NON-INTERVENTIONAL (NI) POST-MARKETING SURVEILLANCE PROTOCOL

Study Information

Title	**Post-Marketing surveillance to observe the safety and efficacy of Duavive tab. 0.45 mg/20 mg**
Protocol Number	B2311067
Protocol Version	Amendment 6.0
Date of Latest Version of Protocol	24 March 2020
Active Substance	PF-05212370
Medicinal Product	Duavive tab. 0.45 mg/20 mg (conjugated estrogens 4.29% 10.4895 mg, bazedoxifene acetate 22.56 mg)
Objective of Study	To observe the safety and efficacy of Duavive tab. 0.45 mg/20 mg during the post-marketing surveillance period.
Created by	PPD Pfizer Pharmaceuticals Korea Ltd. Seoul, Korea

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AEM	Adverse Event Monitoring
EDP	Exposure During Pregnancy
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MFDS	Ministry of Food and Drug Safety
NIS	Non-Interventional Study
PMS	Post-Marketing Surveillance
SAP	Statistical Analysis Plan
SRSD	Single Reference Safety Document

2. RESPONSIBLE PARTIES

Principal Investigator of the Protocol

Name, Degree	Title	Affiliation	Address
PPD M.D.	Non-Interventional Study Lead	Pfizer Pharmaceuticals Korea Ltd.	PPD Korea

3. AMENDMENTS AND UPDATES

Amendment Number	Date	Substantial or administrative amendment	Protocol section changed	Summary of amendment(s)	Reason
Final version 1.0	28 Nov 2014	Not applicable	Not applicable	Not applicable	Not applicable
Amendment 2.0	04 Mar 2015	Substantial Amendments	(1) 7.2.1. Inclusion Criteria	(1) In the inclusion criteria, the item "Women administered for at least one month" was amended to "Women administered at least once".	(1) To include all the patients whose data must be collected in this study
			(2) 7.2.4. Study Procedure	(2) Sections of data to be collected were added and clarified.	(2) To reflect the supplementary opinions of MFDS and maintain the consistency with the case report form
			(3) 7.3.1. Safety Variables	(3) The safety variable section was added.	(3) To maintain consistency with the case report form
			(4) 7.3.2. Safety Evaluation	(4) The description related to the 'serious adverse events' was corrected.	(4) To comply with the standard requirements of Pfizer
			(5) 7.3.3. Efficacy Variables	(5) The descriptions related to efficacy variables were divided according to the purpose of administration.	(5) The efficacy variables were clarified.
			(6) 7.7. Data Analysis	(6) Additional interpretation items and interpretation methods were described.	(6) To reflect the supplementary opinions of MFDS
			(7) 9.1. Single Reference Safety Document	(7) New section was added.	(7) To comply with the protocol template of Pfizer
Amendment 3.0	30 Apr 2015	Substantial Amendments	(1) 7. Study Methods	(1) Corrections and additions were made to make it fit for the prospective study, and definitions of the inclusion criteria and the study end time were clarified.	To perform the study as a prospective study following the review opinion of MFDS
			(2) 8. Protection of Human Subjects	(2) Requirements for the acquisition of the Data Privacy Statement and withdrawal were specified.	
			(3) 9. Report of Adverse Events	(3) The content was corrected to correspond to a prospective study.	

Amendment 4.0	16 Sep 2015	Substantial Amendments	(1) 7.2.4. Study Procedure (2) 7.2.4.3. Status of Administration of Duavive Tab. (3) 7.3.2.1. Efficacy Evaluation (4) 7.7.1.3. Section Related to Efficacy	(1) The content of the follow-up for long-term administration subjects was added. (2) Since the long-term administration subjects are included, the definition of study end time was deleted. (3) The content of the evaluation for long-term administration subjects was added. (4) The efficacy interpretation section for long-term subjects was added.	To reflect the review opinion of MFDS on the collection of information related to the follow-ups for long-term administration subjects
Amendment 5.0	05 Aug 2016	Substantial Amendments	7.2.4.4. Status of Administration of Hormone therapy	The status of administration of Hormone therapy before the Duavive Tab. administration was added.	To add the contents whether the patients have an experience about Hormone therapy or not and the reason why the Hormone therapy was discontinued.
Amendment 6.0	24 Mar 2020	Administrative amendment	Cover	Change of Principal Investigator(s) of the Protocol	Change of of responsible colleague
		Administrative amendment	2. RESPONSIBLE PARTIES	Change of Principal Investigator(s) of the Protocol	Change of of responsible colleague
		Substantial Amendments	7.3.1.1. Collection of Adverse Events Data	Change of AE Coding Dictionary	Change of Coding Dictionary according to New Drug Re-examination Guidelines
		Substantial Amendments	7.6. Data Management	Change of AE Coding Dictionary	Change of Coding Dictionary according to New Drug Re-examination Guidelines

4. MILESTONES

Milestones	Planned date
Start date of data collection	01 January 2016
End date of data collection	01 December 2018
First year (1-1) periodic report (MFDS)	24 March 2015
First year (1-2) periodic report (MFDS)	24 September 2015
Second year (2-1) periodic report (MFDS)	24 March 2016
Second year (2-2) periodic report (MFDS)	24 September 2016
Third year annual report (MFDS)	24 September 2017
Fourth year annual report (MFDS)	24 September 2018
Fifth year annual report (MFDS)	24 September 2019
Re-examination report (MFDS)	24 October 2020

Abbreviation: MFDS = Ministry of Food and Drug Safety.

5. RATIONALE AND BACKGROUND

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 uterus[1].

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.

6. OBJECTIVE OF STUDY

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.

7. RESEARCH METHODS

7.1. 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).

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.

7.2. Setting

7.2.1. 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

2) Post-menopausal women

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.

3) Women who have consented to participate in this study by signing the data privacy statement

7.2.2. 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

7.2.3. Duration of the Study

As specified in the product approval issued by the Ministry of Food and Drug Safety, the study will be conducted for 6 years from the approval date of 25 July 2014 to 24 July 2020.

7.2.4. Study Procedure

This study doesn't require a screening procedure. All the subjects who consented to participate in this study by being administered with Duavive tab. for the first time according to the local product document after the start of the study at a study site and by signing the data privacy statement and who don't fall under the exclusion criteria will be enrolled sequentially.

Since this study aims to collect data under usual clinical practice, Duavive tab. will be administered according to the investigator's prescription and Pfizer will not provide the investigational product. The investigators will collect data on the basis of the medical data obtained by observing from the time of initial administration of Duavive tab. until 3 months (±2 weeks). If the subject does not complete 3 months (±2 weeks) of treatment, its reason should be recorded and relevant data should be collected based on the medical data observed until the time of treatment discontinuation.

Study of long-term use: The subjects who have been administered Duavive Tab. for at least 6 months (±2 weeks) will be evaluated additionally. The investigator will be recommended to evaluate the relevant subjects at 6 months (±2 weeks) after the treatment.

7.2.4.1. Basic Information

The following will be recorded on the CRF for each subject:

- Name of Institution: Enter the name of the institution.
- Department: Enter the department name of the institution.
- Name of Investigator: Enter the name of the contracted investigator.
- Subject Number: The investigator will sequentially assign each subject a subject identification number, which will be a 4-digit number. The total number of cases that need to be collected will be allocated to each study site by Pfizer at the time of execution of the contract with each site.
- Date of CRF Completion: Record the date of CRF completion.
- Signature of Investigator: The contracted investigator must sign the CRF after reviewing it.
- Inclusion and Exclusion Criteria: Whether or not a subject is eligible for enrollment in the study according to the inclusion and exclusion criteria of this study will be indicated by 'Yes' or 'No'.

7.2.4.2. Demography and Baseline Characteristics

The following will be recorded on the CRF for each subject:

- Age: Record the age of the subject at the time of enrollment. The age should be calculated by the date of birth.
- Purpose of treatment: Between 'treatment for moderate to severe vasomotor symptoms associated with menopause' and 'prevention of post-menopausal osteoporosis', select one that is applicable, but both can be selected.
- Presence and characteristics of the vasomotor symptoms associated with menopause: Select 'Yes' or 'No'. If 'Yes' is selected, select 'moderate' or 'severe' for the severity and record the duration of the disease (years/months).
- Other past/present diseases: Past or present diseases (including liver disorder and renal disorder) will be determined based on the date of the first dose of Duavive tab. Record 'Yes' or 'No'. If 'Yes', record the adequate full name of the disease as specified in the Medical Terminology Dictionary (published by the Korean Medical Society), and indicate whether it is 'Past disease' or 'Present disease'. 'Past disease' refers to a disease occurred in the past of which the condition has been recovered by the time of the administration of Duavive tab., whereas 'Present disease' refers to a disease that is present at the time of the first administration of Duavive tab.
- Allergic history: Record the history of all allergies.

7.2.4.3. Status of Administration of Hormone therapy

Checking whether there were any Hormone therapy not before administration of Duavive Tab.. The following will be recorded on the CRF for each subject if they had history of hormone therapy: the name of drug, daily dose (unit), route of administration, duration of the administration and the reason of stopping the administration.

7.2.4.4. Concomitant Medications

Any concomitant medications should be recorded on the CRF for each subject together with the name of the drug, daily dose (unit), route of administration, duration of the treatment and purpose of the treatment.

7.2.4.5. Status of Administration of Duavive Tab.

The following will be recorded on the CRF for each subject:

- Treatment period: Record the start date and discontinuation date of the treatment. If the medication is being continued at the completion of the study, record the start date only and check 'Medication is continued'.
- Daily dose: Select 0.45 mg/20 mg or 'Other'. If 'Other' is selected, record the daily dose.

7.2.4.6. Safety and Efficacy Data

Please refer to Section 7.3 for safety and efficacy data collection.

7.3. Variables

7.3.1. Safety Variables

The type of adverse events (adverse event name), incidence rate, duration (start date and recovery date), severity, measures taken for the adverse event, results and causal relationship with Duavive tab. (based on the investigator's assessment), seriousness and predictability will be investigated in this study.

7.3.1.1. Collection of Adverse Events Data

Please refer to Section 9 for the definition of adverse event (AE) and serious adverse event (SAE).

All AEs occurring within the adverse event reporting period will be recorded on the CRF by the investigator after the investigator reviews each subject's medical data.

Check either 'Yes' or 'No' in the AE section of CRF. If 'Yes', record the details.

- Adverse event: Record the pertinent name of the AE. Record the name of the AE by selecting an appropriate term among the Preferred Terms of the MedDRA. If no appropriate terms are found, use an optimal term listed in the Medical Terminology Dictionary (Korean Medical Society).
- Date of onset: Record the onset date of the AE. Record an approximate date if the actual date is unknown.
- Severity: Severity of the AE must be evaluated according to the following categories:

  - Mild: Not causing any significant problem to the subject. Administration of medicinal product continues without dose adjustment.
  - Moderate: Causing a problem that does not interfere significantly with usual activities or the clinical status. Dose of the medicinal product is adjusted or other therapy is added due to the AE.
  - Severe: Causing a problem that interferes significantly with usual activities or the clinical status. The medicinal product is discontinued due to the AE.

- Measures taken in relation to Duavive tab.: Select among the following options:

  - Permanently discontinued
  - Temporarily discontinued or delayed
  - Dose reduced
  - Dose increased
  - No change
  - Not applicable

- Other measures: Other measure taken after the onset of an adverse event is to be indicated in the following pertinent number and its content is to be described.

  - Prescription of treatment drug (Record the details in the Concomitant Medications section)
  - Other (Provide details)
  - Untreated

- Seriousness: In response to the question 'Is any of the seriousness criteria applicable?', check either 'Yes' or 'No'. If 'Yes', enter an applicable number among the definitions of serious adverse events. When a death has been caused, enter the date of death.
- Outcome: The evaluation of outcome will include: Record the date of recovery in case of 'Recovered' or 'Recovered with sequelae'.

- Recovered
- Recovered with sequelae
- Recovering
- Not recovered
- Unknown

- Causal relationship of the adverse event with the drug: The investigator must determine the causal relationship of AEs to the investigational product according to the following criteria in compliance with the MFDS requirements and check the applicable number.

(1) Certain

- The time sequence is reasonable after administration/use of the drug.
- It cannot be explained by any other drugs, chemical substances or accompanying diseases.
- It has clinically reasonable reaction on discontinuation of the drug.
- It has pharmacological or phenomenological reaction to re-administration of the drug, where necessary.

(2) Probable/Likely

- The time sequence is reasonable after administration/use of the drug.
- It cannot be explained by any other drugs, chemical substances or accompanying diseases.
- It has clinically reasonable reaction on discontinuation of the drug (no information on re-administration).

(3) Possible

- The time sequence is reasonable after administration/use of the drug.
- It may also be explained by other drugs, chemical substances or accompanying diseases.
- It lacks information or has unclear information on discontinuation of the drug.

(4) Unlikely

- It is not likely to have a reasonable causal relationship with administration/use of the drug, but it is temporary.
- It may also be reasonably explained by other drugs, chemical substances or latent diseases.

* Existence of Other Causal Relationship: When the causal relationship of the adverse event with this drug is determined to be 'Unlikely', mark the most reliable cause of the adverse event with one of the following numbers and enter its content:

1. Target Disease
2. Other diseases (Provide details)
3. Combination therapy - medication or non-medication (Provide details)
4. Other (Provide details)

(5) Conditional/Unclassified

- It needs more data to make an appropriate assessment or additional data are under review.

(6) Unassessible/Unclassifiable

- If insufficient information or conflicting information hampers accurate causality assessment, and supplementation or confirmation is unavailable.

All the AEs, except for those with a causal relationship of 'Unlikely', are considered as AEs whose causal relationship to Duavive tab. cannot be excluded, i.e., adverse drug reactions (ADRs).

Please refer to Section 9 for the requirements for reporting safety events to Pfizer Safety during the study.

7.3.1.2. Laboratory Test Data

When the investigator conducts laboratory tests for diagnosis and monitoring according to general medical practice, the results can be collected. First, check either 'Test not conducted' or 'Test conducted' to indicate whether or not test has been conducted. If 'Test conducted' is checked, check either 'Yes' or 'No' to indicate whether there has been any test measurements that have been changed abnormally after the administration compared to before administration. If 'Yes' is checked, record details for the following items:

- Test items: Record the items for which an abnormal test measurement has been found.

- Normal range (unit): Record the normal range of the relevant institution with unit for each item entered.

- Date of test: Record in the order of year/month/day.

- Pre-dose/post-dose: Record test measurements.

Refer to Section 9.4.1 for the criteria for determining whether to report an abnormal test result as an adverse event. If it meets the relevant criteria, record this information in the Adverse Event section of the case report form.

7.3.2. Efficacy Variables

Efficacy variables are the results of the investigator's evaluation.

7.3.2.1. Efficacy Evaluation

Efficacy evaluation will be performed by the investigator on the basis of the medical data observed under usual clinical practice. The investigator will record the result of evaluation after 3 months (± 2 weeks) of treatment on each subject's case report form. If evaluation is not possible, select either 'Duration of treatment of less than 3 months (± 2 weeks)' or 'Other' as its reason. If 'Other' is selected, record its reason in detail.

1) Treatment for moderate to severe vasomotor symptoms associated with menopause: Investigator's judgment on the improvement of the symptom recorded during the treatment – improved, no change, aggravated

2) Prevention of post-menopausal osteoporosis: If the following laboratory test results related to osteoporosis exist both at baseline (data within 1 month prior to the administration of Duavive tab.) and after the administration (data at 3 months (± 2 weeks) after the administration of Duavive tab.), the investigator's evaluation of preventive effect based on this information – Effective in prevention, ineffective in prevention

   - X-ray examination
   - Bone density test record
   - Other blood test record related to resorption of bone and osteogenesis

Efficacy evaluation on long-term use: Record the results of the evaluation of the subjects who have been administered Duavive tab. for 6 months (± 2 weeks) or more on the case report form. If evaluation is not possible, record the pertinent reason in detail.

1) Treatment for moderate to severe vasomotor symptoms associated with menopause: Investigator's judgment on the improvement of the symptom recorded during the treatment – improved, no change, aggravated

2) Prevention of post-menopausal osteoporosis: If the following laboratory test results related to osteoporosis exist both at baseline (data within 1 month prior to the administration of Duavive tab.) and after the administration (data at 6 months (± 2 weeks) after the administration of Duavive tab.), the investigator's evaluation of preventive effect based on this information - Effective in prevention, ineffective in prevention

   - X-ray examination
   - Bone density test record
   - Other blood test record related to resorption of bone and osteogenesis

7.4. Data sources

7.4.1. Case Report Form

The investigator will review source documents and complete the electronic CRF for each included subject. The completed original CRFs are the sole property of Pfizer and shall not be made available in any form to the third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for collection and reporting of all clinical, safety, and laboratory data entered on the CRFs, and must ensure accuracy, authenticity/originality, attributability, completeness, consistency, legibility, timeliness (contemporaneity), endurance, and availability upon request. The CRFs must be signed by the investigator or an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries on the CRFs must be dated, initialed and explained (if necessary) and should not obscure the original entries.

In most cases, the source documents are the hospital's or the investigator's medical records. In this case, data collected on the CRFs must match the data in the medical records.

7.4.2. Record Retention

To enable evaluations and/or audits from the regulatory authorities or Pfizer, the investigator should agree to keep records, including the identity of all participating subjects (sufficient information associated with records, e.g., CRFs and hospital records), copy of all CRFs, SAE forms, records such as source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondences (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to the local regulations, or as specified in the Clinical Study Agreement (whichever is longer).

If the investigator becomes unable for any reason to continue to retain study records for the required period (e.g., retirement, transfer), Pfizer should be notified beforehand. The study records must be transferred to a designee acceptable to Pfizer, such as another investigator, another institution, or to an independent third party arranged by Pfizer. The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements are met.

7.5. Study Size

Sample size calculation is not applicable for this study. At least 600 subjects will be enrolled in this study to meet the MFDS requirements.

7.6. Data Management

CRF data collected by the investigator will be entered into the clinical database. Validation will be performed after comparison of the double data entry. All missing data or data for review will be reported on a query sheet for further validation at the study site. Any data modifications will be recorded.

AEs will be coded using the MedDRA. Medical history will be coded using the classification of Korea National Statistical Office, and concomitant medications will be coded via www.kimsonline.co.kr, which is supplied by KIMS Co. Ltd.

Statistical analysis will be carried out using SAS software version 9.2 or above.

7.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in the Statistical Analysis Plan (SAP), which will be dated, filed and maintained by Pfizer. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses will be reflected in the protocol amendment.

7.7.1. Interpretation items

7.7.1.1. Items related to the composition of cases

- Descriptive analysis will be conducted with respect to the number of subjects whose case report forms are collected, the number of subjects that are evaluated for safety, the number of subjects who withdraw and the reasons, etc.

7.7.1.2. Items Related to Safety

- Status of the onset of adverse events by system organ class and disease/symptom

- Sub analysis can be conducted for each factor considered to have an effect on safety.

7.7.1.3. Item Related to Efficacy

- Treatment for moderate to severe vasomotor symptoms associated with menopause: The investigator's judgment on the improvement of symptom recorded during the treatment (improved, no change, aggravated) is summarized as descriptive statistics, and an effective ratio is provided by considering 'improved' as "Effective" and 'no change' and 'aggravated' as "Ineffective".

- Prevention of post-menopausal osteoporosis: The investigator's evaluation of preventive effect (effective in prevention, ineffective in prevention) based on the laboratory test results related to osteoporosis will be summarized as descriptive statistics, and the effective ratio will be presented by considering 'effective in prevention' as "Effective" and 'ineffective in prevention' as "Ineffective".

- Sub analysis can be conducted for each factor considered to have an effect on efficacy.

- If laboratory test data can be collected, the 3 months (±2 weeks) follow-up data will be compared with baseline data. In case of the subjects who are administered Duavive tab. for a long time, i.e. for at least 6 months (±2 weeks) , the 6 months (±2 weeks) follow-up data will be compared with the 3 months (±2 weeks) follow-up data.

- X-ray examination result
- Bone density test record
- Other blood test record related to resorption of bone and osteogenesis

7.7.2. Interpretation Method (Statistical Considerations)

The data collected from each investigator during the re-examination period will be analyzed. The evaluation of data is shown by summarizing the data mainly using descriptive statistics, etc.

Since the frequency of adverse events occurring during the re-examination period is the primary concern of this study, the frequency of each adverse event will be presented at a 95% confidence interval. The status of the onset of serious AEs/ADRs, unexpected AEs/ADRs, and serious and unexpected AEs/ADRs will be summarized in separate tables.

Unexpected AEs/ADRs will be classified by medical review with reference to the local product document. Events already included in the "Precautions for use" section of the local product document will be classified as "expected". All other events that are not included in the "Precautions for use" section of the local product document will be classified as "unexpected". The unexpected AEs include any events that may be symptomatically and pathophysiologically related to the events listed in the local product document, but differ from the labeled event because of greater severity or specificity.

Subgroup analysis will be conducted by factor considered necessary including demographics and baseline characteristics to identify the factors having effects on safety and efficacy.

Total number of participating institutions, number of enrolled and collected cases and number of cases included in the analysis will be presented in the summary table.

7.8. Quality Control

Quality assurance audits at the study site will be performed by Pfizer's own independent quality assurance group or by the clinical research institution. These audits will be conducted according to Pfizer's procedures and the guidelines for Good Pharmacoepidemiology Practices (see Section 8.4).

7.9. Strength and Limitations of the Study Methods

Strength:

- This is a non-interventional study to observe the safety and efficacy of the study drug under the actual condition of use.

Limitations:

- This is a study mandated by the regulatory authority to maintain approval.

- SAP and the number of subjects to be enrolled will be decided not by specific disease and/or characteristics of the medicinal product but by the guidelines for the re-examination of new drugs, etc. of the Ministry of Food and Drug Safety.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Subject Information and Consent

All concerned parties will ensure protection of subject's personal data, and will not include subject names on any sponsor forms, reports, or publications, or will not disclose them in any form, except when required by law. In case of data transfer, Pfizer will maintain strict standards for protection and confidentiality of subject personal data.

The data privacy statement must comply with the local regulatory requirements and legal requirements.

The data privacy statement used in this study and any changes made during the course of the study must be approved beforehand by Institutional Review Board (IRB)/Independent Ethics Committee (IEC) (if applicable) and Pfizer.

The investigator must ensure that each study subject, or his/her legally acceptable representative, is fully informed of the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain the written data privacy statement from each subject or the subject's legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each subject's signed data privacy statement.

8.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own or their legally acceptable representative's request, or they may be withdrawn at any time at the discretion of the investigator or Pfizer for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document the subject outcome, if possible. The investigator must inquire about the reason for withdrawal and follow up with the subject regarding any unresolved AEs.

If the subject discontinues participation and withdraws consent to disclosure of further information, no additional assessments should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study protocol will be submitted to the MFDS prior to the study. The ethical consideration on this study will be evaluated by the IRB/IEC in each study site prior to the study, if the site has the approval procedures for the PMS study according to the local standard operating procedure of the site.

It is the responsibility of the investigator to obtain prospective approval for the study protocol, protocol amendments, data privacy statement, and other relevant documents, if applicable, by the IRB/IEC. All correspondences with the IRB/IEC should be retained in the investigator file. The copy of IRB/IEC approval letters should be forwarded to Pfizer or a Pfizer's designee.

8.4. Ethical Conduct of the Study

This study will be conducted in accordance with the legal and regulatory requirements, scientific purpose, value and rigor, and follow generally accepted research practices described in the guidelines for GPP issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice guidelines issued by the International Epidemiological Association (IEA), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines, and Korea PMS regulations and/or guidelines.

9. REPORT OF ADVERSE EVENTS

9.1. Requirements

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), except occupational exposure	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator regardless of whether the event is determined by the investigator to be related to a drug under study. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.2. Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Duavive tab. or the time of the patient's informed consent if s/he is already exposed to Duavive tab., and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of Duavive tab.; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was

administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.
If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Duavive tab., the SAE also must be reported to Pfizer Safety.

9.3. Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Duavive tab., follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that Duavive tab. has caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Duavive tab. caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that Duavive tab. has not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

9.4. Definition of Safety Events

9.4.1. Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;

- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result requires additional diagnostic testing or medical/surgical intervention, and/or
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

9.4.2. Serious Adverse Event

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms “suspected transmission” and “transmission” are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (e.g., patient has no place to sleep)
- Administrative admission (e.g., for yearly exam)
- Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)
- Hospitalization for observation without a medical AE
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)
- Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

9.4.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

Exposure during pregnancy (EDP) occurs if:

1. A female becomes or is found to be pregnant either while receiving or having been exposed to (e.g., environmental exposure) Duavive tab. or the female becomes or is found to be pregnant after discontinuing and/or being exposed to Duavive tab. (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product of a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).
2. A male has been exposed, either due to treatment or environmental exposure to Duavive tab. prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable, irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Duavive tab., this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to Duavive tab. in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow-up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

<u>Exposure during breastfeeding</u>

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter;

    - A suspect product;

    - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

9.5. Single Reference Safety Document

The local product document will serve as the SRSD during the course of the study, and the investigator will use it to assess all the safety events reported to Pfizer Safety during the course of this study.

The investigator must use the SRSD for prescribing purposes and guidance.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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 (see Section 4).

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator becomes aware of any new information which might influence the evaluation of the benefits and risks of Duavive tab. 0.45 mg/20 mg, it should be reported to Pfizer immediately.

In addition, the investigator must inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the subjects against any immediate hazard, and of any serious breaches of this non-interventional study protocol that the investigator becomes aware of.

11. REFERENCES

1. Local product document

ANNEX 1. LIST OF STAND ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.