Post Marketing Observational Study
Statistical and Analytical Plans

(DUPKST16002)

A SURVEY ON EFFICACY AND SAFETY IN PATIENTS WITH ENDOMETRIOSIS

Ver. 1.0

Changes in the Statistical Analysis Plan

Version 1.0 of the statistical analysis plan was finalized on September 15, 2017. No revisions were made to the plan thereafter.

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1 Introduction

This document provides details of the statistical analysis plan for the "Post Marketing Observational Study of Duphaston Tablets 5 mg - a Survey on Efficacy and Safety in Patients with Endometriosis" (hereinafter referred to as the "study"). The purpose of the statistical analysis plan is to ensure that data are be analyzed properly and efficiently as planned.

2 Outline of the Study

Duphaston tablets have been available for the treatment of endometriosis in Japan since 1965. This study is designed to collect efficacy and safety data in patients with endometriosis to obtain information for the effective and safe use of Duphaston tablets.

Clinical Supply	Duphaston® 5 mg Tablets
Title (Protocol Number)	Post Marketing Observational Study A SURVEY ON EFFICACY AND SAFETY IN PATIENTS WITH ENDOMETRIOSIS (DUPKST16002)
Study Design	Prospective, non-intervention, non-blind, non-control observational study
Observation period	4 cycles
Planned sample size	65 subjects

3 List Of Abbreviations And Definition Of Terms

Term/abbreviation	Definition
The summary statistics	Number of subjects, mean, standard deviation, minimum, median, and maximum

4 Organization for Statistical Analysis Activities

DENSUKE SYSTEMS Co., Ltd. will be contracted by Mylan EPD G.K. to perform the statistical analysis activities planned in this document.

Details of the organization are provided in the "Statistical Analysis Procedure."

5 Study Design

5.1 Study Schedule

Registration Form/Case Report Form	Registration Form	Case Report Form					
Observation time points/cycles	**At enrollment**	**Before treatment initiation**	**At treatment initiation (cycle 1)**	**Cycle 2**	**Cycle 3**	**Cycle 4**	**At the end of the observation period or at discontinuation**
Registration information							
(1) Subject identification No.	○						
(2) Subject initials	○						
(3) Birth date or age	○						
(4) Planned start date of treatment	○						
(5) Oral consent	○						
Patient background characteristics							
(1) Diagnosis		○					
(2) Body height and weight		○					
(3) Pregnancy and lactation status		○					
(4) Menstruation and ovulation status		○					
(5) Complications		○					
(6) Past history		○					
(7) History of allergy		○					
(8) Serious hepatopathy or liver disease		○					
(9) Heart or kidney disease		○					
(10) History of drug treatment		○					
(11) History of surgical treatment		○					
Treatment compliance, clinical course and efficacy							
(1) Observation date (date of confirmation)		○	○		○		○
(2) Start date of treatment		○					
(3) Compliance with Duphaston treatment			○	◎	○	◎	○
(4) Measurement of ovarian chocolate cyst		○			○		○
(5) Severity of dysmenorrhea		○	○	◎	○	◎	○
(6) Use of analgesics		○	○	◎	○	◎	○
(7) VAS for dysmenorrhea		○	○	◎	○	◎	○
(8) Concomitant medications/therapies		○	○	◎	○	◎	○
(9) Date of withdrawal/dropout and its reason							○
Laboratory tests							
(1) Serum CA125		●					●
(2) Others		△					
Adverse events							
Adverse events		○					

One cycle will consist of one menstruation cycle.
Each endpoint will be observed in cycles marked with a symbol. Observation results should be entered in the EDC system.
○: Endpoint
◎: Investigate information on the next observation day, and enter it.
●: Perform the test during a non-menstruation period.
△: Enter information if observed.

5.2 Outcome measures

【Efficacy Variables】

- The volume measurements of ovarian chocolate cysts
- Dysmenorrhea severity
- The use of analgesics
- Dysmenorrhea score
- VAS for dysmenorrhea
- Serum CA125

【Safety Variables】

- Adverse events

5.3 Determination of Sample Size

Planned sample size of the survey: 65 subjects

Rationale for setting:

Whether or not the size of chocolate cyst of the ovary reduced at the end of treatment from baseline will be evaluated using the sign test. When anticipated results would be a decrease-increase ratio of 7:3 and 10% of all subjects being unchanged, a sample size is calculated to be 58 subjects. Assuming a dropout rate of 10%, a necessary sample size of the survey is 65 subjects.

6 Handling of Data

6.1 Analysis Set

The analysis set will consist of all subjects who satisfy inclusion and exclusion criteria and are enrolled in this survey.

The efficacy evaluation will be summarized in the “efficacy analysis set,” which consists of all subjects who receive Duphaston and for whom any of the efficacy variables are observed. The evaluation will also be summarized in the “study completers,” which consists of subjects who complete the treatment without discontinuation.

The safety evaluation will be summarized in the “safety analysis set,” which consists of all subjects who receive the drug.

6.2 Handling of Data by Period

Since the observation period will be set based not on the number of days from the start date of administration but on the menstruation cycle, and the observation data in each menstrual cycle will be obtained from investigation of status per cycle without identifying the first day of menstruation as a base point, the cycles entered in the EDC system will be used as they are and each item will be summarized according to the applicable observation schedule, namely before the start of treatment (cycle -1), at the start of treatment (cycle 1), cycle 2, cycle 3, cycle 4 and at the completion of the observation period (cycle 5). The last observation of the actual evaluations after cycle 1 including those at discontinuation (except for “unknown”) will be summarized as “at last observation.”

Since the recommended regimen of this survey is to start the dosage on the fifth day of each menstrual cycle, the administration can be started during menstruation of cycle 1.

6.3 Handling of Data to Derive Variables

(1) Age

If the birth date and the start date of administration are available, the age at the start date of administration will be calculated. If these dates are not available, the age entered in the EDC system will be used.

(2) Volume of ovarian chocolate cyst

The value used will be automatically calculated by the EDC system with the following conversion formula using the major axis (D1 [cm]) and minor axis (D2 [cm]) of ovarian chocolate cyst.

$$\text{Volume } [cm^3] = \{(D1 + D2) \times 1/2\}^3 \times 0.52$$

(3) Dysmenorrhea score

The dysmenorrhea score used will be a total of a dysmenorrhea severity score and a score for the use of analgesics and automatically calculated by the EDC system. If either of the scores is unknown, the dysmenorrhea score will be handled as unknown.

6.4 Handling of Adverse Event Data

Adverse event terms entered in the EDC system will be replaced with the MedDRA/J terms. The latest version of the MedDRA/J at the time of summarization will be used and clearly specified in each analysis form. If reanalysis is required, the latest version at the time of reanalysis will be used.

7 Matters concerning statistical analysis

7.1 Level of Significance for Statistical Testing and Confidence Level for Interval Estimation

Unless otherwise specified, statistical testing will be performed with a two-sided level of significance of 5%, and a two-sided confidence level of 95% will be used for interval estimation. No multiplicity adjustment will be made.

7.2 Software to be Used for Statistical Analysis

Windows SAS 9.3 will be used for statistical analysis.

Microsoft Excel 2010 will be used to output analytical data sheets but not for the calculation of statistics.

7.3 Statistical Methods

Categorical data including categories of continuous data will be presented using the number and percentage of subjects in each category. Missing values will normally be excluded from the calculation of frequencies. Data in the “Unknown” category will be included in the summarization of patient characteristics but excluded from that of efficacy variables because they are equivalent in nature to missing values.

Improvement rates will be calculated as the percentage of subjects with an improvement of at least one category among those with assessments other than “Unknown” available before and after treatment.

Continuous data will be presented using the following summary statistics: number of subjects, mean, standard deviation, median, minimum, and maximum.

Summary statistics will be reported to one more digit than the significant figures for mean, standard deviation, and median, and to the same number of digits as the significant figures for minimum and maximum.

The following procedures will be used for statistical testing and interval estimation:

1) Testing for comparing pre- and post-treatment values and scores

The UNIVARIATE procedure will be used to compare pairs of pre- and post-treatment values by the sign test, Wilcoxon signed-rank test, etc. In the comparison of scores, values equivalent to “Unknown” will be excluded before testing.

2) Calculation of confidence intervals for incidence rates (improvement rates)

The EXACT BINOMIAL option of the FREQ procedure will be used to calculate exact confidence intervals based on binomial distribution.

8 Statistical Analysis Variables

8.1 Disposition of Subjects

The following data will be presented: numbers of subjects registered, subjects with case report forms collected, subjects included in the safety analysis set, subjects excluded from the safety analysis set, subjects included in the efficacy analysis set, and subjects excluded from the efficacy analysis set.

8.2 Patient Characteristics

Patient characteristics will be summarized in the "safety analysis set," "efficacy analysis set," and "study completers."

Data will be summarized according to section 7.3. The number of subjects with missing values for each item will not be shown.

Item	Categorical data: Data: Presented by category. Continuous data: The summary statistics
Age (years)	≥ 20 and < 30 years old ≥ 30 and < 40 years old ≥ 40 and < 50 years old The summary statistics
Height (cm)	The summary statistics
Weight (kg)	The summary statistics
Diagnosis	Endometriosis
Pregnancy and lactation status	No, Yes, Unknown
Menstruation status	Normal menstrual cycle, No normal menstrual cycle, Unknown
Menstrual cycle (days)	The summary statistics
Ovulation	No, Yes, Unknown
Complications	No, Yes, Unknown
Past history	No, Yes, Unknown
History of allergy	No, Yes, Unknown
History of allergy to	Drug, Other
Hepatopathy or liver disease	No, Yes, Unknown
Severity of hepatopathy or liver disease	Mild, Moderate, Severe
Heart disease	No, Yes, Unknown
Kidney disease	No, Yes, Unknown
History of drug treatment (for endometriosis)	No, Yes, Unknown
History of surgical treatment (for endometriosis)	No, Yes, Unknown

8.3 Efficacy Variables

Pre- and post-treatment values for each variable will be compared by statistical testing.

8.3.1 Study Primary Variables

(1) Change in the volume of ovarian chocolate cyst before and after treatment

For the volume calculated from the major and minor axes of ovarian chocolate cyst, the values before treatment initiation and at last observation will be compared, frequency of increase and decrease will be summarized and the sign test will be performed separately in the "efficacy analysis set" and "study completers."

In the assessment of increase and decrease, the change rate within ±15% of the volume of ovarian chocolate cyst after treatment from before treatment initiation will be defined as "unchanged."

If there are two or more cysts at a given assessment point, the total volume will be considered as the volume at that point and used for the analysis.

(2) Volume of ovarian chocolate cyst over time before and after treatment

For the volume calculated from the major and minor axes of ovarian chocolate cyst (a total volume if there are two or more cysts), the value, difference from the value before treatment and change rate will be calculated using the summary statistics at each measurement point and last observation in each analysis set, namely "efficacy analysis set" and "study completers," and the Wilcoxon signed-rank test will be performed for the difference and change rate.

8.3.2 Study Secondary Variables

(1) Change in the severity of dysmenorrhea

In each analysis set, namely "efficacy analysis set" and "study completers," the frequency of categories compared to the value before treatment will be calculated by cross tabulation, and the improvement rate and its 95% confidence interval (CI) will be calculated, at each observation point and last observation.

(2) Change in the use of analgesics

In each analysis set, namely "efficacy analysis set" and "study completers," the frequency of categories compared to the value before treatment will be calculated by cross tabulation, and the improvement rate and its 95% CI will be calculated, at each observation point and last observation.

(3) Change in the dysmenorrhea score

In each analysis set, namely "efficacy analysis set" and "study completers," the frequency compared to baseline will be calculated by cross tabulation, and the improvement rate and its 95% CI will be calculated, at each observation point and last observation. The score value and difference from the value before treatment will be calculated at the same points using the summary statistics, and the Wilcoxon signed-rank test will be performed.

(4) Change in the severity of dysmenorrhea pain (VAS)

In each analysis set, namely "efficacy analysis set" and "study completers," the difference from the value before treatment and change rate will be calculated using the summary statistics at each observation point and last observation, and the Wilcoxon signed-rank test will be performed for the difference and change rate.

(5) Change in serum CA125

Separately in the "efficacy analysis set" and "study completers," the values before treatment initiation and at last observation will be compared, the value, difference from the value before treatment and change rate will be calculated using the summary statistics, and the Wilcoxon signed-rank test will be performed for the difference and change rate.

8.4 Safety Variables

The following variables will be summarized in the “safety analysis set.”

8.4.1 Adverse Events

Occurrence of adverse events will be summarized using the terms replaced with the MedDRA/J terms.

Assessment of severity and assessment criteria of causal relationship with Duphaston are described in the “Reference” page of the “Implementation Guidance on Specified Drug-use Survey.”

8.4.1.1 Summary of Adverse Event

The number of subjects with AEs, frequency and number of AEs occurring throughout the study will be summarized by System Organ Class (SOC) and Preferred Term (PT) of the MedDRA/J.

The same items will also be summarized for ADRs, serious AEs and serious ADRs in the same manner.

The results of summary will be listed in the internationally agreed order for the SOCs, and in descending order of frequency for the PTs and in order of PT codes for PTs of the same rank.

8.4.1.2 Individual Adverse Events

A list of adverse events will be prepared.