NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	**Korean Post Marketing Surveillance to observe effectiveness and safety of PRISTIQ® in patients with major depressive disorder**
Protocol number	B2061143
Protocol version identifier	Amendment 4
Date of last version of protocol	29Mar2016
Active substance	PF-05212375
Medicinal product	PRISTIQ® (desvenlafaxine)
Research question and objectives	To identify any problems and questions with respect to the safety and effectiveness of PRISTIQ® during the post-marketing period as required by Ministry of Food and Drug Safety(MFDS)'s regulations.
Author	PPD Pfizer Pharmaceuticals Korea Ltd. Seoul, Korea, Republic of

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADR	Adverse Drug Reaction
AE	Adverse Event
CGI-I	Clinical Global Impression-Improvement
CRF	Case Report Form
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LSLV	Last Subject Last Visit
MDD	Major Depressive Disorder
MFDS	Ministry of Food and Drug Safety
PCD	Primary Outcome Completion Date
PMS	Post Marketing Surveillance
SAE	Serious Adverse Event
SRSD	Single Reference Safety Document

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , MD	Non-Interventional Study Lead	Pfizer Pharmaceuticals Korea Ltd.	Seoul, Korea, Republic of

3. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
Amendment 1	5Mar2015	Substantial	7.1. 7.3.3.1. 7.7.	Convert study design prospectively. Add long-term use study. Add separate analysis in special subject group.	following the guideline of post-marketing surveillance
Amendment 2	11Nov2015	Substantial	1. 4. 6. 7. 8. 9. Entire document	Add abbreviations. Add milestones and modify planned dates. Change MFDS Notification No. Clarify descriptions for research methods, subject exclusion criteria, subject observation period, effectiveness and safety assessment and modify/add minor wording. Modify minor wording. Modify/add/delete some phrases following the Pfizer template and modify minor wording. Change MFDS Notification No. Modify terminology following the revised MFDS Notification.	Modifying contents requiring clear description among the protocol contents
Amendment 3	14Jan2016	Substantial	7.4.9.1. Entire document	Modify the period within which CGI-I evaluation is allowed in case of withdrawal from 'within 6 weeks of the last administration' to 'within 2 weeks of the last administration'. Modify '28 calendar days' to '28 days'.	Reflecting MFDS recommendations
Amendment 4	29Mar2016	Administrative	7.4.10.2 9.1 9.4.3	Clarify the Korean translation of some phrases following the Pfizer template (English) regarding the safety reporting requirement (Korean version only). Clarify the Korean translation of some phrases following the Pfizer template (English) regarding the safety reporting requirement (Korean version only). Modify or add some phrases following the Pfizer template (English) regarding the safety reporting requirement. Modify the Korean translation of some phrases following the Pfizer template (English) regarding the safety reporting requirement (Korean version only). Add the definition of 'lack of efficacy'.	Keeping consistency with the Pfizer template (English) regarding the safety reporting requirement and clarifying the definition of 'lack of efficacy'

4. MILESTONES

Milestone	Planned date
Data collection start date	01 Dec 2015
Data collection end date	01 Dec 2018
MFDS interim report 1-1	05 Oct 2014
MFDS interim report 1-2	05 Apr 2015
MFDS interim report 2-1	05 Oct 2015
MFDS interim report 2-2	05 Apr 2016
MFDS interim report 3	05 Apr 2017
MFDS interim report 4	05 Apr 2018
MFDS interim report 5	05 Apr 2019
MFDS re-examination report	05 May 2020

5. RATIONALE AND BACKGROUND

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 effectiveness information about the product in general practice (usually for a period of 6 years after the product is registered).

PRISTIQ® (desvenlafaxine) is classified as a dual acting Serotonin and Norepinephrine Reuptake Inhibitor (SNRI). Desvenlafaxine extended-release tablets are indicated for the treatment of major depressive disorder (MDD) in adults and for the treatment of moderate to severe vasomotor symptoms (VMS) associated with menopause.

PRISTIQ® was approved by Ministry of Food and Drug Safety (MFDS) in Korea on 06 Feb 2014 for the treatment of Major Depressive Disorder (MDD). This surveillance is conducted for preparing application material for re-examination under the Pharmaceutical Affairs Laws and its Enforcement Regulation, and observation of safety and effectiveness of PRISTIQ® in usual practice according to the Re-examination Guideline of New Drugs, Etc.

The re-exam period for PRISTIQ® is from 06 February 2014 to 05 February 2020, and the final study report should be submitted by 05 May 2020. The analyzed study report based on collected data of 6 years must be submitted to MFDS within 3 months after the end of specified re-examination period (from the product approval date to 6 years afterwards).

6. RESEARCH QUESTION AND OBJECTIVES

The objectives of this study are to determine any problems or questions associated with PRISTIQ® after marketing, with regard to the following clauses under conditions of general clinical practice, in compliance with the regulation "Re-examination Guideline of New Drugs, Etc" (Ministry of Food and Drug Safety Notification 2015-79, 2015.10.30, amended).

(1) Serious adverse event/adverse drug reaction

(2) Unexpected adverse event/adverse drug reaction that has not been reflected in the approved drug label.

(3) Known adverse drug reaction

(4) Non-serious adverse drug reaction

(5) Other safety and effectiveness information

7. RESEARCH METHODS

7.1. Study Design

This study is open-label, non-comparative, observational, non-interventional, prospective and multi-center study in which subjects are administered PRISTIQ® as part of routine practice at Korean health care centers by accredited psychiatrists. The observation period for each subject is from initiating administration of PRISTIQ® until week 8. If administration is discontinued before week 8, observation should be done for at least 28 days from the last administration day. There will be no visit or activity mandated by this study and routine observation will be done during the above-mentioned period.

7.2. Study Size

600 patients will be enrolled in approximately 20 study centers in this study based on the MFDS re-examination regulation (Section 7.3.3). Most of the study centers would be general hospitals or psychiatric hospitals which have the accredited psychiatrists eligible for conducting PMS study.

Subjects will be enrolled by continuous registration method. It means that the physician should consecutively enroll all patients who are administered PRISTIQ® for the first time and satisfy the inclusion and exclusion criteria after contract is made and the study is initiated.

7.3. Setting

7.3.1. Inclusion criteria

1) Adults 19 years of age or older, who have been administered at least one dose of PRISTIQ® for the treatment of Major depressive disorder (MDD).

2) Patients who have been administered PRISTIQ® for the first time after signing the data privacy statement.

7.3.2. Exclusion criteria

Patients to whom PRISTIQ® is contraindicated as per the local labeling;

1) Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the PRISTIQ® formulation.

2) This drug must not be used in combination with a MAOI, or within at least 14 days of discontinuing treatment with a MAOI.

7.3.3. Duration of the study

According to MFDS re-examination regulation, the re-examination report based on collected data of 6 years must be submitted to MFDS within 3 months after the end of specified re-examination period (from the product approval date to 6 years afterwards). The re-exam period is from 06 February 2014 to 05 February 2020, and the final study report should be submitted by 05 May 2020.

The data collection period of this study is until the required subject number (600 patients) is collected. The observation period for each subject is from initiating administration of PRISTIQ® until week 8. If administration is discontinued before week 8, observation should be done for at least 28 days from the last administration day. All the data collected during the observation period should be recorded in the case report form (CRF). In case of an adverse event/safety event recognized after the observation period ends, it should be recorded in the CRF as specified in Section 9.

7.3.3.1. Long-term use study

As PRISTIQ® could be used in a long time considering its indication, data from the patients administered in a long time out of enrolled patients will be collected and analyzed separately. Safety and effectiveness data of at least 60 subjects who have been administered PRISTIQ® over 6 months out of enrolled subjects will be collected.

7.3.4. Dosage and administration

The use and dosage recommendations for PRISTIQ® should take place on the basis of the approved local product document. If subjects have been administered PRISTIQ® off label, they should be excluded from the safety analysis set and analyzed separately.

Refer to the most updated local product document for the detailed information on prescription.

7.4. Study Procedures

All patients who are eligible for this study will be enrolled and evaluated.

There will be no visit mandated, but at least once safety information should be followed up by visit, telephone, e-mail or fax etc. during the study. The investigator should record the following information on the patient's CRF:

7.4.1. Information of institution

The following will be recorded in the CRF for each patient:

- CRF number (Patient number): The investigator will sequentially assign each patient a patient identification number, which will be a 4-digit number. It will be combined with code number of institution by sponsor.
- Name of institution
- Name of department
- Name of investigator
- Date of signing data privacy statement
- Signature of investigator: Contracted investigator must sign after identifying the CRF.

7.4.2. Patient information (Baseline)

The following will be recorded in the CRF for each patient:

- Inclusion criteria: Subjects can be enrolled with satisfying all inclusion criteria.
- Exclusion criteria: Subjects cannot be enrolled with meeting any of exclusion criteria.
- Age
- Sex
- Pregnancy: If 'yes', then record the week of pregnancy.
- Breast-feeding
- Diagnosis
- Diagnosis date
- Severity of the disease

7.4.3. Medical history

Select among 'yes' or 'no' for medical history of followings. Past or present disease (including hepatic and renal impairment) will be determined based on the first PRISTIQ®

administration date. Record adequate full name of the disease down as the Medical Terminology Dictionary indicates (written by Korean Medical Society).

7.4.3.1. Renal disorder / Hepatic disorder

If 'yes', record the name of the disease, severity and status.

7.4.3.2. Allergic history

If 'yes', record the allergen and status.

7.4.3.3. Other diseases / symptoms

If 'yes', record the name of the disease and status.

7.4.4. Recent past psychotropic medication

Select among 'yes' or 'no' for past psychotropic medications which were terminated within 30 days before the first administration of PRISTIQ®. The following will be recorded in the CRF for each patient:

- Name of medication
- Route of administration
- Treatment start date
- Treatment stop date

7.4.5. Administration status for PRISTIQ®

Record the followings with regard to administration status for the study drug. If the posology is changed (including wash-out), please record in a separate row and the reason.

- Treatment start date
- Treatment stop date
- Daily dosage and frequency
- Reason for dose adjustment: Select one among 'planned dose increase or decrease', 'cure or improvement', 'occurrence of adverse event', 'withdrawal due to lack of efficacy' or 'other'. If 'other', record the specific reason.

7.4.6. Concomitant medications

Record the medicated drug while PRISTIQ® is being administrated. First select either 'yes' or 'no' then record in more details if selected 'yes'.

- Name of medication (generic name)

- Treatment start date
- Treatment stop date
- Ongoing: If the treatment is not terminated until the timing of CRF completion, check 'ongoing'.
- Purpose of treatment: Select one among 'treatment for major depressive disorder', 'treatment for other diseases', 'treatment for an adverse event', 'prevention of drug side effect', or 'other'. If 'other', record the specific reason.

7.4.7. Blood Pressure

If the physician performed blood pressure check for diagnostics or monitoring in usual medical practice, check 'done' and record the results. If there is any clinically significant abnormal result in blood pressure during or after administration compared to one before administration, please check 'yes' and record the abnormality in "9. Safety evaluation" clause.

- Date of blood pressure check (before / during / after)
- Results (sBP / dBP)

7.4.8. Clinical laboratory

If the physician performed laboratory test for diagnostics or monitoring in usual medical practice, check 'done' and record the results. If there are any clinically significant abnormality in laboratory test results during or after administration compared to one before administration, please check 'yes' and record the abnormality in "9.Safety evaluation" clause.

- Laboratory test item
- Normal range (unit)
- Date of laboratory test
- Test results (before / during / after)

7.4.9. Effectiveness Evaluation

7.4.9.1. CGI-I scale (Clinical Global Impression – Improvement scale)

Clinical effectiveness will be evaluated after 8 weeks treatment (within 2 weeks of the last administration) using CGI-I scale as follows. In case of long-term use study subject, the result will be also assessed after 6 months treatment of PRISTIQ® (within 2 weeks of the last administration).

- 1. Very much improved

- 2. Much improved
- 3. Minimally improved
- 4. No change
- 5. Minimally worse
- 6. Much worse
- 7. Very much worse

7.4.9.2. Final effectiveness evaluation

Final effectiveness will be evaluated at completing the administration of PRISTIQ® or at around 8 weeks treatment if PRISTIQ® has been still administered. In case of long-term use study subject, the result will be assessed after 6 months treatment of PRISTIQ®. Final effectiveness will be evaluated as 'improved', 'no change', 'worse' or 'unevaluable' based on overall patient's clinical response, CGI-I scale and investigator's judgment.

- Improved: In the case of judgment that there is the improvement of symptoms related to MDD.
- No change: In the case that there is no significant change compared to patient's status before PRISTIQ® administration.
- Worse: In the case that symptoms are getting worse compared to patient's status before PRISTIQ® administration.
- Unevaluable: In the case that the medical charts do not have adequate progress notes to make a judgment on clinical response.

7.4.10. Safety Evaluation

Safety will be assessed based on adverse events reported for all patients who received at least one dose of PRISTIQ® and completed safety follow-up. Any adverse events will be recorded in the CRF including the information of the specific conditions or events, duration of the event persisted, seriousness, severity, causal relationship to PRISTIQ®, actions taken, and outcome.

7.4.10.1. Definition of 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 AE);

- 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.

7.4.10.2. Definition of serious adverse events (SAEs)

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.

- Is important medical event (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)

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)

7.4.10.3. Adverse events data collection

The investigator collects data on safety events as specified in Section 9 including all adverse events that occur during the observation period regardless of causal relationship to PRISTIQ®. The information on adverse events should include the specific conditions or events, duration of the events (start date and stop date), seriousness (serious or non-serious), severity, causal relationship to PRISTIQ®, actions taken, and outcome.

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

- Adverse event: Record the term of adverse event. If possible, specify diagnosis, not individual symptoms.
- Date of onset: Record the date of onset.
- 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) PRISTIQ®: Check the appropriate number for the adjustment of PRISTIQ® resulted from the adverse event.

  1. Withdrawn (temporarily or permanently, or delayed)

  2. Dose reduced

  3. Dose increased

  4. Dose not changed

  5. Unknown

  6. Not applicable

  2) Others: After the onset of adverse event, the investigator 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 at any dose that:

  - results in death;

- is life-threatening;
- requires inpatient hospitalization or prolongation of hospitalization;
- results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- results in congenital anomaly/birth defect.
- Is important medical event (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)

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.

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

- Outcome: Select among ‘yes’, ‘unknown’, or ‘no-resolved’ as a reply to a question, ‘Is the adverse event still present?’ If ‘no-resolved’, record the resolved date.
- Causality of adverse event to the study drug: The causal relationship of adverse event to the study drug must be allocated by the psychiatrist 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, psychiatrists 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.

7.5. Data Sources

7.5.1. Case report forms

The investigator will review source documents and complete an electronic CRF for each included patient. The completed original CRFs are the sole property of Pfizer and should 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 the collection and reporting of all clinical, safety, and laboratory data entered on the CRFs, 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 investigator or by an authorized staff member to attest that the data contained on the CRFs is true. Any corrections to entries made on the CRFs must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the hospital's or the physician's patient chart. In these cases data collected on the CRFs must match the data in those charts.

7.5.2. Record retention

To enable evaluations and/or audits from regulatory authorities or Pfizer, the investigator agrees to keep records, including the original signed data privacy statement, identity of all participating patients (sufficient information to link records, e.g., CRFs and hospital records), copies of all CRFs, SAE 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 investigator according to 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, relocation), Pfizer should be prospectively notified. 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 have been met.

7.6. Data Management

CRF data collected by the investigator will be entered into the clinical database. Verifications will be performed after comparison of the double data entry. All missing data or data to be checked will be reported on a query sheet for further verification at the study site. Any data modification will be recorded.

AEs will be coded using World Health Organization - Adverse Reaction Terminology. Medical history will be coded using Classification of Korea national statistical office. Concomitant drugs will be coded via www.kimsonline.co.kr provided by KIMS Co. Ltd.

Statistical analysis will be carried out with SAS software version 9.2 or a more recent version.

7.7. Data Analysis

The data collected in this study will be documented in a Statistical Analysis Plan, which will be maintained by the sponsor. This document may modify the plans outlined in the protocol; however, any major modifications of primary endpoint definitions or their analyses will be reflected in a protocol amendment.

No formal sample size calculations were performed for this study. Six hundred (600 patients) or more will be collected as per the requirement by MFDS. Safety summaries will be based on the safety analysis set defined as those patients who met inclusion / exclusion criteria and completed safety follow-up. Effectiveness summaries will be based on the effectiveness analysis set, defined as those patients who took at least 8 weeks of PRISTIQ® and completed effectiveness evaluation.

In addition, special subject groups -elderly group (more than or equal to 65 years old), hepatic disorder group, renal disorder group and pregnancy group- will be analyzed separately.

7.7.1. Safety analysis

- Count and frequency of occurrence of adverse event, serious adverse event, adverse drug reaction or unexpected adverse event by category.

- Count and frequency of occurrence of adverse events by subject baseline factor and by treatment factor to determine factors affecting the safety.

- If there is any particular pattern in abnormal findings (including clinical laboratory abnormalities) occurring during or after the treatment which were considered unrelated to PRISTIQ®, the count and frequency of the events will be tabulated and analyzed to determine the casual relationship to the relevant study drug.

7.7.2. Effectiveness analysis

Effectiveness endpoints include following variables: CGI-I scale and final effectiveness evaluation result at the date of effectiveness evaluation. Descriptive statistics (cell counts and percents) will be used to summarize this variable within the effectiveness analysis set population; the CGI-I scale and final effectiveness evaluation will also be summarized within subgroups of the effectiveness analysis set formed by demographic and other baseline factors such as sex, age and diagnosis date of MDD, etc. Comparisons across subgroups may be conducted using chi-squared tests at the 0.05 level of significance.

7.7.3. Statistical consideration

The significance of the difference between sub-categories with regard to safety and effectiveness will be statistically analyzed using χ^2 test ($p \leq 0.05$), etc. The frequency of occurrence of each adverse event will be presented with its 95% confidence interval.

To determine factors affecting the safety, the count and frequency of occurrence of all adverse events will be tabulated by type of the event and subject's baseline factor (gender, age, presence of concurrent disease, etc.), and factors considered potentially affecting the safety will be analyzed using categorical data analysis method (Chi-square test, Fisher's Exact test), etc. Serious adverse events, adverse drug reaction and unexpected adverse events, etc. will be also tabulated and summarized.

7.8. Quality Control

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

7.9. Limitations of the Research Methods

This is a non-interventional PMS study conducted in the Republic of Korea to satisfy the requirements of MFDS. The protocol is determined by regulation of MFDS and not the specific disease and drug characteristics. The observational, non-controlled, and non-randomized design of this study has intrinsic limitations.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient 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 patient 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 Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient, or his/her legally acceptable representative, is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written data privacy statement from each patient or the patient's

legally acceptable representative before any study-specific activity is performed. The investigator will retain the original of each patient'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 sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient 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.

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

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

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and other relevant documents, if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer or its designee.

8.4. 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 Guidelines for GPP issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA), Pharmaceutical Research and Manufacturers Association (PhRMA) guidelines, and Korea PMS regulations and/or guidelines.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS

9.1. Requirements

The table below summarizes the requirements for recording safety events on the CRF 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 CRF	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 CRF. 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 PRISTIQ ®, and lasts through the end of the observation period of the study, which must include at least 28 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 days following the end of observation.

Most often, the date of data privacy statement is the same as the date of enrollment. In some situations, there may be a lag between the dates of data privacy statement and enrollment. In these instances, if a patient provides data privacy statement 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 PRISTIQ ®, 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 PRISTIQ ®, 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 PRISTIQ ® caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether PRISTIQ ® 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 PRISTIQ ® did not cause the event, this should be clearly documented on the CRF and the NIS AEM Report Form.

9.4. Definitions of Safety Events

9.4.1. Adverse events

Refer to the '7.4.10.1. Definition of adverse events' clause.

9.4.2. Serious adverse events

Refer to the '7.4.10.2. Definition of serious adverse events (SAEs)' clause.

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

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) PRISTIQ®, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to PRISTIQ® (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 PRISTIQ® 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 exposures 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 PRISTIQ®, 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 PRISTIQ® 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

Lack of efficacy is defined as the failure of expected pharmacologic action or therapeutic benefit.

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.

Based on the “Safety Information Management Regulations for Drugs, Etc.”, the staff in charge of safety information at Pfizer Korea reports to the Director of Korea Institute of Drug Safety and Risk Management via website, telephone, fax, mail or in the form of electronic document using Appendix Form no. 1 in the Safety Information Management Regulations for Drugs, Etc. (MFDS Notification) within 15 days of awareness or being notified of the serious adverse event/adverse drug reaction in accordance with Article 5 Paragraph 4 of the Re-examination Guideline of New Drugs, Etc (MFDS Notification no. 2015-79). Therefore, in case of a serious adverse event/adverse drug reaction, the investigator immediately notifies the staff in charge of safety information at Pfizer Korea. The investigator completes the

'Non-Interventional Study Adverse Event Report Form' and must fax it within 24 hours of awareness of the applicable serious adverse event/adverse drug reaction.

9.5. Single Reference Safety Document

The local product document will serve as the SRSD during the course of the study, which will be used by Pfizer to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The SRSD should be used by the investigator 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 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 MFDS annually. Final study report (i.e., re-examination report) will be submitted to MFDS in the 6th year to include all data collected during the whole study period (see Section 4).

11. 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 is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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

12. PUBLICATION OF STUDY RESULTS

Pfizer fulfils its commitment to publicly disclose study results through posting the results of this study on www.clinicaltrials.gov. Pfizer posts the results of all studies that is has registered on ClinicalTrials.gov regardless of the reason for registration.

The results are posted in a tabular format called Basic Results.

- Basic Results are due within one anniversary year of the PCD and/or LSLV.
- When PCD and LSLV are not the same date, Basic Results are posted one anniversary year from the PCD and the record is updated one anniversary year from the LSLV. The PCD cannot occur after the LSLV.