SPONSOR: **CHRU DE TOURS** 2 Boulevard Tonnellé 37044 Tours cedex 9	
CLINICAL RESEARCH PROTOCOL	
STUDY CODE	**PHRN15 – FP / MAGPOP**
PROJECT TITLE (English version)	Propess® versus double balloon for cervical ripening of prolonged pregnancies: a randomised controlled trial
PROJECT TITLE (French Version)	Propess® versus double ballonnet pour les maturations cervicales en cas de grossesse prolongée : un essai randomisé contrôlé
ACRONYM	MAGPOP **M**echanical cervic**A**l ripenin**G** for women with **Pr**O**l**onged **P**regnancies
COORDINATING INVESTIGATOR	Pr Franck PERROTIN
CO-COORDINATING INVESTIGATOR	Dr Caroline DI GUISTO
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Version number (after amendment)	**Date**	**Amendment justification**
2.0	10.08.16	1st amendment
3.0	07.11.16	2nd amendment

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PROJECT TITLE

Propess® versus double balloon for cervical ripening of prolonged pregnancies: a randomised controlled trial

MAGPOP

*(**M**echanical cervic**A**l ripenin**G** for women with **P**r**O**longed **P**regnancies)*

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ABSTRACT (English Version)

TITLE	Propess® versus double balloon for cervical ripening of prolonged pregnancies: a randomised controlled trial
SPONSOR	University Hospital Center of Tours
COORDINATOR	Pr Franck PERROTIN Department of Obstetrics and fetal medicine University Hospital Center of Tours
CO-COORDINATOR	Dr Caroline DI GUISTO Department of Obstetrics and fetal medicine University Hospital Center of Tours
BACKGROUND / RATIONALE	A pregnancy is considered "prolonged" from 41 weeks of gestation. Prolonged Pregnancies (PP) are associated with increased maternal morbidity: emergency caesarean, 3rd and 4th degree perineal lesions and postpartum haemorrhage. Foetuses are at increased risk of oligohydramnios, meconium-staining and Fetal Heart Rate (FHR) anomalies. Around 15% of all pregnancies are prolonged. A Cochrane review on induction of labour showed that a policy of labour induction at or beyond 41 weeks was associated with significantly fewer perinatal deaths. Thus the French College of Obstetricians and Gynaecologists stated, "induction of labour can be proposed to patients between 41+0 and 41+6 weeks of gestation». In cases where labour is induced and cervix is unfavourable, cervical ripening is advised. Methods of cervical ripening include pharmacological (prostaglandins) and mechanical (Foley catheter or trans-cervical double balloon) methods. Those two methods were compared in the PROBAAT trial among women with term pregnancies (beyond 37+0). The rates of caesarean section with these two strategies were identical, however uterine hyper stimulation with FHR anomalies occurred less when cervical ripening was mechanical. Considering pharmacological cervical ripening is associated with more uterine hyper stimulation and more FHR anomalies, it may not be the most appropriate in cases of fragile foetuses that include cases of prolonged pregnancies. Considering prolonged pregnancies are associated with a risk of FHR anomalies and that cervical ripening with a pharmacological method is another factor which increases this risk: women with prolonged pregnancies could benefit from a more "gentle" cervical ripening. At present, no particular method is recommended in cases of cervical ripening and prolonged pregnancies. We hypothesise that, in cases of prolonged pregnancies, mechanical cervical ripening, with less uterine hyperstimulation and fewer FHR anomalies, could be more appropriate and could reduce the rate of caesarean section for suspicion of fetal distress.
PRIMARY OBJECTIVE	To demonstrate that mechanical cervical ripening (with a Cook® Cervical Ripening balloon) in comparison with pharmacological cervical ripening (Propess®) significantly reduces the rate of caesarean section for non-reassuring fetal status in cases of prolonged pregnancies
SECONDARY OBJECTIVES	To demonstrate that mechanical cervical ripening (with a Cook® Cervical Ripening balloon) in comparison with pharmacological cervical ripening (Propess®) significantly reduces maternal and neonatal morbidity in cases of prolonged pregnancies.
STUDY DESIGN	Multicentre, open label, randomized, parallel group, controlled trial
PRIMARY OUTCOME	Caesarean section rate for non-reassuring fetal status. Indication of the caesarean section will be settled by an adjudication committee at the end of the study.

SECONDARY OUTCOMES	✓ Time between cervical ripening and delivery in hours ✓ Delivery rate after 12 and 24 hours of cervical ripening ✓ Necessity of induction with oxytocin ✓ Total dose of oxytocin required for induction of labour ✓ Uterine hyper stimulation defined as more than 6 contractions by 10 minutes over a 30 minutes period ✓ Requirement for tocolysis during cervical ripening or during labour ✓ Suspicious or pathological fetal heart rate (see Appendix 1) ✓ Uterine rupture ✓ Use of analgesics during labour ✓ Use of antibiotics during labour ✓ Indication for caesarean delivery other than non-reassuring FHR (failure to progress in first or second stage of labour or maternal indication) ✓ In cases of vaginal delivery: • Spontaneous or instrumental • Indication for instrumental delivery ✓ Maternal morbidity defined by the occurrence of one of the following events: • Suspicion of maternal intra partum infection • Suspicion of post partum infection • Post partum haemorrhage defined as estimated blood loss› 500 cc • Blood transfusion ✓ Neonatal morbidity: • Apgar score at 1, 3, 5 and 10 minutes • Arterial pH at delivery • Admission in an intensive care unit • Respiratory insufficiency with necessity of any respiratory support • Birth asphyxia
PARTICIPANTS	<u>Inclusion criteria</u> ✓ Pregnant women ✓ ≥ 18 years old ✓ With a singleton cephalic pregnancy between ≥41+0 weeks and ≤ 42+0 weeks of gestation ✓ Gestational age estimated from the first trimester ultrasound (realized between 11 and 13+6 weeks of gestation) ✓ With a decision of induction of labour (*see paragraph 6.1.1.*) ✓ Written informed consent obtained from subject ✓ Subject covered by or having the rights to the French Social Security system <u>Exclusion criteria</u> ✓ Bishop score ≥ 6 (favourable cervix) ✓ Non cephalic presentation (breech, transverse) ✓ Severe preeclampsia defined as the presence of preeclampsia with at least one of the following items : - Severe maternal hypertension (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg) - Renal failure with oliguria (‹ 500 ml/24h) or creatinine › 135µmol/L, or proteinuria › 5 g/day - Pulmonary oedema, epigastric pain or HELLP syndrom (hemolysis, elevated liver enzyme, low platelets) - Eclampsia or neurologic persisting symptoms (visual disturbances, headache, increased reflexes) - Thrombopenia ‹ 100 G/L

	✓ Prior caesarean section or uterine scar ✓ Placenta praevia ✓ Suspected genital herpes infection ✓ Known VIH seropositivity (confirmed by blood serology) ✓ Premature rupture of membranes (PROM - continual leaking of amniotic fluid or positive test in favour of PROM) ✓ Foetus with suspected severe congenital abnormalities ✓ Pathological fetal heart rate (see appendix 1) ✓ Contra-indications to Propess® (*see paragraph 7.2.3.*) ✓ Contra-indications for using Cook® Cervical Ripening Balloon (*see paragraph 7.1.3.)* ✓ Women under guardianship or trusteeship
INTERVENTIONS	Experimental group: mechanical cervical ripening with a Cook® Cervical Ripening Balloon Control group: pharmacological cervical ripening with a 10mg slow releasing system of Dinoprostone (Propess®)
PARTICIPANT TIMELINE	Day -1 Selection Day 0 Inclusion, randomization and intervention (cervical ripening) Day 1 Induction of labour in cases where labour has not started Day X Discharge of mother and new-born
RANDOMIZATION AND BLINDING	Randomization 1:1 ratio - Stratification on maternity units, and parity (nulliparas vs multiparas) The nature of the two interventions does not allow blinding, neither of the patients, nor of the care provider who is also the outcome assessor. To compensate the absence of blinding, at the end of the study, an adjudication committee blinded from the method of cervical ripening, will review all FHR of all caesarean deliveries and all FHR of all cases of neonatal asphyxia.
SAMPLE SIZE	1220 women
EXPECTED DURATION OF THE STUDY	Expected duration of enrolment: 36 months Expected duration of the study for a participant: until discharge of the mother and new born Total duration of the study: about 37 months Included participants will not have the authorisation to be involved in another study during the whole follow-up.
FEASIBILITY	All participating maternity units and physicians already regularly do mechanical and pharmacological cervical ripening and have already been successfully involved in several multicentre trials.
EXPECTED RESULTS	Our aim is to show that mechanical cervical ripening methods (with Cook® Cervical Ripening Balloon) for induction of labour in cases of "fragile foetuses" (i.e. premature foetuses or foetuses small for their gestational age) are more appropriate than pharmacological ones (with Propess®). The aim is to prove that mechanical methods could lower the caesarean rate for non-reassuring fetal status in such cases. If this was proved, our aim would be to extend the use of mechanical methods for cervical ripening to other situations of "fragile foetuses" like intra uterine growth restriction or indicated preterm delivery. By lowering the rate of caesarean, the aim is to reduce maternal and fetal morbidity and mortality. Reducing the rate of caesarean would mean reducing the length of hospitalisation of women, reducing their thrombo-embolic risk, reducing the risk of post-operative wound infection and also reducing the cost of the care for women. Reducing the caesarean rate would also improve neonatal health as the risk for neonatal respiratory distress, admission to neonatal ward and neonatal mortality would also be reduced. Reducing neonatal morbidity and mortality would reduce the global cost of perinatal care.

LIST OF ABBREVIATIONS

CHRU	Regional University Hospital Center
PP	Prolonged Pregnancy
FHR	Fetal Heart Rate
SGA	Small for Gestational Age
IUGR	Intra uterine Growth restriction
PROM	Premature Rupture of the Membranes
CTG	Cardiotocography
AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
AMM	Autorisation de Mise sur le Marché
CPP	Comité de Protection des Personnes
CNIL	Commission Nationale de l'Informatique et des Libertés
CNGOF	French national college of obstetricians and gynaecologists
CRA	Clinical Research Assistant
DSUR	Development Safety Update Report
e-CRF	Electronic Case Report Form
GCP	Good Clinical Practices
ICH	International Conference on Harmonization
IP	Investigational Product
INSERM	Institut National de la Santé et de la Recherche Médicale
ITT	Intention To Treat
MR	Méthodologie de référence
PHRC	Protocole Hospitalier de Recherche Clinique
REC	Research Ethics Committee
SAE	Serious Adverse Event
SCP	Summary of Product Characteristics
SOP	Standard Operating Procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction

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1 Background and rational

1.1 Background

1.1.1 Prolonged pregnancies

A pregnancy is considered "prolonged" from 41 weeks of gestation, provided that it was correctly dated on the first trimester ultrasound between 11 and 13+6 weeks of gestation (1). Prolonged Pregnancies (PP) are associated with increased neonatal mortality: according to a study set among 1 815 811 normal weight term births, infants born after 41 weeks have greater odds of neonatal mortality (OR: 1.34, 95% CI, 1.08-1.65) than those born between 38 and 40 weeks (2). In cases of prolonged pregnancies, risks of fetal complications also include macrosomia, oligohydramnios, abnormal fetal heart rate (FHR) and meconium-stained fluid (3).
Maternal morbidity is also increased in prolonged pregnancies: beyond 41 weeks, the rate of caesarean section is multiplied by approximately 1,5; third and 4th degree perineal lesions and postpartum haemorrhage are also more frequent (4).

In 2010 in France, 15 % of pregnancies were prolonged (4). Considering the frequency, the mortality and morbidity it causes, prolonged pregnancies are a major public health issue and should be a priority topic for research.

1.1.2 Management of prolonged pregnancies

In 2012, a Cochrane review entitled "Induction of labour for improving birth outcomes for women at or beyond term" showed that women, beyond term, who underwent induction of labour, had a lower rate of caesarean delivery compared with those who received expectant treatment (5). Compared with a policy of expectant management, a policy of labour induction was associated with fewer perinatal deaths. In the labour induction group, fewer babies had meconium aspiration syndrome and fewer women delivered by caesarean section.

Therefore clinical guidelines usually recommend induction of labour from 41 weeks of gestation: the French National College of Obstetricians and Gynaecologists stated in 2013 that "induction of labour can be proposed to patients between 41+0 and 42+6 weeks» (6). The American College of Obstetricians Gynaecologists stated in 2014 that "before 41 weeks of gestation, induction of labour generally should be performed based on maternal and fetal medical indications; inductions at 41 weeks of gestation should be performed to reduce risk of caesarean delivery and risk of perinatal morbidity and mortality»(7). In Canada, national clinical practice guidelines for management of post-dates pregnancies are non-prescriptive, stating only that women should be 'offered' induction as of 41+0 weeks (8).

1.1.3 Induction of labour

In France, 20% of deliveries are induced meaning that each year approximately 160 000 deliveries follow an induction of labour (9). In cases where labour is induced and cervix is unfavourable, cervical ripening is advised (10). According to a national survey, methods of cervical ripening (protocols of administration and surveillance) vary widely from one maternity unit to another (11). Methods of cervical ripening include pharmacological (prostaglandins) and mechanical (Foley catheter or trans-

cervical double balloon) methods.

Pharmacological agents for cervical ripening are prostaglandins. The most frequently used is Dinoprostone. It can be administered in the cervix or in the vagina, with a slow releasing system or with gel. All systems proved to increase the chances of vaginal delivery in 24 hours and none has proved to be more efficient than the other (12).
Mechanical methods for cervical ripening consist in introducing a catheter through the cervix into the extra-amniotic space. For this technique two main devices exist: the Foley catheter and the trans-cervical double balloons designed specifically for cervical ripening (Cook® Cervical Ripening Balloon). According to a Cochrane review, none of these two methods has proved to be more efficient than the other for cervical ripening (13).

1.2 Study rationale

Recently, pharmacological and mechanical methods for cervical ripening were compared in the PROBAAT trial among women with term pregnancies. The rates of caesarean section with these two strategies were identical. Indications for caesarean deliveries were not significantly different between the two groups. However uterine hyper stimulation with fetal heart anomalies occurred less when cervical ripening was mechanical (14).

Uterine hyper stimulation associated with fetal heart rate anomalies is a frequent side effect when using pharmacological cervical ripening (15). As they increase the risk of non-reassuring FHR, pharmacological methods may not be the most appropriate in cases of foetuses that already present a risk of FHR abnormalities.

At present, no particular method is recommended in cases of cervical ripening and prolonged pregnancies: both strategies, mechanical and pharmacological, are used in daily practice.

We hypothesise that mechanical cervical ripening, with less uterine hyper stimulation and fetal heart rate anomalies, would be better tolerated by fragile foetuses (i.e. premature foetuses or foetuses small for their gestational age) and could be more appropriate in situations of prolonged pregnancies. This is why we aim to conduct a randomized controlled trial in which women beyond 41 weeks of gestation would be randomized to either a pharmacological (Propess®) or a mechanical cervical ripening (Cook® Cervical Ripening Balloon).

1.3 Benefit and risk assessment

1.3.1 Induction of labour

As previously mentioned, it is recommended in France to induce labour from 41 weeks in cases of PP (6). If physicians of the maternity unit follow the clinical guidelines, labour should be induced even if the patient does not participate in the trial. It was also demonstrated recently by Hutcheon et al that routine induction at 41 weeks, in comparison with expectative management, did not affect maternal or neonatal health outcomes (16). More specifically, systematic induction of labour at 41 weeks was not associated with a higher risk of caesarean. So no specific risk is taken due to induction of labour.

1.3.2 Pharmacological and mechanical methods

Described adverse events for pharmacological methods are uterine hyperstimulation associated with fetal heart rate anomalies and uterine rupture in case of prior caesarean. Women randomized in the pharmacological group will not be at risk of uterine rupture as a prior caesarean will be one of the exclusion criteria. However, women randomized in the pharmacological group will have higher risk of uterine hyper stimulation and fetal heart rate anomalies.

A meta analysis comparing mechanical and pharmacological methods for cervical ripening showed multiparous women had a higher risk of not achieving delivery within 24 hours with mechanical methods, in comparison with pharmacological ones (14). So multiparous women may be at higher risk of not achieving delivery within 24 hours and may require more oxytocin. However, the same meta analysis showed that chances of achieving delivery within 48 hours and the risk for caesarean section were the same for the two methods. The only risk may be to slightly delay delivery among multiparas in the mechanical group.
In a Cochrane review on mechanical and pharmacological cervical ripening, serious neonatal or maternal morbidity was infrequently reported and did not differ between pharmacological and mechanical methods, meaning both procedures are safe (13).

2 Objectives

2.1 Primary objective of the study

To demonstrate that mechanical cervical ripening using a Cook® Cervical Ripening Balloon, in comparison with pharmacological cervical ripening using a vaginal prostaglandin E2 slow releasing system (Propess®), significantly reduces the rate of caesarean section for non-reassuring fetal status in cases of prolonged pregnancies.

2.2 Secondary objectives of the study

To demonstrate that mechanical cervical ripening using a Cook® Cervical Ripening Balloon, in comparison with pharmacological cervical ripening using a vaginal prostaglandin E2 slow releasing system (Propess®), significantly reduces maternal morbidity (uterine rupture, suspicion of intra/post partum infection, post partum haemorrhage, blood transfusion) and neonatal morbidity (neonatal acidosis, admission in an intensive care unit, respiratory insufficiency) in cases of prolonged pregnancies.

3 Study design

Multicentre, open label, randomized, parallel group, controlled trial with an adjudication committee blinded from the intervention who will settle the main outcome.

4 Outcomes

4.1 Primary Outcome

To make the trial comparable to published studies on the topic we chose the caesarean section rate for non-reassuring fetal status (with or without arrest of labour) as the primary endpoint.

If caesarean is an objective outcome, the decision to perform the caesarean is not. Two different physicians can take different decisions for the same obstetrical situation and it is frequent physicians disagree on caesarean indications. Similarly the same physician facing the same situation twice can take different decisions. The outcome is considered as an "objectively measured but potentially influenced by clinician judgment outcome", as defined by Savovic et al (17).

This is the reason why, caesarean indications will be adjudicated by a blinded committee at the end of the study, the primary outcome being focused on caesarean for non-reassuring fetal status.
So, once inclusions are over and that all the data will be collected, the adjudication committee will review all the cases of caesarean deliveries to settle the indication (main outcome) with the codified monitorings of FHR 2 hours prior delivery.
The adjudication committee will also review, at the end of the study, all the FHR of all the cases of fetal asphyxia (2 hours prior delivery).
The monitorings of FHR will be codified (with inclusion code of women) before being analyzed by adjudication committee who will be blinded from the cervical ripening method.
In the end, this study is a PROBE study: Prospective, Randomized, Open, with Blinded Evaluation.

4.2 Secondary Outcomes

- ✓ Time between cervical ripening and delivery in hours
- ✓ Delivery rate after 12 and 24 hours of cervical ripening
- ✓ Necessity of induction with oxytocin
- ✓ Total dose of oxytocin required for induction of labour
- ✓ Uterine hyper stimulation defined as more than 6 contractions by 10 minutes over a 30 minutes period
- ✓ Requirement for tocolysis during cervical ripening or during labour
- ✓ Suspicious or pathological fetal heart rate (see Appendix 1)
- ✓ Uterine rupture
- ✓ Use of analgesics during labour
- ✓ Use of antibiotics during labour
- ✓ Indication for caesarean delivery other than non-reassuring FHR (failure to progress in first or second stage of labour or maternal indication)
- ✓ In cases of vaginal delivery: spontaneous or instrumental, indication for instrumental delivery
- ✓ Maternal morbidity defined by the occurrence of one of the following events:
    - o Suspicion of maternal intra partum infection
    - o Suspicion of post partum infection
    - o Post partum haemorrhage defined as estimated blood loss › 500 cc
    - o Blood transfusion
- ✓ Neonatal morbidity:
    - o Apgar score at 1, 3, 5 and 10 minutes
    - o Arterial pH at delivery
    - o Admission in an intensive care unit
    - o Respiratory insufficiency with necessity of any respiratory support
    - o Birth asphyxia defined as pH‹7, Base Excess ›12 mmol/l and encephalopathy.

5 Study setting

The study will be set in 09 French University Hospitals or general Hospitals, all used to participating in clinical trials and also all used to mechanical cervical ripening in their daily practice. The list of study sites is provided in Appendix 3.

6 Participants

6.1 Eligibility criteria

6.1.1 Inclusion criteria

- ✓ Pregnant women
- ✓ ≥ 18 years old
- ✓ With a singleton cephalic pregnancy between ≥41+0 weeks and ≤ 42+0 weeks of gestation
- ✓ Gestational age estimated from the first trimester ultrasound (realized between 11 and 13+6 weeks of gestation)
- ✓ With a decision of induction of labour *
- ✓ Written informed consent obtained from subject
- ✓ Subject covered by or having the rights to the French Social Security system

** Indications for induction of labour may vary between centres.*

Guidelines for induction of labour are summarized in two documents: one from the "Haute Autorité de Santé - Déclenchement artificiel du travail à partir de 37 semaines d'aménorrhée" (10) and one from the "Collège national de Gynécologie Obstétrique - [Prolonged pregnancy term and beyond: guidelines for clinical practice - text of the guidelines (short text)]. J Gynecol Obstet Biol Reprod (Paris). 2011 Dec;40(8):818-22. doi: 10.1016/j.jgyn.2011.09.026. Epub 2011 Nov 9. French. PubMed PMID: 22078138.

This latter document states that in case of prolonged pregnancies, induction of labour should be considered from 41 weeks of gestation.

Considering that in our study, all women will be at 41 weeks of gestation or more, the main indication for induction of labour will be "prolonged pregnancy". In addition to this main indication, clinicians may indicate a second indication for induction of labour which may include: abnormal fetal heart rate, prolonged pregnancy, oligoamnios, reduction of the fetal movements, hypertension, foetus small for its gestational age, growth retardation, diabetes, pathologic doppler findings, gestational thrombocytopenia, cholestasis of pregnancy, personal convenience.

6.1.2 Exclusion criteria

- ✓ Bishop score ≥ 6 (favourable cervix)

If the HAS (French National Authority for Health) usually defines a favourable cervix when the bishop score is greater than or equal to 7 (see appendix 2); we chose to exclude women with a bishop score greater than or equal to 6, to be comparable with other trials evaluating cervical ripening (PROBAAT trial).

- ✓ Non cephalic presentation (breech, transverse)
- ✓ Severe preeclampsia defined as the presence of preeclampsia with one of the following items:
  - Severe maternal hypertension (systolic blood pressure ≥ 160 mm Hg and/or diastolic blood pressure ≥ 110 mm Hg)
  - Renal failure with oliguria (< 500 ml/24h) or creatinine > 135µmol/L, or proteinuria > 5 g/day

- Pulmonary oedema, epigastric pain or HELLP syndrom (hemolysis, elevated liver enzyme, low platelets)
- Eclampsia or neurologic persisting symptoms(visual disturbances, headache, increased reflexes)
- Thrombopenia < 100 G/L

✓ Prior caesarean section or uterine scar
✓ Placenta praevia
✓ Suspected genital herpes infection
✓ Known VIH seropositivity (confirmed by blood serology)
✓ Premature rupture of membranes (PROM - continual leaking of amniotic fluid or positive test in favour of PROM)
✓ Foetus with suspected severe congenital abnormalities
✓ Pathological fetal heart rate (see appendix 1)
✓ Contra-indications to Propess® (*see paragraph 7.2.3.*)
✓ Contra-indications for using Cook® Cervical Ripening Balloon (*see paragraph 7.1.3.)*
✓ Women under guardianship or trusteeship

6.2 Exclusion period

Included participants will not have the authorisation to be involved in another study during the whole follow-up.

7 Interventions

In the experimental group and the control group, both midwives and physicians should be able to administer the products.

7.1 Experimental group : mechanical cervical ripening

7.1.1 Device characteristics

The mechanical cervical ripening is a double transcervical balloon. The device used in the study is the Cook® Cervical Ripening Balloon with CE marked (commercialized by the Cook® laboratory, ref J-CRBS-184000). It is a silicone double balloon catheter. Maximum balloon inflation is 80 mL/balloon.

7.1.2 Administration

To insert the Cook® Cervical Ripening Balloon, the patient should be in gynaecologic position.
It will be used in accordance with user manual (see Appendix 4).

In case of uterine hyperstimulation during the cervical ripening procedure, the device should be removed. To remove the device both balloons should simply be deflated. After the deflation of the balloons a gentle traction on the device is enough to remove it.
If uterine hyperstimulation is associated with abnormal fetal heart rate, tocolysis could be considered.

7.1.3 Contra-indications

✓ Patient receiving or planning to undergo exogenous prostaglandin administration
✓ Placenta previa, vasapraevia or placenta percreta

- ✓ Transverse or breech presentation
- ✓ Prolapsed umbilical cord
- ✓ Prior hysterotomy classic uterine incision, myomectomy or any other full-thickness uterine incision
- ✓ Pelvic structural abnormality
- ✓ Active genital herpes infection
- ✓ Invasive cervical cancer
- ✓ Abnormal fetal heart rate patterns
- ✓ Maternal heart disease
- ✓ Multiple gestational pregnancy
- ✓ Polyhydramnios
- ✓ Presenting part above the pelvic inlet
- ✓ Severe maternal hypertension
- ✓ Any contraindication to labour induction
- ✓ Ruptured membranes

7.2 Control group : pharmacological cervical ripening

7.2.1 Drug characteristics

The comparative pharmacological procedure is a vaginal slow releasing system of dinoprostone. The form used in the study is Propess® (Ferring pharmaceuticals) containing 10mg of dinoprostone (prostaglandin E2).

7.2.2 Administration

The slow releasing system of dinoprostone should be inserted in the vagina, against the cervix. To do so the patient should be in lithotomy position.
It will be used in accordance with Summary of Product Characteristics (see appendix 5).

In case of uterine persistent hyperstimulation with normal cardiotocography (CTG), the tampon can be removed by gently pulling on the tampon.
If uterine hyperstimulation is associated with abnormal fetal heart rate, tocolysis could be considered.

The slow releasing system should be removed immediately, if:
- ruptured membranes (caused or spontaneous)
- the mother has systemic adverse events related to prostaglandin like nausea, vomiting, hypotension or tachycardia

7.2.3 Contra-indications

Propess® should not be used or left in place:
1. When labour has started.
2. In case of concomitant use of IV oxytocic drugs and non steroidal anti-inflammatory drugs including aspirin
3. When strong prolonged uterine contractions would be inappropriate such as in patients:
   a) who have had previous major uterine surgery, e.g. caesarean section, myomectomy etc.

b) with cephalopelvic disproportion
c) with fetal malpresentation
d) with suspicion or evidence of fetal distress
e) who have had more than three full term deliveries
f) previous surgery or rupture of the cervix

4. When there is current pelvic inflammatory disease, unless adequate prior treatment has been instituted.
5. When there is hypersensitivity to dinoprostone, prostaglandins or to any of the excipients (Crosslinked polyethylene glycol (hydrogel), Polyester yarn)
6. When there is placenta previa or unexplained vaginal bleeding during the current pregnancy.
7. In case of glaucoma or raised intraocular pressure, asthma or history of asthma
8. In case of maternal cardiac, or hepatic or pulmonary or renal disease or dysfunction.

7.3 Investigational product management

7.3.1 Supply of products

The Tours Hospital pharmacy will supply the Cook® Cervical Ripening Balloon and the Propess® in each investigational site.

7.3.2 Packaging and labelling

Commercial packaging will be used. The experimental product (Cook® Cervical Ripening Balloon) and the control product (Propess®) will be labelled in accordance with the clinical trials regulatory guidelines by the hospital Pharmacy of CHRU of Tours.

7.3.3 Storage conditions

Experimental and control products will be supplied to the pharmacist of each investigational site, who will be in charge of the traceability and the storage.
The study products will be stored in accordance with regulations, in a different place to the other drugs of the pharmacy, with restricted access and according to the storage conditions recommended by the manufacturer:

- ✓ The Cook® Cervical Ripening Balloon must be stored in a dry place and away from light.
- ✓ The Propess® slow releasing system must be stored in freezer (-20°c to -10°C).

7.3.4 Products accountability

The investigator is responsible for ensuring that all study products received at the site are inventoried and accounted throughout the study. Local pharmacy will be in charge of the accountability of the study treatments. The dispensing of study product to the subject must be documented on the product accountability form. Unused study product must be available for verification by the sponsor's site monitor during on-site monitoring visits.

7.3.5 *Return and destruction of unused products*

All remaining IPs, used and unused containers, will be collected and destroyed at the end of the study. IPs will be kept at the local pharmacy until the monitoring visit by the CRA. Then they will be destroyed on site after a written agreement by the CRA.

7.4 Intervention concomitant care

7.4.1 *Intervention modifications during the study*

If cervical ripening (mechanical or pharmacological) is not sufficient to induce labour, labour should be induced the next day with oxytocin. If it is required, a caesarean section can be performed at any time during the study if the physician in charge of the patient estimates it is necessary.

7.4.2 *Authorized concomitant care*

Antibiotics

All type of antibiotics may be required in cases of suspicion of infection during cervical ripening or labour. They may also be required depending on the status for group B streptococcus or if the patient has fever.

Tocolysis

Tocolysis (Betamimetics or calcium channel blockers) may be required in case of uterine hyperstimulation and FHR anomalies during cervical ripening and during labour.

Analgesics

If the patient experiences severe pain during the cervical ripening, without uterine hyperstimulation, pain management should be done according to the local protocols and may include: massages, shower, paracetamol, phloroglucinol, nalbuphine or nitrous oxide.
During labour, nitrous oxide and epidural may be prescribed if requested by the participant.

Induction of labour

- *Oxytocin :* The day after cervical ripening (Day 1) if delivery has not occurred and if the patient is not in labour, women should have induction of labour with intravenous oxytocin.
Oxytocin should be administered according to his Summary of Product Characteristics and French guidelines (Haute Autorité de Santé, Recommandations "Déclenchement artificiel du travail à partir de 37 semaines d'aménorrhée" Avril 2008) for induction of labour (18).
Once uterine contractions are regular, the oxytocin infusion rate can be reduced and even stopped as long as labour progresses. Continuous fetal monitoring is recommended. Maximum oxytocin used should not exceed 10 UI.
- *Amniotomy* should be done as early as possible. Assuming that in France cervical examination is recommended every hour, every hour the feasibility of amniotomy should be re-evaluated.

Prostaglandins may be required in cases of post partum haemorrhage.

All drugs, devices or surgical/embolization procedures required in case of a post partum haemorrhage may be administrated as required and described by national guidelines.

7.4.3 *Prohibited concomitant care*

Apart for the technique of cervical ripening usual care and usual drugs should be administrated to patients according to the local and national guidelines, however all concomitant care should be reported in a special section of the electronic Case Report Form (eCRF).

For dinoprostone: concomitant use of oxytocic drugs, nonsteroidal inflammatory drugs including aspirin and methylergometrin is prohibited.

8 Participant timeline

8.1 Participant selection and recruitment

Recent guidelines recommend that, in cases of prolonged pregnancies, fetal wellbeing should be evaluated every two days by fetal heart rate monitoring (6). Guidelines on prolonged and post-dated pregnancies also suggest an ultrasound monitoring of the quantity of amniotic fluid (measurement of the largest amniotic fluid pocket).

Therefore in all the participating centres, women with prolonged pregnancies require specific monitoring by midwives, sonographers and physicians. Accordingly those three should be responsible of patient screening in the participating centres.

Therefore, once the decision of induction of labour is taken, the screening should begin.

So women who fulfil inclusion criteria will be informed of the study's objectives by sonographers/midwives/physicians and all their questions will be answered.

Women should be allowed to have as much time as necessary to decide whether or not they wish to participate to the study.

8.2 Practical issues

Because some women are likely to go into labour spontaneously, and because bishop score in case of uterine contractions is likely to change, inclusion and randomization should be done the morning of cervical ripening.

8.2.1 Inclusion and randomization

Women should be admitted in the morning, with an empty stomach (Day 0). Just before cervical ripening, two inclusion criteria should be verified (as they may have changed since the screening visit, the day before). A cervical examination (which will determine the Bishop score) and a fetal CardioTocoGraphy (CTG) (which will allow studying the fetal heart rate) should be done to check the absence of the two following items:

- ✓ Bishop score ≥ 6 (favourable cervix)
- ✓ Non reassuring fetal heart rate

To this point, inclusion will be made:

- Consent: investigators/midwives must obtain the consent of the women. It must be dated and signed by the women and investigators/midwives before any further assessment.
- Randomization is done.

The results of randomization should be "pharmacological" or "mechanical" cervical ripening.

Randomization will be stratified on:

- ✓ Maternity units
- ✓ Parity (nulliparas vs multiparas)

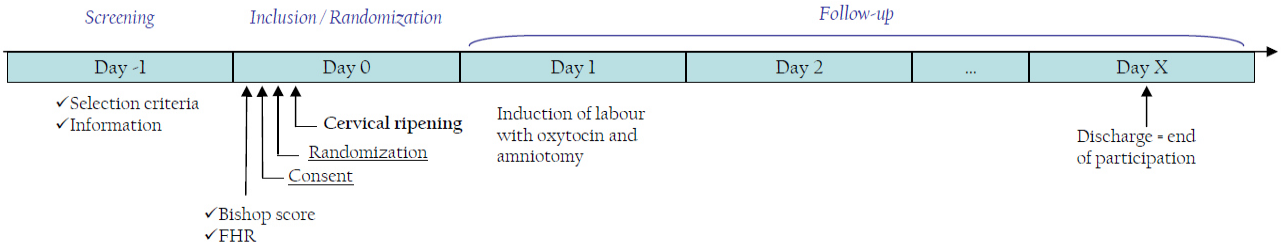


Figure 1: patient's route during the study

8.2.2 *Intervention delivery*

After randomization, cervical ripening will be either mechanical or pharmacological. After the pharmacological or the mechanical device has been administered, the fetal heart rate should be monitored continuously during 120 minutes as recommended (*French National Authority for Health – Recommendations for "Déclenchement artificiel du travail à partir de 37 semaines d'aménorrhée" - Avril 2008*).

Induction of labour, whichever the technique, should always be performed near an operating room in case of the need for an urgent caesarean.

During cervical ripening, foetal condition and uterine activity will be regularly monitored by an external cardiotocography.
If premature rupture of the membranes occurs the double cervical balloon or the vaginal device should be removed.

After cervical ripening, if labour is not instantly induced and if the FHR is reassuring, FHR can be monitored intermittently as recommended by the national guidelines.

At any time, if labour starts, the patient is transferred to labour ward. Epidural analgesia is done according to the patient's wishes and according usual medical indications and contraindications (*see paragraph 7.4.2.*).

8.2.3 *Follow-up assessment*

The day following cervical ripening (i.e. day 1) if labour has not started, the device should be removed in order to start induction of labour with oxytocin. As recommended, perfusion of oxytocin should start at least 30 minutes after the device has been removed.

8.3 Collected data

No assessment visit required but primary and secondary outcome parameters will be retrieved from patient data forms, this will consist on:
- Clinical exam (height, weight, ...)
- Ethnicity* (Sub-Saharian African/Caribbean, North African, Asian, Caucasian, Hispanic)
- Past medical (addictions, medical background, obstetric history)

- Current pregnancy (pathologies, hospitalizations, pharmacological treatment)
- FHR (before and during cervical ripening, during labour)
- Labour (induction, progress, monitoring and treatment)
- Delivery (anesthesia, complications, type (vaginal, instrumental extraction, caesarean))
- Post-partum (hemorrhage, pre-eclampsia…)
- Newborn (apgar score, transfer to reanimation unit…)

**The structure and composition of the cervix is complex. The cervical tissue is composed of connective tissue (collagen, elastin) and smooth muscles. It synthesizes the cervical extracellular matrix, which contains the vaginal flora.*
Cervical length measured by ultrasound during pregnancy and the risk of spontaneous preterm birth are two elements which vary according to ethnicity (Epidemiologic factors and urogenital infections associated with preterm birth in midwestern US population Agger WA et al Obstet Gynecol 2014; Is cervical lenght associated with maternal characterisitcs? Van der Ven AJ EJOG 2015).
This suggests that histological, biochemical or biological composition of the cervix could vary with ethnicity of women. Thus efficiency of the different cervical ripening techniques could depend on ethnicity. This is why we wanted to study this characteristic of women.
Ethnicity is systematically reported in several publications and recent prospective trials on cervical ripening. To be able to compare our results to other studies, we need to study the ethnic distribution of our population. We therefore estimated that this data was important to collect.

8.4 Study schedule

Expected duration of recruitment and total duration of the study: 36 months

Duration of the study for a participant: until discharge of the mother and new born

	Screening (= Decision of induction)	**Intervention**	**Follow-up until discharge (of the mother and new born)**
	Day-1	**Day 0**	**Day 1 => Day X**
Patient information	X		
Criteria for inclusion / non-inclusion	X		
Bishop score / FHR		X (before cervical ripening)	
Signature of consent		X (before cervical ripening)	
Randomization		X (before cervical ripening)	
Clinical examination	X	X (before and during cervical ripening)	X
Cervical ripening (mechanical/pharmacological)		X	
External cardiotocography *- foetal condition (FHR)* *-uterine activity*	X	X X	X until delivery
Induction of labour		X (if applicable)	X (if applicable)
Adverse events and concomitant medications		X	X

8.5 Discontinuation and withdrawal

Once a subject will be randomized in the study, every reasonable effort will be made to follow the subject for the entire study period even if there is a deviation from the intervention protocols.

No subjects should be lost-to-follow-up as every woman will deliver after cervical ripening.

A subject may be discontinued from study at any time if the subject, the investigator, or the Sponsor feels that it is not in the subject's best interest to continue. If a subject is withdrawn from treatment or device due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized. Early discontinuation is not a reason for withdrawal from the study.

All subjects are free to withdraw consent from participation at any time, for any reason, specified or unspecified, and without prejudice. Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents. Nevertheless, data collected for this participant will be used except if the participant refuses.

9 Randomization

9.1 Sequence generation

A computer process will be used to generate allocation sequences in a 1:1 ratio.

Randomization will be stratified on centre and parity using permuted blocks of random sizes. The block sizes will not be disclosed to study investigators.

9.2 Allocation concealment mechanism

Participants will be randomized using CSonline of Ennov Clinical ®, an online central randomization procedure. To insure allocation concealment, randomization procedure will not be possible until the participant has been recruited into the trial, especially all selection criteria must be collected and met.

9.3 Implementation

A statistician who will not be involved in recruiting or follow-up of the participants will generate allocation sequence.

10 Blinding

Blinding is not possible due to the nature of the assessed procedures for three main reasons:

1. Required material for the two procedures is different. The pharmacological method (Propess®) is introduced in the vagina with or without a speculum, depending on the physician's usual practice. The device for mechanical cervical ripening is a 40 cm long silicone double balloon catheter which should be introduced with a speculum and requires to inflate the two balloons.
2. Once cervical ripening has started, women from the mechanical group can see and feel the device. Physicians can also see the device
3. Both mechanical and pharmacological devices need to be removed, but the pharmacological can fall without the patient noticing.

None of the participants or care providers will be blinded.

However the adjudication committee in charge of defining the primary outcome will be blinded from the cervical ripening method.

11 Data handling

11.1 Data collection

11.1.1 Access to data

The investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject of the study.

The sponsor is responsible for obtaining the agreement of all the parties involved in the study in order to guarantee direct access in all the sites where the study is being conducted to source data, source documents and reports, so that he can control their quality and audit them.

The investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

11.1.2 Source data and source document

Any original document or object helping to prove the existence or accuracy of a piece of information or fact recorded during the study is defined as a source document.

11.2 Data collection tool

Study personnel with their own access right to the study database, will enter/capture data from source documents corresponding to a subject into the protocol-specific electronic Case Report Form (eCRF).

All the information required by the protocol will be entered in an eCRF and an explanation will be provided for each missing piece of information. The data must be collected as they are obtained and transcribed into these forms in a clear manner.

If a correction is required for an eCRF, the time and date stamps track the person entering or updating eCRF data and create an electronic audit trail.

11.3 Confidentiality of data

In accordance with the legislative provisions in force (articles L.1121-3 and R.5121-13 of the French Public Health Code), people with direct access to source data will take all necessary precautions to ensure the confidentiality of information relating to study intervention, research studies and people taking part in them, particularly as regard to their identity and the results obtained. These people, such as investigators themselves, are subject to professional secrecy.

During the biomedical research study or when it is over, the information collected on the people taking part in it and forwarded to the sponsor by the investigators (or any other specialized staff member involved) will be made anonymous. Under no circumstances may the uncoded names or addresses of the people concerned appear in it.

For coding subjects in the database or any study documents, the first letter of the first name and first letter of the last name of the subject will be recorded, accompanied by a code showing the order of inclusion of the subject in a centre.

The sponsor will ensure that each person taking part in the study has given his agreement in writing for access to the individual data concerning him which is strictly necessary for quality control of the study.

11.4 Data management procedures

Data management will be performed by the INSERM CIC-P 1415. An eCRF will be developed using the Ennov Clinical® software. eCRF management will be managed in agreement with the INSERM CIC-P 1415 Standardized Operating Procedures (SOP). Clinical Research Associate in charge of the study will be formed to the eCRF and in charge of the investigator's formation. Data will be entered in investigating centers through a secure web site, monitored by CRAs and queries will be edited by data managers, in agreement with a specified data management plan.

A data review will be done prior locking the database. The database will be locked in agreement with the INSERM CIC-P 1415 SOPs and data will be extracted in a SAS format or other, according to statistical requirements.

11.5 Data validation

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. After inconsistencies review, queries are entered, tracked, and resolved through the electronic data capture system directly (omissions and discrepancies will be forwarded to investigator for resolution). The study database will be updated in accordance with the resolved queries. All changes will be documented.

11.6 Security and archival of data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

12 Statistical considerations

12.1 General principles of study analysis

Statistical analyses will be supervised by Bruno Giraudeau from the methodological unit CIC Inserm 1415 CHRU de Tours, 2 boulevard Tonnellé, 37044 TOURS Cedex. A detailed analysis plan will be *a priori* defined. SAS 9.2 and R 2.15.0 (or latest versions) softwares will be used. The level of statistical significance will be set at 5%. A statistical report will be reported according to international guidelines: CONSORT (http://www.consort-statement.org/ - Consultation: 2016.04.01). A flow diagram will be done.

12.2 Analysis population definition

The ITT principle will be applied.

Because the primary outcome is the caesarean rate for non-reassuring fetal status, we expect to have no missing data for the primary outcome. In case we would however have some, multiple imputation methods would be applied.

12.3 Baseline characteristics

Baseline characteristics will be reported per group using descriptive statistics. No statistical test will be performed on baseline measures.

12.4 Statistical analysis of the primary outcome

The caesarean rate will be compared using the chi-square test.

12.5 Statistical analysis of secondary outcomes

- ✓ Time between cervical ripening and delivery in hours: The time between cervical ripening and delivery will be compared between the two groups using the Wilcoxon test.
- ✓ Delivery rate after 12 and 24 hours of cervical ripening: The Delivery rate after 12 hours of cervical ripening will be compared using the chi-square test. The same analysis will be performed for the Delivery rate after 24 hours of cervical ripening.
- ✓ Necessity of induction with oxytocin: The administration of oxytocin (binary outcome: Yes/no) will be compared between the two groups using the chi-square test.
- ✓ Total dose of oxytocin required for induction of labour: In case of administration of oxytocin, the total dose of oxytocin will be compared using the Wilcoxon test.
- ✓ Uterine hyper stimulation defined as more than 6 contractions by 10 minutes over a 30 minutes period: The presence of uterine hyper stimulation will be compared using the chi-square test.
- ✓ Requirement for tocolysis during cervical ripening or during labour: the requirement for tocolysis will be compared using the chi-square test.
- ✓ Suspicious or pathological fetal heart rate (see Appendix 1): the rate of Suspicious or pathological fetal heart rate will be compared using the chi-square test.
- ✓ Uterine rupture: the rate of uterine rupture will be compared using the chi-square test.
- ✓ Use of analgesics during labour: the administration of analgesics will be compared using the chi-square test.
- ✓ Use of antibiotics during labour: the administration of antibiotics will be compared using the chi-square test.
- ✓ Indication for caesarean delivery other than non-reassuring FHR (failure to progress in first or second stage of labour or maternal indication): the Indication for caesarean delivery will be compared using chi-square test.
- ✓ In cases of vaginal delivery, spontaneous or instrumental delivery and indication for instrumental delivery: In cases of vaginal delivery, the rate of spontaneous or instrumental delivery will be compared using the chi-square. In cases of instrumental delivery, indication will be compared using chi-square tests.
- ✓ Suspicion of maternal intra partum infection: the rate of Suspicion of maternal intra partum infection will be compared using the chi-square test.
- ✓ Suspicion of post partum infection: the rate of Suspicion of post partum infection will be compared using the chi-square test.
- ✓ Post partum haemorrhage defined as estimated blood loss › 500 cc: the rate of Post partum haemorrhage will be compared using the chi-square test.
- ✓ Blood transfusion: the rate of blood transfusion will be compared using the chi-square test.
- ✓ Apgar score at 1, 3, 5 and 10 minutes: the Apgar score at 1 minute will be compared using the Wilcoxon test. The same analysis will be performed for Apgar score at 3, 5 and 10 minutes. The

evolution of Apgar score will be studied also in the framework of a mixed model (several measures per newborn).

- ✓ Arterial pH at delivery: the Arterial pH at delivery will be compared using the Wilcoxon test.
- ✓ Admission in an intensive care unit: the rate of admission in an intensive care unit will be compared using the chi-square test.
- ✓ Respiratory insufficiency with necessity of any respiratory support: the rate of Respiratory insufficiency will be compared using the chi-square test.
- ✓ Neonatal birth asphyxia: events will be reported per group using descriptive statistics.

12.6 Sample size

The NOCETER trial was set in French maternity units and concerned a population of women with prolonged pregnancies and a bishop score of less than 6. The rate of caesarean delivery was 27% of which 17,7% were performed for fetal distress (5). Many of the participating centres in the NOCETER trial would participate in the present trial so we estimated we could use these percentages as a reference.

We hypothesize that mechanical cervical ripening could reduce the rate of caesarean for suspected fetal distress from 17,7% to 12%.

To detect a reduction from 17,7% to 12% of the main outcome (caesarean for fetal distress) With a power at 80% and a two tailed type I error at a 5%, we need to include a total of 1220 women (610 in each group)

13 Project feasibility

All participating maternity units and physicians already regularly do mechanical and pharmacological cervical ripening and have already been successfully involved in several multicentre trials.

Considering :

- ✓ All the participating maternity units are used to clinical trials in their daily practice
- ✓ Prolonged pregnancy concerns around 15% of all pregnancies in France
- ✓ According to the number of deliveries over the last years, we estimate that the 9 participating maternity units will enable us to assess about 100 000 deliveries over the 36 months recruiting period
- ✓ Observing 100 000 deliveries could allow us to have 100 000 x 0.15= 15 000 eligible women with prolonged pregnancies.
- ✓ At least 1/10 women will agree to participate, meaning that at least 15000 x 1/10= 1500 women should agree to participate.

Accordingly, recruitment of 1220 women appears feasible within a 36 months period.

14 Expected results/benefits

Our aim is to show that mechanical cervical ripening methods for induction of labour in cases of foetuses at high risk of FHR abnormalities is more appropriate than pharmacological ones and that these methods could be associated with a lower caesarean rate for non-reassuring fetal status. If this was proved, our aim would be to extend the use of mechanical methods for cervical ripening to other situations of "fragile foetuses" (i.e. premature foetuses or foetuses small for their gestational age) like

intra uterine growth restriction or indicated preterm delivery. By lowering the rate of caesarean, the aim is to reduce maternal and fetal morbidity and mortality.
Around 20% of deliveries are caesarean sections in France. Reducing the rate of caesarean would mean reducing the length of hospitalisation of women, reducing their thrombo-embolic risk, reducing the risk of post-operative wound infection and also reducing the cost of the care for women.
Reducing the caesarean rate would also improve neonatal health as the risk for neonatal respiratory distress; admission to neonatal ward and neonatal mortality would also be reduced. Reducing neonatal morbidity and mortality would reduce the global cost of perinatal care.

15 Evaluation of security

Terminology used in this section is defined in Appendix 6, 7 and 8.

15.1 Description of safety evaluation parameters

The major expected serious adverse reactions are those listed in the summary of product of Propess® (for pharmacological group), or those listed in the instructions for use of Cook® Cervical Ripening Balloon (for mechanical group).

15.2 Procedures and timing for the measurement, collection and analysis of the safety parameters

After the pharmacological or the mechanical device has been administered, the fetal heart rate should be monitored continuously during 120 minutes as recommended.

If labour is not instantly induced and if the FHR is reassuring, FHR can be monitored intermittently as recommended by the national guidelines; it would be monitored until the delivery.

During cervical ripening and labour, some elements will be monitored: pain, uterine hyperstimulation, fetal cardiac rhythm, temperature, bleeding, blood pressure.

15.3 Reporting and documentation of serious adverse events

15.3.1 Investigator's responsibilities

15.3.1.1 Notification of serious adverse events

15.3.1.1.1 Information to be reported to the sponsor

Each serious adverse event will be reported in the dedicated CRF pages, (initial or follow-up declaration), as thoroughly as possible.

The following information must be transmitted:

- ✓ subject identification (number, code, date of birth, date of inclusion, weight, height),
- ✓ severity criteria of the AE,
- ✓ start and end date of the AE,
- ✓ a clear and detailed description of the AE (diagnosis, symptoms, intensity, timing, actions and results),
- ✓ changes to the AE with time,
- ✓ disease course or relevant subject history,

- ✓ treatment received by the subject,
- ✓ whether the adverse event is related to the medical product, or to any associated treatments or other criteria.

Whenever possible, the investigator shall also attach to the adverse event report documents:

- ✓ a copy of the report of hospitalization or prolongation of hospitalization,
- ✓ a copy of the autopsy report (if applicable),
- ✓ a copy of all the results of additional tests, including those showing normal laboratory values,
- ✓ any other documents if necessary and appropriate.

These documents will be anonymized and coded with the identification number of the participant.

15.3.1.1.2 Procedure for SAE reporting to the sponsor

A report of every serious adverse event, regardless of whether the material device, the study procedures or the research is suspected to have caused it (with the exception of those listed in the protocol as not requiring immediate notification), will be faxed to the CHRU of Tours on the following numbers 02 47 47 46 62.

A vigilance expert (Céline LENGELLE, Marie-Sara AGIER, Annie-Pierre JONVILLE-BERA) can be reached by telephone (02 47 47 80 37, 02 47 47 43 15, 02 47 47 36 01).

15.3.1.1.3 Time limit for SAE reporting to the sponsor

The investigator has to report to the sponsor immediately (real time reporting) and within a maximum of 24 hours after learning of the occurrence of a serious adverse event in the trial (with the exception of those listed in section 15.3.1.2 of the protocol which do not require immediate notification).

This initial notification must be provided in writing and should be quickly followed by a detailed written supplementary report.

15.3.1.1.4 Reporting period of SAE to the sponsor

The investigator will record and report all serious adverse events that occur during the study, from the day that written informed consent is provided. This includes all events that occur during the follow-up period of the clinical trial, so until discharge.

Moreover, all serious adverse events occurring after the study and that may be due to the research must be reported to the sponsor (e.g. serious events that may occur a long time after drug exposure, such as cancer or birth defects).

The investigator has the responsibility to record and report all serious adverse events occurring during the entire study:

- ✓ From the day of the written informed consent,
- ✓ For the duration of monitoring of the participant under the test.

Moreover, regardless of the time of occurrence after the end of the study, all serious adverse events likely to be due to the research must be reported to the sponsor, since no other cause that the research cannot reasonably be attributed (e.g. serious events that may occur at great distances from study treatment, such as cancer or birth defects).

All these events must be monitored until they are completely resolved. The investigator will send the sponsor additional information (additional declaration form) concerning the evolution of the event not mentioned in the initial report.

15.3.1.1.5 Reporting of non-serious adverse events

Non-serious adverse events must also be reported in the e-CRF with their date of occurrence, a description, their intensity evaluation (using the classification provided in Appendix 7) and duration, method of resolution, aetiology, causal relationship (using the classification provided in Appendix 8) with the research and any decisions made.

15.3.1.2 Specificities of the protocol

Some circumstances requiring hospitalization that are not covered by the "hospitalization / prolongation of hospitalization" section under “serious adverse events" and not need to be reported, that include :

- ✓ hospitalization related to the study procedures and planned in the protocol,
- ✓ admission for social or administrative reasons,
- ✓ short stays lasting less than 24 hours,
- ✓ hospitalization for routine treatment or monitoring of the disease studied that is not related to the deterioration of the participant's condition,
- ✓ hospitalization for medical or surgical treatment scheduled before the start of the research.

Caesarean delivery is a serious adverse events expected, related to the pathology of patients. In so far as it is the primary outcome, it will be recorded, as soon as possible, in the e-CRF, on a specific page and will be included in the annual safety report.

15.3.2 Sponsor's responsibilities

15.3.2.1 Analysis of serious adverse events

The sponsor must evaluate the following:

- ✓ The causal relationship between serious adverse events according to ICH guidelines (as defined in Appendix 8) and the medical device or the study procedures. If the investigator or the sponsor considers that a causal relationship may exist with the study procedures, then serious adverse events are considered to be suspected adverse reactions. If there is a difference in opinion between the sponsor and the investigator, both opinions are mentioned in the statement sent to the competent authority (if a statement is required).
- ✓ The expected or unexpected features of the serious adverse reactions, using the reference document in force: the instruction for use of the Cook® Cervical Ripening Balloon and the Summary of Product Characteristics (SCP) of Propess®.
- ✓ Adverse events whose relationship with the study procedures is doubtful, possible, probable or highly probable will be considered to be related to the study procedures.

If they are unexpected, they will be classified as SUSAR and notified in a report by the sponsor (see following paragraph).

15.3.2.2 Declaration of suspected unexpected serious adverse reaction and serious adverse event possibly related to the implementation process of the experimental medical device

The sponsor will report all

- suspected unexpected serious adverse reactions (SUSAR)
- serious adverse event possibly related to the implementation process of the experimental medical device

to the French Health Authorities (ANSM), the ethics committee (CPP) and the investigators within the regulatory time limits for reporting, which are a maximum of:

- ✓ Seven calendar days for serious adverse unexpected or serious adverse event possibly related to the implementation process of the experimental medical device, fatal or life-threatening. In such cases, additional relevant information should be sought and transmitted within a further period of 8 days.
- ✓ 15 calendar days for all other serious unexpected effects or serious adverse event possibly related to the implementation process of the experimental medical device. Additional relevant information should be sought and transmitted within a further period of 8 days.

15.3.2.3 Transmission of annual safety reports

At the anniversary of the start of the study (first inclusion), the sponsor will write a safety report containing:

- ✓ a safety analysis of subjects included in the study,
- ✓ the list of serious adverse reactions (including expected and unexpected serious reactions) that will have occurred in the trial concerned both in France and abroad (including in non UE member countries) during the period covered by the report,
- ✓ summary tables of all serious adverse events and serious adverse reactions that occurred in the trial concerned since the start of the research.

This will be sent to French Health Authorities (ANSM) and to the ethics committee (CPP) within 60 days following the anniversary date of the authorization of the study.

15.3.2.4 Declaration of other safety data

The sponsor will notify the ANSM and the CPP of any safety data or new fact as soon as possible and at the latest within 15 calendar days of when the sponsor first became aware of them.

Additional relevant information will be provided within 8 days of the end of this initial 15 day period.

15.3.2.5 Data and Safety Monitoring Board

Although this study is conducted in pregnant women, this study presents a low risk to the extent that the Cook® Cervical Ripening Balloon and Propess® are used in this protocol in strict accordance with their marketing authorization. Furthermore, no interim analysis is planned in this study.

So, the constitution of a DSMB is not provided.

16 Practical issues on study sites

A clinical research technician will be responsible for:

- ✓ logistics of the study,
- ✓ producing reports concerning its state of progress,
- ✓ ensuring e-CRF completion and update (request for additional information, corrections, etc.),
- ✓ transmitting SAEs to the sponsor.

He/she will works in accordance with the standard operating procedures, in cooperation with the clinical research associate appointed by the sponsor.

17 Quality control – Monitoring visits

A clinical research associate appointed by the sponsor will regularly visit each study centre during the process of setting up the study, one or more times during the study depending on the frequency of inclusions, and at the end of the study. During these visits, the following aspects will be reviewed:

- ✓ informed consent,
- ✓ compliance with the study protocol and the procedures set out in it,
- ✓ quality of the data collected in the case report form: its accuracy, missing data, consistency of the data with the source documents (medical records, the originals of laboratory results etc.),
- ✓ adequate management of products.

Each monitoring visit will be performed according to the monitoring plan and then, a monitoring report will be written.

18 Audit and inspection

An audit may be performed at any time by people appointed by the sponsor who are independent of those responsible for the study. The aim of an audit is to ensure the good quality of the study, that its results are valid and that the law and regulations in force are being observed.

The investigators agree to comply with the requirements of the sponsor and the relevant authority for an audit or an inspection of the study.

The audit can apply to all stages of the study, from development of the protocol to publication of the results and filing the data used or produced in the study.

19 Storage of documents and data at the end of the study

The following documents relating to this study are archived in accordance with Good Clinical Practice.

19.1 By the investigators:

For a period of 15 years following the end of the study:

- ✓ The protocol and any amendments to the protocol.
- ✓ The case record forms.
- ✓ The source files of participants who signed a consent form.
- ✓ All other documents and letters relating to the study.

For a period of 30 years following the end of the study

- ✓ The original copies of informed consent forms signed by participants

The investigator is responsible for all these documents for the regulation period of archiving.

19.2 By the sponsor

For a period of 15 years following the end of the study:

- ✓ The protocol and any amendments to the protocol.
- ✓ The originals of the case record files.
- ✓ All other documents and letters relating to the study.

For a period of 30 years following the end of the study:

- ✓ A copy of the informed consent forms signed by the participants
- ✓ Documents relating to serious adverse events

The sponsor is responsible for all these documents for the regulation period of archiving.

No removal or destruction may be carried out without the sponsor's agreement. At the end of the regulation archiving period, the sponsor will be consulted regarding destruction. All the data, all the documents and reports could be subject to audit or inspection.

20 Administrative, ethical, regulatory considerations

The sponsor and the investigator or investigators undertake to conduct this study in compliance with French law n° 2004-806 of 9th August 2004 and following Good Clinical Practice (I.C.H. version 4 of 1st May 1996 and the decision of 24th November 2006) and the Helsinki Declaration (Ethical Principles for Medical Research involving Human Subjects, Tokyo 2004).

The study is being conducted in accordance with this protocol. With the exclusion of emergency situations necessitating taking specific therapeutic actions, the investigator or investigators undertake to observe the protocol in all respects, in particular as regards obtaining consent and the notification and follow-up of serious adverse events.

This research will be registered in the European EudraCT database under n° *registration number* in accordance with art. L1121.15 of the French Public Health Act.

20.1 Information and consent forms

Participants will be informed of the objectives of the study and their informed sign consent will be obtained by midwives or physicians. Patients' care will not be affected by their decision to participate or not in the study.

20.2 CNIL

The data recorded in this study will be subject to computer processing by INSERM CIC-P 1415 – CHRU Tours in compliance with law n°78-17 of 6th January 1978 concerning data processing, files and civil liberties modified by law 2004-801 of 6th August 2004.
This research falls within the framework of the "Reference methodology" (MR-001) in application of the provisions of article 54 paragraph 5 of the modified law of 6th January 1978 relating to information, files and civil liberties. This change has been approved by the decision of 5th January 2006. CHRU Tours signed a commitment to comply with this "Reference methodology".

20.3 Research ethics committee

The protocol, informed consent form, subject information sheet will be reviewed and approved by a French ethic committee (CPP) prior to study initiation.

20.4 Regulatory authorities

The sponsor will send an authorization request to French health authority (ANSM).

The Coordinating Investigator will provide regularly to the Ethics Committee and Regulatory Authorities (ANSM), any reports, updates or appropriate information (e.g.., amendments, administrative letters, Adverse Events reports) according to regulatory requirements. Deviations from, or significant changes of the protocol should not be initiated without prior written approval from Ethics Committee and from Regulatory Authorities.

20.5 Protocol amendments

Any substantial modification, i.e. any modification of a nature likely to have a significant impact on the safety of the people involved, the conditions of validity and the results of the study, on the quality and safety of the study procedures, on interpretation of the scientific documents which provide support for the study or the methods for conducting it, will be the subject of a written amendment to be submitted to the sponsor; prior to implementing it, the latter must obtain approval from the ethics committee and authorisation from ANSM.

Non-substantial modifications, i.e. those not having a significant impact on any aspect of the study whatsoever, will be communicated to the ethics committee for information purposes.

Any amendments to the protocol must be made known to all the investigators participating in the study. The investigators undertake to comply with the contents.

Any amendment modifying the management of participants or the benefits, risks or constraints of the study will be the subject of a new Participant Information and Informed Consent form which must be completed and collected according to the same procedure as used for the previous one.

20.6 Registration

The study protocol will be registered on ClinicalTrials.gov. Recorded data will be updated regularly. The study results will be posted on the registry Results section.

20.7 Insurance

CHRU Tours, the sponsor of this study, will take out an insurance policy covering third party liability with SHAM complying with the provisions of article L1121-10 of the French Public Health Act.

21 Dissemination policy

21.1 Authorship

Any written or oral communication of the results of the study will be previously agreed by the coordinating investigator and, if necessary, by the scientific committee constituted for the study.

Publication of the main results will mention the sponsor and the funding source. We will follow the Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals (updated in December 2014) from the International Committee of Medical Journal Editors (ICMJE). All investigators not-cited in the authorship will be listed as non-author contributors.

21.2 Communication of the results to participants

In accordance with the law n° 2002-303 of 4th March 2002, participants will be informed, at their request, of the overall results of the study.

22 Financial data

22.1 Budget of the study

This trial is funded through a grant from the French Ministry of Health. Funding will be managed by the Direction of Medical Affairs & Research, University Hospital Center of Tours.
It is noted that the pharmaceutical company "Cook® medical", agreed to reduce the price of the Cook® Cervical Ripening Balloon for the study.

22.2 Compensation for participants

This study does not give rise to compensation for participants.

APPENDIX

Appendix 1. FIGO Intrapartum Fetal Monitoring Guidelines – CTG classification table (October 2015)

CTG classification

2015 revised FIGO guidelines on intrapartum fetal monitoring

	Normal	Suspicious	Pathological
Baseline	110-160 bpm	Lacking at least one characteristic of normality, but with no pathological features	< 100 bpm
Variability	5-25 bpm		Reduced variability. Increased variability. Sinusoidal pattern.
Decelerations	No repetitive* decelerations		Repetitive* late or prolonged decelerations for > 30 min (or > 20 min if reduced variability). Deceleration > 5 min
Interpretation	No hypoxia/acidosis	Low probability of hypoxia/acidosis	High probability of hypoxia/acidosis
Clinical management	No intervention necessary to improve fetal oxygenation state	Action to correct reversible causes if identified, close monitoring or adjunctive methods	Immediate action to correct reversible causes, adjunctive methods, or if this is not possible expedite delivery. In acute situations immediate delivery should be accomplished

*Decelerations are repetitive when associated with > 50% contractions.
Absence of accelerations in labour is of uncertain significance.

Appendix 2. Assessment of cervix maturation by Bishop score

(French National Authority for Health – « Recommendations for Déclenchement artificiel du travail à partir de 37 semaines d'aménorrhée »)

Paramètres	0	1	2	3
Dilatation du col utérin	fermé	1 – 2 cm	3 – 4 cm	≥ 5
Effacement du col utérin	0 – 30 %	40 – 50 %	60 – 70 %	> 80 %
Consistance du col utérin	ferme	moyenne	molle	
Position du col utérin	postérieure	centrale	antérieure	
Positionnement de la présentation fœtale par rapport aux épines sciatiques	mobile (3 cm au-dessus)	amorcée (2 cm au-dessus)	fixée (< 1 cm au-dessus)	engagé (1 – 2 cm au-dessous)

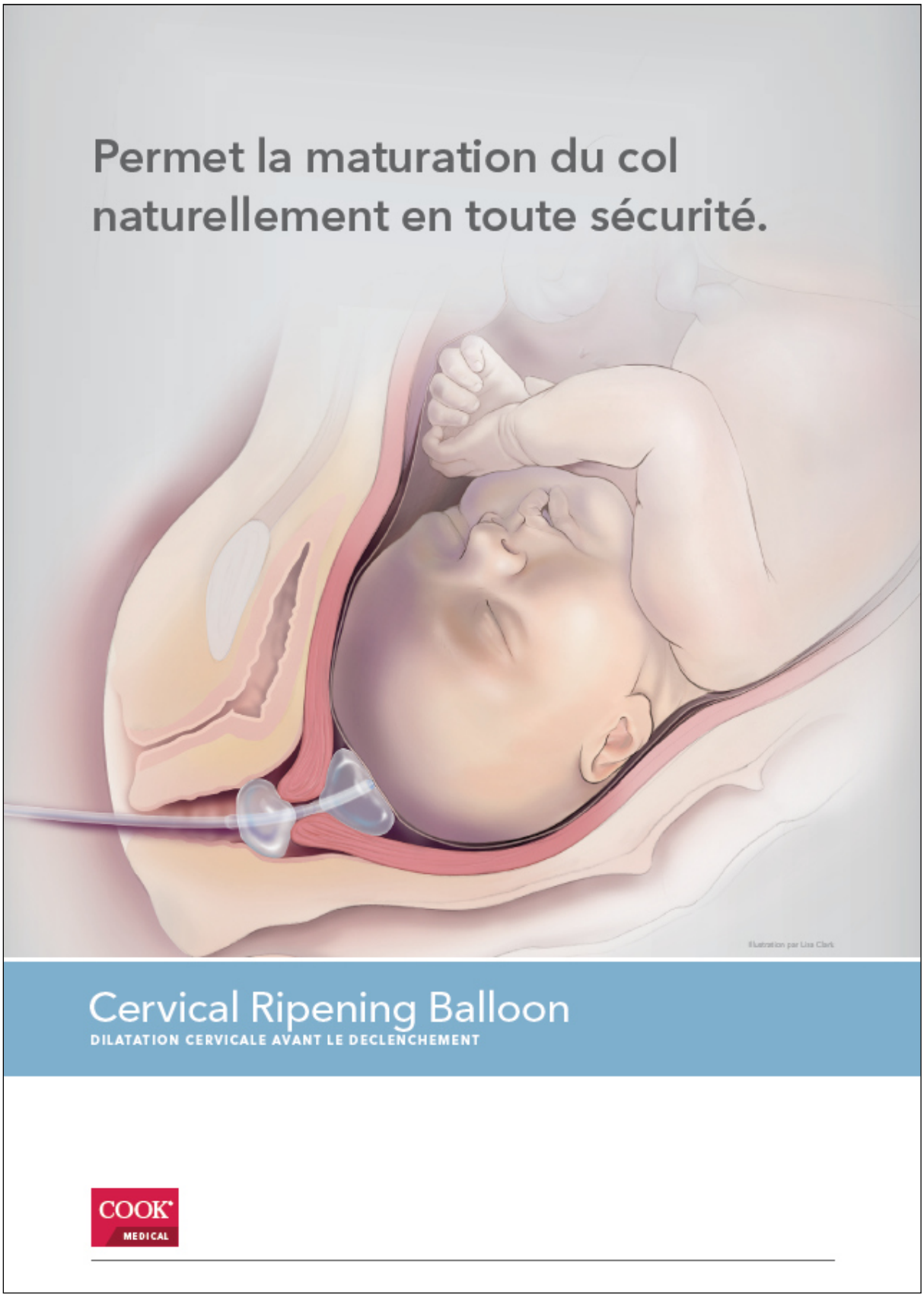
Valeurs du score : de 0 à 13 ; score ≥ 7 : pronostic favorable (travail de moins de 4 heures chez les multipares).

Appendix 3. List of participating maternity units and principal investigators

Institution name	Name and first name of investigators	Address	E-mail
CH Pontoise	**Pr PONCELET Christophe**	Service de Gynécologie-Obstétrique Hôpital René Dubos, CH de Pontoise 6 Avenue de l'Île de France CS 90079 Pontoise 95303 CERGY PONTOISE	christophe.poncelet@ch-pontoise.fr
CHU Saint Etienne	**Pr CHAULEUR Céline**	Service de Gynécologie-Obstétrique Hôpital Nord, CHU de St Etienne Avenue Albert Raimond 42270 SAINT-PRIEST EN JAREZ	celine.chauleur@chu-st-etienne.fr
CHRU Tours	**Pr PERROTIN Franck**	Pôle de Gynécologie-Obstétrique, Centre Olympe de Gouges Hôpital Bretonneau, CHRU de Tours 2 boulevard Tonnellé 37044 TOURS Cedex 9	franck.perrotin@med.univ-tours.fr
CHU Brest	**Dr HANNIGSBERG Jacob**	Hôpital Femme-Mère-Enfant Hôpital Morvan, CHU Brest 2 Avenue Maréchal Foch 29200 BREST	jacob.hannigsberg@chu-brest.fr
CHU Nantes	**Dr WINER Norbert**	Service de Gynécologie-Obstétrique Hôpital femme-enfant-adolescent, CHU de Nantes 38 boulevard Jean-Monnet 44093 NANTES Cedex 1	norbert.winer@chu-nantes.fr
CH Départemental de Vendée	**Dr DUCARME Guillaume**	Service de Gynécologie-Obstétrique Les Oudairies, CH Départemental de Vendée 85925 LA ROCHE SUR YON Cedex 9	guillaume.ducarme@chd-vendee.fr
CHU Clermont-Ferrand	**Pr GALLOT Denis**	Pôle Femme-Enfant Service de Gynécologie-Obstétrique Hôpital d'Estaing, CHU de Clermont-Ferrand 1 place Lucie et Raymond Aubrac 63001 CLERMONT-FERRAND Cedex 1	dgallot@chu-clermontferrand.fr
CHU Reims	**Pr GABRIEL René**	Service de Gynécologie-Obstétrique Hôpital Maison Blanche, CHU de Reims 45, rue Cognacq-Jay 51 092 REIMS Cedex	rgabriel@chu-reims.fr
CHR Orléans	**Dr RAMOS Anna**	Service de Gynécologie Bâtiment Nouvel Hôpital, Hôpital de La Source, CHR Orléans 14 Avenue de l'Hôpital 45100 ORLEANS	anna.ramos@chr-orleans.fr
Hôpital St Joseph	**Dr DESBRIERE Raoul**	Service de Gynécologie-Obstétrique et chirurgicale, médecine et biologie de la reproduction Hôpital St Joseph 26 Bd de Louvain 13008 MARSEILLE	raoul.desbriere@orange.fr
CHU Caen	**Dr BEUCHER Gaël**	Service de Gynécologie-Obstétrique Pôle Femme-Enfant Bâtiment Femme-Enfant-Hématologie, CHU de Caen Avenue de la Côte de Nacre CS 30001 14033 CAEN Cedex 9	beucher-g@chu-caen.fr
CH Chartres	**Dr Alexis BALAGNY**	Service de gynécologie-obstétrique Les Hôpitaux de Chartres 34, rue du Docteur Maunoury - BP 30407 28018 CHARTRES	abalagny@ch-chartres.fr

Institution name	**Name and first name of investigators**	**Address**	**E-mail**
CHU Rennes	**Dr Hélène ISLY**	Service d'Obstétrique Hôpital Sud, CHU de Rennes 16, boulevard de Bulgarie 35203 RENNES cedex 2	helene.isly@chu-rennes.fr
CHU Toulouse	**Pr Olivier PARANT**	Échographie et diagnostic prénatal Pôle femme mère couple Hôpital Paule de Viguier, CHU de Toulouse 330, avenue de Grande Bretagne TSA 70034 31059 TOULOUSE Cedex 9	parant.o@chu-toulouse.fr
CH Intercommunal Poissy St-Germain-en-Laye	**Pr Patrick ROZENBERG**	Service Obstétrique, grossesses à risque, échographie obstétricale Site de Poissy 10 rue du Champ Gaillard - Poissy 78303 POISSY CEDEX	prozenberg@chi-poissy-st-germain.fr

Appendix 4. User manual of Cook® Cervical Ripening Balloon (October 2014)



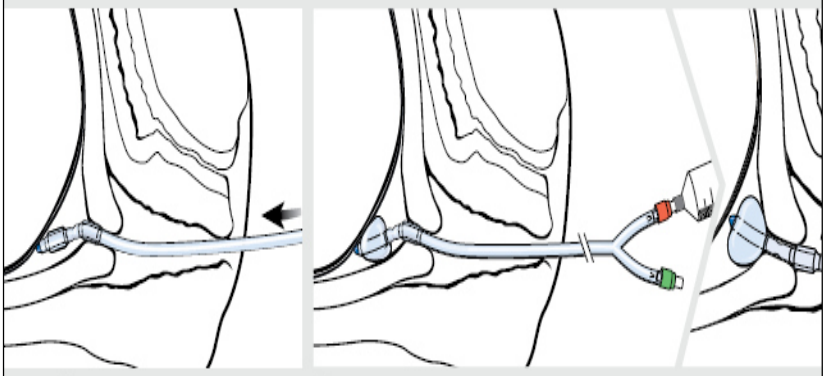
Cervical Ripening Balloon

DILATATION CERVICALE AVANT LE DECLENCHEMENT

Le ballonnet Cook pour maturation du col offre une technique simple de maturation du col en présence d'un col défavorable, sans les effets secondaires potentiels des autres méthodes de maturation.

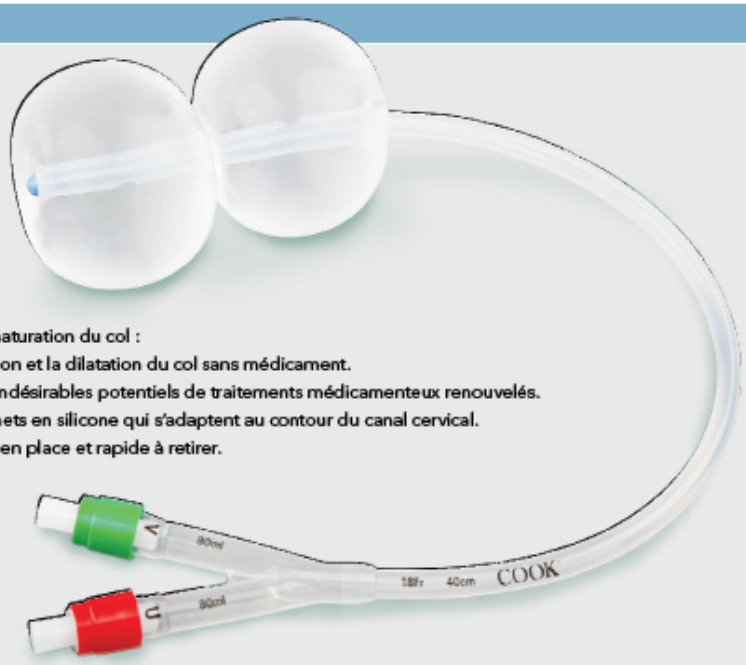
Il n'est pas facile de déclencher le travail des patientes présentant un col défavorable. La méthode de maturation que vous utilisez peut compliquer le déclenchement du travail. Certains traitements médicaux, comme l'utilisation des prostaglandines, peuvent entraîner des effets secondaires et des taux élevés d'échec du déclenchement du travail donnant lieu à des accouchements par césarienne non désirés.

Le ballonnet Cook pour maturation du col est conçu pour dilater naturellement et progressivement le col et faciliter le déclenchement du travail. La maturation et la dilatation sont obtenues par la pression légère et constante exercée par les ballonnets au niveau des orifices interne et externe du col.



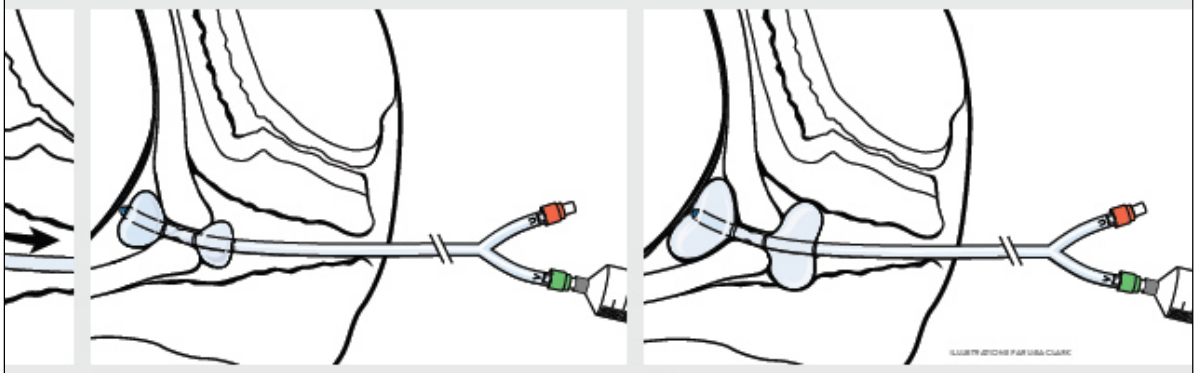
1 Avancer le ballonnet pour maturation du col à travers le col jusqu'à ce que les deux ballonnets entrent dans le canal cervical.

2 Gonfler le ballonnet utérin avec 40 mL de sérum physiologique. Lorsque le ballonnet utérin est gonflé, reculer le dispositif jusqu'à ce que le ballonnet bute contre l'orifice interne du col.



Le ballonnet pour maturation du col :

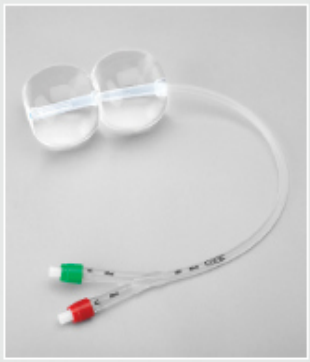
- Permet la maturation et la dilatation du col sans médicament.
- Elimine les effets indésirables potentiels de traitements médicamenteux renouvelés.
- Utilise des ballonnets en silicone qui s'adaptent au contour du canal cervical.
- Est facile à mettre en place et rapide à retirer.



3 Le ballonnet vaginal doit être visible à l'extérieur de l'orifice externe du col. Gonfler le ballonnet vaginal avec 20 mL de sérum physiologique.

4 Lorsque les ballonnets sont positionnés de chaque côté du col, ajouter du sérum physiologique, au maximum 80 mL par ballonnet. L'heure de mise en place du ballonnet doit être établie de manière à ce qu'il ne reste pas en place pendant plus de 12 heures avant le déclenchement du travail actif.

Pour des informations supplémentaires sur la prise en charge du travail à l'aide du ballonnet Cook pour maturation du col, consulter le mode d'emploi.



Cervical Ripening Balloon

DILATATION CERVICALE AVANT LE DECLENCHEMENT

Le ballonnet Cook pour maturation du col est indiqué pour la dilatation mécanique du canal cervical avant le déclenchement du travail à terme lorsque le col est défavorable. Consulter le mode d'emploi pour obtenir des informations détaillées sur l'utilisation, les indications et les contre-indications de ce produit. Vendu par boîtes de 10.

Numéro de commande	Référence produit	Fr	Longueur cm	Volume du ballonnet mL
G48149	J-CRB-184000	18	40	80

Ressources

Atad J, Hallak M, Ben-David Y, et al. Ripening and dilatation of the unfavourable cervix for induction of labour by a double balloon device: experience with 250 cases. *Br J Obstet Gynaecol.* 1997;104(1):29-32.

Atad J, Hallak M, Auslender R, et al. A randomized comparison of prostaglandin E2, oxytocin, and the double-balloon device in inducing labor. *Obstet Gynecol.* 1996;87(2):223-227.

Couverture : Illustration par Lisa Clark

Service Clientèle

FRANCE : +33 171230269, fr.orders@cookmedical.com
BELGIUM : +32 27001633, be.orders@cookmedical.com
SWITZERLAND : +41 448009609, fr.orders@cookmedical.com

NOM DU PRODUIT : Cook® Cervical Ripening Balloon - Ballonnet Cook pour maturation du col, **DESTINATION :** Le ballonnet Cook pour maturation du col est indiqué pour la dilatation mécanique du col de l'utérus avant le déclenchement du travail à terme lorsque le col est défavorable. **CLASSE DU DISPOSITIF MEDICAL :** Classe IIa, **ORGANISME NOTIFIE :** LRQA 0088, **FABRICANT :** Cook Incorporated, **MODE D'EMPLOI :** Veuillez lire attentivement les instructions figurant sur la notice ou l'étiquetage du dispositif médical, **REMBOURSEMENT (FRANCE) :** Pris en charge par l'assurance maladie. **DATE DE PUBLICATION :** 2014 Octobre

Appendix 5. User manual of Propess® (September 2015)

Dénomination du médicament

PROPESS 10 mg, système de diffusion vaginal

Dinoprostone

Encadré

Veuillez lire attentivement l'intégralité de cette notice avant d'utiliser ce médicament.

· Gardez cette notice, vous pourriez avoir besoin de la relire.

· Si vous avez toute autre question, si vous avez un doute, demandez plus d'informations à votre médecin ou à votre pharmacien.

· Ce médicament vous a été personnellement prescrit. Ne le donnez jamais à quelqu'un d'autre, même en cas de symptômes identiques, cela pourrait lui être nocif.

· Si l'un des effets indésirables devient grave ou si vous remarquez un effet indésirable non mentionné dans cette notice, parlez-en à votre médecin ou à votre pharmacien.

Sommaire notice

Dans cette notice :

1. QU'EST-CE QUE PROPESS 10 mg, système de diffusion vaginal ET DANS QUELS CAS EST-IL UTILISE ?

Classe pharmacothérapeutique

Prostaglandine E_2

Indications thérapeutiques

PROPESS 10 mg, système de diffusion vaginal est indiqué dans le déclenchement du travail (maturation et/ou la dilatation du col de l'utérus) lorsque la grossesse est à terme.

2. QUELLES SONT LES INFORMATIONS A CONNAITRE AVANT D'UTILISER PROPESS 10 mg, système de diffusion vaginal ?

Liste des informations nécessaires avant la prise du médicament

Sans objet.

Contre-indications

N'utilisez jamais PROPESS :

· si vous êtes allergique (hypersensible) à la substance active ou à l'un des autres composants contenus dans ce médicament, mentionnés dans la rubrique 6 ;

· lorsque le travail a commencé ;

· lorsqu'un traitement par ocytocine est administré ;

· lorsque des contractions utérines fortes et prolongées ne sont pas souhaitables, et notamment en cas :

- o d'antécédent de chirurgie utérine majeure, par exemple une césarienne, une myomectomie ;
- o de disproportion fœto-pelvienne ;
- o d'anomalie de présentation du fœtus autre que céphalique ;
- o de souffrance fœtale suspectée ou confirmée ;
- o d'antécédents de plus de trois accouchements à terme ;
- o d'antécédent de chirurgie ou de rupture du col ;

· en présence de maladie inflammatoire génitale récente, à moins qu'un traitement adéquate n'ait été instauré ;

· placenta praevia ou saignement vaginal inexpliqué pendant la grossesse.

Précautions d'emploi ; mises en garde spéciales

Faites attention avec PROPESS 10 mg, système de diffusion vaginal:

L'état du col de l'utérus sera évalué avec soin avant toute administration de ce médicament.

Un contrôle de l'activité utérine et de la vitalité du fœtus sera effectué régulièrement après l'introduction du système de diffusion vaginal.

Le système sera retiré immédiatement:

· en cas de contractions utérines prolongées ou excessives;

· en cas de rupture des membranes;

· en cas de signe d'intolérance fœtale;

· en cas de survenue d'effets indésirables chez la mère (nausées, vomissements, baisse de la pression artérielle, tachycardie);

· au moins 30 minutes avant l'administration d'ocytocine.

Le produit sera utilisé avec précaution en cas:

· d'hypertonie utérine;

· de glaucome;

· d'asthme;

· de grossesse multiple

· lorsqu'il y a eu rupture des membranes.

PROPESS doit être utilisé avec prudence chez les patients ayant une rupture des membranes. L'activité utérine ainsi que l'état fœtal doivent être particulièrement suivis.

La réadministration de PROPESS 10 mg, système de diffusion vaginal n'est pas recommandée car les effets d'une seconde insertion n'ont pas été étudiés.

Le système de diffusion vaginal doit être retiré lorsque la maturation du col est considérée comme complète dès le début du travail.

Les effets de ce produit chez des patientes présentant des maladies susceptibles d'affecter le métabolisme ou l'excrétion de la PGE_2, comme par exemple les maladies pulmonaires, hépatiques ou rénales, n'ont pas été étudiés spécifiquement. L'administration de ce médicament chez ces patientes n'est pas recommandée.

Les femmes âgées de plus de 35 ans, les femmes ayant rencontré des complications durant leur grossesse ou dont l'âge gestationnel de la grossesse est supérieur à 40 semaines ont un plus grand risque de développer une Coagulation Intravasculaire Disséminée (CIVD). Ce risque est d'autant plus élevé chez celles pour lesquelles le travail a été déclenché. Ainsi, ce médicament devrait être utilisé avec précaution chez ces femmes. Dans la phase de post-partum qui suit immédiatement l'accouchement, le médecin devrait porter une attention particulière à tous les signes cliniques qui pourraient évoquer une CIVD (ex. fibrinolyse).

Interactions avec d'autres médicaments

Prise ou utilisation d'autres médicaments

L'administration de médicaments anti-inflammatoires non-stéroïdiens, y compris l'aspirine, doit être interrompue avant l'administration de PGE_2.

Les prostaglandines augmentent les effets de l'ocytocine. Par conséquent, PROPESS 10 mg, système de diffusion vaginal ne doit pas être utilisé en même temps que l'ocytocine.

Si vous prenez ou avez pris récemment un autre médicament, y compris un médicament obtenu sans ordonnance, parlez-en à votre médecin ou à votre pharmacien.

Interactions avec les aliments et les boissons

Sans objet.

Interactions avec les produits de phytothérapie ou thérapies alternatives

Sans objet.

Utilisation pendant la grossesse et l'allaitement

Grossesse et allaitement

Ce médicament ne sera utilisé en fin de grossesse que sur les conseils de votre médecin. L'allaitement est possible au décours de l'utilisation de ce médicament.

Demandez conseil à votre médecin ou à votre pharmacien avant de prendre tout médicament.

Sportifs

Sans objet.

Effets sur l'aptitude à conduire des véhicules ou à utiliser des machines

Sans objet.

Liste des excipients à effet notoire

Sans objet.

3. COMMENT UTILISER PROPESS 10 mg, système de diffusion vaginal ?

Instructions pour un bon usage

Sans objet.

Posologie, Mode et/ou voie(s) d'administration, Fréquence d'administration et Durée du traitement

Un système de diffusion vaginal doit être introduit haut dans le cul-de-sac postérieur du vagin. Après insertion, vous devez rester allongée pendant 20 à 30 minutes.

Si la maturation cervicale est insuffisante après 24 heures, le système doit être retiré.

Après le retrait du système, il est recommandé de respecter un intervalle de temps d'au moins 30 minutes avant l'utilisation ultérieure d'ocytociques.

PROPESS 10 mg, système de diffusion vaginal doit être conservé dans le sachet et sorti du congélateur

immédiatement avant utilisation.

Administration

Le système de diffusion vaginal doit être introduit haut dans le cul-de-sac postérieur du vagin. De petites quantités de lubrifiants peuvent être utilisées afin de faciliter l'insertion du système.

Une fois le système de diffusion vaginal inséré, le ruban de retrait pourra être coupé avec des ciseaux, en s'assurant que la longueur de ruban soit suffisante pour permettre le retrait du système. Aucune tentative ne doit être faite pour introduire le bout du ruban dans le vagin, le retrait du système serait alors plus difficile.

Après insertion, la patiente doit rester allongée pendant 20 à 30 minutes.

Comme la prostaglandine est diffusée en continu pendant 24 heures, il est important de surveiller à intervalles fréquents et réguliers les contractions utérines ainsi que l'état du fœtus.

Retrait

Le système de diffusion vaginal peut être retiré rapidement et facilement en tirant doucement sur le ruban de retrait.

Symptômes et instructions en cas de surdosage

Sans objet.

Instructions en cas d'omission d'une ou de plusieurs doses

Sans objet.

Risque de syndrome de sevrage

Sans objet.

4. QUELS SONT LES EFFETS INDESIRABLES EVENTUELS ?

Description des effets indésirables

Comme tous les médicaments, ce médicament peut provoquer des effets indésirables, mais ils ne surviennent pas systématiquement chez tout le monde.

Les effets indésirables obtenus sont ceux habituellement associés à l'administration vaginale de prostaglandine.

Les événements secondaires suivants ont été observés:

· modifications du rythme cardiaque fœtal et détresse fœtale non spécifique,

· anomalies de la contractilité utérine associées avec ou non une détresse fœtale,

· dans l'essai clinique d'efficacité, 5 (4,9 %) des 102 patients ont présenté une hypercontractilité utérine; dans 3 cas une détresse fœtale était associée. Chez quatre des 5 cas, l'hypercontractilité s'est résolue après le retrait du système,

· nausées, vomissements et diarrhée,

· réactions allergiques.

Une augmentation du risque post-partum de coagulation intravasculaire disséminée a été rapportée chez des patientes chez lesquelles le travail avait été provoqué de façon médicamenteuse avec de la dinoprostone ou de l'ocytocine (Mises en garde et précautions d'emploi).

· Passage du liquide amniotique dans la circulation maternelle (embolie amniotique). Fréquence non connue, ne peut être estimée à partir des données disponibles.

Si vous remarquez des effets indésirables non mentionnés dans cette notice, ou si certains effets indésirables deviennent graves, veuillez en informer votre médecin ou votre pharmacien.

Déclaration des effets secondaires

Si vous ressentez un quelconque effet indésirable, parlez-en à votre médecin ou votre pharmacien. Ceci s'applique aussi à tout effet indésirable qui ne serait pas mentionné dans cette notice. Vous pouvez également déclarer les effets indésirables directement via le système national de déclaration : Agence nationale de sécurité

du médicament et des produits de santé (ANSM) et réseau des Centres Régionaux de Pharmacovigilance - Site internet: www.ansm.sante.fr

En signalant les effets indésirables, vous contribuez à fournir davantage d'informations sur la sécurité du médicament.

5. COMMENT CONSERVER PROPESS 10 mg, système de diffusion vaginal ?

Tenir hors de la portée et de la vue des enfants.

Date de péremption

Ne pas utiliser PROPESS 10 mg, système de diffusion vaginal après la date de péremption figurant sur la boîte.

Conditions de conservation

A conserver dans le sachet non ouvert au congélateur entre -10°C et -20°C.

Si nécessaire, mises en garde contre certains signes visibles de détérioration

Les médicaments ne doivent pas être jetés au tout-à-l'égout ou avec les ordures ménagères. Demandez à votre pharmacien ce qu'il faut faire des médicaments inutilisés. Ces mesures permettront de protéger l'environnement.

6. INFORMATIONS SUPPLEMENTAIRES

Liste complète des substances actives et des excipients

Que contient PROPESS 10 mg, système de diffusion vaginal ?

La substance active est:

Dinoprostone ..... 10 mg

Pour 1 système de diffusion vaginal.

Les autres composants sont:

Hydrogel polymérique (macrogol 8000, dicyclohexyl-méthane-4,4'-diisocyanate, hexanetriol).

Forme pharmaceutique et contenu

Qu'est-ce que PROPESS 10 mg, système de diffusion vaginal et contenu de l'emballage extérieur ?

Ce médicament se présente sous forme d'un système de diffusion vaginal en sachet. Boîte de 5.

Nom et adresse du titulaire de l'autorisation de mise sur le marché et du titulaire de l'autorisation de fabrication responsable de la libération des lots, si différent

Titulaire

FERRING SAS
7, rue Jean-Baptiste Clément
94250 Gentilly
FRANCE

Exploitant

FERRING SAS
7 RUE JEAN-BAPTISTE CLEMENT
94250 GENTILLY
FRANCE

Fabricant

FERRING GmbH
WITTLAND 11
24109 KIEL
ALLEMAGNE

Ou
FERRING CONTROLLED THERAPEUTICS Ltd
1 Redwood Place, Peel Park Campus
East Kilbride, G57 5PB
Ecosse

Noms du médicament dans les Etats membres de l'Espace Economique Européen

Sans objet.

Date d'approbation de la notice

La dernière date à laquelle cette notice a été approuvée est le {date}.

AMM sous circonstances exceptionnelles

Sans objet.

Informations Internet

Des informations détaillées sur ce médicament sont disponibles sur le site Internet de l'Afssaps (France).

Informations réservées aux professionnels de santé

Sans objet.

Autres

Sans objet.

Appendix 6. Safety evaluation terminology

Adverse Event (AE) (article R.1123-39 of the French Public Health Act): any harmful event occurring in a person taking part in a biomedical research study, whether or not that event is linked to the study or to the product being investigated in the study.

Serious Adverse Event (SAE) (article R.1123-39 of the Public Health Act and the ICH E2B guide): the severity is defined by one of the following observations:

- death,
- threatening life of the person taking part in the research study (immediate threat to life at the time of the event, regardless of the consequences of corrective or palliative therapy),
- disability or significant or lasting handicap,
- hospitalization,
- prolongation of hospitalization,
- malformation/birth defect,
- potentially serious event (adverse clinical event or laboratory test result considered serious by the investigator).

Adverse Reaction (AR): any untoward and unintended reaction to an investigational medicinal product, whatever the dose administered.

Serious Adverse Reaction (SAR): serious adverse events potentially caused by a medicinal product.

Suspected Unexpected Serious Adverse Reaction (SUSAR) (article R.1123-39 of the French Public Health Act): serious adverse reaction, the type, severity, intensity or progression of which is inconsistent with the information contained in the summary of product characteristics for an authorized medicinal product or, in the case of an unauthorized medicinal product, in the investigator's brochure.

New fact (order dated 24 May 2006): new safety information which could lead to (1) re-evaluation of the benefit/risk ratio of the study; or (2) modifications to documents concerning the study, to the way the study is conducted, or, if necessary, to the way the product is used. This includes:

- any clinically significant increase in the incidence of a known serious adverse effect,
- the occurrence of SUSAR among participants who completed the trial as reported by the investigator to the sponsor, as well as any potential follow-up reports,
- any new findings concerning the progress of the clinical trial or the development of investigational medicinal products, if this finding is likely to affect the safety of participants.

Causal relationship: relationship between the adverse event and the treatment. An adverse event related to an investigational medicinal product will be classified as an adverse reaction. Factors to consider when determining the cause of an adverse event are:

- the chronological order of events,
- the disappearance of the AE at the time of drug discontinuation and/or the reappearance upon re-administration,
- the pharmacodynamic and pharmacokinetic properties of the drug,
- history of similar event occurring during the administration of the drug or a drug of the same class,
- other potential causes of the AE.

Appendix 7. Severity evaluation of adverse events

Severity (Toxicity Grade)	**Description**
Mild	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe or life threatening	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

Appendix 8. Causal relationship evaluation

In accordance with ICH guidelines on the management of adverse events in clinical trials- ICHE2B(R3)12 May 2005 version- the relationship between all notified SAE and the research must be assessed.

The method used to evaluate the relationship of the event is as follows:

Unrelated: the event occurred within a time period that is not compatible with the administration of the medicinal product, and/or sufficient information exists showing that the observed reaction is unrelated to the medicinal product, and/or a probable alternative explanation exists.

Doubtful: the timing of the event (occurrence, outcome) is inconsistent with the administration of the medicinal product. The event is most likely related to factors other than the medicinal product such as the participant's clinical condition or concomitant administration of other medicinal products.

Possible: the event occurred within a period that is compatible with the administration of the medicinal product. Although a causal effect of the product cannot be ruled out, other factors can be implicated, such as the subject's clinical condition or the concomitant administration of other medicinal products. Information about the outcome upon discontinuation of the studied treatment can be absent or inconclusive.

Probable: the event occurred within a period that is compatible with the administration of the medicinal product. It cannot reasonably have been caused by another factor, such as the subject's clinical condition or the concomitant administration of other medicinal products. The outcome upon discontinuation of the medicinal product must be clinically compatible. Information about re-challenge with the medicinal product is not essential.

Highly probable: the event occurred within period that is highly compatible with the administration of the medicinal product. It cannot be explained by another factor such as the subject's clinical condition or the concomitant administration of other medicinal products. The outcome upon discontinuation of the medicinal product must be clinically compatible. The event should have a pharmacological or pathophysiological explanation, or recurs upon re-challenge with the medicinal product.

Appendix 9. References

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