

Protocol A6791040

**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**

**Statistical Analysis Plan
(SAP)**

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

Amendment Number	Date	Section Changed	Summary of Changes
1	31August2018	6.1 Analysis of Primary Endpoint	<ul style="list-style-type: none"> Added plans for a sensitivity analysis. A sensitivity analysis will be conducted for the primary endpoint; this analysis will exclude primary endpoint data for sites that required closure during the study due to Good Practice violations. Clarified definition of repeated attempts in a single visit.
	31August2018	6.3 Analysis of Other Endpoint	<ul style="list-style-type: none"> Clarified that, endpoints will be summarized by visit and by who administered injection at clinic.
	31August2018	6.7.1. Adverse Events	<ul style="list-style-type: none"> Clarify language regarding analysis, AEs will be summarized by injection method.
	30August2018	Appendix 2	<ul style="list-style-type: none"> Removal of Visit windows.

2. INTRODUCTION

Study A6791040 is a Phase IV Open Label Single Group one year Study of Home Self-Injection with Sayana® Press in adult women of reproductive age, to be run in the United Kingdom.

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 Marketing Commitment (PMC) required by MHRA.

The application for approval of self-injection with Sayana Press was primarily based on a 1-year investigator-initiated study (Study GA67815) 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 from 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 SAP provides the detailed methodology for summary and statistical analyses of the data collected in study A6791040. This document may modify the plans outlined in the protocol; however, any major modifications of the primary endpoint definition or its analysis will also be reflected in a protocol amendment.

2.1. Study Objectives

Primary Objective:

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

Secondary Objective:

- Assess continuation rate for the method at 1 year.

CCI [REDACTED]

I [REDACTED]

I [REDACTED]

I [REDACTED]

I [REDACTED]

2.2. Study Design

This is an open-label, single-arm, non-randomized, 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. 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.

At the Month 12 Final Visit or premature discontinuation, subjects will be asked to complete the CCI [REDACTED] and the HCP will also complete a CCI [REDACTED].

2.3. Sample Size

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 (GA678151) 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, 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.

3. ENDPOINTS AND BASELINE VARIABLES: DEFINITIONS AND CONVENTIONS

3.1. Primary Endpoint(s)

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).

3.2. Secondary Endpoint(s)

- Continuation rate for method at 1 year.

CCI

No baseline covariates in the planned analysis.

Adverse events (AEs), including unplanned pregnancy and persistent injection site reactions, premature discontinuations, concomitant medications, vital signs and laboratory parameter (urine pregnancy test).

4. ANALYSIS SETS

Data for all subjects will be assessed to determine if subjects meet the criteria for inclusion in each analysis population prior to unblinding and releasing the database and classifications will be documented per standard operating procedures.

4.1. Full Analysis Set

The Full Analysis Set (FAS) will be defined as subjects who enroll into the study. All summaries of efficacy parameters will be reported within the FAS population.

4.2. Per Protocol Analysis Set

No per protocol analysis set is planned for this study.

4.3. Safety Analysis Set

The safety population will be defined exactly the same as the FAS population above. The safety population will be used for all safety summaries.

4.4. Other Analysis Sets

No other analysis sets are planned for this study.

5. GENERAL METHODOLOGY AND CONVENTIONS

5.1. Hypotheses and Decision Rules

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

5.2. General Methods

5.2.1. Analyses for Binary Correlated Data

The primary endpoint is the mean percent of self-injections that were successfully administered (ie, combined across visits). 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.

5.2.2. Analyses for Binary Data

For dichotomous categorical variable (continuation rate and proportion of attempted home self-injections where subject returned to clinic for the injection), the number of subjects and proportion will be presented, as well as a 95% confidence interval (using normal approximation to binomial).

5.2.3. Analyses for Categorical Data

For categorical variables (such as Subject and HCP questions), the counts and percent of subjects responding to each category will be presented.

5.3. Methods to Manage Missing Data

Subjects with missing value for a given efficacy variable will not contribute to the analysis of that variable.

6. ANALYSES AND SUMMARIES

All efficacy summaries and analyses will be conducted within the FAS population. Analyses will be primarily descriptive in nature. No interim analyses are planned.

6.1. Analysis of Primary Endpoint

The primary endpoint is the mean percent of home self-injections that were successfully administered (ie, combined across visits). 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. When several home attempts occurred at a visit, the last attempt is counted at a visit.

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 working correlation structure of independence. This GEE model will include only the intercept term and is used to obtain a 95% CI based on standard error estimates that take into account the correlation of binary observations within the patient; the point estimate and 95% CI for the intercept will be back-transformed (anti-logit transformation) to obtain the point estimate and 95% CI on the proportion scale. The proportion estimate and 95% CI will be subsequently multiplied by 100 to obtain results on the percent scale. Note that proportion estimate from the GEE model equals:

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

A sensitivity analysis will be conducted for the primary endpoint; this analysis will exclude primary endpoint data for sites who required closure during study due to Good Clinical Practice violations.

6.2. Analysis of Secondary Endpoint(s)

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

The number and percentage of subjects completing 0 months (receiving 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 summarized. 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:

$$(\# \text{ subjects who have not discontinued by 12 months}) / (\text{total } \# \text{ of subjects in study}).$$

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.

CCI [REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]

[REDACTED]

CCI [REDACTED]

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CCI
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6.4. Correlation Analyses

To describe the degree of relationship between the subject educational level to the subject's rating of the usefulness of training materials (based on Question 1 and Question 2 of subjects questionnaire), an analysis of correlation will be performed between these two categorical variables, the chi-square test and the resulting p-value, as well as the Cramér's V (ϕ_c) will be reported as a measure of correlation between these two variables.

6.5. Subset Analyses

No subset analysis are planned for this study.

6.6. Baseline and Other Summaries and Analyses

6.6.1. Baseline Summaries

All demographic, baseline characteristics and pre-treatment conditions will be summarized using the safety population. Descriptive statistics, including number of patients, mean, standard error, median, and range for continuous variables, and frequency and percent for categorical variables, will be provided for all demographic, baseline characteristics, and pre-treatment conditions.

6.6.2. Study Conduct and Subject Disposition

The number and percentage of patients, enrolled and treated in the study will be presented, together with the number and percentage of patients who withdrew from the study or study medication prematurely. A breakdown of the corresponding reasons for premature withdraw from study or study medication will be provided.

A tabulation of the number and percentage of patients included in each analysis population will be provided. Reasons for exclusion from analysis population will also be provided.

Details on the subject disposition will be provided in subject listings.

6.7. Safety Summaries and Analyses

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.

6.7.1. Adverse Events

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 (lack of efficacy) 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.

Adverse events will also be summarized by injection method (ie, Self-injection at home, Supervised self-injection at clinic by health care provider and Other injections (including the injection performed by a friend).

An adverse event is considered treatment emergent relative to a given treatment if:

- The event occurs for the first time during the effective duration of treatment and was not seen prior to the start of treatment (for example, during the baseline or run-in period), or
- The event was seen prior to the start of treatment but increased in severity during treatment.

AE reporting timeframe for this study will be 14 weeks after the last injection, or until the end of study visit, whichever is the earliest.

6.7.2. Vital Signs

Vital signs will be summarized and described at each visit. Vital signs including heart rate, sitting systolic and diastolic blood pressure will be taken at Screening, Baseline and Final Visits. Weight and height measurements will be conducted at Baseline and Final Visit.

6.7.3. 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.

7. INTERIM ANALYSES

No interim analyses are planned in this study. The final analyses will be performed after database release.

8. REFERENCES

1. 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.
2. Generalized Linear Models, 2nd Edition (*Chapman & Hall Monographs on Statistics and Applied Probability* 37) by P. McCullagh (Author), John A. Nelder (Author).
3. Lui, K.J., Mayer, J.A., and Eckhardt, J. (2000), Confidence Intervals for the Risk Ratio under Cluster Sampling based on the Beta-Binomial Model, *Statistics in Medicine*, 19, 2933-2942.
4. Liang, K.Y. and Zeger, S.L. (1986), Longitudinal Data Analysis using Generalized Linear Models, *Biometrika*, 78, 13-22.

9. APPENDICES**Appendix 1. SUMMARY OF EFFICACY ANALYSES**

Endpoint/Variable	Analysis Set	Statistical Method	Timepoint	Interpretation
the proportion of all attempted home self-injections that were successfully performed by the study participant at home	FAS	GEE model (PROC GENMOD)	EOT	Primary Endpoint
Continuation rate for method at 1 year.	FAS	Proportion & CI	EOT	Secondary Endpoint
CCI [REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

Appendix 2. DATA SET DESCRIPTIONS

CCI [REDACTED] will not be collected in the CRF; this dataset will be provided by sites and then converted into SAS data set for analysis.

Appendix 3. STATISTICAL METHODOLOGY DETAILS

Sample SAS code to fit the GEE model repeated measures specified in [Section 6.1](#). will be presented in the programming plan.