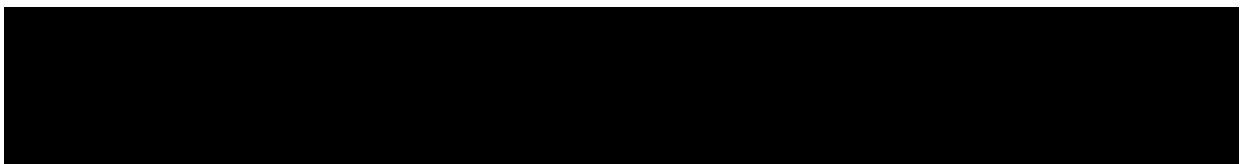




NON-INTERVENTIONAL (NI) DRUG STUDY PROTOCOL

POST MARKETING SURVEILLANCE FOR GENERAL DRUG USE TO ASSESS THE SAFETY AND EFFICACY PROFILE OF VIVIAINT IN USUAL PRACTICE

Compound Number:	PF-05208749
Compound Name:	Viviant Tablet 20 mg (Bazedoxifene Acetate)
Study Number:	B1781047
Version and Date:	Final 23 Jul 2012
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	Amendment 6 26 Mar 2015
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ABBREVIATIONS AND DEFINITION OF TERMS

Abbreviation	Definition
AE	Adverse Event
SAE	Serious Adverse Event
BMD	Bone Mineral Density
CRF	Case Report Form
eCRF	Electronic Case Report Form
CTX	C-telopeptide of collagen cross links
DVP	Data Validation Plan
DXA	Dual energy X-ray Absorptiometry
EIU	Exposure in Utero
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LSLV	Last Subject Last Visit
MFDS	Ministry of Food and Drug Safety
NTX	N-telopeptide of collagen cross links
PCD	Primary Completion Date
QUS	Quantitative Ultrasound
SAP	Statistical Analysis Plan
SRSD	Single Reference Safety Document

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1. RATIONALE AND BACKGROUND

Viviant 20 mg was approved as a new medicine on 16 Nov 2011. As required for any new medicine approved by the Ministry of Food and Drug Safety (MFDS), safety and efficacy information of the medicine should be provided in the setting of routine practice during the re-examination period of 6 years from the approval date (16 Nov 2011 ~ 15 Nov 2017).

The objective of the Re-examination system in Korea is to re-confirm the clinical usefulness of the product through collecting, reviewing, identifying and verifying the safety and efficacy information about the product in general practice (usually for a period of 6 years after the product is registered.).

This survey is conducted for preparing application material for re-examination under the Pharmaceutical Affairs Laws and its Enforcement Regulation, and assessing the safety and efficacy profiles of Viviant 20 mg in usual practice according to the Re-examination Regulation for New Drugs.

2. RESEARCH QUESTION AND OBJECTIVES

This study is to observe safety and efficacy of Viviant 20 mg in the setting of routine practice.

The objectives of this survey are:

- 1) To examine the safety and efficacy profiles of Viviant 20 mg in Korean patients
- 2) To identify factors that might have an influence on the safety and efficacy profiles of Viviant 20 mg in Korean patients.

3. RESEARCH METHODS

3.1. Study Design

This study is an observational, non-interventional, multi-center study in which subjects will be treated as part of routine practice at Korean health care centers by accredited physicians. The study can be performed in primary, secondary or tertiary care medical center including the departments below where Viviant 20 mg is mainly prescribed for treatment and prevention of postmenopausal osteoporosis which is the indication for Viviant 20 mg.

- Primary care medical center: Department of obstetrics and gynecology, endocrinology, orthopedics, family medicine and rehabilitation
- Secondary care medical center: Department of obstetrics and gynecology,

endocrinology, orthopedics, family medicine, rheumatology, neurosurgery and rehabilitation

- Tertiary care medical center: Department of obstetrics and gynecology, endocrinology, orthopedics, neurosurgery and rheumatology

Surveillance for long-term use: Patients who are treated with Viviant 20 mg for at least 6 months (\pm 2 weeks) will be evaluated additionally if collected. The physician will be recommended to evaluate those subjects at 6 months (\pm 2 weeks) after the treatment.

3.2. Study Population

Subjects will be enrolled by continuous registration method. It means that the physician should enroll all postmenopausal women who are received Viviant 20 mg for the first time and agree to participate in this study by signing the ‘data privacy statement’ after contract is made with the physician or the institution.

3.2.1. Inclusion Criteria

Indication

Treatment and prevention of postmenopausal osteoporosis in women

A significant reduction in the incidence of vertebral fracture has been demonstrated, but efficacy on non-vertebral fracture has not been established.

Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study.

1. Patients who is indicated in the current VIVIANT local label
2. Evidence of a personally signed and dated data privacy statement indicating that the subject (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

Special patients with known hepatic disorder or renal disorder which was medically diagnosed or older (\geq 65 years) will be evaluated if collected.

The following subjects should be treated with caution.

1. Patients with hypertriglyceridemia (This drug has not been studied in women with triglyceride levels $>$ 300mg/dl ($>$ 3.4 mmol/L). It may increase serum triglyceride levels.)

2. Patients with severe renal impairment.
3. Patients with hepatic impairment (patients with hepatic impairment showed a 4.3-fold increase in area under the curve (AUC) compared with controls. Use in this population is not recommended.)

3.2.2. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study.

1. Patients with hypersensitivity to the active substance or to any of the excipients.
2. Patients with active or past history of venous thromboembolic events, including deep vein thrombosis, pulmonary embolism, and retinal vein thrombosis
3. Pregnant women and women of child-bearing potential.
4. Lactating women
5. Patients with unexplained uterine bleeding.
6. Patients with signs or symptoms of endometrial cancer (safety in this patient group has not been adequately studied).
7. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

3.3. Data Sources

The followings are data sources for the study:

1. Medical records
2. Laboratory test results
3. Subject interview

3.4. Variables

Variable	Role	Data source(s)	Operational definition
Demographic Characteristics	Baseline characteristics	Medical records	
Basic Laboratory data	Baseline characteristics	Laboratory test results	
Concomitant medication	Baseline characteristics	Medical records and interview	
BMD and biochemical markers	outcome	Laboratory test results	
Efficacy result by the physician	outcome	Medical records and interview	

Adverse events	outcome	Medical records and interview	
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Detailed instruction of variable will be included Statistical Analysis Plan (SAP) and CRF.

3.5. Study Procedures

3.5.1. Study Duration

As specified in the product license given by the MFDS, this study will be conducted for 6 years from the approval date of 16 Nov 2011 to 15 Nov 2017.

3.5.2. Study Treatment

The use and dosage recommendations for Viviant 20 mg will take place on the basis of the approved Local Product Document. The indication for Viviant 20 mg is treatment and prevention of postmenopausal osteoporosis in women. One tablet once daily, at any time of day, with or without food.

3.5.3. Planned Numbers of Patients

Planned number of patients: 3,000 patients

The number of total subjects required for re-examination is at least 3,000 according to the Re-examination Regulation for New Drugs and Others.

3.5.4. Endpoints

3.5.4.1. Safety Endpoints

The drug safety is evaluated through the following items:

- Serious adverse event
- Unexpected adverse drug reaction
- Identification of AE profile in usual practice
- Non-serious adverse event

3.5.4.2. Efficacy Endpoint

1. The drug efficacy is evaluated through the overall efficacy evaluation by the physician
: Improved, No change, Worsened, Unevaluable
2. Osteoporosis related fractures incident

3. If laboratory data will be collectable, 3 month (\pm 2 weeks) F/U data will be compared with the baseline data
- Any X-ray result by the physician.
 - Any bone mineral density result: dual energy x-ray absorptiometry (DXA), quantitative ultrasound (QUS), etc
 - Biochemical markers of bone turnover: Deoxypyridinoline, N-telopeptide of collagen cross links (NTX), C-telopeptide of collagen cross links (CTX), osteocalcin, bone specific alkaline phosphatase, etc.

3.5.5. Investigating Matters

The physician is required to monitor any adverse events of all enrolled subjects during at least one follow up visit. Generally, this will be done during the subject's next visit. Efficacy will be evaluated at 3 months (\pm 2 weeks) after the initiation of Viviant treatment regardless of whether the treatment is ongoing or not at the time of evaluation. Safety, that is, the occurrence of adverse event, will be observed by 3 months (\pm 2 weeks) after the initiation of Viviant treatment if the treatment is continued for at least 3 months (\pm 2 weeks). If the treatment is discontinued earlier than 3 months (\pm 2 weeks), safety will be observed by one month after the discontinuation. If subject's next visit is not expected during the evaluation timeframe, the physician should contact subjects via phone to collect the information. The information collected during the follow up visit (including telephone contact) should be recorded in the subject's medical chart and Case Report Form (CRF).

Any clinical and/or laboratory adverse events observed or reported from the time of the subject's first dosing in the observational period as per study design through and including 28 calendar days after the last administration of the study drug within the observational period will be collected by the physician.

Targeted investigational population

- Targeted safety evaluation population: Patients who have had experience to be taken Viviant 20 mg at least one time and be completed follow up
- Targeted efficacy evaluation population: Patients who are completed efficacy evaluation based on the protocol in the targeted safety evaluation population

3.5.5.1. Basic Information

- Name of Institution
- Name of Physician
- Department
- Subject ID
- Height/Weight: Record by cm / kg unit.
- Month of Birth: Record the month of birth of the subject.
- Confirmation of Data Privacy Statement: If all agreement for using subject's personal and medical information, signature and date are obtained from the subject or legally acceptable representative, then check the box of 'yes' and record the date of signature by the subject or legally acceptable representative. If not, check 'no' which means that case is excluded from this study.

3.5.5.2. Diagnosis

- Date of diagnosis for osteoporosis: Record the date of diagnosis for osteoporosis

3.5.5.3. Medical History

Select either 'yes' or 'no' for past/present disease. If 'yes' then write adequate full name of the disease down as Medical Terminology Dictionary indicates (written by Korean Medical Society) and select either 'past disease' or 'present disease' at each disease clause. Additionally, check either 'yes' or 'no' for 'complication of osteoporosis'.

- Past disease: Disease occurred past, but recovered before Viviant 20 mg administration
- Present disease: Accompanied disease at the time of the first Viviant 20 mg administration
- Complication of osteoporosis: Disease whose immediate cause is osteoporosis

3.5.5.4. Concomitant Medication / Therapy

The physician records the medication/therapy which has been administered/conducted continuously at the point of being enrolled in this study or administered/conducted newly after being enrolled. Check either 'yes' or 'no'. If 'yes', record in detail.

- Name of drug / Therapy name: Record generic name in case of single product and record trade name in case of combination product. Also, record name of concomitant therapy.

- Daily total dosage / Frequency: Record the daily total dosage as unit. If not combination drug, avoid recording in tablets, capsules or vials. Record the frequency of concomitant therapy.
- Duration of administration / Duration of therapy: Record the starting/ending date of the medicated drug and concomitant therapy (year/month/day). If the medication and therapy are being continued at the completion of the study, record the starting date only and check 'ongoing'.
- Purpose of administration / Purpose of therapy: Record the purpose of administration or therapy.

3.5.5.5. Administration Status and Evaluation of Viviant

Record the following with regard to administrative status of Viviant 20 mg.

- Duration of administration: Record the starting/ending date of Viviant 20 mg therapy (year/ month/day).
- Date of Visit: Record the date of visit (year/ month/day).
- Daily total dosage: Record the daily total dosage.
- Laboratory test for Viviant treatment: Check either 'yes' or 'no'. If 'yes', select among 'X-ray', 'bone mineral density' or 'biochemical marker of bone turnover' and record the details in the section of laboratory test.
- Phone contact: If the subject did not visit the physician's site during the follow-up period, phone contact should be made to collect any relevant information. Check either 'yes' or 'no'. If 'yes', record the date of phone contact and the collected information. If 'no', record the reason of not being able to have a phone contact.
- Osteoporosis related fracture: Check either 'yes' or 'no' for the question, 'Has the subject experienced an osteoporosis related fracture after the initiation of Viviant 20 mg administration?'. If 'yes', record the details in the section of adverse event.

3.5.5.6. Safety

3.5.5.6.1. Adverse Event

Every observed and reported adverse event, regardless of the causal relationship with the study drug, must be recorded on an adverse event section in case report forms. The query

pattern of experience of adverse event to the subjects is as follow;

“Have you had any health problem since last visit?”

For adverse events repeating before and after administrating the study drug, record the first appearing date and the last disappearing date. Background information on Viviant 20 mg can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to Viviant 20 mg.

Check either ‘yes’ or ‘no’ in adverse event section. If ‘yes’, record in detail.

- Adverse event: Record the term of adverse event. If possible, specify diagnosis, not individual symptoms. Record the term according to the term in the local product document or the Preferred Term in the WHO Preferred Terminology Standard (distributed by Korean Ministry of Health and Welfare). If there is no preferred term, look up the Medical Terminology written by Korean Medical Society.
- Date of onset: Record the date of onset. Just record the year or year and month if an actual date is unknown.
- Severity: Severity evaluation of adverse events must be done according to the following category.
 1. Mild- Not causing any significant problem to the subject
Continuous medication of study drug is possible without dose adjustment.
 2. Moderate- Cause a problem that does not interfere significantly with usual activities or the clinical status
Dose adjustment of study drug or other therapy is needed due to adverse event.
 3. Severe- Cause a problem that interferes significantly with usual activities or the clinical status
Study drug should be stopped due to adverse event.

If the severity of an adverse event changed, the adverse event must be entered separately. Record stop date of previous severity and onset date of new severity – along with completion of all other items.

- Action: Check all relevant actions.

- 1) Viviant: Check the appropriate number for the adjustment of Viviant resulting from the adverse event.
 1. no action taken
 2. dosage reduced
 3. dosage increased
 4. stopped temporarily
 5. permanently discontinued
 6. not applicable
 - 2) Withdrawal: Check either 'yes' or 'no' for the question, 'Was the subject withdrawn from the study due to the adverse event?'
 - 3) Others: After the onset of adverse event, the physician should indicate other actions taken and record in detail.
 1. Treatment given (please specify in concomitant medication section)
 2. Others (please specify)
 3. No action taken
- Seriousness: Check either 'yes' or 'no' for the question, 'Is this case under the criteria of serious adverse event?' If 'yes', record the appropriate number for the category of seriousness.

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

- (1) results in death;
- (2) is life-threatening;
- (3) requires inpatient hospitalization or prolongation of hospitalization;
- (4) results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- (5) results in congenital anomaly/birth defect;
- (6) is an important medical event

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 subject 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 subject exposed to a Pfizer product. The terms “suspected transmission via product” and “transmission via product” 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.

In case of serious adverse event, the Drug Safety Unit of the Pfizer Pharmaceuticals Korea Ltd. is to be notified promptly by the physician (Telephone No. 02-317-2146 (working hours), 010-8771-7114 (24 hours) / Fax No. Toll-Free 0079814206-4512, Toll 02-317-2135 / E-mail: KOR.AEreporting@pfizer.com). The physician should complete the ‘Non Interventional Study Adverse Event Report Form’ and fax it within 24 hours of awareness of the adverse event.

Record the followings at the end of the study or after the resolution of the adverse event.

- Outcome: Select among ‘yes’, ‘unknown’, or ‘no-resolved’ as a reply to a question, ‘Is the adverse event still present?’ If the subject died without resolution of the AE, ‘yes’ should be checked. If ‘no-resolved’, record the resolved date. Just record the year or year and month if an actual date is unknown.
- Causality of adverse event to the study drug: The causal relationship of adverse event to the study drug must be allocated by the physician according to the following criteria.

(1) Certain

- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug.
- It has pharmacological or phenomenological reaction to re-administration of the drug, where necessary.

(2) Probable/likely

- It follows a reasonable time sequence from administration of the drug (before and after the study medication).
- It could not be explained by other drugs, chemical substance or accompanying diseases.
- It has clinically reasonable reaction on cessation of the drug.

(No information on re-administration)

(3) Possible

- It follows a reasonable time sequence from administration of the drug.
- It could also be explained by other drugs, chemical substance 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 from administration of the drug. Rather, it seems to be temporary.
- It could also be reasonably explained by other drugs, chemical substances or latent diseases.

* Other causality of adverse event: If the adverse event is not related to the study drug, the physician should indicate the most appropriate cause from the followings and record in detail.

1. Disease under the study
2. Other disease (please specify)
3. Concomitant treatment –drug or non-drug (please specify)
4. Others (please specify)

(5) Conditional/unclassified

- It needs more data to make an appropriate assessment or its additional data are being reviewed.

(6) Unaccessible/unclassifiable

- Lack of sufficient information or conflicting information hampers accurate causality assessment or supplementation or confirmation.

3.5.5.6.2. Laboratory Test

Laboratory testing is not mandatory because this study is a non-interventional study. If the physician performed a laboratory test for diagnostics and monitoring in usual medical practice, the results can be collected. Check ‘not done’ if it is not performed. If ‘done’, record the following in detail.

- Normal Range
- Date of clinical laboratory test before administration

- Date of clinical laboratory test during administration
- Date of clinical laboratory test after administration
- Result: Record the lab result of each test.
- Remark

Refer to [Section 5.1.4.] of the criteria for determining whether an abnormal objective test finding should be reported as an adverse event. If it meets the criteria, it has to be recorded in adverse event section of a case report form.

3.5.5.7. Final Evaluation

- 3-month (± 2 weeks) treatment: Check either ‘yes’ or ‘no’ for the question, ‘Has the subject been administered Viviant for at least 3 months (± 2 weeks)?’ If ‘no’, check among ‘adverse event’, ‘lack of efficacy’ or ‘other (please specify)’ for the reason.
- Date of last safety observation: Record the date by when safety is observed. Safety, that is, the occurrence of adverse event, will be observed by 3 months (± 2 weeks) after the initiation of Viviant treatment if the treatment is continued for at least 3 months (± 2 weeks). If the treatment is discontinued earlier than 3 months (± 2 weeks), safety will be observed by one month after the discontinuation.
- Date of efficacy evaluation: Record the date of efficacy evaluation. Efficacy will be evaluated at 3 months (± 2 weeks) after the initiation of Viviant treatment regardless of whether the treatment is ongoing or not at the time of evaluation.
- Efficacy evaluation: Select among ‘improved’, ‘no change’, ‘worsened’ or ‘unevaluable’. If ‘unevaluable’, check either ‘follow-up lost’ or ‘other (please specify)’ for the reason.

Additionally, follow-up information will be collected for subjects treated with Viviant for the long term.

- 6-month (± 2 weeks) treatment and follow-up: Check either ‘yes’ or ‘no’ for the question, ‘Has the subject been administered Viviant for at least 6 months (± 2 weeks)?’ If ‘yes’, check either ‘yes’ or ‘no’ for the question, ‘Was the follow-up made by 6 months (± 2 weeks) after the initiation of Viviant treatment for the subject?’. If ‘yes’, record the date when the follow-up is completed.
- Long-term efficacy evaluation: Select among ‘improved’, ‘no change’, ‘worsened’ or

‘unevaluable’. If ‘unevaluable’, record the reason.

- Safety observation: If the subject has been administered Viviant for more than 6 months (± 2 weeks), Perform the safety observation until 6 months (± 2 weeks) after the 1st Viviant treatment.

3.6. Power and Sample Size

Safety evaluation should be conducted for at least 3000 subjects in compliance with the MFDS regulation.

3.7. Data Collection and Data Management

3.7.1. Data Collection

As used in this protocol, the term case report form (CRF) should be understood to refer to either a paper form or an electronic data record or both, depending on the data collection method used in this study (“eCRF” may be used to describe an electronic data record).

A CRF should be completed for each included subject. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

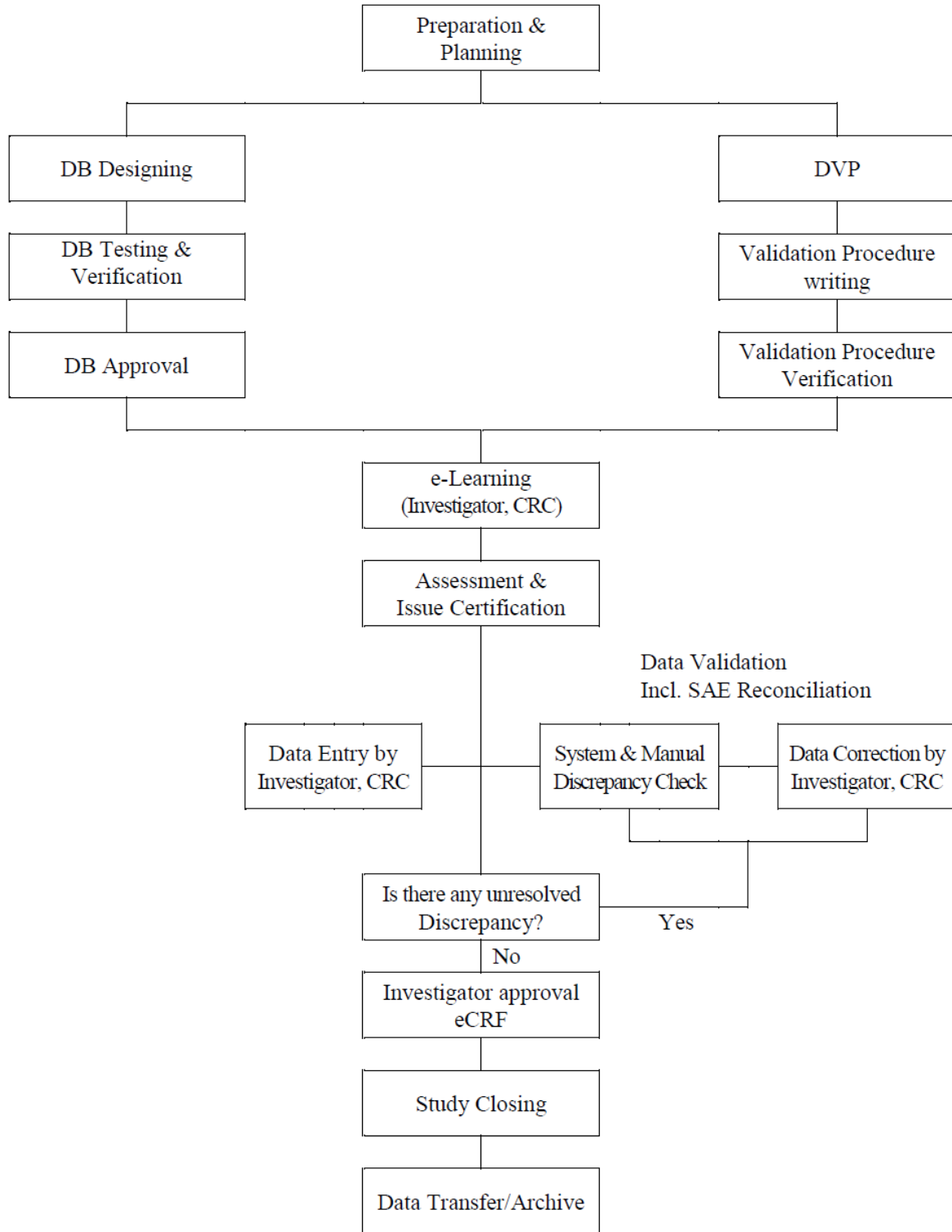
Each study physician has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection forms (source documents) and ensuring that they are accurate, authentic / original, attributable, complete, consistent, legible, timely (contemporaneous), enduring and available when required. The CRFs must be signed by the study physician or by an authorized staff member to attest that the data contained on the CRFs are correctly recorded. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry. For studies using electronic data capture systems, an audit trail of any corrections to original data entry must be ensured.

In many cases, the source document is the subject medical chart. In these cases, data collected on the CRFs must match the data in the chart.

In some cases (e.g., subject interview), the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the physician’s site as well as

at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

3.7.2. Data Management



<Figure 1> Data Management Flow Chart

3.7.2.1. Data Cleaning

Data will be cleaned through the system and/or manual discrepancy check process as shown in the Figure 1.

3.8. Data Analysis

3.8.1. Assessment Parameter

3.8.1.1. Parameter on Cases

- Descriptive analysis will be done pertaining to total collected cases, safety evaluable cases, efficacy evaluable cases, discontinuation cases and the cause for it.

3.8.1.2. Parameter on Safety

- Safety parameter will be evaluated.
- Incidence of adverse event categorized according to physical organ and disease/symptom and 95% confidence interval will be presented.
- Sub-analysis could be done by factors which are considered to affect safety. If necessary chi-square test (χ^2 -test), Fisher's exact test or Logistic Regression Analysis will be used for subgroup analysis.
- Clinically significant abnormality from laboratory test (if any). If data are applicable, paired t-test, descriptive analysis and other statistical method will be used.

3.8.1.3. Parameter on Efficacy

- The four point scale: Improved, No Change, Worsened, Unevaluable will be descriptively summarized. Efficacy and 95% confidence interval of efficacy rate will be presented. Sub-analysis could be done by factors which are considered to affect efficacy. If necessary, χ^2 -test, Fisher's exact test or Logistic Regression Analysis will be used.
- Osteoporosis related fractures incident.
- If laboratory data will be collectable, 3 month (\pm 2 weeks) F/U data will be compared with the baseline data
 - Any X-ray result by the physician.
 - Any bone mineral density result: dual energy x-ray absorptiometry(DXA), quantitative ultrasound(QUS), etc

- Biochemical markers of bone turnover: Deoxypyridinoline, N-telopeptide of collagen cross links (NTX), C-telopeptide of collagen cross links (CTX), osteocalcin, bone specific alkaline phosphatase, etc.

3.8.2. Statistical Consideration

Analysis will be performed for the pooled data from each physician collected during the re-examination period. Evaluation of data will primarily consist of summary displays (e.g., descriptive statistics, tables, graphs).

The primary interest of this study is any adverse event, unexpected adverse event, serious adverse event, each adverse drug reaction and the frequency of them reported during the re-examination period. They will be presented with 95% confidence interval. Adverse events will be categorized according to physical organs/cases will be separately summarized as 'overall adverse events and adverse drug reaction', 'serious adverse event and serious adverse drug reaction' and 'unexpected adverse and unexpected adverse drug reaction'.

if necessary, the adverse event analysis and evaluation could be conducted for the subjects who are excluded from safety evaluation due to the off-label use.

To identify any factor that affect safety and efficacy rate, subgroup analysis will be performed by the following factors: age, presence of concurrent diseases, presence of concomitant medication, etc.

Total number of participating institutions, enrolled and retrieved cases, and the number of cases included in the analysis will be presented as summary tables.

3.8.3. Interim Analysis

As required by the MFDS regulations, the periodic report should be submitted to the MFDS every 6 months for the first two years and then annual report should be submitted to the MFDS for the third, fourth and fifth year. The final report should be submitted in the sixth year. Interim analysis will be performed in time for the report submission.

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

3.9. Quality Control

Detailed process for quality control will be documented in a Data Management Plan (DMP), which will be dated, filed and maintained by the sponsor. Validation procedure will be installed to eCRF based on the Data Validation Plan (DVP). Data will be cleaned through the system and/or manual discrepancy check process as shown in the Figure 1.

3.9.1. Record Retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the physician agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed data privacy statements, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the physician according to local regulations, or as specified in the Clinical Study Agreement, whichever is longer.

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

3.10. Strengths of the Research Methods

- Large scale non interventional real world study for evaluating efficacy and safety of study drug
- Subjects will be enrolled in a consecutive manner

3.11. Limitations of the Research Methods

- Regulatory required study for maintaining license and exclusivity.
- SAP and number of subjects are ruled by PMS guideline of the MFDS, not specific disease and/or drug characteristics.

4. PROTECTION OF HUMAN SUBJECTS

4.1. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subject personal data.

The data privacy statement must be in compliance with 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 prospectively approved by both the IRB/IEC if applicable and Pfizer before use.

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

4.2. Subject Withdrawal

Subjects 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 physician or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The physician should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations 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.

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

It is the responsibility of the physician to have prospective approval of the study protocol, protocol amendments, and data privacy statements, and other relevant documents, if

applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Physician File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

4.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidances, Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines and similar.

5. ADVERSE EVENT REPORTING

5.1. 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
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.

5.1.1. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Viviant or the time of the patient's informed consent if s/he is already exposed to Viviant, 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 a drug under study; 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 Viviant, the SAE also must be reported to Pfizer Safety.

5.1.2. 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 Viviant, 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 Viviant caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Viviant 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 Viviant did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

5.2. DEFINITIONS OF SAFETY EVENTS

5.2.1. 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.

5.2.2. Serious adverse events

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)

5.2.3. 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

An 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) Viviant, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Viviant (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in 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 Viviant 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 Viviant, 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 Viviant 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.

Exposure during breastfeeding

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.

6. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the physician is aware of any new information which might influence the evaluation of the benefits and risks of Viviant 20 mg, Pfizer should be informed immediately.

In addition, the physician will inform Pfizer immediately of any urgent safety measures taken by the physician to protect the study subjects against any immediate hazard, and of any serious breaches of this NI study protocol that the physician becomes aware of.

7. Single Reference Safety Document

Background information on Viviant 20 mg can be obtained from the current version of the local product document, which is the single reference safety document (SRSD) for information relating to Viviant 20 mg in this study.

8. STUDY DISCLOSURE

Pfizer fulfils its commitment to publicly disclose the results of studies through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov). Pfizer registers study protocols and posts Basic Results on ClinicalTrials.gov for Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product and for Pfizer sponsored NI studies, regardless of design or data source, that evaluate the safety and efficacy of a Pfizer product.

The results are posted in a tabular format called Basic Results and the posting timelines are:

- Newly FDA approved products:
Basic Results must be submitted within 30 calendar days of the FDA marketing approval for studies whose PCD occurred prior to 1 anniversary year or more from the date of marketing approval.
- FDA-previously approved products:
Basic Results are due within 1 anniversary year of the PCD and/or LSLV.
When PCD and LSLV are not the same date, Basic Results are posted 1 anniversary year from the PCD and the record is updated 1 anniversary year from LSLV. PCD cannot occur after LSLV.
- Discontinued products:
Basic Results are due within 1 anniversary year of the decision to discontinue the product for all indications if there are no plans to out license the product or within 2 anniversary years if out licensing plans are not completed.
- Marketed outside of the United States (US) only:

Basic Results are due within 1 anniversary year of the ex-US approval or for already approved products, within 1 anniversary year of LSLV.

For products marketed in the US and ex-US, the US timelines are followed.

Primary Completion Date (PCD) is defined as the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol, was terminated or ongoing.

9. LIST OF FIGURES

<Figure 1> Data Management Flow Chart

10. REFERENCES

1. 골다공증 진단 및 치료 지침 2008 (대한골대사학회 지침 위원회)
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3. Safety and tolerability of bazedoxifene in postmenopausal women with osteoporosis : results of 5-year, randomized, placebo-controlled phase 3 trial. 2011 Feb;22(2):567-76. Epub 2010 Jun 10.
4. Future long-term trials of postmenopausal hormone replacement therapy - what is possible and what is the optimal protocol and regimen? Climacteric. 2012 Jun;15(3):288-93
5. Sustained efficacy and safety of bazedoxifene in preventing fractures in postmenopausal women with osteoporosis: results of a 5-year, randomized, placebo-controlled study. Osteoporos Int (2012) 23:351–363

APPENDIX 1. RESPONSIBLE PARTIES

Protocol Contact

Name, degree(s)	Title	Affiliation	Address
PPD [REDACTED], MD	Sr. Medical Manager	Pfizer Pharmaceuticals Korea Ltd	Pfizer Tower, 1-11, Hoehyun-Dong 3-Ga, Jung-Gu, Seoul, Korea

Country Coordinating Physicians

NA

APPENDIX 2. AMENDMENTS

Current amendment: 7

Amendment number	Date	Rationale for amendment	Protocol section(s) changed
1	18 Jan 2013	Clarification of the type of study sites	3.1. Study Design
		Clarification of inclusion criteria	3.2.1. Inclusion Criteria
		Addition of number of subjects	3.5.3. Planned Numbers of Patients
		Clarification of efficacy evaluation time point	3.5.5. Investigating Matters
		Addition of medical history item	3.5.5.3. Medical History
		Addition of statistical analyses method	3.8.1.2. Parameter on Safety
		Addition of statistical analyses method	3.8.1.3. Parameter on Efficacy
2	04 Mar 2013	Clarification of the analysis set	3.5.5. Investigating Matters
3	13 Aug 2013	Correction of the follow-up period for long-term surveillance	3.1. Study Design
		Clarification of safety observation and efficacy evaluation time point	3.5.5. Investigating Matters
		Clarification of medical history item	3.5.5.3. Medical History
		Addition of concomitant therapy	3.5.5.4. Concomitant Medication / Therapy
		Clarification of evaluation item (incl. long-term surveillance)	3.5.5.5. Administration Status and Evaluation of Viviant 3.5.5.7. Final Evaluation
		Addition of 'not applicable' for the action taken for an AE	3.5.5.6.1. Adverse Event
		Reflection of the data management related process applicable to an eCRF study	3.7.2. Data management 3.7.2.1 Data Cleaning 3.9. Quality control
		Reflection of the current disclosure requirements	6. Study Disclosure
		Other administrative, non-substantive, stylistic changes were made.	Not specified
4	28 Oct 2013	Reflection of SOP amendment	5.1.3. Definition of an Adverse Event

5	28 Nov 2013	Addition of the details of study sites	3.1. Study Design
		Addition of daily total dosage	3.5.5.5. Administration Status and Evaluation of Viviant
		Clarification of the term used.	3.5.5.6.1. Adverse Event
		Addition of the safety evaluation date and details for long term evaluation	3.5.5.7. Final Evaluation
		Clarification of the sample size	3.6. Power and Sample Size
		Clarification of the analysis method	3.8.1.2. Parameter on Safety
		Clarification of the analysis method	3.8.1.3. Parameter on Efficacy
		Clarification of the analysis method	3.8.2. Statistical Consideration
		Clarification of the term used.	5.1.2. Reporting Period
		Clarification of the term used.	5.1.5. Serious Adverse Events
Clarification of the term used.	5.1.8. Exposure during Pregnancy		
6	26Mar2015	Reflection of SOP amendment	5. Adverse Event Reporting
		Content numbering updated. (Content is same as Amend #5.)	6. Communication of Issues
		Content numbering updated. (Content is same as Amend #5.)	7. Single Reference Safety Document
		Content numbering updated. (Content is same as Amend #5.)	8. Study Disclosure
		Content numbering updated. (Content is same as Amend #5.)	9. List Of Figures
		Content numbering updated. (Content is same as Amend #5.)	10. References
7	22Jun2016	Korean term of “Adverse Event” is changed in accordance with updated MFDS Re-Examination guideline.	Not specified but overall protocol.
		Revision of subject’s personal data collection; Month of Birth	3.5.5.1 Basic Information
		Revision of 24 hours contact information; Drug Safety Unit of the Pfizer Pharmaceuticals Korea Ltd.	3.5.5.6.1 Adverse Event
		Change of Protocol Contact	Appendix 1. Responsible Parties

APPENDIX 3. MILESTONES

Milestone	Planned date
Start of data collection	Oct 2013
End of data collection	15 Nov 2017
Interim reports	15 Jul 2012
	15 Jan 2013
	15 Jul 2013
	15 Jan 2014
	15 Jan 2015
	15 Jan 2016
	15 Jan 2017
Final study report	15 Feb 2018