STATISTICAL ANALYSIS PLAN

Protocol Name

Pergoveris™ Post-Marketing Surveillance (PMS)

Version No. (Date)

2.0 (15 FEB 2017)

Written By

PPD / Biostatistician

PPD

Signature page

The Statistical Analysis Plan was written by PPD according to ICH guideline, Local regulation and a related SOP (SOP PPD Statistical Analysis Plan), after training related SOPs.

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The Statistical Analysis Plan was approved by Sponsor.

Approved by:

PPD PPD	Approved by e-mail Merck KGaA	21 FEB 2017 Date
PPD Medical Responsible	Approved by e-mail Merck Korea	21 FEB 2017 Date
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Version Information (Document revision history)

Version	Effective Date	Prepared by Name	Details
1.0	06 Apr 2012	PPD	First Version
2.0	Sponsor's approval date	PPD	Second Version

Abbreviation

Term	Definition
ADR	Adverse Drug Reaction
AE	Adverse Events
ATC code	Anatomical Therapeutic Chemical code
ICH	International Conference on Harmonization
KGCP	Korea Good Clinical Practice
MedDRA	Medical Dictionary for Regulatory Activities
MFDS	Ministry of Food and Drug Safety
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
UAE	Unexpected Adverse Event
WHOART	WHO Adverse Reactions Terminology

Contents

1. Objective of PMS

To analyze safety and efficacy information on Pergoveris™ in post-marketing uses, as well as factors likely to influence safety and efficacy

Primary objective: To get safety information in subjects using Pergoveris™

1) Serious Adverse Event (SAE)
   ① If causing death or threatening one's life
   ② If hospitalization or prolonged duration of hospitalization is necessary
   ③ If causing continuous or significant disability or dysfunction
   ④ If causing congenital malformation or abnormality
   ⑤ Other medically critical conditions
2) Adverse event/adverse drug reaction unexpected in precautions
3) Already known adverse drug reaction
4) Non-serious adverse drug reaction
5) Other safety/efficacy related information (influence upon clinical laboratory value, etc.)

2. Patient population

Women with serious deficiency of Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH) at less than 1.2 IU/L of endogenous serum LH

3. Sample size

A total of 600 cases or more shall be reported as per the number of report cases pursuant to the Paragraph 3 of Article 6 of the 'Re-examination Standards for New Drugs Etc.' (Ministry of Food and Drug Safety Notification No. 2014-61).

4. Study items

4.1 Basic information of subject

1) Date of birth

4.2 Medical history of subject

1) Concurrent disease
2) Allergic history

3) Period for infertility
4) Causes for infertility
   ① Ovary factor
   ② Cervical factor
   ③ Uterine factor
   ④ Oviduct factor
   ⑤ Intra-abdominal abnormality
   ⑥ Male infertility factor
   ⑦ Immunological factor
   ⑧ Unknown cause.
5) Previous ART experience
6) ART procedure
   ① OI (Ovulation Induction)
   ② IUI (Intra Uterine Insemination)
   ③ IVF-ET (In Vitro Fertilization - Embryo Transfer)
   ④ GIFT (Gamete Intra-Fallopian Transfer)
   ⑤ ZIFT (Zygote Intra-Fallopian Transfer)
   ⑥ ICSI (Intra Cytoplasmic Sperm Injection)
   ⑦ Others

4.3 Indication for Pergoveris™

1) The levels of serum LH and FSH
2) The measured date of LH and FSH

4.4 Previous treatments for infertility

1) Presence or absence of previous treatment for infertility
2) The name and the administration cycle of drug (product) used

4.5 Current Pergoveris™ uses

1) Daily dose
2) Administration period: The administration start date and the administration end date

4.6 Concomitant medication

1) The name of concomitant medication (product)
2) Daily dose
3) Route of administration
   - ① PO (Per os)
   - ② IV (Intravenous)
   - ③ IM (Intramuscular)
   - ④ SC (Subcutaneous)
   - ⑤ SL (Sublingual)
   - ⑥ Ophthalmic
   - ⑦ TD (Transdermal)
   - ⑧ Others
4) Administration period: The administration start and end dates

4.7 Safety items

Adverse event (including side effect) and serious adverse event, including onset date, disappearance date, severity, causal relationship with Pergoveris™, measures on administration of Pergoveris™, and progress

4.8 Efficacy items

1) HCG administration
2) Follicular growth
3) Clinical pregnancy
4) Urine HCG test
5) Ultrasonography

5. Statistical methodology

5.1 Analysis dataset

5.1.1 Safety analysis dataset

Safety analysis will be conducted for all subjects who have been administered Pergoveris™ for at least once and followed up, except the following subjects.

- Subjects who have been treated Pergoveris™ before the contract

- Subjects with double enrollments
  (If it is identified that the subject has been enrolled more than once at the same site, under the sponsor's confirmation, the one whose start date of Pergoveris™ administration is earlier will be selected and included for safety assessment.)
- Subjects who do not have any record of Pergoveris™ administration
- Subjects who administer Pergoveris™ for causes other than permitted usage

5.1.2 Efficacy analysis dataset

Among those subjects in safety analysis dataset, efficacy analysis will be conducted for subjects who have been evaluated for follicular growth after administration of Pergoveris™, except the following subjects.

- Subjects who were not assessed for follicular growth
- Subjects whose assessments of follicular growth were considered as 'undecidable'

5.2 General principle

Continuous variables will be presented as descriptive statistics (mean with standard deviation, median, minimum and maximum values). For categorical variables, the number and percentage of subjects for each category and overall will be reported. Percentages will be based on the number of subjects observed at each category. All p-values will be presented as four decimal places. Values other than p-value such as mean, standard deviation, percentage, etc. will be presented as two decimal places.

5.3 Handling of missing data

No imputation of missing data will be performed for statistical analysis except for administration start date and end date.

If only partial information of administration start date or end date is available and is required for calculation of administration period, total dose as well as the average daily dose, the following methods will be used.

- If day is missing, the day will be imputed as day 1.
- If month is missing, the month will be imputed as January.
- If year is missing, the date will be considered as missing.

5.4 Demographics and baseline characteristics

Demographics and baseline characteristics will be analyzed as below.

- **Variables that will be presented by frequency and percentage**

  Age group, concurrent disease, allergic history, period for infertility, causes for infertility*, previous ART experience, ART procedure*, levels of serum Luteinizing Hormone (LH), levels of serum Follicle Stimulating Hormone (FSH), previous treatments for infertility

  * Multiple responses

- **Variables that will be presented by descriptive statistics (mean with standard deviation, median, minimum and maximum values)**

  Age, period for infertility, previous ART experiences, serum Luteinizing Hormone (LH), serum Follicle Stimulating Hormone (FSH)

- **Variables that will be classified by ATC code**

  - Previous treatments for infertility: The frequencies and percentages of subjects having previous treatments for infertility as well as previous treatments for infertility classified by ATC (Anatomical Therapeutic Chemical) code will be presented.

  - Concomitant medication: The frequencies and percentages of subjects having concomitant medications as well as concomitant medications classified by ATC code will be presented.

5.5 Pergoveris™ exposure

Pergoveris™ exposure will be analyzed as below.

- **Administration period**

  Administration period is defined as the sum of each administration period and will be summarized as descriptive statistics. Also, the administration period will be classified as two levels (≤ median, > median) and presented by the frequency and percentage for each level.

- **Total dose**

  Total dose is defined as the sum of total doses on each administration period and will be summarized as descriptive statistics. Also, the total dose will be classified as two levels (≤ median, > median) and presented by the frequency and percentage for each level.

- **Average daily dose**

Average daily dose is defined as total dose divided by administration period and will be summarized as descriptive statistics. Also, the average daily dose will be classified as two levels (≤ median, > median) and presented by the frequency and percentage for each level.

5.6 Definition of special population

Definition of special population is defined as below.

- **Children and adolescent and geriatrics**

Special population	Chinese character	Age
Children and adolescent	小兒	18 years or younger
Geriatrics	高齡者(老人)	65 years or older

- **Hepatic impairment**

Hepatic impairment in concurrent disease was recorded as 'Yes'.

- **Renal impairment**

Renal impairment in concurrent disease was recorded as 'Yes'.

5.7 Safety evaluation

- **Occurrence of adverse event**
  - For adverse event (AE), adverse drug reaction (ADR), unexpected adverse event (UAE) and serious adverse event (SAE), the total number of subjects, the number of events, the occurrence rate and 95% confidence interval will be summarized.
  - AE and ADR will be classified by the system-organ class (SOC) and preferred term (PT) using WHOART (WHO Adverse Reactions Terminology) for n^{th} investigation report and MedDRA (Medical Dictionary for Regulatory Activities) for re-examination report, and summarized by the number of subjects, the occurrence rate and the number of events.
  - The details of unexpected adverse event, serious adverse event and adverse event of subjects who are excluded from safety evaluation in accordance with paragraph 5.1.1 will be listed.
  - Severity, causal relationship, actions taken regarding Pergoveris™ administration and progress of AE categorized by SOC and PT using WHOART for n^{th} investigation report and MedDRA for re-examination report will be analyzed by presenting the number of events and

percentage. If there are several levels for severity, causal relationship, actions taken regarding Pergoveris™ administration and progress of the same AEs, the level that will be used for the analysis will be the worst one on subject level.

- **Factors that might affect the safety evaluation**

The occurrence of adverse event for each factor o f demographics (age), baseline characteristics (concurrent disease, period for infertility, allergic history, previous assisted reproductive technology experience, luteinizing hormone, follicle stimulating hormone, previous treatments for infertility, concomitant medication), Pergoveris™ exposure (average daily dose, total duration, total dose) and special population (hepatic impairment, renal impairment) will be presented by the frequency and rate with 95% confidence interval. The AE rate for each factor will be analyzed using Pearson's chi-squire test or Fisher's exact test.

Additionally, the occurrence of adverse event for all factors described above will be analyzed using multivariable logistic regression.

5.8 Efficacy evaluation

- **Follicular growth and clinical pregnancy**
  - Follicular growth: The frequency and percentage of subjects who are thought to be 'effective' (at least one follicle in more than 17mm of mean diameter on ultrasonography) will be presented.
  - Clinical pregnancy: For the subjects who underwent clinical pregnancy test (urine HCG test or ultrasonography), the frequency and percentage of subjects who are pregnant (urine HCG test 'Positive' or ultrasonography 'Yes') will be presented.

- **Factors that might affect the effectiveness in follicular growth**

The effectiveness in follicular growth for each factor of demographics (age) and baseline characteristics (concurrent disease, period for infertility, allergic history, previous assisted reproductive technology experience, luteinizing hormone, follicle stimulating hormone, previous treatments for infertility, concomitant medication), Pergoveris™ exposure (average daily dose, total duration, total dose) and special population (hepatic impairment, renal impairment) will be presented by the frequency and percentage. The effective rate for each factor will be analyzed using Pearson's chi-squire test or Fisher's exact test.

Additionally, the effectiveness for all factors described above will be analyzed using multivariable

logistic regression.

5.9 Appendix

- **Appendix 2**

The total number of enrolled subjects, the total number of subjects who are included in safety analysis dataset and efficacy analysis dataset and the total number of subjects who excluded from safety analysis dataset and efficacy analysis dataset and the primary reason for exclusion will be resented on Ministry of Food and Drug Safety (MFDS) Appendix 2 form.

- **Appendix 3-1**

ADR categorized by SOC and PT using WHOART for n^{th} investigation report and MedDRA for re-examination report will be summarized by presenting the total number of occurrence, the number of events and the occurrence rate on MFDS Appendix 3-1 form.

- **Appendix 3-2**

SAE categorized by SOC and PT using WHOART for n^{th} investigation report and MedDRA for re-examination report will be summarized by presenting the total number of occurrence, the number of events and the occurrence rate on MFDS Appendix 3-2 form.

- **Appendix 4**

All of the safety information (study reports, spontaneous reports and literature reports, etc.) collected during the study period will be will be summarized by presenting the total number of occurrence, the number of events and the occurrence rate categorized by SOC and PT using WHOART for n^{th} investigation report and MedDRA for re-examination report on MFDS Appendix 4 form.

- **Appendix 5**

The details of all of the safety information (study reports, spontaneous reports and literature reports, etc.) collected during the study period will be listed on MFDS Appendix 5 form.

6. Dummy table

<Annex>

7. Role & responsibility

Role	Name	Responsibility
Biostatistician	PPD	Statistical Analysis

8. Applied SOPs

SOP No.	SOP Version_Effective date	SOP Name
PPD		Statistical Analysis Plan
		Statistical Analysis Process