Non-Interventional Study Protocol
B2311067

Post-Marketing surveillance to observe the safety and efficacy of Duavive tab. 0.45 mg/20 mg

Statistical Analysis Plan
(SAP)

Version: Version 3.0

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date of Revision	Reason for change	Author name
Version 1.0	04-APR-2016	1st Version	PPD
Version 2.0	08-SEP-2016	Add analysis of hormone therapy related to menopause before administration of Duavive Tab.	PPD
Version 3.0	TBD	1) Addition of calculation method of 'Duration of disease' 2) Addition of AE listings 3) Addition of SAE/SADR, unexpected AE/unexpected ADR by preferred terms according to the frequency categories in the approved local label 4) Addition of Basic Results Tables 5) Change of AE coding dictionary	PPD

2 INTRODUCTION

Note: In this document any text taken directly from the protocol is *italicized.*

Duavive tab. is a tissue selective estrogen complex (TSEC) made by combining bazedoxifene, a selective estrogen receptor modulator (SERM), with conjugated estrogen (CE). Duavive tab. was approved by the Ministry of Food and Drug Safety on 25 July 2014 for the treatment for moderate to severe vasomotor symptoms associated with menopause and the prevention of post-menopausal osteoporosis in women with a uterus1.

As required for new medications approved by the MFDS, safety and efficacy information should be provided for a minimum of 600 subjects treated in the setting of routine practice during 6 years following the approval (25 July 2014 to 24 July 2020). This non-interventional post-marketing surveillance (PMS) study is an obligation to the MFDS.

Background information on Duavive tab. can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to Duavive tab. in this study.

2.1 STUDY DESIGN

This is an open-label, non-comparative, non-interventional, prospective, and multi-center study conducted in Korean health care centers by accredited physicians (i.e., investigators). The study will be conducted with those subjects administered with Duavive tab. as a part of routine treatment who comply with the local labeling. Duavive tab. will be administered according to the "Dosage and Administration" specified in the approved

local product document. Since this study intends to observe routine treatment situation, there is no visit or activity mandated by this study. The investigator will collect data by observing enrolled subjects and record the information on each subject's case report form (CRF).

Study population

At least 600 subjects will be enrolled in about 20 study sites in this study based on the MFDS re-examination regulation. Each investigator will sequentially enroll all female subjects who are administered Duavive tab. for the first time according to the local product document after the start of the study at a study site and who agree to participate in this study by signing the data privacy statement until the total requested cases per site are collected for this study.

[Inclusion criteria]

To be eligible to enroll in this study, a patient will have to meet the following inclusion criteria:

1) *Women who have been administered Duavive tab. for the first time according to the current local labeling (indications, administration and dosage) of Duavive tab. after the start of the study at a study site*

Indications

This drug is used to treat the following diseases in women with a uterus for:

1) *Treatment for moderate to severe vasomotor symptoms associated with menopause*
2) *Prevention of post-menopausal osteoporosis*

Administration and Dosage

1) *Treatment for moderate to severe vasomotor symptoms associated with menopause*
   The recommended dosage is one DUAVIVE tablet daily.
2) *Prevention of post-menopausal osteoporosis*
   The recommended dosage is one DUAVIVE tablet daily.
3) *General dosing information*
   Take DUAVIVE once daily, without regard to meals. Tablets should be swallowed whole. They should not be chewed or crushed.
4) *Recommendation for Calcium or Vitamin D supplementation*
   Women taking DUAVIVE for prevention of post-menopausal osteoporosis should add supplemental calcium and/or vitamin D to their diet if daily intake is inadequate.
5) *Administration Instructions for Missed Doses*
   If a dose of DUAVIVE is missed, instruct patients to take it as soon as remembered unless it is almost time for the next scheduled dose. They should not

take two doses at the same time.

2) *Post-menopausal women*
3) *Women who have consented to participate in this study by signing the data privacy statement*

[Exclusion criteria]

Patients, who meet at least one of the following criteria, will not be included in the study:

1) *Women who have deviated from local labeling in taking this drug*
2) *Women with undiagnosed abnormal uterine bleeding*
3) *Women with known, suspected, or past history of breast cancer*
4) *Women with known or suspected estrogen-dependent neoplasia*
5) *Women with active deep venous thrombosis, pulmonary embolism, or history of these conditions*
6) *Women with active arterial thromboembolic diseases (e.g.: stroke, myocardial infarction) or history of these conditions*
7) *Women taking progestins, estrogens, or estrogen agonist/antagonists*
8) *Women with hypersensitivity (e.g.: anaphylaxis, angioedema) to estrogens, bazedoxifene, or any ingredients*
9) *Women with known hepatic impairment or diseases*
10) *Women with known protein C, protein S, or antithrombin deficiency or other known thrombophilic disorders*
11) *Pregnancy, women who may become pregnant and nursing mothers*
12) *Patients with hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption*

2.2 STUDY OBJECTIVES

In this study, the safety and efficacy of Duavive tab. 0.45 mg/20 mg will be observed under the actual condition of use.

The objectives of this post-marketing surveillance are as follows:

1) *To observe the safety and efficacy profile of Duavive tab. 0.45 mg/20 mg in the Korean subjects.*
2) *To identify the factors that can have an effect on the safety and efficacy profile of Duavive tab. 0.45 mg/20 mg in the Korean subjects.*

3 INTERIM AND FINAL ANALYSES

This Statistical Analysis Plan (SAP) details the analyses and outputs to be produced for the interim and final analyses.

For the first 2 years, 6-month reports will be submitted to the MFDS (i.e., Reports 1-1, 1-2, 2-1, and 2-2). Thereafter, data collected in the 3rd, 4th, and 5th year will be reported to the MFDS annually. The final study report (i.e., re-examination report) will be submitted to the MFDS in the 6th year to include all data collected during the whole study period The first interim analysis will be performed once this SAP is finalized.

All analyses outlined in this SAP, except for those described below, will be performed for each interim analysis for the periodic report annually.

- Type of medical history (Past disease, Present disease)
- Type of concomitant medications
- Type of Hormone therapy related to menopause before administration of Duavive Tab.
- SAE/SADR, unexpected AE/unexpected ADR by preferred terms according to the frequency categories in the approved local label
- Basic Results Tables

4 HYPOTHESES AND DECISION RULES

Not Applicable

5 ANALYSIS SETS/ POPULATIONS

All subjects entered into this study will be evaluated as to whether they are eligible to be in the Safety Analysis Set and the Effectiveness Analysis Set.

All subjects excluded from the Safety Analysis Set will be accounted for as part of the subject accounting in the Clinical Study Report. Any adverse events reported for subjects excluded from the Safety Analysis Set will also be described.

5.1 SAFETY ANALYSIS SET

Subject who have been administered Duavive tab. at least once and completed follow up will be included in the safety analysis set.

The following exclusions from the Safety Analysis Set are to ensure that the subjects who are not providing data to the analyses but have some record of treatment do not over-inflate the denominator for the analyses.

The following cases are excluded from the safety analysis set:

1) Subjects who were enrolled in the study prior to the starting date of the study period at the site
2) Subjects who didn't receive Duavive tab.

3) Follow-up failure: Subjects for whom adverse event status (Adverse Events status is unknown or missing in the CRF) could not be established
4) Subjects who violated inclusion/exclusion criteria (see section 2.1)

Statistical analysis on safety parameters will be performed on the safety analysis set.

5.2 EFFECTIVENESS ANALYSIS SET

The effectiveness analysis set is a subset of the safety analysis set.

The following cases are excluded from the effectiveness analysis set:

1) Subjects excluded from safety analysis set listed in section 5.1
2) Subjects whose items on the clinical response of "Treatment for moderate to severe vasomotor symptoms associated with menopause" in effectiveness evaluation on the CRF are not completed†
3) Subjects whose items on the clinical response of "Prevention of post-menopausal osteoporosis" in effectiveness evaluation on the CRF are not completed‡
4) Subjects who are assessed as "unevaluable" on the clinical response of "Treatment for moderate to severe vasomotor symptoms associated with menopause" in effectiveness evaluation on the CRF†
5) Subjects who are assessed as "unevaluable" on the clinical response of "Prevention of post-menopausal osteoporosis" in effectiveness evaluation on the CRF‡

† Only if main indication is "Treatment for moderate to severe vasomotor symptoms associated with menopause"
‡ Only if main indication is "Prevention of post-menopausal osteoporosis"

Statistical analysis on effectiveness parameters will be performed on the effectiveness analysis set.

6 ENDPOINTS AND COVARIATES

6.1 SAFETY ENDPOINTS

Adverse Event Occurrence

6.2 EFFECTIVENESS ENDPOINT(S)

1) Treatment for moderate to severe vasomotor symptoms associated with menopause: Investigator's judgment on the improvement of the symptom recorded during the treatment

2) Prevention of post-menopausal osteoporosis:
   - The investigator's evaluation of preventive effect based on this information.
   - Laboratory test results (if any)
     - X-ray examination
     - Bone density test record (Bone mineral density)
     - Other blood test record related to resorption of bone and osteogenesis (Biochemical marker of bone turnover)

7 HANDLING OF MISSING VALUES

No imputation of missing data will be performed. Missing or incomplete dates will be excluded from the analysis.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

All test statistics will be the results of two-sided tests with the statistical significant level of 0.05.

8.1.1 Analysis for Continuous Data

Descriptive summary statistics for continuous variables will include the following:
- number of subjects (n), mean, standard deviation (SD), median, minimum and maximum.

8.1.2 Analysis for Categorical Data

Descriptive statistics for categorical variables will be given as frequencies and percentages. The denominator will be the number of subjects included either in the safety analysis set or effectiveness analysis set depending on where the analysis is presented.

Where appropriate, the percentages will be presented with a corresponding 95% confidence interval. Comparisons between subcategories of each baseline characteristic will be made using chi-square test or Fisher's exact test. Test statistics include p-value. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of chi-square test.

8.2 STATISTICAL ANALYSES

8.2.1 Safety Analyses

8.2.1.1 Baseline Characteristics

Baseline characteristics for this study are defined as follows:

- Continuous measurements will be presented Mean (SD) :
  - Age
  - Duration of disease†
  - Total administration period of Duavive tab. ‡

- Categorized measurements will be presented n(%) :
  - Main indication (Treatment for moderate to severe vasomotor symptoms associated with menopause, Prevention of post-menopausal osteoporosis, both)
  - Geriatric status (<65 years, ≥65 years)
  - Age (<50 years, ≥50 years and ≤59 years, ≥60 years and ≤69 years, ≥70 years*)
  - Allergy history (Yes, No)
  - Duration of disease† (<3 months, ≥3 months and <6 months, ≥6 months*)
  - Medical history (Past disease, Present disease/Yes, No)
  - Total administration period of Duavive tab. (<3 months, ≥3 months and <6 months, ≥6 months*)
  - Long-term administration (<22 weeks, ≥22 weeks of total administration period of Duavive tab.)
  - Kidney disorder (Yes, No)
  - Liver disorder (Yes, No)
  - Concomitant medication (Yes, No)
  - Hormone therapy related to menopause before administration of Duavive Tab. (Yes, No)

† Only if main indication is "Treatment for moderate to severe vasomotor symptoms associated with menopause"
Duration of disease (months) = (number of years after diagnosis)×12+(number of months after diagnosis)

‡ Total administration period of Duavive tab.= Sum of each administration period
: Each administration period = (Administration end date) – (Administration start date) + 1
If the medication is being continued at the completion of the study, administration end date is replaced with effectiveness evaluation date at last visit.

* The categories can be altered depending on the data distribution.

8.2.1.2 Adverse Events

All adverse events reported after start of administration of Duavive tab. will be considered as on-treatment and summarised. Adverse events reported with partial dates of onset will be assumed as on-treatment, unless month/year of AE onset date is before start date of Duavive tab.

In the safety analysis set, the number of subjects to whom AE occurred and the number of AEs will be calculated and the incidence rate of AEs will be estimated with its 95% confidence interval.

8.2.1.3 Adverse Events by Baseline Characteristics

The following will be presented for AEs, split by the baseline characteristics using the safety analysis set:

- The number of subjects to whom AE occurred and the number of AEs will be calculated.
- The proportion of subjects to whom AE occurred and its 95% confidence interval will be estimated and compared between subcategories of each baseline characteristic using chi-square test or Fisher's exact test. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of chi-square test.
- Adverse event presentations will be split by the following baseline characteristics (See Categorized measurements of Section 8.2.1.1)

8.2.1.4 Adverse Events by Preferred Terms (AEs/ADRs/SAEs)

All AEs recorded in CRFs will be classified into the system organ class (SOC) and the terms of AE will be coded according to the classification of AEs in 'MedDRA'. All AEs, except for 'Unlikely', will be considered as AE whose causal relationship to study drug cannot be excluded (hereinafter "Adverse Drug Reaction (ADR)").

- The number and percentage of AE will be presented overall and by preferred term. This will be repeated by:
  - Severity
  - Measures taken in relation to Duavive tab.
  - Other measures
  - Seriousness
  - Outcome
  - Causal relationship of the adverse event with the study drug
  - Other causal relationship of the adverse event with the study drug
- The number of subjects and the number of unexpected AE/ADR, Serious AE (SAE)/Serious ADR (SADR), unexpected SAE/SADR, AE/ADR will be calculated according to the preferred terms. Also, the proportion of subjects to whom AE/ADR occurred will be estimated. In re-examination report, SAE/SADR and unexpected AE/unexpected ADR in accordance with preferred terms will be presented respectively according to the frequency categories of adverse events in the approved local label.
- The subjects with SAE, unexpected AE, unexpected SAE, AE of geriatric, renal disorder, hepatic disorder will be listed for safety analyses set.For subjects excluded from safety analysis set*, the number of subjects and the number of

unexpected AE/ADR, Serious AE (SAE)/Serious ADR (SADR), unexpected SAE/SADR, AE/ADR will be calculated according to the preferred terms. Also, the proportion of subjects to whom AE occurred will be estimated.

* Subjects excluded from safety analysis set: Subjects excluded from safety analysis set except for 'Subjects who didn't receive Duavive tab.' and 'Follow-up failure: Subjects for whom adverse event status (Adverse Events status is unknown or missing) could not be established'.

Note: Unexpected AEs/ADRs will be classified by medical review and with reference to the local product document. Terms already included in the local product document are classified as 'expected'. All other terms that are not included in the local product document will be classified as 'unexpected'.

- The subjects with SAE, unexpected AE, unexpected SAE, AE of geriatric, renal disorder, hepatic disorder will be listed for subjects excluded from safety analyses set.

8.2.2 Effectiveness Analyses

Final effectiveness will be analyzed based on the evaluation of investigator for clinical response. Effectiveness analyses will be conducted for each indication. Because both indications can be selected, subjects can include in effectiveness analysis in duplicate.

1) Treatment for moderate to severe vasomotor symptoms associated with menopause:

   Subjects who were assessed as 'improved' in "effectiveness evaluation" would be considered as "Effectiveness" and 'no change', 'aggravated' in "effectiveness evaluation" would be considered as "Ineffectiveness". The effectiveness rate at last visit, which is defined as the proportion of subjects classified as 'effectiveness' in the final effectiveness evaluation, will be estimated with its 95% confidence interval.

   For at last visit, the effectiveness rate according to the baseline characteristics listed in categorized measurements of section 8.2.1.1 (except for "Main indication" item) will be analyzed. Chi-square test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of chi-square test.

   The frequency and percentage of clinical response evaluation at 3 months (±2 weeks), 6 months (±2 weeks), last visit ('Effectiveness (improved)', 'Ineffectiveness (no change, aggravated)') will be summarized.

2) Prevention of post-menopausal osteoporosis:

Subjects who were assessed as 'effective in prevention' in "effectiveness evaluation" would be considered as "effectiveness" and 'ineffective in prevention' in "effectiveness evaluation" would be considered as "ineffectiveness". The effectiveness rate at last visit, which is defined as the proportion of subjects classified as 'effectiveness' in the final effectiveness evaluation, will be estimated with its 95% confidence interval.

For at last visit, the effectiveness rate according to the baseline characteristics listed in categorized measurements of section 8.2.1.1 (except for "Main indication" item) will be analyzed. Chi-square test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of chi-square test.

The frequency and percentage of clinical response evaluation at 3 months (±2 weeks), 6months (±2 weeks), last visit ('Effectiveness(effective in prevention)', 'Ineffectiveness(ineffectiveness in prevention)') will be summarized.

Also, if laboratory test data can be collected, the follow-up data at last visit will be compared with baseline data.

- X-ray examination
- Bone density test record (Bone mineral density)
- Other blood test record related to resorption of bone and osteogenesis (Biochemical marker of bone turnover)

8.2.3 Other Analyses

The following Basic Results Tables will also be produced for the final study report:

- Baseline Characteristics in safety analysis set
- Summary of Baseline Characteristics in safety analysis set
- All Adverse Events in safety analysis set
- Summary of Each SOC/PT of Adverse Events in safety analysis set
- Summary of Effectiveness Evaluation in effectiveness analysis set
- Subjects Flow Chart (the number of subjects who started the study, the number of subjects in safety analysis set, the number of subjects in effectiveness analysis set)

9 APPENDICES

9.1 APPENDIX 1: NOTES

- Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.
- Ambiguous data such as “≥20”, “>20” will be excluded from analysis.