Integrated Analysis Plan

Clinical Study Protocol Identification No.	MS200113_0005
Title	Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study
Study Phase	IV
Investigational Medicinal Product(s)	Not applicable
Clinical Study Protocol Version	10 October 2018/Version 1.0
Integrated Analysis Plan Author	**Coordinating Author** PPD Merck PPD **Function** / **Author(s) / Data Analyst(s)** PPD / PPD
Integrated Analysis Plan Date and Version	26 April 2019/ Version 1.0
Integrated Analysis Plan Reviewers	**Function** / **Name** PPD Merck / PPD PPD, Merck / PPD PPD, Merck / PPD PPD / PPD

Confidential
This document is the property of Merck KGaA, Darmstadt, Germany, or one of its affiliated companies.
It is intended for restricted use only and may not - in full or part - be passed on, reproduced, published or used without express permission of Merck KGaA, Darmstadt, Germany or its affiliate.
Copyright © 2019 by Merck KGaA, Darmstadt, Germany or its affiliate. All rights reserved.

Approval Page

Integrated Analysis Plan: MS200113_0005

Comparison of Crinone® versus combination medication for luteal phase support on the ongoing pregnancy rate of frozen-thawed cycle in Chinese population: a randomized, interventional, open-label, Phase IV, single center, pilot study

PPD PPD

PPD

Merck, 25F NUO Center Office, Beijing China

PPD PPD PPD

PPD

Merck, 23F NUO Center Office, Beijing China

PPD PPD PPD

PPD

PPD PPD

PPD

1 Table of Contents

Integrated Analysis Plan 1
Approval Page 2
1 Table of Contents 3
2 List of Abbreviations and Definition of Terms 5
3 Modification History 6
4 Purpose of the Integrated Analysis Plan 6
5 Objectives and Endpoints 6
6 Overview of Planned Analyses 7
7 Changes to the Planned Analyses in the Clinical Study Protocol 7
8 Protocol Deviations and Analysis Populations 8
8.1 Definition of Protocol Deviations 8
8.2 Definition of Analysis Populations and Subgroups 8
9 General Specifications for Data Analyses 9
10 Study Subjects 11
10.1 Disposition of Subjects and Discontinuations 11
10.2 Protocol Deviations 12
10.2.1 Important Protocol Deviations 12
10.2.2 Reasons Leading to the Exclusion from an Analysis Population 12
11 Demographics and Other Baseline Characteristics 12
11.1 Demographics 12
11.2 Medical History 13
11.3 Other Baseline Characteristics 13
12 Concomitant Medications/Procedures 15
13 Study intervention Compliance and Exposure 15
14 Efficacy Analyses 16
14.1 Primary Endpoint: Ongoing Pregnancy 16
14.1.1 Primary Objective: Analysis of the primary endpoint Ongoing Pregnancy 17
14.1.2 Subgroup Analyses of the primary endpoint Ongoing Pregnancy 17
14.2 Secondary endpoint 17
15 Safety Analyses 20

15.1 Adverse Events 20
15.1.1 All Adverse Events 21
15.1.2 Adverse Events Leading to Study Intervention Discontinuation 22
15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events 22
15.2.1 Deaths 22
15.2.2 Serious Adverse Events 22
15.2.3 Bleeding 22
15.3 Clinical Laboratory Evaluation 24
15.4 Vital Signs 24
16 Analyses of Other Endpoints 24
17 References 24
18 Appendices 24

2 List of Abbreviations and Definition of Terms

ADaM	Analysis Data Model
AE	Adverse event
ATC	Anatomical Therapeutic Chemical classification
CI	Confidence Interval
(e)CRF	(electronic) Case Report Form
CSR	Clinical Study Report
EDC	Electronic data capture
ET	Embryo transfer
FET	Frozen-thawed embryo transfer
β-hCG	Beta human chorionic gonadotrophin
IAP	Integrated Analysis Plan
ICH	International Council for Harmonization
ITT	Intention-to-treat
IVRS	Interactive Voice Response System
LOCF	Last Observation Carried Forward
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable
PD	Protocol Deviation
PT	Preferred Term
PP	Per protocol
SAE	Serious adverse event
SCR	Screening analysis population
SD	Standard Deviation
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
TLF	Tables, Listings, and Figures
WHO-DD	World Health Organization Drug Dictionary
MedDRA	Medical Dictionary for Regulatory Activities

3 Modification History

Unique Identifier for Version	Date of IAP Version	Author	Changes from the Previous Version
1.0	26 April 2019	PPD	new

4 Purpose of the Integrated Analysis Plan

The purpose of this IAP is to document technical and detailed specifications for the final analysis of data collected for protocol MS200113_0005. Results of the analyses described in this IAP will be included in the Clinical Study Report (CSR). Additionally, the planned analyses identified in this IAP will be included in future manuscripts. Any post-hoc, or unplanned analyses performed to provide results for inclusion in the CSR but not identified in this prospective IAP will be clearly identified in the CSR.

The IAP is based upon section 9 (Statistical Consideration) of the study protocol and is prepared in compliance with ICH E9. It describes analyses planned in the protocol.

The first version (version 1.0) focused on the detailed description of the planned explorative analyses of efficacy and safety variables.

5 Objectives and Endpoints

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
Primary			
To investigate the ongoing pregnancy rate of Crinone® compared to Crinone® in combination with Duphaston® during artificial FET cycles in Chinese population.	Ongoing pregnancy	At 10-12 weeks of pregnancy [8-10 weeks after ET]	14.1
Secondary			
To evaluate the efficacy of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• β-hCG positive	At 4 weeks of pregnancy [2 weeks after ET]	14.2
	• Implantation • Clinical pregnancy	At 6-8 weeks of pregnancy [4-6 weeks after ET]	14.2

Objectives	Endpoints (Outcome Measures)	Endpoints (Outcome Measures) Timeframe	IAP section
	• Early abortion	Time from ET to 12 weeks of pregnancy	14.2
To evaluate the safety of Crinone® compared to Crinone® in combination with Duphaston® for luteal phase support in artificial FET cycles.	• Luteal phase bleeding	Time from ET to β-hCG positive assessment	15.2.3
	• Vaginal bleeding	Time after β-hCG positive assessment	15.2.3
	• The safety profile of the study intervention	Time from the first day of study intervention after randomization to last dose of study intervention date or the clinical cut-off date, whatever occurs earlier.	15

6 Overview of Planned Analyses

No formal interim analyses are planned.

Cut-off date

The final planned analysis identified in the Clinical Study Protocol and in this IAP will be performed only after the last subject has completed the study with all study data in-house, all data queries resolved, and the database locked.

7 Changes to the Planned Analyses in the Clinical Study Protocol

Protocol	IAP	
Original	**Change**	**Rationale**
• The CI for the difference between the two treatment groups will be calculated with the Pearson chi-square test	The CI for the difference between the two treatment groups will be calculated with the stratified "Miettinen-Nurminen" method	There is stratification randomization in this study, previous proposed Pearson chi-square test cannot provide the CI for stratified data, thus calculation method was changed to be stratified "Miettinen-Nurminen" method
• Early abortion was listed as safety secondary endpoint in the synopsis.	Early abortion is listed in the efficacy secondary endpoint section	Early abortion is a failure to pregnancy, so move it under the efficacy endpoint.

8 Protocol Deviations and Analysis Populations

8.1 Definition of Protocol Deviations

Important protocol deviations are protocol deviations that might significantly affect the completeness, accuracy, and/or reliability of the study data or that might significantly affect a subject's rights, safety, or well-being.

The following deviations will be identified and confirmed prior to or at the Data Review Meeting at the latest.

Important protocol deviations include:

- Deviations from the inclusion and exclusion criteria
- Deviations post inclusion
- Subset of these important protocol deviations are clinically important, if leading to the exclusion of a subject from an analysis population (see section 8.2)

All important protocol deviations based on eCRF database are documented in ADaM datasets whether identified through site monitoring, medical review or programming.

8.2 Definition of Analysis Populations and Subgroups

The analysis populations are specified below. The final decision to exclude subjects from any analysis population will be made during a data review meeting prior to database lock.

Analysis Population	Description
Intention-to-Treat (ITT) Population	The ITT Population will include all subjects who receive at least one dose of randomized study intervention after randomization. Subjects will be analyzed according to the study intervention they were initially assigned.
Per-Protocol (PP) Population	Includes all subjects in ITT population without any important protocol violations.
Safety Population	Include all subjects who have received at least one dose of study intervention after randomization. Subjects will be analyzed according to the actual study intervention they received.

The general use of the analysis populations in the different analyses are summarized as below.

	Analysis Population		
Analyses	**Intent-to-Treat**	**Per Protocol**	**Safety**
Baseline Assessments	✓		
Concomitant Therapies	✓		
Compliance and Exposure			✓

	Analysis Population		
Analyses	**Intent-to-Treat**	**Per Protocol**	**Safety**
Efficacy: Primary	✓	✓	
Efficacy: Secondary	✓	✓	
Safety			✓

If the Per Protocol analysis population includes at least 90% of subjects in the ITT analysis population, additional efficacy analyses on the Per Protocol analysis population will be omitted as the differences in the results based upon these two analysis populations are expected to be negligible.

Additional Subgroup Analysis Populations

Subgroup analyses of the primary endpoint will be performed on subgroups as defined below if needed. For the definition of subgroup, data as documented in the electronic case report form (eCRF) will be taken.

Subgroups:

The following subgroups will be defined if the data suggest a possible imbalance between the two arms:

- the number of embryos transferred
  - 1 embryo transferred
  - 2 embryos transferred

9 General Specifications for Data Analyses

Study intervention groups

Study intervention groups are defined and labelled as Crinone® and combination medication (Crinone® plus Duphaston®).

Unless otherwise indicated all analyses will be presented separately for the two study intervention groups.

Data handling after cut-off date

Data after cut-off do not undergo the cleaning process.

Data obtained after the cut-off will not be displayed in any listings or used for summary statistics, e.g. laboratory values of samples taken after data cut-off, AEs with onset date after data cutoff, etc. will not be included in any analysis or listing.

Stop dates are not affected by this rule, e.g. a stop date of AEs, which starts prior to the cut-off, but stops after date of cut-off, will not be changed.

Significance level

There is no formal statistical hypothesis testing in this study. For treatment difference, two sided 90% confidence intervals will be calculated, unless otherwise in this IAP specified.

Presentation of continuous and qualitative variables

Continuous variables will be summarized using descriptive statistics, i.e.

- number of subjects, number of subjects with non-missing values,
- mean, standard deviation,
- median, 25th Percentile - 75th Percentile (Q1-Q3),
- minimum, and maximum.

Qualitative variables will be summarized by counts and percentages.

Unless otherwise stated the calculation of proportions will be based on the number of subjects of the analysis population of interest. Therefore, counts of missing observations will be included in the denominator and presented as a separate category.

In case the analysis refers only to certain visits percentages will be based on the number of subjects still present in the study at that visit, unless otherwise specified.

Definition of baseline

In general, the last non-missing measurement prior to (≤) randomization date will serve as the baseline measurement. If no such a value is available, the last measurement prior to (≤) the first study intervention administration date after randomization date will be used as the baseline measurement.

Conversion factors

The following conversion factors will be used to convert days into months or years: 1 month = 30.4375 days, 1 year = 365.25 days.

Handling of missing data

Unless otherwise specified, missing data will not be replaced.

In all subject data listings, imputed values will be presented. In all listings imputed information will be flagged.

Missing statistics, e.g. when they cannot be calculated, should be presented as “nd”. For example, if n=1, the measure of variability (SD) cannot be computed and should be presented as “nd”.

Time window

Day 1 is the day of start of study intervention after randomization, the day before is Day -1 (no Day 0 is defined).

Study day is defined relative to Day 1.

Software(s)

All analyses will be performed using SAS® Software version 9.4 or higher.

10 Study Subjects

The subsections in this section include specifications for reporting subject disposition and study intervention/study discontinuations. Additionally, procedures for reporting protocol deviations are provided.

10.1 Disposition of Subjects and Discontinuations

- Total number of subjects screened (i.e. subjects who gave informed consent)
- Number of subjects who discontinued from the study prior to randomization overall and grouped by the main reason (e.g. the failed specific inclusion or exclusion criteria, withdraw of consent)
- Number of randomized subjects.
- Number of randomized subjects who received at least one dose of study intervention after randomization
- Number of randomized subjects who completed study after randomization, grouped by study intervention group and main reason.
- Number of randomized subjects who discontinued the study after randomization, grouped by study intervention group and main reason

The number and percentage of subjects in each of the above disposition categories will be presented by randomized study intervention group (if applicable) and overall. Percentages will be presented with respect to the number of randomized subjects. Study completion or discontinuation and their corresponding reasons will be summarized from "Study Termination" eCRF page.

Disposition of subjects by allocated study intervention group will be presented in a CONSORT Flow Diagram.

The results of the randomization algorithm (according to IVRS) will be summarized as follows:

- Number of subjects by randomization stratum (IVRS)

10.2 Protocol Deviations

10.2.1 Important Protocol Deviations

The following summary tables and listings of important protocol deviations will be provided (separately for pre-/post inclusion deviations):

- Frequency table per reason of important protocol deviations
- Listing of important protocol deviations

10.2.2 Reasons Leading to the Exclusion from an Analysis Population

For subjects excluded from the PP, the reasons for exclusion will be summarized and listed;

- Frequency table per reason of exclusion from the PP population
- Listing of reasons of exclusion from the PP population

11 Demographics and Other Baseline Characteristics

If not stated otherwise, summaries will be presented on the ITT analysis population, by randomized study intervention group and overall.

11.1 Demographics

Demographic characteristics will be summarized using the following information from the "Visit 1 (Baseline Evaluation)" eCRF pages.

- Demographic characteristics
  - Age at freezing (years)
  - Age at transfer (years)
  - Age categories at transfer:
    - < 35 years and ≥ 20 years
    - ≥ 35 years
  - Race: Asian, other, not collected at this site
- Weight at Baseline
- BMI at Baseline

Specifications for computation in EDC:

- Age at transfer (years)
  - Formula: (date of given informed consent - date of birth) / 365.25.
  - In case of missing day for at least one date, but month and year available for both dates:

    For the derivation of age, the day of informed consent and the day of birth will be set to 1 and the formula above will be used
  - In case of missing month for at least one date, but year available for both dates:

    For the derivation of age, the day and the month of informed consent and the day and month of birth will be set to 1 and the formula above will be used
- BMI (kg/m^2) = weight (kg) / [height (cm) x height (cm)] x 10000

Deviation:

- Age at freezing (years)
  - Formula: (date of frozen embryo- date of birth) / 365.25.
  - Data Source: date of frozen embryo is from "Embryo Transfer" eCRF page.
  - Missing date imputation: same as the way as the one for age at transfer.

11.2 Medical History

The medical history will be summarized from the "Medical History" eCRF page, using MedDRA, current version, preferred term as event category and system organ class (SOC) body term as Body System category.

Medical history will be displayed in terms of frequency tables: ordered by primary SOC and PT in alphabetical order.

11.3 Other Baseline Characteristics

Information on disease characteristics and ET preparation collected at the baseline evaluation visit will be summarized by study intervention group and overall. Summary statistics will be presented for:

Disease history

- Subjects with pelvic surgery history ("Pelvic Surgery History" eCRF page)
- Previous pregnancies ('Yes' or 'No') ("OBSTETRICAL HISTORY" eCRF page)
  - Definition: subjects with number of previous pregnancies >0 will be categorized to be 'Yes', otherwise 'No'

  - If Yes, number of previous pregnancies will be provided and displayed by number category.

- Live births ('Yes' or 'No') ("OBSTETRICAL HISTORY" eCRF page)
  - Definition: subjects with number of live births >0 will be categorized to be 'Yes', otherwise 'No'
  - If Y, number of live births will be provided and displayed by number category.
- Spontaneous abortions ("OBSTETRICAL HISTORY" eCRF page)
  - Definition: subjects with number of spontaneous abortions>0 will be categorized to be 'Y', otherwise 'N'
  - If Y, number of spontaneous abortions will be provided and displayed by number category.
- Therapeutic/elective abortions ("OBSTETRICAL HISTORY" eCRF page)
  - Definition: subjects with number of therapeutic/elective abortions>0 will be categorized to be 'Y', otherwise 'N'
  - If Y, number of therapeutic/elective abortions will be provided and displayed by number category.
- Infertility (primary or secondary) ("Infertility History" eCRF page)
- Duration of Infertility (Months) ("Infertility History" eCRF page)
- Type of Infertility ("Infertility History" eCRF)
  - Causes of female infertility

Embryo transfer related baseline characteristics

- Endometrial thickness at baseline ("Ultrasound Scan Assessment -Screening" eCRF page at visit 1)
- Duration of Estradiol Valerate prior to randomization date (day)
  - Derivation: randomization date - the date of Estradiol Valerate initiation + 1
  - Data source:
    - The date of Estradiol Valerate initiation: the first dose date in "Administration of Estradiol Valerate" eCRF page
    - Randomization date: randomization date in the "Randomization" eCRF page at visit 4
- Endometrial thickness prior to initiation of Crinone ("Ultrasound Scan Assessment-1" eCRF page at visit 3)
- Endometrial thickness at transfer day ("Ultrasound Scan Assessment-2" eCRF page at visit 4)
- Number of D5 embryos transferred (displayed by number category) ("Embryo Transfer" eCRF page)

- Duration of embryo frozen (months)
  - Formula: =embryo transfer date – the date of frozen embryo + 1
  - Data source: "Embryo Transfer" eCRF page
- Good quality embryo
  - Derivation: for each subject, it is the number of embryos graded in AA, AB, BA or BB (inner cell mass is not equal to 'C' and trophectoderm is not equal to 'C') according to the Gardner Embryo Grading System.
  - Data source: "Embryo Transfer" eCRF page

12 Concomitant Medications/Procedures

Concomitant treatments are medications, other than study interventions and estradiol valerate, which are taken by subjects any time on-study (on or after the first day of study intervention after randomization for each subject) or prior to last dose of trial drug.

Concomitant treatment will be summarized from the "Concomitant Medication" eCRF page. ATC-2nd level and preferred term will be tabulated as given from the WHO-DD dictionary current version. In case multiple ATC's are assigned to a drug, all ATC-2nd level will be used for reporting. In case the date values will not allow to unequivocally allocate a medication to concomitant medication, the medication will be considered as concomitant medication.

All **Concomitant procedures**, which were undertaken any time on study, will be summarized according to the eCRF page "Concomitant Procedures". Concomitant procedures will be classified by medical review.

Number of subjects with concomitant procedures (on or after the first day of study intervention after randomization or prior to last dose of study intervention) will be presented by overall and by type of procedure (as classified by medical review)

13 Study intervention Compliance and Exposure

All dosing calculations and summaries will be based on "Administration of Crinone" and "Administration of Duphaston" eCRFs pages.
Crinone will be administered prior to randomization, but first dose date after randomization will be used as start date in the following calculation.

Analysis Population to be used for summaries:

- Safety population

Compliance

- Compliance (%) = 100 * actual dose/planned dose for study intervention duration.
  - Crinone Planned Dose: 90mg/gel, q.d
  - Duphaston Planned Dose: 10mg/tablet, b.i.d

14 Efficacy Analyses

14.1 Primary Endpoint: Ongoing Pregnancy

14.1.1 Primary Objective: Analysis of the primary endpoint Ongoing Pregnancy

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Primary endpoint: Ongoing pregnancy assessment at 10-12 weeks of pregnancy [8-10 weeks after ET]			
Primary (ITT) Supportive (PP)	**Ongoing pregnancy rate (%)**: =100 * number of subjects with ongoing pregnancy/number of subjects with ET cycle. • **Time window**: from the start date of first ET to the end of study. • **Numerator**: The subjects with ongoing pregnancy will be determined to be those with positive ongoing pregnancy result in the "Ongoing Pregnancy Assessment" eCRF page • **Denominator**: The subjects with ET cycle will be determined as those with ET date in "Embryo Transfer" eCRF page.	• Point estimate and 95%CI for each study intervention groups (Clopper-Pearson) • Point estimate and 90%CI for difference between two study intervention groups (stratified Miettinen & Nurminen (MN) method (see Miettinen & Nurminen, 1985)) o It will be computed with the SAS® 9.4 FREQ procedure, using the riskdiff (COMMON) option in the Table statement and speicified alpha=0.1. The results could be found in the ODS CommonPdiff table (method=' Summary Score')	Missing=Failure

14.1.2 Subgroup Analyses of the primary endpoint Ongoing Pregnancy

Since the number of embryos transferred is medically known to have an impact on the chance of achieving an ongoing pregnancy rate, the rate of subjects with only 1 embryo transferred within each arm will be examined by fisher exact test. If the data suggest a possible imbalance between the two arms ($p<0.05$), then subgroup analyses of the primary endpoint in subjects with only 1 embryo transferred and in subjects with 2 embryos transferred may be performed with the method same in 14.1.1.

14.2 Secondary endpoint

Analysis (Analysis Population)	Derivation	Statistical Analysis Methods	Missing data handling
Secondary Endpoint: β-hCG positive			
Secondary (ITT) Supportive (PP)	**β-hCG positive rate (%)**: =100 * number of subjects with positive β-hCG /number of subjects with ET cycle. • **Time window**: from the start date of first ET to the end of study. • **Numerator:** The subjects with positive β-hCG will be determined to be those with positive β-hCG result in the "β-hCG Level" eCRF page at β-hCG positive assessment visit. • **Denominator:** The subjects with ET cycle will be determined as those with ET date in "Embryo Transfer" eCRF page.	Same as method in the section 14.1.1	Next observation carried backward (NOCB). Missing assessment outcomes prior to positive pregnancy assessment outcome will be imputed to be positive. Note: imputation is only valid for those subjects with following positive assessment outcomes and carried backward. Otherwise, missing=failure.
Secondary Endpoint: Implantation			
Secondary (ITT) Supportive (PP)	**Implantation rate (%)**: =100 * number of gestational sacs observed / number of embryos transferred. • **Time window**: from the start date of first ET to the end of study. • **Numerator:** The number of gestational sacs will be obtained in the "Clinical Pregnancy Assessment" eCRF page. • **Denominator:** The number of embryos transferred will be obtained in the "Embryo Transfer" eCRF page.	Same as method in the section 14.1.1	Same as above
Secondary Endpoint: Clinical pregnancy			
Secondary (ITT) Supportive (PP)	**Clinical pregnancy rate (%)**: =100 * number of subjects with clinical pregnancy/number of subjects with ET cycle. • **Time window**: from the start date of first ET to the end of study.	Same as method in the section 14.1.1	Same as above

	• **Numerator**: The subjects with clinical pregnancy will be determined to be those with positive clinical pregnancy result in the "Clinical Pregnancy Assessment" eCRF page • **Denominator**: The subjects with ET cycle will be determined as those with ET date in "Embryo Transfer" eCRF page.		
Secondary Endpoint: Early abortion			
Secondary (ITT) Supportive (PP)	**Early abortion rate (%)**: =100 * number of subjects with Early abortion/number of subjects with clinical pregnancy. • **Time window**: from the start date of first ET to the end of study. • **Numerator**: The subjects with Early abortion will be determined to be those with early miscarriage date in "early miscarriage" eCRF page. • **Denominator**: The subjects with clinical pregnancy will be determined to be those with positive clinical pregnancy result in the "Clinical Pregnancy Assessment" eCRF page.	Same as method in the section 14.1.1	Missing=not occurred

15 Safety Analyses

The subsections in this section include specifications for summarizing safety endpoints that are common across clinical studies such as adverse events, laboratory tests and vital signs.

Safety analyses will be done on the safety analysis population and according to the as-treated principle.

15.1 Adverse Events

Unless otherwise stated AE will be assessed via summary statistics.

Definitions

Treatment-emergent adverse events (TEAEs): those events with onset dates occurring within the treatment periods. The **treatment period** is defined from the first day of study intervention after randomization until last dose of study intervention date or the clinical cut-off date, whatever occurs earlier.

All analyses described in Section 15.1 will be based on TEAEs if not otherwise specified.

Adverse events **related to study intervention** are those events with relationship missing, unknown or yes.

Missing data handling

Incomplete AE-related dates will be handled as follows:

- In case the onset date is missing completely or missing partially but the onset month and year, or the onset year are equal to the start of study intervention then the onset date will be replaced by the minimum of start of study intervention and AE resolution date.
- In all other cases, the missing onset day or missing onset month will be replaced by 1.
- Incomplete stop dates will be replaced by the last day of the month (if day is missing only), if not resulting in a date later than the date of subject's death. In the latter case, the date of death will be used to impute the incomplete stop date.
- In all other cases, the incomplete stop date will not be imputed. If Stop date of AE is after date of cut-off outcome of AE is ongoing at cut-off.
- Further information after cut-off (like fatal outcome) might be taken from Safety data base and included separately into CSR.

15.1.1 All Adverse Events

Unless otherwise stated, adverse events will be displayed in terms of frequency tables: by primary system organ class (SOC) in alphabetical order and preferred term (PT) in incidence descending order.

If an adverse event is reported for a given subject more than once during study intervention, the worst severity and the worst relationship to study intervention will be tabulated.

In addition, the following overall frequency table will be prepared by primary SOC in alphabetical order and PT in incidence descending order:

- Any TEAE
    - Any either trial drug related TEAEs
    - Any Crinone only related TEAEs
    - Any Duphaston only related TEAEs
    - Any TEAEs related to both drugs
- Any serious TEAEs
    - Any either trial drug related serious TEAEs
    - Any Crinone only related serious TEAEs
    - Any Duphaston only related serious TEAEs
    - Any serious TEAEs related to both drugs
- Any AE by worst severity
    - Any either trial drug related TEAEs by worst severity
    - Any Crinone only related TEAEs by worst severity
    - Any Duphaston only related TEAEs by worst severity
    - Any TEAEs related to both drugs by worst severity
- AEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
    - Any either trial drug related TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
    - Any Crinone only related TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
    - Any Duphaston only related TEAEs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)
    - Any TEAEs related to both drugs leading to death (AEs with Grade 5 or outcome "fatal" if grade 5 not applicable)

15.1.2 Adverse Events Leading to Study Intervention Discontinuation

The following overall frequency tables will be prepared for the adverse event actions for the first study intervention by PT and primary SOC in alphabetical order.

- AEs causing discontinuation of at least one study intervention (either Crinone or Duphaston)
- AEs causing discontinuation of Crinone
    - Crinone only related AEs causing discontinuation of Crinone
- AEs causing discontinuation of Duphaston
    - Duphaston only related AEs causing discontinuation of Duphaston

15.2 Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

15.2.1 Deaths

If there is death reporting in this study, all deaths will be tabulated based on information from the "Study Termination" eCRF page.

- Number of Deaths

In addition, date and cause of death will be provided in individual subject data listing together with selected dosing information (date of first / last administration after randomization) if applicable

- Subject listing of deaths
- Include columns for:
    - AEs with fatal outcome (list preferred terms of AEs with outcome=fatal)

15.2.2 Serious Adverse Events

Please refer to Section15.1.1. For these AEs, subject listings will be provided in addition.

15.2.3 Bleeding

Secondary Endpoint: Luteal phase bleeding			
Secondary (ITT) Supportive (PP)	**Luteal phase bleeding rate (%)**: =100 * number of subjects with Luteal phase bleeding /number of subjects with ET cycle. • **Time window**: from the start date of first ET to β -hCG positive assessment visit. • **Numerator:** The subjects with luteal phase bleeding will be determined to be those with luteal phase bleeding record in the "Bleeding Assessment (Luteal Phase)" eCRF page. • **Denominator:** The subjects with ET cycle will be determined as those with ET date in "Embryo Transfer" eCRF page. • **Additional display:** calculated separately according to the pregnancy outcomes o β-hCG positive o β-hCG negative	Same as method in the section 14.1.1	Missing=not occurred
Secondary Endpoint: Vaginal bleeding			
Secondary (ITT) Supportive (PP)	**Vaginal bleeding rate (%)**: =100 * number of subjects with vaginal bleeding /number of subjects with ET cycle. • **Time window**: from the start date of β-hCG positive assessment visit to the end of study. • **Numerator:** The subjects with vaginal bleeding will be determined to be those with vaginal phase bleeding record in the "Bleeding Assessment (vaginal)" eCRF page. • **Denominator:** The subjects with ET cycle will be determined as those with ET date in "Embryo Transfer" eCRF page. • **Additional display:** calculated separately by pregnancy assessment visit o Visit 6 (Clinical pregnancy assessment) o Visit 7 (Ongoing pregnancy assessment)	Same as method in the section 14.1.1	Missing=not occurred

15.3 Clinical Laboratory Evaluation

β-hCG concentration listing will be provided.

15.4 Vital Signs

Baseline characteristics with respect to vital signs will be part of Section 11.1 (Demographics). There is no post-baseline vital signs data collection.

An additional subject data listing will present all records.

16 Analyses of Other Endpoints

NA

17 References

Miettinen O, Nurminen M. Comparative analysis of two rates. Stat Med 1985;4(2):213-26

18 Appendices

NA