PHASE IV OPEN LABEL SINGLE GROUP ONE YEAR STUDY OF HOME SELF-INJECTION WITH SAYANA® PRESS IN ADULT WOMEN OF REPRODUCTIVE AGE- A PRAGMATIC CLINICAL TRIAL

Medicinal Product Number:	PN-008839
Medicinal Product Name:	Sayana® Press (Depot -medroxyprogesterone Acetate)
United States (US) Investigational New Drug (IND) Number:	Not Applicable (N/A)
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Protocol Number:	A6791040
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[redacted]

Document History

Document	Version Date	Summary of Changes
Original Protocol	26 January 2017	Not applicable (N/A)

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APPENDICES

PROTOCOL SUMMARY

Background

Intramuscular (IM) depot medroxyprogesterone acetate (DMPA), 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection, has been marketed for many years as DEPO-PROVERA®. A new, low dose formulation for subcutaneous (SC) injection of depot medroxyprogesterone acetate (DMPA-SC) has been approved by regulatory agencies for the prevention of pregnancy in women. DMPA-SC is available in pre-filled syringes and is administered by SC injection to the anterior thigh or abdomen, once every 3 months (13 weeks +/- 1 week).

For many years, the syringe has been the standard way to deliver solutions and suspensions for parenteral use. The syringe design, however, is relatively bulky and the potential to attempt re-use of syringes increases the risk of transmission of blood borne diseases.

The Uniject™ delivery system is a simple single use prefilled injection system designed for SC injections and has been approved for use as a contraceptive under the name Sayana® Press.

Study Objectives and Endpoints

Primary Objectives

- Determine the proportion of women who are able to self-inject Sayana Press successfully over a 1-year period.

Secondary Objectives

- Assess continuation rate for the method at 1 year.

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Primary Endpoint

The primary endpoint will be the proportion of all attempted home self-injections that were successfully performed by the study participant at home (ie, not in the clinic under direct HCP supervision) and on schedule (13 week interval +/- 1 week). If a subject decides to discontinue Sayana Press as her contraceptive method, and therefore does not attempt one or more injections, these scheduled injections would not be included in the denominator for the primary endpoint.

Secondary Endpoint

- Continuation rate for method at 1 year.

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- HCP Questionnaire:
    - Percentage of suitable patients, based on Question 1;
    - Percentage of willing patients, based on Question 2;
    - Usefulness of training materials, based on Question 3;
    - Ease to teach a patient to self-inject, based on Question 4;
    - Overall experience/other information and input, based on Questions 5, 6 and 7.

CCI [redacted]

[redacted]

Safety Analysis

Safety data, consisting of all adverse events, including unplanned pregnancies, persistent injection site reactions, SAEs, premature discontinuations, concomitant medications, vital signs, height and weight, and laboratory parameters, will be tabulated and listed according to Pfizer's standard reporting algorithms.

Study Design

This is an open-label, single-arm, 1-year study to assess home self-administration of Sayana Press in women who desire long-acting reversible contraception (LARC), are interested to attempt DMPA self-injection at home and are judged by their HCP to be good candidates for self-injection. Following training and a supervised initial self-injection at the clinic, study participants will self-inject Sayana Press in the home setting every 3 months (at Month 3, Month 6 and Month 9) and return for a final study visit at Month 12.

Approximately 160 adult women subjects of reproductive age (18 to 45) will be enrolled to ensure that at least 100 women will complete the study.

Participants will attend 2 or 3 study visits at the clinic: a Screening/Baseline Visit or Screening and Baseline visit separately and a Final Visit. At Months 3, 6 and 9, participants will be asked to contact the clinic by phone after performing each scheduled home self-injection in order to confirm the date of injection and to report any AEs, and/or injection difficulties or problems with the device. Should the injection site reactions occur, the centre staff will collect detailed information about these reactions. Reasons for self-injection failure will also be recorded in the case report form (CRF).

At the Month 12 Final Visit or premature discontinuation, subjects will be asked to complete the CCI [redacted]

If an unplanned pregnancy occurs during the trial it will be collected on the AE Case Report Form (CRF) page.

Statistical Analysis

As this is a single arm study, there will be no treatment comparisons, and all analyses will be descriptive.

The primary endpoint is the mean percent of self-injections that were successfully administered. Each subject will have a maximum of 3 self-injections, each of which will be defined as a success or failure. A success is defined as a home self-injection that was successfully performed by the study participant at home and on schedule (13 week interval +/- 1 week). If the subject attempts but is unable to administer the self-injection at home and had it performed instead at the clinic, then these are classed as failures. If a subject discontinues from the study prior to attempting all 3 injections, or chooses not to attempt the injection at home, but have it performed in the clinic, then only the injections that were attempted at home will be evaluated and included in the analysis. These binary outcomes are correlated within the subject, and they will therefore be analyzed with a generalized estimating equation (GEE) model for clustered binomial data, using subject as the clustering variable, to provide a proportion along with 95% confidence interval.

The secondary endpoint is the continuation rate for the method at 1 year. Subjects had completed 12 months if they received all 4 injections, had a follow-up visit and were not recorded as discontinuing during the 12 month period. The total proportion of subjects who have not discontinued by 12 months (the follow-up visit) will be estimated along with a 95% confidence interval (CI).

Endpoints from the questionnaires will be summarized either as categorical frequencies by counts and percentages.

Safety data will be tabulated and listed according to Pfizer's standard reporting algorithms.

SCHEDULE OF ACTIVITIES

The schedule of activities table provides an overview of the protocol visits and procedures. Refer to the Study Procedures and Assessments sections of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed on the schedule of activities, in order to conduct evaluations or assessments required to protect the well-being of the subject.

Visit Identifier **Protocol Activity**	**Screening (Days -14 to 1)**	**Baseline (Day 1)**	**Month 3 (Subject Phone Assessment)**	**Month 6 (Subject Phone Assessment)**	**Month 9 (Subject Phone Assessment)**	**Final Visit (Month 12) or PD[f]**
Informed Consent	X					
General Medical History	X					
General Physical Examination	X					X
Demography	X					
Weight and Height		X				X
Vital Signs (sitting Blood Pressure [BP], Heart Rare [HR]	X	X				X
Urine Pregnancy Test	X	X				X
Pregnancy Test (If Self-Injection is Delayed)[g]			X	X	X	
Registration in Study		X				
Record Subject's Educational Level		X				
Self-injection Training (including first self-injection and recording problems with the device, if any)		X				
Investigator Approval of Self-injection Proficiency		X				
Drug Dispensing		X				
Adverse Events[h]	X	X	X[a]	X[a]	X[a]	X
Self-Injection at Home			X	X	X	
Self-Report Injection Difficulties or Problems with the Device			X[a]	X[a]	X[a]	
Prior[b]/Concomitant	X	X	X	X	X	X

Medications[c]						
CCI [redacted]						[redacted]
						[redacted]
End of Study[e]						X

Abbreviations: Pharmacodynamic (PD), Blood Pressure (BP), Heart Rate (HR), CCI [redacted]

a. At Months 3, 6 and 9, participants will be asked to contact the clinic by phone after performing each scheduled self-injection in order to confirm the date of injection, report any adverse events and/or injection difficulties or problems with the device, including injection site reactions, and unplanned pregnancy. If at least 1 week has passed from the scheduled self-injection date and the clinic has not heard from the subject, the clinic staff will contact the subject to obtain the necessary information and provide appropriate instructions to the subject. Reasons for self-injection failure will also be recorded in the CRF.

b. Prior/current medications for the 2-week period prior to Baseline Visit.

c. Concomitant medications taken after first administration of study drug.

d. CCI [redacted]

e. End of study form and study drug accountability.

f. Premature Discontinuation visit.

g. Whenever a scheduled injection has been delayed beyond the protocol-specific window (scheduled injection date ± 1 week), the subject should be advised to contact the clinic and speak to a healthcare professional regarding the need to exclude pregnancy before any additional injections, advice regarding additional contraception, and also for the timing of the next injection. A pregnancy test is to be conducted if the Sayana Press injection is delayed outside the protocol study drug administration window. This could be either a home pregnancy test or test conducted in the clinic. If the subject has a positive pregnancy test result, she is not to inject Sayana Press and must inform the study centre immediately, to conduct a final study visit (subject will be prematurely terminated). The study centre must complete and submit an Exposure During Pregnancy Form to Pfizer within 24 hours of awareness of the pregnancy. The study centre will follow all protocol required pregnancy in utero procedures (See Section 8.10).

h. AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the last subject visit.

1. INTRODUCTION

1.1. Mechanism of Action

Medroxyprogesterone acetate (MPA) is a synthetic analogue of 17 α-hydroxyprogesterone, which has antioestrogenic, anti-androgenic, and anti-gonadotropic effects. MPA inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation. The primary mechanism for MPA's contraceptive effect is suppression of ovulation. Secondary mechanisms, which may also aid the contraceptive effect, include endometrial thinning and thickening of the cervical mucus.

1.2. Background and Rationale

Intramuscular (IM) depot medroxyprogesterone acetate (DMPA), 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection, has been marketed for many years as DEPO-PROVERA®. A new, low dose formulation for subcutaneous (SC) injection of depot medroxyprogesterone acetate (DMPA-SC) has been approved by regulatory agencies for the prevention of pregnancy in women. DMPA-SC is available in pre-filled syringes and is administered by SC injection to the anterior thigh or abdomen, once every 3 months (13 weeks +/- 1 week).

For many years, the syringe has been the standard way to deliver solutions and suspensions for parenteral use. The syringe design, however, is relatively bulky (especially if pre-filled with drug) and the potential to attempt re-use of syringes increases the risk of transmission of blood borne diseases.

The Uniject™ delivery system is a simple single use prefilled injection system designed for IM and SC injections. Uniject was originally developed by the international non-profit organization Program for Appropriate Technology in Health (PATH) and the device is manufactured by Becton, Dickinson and Co. DMPA-SC in the Uniject™ is now approved in a number of countries and is available as Sayana® Press. In Europe, Sayana Press has been recently (July 2015) approved under the Mutual Recognition Procedure (MRP) to allow women the option of home self-injection, when this option is considered appropriate by their physician; the Medicines and Healthcare products Regulatory Agency (MHRA) have granted approval for this variation in the United Kingdom (UK).

Several studies by independent researchers have evaluated the feasibility and acceptability of self-injected DMPA-SC.[1-5] Overall, women who performed self-injections in these studies found DMPA-SC self-injection to be easy and convenient and would recommend the method to other women. These independent studies also support home-based self-administration of DMPA-SC.

The approval of self-injection with Sayana Press was primarily based on a 1-year investigator-initiated study (Cameron, et al Study GA67815[2]) that used Sayana (DMPA-SC in a pre-filled syringe) and a usability study that used Sayana Press (DMPA-SC in Uniject™) in which participants (volunteers) performed simulated injections into an injection trainer and

assessed the functionality or usability of the device and the instructions for use for the device. While the GA67815 study showed that women can perform independent (at home) self-injection when using the pre-filled syringe, the Uniject™ device is fundamentally different to the syringe and MHRA has identified a need for a post-approval study that shows that women can similarly self-inject successfully when using the Uniject™ device rather than a standard pre-filled syringe.

This study is intended to provide information on the use of Sayana Press by women who self-inject the product at home over a 1-year period as part of Post Authorization Safety Study (PASS) required by MHRA.

This protocol and study procedures are intended to mirror standard clinical practice as closely as possible in order to provide information that is most relevant to the use of Sayana Press in the community.

The most important positive aspect of self-injection is that it is simply convenient for the patient. The potential risks of permitting home self-injection include a concern for the timeliness of injection. With self-administration on such an infrequent schedule (every 3 months), it is possible the patient will forget to administer the injection and could experience a contraceptive failure. It is a certainty that some patients will not be timely, but DMPA is rather forgiving in this respect. One of the characteristics of this Long Acting Reversible Contraception (LARC) is that the return to fertility, after stopping treatment, generally takes at least 6 months and often up to a year. The reminder techniques should be used to ensure subjects would to maintain their scheduled administrations at home. The other principal risk with unsupervised self-injection is that the woman will be unable to properly perform the injection. The availability of effective training materials and other aids will be important to achieving this goal. It should be noted, that a patient who is unable to demonstrate proficiency in the clinic should not be considered as a candidate for self-injection.

In consideration of all the above factors, the benefit-risk profile for permitting self-injection by suitably selected and trained patients is favorable.

Complete information for this compound may be found in the single reference safety document (SRSD), which, for this study, is the current approved Summary of Product Characteristics (SmPC) for Sayana Press.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Objectives

Primary Objectives

- Determine the proportion of women who are able to self-inject Sayana Press successfully over a 1-year period.

Secondary Objectives

Assess continuation rate for the method at 1 year.

[redacted]

2.2. Endpoints

Primary Endpoint

The primary endpoint will be the proportion of all attempted home self-injections that were successfully performed by the study participant at home (ie, not in the clinic under direct HCP supervision) and on schedule (13 week interval +/- 1 week). If a subject decides to discontinue Sayana Press as her contraceptive method, and therefore does not attempt 1 or more injections, these scheduled injections would not be included in the denominator for the primary endpoint.

Secondary Endpoint

- Continuation rate for method at 1 year.

[redacted]

- Ease of self-injection, based on Question 10 of Subject Questionnaire (including any post-baseline self-injections that were performed under HCP supervision, which would not have been included in the primary analysis);
- Usefulness and type of reminder techniques used, based on Questions 5 and 6 of Subject Questionnaire;
- Proportion of attempted home self- injections where subject returned to clinic for the injection (to be administered by the a HCP or under supervision of one);
- Evaluate end of study plasma concentration of MPA;
- Reasons for electively discontinuing self-injection of Sayana Press (where the subject elects to continue to receive DMPA administered by a HCP at the clinic), based on Question 17 of Subject Questionnaire;
- Reasons for electively discontinuing Sayana Press altogether, based on Question 18 of Subject Questionnaire;
- Adverse Events (AEs), including unplanned pregnancy and persistent injection site reactions;
- Other information provided in Subject Questionnaire;
- HCP Questionnaire:
    - Percentage of suitable patients, based on Question 1;
    - Percentage of willing patients , based on Question 2;
    - Usefulness of training materials, based on Question 3;
    - Ease to teach a patient to self-inject, based on Question 4;
    - Overall experience/other information and input, based on Questions 5, 6, and 7

CCI [redacted]

[redacted]

Safety Analysis

Safety data, consisting of all adverse events, including unplanned pregnancies, persistent injection site reactions, SAEs, premature discontinuations, concomitant medications, vital signs, height and weight, and laboratory parameters, will be tabulated and listed according to Pfizer's standard reporting algorithms.

The study will be registered in the European Union (EU) in the EU Clinical Trials Register and in the United States in the ClinicalTrials.Gov registry, according to local requirements.

3. STUDY DESIGN

This is an open-label, single-arm, 1-year study to assess home self-administration of Sayana Press in women who desire long-acting reversible contraception (LARC), are interested to attempt DMPA self-injection at home and are judged by their HCP to be good candidates for the self-injection option. Following training and a supervised initial self-injection at the clinic, study participants will self-inject Sayana Press in the home setting every 3 months (at Month 3, Month 6 and Month 9) and return for a final study visit at Month 12.

Approximately one hundred sixty (160) adult women subjects of reproductive age (18 to 45) will be enrolled at approximately 10 study centres in the UK (and other countries in Europe if required) with approximately 16 subjects per study centre, to ensure that at least 100 women will complete the study.

Participants will attend 2 or 3 study visits at the clinic: a Screening/Baseline Visit (or Screening and Baseline visits separately) and a Final Visit. At Months 3, 6 and 9, participants will be asked to contact the clinic by phone after performing each scheduled home self-injection in order to confirm the date of injection and to report any AEs, and/or injection difficulties or problems with the device. Should the injection site reactions occur, the centre staff will collect detailed information about these reactions. If at least 1 week has passed from the scheduled self-injection date and the clinic has not heard from the subject, the clinic staff will contact the subject to obtain the necessary information and provide appropriate instructions to the subject, depending on the circumstances. All AEs, including pregnancy and injection site reactions will be recorded on the AE Case Report Form (CRF) page. Reasons for self-injection failure will also be recorded in the CRF.

At the Month 12 Final Visit or Premature Discontinuation, subjects will be asked to complete the [redacted]

If a subject does not perform a scheduled self-injection at home for any reason, the subject should immediately contact the clinic to explain the reason why the injection was not performed. The HCP at the clinic must provide instructions to the subject regarding how the scheduled injection will be provided:

- An unscheduled visit will need to be conducted if the subject would prefer to have the scheduled injection performed at the clinic. If so, additional training in the self-injection technique should be provided to the subject during the unscheduled visit.

- If the reason why the self-injection did not occur was due to malfunction or damage to the Sayana Press injector, a replacement Sayana Press injector should be provided to the subject at the unscheduled visit to replace it and the subject should self-inject immediately upon returning home.
- If the subject did not self-inject at home due to desire to discontinue participation in the study, they should complete the final/premature discontinuation visit assessments. If the subject prematurely discontinues from the study, another contraceptive method should be prescribed to the subject.

Whenever a scheduled injection has been delayed beyond the protocol-specified window (scheduled injection date ±1 week), the subject should be advised to contact the clinic and speak to a healthcare professional regarding the need to exclude pregnancy before any additional injections, advice regarding additional contraception, and also for the timing of the next injection. A pregnancy test should also be conducted prior to the next scheduled injection.

The study centres will record any instances where a study participant was unable to self-inject at home and needed to make an unscheduled clinic visit in order to receive the injection (irrespective of who performs the injection at the clinic: self-injected or HCP-injected).

If an unplanned pregnancy (lack of efficacy) occurs during the trial it will be collected on the AE CRF page. All adverse safety events will be collected and reported in the normal manner, according to Pfizer standard safety reporting procedures for clinical trials.

Details regarding subject self-injection issues and reasons for self-injection failure must be documented in the subject's primary source records.

4. SUBJECT SELECTION

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for the protocol intervention is considered appropriate by their healthcare provider.

4.1. Inclusion Criteria

Subject eligibility should be reviewed and documented by an appropriate member of the investigator's study team before subjects are included in the study.

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Women aged 18 to 45 years of age who are willing to attempt Sayana Press self-injection at home;

2. Women who are likely to be successful on a DMPA self-injection program, based on the opinion of the investigator;

3. Not planning to move out of the area for at least 12 months;

4. Willing to be contacted by the clinic staff at work or at home;

5. Evidence of a personally signed and dated Informed Consent Document (ICD) indicating that the subject has been informed of all pertinent aspects of the study;

6. Subjects who are willing and able to comply with scheduled visits, treatment plan and other study procedures.

4.2. Exclusion Criteria

Subjects presenting with any of the following will not be included in the study:

1. A preexisting medical condition that would interfere with participation in the study or pose a risk to the subject, including hypersensitivity to MPA or any constituents of Sayana Press;

2. Known or suspected malignancy of genital organs;

3. Known or suspected malignancy of the breast;

4. History of cerebrovascular disease;

5. Metabolic bone disease;

6. A contraindication to DMPA (UK Medical Eligibility Criteria – Category 3 or 4),[6] such as:

    - Multiple risk factors for cardiovascular disease (eg, older age, smoking, diabetes, obesity hypertension)
    - Current and history of ischaemic heart disease
    - Stroke (history of cerebrovascular accident, including transient ischaemic attack)
    - Unexplained vaginal bleeding
    - Current or history of breast cancer
    - Diabetic nephropathy, neuropathy, retinopathy or other diabetic vascular disease
    - Severe (decompensated) liver cirrhosis
    - Hepatocellular adenoma
    - Hepatoma
    - Systemic Lupus Erythematosus (positive or unknown antiphospholipid antibodies; severe thrombocytopenia)

7. Subjects who are investigational centre staff members directly involved in the conduct of the study and their family members, centre staff members otherwise supervised by the investigator, or subjects who are Pfizer employees directly involved in the conduct of the study;

8. Participation in other studies involving investigational drug(s) (Phases 1-4) within 30 days prior to study entry and/or during study participation;

9. Patients who plan to get pregnant within two years of study;

10. Breastfeeding female subjects and pregnant female subjects;

11. Other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

4.3. Randomization Criteria

This will be a single-arm, non-randomized study.

4.4. Lifestyle Guidelines

All subjects in this study will be women, aged 18-45, who are willing to use Sayana Press at home. Study subjects will self-inject Sayana Press at home according to study schedule (13 week interval +/- 1 week). If the subject fails to self-inject or report to clinic for an injection (supervised or administered by HCP) within this +/- 1 week treatment window, she should be advised to use a barrier method of contraception as instructed by the study investigator until she administers the next injection or, in cases when the subject decides to discontinue Sayana Press altogether, until the new contraceptive regimen is established. A pregnancy test should also be conducted prior to the next scheduled injection.

4.5. Investigator Approval for Self-Injection

Subjects who meet all inclusion criteria and none of the exclusion criteria will undergo training in self-injection at the Baseline Visit which will culminate in the subject attempting to perform the first self-injection of Sayana Press under the supervision of the investigator (or suitable designee). At this point, the investigator will approve (or not approve) the subject to go forward in the study and be permitted to attempt the 3 subsequent self-injections at home, based on the investigator's assessment of the subject's proficiency at self-injection. Subjects who are not approved for self-injection at this point will be discontinued from the study.

4.6. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, subjects are provided with a contact card. The contact card contains, at a minimum, protocol and investigational compound identifiers, subject study numbers, contact information for the investigational centre, and contact details for a contact centre in the event that the investigational centre staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the subject's participation in the study. The contact number can also be used by investigational staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigational centre and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigational centre and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the subject directly, and if a subject calls that number, he or she will be directed back to the investigational centre.

5. STUDY INTERVENTION

For the purposes of this study, and per International Conference on Harmonization (ICH) guidelines study drug is defined as a pharmaceutical form of an active ingredient or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH E6 1.33). Study drug in this study will be the currently marketed, commercial Sayana Press.

5.1. Allocation to Treatment

This is a non-randomized single arm study and all study subjects will be receiving the same treatment.

5.2. Subject Compliance

To document compliance, study participants will be asked to contact the clinic by phone after performing each scheduled self-injection in order to confirm the date of injection. If at least 1 week has passed from the scheduled self-injection date and the clinic has not heard from the subject, the clinic staff will contact the subject to obtain the necessary information and provide appropriate instructions to the subject, depending on the circumstances.

The investigator will provide training to the study subjects regarding the safe and correct use of Sayana Press according to standard of care, using currently available training materials that will include tools designed to facilitate the training of subjects in self-injection and that assist subjects in remembering the scheduled injection dates. Since this study is intended to be relevant to clinical practice, and with respect to materials intended to remind study subjects of the proper injection date (reminder materials), Investigators should use reminder materials and techniques that may be employed in their practice for patients using 3-monthly DMPA (eg, an appointment card or reminder phone call or other electronic methods for

reaching out to patients to encourage compliance with the standard DMPA 3-monthly visit schedule).

5.3. Study Drug Supplies

5.3.1. Dosage Form(s) and Packaging

Sayana® Press delivery system is commercially available. The sponsor will centrally supply this product to be used in accordance with local regulations and according to the commercial usage instructions.

5.3.2. Preparation and Dispensing

See the included commercial package leaflet for instructions on how subjects will administer the study drug. Each unit will be individually packaged in single-use foil pouches. The pouches should not be opened until the study drug is to be administered. Each subject will receive enough product units to cover the required number of doses for the length of the study.

5.3.3. Administration

The product will be administered in accordance with the label.

Study participants will be taught how to self-administer Sayana Press by the investigator or study centre staff using the training materials used according to standard of care in their practice, which are based on the approved Instructions for Use (IFU) for Sayana Press (Appendix 2). If the subject is comfortable attempting the Baseline Visit self-injection, the first self-injection will be performed at the clinic under the supervision of the study centre staff. If the subject adequately performs the first self-injection, and the investigator approves the subject to continue in the study, based on the subject's proficiency exhibited during the first self-injection, the subject will be then provided with 3 Sayana Press delivery system packages to take home. Subjects will be also given a copy of the Sayana Press IFU and contact information for the clinic. Subjects may also be given a reminder card or other reminder tools at the discretion of the Investigator.

If a self-injection did not occur due to malfunction or damage to the Sayana Press injector, a replacement Sayana Press injector should be provided to the subject at an unscheduled visit to replace it and the subject should self-inject immediately upon returning home.

If a scheduled injection is been delayed beyond the protocol-specified window (scheduled injection date ±1 week), the subject should be advised to contact the clinic and speak to a healthcare professional regarding the need to exclude pregnancy before any additional injections, advice regarding additional contraception, and also for the timing of the next injection. A pregnancy test should also be conducted prior to the next scheduled injection.

Details regarding subject self-injection issues and reasons for self-injection failure must be documented in the subject's primary source records.

Following self-injection, the used Sayana Press injector should be immediately disposed of into a suitable container in accordance with the local regulatory authority requirements or per instructions from the Investigator.

5.4. Study Drug Storage

The investigator, or an approved representative, eg, pharmacist, will ensure that all study drugs are stored in a secured area with controlled access under required storage conditions and in accordance with applicable regulatory requirements.

Study Drug should be stored in its original container and in accordance with the label. See the Summary of Product Characteristics for storage conditions of the product. Storage conditions stated in the SRSD will be superseded by the storage conditions stated in the labeling.

Centre systems must be capable of measuring and documenting (for example, via a log), at a minimum, daily minimum and maximum temperatures for all centre storage locations (as applicable, including frozen, refrigerated and/or room temperature products). This should be captured from the time of investigational product receipt throughout the study on all business days. Even for continuous monitoring systems, a log or centre procedure that ensures active daily evaluation for excursions should be available. The operation of the temperature monitoring device and storage unit (for example, refrigerator), as applicable, should be regularly inspected to ensure it is maintained in working order.

Any excursions from the product label storage conditions should be reported upon discovery. The centre should actively pursue options for returning the product to the storage conditions, as soon as possible. Deviations from the storage requirements, including any actions taken, must be documented and reported to the sponsor. Once an excursion is identified, the study drug must be quarantined and not used until the sponsor provides documentation of permission to use the investigational product. It will not be considered a protocol deviation if the sponsor approves the use of the study drug after the temperature excursion. Use of the investigational product prior to sponsor approval will be considered a protocol deviation.

Specific details regarding information the centre should report for each excursion will be provided to the centre.

Centre staff will instruct subjects on the proper storage requirements for take home study drugs including how to report temperature excursions. In the event of any significant temperature changes (eg, left study drug in a hot car for several hours) after the subject takes the study drug home from the study centre, the subject is not to use this study drug and should contact the study centre immediately to return that study drug and obtain a replacement supply. The study centre will quarantine any study drug that was returned by a subject due to significant temperature changes and not redispense it.

5.5. Study Drug Accountability

The investigative centre must maintain adequate records documenting the receipt, use, loss, or other disposition of the study drug supplies. All unused study drug product will be returned to the investigator by the subject upon completion of the study or discontinuation.

5.6. Destruction of Study Drug Supplies

The sponsor or designee will provide guidance on the destruction of unused study drug (eg, at the centre). If destruction is authorized to take place at the study centre, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer, and all destruction must be adequately documented.

5.7. Concomitant Treatment(s)

Medications that are contraindicated with Sayana Press (as per current prescribing information) will be prohibited.

6. STUDY PROCEDURES

6.1. Screening (Days -14 to 1)

Screening visit may take place on the same day as Baseline Visit or on a different day (within 14 days prior to Baseline Visit).

The investigator (or an appropriate designee) will obtain written informed consent from each participant in accordance with the approved ICD. Participants will be screened prior to enrollment to confirm that they meet the enrollment criteria for the study. The following screening procedures will be performed:

- Written, informed consent obtained prior to performance of any testing, examination or treatment;
- Medical history;
- Demographics
- AE assessment;
- Prior medications;
- Physical examination;
- Vital signs (sitting blood pressure and heart rate);
- Urine pregnancy test.

6.2. Study Period

Baseline Visit (Day 1)

Baseline Visit may take place on the same day as Screening Visit or on different days.

Following procedures will be performed at this visit:

- Registration in the study;
- AE assessment;
- Vital signs (sitting blood pressure and heart rate);
- Height and Weight;
- Prior medications for the 2-week period prior to Baseline Visit;
- Urine pregnancy test;
- Record subject's educational level;
- Self-injection training including first self-injection;

  The baseline training and patient-directed training materials given to study participants will be those used according to standard of care for patients in their practice.

  The training materials should include suggested methods for remembering the scheduled injection dates per standard of care. Investigators may also utilize patient reminder techniques in this study that align closely with techniques they normally use in their practice for women receiving DMPA injections every 3 months in the clinic (eg, an appointment card, phone call, text message or other electronic methods for reaching out to patients to encourage compliance with the standard DMPA 3-monthly visit schedule). However, under this protocol investigators are not required to utilize any such outreach method to encourage compliance. Because training techniques, training materials and reminder techniques might differ from centre to centre, such methods and the way they were delivered will be documented for each centre;

- Injection difficulties or any problems with the device will be recorded in the CRF;
- Investigator approval of self-injection proficiency;

Three packages containing Sayana Press delivery system will be distributed to each study subject for home self-injection.

Months 3, 6 and 9 (subject phone assessment)

Study subjects will self-inject Sayana Press at home according to schedule (13 week interval +/- 1 week). They will be asked to contact the clinic by phone after performing each self-injection in order to confirm the date on which the injection was performed and report any AEs, including unplanned pregnancy, concomitant medications and injection site reactions. During this phone call, the clinic staff will also record whether the subject had any difficulties in performing the injection or had problems operating the device and what those issues were. In case the subject reports any injection site reactions, clinic staff will collect detailed information about the reaction (eg, timing; persistence; appearance; is it getting worse or better; how large or deep is it; how bothersome, etc.). All AEs, including unplanned pregnancy and injection site reactions will be recorded on AE CRF page. Reasons for self-injection failure will also be recorded in the CRF.

If a participant fails to contact the clinic to report the injection date, the study centre personnel shall not contact the patient until after the treatment window (+/- 1 week) for that planned injection has expired. If at least 1 week has passed from the scheduled self-injection date and the clinic has not heard from the subject, the clinic staff will contact the subject to obtain the necessary follow-up information and provide appropriate instructions to the subject, depending on the circumstances.

If the subject fails to self-inject or report to clinic for an injection (supervised or administered by HCP) within the +/- 1 week treatment window, the subject should be advised to contact the clinic and speak to a healthcare professional regarding the need to exclude pregnancy before any additional injections, advice regarding additional contraception, and also for the timing of the next injection. She should be advised to have a pregnancy test conducted prior to administering her next Sayana Press injection either at home or at the clinic. The study centre must be informed if the subject has a positive at home pregnancy test and report to the clinic immediately. An Exposure During Pregnancy Form must be completed and submitted to Pfizer within 24 hours of awareness. The subject should also use a barrier method of contraception as instructed by the study investigator until she administers the next injection or, in cases when the subject decides to discontinue Sayana Press altogether, until the new contraceptive regimen is established.

Final Visit (Month 12 +/- 1 week) or Premature Discontinuation Visit

Subjects will return to the clinic for their final visit and the following procedures will be performed:

- AE assessment;
- Concomitant medications;
- CCI [redacted]

[redacted]

- Physical examination;
- Height and Weight;
- Vital signs (sitting blood pressure and heart rate);
- Urine pregnancy test;
- Plasma sample for analysis of MPA (at select sites);
- Drug accountability;
- End of study form procedures (administrative).

CCI [redacted]

6.4. Subject Withdrawal

Subjects 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 or behavioral reasons, or the inability of the subject to comply with the protocol-required schedule of study visits or procedures at a given study centre.

If a subject does withdraw they should return to the clinic to complete the Final Visit assessments. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. All attempts to contact the subject and information received during contact attempts must be documented in the subject's medical record). In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal, request that the subject return all unused study drug, request that the subject return for a final visit, if applicable, and follow up with the subject regarding any unresolved AEs.

If the subject withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

7. ASSESSMENTS

Every effort should be made to ensure that the protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances, outside of the control of the investigator, which may make it unfeasible to perform the test. In these cases the investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible. The study team will be informed of these incidents in a timely fashion.

7.1. Pregnancy Testing

Urine pregnancy test, with sensitivity of at least 25 mIU/mL, will be performed at Screening, before Sayana Press administration at the Baseline Visit, and at the Final Visit. A negative pregnancy result is required before the subject may receive the first Sayana Press injection. Pregnancy test will also be done in any instance when potential pregnancy is suspected, if the Sayana Press injection is not conducted per the required schedule and at the end of the study to confirm the subject has not become pregnant during the study. Pregnancy tests may also be repeated as per request of institutional review boards (IRBs)/ethics committees (ECs) or if required by local regulations. In the case of a positive confirmed pregnancy, the subject will be withdrawn from administration of the Sayana Press product and from the study.

If the subject fails to self-inject or report to clinic for an injection (supervised or administered by HCP) within the +/- 1 week treatment window, the subject should be advised to contact the clinic and speak to a healthcare professional regarding the need to exclude pregnancy before any additional injections, advice regarding additional contraception, and also for the timing of the next injection. She should be advised to have a pregnancy test conducted at home or at the clinic prior to administering her next Sayana Press injection. The study centre must be informed if the subject has a positive at home pregnancy test and report to the clinic immediately. An Exposure During Pregnancy Form must be completed and submitted to Pfizer within 24 hours of awareness. The subject should also use a barrier method of contraception as instructed by the study investigator until she administers the next injection or, in cases when the subject decides to discontinue Sayana Press altogether, until the new contraceptive regimen is established.

7.2. Assessments Questionnaires

CCI [redacted]

[redacted]

[redacted]

CCI [redacted]

[redacted]

7.3. Safety Assessments

Vital Signs

Vital signs including heart rate, sitting systolic and diastolic blood pressure will be taken at Screening, Baseline and Final Visits.

Weight and Height

Weight and height measurements will be conducted at Baseline and Final Visit.

General Physical Examination

General physical examination, including general appearance, vascular, nervous system, cardiovascular system and gastrointestinal system will be conducted at Screening and at the Final Visit.

Adverse Events Assessment

AE assessment will be performed at Screening, Baseline and Final Visits. During the "at home" portion of the study, study subjects will contact the clinic by phone after performing each self-injection to report any AEs, including unplanned pregnancy and injection site reactions. In case the subject reports any injection site reactions, the clinic staff will collect detailed information about the reaction (eg, timing; persistence; appearance, is it getting worse or better; how large or deep is it; how bothersome, etc.). The physical examination at the end of study will allow evaluation of the injection sites, and investigators should determine any sequelae at the injection sites that may be due to a persistent injection site reaction and report them as AEs or serious adverse events (SAEs) accordingly.

CCI [redacted]

[redacted]

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8. ADVERSE EVENT REPORTING

8.1. Adverse Events

All observed or volunteered AEs regardless of treatment group or suspected causal relationship to the investigational product(s) will be reported as described in the following sections.

For all AEs, the investigator must pursue and obtain information adequate both to determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE requiring immediate notification to Pfizer or its designated representative. For all AEs, sufficient information should be obtained by the investigator to determine the causality of the AE. The investigator is required to assess causality. Follow-up by the investigator may be required until the event or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

As part of ongoing safety reviews conducted by the sponsor, any non-serious AE that is determined by the sponsor to be serious will be reported by the sponsor as an SAE. To assist in the determination of case seriousness, further information may be requested from the investigator to provide clarity and understanding of the event in the context of the clinical study.

8.2. Reporting Period

For SAEs, the active reporting period to Pfizer or its designated representative begins from the time that the subject provides informed consent, which is obtained prior to the subject's participation in the study, ie, prior to undergoing any study-related procedure and/or receiving investigational product, through and including 28 calendar days after the last administration of the investigational product. SAEs occurring to a subject after the active reporting period has ended should be reported to the sponsor if the investigator becomes aware of them; at a minimum, all SAEs that the investigator believes have at least a reasonable possibility of being related to investigational product are to be reported to the sponsor.

AEs (serious and non-serious) should be recorded on the case report form (CRF) from the time the subject has taken at least 1 dose of investigational product through the last subject visit.

8.3. Definition of an Adverse Event

An AE is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- Abnormal test findings;
- Clinically significant symptoms and signs;

Unplanned pregnancy; Changes in physical examination findings;

- Hypersensitivity;
- Progression/worsening of underlying disease;
- Drug abuse;
- Drug dependency.

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

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy (EDP);
- Exposure via breastfeeding;
- Medication error;
- Occupational exposure.

8.4. Medication Errors

Medication errors may result, in this study, from the administration or consumption of the wrong product, by the wrong subject, at the wrong time, or at the wrong dosage strength. Such medication errors occurring to a study participant are to be captured on the Adverse Event page of the case report forms (CRFs), and on the SAE form when appropriate. In the event of medication dosing error, the sponsor should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving subject exposure to the investigational product;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error and, if applicable, any associated AE(s) are captured on an AE CRF page (refer to the Adverse Event Reporting Section for further details).

8.5. Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an AE 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 AE by the investigator or sponsor.

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

8.6. Serious Adverse Events

A Serious Adverse Event is any untoward medical occurrence at any dose that:

- Results in death;
- Is life-threatening (immediate risk of death);
- Requires inpatient hospitalisation or prolongation of existing hospitalisation;
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

- Lack of efficacy in an approved indication should be reported as an SAE.

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 hospitalisation. The important medical event should be reported as serious, if it is determined that the event may jeopardize the subject or may require intervention to prevent one of the other AE outcomes.

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 hospitalisation; or development of drug dependency or drug abuse.

Medical device complaints may meet the SAE reporting requirement criteria (see the section on Medical Device Complaint Reporting Requirements). An incident is any malfunction (ie, the failure of a device to meet its performance specifications or to perform as intended; performance specifications include all claims made in the labeling for the device) that, directly or indirectly, might lead to or might have led to the death of a subject, or user, or of other persons, or to a serious deterioration in their state of health.

A serious injury that can cause a serious deterioration in state of health can include:

- A life-threatening illness, even if temporary in nature;
- A permanent impairment of a body function or permanent damage to a body structure;
- A condition necessitating medical or surgical intervention to prevent the above 2 bulleted items;

  Examples: clinically relevant increase in the duration of a surgical procedure; a condition that requires hospitalisation or significant prolongation of existing hospitalisation;
- Any indirect harm as a consequence of an incorrect diagnostic or in vitro diagnostic device test results when used within the manufacturer's instructions for use;
- Fetal distress, fetal death, or any congenital abnormality or birth defects.

8.6.1. Protocol-Specified Serious Adverse Events

There are no protocol-specified SAEs in this study. All SAEs will be reported by the investigator as described in previous sections, and will be handled as SAEs in the safety database (see the section on Serious Adverse Event Reporting Requirements).

8.6.2. Potential Cases of Drug-Induced Liver Injury

Liver function tests (LFTs) are not required as a routine safety monitoring procedure in this study. However, should an investigator deem it necessary to perform LFTs because of clinical sign/symptom presenting in a subject, such LFT results should be handled and followed up as described below.

Abnormal values in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) levels concurrent with abnormal elevations in total bilirubin level that meet the criteria outlined below in the absence of other causes of liver injury are considered potential cases of drug-induced liver injury (potential Hy's law cases) and should always be considered important medical events.

The threshold of laboratory abnormalities for a potential case of drug-induced liver injury depends on the subject's individual baseline values and underlying conditions. Subjects who present with the following laboratory abnormalities should be evaluated further to definitively determine the etiology of the abnormal laboratory values:

- Subjects with AST or ALT and total bilirubin baseline values within the normal range who subsequently present with AST or ALT values ≥3 times the upper limit of normal (× ULN) concurrent with a total bilirubin value ≥2 × ULN with no evidence of hemolysis and an alkaline phosphatase value ≤2 × ULN or not available;

- For subjects with preexisting ALT **OR** AST **OR** total bilirubin values above the ULN, the following threshold values should be used in the definition mentioned above:

    - For subjects with preexisting AST or ALT baseline values above the normal range: AST or ALT values ≥2 times the baseline values and ≥3 × ULN, or ≥8 × ULN (whichever is smaller).

    Concurrent with

    - For subjects with preexisting values of total bilirubin above the normal range: Total bilirubin level increased by 1 × ULN **or** ≥3 × ULN (whichever is smaller).

The subject should return to the investigational centre and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT, laboratory tests should include albumin, creatine kinase, total bilirubin, direct and indirect bilirubin, gamma-glutamyl transferase, prothrombin time (PT)/international normalized ratio (INR), and alkaline phosphatase. A detailed history, including relevant information, such as review of ethanol, acetaminophen, recreational drug, and supplement consumption, family history, occupational

exposure, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and work exposure, should be collected. Further testing for acute hepatitis A, B, or C infection and liver imaging (eg, biliary tract) may be warranted. All cases confirmed on repeat testing as meeting the laboratory criteria defined above, with no other cause for LFT abnormalities identified at the time, should be considered potential Hy's law cases irrespective of availability of all the results of the investigations performed to determine etiology of the abnormal LFTs. Such potential Hy's law cases should be reported as SAEs.

8.7. Hospitalisation

Hospitalisation is defined as any initial admission (even less than 24 hours) in 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 (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, or neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalisation; however, the event leading to the emergency room visit should be assessed for medical importance.

Hospitalisation does not include the following:

- Rehabilitation facilities;
- Hospice facilities;
- Respite care (eg, caregiver relief);
- Skilled nursing facilities;
- Nursing homes;
- Same-day surgeries (as outpatient/same-day/ambulatory procedures).

Hospitalisation or prolongation of hospitalisation in the absence of a precipitating, clinical AE is not in itself an SAE. Examples include:

- Admission for treatment of a preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition (eg, for workup of persistent pretreatment laboratory abnormality);
- Social admission (eg, subject has no place to sleep);
- Administrative admission (eg, for yearly physical examination);
- Protocol-specified admission during a study (eg, for a procedure required by the study protocol);

- Optional admission not associated with a precipitating clinical AE (eg, for elective cosmetic surgery);
- Hospitalisation for observation without a medical AE;
- Preplanned treatments or surgical procedures. These should be noted in the baseline documentation for the entire protocol and/or for the individual subject;

Diagnostic and therapeutic noninvasive and invasive procedures, such as surgery, should not be reported as AEs. However, the medical condition for which the procedure was performed should be reported if it meets the definition of an AE. For example, an acute appendicitis that begins during the AE reporting period should be reported as the AE, and the resulting appendectomy should be recorded as treatment of the AE.

8.8. Severity Assessment

If required on the AE CRFs, the investigator will use the adjectives MILD, MODERATE, or SEVERE to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
MILD	Does not interfere with subject's usual function.
MODERATE	Interferes to some extent with subject's usual function.
SEVERE	Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily an SAE. For example, a headache may be severe (interferes significantly with the subject's usual function) but would not be classified as serious unless it met one of the criteria for SAEs, listed above.

8.9. Causality Assessment

The investigator's assessment of causality must be provided for all AEs (serious and non-serious); the investigator must record the causal relationship in the CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements if applicable. An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an AE; generally the facts (evidence) or arguments to suggest a causal relationship should be provided. If the investigator does not know whether or not the investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes, as defined by the sponsor (see the section on Reporting Requirements). If the investigator's causality assessment is "unknown but not related to investigational product," this should be clearly documented on study records.

In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, as appropriate, and report such an assessment in accordance with the SAE reporting requirements, if applicable.

8.10. Exposure During Pregnancy

For investigational products and for marketed products, an exposure during pregnancy occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed (eg, because of treatment or environmental exposure) to the investigational product; or the female becomes or is found to be pregnant after discontinuing and/or being exposed to the investigational product;

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male subject has been exposed (eg, because of treatment or environmental exposure) to the investigational product prior to or around the time of conception and/or is exposed during his partner's pregnancy.

If a study subject or study subject's partner becomes or is found to be pregnant during the study subject's treatment with the investigational product, the investigator must submit this information to the Pfizer drug safety unit on an SAE report form and an EDP supplemental form, regardless of whether an SAE has occurred. In addition, the investigator must submit information regarding environmental exposure to a Pfizer product in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) using the EDP supplemental form. This must be done irrespective of whether an AE has occurred and within 24 hours of awareness of the exposure. The 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 and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer of the outcome as a follow-up to the initial EDP supplemental form. 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 (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live-born baby, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the investigator should follow the procedures for reporting SAEs.

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 the investigational product.

Additional information regarding the EDP may be requested by the investigator. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the study subject with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the subject was given the Pregnant Partner Release of Information Form to provide to his partner.

8.11. Withdrawal Due to Adverse Events (See Also the Section on Subject Withdrawal)

Withdrawal due to AEs should be distinguished from withdrawal due to other causes, according to the definition of AE noted earlier, and recorded on the appropriate AE CRF page.

When a subject withdraws because of an SAE, the SAE must be reported in accordance with the reporting requirements defined below.

8.12. Eliciting Adverse Event Information

The investigator is to report all directly observed AEs and all AEs spontaneously reported by the study subject. In addition, each study subject will be questioned about AEs.

8.13. Reporting Requirements

Each AE is to be assessed to determine if it meets the criteria for SAEs. If an SAE occurs, expedited reporting will follow local and international regulations, as appropriate.

8.13.1. Serious Adverse Event Reporting Requirements

If an SAE occurs, Pfizer is to be notified within 24 hours of investigator awareness of the event.

In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available AE information. This time frame also applies to additional new information (follow-up) on previously forwarded SAE reports as well as to the initial and follow-up reporting of EDPand exposure via breastfeeding.

In the rare event that the investigator does not become aware of the occurrence of an SAE immediately (eg, if an outpatient study subject initially seeks treatment elsewhere), the investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the AE.

For all SAEs, the investigator is obligated to pursue and provide information to Pfizer in accordance with the time frames for reporting specified above. In addition, an investigator may be requested by Pfizer to obtain specific additional follow-up information in an expedited fashion. This information collected for SAEs is more detailed than that captured on the AE CRF. In general, this will include a description of the AE in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information on other possible causes of the event, such as concomitant medications, vaccines, and/or illnesses, must be provided. In the case of a subject death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

8.13.2. Non-serious Adverse Event Reporting Requirements

All AEs will be reported on the AE page(s) of the CRF. It should be noted that the form for collection of SAE information is not the same as the AE CRF. Where the same data are collected, the forms must be completed in a consistent manner. For example, the same AE term should be used on both forms. AEs should be reported using concise medical terminology on the CRFs as well as on the form for collection of SAE information.

8.13.3. 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 incidents or malfunctions associated with the use of a medical device product. An 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 the investigator's awareness of the event.

8.13.4. Sponsor's Reporting Requirements to Regulatory Authorities

AE reporting, including suspected unexpected serious adverse reactions, will be carried out in accordance with applicable local regulations.

9. DATA ANALYSIS/STATISTICAL METHODS

9.1. Sample Size Determination

The primary endpoint for this study is the proportion of all attempted home self-injections that were successfully performed by the study participant at home and on schedule. This will be presented as mean percentage of self- injections that were successfully administered, along with a 95% confidence interval using a clustered binomial analysis approach. The self-administration success rate in a 1-year IIR study (GA67815[2]) using data from 56 subjects who each had up to 3 injections, was estimated to be 88.8%, with 95% confidence interval 83.1% to 92.7%. This was determined using the generalized estimating equation (GEE) model for clustered binomial data, and estimated the intra-class correlation (ICC) to be 0.043.

Using a GEE model for clustered binomial data, and assuming the ICC to be 0.05, then for 100 subjects, the half-width of the 95% confidence interval for different success rates is simulated to be the following:

Response rate	Half-width of 95% confidence interval
85%	4.6%
90%	3.8%
95%	2.8%

To allow for subjects who have never used Sayana previously, some subjects who may not be proficient at self-injection after the training and to allow for some subjects who may discontinue the study due to being lost to follow up, approximately 160 subjects will be enrolled to provide a sample size of at least 100 women who will perform the required self-injections at home and complete the follow-up questionnaires.

9.2. Statistical Methods

As this is a single arm study, there will be no treatment comparisons, and all analyses will be descriptive.

9.2.1. Analysis of Primary Endpoint

The primary endpoint is the mean percent of home self-injections that were successfully administered. Each subject will have a maximum of 3 home self-injections, each of which will be defined as a success or failure. A success is defined as a home self-injection that was successfully performed by the study participant at home and on schedule (13 week interval +/- 1 week). If the subject attempts but is unable to administer the self-injection at home and had it performed instead at the clinic, then that attempted self-injection would be classified as a failure. If a subject discontinues from the study prior to attempting all 3 home

self-injections, or chooses not to attempt an injection at home, but has it performed in the clinic, then only the injections that were attempted at home will be evaluated and included in the analysis; ie, all attempts are included in the denominator.

For each subject we will calculate:

Proportion of attempted self-injections successfully administered at home= (# of successful home self-injections) / (total # of home self-injection attempts)

These binary outcomes are correlated within the subject, and they will therefore be analyzed with a GEE model for clustered binomial data, using subject as the clustering variable. The GEE model for this single-group analysis will use the logit link and will contain an intercept term; the 95% confidence interval for the intercept will be transformed to a 95% confidence interval for the self-injection success rate.

9.2.2. Analysis of Secondary Endpoint

The secondary endpoint is the continuation rate for the method at 1 year. This is similar to the primary endpoint in study GA67815.[2]

The number and percentage of subjects completing 0 months (receiving only first injection), 3 months (receiving first and second injections), 6 months (receiving first, second and third injections), and 9 months (receiving all 4 injections but not returning for follow-up visit) will be determined. Subjects had completed 12 months if they received all 4 injections, had a follow-up visit and were not recorded as discontinuing during the 12 month period.

The continuation rate equals:

- (# subjects who have not discontinued by 12 months) / (total # of subjects in study)

The total proportion of subjects who have not discontinued by 12 months (the follow-up visit) will be estimated along with a 95% confidence interval (CI), calculated using the normal approximation to the binomial.

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9.2.5. Safety Analysis

Safety data, consisting of all adverse events, including unplanned pregnancies, persistent injection site reactions, SAEs, premature discontinuations, concomitant medications, vital signs, height and weight, and laboratory parameters, will be tabulated and listed according to Pfizer's standard reporting algorithms.

10. QUALITY CONTROL AND QUALITY ASSURANCE

During study conduct, Pfizer or its agent will conduct periodic monitoring visits to ensure that the protocol and Good Clinical Practices (GCPs) are being followed. The monitors may review source documents to confirm that the data recorded on CRFs are accurate. The investigator and institution will allow Pfizer monitors/auditors or its agents and appropriate regulatory authorities direct access to source documents to perform this verification.

The study centre may be subject to review by the institutional review board (IRB)/ethics committee (EC), and/or to quality assurance audits performed by Pfizer, or companies working with or on behalf of Pfizer, and/or to inspection by appropriate regulatory authorities.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

11. DATA HANDLING AND RECORD KEEPING

11.1. Case Report Forms/Electronic Data Record

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.

A CRF is required and 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.

The 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 investigator or by an authorized staff member to attest that the data contained on the CRFs are true. Any corrections to entries made in the CRFs or source documents must be dated, initialed, and explained (if necessary) and should not obscure the original entry.

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

In some cases, the CRF, or part of the CRF, may also serve as source documents.

11.2. 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 documents, copies of all CRFs, safety reporting forms, source documents, and detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, and telephone call reports). The records should be retained by the investigator according to the International Conference of Harmonisation (ICH), according to local regulations, or as specified in the clinical study agreement (CSA), whichever is longer.

If the investigator becomes unable 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 an independent third party arranged by Pfizer. Investigator records must be kept for a minimum of 15 years after completion or discontinuation of the study or for longer if required by applicable local regulations.

The investigator must obtain Pfizer's written permission before disposing of any records, even if retention requirements have been met.

12. ETHICS

12.1. Institutional Review Board/Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, eg, recruitment advertisements, if applicable, from the IRB/EC. All correspondence with the IRB/EC should be retained in the investigator file. Copies of IRB/EC approvals should be forwarded to Pfizer.

The only circumstance in which an amendment may be initiated prior to IRB/EC approval is where the change is necessary to eliminate apparent immediate hazards to the subjects. In that event, the investigator must notify the IRB/EC and Pfizer in writing immediately after the implementation.

12.2. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as the general principles set forth in the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Council for International Organizations of Medical Sciences 2002), Guidelines for GCP (ICH 1996), and the Declaration of Helsinki (World Medical Association 1996 & 2008).

In addition, the study will be conducted in accordance with the protocol, the ICH guideline on GCP, and applicable local regulatory requirements and laws.

12.3. Subject Information and Consent

All parties will ensure protection of subject personal data and will not include subject names or other identifiable data in any reports, publications, or other disclosures, except where required by law.

When study data are compiled for transfer to Pfizer and other authorized parties, subject names, addresses, and other identifiable data will be replaced by a numerical code consisting of a numbering system provided by Pfizer in order to de-identify study subjects. The study centre will maintain a confidential list of subjects who participated in the study, linking their numerical code to the subject's actual identity. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of subjects' personal data consistent with applicable privacy laws.

The informed consent documents must be in compliance with ICH GCP, local regulatory requirements, and legal requirements, including applicable privacy laws.

The informed consent documents used during the informed consent process must be reviewed by the sponsor, approved by the IRB/EC before use, and available for inspection.

The investigator must ensure that each study subject 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 subject before any study-specific activity is performed. The investigator will retain the original of each subject's signed consent document.

12.4. Subject Recruitment

Study centres will recruit study subjects from their clinic who they determine appropriate for study entry. Additionally, advertisements and posters may be used as recruitment procedures. Pfizer will provide study centres a template advertisement and template poster, if they choose to use them, and must be reviewed and approved by the local Ethics Committee prior to utilization. Additional sites may be included if needed.

Pfizer will have an opportunity to review and approve the content of any study recruitment materials directed to potential study subjects before such materials are used.

12.5. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the investigational product, Pfizer should be informed immediately.

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

13. DEFINITION OF END OF TRIAL

13.1. End of Trial in a Member State

End of trial in a Member State of the European Union (EU) is defined as the time at which it is deemed that a sufficient number of subjects have been recruited and completed the study as stated in the regulatory application (ie, clinical trial application [CTA]) and ethics application in the Member State. Poor recruitment (recruiting less than the anticipated number in the CTA) by a Member State is not a reason for premature termination but is considered a normal conclusion to the study in that Member State.

14. SPONSOR DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the IRB/EC, or study drug safety problems, or at the discretion of Pfizer.

If a study is prematurely terminated or discontinued, Pfizer will promptly notify the investigator. After notification, the investigator must contact all participating subjects and the hospital pharmacy (if applicable) within 15 days. As directed by Pfizer, all study materials must be collected and all CRFs completed to the greatest extent possible.

15. PUBLICATION OF STUDY RESULTS

15.1. Communication of Results by Pfizer

Pfizer fulfills its commitment to publicly disclose clinical trial results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), www.pfizer.com, and/or the European Clinical Trials Database (EudraCT), and other public registries in accordance with applicable local laws/regulations.

www.clinicaltrials.gov

Pfizer posts clinical trial Basic Results on www.clinicaltrials.gov for all Pfizer-sponsored interventional studies that evaluate the safety and/or efficacy of a Pfizer product.

15.2. Publications by Investigators

Pfizer has no objection to publication by investigator of any information collected or generated by investigator, whether or not the results are favorable to the investigational drug. However, to ensure against inadvertent disclosure of confidential information or unprotected inventions, investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

The investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, the investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

The investigator will, on request, remove any previously undisclosed confidential information (other than the Study results themselves) before disclosure.

If the study is part of a multicenter study, the investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the study at all participating sites, investigator is free to publish separately, subject to the other requirements of this section.

For all publications relating to the study, institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

16. REFERENCES

1. Prabhakaran S and Sweet A. Self-administration of subcutaneous depot medroxyprogesterone acetate for contraception: feasibility and acceptability. Contraception 2012; 85:453-457.

2. Cameron ST, Glasier A and Johnstone A. Pilot study of home self-administration of subcutaneous depot-medroxyprogesterone acetate for contraception. Contraception 2012; 85:458-464.

3. Beasley A and Westoff C. Self- versus clinical administration of depot medroxyprogesterone acetate (DMPA): A randomized clinical trial. Contraception 2012; 86: 315.

4. Williams R, Hensel D and Fortenberry JD. Self-administration of subcutaneous depot-medroxyprogesterone acetate by adolescent women. Journal of Adolescent Health Abstracts 2010; 46:S17-S81.

5. Beasley A, White KO, Cremers S, Westhoff C. Randomised clinical trial of self-versus clinical administration of subcutaneous depot medroxyprogesterone acetate. Contraception 2014; 89:352-6.

6. UK Medical Eligibility Criteria (UKMEC 2009) www.fsrh.org

Appendix 1. Abbreviations

This is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CI	confidence interval
CRF	case report form
CSA	clinical study agreement
CTA	clinical trial application
DMPA	depot medroxyprogesterone acetate
EC	ethics committee
EDP	exposure during pregnancy
EU	European Union
EudraCT	European Clinical Trials Database
GCP	Good Clinical Practice
GEE	generalized estimating equation
HCP	health care professional
ICC	intra-class correlation
ICD	informed consent document
ICH	International Conference on Harmonisation
IFU	instructions for use
IND	Investigational New Drug
INR	international normalised ratio
IM	intramuscular
IRB	institutional review board
IUD	intrauterine device
LARC	long-acting reversible contraception
LFT	liver function test
MHRA	Medicines and Healthcare products Regulatory Agency
MPA	medroxyprogesterone acetate
MRP	Mutual Recognition Procedure
N/A	not applicable
PATH	Program for Appropriate Technology in Health
PMC	Post Marketing Commitment
PD	premature discontinuation
PK	Pharmacokinetic
PT	prothrombin time
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SOP	standard operating procedure

Abbreviation	Term
SmPC	summary of product characteristics
SRSD	single reference safety document
ULN	upper limit of normal
UK	United Kingdom
US	United States

Appendix 2. Instructions for Use. Preparing and giving an injection with Sayana Press

Sayana Press is a disposable injector that contains a single dose of medicine sealed in a reservoir. These instructions show step-by-step how to prepare and give the injection.

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Step 1: Getting ready

You will need:

– A Sayana Press injector (in its sealed foil pouch).
– A suitable container for the used injector.
– A clean cotton pad or clean paper tissue.

- Wash and dry your hands thoroughly before starting.
- Check that the pouch does not appear to be damaged.
- Check that the expiry date has not passed.
- Ensure the pouch is at room temperature.

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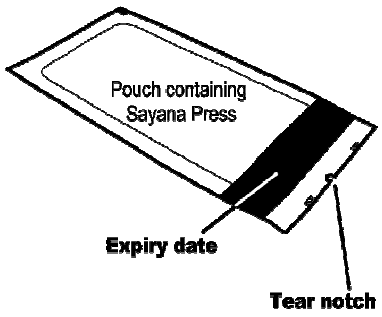

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Step 2: Selecting an injection area

- Choose a suitable area for the injection, either the abdomen or the front upper thigh. Avoid bony areas and the navel (belly button).
- The area of skin must be free from scars and skin conditions such as eczema or psoriasis.
- Change the site with each injection
- Clean the area of skin as your healthcare provider has told you.

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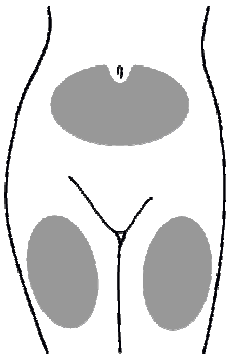

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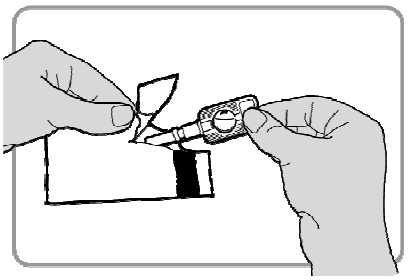
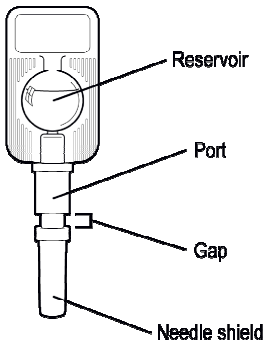
Step 3: Preparing the injector

- Carefully tear open the foil pouch at the tear notch.
- Take out the injector. Do not remove the needle shield from the injector yet.



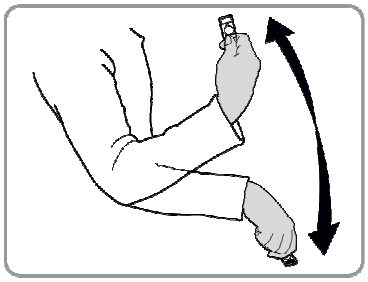
- Check the injector. There should be a gap between the needle shield and the port.
- Discard the injector and use a new one if :
  - There is no gap.
  - The injector is damaged.

The needle shield has come off or is missing.

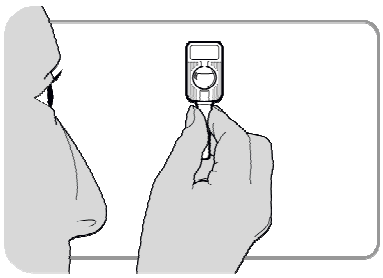


Step 4: Mixing the medicine

- Hold the injector firmly by the port.
- Shake the injector vigorously for at least 30 seconds to mix the medicine.

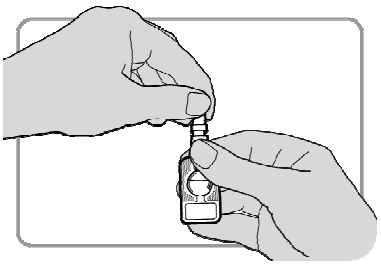


- The medicine should appear white and uniform. If it is not, discard the injector and use a new one.
- If you see liquid leaking out or any other problem, discard the injector and use a new one.
- If there is a delay before injecting, you must repeat the mixing step.

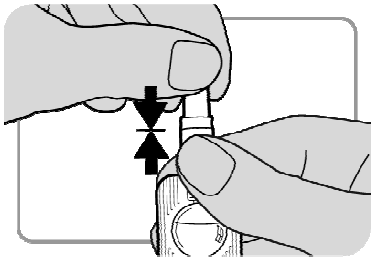


Step 5: Activating the injector

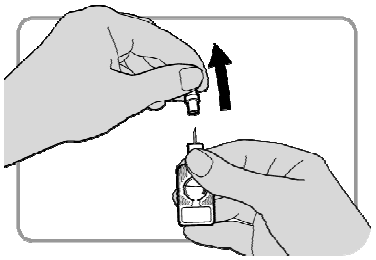
- Hold the injector firmly by the port, making sure the needle shield is pointing upwards. Take care not to squeeze the reservoir.
- Hold the needle shield with the other hand.



- Push the needle shield firmly towards the port until it will go no further. The injector is now activated.



- Pull the needle shield off, and discard it in the sharps disposal container



Step 6: Injecting the dose

- Gently pinch a large area of skin. Keep the skin pinched all through this step.
- Hold the injector by the port with the needle pointing straight downwards.
- Insert the needle into the skin so that the port just touches the skin.
- Squeeze the reservoir slowly to inject the medicine. You should take about **5-7 seconds** to do this.
- Gently pull the needle out of the skin. Let go of the skin.
- Check whether any medicine has leaked out of the injector or has appeared on the skin.
- Do not replace the needle shield.
- Use a clean cotton pad to press lightly on the injection area for a few seconds. Do not rub the area.

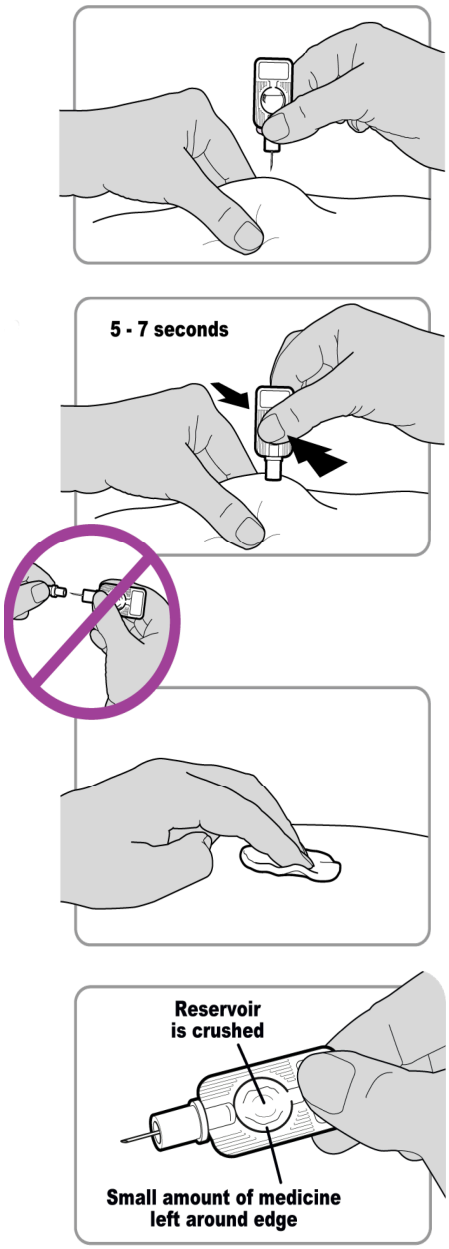
Important advice

- After the injection a small amount of medicine will be left around the inside edge of the reservoir. This is normal.
- However, if any medicine has leaked out of the injector or appeared on the skin, then a problem may have occurred.
- If you believe for any reason that the full dose has not been given, speak to your healthcare provider about alternative methods of contraception until the next scheduled injection.
- **Do not inject an additional dose.**

After injection care:

- If you get any symptoms of allergic reaction (see leaflet Section 4 above) seek medical help immediately.

Monitor the appearance of the injection site until the next injection. If you notice any skin indentation or dimpling at the injection site, tell your healthcare provider.



Step 7: Disposing of the injector • Immediately dispose of the used injector into a suitable container in accordance with your local authority requirements or as you have been told by your healthcare provider. • The injector is for a single injection only and must not be re-used.	
Step 8 • Record the date of your injection and should you wish to continue, calculate the date of your next scheduled injection of Sayana Press	

Retain this leaflet for your records.

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