Non-Interventional Study Protocol
B2061143

Korean Post Marketing Surveillance to observe effectiveness and safety of PRISTIQ® in patients with major depressive disorder

Statistical Analysis Plan
(SAP)

Version: Version 4.0

Author: PPD (PPD - DreamCIS)

Date: 08-NOV-2019

TABLE OF CONTENTS

1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date of Revision	Reason for change	Author name
Version 1.0	11-MAY-2016	1st Version	PPD
Version 2.0	10-JUL-2016	1) Deletion duplicated exclusion criteria in Safety Analysis Set • The contents of "Subjects who didn't receive PRISTIQ®" are included in "Subjects who violated inclusion/exclusion criteria) item 2) Addition the exclusion criteria in Long-term Effectiveness Analysis Set • Addition "Subjects whose each drug-free period is greater than 14 days" item 3) Modification for analysis method and category • Pregnancy • Breast-feeding • Severity of disease • Mean daily dose of PRISTIQ® 4) Modification of calculation method • "Total administration period of PRISTIQ®" 5) Addition the analysis • Other Analyses (Blood Pressure)	PPD
Version 3.0	15-NOV-2018	1) Modification of calculation of Total administration period of PRISTIQ® according to analysis set 2) Clarification the definition of subjects excluded from safety analysis set 3) Addition items of Basic Results Tables	PPD
Version 4.0	08-NOV-2019	1) Exclusion of subjects who are assessed on the final effectiveness evaluation before 8 weeks treatment with PRISTIQ® from the Effectiveness Analysis Set (Section 5.2) 2) Clarification on the derivation of the mean daily dose of PRISTIQ® excluding days of missed doses (Sections 8.2.1.1) 3) Addition of categories for the Total administration period of PRISTIQ®: <12 weeks, ≥12 weeks (Sections 8.2.1.1 and 8.2.1.3) 4) Addition of AE Listings (Section 8.2.1.4) 5) Addition the analysis	PPD

		• AE analysis according to the frequency categories of adverse events in the approved local label (Section 8.2.1.4) 6) Clarification that the effectiveness analyses will be conducted for the periods after 8 weeks and after 6 months of treatment with PRISTIQ® (Section 8.2.2)	

2 INTRODUCTION

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

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).

2.1 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.

Study population

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.

[Inclusion criteria]

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

[Exclusion criteria]

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

- *Hypersensitivity to desvenlafaxine succinate, venlafaxine hydrochloride or to any excipients in the PRISTIQ® formulation.*
- *This drug must not be used in combination with a MAOI, or within at least 14 days of discontinuing treatment with a MAOI.*

2.2 STUDY 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).

- *Serious adverse event/adverse drug reaction*
- *Unexpected adverse event/adverse drug reaction that has not been reflected in the approved drug label.*
- *Known adverse drug reaction*
- *Non-serious adverse drug reaction*
- *Other safety and effectiveness information*

3 INTERIM AND FINAL ANALYSES

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

Note: 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.

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

- Type of medical history
- Type of concomitant medications
- Blood Pressure(SBP, DBP)
- Basic Results Tables

4 HYPOTHESES AND DECISION RULES

Not Applicable

5 ANALYSIS SETS/ POPULATIONS

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

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

5.1 SAFETY ANALYSIS SET

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

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

The following cases are excluded from the safety analysis set:

- Subjects who were enrolled in the study prior to the site initiating contract date

- Follow-up failure: Subjects for whom adverse event status (Adverse Events status is unknown or missing in the CRF) could not be established
- Subjects who violated inclusion/exclusion criteria (see section 2.1)
- Subjects who did not follow dosage and administration indicated in the local product document
  To exclude subjects who have ever taken more than 200mg/day

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

5.2 EFFECTIVENESS ANALYSIS SET

Subject who have been administered PRISTIQ® at least once and evaluated upon its related effectiveness endpoints at least once will be included in the effectiveness analysis set. The effectiveness analysis set is a subset of the safety analysis set.

The following cases are excluded from the effectiveness analysis set:

- Subjects excluded from safety analysis set listed in section 5.1
- Subjects who are assessed as "Unevaluable" on the final effectiveness evaluation on the CRF
- Subjects who administrated PRISTIQ® less than 8 weeks
- Subjects who are assessed on the final effectiveness evaluation before 8 weeks treatment of PRISTIQ®

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

5.3 LONG-TERM EFFECTIVENESS ANALYSIS SET

Subject who have been administered PRISTIQ® over 6 months out of enrolled patients will be included in the long-term effectiveness analysis set. The long-term effectiveness analysis set is a subset of the effectiveness analysis set.

The following cases are excluded from the long-term effectiveness analysis set:

- Subjects excluded from effectiveness analysis set listed in section 5.2
- Subjects who administrated PRISTIQ® less than 6 months(180 days)
- Subjects whose each drug-free period is more than 14 days
- Subjects who are assessed on the final effectiveness evaluation before 6 months(180 days) treatment of PRISTIQ®

6 ENDPOINTS AND COVARIATES

6.1 SAFETY ENDPOINT(S)

- *Occurrence of Adverse Event*

6.2 EFFECTIVENESS ENDPOINT(S)

- *[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.*

- *[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 HANDLING OF MISSING VALUES

Not Applicable

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

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

8.1.1 Analysis for Continuous Data

Descriptive summary statistics for continuous variables will include the following:

- number of subjects (n), mean, standard deviation (SD), median, minimum and maximum.

8.1.2 Analysis for Categorical Data

Descriptive statistics for categorical variables will be given as frequencies and percentages. The denominator will be the number of subjects included either in the safety analysis set or effectiveness analysis set depending on where the analysis is presented. But in case of pregnancy and breast-feeding analysis, subjects who collected "Not Applicable (male)" are excluded from the denominator and footnote will be added to the relevant outputs to indicate the number of subjects collected "Not Applicable (male)". Likewise, in analysis of severity of disease, subjects who collected "Unknown" are excluded from the denominator and footnote will be added to the relevant outputs to indicate the number of subjects collected "Unknown".
Where appropriate, the percentages will be presented with a corresponding 95% confidence interval. Comparisons between subcategories of each baseline characteristic will be made using chi-square test or Fisher's exact test. Test statistics include p-value. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test should be used instead of chi-square test.

8.2 STATISTICAL ANALYSES

8.2.1 Safety Analyses

8.2.1.1 Demographic and Baseline Characteristics

Baseline characteristics for this study are defined as follows:

- Continuous measurements:
  - Age
  - Duration of disease†
  - Total administration period of PRISTIQ®‡
  - Total dose of PRISTIQ®¶

- Mean daily dose of PRISTIQ® excluding days of missed doses§

- Categorized measurements:
  - Age (< 30 years, ≥30 years and ≤49 years, ≥50 years and ≤69 years, ≥70 years*)
  - Geriatric status (<65 years, ≥65 years)
  - Sex (Male, Female)
  - Pregnancy (Yes, No)
  - Breast-feeding (Yes, No)
  - Duration of disease† (<3 months, ≥3 months and <6 months, ≥6 months*)
  - Severity of disease (Mild, Moderate, Severe)
  - Medical History (Past Disease, Present Disease/Yes, No)
  - Allergic history (Yes, No)
  - Recent past psychotropic medication (Yes, No)
  - Total administration period of PRISTIQ®‡ (< 4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks*)
  - Mean daily dose of PRISTIQ® excluding days of missed doses (<50 mg/day, ≥50 mg/day and <100 mg/day, ≥100 mg/day and ≤200 mg/day *)
  - Renal disorder (Yes, No)
  - Hepatic disorder (Yes, No)
  - Long-term administration (<6 months (180 days), ≥6 months (180 days) of total administration period of PRISTIQ®)
  - Concomitant medication (Yes, No)

† Duration of disease = First start date of PRISTIQ®– Diagnosis Date + 1
Subjects whose diagnosis date is included 'Unknown' are excluded from the analysis (Footnote will be added to the relevant outputs to indicate the number of subjects collected 'Unknown')

‡ Total administration period of PRISTIQ® = Sum of each period of administration
- In safety analysis set
  Sum of each period of administration = (Last administration end date) – (First administration start date) + 1
  If the medication is being continued at the completion of the study, last administration end date is replaced with last date collected in data.
- In effectiveness analysis set
  - If final effectiveness evaluation is evaluated after last administration end date,
    Sum of each period of administration = (Last administration end date) – (First administration start date) + 1
  - If final effectiveness evaluation is evaluated before last administration end date or the medication is being continued at the completion of the study,
    Sum of each period of administration = (Date of final effectiveness evaluation) – (First administration start date) + 1

¶ Total dose of PRISTIQ® = Sum of each dose of administration

: Each dose of administration = (Administration end date - Administration start date +1)*(Total daily dose)
§ Mean daily dose of PRISTIQ® excluding days of missed doses = Total dose of PRISTIQ® / Total administration period of PRISTIQ® excluding days of missed doses
* The above categories can be altered depending on the data distribution.

8.2.1.2 Adverse Events

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

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

8.2.1.3 Adverse Events by Baseline Characteristics

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

- The number of subjects to whom AE occurred and the number of AEs will be calculated.
- The proportion of subjects to whom AE occurred and its 95% confidence interval will be estimated and compared between subcategories of each baseline characteristic using chi-square test or Fisher's exact test.
- Adverse event presentations will be split by the following baseline characteristics:
  - Age (< 30 years, ≥30 years and ≤49 years, ≥50 years and ≤69 years, ≥70 years)
  - Geriatric status (<65 years, ≥65 years)
  - Sex (Male, Female)
  - Pregnancy (Yes, No)
  - Breast-feeding (Yes, No)
  - Duration of disease (<3 months, ≥3 months and <6 months, ≥6 months)
  - Severity of disease (Mild, Moderate, Severe)
  - Medical History (Past Disease, Present Disease/Yes, No)
  - Allergic history (Yes, No)
  - Recent past psychotropic medication (Yes, No)
  - Total administration period of PRISTIQ® (< 4 weeks, ≥4 weeks and <8 weeks, ≥8 weeks and <12 weeks, ≥12 weeks)
  - Mean daily dose of PRISTIQ® excluding days of missed doses (<50 mg/day, ≥50 mg/day and <100 mg/day, ≥100 mg/day and ≤200 mg/day)
  - Renal disorder (Yes, No)
  - Hepatic disorder (Yes, No)

- Long-term administration (<6 months (180 days), ≥6 months (180 days) of total administration period of PRISTIQ®)
- Concomitant medication (Yes, No)

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

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

- The number and percentage of AE will be presented overall and by preferred term. This will be repeated by:
  - severity
  - action
  - other action
  - seriousness
  - outcome
  - causality of adverse event to the study drug
  - other causality of adverse event to the study drug
- The number of subjects and the number of unexpected AE/ADR, Serious AE (SAE)/Serious ADR (SADR), unexpected SAE/SADR, AE/ADR will be calculated according to the preferred terms. Also, the proportion of subjects to whom AE occurred will be estimated.
- The subjects with Serious AE, unexpected AE, unexpected serious AE, AE of Geriatric, pregnant, breast-feeding, renal disorder, hepatic disorder and long term subjects will be listed for safety analyses sets.
- For subjects excluded from safety analysis set*, the number of subjects and the number of unexpected AE/ADR, Serious AE(SAE)/Serious ADR (SADR), unexpected SAE/SADR, AE/ADR will be calculated according to the preferred terms. Also, the proportion of subjects to whom AE occurred will be estimated.
  * Subjects who enrolled for duplication or Subjects who have not taken PRISTIQ® or Subjects for whom adverse event status could not be established (Adverse Events status is unknown or missing in the CRF) will be excluded from this analysis.
  Note: Unexpected AEs/ADRs will be classified by medical review and with reference to the local product document. Terms already included in the local product document are classified as 'expected'. All other terms that are not included in the local product document will be classified as 'unexpected'. These can't be classified without the local product document.
- For subjects excluded from safety analysis set, Serious AE, unexpected AE, unexpected serious AE will be listed for subjects excluded from safety analysis set.

- In re-examination report, SAE/SADR and unexpected AE/unexpected ADR in accordance with PT will be presented respectively according to the frequency categories of adverse events in the approved local label.

8.2.2 Effectiveness Analyses

Statistical analysis on effectiveness parameter after 8 weeks treatment of PRISTIQ® will be done on effectiveness analysis set.

For collected data separately,

- The overall improvement rate (the proportion of patients considered "Improved") will be estimated with its 95% confidence interval.
- Frequency and percentage of results for Final Effectiveness ('Improved', 'No change', 'Worse') will be summarized.

The improvement rate according to the baseline characteristics listed in section 8.2.1.3 will be analyzed. Chi-square test or Fisher's exact test will be used for comparing between subcategories of each baseline characteristic

Additionally, the distribution of subjects according to the CGI-I scale ('1. Very much improved', '2. Much improved', '3. Minimally improved', '4. No change', '5. Minimally worse', '6. Much worse', '7. Very much worse') at last visit will be summarized.

Following statistical analysis on effectiveness parameter after 6 months(180 days) treatment of PRISTIQ® will be done on long-term effectiveness analysis set.

- Frequency and percentage of results for Final Effectiveness ('Improved', 'No change', 'Worse') will be summarized.
- Distribution of subjects according to the CGI-I scale ('1. Very much improved', '2. Much improved', '3. Minimally improved', '4. No change', '5. Minimally worse', '6. Much worse', '7. Very much worse') at last visit will be summarized.

8.2.3 Other Analyses

Statistical analysis on blood pressure will be done on safety analysis set.

For Blood Pressure (SBP, DBP),

- Descriptive summary statistics (number of subjects (n), mean, standard deviation (SD), median, minimum and maximum) of blood pressure at before and after administration will be summarized.
- The change of after administration compared before administration for blood pressure will be analyzed using paired t-test.

In addition to the above summaries and analyses, the following Basic Results Tables will also be produced for the final study report.:

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

9 APPENDICES

9.1 APPENDIX 1: NOTES

- Each statistical analysis will be carried out with SAS Software version 9.4 or more recent version.
- Ambiguous data such as "≥20", ">20" in 'Diagnosis Date', 'Daily dosage' variable will be excluded from analysis.