NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study information

Title	POST MARKETING SURVEILLANCE TO OBSERVE SAFETY AND EFFECTIVENESS OF SAYANA® USED FOR CONTRACEPTION AND MANAGEMENT OF ENDOMETRIOSIS-ASSOCIATED PAIN
Protocol number	A6791036
Protocol version identifier	Amendment 8, 21Mar2018
Date of last version of protocol	Final, 24May2013 Amendment1, 22Jul2013 Amendment 2, 06 Dec 2013 Amendment 3, 26 Mar 2015 Amendment 4, 08 Jul 2016 Amendment 5, 24 Aug 2016 Amendment 6, 21 Feb 2017 Amendment 7, 30Jan2018
Active substance	Medroxyprogesterone acetate (ATC code: G03DA02)
Medicinal product	Sayana®
Research question and objectives	This study is to describe the safety and effectiveness of Sayana® during the usual care setting.
Author	PPD

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
SAE	Serious Adverse Event
CRF	Case Report Form
eCRF	Electronic Case Report Form
CDC	Clinical Data Coordinator
DC	Data Coordinator
DCF	Data Clarification Form
DMPA	Depot Medroxyprogesterone Acetate
DVP	Data Validation Plan
EIU	Exposure in Utero
IRB/IEC	Institutional Review Board/Independent Ethics Committee
LSLV	Last Subject Last Visit
MFDS	Ministry of Food and Drug Safety
NA	Not Applicable
ODC	Obvious Data Correction
PV	Pharmacovigilance
SAP	Statistical Analysis Plan

2. RESPONSIBLE PARTIES

Name, degree(s)	Title	Affiliation	Address
PPD , MD, MPH	PPD	PPD	PPD Korea
PPD MD	PPD / PPD	PPD	PPD Korea

3. AMENDMENTS AND UPDATES

Document	Version Date	Substantial amendment or Administrative amendment	Summary of Changes
Original protocol	24 May 2013	N/A	N/A
Amendment 1	22 July 2013	Substantial	Responsible parties amended: **1.** PPD Amendment due to regulatory requirements: **1.** Section 8.2.1. Inclusion Criteria: Women subjects who are currently being treated with Sayana® has been omitted. **2.** Section 8.3.1.1. General Information: Addition of date of contract. **3.** Section 8.3.1.2. Demographic information: "Classification" has been deleted. **4.** Section 8.7.2. Statistical Consideration: Use of 95% confidence intervals has been added where necessary. **5.** Section 8.7.2.1. Safety Analysis & 8.7.2.2. Effectiveness Analysis: Statistical method has been added or modified. Others: **1.** Section 8.1.2. Effectiveness endpoint amended: "treatment failure cumulative pregnancy" amended to "cumulative percent of patients who become pregnant by month 6 and rate of pregnancies per 100 person-years of follow-up." **2.** Section 8.1.2. Method of effectiveness endpoint (endometriosis pain management) measurement amended to visual analogue scale.
Amendment 2	06 Dec 2013	Substantial	Responsible parties amended: 1. PPD Amendment for clarification. 1. Section 8.3.1.2. Demographic information: Collection of method for pregnancy test, purpose of administration and VAS at Baseline have been added. 2. Section 10.1.5. SERIOUS ADVERSE EVENTS: The meaning of 'Transmission'

Document	Version Date	Substantial amendment or Administrative amendment	Summary of Changes
			has been clarified. 3. Section 8.7.1.2. Safety Parameters: Additional instruction was added. Amendment due to SOP requirement: 1. Section 10.1.3. DEFINITION OF AN ADVERSE EVENT: The detail to report overdose, misuse, extravasation associated with the use of a Pfizer product has been added. 2. Section 11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS: It has been amended per SOP. 3. Section 10.1.1.5: Lack of efficacy reporting requirement was changed. Others: 1. Section 5. MILESTONE: Typo correction. 2. Section 8.2. Setting: Correction per local regulation 3. Section 8.3.1.1. General Information: "Initial of subject", which would not be collected, has been deleted. 4. Section 8.3.1.4. Concomitant Medication/ Therapy: Typo correction. 5. Section 8.3.1.5 Administrative Status for Sayana®: CRF change was applied.
Amendment 3	26 Mar 2015	Substantial	Amended per SOP; 1. Section 10. Averse Event Reporting: Amended with Safety Reporting Language (effective date: 31 Dec 2013) SOP Update.
Amendment 4	08 Jul 2016	Substantial	Amended the total target enrollment number in accordance with MFDS Appeal Letter. Terms revision; Korean term of "Adverse Event" is changed in accordance with updated MFDS Re-Examination Guideline. Others: 1. "Table of Contents" number correction.
Amendment 5	24 Aug 2016	Substantial	Amended the total target enrollment number to submit the complemented document for Appeal letter to MFDS.
Amendment 6	21 Feb 2017	Substantial	1. Section 5. RATIONALE AND BACKGROUND & Section 7.5. Study size: Amended target enrollment number to initial number

Document	Version Date	Substantial amendment or Administrative amendment	Summary of Changes
			2. Section 7.2. Setting: Amended the subject enrollment method from continuous registration method to whole case enrollment method. 3. 7.2.1 Inclusion criteria: Amended the subject enrollment criteria (After the site initiation, women subjects who are/were in treatment with Sayana® as per the local product document for usage).
Amendment 7	30 Jan 2018	Substantial	Author change: PPD PPD RESPONSIBLE PARTIES addition: PPD PPD Protocol amendment 1. Section 5. RATIONALE AND BACKGROUND & Section 7.5. Study size: Amended target enrollment number for supplementation document submission to MFDS 2. Section 7.2. Setting: Amended the subject enrollment method from whole case enrollment method to continuous registration method. 3. 7.2.1 Inclusion criteria: Amended the subject enrollment criteria 4. Protocol template change
Amendment 8	21 Mar 2018	Substantial	Section 4. MILESTONES: Amended milestones of Interim reports & Final study report in accordance with study period extension. Section 5. RATIONALE AND BACKGROUND & Section 7.5. Study size: Amended target enrollment number to initial number in accordance with re-examination period extension.

4. MILESTONES

Milestone	Planned date
Start of data collection	01 April 2014
End of data collection	28 January 2019
Interim report 1 -1	29 July 2013~28 September 2013
Interim report 1-2	29 January 2014~28 March 2014
Interim report 2-1	29 July 2014~28 September 2014
Interim report 2-2	29 January 2015~28 March 2015
Interim report 3	29 January 2016~28 March 2016
Interim report 4	29 January 2017~28 March 2017
Interim report 5	29 January 2018~28 March 2018
Re-Examination application report	29 January 2019~28 April 2019
Interim report 7	29 January 2020~28 March 2020
Final Study Report (8)	29 January 2021~28 April 2021
Product Market Launching	01 July 2013

5. RATIONALE AND BACKGROUND

In light of the number of unplanned pregnancies, women recognize the need for contraception and family planning.[1,2,3] 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.[4] Nondaily contraceptives offer dosing options that reduce the likelihood of missed dose.[5]

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.[6]

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.[6]

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.[7,8]

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.[9]

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 effectiveness 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.

6. RESEARCH QUESTION AND OBJECTIVES

This study is to describe the safety and effectiveness 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 effectiveness.

7. RESEARCH METHODS

7.1. 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.

7.1.1. Safety Endpoints

- Incidence of adverse events categorized according to physical organ and disease/symptom.

7.1.2. Effectiveness Endpoints

- Cumulative percent of patients who become pregnant over the 6 month observation period and rate of pregnancies per 100 person-years of follow-up.

- The patient response to endometriosis pain treatment: endometriosis pain treatment effect will be measured by visual analogue scale scores recorded by the subjects at each visit. The subject will be asked to indicate the subjective level of endometriosis pain looking back at the last 3 months and mark it with a single vertical mark on the 100mm horizontal visual analogue scale, where 0 mm represents absence of pain and 100mm indicates unbearable pain.

7.2. Setting

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.

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.

7.2.1. 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).

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.

7.2.2. 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.

7.3. Variables

Variable	Role	Data source(s)	Operational definition
Demographic Characteristics	Baseline characteristics	Medical records	*
Basic Laboratory data	Baseline characteristics	Laboratory test results	*
Concomitant medication	Baseline characteristics	Medical records	*

Variable	Role	Data source(s)	Operational definition
Effectiveness result by investigator	Outcome	Medical records	*
Adverse Event (AE)	Outcome	Medical records	*

* Refer to Section 7.3.1 data collection

Detail instruction of variable will be included in the CRF.

7.3.1. Data Collection

The investigator will observe each enrolled subject for 6 months, prospectively, from the enrollment date. There is no specified visit schedule, because this study is not an interventional study. Safety information will be collected at every visit performed for the subject during the observation period.

7.3.1.1. General Information

- Name of Institution: Record the name of the institution.
- Name of Investigator: Record the name of the physician contracted to conduct the study.
- Department: Record the medical department conducting the study.
- Subject ID: Record 4 digit number per subject registration sequence.
- Confirmation of Data Privacy Statement: If all agreement for using subject's personal and medical information, signature and date are obtained by subject or legally authorized representative, then check the box of 'yes'. If not, check 'no' which means that case is excluded from this study.
- Date of contract: Record the date of contract between the Investigator/Institution and the Sponsor.

7.3.1.2. Demographic Information

- Age: Record the age of the subject.
- Sex: Check 'female'.
- Pregnancy: Check the box next to 'yes' or 'no' and record the method of pregnancy test.
- Weight: Record by kg unit.
- Height: Record by cm unit.
- Purpose of administration: Check either the prevention of pregnancy in women of child bearing potential or management of endometriosis-associated pain.
- VAS at Baseline: If the purpose of administration was management of endometriosis-associated pain, visual analogue scale scores recorded by the subject.

7.3.1.3. Medical History

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

7.3.1.4. Concomitant Medication/Therapy

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

- Name of drug/Therapy name: Record generic name in case of single product and record trade name in case of combination product. Also, record name of concomitant therapy.
- Daily total dosage/Frequency: Record the daily total dosage as unit. If not combination drug, avoid recording in tablets, capsules or vials. Record the frequency of concomitant therapy.
- Duration of administration/Duration of therapy: Record the starting/ending date of the medicated drug and concomitant therapy (year/month/day). If the medication and therapy are being continued at the completion of the study, record the starting date date and check in the box next to 'Ongoing'.
- Purpose of administration/Purpose for therapy: Record the purpose of administration or therapy.

7.3.1.5. Administrative Status for Sayana®

Sayana® is provided by the investigator's prescription, and Pfizer Korea will not provide Sayana® for this study.

Record the following with regard to administrative status of Sayana®.

- Date of administration: Record the date of each Sayana® therapy (year/ month/day.
- Dose: Record the dose (ml).
- Outcome of administration:
  Record the evaluation date. If the purpose of administration was the prevention of pregnancy in women of child bearing potential, check either pregnant or not pregnant with the method of pregnancy check. If the subject is pregnant, record the first day of last menstrual period to collect the time to pregnancy. (At the time of first Sayana® administration, investigator must ensure the subject is non-pregnant. Also if a sexually active subject is having regular menstrual cycle and was previously not being administered with other contraceptive agent (therefore is having normal menstrual cycle), investigator must ensure that the first Sayana® injection is within 5 days of the subject's normal menstrual cycle. If the subject was previously being administered with other contraceptive agent(s) and is not having normal menstrual cycle, investigator must ensure that the subject is not pregnant by a method decided by the investigator).

If the purpose of administration was management of endometriosis-associated pain, visual analogue scale scores recorded by the subject.

7.3.1.6. Safety

7.3.1.6.1. Adverse Event

Refer to Section 9 of this protocol and Case Report Form blank form.

7.3.1.6.2. Laboratory Test

Laboratory test is not mandatory because this study is a non-interventional study. If investigator performed a laboratory test (eg, Serum HCG, CBC, Chemistry and Urine) under their usual practice, the results can be collected. Check 'not done' if it is not performed. If 'done', record the following in detail.

- Name of laboratory test: Record the item of laboratory test.
- Normal range (unit): Record the normal range and its unit for each recorded item in each institution.
- Date for laboratory test: Record the date with year / month / day.
- Test result before / after medication: Record the test result.

Refer to [Section **Error! Reference source not found.**.] of the criteria for determining whether an abnormal objective test finding should be reported as an adverse event. If it meets the criteria, it has to be recorded in the adverse event section of the case report form.

7.4. Data sources

The followings are data sources for the study:

1. Medical and nurse records;
2. Laboratory test results.

7.5. Study size

More than 600 subjects should be observed per "Basic Standards for the Re-examination of New Medicines" (Korea MFDS notification No. 2016-97, 2016.9.6., Amendment)

7.6. Data management

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

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

Each study investigator has ultimate responsibility for the collection and reporting of all clinical, safety and laboratory data entered on the CRFs and any other data collection

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

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

In some cases (eg, subject interview), the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

Figure 1. Data Management Flow Chart

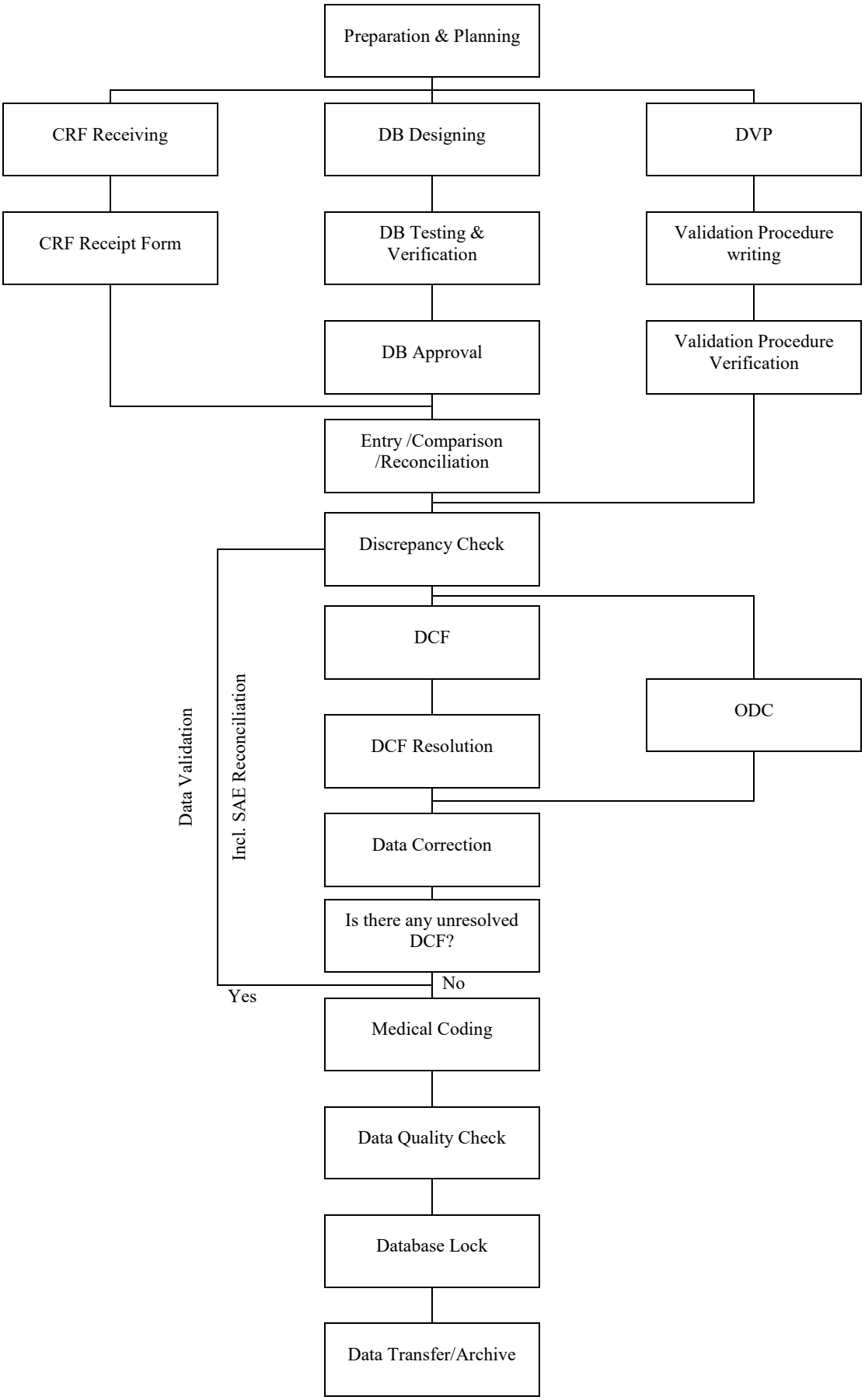
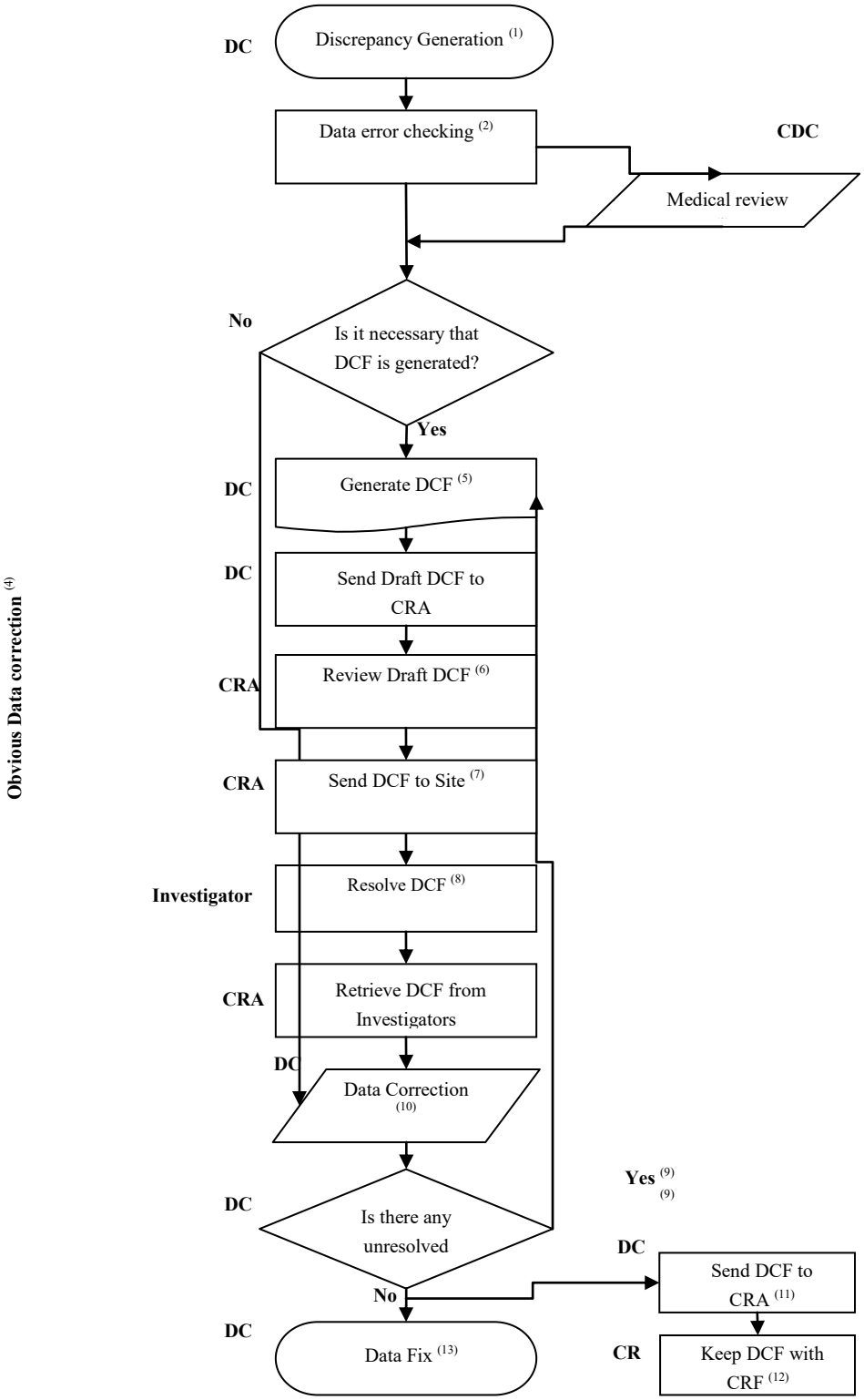


Figure 2. Data Validation Flow Chart



7.7. Data analysis

7.7.1. Assessment of Safety and Effectiveness Parameters

7.7.1.1. Analysis Populations

All analyses will be performed on the safety population, defined as those patients who took at least one dose of study medication.

7.7.1.2. Safety Parameters

Safety parameters include:

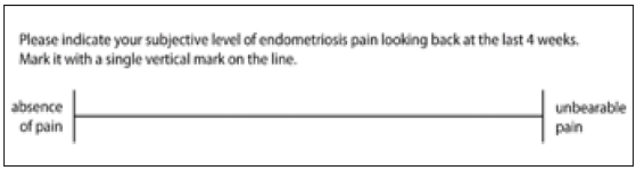
- Adverse events and serious adverse events;
- Premature discontinuations from the study due to adverse events;
- Use of concomitant medications due to adverse events;
- Clinically significant abnormalities from laboratory test.

7.7.1.3. Effectiveness Parameters

Effectiveness parameters include:

- Cumulative percent of patients who become pregnant over the 6 month observation period.
- Rate of the number of pregnancies per 100 per-years of follow-up.
- Change from baseline in visual analogue scale (VAS) endometriosis pain scores at each visit.

Figure 3. Visual Analogue Scale



Source: Gerlinger C, Schumacher U, Wentzeck R, et al [10]

7.7.2. Statistical Considerations

Statistical analyses of safety and effectiveness parameters will be primarily descriptive in nature; no statistical hypotheses will be tested. No imputations for missing data are planned.

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.

7.7.2.1. Safety Analyses

All safety parameters will be summarized in accordance with Pfizer Data Standards (PDS) for safety reporting. Medical histories and patient demographics will also be summarized using PDS. Selected and/or common adverse events will be further described using a 95% confidence interval for binomial proportions.

The dosage and number of injections of study medication will be summarized using descriptive statistics.

7.7.2.2. Effectiveness Analyses

- 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 accompanied by an 95% confidence interval; this confidence interval will be based on the Poisson distribution.

- Mean change in VAS scores from baseline will be tested against zero change using the paired t-test; p-values $\leq$ 0.05 will indicate statistically significant change. Mean change will also be described using a 95% confidence interval.

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

7.8. Quality control

Data Quality Measurement is performed by Data QC Coordinator to define the level of data quality and evaluate the data quality.

For all items, 10% Data Quality Check is conducted before the DB lock. If error rate is satisfied less than 0.05%, Data Quality Check is stopped, if not, 10% sampling and Data Quality Check is repeated. In repeated Data Quality Check, if error rate is satisfied less than 0.05%, Data Quality Check is stopped, if not, 100% Data Quality Check is made. As a result of 10% sampling, only if more than 100 subjects is sampled, Data Quality Check is conducted for 100 subjects.

CRF-to-Database Inspection outcomes will be approved by Pfizer Korea.

7.8.1. Record retention

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

If the investigator becomes unavailable for any reason to continue to retain study records for the required period (eg, 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.

7.9. Limitations of the research methods

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

7.10. Other aspects

Not applicable.

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 informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/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 informed consent 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 consent form.

8.2. Patient withdrawal

Patients may withdraw from the study at any time at their own 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)

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), 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.

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 *Good Pharmacoepidemiology Practices* (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), Good Epidemiological Practice (GEP) guidelines issued by the International Epidemiological Association (IEA).

9. ADVERSE EVENT REPORTING

9.1. Requirements

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

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

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

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

9.1.1. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Sayana® or the time of the patient's informed consent if s/he is already exposed to Sayana®, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation), the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Sayana®, the SAE also must be reported to Pfizer Safety.

9.1.2. Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to Sayana®, 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 Sayana® caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether Sayana® 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 Sayana® did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

9.2. Definitions of Safety Events

9.2.1. Adverse events

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

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

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;

- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

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

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

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

9.2.2. Serious adverse events

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

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

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

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

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

Hospitalization

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

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

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

9.2.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

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

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) Sayana®, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to Sayana® (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 Sayana® prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

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

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with Sayana®, 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 Sayana® in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;

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

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

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

Exposure during breastfeeding

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

Medication error

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

Medication errors include:

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

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

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

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

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

  - An identifiable reporter;

- A suspect product;
- The event medication error.

Overdose, Misuse, Extravasation

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

Lack of Efficacy

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

Occupational Exposure

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

9.2.4. Medical Device Complaint Reporting Requirements

All medical device complaints, regardless of whether the medical device complaint is associated with an AE, will be collected on the applicable pages within the CRF. This includes potential near incident or malfunctions associated with the use of a medical device product. A near incident or malfunction is an event that might have led to death or serious deterioration in health, or if it occurred again, might have led to death or serious deterioration in health.

Pfizer is to be notified of all medical device complaints within 24 hours of awareness of the event by the investigator.

Medical device complaints that are not associated with an SAE are forwarded to Pfizer Global Manufacturing.

9.2.5. Communication of Issues

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of Sayana®, 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 NI study protocol that the investigator becomes aware of.

9.3. Single reference safety document

Investigator should use the single reference safety document (SRSD) for purpose of prescription and guidance checking.

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

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

- Newly FDA approved products:

  Basic Results must be submitted within 30 calendar days of the FDA marketing approval for studies whose PCD occurred prior to 1 anniversary year or more from the date of marketing approval.

- FDA-previously approved products:

  Basic Results are due within 1 anniversary year of the PCD and/or LSLV.

  When PCD and LSLV are not the same date, Basic Results are posted 1 anniversary year from the PCD and the record is updated 1 anniversary year from LSLV. PCD cannot occur after LSLV.

- Discontinued products:

  Basic Results are due within 1 anniversary year of the decision to discontinue the product for all indications if there are no plans to out license the product or within 2 anniversary years if out licensing plans are not completed.

- Marketed outside of the United States (US) only:

  Basic Results are due within1 anniversary year of the ex-US approval or for already approved products, within 1 anniversary year of LSLV.

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

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

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12. LIST OF TABLES

None.

13. LIST OF FIGURES

1. <Figure 1> Data Management Flow Chart
2. <Figure 2> Data Validation Flow Chart
3. <Figure 3> Visual Analogue Scale

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.