PROTOCOL SYNOPSIS PPL17

Working title	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Proof of Concept Study (Part A (Section A)) with a conditional dose finding follow up (Part A (Section B)) to Evaluate the Efficacy on Cervical ripening, Safety, Tolerability and dose response of Subcutaneously Administered Tafoxiparin in Term Pregnant, Nulliparous Women with an unripe cervix undergoing Labor Induction.	
Sponsor Protocol No. PPL17		Eudract number: 2019-000620-17
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Trial period First subject to be enrolled in Q-2 2019 Last subject's last visit Q-2 2021 (POC) Last subject's last visit Q-2 2022 (Dose-finding)		Phase of development - II
Objectives	*Primary:* To assess the Efficacy of tafoxiparin on cervical ripening. *Secondary:* To assess the maternal and neonatal safety, tolerability and dose response of tafoxiparin as a supplement therapy in term pregnant, nulliparous women with an unripe cervix undergoing labor induction	
Study design	A randomized, double-blind, placebo-controlled, parallel-group, multi-center Proof of Concept study (Part A) with a conditional dose-finding add-on (Part B). Part B will be added conditional to both statistically significant difference between the treatment groups and a satisfactory safety profile of tafoxiparin in Part A. See also Flow Charts in appendix 14.1 of the protocol	

Endpoints	Efficacy	<u>*Primary Efficacy endpoint*</u>: Cervical ripening rate during up to the first seven days of treatment, measured by Bishop score <u>*Secondary Efficacy endpoints include:*</u> i) Time from start of treatment to increase in Bishop score of ≥ 2 points or spontaneous onset of labor, whichever comes first ii) Time from start of treatment to increase in Bishop score of ≥ 3 points or spontaneous onset of labor, whichever comes first iii) Time from start of treatment to increase in Bishop score of ≥ 4 points or spontaneous onset of labor, whichever comes first iv) Cervical ripening as measured by change from baseline to end of treatment in Bishop Score v) Time from onset of labor to partus. Onset of labor is defined as last record of 4 cm cervical dilatation visualized in the partogram and progress of labor or last record of 4 cm of cervical dilatation in combination with amniotomy and intravenous administration oxytocin vi) Proportion of women with established labor ≤ 6 hours vii) Proportion of women with labor time ≤ 8 hours viii) Proportion of women with established labor ≥ 12 hours ix) Total dosages of study drug (IMP) x) Proportion of women with spontaneous labor (response group I) xi) Proportion of women with a ripe cervix (response group I+II) xii) Proportion of women in response groups (I-IV)
	Safety and tolerability	<u>Secondary Safety and tolerability endpoints include:</u> Safety and tolerability will be evaluated through rate and frequency of adverse events and serious adverse events, complete and symptom-directed physical evaluations, vital signs, safety blood samples (hematology and clinical chemistry) and rate of withdrawals from the study and/or the study medication and by the following safety variables:

		i) Proportion of patients undergoing caesarean sections (CS) ii) Indications for CS iii) Proportion of patients undergoing instrumental deliveries (vacuum extraction (VE)/forceps delivery) iv) Indications for VE and forceps deliveries v) Fetal outcome measured as Birth weight, Apgar score, Acidosis (pH<7.10) and/or Base Excess < -12 mmol/L arterial or venous in umbilical cord blood vi) Indication for referral to neonatal intensive care unit (NICU) vii) Proportion of infants staying in the NICU for > 48 hours. viii) Uterine hyper stimulation in demand of tocolytic treatment ix) Proportion of patients with Postpartum Hemorrhage (PPH) > 2000 ml
Selection criteria	Inclusion	In order to participate in this study, the subjects must meet <u>all</u> of the following inclusion criteria: i) Pregnant women of ≥18 and ≤ 64 years of age ii) Nulliparous iii) Unripe cervix with ≤ 4points according to Bishop/Westin score (0-10 points scale) iv) Planned for labor induction after 4-7 days of IMP treatment <u>Examples of diagnosis as a basis for induction:</u> Post term pregnancy (40-41 weeks of gestation) Gestational diabetes Diabetes type 1 - well controlled Pre-eclampsia (BP diastolic <100, systolic <140) Hypertension - well controlled Hepatosis (without clinically significantly elevated serum bile acids) Maternal age ≥ 40 years Humanitarian-psycho social reasons Oligohydramnios v) Gestational age <u>≥</u> 37 weeks confirmed by ultrasound before 21 weeks of gestation vi) Singleton pregnancy vii) Subject is, as per the discretion of the Investigator, able to comply with the

		requirements of the protocol including an ability to be present at all required controls viii) Subject can understand and sign an informed form ix) Provision of written informed consent
	Exclusion	i) Subjects who are unable to understand the written and verbal instructions in local language ii) Breech presentation and other abnormal fetal presentations iii) Previous uterine scar iv)Spontaneous rupture of membranes at inclusion v) Pathologic CTG at inclusion vi)Fetal estimated weight > 2SD of normal fetal estimated weight earlier diagnosed by ultrasound and documented in patient record vii) Mother's BMI > 35 at early pregnancy viii) Known IUGR defined as ≤ 2SD of normal ix)Presence of eclampsia x) Severe Pre-eclampsia xi)HELLP syndrome (hemolysis, elevated liver enzymes, and low platelets) xii) Clinically significant vaginal bleeding in need of hospitalization in the third trimester xiii) Placenta previa xiv) Previously known coagulation disorders (Leiden, heterozygote - OK) xv) Treatment with a heparin/LMWH product during the previous six months xvi) Current use of any drugs that interfere with hemostasis such as oral anti-coagulant medication, non-steroidal anti-inflammatory drugs (NSAID) compounds and vitamin K antagonists. xvii) Current use of acetylsalicylic acid (ASA) compounds or use within the week preceding inclusion xviii) Diagnosed with HIV or Acute hepatitis xix) Known history of allergy to standard heparin and/or LMWH heparin xx) History of heparin-induced thrombocytopenia xxi) Current drug or alcohol abuse which in the opinion of the Investigator should preclude participation in the study.

		xxii) Current participation in other interventional medicinal treatment studies xxiii) Subject has a fear of needles which is believed by the Investigator to affect study medication compliance xxiv) Any relevant condition, laboratory value or concomitant medication which, in the opinion of the investigator, makes the subject unsuitable for entry into the study
Methods & procedures		Subjects who enter into ≥ 37 weeks of gestation may be subject to the informed consent procedure. If the subject is found to be eligible for the study, she will be randomized to study treatment with the Investigational Medicinal Product (IMP) *Part A - a proof of concept study* The daily study treatment will be 300 mg of tafoxiparin or placebo for at least 4 days and up to 7 days *Part B - to be initiated after a positive result from Part A study* The daily study treatment will be 150 mg tafoxiparin or 75 mg of tafoxiparin/placebo for up to at least 4 days and up to 7 days After Randomization/inclusion in the study the following must be recorded at any stage during the study: • new adverse event or changes to pre-existing adverse events according to instructions • concomitant medications according to instructions ***Screening and Baseline*** Upon the provision of informed consent, the subject will undergo the study-specific screening procedures where cervical palpation, vital signs (BP and HR) will be recorded. Data regarding demographics and habits, expected date of delivery and gestational age, medical history and previous/concomitant medication will be collected by interview and from subject's records. The Investigator will perform a review of the eligibility criteria. Blood samples will be collected for laboratory determination of hematology and clinical chemistry A cardiotocographic (CTG) tracing according to clinical practice should be carried out. The subject will be randomized to study treatment, included in the study and given the first dose of IMP (tafoxiparin/placebo)

	If more than 24 hours has passed between screening and randomization, a CTG tracing, cervical palpation and BP and HR recordings will be repeated prior to treatment with IMP. The subject is included in the study when study treatment is initiated by the first injection of the IMP ***Study treatment and Induction of Labor*** Before every daily dosing instance, a cardiotocographic (CTG) tracing according to clinical practice should be carried out and BP and HR recordings performed. Thereafter the subject will receive the SC injections of the IMP. Cervical palpation should be performed daily. Membrane sweeping to initiate labor should not be done. *Part A* The daily dose of tafoxiparin will be 300 mg *Part B* The daily dose of tafoxiparin will be 150 mg tafoxiparin or 75 mg of tafoxiparin The study medication will be administered subcutaneously in the abdominal or hip region for up to a total of 7 days or until partus. After the fifth dose of IMP has been given, prior to labor induction and immediately prior to any epidural anesthesia, a blood sample for hematology status, including thrombocyte count, should be taken. The result from the fifth dose sample should be reviewed before the next dose is given. If one of the following two criteria are fulfilled, the IMP treatment should be terminated: 1. The thrombocyte count value is reduced by 50% or more from the screening/baseline value. 2. The actual thrombocyte count value is below $70x10^9$/L. The result from the blood sample taken prior to epidural anesthesia should be reviewed before the epidural anesthesia procedure is initiated. In a situation where HIT is suspected, a HIT antibody test should be performed, and if positive, a hematologist shall be contacted for further testing and appropriate treatment If the HIT test is positive, the event should be classified and reported as a SAE.

	Response group I Subjects who enter into spontaneous labor after 1-7 doses of IMP should be managed according to clinical practice *Response group II* Subjects who are given 4-7 doses without entering into spontaneous labor, but with a ripe cervix (Bishop/Westin score ≥6) should be induced into labor by amniotomy and oxytocin treatment, but preferably not before 4 treatment doses have been given. *Response group III* Subjects who are given 7 doses of IMP without entering into spontaneous labor and with an unripe cervix shall be treated with a cervical balloon catheter provided by the hospital according to instructions provided by the sponsor. The balloon should stay in the cervix until it is expelled or up to 24 hours. If the cervix is still unripe after 24 hours of balloon treatment, the subject should be given PGE-1 treatment orally according to clinical routine. When the cervix is ripe (Bishop/Westin score ≥6), they should be induced into labor according to clinical practice. If they do not enter into labor after PGE-1 and oxytocin treatment they should be managed at the discretion of the treating physician. A CTG recording should be performed in relation to PGE-1 treatment according to clinical practice. Abnormal CTG with signs of hypercontractility will be treated according to clinical routines and with tocolytics if needed. *Response group IV* The subject must be induced into labor due to medical reasons or subjects demand before 7 doses of IMP have been given and the cervix is still unripe. They should be managed according to clinical practice. ***Labor*** Onset of labor is defined as last record of 4 cm cervical dilatation visualized in the partogram and progress of labor or last record of 4 cm of cervical dilatation in combination with amniotomy and intravenous administration oxytocin CTG registration will be performed continuously during established labor according to clinical practice. If slow progress of labor (cervical dilation < 1cm per/hour during 3 hours) or labor arrest (no progress during 3 hours) occur in patients who are not yet on oxytocin treatment, they should be given oxytocin treatment according to clinical practice. The characteristics of the new-born baby will be evaluated and recorded. Blood sample from arterial or venous umbilical cord will be collected for analyses of pH and/or Base Excess. After labor, the subject will remain at the clinic as per clinical practice until the Discharge.

Study drug injection site reactions (Skin discoloration < 3 cm in diameter should not be reported as AE)

Discharge
At discharge, evaluations specific for the Discharge shall be performed.
Any changes to, or new concomitant medications or the occurrence or changes to any pre-existing adverse events for both the mother and the infant will be evaluated and reported.
The mother's BP and HR should be recorded

A blood sample for hematology status including thrombocyte count should be taken.

If one of the following two criteria are fulfilled, a HIT antibody test should be performed.
1. The thrombocyte count value is reduced by 50% or more from the baseline value.
2. The actual thrombocyte count value is below 70 109/L.

In a situation where HIT is suspected, a HIT antibody test should be performed, and if positive, a hematologist shall be contacted for further testing and appropriate treatment.

If the HIT test is positive, the event should be classified and reported as a SAE.

Any potential events requiring NICU admission and neonatal diagnoses will be specifically recorded.
Permission to review the infant's hospital charts from the pediatric and other relevant departments will be requested.

Withdrawal from Treatment and Study
There will be two types of withdrawals from the study:
- complete withdrawal (e.g., due to withdrawal of informed consent or lost to follow-up) or
- withdrawal from study medication (e.g., unacceptable adverse events or Investigator's discretion).

The adherence to the protocol may be aborted if there is significant deterioration in the condition of the mother or the fetus that would make it unwise to continue the induction attempt.
All subjects who prematurely discontinue participation in the study (complete withdrawal) should not receive any additional doses of study medication or perform any subsequent clinic visits. The Investigator should, however, make an effort to contact the patient and obtain the reason for discontinuation from

		the study. All subjects who prematurely discontinue the study for whichever reason (withdrawals from investigational product), shall not receive any additional doses of study medication, independent of the reason for withdrawal. However, they will be asked to complete all subsequent planned safety and efficacy evaluations. Subjects who are withdrawn for whichever reason after randomization but prior to receiving the first dose of study drug may be replaced at the discretion of the Sponsor. ***Medications and Procedures Excluded during the Study*** The medications, devices and procedures which are prohibited from use during the study include, but are not limited to, the following: • Use of drugs that interfere with hemostasis, including heparin / LMWH, direct oral anti-coagulant drugs, non-steroidal anti-inflammatory drugs (NSAID) compounds and vitamin K antagonists • Use of acetylsalicylic acid (ASA) from one week prior to Screening until partus. NSAID and heparin/LMWH may be used postpartum according to clinical practice.
Medication (dose, route, duration)	Test/ placebo Part A	Tafoxiparin/Placebo will be supplied to the site as kits designed to constitute 300 mg of tafoxiparin or placebo to be given as SC injection daily for up to 7 days. The active substance will be delivered in 2 ml vials containing a minimum extractable volume of 1.6 ml of 150mg/ml of tafoxiparin. Apart from tafoxiparin, each ml of study drug will constitute 0.015 M phosphate buffer. The study medication kit for each patient will contain 8 doses (2 vials per dose) with one dose labeled reserve dose in case a dose is rendered unusable. The investigational product will be administered subcutaneously every 24±3 hours by the site staff for up to 7 days. At each dosing time 1.0 ml of the drug will be extracted from each of the two vials and injected as separate s.c. injections.
	Test/ placebo Part B	Tafoxiparin/Placebo will be supplied to the site as kits designed to constitute 150 mg or 75 mg of tafoxiparin or placebo to be given daily by SC injection. The active substance will be delivered in 2 ml vials containing a minimum extractable volume of 1.6 ml of 150mg/ml of tafoxiparin. Apart from the active substance, each ml of study drug will constitute 0.015 M phosphate buffer. The study medication kit for each patient will contain 8 doses (2 vials per dose). For the subjects randomized to 150 mg of tafoxiparin per day the IMP kits will contain two vials of tafoxiparin. For the subjects randomized to 75 mg of

		tafoxiparin per day the IMP kits will contain one vial of tafoxiparin and one vial of placebo. The investigational product will be administered subcutaneously every 24±3 hours by the site staff for up to 7 days. At each dosing occasion 0.5 ml of the drug will be extracted from each of the vial and injected as separate s.c. injections.
	Comparator	Matching placebo saline solution will be supplied to the site containing of 9 mg/ml of sodium chloride (NaCl) solution. The placebo saline solution will be indistinguishable from the active solutions in appearance, smell and packaging.
	Non-investigational product	PGE-1 medications for oral administration will be supplied by the investigators. The treatment will be given according to clinical practice. Cervical balloon catheters will be supplied by the hospital and used as described in the protocol.
Statistics	Sample size	The sample size estimation for the PPL17 study is based on a parallel-group comparison of effect between placebo and tafoxiparin on the primary endpoint. Thus, the sample size is based on Part A (the efficacy part of the study). Sample size calculation is based on the following: Totally 170 patients (85 in each group) are required to have an 80% power of detecting, as significant at the 5% level, an increase in the primary endpoint from 0.5 Bishop score points per 7 days in the placebo group to 1.5 Bishop score points per 7 days in the tafoxiparin group assuming a common standard deviation (SD) of 2.3 Bishop score points. If the efficacy and safety profiles of Part A are conclusive in favor of tafoxiparin, 82 women will be included in each of two additional tafoxiparin dose groups in Part B.
	Methods	The main analysis is planned when all patients have completed the study, all data have been entered, verified and validated, and the database has been locked. ***Primary analyses (Efficacy):*** The primary efficacy endpoint is "Cervical ripening rate during up to the first seven days of treatment, measured by Bishop score" The primary efficacy endpoint will be analyzed using a linear mixed effects model with random intercept and random slope. Time-to-event outcomes will be analyzed using a Weibull model with treatment and stratification factors as independent factors. Kaplan-Meier plots of the time from onset of labor to partus for

		each treatment group will be presented. Cox regression will also be performed as sensitivity analyses. Dichotomous endpoints will be analyzed using logistic regression. Other efficacy and safety variables will be presented with descriptive statistics such as mean, standard deviation, median, minimum and maximum for continuous variables, and number and percentages for discrete variables. ***Secondary analysis (Safety and Tolerability):*** Safety and tolerability will be analyzed using descriptive statistics on the primary endpoints. No formal statistical tests will be performed. Means, medians, ranges and standard deviations will be presented by treatment group for continuous endpoints, while counts and percentages will be presented for categorical endpoints. ***Statistical Analysis Plan*** In addition to the summarized analysis plan outlined above, a separate document - Statistical Analysis Plan for PPL17 - will detail all analysis to be performed. ***Subgroup analyses:*** The subgroups and the analyses performed on the subgroups will be elaborated in the Statistical Analysis Plan.

Schedule of events

Control/visit	Screening - 24-0h	Baseline 0h	Day 5	IMP treatment for up to 7 days	Induction (if relevant) EDA if relevant	Established Labor	Discharge
Informed Consent	X						
Inclusion/Exclusion Criteria	X	X[a]					
Medical History and Concomitant Diseases	X						
Vital Signs	X	X[a]		X	X	X	X
Cervical Palpation	X	X[a]		X	X	X	
Randomization		X					
Study Drug Administration		X		X			
Injection site reactions				X	X		X
Induction of Labor					X		
Labor Characteristics - Partogram						X	
Fetus/Infant Status including CTG	X	X[a]		X[c]	X	X	X[b]
Hematology and Clinical Chemistry	X		X[d]		X, X[e]		X[d]
Umbilical cord blood						X	
Concomitant Medication (Mother)	X	X[a]		X	X	X	X
Concomitant Medication (Infant)						X	X
Adverse Events (Mother and Fetus/Infant)				X	X	X	X

[a] If Baseline occurs ≤ 24 hours after Screening, these data will not be re-checked, [b] No CTG, [c] Prior to dosing [d] Hematology status including thrombocyte count [e] Only hematology prior to labor induction and immediately prior to epidural anesthesia