A Randomized, Open-Label, Controlled, Multi-Center Study on the Efficacy of a Sustained Release Progesterone Cerclage Cervical Pessary at Doses of 6.3 g or 7.7 g for the Prevention of Preterm Birth and a Maximum Duration of 20 Weeks.

NCT Number: 02225353

Protocol ID: EC12012/10IEI-9339

Date of Document: 16 May 2016

Clinical Protocol: PCP 002

A Randomized, Open-Label, Controlled, Multi-Center Study on the Efficacy of a Sustained Release Progesterone Cerclage Cervical Pessary at Doses of 6.3 g or 7.7 g for the Prevention of Preterm Birth and a Maximum Duration of 20 Weeks

Research Sites:

Instituto de Investigación Materno Infantil (IDIMI) – Maternidad Hospital Clínico San Borja Arriarán (HCSBA).

UNICERH, South Department of Obstetrics & Gynecology – School of Medicine *UCH Hospital Barros Luco-Trudeau.*

Centro de Investigación e Innovación en Medicina Materno Fetal (CIMAF) - Complejo Asistencial Dr. Sótero del Río (CASR)

East Department of Obstetrics & Gynecology – School of Medicine *UCH Hospital Dr. Luis Tisné Brousse.*

Study Phase: II

Sponsor:
Laboratorio Andrómaco S.A.
Avenida Quilín N° 5273, Peñalolén, Santiago

Version 3 - May 16, 2016

Medical Advisor
Germán Campos P, M.D.
[redacted]
Av. Francia N°1655, Suite 303
[redacted]
Valdivia
Valdivia, Chile

Principal Investigator
IDIMI-HCSBA
Ariel Fuentes G, M.D.
[redacted]
Av. Santa Rosa N° 1234, 2nd floor
[redacted]
Santiago, Chile

Principal Investigator
South Department of Obstetrics & Gynecology – School of Medicine
UCH Hospital Barros Luco
Pablo Lavín Acevedo, M.D.
[redacted] Gran Av. José Miguel
Carrera 3100
[redacted]
San Miguel
Santiago, Chile

Principal Investigator
CIMAF-CASR
Christian Figueroa Lassalle, M.D.
Professor, School of Medicine - PUC
[redacted]
Concha y Toro 3459
[redacted]
Puente Alto
Santiago, Chile

Principal Investigator
East Department of Obstetrics & Gynecology
UCH School of Medicine
Hospital Luis Tisné Brousse
Angélica Díaz, M.D.
[redacted]
Av. Las Torres N° 5150
[redacted]
Peñalolén
Santiago, Chile

Sponsor
Laboratorios Andrómaco S.A.
Avenida Quilín N° 5273,
Tel: +56 594 8479
[redacted]
Peñalolén, Santiago
Santiago, Chile

Study Coordinators
[redacted]
Avenida Quilín N° 5273,
[redacted]
Peñalolén, Santiago
Santiago, Chile.

[redacted]
Avenida Quilín N° 5273,
[redacted]
Peñalolén, Santiago
Santiago, Chile.

Technical Director Manager
[redacted]
Peñalolén, Santiago
Santiago, Chile.

Pharmacovigilance Manager
Laboratorios Andrómaco S.A.
[redacted]
Peñalolén, Santiago
Santiago, Chile.

Medical Director
Laboratorios Andrómaco S.A.
[redacted]
Peñalolén, Santiago
Santiago, Chile.

SYNOPSIS

Protocol Number	**PCP 002**
Title	A Randomized, Open-Label, Controlled, Multi-Center Study on the Efficacy of a Sustained Release Progesterone Cerclage Cervical Pessary at Doses of 6.3 g or 7.7 g for the Prevention of Preterm Birth and a Maximum Duration of 20 Weeks
Sponsor and Phase	Andrómaco - Phase II
Type of Investigation	Medical Device
Type of Study	Interventional
Study location	1. Instituto de Investigación Materno Infantil (IDIMI) – Maternidad Hospital Clínico San Borja Arriarán (HCSBA). 2. UNICERH, South Department of Obstetrics & Gynecology – School of Medicine *UCH Hospital Barros Luco* 3. *Centro de Investigación e Innovación en Medicina Materno Fetal (CIMAF) - Complejo Asistencial Dr. Sótero del Río (CASR).* 4. East Department of Obstetrics & Gynecology – School of Medicine *UCH Hospital Dr. Luis Tisné Brousse*.
Primary Objective of the Study	To assess the efficacy of Cerclage Pessaries containing 6.3 g or 7.7 g of micronized progesterone for the Prevention of Preterm Birth, established through spontaneous parturition before gestation weeks 32 (31 6/7) and 34 (33 6/7), when the pessary is inserted between weeks 16 and 24 and removed at 36 6/7 weeks of gestation in pregnant women at risk of preterm birth.
Secondary Objectives of the Study	• To record the occurrence of premature rupture of membranes before gestation weeks 32 (31 6/7) and 34 (33 6/7). • To assess anatomical cervix features in pregnant women: position and length. • To establish the acceptability and tolerance of the use of the Cerclage Pessary by pregnant women. • To evaluate local and systemic safety in pregnant women using the Cerclage Pessary.
Study Design	Randomized, open-label, controlled clinical study of efficacy.
Study population Inclusion Criteria Exclusion Criteria	**Voluntary patients:** 1. Women with single pregnancy and a cervical length of 10 mm - 25 mm between 16 and 24 weeks of gestation, without any previous risk factors. 2. Women with single pregnancy and a cervical length ≥ 10 mm between 16 and 24 weeks of gestation, and pre-existing risk factors for preterm birth: • Previous preterm birth before week 35. • Previous rupture of membranes before week 35. 1. Pregnancies with: • Major fetal abnormalities, such as lethal malformations or malformations requiring pre- or post-natal surgery, and fetal death before randomization. • History of rupture of membranes or prophylactic

	cerclage in the current pregnancy before inclusion into the study.
	2. Cervical or vaginal injuries prior to insertion of the pessary (e.g. cervical erosion secondary to trauma, infection or carcinoma, vesicovaginal or rectovaginal fistulas). 3. Unconscious, severely ill, mentally disabled patients, or under 16 years of age. 4. Patients for whom use of progesterone is contraindicated. 5. Patients with history of thrombosis.
Planned number of participants	A sample consisting of 270 pregnant women at risk of preterm birth, with useful information for the analysis and recruited in the 4 participating sites. This population will be divided into 3 groups of treatment, with 90 participants each. The 3 groups of the clinical trial are: One control group with progesterone 200 mg vaginal capsules and 2 study groups with 2 different doses of progesterone in the pessaries.
Investigational Product	Cerclage pessaries containing 6.3 g or 7.7 g of sustained-release micronized progesterone each.
Outcomes to be evaluated Primary Secondary	Determination of the effective dose of progesterone in the cerclage pessary through the occurrence of spontaneous birth before 32 (31 6/7) and 34 (33 6/7) weeks of gestation. **Occurrence of rupture of membranes:** Premature rupture of membranes before 32 (31 6/7) and 34 (33 6/7) weeks of gestation. **Cervical anatomic changes** 1. Cervical length and internal cervical os dilation before and after inserting the pessary. 2. Cervical position in relation to the uterus longitudinal axis before and after inserting the medicated pessary. **Acceptability:** 1. Ease of insertion 2. Pain of the patient at the time of insertion 3. Assessment based on the VAS during use 4. Spontaneous expulsion of the pessary 5. Request for early removal of the pessary 6. Subjective changes of vaginal discharge **Local safety:** Major maternal complications attributable to the pessary (chorioamnionitis, severe vaginal or cervical trauma).
Length of the Study	21 – 48 months

2 RATIONALE

Nowadays, prematurity is a central issue both for obstetrics as well as for public health worldwide, as it is a highly incident clinical situation (affecting approximately 7% to 10% of births), and is involved in around 50 - 75% of neonatal morbidities and mortalities, mainly in neonates born before 32 weeks of gestation. Sequelae in premature neonates also impact on the increase of healthcare costs and infant mortality during the first year of life (1).

The rate of preterm births has not declined over the last 20 years, and in most developed countries it remains high despite advances in the knowledge about risk factors and mechanisms related to preterm births (2). Essentially, there are two reasons that explain the failure to reduce preterm births: first, the absence of a screening method effective for the identification of women at high risk for this event; and second, the lack of effective intervention to prevent this complication.

The most commonly adopted approach for identification of pregnancies at high risk for preterm birth has been the use of obstetrical history and mother's demographics.

In published screening studies where over 60,000 women with single pregnancies were included, the preterm birth rate by week 34 in England was 1.8%, very similar to that found in our country (1.3%). Preterm births were spontaneous in two-thirds of the cases (1.2% of the total), whereas one-third were iatrogenic. Only in 3% of cases, the patients had a history of preterm birth and this group accounted for 15% of the total number of spontaneous deliveries by week 34 only. This demonstrates that identification of patients at risk of delivery before week 34 based on obstetric history leaves most of these patients outside of the risk group, and therefore, not covered by preventive measures.

An effective method for prenatal screening to detect the risk of preterm birth is the measurement of the cervical length by ultrasound between gestation weeks 20 and 25. The risk of preterm birth both for single-fetus as well as for twin pregnancies is inversely related to the cervical length. Therefore, a woman with a cervical length (CL) between 1-10 mm has a risk of preterm birth of 44%, whereas a woman with a CL between 26-30 mm has a risk of 1.3%. The group with cervix measures of 1 to 15 mm corresponded to 28% of all spontaneous deliveries before week 34, and the group with a cervix measure of 16 to 25 mm corresponded to 21% (3).

In addition to the myriad of scientific evidence available from the studies above, they allow to state that the lower a certain cervical length in the second trimester of pregnancy, the higher the risk of spontaneous preterm birth both in single and twin pregnancies (4). However, there is still no consensus on the accurate definition for "short cervix" during gestation related to preterm birth risk prediction. Almost every women before 14 weeks of gestation including those at increased risk of preterm birth will have a normal cervical length (CL). A CL of 25 mm at this gestational age is only seen in women with a history of miscarriage in the second trimester, or who have undergone cervical surgery (cone). A CL in the range of 25-50 mm is normal between 14 and 24 weeks in all pregnant women. In women at low risk of preterm birth, the mean CL between 14-30 weeks of gestation is 35-40 mm, and the 10th percentile is 25 mm, while the 90th percentile lies in 50 mm. The optimal timing for measurement of the CL by transvaginal ultrasound should be accurately established since, if performed before 14 weeks, a separate visualization of the cervix from the lower uterine segment may be very difficult. In addition, after week 30, the cervix is

progressively shortened in preparation for a full-term delivery, so in asymptomatic women, a CL <25 mm after 30 weeks is physiological and indicative of a non-preterm birth (5).

Most women who have a preterm birth display a shortened neck for the first time approximately between 18-22 weeks of gestation, so the initial examination should be conducted at least within that period. Besides the already established inverse relationship between CL and the risk of preterm birth, the earlier the cervix is shortened during gestation, the higher the likelihood of a preterm birth. In women at higher risk, a CL <25 mm has a positive predictive value of 70% for preterm birth before 35 weeks when detected at 14-18 weeks, and 40% when detected at 18-22 weeks (5). In the same line of evidence, Vaisbuch *et al*. (4) recently demonstrated an approximate two-fold risk of delivery before 28 or 32 weeks if CL is ≤15 mm before 20 weeks (76.9% and 80.8%) versus 20-24 weeks (30.9% and 48.1%). Overall, this evidence suggests that starting the screening of patients with cervix measurements earlier than week 18 and using a 25-mm CL limit to determine the need for an intervention as discussed in this clinical study might entail a greater advantage.

Preventing the Preterm Birth

The traditional practice for prevention of preterm birth is the administration of tocolytics to patients threatened to, or into premature labor. Although tocolytics administration has been used for several decades, systematic reviews of randomized studies have reported no improvement in the neonatal outcome with the administration of such agents or a decrease in the frequency of preterm births (7). Prophylactic administration of progesterone to women with a history of preterm birth and to those with short cervix and single-fetus pregnancy in mid-gestation has shown to significantly reduce the rate of spontaneous preterm birth (about 40-45% less) before week 33-34. However, there are 55-60% of patients remaining with shortened cervix who likewise and despite progesterone administration, gave birth by week 34 (8-10), which is in line with the multi-causal nature of this condition in humans.

Progesterone mechanism of action to prevent preterm births seems to be related in part with a local anti-inflammatory effect that stops or slows-down the pathway of biochemical events involved in cervical maturation and, on the other hand, by means of a mild inhibitory effect of uterine contractions (13).

The cervical cerclage surgical procedure has also been proposed as a prevention alternative in pregnant patients with single-fetus and short cervix. However, results in patients without previous history of cervical incompetence are still controversial. A recent publication shows that results in the prevention of preterm birth using cerclage for the indication of short cervix are similar in the group in which cerclage is indicated on the basis of the obstetric history. Thus, there would not be a rationale for expecting the cervical shortening to occur in order to perform the procedure (14). On the other hand, multiple observational studies and a recent randomized clinical study in patients with short cervix before 24 weeks of gestation show that the placement of a cerclage pessary (without surgery) significantly reduces the risk of preterm birth as compared to control patients (15-17). Previous evidence suggests that a mechanical factor—probably a cervical distension and/or pressure on the inner cervical os—seems to be also related to early cervical maturity and the risk of preterm birth.

Under normal conditions, an immature cervix in a pregnant woman is displaced posteriorly toward the sacrum, whereby the intrauterine and fetal presentation pressure are exerted on the uterine segment and not on the inner cervical os

(18), thus preventing early dilatation.

Cerclage Pessary without Drug Substance

The cerclage pessary mechanism of action in the prevention of preterm birth has not been fully elucidated. Theoretically, the effect of the pessary is based on its mechanical capability to displace the cervix posteriorly, hence slightly increasing the cervix length and changing the angle of the cervical uterus. All these variations not only reinforce the cervical canal, but also reduce the likelihood for membranes to make contact with the vaginal environment, thus contributing to preserve its integrity (20). An additional benefit of the cerclage pessary may be that it contributes to maintain the immunological barrier between the extraovular chorio-amniotic space and the microbiology flora in the vagina–a mechanism similar to that postulated for surgical cerclage.

[redacted] In a paired-analysis, retrospective study on women with twin pregnancies and a cervical length below the 10th percentile by routine ultrasound, 23 cases were treated with the pessary and 23 received expectant management. The spontaneous delivery rate before week 32 was 0% in the group with pessary and 30% in the control group ($p < 0.001$). In the same study, 12 women with single pregnancies were treated with the pessary and other 12 were treated with expectant management. The spontaneous preterm birth rate before week 36 was 0% in the group with pessary and 50% in the control group ($p < 0.001$) (16). There are many other observational or case-control studies about the use of pessaries for preventing preterm birth. These studies date back to 1959 and have resulted in a promising absence of severe adverse effects (23).

A recent study that included 385 patients with single-fetus pregnancies and shortened cervix confirms the findings above, even though the magnitude of reduction in the prematurity rate for the control group appears to be disproportionately high (17, 20).

[redacted]

Development of a Cerclage Pessary containing Sustained-Release Progesterone

[redacted]

[redacted]

[redacted]

On the basis of the same principle, the development of a cerclage pessary containing progesterone, which is released in a sustained manner upon implantation around the cervix, has been initiated. [redacted]

Characteristics of the Cerclage Pessary with Sustained-Release Progesterone

[redacted]

3 STUDY OBJECTIVES

Primary Objective: This is a Phase II clinical study to assess the efficacy of two cerclage pessaries containing 6.3 g and 7.7 g of sustained-release micronized progesterone for the prevention of preterm birth, established by spontaneous delivery before gestation weeks 32 (31 6/7) and 34 (33 6/7) when the pessary is inserted between weeks 16 and 24 and removed in gestation week 36 6/7, in pregnant women at risk of preterm birth.

Secondary Objectives:

- To record occurrence of premature rupture of membranes before gestation weeks 32 and 34.
- To assess anatomical cervix features in pregnant women: position and length.
- To establish acceptability and tolerance in pregnant women using the Cerclage Pessary.
- To evaluate local and systemic safety in pregnant women using the Cerclage Pessary.

4 STUDY DESIGN

The study will be conducted in compliance with the protocol, the good clinical practice standards, and the provisions of the corresponding ethics committee.

This will be a randomized, open-label, controlled, multicenter, exploratory Phase II study of efficacy. Pregnant patients with a single fetus who after reading the informed consent voluntarily agree to participate in the study will be included.

For secondary outcomes, patients will be their own controls on the following endpoints to be tested: cervix anatomical features—position and length—; plasma and endometrial progesterone concentrations in non-pregnant menopausal women; surveys on pregnant women to establish the acceptability and tolerance of the intervention; and local and systemic safety issues.

4.1. Pregnant Volunteers: 270 + 10% pregnant women at risk of preterm birth from the 4 participating sites will be recruited. This population will be divided into 3 treatment groups with 90 participants each.

They will be informed and invited to participate in the study at prenatal and/or ultrasound control between 16 and 24 weeks of gestation. Volunteers will be included in all cases up to 24 (0/0) weeks of gestation. Volunteers will be selected on the basis of their clinical history and by transvaginal ultrasound performed between weeks 16 and 24. All volunteers with a single pregnancy and cervical length ≤25 mm but ≥10 mm will be invited to participate in the study. Prior to inclusion in the study, fetal vitality or other exclusion factors discussed in detail below will be confirmed. Those patients who do not agree to participate in the study will receive the current standard care at each participating site depending on their condition.

4.1.1. Inclusion criteria in pregnant volunteers:

- Pregnant women with a single fetus with a cervical length of 10-25 mm between 16 and 24 weeks of gestation with no pre-existing risk factors.
- Women with ongoing pregnancy between 16 and 24 weeks of gestation with a single fetus and cervical length ≥10 mm, and having pre-existing risk factors in the immediately previous pregnancy characterized by:
  - Preterm birth before week 35 (with a viable fetus).
  - Premature rupture of membranes before week 35 (with a viable fetus).

4.1.2. Exclusion criteria in pregnant volunteers

- Pregnancies with:
  - Major fetal abnormalities in the current pregnancy such as: lethal malformations, or requiring pre- or post-natal surgery; and fetal death prior to randomization.
  - History of rupture of membranes or prophylactic cerclage in the current pregnancy before inclusion into the study.
    - Cervical and/or vaginal injuries prior to insertion of the pessary (e.g., cervical erosion secondary to trauma, infection or carcinoma, vesicovaginal or rectovaginal fistulas).
    - Unconscious, severely ill, mentally disabled patients, or under 16 years of age.
    - Patients for whom use of progesterone is contraindicated.
    - Participants with history of thrombosis.

5 PROCEDURES

5.1. Recruitment and Screening

Patients will participate voluntarily and under informed consent. Participant selection will be performed by screening the general population of pregnant women with single fetus monitored by the Hospital Healthcare Network, to investigate by serial transvaginal ultrasound performed between gestation weeks 16 (0/7) and 24 (0/7) those patients who have a cervical length between 10 mm and 25 mm, and/or women with a single fetus and cervical length ≥10 mm presenting one or more of the following risk factors: a) preterm birth prior to 35 (34 6/7) weeks of gestation; b) premature rupture of membranes prior to 35 (34 6/7) weeks of gestation.

Gestational age will be determined by the last menstruation date and will be confirmed by measurement of the craniocaudal length obtained in the first trimester ultrasound, or by measurement of the cephalic circumference in the second trimester ultrasound predominating the actual date of the last menstrual period (LMPad).

The selected volunteers will be examined and those with vaginal discharge will undergo clinical examination and/or bacteriological investigation and if confirmed for infection, this will be treated with the appropriate antibiotic. In these cases, insertion of the sustained-release progesterone cerclage pessary will be performed subsequent to the end of treatment although before 24 (0/1) weeks of gestation.

5.2. Study groups

Patients will be randomly assigned to the following 3 study groups:

- Control study group: They will be instructed to administer a micronized progesterone 200 mg capsule by vaginal route on a daily basis.
- Pessary study group A: They will have a pessary with 6.3 g of sustained-release progesterone inserted for a period of about 4 to 5 months. This procedure will be performed by a professional qualified and trained for these purposes.
- Pessary study group B: They will have a pessary with 7.7 g of sustained-release progesterone inserted for a period of about 4 to 5 months. This procedure will be performed by a professional qualified and trained for these purposes.

5.3. Randomization

The randomization program will be generated by an independent statistician. This program will be linked in sequential numbers with the treatment code randomly assigned. The randomization plan will be kept by a qualified person from Laboratorio Andromaco until the database is clean and ready for analysis. Treatment will be dispensed according to the randomization plan. Women with single pregnancy chosen will be randomized to receive one of the vaginal formulations of the study. For the next volunteer, the Site will have the next randomized number available. Each woman will receive only the formulation corresponding to their randomization number. The investigator will record on the file the randomization number and the code printed on every formulation container. The coordinator of each site will assign the randomization code to the volunteers.

5.4. Intervention and follow-up

The intervention and follow-up of participants will begin after the conditions eligible to participate in the study are verified, proceeding as follows:

5.4.1. For selected participants with pre-existing risk factors, these are: immediately previous pregnancy terminated prematurely with preterm birth, or premature rupture of membranes before 35 weeks of gestation; placement of a progesterone cerclage pessary, or treatment with progesterone capsules will start at week 16 (0/7) but not beyond 24 (0/7) weeks of gestation. These participants will have a transvaginal ultrasound performed to document the length (≥10 mm) and position of the cervix at the placement of the pessary or the start of treatment with vaginal progesterone capsules.

5.4.2. For pregnant patients with a single fetus, selected for the presence of a shortened cervix (between 10 mm and 25 mm), the pessary will be inserted or the vaginal administration of progesterone capsules will be started at the time of the investigation, but not before 16 (0/7) weeks of gestation and not after 24 (0/7) weeks of gestation. The cervix angulation relative to the uterus body using the intersection of the uterus posterior wall longitudinal axis with the cervical canal axis in addition to a measurement of the cervical length will be performed on 60% of the study participants assigned to one of the two groups with medicated pessary, prior to insertion of the pessary and after its insertion, by means of a transvaginal ultrasound technique recently described (25). The transvaginal ultrasonography post-insertion of the pessaries may be performed at visit one or at visit two at the latest.

5.4.3. After insertion of the pessary or beginning of the administration with vaginal progesterone capsules and until 28 weeks of gestation, participants in the 3 treatment groups will be monitored every 4 weeks at the most or more often, if the site has established so as a control standard. After 28 weeks, patients should be monitored every 2 weeks. At every control visit, procedures applicable to their prenatal control and a transvaginal ultrasound by standard technique will be performed (patients receiving vaginal capsules), if considered necessary by the physician, or transvaginal using the technique recently described (25) (in patients with medicated pessary) to measure and record cervical length. The occurrence of possible side effects, adherence to treatment, and visits or hospitalizations due to threat or preterm labor will also be recorded, as well as the existence of potential causes for *ex-post* exclusion from the study. In addition, concomitant medication will be recorded at each visit.

5.4.4 Management of participants consulting due to a threat or premature labor will be conducted according to the diagnostic and therapeutic guidelines of the Ministry of Health (MINSAL) (Clinical Guide for Preventing Preterm Birth - MINSAL 2010) and the respective hospital's Obstetrics and Gynecology Service. In these cases, the treating physician will be provided with information about the progesterone treatment the patient is receiving in the study, and the decision for her continuation in the clinical study will be made jointly as far as possible, since the opinion of the treating physician shall predominate.

5.4.5 Every case will be closed at 36 6/7 weeks of gestation, or at the time of preterm birth. Data on the birth, condition at birth, and evolution of infants born preterm will be analyzed, recording morbidity and mortality through the time of discharge from the hospital.

The participant's attending health team (physicians and midwives) will be informed in writing about the participation of these women in the study by means of an identification

card that will be given to every woman participating in the study. In the pregnancy card, participation of these subjects in the study will be emphasized by means of a self-adhesive sticker detailing their participation in one of the treatment groups (pessary or capsule) and recorded in the medical history.

5.5. Placement and repositioning of the cerclage pessary containing sustained-release progesterone

Once the cervix length and positioning have been examined by transvaginal ultrasound, and any vaginal infection has been ruled out or treated, the progesterone pessary should be implanted by a professional qualified and trained for that purpose. For placement, the participant must be lying in supine position. [redacted] The removal of the pessary will be done by vaginal examination at week 36 6/7 or earlier, if there is any medical indication for induction of premature labor or elective cesarean section. The pessary will also be removed from participants in preterm birth labor not responding to treatment with tocolytics.

During controls or visits to emergency departments or medical offices, participants who report vaginal discharge should be examined by a physician to rule out infection by relevant testing (vaginal discharge smears for PCR), and deliver the appropriate treatment without the need to remove the pessary. This condition will be considered an adverse event.

In the event that the medicated cerclage pessary is spontaneously expelled it, will be repositioned within maximum 72 hours; if this does not occur, the patient will be withdrawn from the study but considered in the final statistical analysis under the intention-to-treat principle.

5.6. Adherence and resuming the treatment in patients assigned to the group treated with vaginal progesterone capsules.

Use of capsules at least during 80% of the exposure time, and resuming the treatment not later than 72 hours after discontinuation for any cause will be considered an acceptable adherence to treatment. If adherence of a patient is below 80% or the treatment is interrupted for more than 72 hours, she will be withdrawn from the study but considered in the final statistical analysis.

5.7. Study participant withdrawal

The progesterone cerclage pessary will be removed if the patient requests so, or if there is any adverse event not responding to treatment alternatives such as pathological vaginal discharge non-responsive to antibiotic therapy. These participants will not be replaced and the information collected from them will be included in the analysis since this is based on the intention-to-treat principle.

Follow-up of subjects withdrawn from the investigational product will be the same as the standard follow-up.

5.8. Recording, quality control, and data management

Information about the characteristics of the participants, including demographics (race, age, parity, measures for calculation of body mass index [BMI]), and the medical and obstetrical records will be obtained directly from the participants and recorded in the study file. Information about the outcome of the pregnancy will be obtained from the hospital's medical records file or treating physician. Medical records of participants experiencing preterm birth labor before weeks 32 and 34 will be reviewed to determine the cause and establish whether the delivery was because of medical indication or spontaneous. Spontaneous deliveries will include those with prior preterm labor and those with rupture of membranes before the onset of labor. Quality control for screening, information management, and monitoring of adherence to protocol across the four sites will be performed regularly by the clinical study monitor.

6 MATERIALS AND SUPPLIES

Cerclage pessaries containing sustained-release progesterone will be manufactured by Laboratorios Andrómaco S.A. Both the pessaries as well as the 200 mg progesterone soft capsules to be administered by vaginal route will be supplied to participants free of charge by Laboratorios Andrómaco S.A.

- Vaginal formulations of the study:
  - Capsules containing 200 mg of micronized progesterone for vaginal administration.
  - Vaginal device consisting of a cerclage pessary containing 6.3 g of sustained-release progesterone.
  - Vaginal device consisting of a cerclage pessary containing 7.7 g of sustained-release progesterone.

Laboratorios Andrómaco S.A. will be responsible for printing the applicable codes on every container of study formulation.

7 OUTCOMES OF INTEREST

7.1. Primary Outcomes:

Determination of the progesterone effective dose in the cerclage pessary by non-occurrence of spontaneous delivery before 32 and 34 weeks of gestation.

7.2. Secondary Outcomes:

7.2.1. Occurrence of rupture of membranes:

7.2.1.1. Premature rupture of membranes before 32 and 34 weeks of gestation.

7.2.2. Cervical anatomic changes

7.2.2.1. Cervical length before and after the insertion of the progesterone pessary.

7.2.2.2. Cervix position *relative to the longitudinal axis of the uterus* before and after insertion of the progesterone pessary considering that this measurement may be performed on the same day of the pessary insertion or at Visit 2.

7.2.2.3. Measurement of the utero-cervical angle formed by the posterior wall of the uterus and the longitudinal axis of the cervix before and after insertion of the progesterone pessary.

7.2.3 Acceptability

7.2.3.1 Ease of insertion. Measured by means of a questionnaire.

7.2.3.2. Pain of the patient at the time of insertion and during use of the pessary. The VAS will be applied from 1 to 10 at Visit 1 (admission, where questions 1 to 3 will be answered) and at the final study visit (where questions 4 and onwards will be answered).

7.2.3.3. Request for early removal of the pessary. Date, gestational age and reason for the pessary removal request will be recorded in the data record file.

7.2.3.4. Spontaneous expulsion of the pessary: Date and gestational age at the time of expulsion of the pessary without replacement will be recorded in the data record file.

7.2.3.5. Changes in vaginal discharge. The participant will be questioned about the presence, quantity, and physical characteristics of the discharge at every control visit. The clinical signs and symptoms of the patient will also be recorded.

7.2.4. Local safety

7.2.4.1. Pain, irritation, pruritus, infection occurring in the patient during treatment.

7.2.4.2. Major maternal complications attributable to the pessary such as chorioamnionitis, severe vaginal or cervical trauma.

8 ADVERSE EVENTS

An adverse experience is defined as an unfavorable and unexpected change in the structure, function, or chemistry of the body, transiently associated with the use of the study product, whether or not related to the use of the drug. Any worsening (i.e., any adverse change clinically significant in terms of frequency or severity) of a pre-existing condition that is transiently associated with use of the study product is also an adverse experience.

Adverse events will be documented from the time of enrollment (i.e., at the time of signing the informed consent form) through the last scheduled contact as per the protocol, i.e., the date of the last visit/contact (may be a phone call, for example, in case the participant withdraws from the study).

Definition of Serious Adverse Event (SAE)

A SAE is any medical incidence that, at any dose:

- Results in death; or
- Is life-threatening (puts the subject, from the investigator's perspective, in an immediate risk of death due to the experience that took place. This includes direct life-threatening experiences but not those that could potentially put life at risk), or
- Requires or prolongs hospitalization of the patient (hospitalization is defined as an admission, regardless of length of stay, even if hospitalization is a precautionary measure in order to continuously monitor the patient). If this hospitalization is due to a non-worsening pre-existing condition, it is not to be considered as a serious adverse experience.

- Results in persistent or significant inability/disability (major impairment to the ability to perform daily life functions); or
- Is an abnormal congenital defect or birth defect
- Is considered a clinically significant medical event

A scheduled hospital admission, for example, for elective surgery, is not considered a SAE if documented at the time of enrollment.

All patients randomized in the study are pregnant women, therefore, hospitalizations related to scheduled parturitions/full term deliveries will not be considered as adverse events nor as serious or relevant adverse events.

Definition of Adverse Event of Special Interest

Adverse events of special interest are adverse events considered important for assessment of the safety profile regardless of seriousness, expectancy, and severity classification.

Preterm birth is the birth of a fetus before 37 weeks of pregnancy. Preterm birth will be considered an event of special interest and should consequently be reported within 24 hours.

Expected Adverse Events

Expected Adverse Events will be evaluated by the Sponsor.

An unexpected adverse event is one where the nature or severity is not consistent with the information contained in the relevant source document, i.e. the Investigator Brochure.

In addition, reports that add significant information about the specificity or seriousness of a known, already documented adverse reaction are unexpected adverse events. For example, an adverse event more specific or more serious than expected would be considered "unexpected."

Definition of Adverse Drug Reactions

An Adverse Drug Reaction is any harmful and undesirable response to an Investigational Medicinal Product (IMP) or drug, regardless of the dose administered.

All adverse events reported by subjects spontaneously at any time point should also be documented.

All adverse events should be documented in the CRF with the following information according to the case:

- Description (adverse events reported within the term)
- Start date
- End date or continuation
- Whether the adverse event was serious
- Severity

- Outcome
- Mitigation actions
- Causal relationship with the IMP
- Definition of severity

The clinical severity of an adverse event will be classified as:

Mild:	The signs and symptoms can be easily tolerated. Symptoms may be ignored and disappear when the subject is distracted.
Moderate	Symptoms cause discomfort but are tolerable, not ignorable, impairing concentration ability
Severe	Symptoms affecting daily life activities.

For adverse events where intensity changes over time, the maximum intensity observed throughout the adverse event will be documented.

Adverse events that occur during the enrollment period, but prior to the first administration of the IMP and worsen during or after administration of the IMP will be documented as new adverse events.

Definition of outcomes at the time of the last observation of the adverse event

The outcome at the time of the last observation will be classified as:

- Recovered/Resolved
- Recovering/Resolving
- Not recovered/Not resolved
- Recovered/Resolved with sequelae
- Fatal
- Unknown (unknown should only be used if, at the time of the subject's last visit in a trial, the outcome of the adverse event is unknown to the investigator, for example, because the subject was a lost to follow-up)

Definition of the mitigation actions:

• None:	No mitigation actions have been provided
• Start of new medication:	Start of new medication or change in the dosage or route of administration of a drug due to an adverse event (which will be listed before/concomitantly with the medication sheet) that is used as a mitigation action.
• Interruption of the study:	Discontinuation of the subject participation in the study was required due to an adverse event.
• Other:	All other mitigation actions, e.g., physical therapy, surgery.

With the exception of "none", multiple mitigation actions can be taken for an adverse event.

Classification of causality:

The causal relationship of an adverse event to the investigational product will be classified according to terminology as follows. The proposed criteria for each term are to be considered and not exhaustive and neither are required to be entirely fulfilled for choosing the respective term:

Terms for classification of causality	Criteria for choosing causality classification terms
Conditional/Unclassified	Additional data for proper evaluation are under examination.
Not Evaluable/Not Classifiable:	Assessment of available data may not be performed because the information is insufficient or contradictory, and may not be supplemented or verified.
Unrelated:	Data with sufficient evidence to accept that there is no causal relationship with the administration of the IMP (i.e., there is no time relationship with the administration of the investigational product or another cause has been proved).
Not possible:	Data without sufficient evidence to accept that there is no causal relationship to the administration of the IMP, though neither with evidence or argument to suggest a causal relationship (e.g., the temporal relationship with the administration of the investigational product makes a causal relationship unlikely and other drugs, chemicals, or underlying disease[s] provide plausible explanations).
Possible:	Data or a foundation with limited evidence suggesting a causal relationship (e.g. existence of a reasonable time sequence with the administration of the drug, but the adverse event could also be explained by concurrent disease[s] or other drugs or chemicals. Information regarding drug abstinence may not exist or be unclear).
Probable/Possible	Data or a foundation of enough evidence to suggest a causal relationship (e.g. existence of a reasonable time sequence with administration of the drug, the adverse event is unlikely to be attributed to concurrent disease[s] or other drugs or chemicals, and the response regarding dechallenge is clinically reasonable).
Certain	Data with evidence of a causal relationship (i.e., a clinical event, including alterations in laboratory tests, occurs under a plausible relationship with the time of administration of the drug, and simultaneous disease or other drugs or chemical substances may not explain it. Response to drug dechallenge should be well-defined and clinically plausible, using a successful rechallenge procedure where appropriate).

Follow-up of subjects with an adverse event

Follow-up on any clinically relevant, laboratory abnormality, or vital signs result adverse event will be performed until a satisfactory solution or stabilization is reached, or the clinical evaluation indicates that an additional evaluation is not warranted.

Reporting serious adverse events

Any serious adverse event (SAE) regardless of cause, occurring to any woman admitted into the study, must be notified by the Principal Investigator within 24 hours to **DrugSafetyCOE@grunenthal.com**, and to the respective Institutional Review Boards. These reports should include all supporting documentation available (with the name of the subject crossed out) for each event, the summary of the hospital discharge.

The Technical Director of Laboratorios Andrómaco S.A., Rodrigo Jara [redacted] will communicate the SAE to the local health regulatory authorities. Every SAE must be followed until it is completely characterized. This report must be sent earlier than 2 days after the study staff were notified of the event.

The Principal Investigator must submit a report called a Security Report Form (SRF), which includes a description of the event, the therapy initiated, and the testing procedures. The following information must be reported with the first report of a SAE:

- Study identification
- Subject identification
- Subject's date of birth (if available) or age (at the onset of the adverse event)
- Gender of the subject
- Indicate whether the condition was pre-existing or not, and if so, if it worsened
- First administration of the IMP (date and time, if available)
- Last administration of the IMP (date and time, if available)
- Brief description of the event, and mitigation arrangements taken, actions undertaken (does the adverse experience cause the study drug to be discontinued or interrupted?)
- Maximum intensity
- SAE severity criteria
- Outcome
- Concomitant medication at the onset of the event and if one of the concomitant medications is also suspected of having caused the event
- Relevant history/pre-existing medical condition
- The relationship with the study drug evaluated by the Investigator (determination of causality: Is the study drug the cause of the adverse experience?)

Any additional information relating to the adverse event until the termination of the trial or the final result shall be reported in the follow-up report without delay.

9 STATISTICS

This project aims to conduct a randomized, open-label, controlled, clinical-exploratory phase II study evaluating the efficacy of a cerclage pessary containing one of 2 doses of sustained-release micronized progesterone for prevention of preterm birth, compared to the treatment method currently used by obstetrics-gynecology specialists, which comprises the administration of one daily capsule by vaginal route of 200 mg of progesterone. A total of

270 pregnant participants at risk of preterm birth will be enrolled, screened, and randomized to the 3 groups of treatment previously described. The number of patients listed (n = 270) refers to the number of patients who effectively are enrolled and successfully complete the study. Therefore, an enrollment of at least 10% over that number (27 patients or more) should be considered due to the eventual withdrawal or early loss to follow-up of patients initially recruited.

As primary results, the proportions of spontaneous preterm delivery before gestation weeks 32 and 34 will be compared between the control group and the 2 groups with the pessaries containing different doses of progesterone. The risk of spontaneous preterm birth from the time of inclusion in the study through the gestation weeks 32 and 34 will be determined by a Kaplan-Meier analysis[21], where gestational age will be the time scale and spontaneous delivery will be the event; elective parturitions will be censored. For the purpose of this analysis, pregnancies will no longer be considered as high risk for the event if delivery occurs at the week of gestation 34 (34 0/7) or beyond.

As secondary outcomes, those qualitative variables in pregnant participants at risk of preterm birth will be evaluated, and the percentage distribution of acceptability responses or side effects recorded will be determined. For the quantitative variables (measurements of length and cervical angulation), the averages and standard deviations of the values found will be compared. Accordingly, each participant will work as her own control.

9.1. Sample Size

The calculation of the sample size is based on the power to detect differences in the proportion of spontaneous delivery before 32 and 34 weeks of gestation between the cerclage pessary formulations with respect to the control group (vaginal capsules containing 200 mg progesterone). Collecting data from at least 90 women in each group will provide a power of at least 80% to detect differences at a rate of 40% or more using a two-tailed test with α=0.05 for a non-corrected Chi square.

We estimate that up to 10% of enrolled women may not complete the study, so it is planned to enroll at least 99 pregnant women per group to reach at least 198 treated with the cerclage pessaries, and 99 treated with soft progesterone capsules as control group (i.e., 99 per vaginal formulation).

9.2. Statistical analysis

For quantitative variables, descriptive statistics will be used (mean, standard deviation, minimum, median, maximum, 95% CI, and number of observations), whereas for categorical variables, frequencies and percentages analyses will be carried out. Results will be tabulated by treatment arm and pooled. The different vaginal formulations and progesterone will be formally compared. Results on efficacy and safety will be studied for each group separately and pooled, if relevant.

The proportion of women reporting adverse events during treatment will be cross-compared between the different doses using the Fisher's exact test or the Chi-square test.

All statistical analyses will be performed using the statistical software SPSS (Version 12) or Epistat 4.0.

10 STUDY OVERSIGHT

A Study's Steering Committee will be established and constituted by the medical advisor, clinical monitor, CORFO project Director, [redacted] The Study's Steering Committee is responsible for overseeing the progress of the study, adherence to the protocol, safety of the participants and discussion of new information relevant to the study.

Study Coordinators/CORFO project Director, code [redacted]

Medical advisor [redacted]

Principal Investigator

At each participating site, a physician specialized in Obstetrics and Gynecology will be fully responsible for conducting the study at his/her site. The Principal Investigator will also be responsible for recruiting patients and ensuring that the study is conducted in accordance with the protocol and the Good Clinical Practice guidelines.

- Dr. Ariel Fuentes García at the Instituto de Investigación Materno Infantil (IDIMI) – Maternidad, Hospital Clínico San Borja Arriarán (HCSBA).
- Dr. Pablo Lavín Acevedo at the UNICERH, South Department of Obstetrics & Gynecology – School of Medicine *UCH Hospital Barros Luco*
- Dr. Christian Figueroa Lassalle at the CIMAF-CASR
- Dr. Angélica Díaz at the Department of Obstetrics & Gynecology located at the *Hospital Luis Tisné Brousse*

11 ETHICAL CONSIDERATIONS

The sponsor of the study is Laboratorios Andrómaco S.A.

According to the established in Chile, recruitment of patients for this type of studies is governed by Act 20120. Before any procedure or intervention takes place, the informed consent form must be signed.

According to scientific evidence currently available, this study is classified as a "minimum risk" study for the patients and their unborn children.

12 PROTOCOL AMENDMENTS

Any substantial amendment to this protocol requires approval from the Independent Ethics Committee prior to its implementation.

13 ACCESS TO THE DATABASE/DOCUMENTS

Participating investigators and institutions will have access to controls, audits, reviews, and regulatory inspections by the entities governing the study, and will provide required data and documents safeguarding the identity of the participating patients.

References

1. Guía Clínica Prevención Parto Prematuro MINSAL 2010: http://www.minsal.gob.cl/portal/url/item/721fc45c972f9016e04001011f0113bf.pdf
2. To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH: Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol. 2006; 194:1360-5.
3. To MS, Skentou CA, Royston P, Yu CK, Nicolaides KH. Prediction of patient-specific risk of early preterm delivery using maternal history and sonographic measurement of cervical length: a population-based prospective study. Ultrasound Obstet Gynecol 2006; 27: 362-7
4. Vaisbuch E, Romero R, Erez O, Kusanovic JP, Masaki-Tovi S, Gotsch F, Romero V, Ward C, Chaiworapongsa T, Mittal P, Sorokin Y and Hassan S. Clinical significance of early (<20 weeks) vs. late (20–24 weeks) detection of sonographic short cervix in asymptomatic women in the midtrimester. Ultrasound Obstet Gynecol 2010; 36: 471-481
5. Maria Teresa Mella, MD, and Vincenzo Berghella, MD. Prediction of Preterm Birth: Cervical Sonography. Sem Perinatol 2009; 33: 317-324
6. To MS, Fonseca EB, Molina FS, Cacho AM, Nicolaides KH: Maternal characteristics and cervical length in the prediction of spontaneous early preterm delivery in twins. Am J Obstet Gynecol. 2006; 194:1360-5.
7. A.P. Kenyon, D. Peebles. Myth: Tocolysis for prevention of preterm birth has a major role in modern obstetrics. Seminars in Fetal & Neonatal Medicine 2011; 16: 242-246
8. Dodd JM, Crowther CA, Cincotta R, Flenady V and Robinson JS. Progesterone supplementation for preventing preterm birth: a systematic review and meta-analysis. Acta Obstet Gynecol Scand 2005; 84: 526-533
9. Berghella V. Novel developments on cervical length tamizaje and progesterone for preventing preterm birth. BJOG 2009;116:182–187.
10.S. S. Hassan, R. Romero, D. Vidyadhari, S. Fusey, J. K. Baxter et al. Vaginal progesterone reduces the rate of preterm birth in women with a sonographic short cervix: a multicenter,
randomized, double-blind, placebo-controlled trial. Ultrasound in Obstetrics & Gynecology, 2011; 38, (1):18–31.
11.Suneet P. Chauhan, MD; James A. Scardo, MD; Edward Hayes, MD; Alfred Z. Abuhamad, MD; Vincenzo Berghella, MD. Twins: prevalence, problems, and preterm births. American Journal of Obstetrics & Gynecology, 2010 Oct; 203(4): 305-15
12.Rouse DJ, Caritis SN, Peaceman AM, Sciscione A, Thom EA, Spong CY, Varner M, Malone F, Iam JD, Mercer BM, Thorp J, Sorokin Y, Carpenter M, Lo J, Ramin S, Harper M, Anderson G; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. A Trial of 17 Alpha-Hydroxyprogesterone Caproate to prevent prematurity in twins. N Engl J Med 2007; 357:454-61.
13.Jayasooriya, GS and Lamont, RF . The use of progesterone and other progestational agents to prevent spontaneous preterm labour and preterm birth. Expert Opin. Pharmacother. 2009; 10(6): 1007-1016
14.Simcox R, Seed PT, Bennett P, et al. A randomized controlled trial of cervical scanning vs history to determine cerclage in women at high risk of preterm birth (CIRCLE trial). Am J Obstet Gynecol. 2009; 200(6):623.e1-6.
15.Newcomer J. Pessaries for the treatment of incompetent cérvix and premature delivery. Obstet Gynecol Surv 2000; 55: 443-48
16.Arabin B, Halbesma JR, Vork F, Hübener M, van Eyck J. Is treatment with vaginal pessaries an option in patients a sonographically detected short cervix? J Perinat Med 2003; 31: 122-33
17.Maria Goya, Laia Pratcorona, Carme Merced, Carlota Rodó, Leonor Valle, Azahar Romero, Miquel Juan, Alberto Rodríguez, Begoña Muñoz, Belén Santacruz, Juan Carlos Bello-Muñoz, Elisa Llurba, Teresa Higueras, Luis Cabero, Elena Carreras, on behalf of the Cervical Pessary to Avoid Prematurity (PECEP) Trial Group. Cervical pessary in pregnant

women with a short cérvix (PECEP): an open-label randomised controlled trial. Lancet 2012; 379, (9828): 1800-6
18.Berghella V, Bega G, Tolosa JE, Berghella M. Ultrasound assessment of the cervix. Clin Obstet Gynecol. 2003 Dec;46(4):947-62.
19.Induction of Labor. ACOG Practice Bulletin. Obstetrics&Gynecology August 2009; Vol. 114, No. 2, Part 1.
20.Caritis, SN. Cervical pessary use and preterm birth: how little we know. Lancet 2012; 379, (9828): 1769-70
21.Sivin, I., Mishell, DR Jr., et al. A multicenter study of levonorgestrel-estradiol contraceptive vaginal rings. I. Use effectiveness". Contraception 1981; 24:341-348.
22.Díaz, S., Jackanicz, T.M. et al. Fertility regulation in nursing women.VIII. Progesterone plasma levels and contraceptive efficacy of a progesterone-releasing vaginal ring. Contraception 1985; 32:603-622.
23.Cross RG. Treatment of habitual abortion due to cervical incompetence. Lancet 1959; 2: 127.
24.Lachelin G, McGarrigle H, Seed P, Briley A, Shennan A, Poston L. Low saliva progesterone concentrations are associated with spontaneous early preterm labour (before 34 weeks of gestation) in women at increased risk of preterm delivery. BJOG 2009;116(11):1515-9
25.Goya M, Pratcorona L, Higueras T, Perez-Hoyos S, Carreras E, Cabero L. Sonographic cervical length measurement in pregnantwomen with a cervical pessary. Ultrasound Obstet Gynecol 2011; 38: 205–9.