ABBOTT

Statistical Analysis Plan

Module 1
(Non-standard data and analyses)

Version 3.0, Date 19Sep2017

Study: DYDR3004 (formerly M13-625)

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**)

[redacted]

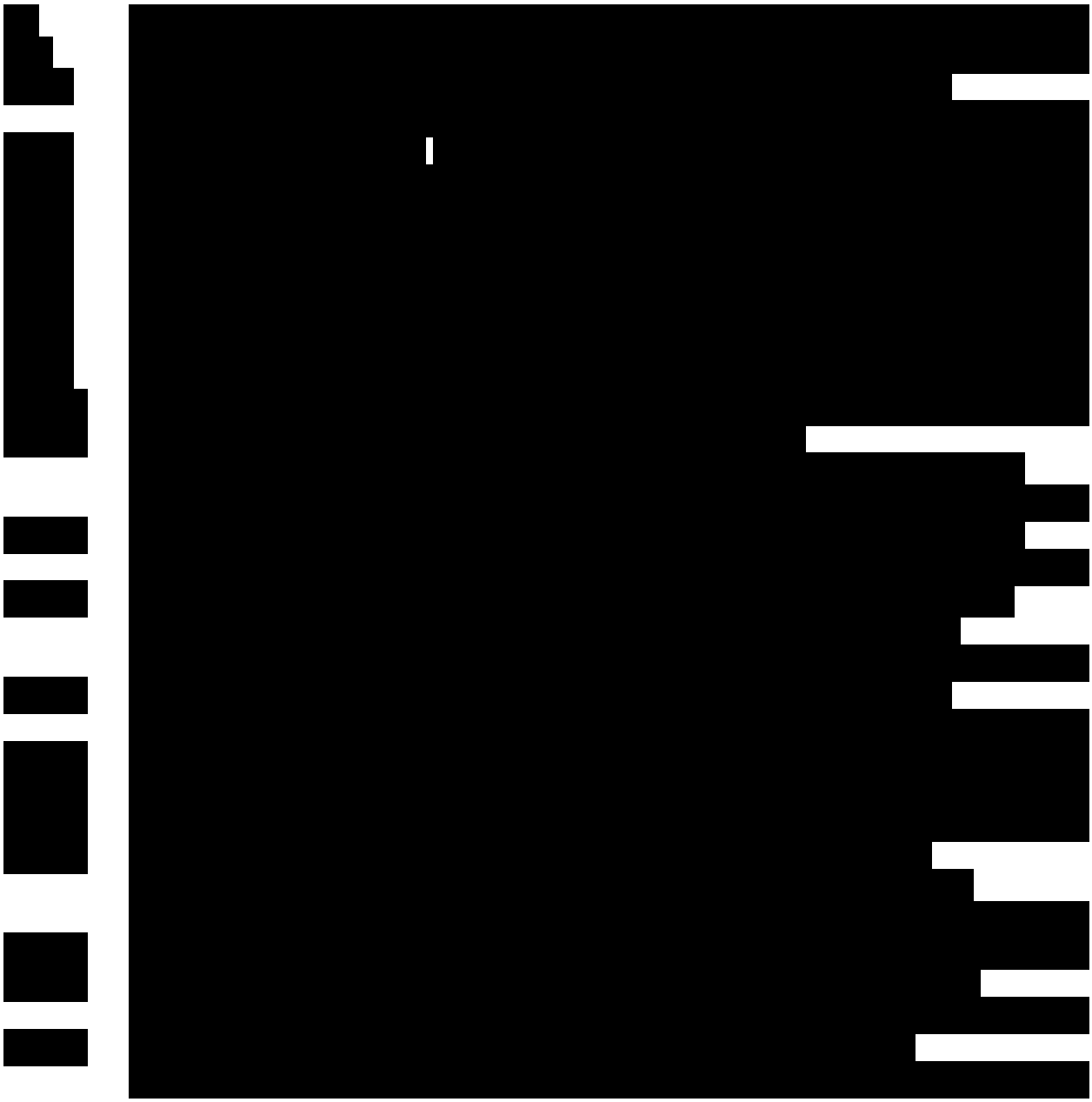
[redacted]

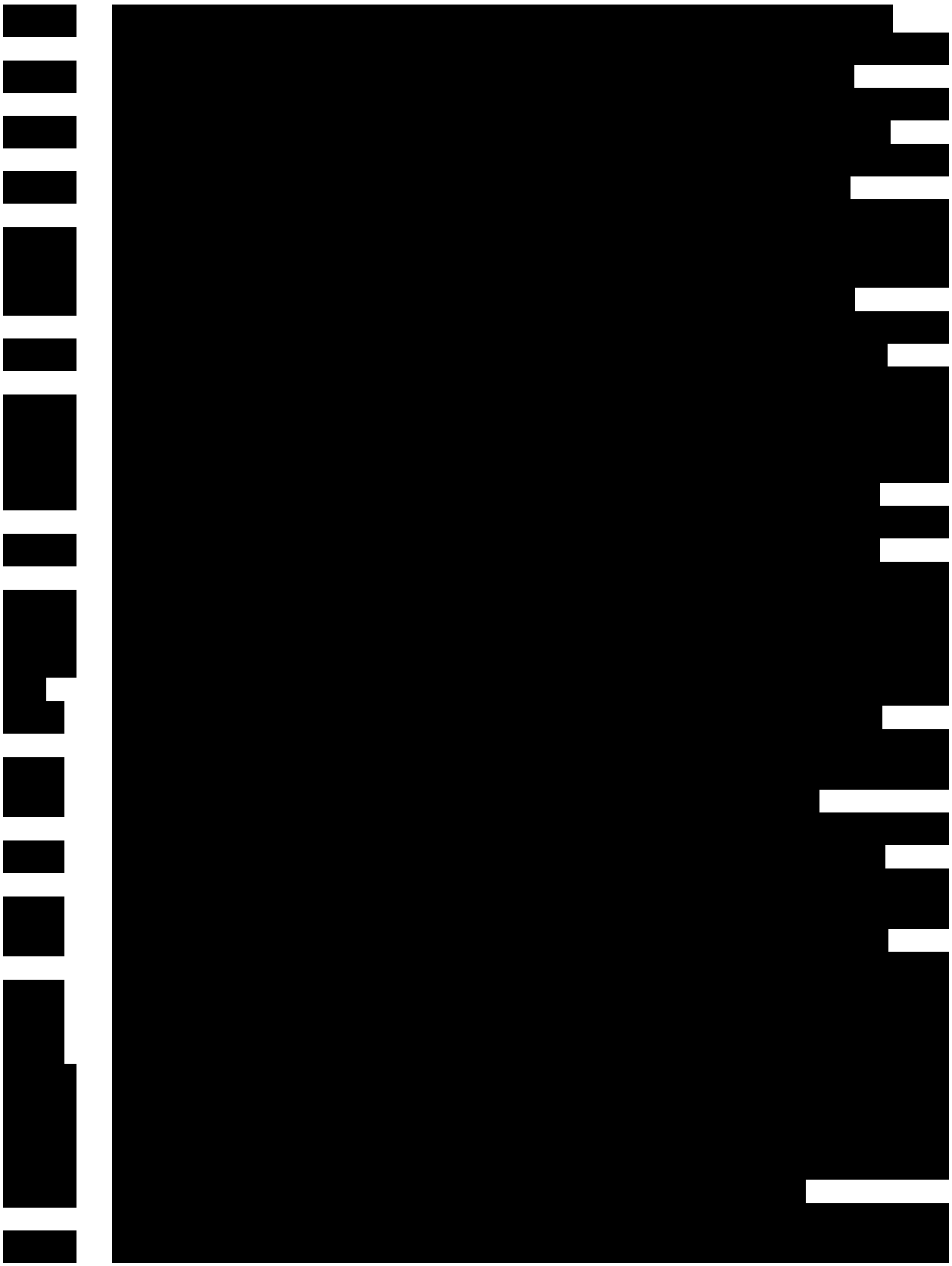
Statistical Analysis Plan is based on the Abbott template for clinical studies. Template Version 3.0

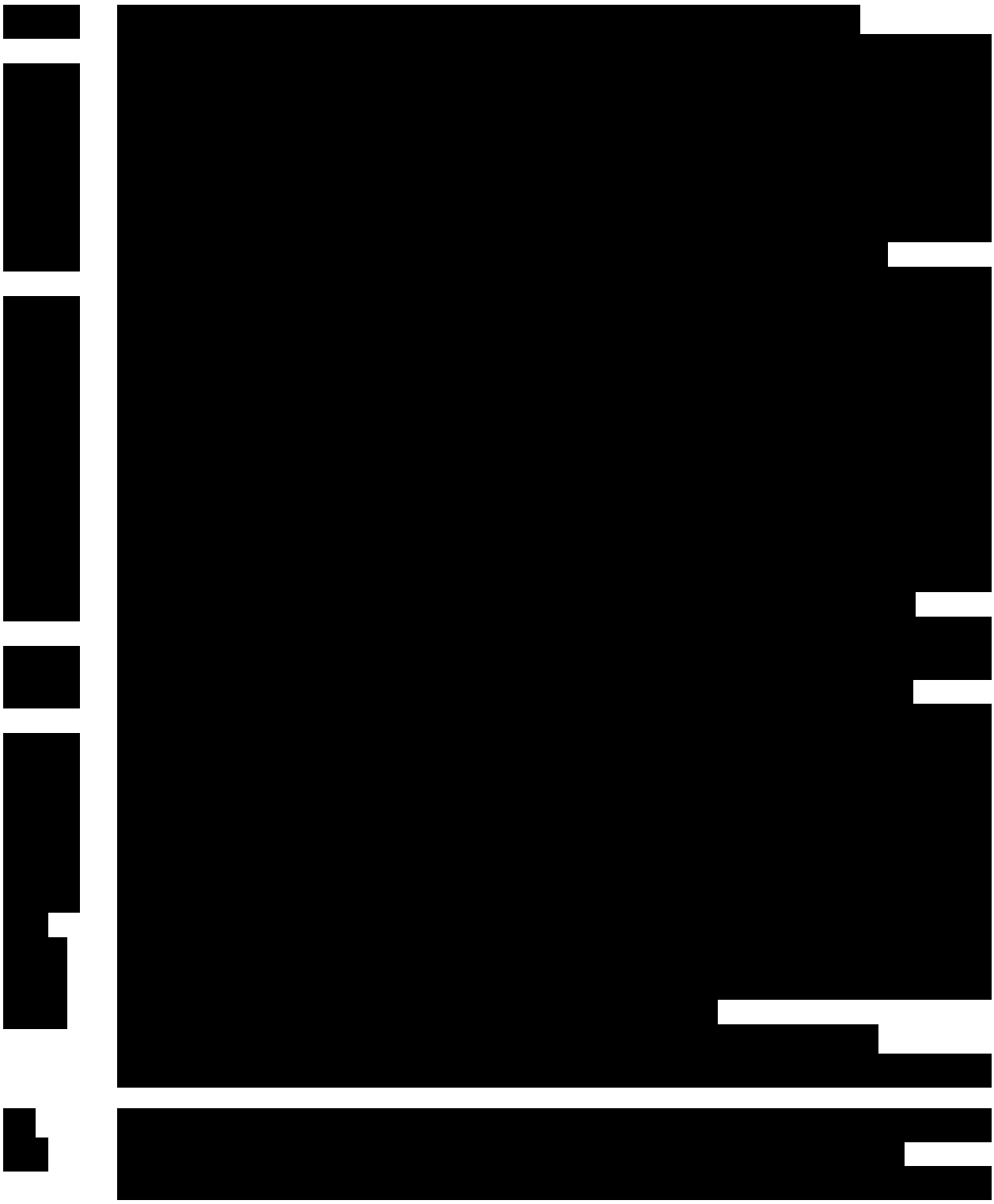
[redacted]

[redacted]

TABLE OF CONTENTS







1. ABBREVIATIONS

1.1 Standard Abbreviations

AE	adverse event
ALAT	alanine aminotransferase
ASAT	aspartate aminotransferase
APGAR	Appearance, Pulse, Grimace, Activity, Respiration
BMI	body mass index
bpm	beats per minute
CRF	case report form
CRO	contract research organization
DBP	diastolic blood pressure
ET	embryo transfer
eCRF	Electronic case retrieval form
FA	Full Analysis
HCG	human chorionic gonadotropin
HLGT	High Level Group Term
HLT	High Level Term
ICH	International Conference on Harmonization
IVF	in vitro fertilization
IWRS/IRT	interactive web response system
LDA	day number of the last day of drug administration
LH	luteinizing hormone
LLT	Lowest Level Term
max	maximum
MedDRA	Medical Dictionary for Regulatory Activities
min	minimum
N,n	number of observations
NA	not applicable
PP	Per Protocol
PRL	Prolactin
PT	Preferred Term
RBC	red blood cells
SAE	serious adverse event
SAP	statistical analysis plan
SBP	systolic blood pressure
SD	standard deviation
SOC	System Organ Class
SOP	standard operating procedure
T	Testosterone
TEAE	treatment-emergent adverse event
TESAE	treatment-emergent serious adverse event
tid	three times daily
TLF/T,L,F	tables, listings and figures
TSH	thyroid-stimulating hormone
WBC	white blood cells

WHO-DD(E)	World Health Organization – Drug Dictionary (enhanced)

3. SUMMARY OF THE PROTOCOL

3.1 Overall Study Plan

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:

- Visit 1 (Day -40 to -1 (according to amendment 2)/or Day -14 to -1 if the study is conducted according to amendment 1[day of downregulation/ovarian follicle stimulation]): Screening and Enrollment

  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. For patients conducting the study according to amendment 3 hormone testing should also be performed for subjects where FSH, estradiol ($E_{2)}$, LH (luteinizing hormone), PRL (Prolactin), T (Testosterone) and TSH (thyroid-stimulating hormone) are not available prior screening.

- Treatment period (Day 1 to Week 10):

  Luteal support starts on Day 1 (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) (Duphaston)
  or
  Group II
  Crinone 8%, intravaginal progesterone gel 90 mg, once daily

- Visit 3 (Day 3 - 6): Day of embryo transfer

  This interventional treatment is following the clinic specific in vitro fertilization (IVF) protocol.

- Visit 4 (Day 17 – 20 (according to amendment 2)/or Day 15 +/- 3 days if the study is conducted according to amendment 1): Day to confirm biochemical pregnancy.

  On day 15 after embryo transfer, subjects will have a routine pregnancy test (serum β-hCG) to confirm subject's pregnancy. If the test is positive, luteal support is continued up to week 10 of the 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.

- Visit 5 (Day 43 +/- 3 days – Week 6): Day to confirm ongoing pregnancy

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, patient 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, whatever 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 patient will return the remaining study medication.

- Visit 6 (Day 71 +/- 3 days – Week 10 [12 weeks of gestation]): End of treatment

  A transvaginal ultrasound examination will be performed to establish an ongoing pregnancy defined as the presence of fetal heart beats. Data on vital signs, routine laboratory values, TEAEs, and concomitant medication will be recorded. Patients return their study medication.

- Visit 7 and 8 (Day 101 +/- 3 days and Day 157 +/- 3 days): Post treatment surveillance calls

  Subjects will be followed during the pregnancy by routine pregnancy supervision program until the date of delivery. In addition 2 telephone calls (on Day 101 +/- 3 days and on Day 157 +/- 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.

- Visit 9: After successful delivery

  The time of delivery (gestational age) and the following parameters of the newborn(s) will be obtained: gender, APGAR Score, weight, height, head circumference, abnormal findings of physical examination.

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

3.2 Study Flowchart

The flowchart of the study can be found in Appendix 9.1.

3.3 Study Objectives

Primary Efficacy Objective(s):

The primary objective is to demonstrate non-inferiority of the oral dydrogesterone treatment versus the comparator micronized progesterone vaginal gel. The primary efficacy parameter is the pregnancy rate defined as the presence of fetal heart beats at 12 weeks gestation (10 weeks pregnancy) determined by transvaginal ultrasound.

Secondary Efficacy Objective(s):

The secondary objectives and parameters are a positive pregnancy test on Day 15 after embryo transfer and the incidence of live births and healthy newborns.

Safety Objective(s):

The safety objective is to obtain safety and tolerability data by means of documentation of treatment emergent adverse events (TEAEs) 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 (gestational age) 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.

3.4 Sample Size and Randomization

Assuming a 35% pregnancy rate for the dydrogesterone and the micronized progesterone gel group, a sample size of about 479 patients per group will provide 90% power to reject the null hypothesis of H_0: $p_{dupha} - p_{crinone} \leq -0.1$ in favor of the alternative: H_1: $p_{dupha} - p_{crinone} > -0.1$ 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 will be required, resulting in a total sample size of 1066 subjects in order to show non inferiority in the primary efficacy parameter.

Subjects will be assigned to a treatment group using a centralized electronic system (interactive web response system; IWRS/IRT). The IWRS/IRT assigns a 5-digit randomization number to each subject. Subjects will be allocated in a 1:1 ratio of both treatments in blocks of 4 subject numbers per block. Randomization will be stratified by age group (< 35 years, >= 35 years) and country.

4. STATISTICAL ANALYSIS

4.1 Subject samples

There will be six subject samples.

The Re-Randomized subject sample will consist of all subjects who:

- gave their informed consent
- have been randomized for this study before and are re-randomized
- have been allocated to treatment

The All Subjects Consented subject sample will consist of all subjects who:

- gave their informed consent.
- are not included in the Re-Randomized subject sample. All screen failures are kept regardless if they were re-screened or re-randomized.

The All Subjects Allocated to Treatment subject sample will consist of all subjects who:

- are in the All Subjects Consented sample
- were allocated to treatment.

The Safety subject sample will consist of all subjects who:

- are in the All Subjects Allocated to Treatment subject sample
- received at least one dose of study medication.

The Full Analysis (FA) subject sample will consist of all subjects who:

- are included in the Safety subject sample
- had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 (Day 3 to 6) due to study drug related issues, which means that an AE with causality "possible" or "probable" leading to study termination was reported. (Those subjects that discontinued prematurely due to reasons independent of study drug do not contribute to the treatment effect assessment because they did not get an embryo transfer and, therefore, could not get pregnant in their cycle, and the reason for that had nothing to do with any sort of treatment effect).

The Per Protocol (PP) subject sample will be defined through blind data review and will consist of all subjects who:

- are included in the Full Analysis sample
- did not present any major protocol deviations
- had a successful embryo transfer at Visit 3 (Day 3 to 6)

4.2 Efficacy analysis

The FA and the PP subject samples will be used for the analysis of the efficacy data. The primary efficacy analysis is to be performed on the PP subject sample (in line with the objective of non-inferiority) and repeated for the FA subject sample. Further statistical tests will be performed, also on secondary variables. All efficacy parameters will be summarized by standard descriptive methods.

The following subgroups are defined for key efficacy analyses:

Age Group:

- < 35 Years
- >= 35 Years

Age (Years) is calculated relative to Screening.

Country:

- Australia
- Belgium
- China
- Germany
- Hong Kong
- India
- Russia
- Singapore
- Thailand
- Ukraine

Baseline BMI (kg/m2):

- < 24
- >= 24 to < 28
- >= 28

Number of embryos transferred:

- One
- Two
- Three

Race:

- Asian
- White

- Other (American Indian or Alaskan Native, Black, of African heritage or African American, Native Hawaiian or Other Pacific Islander)

Weight at baseline:

- < 55 kg
- 55 - < 65 kg
- 65 - < 75 kg
- >= 75 kg

4.2.1 Calculation of Pregnancy Rates

- Denominator

FA subject sample: The rates for the efficacy variables are calculated relative to the number of subjects who:

- Received at least one administration of study drug.
- Had a successful embryo transfer performed at Visit 3 (Day 3 to 6) or prematurely discontinued prior to embryo transfer at Visit 3 (Day 3 to 6) due to study drug related issues.

PP subject sample: The rates for the efficacy variables are calculated relative to the number of subjects who:

- Received at least one administration of study drug.
- Had a successful embryo transfer performed at Visit 3 (Day 3 to 6).
- Did not present any major protocol deviations

- Numerator

A detailed list of subjects who prematurely discontinued, with reasons for discontinuation will be used in the BDR meeting in order to decide which subjects can be included as successes or failures (i.e. not pregnant at Visit 6 (Week 10)).

The numerator for the pregnancy rates will consist of the following subjects counted as successes or failures:

	After a pregnancy test was performed	
Pregnancy Test	**Subjects counted as success if:**	**Subjects counted as failures if:**
β-HCG (Visit 4)	Pregnant at Visit 4 (Day 17 to 20) (if the serum ß-HCG test is positive the subject will be counted as pregnant) Only for PP: No additional Progesterone was given before visit 4.	Not pregnant at Visit 4 (Day 17 to 20) or ß-HCG test assessments or results is missing (due to test being not performed or subject discontinued prior to visit 4) Only for PP: Additional Progesterone was given before visit 4.
Ultrasound (Visit 6)	Pregnant at Visit 6 (Week 10) (gestational sac with viable fetal heart beats) Only for PP: No additional Progesterone was given before visit 6.	Not pregnant at Visit 6 (Week 10) Only for PP: Additional Progesterone was given before visit 6.
	Pregnancy Status at Visit 5 (Week 6) carried forward if: - Data for Visit 6 (Week 10) not available -	
	Pregnant at Visit 5 (Week 6) and no discontinuation data as in right column present	- Not pregnant at Visit 5 (Week 6) - Subject prematurely discontinued after Visit 4 (Day 17 to 20) or Visit 5 (Week 6) due to an AE Subject prematurely discontinued after Visit 4 (Day 17 to 20) or Visit 5 (Week 6) with reason of lack of efficacy Only for PP: Additional Progesterone was given before visit 5
	Pregnancy Status at Visit 4 (Day 17 to 20) carried forward if: - Data for Visit 5 (Week 6) and Visit 6 (Week 10) not available -	
	Pregnant at Visit 4 (Day 17 to 20) and no discontinuation data as in right column present	- Not pregnant at Visit 4 (Day 17 to 20) - Subject prematurely discontinued after Visit 4 (Day 17 to 20) due

		to an AE - Subject prematurely discontinued after Visit 4 (Day 17 to 20) with reason of lack of efficacy or pregnancy not confirmed at Visit 4 (Day 17 to 20) Only for PP: Additional Progesterone was given before visit 4.

- Subject who prematurely discontinued after Visit 4 (Day 17 to 20) or Visit 5 (Week 6) with reasons, "withdrawal of consent, administrative, lost to follow up and protocol violation" will be discussed on a case by case basis during the BDR meeting.
- For each subject, the reason for premature discontinuation, the time point and any further information will be discussed during the BDR meeting to decide whether the subjects can be counted as a failure or success in the primary analysis.
- The results of the final BDR indicated no such cases to decide on.

4.2.2 Primary Efficacy Analysis

The primary efficacy parameter is the comparison of ongoing pregnancy rates, defined as the presence of fetal heart beats at 12 weeks gestation by transvaginal ultrasound. 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.

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

The following hypotheses are tested at a one-sided significance level of 2,5%:

- H_0: $p_{dupha} - p_{crinone} \leq -\Delta$
- H_1: $p_{dupha} - p_{crinone} > -\Delta$

with p_{dupha} and $p_{crinone}$ as the probabilities of pregnancy under Duphaston treatment and Crinone, respectively, and Δ=10% as the 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 (randomization was stratified by country and age group). If Mantel Haenszel estimators cannot be computed, since not both treatment groups are present for an age group in a specific country, the test will only be stratified by age group. The two age groups were defined as patients either older or younger than 35 years. Mantel-Haenszel estimators $\hat{d}_{MH}$ for the differences of proportions using Cochran's weights are defined as:

$$\hat{d}_{MH} = \left(\sum_h \hat{d}_h w_h\right) / \left(\sum_h w_h\right)$$

with $\hat{d}_h = \hat{p}_{dupha,h} - \hat{p}_{crinone,h}$ the risk difference in stratum h, $w_h = n_{dupha,h} * n_{crinone,h}/n_h$ the weight in stratum h and n_h the number of patients in stratum h. The variance of each stratum specific proportion difference $p_{dupha} - p_{crinone}$ will be estimated as $\hat{p}_{dupha}(1-\hat{p}_{dupha})/n_{dupha} + \hat{p}_{crinone}(1-\hat{p}_{crinone})/n_{crinone}$.

Assuming that $\hat{d}_{MH}$ is normally distributed by approximation, $\left(\hat{d}_{MH} \pm (z_{1-\alpha/2} * \sigma(\hat{d}_{MH})/\sqrt{n})\right)$ is the 95% confidence interval for the difference of pregnancy rates in each treatment group (with alpha=5%), which will be compared to Δ. In order to declare non-inferiority, the lower bound of the two-sided 95% confidence interval, actually the 97.5% lower confidence bound, should exclude a difference greater than 10% in favor of Duphaston. When that is the case H_0 can be rejected. Since no multiple testing is performed, the type I error alpha does not have to be adjusted.
If the null hypothesis of inferiority can be rejected, a second hypothesis of superiority will be tested with the following hypothesis:

- H_0: $p_{dupha} - p_{crinone} \leq 0$
- H_1: $p_{dupha} - p_{crinone} > 0$

To show superiority the lower bound of the 95% confidence interval calculated above should be greater than 0%, for H_0 to be rejected. If non-inferiority can not be established, no further test for superiority will be conducted.

The p-value will be computed for the non-inferiority and if applicable for the superiority test.

The p-value for the hypothesis of non-inferiority is defined as $P(\hat{d}_{MH} \geq d)$, with d being the realization of $\hat{d}_{MH}$ given the specific data, under the assumption that H_0 is correct. Since the normal distribution is invariant under linear transformations, $\hat{d}_{MH}/\hat{\sigma}(\hat{d}_{MH})$ is standard normally distributed. Therefore the p-value can be written as

$$1 - \phi\left(\frac{\hat{d}_{MH} + \Delta}{\hat{\sigma}(\hat{d}_{MH})/\sqrt{n}}\right).$$

Point estimate and 95% confidence intervals for each treatment group separately will be displayed for each rate separately. These confidence intervals are not stratified.

Subgroup analyses:

The primary analysis will be repeated for each of the subgroups defined.

4.2.3 Secondary efficacy analysis

The secondary efficacy parameters analyzed are:

- chemical pregnancy rate (β-HCG test) on Day 15 after embryo transfer
- pregnancy rate at visit 5
- biochemical pregnancy rate
- abortion and preterm birth rates
- incidence of live birth and healthy newborns
- gestational age

Gestational age is derived as (date of birth - date of embryo transfer +1day) / 7 + 2 weeks. It will be presented in weeks, rounded to two decimal points.

For the calculation of abortion, preterm birth and biochemical rates derived variables will be used instead of qualitative CRF data .A pregnancy outcome is defined as an abortion if the pregnancy is ongoing at visit 5 and gestational age is <= 22 weeks.

Preterm birth is defined as a pregnancy outcome with gestational age greater 22 weeks and less than 37 weeks. Pregnancy outcomes with gestational age >= 37 weeks will be counted as birth. The pregnancy outcome is defined as biochemical pregnancy for all subjects who have an AE "biochemical pregnancy".

The rates for the efficacy variables are calculated relative to the number of subjects who had an embryo transfer done at Visit 3 (Day 3 to 6).

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.

For the pregnancy rate as well as the rates of live births and healthy newborns p-values will be computed using the same method as for the primary analysis. For the abortion, preterm birth and biochemical pregnancy rates p-values will be calculated with the same methods for the following hypothesis of non-inferiority:

- H_0: $p_{crinone} - p_{dupha} \leq -\Delta$
- H_1: $p_{crinone} - p_{dupha} > -\Delta$

The point estimate and 95 % confidence interval (using the stratified CMH approach) for the difference in treatment group for each of the following variables will be presented graphically using forest plots:

- Pregnancy rate (Ultrasound) at visit 6
- Pregnancy rate (ß-HCG) at visit 4
- Pregnancy rate at visit 5
- Biochemical pregnancy rate
- Abortion rate
- Preterm birth rate

- Live birth rate (sum of pre-term births and births)
- Healthy newborn rate

Subjects who give birth to more than one healthy newborn will be counted only once.

For each treatment group all efficacy parameters will be summarized by standard descriptive methods.

4.2.4 Other efficacy analysis

For the Chinese sub-report the efficacy analysis will be performed on specifically defined patients. Outputs will be produced for all patients from Chinese sites, Asian sites (which include China, Hong-Kong, India, Singapore and Thailand) and for all patients of Asian race respectively. The analysis is the same as described for the primary and secondary variables.

4.3 Safety analysis

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

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. This first day of drug administration is referred to as Day 1. All assessment dates will be related to the first day of study drug administration.

A gap period of infinity will be defined for all safety variables.

Adverse Events:

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 (Duphaston)
- 8% micronized progesterone gel 90 mg (Crinone)

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.

Adverse Events are recorded for the mother and the foetus/newborn and will be analyzed separately.

Adverse Events of special interest include: Preterm Birth, Abortion/Miscarriage, Signs and Symptoms of Threatened Abortion.

Adverse Events of Special Interest by Visit Interval include but are not limited to: Abortion, Miscarriage and Malformations.

Adverse Events are coded using Medical Dictionary for Regulatory Activities (MedDRA) version 18.1.

For the Chinese sub-report some tables and listings will also be produced for all patients from Chinese sites, Asian sites and for all patients of Asian race respectively.

Vital Signs:

Vitals signs, including changes from baseline will be summarized for baseline, visit 6 and end of treatment. End of treatment is the last assessment (scheduled or unscheduled) and includes data from patients who had the vital signs assessment at their early discontinuation visit. A frequency table will be presented for markedly abnormal values.

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.

Routine Laboratory:

Laboratory variables, including changes from baseline will be summarized for baseline, visit 6 and end of treatment. End of treatment is the last assessment (scheduled or unscheduled) and includes data from patients who had the laboratory assessment at their early discontinuation visit. A frequency table will be presented for markedly abnormal values. Shift tables will be presented according to the reference ranges (low, normal or high).

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 and potassium.

Urine analysis: Urine sample collection for routine urine analysis of pH, nitrite, specific gravity, blood, protein and glucose will be performed, as well as for pregnancy test (strip test).

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

Physical Examination:

A physical examination should be performed and any relevant findings are to be recorded on the Medical History form in the case report form (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.

4.4 Interim Analysis

No interim analysis is planned.

4.5 Data Safety Monitoring Board

Not applicable.

4.6 Safety Management Team

Not applicable.

5. DESCRIPTION OF NON-STANDARD DATA COLLECTED AND DERIVED VARIABLES

5.1 Other Non-Standard Baseline Characteristics

Not applicable.

5.2 Non-Standard Disease History

For the non-standard disease history the number of previous IVF attempts in the subject's life and for this child wish are recorded.

5.3 Efficacy data

The following non-standard efficacy parameters are analyzed:

- pregnancy rate (transvaginal ultrasound)
- chemical pregnancy rate (β-HCG test) on Day 15 after embryo transfer
- abortion rate
- biochemical pregnancy rate
- preterm birth rate
- live birth rate
- healthy newborn rate
- gestational age

The following non-standard efficacy data are collected on the newborn:

- Gender:
  - Male
  - Female
- Height at birth (cm)
- Weight at birth (g)
- Head circumference at birth (cm)
- Abnormal findings of physical examination:
  - Yes/Specifications
  - No
- Malformations:
  - Yes/Specifications
  - No
- APGAR score:
  - 1 min postpartal

- 5 min postpartal

Newborn efficacy data recorded on the "Status at End of Pregnancy" form will be summarized using descriptive statistic displaying mean, SD, median, min and max values for each applicable safety variable. For qualitative newborn efficacy data, per category the number and frequencies of newborns with non-missing data (n, %) will be the default summary presentation. This data will also be presented in a listing.

5.4 Non-standard Safety Data

Not applicable.

5.5 Drug Accountability and Exposure

5.5.1 Drug Accountability

Treatment compliance/drug accountability is defined as the number of tablets/gel applicators that were actually taken relative to the number of tablets/gel applicators that should have been taken for the duration of actual treatment exposure.

The overall compliance, assessed by tablet/gel applicator count, will be calculated as follows:

$$\text{Compliance (\%)} = \frac{\text{(N of tablets/gel applicators dispensed - N of tablets/gel applicators returned)}}{\text{(Duration * N of tablets/gel applicators prescribed per day)}} * 100$$

Interval Treatment Duration = (Dispensing Date at end of interval – (Dispensing Date at start of interval + 1 day))+1. For the first interval first day of study drug is used as start of interval and for the last interval last day of study drug is used as end of interval.

Overall Treatment Duration = (Last day of study drug administration – First day of study drug administration) + 1.

The calculated percentage compliance will be categorized as:

- Too Low: $< 80\%$ compliance.
- Adequate: $\geq 80\%$ to $\leq 120\%$ compliance.
- Too High: $> 120\%$ compliance.

5.5.2 Exposure

Exposure duration to treatment is equal to the day number of the last day of drug administration, calculated relative to the start of study drug administration.

Scheduled Treatment Duration Per Treatment Group (Days)		
Visit Interval	**Duphaston**	**Crinone**
Visit 2 to Visit 4	17 to 20	17 to 20
Visit 4 to Visit 5	21 to 30	21 to 30

Visit 5 (Week 6) to Visit 6 (Week 10)	29	29
Overall	71	71

6. FURTHER SPECIFICATIONS TO THE STANDARD ANALYSES IN MODULE 2

6.1 Trial Design [2]

6.1.1 Trial Periods

The combination of trial arms and trial periods for the current trial is presented in the following diagram:

Treatment Arm	Screening Period	Treatment Period	Follow-up Period
Duphaston	**Amendment1** 1-14 days **Amendment2** 1-40 days	70 days (+/- 3 days)	From visit 6 (end of treatment period or early discontinuation) until visit 10 (30 days after end of treatment or after delivery)
Crinone	**Amendment1** 1-14 days **Amendment2** 1-40 days	70 days (+/- 3 days)	From visit 6 (end of treatment period or early discontinuation) until visit 10 (30 days after end of treatment or after delivery)

Screening Period

Screening period is defined as the period from informed consent to randomization and first study drug administration at Day 1.

Treatment Period

Treatment period is defined as the period from first dose of study drug at Visit 2 up to and including last day of study drug at Visit 6 or early discontinuation.

Follow-up Period

The follow-up period consists of Visits 6 to 10. Visits 7 and 8 are post treatment surveillance calls, which take place every two months. Visit 7 will be at Day 101 (+/- 3 days) and Visit 8 at Day 157 (+/- 3 days). Visit 9 will be performed after delivery, if applicable. Visit 10 is the final follow-up call 30 days after delivery or end of treatment.

6.1.2 Trial Elements

The start time of each intervention will be expressed relative to the first administration of investigational study drug closest to that intervention.

The Trial Elements are presented in the following diagram:

Trial Element	Description of Element	Rule for Start of Element	Rule for End of Element	Planned Duration of Element
SCRN	Screening	Informed consent	Day before first dose of randomized treatment	**Amendment1** up to 14 days **Amendment2** up to 40 days
Duphaston	Dydrogesterone 30 mg daily	Day of first dose of Duphaston	Day of last dose of Duphaston	70 (+/- 3 days)
Crinone	Intravaginal progesterone gel 90 mg daily	Day of first dose of Crinone	Day of last dose of Crinone	70 (+/- 3 days)
FU	Follow-up	End of treatment or early discontinuation	30 Days after end of treatment or delivery	

6.1.3 Trial Arms

The trial arms for this study are made up of the following trial elements:

Trial Arm	Elements		
Duphaston	SCRN	Duphaston	FU
Crinone	SCRN	Crinone	FU

6.1.4 Unique Treatments

The trial arms for this study are made up of the following unique treatments:

Unique treatment		Arm	Elements
Description	**Label**		
Duphaston	Duphaston	Duphaston	Duphaston
Crinone	Crinone	Crinone	Crinone

6.1.5 Visits and related definitions

Tests and examinations that were scheduled in the protocol will be related to the general time axis of the trial by relating the visit date on which a test or examination is performed to the start date of the trial element that describes the first administration of investigational study drug closest in time to the visit date of that test or examination (Reference Start Date/ Time).

Test / Examination	Visit name	Visit Label	Visit Number	Reference Start Date/Time	Relative Day Number
See App. 9.1	Visit 1 (Screening and Enrollment)	Screening	1		**Amendment1** -14 to -1 **Amendment 2** -40 to -1
See App. 9.1	Visit 2 (Start of treatment/ Day of oocyte retrieval)	Start of treatment	2	Date of first dose of study medication	1
See App. 9.1	Visit 3 (Day of embryo transfer (ET))	Embryo transfer	3	Date of first dose of study medication	3 to 6
See App. 9.1	Visit 4 (Day to confirm biochemical pregnancy)	Biochemical pregnancy	4	Date of first dose of study medication	17 to 20
See App. 9.1	Visit 5 (Day to confirm ongoing pregnancy)	Ongoing pregnancy	5	Date of first dose of study medication	43 (+/- 3)
See App. 9.1	Visit 6 (End of treatment/ early discontinuation)	End of treatment	6	Date of first dose of study medication	71 (+/- 3)
See App. 9.1	Visit 7 (Post treatment surveillance call)	First phone call	7	Date of first dose of study medication	101 (+/- 3)
See App. 9.1	Visit 8 (Post treatment surveillance call)	Second phone call	8	Date of first dose of study medication	157 (+/- 3)
See App. 9.1	Visit 9 (After delivery case notes)	After delivery	9		
See App. 9.1	Visit 10 (Phone call 30 days	Final phone call	10	Date of	30

	after delivery)				

6.2 Further Specifications to the Standard Tables in Module 2

Not applicable

6.3 Other Further Specifications

Not applicable.

7. CHANGES TO PLANNED ANALYSES

7.1 Changes to the Analysis as Laid Down in the Protocol

For the subgroup analysis baseline BMI is used instead of baseline weight to align analysis with LOTUS I. Number of embryos transferred was added as a further subgroup. In the protocol of study M13-625 it is mentioned that the day of first study drug administration is Day 0. In this SAP the day of first study drug administration will be defined as Day 1.

Subjects are only included in the study with their first attempt. A sixth subject sample (Re-Randomized subject sample) is introduced consisting of all subjects who gave their informed consent and have been randomized for this study before. The all subject consented subject sample will only consist of patients who gave their informed consent and have not been randomized for this study before. Only demography and AEs listings will be produced for the Re-Randomized subject sample, the data will not be analyzed. Data from re-randomized patients that are screening failures will not be listed or analyzed. Gestational Age will be derived instead of using recorded pregnancy week + 2 weeks.

7.2 Changes from SAP Version 2.0 to Version 3.0

No changes will be made to the final SAP, Version 3.0. If the actual analysis deviates from the final planned analysis, this will be discussed in the Clinical Study Report.

8. REFERENCE

1. Abbott SAP Module 2
2. CDISC terminology, see http://www.cdisc.org.

9. APPENDICES

9.1 Study Flowchart

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 delivery Case notes	Phone call 30 days after delivery
Visit	1	2	3	4**	5	6	7 + 8	9	10
Day	-40 to -1	1	3 to 6	17 to 20	43 (+/- 3 days)	71 (+/- 3 days)	101 (+/- 3 days) 157 (+/- 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			
β-HCG Test				X					
Urine analysis HCG test (strip test)	X			X X		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 delivery 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 hormones 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.

9.2 Tables, Listings and Figures

9.2.1 Tables

For the shells of the non-standard tables, see Section 10.1.

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
DST001	Subject Disposition	10.1.1.1.1	Subject Disposition - All Subjects Allocated to Treatment Subject Sample	x
DST001	Subject Disposition	10.1.1.1.1.1	Subject Disposition: Chinese Sites - All Subjects Allocated to Treatment Subject Sample	
DST001	Subject Disposition	10.1.1.1.1.2	Subject Disposition: Asian Sites - All Subjects Allocated to Treatment Subject Sample	
DST001	Subject Disposition	10.1.1.1.1.3	Subject Disposition: Asian Race - All Subjects Allocated to Treatment Subject Sample	
DST001	Subject Disposition	10.1.1.1.2	Subject Disposition by Country - All Subjects Allocated to Treatment Subject Sample	
DST001	Subject Disposition	10.1.1.1.3	Subject Disposition by Age Group - All Subjects Allocated to Treatment Subject Sample	
DVT001	Protocol Deviations	10.1.1.2	Major Protocol Deviations – All Subjects Allocated to Treatment Subject Sample	
DVT002	Protocol Deviations	10.1.1.3	Subject Samples - All Subjects Allocated to Treatment Subject Sample	x
DMT002	Demographic Data	10.1.1.4.1	Demographics – Full Analysis Subject Sample	x
DMT002	Demographic Data	10.1.1.4.2	Demographics by Country – Full Analysis Subject Sample	
DMT002	Demographic Data	10.1.1.4.3	Demographics– Safety Subject Sample	
DMT002	Demographic Data	10.1.1.4.3.1	Demographics: Chinese Sites – Safety Subject Sample	
DMT002	Demographic Data	10.1.1.4.3.2	Demographics: Asian Sites – Safety Subject Sample	
DMT002	Demographic Data	10.1.1.4.3.3	Demographics: Asian Race – Safety Subject Sample	
VST003	Vital Signs	10.1.1.5	Other Baseline Characteristics – Full Analysis Subject Sample	
MHT001	Medical History	10.1.1.6	Medical History – Full Analysis Subject Sample	
CMT001	Concomitant Medications	10.1.1.7	Concomitant Medication: Subject – Full Analysis Subject Sample	
SCT001	Subject Characteristics	10.1.1.8	Number of IVF Attempts – Full Analysis Subject Sample	
DAT001	Treatment Compliance	10.1.1.8.1	Compliance to Study Drug – Safety Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
DAT001	Treatment Compliance	10.1.1.8.2	Compliance to Study Drug – Full Analysis Subject Sample	
DAT001	Treatment Compliance	10.1.1.8.3	Compliance to Study Drug – Per Protocol Subject Sample	
EXT001	Exposure	10.1.1.9.1	Exposure to Study Drug – Safety Subject Sample	
EXT001	Exposure	10.1.1.9.1.1	Exposure to Study Drug: Chinese Sites – Safety Subject Sample	
EXT001	Exposure	10.1.1.9.1.2	Exposure to Study Drug: Asian Sites – Safety Subject Sample	
EXT001	Exposure	10.1.1.9.1.3	Exposure to Study Drug: Asian Race – Safety Subject Sample	
EXT001	Exposure	10.1.1.9.2	Exposure to Study Drug – Full Analysis Subject Sample	
EXT001	Exposure	10.1.1.9.3	Exposure to Study Drug – Per Protocol Subject Sample	
EFT001	Efficacy	10.1.2.1.1	Pregnancy Confirmation at Visit 4 – Full Analysis Subject Sample	x
EFT001	Efficacy	10.1.2.1.1.1	Pregnancy Confirmation at Visit 4: Chinese Sites – Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1.2	Pregnancy Confirmation at Visit 4: Asian Sites – Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1.3	Pregnancy Confirmation at Visit 4: Asian Race – Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1a	Pregnancy Confirmation at Visit 4 by Country– Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1b	Pregnancy Confirmation at Visit 4 by Age Group - Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1c	Pregnancy Confirmation at Visit 4 by Race - Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1d	Pregnancy Confirmation at Visit 4 by BMI - Full Analysis Subject Sample	x
EFT001	Efficacy	10.1.2.1.1e	Pregnancy Confirmation at Visit 4 by Number of embryos transferred - Full Analysis Subject Sample	
EFT001	Efficacy	10.1.2.1.1f	Pregnancy Confirmation at Visit 4 by Weight - Full Analysis Subject Sample	
EFT002	Efficacy	10.1.2.1.2	Pregnancy Status at Visit 5 – Full Analysis Subject Sample	x
EFT002	Efficacy	10.1.2.1.2a	Pregnancy Status at Visit 5 by Country– Full Analysis Subject Sample	
EFT002	Efficacy	10.1.2.1.2b	Pregnancy Status at Visit 5 by Age Group– Full Analysis Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
EFT002	Efficacy	10.1.2.1.2c	Pregnancy Status at Visit 5 by Race– Full Analysis Subject Sample	
EFT002	Efficacy	10.1.2.1.2d	Pregnancy Status at Visit 5 by BMI – Full Analysis Subject Sample	
EFT002	Efficacy	10.1.2.1.2e	Pregnancy Status at Visit 5 by Number of embryos transferred – Full Analysis Subject Sample	
EFT002	Efficacy	10.1.2.1.2f	Pregnancy Status at Visit 5 by Weight – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3	Pregnancy Status : Transvaginal Ultrasound at Visit 6 – Full Analysis Subject Sample	x
EFT003	Efficacy	10.1.2.1.3.1	Pregnancy Status : Transvaginal Ultrasound at Visit 6: Chinese Sites – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3.2	Pregnancy Status : Transvaginal Ultrasound at Visit 6: Asian Sites – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3.3	Pregnancy Status : Transvaginal Ultrasound at Visit 6: Asian Race – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3a	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Country– Full Analysis Subject Sample	x
EFT003	Efficacy	10.1.2.1.3a.1	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Country: Chinese Sites – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3a.2	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Country: Asian Sites – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3a.3	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Country: Asian Race – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3b	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Age Group– Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3c	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Race– Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3d	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by BMI – Full Analysis Subject Sample	
EFT003	Efficacy	10.1.2.1.3e	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Number of embryos transferred – Full Analysis Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
EFT003	Efficacy	10.1.2.1.3f	Pregnancy Status : Transvaginal Ultrasound at Visit 6 by Weight – Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4	Efficacy Analysis – Full Analysis Subject Sample	x
EFT004	Efficacy	10.1.2.1.4.1	Efficacy Analysis: Chinese Sites – Full Analysis Subject Sample	x
EFT004	Efficacy	10.1.2.1.4.2	Efficacy Analysis: Asian Sites – Full Analysis Subject Sample	x
EFT004	Efficacy	10.1.2.1.4.3	Efficacy Analysis: Asian Race – Full Analysis Subject Sample	x
EFT004	Efficacy	10.1.2.1.5	Efficacy Analysis – Per Protocol Subject Sample	x
EFT004	Efficacy	10.1.2.1.5.1	Efficacy Analysis: Chinese Sites – Per Protocol Subject Sample	x
EFT004	Efficacy	10.1.2.1.5.2	Efficacy Analysis: Asian Sites – Per Protocol Subject Sample	x
EFT004	Efficacy	10.1.2.1.5.3	Efficacy Analysis: Asian Race – Per Protocol Subject Sample	x
EFT004	Efficacy	10.1.2.1.4a	Efficacy Analysis by Country– Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4b	Efficacy Analysis by Age Group - Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4c	Efficacy Analysis by Race – Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4d	Efficacy Analysis by BMI – Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4e	Efficacy Analysis by Number of embryos transferred – Full Analysis Subject Sample	
EFT004	Efficacy	10.1.2.1.4f	Efficacy Analysis by Weight – Full Analysis Subject Sample	
EFT005	Efficacy	10.1.2.1.6	Gestational Age – Full Analysis Subject Sample	
EFT005	Efficacy	10.1.2.1.6.1	Gestational Age: Chinese Sites – Full Analysis Subject Sample	
EFT005	Efficacy	10.1.2.1.6.2	Gestational Age: Asian Sites – Full Analysis Subject Sample	
EFT005	Efficacy	10.1.2.1.6.3	Gestational Age: Asian Race – Full Analysis Subject Sample	
EFT006	Efficacy	10.1.2.1.7	Status at End of Pregnancy: Newborn - Full Analysis Subject Sample	x
EFT006	Efficacy	10.1.2.1.7.1	Status at End of Pregnancy: Newborn Chinese Sites - Full Analysis Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
EFT006	Efficacy	10.1.2.1.7.2	Status at End of Pregnancy: Newborn Asian Sites - Full Analysis Subject Sample	
EFT006	Efficacy	10.1.2.1.7.3	Status at End of Pregnancy: Newborn Asian Race - Full Analysis Subject Sample	
EFT007	Efficacy	10.1.2.1.8	Number of Live Births - Full Analysis Subject Sample	
EFT007	Efficacy	10.1.2.1.8.1	Number of Live Births: Chinese Sites - Full Analysis Subject Sample	
EFT007	Efficacy	10.1.2.1.8.2	Number of Live Births: Asian Sites - Full Analysis Subject Sample	
EFT007	Efficacy	10.1.2.1.8.3	Number of Live Births: Asian Race - Full Analysis Subject Sample	
AET001	Adverse Events	10.1.3.1.1	Overall Summary of Adverse Events: Subject – Safety Subject Sample	x
AET001	Adverse Events	10.1.3.1.1.1	Overall Summary of Adverse Events: Subject Chinese Sites – Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1.2	Overall Summary of Adverse Events: Subject Asian Sites – Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1.3	Overall Summary of Adverse Events: Subject: Asian Race – Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1a	Overall Summary of Adverse Events: Subject by Country– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1b	Overall Summary of Adverse Events: Subject by Age Group– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1c	Overall Summary of Adverse Events: Subject by Race– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1d	Overall Summary of Adverse Events: Subject by BMI– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1e	Overall Summary of Adverse Events: Subject by Number of embryos transferred– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.1f	Overall Summary of Adverse Events: Subject by Weight– Safety Subject Sample	
AET001	Adverse Events	10.1.3.1.2	Overall Summary of Adverse Events: Newborn – Full Analysis Subject Sample	
AET002	Adverse Events	10.1.3.1.3	Incidence of TEAEs – Safety Subject Sample	x
AET002	Adverse Events	10.1.3.1.3.1	Incidence of TEAEs: Chinese Sites – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3.2	Incidence of TEAEs: Asian Sites – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3.3	Incidence of TEAEs: Asian Race – Safety Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
AET002	Adverse Events	10.1.3.1.3a	Incidence of TEAEs by Country – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3b	Incidence of TEAEs by Age Group – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3c	Incidence of TEAEs by Race – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3d	Incidence of TEAEs by BMI - Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3e	Incidence of TEAEs by Number of embryos transferred – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.3f	Incidence of TEAEs by weight – Safety Subject Sample	
AET002	Adverse Events	10.1.3.1.4	Incidence of TEAEs - Newborn – Full Analysis Subject Sample	
AET003	Adverse Events	10.1.3.1.5	Incidence of TEAEs in 5% of the Subjects in Any Treatment Group – Safety Subject Sample	
AET003	Adverse Events	10.1.3.1.5.1	Incidence of TEAEs in 5% of the Subjects in Any Treatment Group: Chinese Sites – Safety Subject Sample	
AET003	Adverse Events	10.1.3.1.5.2	Incidence of TEAEs in 5% of the Subjects in Any Treatment Group: Asian Sites – Safety Subject Sample	
AET003	Adverse Events	10.1.3.1.5.3	Incidence of TEAEs in 5% of the Subjects in Any Treatment Group: Asian Race – Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6	Incidence of TEAEs of Special Interest - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6.1	Incidence of TEAEs of Special Interest: Chinese Sites - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6.2	Incidence of TEAEs of Special Interest: Asian Sites - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6.3	Incidence of TEAEs of Special Interest: Asian Race - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6a	Incidence of TEAEs of Special Interest by Country - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6b	Incidence of TEAEs of Special Interest by Age Group - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6c	Incidence of TEAEs of Special Interest by Race – Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6d	Incidence of TEAEs of Special Interest by BMI – Safety Subject sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
AET004	Adverse Events	10.1.3.1.6e	Incidence of TEAEs of Special Interest by Number of embryos transferred - Safety Subject Sample	
AET004	Adverse Events	10.1.3.1.6f	Incidence of TEAEs of Special Interest by Weight - Safety Subject Sample	
AET005	Adverse Events	10.1.3.1.7	Incidence of TEAEs With a Reasonable Possibility for a Causal Relationship (Investigator's Judgment) – Safety Subject Sample	
AET005	Adverse Events	10.1.3.1.7.1	Incidence of TEAEs With a Reasonable Possibility for a Causal Relationship (Investigator's Judgment): Chinese Sites – Safety Subject Sample	
AET005	Adverse Events	10.1.3.1.7.2	Incidence of TEAEs With a Reasonable Possibility for a Causal Relationship (Investigator's Judgment): Asian Sites – Safety Subject Sample	
AET005	Adverse Events	10.1.3.1.7.3	Incidence of TEAEs With a Reasonable Possibility for a Causal Relationship (Investigator's Judgment): Asian Race – Safety Subject Sample	
AET006	Adverse Events	10.1.3.1.8	Incidence of TEAEs by Maximum Severity (Investigator's Judgment) – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9	Incidence of TESAEs: Subject – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9.1	Incidence of TESAEs: Chinese Sites – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9.2	Incidence of TESAEs: Asian Sites – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9.3	Incidence of TESAEs: Asian Race – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9a	Incidence of TESAEs by Country – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9b	Incidence of TESAEs by Age Group – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9c	Incidence of TESAEs by Race - Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9d	Incidence of TESAEs by BMI– Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9e	Incidence of TESAEs by Number of embryos transferred – Safety Subject Sample	
AET007	Adverse Events	10.1.3.1.9f	Incidence of TESAEs by Weight – Safety Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
AET007	Adverse Events	10.1.3.1.15	Incidence of TESAEs: Newborn – Full Analysis Subject Sample	
AET008	Adverse Events	10.1.3.1.10	Incidence of TEAEs Leading to Study Termination – Safety Subject Sample	
AET008	Adverse Events	10.1.3.1.10.1	Incidence of TEAEs Leading to Study Termination: Chinese Sites – Safety Subject Sample	
AET008	Adverse Events	10.1.3.1.10.2	Incidence of TEAEs Leading to Study Termination: Asian Sites – Safety Subject Sample	
AET008	Adverse Events	10.1.3.1.10.3	Incidence of TEAEs Leading to Study Termination: Asian Race – Safety Subject Sample	
AET009	Adverse Events	10.1.3.1.11	Incidence of Non-Serious TEAEs – Safety Subject Sample	
AET010	Adverse Events	10.1.3.1.12	Incidence of Non-Serious TEAEs in >= 5% of the Subjects in Any Treatment Group – Safety Subject Sample	
AET011	Adverse Events	10.1.3.1.13	Incidence of TEAEs Leading to Discontinuation of Study Drug – Safety Subject Sample	
AET0012	Adverse Events	10.1.3.1.14	Adverse Events of Special Interest by Visit Interval – Safety Subject Sample	
LBT001	Laboratory Tests	10.1.3.2.1	Summary of Quantitative Safety Laboratory Variables– Safety Subject Sample	
LBT002	Laboratory Tests	10.1.3.2.2	Summary of Qualitative Safety Urinalysis Variables– Safety Subject Sample	
LBT003	Laboratory Tests	10.1.3.2.3	Shifts of Quantitative Safety Laboratory Variables From Baseline to Each Post-Baseline Visit Based on Reference Ranges – Safety Subject Sample	
LBT004	Laboratory Tests	10.1.3.2.4	Incidence of Markedly Abnormal Safety Laboratory Variables – Safety Subject Sample	
LBT005	Laboratory Tests	10.1.3.2.5	Changes From Baseline of Qualitative Safety Laboratory Variables – Safety Subject sample	
VST001	Vital Signs	10.1.3.3.1	Summary of Vital Signs – Safety Subject Sample	
VST002	Vital Signs	10.1.3.3.2	Incidence of Markedly Abnormal Vital Signs – Safety Subject Sample	

Note: A missing output code denotes a non-standard output.

9.2.2 Listings

For the shells of the non-standard listings, see Section 10.2.

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
DSL001	Subject Disposition	12.2.1.1	Subjects Who Prematurely Terminated the Study Prior to Treatment Allocation - All Subjects Consented Subject Sample	
DSL001	Subject Disposition	12.2.1.1.1	Subjects Who Prematurely Terminated the Study Prior to Treatment Allocation: Chinese Sites - All Subjects Consented Subject Sample	
DSL001	Subject Disposition	12.2.1.1.2	Subjects Who Prematurely Terminated the Study Prior to Treatment Allocation: Asian Sites - All Subjects Consented Subject Sample	
DSL001	Subject Disposition	12.2.1.1.3	Subjects Who Prematurely Terminated the Study Prior to Treatment Allocation: Asian Race - All Subjects Consented Subject Sample	
DSL002	Subject Disposition	12.2.1.2	Subjects Allocated to Treatment - All Subjects Allocated to Treatment Subject Sample	
DSL003	Subject Disposition	12.2.1.3	Subjects Allocated to Treatment Who Prematurely Terminated the Study - All Subjects Allocated to Treatment Subject Sample	
DSL004	Subject Disposition	12.2.1.4	Subjects Allocated to Treatment Who Prematurely Terminated the Study due to a Protocol Violation- All Subjects Allocated to Treatment Subject Sample	
DVL001	Major Protocol Deviations	12.2.2.1	Subjects With Major Protocol Deviations - All Subjects Allocated to Treatment Subject Sample	
IEL002	Inclusion/Exclusion	12.2.2.2	Subjects With Deviations from Inclusion or Exclusion Criteria - All Subjects Allocated to Treatment Subject Sample	
DVL002	Major Protocol Deviations	12.2.2.3	Subjects Excluded From the Subject Samples - All Subjects Allocated to Treatment Subject Sample	
DML002	Demographic Data	12.2.4.1	Demographics - All Subjects Allocated to Treatment Subject Sample	
DML002	Demographic Data	12.2.4.1.1	Demographics: Chinese Sites - All Subjects Allocated to Treatment Subject Sample	
DML002	Demographic Data	12.2.4.1.2	Demographics: Asian Sites - All Subjects Allocated to Treatment Subject Sample	
DML002	Demographic Data	12.2.4.1.3	Demographics: Asian Race - All Subjects Allocated to Treatment Subject Sample	
DML002	Demographic Data	12.2.4.1a	Demographics – Re-Randomized Subject Sample	
VSL003*	Vital Signs	12.2.4.2	Other Baseline Characteristics - All Subjects Allocated to Treatment Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
MHL001	Medical History	12.2.4.3	Medical History: General - All Subjects Allocated to Treatment Subject Sample	
MHL002	Medical History	12.2.4.4	Medical History: MedDRA Coding - All Subjects Allocated to Treatment Subject Sample	
SCL001	Subject Characteristics	12.2.4.5	IVF Attempts – All Subjects Allocated to Treatment Subject Sample	
CML001	Concomitant Medications	12.2.4.6	Concomitant Medication: General - All Subjects Allocated to Treatment Subject Sample	
CML002	Concomitant Medications	12.2.4.7	Concomitant Medication: Subject: WHO-DD Coding - All Subjects Allocated to Treatment Subject Sample	
CML003	Concomitant Medications	12.2.4.8	Concomitant Medication: Newborn – Full Analysis Subject Sample	
CML002	Concomitant Medications	12.2.4.9	Concomitant Medication: Newborn: WHO-DD Coding – Full Analysis Subject Sample	
DAL001	Drug Accountability	12.2.5.1	Drug Accountability and Compliance - Safety Subject Sample	
EFL001	Efficacy	12.2.6.1	Embryo Transfer – Safety Subject Sample	
EFL001	Efficacy	12.2.6.1.1	Embryo Transfer: Chinese Sites – Safety Subject Sample	
EFL001	Efficacy	12.2.6.1.2	Embryo Transfer: Asian Sites – Safety Subject Sample	
EFL001	Efficacy	12.2.6.1.3	Embryo Transfer: Asian Race – Safety Subject Sample	
EFL002	Efficacy	12.2.6.2	Pregnancy Confirmation– Full Analysis Subject Sample	
EFL002	Efficacy	12.2.6.2.1	Pregnancy Confirmation: Chinese Sites– Full Analysis Subject Sample	
EFL002	Efficacy	12.2.6.2.2	Pregnancy Confirmation: Asian Sites– Full Analysis Subject Sample	
EFL002	Efficacy	12.2.6.2.3	Pregnancy Confirmation: Asian Race– Full Analysis Subject Sample	
EFL003	Efficacy	12.2.6.3	Pregnancy Confirmation: Transvaginal Ultrasound – Full Analysis Subject Sample	
EFL003	Efficacy	12.2.6.3.1	Pregnancy Confirmation: Transvaginal Ultrasound: Chinese Sites – Full Analysis Subject Sample	
EFL003	Efficacy	12.2.6.3.2	Pregnancy Confirmation: Transvaginal Ultrasound: Asian Sites – Full Analysis Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
EFL003	Efficacy	12.2.6.3.3	Pregnancy Confirmation: Transvaginal Ultrasound: Asian Race – Full Analysis Subject Sample	
EFL004	Efficacy	12.2.6.4	Pregnancy Status – Full Analysis Subject Sample	
EFL004	Efficacy	12.2.6.4.1	Pregnancy Status: Chinese Sites – Full Analysis Subject Sample	
EFL004	Efficacy	12.2.6.4.2	Pregnancy Status: Asian Sites – Full Analysis Subject Sample	
EFL004	Efficacy	12.2.6.4.3	Pregnancy Status: Asian Race – Full Analysis Subject Sample	
EFL005	Efficacy	12.2.6.5	Status at End of Pregnancy: Subject – Full Analysis Subject Sample	
EFL005	Efficacy	12.2.6.5.1	Status at End of Pregnancy: Subject Chinese Sites – Full Analysis Subject Sample	
EFL005	Efficacy	12.2.6.5.2	Status at End of Pregnancy: Subject Asian Sites – Full Analysis Subject Sample	
EFL005	Efficacy	12.2.6.5.3	Status at End of Pregnancy: Subject Asian Race – Full Analysis Subject Sample	
EFL006	Efficacy	12.2.6.6	Status at End of Pregnancy: Newborn – Full Analysis Subject Sample	
EFL006	Efficacy	12.2.6.6.1	Status at End of Pregnancy: Newborn Chinese Sites – Full Analysis Subject Sample	
EFL006	Efficacy	12.2.6.6.2	Status at End of Pregnancy: Newborn Asian Sites – Full Analysis Subject Sample	
EFL006	Efficacy	12.2.6.6.3	Status at End of Pregnancy: Newborn Asian Race – Full Analysis Subject Sample	
EFL006	Efficacy	12.2.6.7	Status at End of Pregnancy: Newborn – for Patients from Russia – Full Analysis Subject Sample	
EFL009	Efficacy	12.2.6.8	Phone Contacts– Full Analysis Subject Sample	
EFL010	Efficacy	12.2.6.9	Final Phone Contact - Full Analysis Subject Sample	
AEL008	Adverse Events	12.2.7.1	AEs: General: Subject - All Subjects Consented Subject Sample	
AEL008	Adverse Events	12.2.7.1a	AEs: General: Subject – Re-Randomized Subject Sample	
AEL003	Adverse Events	12.2.7.2	AEs: General: Newborn – Full Analysis Subject Sample	
AEL002	Adverse Events	12.2.7.3	AEs: MedDRA Coding - All Subjects Consented Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
AEL002	Adverse Events	12.2.7.3.1	AEs: MedDRA Coding: Chinese Sites - All Subjects Consented Subject Sample	
AEL002	Adverse Events	12.2.7.3.2	AEs: MedDRA Coding: Asian Sites - All Subjects Consented Subject Sample	
AEL002	Adverse Events	12.2.7.3.3	AEs: MedDRA Coding: Asian Race - All Subjects Consented Subject Sample	
AEL002	Adverse Events	12.2.7.3a	AEs: MedDRA Coding: - Re-Randomized Subject Sample	
AEL002	Adverse Events	12.2.7.4	AEs: MedDRA Coding: Newborn – Full Analysis Subject Sample	
AEL002	Adverse Events	12.2.7.4.1	AEs: MedDRA Coding: Newborn Chinese Sites – Full Analysis Subject Sample	
AEL002	Adverse Events	12.2.7.4.2	AEs: MedDRA Coding: Newborn Asian Sites – Full Analysis Subject Sample	
AEL002	Adverse Events	12.2.7.4.3	AEs: MedDRA Coding: Newborn Asian Race – Full Analysis Subject Sample	
AEL009	Adverse Events	10.1.3.1.22	Listing of Deaths: Subject - All Subjects Consented Subject Sample	
AEL009	Adverse Events	10.1.3.1.22.1	Listing of Deaths: Subject Chinese Sites - All Subjects Consented Subject Sample	
AEL009	Adverse Events	10.1.3.1.22.2	Listing of Deaths: Subject Asian Sites - All Subjects Consented Subject Sample	
AEL009	Adverse Events	10.1.3.1.22.3	Listing of Deaths: Subject Asian Race - All Subjects Consented Subject Sample	
AEL010	Adverse Events	10.1.3.1.23	Listing of Other SAEs: Subject - All Subjects Consented Subject Sample	
AEL010	Adverse Events	10.1.3.1.23.1	Listing of Other SAEs: Subject Chinese Sites - All Subjects Consented Subject Sample	
AEL010	Adverse Events	10.1.3.1.23.2	Listing of Other SAEs: Subject Asian Sites - All Subjects Consented Subject Sample	
AEL010	Adverse Events	10.1.3.1.23.3	Listing of Other SAEs: Subject Asian Race - All Subjects Consented Subject Sample	
AEL010	Adverse Events	10.1.3.1.26	Listing of Other SAEs: Newborn – Full Analysis Subject Sample	
AEL011	Adverse Events	10.1.3.1.24	Listing of TEAEs Leading to Study Termination – Safety Subject Sample	
AEL011	Adverse Events	10.1.3.1.24.1	Listing of TEAEs Leading to Study Termination: Chinese Sites – Safety Subject Sample	
AEL011	Adverse Events	10.1.3.1.24.2	Listing of TEAEs Leading to Study Termination: Asian Sites – Safety Subject Sample	

Output Code	Clinical Domain	Output Number	Title	Produced for: Headline Results
AEL011	Adverse Events	10.1.3.1.24.3	Listing of TEAEs Leading to Study Termination: Asian Race – Safety Subject Sample	
AEL012	Adverse Events	10.1.3.1.25	Listing of TEAEs Leading to Discontinuation of Study Drug – Safety Subject Sample	
AEL012	Adverse Events	8.3.2	Data Portion for Subject Narratives	
LBL008	Laboratory Data	12.2.8.1	Markedly Abnormal and/or Clinically Significant Safety Laboratory Variables – Safety Subject Sample	
LBL002	Laboratory Data	12.2.8.2	Qualitative Safety Laboratory Variables - All Subjects Allocated to Treatment Subject Sample	
LBL003	Laboratory Data	12.2.8.3	Quantitative Safety Laboratory Variables - All Subjects Allocated to Treatment Subject Sample	
VSL004	Vital Signs	12.2.8.4	Markedly Abnormal Vital Signs – Safety Subject Sample	
VSL005	Vital Signs	12.2.8.5	Vital Signs - All Subject Allocated to Treatment Subject Sample	
SVL001	Subject Visits	12.2.8.6	Subject Visits – All Subject Allocated to Treatment Subject Sample	
COL001	Comments	12.2.9.1	Comments – All Subjects Consented Subject Sample	

Note: A missing output code denotes a non-standard output.

9.2.3 Figures

For the shells of the non-standard figures, see Section 10.3.

Output Code	Clinical Domain	Output Number	Title	Produced for:
				Headline results
DSF001	Subject Disposition	10.1.4.1	Flowchart of Subject Disposition	
DSF001	Subject Disposition	10.1.4.1.1	Flowchart of Subject Disposition: Chinese Sites	
DSF001	Subject Disposition	10.1.4.1.2	Flowchart of Subject Disposition: Asian Sites	
DSF001	Subject Disposition	10.1.4.1.3	Flowchart of Subject Disposition: Asian Race	
DSF002	Subject Disposition	10.1.4.2	Flowchart of Subject Samples	
EFF001	Efficacy	10.1.5.1	Impact of Treatment on Pregnancy Rates – Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.2	Impact of Treatment on Pregnancy Rates – Per Protocol Subject Sample	
EFF001	Efficacy	10.1.5.1a	Impact of Treatment on Pregnancy Rates by Country - Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.1b	Impact of Treatment on Pregnancy Rates by Age Group – Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.1c	Impact of Treatment on Pregnancy Rates by Race– Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.1d	Impact of Treatment on Pregnancy Rates by BMI – Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.1e	Impact of Treatment on Pregnancy Rates by Number of Embryos transferred– Full Analysis Subject Sample	
EFF001	Efficacy	10.1.5.1f	Impact of Treatment on Pregnancy Rates by Weight – Full Analysis Subject Sample	

Note: A missing output code denotes a non-standard output.