Substantial Amendment Notification Form (Cf. Section 3.7.b of the *Detailed guidance on the request to the competent authorities for authorisation of a clinical trial on a medicinal product for human use, the notification of substantial amendments and the declaration of the end of the trial*[1])

NOTIFICATION OF A SUBSTANTIAL AMENDMENT TO A CLINICAL TRIAL ON A MEDICINAL PRODUCT FOR HUMAN USE TO THE COMPETENT AUTHORITIES AND FOR OPINION OF THE ETHICS COMMITTEES IN THE EUROPEAN UNION

For official use:

Date of receiving the request :	Grounds for non acceptance/ negative opinion **:** ☐ Date :
Date of start of procedure:	Authorisation/ positive opinion **:** ☐ Date :
Competent authority registration number of the trial: Ethics committee registration number of the trial :	Withdrawal of amendment application ☐ Date :

To be filled in by the applicant:

This form is to be used both for a request to the Competent Authority for authorisation of a **substantial** amendment and to an Ethics Committee for its opinion on a **substantial** amendment. Please indicate the relevant purpose in Section A.

A TYPE OF NOTIFICATION

A.1 Member State in which the substantial amendment is being submitted: Sweden	
A.2 Notification for authorisation to the competent authority:	**x**
A.3 Notification for an opinion to the ethics committee:	**x**

B TRIAL IDENTIFICATION *(When the amendment concerns more than one trial, repeat this form as necessary.)*

B.1 Does the substantial amendment concern several trials involving the same IMP?[2] yes ☐ no x

B.1.1 If yes repeat this section as necessary.

B.2 Eudract number: 2020-000233-41

B.3 Full title of the trial : OPTION – OutPatienT InductiON:
Labour induction in an outpatient setting - a multicenter randomized controlled trial.

B.4 Sponsor's protocol code number, version, and date: version 11, 22nd December 2022

C IDENTIFICATION OF THE SPONSOR RESPONSIBLE FOR THE REQUEST

C.1	**Sponsor**
C.1.1	Organisation: Sahlgrenska University Hospital, Gothenburg, Sweden, Västra Götalandsregionen
C.1.2	Name of person to contact: Verena Sengpiel
C.1.3	Address : Verksamhet obstetrik, Sahlgrenska Universitetssjukhuset Diagnosvägen 15, 416 50 Göteborg
C.1.4	Telephone number : +46 704 223475
C.1.5	Fax number : /
C.1.6	e-mail: verena.sengpiel@obgyn.gu.se

C.2	**Legal representative[3] of the sponsor in the European Union for the purpose of this trial (if different from the sponsor)**
C.2.1	Organisation: Sahlgrenska University Hospital, Gothenburg, Sweden, Västra Götalandsregionen
C.2.2	Name of person to contact: Corinne Pedroletti
C.2.3	Address : Verksamhet obstetrik, Sahlgrenska Universitetssjukhuset Diagnosvägen 15, 416 50 Göteborg
C.2.4	Telephone number : +46 72-2096857
C.2.5	Fax number : /
C.2.6	e-mail: corinne.pedroletti@vgregion.se

D APPLICANT IDENTIFICATION (please tick the appropriate box)

---

1 OJ, C82, 30.3.2010, p. 1; hereinafter referred to as 'detailed guidance CT-1'.

2 Cf. Section 3.7. of the detailed guidance CT-1.

3 As stated in Article 19 of Directive 2001/20/EC.

D.1	Request for the competent authority	
D.1.1	Sponsor	x
D.1.2	Legal representative of the sponsor	☐
D.1.3	Person or organisation authorised by the sponsor to make the application.	☐
D.1.4	Complete below:	
D.1.4.1	Organisation :	
D.1.4.2	Name of person to contact :	
D.1.4.3	Address :	
D.1.4.4	Telephone number :	
D.1.4.5	Fax number :	
D.1.4.6	E-mail	

D.2	Request for the Ethics Committee	
D.2.1	Sponsor	x
D.2.2	Legal representative of the sponsor	☐
D.2.3	Person or organisation authorised by the sponsor to make the application.	☐
D.2.4	Investigator in charge of the application if applicable[4]:	
	• Co-ordinating investigator (for multicentre trial)	☐
	• Principal investigator (for single centre trial):	☐
D.2.5	Complete below	
D.2.5.1	Organisation :	
D.2.5.2	Name :	
D.2.5.3	Address :	
D.2.5.4	Telephone number :	
D.2.5.5	Fax number :	
D.2.6	E-mail :	

E SUBSTANTIAL AMENDMENT IDENTIFICATION

E.1	**Sponsor's substantial amendment code number, version, date for the clinical trial concerned:** ( )

E.2	Type of substantial amendment	
E.2.1	**Amendment to information in the CT application form**	yes ☐ no x
E.2.2	**Amendment to the protocol**	yes x no ☐
E.2.3	**Amendment to other documents appended to the initial application form**	yes x no ☐
E.2.3.1	If yes specify:	
E.2.4	**Amendment to other documents or information:**	yes ☐ no ☐
E.2.4.1	If yes specify: FPI_Kvinnan RCT_OPTION, FPI_Partner RCT_OPTION, 6.1_DSMB-Charter-OPTION	
E.2.5	**This amendment concerns mainly urgent safety measures already implemented[5]**	yes ☐ no X
E.2.6	**This amendment is to notify a temporary halt of the trial[6]**	yes ☐ no x
E.2.7	**This amendment is to request the restart of the trial[7]**	yes ☐ no x

4 According to national legislation.
5 Cf. Section 3.9. of the detailed guidance CT-1.
6 Cf. Section 3.10. of the detailed guidance CT-1.
7 Cf. Section 3.10. of the detailed guidance CT-1.

E.3	Reasons for the substantial amendment:	
E.3.1	**Changes in safety or integrity of trial subjects**	**yes ☐ no x**
E.3.2	**Changes in interpretation of scientific documents/value of the trial**	**yes ☐ no x**
E.3.3	**Changes in quality of IMP(s)**	**yes ☐ no x**
E.3.4	**Changes in conduct or management of the trial**	**yes x no ☐**
E.3.5	**Change or addition of principal investigator(s), co-ordinating investigator**	**yes x no ☐**
E.3.6	**Change/addition of site(s)**	**yes x no ☐**
E.3.7	**Other change**	**yes x no ☐**
E.3.7.1	**If yes, specify:** Change regarding where labelling of study medication will happen, change regarding DSMB members and chair of DSMB, new information material, a small update in the consent form, request that even midwives with appropriate education and GCP certification can sign informed consent.	
E.3.8	**Other case**	**yes ☐ no x**
E.3.8.1	**If yes, specify**	

E.4	Information on temporary halt of trial[8]	
E.4.1	**Date of temporary halt** (YYYY/MM/DD)	
E.4.2	**Recruitment has been stopped**	yes ☐ no ☐
E.4.3	**Treatment has been stopped**	yes ☐ no ☐
E.4.4	Number of patients still receiving treatment at time of the temporary halt in the MS concerned by the amendment ( )	
E.4.5	**Briefly describe (free text)**:	

- Justification for a temporary halt of the trial
- The proposed management of patients receiving treatment at time of the halt *(free text)*.

The consequences of the temporary halt for the evaluation of the results and for overall risk benefit assessment of the investigational medicinal product *(free text)*.

F DESCRIPTION OF EACH SUBSTANTIAL AMENDMENT[9] *(free text)*:

Previous and new wording in track change modus	New wording	Comments/explanation/reasons for substantial amendment
In the study protocol:		
Anna Hagman, DSMB	Anna Hagman, chair of DSMB	The former chair cannot continue due to personal reasons, vice chair takes over as chair.
Ellika Andolf, vice chair of DSMB	/	New DSMB member as Charlotta Grunewald had to quite due to personal reasons.
New study sites (Skellefteå and Visby) and new local PIs for Jönköping, Norrköping and Trollhättan as presented on page 10 in the study protocol	10 Jönköping Region Jönköpings län Anna Cala 18 Norrköping Region Östergötland Ushani Mohapatra 20 Skellefteå Region Västerebotten Linda Mikaelsson 30 Trollhättan Västra Götelandregioneen Martin Berndtsson 33 Visby Region Gotland Jan Wesström	
6.1 Inclusion criteria To be included in the study, subjects must meet the following criteria:	Eligible participants are healthy women between ≥37+0 and 41+6 gestational weeks with a modified Bishop score <6	Please see even attachment "Signering FPI OPTION 221222": Patient evaluation and induction of

[8] Cf. Section 3.10. of the detailed guidance CT-1.

[9] Cf. Section 3.7.c. of the detailed guidance CT-1. The sponsor may submit this documentation on a separate sheet.

Eligible participants are healthy women between ≥37+0 and 41+6 gestational weeks with a modified Bishop score <6 (<5 in parous women) planned for induction at one of the participating hospitals. Study participants will receive written and oral information on the study and will be included into the study by the responsible medical doctor or midwife according to good clinical practice. The subject has given written consent to participate in the study.	(<5 in parous women) planned for induction at one of the participating hospitals. Study participants will receive written and oral information on the study and will be included into the study by the responsible medical doctor or midwife according to good clinical practice. The subject has given written consent to participate in the study.	low-risk pregnancies such as eligible for the OPTION study lies within the midwives' area of competence and duty
7.1 […] Angusta® Tablett 25 microgram misoprostol 8 tablett(er) Blister Varunummer: 044492 Tillverkare: Azanta Danmark A/S/ Norgine B.V. ~~Angusta® will be will be labeled as study medication and delivered to the pharmacy, by Norgine B.V..~~ Angusta® will be delivered to the pharmacy by Norgine and labeled as study medication by the pharmacy.	7.1 […] Angusta® Tablett 25 microgram misoprostol 8 tablett(er) Blister Varunummer: 044492 Tillverkare: Azanta Danmark A/S/ Norgine B.V. Angusta® will be delivered to the pharmacy by Norgine and labeled as study medication by the pharmacy.	Change according to request from both Norgine and Tamro, please find documentation from Tamro attached: "Certificate of GMP-compliance Gothenburg" and "Tillstånd 6.2.1-2022-051529 Tamro AB Importgatan tillverkning prövningsläkemedel människa"
9.3.1 […] ~~1.~~ Ove Axelsson, ~~chair of DSMB~~ 2. Anna Hagman, ~~vice~~ chair of DSMB ~~3. Charlotta Grunewald~~ Ellika Andolf, vice chair of DSMB 4. Göran Wennergren 5. Max Petzold 6. Annika Strandell 7. Lotta Selin	9.3.1 […] 1. Anna Hagman, chair of DSMB 2. Ellika Andolf, vice chair of DSMB 3. Ove Axelsson 4. Göran Wennergren 5. Max Petzold 6. Annika Strandell 7. Lotta Selin	Personal reasons.
10.4.1 […]The primary, non-inferiority hypothesis will be tested by constructing a two-sided 95.7% confidence interval (CI) for the difference in percentage of primary outcome between outpatient and inpatient induction.	10.4.1 […]The primary, non-inferiority hypothesis will be tested by constructing a two-sided 95.7% confidence interval (CI) for the difference in percentage of primary outcome between outpatient and inpatient induction.	Writing mistake noticed when preparing the protocol for this submission, calculations have always been performed for two-sided 95.7% CI.
10.4.2. […]Assuming a vaginal delivery rate of 90% in the outpatient arm, calculating with 80% power, a two sided 99.3% CI, a non-inferiority margin of 0.015 and a 5% drop-out rate, 2119 women need to be randomized to each arm induced with either balloon catheter or prostaglandin.	10.4.2. […]Assuming a vaginal delivery rate of 90% in the outpatient arm, calculating with 80% power, a two sided 99.3% CI, a non-inferiority margin of 0.015 and a 5% drop-out rate, 2119 women need to be randomized to each arm induced with either balloon catheter or prostaglandin.	Writing mistake noticed when preparing the protocol for this submission, calculations have always been performed for a two sided CI.
In "FPI_Kvinnan RCT_OPTION v4 221222" and "FPI_Partner RCT_OPTION v2 221222"		
Men om det är lika säkert och effektivt att vara hemma som på sjukhus under denna fas har hittills inte studerats ~~på ett~~ tillräckligt på vetenskapligt sätt.	Men om det är lika säkert och effektivt att vara hemma som på sjukhus under denna fas har hittills inte studerats tillräckligt på vetenskapligt sätt.	Better text/wording.
In "FPI_Kvinnan RCT_OPTION v4 221222"		

Vi kontrollerar ditt blodtryck, ~~urinprov~~ och hälsotillstånd, evtl ett urinprov	Vi kontrollerar ditt blodtryck, och hälsotillstånd, evtl ett urinprov	More correct as urin test will only be performed if indicated – not on all women as is suggested by the former wording.
Kvinnorna som blir lottade till igångsättning hemma har då större möjlighet att röra sig fritt och leva som vanligt med dusch, ~~bad,~~ mat, vila och sömn - på samma sätt som kvinnor vars förlossning startar av sig själv.	Kvinnorna som blir lottade till igångsättning hemma har då större möjlighet att röra sig fritt och leva som vanligt med dusch, mat, vila och sömn - på samma sätt som kvinnor vars förlossning startar av sig själv.	As bath is not allowed for women who are induced due to prelabour rupture of the membranes which are eligible for OPTION, we chose to remove the word "bath".
In "6.1_DSMB-Charter-OPTION_v3_221222":		
1.Anna Hagman, ~~Ove Axelsson~~, chair of DSMB 2. ~~Anna Hagman~~, Ellika Andolf, vice chair of DSMB 3. ~~Charlotta Grundwald~~ Ove Axelsson 4. Göran Wennergren 5. Max Petzold 6. Annika Strandell 7. Lotta Selin	1.Anna Hagman, chair of DSMB 2. Ellika Andolf, vice chair of DSMB 3. Ove Axelsson 4. Göran Wennergren 5. Max Petzold 6. Annika Strandell 7. Lotta Selin	

G CHANGE OF CLINICAL TRIAL SITE(S)/INVESTIGATOR(S) IN THE MEMBER STATE CONCERNED BY THIS AMENDMENT

G.1 Type of change

G.1.1 **Addition of a new site: Skellefteå**
G.1.1.1 **Principal investigator** (provide details below)
G.1.1.1.1 Given name Linda
G.1.1.1.2 Middle name (if applicable)/
G.1.1.1.3 Family name Mikaelsson
G.1.1.1.4 Qualifications (MD……..) MD
G.1.1.1.5 Professional address Lsarettsvägen 29D, 93186 Skellefteå
G.1.2 **Addition of a new site: Visby**
G.1.2.1 **Principal investigator** (provide details below)
G.1.2.1.1 Given name Jan
G.1.2.1.2 Middle name (if applicable)/
G.1.2.1.3 Family name Wesström
G.1.2.1.4 Qualifications (MD……..) MD
G.1.2.1.5 Professional address S:t Göransgatan 5, 62184 Visby
G.1.3 **Removal of an existing site /**
G.1.3.1 **Principal investigator** (provide details below)
G.1.3.1.1 Given name
G.1.3.1.2 Middle name (if applicable)
G.1.3.1.3 Family name
G.1.3.1.4 Qualifications (MD……..)
G.1.3.1.5 Professional address
G.1.4 **Change of co-ordinating investigator** (provide details below of the new coordinating investigator) /
G.1.4.1 Given name
G.1.4.2 Middle name
G.1.4.3 Family name
G.1.4.4 Qualification (MD…….)
G.1.4.5 Professional address
G.1.4.6 Indicate the name of the previous co-ordinating investigator:
G.1.5 **Change of principal investigator at an existing site** (provide details below of the new principal investigator) Jönköping
G.1.5.1 Given name Anna
G.1.5.2 Middle name /
G.1.5.3 Family name Cala
G.1.5.4 Qualifications (MD……..) MD
G.1.5.5 Professional address Sjukhusgatan, Jönköping

G.1.5.6 Indicate the name of the previous principal investigator: Malin Dögl
G.1.6 **Change of principal investigator at an existing site** (provide details below of the new principal investigator) Norrköping
G.1.6.1 Given name Ushani
G.1.6.2 Middle name /
G.1.6.3 Family name Mohapatra
G.1.6.4 Qualifications (MD……..) MD
G.1.6.5 Professional address Gamla Övägen 25, 60379 Norrköping
G.1.6.6 Indicate the name of the previous principal investigator: Linda Hjertberg
G.1.7 **Change of principal investigator at an existing site** (provide details below of the new principal investigator) Trollhättan
G.1.7.1 Given name Martin
G.1.7.2 Middle name /
G.1.7.3 Family name Berndtsson
G.1.7.4 Qualifications (MD……..) MD
G.1.7.5 Professional address Kvinnokliniken NÄL, 46173 Trollhättan
G.1.7.6 Indicate the name of the previous principal investigator: Dag Prebensen

H CHANGE OF INSTRUCTIONS TO CA FOR FEEDBACK TO SPONSOR

H.1	**Change of e-mail contact for feedback on application***	
H.2	Change to request to receive an .xml copy of CTA data	☐ yes x no
H.2.1	Do you want a .xml file copy of the CTA form data saved on EudraCT?	☐ yes ☐ no
H.2.1.1	If yes provide the e-mail address(es) to which it should be sent (up to 5 addresses):	
H.2.2	Do you want to receive this via password protected link(s)[10]?	☐ yes x no
	If you answer no to question H.2.2 the .xml file will be transmitted by less secure e-mail link(s)	
H.2.3	Do you want to stop messages to an email for which they were previously requested?	☐ yes x no
H.2.3.1	If yes provide the e-mail address(es) to which feedback should no longer be sent:	

(*This will only come into effect from the time at which the request is processed in EudraCT).

I LIST OF THE DOCUMENTS APPENDED TO THE NOTIFICATION FORM (cf. Section 3.7 of detailed guidance CT-1)

Please submit only relevant documents and/or when applicable make clear references to the ones already submitted. Make clear references to any changes of separate pages and submit old and new texts. Tick the appropriate box(es).

I.1 Cover letter	x
I.2 Extract from the amended document in accordance with Section 3.7.c. of detailed guidance CT-1 (if not contained in Part F of this form)	☐
I.3 Entire new version of the document[11]	☐
I.4 Supporting information	X
I.5 Revised .xml file and copy of initial application form with amended data highlighted	☐
I.6 Comments on any novel aspect of the amendment if any :	

J SIGNATURE OF THE APPLICANT IN THE MEMBER STATE

[10] This requires a EudraLink account. (See https://eudract.ema.europa.eu/ for details)
[11] Cf. Section 3.7.c. of the detailed guidance CT-1.

J.1	I hereby confirm that/ confirm on behalf of the sponsor that (delete which is not applicable) • The above information given on this request is correct; • The trial will be conducted according to the protocol, national regulation and the principles of good clinical practice; and • It is reasonable for the proposed amendment to be undertaken.

J.2	**APPLICANT OF THE REQUEST FOR THE COMPETENT AUTHORITY**(as stated in section D.1):☐
J.2.1	Signature [12]: 
J.2.2	Print name : Verena Sengpiel
J.2.3	Date : 7th February 2023

J.3	**APPLICANT OF THE REQUEST FOR THE ETHICS COMMITTEE (**as stated in section D.2): ☐
J.3.1	Signature [13]:
J.3.2	Print name:
J.3.3	Date :

[12] On an application to the Competent Authority only, the applicant to the Competent Authority needs to sign.
[13] On an application to the Ethics Committee only, the applicant to the Ethics Committee needs to sign.