CLINICAL STUDY PROTOCOL

WORKING PROTOCOL INCLUDING AMENDMENT 01, 02 and 03

Cover Page

Protocol No.:	M13-625	**Protocol Date:**	19 June 2013
		Amendment 01:	31 March 2015
		Amendment 02:	7 September 2015
		Amendment 03:	4 January 2016
Study Title:	A Randomized, Open-label, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg daily versus Crinone 8% intravaginal progesterone gel 90 mg daily for Luteal Support in In-Vitro Fertilization (**LOTUS II**)		
IND No.:			
EudraCT No.:	2012-002993-29		
Phase of Development:	III		
Sponsor:	Abbott Laboratories GmbH Freundallee 9A D-30173 Hannover		
Global Clinical Director / Strategic Medical Affairs Medical Director / Head Clinical Pharmacology:	[redacted]		
Protocol Author(s):	[redacted]		

[redacted]

SYNOPSIS

Name of Sponsor: Abbott Laboratories	**Name of Finished Product:** Duphaston®	**Name of Active Ingredient(s):** Dydrogesterone
Title of Study: A Randomized, Open-label, Two-arm, Multicenter Study Comparing the Efficacy, Safety and Tolerability of Oral Dydrogesterone 30 mg daily versus Crinone 8% intravaginal progesterone gel 90 mg daily for Luteal Support in In-Vitro Fertilization		
Study Center(s) (Planned): Approximately 30 to 40 study sites		
Study Duration: The planned study period from First Subject First Visit until Last Subject Last Visit is August 2015 until April 2017 (End of Study is defined as Last Subject Last Visit.) The treatment phase is up to 12 weeks of gestation with an observation phase until 1 month after delivery.	Phase of Development: III	

Objectives:

- Efficacy Objectives: The primary objective is to demonstrate non-inferiority of oral dydrogesterone versus micronized progesterone as vaginal gel. The primary efficacy parameter is the presence of fetal heart beats at 12 weeks'gestation (10 weeks´ pregnancy) determined by transvaginal ultrasound. The secondary parameters are a positive pregnancy test on Day 14 after embryo transfer and the incidence of live births and healthy newborn(s).
- Safety and Tolerability Objectives: To obtain safety and tolerability data by means of documentation of treatment emergent adverse events (TEAE) during the entire study period. In addition, data on vital signs, physical examination findings, and routine laboratory values will be obtained. Furthermore, signs and symptoms of threatened abortion will be recorded. The time of delivery (pregnancy week) and the following parameters of the newborn (s) will be obtained at delivery: gender, APGAR Score, weight, height, head circumference, abnormal findings of physical examination and any malformations.

This is a prospective randomized, open-label, two-arm, multicenter study comparing the efficacy, safety and tolerability of the oral dydrogesterone treatment regime versus an intravaginal micronized progesterone gel treatment for the luteal support in in-vitro fertilization (IVF).

The study will be conducted according to the following scheme:

1. Screening and Enrollment (Day -40 to -1 [day of downregulation/ ovarian follicle stimulation], Visit 1): Subjects signing the informed consent form will be evaluated for eligibility. They will undergo a physical examination including vital signs; a review of their medical history and concomitant medication. A transvaginal ultrasound will be done, if the last transvaginal examination is older than 14 days. Blood samples will be taken for baseline routine laboratory values and in addition, for subjects where the following hormone values, FSH, estradiol (E_2) LH (luteinizing hormone), PRL (Prolactin), T (testosterone) and TSH (thyroid-stimulating hormone), are not available prior screening, a hormone testing should be performed.
2. Treatment period (Day 0 to Week 10): Luteal support starts on Day 0 (Visit 2), the day of oocyte retrieval. Subjects will be treated with one of the following treatment regimens:

Name of Sponsor:	Name of Finished Product:	Name of Active Ingredient(s):
Abbott Laboratories	Duphaston®	Dydrogesterone

Group I
Oral Dydrogesterone 10 mg tablets three times daily (tid)
or
Group II
Crinone 8% intravaginal progesterone gel 90 mg once daily

3. At Visit 3 (Day 2-5): The day of embryo transfer, this interventional procedure is following the clinic specific IVF protocol.

4. At Visit 4 (Day 16-19 days). On day 14 after embryo transfer, subjects will have a routine pregnancy test (serum β-HCG) to confirm subject's biochemical pregnancy. If the test is positive, luteal support treatment is continued up to week 10 pregnancy (week 12 of gestation).

   If pregnancy is not confirmed on Visit 4 the early discontinuation visit should be performed including physical examination and vital signs. Blood samples will be taken for routine laboratory values.

5. At Visit 5 (Day 42 + /- 3 days – Week 6): Study medication packages should be returned. If pregnancy is confirmed according to clinical evidence then the new study medication packages will be dispensed. Pregnancy related TEAEs and concomitant medication will be recorded.

   If an event of miscarriage occurs between the Visits 4 and 6, subject should return to the study site for the early discontinuation visit within 30 days of the last treatment dose or keep their appointment for Visit 6, whichever occurs first. A physical examination including vital signs will be performed; blood samples will be taken for routine laboratory values. Concomitant medication and any TEAEs will be recorded; the subject will return the remaining study medication.

6. End of treatment on Visit 6 (Day 70 (+ /-3 days)-Week 10): A transvaginal ultrasound examination will be performed to confirm ongoing pregnancy defined as the presence of fetal heart beats. Data on vital signs, routine laboratory values, TEAEs, and concomitant medication will be recorded. Subjects return their study medication.

7. Post treatment surveillance calls (Visit 7 and 8): Subjects will be followed during the pregnancy by routine pregnancy supervision program until the date of delivery. In addition 2 telephone calls (on Day 100 +/- 3 days and on Day 156 +/-3 days)) will be done to record any concomitant treatment and medications and any TEAEs. Especially events of miscarriage and preterm delivery will be recorded.

8. After successful delivery (Visit 9), the time of delivery (pregnancy week) and the following parameters of the newborn(s) will be obtained: gender, APGAR Score, weight, height, head

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circumference, abnormal findings of physical examination and any malformations.

9. At Visit 10 (Day 30 +/- 3 days after delivery): A phone call will be performed to record both mother' and newborn's safety and wellbeing.

Number of Subjects (Planned):
Number of subjects to be allocated to treatment: 1066
Number of subjects to be screened: 1250

Diagnosis and Main Criteria for Inclusion:

Inclusion Criteria:

- Signed informed consent
- Premenopausal females, age > 18 years < 42 years
- Non-smokers. For females who were past smokers, they must have stopped tobacco usage for at least 3 months prior screening visit
- Early follicular phase (Day 2-4) FSH (Follicle stimulating hormone) less than or equal to 15 IU/L and estradiol (E_2) within normal limits at screening
- LH (luteinizing hormone), PRL (prolactin), T (testosterone) and TSH (thyroid-stimulating hormone), within the normal limits for the clinical laboratory, or considered not clinically significant by the Investigator within 6 months prior or at screening
- Documented history of infertility (e.g., unable to conceive for at least one year or for 6 months for women ≥ 38 years of age or bilateral tubal occlusion or absence)
- Normal transvaginal ultrasound at screening (or within 14 days prior of screening) without evidence of clinically significant abnormality consistent with finding adequate for ART with respect to uterus and adnexa (no hydrosalpinx or clinically relevant uterine fibroids)
- Subject is not pregnant, confirmed by negative pregnancy test or by investigator judgment
- Clinical indicated protocol for induction of IVF with a fresh embryo
- Single or dual embryo transfer
- BMI ≥18 and ≤ 30 kg/m^2

Test Product, Dose and Mode of Administration:

Dydrogesterone 10 mg oral tablets three times daily (tid)

Duration of Treatment:

The treatment duration is 10 weeks plus a safety follow-up.

Name of Sponsor: Abbott Laboratories	**Name of Finished Product:** Duphaston®	**Name of Active Ingredient(s):** Dydrogesterone

Reference Therapy, Dose and Mode of Administration:

Crinone 8% intravaginal progesterone gel 90 mg daily.

Criteria for Evaluation:

Efficacy:

The primary efficacy parameter is the pregnancy rate defined as the presence of fetal heart beats at 12 weeks' gestation determined by transvaginal ultrasound. The secondary parameters are a positive pregnancy test on Day 14 after embryo transfer and the incidence of live births and healthy newborns.

Safety:

Safety and Tolerability Criteria: To obtain safety and tolerability data by means of documentation of treatment emergent adverse events (TEAE) during the entire study period. In addition, data on vital signs, physical examination findings, and routine laboratory values will be obtained. Furthermore, signs and symptoms of threatened abortion will be recorded. The time of delivery (pregnancy week) and the following parameters of the newborn baby will be obtained at delivery: gender, APGAR Score, weight, height, head circumference, abnormal findings of physical examination and any malformations. A phone call 30 days after delivery to establish both mother' and newborn's safety and wellbeing.

Statistical Methods:

Efficacy:

The primary endpoint is the comparison of ongoing pregnancy rates between the active comparator and the dydrogesterone treatment regime.

The primary efficacy analysis is using a two-sided 95% confidence interval with a non-inferiority margin of 10% for the pregnancy rates in the two treatment groups. The dydrogesterone group will be compared against intravaginal micronized progesterone gel. So in order to declare non-inferiority, the lower bound of the two-sided 95% confidence interval should exclude a difference greater than 10% in favor of the comparator. In order to calculate the confidence intervals a Cochran-Mantel-Haenszel test stratified for country and age groups will be used. Two age groups will be defined, subjects older or younger than 35 years.

For the primary efficacy analysis, the full analysis FA sample will be used. In addition, further statistical tests may be performed, also on secondary variables. All efficacy and safety parameters will be summarized by standard descriptive methods.

Safety:

The safety sample will be used for the analysis of the safety and tolerability data. Safety variables will be summarized by standard descriptive statistics.

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Treatment emergent AEs are summarized by unique treatment. Severity and drug-event relationship of treatment emergent AEs are summarized separately.

Laboratory variables, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values. Shift tables will be presented according to the reference ranges (low, normal or high).

Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values.

Sample size

Several studies can be found in literature investigating the use of dydrogesterone, intravaginal micronized progesterone capsules (Utrogestan®) or micronized progesterone gel (Crinone®) treatment in IVF. The following table displays the 8- or 12-week pregnancy rate for several studies.

	8-week pregnancy rate			**12-week pregnancy rate**		
	Dydro-gesterone	**Intravaginal micronized progesterone capsules**	**micronized progesterone gel**	**Dydro-gesterone**	**Intravaginal micronized progesterone capsules**	**micronized progesterone gel**
Ganesh 2011[3]				29% (121/422)	23% (104/459)	29% (138/482)
Patki 2007[10]	41% (150/366)	30% (91/309)				
Kleinstein 2005[11]					25% (55/218)	22% (47/121)
Tomic 2011[12]			33% (62/185)			
Simunic 2007[13]		30% (42/136)	33% (43/130)			
Ludwig 2002[14]					17% (9/53)	25% (18/73)
Baruffi 2003[15]		28% (29/103)				
Pouly 1996[16]		25% (36/144)	29% (40/139)			
Lutinus/Endometrin program 2006[17]		42.3 % (171/404)	42.2% (170/403)			

The largest study from Ganesh et al. showed comparable results for micronized progesterone gel and dydrogesterone and only a small, non-significant difference in rates between dydrogesterone and micronized progesterone capsules. Both the study from Kleinstein and Ludwig conclude that both micronized progesterone gel and micronized progesterone capsules will give similar results. Therefore, it is assumed that dydrogesterone and micronized progesterone gel will have similar results with about 35% pregnancy rate at week 12.

A non-inferiority margin of 10% was chosen based on data from the previously approved

Name of Sponsor: Abbott Laboratories	**Name of Finished Product:** Duphaston®	**Name of Active Ingredient(s):** Dydrogesterone
Lutinus®/Endometrin® drug. Assuming a 35% pregnancy rate for the dydrogesterone and the micronized progesterone gel study group, a sample size of about 479 subjects per group would provide 90% power to reject the null hypothesis of H_0: $p_{dydro} - p_{progesterone} \leq -0.1$ in favor of the alternative: H_1: $p_{dydro} - p_{progesterone} > -0.1$ with a one-sided significance level of 2.5%. Assuming a dropout rate of 10%, a total sample size of 533 subjects per treatment group would be required, resulting in a total sample size of 1066 subjects in order to show non inferiority in the primary efficacy parameter.		

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR adverse drug reaction

AE adverse event

APGAR score assessing the health of newborn, done one and five minutes after birth (heart rate, skin color, reflex irritability, muscle tone, respiratory effort)

ATC Anatomical Therapeutic Chemical

ART Assisted Reproductive Technology

Beta-hCG human chorionic gonadotropin

CFR Code of Federal Regulations

CRF case report form (paper or other media)

C_{trough} observed predose (trough) plasma concentration

CV coefficient of variation

CYP cytochrome P450

DHEA-S Dehydroepiandrosterone sulfate

DBP diastolic blood pressure

DMC Data Monitoring Committee

E_2 estrogen

ECG electrocardiogram

EDC Electronic Data Capture

EEG electroencephalogram

EU European Union

EudraCT European clinical trials database

FA full analysis

FDA Food and Drug Administration

FSH follicle stimulating hormone

GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GPRM	Global Pharmacovigilance and Risk Management
HLGT	high level group term
HLT	high level term
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IND	Investigational New Drug
IRB	Institutional Review Board
IVF	in vitro fertilization
IRT	Interactive Response Technology
LH	luteinizing hormone
LPD	luteal phase deficiency
LLOQ	lower limit of quantification
LLT	lowest level term
Max	Maximum
MedDRA	Medical Dictionary for Regulatory Activities
Min	Minimum
MRT	mean residence time
N/A	not applicable
PD	pharmacodynamic
PK	pharmacokinetic

PP	per-protocol
PT	preferred term
PTF	peak trough fluctuation
SADR	serious adverse drug reaction
SAE	serious adverse event
SBP	systolic blood pressure
SD	standard deviation
SOC	system organ class
SPC	Summary of Product Characteristics
SUSAR	suspected unexpected serious adverse drug reaction
TEAE	treatment emergent adverse event
TSH	Thyroid-stimulating hormone
WHO	World Health Organization

1 ETHICS

1.1 Independent Ethics Committee or Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for obtaining written approval for the clinical study protocol (including all substantial protocol amendments), the written subject informed consent form (including written assent, when applicable), informed consent updates, subject recruitment procedures (e.g., advertisements) and any other written information to be provided to subjects from an Independent Ethics Committee (IEC) / Institutional Review Board (IRB) that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IEC/IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of subjects). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IEC/IRB annually, or more frequently if requested by the IEC/IRB. A final study notification should be forwarded to the IEC/IRB within 90 days after the study has completed, or in the event of premature termination of the study, within 15 days with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

In accordance with national provisions and the rules of the EU Clinical Trial Directive, the Sponsor (or an authorized representative) will inform all participating IECs/IRBs and national authorities of all SAEs/SADRs/SUSARs or other safety-related information, which occur during the clinical study.

1.2 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subject. The study will be conducted in compliance with GCP and the applicable national regulations to assure that the rights, safety, and well-being of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

Data Monitoring Committee

Not applicable

1.3 Subject Information and Consent

Voluntary written informed consent will be obtained from each subject prior to performing any study-related procedures. Each subject will be given both verbal and written information describing the nature and duration of the clinical study. The informed consent process will take place under conditions where the subject has adequate time to consider the risks and benefits associated with his/her participation in the study. Subjects will not be screened or treated until the subject has signed an approved informed consent written in a language that is understandable to the subject.

The IEC/IRB approved informed consent form will be signed and personally dated by the subject (or legally acceptable representative, when appropriate) and the person who conducted the informed consent discussion. Each subject is to receive a copy of the signed and dated written informed consent form and any other written subject information.

The signature of an impartial witness is to be obtained in the event the subject or the subject's legally acceptable representative is unable to read. Additional signatures on the informed consent form may be required in accordance with IEC/IRB requirements or those of the Sponsor (or an authorized representative).

The Investigator is responsible for assuring the appropriate content of the informed consent form and that informed consent is obtained from each subject in accordance with the applicable regulations and guidelines. The original signed informed consent is to be retained in the study documentation files.

The Investigator shall maintain a log of all subjects who sign the informed consent form and indicate if the subject received study drug or, if not, the reason why. The subject´s medical records should also document that the informed consent form was signed and dated prior to any study-related procedures being performed.

2 INTRODUCTION

Assisted reproductive technology (ART) is a general term referring to methods to achieve pregnancy by artificial or partial artificial means. Technically, the term ART refers only to fertility treatments, such as in vitro fertilization (IVF) and its variants (e.g., intracytoplasmic sperm injection (ICSI), frozen embryo replacement (FER), egg donation (ED) etc.). More than 4 million babies have been conceived by ART methods since the birth of the first IVF baby Louise Brown in 1978 (EIM Consortium 2010).

Most assisted reproductive technologies procedures use in-vitro fertilization (IVF).

As part of the Assisted Reproductive Therapy procedures (ART), gonadotroping releasing hormones (GnRH) are used to induce ovarian stimulation. The use of GnRHs causes a suppression of luteinizing hormone (LH) secretion, which results in a dysfunctional corpus luteum and leads to inadequate ovarian progesterone production. Low progesterone levels lead to an incomplete secretory endometrium and ineffective ovum implantation. Luteal deficiency was first proposed as a cause of infertility in 1949.2

The modulating effect of progesterone on endometrial structure and function are essential for the success of human reproduction. After ovulation, progesterone produced by the corpus luteum induces secretory maturation of the endometrium, involving a cascade of molecular events that ultimately renders the endometrium receptive to implantation of the embryo. After nidation, continued progesterone stimulation, driven by rapidly increasing concentration of hCG, decidualizes the endometrial stoma and supports early embryonic development.

Progesterone or hCG treatment has become an established supplement to support the corpus luteum progesterone production, to support the luteal phase of the artificial cycle, promote the maintenance of the endometrium and enhance the likelihood of implantation of a fertilized egg.

The luteal support causes a considerable improvement in the pregnancy rates as compared to IVF cycles without luteal support.3,4

Progesterone has become the agent of choice for luteal support because hCG is associated with a higher risk of ovarian hyperstimulation syndrome (OHSS), particulary in younger women, good responders, and women with polycystic ovary syndrome.

The evidence for the beneficial use of progesterone and other progestogens in LPD is largely empirical. 5 The range of success rates is between 30 and 60%.6,7 The low success rates in some publications may at least partly be explained by the poor selection of cases with the diagnosis of luteal deficiency made in a haphazard manner. In addition, the doses might not always have been high enough.

When progestogene supplementation is the therapy of choice in luteal support, dydrogesterone is frequently used in infertility as it has no inhibitory effect on ovulation, it

does not inhibit the formation of progesterone in human placenta during early pregnancy, and does not cause masculinization of the fetus.[8,9]

In most ART centers worldwide the use of micronized progesterone, as vaginal gel formulation, has become a routine practice. The usual dose for luteal-phase support with the micronized progesterone gel is 90 mg once daily.
The main side effects associated with vaginal preparation are vaginal irritation, discharge, and dyspareunia. Several research groups believe that due to the local side effects the vaginal application is not very well accepted by all subjects.

Dydrogesterone, a retroprogesterone derivate, has a good bioavailability combined with all of the clinical properties of endogenous progesterone, as well as being devoid of local side effects. Dydrogesterone has been used effectively in various gynecological disease, e.g. premenstrual disease, endogenous progesterone deficiency, menstrual abnormalities, endometriosis and in combination with estrogen in hormone replacement therapy.

3 STUDY OBJECTIVES

3.1 Primary Objective(s)

The primary objective is to demonstrate non-inferiority of oral dydrogesterone versus micronized progesterone as vaginal gel. The primary efficacy parameter is the presence of fetal heart beats at 12 weeks' gestation determined by transvaginal ultrasound.

3.2 Secondary Objective(s)

The secondary objectives and parameters are a positive pregnancy test on Day 14 after embryo transfer and the incidence of live births and healthy newborns.

3.3 Safety Objective(s)

The safety objective is to obtain safety and tolerability data by means of documentation of treatment emergent adverse events (TEAE) during the entire study period. In addition, data on vital signs, physical examination findings, and routine laboratory values will be obtained. Furthermore, signs and symptoms of threatened abortion will be recorded. The time of delivery (pregnancy week) and the following parameters of the newborn will be obtained at delivery: gender, APGAR Score, weight, height, head circumference, abnormal findings of physical examination and any malformations.

4 STUDY DESIGN

4.1 Overall Study Design and Plan-Description

This is a prospective open label, randomized, two-arm, multicenter study comparing the efficacy, safety and tolerability of the oral dydrogesterone treatment regimen versus an intravaginal micronized progesterone gel treatment for the luteal support in in-vitro fertilization (IVF).

The study will be conducted according to the following scheme:

- Screening and Enrollment (Day -40 to -1 [day of downregulation/ovarian follicle stimulation], Visit 1): Subjects signing the informed consent form will be evaluated for eligibility. They will undergo a physical examination including vital signs; a review of their medical history and concomitant medication. A transvaginal ultrasound will be done, if the last transvaginal examination is older than 14 days. Blood samples will be taken for baseline routine laboratory values and in addition, for subjects where the following hormone values, FSH, estradiol (E_2), LH (luteinizing hormone), PRL (Prolactin), T (testosterone) and TSH (thyroid-stimulating hormone), are not available prior screening, a hormone testing should be performed.
- Treatment period (Day 0 to Week 10): Luteal support starts on Day 0 (Visit 2), the day of oocyte retrieval. Subjects will be treated with one of the following treatment regimens:
  Group I
  Oral Dydrogesterone 10 mg tablets three times daily (tid)
  or
  Group II
  Crinone 8%, intravaginal progesterone gel 90 mg, once daily

- At Visit 3 (Day 2 - 5): The day of embryo transfer, this interventional treatment is following the clinic specific IVF protocol.
- At Visit 4 (Day 16 - 19 days). On day 14 after embryo transfer, subjects will have a routine pregnancy test (serum β-hCG) to confirm subject´s biochemical pregnancy. If the test is positive, luteal support is continued up to week 10 pregnancy (week´12 gestation).

  If pregnancy is not confirmed on Visit 4 the early discontinuation visit should be performed including physical examination and vital signs. Blood samples will be taken for routine laboratory values.

- At Visit 5 (Day 42 +/ 3 days – Week 6): Study medication packages should be returned. If pregnancy is confirmed according to clinical evidence then the new study medication packages will be dispensed. Pregnancy related TEAEs and concomitant medication will be recorded.

  If an event of miscarriage occurs between the Visits 4 and 6, subject should return to the study site for the early discontinuation visit within 30 days of the last treatment dose or keep their appointment for Visit 6, whichever occurs first. A physical examination

including vital signs will be performed; blood samples will be taken for routine laboratory values. Concomitant medication and any TEAEs will be recorded; the subject will return the remaining study medication.

- End of treatment on Visit 6 (Day 70 +/- 3 days – Week 10): A transvaginal ultrasound examination will be performed to determine the pregnancy defined as the presence of fetal heart beats. Data on vital signs, routine laboratory values, TEAEs, and concomitant medication will be recorded. Subjects return their study medication.
- Post treatment surveillance calls (Visit 7 and 8): Subjects will be followed during the pregnancy by routine pregnancy supervision program until the date of delivery. In addition 2 telephone calls (on Day 100 +/- 3 days and on Day 156 +/- 3 days) will be done to record any concomitant treatment and medications and any TEAEs. Especially events of miscarriage and preterm delivery will be recorded.
- After successful delivery (Visit 9), the time of delivery (pregnancy week) and the following parameters of the newborn(s) will be obtained: gender, APGAR Score, weight, height, head circumference, abnormal findings of physical examination.
- At Visit 10 (Day 30 +/- 3 days after delivery): A phone call will be performed to record both mother' and newborn's safety and wellbeing.

4.2 Discussion of Study Design, Including the Choice of Control Groups

The aim of this study is to substantiate the empirical use of dydrogesterone in a prospective open-label, randomized clinical study. With this objective non-inferiority to the current standard of care should be demonstrated. Intravaginal progesterone gel, one of the current standard of care products for the luteal support in IVF, is included in this study as comparator.

5 SELECTION OF STUDY POPULATION

5.1 Inclusion Criteria

1. Signed informed consent
2. Premenopausal females, age > 18 years < 42 years
3. Non-smokers. For females who were past smokers, they must have stopped tobacco usage for at least 3 months prior screening visit
4. Early follicular phase (Day 2-4) FSH (Follicle stimulating hormone) less than or equal to 15 IU/L and estradiol (E_2) within normal limits at screening
5. LH (luteinizing hormone), PRL (prolactin), T (testosterone) and TSH (thyroid-stimulating hormone), within the normal limits for the clinical laboratory, or considered not clinically significant by the Investigator within 6 months prior or at screening
6. Documented history of infertility (e.g., unable to conceive for at least one year or for 6 months for women ≥ 38 years of age or bilateral tubal occlusion or absence)
7. Normal transvaginal ultrasound at screening (or within 14 days prior of screening) without evidence of clinically significant abnormality consistent with finding adequate for ART with respect to uterus and adnexa (no hydrosalpinx or clinically relevant uterine fibroids)
8. Subject is not pregnant, confirmed by negative pregnancy test or by investigator judgment
9. Clinical indicated protocol for induction of IVF with a fresh embryo
10. Single or dual embryo transfer
11. BMI ≥18 and ≤ 30 kg/m^2

5.2 Exclusion Criteria

1. Evidence of cardiovascular, respiratory, urogenital, gastrointestinal/hepatic, hematologic/immunologic, HEENT (head, ears, eyes, nose, throat), dermatologic/connective tissue, musculoskeletal, metabolic/nutritional, endocrine, neurologic/psychiatric, allergy, recent major surgery (< 3 months), or other relevant diseases as revealed by history, physical examination and/or laboratory assessments which could limit participation in or completion of the study;
2. Acute urogenital disease
3. Known allergic reactions to progesterone products
4. Intake of any experimental drug or any participation in any other clinical trial within 30 days prior to study start.
5. Mental disability or any other lack of fitness, in the Investigator's opinion, to preclude subjects in or to complete the study
6. Current or recent substance abuse, including alcohol and tobacco (Note: Patients who stopped tobacco usage at least 3 months prior to screening visit would be allowed)
7. History of chemotherapy
8. Patients with more than 3 unsuccessful IVF attempts
9. Contraindication for pregnancy

10. Refusal or inability to comply with the requirements of the study protocol for any reason, including scheduled clinic visits and laboratory tests
11. History of recurrent pregnancy loss defined as 3 or more spontaneous miscarriages

5.3 Rationale for Diagnosis and Criteria

The evidence for the beneficial use of progesterone and other progestogens in treatment of luteal phase deficiency (LPD) is largely empirical.[5] The range of success rates is between 30% and 60%.[6,7] The low success rates in some publications may at least partly be explained by the poor selection of cases with the diagnosis of luteal deficiency made in a haphazard manner. In addition, the doses might not always have been high enough.

When progestogen supplementation is the therapy of choice for IVF, then also dydrogesterone could be used in infertility as it has no inhibitory effect on ovulation, does not inhibit the formation of progesterone in human placenta during early pregnancy, and does not cause masculinization of the fetus.[8,9]

The aim of this study is to substantiate the empirical use of dydrogesterone in a prospective open-label, two-arm, randomized clinical study. With this objective non-inferiority to the current standard of care should be demonstrated.

6 REMOVAL OF SUBJECTS FROM THERAPY OR ASSESSMENT

All subjects are free to withdraw from participation in this study at any time, for any reason, specified or unspecified, and without penalty or loss of benefits to which the subject is otherwise entitled.

The Study Termination form must be completed for all subjects who have entered the study (i.e., have signed Informed Consent form), including subjects dropping out prior to any study drug administration.

In case of premature termination of the subject from the study, the primary reason for this premature termination is to be indicated according to the following definitions:

- If pregnancy is not confirmed at Visit 4, the day of the biochemical pregnancy test (14 days after embryo transfer).
- Adverse event: discontinuation due to any adverse event (AE) with a corresponding entry reflected on the Adverse Events form in the CRF
- Lack of efficacy: subject fails to respond to the study drug at an acceptable level where the subject or the Investigator feels it is in the best interests of the subject to seek another treatment.
- Lost to follow-up: the subject fails to return to the study site for scheduled visits and does not respond to telephone or written attempts to contact.
- Withdrew consent: subject decides to stop her participation in the study for any reason other than an AE, or is unable to complete the study as described in the clinical study protocol (e.g., subject is relocating to another location).
- Administrative: the Sponsor decides to terminate an individual subject or decides to discontinue the study (either at the study site or the entire study), e.g., general safety problems leading the Sponsor to entirely stop the study.
- Protocol violation – anything which is in direct violation of the clinical study protocol (e.g., inclusion/exclusion violation).

7 TREATMENTS

The investigator receives the information of the treatment allocation number from the IRT system. The subject will receive her study medication package from the study site or from the pharmacy of the institution.

7.1 Treatments to be administered

Luteal support starts on Day 0 (Visit 2), the day of oocyte retrieval. Subjects will be treated from Day 0 to Week 10 with any of the following two regimens:

- Oral Dydrogesterone 10 mg tablets tid *or*
- Crinone 8%, intravaginal micronized progesterone gel 90 mg, once daily

Treatment should we stopped at Visit 4 (Day 14 +/ - 3 days) if pregnancy is biochemically (β-hCG test) not confirmed.

7.2 Packaging and Labeling

Packaging and labeling will be controlled by Clinical Supply Management (Drug Product Development) of Abbott Healthcare Products BV, Weesp, The Netherlands.
All packaging and labeling as well as the production of study drug will be in compliance with Good Manufacturing Practices (GMP) specifications, as mentioned in the Manufacturing of Investigation and Medicinal Products Volume 4 Annex 13 and in accordance with other applicable laws or local regulations.
Details on the packaging and labeling will be specified in the Packaging and Labeling Specifications and Supply Request.

An Abbott Qualified Person will release all the clinical supplies prior to shipment to investigational sites. A Certificate of Compliance will be issued stating the expiry date of the clinical supplies.

7.3 Storage and Dispensing of Study Drug

All clinical drug supplies are to be stored in a secure, monitored, limited-access area in accordance with labeled storage conditions. The temperature of the room should be below 25 degrees C. Keeping the blister in the outer carton, in order to protect from moisture and light. The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study. These records shall include the amounts of drug supplies and the dates on which drug supplies were received from the Sponsor (or an authorized representative), dispensed to the subject, returned by the subject and returned to the Sponsor (or an authorized representative). If errors or damages in the clinical drug supply shipments occur, the Investigator must contact the Sponsor (or an authorized representative) immediately.

7.4 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to a treatment group using a centralized electronic system (interactive voice/web response system; IRT). The IRT assigns a 5-digit randomization number to each subject according to a randomization scheme.

The randomization scheme will be provided by Clinical Supply Management (Drug Product Development) of Abbott Healthcare Products BV.

7.5 Selection of Doses in the Study

The selection of the doses of the treatment medication is based on the doses recommended by specialists for the treatment of luteal support in IVF and from published study reports.[10]

7.6 Selection and Timing of Dose for Each Subject

Subjects will be randomly assigned to a selected fixed dose regimen as described in Section 7.1. Subjects will start their treatment on the day of oocyte retrieval (Visit 2/Day 0) and if pregnancy is confirmed at Visit 4 (Day 14 +/- 3 days), treatment will be continued until Day 70. The dydrogesterone tablets will be taken orally evenly distributed over the day. The micronized progesterone gel will be administered once daily via intravaginal application.

7. 7 Blinding and Treatment Code Information

Not applicable

7.8 Prior and Concomitant Therapy

Any intake of further progesterone products during the treatment phase is not allowed and leads to the exclusion of the subject.

Any intake of other medication, which does not interfere with the study medication or its evaluation, is allowed as judged appropriate by the Investigator.

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) will be recorded on the Concomitant Medication form, except for study drug.

7.9 Treatment Compliance

Drug Accountability

The Investigator is accountable for all clinical drug supplies shipped to his/her study site for the duration of the study. A final accounting of the clinical drug supplies will be required at the completion/termination of the study. The Investigator is required to provide written explanation for any discrepancies. All unused clinical drug supplies (except required

retention samples) will be inventoried and returned to the Sponsor (or an authorized representative) by a designated monitor. The Investigator will not be permitted to return or destroy (un)used clinical drug supplies or packaging materials unless authorized by the Sponsor (or authorized representative). The subjects should return their used/unused study medications to the pharmacy or study nurse.

8 STUDY ASSESSMENTS AND FLOW CHART

8.1 Efficacy Measurements

Pregnancy Rate

The primary efficacy parameter is the pregnancy rate defined as the presence of fetal heart beats at 12 weeks' gestation determined by transvaginal ultrasound.

Rate of successful completion of pregnancy

The secondary parameters are a positive pregnancy test on Day 14 after embryo transfer and the incidence of live birth and healthy newborns.

Status Newborn

Further secondary parameters are the incidence of life birth and healthy newborns. The gender and APGAR score will be recorded, as well as the height, weight and head circumference of the newborn.

In addition, a physical examination of the newborn will be performed and any malformations will be recorded.

8.2 Safety Measurements

Adverse Events

Requirements for collecting, recording and reporting of AEs are described in Section 9. Each subject is to be evaluated at the termination visit. Should any AE be identified at this visit, the Investigator will continue to follow the subject as described in Section 9.1.2

Biochemical pregnancy

Is defined as a rise in β-hCG with no further clinical evidence of pregnancy at Visit 5 (Day 42 -/+ 3 days) as determined and confirmed by investigator at the routine control.

Miscarriage

Is defined as a pregnancy loss after the confirmation of pregnancy.

Routine laboratory

Blood will be collected for the determination of the following parameters:

Baseline routine laboratory values (hematology: hemoglobin, hematocrit, RBC count, WBC count, platelet count; biochemistry: glucose (if possible fasting), creatinine, alkaline phosphatase, total bilirubin, ALAT, ASAT, gamma-glutamyl transferase, uric acid, calcium, phosphate, potassium.

For subjects where the hormone values are not available prior screening a hormone testing including, FSH, estradiol (E_2), LH (luteinizing hormone), PRL (Prolactin), T (testosterone) and TSH (thyroid-stimulating hormone) should be performed.

Urine analysis (Dipstick)

Urine sample collection for routine urine analysis of pH, nitrite, specific gravity, blood, protein and glucose will be performed.

Urine sample collection for pregnancy test (strip test).

For values outside the normal range (or abnormal results) the clinical significance is to be judged by the Investigator.

Vital Signs

Height and weight must be recorded during the treatment phase.

Systolic blood pressure (SBP), diastolic blood pressure (DBP) and pulse rate are to be measured while the subject is in sitting position after 3-5 minutes rest.

Physical Examination

A physical examination should be performed and any relevant findings are to be recorded on the Medical History form in the CRF (for findings from the past that occurred prior to first screening visit), or on the Adverse Events form in the CRF for findings presently occurring.

8.3 Other Assessments

Informed Consent

Voluntary written informed consent must be obtained from each subject (or their legally acceptable representative) prior to performing any study-related procedures (see Section 1.3).

Demographic Data

Demographic data (gender, date of birth, ethnicity, and race) will be collected for all subjects.

Medical History

Any clinical event, including diagnosis, condition, or surgery, that occurred prior to the screening visit (before the informed consent is signed), is to be recorded on the Medical History form. In case a clinical event concerns a chronic disorder, which means it started in the past and it is still present at the screening visit, it should also be recorded on the Medical History Form. Examples of these events are diabetes, migraine, and hay fever.

Concomitant Medication

All medication taken by the subject during the study (from signing the informed consent form through post-study follow-up) is to be recorded on the Concomitant Medication form, except for study drug.

8.4 Appropriateness of Measurements

All measurements will be performed using standard methods which are generally recognized as being reliable, accurate, and relevant.

8.5 Primary Efficacy Variable

The primary efficacy parameter is the pregnancy rate defined as the presence of gestational sac(s) with viable fetal heart beats at 12 weeks' gestation by transvaginal ultrasound.

8.6 Flow Chart of Study Assessments

All study assessments will be conducted as indicated in Table 1, which displays the frequency and timing of all measurements.

Table 1. Flow Chart of Study Assessments

Period	Screening and Enrollment	Start of treatment Day of oocyte Retrieval	Day of embryo transfer (ET)	Day to confirm biochemical pregnancy	Day to confirm ongoing pregnancy	End of Treatment/ Early discontinuation ***	Post treatment surveillance calls every 2 months	After delive ry Case notes	Phone call 30 days after delivery
Visit	1	2	3	4**	5	6	7 + 8	9	10
Day	-40 to -1	0	2 to 5	16 to 19	42 (+/- 3 days)	70 (+/- 3 days)	100 (+/- 3 days) 156 (+/- 3 days)		
Informed consent	X								
Demographic data	X								
Medical history	X								
Physical examination	X					X			
Transvaginal ultrasound examination	X					X should not be performed at the early discontinuation visit			
Inclusion/exclusion criteria	X								
Blood samples for routine laboratory values *	X					X			
Serum β-hCG Test				X					
Urine analysis	X			X		X			
β-hCG test (strip test)				X					
Vitals signs	X					X			

Period	Screening and Enrollment	Start of treatment Day of oocyte Retrieval	Day of embryo transfer (ET)	Day to confirm biochemical pregnancy	Day to confirm ongoing pregnancy	End of Treatment/ Early discontinuation ***	Post treatment surveillance calls every 2 months	After delive ry Case notes	Phone call 30 days after delivery
Subject to collect study drug at pharmacy		X		X	X				
Return unused medication				X	X	X			
Concomitant medication	X	X	X	X	X	X	X		X
Compliance check				X	X	X			
Adverse events		X	X	X	X	X	X	X	X
Infant assessment****: gender, weight/ height, APGAR, physical examination								X	

* For subjects where the hormone values are not available prior screening a hormone testing including FSH, estradiol (E_2), LH (luteinizing hormone), PRL (Prolactin), T (testosterone) and TSH (thyroid-stimulating hormone) should be performed.

**if pregnancy is not confirmed on visit 4 an early discontinuation should be performed including physical examination and blood sampling for routine laboratory testing

*** If an event of miscarriage occurs between the Visits 4 and 6, patient should be return to the study site for the early discontinuation visit within 30 days of the last treatment dose or on their appointment for Visit 6, whatever occurs first. A physical examination including vital signs will be performed; blood samples will be taken for routine laboratory values

**** After successful delivery, the time of delivery (pregnancy week) and the following parameters of the newborn baby will be obtained: gender, APGAR score, weight, height, physical examination.

9 ADVERSE EVENTS

9.1 Adverse Events and Adverse Drug Reactions

Definition of Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom (including an AE occurring from drug abuse, an AE occurring from drug withdrawal and any failure of expected pharmacological action), or disease temporally associated with the use of a pharmaceutical product, whether or not considered related to the pharmaceutical product.

An elective surgery/procedure scheduled to occur during a study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Definition of Adverse Drug Reaction (ADR)

In the pre-approval clinical experience with a new pharmaceutical product or its new usages, particularly as the therapeutic dose(s) may not be established, all noxious and unintended responses to a pharmaceutical product related to any dose should be considered ADRs. The phrase “response to a pharmaceutical product” means that a causal relationship between a pharmaceutical product and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

Regarding marketed pharmaceutical products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for modification of physiological function.

An unexpected ADR is an ADR, the nature or severity of which is not consistent with the applicable product information, such as the Investigator’s Brochure (IB) or the Summary of Product Characteristics (SPC).

9.1.1 Recording of Adverse Events

Any AE should be recorded on the Adverse Events form in the CRF and source documents. In order to avoid vague, ambiguous or colloquial expressions, the AE should be recorded in standard medical terminology rather than the subject’s own words. Whenever possible, the Investigator should group together into a single term signs and symptoms which constitute a single diagnosis.

The existence of or change in an AE may be concluded due to the necessity to administer a concomitant medication, from a spontaneous report of the subject, from the physical examination or from special tests like ECG, EEGs, laboratory assessments or other study specified tests (source of AE).

AEs, which occur from the time the subject signed the study specific informed consent, regardless of the interval prior to the first administration of the study drug, and/or in the specified post-therapy AE collection period and/or in the post-protocol period until last visit will be handled as any other AE occurring during the treatment with study drug.

Each AE is to be evaluated for duration, severity, seriousness and causal relationship to the investigational drug. The action taken with study drug, the concomitant treatment/therapy introduced and the outcome as well as whether the event led to study termination will also be recorded.

Severity

The severity of the AE should be characterized as “mild, moderate or severe” according to the following definitions:

- Mild events are usually transient and do not interfere with the subject’s daily activities.
- Moderate events introduce a low level of inconvenience or concern to the subject and may interfere with daily activities.
- Severe events interrupt the subject’s usual daily activity.

Drug-Event Relationship

The causal relationship between the study drug and the AE should be characterized according to the following:

- Unrelated – there is not a reasonable possibility that the study drug caused the AE.
- Unlikely – suggests that only a remote connection exists between the study drug and the event. Other conditions, including concurrent illness, progression or expression of the disease state or reaction to concomitant medication, appear to explain the AE.
- Possible – suggests that the association of the AE with the study drug is unknown, however the event is not reasonably supported by other conditions.
- Probable – suggests that a reasonable temporal sequence of the AE with drug administration exists and, in the Investigator’s clinical judgment, it is likely that a causal relationship exists between the drug administration and the AE, and other conditions (concurrent illness, progression or expression of the disease state, or concomitant medication reactions) do not appear to explain the AE.

Outcome

The outcome of the adverse event should be classified according to the following definitions:

- Recovered / resolved: the event has resolved (no further symptoms are present and no treatment is being received by the subject).
- Recovered / resolved with sequelae: the event has resolved but there may be lingering effects present (e.g., a scar following a cut or abrasion).
- Fatal: the subject died as a result of the event. This code should only be used for the event that caused the death, not any event that was present at the time of the subject's death. Fatal events require immediately reporting to the Sponsor (or an authorized representative).
- Unknown: may only be used in the event that the subject is lost to follow-up and no reliable data can be obtained.

All efforts should be made to classify the AE according to the above categories. Especially, an assessment of the drug-event relationship should be available from the reporter.

Note: when the AE is ongoing, the outcome will remain blank on the Adverse Events form in the CRF.

9.1.2 Follow-up of Adverse Events

All AEs occurring during the study are to be followed up in accordance with good medical practice until resolved or judged no longer clinically significant, or if a chronic condition, until fully characterized. All follow-up results are to be reported to the Sponsor (or an authorized representative).

9.2 Serious Adverse Events (SAEs) and Serious Adverse Drug Reactions (SADRs)

Definitions of Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR)

Any untoward medical event that occur during any study phase at any dose:

- results in death,
- is life-threatening (an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe),
- requires inpatient hospitalization or prolongation of an existing hospitalization,
- results in persistent or significant disability/incapacity,
- is a congenital anomaly/birth defect,
- is considered an important medical event (an event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any

of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse as well as spontaneous or elective abortions, stillbirths and ectopic pregnancies).

9.2.1 Reporting Serious Adverse Events

Any SAE, whether or not related to the study drug, must be reported immediately (within 24 hours of the investigator's awareness of the event) by telephone or faxing the appropriate SAE forms to the numbers specified on each country specific SAE form.

9.2.2 Reporting of Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) to Regulatory Authorities and Investigators

Adverse reactions will be considered as unexpected if the nature, seriousness, severity or outcome of the reaction(s) is not consistent with the reference information. The expectedness of adverse reactions for this study is detailed for Dydrogesterone in the current Investigator brochure. For the comparative study drug, Crinone 8% intravaginal gel 90 mg, the reference safety information is the current SmPC issued in United Kingdom.

All SUSARs will be subject to expedited reporting. Additionally, post-study SUSARs that occur after the subject has completed a clinical study and are reported by the Investigator to the Sponsor (or an authorized representative) qualify for expedited reporting.

The Sponsor (or an authorized representative) is responsible for submitting reports of SUSARs to the appropriate national regulatory authorities within the required reporting period. All Investigators participating in ongoing clinical studies with the study drug will be notified by the Sponsor (or an authorized representative) of all SUSARs that require prompt submission to the IEC/IRB. The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for notifying the IECs/IRBs in writing of the SUSARs within the required reporting timelines. Copies of the notification will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

Reports of miscarriage before presence of fetal heart beats at 12 weeks' gestation (10 weeks´ pregnancy) primary endpoint efficacy; determined by transvaginal ultrasound) will be generally assessed (company assessment) with "no reasonable possibility" and as "expected" as it is awaited in the indication that less than 35% of the women will become pregnant (protocol: it is assumed that both dydrogesterone and micronized progesterone gel will have similar results with about 35% pregnancy rate at week 12).

9.2.3 Reporting of Pregnancy Adverse Event/Outcome

Pregnancy in a study subject is not considered an AE. However, all data regarding pregnancy, the evolution and the outcome, i.e., the health status of the newborn, have to be collected and documented in the CRF.

Any AE in the mother and/or fetus/newborn(s) (e.g. premature birth, low birth weight) should be checked for seriousness. Biochemical pregnancy as defined in section 8.2 is generally not considered a SAE. At least any complication of pregnancy after Visit 5 (Day 42 +/- 3 days-Week 6: new study medication packages will be dispensed if patient pregnancy is ongoing) such as elective or spontaneous abortion, missed abortion, stillbirth, or congenital anomaly is considered a SAE and must be reported to the Sponsor (or an authorized representative) within 24 hours of the investigator becoming aware of the event and followed-up as described in Section 9.2.1.

Without any complications (mother and/or child) hospital birth and prophylactic/elective caesarean section are generally not considered a reportable SAE.

10 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

Data handling will be the responsibility of the CRO. The data will be inspected for inconsistencies by performing validation checks. Any inconsistencies found will be resolved by the monitor after contacting the Investigator. When the data in the database are considered clean and the subjects allocated to subject samples in a blind data review, the database will be locked to prevent unauthorized access. Next, the database will be made available as SAS® files for statistical analysis.

All details regarding the statistical analysis and the preparation of tables, listings and figures will be described in the Statistical Analysis Plan prepared by the CRO and approved by Abbott before breaking the blind or database lock.

The statistical analysis will be performed by the CRO.

10.1 General Definitions and Conventions

Time-Related Definitions

All assessment dates will be related to the first day of study drug administration. This first day of drug administration is referred to as Day 0.

The baseline period will be defined as the period from informed consent to the first study drug administration. The baseline value for a variable is defined as the last non-missing value collected before first study drug administration.

The endpoint value for efficacy variables is defined as the last non-missing value assigned to treatment for the subject.

All variables planned to be measured at one or more time points and supposed to be time-related will be windowed.

Coding Systems

AEs and medical history Investigator terms will be assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and primary system organ class (SOC) according to the MedDRA thesaurus.

Concomitant medications will be classified according to active drug substance using the WHO drug dictionary. The generic name, the preferred name and the WHO name will be assigned.

In addition, the Anatomical Therapeutic Chemical (ATC) classes will be assigned to the drug ID. ATC codes are defined to the 4th level. For each medication, the primary ATC class will be assigned manually based on the generic name and the reason for use.

Default Summary Statistics

The default summary statistics for quantitative and ordinal variables will be the number of observations (n), mean, standard deviation (SD), median, minimum (Min) and maximum (Max) for subjects with data. Any other summary statistics will be described on an individual basis.

Default Frequency Tabulations

For qualitative variables, per category the numbers and frequencies of subjects with non-missing data (n, %) will be the default summary presentation, and if appropriate and present, the number of missing values.

For AEs, medical history and concomitant medications, however, the denominator for the percentage calculation will be the number of subjects at risk for the particular treatment arm. A subject will be considered at risk if the subject is in the safety sample and entered the respective study period.

Subject Listings

Individual subject listings will be produced for all raw data and a selection of the derived data.

10.2 Subject Samples

The main subject samples of interest are defined as follows.

The all subjects consented sample will consist of all subjects who:

- Gave their informed consent.

The all subjects allocated to treatment sample will consist of all subjects who:

- Were in the all subjects consented sample; and
- Were allocated to treatment.

The safety sample will consist of all subjects who:

- Were in the all subjects allocated to treatment sample; and
- Had at least one dose of study medication administered.

The full analysis (FA) sample will consist of all subjects who:

- Were included in the safety sample; and
- Had data for at least one post-baseline assessment of any efficacy measurement.

The per-protocol (PP) sample will be defined through blind data review and will consist of all subjects who:

- Were included in the FA sample; and
- Did not present any major protocol violation.

10.3 Efficacy

The primary efficacy parameter is the pregnancy rate defined as the presence of fetal heart beats at 12 weeks' gestation by transvaginal ultrasound. The dydrogesterone group will be compared against the intravaginal micronized progesterone gel.

The primary endpoint is the comparison of ongoing pregnancy rates between the two treatment groups. The primary efficacy analysis is using a two-sided 95% confidence interval with a non-inferiority margin of 10% for the difference in pregnancy rates in the two treatment groups. For the primary efficacy analysis, the full analysis (FA) sample will be used.

The following hypotheses are tested:

H_0: $p_{dydro} - p_{crinone} \leq -\Delta$

H_1: $p_{dydro} - p_{crinone} > -\Delta$

Δ is clinically non-relevant difference accepted as the lower bound of non-inferiority.
In order to calculate the confidence intervals, a Cochran-Mantel-Haenszel test stratified for country and age groups will be used. Two age groups will be defined, subjects older or younger than 35 years. Mantel-Haenszel type estimators will be computed for the differences of proportions using Cochran's weights. With n1 subjects in the dydrogesterone group and n2 subjects in the comparator group within a given stratum, the weights for the stratum-specific proportion differences will be proportional to n1*n2/(n1+n2), and the variance of each stratum-specific proportion difference p1−p2 will be estimated as

$$p1*(1-p1) / n1 + p2*(1-p2) / n2 .$$

The 95% confidence interval for the difference of pregnancy rates in each treatment group will be compared to Δ. In order to declare non-inferiority, the lower bound of the two-sided 95% confidence interval should exclude a difference greater than 10% in favor of the comparator. If the hypothesis of inferiority can be rejected, a second hypothesis of superiority will be tested.

The following parameters will be analyzed as secondary efficacy variables:

- chemical pregnancy rate (β-HCG test) on Day 14 after embryo transfer

- abortion and preterm birth rates
- incidence of live birth and healthy newborns.

The following parameters of the newborn will be analyzed:

- APGAR score, as well as gender, height, weight and head circumference.
- any malformations and abnormal findings of a physical examination of the newborn.

Further statistical tests may be performed on secondary variables. All efficacy and safety parameters will be summarized by standard descriptive methods.

An efficacy report will be written when all efficacy data are available and will be later included in the overall study report.

10.4 Safety

The safety sample will be used for the analysis of the safety and tolerability data. The safety and tolerability data collected during this study include vital signs, routine laboratory values and adverse events. Safety variables will be summarized by standard descriptive statistics.

For concomitant medication, the WHO thesaurus will be used to assign them to a major therapeutic class. Adverse experiences will be classified by preferred term and body system according to the MedDRA dictionary.

An AE that starts during a unique treatment or that already exists before the start of that unique treatment but worsens during the treatment, including any subsequent wash-out or post-treatment period will be considered as treatment emergent for that unique treatment.

For the definition of treatment emergent, the following unique treatments are distinguished by applicable study period:

- 30 mg dydrogesterone
- 8% micronized progesterone gel 90 mg

AEs will be reported on a per-subject basis, i.e. counting subjects rather than events. This means that if a subject suffers the same AEs repeatedly during the applicable study period, the event will be counted only once for that period. Repeated events per subject will be summarized according to the following rule: if a subject suffered the same AE more than once, the event will be assigned the worst severity, the closest relationship to the study drug and the earliest starting date. Only treatment emergent AEs will be reported. In the listings, however, all occurrences of the AEs will be presented.

For each unique treatment, treatment emergent AEs will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC. Severity and drug-event relationship of treatment emergent AEs are summarized separately.

Vitals signs, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values.

Laboratory variables, including changes from baseline will be summarized. A frequency table will be presented for markedly abnormal values. Shift tables will be presented according to the reference ranges (low, normal or high).

10.5 Other Assessments

The assignment of subjects to subject samples, the disposition of subjects with respect to premature termination, reason for premature termination, drug exposure and treatment compliance will be summarized per treatment group.

Demographics and other baseline characteristics will be summarized per treatment group.

Medical history, including coding data will be summarized per primary SOC, per HLT by primary SOC and per PT by HLT and primary SOC.

Major protocol deviations will be listed.

Concomitant medication, including coding data will be summarized per assigned treatment period for incidence per subject, for primary therapeutic subgroup (3rd level ATC code) and for generic name by therapeutic subgroup.

10.6 Subgroup Analysis

Subgroup analyses according to weight and race will be performed.

10.7 Interim Analysis

For this study, no interims analysis is planned.

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10.8 Determination of Sample Size

Several studies can be found in literature investigating the use of dydrogesterone, micronized progesterone capsules (Utrogestan®) or micronized progesterone gel treatment (Crinone®) in IVF. The following table displays the 8- or 12-week pregnancy rate for several studies.

	8-week pregnancy rate			12-week pregnancy rate		
	Dydro-gesterone	**Intravaginal micronized progesterone capsules**	**micronized progesterone gel**	**Dydro-gesterone**	**Intravaginal micronized progesteron e capsules**	**micronized progestero ne gel**
Ganesh 2011[3]				29% (121/422)	23% (104/459)	29% (138/482)
Patki 2007[10]	41% (150/366)	30% (91/309)				
Kleinstein 2005[11]					25% (55/218)	22% (47/121)
Tomic 2011[12]			33% (62/185)			
Simunic 2007[13]		30% (42/136)	33% (43/130)			
Ludwig 2002[14]					17% (9/53)	25% (18/73)
Baruffi 2003[15]		28% (29/103)				
Pouly 1996[16]		25% (36/144)	29% (40/139)			

The largest study from Ganesh et al. showed comparable results for micronized progesterone gel and dydrogesterone and only a small, non-significant difference in rates between dydrogesterone and micronized progesterone capsules.[3] Both the study from Kleinstein[11] and Ludwig[14] conclude that both micronized progesterone gel and micronized progesterone capsules will give similar results. Therefore, it is assumed that dydrogesterone and micronized progesterone gel will have similar results with about 35% pregnancy rate at week 12.

A non-inferiority margin of 10% was chosen based on data from the previously approved Lutinus®/Endometrin® drug.[17]

Assuming a 35% pregnancy rate for the dydrogesterone and the micronized progesterone gel group, a sample size of about 479 subjects per group would provide 90% power to reject the null hypothesis of H_0: $p_{dydro} - p_{crinone} \leq -0.1$ in favor of the alternative: H_1: $p_{dydro} - p_{crinone} > -0.1$ with a one-sided significance level of 2.5%.

Assuming a dropout rate of 10%, a total sample size of 533 subjects per treatment group would be required, resulting in a total sample size of 1066 subjects in order to show non inferiority in the primary efficacy parameter.

11 INVESTIGATOR OBLIGATIONS

The Investigator agrees to conduct the clinical study in compliance with this protocol after being approved by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol to confirm this agreement.

11.1 Essential Study Documents

The Investigator is responsible for providing and maintaining essential study documents. Essential study documents are those documents that individually and collectively permit the evaluation of the conduct of the study and the quality of the data produced. These documents serve to demonstrate the compliance of the Investigator and the Sponsor (or an authorized representative) with the standards of GCPs and with all applicable national regulatory requirements.

Essential study documents will include regulatory documents as well as source documents which are original documents, data and records of clinical findings, observations and other activities in a clinical study necessary for the reconstruction and evaluation of the study. Source documents will include hospital records, clinical and office charts, laboratory notes, memoranda, subject diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate copies, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files and records kept at the pharmacy, at the laboratories and at medical/technical departments involved in the clinical study.

The Investigator agrees to allow direct access to all essential clinical study documents for the purpose of monitoring and/or auditing by the Sponsor (or an authorized representative) and inspection by the appropriate national and foreign regulatory authorities.

11.2 Case Report Form (CRF) Completion

Data reflecting the subject´s participation with the study drug under investigation will be reported to the Sponsor (or an authorized representative). The data will be recorded on the designated CRFs (paper or other media) provided or approved by the Sponsor. The CRF is essentially considered a data entry form and will not constitute the original (or source) medical records unless otherwise specified.

The Investigator will be required to submit a completed CRF for each subject who receives study drug, regardless of duration.

For each subject that has signed the informed consent but does not qualify for allocation to treatment, i.e. Screen Failure, only the following information is required to be collected:

- Informed Consent information
- Reason for Termination information

- Screen Fail Identifier question -YES/NO
- Adverse Event information in case of a SAE reported to GPRM.

Electronic Data Capture (EDC) will be used for this trial, meaning that all CRF data will be entered in electronic forms at the investigational site. Data collection will be completed by authorized study site personnel designated by the Investigator. Appropriate training and security measures will be completed with the Investigator and all authorized study site personnel prior to the study being initiated and any data being entered into the system for any study subjects.

All data must be entered in English. The eCRFs should always reflect the latest observations on the subjects participating in the trial. Therefore, the eCRFs are to be completed as soon as possible during or after the subject´s visit. To avoid inter observer variability; every effort should be made to ensure that the same individual who made the initial baseline determinations completes all efficacy and safety evaluations. The Investigator must verify that all data entries in the eCRFs are accurate and correct. If some assessments are not done, or if certain information is not available or not applicable or unknown, the Investigator should indicate this in the eCRF. The Investigator will be required to electronically sign off on the clinical data.

The monitor will review the eCRFs and evaluate them for completeness and consistency. The eCRF will be compared with the source documents to ensure that there are no discrepancies between critical data. All entries, corrections and alterations are to be made by the responsible Investigator or his/her designee. The monitor cannot enter data in the eCRFs. Once clinical data of the eCRF have been submitted to the central server, corrections to the data fields will be audit trailed, meaning that the reason for change, the name of the person who performed the change, together with time and date will be logged. Roles and rights of the site personnel responsible for entering the clinical data into the eCRF will be determined in advance. If additional corrections are needed, the responsible monitor or Data Manager will raise a query in the EDC application. The appropriate investigational staff will answer queries sent to the Investigator. This will be audit trailed by the EDC application meaning that the name of investigational staff, time and date stamp are captured.

The eCRF is essentially considered a data entry form and should not constitute the original (or source) medical records unless otherwise specified. Source documents are all documents used by the Investigator or hospital that relate to the subject´s medical history, that verify the existence of the subject, the inclusion and exclusion criteria and all records covering the subject´s participation in the study. They include laboratory notes, ECG results, memoranda, pharmacy dispensing records, subject files, etc.

The Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. The Investigator must submit a completed eCRF for each subject who receives study medication, regardless of duration. All supportive documentation submitted with the eCRF, such as laboratory or

hospital records, should be clearly identified with the study and subject number. Any personal information, including subject name, should be removed or rendered illegible to preserve individual confidentiality.

Electronic case report form records will be automatically appended with the identification of the creator, by means of their unique UserID. Specified records will be electronically signed by the Investigator to document his/her review of the data and acknowledgement that the data are accurate. This will be facilitated by means of the Investigator's unique UserID and password; date and time stamps will be added automatically at time of electronic signature. If an entry on an eCRF requires change, the correction should be made in accordance with the relevant software procedures. All changes will be fully recorded in a protected audit trail, and a reason for the change will be required.

11.3 Essential Records Retention

The Investigator should maintain the essential clinical study documents (including CRFs, source documents, clinical drug disposition records, signed subject informed consent forms, AE reports and other regulatory documents) as required by the applicable national regulatory requirements. The Investigator is to take adequate measures to prevent accidental or premature destruction of these documents. In the event of accidental destruction, the Investigator should notify the Sponsor (or an authorized representative) immediately.

Essential clinical study documents will be retained at least two (2) years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region OR at least two (2) years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents shall be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor (or an authorized representative).

The Investigator is required to notify the Sponsor (or an authorized representative) prior to changing the location or status of any essential clinical study documents. The Sponsor (or an authorized representative) will be responsible for informing the Investigator as to when these documents no longer need to be retained.

11.4 Investigator Agreement

The Investigator is responsible for assuring the proper implementation and conduct of the clinical study including those study-related duties delegated to other appropriately qualified individuals. The Investigator and his/her staff will cooperate with the Sponsor (or an authorized representative) during monitoring and auditing visits to assist with the review of the study data and resolve any discrepancies.

The Investigator will demonstrate due diligence in recruitment and screening of potential study subjects. The enrollment rate should be sufficient to complete the study as agreed with

the Sponsor (or an authorized representative). The Sponsor (or an authorized representative) is to be notified of any projected delays, which may impact the completion of the study.

The Sponsor retains the right to terminate the clinical study at any time for any reason. In such an event, instructions on the requirements for the discontinuation of subjects will be provided by the Sponsor (or an authorized representative).

12 SPONSOR OBLIGATIONS

12.1 Protocol Amendments

Only the Sponsor (or an authorized representative) will make modifications to the clinical study protocol, which will be documented in a written amendment that describes all changes that will be implemented. Protocol amendments will be categorized as either substantial or non-substantial.

Protocol amendments will be considered substantial when the changes have significant impact on:

- The safety of physical or mental integrity of the subjects
- The scientific value of the study
- The conduct or management of the study
- The quality or safety of any investigational medicinal product or control used in the study

Protocol amendments will be considered non-substantial when the changes affect only administrative issues with the conduct of the study, i.e., changes in telephone numbers or addresses.

The Sponsor (or an authorized representative) will be responsible for notifying the appropriate national regulatory authorities in writing of any amendments to the protocol prior to the changes being implemented except in those cases where the changes are necessary to eliminate an immediate hazard to the clinical study subjects.

Substantial amendments will require written approval by the IEC/IRB prior to being implemented by the Investigator at the study site except under those circumstances described previously. Non-substantial amendments will not require approval by the IEC/IRB unless requested by the IEC/IRB.

12.2 Study Monitoring

The study will be monitored by authorized representatives of the Sponsor throughout its duration by means of personal visits to the Investigator's facilities and through other communications (e.g., telephone calls, written correspondence). Monitoring visits will be scheduled at mutually agreeable times periodically throughout the study and at frequency deemed appropriate for the study.

These visits will be conducted to evaluate the progress of the study, ensure the rights and well-being of the subjects are protected, check that the reported clinical study data are accurate, complete and verifiable from source documents, and the conduct of the study is in compliance with the approved protocol and amendments, GCPs and applicable national regulatory requirements. A monitoring visit will include a review of the essential clinical

study documents (regulatory documents, CRFs, source documents, drug disposition records, subject informed consent forms, etc.) as well as discussion on the conduct of the study with the Investigator and staff. The Investigator and staff should be available during these visits to facilitate the review of the clinical study records and resolve/document any discrepancies found during the visit.

12.3 Quality Assurance Audits

The Sponsor's (or an authorized representative's) Quality Assurance department may conduct on-site audits of all aspects of the clinical study either during the study or after the study has been completed.

The clinical study may also be subject to inspection by regulatory authorities (national or foreign) as well as the IECs/IRBs to ascertain that the study is being or has been conducted in accordance with protocol requirements, GCPs, as well as the applicable regulatory requirements.

13 PUBLICATION POLICY

The data generated by this study are confidential information of the Sponsor. The Sponsor will publicly disclose the results of all applicable clinical trials following legal and regulatory requirements. The publication policy with respect to the Investigator and study center will be set forth in the Clinical Trial Agreement.

14 INSURANCE

The Sponsor has taken out a liability insurance, which covers this study as required by local law and/or national regulations and/or ICH guidelines whichever is applicable.

15 REFERENCES

1. Mouzon J; Lancaster P, Nygren K et al: World collaborative Report on Assisted Reproductive Technology, 2002. Hum Reprod 2009: 24 (9) 2310-2320.

2. Jones GE. Some newer aspects of management of infertility. J Am Med Assoc 1949;141(16):1123-29, illust.

3. Ganesh A. et al: Comparison of oral dydrogesterone with progesterone gel and micronized progesterone for luteal support in 1,373 women undergoing in vitro fertilization: a randomized clinical study. Fertility and Sterility, 2011, May; 95(6): 1961-5

4. Soliman S; Daya S, Collins J, Hughes, EG. The role of luteal phase support in the infertility treatment: a meta-analysis of the randomized trails. Hum Reprod 2002;17:2287-99

5. Sauer MV. Use of progesterone in assisted reproduction. J Reprod Med 1999;44 Suppl 2:197-202

6. Gellé P, Schaeffer Ph. Apropos of the use of dydrogesterone in gynecology and obstetrics; clinical experience [French]. Bull Fed Soc Gynecol Obstet Lang Fr. 1965;17(4):369-70.

7. Taubert HD. Jürgensen O, Becker H. Clinical observations on luteal phase inadequacy. Bull Schweiz Akad Med Wiss 1969;25(4-6):586-94

8. Wesselius-DeCasparis A, Duphaston. Revised summary of pharmacological properties and clinical results, 1971, Abbott report

9. Saure A, Teräväinen T, Karjalainen O. The effect of synthetic gestagens on progesterone formation in vitro in human placenta of early pregnancy. J Reprod Fertil. 1977;51(2):369-73.

10. Patki A, et al: Modulating fertility outcome in assisted reproductive technologies by the use of dydrogesterone. Gynecological Endocrinology, October 2007; 23 (S1): 68-72

11. Kleinstein et al: Efficacy and tolerability of vaginal progesterone capsules compared to progesterone gel for luteal phase support during assisted reproduction, 2005. Fertility and Sterility, 83 (6) 1641-1649

12. Tomic V et al: Oral micronized progesterone combined with vaginal progesterone gel for luteal support, 2011. Gynecological Endocrinology 27(12): 1010-1013

13. Simunic V et al: Comparative study of the efficacy and tolerability of two vaginal progesterone formulations, Crinone 8% gel and Utrogestan capsules, used for luteal support 2007 Fertility and Sterility, 87 (1) 83-87

14. Ludwig M et al: Luteal support using either Crinone 8% or Utrogest: results of a prospective, randomized study, 2002. European Journal of Obstretics & Gynecology and Reproductive Biology 103: 48-52

15. Baruffi R et al: Effects of Vaginal Progesterone Administration Starting on the Day of Oocyte Retrieval on Pregnancy Rates, 2003. Journal of Assisted Reproduction and Genetics 20 (12), 517-520

16. Pouly JL et al: Luteal support after in-vitro fertilization: Crinone 8%, a sustained release vaginal progesterone gel, versus Utrogestan, anoral micronized progesterone, 1996. Human Reproduction 11 (10): 2085-2089.

17. Center for drug evaluation and research, medical review 22-057.

16 APPENDICES

16.1 Appendix – Participating Countries' National Insurance Requirements

Not part of the protocol

16.2 Appendix – Coordinating Investigator Signature of Clinical Study Report

The following Investigator is regarded to be the coordinating Investigator who should sign the Investigator signature page of the clinical study report:

<insert name or define the process of designating the signatory coordinating Investigator>.