Non-Interventional Study Protocol
A6791036

Sayana®
(POST MARKETING SURVEILLANCE TO OBSERVE SAFETY AND EFFICACY OF SAYANA® USED FOR CONTRACEPTION AND MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN)

Statistical Analysis Plan
(SAP)

Version: 2.0

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1 AMENDMENTS FROM PREVIOUS VERSION(S)

Version	Date of Revision	Reason for change	Author name
Version 1.0	23-JUL-2014	1st Version	PPD
Version 2.0	27-APR-2020	- Amended study period extension in accordance with Protocol change. - Added unexpected SAE/SADR according to the preferred terms - Added AE/SADR, unexpected AE/unexpected ADR by preferred terms according to the frequency categories in the approved local label - Added AE Listings - Detailed Basic Results Tables	PPD

2 INTRODUCTION

Note: in this document any text taken directly from the Protocol is ***italicised***.

In light of the number of unplanned pregnancies, women recognize the need for contraception and family planning. In addition to controlling the size of their families, couples also want to control the timing and spacing of births. Moreover, the job of family planning will never be finished. With each new generation, comes a new set of parameters affecting use of contraception.

Barriers to using contraception include worries about side effects, health concerns, social disapproval or partner's opposition, financial limitations and lack physical access. In addition, lack of information about nondaily hormonal contraceptives may also be a barrier for women considering contraception. The success of many family planning programs has been linked to removing administrative and medical barriers. Nondaily contraceptives can increase compliance. With oral contraceptives, missed pills are common and contribute to unintended pregnancies. Nondaily contraceptives offer dosing options that reduce the likelihood of missed dose.

Sayana®, revised formulation of depot medroxyprogesterone acetate (DMPA), is specifically formulated for subcutaneous administration. The contraceptive efficacy of Sayana® has been demonstrated in 2 large, multinational contraceptive trials, in which Sayana® was highly effective and generally well tolerated Zero pregnancies were reported in both trials (N=1,787) under perfect use conditions.

In addition to its high efficacy, Sayana® delivers a lower dose of medroxyprogesterone acetate than Depo-Provera Contraceptive Injection 150 mg/mL (medroxyprogesterone acetate injectable suspension, 150 mg/mL) and offers subcutaneous administration once every 3 months, thereby eliminating the need for the discipline of daily dosing.

Sayana® benefits from the established clinical history of Depo-Provera CI 150 mg for intramuscular administration, which contains the same active ingredient in a different formulation. Depo-Provera CI 150 mg has been available worldwide for decades and in the United States since 1992. Over 68 million women in over 114 countries worldwide have used Depo-Provera CI 150 mg, and the years of experience with Depo-Provera CI 150 mg worldwide provide a large body of long-term data regarding its safety and efficacy.

In December 2004, the FDA approved Sayana® for use as a contraception. Sayana® was approved in 48 countries over the world, among which 33 countries marketed Sayana® while 15 countries are under preparation for marketing.

Women who use Sayana® may lose significant bone mineral density. Bone loss is greater with increasing duration of use and may not be completely reversible. It is unknown if use of Sayana® during adolescence or early adulthood, a critical period of bone accretion, will reduce peak bone mass and increase the risk for osteoporotic fracture in later life. Sayana® should be used long-term (eg, longer than 2 years) only if other methods of birth control are inadequate.

In South Korea, Sayana® was first approved as new medicine on 29 Jan 2013 by Ministry of Food and Drug Safety (MFDS). As required for any new medication approved by MFDS of Korea, Republic of, safety and efficacy information of new medication should be provided at minimum 600 subjects administered in the setting of routine practice during the initial 6 years after the approval (29 Jan 2013 ~ 28 Jan 2019) through Post-Marketing Surveillance study.

However, as of 05 Mar 2018, MFDS approved 2 more years re-examination period extension due to low sales trend and enrollment difficulty after marketing. This study will be conducting by 28 Jan 2021 then safety and effectiveness information will be provided from these minimum 600 subjects.

2.1 STUDY DESIGN

This study is an open-label, non-comparative, observational, non-interventional, prospective and multi-center study in which subjects administered Sayana® (administered as part of routine practice in Korean health care centers by accredited physicians) will be observed prospectively for a period of 6 months from the enrollment date. The visit schedule or interval will be decided by the investigator.

Subject Enrollment

Subjects will be enrolled by continuous registration method. The investigators will assess all the subjects in their practice who receive at least 1 dose of Sayana® 104mg/0.65mL agreed to participate in this study by signing the 'data privacy statement'. All subjects enrolled should meet the usual prescribing criteria for as Sayana® per the local product document and should be entered into the study at the investigator's discretion.

A written, Pfizer and institutional review board (IRB)/independent ethics committee (IEC)-approved, informed consent (ie, Data privacy statement) must be obtained before initiating study procedures.

Subject selection

The eligibility of the subject will be evaluated. After inclusion of the subject and after obtaining written informed consent (ie, Data privacy statement) (prior to any procedure being performed) from the subject or subject's parents/ legal representative (as appropriate), the investigator or site staff will record the subject data into source documents and into a Case Report Form (CRF). Enrollment visit is the visit when subject signs on informed consent (ie, Data privacy statement). Following the baseline data collection , the visits are at the discretion of the investigator and may follow the local usual standard of care, however, the sponsor recommends safety and treatment data assessments at 3 month intervals (every 12~14weeks) at a minimum during the 6 months of participation. A Follow-up Call is to be conducted by investigator or delegated staffs at least 28 calendar days after the last administration of the study drug within the observational period in order to collect information on the occurrence of adverse events and concomitant medications.

[Inclusion criteria]

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

1) *Subjects or legally authorized representatives of pediatric subjects agree to provide written informed consent form (ie, data privacy statement).*
2) *Women subjects who are initiating treatment with Sayana® for the first time as per the local product document for usage*

Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study is required.

[Exclusion criteria]

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

1) *Known or suspected pregnancy.*
2) *Undiagnosed vaginal bleeding.*
3) *Known or suspected malignancy of breast.*
4) *Active thrombophlebitis, or current or past history of thromboembolic disorders, or cerebral vascular disease.*
5) *Significant liver disease.*
6) *Known hypersensitivity to medroxyprogesterone acetate or any of its other ingredients.*
7) *Women who are before menarche or who are post-menopausal.*

8) Treatment with any investigational agent or device within 30 days prior to the enrollment visit.

2.2 STUDY OBJECTIVES

This study is to describe the safety and efficacy of Sayana® during the usual care setting.

The objective can be specified as below:

- *To detect serious adverse events and adverse drug reactions.*
- *To detect unexpected adverse events and adverse drug reactions that are not included in precaution of local product document.*
- *To observe already known adverse drug reactions.*
- *To observe non-serious adverse drug reactions.*
- *To detect other information on safety and efficacy.*

3 INTERIM ANALYSES

As required by MFDS regulations, the periodic report should be submitted to MFDS every 6 months for the first two years and then annual report should be submitted to 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.

However, according to re-examination period extension, additional annual reports will be submitted to MFDS in the sixth and seventh year and the final report will be submitted in the eighth year.

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

The analyses for types of medical history(past/present disease), types of concomitant medications, any clinically significant abnormal finding from laboratory test reported as an AE (if necessary and data are applicable), the classification of AE by preferred term according to severity, action, seriousness, outcome, causal relationship to Sayana® and other causal relationship regarding occurred AE and estimation of 95% confidence interval for AEs by baseline characteristics, System Organ Classes and Preferred Term of Serious AE/Serious ADR, unexpected AE/ unexpected ADR according to the frequency of AEs in the prescribing information, Basic Results Tables will be performed for the re-examination report (i.e. final report) only.

Note: Although it was planned that interim analyses would be performed for the report submission to the MFDS annually, interim analyses were not performed for the annual reports for the first one year. The first interim analysis will be performed once this SAP is finalized.

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 Efficacy Analysis Set.

All subjects excluded from the Safety Analysis Set will be counted for as part of the subject enrolled 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 Sayana® at least once 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 have taken Sayana® prior to the contract date
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- Subjects who didn't receive Sayana® for this study
- Follow-up failure: Subjects for whom adverse event status (Adverse Events status is unknown or missing in CRF) could not be established
- Subjects who violate the inclusion/exclusion criteria (see section 2.1)
- Subjects who were prescribed for other indications except indications in the local product document:
  [Indications]
  - Prevention of pregnancy in women of child bearing potential
  - Management of endometriosis associated pain
- Subjects who violate the dosage
  [Dosage]
  Sayana® is injected under the skin into the front upper thigh or abdomen every 3 months (12 to 14 weeks).

Unless specified otherwise, safety summaries and analyses will be presented for the safety analysis set.

5.2 EFFICACY ANALYSIS SET

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

The following cases are excluded from the efficacy analysis set:

- Subjects excluded from safety analysis set listed in section 5.1
- If the purpose of administration was the prevention of pregnancy in women of child bearing potential, subjects whose check either pregnant or not pregnant at evaluation date on the CRF are not completed
- If the purpose of administration was management of endometriosis-associated pain, subjects whose record VAS score at baseline or evaluation date on the CRF are not completed

Unless specified otherwise, statistical analysis on efficacy parameters will be performed on the efficacy analysis set.

6 ENDPOINTS AND COVARIATES

6.1 SAFETY ENDPOINTS

- All Adverse Events (AEs) Occurrence

6.2 EFFICACY/ EFFECTIVENESS ENDPOINT(S)

- *Cumulative percent of patients who become pregnant over the 6 month observation period*
- *Rate of pregnancies per 100 person-years of follow-up*
- *The patient response to endometriosis pain treatment*

7 HANDLING OF MISSING VALUES

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

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

8.1.1 Analysis for Continuous Data

Descriptive summary statistics for continuous variables will include the following:

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

No formal statistical analyses will be performed on continuous data.

8.1.2 Analysis for Categorical Data

Descriptive statistics for categorical variables will be given as frequencies and percentages. Unless specified otherwise, the denominator will be the number of subjects included in the safety analysis set or the efficacy analysis set depending on what analysis is presented. Where appropriate, percentages will be presented with a corresponding 95% confidence interval. Comparisons between subcategories of each baseline characteristic will be made using a chi-square test or Fisher's exact test as appropriate. When more than 20% of expected frequency of the cell count is less than 5, Fisher's exact test will be used instead of the chi-square test.

8.2 STATISTICAL ANALYSES

8.2.1 Safety Analysis

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

8.2.1.1 Baseline Characteristics

Baseline characteristics for this study are defined as follows:

- Age[†] (≤19 years, ≥20 years and ≤29 years, ≥30 years and ≤39 years, ≥40 years and ≤49 years, ≥50 years and ≤59 years, ≥60 years and ≤69 years, ≥70 years)
- Weight
- Height
- Purpose of administration (Prevention of pregnancy in women of child bearing potential, Management of endometriosis associated pain)
- Medical history (Past, Present / Yes, No)
- Concomitant medication (Yes, No)
- Concomitant therapy (Yes, No)
- Total number of injections of Sayana® (1, 2, 3, 4, >4)
- Dose per injections of Sayana® (1 pre-filled syringe(2.25ml), Other)
- Paediatric status (<19 years, ≥19 years)

- Geriatric status (<65 years, ≥65 years)
- Kidney disorder (Yes, No)
- Liver disorder (Yes, No)

† Age = Using the information recorded in CRFs

8.2.1.2 Adverse Events

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

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 a chi-square test or Fisher's exact test. When more than 20% of the expected frequency of the cell count is less than 5, Fisher's exact test will be used instead of the chi-square test.
- Adverse event presentations will be split by the following baseline characteristics: age, purpose of administration, medical history (past/present), concomitant medication, concomitant therapy, total number of injections of Sayana®, dose per injections of Sayana®, paediatric status, geriatric status, kidney disorder, liver disorder (see section 8.2.1.1).

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

All AEs recorded in CRFs will be classified into the system organ class (SOC) and the terms of AE will be coded according to the classification of AEs in 'Precautions of Use' in the local product document of Sayana®/'WHO-ART'/'MedDRA' order. All AEs, except for those with causality of adverse event to the study drug classified as 'Unlikely', will be considered as AEs whose causal relationship to the 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
  - seriousness
  - outcome
  - causal relationship to Sayana®
  - other causal relationship regarding occurred AE
- The number of subjects and the number of unexpected AE/ADR, 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. In re-examination report, SAE/SADR and unexpected AE/unexpected ADR in accordance with preferred terms will be presented respectively according to the frequency categories of adverse events in the approved local label.
- The subjects with Serious AE, Unexpected AE, Unexpected Serious AE, AE of G eriatric, kidney disorder, liver disorder will be listed for safety analyses sets.
- For subjects excluded from the safety analysis set*, the number of subjects and the number of unexpected AE/ADR, SAE/Serious ADR (SADR), unexpected SAE/SADR, AE/ADR will be calculated according to the preferred terms. Also, the proportion of subjects to whom AE occurred will be estimated.

  * Subjects excluded from safety analysis set: Subjects excluded from safety analysis set except for 'subjects who didn't receive Sayana®' and 'subjects for whom adverse event status (Adverse Events status is unknown or missing) could not be established'.

  Note: Unexpected AEs/ADRs will be classified by medical review and with reference to the local product document. Terms already included in the local product document are classified as 'expected'. All other terms that are not included in the local product document will be classified as 'unexpected'. These can't be classified without the local product document.
- For subjects excluded from safety analysis set, Serious AE, unexpected AE, Unex pected Serious AE will be listed.

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

- Demographic Characteristics in safety analysis set
- Summary of Demographic 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)

8.2.2 Efficacy Analysis

The cumulative percent of patients who become pregnant by month 6 will be calculated as 100*(1 – Kaplan-Meier curve at month 6), where the Kaplan-Meier (KM) method for estimating survival function will be applied to time-to-pregnancy. Patients who did not become pregnant will be censored at the time of their last follow-up. The KM method will also be used to calculate a 95% confidence interval for this cumulative percent at month 6.

The rate of pregnancies per 100 person-years of follow-up will be summarized by a 95% confidence interval.

For the rate of pregnancies per 100 person-years of follow-up defined as major events, incidence rate will be calculated as follows:
100×(total number of patients with effectiveness endpoint)/(total person-years of patients included in the effectiveness analysis set) where total person-years is equal to (last evaluation date of outcome - first date of administration +1)/365.25 for all patients in the effective analysis set

The difference between the visual analogue scale (VAS) endometriosis pain scores measured at each visit and the measurement taken before the administration of Sayana® will be analyzed using paired t-test.

9 APPENDICES

9.1 APPENDIX 1: NOTES

- All statistical summaries and analyses will be carried out using SAS Software version 9.2 or higher.
- Where formal statistical tests are performed, significance will be declared using a 2-sided 5% level of significance