Version: Final 2.0

Version History

Version	Description
Draft 0.1	Initial version
Draft 0.2	Updated version
Draft 0.3	Updated version according to discussions after meeting of 22th September 2015.
Draft 0.4	Updated version
Draft 0.5	Updated version
Draft 1.0	Updated version
Draft 1.1	Updated version following JMG's review
Draft 1.2	Updated version
Draft 1.3	Updated version
Draft 1.4	Updated version (hierarchisation of secondary endpoints)
Draft 1.5	Updated version (definition of key secondary endpoints)
Draft 1.6	Updated version (number of days with assisted ventilation, duration of hospitalization, reference level definition were added)
Draft 1.7	Last updated version following blind review meeting.
Final 2.0	Final version

Fibrinogen in haemorrhage of DELivery: FIDEL LFB BIOMEDICAMENTS

SIGNATURE PAGE

Statistical analysis plan

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December 20th, 2018, Final2.0 Euraxi Strictly Confidential 3

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List of Abbreviations

AE	Adverse Event
ATC	Anatomical Therapeutic Chemical
BMI	Body Mass Index
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
FCS	Fully Conditional Specification
FFP	Fresh Frozen Plasma
Hb	Haemoglobin
Ht	Haematocrit
HES	Hydroxyethylstarch
IMP	Investigational Medicinal Product
ITT	Intent To Treat
LFB	Laboratoire français du Fractionnement et des Biotechnologies
MAR	Missing at Random
MCAR	Missing Completely at Random
MedDRA	Medicinal Dictionary for Regulatory Activities
MI	Multiple Imputation
MMRM	Mixed Model for Repeated Measures
MNAR	Missing Not at Random
PICU	Post-Interventional Care Unit
PP	Per Protocol
PPH	Post-Partum Haemorrhage
PT	Preferred Term
RBC	Red Blood Cells

SAE	Serious Adverse Event
SOC	System Organ Class
SOFA	Single Or Multiorgan Failure
SPC	Summary of Product Characteristics
SS	Safety Set
TEAE	Treatment Emergent Adverse Event
VIF	Variance Inflation Factor
WHO	World Health Organisation

1. INTRODUCTION

1.1 Study Objectives

1.1.1 Main 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.

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

1.2 Study Design

1.2.1 Experimental Design

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

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

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

1.3 Flow chart

An outline of the study procedures is presented in the table below.

Table 1 Study flow-chart

	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		
Treatments								

FIDEL Fibrinogen in haemorrhage of DELivery	CONSENT FORM	INCLUSION	TREATMENT	FOLLOW-UP				END OF STUDY
	Visit 1		Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7
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

1.4 TREATMENT

The investigational medicinal product (IMP) is either Clottafact® or placebo.

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

It is administered as a single-dose. A total volume of 200 mL of IMP (2 vials of 100 mL of reconstituted IMP) is injected to every patient.

Only one injection of IMP is performed to the patient throughout the study.

Following the administration of IMP, the therapeutic management is totally left to the discretion of the investigator. However, some concomitant treatments may be administered in accordance with the following recommendations:

- Fibrinogen concentrate as rescue therapy: if administered, it can't be administered:
  - within 60 minutes following the start of IMP administration,

  OR
  - before at least 2 units of packed red blood cells (RBCs) have been administered to the patient.

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

- Transfusional strategy: in accordance with the following objectives:
  - Haemoglobin (Hb) ≥ 8 g /100 ml,
  - Prothrombin time ≥ 40%,
  - Platelets count ≥ 50 000/mm3,
  - Transfusions of RBC, FFP and platelets units can be performed before availability of laboratory results, when indicated.

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

1.5 ELIGIBILITY CRITERIA

Before any study-related procedure is undertaken, a written informed consent must be obtained. For a patient to be eligible, all of the inclusion criteria and none of the exclusion criteria must be met.

1.5.1 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.

1.5.2 Non-inclusion criteria

Patients are not 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 accrete,
d. Hb level < 10 g/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 within 24 hours prior 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 fresh frozen plasma (FFP), platelets units or prohaemostatic drugs, tranexamic acid and recombinant activitated factor VII or prothrombin complex concentrate within 48 hours prior to the inclusion,
l. Administration of RBC 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 judgment,
t. Patients who are unlikely to survive through the treatment period and evaluation,
u. Patients transferred from another service after the delivery.

1.6 DURATION OF PATIENT PARTICIPATION

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

1.7 NUMBER OF INVESTIGATORS

The study was expected to be conducted in approximately 25 French investigational centers.

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

1.8 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:

-Non randomised patient,

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

-Withdrawal of consent for any reason, at any time,

-Lost to follow-up.

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 is to 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).

1.9 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 have to be documented in the patient's medical record.

1.10 EFFICACY AND SAFETY ENDPOINTS

1.10.1 Primary endpoint

The primary endpoint is a composite binary failure endpoint. Failure is defined when a patient:

- Loses at least 4 g/dL of Hb, compared to the reference Hb level, within the 48 hours following IMP administration

AND/OR

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

The reference Hb level is the most recent Hb value recorded within the third trimester of pregnancy. 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 primary endpoint is 48h (H48) after IMP administration (H0). A 20h time window (from H32 to H52) is authorized to account for the time of delivery that may occur during the night.

1.10.2 Secondary endpoints

1.10.2.1 Evolution of haemorrhage

- Percentage of patients losing at least 4 g/dL of Hb within 48 hours following IMP administration with regards to the Hb reference level.
- Percentage of patients losing at least 3 g/dL of Hb within 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 within 48 hours following IMP administration.
- Percentage of patients losing at least 4 g/dL of Hb within 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 48 hours following IMP administration.
- Number of units of transfused blood products within 48 hours following IMP administration.
- Calculated volume of total blood loss, 48 hours following 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
    - 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%).

1.10.2.2 Need for haemostatic intervention

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

1.10.2.3 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.

1.10.2.4 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.

1.10.2.5 Biological effects of fibrinogen concentrate administration

- Change in plasma fibrinogen level between H0 (start if IMP infusion) and D2;
- Evolution of hemoconcentration between H0 and D2
    - 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

1.10.2.6 Tolerance of fibrinogen concentrate administration

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

1.11 SAMPLE SIZE CALCULATION

It has been 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 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 is needed per treatment group. 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 is 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) to maintain the power to 90% while still considering the same originally planned difference in failure rates, i.e. 15%. Given an estimated overall rate of failures higher than expected, the sample size was re-estimated at 470 patients to maintain the power to 90%. The recruitment period ended on June 30th, 2018 with 448 patients at this date. Based on this sample size of 448, and assuming that 1.55% of patients excluded from the ITT analysis (i.e. patients without receiving at least a dose of the IMP) the current power of the trial is 89.6%, which remains very close to the targeted power of 90%.

2. CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

2.1 PROTOCOL AMENDMENTS

2.1.1 Amendment 1 - 12/15/2014

- **Bakri balloon**

The term of Bakri balloon (brand name) is replaced by the term intrauterine balloon (generic name). To date the Bakri balloon is no longer the only device available.

- **Intrauterine balloon in the PPH management**

The place of the intrauterine balloon in the PPH management has changed since the initial protocol writing. To date it may be used earlier in the management of PPH as it was before. Then it can no longer be considered as a final haemostatic intervention in the same way as these which are mentioned in the 3.2.2.2 section of the protocol. The use of an intrauterine balloon will be analyzed as a Secondary Endpoint separately from the other haemostatic interventions.

- **Informed Consent Form**

As it has been anticipated, investigational sites confirmed that informed consent signature by the patients in an emergency situation, as PPH, is an extremely sensitive procedure. The very short timing requested by the protocol makes it even

more complicate. In a purpose to facilitate the emergency procedure, the information sheet and the informed consent have been simplified in terms of both content and form, without modifying the meaning and the purpose of the provided information.
Precisions have been added in the post-inclusion information sheet and consent form in order to be compliant with the updated version of LFB Informed Consent Form template.

- **Non-inclusion criteria**

The non-inclusion criteria « m » and « u » have been clarified following investigator's request.

- **Blood sampling timing**

For feasibility reasons, the authorized time frame for blood sampling has been extended from 15 min to 30 min for H2 and H6 assessments.

2.1.2 Amendment 2 - 11/13/2015

Only administrative changes (recruitment period extended and number of sites increased)

2.1.3 Amendment 3 - 07/11/2016

- **Sample size determination**

The purpose of this amendment is to estimate the overall failure rate (i.e. both treatment groups confounded) in a blind way during the trial and therefore re-estimate the possible variance of the difference in failure rates between both treatment groups compared. A new sample size will be accordingly calculated so as to maintain the power to 90% while assuming the same planned expected treatment difference in the primary endpoint between both treatment groups (i.e. Clottafact versus placebo).
Assuming the same expected 15% difference in failure rates, an expected failure of 57.5% in the control group and an expected rate of 42.5% in the Clottafact treated group, the variance of the Z test becomes higher and this increase in variance requires a sample size of 2 x 229 =458 patients to maintain the power to 90%, compared to the 2x 206 = 412 patients initially planned in the protocol. Of note, this is the configuration of failure rates (57.5% vs 42.5%) that leads to the largest variance of the statistics. Hence, in the worst configuration, the increase in sample

size should not exceed 2x23 = 46 evaluable patients and if a drop-out rate of 5% is still assumed, 484 = 2 x 242 are needed and the increase in sample size adjusted for drop-outs will not exceed 2x25 =50 patients (50 = 484-434).

Hence, this amendment to the protocol aims to estimate the Overall Failure Rate (i.e. both groups confounded), denoted as OFRinterim below, at a blind interim analysis performed at 80% of the initially planned sample size, i.e. when the primary endpoint is available on approximately 326 evaluable patients or 348 patients with adjustment for a 5% drop-out rate.

Given this estimated overall failure rate at this interim stage and assuming the same expected difference in failure rates of 15% in the Clottafact® treated group compared to the control group (as planned in the protocol), the variance of the Z statistics will be reestimated assuming an expected failure rate of OFRinterim – 7.5% in the Clottafact treated group and an expected failure rate of OFRinterim + 7.5% in the control group. The sample size will be subsequently reassessed so as to maintain a 90% power for the primary analysis. As mentioned above, the increase in sample size adjusted for drop-outs will not exceed 50 additional 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.

2.1.4 Amendment 4 - 04/13/2017

No impact on the statistical analysis (recruitment period extended, status of the investigator and SAE reporting timeframe precised).

2.1.5 Amendment 5 - 10/26/2017

The purpose of this amendment is to update the patient information leaflet (emergency and post-inclusion) according to the new version of the Clottafact SPC (version 237119/1.0).

2.1.6 Amendment 6 - 11/24/2017

Administrative changes:

- Recruitment period extended until the date of the inclusion of the 470th patient if this inclusion occurs before June 30th, 2018 or until June 30th, 2018 considered as the end date for inclusions;
- The investigator can delegate completion of the CRFs to qualidied and trained staff, but the signature of CRFs can only be delegated to physicians or midwives).

2.1.7 Amendment 7 - 03/06/2018

The purpose of this amendment is to update the patient information leaflet (emergency and post-inclusion) according to the new version of the Clottafact SPC (version February 2018).

2.2 CHANGES IN THE STATISTICAL ANALYSIS PLAN

Section	Protocol	SAP and rationale for changes
Analysed data sets	12.6. Protocol Deviations and Analysis Set "ITT set : all randomized patients"	SAP: "ITT set: all randomized patients considered as randomized patients (i.e. regardless of allocation errors) and having received at least one dose of the IMP." Rationale for change: this definition of the ITT set is the most commonly accepted. As specified in ICH E9, In some situations, it may be reasonable to eliminate from the set of all randomised subjects any subject who took no trial medication. The intention-to-treat principle would be preserved despite the exclusion of these patients provided, for example, that the decision of whether or not to begin treatment could not be influenced by knowledge of the assigned treatment. This assumption should hold in this double blind randomized trial.
	"Safety set : all patients who received at least one dose of IMP"	SAP : all patients receiving at least one dose of IMP and considered 'as treated' (i.e. assigned to the 'as treated' group regardless of randomization errors). If all randomized patients received their allocated treatment and if there is no randomization error, the 'as treated' analysis will be the same 'as randomized' analysis and Safety set will be the same than Intent-to-treat set.
Demographics and other baseline	"If the PP set represents less than 80% of the ITT set, demographic and	SAP: "Demographic and baseline characteristics of patients will be analysed on the ITT and PP

characteristics	baseline characteristics will also be presented on the PP set."	set."
Handling missing data	12.7. General Rules for Handling of Missing or Inconsistent Data "Concerning the primary efficacy endpoint, missing data (including incomplete dates) will be estimated as failures."	SAP: "No imputation of missing data will be proposed for the primary analysis of the primary endpoint. " Rationale for change: There is no best method for handling missing data. The approach for handling missing data as recommended by the EMA guideline on missing data in confirmatory trials (EMA, 2010) should consider various missingness mechanisms along with subsequent analyses. Three methods for handling missing data will be considered. - The method n°1 considers no replacement of missing data (which is considered as the primary method). - The method n°2 replaces missing data by failures regardless of the randomized treatment (which is considered as a sensitivity method). This method relies on strong assumptions corresponding to a particular MNAR missingness mechanism, and should thus not be envisaged in first place. - The method n°3 (which is considered as another sensitivity method) performs multiple imputations (MI) for missing data, assuming a MAR missingness mechanism. As there is no other post randomization assessment of the primary endpoint when this latter is missing, the multiple imputation process must be based on baseline and post randomization covariates other than intermediate assessments of the primary endpoint. Blinded simulations have shown that important prognostic factors (such as country) could not be fitted as the model could not converge. Hence, this method based on multiple imputations relies on a somewhat subjective choice of covariates and should not be considered as the primary one.
Primary Analysis	12.10.1.2. Primary analysis "The primary model analysis will be an exact logistic regression adjusting for treatment, centre, and baseline fibrinogen (categorized into three classes, ≤ 2 g/L,]2 g/L; 4g/L], > 4g/L)"	SAP: The primary model of analysis will be a logistic regression to assess the association between a binary exposure variable treatment (variable "_trt") and the binary outcome (variable "_resp"), adjusting for centre and baseline fibrinogen (variable "_b_fibrinogen",

	12.10.1.2.2. Prognistic factors and covariates "Stratified center and baseline fibrinogen are considered as major prognostic factors for the primary outcome"	categorized into four classes (≤ 2 g/L,]2;3] g/L,]3,4] g/L, > 4 g/L)". Rationale for change: as some centers would enroll too few patients, centres with small number of enrolled patients (< 20 patients) will be pooled into one group of centers. The interaction of adjusted variables with treatment effect will be estimated in another standard logistic regression models. If feasible, Influence of centre will be secondarily studied in a logistic regression model adjusting for center as an additional term.
Prognostic factors and covariates	12.10.1.2.2. Prognistic factors and covariates "Stratified center and baseline fibrinogen" "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"	SAP: "Baseline fibrinogen will be considered as a major prognostic factor of the primary outcome. Baseline fibrinogen will be adjusted in the primary model as described above. As the linear relationship between baseline fibrinogen and the primary binary outcome (on the logit scale) is a priori ascertained, baseline fibrinogen will be categorized into four classes (≤ 2 g/L,]2;3] g/L,]3,4] g/L, > 4 g/L). Other possible prognostic factors will be considered as secondary and listed as follows : *Other baseline covariates :* -Center, -Tranexamic acid intake, -Lost of at least 2g/dl of haemoglobin (at the inclusion) compared to the reference level, -Heart rate ≥100beats/min at the inclusion, -Measured/estimated total blood loss volume. *Post-randomization covariates:* -Fibrinogen concentrate as rescue therapy, -Tranexamic acid intake, -Fresh frozen plasma, -Administration of platelet units, -Haemostatic intervention by bakri balloon, -Haemostatic invasive procedures, -Transfer to intensive care unit, -Heart rate ≥ 100 beats/min " Rationale for change:: See primary analysis
Individual analyses of the composite primary endpoint	None	SAP: "[…] logistic regression adjusting for baseline fibrinogen value (categorized) will be used to compare Clottafact® and placebo groups." Each component of the primary endpoint will be analyzed separately according to the same logistic regression analyses planned for the primary endpoint.
Secondary analyses	"[…] all secondary efficacy variables will be compared between the 2groups using chi-square for categorical data and using t test for continuous quantitative data or other appropriate	SAP: "The change in plasma fibrinogen level, Hb and Ht will be analysed at H2, H6 and D2 following IMP administration with a Mixed Model for Repeated Measures (MMRM) comparing the Clottafact® group and placebo

	tests."	group."
Multiplicity	None	SAP: "No multiplicity adjustment is necessary for the primary analysis as there is only one primary criterion and two arms compared. The 2-sided nominal alpha level of significance is set to 5%. Results for the two components of the composite primary endpoint will be individualy examined without statistical hypothesis testing. Secondary efficacy parameters will be tested for superiority at the 5% level of the Clottafact® arm, compared to the placebo arm. Secondary efficacy variables willl be examined and may contribute to supportive information to the effectiveness. We distinguish two types of secondary endpoints: (1) Key secondary endpoints are defined as highly clinically relevant endpoints. Statistical methods for addressing multiplicity issues will be used to test sequentialy key secondary endpoints (ie. Hochberg procedure); (2) other secondary endpoints will be analysed in an exploratory purpose."

3. STATISTICAL METHODS

3.1 DEFINITION OF THE ANALYSED DATA SETS

According to the proposed analysis, several analysis sets have been defined as follows:

3.1.1 Efficacy sets

3.1.1.1 Intent-To-Treat Set (ITT)

This set is defined as all randomized patients considered as randomised (i.e. regardless of allocation errors) patients and having received at least one dose of the IMP.

3.1.1.2 Per Protocol Set (PP)

It includes all ITT patients without any major protocol deviation. These major deviations will be reviewed by the data review committee and listed in the final version SAP prior to final database lock.

3.1.2 Safety set (SS)

This set is defined as all patients receiving at least one dose of IMP and considered 'as treated' (i.e. assigned to the 'as treated' group regardless of randomization errors). If all randomized patients received their allocated treatment and if there is no

randomization error, the 'as treated' analysis will be the same 'as randomized' analysis and Safety set will be the same than Intent-to-treat set.

3.2 DATA REVIEW COMMITTEE

The members of the data review committee are the study coordinator, members of the scientific committee, representatives of the sponsor, members of the CRO (project manager, data manager, statistician, medical writer).

The data will be reviewed during a meeting in a blinded manner.

The data review committee will define :

1) the deviations to the protocol as minor and major, thus enabling the specific definition of each of the populations.
2) Missing data for the primary endpoint: missing data will be confirmed by the scientific committee.

Final decisions will be taken by the scientific committee only.

3.3 STATISTICAL ANALYSES

3.3.1 Generalities

The analysis is carried out on a PC provided with Windows Seven operating system.

The analysis is performed with the software SAS® version 9.4.

The inferential analyses are preceded by descriptive analyses.

The quantitative variables are described by number of data available and missing, mean, standard deviation, the 1st and the 3rd quartile, median, minimum and maximum.

The qualitative variables are described by number of data available and missing, frequency and percentage per modality. The category missing are displayed only if there are actually missing values. Percentages are calculated on the total of non-missing recorded categories.

3.3.2 Interim analyses and Multiplicity issue

No interim analysis is planned.

No multiplicity adjustment is necessary for the primary analysis as there is only one primary criterion and two arms compared. The 2-sided nominal alpha level of

significance is set to 5%. Results for the two components of the composite primary endpoint will be individualy examined without statistical hypothesis testing.

Secondary efficacy parameters will be tested for superiority at the 5% level of the Clottafact® arm, compared to the placebo arm. Secondary efficacy variables willl be examined and may contribute to supportive information to the effectiveness. We distinguish two types of secondary endpoints: (1) Key secondary endpoints are defined as highly clinically relevant endpoints (ie. based on clinical practices). Statistical methods for addressing multiplicity issues will be used to test sequentialy key secondary endpoints (ie. Hochberg procedure); (2) other secondary endpoints will be analysed in an exploratory purpose.

3.3.3 Handling of Missing Data

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

Missing data for the primary endpoint occurs when the primary endpoint cannot be evaluated. Missing data will be confirmed by the scientific committee during the data review meeting (see 3.2). When the Hb level within the 48 hours following IMP administration is missing, the Hb value in the 48 hours following inclusion that not be collected as part of the study will be used to calculate the lose of Hb compared to the reference Hb level and for the primary endpoint evaluation.

No imputation of missing data will be proposed for the primary analysis of primary endpoint. The primary analysis will thus be performed on the Full analysis set (FAS), which will be as close as possible to the randomized set.

Sensitivity analyses of the primary endpoint will be proposed as follows:

- Primary sensitivity analysis (MAR assumption): a multiple imputation approach (MI) will be used assuming a missing at random (MAR) mechanism will be used to handle missing data. A multiple imputation approach by Fully Conditional Specification (FCS) will be used to handle missing data of the primary efficacy endpoint.

  .

- Secondary sensitivity analysis (MNAR assumption): all missing data for the primary endpoint will be estimated as failures assuming a missing not at random mechanism.

When needed, to be able to calculate durations, incomplete dates will be estimated according rules specified in the section 6.1.1. and will be reviewed by the scientific committee.
All estimated or replaced data will be edited along with a flag in the statistical appendices.

3.3.4 Study Patients

3.3.4.1 Patient Disposition

The number of patients who were enrolled and having been treated at least once by the IMP as well as those who fulfilled the inclusion and exclusion criteria will be summarised overall.
The number of patients in each center will be displayed overall and by group by means of contingency table in the ITT Set.

3.3.4.2 Protocol deviations

The number and percentage of patients with any protocol deviation, which is listed by deviation category, will be tabulated overall and by study treatment group in the ITT Set.

3.3.4.3 Analysis set

The number and percentage of patients in each analysis set will be displayed overall and by group in the ITT Set. The number and percentage of patients with definitive discontinuation and their reasons will be tabulated overall and by group in the ITT Set.

3.3.5 Demographics and Other Baseline Characteristics

Demographic and baseline characteristics of patients will be analysed on the ITT and PP 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 point of view only.

3.3.5.1 Demographic Characteristics, Medical History and Diagnoses

All demographic characteristics and all medical history data will be presented per randomisation group. Medical and surgical history data recorded at inclusion visit will be coded using the MedDRA dictionary version 17.1. All data will be summarised by Primary System Organ Class (SOC) and Preferred Term (PT) according to treatment group.

Pregnancy and data related to the delivery up to randomisation will also be presented in this section.

3.3.5.2 Previous Treatments

All previous treatments will be listed by patient with the associated Anatomical Therapeutic Chemical (ATC) codes for the WHO drug dictionary March 1, 2014 version.

Descriptive statistics will be produced to describe the previous treatments by anatomical therapeutic (ATC) name and preferred name according to treatment group.

Intravenous fluids and tranexamic acid before study treatment administration will be described according to treatment group.

Volume administered (mL), dose (g), duration of treatment administration and duration since start of delivery will be also presented.

3.3.5.3 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.

3.3.5.4 Baseline Safety Variables

All safety variables will be presented by study treatment 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.

3.3.5.5 Investigational Product (IMP) and Concomitant Treatments

3.3.5.5.1 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.

3.3.5.5.2 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 “as treated” set (SS set) in each treatment group.

3.3.5.5.3 Concomitant Treatment

Concomitant treatments will be coded using the WHO DDE March 1, 2014 version.

The number and percentage of patients with at least one concomitant medication will be summarised by group. Concomitant medications will be described on SS set by anatomical therapeutic chemical (ATC) name, overall and by group.

3.3.6 Efficacy analyses

3.3.6.1 Primary Efficacy Variable(s) and prognostic factors

3.3.6.1.1 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 compared to the reference Hb level,

and/or

- requires the transfusion of at least 2 units of packed 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.

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

3.3.6.1.2 Description of prognostic factors and covariates of the primary efficacy variable(s)

Baseline fibrinogen will be considered as a major prognostic factor of the primary outcome. Baseline fibrinogen and centre (Centres with small number of enrolled patients (<20 patients) will be pooled arbitrary into one) will be adjusted in the primary model as described below. As the linear relationship between baseline fibrinogen and the primary binary outcome (on the logit scale) is a priori ascertained, baseline fibrinogen will be categorized into four classes (≤ 2 g/L,]2;3] g/L,]3,4] g/L, > 4 g/L).

Other possible prognostic factors will be considered secondarily and listed as follows:

- Other baseline covariates :
    - tranexamic acid intake (Yes/No),
    - lost of at least 2g/dl of haemoglobin (at V1) compared to the reference level (the last assessment during the third trimester),
    - heart rate at the inclusion (<100 beats/min vs. ≥100 beats/min)
    - measured/estimated total blood loss volume (<1000 ml vs. ≥1000 ml).

Raw percentages of failures will also be provided by centre, by tranexamic acid intake. (Yes versus No), by baseline fibrinogen (categorized into four classes: ≤ 2 g/L,]2;3] g/L,]3,4] g/L, > 4 g/L and by other covariates levels identified above.

- Post-randomization covariates (within the 48 hours following IMP administration):
    - fibrinogen concentrate as rescue therapy,
    - tranexamic acid intake,

- administration of fresh frozen plasma,
- administration of platelet units,
- haemostatic intervention by bakri balloon,
- haemostatic invasive procedures,
- transfer to intensive care unit,
- heart rate ≥ 100 beats/min.

Post-randomization covariates will be mainly used to implement the multiple imputation model for the primary analysis. Although partially confounded with the treatment effect, these post-randomization covariates will also be investigated to check whether they are treatment effect modifiers. Raw percentages of failures will be provided by post-randomization covariates levels.

3.3.6.2 Primary analysis of the primary endpoint

3.3.6.2.1 Hypothesis

- 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 primarily in the ITT set.

3.3.6.2.2 Model of analysis of the primary endpoint

The primary model of analysis will be a logistic regression to assess the association between a binary exposure variable treatment (variable "_trt") and the binary outcome (variable "_resp"), adjusting for baseline fibrinogen (variable "_b_fibrinogen", categorized into four classes (≤ 2 g/L,]2;3] g/L,]3,4] g/L, > 4 g/L) and centre (see SAS code in §7.1). Missing data will be not imputed, assuming the missing completely at random (MCAR) assumption.

The treatment effect (odds ratio of failure) with its 95% confidence interval (95%CIs) will be provided by treatment group and tested at the 5% two-sided level of significance in this model.

Validity of the primary analysis: A graphical analysis of residuals will be done for verifying that assumptions for the primary analysis are met. If adjusting for centre effects lead to convergence issues or unstable estimates, centre effect will be ignored in the analysis.

3.3.6.2.3 Sensitivity Analyses of the primary endpoint

3.3.6.2.3.1 Primary sensitivity analysis (MAR assumption)

Assuming the missing at random (MAR) mechanism, multiple imputation (MI) approach by Fully Conditionnal Specification (FCS) will be used to handle missing data of the primary efficacy endpoint.

A stepwise logistic regression will be done to identify relevant covariates by a backward elimination analysis based on iterative maximum likelihood with the Newton-Raphson algorithm using a significance level of 0.2 to retain variables in the model. Only relevant covariates will be introduced in the MI process. The number of imputations needed will be verified with relative efficiency (RE) for the fully efficient imputation (in unit of variance) and by replicating sets of imputations checking whether the estimates are stable between imputation sets. With a little of missing information (10%), only a small number of imputations are necessary.

The final set of key covariates (referenced here below in the SAS syntax as “key_covariates_for_MI”, see §7.2 for SAS code) to be accounted for in the MI model in addition to treatment and categorized baseline fibrinogen will be defined <u>before</u> breaking the blind.

3.3.6.2.3.2 Secondary sensitivity analysis (MNAR assumption)

All missing data for the primary endpoint will be estimated as failures assuming a missing not at random (MNAR) mechanism. The same model as the one proposed for the primary analysis will be fitted on the new data set considering missing data as failures.

3.3.6.2.3.3 Per Protocol analyses

Same primary model analyses will also be performed in the PP set assuming the MAR, MCAR and MNAR assumptions to handle missing data of the primary efficacy endpoint.

3.3.6.2.4 Other efficacy analyses of the primary endpoint

- *Analysis of the baseline fibrinogen as continuous:*

A logistic model will be fitted adjusting linear and quadratic effects of baseline fibrinogen.

- *Analysis of the centre and baseline fibrinogene interactions with treatment:*

Treatment by center and treatment by categorized baseline fibrinogen interactions will be investigated in a logistic regression adjusting for baseline fibrinogen, centre and interactions (see §7.3 for SAS code).

Odds ratios with their 95%CIs will be provided by centre and treatment group and illustrated in forest plots.

3.3.6.2.5 Individual component analyses of the primary endpoint

The analysis of the contribution of each component of the composite primary endpoint will be considered as descriptive analyses. Odds ratios and 95%CIs will be provided.

3.3.6.2.5.1 Administration of RBCs from H0 to D2

The percentage of patients requiring the transfusion of at least 2 units of RBCs within 48 hours following IMP administration will be calculated and logistic regression adjusting for baseline fibrinogen value (categorized) will be used to compare the Clottafact® group and placebo group.

The same subgroup analyses planned for the primary endpoint will be performed as well.

3.3.6.2.5.2 Percentage of patients losing at least 4g/dL of haemoglobin from H0 to D2

The percentage of patients losing at least 4 g/dL of haemoglobin within 48 hours following IMP administration with regards to the haemoglobin reference level will be calculated. A logistic regression adjusting for baseline fibrinogen value (categorized) will be used to compare the Clottafact® group and placebo group.

The same subgroup analyses planned for the primary endpoint will be performed as well.

3.3.6.2.6 Subset analyses

Subset analyses will be performed to estimate the percentage of failure by treatment group and by baseline covariates level in ITT and PP sets.

Baseline covariates will be tested separately in univariate logistic regression models which will be the primary model to estimate the treatment effect by covariate level with its 95%CI (see §7.4 for SAS code). Forest plots displaying treatment effects (odds ratios) along with their 95%CIs will be displayed across covariates levels.

A multivariate analysis will be done to test in the model the following relevant covariates and interactions. Center, the total blood lost, the tranexamic acid intake, lost of haemoglobin compared to the reference level, heart rate and their interactions will be analysed in a stepwise logistic regression model.

3.3.6.3 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.

3.3.6.3.1 Description of secondary efficacy variables

Secondary efficacy variables are detailed in §1.10.2. We distinguish two types of secondary endpoints:

- ***Key secondary efficacy variables :***
  1- *Calculated and adjustment of total blood loss 48 hours following IMP administration*

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

Total blood loss (mL) = blood loss calculated + blood loss compensated by transfusion

With:

-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
- 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%).

2- Percentage of patients requiring any need for rescue procedure

The percentage of patients requiring any need for rescue procedure is defined as follows:

- at least one of the following invasive procedure within 48 hours following IMP administration :
  - pelvic arteries embolization,
  - surgical vascular ligation,
  - uterine ligation (B Lynch or other techniques),
  - hysterectomy
  - intrauterine ballon
- and/or administration of recombinant active Factor VII (rFVIIa),
- and/or fibrinogen rescue.

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

- ***Other secondary efficacy variables :***
  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 haemoorhage (hours): end time of haemorrhage – start time of haemorrhage

6- Duration in the obstetrics room (from arrival hour in obstetrics room to delivery hour)
7- Duration of hospitalization (from arrival date in obstetrics room to hospital 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

3.3.6.3.2 Analyses of secondary efficacy variables

3.3.6.3.2.1 Analyses of key secondary variables

The analyses of key secondary variables will be tested with the Hochberg step-up method:

1- Calculated/estimated volume of total blood loss, 48 hours following IMP administration

   The estimated/calculated volume of total blood loss 48 hour after IMP administration will be compared between the Clottafact® group and placebo group by a t test or non parametric test.

2- Percentage of patients requiring any need for rescue procedure

   The percentage of patients requiring any need for rescue procedure within 48 hours following IMP administration will be calculated and chi-square or Fisher exact tests will be used to compare between the Clottafact® group and placebo group.

3- Percentage of patients requiring the use of intrauterine balloon within 48 hours following IMP administration

   The percentage of patients requiring the use of intrauterine balloon within 48 hours following the administration will be calculated and chi-square or Fisher exact tests will be used to compare between the Clottafact® group and placebo group.

3.3.6.3.2.2 Other analyses of secondary variables

Other secondary endpoints will be analysed in an exploratory purpose.

3.3.6.3.2.2.1 Analyses of the change from baseline in plasma fibrinogen level, Hb and Ht

The evolution in plasma fibrinogen level, Hb and Ht will be analysed at H2, H6 and D2 following IMP administration with a Mixed Model of Repeated Measurements comparing the Clottafact® group and placebo group.

3.3.6.3.2.2.2 Analyses of the evolution of haemorrhage

3.3.6.3.2.2.2.1 Analyses of haemoglobin level

- The percentage of patients losing at least 3 g/dL of Hb within 48 hours following IMP administration with regards to the Hb reference level will be calculated and chi-square or Fisher exact tests will be used to compare between the Clottafact® group and placebo group.
- The percentage of patients with an occurrence of Hb level < 9 g/dL within 48 hours following IMP administration will be calculated and chi-square or Fisher exact tests will be used to compare between the Clottafact® group and placebo group.

3.3.6.3.2.2.2.2 Analyses of the number of units of transfused blood units

The number of units of transfused blood products within 48 hours following IMP administration with be calculated for the Clottafact® group and placebo group and compared using a Chi-square or generalized Fisher exact test.

3.3.6.3.2.2.2.3 Duration of haemorrhage

The time to the end of haemorrhage (hours) will be summarised by treatment group. The duration of the haemorrhage will be presented using Kaplan-Meier estimates to the end of haemorrhage. A log rank test will be used to compare the duration of haemorrhage curves between the Clottafact® group and placebo group.

3.3.6.3.2.2.3 Description of haemostatic intervention

The percentage of patients with haemorrhage leading to the occurrence of morbidity will be compared by treatment group using Fisher exact test. The percentage of patients requiring at least pelvic arteries embolization, surgical vascular ligation, uterine ligation, administration of recombinant activated Factor VII, intrauterine

ballon, and hysterectomy within 48 hours following the IMP administration will be calculated by group.

The time of intrauterine balloon placement will be described as other haemostatic interventions.

Fisher exact tests will be performed to compare the occurrence of heamostactic interventions by treatment groups.

3.3.6.3.2.2.4 Description of maternal morbidity

The maternal morbidity will be analyzed in the subgroup of patients transferred in resuscitation and/or intensive care and/or PICU and/or continuous care units with:

1. *Duration (days) in resuscitation and/or intensive care and/or PICU and/or continuous care units.*
2. *The maximal SOFA score,*
3. *Duration of admission in obstetrics room (hours), duration of hospitalization and number of days with assisted ventilation*

Chi-square or Fisher exact tests will be performed for categorical data and t test for continuous quantitative data or other appropriate tests (ie non parametric tests).

4. SAFETY EVALUATION

Analyses of safety endpoints will be conducted in the safety set (SS).

Missing data will not be replaced.

The standard dictionary for coding adverse events will be the MedDRA (version 17.1).

All AEs will be classified as emergent (i.e. happening or worsening after the time of start of IMP perfusion, defined as treatment-emergent adverse event, TEAEs) or not emergent.

4.1 Summary of AEs and TEAEs

Numbers and percentages of patients will be summarised overall by treatment group, with at least one AE, one serious AE (SAE), one maximal severity AE, one strongest relationship AE, the action taken, the treatment provided and the outcome. The duration of AE will be also presented.

Summary of TEAEs will include the same information as the summary AEs.

4.2 AEs and TEAEs by System Organ Class and Preferred Term

Numbers and percentages of patients with at leat one AE and numbers and percentages of patients with at leat one emergent AE will be presented by treatment group according to SOC and PT :

- for all AEs,
- for SAEs,
- for AEs related to study treatment,
- for AEs leading to study treatment discontinuation.

The duration of the AE and the duration between the last dose of IMP and onset of the adverse event will be calculated.

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

No statistical tests will be performed on other variables.

The following listings will be produced:

- Individual data listing of related adverse events,
- Individual data listing of adverse events leading to Treatment discontinuation,
- Individual data listing of SAEs,
- Individual data listing of deaths.

4.3 Laboratory Data

Raw laboratory variables (including baseline data) will be presented by treatment group at each determination (H0, H2, H6 and D2) and contengency tables will also be displayed at the same periods.

Descriptive statistics will be presented graphically by visit according to treatment group for a selection of haematological, biochemistry and coagulation test parameters:

- Haematology: Haemoglobin (g/dL), Red cells (count/L), Hematocrit (%), Leucocytes (/mm^3) and Platelets (10^9/L);

Biochemistry: Urea (mmol/L) and Creatinin (µmol/L);

- Coagulation tests: Fibrinogen (g/L), Prothrombin (%), Quick's time (sec), Activated Thromboplastin Time Ratio and D-Dimer. The activated thromboplastin time ratio will be computed as the ratio beween activated thromboplastin time "patient" (sec) and activated thromboplastin time "control" (sec).
- Factor II, Factor V and Fibrin monomer

The change from baseline for each laboratory parameter will be analysed at D2 by t test for comparing treatment groups.

4.4 Vital signs

Vital sign parameters will be described at inclusion visit, H2, H6, discharge from the obstetrics room, D2, intensive care unit discharge (if applicable) and hospital discharge :

- Systolic blood pressure (mmHg) at each visit and minimal value since last visit
- Diastolic blood pressure (mmHg) at each visit and minimal value since last visit
- Heart rate (beats/min) at each visit and minimal value since last visit

4.5 Physical examination

Physical examination will be described at inclusion and at hospital discharge.

5. TABLES, FIGURES AND GRAPHS

5.1 General Remarks about Tables

This section lists all tables and figures in the order in which they are expected to appear in the statistical report.

Table templates may be adapted as needed at the time the statistical analyses are performed.

5.2 List of tables

Table	Number	Title
HEADING	**14.1**	**STUDY PATIENTS**
HEADING	**14.1.1**	**DISPOSITION OF PATIENTS**
Table	14.1.1.1	Recruitment of Patients - ITT Set
Table	14.1.1.2	Overall Patient Disposition - ITT Set
Table	14.1.1.3	Disposition by Visit, withdrawal and reasons - ITT Set
HEADING	**14.1.2**	**PROTOCOL DEVIATIONS**
Table	14.1.2.1	Number (%) of Patients by Reason for Exclusion from the Per Protocol Set (Major Deviations) - ITT Set
Table	14.1.2.2	Number (%) of Patients by Protocol Deviation Other than Major Protocol Deviations (Minor Deviations) - ITT Set
HEADING	**14.1.3**	**DEFINITION OF ANALYSIS SETS**
Table	14.1.3.1	Number (%) of Patients in Each Analysis Population / ITT Set
HEADING	**14.1.4**	**DEMOGRAPHIC AND BASELINE CHARACTERISTICS** [a]
Table	14.1.4.1	Demographic Data by Treatment Group - ITT Set
Table	14.1.4.2	Physical Examination by Treatment Group – ITT Set
Table	14.1.4.3	Pregnancy Parameters by Treatment Group - ITT Set
Table	14.1.4.4	Obstetrical History by Treatment Group - ITT Set
Table	14.1.4.5	Surgical and Medical History by Treatment Group - ITT Set
Table	14.1.4.6	Surgical and Medical History by Treatment Group, System Organ Class and Preferred Term - ITT Set
Table	14.1.4.7	Delivery Parameters by Treatment Group - ITT Set
Table	14.1.4.8	Post-Partum Haemorrhage Parameters at Inclusion by Treatment Group - ITT Set
Table	14.1.4.9	Prostaglandin infusion by Treatment Group – ITT Set
Table	14.1.4.10	Previous Treatments - Intravenous Fluids Before Study Treatment Administration by Treatment Group - ITT Set
Table	14.1.4.11	Previous Treatments - Tranexamic Acid Before Study Treatment Administration by Treatment Group - ITT Set
Table	14.1.4.12	Other Previous Treatments According to ATC and Preferred Name by Treatment Group - ITT Set
HEADING	**14.1.5**	**INVESTIGATIONAL PRODUCT (IMP) AND CONCOMITANT TREATMENTS**

[a] Demographic and baseline characteristics for ITT and PP set will be presented in appendix in the same order they are mentioned in the list of table.

Table	Number	Title
Table	14.1.5.1	Number and percentage of patients exposed by Treatment Group - ITT Set
Table	14.1.5.2	Study Treatment Administration by Treatment Group - ITT Set
Table	14.1.5.3	Duration of exposure by Treatment Group - ITT Set
Table	14.1.5.4	Compliance by Treatment Group – ITT Set
Table	14.1.5.5	Number and percentage of patients receiving receiving at least one transfusion of RBCs – ITT Set
Table	14.1.5.6	Number and percentage of patients receiving FFP and platelet units – ITT Set
Table	14.1.5.7	Number and percentage of patients receiving fibrinogen concentrate as rescue therapy – ITT Set
Table	14.1.5.8	Number and percentage of patients with tranexamic acid adminstration – ITT Set
Table	14.1.5.9	Chronological order of administration of concomitant treatments – ITT Set
Table	14.1.5.10	Concomitant Treatments According to to Anatomical Therapeutic Chemical Classification and Preferred Name by Treatment Group – ITT Set
HEADING	**14.2**	**EFFICACY ANALYSIS**
HEADING	**14.2.1**	**PRIMARY EFFICACY ANALYSIS OF THE PRIMARY ENDPOINT**
Table	14.2.1.1	Primary Efficacy Analysis of the Primary Endpoint - Logistic regression model adjusting for treatment, centre and baseline fibrinogen – ITT Set without imputation of missing data
Table	14.2.1.2	Validity of the Primary Efficacy Analysis – ITT Set without of missing data
HEADING	**14.2.2**	**SECONDARY MAJOR ANALYSES OF THE PRIMARY ENDPOINT AND SENSITIVITY ANALYSES**
Table	14.2.2.1	Secondary Major Efficacy Analysis of the Primary Endpoint assuming MAR missingness mechanism – ITT Set
Table	14.2.2.2	FCS multivariate imputation estimations – ITT Set
Table	14.2.2.3	Sensitivity analysis Efficacy Analysis of the Primary Endpoint assuming missingness mechanism as failure – ITT Set
Table	14.2.2.4	Per protocol analyses of the primary efficacy endpoint – PP Set
HEADING	**14.2.3**	**OTHER EFFICACY ANALYSES OF THE PRIMARY ENDPOINT**
Table	14.2.3.1	Logistic regression model adjusting for treatment, centre and continuous baseline fibrinogen – ITT Set without imputation of missing data
Table	14.2.3.2	Logistic regression model adjusting for treatment, categorized fibrinogen at baseline, treatment * categorised fibrinogen and centre * treatment interactions – ITT Set without imputation of missing data
Heading	**14.2.4**	**INDIVIDUAL COMPOMENT ANALYSES OF THE PRIMARY ENDPOINT**
Table	14.2.4.1	Analyses of administration of at least 2 units of RBCs from H0 to D2 - ITT SET
Table	14.2.4.2	Analyses of the percentage of patients losing at least 4g/dL of Hb from H0 to D2 - ITT SET
HEADING	**14.2.5**	**SUBGROUP ANALYSES** [b]
Table	14.2.5.1	Analyses of failure rate by treatment group and level of categorized prognostic factors – ITT Set without imputation of missing data
Table	14.2.5.2	Univariate logistic regression of the influence of prognostic factors – ITT Set without imputation of missing data
Table	14.2.5.3	Stepwise logistic regression of the influence of prognostic factors and interactions – ITT Set without imputation of missing data
HEADING	**14.2.6**	**SECONDARY EFFICACY ANALYSES** [b]

[b] All secondary efficacy tables will be duplicated to the description of PP set.

Table	Number	Title
Heading	**14.2.6.1**	**Analyses of the key secondary efficacy variables**
Table	14.2.6.1.1	Calculated volume of total blood loss, 48 hours following IMP administration – ITT set
Table	14.2.6.1.2	Percentage of patients requiring any need for rescue procedure – ITT set
Table	14.2.6.1.3	Percentage of patients requiring the use of intrauterine balloon within 48 hours following the IMP administration – ITT set
Hedling	**14.2.6.2**	**Analyses of the other secondary efficacy variables**
Heading	**14.2.6.2.1**	**Change from baseline in plasma fibrinogen level (g/L) at H2, H6 and D2 compared between treatment groups**
Table	14.2.6.2.1.1	Descriptive statistics of plasma fibrinogen paramenter at each time - ITT set
Table	14.2.6.2.1.2	Analyses of change from baseline – Student t test - ITT set
Heading	**14.2.6.2.2**	**Change from baseline for Hb, Ht and RBCs parameters at H2, H6 and D2 compared between treatment groups**
Table	14.2.6.2.2.1	Descriptive statistics of Hb, Ht and RBCs parameters at each time - ITT set
Table	14.2.6.2.2.2	Analyses of change from baseline – Student t test - ITT set
Heading	**14.2.6.2.3**	**Analyses of the evolution of haemorrhage**
Table	14.2.6.2.3.1	Analyses of the evolution of haemorrhage by treatment group - ITT set
Table	14.2.6.2.3.2	Analyses of the number of units of transfused blood units – ITT set
Table	14.2.6.2.3.3	Analyses of the duration of haemorrhage by treatment group - ITT set
Heading	**14.2.6.2.4**	**Haemostatic intervention and maternal morbidity**
Table	14.2.5.5.1	Description of haemostatic interventions by treatment group - ITT set
Table	14.2.5.5.2	Analysis of length of stay in the obstetrics room, duration of hospitalization and number of days with assisted ventilation by treatment group – ITT set
Table	14.2.5.5.3	Analysis of the number of days in resuscitation and/or intensive care and/or PICU and/or continuous care units – Student t test - ITT set
Table	14.2.5.5.4	Descriptive statistics of maximal SOFA score by treatment group - ITT set
Heading	**14.2.6.2.5**	**Laboratory parameters (Haematology, Biochemistry and coagulation tests)**
Table	14.2.6.2.5.1	Descriptive statistics of haematology parameters at each time
Figure	1	Graphical representation of heamoglobin (g/dL) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	2	Graphical representation of red cells (count/L) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	3	Graphical representation of hematocrit (%) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	4	Graphical representation of Leucocytes (/mm^3) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
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Table	14.2.6.2.5.2	Descriptive statistics of biochemistry parameters at each time
Figure	6	Graphical representation of Urea (mmol/L) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
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Table	Number	Title
Table	14.2.6.2.5.3	Descriptive statistics of coagulation parameters at each time - ITT SET
Figure	8	Graphical representation of Prothrombin (%) paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	9	Graphical representation of Activated Thromboplastin Time Ratio paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	10	Graphical representation of D-Dimer paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	11	Graphical representation of factor II paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	12	Graphical representation of factor V paramater by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline - ITT set
Figure	13	Graphical representation of fibrin monomer parameter by visit and by group (Inclusion, Hour 2, Hour 6 and Day 2) and change from baseline – ITT set
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Listing	14.3.5.1	Listing of Aes related to treatment – SS
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Listing	14.3.5.3	Listing of SAEs – SS

Table	Number	Title
Listing	14.3.5.4	Listing of deaths – SS

6. DOCUMENTATION OF STATISTICAL METHODS

6.1 General Remarks

6.1.1 Missing and Partially Known Dates

Missing dates will not be replaced. Unless specified otherwise, partially known dates will be defined as follows for duration computation:

- Partially known begin date:
  - If only the day is missing, it is estimated as the first day of the month or the day of the inclusion date (if the month of the inclusion date is the same as the month of the begin date).
  - If month and day are missing, they are estimated as January 1 or the month and day of the inclusion date (if the month and day of the inclusion date are the same as the month and day of the begin date).
- Partially known end date:
  - If only the day is missing, it is estimated as the last day of the month or the day of the last visit date (if the month of the last visit date is the same as the month of the end date).
  - If month and day are missing, they are estimated as December 31 or the month and day of the last visit date (if the month and day of the last visit date are the same as the month and day of the end date).

Partially known dates and duration calculations with day/month imputations will be presented during the data review meeting for reviewed in a blinded manner.

6.2 Demographics

The following rules will be applied for the computation of age and BMI:

- **Age** will be calculated in years using the following formula: age = (initial visit date – birth date) / 365.25. Date of initial visit will be taken at inclusion visit (Visit 1). Results will be expressed with two decimals.
- **BMI** will be calculated in kg/m² using the following formula: [Last known weight (Kg) / Height (cm) * Height (cm)] * 10000. Results will be expressed with two decimals.

6.3 Durations

The following durations will be computed for the analyses:

- **Duration of delivery** will be defined in hours as: end date/time of delivery – start date/time of delivery.
- **Duration since start of delivery until start of previous/concomitant treatment administration** will be defined in hours as: start date/time of treatment administration – start date/time of delivery.
- **Follow-up duration in the study** will be defined in days as: hospital discharge or premature withdrawal date – date of V1.
- **Duration of haemorrhage** will be defined in hours as: end date/time of haemorrhage – start date/time of haemorrhage.
- **Duration since H0 before haemostatic intervention** will be defined in hours as: date/time of haemostatic intervention – start date/time of study treatment administration (H0).

6.4 Previous and Concomitant Treatments

Descriptive statistics for treatments collected on an ongoing basis during the study and coded with the WHO Drug dictionary will be presented by treatment group according to the pharmacological class of the ATC classification system (four first letters of ATC code) and the drug generic name (preferred name).

Previous and concomitant treatments will be distinguished as follows:

- A **previous treatment** is a treatment, whether ongoing or not, which was started before the start of IMP administration: treatment start date/time < study treatment administration start date/time (H0).
- A **concomitant treatment** is a treatment which started after the start of IMP administration: treatment start date/time ≥ study treatment administration start date/time (H0).

6.5 Adverse Events

All Aes will be categorised as emergent (TEAEs) or not emergent as follows:

- **Not emergent**: start date/time before the start date/time of IMP perfusion (H0) or after the date of hospital discharge (Visit 6).
- **Emergent**: start date/time on or after the start date/time of IMP perfusion (H0) and on or before the date of hospital discharge (Visit 6).

The period between the start date/time of IMP perfusion (H0) and the date of hospital discharge is retained for the definition of an emergent AE as it is expected to cover the duration of Clottafact® exposure (including elimination half-life).
If start and/or end dates/times of an AE are missing, partially missing or unknown, the AE will be considered as emergent.

The **duration of the AE** will be computed in days as the difference between the end and start dates/times using the following formula: AE end date/time – start date/time + 1.

Treatment-related Aes are those described by the investigator as possibly related to study treatment or as Aes with unknown relationship**.**

6.6 Laboratory Data

Haematology, biochemistry and coagulation test laboratory parameters and corresponding units are listed below.

- Haematology parameters:

Parameter	Unit
Hb	g/dL
Red cell	Count/L
Ht	%
Leucocyte	/mm^3
Platelets	10^9/L

- Biochemistry parameters:

Parameter	Unit
Urea	mmol/L
Creatinine	µmol/L

- Coagulation tests

Parameter	Unit
Prothrombin	%
Activated thromboplastin time ratio	-
D-Dimer	ng/mL
Factor II	%
Factor V	%
Fibrin monomer	µg/mL

The activated thromboplastin time ratio will be computed as the ratio beween activated thromboplastin time “patient” (sec) and activated thromboplastin time “control” (sec).

6.7 Vital Signs

Vital sign parameters and corresponding units are listed below.

Parameter	Unit
Systolic blood pressure	mmHg
Diastolic blood pressure	mmHg
Heart rate	Beats/minute
Peripheral oxygen saturation	%

7. SAS CODE

7.1 SAS code fragments for primary analysis of the primary endpoint

The SAS code for the primary model is written as follows:

```
/*************************************************************************/
/* EURAXI PHARMA - SAS version 9.4  Programme created by B.BERGE         */
/* Date: 26/10/2018    Last modifications:                               */
/* Risk level :   IIb                                                    */
/*                                                                       */
/* PROGRAM : F:\Data-Management\01 - Etudes\1016 - Fidel\11 -
Stat\Programmes\1016_FIDEL_EFFICACY_I.sas                                 */
/*                                                                       */
/* MACRO:   %detect, %Stat_des                                           */
/*                                                                       */
/* Description :  PRIMARY ANALYSIS (logistic model)                      */
/*************************************************************************/

ods graphics on;

ods output ParameterEstimates =_est  OddsRatios =_or;

proc logistic data = Main_analysis descending;

class _trt centre  _b_fibrinogen(PARAM=REF REF="> 4 g/L") / param=glm;

model _resp = _trt centre _b_fibrinogen /influence iplots;

run;

ods graphics off;
```

7.2 SAS code fragments for sensitivity analyses (FCS model) of the primary endpoint

The SAS code for MI imputation with FCS model is written as follows:

```
/* Model MI FCS */

Proc MI data= Main_analysis  seed =xxx nimpute =100 out = logistic_ficout;

Var _trt centre  _b_fibrinogen_ key_covariates_for_MI Resp;

class _trt centre  _b_fibrinogen_ key_covariates_for_MI  resp;

fcs logistic(resp  = _trt centre _b_fibrinogen key_covariates_for_MI

/details) ;

run;

/* PRIMARY MODEL OF ANLYSIS */

proc logistic data = logistic_ficout descending;

class _trt centre _b_fibrinogen(PARAM=REF REF="> 4 g/L") / param=glm;

model _resp = _trt centre  _b_fibrinogen  /influence iplots;

ods output ParameterEstimates =_ logistic_parms  ;

by _imputation_;

run;
```

```
/* COMBINE RESULTS OF MULTIPLE IMPUTATIONS, INFERENCES */
proc mianalyze parms (classvar =classval) = logistic_parms;
class _trt;
modeleffects _trt;
ods output parameterestimates=  logistic_outcome;
run;
data res;
set logistic_outcome;
estimate_back=exp(estimate);
lcl_back= exp(estimate -1.96*stderr);
ucl_back= exp(estimate +1.96*stderr);
run;
proc print data= res;run;
```

7.3 SAS code fragments for other efficacy analyses (interactions testing)

```
ods graphics on;
ods output ParameterEstimates =_est  OddsRatios =_or;
proc logistic data = Main_analysis descending;
class _trt centre  _b_fibrinogen(PARAM=REF REF="> 4 g/L") / param=glm;
model _resp = _trt centre _b_fibrinogen centre*_trt centre*_b_fibrinogen
_b_fibrinogen*_trt /influence iplots;
run;
ods graphics off;
```

7.4 SAS code fragments for other efficacy analyses (subgroup analyses)

```
ods output ParameterEstimates =_est  OddsRatios =_or;
proc logistic data = Main_analysis descending;
class _trt _covariate(PARAM=REF REF="covariate ref class") / param=glm;
model _resp = _trt _covariate _covariate *_trt ;
run;
```