Public Assessment Report

Mutual Recognition Procedure

SAYANA PRESS 104 mg/0.65 ml suspension for injection

PL 00057/1093; UK/H/0960/002/DC

Medroxyprogesterone acetate

Pfizer Limited

Medicines and Healthcare Products Regulatory Agency

LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for SAYANA PRESS 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/002/DC). It explains how SAYANA PRESS 104mg/0.65ml suspension for injection was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use this product. For ease of reading, throughout this PAR, the product SAYANA PRESS 104mg/0.65ml suspension for injection will be called SAYANA PRESS.

For practical information about using SAYANA PRESS, patients should read the Package Leaflet or contact their doctor or pharmacist.

What is SAYANA PRESS and what is it used for?
SAYANA PRESS is a line-extension of the existing product licence for SAYANA 104mg/0.65ml suspension for injection in prefilled syringe (PFS) (PL 00057/0589), using the "Uniject" delivery system.

SAYANA PRESS is a contraceptive injection containing the active substance medroxyprogesterone acetate. It can be used:

- For long-term contraception where you and the person who provides your contraception (e.g. your doctor, nurse or healthcare provider) have decided that this method is the most suitable for you. However, if you wish to use SAYANA PRESS for more than 2 years, your health professional/doctor/nurse may wish to re-evaluate the risks and benefits of using SAYANA PRESS to make sure that it is still the best option for you.
- By teenagers, but only after other methods of contraception have been discussed with the person who provides your contraception and are considered unsuitable or unacceptable.

How does SAYANA PRESS work?
The active ingredient in SAYANA PRESS, medroxyprogesterone acetate (MPA), is similar to (but not the same as) the natural hormone progesterone that is produced in the ovaries during the second half of your menstrual cycle. SAYANA PRESS acts by preventing an egg from fully developing and being released from the ovaries during your menstrual cycle. If an egg is not released it cannot become fertilised by sperm and result in pregnancy.

How is SAYANA PRESS used?
Administration of SAYANA PRESS is initiated by a healthcare professional (HCP). If considered appropriate by the HCP, you may be able to self-inject your injections following suitable instruction and training on injection technique and schedule of administration.

SAYANA PRESS is injected under the skin into the front upper thigh or abdomen. The first injection should be performed under the supervision of your doctor, nurse, or healthcare provider. If your doctor considers it appropriate you may choose to give yourself the injections. You will be shown how to give yourself the injection under supervision before you do this on your own at home. The detailed instructions on the injection procedure are provided at the end of this leaflet and should be followed very carefully. You should continue to receive SAYANA PRESS for as long as instructed by your doctor or until you want to have a baby or switch to a different method of contraception.

Please read Section 3 of the Package Leaflet for detailed information on dosing recommendations, the route of administration and the duration of treatment.

How has SAYANA PRESS been studied?
A clinical study has been performed in volunteers with this product, which uses the "Uniject" single-dose delivery system, which delivers the same dose as the current approved product, which uses the "PFS" delivery system.

What are the possible side effects of SAYANA PRESS?
The possible side effects observed with this product are the same as those observed with other marketed SAYANA products. Very common side effects (affecting more than one in 10) are weight decrease and weight increase. Common side effects (affecting up to one in 10 people) include abdominal pain (cramps), nausea, acne, amenorrhea (very light or no period), heavy, frequent or unexpected bleeding, irregular periods; period pain; breast pain/tenderness, depression, weakness or tiredness, headache, injection site reactions, irritability, anxiety, decreased sexual feeling, vaginal irritation or itching, mood changes, dizziness, back pain, pain in limbs, abnormal cervical smear.

For further information, please see Section 4 the Package Leaflet.

Why is SAYANA PRESS approved?
It was concluded that, in accordance with EU requirements, SAYANA PRESS 104mg/0.65ml suspension for injection is an effective contraceptive, with a suitable side-effect profile that was similar to other marketed contraceptives. The benefit-risk profile for this product was considered to be favourable and a product licence was granted.

What measures are being taken to ensure the safe and effective use of SAYANA PRESS?
A risk management plan (RMP) has been developed to ensure that SAYANA PRESS 104mg/0.65ml suspension for injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for SAYANA PRESS 104mg/0.65ml suspension for injection includes the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about SAYANA PRESS
Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway, Poland and the UK agreed to grant marketing authorisations for this product on 22 May 2011. The UK granted a marketing authorisation for SAYANA PRESS 104mg/0.65ml suspension for injection on 21 June 2011.

The full PAR for SAYANA PRESS 104mg/0.65ml suspension for injection follows this summary.

For more information about treatment with SAYANA PRESS 104mg/0.65ml suspension for injection, read the Package Leaflet or contact your doctor or pharmacist.

This summary was last updated in August 2015.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway, Poland and the UK agreed to grant marketing authorisations for this product on 22 May 2011 (UK/H/0960/002/DC). The UK granted a marketing authorisation for SAYANA PRESS 104mg/0.65ml suspension for injection on 21 June 2011 (PL 00057/1093).

This product is a prescription-only medicine intended for long-term female contraception. In this line extension application, the only change in the product is the introduction of a new injection device; the product has an injection system that is based on Uniject® technology. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

This product contains the active substance medroxyprogesterone acetate (MPA). MPA is a synthetic analogue of 17α-hydroxyprogesterone, with antiestrogenic, antiandrogenic and antigonadotropic effects. MPA belongs to the progestagen pharmacological class of drugs (ATC code: G03AC). It acts by inhibiting the secretion of gonadotropins (luteinizing hormone and follicle-stimulating hormone) from the anterior pituitary. This inhibition, in turn, prevents follicular maturation and ovulation and results in endometrial thinning. These actions collectively produce its contraceptive effect. MPA has well established use in contraception by intramuscular injection and sub-cutaneous injection.

This application was made under Article 8(3) of Directive 2001/83/EC, as amended, a line-extension to the current granted licence for Sayana 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/001/DC), using a prefilled, single-use syringe system.

The RMS for these procedures was the UK and the CMSs were Austria, Belgium, Czech Republic, Germany, Hungary, Ireland, the Netherlands, Norway and Poland.

No new non-clinical studies were conducted, which is acceptable given that the application is for a product containing an existing formulation of a well-known active substance.

Since this product will be used in place of other products that are currently on the market and (with the exception of the delivery system) is identical to the current approved Sayana 104mg/0.65ml suspension for injection (PL 00057/1093; UK/H/0960/001/DC), no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

A randomized, open-label, parallel group study of the pharmacokinetics of medroxyprogesterone acetate in 68 healthy volunteers following subcutaneous administration using the Uniject™ delivery system or depo-subQ provera 104 pre-filled syringe (PFS). The study was conducted in-line with current Good Clinical Practice.

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place for this product type at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, as certification that acceptable standards of GMP are in place at those non-Community sites.

A Risk Management Plan (RMP) and a summary of the pharmacovigilance system have been provided with this application and are satisfactory.

II QUALITY ASPECTS

II.1 Introduction

This is an Article 8(3) line extension application, the only change in the product is the introduction of a new injection device; the proposed product has an injection system that is based on Uniject® technology. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

SAYANA PRESS suspension for injection is supplied in a single-dose container in the form of a pre-filled injector containing 0.65 ml suspension. The injector comprises a linear low-density polyethylene laminate reservoir with a siliconized AISI type-304 stainless steel 23 gauge ultra-thin wall needle attached via a low density polyethylene port and valve. The pack size is one single-dose container.

One pack of Sayana Press, consists of 104 mg medroxyprogesterone acetate (MPA) in 0.65 mL suspension for injection. In addition to these active substances, Sayana Press also contains the excipients Macrogol 3350, methyl parahydroxybenzoate (E 218), propyl parahydroxybenzoate (E 216), sodium chloride, Polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, hydrochloric acid and/or Sodium Hydroxide (for pH adjustment), and water for injection.

II.2 DRUG SUBSTANCE

INN: Medroxyprogesterone acetate
Chemical name: 6-Methyl-3,20-dioxopregn-4-en-17-yl acetate
Molecular formula: $C_{24}H_{34}O_4$
Molecular weight: 386.5
CAS number: 71-58-9
General Properties: White or almost white, crystalline powder. Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone, sparingly soluble in ethanol (96 per cent)

The drug substance is a well-established compound with a European Pharmacopoeia monograph. The data provided confirm that the drug substance used in this product complies with this monograph. The drug substance is the same as that already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589). This is acceptable.

II.3 DRUG PRODUCT

Pharmaceutical development

The objective of the development programme was to produce the identical product to SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589; UK/H/0960/001/MR). albeit using the Uniject® injection system instead of the PFS system. The formulation, method of manufacture and route of administration of the proposed product are identical to those already approved for SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), which is provided in pre-filled syringes (PFS).

The applicant has provided a suitable product development section.

All excipients comply with their respective European Pharmacopoeia monographs.

No excipients of animal or human origin are used in the final products. None of the excipients are sourced from genetically modified organisms.

Manufacture of the product
A description and flow-chart of the manufacturing method has been provided.

Satisfactory batch formulae have been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated at commercial-scale and has shown satisfactory results. Appropriate in-process controls are in place at suitable points during manufacture.

Finished Product Specification
The finished product specification is satisfactory. Test methods have been described and adequately validated. Batch data have been provided and comply with the release specifications. Certificates of Analysis have been provided for any working standards used.

Stability
Finished product stability studies have been conducted in accordance with current guidelines, using batches of the finished products stored in the packaging proposed for marketing. Based on the results, a shelf-life of 5 years with the storage conditions "Do not refrigerate or freeze" are acceptable. An additional precaution of "use immediately; discard any unused portion" also exists for the product after opening.

Suitable post approval stability commitments have been provided.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of the active substance are well-established. As all active substance are widely used and well-known, the applicant has not provided additional studies and further studies are not required. An overview based on a literature review is, thus, appropriate.

Since this product will be used in place of other products that are currently on the market and contains a well-known active substance that is highly stable with a very low toxic potential, no increase in environmental exposure is anticipated. An Environmental Risk Assessment (ERA) is, therefore, not deemed necessary.

IV CLINICAL ASPECTS

IV.1 Introduction

One pharmacokinetic study has been submitted. It was conducted in-line with current Good Clinical Practice.

IV. 2 Pharmacokinetics

A randomized, open-label, parallel group study of the pharmacokinetics (PK) of MPA in 68 healthy volunteers was conducted to compare the PK of MPA following SC administration using the Uniject™ delivery system or PFS (depo-subQ provera 104).

The study participants were pre-menopausal women aged 18-45 years with confirmed ovulatory cycles who were at low risk of pregnancy.

Primary objective: To compare the PK of MPA following a single SC administration of MPA (DMPA; 0.65 mL [104 mg]) using the Uniject system or PFS.

Secondary objectives:

- To compare the weight of DMPA suspension delivered following a single SC administration of DMPA using the Uniject delivery system or PFS;
- To compare the PD response of the ovaries following a single SC administration of DMPA using the Uniject delivery system or PFS; and
- To evaluate the safety and tolerability of SC administration of DMPA using the Uniject delivery system.

Results

PK results: Eight subjects were excluded from the primary PK analysis for reasons pre-specified in the protocol: 1 subject for an insufficient number of serum samples; 3 subjects for a non-zero serum MPA level at baseline; and 4 subjects for dosing administration errors. Sixty subjects were included in the primary PK analyses.

Table 10. Geometric Mean (CV%) Serum Medroxyprogesterone Acetate Pharmacokinetic Parameter Values

Pharmacokinetic Parameters (Units)	Planned Analysis population (dosing administration errors excluded)		PK Evaluable Subjects (dosing administration errors included)	
	Uniject	Pre-filled Syringe	Uniject	Pre-filled Syringe
N, n	32, 12	28, 9	32, 12	32, 11
AUC_{2136} (ng.hr/mL)	959.0 (37)	919.3 (37)	959.0 (37)	479.6 (45)
AUC_{3576} (ng.hr/mL)	1393 (31)	1368 (36)	1393 (31)	691.6 (45)
AUC_{inf} (ng.hr/mL)	2111 (25)	1385 (47)	2111 (25)	313.6 (58)
AUC_{last} (ng.hr/mL)	1408 (31)	1376 (36)	1408 (31)	680.2 (45)
C_{max} (ng/mL)	0.9539 (47)	0.7897 (50)	0.9539 (47)	0.5564 (56)
T_{max} [a] (hr)	70.9 (17.1 – 2400)	163 (23.9 – 1500)	70.9 (17.1 – 2400)	160 (23.9 – 1500)
$t_{1/2}$ [a] (hr)	1342 (345 – 2750)	1668 (370 – 2470)	1342 (345 – 2750)	1584[b] (370 – 2470)

Source: Tables 13.5.2 and 13.5.3

[a] median (range)

[b] n = 10

CV = Coefficient of variation; PK = pharmacokinetic; N = Number of subjects; n = Number of subjects contributing to the mean for $t_{1/2}$ and AUC_{inf}; AUC_{2136} = AUC Day 0 to Day 90; AUC_{3576} = AUC Day 0 to Day 150. Other parameters are defined in Table 3.

Table 8. Comparative Pharmacokinetic Parameters in the Planned Analysis Population

	Ratio (Uniject/PFS)	90% CI
AUC_{0-150}	1.02	0.78 - 1.34
AUC_{0-90}	1.04	0.80 - 1.36
C_{max}	1.21	0.96 - 1.52

Source: Table 13.5.5
PFS = pre-filled syringe; CI = confidence interval.
Parameters are defined in Table 3

Pharmacodynamic results: Ovarian function: based on serum levels of progesterone, estradiol, LH and FSH, 4 PFS subjects had cyclic ovarian activity prior to day 92; 3 of these subjects had been excluded from PK analysis due to dosing administration errors, while the fourth subject had very low serum MPA levels but no record of a dosing administration error. One Uniject subject had a single progesterone elevation on days 8 to 11; serum MPA levels for this subject were lower than average throughout the treatment period, but always ≥0.2 ng/mL and, therefore, effective for contraception. No subject showed ovarian activity during days 93 to 150.

Expelled weight results: Five subjects in the PFS arm were excluded from this analysis because their recorded weight differences ('before' – 'after') were not physically possible since the recorded value exceeded the amount of drug suspension in the syringe by several hundred mg. No subjects randomized to the Uniject arm were excluded from this analysis.

Table S5. Expelled Weight of Medroxyprogesterone Acetate Suspension by Treatment Arm

	Uniject	Pre-Filled Syringe
N	34	29
Mean (mg)	650.1	685.9
SEM (mg)	6.3	24.7
95% CI for the Mean	(637.2, 663.0)	(635.4, 736.5)

N = number of subjects; SEM = standard error for the mean; CI = confidence intervals

Day 92 Serum MPA Levels (biomarker for contraceptive efficacy): All subjects who were dosed with Uniject had serum levels of MPA above 0.1ng/mL at Day 92**.**

IV.3 Pharmacodynamics

No new studies have been conducted and none are required.

IV.4 Clinical efficacy

No new studies have been conducted and none are required.

IV.5 Clinical Safety

With the exception of data collected during the pharmacokinetic study, no new safety data were collected and none were required. No new or unexpected safety concerns were raised during the pharmacokinetic study.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder has submitted an RMP in accordance with the requirements of Directive 2001/83/EC, as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to SAYANA 104mg/0.65ml suspension for injection.

IV.7 Discussion on the clinical aspects

The grant of a marketing authorisation is recommended for this application.

V User consultation

A user consultation with target patient groups on the PIL has been performed and the results submitted in accordance with Article 59 of Council Directive 2001/83/EC, as amended. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The product is identical in quantitative and qualitative composition to SAYANA 104 mg/0.65 mL suspension for injection (PL 00057/0589), albeit with an injection system that is based on Uniject® technology. The marketing authorisation holder has provided suitable pharmacokinetic data to show that the levels of serum medroxyprogesterone acetate is comparable between this product and Sayana using the pre-filled syringe system (PL 00057/0589).

No new or unexpected safety issues occurred during the pharmacokinetic study.

The benefit/risk assessment is, therefore, considered to be positive.

The Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling are satisfactory with the data collected and consistent with other similar products. In accordance with Directive 2012/84/EU, the current approved UK versions of the SmPCs and PILs for these products are available on the MHRA website.

The currently approved labels are listed below:


5 013457 028119
Pfizer Limited
Ramsgate Road
Sandwich
Kent, CT13 9NJ,
United Kingdom
PL 00057/1093
Ref: SN 2_0
Pfizer
SAYANA® PRESS 104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
0.65 ml suspension for injection
104 mg medroxyprogesterone acetate
Subcutaneous use
1 x Single-dose container
SAYANA® PRESS
104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
SAYANA® PRESS 104 mg/0.65 ml
suspension for injection
medroxyprogesterone acetate
LOT/EXP:
Suspension for injection contains: 104 mg medroxyprogesterone acetate.
Also contains: macrogol, E218, E216, sodium chloride, polysorbate 80, monobasic sodium phosphate monohydrate, disodium phosphate dodecahydrate, methionine, povidone, water for injection, hydrochloric acid and/or sodium hydroxide for pH adjustment.
To be used immediately after opening the foil pouch.
Read the package leaflet before use.
Keep out of the reach and sight of children.
Do not refrigerate or freeze.
Any unused product should be disposed of safely after use, in accordance with local guidance for the disposal of sharps.
POM
GP4493
SP4485

Table of content of the PAR update for MRP and DCP

Steps taken after the initial procedure with an influence on the Public Assessment Report (Type II variations, PSURs, commitments)

Scope	**Procedure number**	**Product information affected**	**Date of start of the procedure**	**Date of end of procedure**	**Approval/ non approval**	**Assessment report attached Y/N (version)**
II	UK/H/0960/ 002/II/029G	SmPC, PIL, RMP			Approval	Yes

Annex I

Reference:	PL 00057/1093-0022 (UK/H/0960/002/II/029G)
Product:	Sayana Press 104mg/0.65ml suspension for injection
Marketing Authorisation Holder:	Pfizer Limited.
Active Ingredients:	Medroxyprogesterone acetate
Reason:	To update the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to include the option for self-injection.

Background
Sayana Press (DMPA-SC in Uniject) was initially approved for use as an injectable contraceptive when administered by a healthcare professional and requires 3-monthly clinic visits by patients. The marketing authorisation holder (MAH) proposes the self-injection of Sayana Press, as an option to women who according to the MAH can independently perform the procedure reliably and safely.

Supporting Evidence
The assessment of the clinical data submitted in support of this variation is presented below. In addition to the clinical data submitted, an updated SmPC, PIL and Risk Management Plan were submitted in support of this variation.

Assessor's Comment
The proposed changes to the SmPC and PIL are satisfactory. The marketing authorisation holder has also updated the Risk Management Plan suitably in-line with the proposed option to self-inject.

Conclusion
The grant of this variation is recommended.

Decision - Granted
Date - 15 July 2015

The final variation assessment report for the change to the SmPC/PIL is presented below.

Type II variation
Final updated variation Assessment Report

Sayana Press suspension for injection 104mg/0.65ml
Medroxyprogesterone acetate

UK/H/0960/002/II/29G

Marketing Authorisation Holder: Pfizer Limited

I. RECOMMENDATION

Based on the review of the data on the safety and efficacy, the RMS considers that the variation for Sayana Press suspension for injection 104mg/0.65ml (Medroxyprogesterone acetate) for contraception, for the proposed changes to section 4.2 of the Summary of Product Characteristics with consequential changes to the Patient Information and instructions for use to introduce the option of self-injection by patients is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

This Grouped Type II C.I.4 variation concerns changes to section 4.2 of the Summary of Product Characteristics with consequential changes to the Patient Information and Instructions for Use for Sayana Press (medroxyprogesterone acetate 104mg/0.65ml) to introduce the option of self-injection by patients.

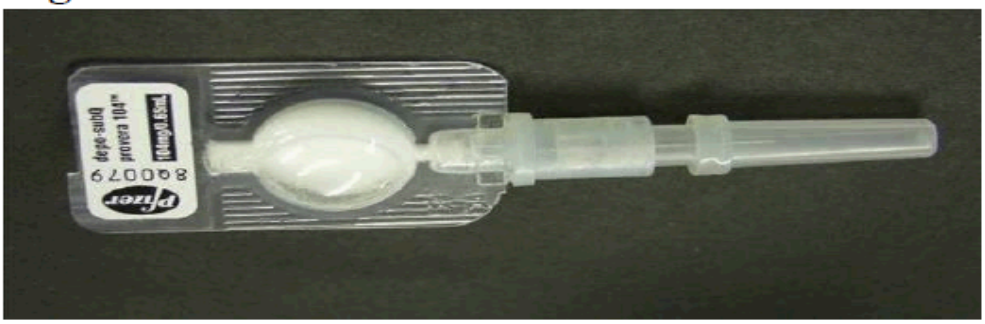
As a consequence of this new proposed mode of administration, the current medroxyprogesterone acetate subcutaneous Risk Management Plan is updated and reformatted in-line with Pharmacovigilance Module V Guidance and to introduce relevant revisions to the Part II: Module SVI section. The RMP is assessed separately to this variation.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

Sayana Press (DMPA-SC in Uniject) is currently approved for use as an injectable contraceptive when administered by an HCP and requires 3-monthly clinic visits by patients. The MAH proposes the self-injection of Sayana Press, as an option to women who according to the MAH can independently perform the procedure reliably and safely. The container closure system for Sayana Press utilises a prefilled plastic reservoir with needle attached, designed for single use and immediate disposal,

Figure 1. SAYANA PRESS



III.3.1 Clinical pharmacology

N/A

III.3.2 Clinical efficacy

To support the application, the MAH provides data from

- Two (2) MAH-sponsored, 1-year, single-arm, Phase 3 safety and efficacy trials of DMPA-SC in prefilled syringes (Study 267 and Study 269). (These studies were used to demonstrate the efficacy and safety of DMPA-SC in the original application for Sayana).

- One (1) Investigator-initiated, non-randomised, independent study that compared the self-injection of DMPA-SC in prefilled syringes versus administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic (Study GA67815);

- One (1) usability study assessing the ability of representative users to correctly operate the Uniject injection delivery system according to the instructions provided (Study A6791035)

- Relevant clinical studies published in the medical literature.

Main studies
Study 269

A 1-year, Phase III, open-label, non-comparative, multicentre study, conducted to assess the safety and efficacy and subject satisfaction with medroxyprogesterone acetate104mg/0.65ml (DMPA-SC) (prefilled syringe) given every 3 months (13 weeks ± week) via the subcutaneous route.

Study objectives
Primary: The primary objective was to assess the efficacy of DMPA-SC contraceptive injection administered every 3 months.

Secondary: The secondary objective was to assess the safety of DMPA-SC contraceptive injection administered every 3 months. Additionally, subject satisfaction with the treatment results and treatment processes of DMPA-SC self-injected at home were evaluated, and the efficacy and safety of DMPA-SC contraception injection self-injected at home were assessed.

Method
This was a phase 3, open-label, non-comparator, multinational, multicentre study designed to assess the efficacy and safety of and subject satisfaction with DMPA-SC given every 3 months for 1 year. The drug was initially to be administered during office visits that were scheduled at 3-month intervals. However, an amendment to the protocol allowed subjects at selected sites to self-inject the drug at home during the last half of the 1-year study. A total of 1065 women were treated in the trial.

Study participants
Women between the ages of 18 and 49 years; being sexually active; desiring long-term contraception who met all of the following criteria were eligible for the study:

- Being between the ages of 18 and 49 years
- Being sexually active and desiring long-term contraception (including women who currently used oral, intrauterine, or barrier methods and wished to switch to DMPA-SC contraception)
- Having been off of oral contraceptives for the 2 months prior to enrolment when applicable and having used a barrier (excluding intrauterine device) method of contraception or having been sexually inactive during this pre-screening period
- Having a negative urine pregnancy test
- Willing to rely upon DMPA-SC for contraception for at least 1 year (4 doses total, with 1 dose at 0, 13, 26, and 39 weeks)
- Menstruating regularly during the 3 months (cycle length of 25 to 35 days) prior to enrolment
- Willing to sign informed consent and able to comply with the study-specific procedures.

Treatments Administered

Women were treated with a 104-mg dose of DMPA-SC at visit 1 and subsequently every 91 ± 7 days for 1 year. Pre-filled syringes with needles supplied separately were utilised in this study as opposed to prefilled plastic reservoir with needle attached also known as Uniject.

Primary Endpoint

The primary efficacy endpoint was the treatment failure cumulative pregnancy rate at 1 year, which was defined as a positive pregnancy test prior to the next scheduled injection.

Secondary Endpoint(s)

The secondary endpoints included a hormone profile and the incidences of amenorrhea, irregular bleeding, and adverse events. Sitting blood pressure, weight, and routine laboratory safety assays were also evaluated. Secondary endpoints at selected sites included endometrial biopsies and endometrial thickness measurements.

Outcomes Research Endpoints:

Patient Satisfaction Questionnaire

The patient satisfaction (PSQ) instrument was administered at visits 1 (the injection visit), 4 (6 months), and 6 (1 year). It was a self - administered instrument containing 5 to 7 items (depending upon the 10. No formal validation of the instrument was undertaken prior to the trial. Evaluation of the treatment processes included the subjects' evaluations of the instruction they received, confidence in the injection technique, unexpected pain associated with injection, convenience of the treatment method, and the difficulty following the injection schedule.

End-of-Treatment Questionnaire

The End-of-Treatment Questionnaire (EOTQ) was administered at visit 6 (1 year). The questionnaire consisted of 27 items and collected information about the subject satisfaction with the self-injection treatment process. A section was also included in the questionnaire to gather information on why subjects who did not elect to self-inject made such a decision. No formal validation of the instrument was undertaken prior to the trial.

It is noted that home self-injection was not originally the subject of this study but was added on as an amendment to the protocol and this allowed subjects at selected sites to self-inject. In addition the option to self-inject was an outcome research endpoint and not a primary or secondary endpoint.

It is also noted that the tools used to measure subjects' satisfaction were not appropriately validated, however, this is not a major concern.

Statistical Methods:

Primary and secondary endpoint analyses used the intent-to-treat (ITT) populations. The ITT efficacy population included all subjects who received at least 1 dose of study medication and had at least 1 visit after the first dose. The ITT safety population included all subjects who received at least 1 dose of study medication.

Sample size was set to accumulate at least 5000 cycles of experience with DMPA-SC (1 cycle = 1 month) and to include for 1 year at least 200 subjects who were 35 years old or younger. Assuming a subject dropout rate of 12% after each clinic visit if 850 subjects were enrolled, after 1 year in the study, the overall dropout rate was calculated to be approximately 40%, with over 7400 cycles accumulated in DMPA-SC-treated subjects.

For data analyses, a skip pattern within the EOTQ was triggered by whether the subject reported that they had or had not self-injected at home during the course of the study. If discrepancies existed between self-reported and study site-reported home self-injection status, those subjects were dropped from the analyses (n = 3). If no site-reported home self-injection data were available, those subjects were kept in the analysis using their self-reported status. Therefore, for these analyses, the denominator of self-injecting subjects was higher than that reported by the study sites. Applying the decision rules left a total of 533 respondents to the EOTQ

Results

Disposition of Subjects:

The ITT population consisted of 1065 subjects who received at least 1 dose of study medication (6 subjects did not return after their first dose, so the efficacy analyses were based on 1059 subjects; adverse event data were based on 1060 subjects). Of these, 80.4% (856/1065) completed the study. Two hundred and nine subjects discontinued the study treatment prior to 1 year. The most common reasons for subject discontinuation were withdrawal of consent, adverse events, and lost to follow-up.

Table 2. Study 269 - Exposure to DMPA-SC (ITT Population)

Subjects Receiving Injections		DMPA-SC N = 1065		
		n	Total	%*
Within protocol-specified range	3-month	936	995	94.1
	6-month	836	905	92.4
	9-month	834	865	96.4
Total self-injections by visit	Enrolment	62	1065	5.8
	3-month	357	994	35.9
	6-month	468	907	51.6
	9-month	571	868	65.8
Clinic self-injections by visit	Enrolment	62	1065	5.8
	3-month	357	994	35.9
	6-month	466	907	51.4
	9-month	366	868	42.2
Home self-injections by visit	6-month	2	228[t]	0.9
	9-month	205	372[t]	55.1

cm = centimetre; DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic.
* % = (n/total reported within visit) x 100.
t. Number of subjects offered a choice of home self-injection.
Source: Study 269 CSR Table 4.

Baseline Characteristics

The mean subject age was 32.2 years; most of the subjects were 35 years of age or younger (69.4%, 739/1065) and almost all of them were white (97.9%; 1043/1065). The mean BMI was 23.2kg/m^2. Most subjects (81.2%, 865/1065) received 4 injections of DMPA-SC.

Table 1. Study 269 - Summary of Demographic Characteristics (ITT Population)

Characteristic	DMPA-SC (N = 1065)
Age (years)	
Mean ±SD	32.2 ± 7.2

Range	18.0 - 49.6
≤35, n (%)	739 (69.4)
>35, n (%)	326 (30.6)
Race, n (%)	
White	1043 (97.9)
Black	1 (0.1)
Asian/Pacific Islander	20 (1.9)
Mixed/Multiracial	1 (0.1)
Weight (kg)	
Mean ± SD	62.6 ± 11.3
Range	35.0 - 113.2
Height (cm)	
Mean ± SD	164.1 ± 6.4
Range	137.2 - 184.0
Body Mass Index (kg/m^2)	
Mean ± SD	23.2 ± 3.9
Range	15.4 - 40.6
≤25, n (%)	779 (73.1)
>25 to 30, n (%)	219 (20.6)
>30, n (%)	67 (6.3)
cm = centimetre; DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; m = metre; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic; SD = standard deviation. Source: Study 269 CSR Table 2.	

Treatment Compliance

More than 92% of the injections were administered within the protocol-specified range. Of the 205 women who self-injected at home, 10 had at least one injection that was out of the compliance range (91 ± 7 days); these injections were outside of the range by 1 or 2 days only.

Efficacy Results

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at 1 year was 0%. =The Pearl Index, the number of pregnancies per 100 woman-years was 0. Therefore, from the information provided it would appear that no pregnancies occurred at all in the study as a whole.

Table 3. Study 269 – Woman-Cycles of Exposure (ITT Population)

Type of Injection	Number of Injections	Woman-Cycles of Exposure	Woman-Cycles of Exposure with Specific Exclusions*		
			Months without consistent barrier use	Months with no consistent or occasional barrier use	Months with intercourse and with no barrier use
Office Injection by Professional	2366	7098	6790	6482	6278
Office Self-Injection	1251	3753	3701	3615	3531
Home Self-Injection	207	621	601	577	566
Total	3824	11472	11093 †	10699†	10407 †

ITT = intent-to-treat.
* In the bleeding pattern diary, subjects were asked each month if they had used a barrier contraceptive (e.g., condom, diaphragm), and if so, how often (every time or sometimes); they were also to note whether they had engaged in sexual intercourse.
†Adding cycle numbers sorted by types of injections will not sum to these totals. If a subject's injection type changed during a given month, exclusion was applied to both types of injections.
Source: Study 269 CSR Table 5.

Self-injection

At least 1 self-injection was performed by 61.6% (656/1065) of the subjects, including self-injections performed at the clinic. Self-injection at home was performed by 19.2% (205/1065) of the subjects. None of the self-injecting subjects experienced a contraceptive failure.

Table 4. Study 269 - Self-Injection Summary by Visit in the ITT Population

Treatment: DMPA-SC (N=1065)		
	Visit	
	Month 6	Month 9
	n	n
Did the Patient Self-Inject?		
Yes	2	205
No	226	167
Total Reported	228	372
Difficulty with injection?		
Yes	No data	7
Total Reported	No data	7
Return to office for assistance with self-injection?		
Yes	No data	3
Total Reported	No data	3

DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study; n = number of subjects with measured characteristic.
Source: Study 269 CSR Table T3.6.

Assessment of the Self-Injection Experience
The EOTQ was completed by 536 subjects. According to the applicant whether the subject had self-injected at home was not always recorded by the clinical sites therefore data for a few subjects is missing. 523 subjects completed the study and 10 who did not (there is a disparity as some subjects (3) were kept in the analysis using their self-reported status even if site reported data was not available for them).

Among those who received training prior to making a decision about whether to self-inject at home, 80.3% (355/442) reported that the training was valuable in helping to make that decision. Subjects who self-injected at home rated their instruction significantly higher with regard to how well it prepared them for home injection and how well the training materials answered questions than did those who did not self-inject at home.

Subjects who self-injected at home also reported significantly greater confidence in their ability to inject themselves correctly and rated how well the office staff answered their questions about the medication's efficacy, safety, and the injection method significantly higher.

Of the subjects who self-injected at home, 78.2% (158/202) reported that they referred to the take-home injection instructions and 71.9% (146/203) indicated that they had not contacted the doctor's office for additional injection instructions.

No significant difference was found between those who chose home self-injection and those who did not with regard to how well the office staff answered their questions about the medication's efficacy, safety, and the injection method.

Table 5. Study 269 – Subject Evaluation of Training, Training Materials and Support for Self-Injection

	N	%	Did Home Inject, mean (SD) N	Did Not Do Home Inject, mean (SD) N	p-value
When self-injection training was given					
After decision to home inject	41	7.9			
Before decision to home inject	452	86.9			
Received no instruction	27	5.2			
Did instruction help to make home injection decision (among those getting training before decision)					
Yes	355	80.3			
No	87	19.7			
Rating of how well instruction prepared you for home injection (among those getting training)*			9.46 (.98) 202	7.60 (2.15) 286	<.001
Rating of confidence in being able to home inject correctly (among those getting training)*			9.51 (.75) 204	6.86 (2.54) 287	<.001
Rating of how well training materials answered questions (among those getting training)*			9.52 (.88) 175	8.04 (2.19) 288	<.001
Did you review take-home instructions before injecting (among those reporting home injection)?					
Yes	158	78.2			
No	44	21.8			
Did you contact the doctor's office before injecting (among those reporting home injection)?					
Yes	57	28.1			
No	146	71.9			
Rating of how well office staff answered questions (all respondents)*			9.91 (.28) 103	9.28 (1.09) 291	<.001

N = total number of subjects participated in study; SD = standard deviation.
* Rating on a scale of 1 (worst) to 10 (best) with appropriate definition for each question.
Source: Study 269 CSR Table T12.3.

Table 6. Study 269 - EOTQ: Evaluation of Self-Injection Procedures and Experiences

EOTQ QUESTION	N	%	mean (SD)
Did you use the injection reminder stickers?			
Yes	138	31.3	
No	63	68.7	
Rating of the efficacy of the reminder stickers (among those using the stickers)*	63		9.51 (1.12)
Rating of the ease of following the injection schedule correctly*	201		9.59 (0.78)
Rating of the ease of doing home Injection*	204		9.26 (1.03)
Rating of the convenience of home injection*	204		9.42 (1.02)
Rating of the injection pain during home injection*	204		9.07 (1.25)
If you continued using the injectable contraceptive, where would you prefer to obtain the syringes?			
Doctor's office	97	48	
Local pharmacy	90	44.6	
Through the mail	15	7.4	
What factors lead to the decision to home inject? (Subjects may indicate >1 factor)			
More convenient	155	47.8	
Feel more independent	84	25.9	
I am a health professional	45	13.9	
I self-inject other medications	34	10.5	
Other	6	1.9	

EOTQ = End-of-Treatment Questionnaire; N = number of subjects participated in study; SD = Standard deviation.
* Ratings used a scale of 1 (worst) to 10 (best), with definitions appropriate for each of the questions; for example, pain was rated as 1="unbearable pain" to 10="no pain".
Source: Study 269 CSR Table T12.4.

The 204 respondents identified 324 factors which led them to make a decision to self-inject (there was an option to select more than one factor). Convenience was cited most frequently as a factor leading to self-injection, accounting for 47.8% (155/324) of the responses. A feeling of greater independence accounted for another 25.9% (84/324) of the responses.

Similarly, those who did not self-inject were asked to identify what factors led them to their decision (Table 7). The 316 respondents identified a total of 482 factors. Among those who did not self-inject, the most frequently cited reason (25.3%, 122/482) was concern that an error during the injection procedure may result in pregnancy. Concern that they would make an error during the injection that would cause pain accounted for 22.8% (110/482) of the responses. Having difficulty inflicting injection pain on themselves and being afraid of the sight of needles accounted for 18.0% (87/482) and 12.2% (59/482) of the responses, respectively. Never being given the opportunity to self-inject was cited by 8.5% (41/482) of the subjects. Only 3.7% (18/482) of the respondents reported that the training had not adequately prepared them for self-injection.

Table 7. Study 269 - EOTQ: Factors Leading to Decision Not to Self-Inject

What Factors Led to the Decision Not to Home Self-Inject?	N	%*
Concerned error might result in pregnancy	122	25.3
Concerned error might cause pain	110	22.8
Difficult to inflict pain on oneself	87	18.0
Afraid of sight of needle	59	12.2
Other	45	9.3
Never given opportunity to home inject	41	8.5
Training didn't prepare me to home inject	18	3.7

EOTQ = end-of-treatment questionnaire; N = number of subjects participated in study.
* Proportion of N=482 responses (provided by N=316 respondents).
Source: Study 269 CSR Table T12.5.

Of the subjects who had self-injected, 78.8% (160/203) indicated a preference to continue self-injection if they chose to use DMPA-SC for future contraceptive needs, whereas 21.4% (67/313) of those who had not self-injected at home stated that they would prefer to self-inject, as shown in Table 8, which also shows the injection preferences when expressed across all of the EOTQ respondents. Self-injections were preferred by 44.0% (227/516) of all respondents, with 35.5% (183/516) preferring that staff at their doctor's office inject them and 20.5% (106/516) preferring to inject themselves at the doctor's office.

Table 8. Study 269 - EOTQ - Preferences for Future Injections (ITT Population)

Injection if Treatment Is Continued	Did Self-Injection		Did not do Self-Inject		Total	
	N	%	n	%	n	%
Home self-injections	160	78.8	67	21.4	227.0	44.0
Injected by staff at doctor's office	22	10.8	161	51.4	183.0	35.5
Self-injection at doctor's office	21	10.3	85	27.2	106.0	20.5
Total	203	99.9*	313	100.0	516.0	100.0

EOTQ = end-of-treatment questionnaire; ITT = intent-to-treat.
*Total does not equal 100% due to rounding.
Source: Study 269 CSR Table T12.6.

Conclusions

Just over half of the subjects who participated in the trial completed the EOTQ. The results suggest that subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided. Overall, however, no firm conclusion can be made regarding the findings of the EOTQ as it was not appropriately validated.

Study 267

A Phase III, open-label, multinational, multicentre 1-year study was conducted to assess the efficacy, safety, and subject satisfaction of DMPA-SC given every 3 months. An amendment to the protocol allowed subjects to self-inject at home during the last half of the 1-year study.

Study participants

Women who met all of the following criteria were eligible for the study: being between the ages of 18 and 49 years; being sexually active; desiring long-term contraception (including women who currently used oral, intrauterine, or barrier methods and wished to switch to DMPA contraception); having been off of oral contraceptives for the 2 months prior to enrolment when applicable and having used a barrier (excluding intrauterine device) method of contraception or having been sexually inactive during this pre-screening period; having a negative urine pregnancy test; willing to rely upon DMPA-SC for contraception for at least 1 year (4 doses total, with 1 dose at 0, 13, 26, and 39 weeks); menstruating regularly during the 3 months (with an average cycle length of 25 to 35 days) prior to enrolment; willing to sign informed consent; and willing and able to comply with the study-specific procedures.

Treatments Administered

Women were treated with a 104-mg dose of DMPA-SC at visit 1 and subsequently every 91 ± 7 days for 1 year.

Endpoints/statistical methods

The endpoints and statistical method used are broadly in line with that of study 269

Results
Baseline Characteristics:

Table 10. Study 267 - Summary of Demographic Characteristics (ITT Population)

Characteristic	DMPA-SC N = 722
Age (years)	
Mean ± SD	28.2 ± 7.0
Range	18.0-49.9
≤35, n (%)	610 (84.5)
>35, n (%)	112 (15.5)
Race, n (%)	
White	485 (67.2)
Black	61 (8.4)
Asian/Pacific Islander	22 (3.0)
Mixed/Multiracial	154 (21.3)
Weight (kg)*	
Mean ± SD	66.5 ± 16.7
Range	38.8-164.9
Height (cm)*	
Mean ± SD	161.7 ± 7.2
Range	129.0-180.3
Body Mass Index (kg/m2)†	
Mean ± SD	25.3 ± 5.7
Range	14.7-57.7
≤25, n (%)	403 (55.8)
>25 to 30, n (%)	189 (26.2)
>30, n (%)	126 (17.5)

cm = centimetre; DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; m = metre; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic; SD = standard deviation.
* N=720; † N=718.
Source: Study 267 CSR Table 2.

Extent of Exposure

Over two-thirds (68.8%, 497/722) of the subjects received 4 injections of DMPA-SC. At least 1 self-injection was performed by 53.2% (384/722) of the subjects, with 10.1% (73/722) receiving 1 home self-injection.

Table 11. Study 267 - Exposure to DMPA-SC (ITT Population)

Subjects Receiving Injections		DMPA-SC N=722		
		n	Total	%*
Within protocol-specified range	3-month	607	636	95.4
	6-month	522	550	94.9
	9-month	483	497	97.2
Total self-injections by visit	Enrolment	12	721§	1.7
	3-month	90	636	14.2
	6-month	203	551	36.8
	9-month	330	497	66.4
Clinic supervised self-injections by visit	Enrolment	12	721§	1.7
	3-month	90	636	14.2
	6-month	203	551	36.8
	9-month	257	497	51.7
Home self-injections by visit	9-month	73†	338††	21.6

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study.
* % = (n/total reported within visit) x 100. § Data missing for 1 subject.
† Number is 72 in Table T5.4 because 1 subject's attempt at home self-injection was unsuccessful.
††Based on the number of subjects offered home self-injection.
Source: Study 267 CSR Table 4.

Table 12. Study 267 - Woman-Cycles of Exposure (ITT Efficacy Population)

Type of Injection	Number of Injections	Woman-Cycles of Exposure	Woman-Cycles of Exposure with Specific Exclusions*		
			Months with no consistent barrier use	Months with no consistent or occasional barrier use	Months with intercourse and with no barrier use
Office Injection by Professional	1768	5304	5082	4793	4023
Supervised Self- Injection	563	1689	1658	1586	1348
Independent Self-Injection	72	216	214	204	173
Total	2403	7209	6960†	6605†	5616†

ITT = intent-to-treat.
* In the bleeding pattern diary, subjects were asked each month if they had used a barrier contraceptive (e.g., condom, diaphragm), and if so, how often (every time or sometimes); they were also to note whether they had engaged in sexual intercourse.
†Adding cycle numbers sorted by types of injections will not sum to these totals. If a subject's injection type changed during a given month, exclusion was applied to both types of injections.
Source: Study 267 CSR Table 5.

Table 13. Study 267 - Self-Injection Summary by Visit in the ITT Population

Treatment: DMPA-SC (N= 722)		
	Visit	
	Month 6	Month 9
	n	n
Did Patient Self-Inject?		
Yes	0	73
No	174	265
Total Reported	174	338
Difficulty with injection?		
Yes	No data	8
Total Reported	No data	8
Return to office for Injection?		
Yes	No data	1
Total Reported	No data	1

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects who participated in the study; n = number of subjects with measured characteristic.
Source: Study 267 CSR Table T3.6.

The primary efficacy endpoint of treatment failure cumulative pregnancy rate at 1 year was 0%. None of the 720 subjects with data became pregnant during the study. The Pearl Index, the number of pregnancies per 100 woman-years, was also 0.

Self-injection

The EOTQ was completed by 396 subjects. Application of the rules that applied to study 269 (mentioned above) left a total of 394 respondents to the EOTQ. These included 374 subjects who completed the study and 20 who did not.

The subjects indicated a high level of satisfaction with the injection training they received from study site personnel. Among those who received training prior to making a decision about whether to self-inject, 72.9% (145/199) reported that the training was valuable in helping them to make that decision. Subjects who self-injected rated their instruction significantly higher with regard to how well it prepared them for self-injection and how well the training materials answered questions than did those who did not self-inject. Subjects who self-injected also reported significantly greater confidence in their ability to inject themselves correctly.

Of the subjects who self-injected, 88.6% (70/79) reported that they referred to the take-home injection instructions and 93.6% (73/78) indicated that they had not contacted the doctor's office for additional injection instructions.

Table 15. Study 267 - EOTQ: Evaluation of Home Self-Injection Procedures and Experiences

EOTQ Question	N	%	Mean (SD)
Did you use the injection reminder stickers?			
Yes	25	31.6	
No	54	68.4	
Rating of the efficacy of the reminder stickers (among those using the stickers)*	25		9.64 (1.11)
Rating of the ease of following the injection schedule correctly*	79		9.63 (0.7)
Rating of the ease of doing home Injection*	79		9.43 (0.81)
Rating of the convenience of home injection*	79		9.73 (0.64)
Rating of the injection pain during home injection*	79		8.47 (1.84)
If you continued using the injectable contraceptive, where would you prefer to obtain the syringes?			
Doctor's office	28	36.8	
Local pharmacy	24	31.6	
Through the mail	24	31.6	
What factors lead to the decision to home inject? (Subjects may indicate >1 factor)			
More convenient	69	53.9	
Feel more independent	40	31.3	
I am a health professional	11	8.6	
I self-inject other medications	3	2.3	
Other	5	3.9	

EOTQ = End of Treatment Questionnaire; N = number of subjects participated in study; SD = standard deviation;
* Ratings used a 1 (worst) to 10 (best) scale with appropriate definition for each question
Source: Study 267 CSR Table T10.4.

The calendar reminder stickers that were provided to the subjects were used by 31.6% (25/79) of those who self-injected. Among the subjects who used them, the reminder stickers were considered to be highly effective. Subjects also highly rated the ease of adhering to the injection schedule, the ease of performing the self-injection, and the convenience of the contraception method. The pain associated with self-injection was considered minor (mean of 8.47, wherein 1 was unbearable pain and 10 was no pain). The respondents indicated that if they continued to use DMPA-SC for contraception, 36.8% (28/76) would prefer to get their syringes from the doctor's office, 31.6% (24/76) from the local pharmacy, and 31.6% (24/76) through the mail.

The respondents who had self-injected were asked what led them to that decision; they could have selected more than 1 factor. A total of 128 factors were identified by the 78 respondents. Convenience was cited most frequently as a factor leading to self-injection, accounting for 53.9% (69/128) of the responses. A feeling of greater independence accounted for another 31.3% (40/128) of the responses. Similarly, those who did not self-inject were asked to identify what factors led them to their decision (Table 16). A total of 330 factors were identified by the 225 respondents. Among those who did not self-inject, the most frequently cited reason (24.5%, 81/330) was that they had never been given the opportunity to do so. Other concerns included the possibility that the injection would cause pain; that an injection error might result in pregnancy; and general uneasiness with needles.

Only 4 responses suggested that the training had not adequately prepared the subject for home self-injection.

Table 16. Study 267 - EOTQ: Factors Leading to Decision Not to Self-Inject

What Factors Led to the Decision Not to Home Self-Inject?	N	%*
Never given opportunity to home inject	81	24.5
Concerned error might cause pain	52	15.8
Difficult to inflict pain on	49	14.8
Afraid of sight of needle	39	11.8
Concerned error might result in pregnancy	34	10.3
Training didn't prepare me to home inject	4	1.2
Other	71	21.5

* Proportion out of N=330 total responses reported by N=225 respondents;
EOTQ = end of treatment questionnaire.
Source: Study 267 CSR Table T10.5.

Of the subjects who had self-injected, 94.9% (74/78) indicated a preference to continue self-injection if they chose to use DMPA-SC for future contraceptive needs, whereas 47.9% (139/290) of those who

had not self-injected would prefer to self-inject. Table 17 provides the preferences for future injections expressed across all of the EOTQ respondents. Self-injections were preferred by 57.9% (213/368) of all respondents, whereas preferences for the other alternatives were nearly equal, with 21.5% (79/368) preferring to inject themselves at the doctor's office and 20.7% (76/368) preferring that the staff at their doctor's office inject them.

Table 17. Study 267 - EOTQ: Preferences for Future Injections (ITT Population)

Injection if Treatment Is Continued	Did Self-Injection		Did not do Self-Injection		Total	
	N	%	n	%	n	%
Home self-injections	74	94.9	139	47.9	213	57.9
Self-injection at doctor's office	3	3.8	76	26.2	79	21.5
Injected by staff at doctor's office	1	1.3	75	25.9	76	20.7
Total	78	100	290	100	368	100.1*

EOTQ = End of Treatment Questionnaire; ITT = Intent to treat population; N = number of subjects who participated in the study; n = number of subjects with the measured characteristic.
*Total does not equal 100% due to rounding
Source: Study 267 CSR Table T10.6.

Conclusion

The results suggest that subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided. However, only about 31% of the subjects used the calendar reminder stickers

Study GA67815

A prospective, open-label, parallel-group, non-randomised study designed to evaluate the feasibility and acceptability of self-administration of DMPA-SC in terms of efficacy, safety and patient perceptions. This study was independently conducted and not sponsored by the MAH although they supplied the pre-filled syringes with separate needles to the investigators.

Objectives:

The study was designed to determine feasibility of self-administration of hormonal injectable contraception by answering the following questions.

1. Whether self-administration of depot medroxyprogesterone acetate administered subcutaneously (DMPA-SC) will result in improved continuation rates compared with depot medroxyprogesterone acetate administered intra-muscularly (DMPA-IM) after 12 months?

2. Whether self-administration will lead to greater satisfaction with this contraceptive?

3. If women who self-administer DMPA-SC will do so at the correct time interval?

4. Which proportion of women, who expressed a theoretical wish to self-administer DMPA-SC, will do so in practice? (It should be noted that this objective is not addressed in this report).

5. Whether self-administration of DMPA-SC will result in the need for increased non-scheduled contact with Family Planning providers?

Study population and selection criteria

Women aged 18 to 40 years; using DMPA-IM for at least the previous 9 months and wishing to continue using DMPA for more than one year were eligible to participate in the study. Subjects were required to fulfil the following criteria:

- No contraindications to DMPA (World Health Organization [WHO] Medical Eligibility Criteria – category 3 or 4);
- Not wishing to conceive within the next 2 years;
- Not planning to move out of the area for at least 12 months;
- Willing to be contacted at work or at home;
- Without significant pre-existing medical conditions;
- Willing and able to give informed consent.

Study Treatment:

Subjects in the DMPA-SC group received the product SC once every 3 months. For the DMPA-SC group, the injection delivery system used in this study consisted of a pre-filled syringe with a separately packaged, sterile, SC needle (26 gauge) that was required to be attached to the syringe body prior to use (Sayana®). The injection delivery system used in this study consisted of a pre-filled syringe with a separately packaged, sterile, SC needle while Sayana Press consists of a prefilled plastic reservoir with a needle already attached.

Primary efficacy endpoint:

- The continuation rate of the method at 12 months compared to a control group of existing users of DMPA-IM (N=64) who continued to attend clinic to receive HCP-administered DMPA-IM (discontinuation rate).
- The proportion of self-injections that were given at the correct scheduled time
- Injection problems
- Patient's satisfaction with the method

Results

Subject Disposition and Demography:

A total of 178 current users of DMPA-IM were approached to participate in the study; 128 agreed to participate; 64 subjects were randomised to self-administer DMPA-SC and 64 were randomised to receive DMPA-IM administered by a clinician.

Table S1. Subject Disposition

Number of Subjects (%)	DMPA-SC	DMPA-IM
Assigned to study treatment	64	64
Treated	64	64
Completed	50 (78.1)	48 (75.0)
Discontinued	14 (21.9)	16 (25.0)
Analyzed for:		
Safety analysis set	64 (100.0)	64 (100.0)
Efficacy analysis set	58 (90.6)	64 (100.0)
Analyzed for adverse events	64 (100.0)	64 (100.0)

Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly; DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously.

Table 19. Study GA67815 Demographics at Baseline in the Safety Analysis Set (N=128)

	DMPA-SC Self-Injection Group	DMPA-IM Clinic Group	p-value
No. of women (n)	64	64	
Age (SD), years	28.8 (5.0)	28.3 (5.7)	0.71
Age category: n (%)			
<18 years	0 (0.0)	0 (0.0)	nd
18 - 25 years	17 (26.6)	21 (32.8)	nd
>25 - 40 years	47 (73.4)	43 (67.2)	nd
>40 years	0 (0.0)	0 (0.0)	nd
BMI category (kg/m^2): n (%)			
<18.5	2 (3.1)	2 (3.1)	nd
18.5 - <25	27 (42.2)	28 (43.8)	nd
25 - <30	14 (21.9)	21 (32.8)	nd
30 - <40	14 (21.9)	10 (15.6)	nd
≥40	1 (1.6)	0 (0.0)	nd
missing	6 (9.4)	3 (4.7)	nd
Deprivation Category Index Scores*	3.8 (1.6)	4.0 (1.5)	0.43
Reproductive History			
Births, per subject	0.22 (0.65)	0.19 (0.53)	0.82
Miscarriages, per subject	0.05 (0.21)	0	0.08
Abortions, per subject	0.34 (0.67)	0.23 (0.46)	0.49
Ectopic, per subject	0	0	nd
Total use of DMPA (months)	51 (33)	55 (38)	0.76
Recent continuous use of DMPA (months)	41 (31)	42 (35)	0.99

BMI = body mass index; DMPA = depot medroxyprogesterone acetate; DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; kg = kilogram; N = total number of subjects participated in study; n = number of subjects with measured characteristic; nd = not done; SD = standard deviation.
* Deprivation Score based on postal code and census data, with score = 1 (affluent) and score = 5 (very poor).
Source: Study GA67815 CSR Tables T14.1.2.1 and T14.1.2.2.

Discontinuation Rate:

In the DMPA-SC group, the study medication expired before the last 6 subjects recruited could complete the study. No replacement study medication was available, so these 6 subjects had to be withdrawn from the study prematurely. These 6 subjects were excluded from efficacy analysis.

5 subjects were withdrawn from the study due to adverse events (AEs - 3 had moderate AEs, and 2 had mild AEs), 2 subjects were lost to follow-up and 1 subject was withdrawn from study due to a protocol violation.

In the DMPA-IM group, 4 subjects discontinued due to AEs (2 moderate, 2 mild); 10 subjects were lost to follow-up; 1 subject discontinued as she wished to start a family and 1 subject withdrew consent

Table 4. Discontinuations From the Study

Reason for Discontinuation	DMPA-SC (N = 64)[a]	DMPA-IM (N = 64)
Adverse event[b]	5 (7.8)	4 (6.3)
Lost to follow-up	2 (3.1)	10 (15.6)
Other	7 (10.9)[a]	1 (1.6)
Withdrew consent[c]	0	1 (1.6)
Total number of subjects discontinued	14 (21.9)	16 (25.0)

Sources: Table 14.1.1.2, Table 16.2.1 and Table 16.2.7.2
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly;
DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects.
a. Six of these subjects were withdrawn due to expiry of study medication. One subject was withdrawn due to protocol violation.
b. A subject is represented here as 'discontinued due to an adverse event' if either Table 16.2.1 and/or Table 16.2.7.2 indicate that the subject discontinued for that reason.
c. Subject who had an AE that resulted in discontinuation has been excluded here.

Table 6. Analysis of 12 Month Discontinuation Rate

Treatment Group	N	n	Discontinuation Rate	Asymptotic Standard Error	Asymptotic 95% Confidence Interval		
					Lower	Upper	p-value†
DMPA-SC	58*	8	13.8	4.5	4.9	22.7	
DMPA-IM	64	16	25.0	5.4	14.4	35.6	
Difference			-11.2	7.1	-25.0	2.6	0.1123

Source: Table 14.2.2.2
* Six subjects received medication that expired prior to the end of the study. As these subjects could not complete the trial with all 4 planned injections, these subjects were excluded from the analysis.
† p-value is for comparison of differences based on normal approximation to the binomial.
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly;
DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects;
n = Total number of subjects discontinued by 12 months.

The total number of subjects included in the study is small. However, there does not appear to be any major difference in the reason for discontinuation between the DMPA-SC and DMPA-IM group. It would also appear that a few more subjects were lost to follow-up in the DMPA-IM group which could imply that women were willing and able to continue DMPA-SC

Injection Problems.

A total of 235 DMPA-SC self-injections by 64 DMPA-SC subjects were attempted in this study. Of these, 64 were self-injections performed at the Baseline visit, in the clinic, under supervision, following the training session. A total of 171 self-injections were attempted at home, at the post-baseline time points (3 months, 6 months, and 9 months. Most of the 235 DMPA-SC self-injections were completed without a reported problem, but there were 33 separate reports of problems occurring in 20 of the 64 DMPA-SC subjects. The incidence of injection problems was low (6% of subjects) at the baseline Visit, when the self-injection was done under supervision of the healthcare professional. It was higher at the first self-injection at Month 3 (21% of subjects), but declined for the subsequent self-injections (9% at 6 months; 8% at 9 months). The most commonly reported injection problem in this study was an injection system issue, reported by 14 of the 20 subjects (70%) who reported injection problems. One issue encountered by these subjects was difficulty with the attachment of the needle to the body of the prefilled syringe.

The other self-injection problem was difficulty expelling the suspension through the 26-gauge needle that was supplied with the prefilled syringe.

There were 3 instances where a subject attempting self-injection encountered a problem that led them to return to the clinic in order to have the injection performed by the healthcare professional: (i) Subject SC050 returned to clinic for assistance with self-injection, but at the clinic was given an injection of DMPA-IM in error and the subject was discontinued from the study at Month 3 due to this dosing error (protocol deviation). (ii) Subjects SC045 and SC054 also experienced difficulty at

home and returned to clinic for assistance, where they successfully self-injected DMPA-SC under supervision.

Table 7. Number of DMPA-SC Self-injections Performed and Incidence of Reported Problems with Self-injection of DMPA-SC

DMPA-SC Subjects	No. of Self-Injections performed, n		No. of subjects reporting a 'problem' with the self-injection, n (%)
	Primary Efficacy Population (N = 58)	Safety Analysis Population (N = 64)*	Safety Analysis Population (N = 64)*
Baseline (at clinic)	58	64	4 (6%)
3 months (at home)	56	62	13 (21%)
6 months (at home)	53	58	5 (9%)
9 months (at home)	51	51	4 (8%)
Total 'at home' self-injections	160	171	20† (31%)

Sources: Tables 14.2.3.1, 14.2.3.2, 14.2.2.1, 16.2.5.1, 16.2.6.1
* Includes subjects who were discontinued due to study drug unavailable (expired); n = 6.
† Twenty (20) DMPA-SC subjects provided 33 separate reports of injection problems: 8/64 subjects (13%) reported injection site reaction; 6/64 subjects (9%) reported injection site skin changes; 14/64 subjects (22%) reported injection system problems; 5 of the 33 reports were recurrences of the same problem by the same subject (but occurring at a different time).

A number of self-injection issues occurred during the study including difficulty with the attachment of the needle to the body of the prefilled syringe and difficulty expelling the suspension through the 26-gauge needle. These issues should not occur with Sayana Press as the needle is already attached.

Timeliness of Self-Injections

138 of 171 (81%) self-injections occurred on the scheduled date, with zero deviation. Overall, the timing of self-injections ranged from 35 days early to 14 days late. Only 2 self-injections were given more than 1 week late, but none of the subjects in either treatment group became pregnant during the study. Most subjects self-injected on schedule.

Table 8. Timeliness of Self-Injection Attempts by Subjects

	Total 'At Home Self-Injections' (N)	On Time (scheduled day; no deviation), n (%)	1 to 7 days Early, n (%)	>7 days Early, n (%)*	1 to 7 days Late, n (%)	>7 days Late, n (%)**
DMPA-SC at home self-injections	171†	138 (81%)	14 (8%)	4 (2%)	13 (8%)	2 (1%)

Sources: Table 16.2.5.1
† Two of the self-administration attempts were unsuccessful at home and the drug was actually self-administered under supervision in the clinic, but this table is intended to address the timeliness of a subject's attempt to perform her self-injection.
* The earliest self-injection was performed 35 days prior to the due date; the other early injections in this column were -21, -9, and -8, for a total of n = 4.
** The latest injection was 14 days after the due date; the only other late injection in this column was: +8, for a total of n = 2.

Satisfaction with Method

At the end of the study, 61 of 64 DMPA-SC subjects completed the end-of-study questionnaire. All 61 subjects in the DMPA-SC group who completed a questionnaire were positive about the training that they had received in self-injection, with 54 (88.5%) subjects agreeing that 'self-injection was easy', 5 (8.2%) were not sure and 2 (3.3%) subjects disagreed. Over 90% of subjects also agreed that they had been confident with the technique of self-injection and that they had received the correct dose of medication and that safe disposal of needles was not a problem. 28 subjects (45.9%) considered that the SC injection was less painful than the IM injection, with the same proportion of respondents being 'unsure' if SC injection was less painful (see table below).

Table 9. Agreement With Ease of Use With Method at End of Study

Statement (Responders, N)	Agreed n (%)	Not Sure n (%)	Disagreed n (%)
'Self-injection was easy' (N = 61)	54 (88.5)	5 (8.2)	2 (3.3)
'Confident received correct dose' (N = 60)	58 (96.7)	1 (1.7)	1 (1.7)
'Safe disposal of the needle and syringe was not a problem' (N = 61)	58 (96.7)	1 (1.7)	1 (1.7)
'Subcutaneous injection was less painful than intramuscular' (N = 61)	28 (45.9)	28 (45.9)	5 (8.2)

Source: Table 14.2.4.1
Abbreviations: N = Total number of subjects; n = Number of subjects.

Questionnaires regarding satisfaction with self-administration of DMPA-SC or clinic administration of DMPA-IM were completed by the 61 subjects in the SC group and 54 in the IM group for whom follow-up was available at exit. There was no significant difference in the proportion of subjects in each group who reported feeling either 'the same or better' on their chosen injectable preparation. Similar proportions of subjects in each group also agreed that overall, they were satisfied with their chosen injectable method, would recommend their treatment to a friend and would want to continue treatment by self-injection.

Table 10. Satisfaction With Method at End of Study

	DMPA-SC (N = 61)[a] n (%)[b]	DMPA-IM (N = 54)[a] n (%)[b]
'I feel same or better'	56 (94.9)	53 (98.1)
'I am extremely or somewhat satisfied'	56 (91.8)	53 (98.1)
'I would recommend this to a friend'(administered in clinic)	51 (85.0)	53 (100)
'I would recommend this to a friend'(self-administered)	57 (95.0)	-
'I want to continue this method'(administered in clinic)	50 (82.0)	45 (84.9)
'I want to continue this method'(self-administered)	54 (90.0)	-

Source: Table 14.2.4.2
Abbreviations: DMPA-IM = Depot medroxyprogesterone acetate administered intra-muscularly; DMPA-SC = Depot medroxyprogesterone acetate administered subcutaneously; N = Total number of subjects; n = Number of subjects.
a. Total number is the number of subjects who have exit questionnaire data.
b. The denominators of percentages are the numbers of subjects who gave answers to the corresponding questions.

Study A6791035

This was an open-label study of the ability of naïve subjects to correctly interpret the IFU and operate the Sayana® Press delivery system.

Primary Objective:
To assess the proportion of subjects who were able to successfully operate the delivery system on Visit 2 (Day 90) when relying on the Instructions for Use (IFU) provided.

Secondary Objectives:

a) To solicit descriptive information from subjects (directly and via the observers) regarding the ease of use of the Sayana® Press delivery system, in order to inform potential revisions to the IFU for the product;

b) To quantitatively determine the weight of suspension expelled from the Sayana® Press delivery system during the injection attempt.

Study participants

Normal healthy female volunteers aged 18 to 45 years (inclusive) who were able to read and comprehend French or Dutch. Subjects with prior training in the use of a syringe for the purpose of administering parenteral medications to humans (including self-injection) or animals were excluded, as were subjects who had any severe acute or chronic medical or psychiatric condition or laboratory

abnormality that may have increased the risk associated with study participation or could reasonably have precluded the subject from successfully operating the Sayana® Press delivery system.

The study population was chosen to be representative of women who might use DMPA-SC in the Uniject delivery system. Half of the women volunteers were randomised to receive a hands-on training demonstration at visit 1 whereas the remainder were randomised to receive no hands-on training, however all women were provided with the written IFU.

Method

Each participant was assessed after receiving training from a staff member and reading the IFU (for those in the 'trained' group) or after reading the IFU (for those in the 'untrained' group). The participants were told to follow the instructions and perform an injection into a rubber/foam injection trainer designed to simulate distinct layers of skin, subcutaneous fat and muscle.

The test sessions were led by an Observer/Moderator who conducted the session as laid out by the written Observer Assessment Tool (OAT) that was divided into segments corresponding to the individual steps in the IFU. The Observer recorded the participant's ability to perform each step and noted any errors made by the participant.

Endpoints

The primary endpoint was the Delivery System Success Rate (DSSR) which was calculated based on the data recorded in the OAT by the staff member who led the participant through the assessment and observed their performance. An overall success rate whose one-sided 95% lower confidence bound is greater than 80% will support a conclusion that the design of the delivery system, together with the accompanying IFU, are fit for purpose.

The secondary endpoints were: categorical responses to questions 2 to 5 on the PAT, comments provided by subjects as part of the PAT, time to perform each step as recorded by the observer to the nearest second, and weight of suspension expelled from the Sayana® Press delivery system following injection.
The time required to perform each step on the OAT was summarized and presented by visit and for each step.

Statistical Methods:

Assuming an underlying DSSR >91%, a sample size of approximately 120 randomized subjects would provide at least 90% power to conclude that the DSSR at Visit 2 (Day 90) for Sayana® Press exceeds the threshold value of 80%, evidenced by the one-sided 95% lower confidence bound exceeding 80%. This target sample size assumed that at least 80% of randomized subjects would contribute to the DSSR calculation at Visit 2 (Day 90).

Results

Subject Disposition and Demography:

A total of 120 subjects were assigned to the 2 groups (trained and untrained) equally (i.e., 60 subjects in each group).

All subjects in the study were female. The mean age was 32.4 years and 32.6 years for the trained group and untrained group, respectively. The majority of the subjects were White

Table S2. Demographic Characteristics

	Trained Group	Untrained Group
Number of subjects (females)	60	60
Hormonal status: premenopausal, n (%)	60 (100.0)	60 (100.0)
Age (years), n (%)		
18-25	13 (21.7)	12 (20.0)
26-35	26 (43.3)	26 (43.3)
36-45	21 (35.0)	22 (36.7)
Mean (SD)	32.4 (7.3)	32.6 (6.7)
Range	21-45	20-45
Race, n (%)		
White	54 (90.0)	55 (91.7)
Black	1 (1.7)	3 (5.0)
Other	5 (8.3)	2 (3.3)
Weight (kg)		
Mean (SD)	66.4 (12.4)	65.3 (15.4)
Range	43.4-111.0	45.0-117.0
Body mass index[a] (kg/m^2)		
Mean (SD)	24.3 (4.3)	24.1 (4.9)
Range	17.3-37.5	18.7-42.5
Height (cm)		
Mean (SD)	165.2 (6.1)	164.4 (6.9)
Range	153-181	149-180

Abbreviations: n = number of subjects, SD = standard deviation
a. Body mass index = weight/(height × 0.01)^2.

Results:

Primary

The one-sided 95% lower confidence bound for the trained group was >80% for both visits but this was not the case in the untrained group suggesting that training prior to operating the delivery system was important in helping subjects operate the delivery system successfully

Table 26. Study A6791035 – Summary of Delivery System Success Rate (DSSR)

Visit Day	Number of Subjects	Number of Success	Percent Success	One-sided 95% CI[a]
Trained Group				
Day 1	60	54	90.0%	(81.81%, 100%)
Day 90	60	58	96.7%	(90.42%, 100%)
Untrained Group				
Day 1	60	46	76.7%	(66.66%, 100%)
Day 90	60	53	88.3%	(79.81%, 100%)
All Subjects[b]				
Day 1	120	100	83.3%	(77.02%, 100%)
Day 90	120	111	92.5%	(87.54%, 100%)

a. Wilson method was used to calculate the 95% CI.
b. the results for all subjects reflects a population in which half are trained and half are not trained, which may or may not correspond to a real clinical situation.
CI = confidence interval; DSSR = delivery system success rate.
Source: Study A6791035 CSR Table 14.2.1.1.

Secondary

In the trained group, there was no difference between visits in the DSSR (CI contained 0: -2.42%, 15.75%). On the other hand, in the untrained group, prior experience was shown to be effective as reflected in the higher percent success at Visit 2 (CI did not contain 0: 1.24%, 22.09%).

Table 27. Study A6791035 - Summary and Analysis of Delivery System Success Rate for Visit Difference

Percent Success at Visit 1	Percent Success at Visit 2	Difference	95% CI[a]
Trained Group			
90.0%	96.7%	6.7%	(-2.42%, 15.75%)
Untrained Group			
76.7%	88.3%	11.7%	(1.24%, 22.09%)
All Subjects			
83.3%	92.5%	9.2%	(2.24%, 16.09%)

a. The asymptotic method was used to calculate the 95% CI for difference dependent proportions.
CI = confidence interval.

Problems Encountered During Injection Attempts

For most of the IFU steps assessed by the observer, there were no important differences in performance (i.e., numbers of errors) between the trained group and the untrained group. However, the step that requires the participant to 'activate' the Uniject delivery system appeared to have more errors in the untrained group,

Table 28. Study A6791035 - Success Rates for the Uniject Activation Step Based on OAT Data

	Participants Assessed (N)	Participants Unable to Active the Uniject (n)	% Successful [(N-n)/Nx100]
Trained Group – Day 1	58	2	96.6
Trained Group – Day 90	60	0	100.0
Untrained Group – Day 1	59	8	86.4
Untrained Group – Day 90	60	3	95.0

OAT = observer assessment tool; N = total number of subjects participated in study; n = number of subjects with measured characteristic.
Source: Study A6791035 CSR Table 14.2.3.

It was observed that approximately 36% of the subjects in both the groups (trained group: 37.5%, untrained group: 35.3%) faced 'noticeable difficulty' while trying to expel the medicine on Day 1. However, when the simulated injection was repeated on Day 90, the proportion of participants having difficulty expelling the drug was lower: trained group: 16.7%, untrained group: 22.8%.

Completeness of Injection – Weight of Suspension Expelled from Sayana Press

Generally, subjects in the trained group were able to expel more of the suspension from the Sayana® Press delivery system, compared to the untrained group. Visit-wise, all subjects were able to expel more of the suspension from the Sayana® Press delivery system at Visit 2,

There were 13 subjects who were listed as "expelling" <10 mg of the dose. However, this apparent "loss" may be attributed to small differences in weighing accuracy of the injector since the majority of these subjects (12/13 subjects) did not actually proceed to the injection step. A majority (10 subjects) stopped at Step 5 (activating the injector).

Study A6791035 is a usability study of the instruction for use (IFU) for Sayana Press and the subjects in the study did not at any time self-inject. The results suggest that women that received training prior to trying out the Uniject system were more likely to succeed on first attempt compared to the women who relied solely on the IFU. It would also appear that errors can occur during the use of the delivery system.

Relevant literature references (as considered by the applicant)
Apparently to the applicant there have been three studies reported in the literature that involved self-administration of DMPA-SC (104 mg every 3 months) by patients, either independently or under supervision at the clinic. DMPA-SC in the prefilled syringe was apparently used in the studies.

Beasley A, White K and Westhoff C (Contraception, 2014)

This study evaluated the feasibility, acceptability and continuation rates following self-administration of DMPA-SC for up to 1 year. In addition, trough MPA levels in women who self-injected at home and women who received their injections at the clinic. 137 women were enrolled in to the study out of which 91 were allocated to self-administration, and 90 were able to correctly self-administer DMPA-SC. Eighty-seven percent (87%) of the subjects completed follow-up. The continuation rate for DMPA use at 1 year was not different between the 2 groups: 71% for the self-administration group and 63% for the clinic group (p=0.47). Uninterrupted (perfect) DMPA use was 47% and 48% for the self-administration and clinic administration groups at 1 year (p=0.70), respectively, serum trough MPA levels in both groups were similar and all participants had therapeutic trough MPA levels.

Table 29. Beasley et al. Serum Trough MPA Levels at 12 Month Visit		
Serum MPA (pg/mL)	Clinic Injection by HCP	Self-Injection At Home
Median	641.0	640.8
Mean	686.2	695.8
Minimum	236.4	227.0
Maximum	1283.2	1519.5
HCP = health care professional; MPA = medroxy progesterone acetate; Source: Beasley et al (2014) Figure 2.		

Prabhakaran and Sweet (Contraception, 2012)

This prospective, single-arm, non-comparative study assessed the feasibility, continuation rates and patient satisfaction during a 1-year period of self-administration of DMPA-SC using prefilled syringes. The women were taught to self-inject DMPA-SC at the first visit and then supplied with an injection kit containing the subsequent doses for self-administration. DMPA continuation at 1 year was 74% [95% CI; 62%–86%]. Of 150 possible self-injections, documentation was collected for 124 injections. Of these, 121 (98%) were independent self-injections, and 3 (2%) were supervised self-injections. None of the patients requested to have clinic staff inject the subcutaneous formulation.

By Injection 4, 26% (n=13) of subjects either discontinued DMPA-SC or were lost to follow-up. Two (2) subjects discontinued DMPA-SC due to side effects, 1 continued DMPA but discontinued self-administration due to the fear of self-injection, 1 desired pregnancy, and 12 were lost to follow-up.

Following the 3 cycles of self-injections, 87% reported self-injection to be ‘very easy’ or ‘easy,’ whereas 7% found it ‘very difficult’ or ‘difficult’; 3% reported ‘no opinion’ and 3% did not provide an answer.

The most frequent complaint from participants related to the needle used with the prefilled syringe, with 17% reporting that they encountered difficulty getting the drug suspension to flow through the needle.

Williams et al (Contraception, 2013)

This study reported a planned secondary analysis of a randomised controlled trial comparing pain between DMPA-IM and DMPA-SC among adolescent and young adult users of DMPA. 55 subjects were randomised to receive DMPA-IM or DMPA-SC as their first study injection. The participants then received the alternate formulation at the 3-Month follow-up visit (cross-over). At the 9-month visit the participant could elect to learn and perform self-administration of DMPA-SC in the clinic, if desired and the study explored participants attitudes towards home self-administration but none self-administered at home as all self-injections were done in clinic. Proficiency level for overall ability to self-administer DMPA-SC was as follows: 42.1% (8/19) ‘independent’, 21.1% (4/19) ‘independent after repeat education’, 21.1% (4/19) ‘with assistance’ and 15.8% (3/19) ‘not competent to self-administer’. The participants were then questioned in a structured interview

Conclusion

The available clinical and usability data suggest that self-injection of Sayana Press could be feasible and effective as a method for contraception, provided that physicians exercise due care in selecting and training appropriate patients for this option. Under no circumstances should a woman who is either not motivated to self-inject, or not capable of self-injecting, be compelled to do so in order to use the method.

The efficacy of DMPC-SC has been previously demonstrated and is not the subject of this variation application.

The MAH provides data from four studies to support the application to allow self-administration of Sayana Press at home unsupervised**;**

- Studies 267 and 269 (both demonstrated the efficacy of DMPA-SC (the option to self-administer at home was available to a proportion of subjects because of a study protocol amendment). Home self-injection was performed at least once by 15.6% (278/1787) of the subjects in these studies [10% (73/722) Study 267 and 19.2% (205/1065) in Study 269]. Self-injection was obtained from 6,279 woman-cycles however most of the women who self-administered did so in the clinic and approximate to 5,442 woman cycles. The experience with at-home self-injection totalled 837 woman-cycles and it would appear that nearly all the subjects who self-injected at home did so for only one injection. The end of treatment questionnaire (EOTQ) assessed subjects' satisfaction with the self-injection process. Even though the questionnaires were apparently not validated, the results suggest that most subjects who received training prior to self-injecting were happy with the training received and able to self-inject using the instructions provided.

- An independent study which compared the self-injection of DMPA-SC in prefilled syringes with administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic (Study GA67815). 128 subjects participated in this study with 64 randomised to DMPA-SC and 64 to DMPA-IM, the results of the study showed that the 12 month discontinuation rate was similar in both groups with a few more subjects lost to follow up in the DMPA-IM group. A total of 171 self-injections were independently attempted, at the post-baseline time-points (3 months, 6 months, 9 months) for the subjects in the DMPA-S group.
- A usability study assessing the ability of representative users to correctly operate the Uniject injection delivery system (the device Sayana Press is contained in) according to the instructions provided (Study A6791035). The results suggest that women that received training prior to trying out the Uniject system were more likely to succeed compared to the women who relied solely on the IFU**.** It is however crucial to note that the participants in this study did not self-inject. It would also appear that errors can occur during the use of the delivery system.

Overall, it would appear that majority of women included in the studies were able to self-inject when trained appropriately as indicated by the results from studies 267, 269 and GA67815 although subjects in studies 267 and 269 self-injected only on one occasion. In addition, the results from study GA67815 suggest that women can self-inject on repeated occasions on schedule even though the numbers included in the study are quite small. The results from the literature references also suggest that women are able to self-inject.

The only drawback with the data provided is that Sayana Press (the subject of this variation) was not utilised in any of the studies. However, the results from the usability study suggest that with prior and adequate training women are able to use the Uniject system but using the instructions for use (IFU) alone did not appear to be adequate in preparing women on how to use the system.

III.3.3 Clinical safety

The safety profile of DMPA-SC injection was demonstrated in three Phase 3 studies Studies 267 and 269 (contraceptive efficacy studies) and Study 267BMD small 3-year BMD safety study

To support this variation application, the company has provided the summaries of the safety findings from Study 267, Study 269 and Study GA67815.

Patient exposure

1060 subjects received at least one dose of DMPA-SC in study 269 out of which 856 completed 12 months of treatment (4 injections). 656 of the subjects self-injected and home self-injection was performed by 205 of the subjects

In study 267, 720 subjects received at least 1 dose of DMPA-SC out of which 489 completed 12 months of treatment. 384 of the subjects self-injected with 73 receiving 1 home self-injection.

In study GA67815, 64 subjects performed self-injection of DMPA-SC at the baseline visit, overall 235 DMPA-SC injections were performed.

Adverse events
Study 269

At least 1 adverse event was reported by 46.5% (493/1060) of the subjects. The most common adverse events (occurring in at least 5% of subjects) were amenorrhea not otherwise specified (NOS) (8.1%, 86/1060), intermenstrual bleeding (7.9%, 84/1060), and headache NOS (5.0%, 53/1060). Vaginal haemorrhage was reported in 4.6% (49/1060) of the subjects and increased weight was reported in 4.3% (46/1060) of the subjects. Depression (combined preferred terms [PT's], depression not elsewhere classified [NEC] and depressed mood) was reported as an adverse event in only 1.2% (13/1060) of the subjects.

There were 17 injection site reaction events **(**1.6% of the subjects) occurred in this study including injection site atrophy, injection site induration, injection site pain, injection site reaction NOS, and lipodystrophy.

Fifty-one (51) adverse events occurred on or after self-injection and were reported in 38 subjects**, o**f these, 8 adverse events in 7 subjects were considered treatment-related. One occurred (atrophy at site of injection anterior thigh) occurred on or within 7 days after self-injection

Thirty-two percent (31.7%, 336/1060) of the subjects were deemed by the investigator to have at least 1 adverse event related to the study drug. Adverse events leading to discontinuation were reported in 5.3% 56/1060) of the subjects; the most common adverse event leading to discontinuation was intermenstrual bleeding (0.9%, 10/1060). Serious adverse events were reported in 1.4% (15/1060) of the subjects.

Table 31. Study 269 - Treatment-Related Adverse Events with Incidence of ≥1% (ITT Population)

System/Organ Class (MedDRA ver. 2.3)	DMPA-SC N=1065	
	n	%
Total Subjects Reported	1060†	100
General Disorders and Administration Site Conditions		
Hemorrhage NOS	12	1.1
Investigations		
Weight Increased	45	4.2
Nervous System Disorders		
Headache NOS	26	2.5
Psychiatric Disorders		
Libido Decreased	16	1.5
Reproductive System and Breast Disorders		
Amenorrhea NOS	85	8
Intermenstrual Bleeding	84	7.9
Menometrorrhagia	33	3.1
Menorrhagia	23	2.2
Menstruation Irregular	19	1.8
Uterine Hemorrhage	14	1.3
Vaginal Hemorrhage	49	4.6
Skin and Subcutaneous Tissue Disorders		
Acne NOS	16	1.5

DMPA-SC = depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; MedDRA = Medical Dictionary for Regulatory Activities; N = total number of subjects participated in study; NOS = Not otherwise specified.
† No follow-up safety data were available for 5 subjects
Source: Study 269 CSR Table 13.

Study 267

At least 1 adverse event was reported by 70.7% (509/720) of the subjects. The most common adverse events (i.e., occurring in ≥5% of subjects) were headache (11.8%, 85/720), weight increased (8.5%, 61/720), intermenstrual bleeding (6.4%, 46/720), amenorrhea (5.8%, 42/720), and libido decreased (5.1%, 37/720). Depression (combined PTs depression NEC and depression aggravated) was reported as an adverse event in 3.5% (25/720) of the subjects.

Injection site reaction was also a common adverse event. A total of 94 injection site reaction adverse events were reported by 9.7% (70/720) of the subjects (some subjects had multiple occurrences of the same adverse event and/or had more than 1 type of injection site adverse event). Most of the events were of mild intensity. 50.0%, 47/94) of the injection site events occurred at the first (enrolment) visit; 74 of 94 events occurred after in-office injection by a professional (78.7% of the events; 4.2% of the 1770 clinic-administered injections in the study); 19 of the 94 events occurred after in-office self-injection (20.2% of the events; 3.4% of the 562 clinic-based self-injections); and 1 of the 94 events occurred after a home self-injection (1.1% of the 94 events; 1.4% of the home self-injections). The location for the majority of the injection site events was the thigh (60.6%, 57/94 events); the remainder were in the abdomen (37.2%, 35/94 events) or were reported as injection site unknown (2.1%, 2/94 events). The most common injection site reactions were injection site pain (2.6%, 19/720 subjects), injection site granuloma (1.9%, 14/720 subjects), and injection site atrophy (1.3%, 9/720 subjects).

A total of 14 treatment-related adverse events were reported by 9 subjects on or after starting self-injections: headache NOS (2 occurrences in 2 subjects); acne NOS, breast pain, mood alteration NOS, vaginitis, pain in limb, menstrual disorder NOS, intermenstrual bleeding, dizziness (excluding. vertigo), proteinuria present, breast neoplasm NOS, dysmenorrhea and depression NEC.

Adverse events leading to discontinuation were reported in 13.9% (100/720) of the subjects; the most common adverse event leading to discontinuation was weight gain (2.5%, 18/720)

Table 33. Study 267 - Treatment-Related Adverse Events with Incidence of ≥1%

System/Organ Class (MedDRA ver. 2.3)	DMPA-SC N=722	
	n	%
Total Subjects Reported	720†	100
Gastrointestinal		
Abdominal Distension	11	1.5
Abdominal Pain NOS	14	1.9
Nausea	8	1.1
General Disorders and Administration Site Conditions		
Fatigue	20	2.8
Injection Site Atrophy	9	1.3
Injection Site Granuloma	12	1.7
Injection Site Pain	19	2.6
Investigations		
Weight Increased	59	8.2
Metabolism and Nutrition Disorders		
Appetite Increased NOS	7	1
Nervous System Disorders		
Dizziness (Excluding Vertigo)	10	1.4
Headache NOS	44	6.1
Insomnia NEC	8	1.1
Psychiatric Disorders		
Anorgasmia	7	1
Depression NEC	12	1.7
Irritability	11	1.5
Libido Decreased	30	4.2
Mood Alteration NOS	8	1.1
Mood Swings	10	1.4
Reproductive System and Breast Disorders		
Amenorrhea NOS	42	5.8
Breast Pain	8	1.1
Breast Tenderness	10	1.4
Intermenstrual Bleeding	44	6.1
Menorrhagia	9	1.3
Vaginal Hemorrhage	19	2.6
Skin and Subcutaneous Tissue Disorders		
Acne NOS	27	3.8
Vascular Disorders		
Hot Flushes NOS	7	1

DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; ITT = intent-to-treat; N = total number of subjects participated in study; NEC: Not Elsewhere Classified; NOS = Not otherwise specified; MedDRA = Medical Dictionary for Regulatory Activities.
† No follow-up safety data were available for 2 subjects.
Source: Study 267 CSR Table 12.

Study GA67815

21 out of 64 DMPA-SC subjects (32.8%) reported a total of 41 adverse events. In the DMPA-IM group, there was a lower incidence of adverse events reported: 12 subjects (18.8%) reported a total of 15 adverse events.

For treatment-related adverse events, 15 out of 64 DMPA-SC subjects (23.4%) reported a total of 30 adverse events. In the DMPA-IM group, there was a lower incidence of adverse events reported: 6 subjects (9.4%) reported a total of 9 adverse events.

Overall, adverse events were reported more frequently in the DMPA-SC self-injection group in Study GA67815 compared with the DMPA-IM clinic group. The most notable differences in the reported AEs were for injection site reactions (14 reports for DMPA-SC and none for the DMPA-IM group.

Table 35. Study GA67815 – Treatment-Related Treatment Emergent Adverse Events

TE AE (treatment-related)	DMPA-SC (N=64)		DMPA-IM (N=64)	
	n	%	n	%
Gastrointestinal Disorders	4	6.3	1	1.6
Abdominal distension	0		1	1.6
Abdominal mass	1	1.6	0	
Abdominal pain	1	1.6	0	
Diarrhoea	1	1.6	0	
Gastritis	0		1	1.6
Nausea	2	3.1	0	
Vomiting	1	1.6	0	
General Disorders and Administration Site Conditions	10	15.6	0	
Feeling abnormal	1	1.6	0	
Injection site induration	1	1.6	0	
Injection site mass	1	1.6	0	
Injection site pain	4	6.3	0	
Injection site reaction	7	10.9	0	
Injection site vesicles	1	1.6	0	
Infections and Infestations	0		2	3.1
Candida infection	0		2	3.1
Investigations	0		1	1.6
Weight increased	0		1	1.6
Musculoskeletal and Connective Tissue Disorders	1	1.6	0	
Pain in extremity	1	1.6	0	
Nervous System Disorders	1	1.6	0	
Tremor	1	1.6	0	
Psychiatric Disorders	2	3.1	1	1.6
Emotional disorder	2	3.1	0	
Irritability	0		1	1.6
Mood swings	0		1	1.6
Reproductive System and Breast Disorders	3	4.7	1	1.6
Breast tenderness	2	3.1	1	1.6
Premenstrual cramps	1	1.6	0	
Vaginal discharge	1	1.6	0	
Skin and Subcutaneous Tissue Disorders	0		1	1.6
Skin disorder	0		1	1.6
Vascular Disorders	1	1.6	0	
Hot flush	1	1.6	0	
Total Preferred Term Events	30		9	

Abbreviations: DMPA-SC = Depot medroxyprogesterone acetate sub cutaneous; DMPA-IM = Depot medroxyprogesterone acetate Intramuscular; ITT = intent-to-treat; N = total number of subjects participated in study; NOS = Not otherwise specified.
Source: Study GA67815 CSR Table 14.3.2.2.6.

Study 267BMD,

Was a 3-year Phase 3 study that randomised women to DMPA-SC (clinic injection) or DMPA-IM (clinic injection) and has been included by the applicant to explore the possibility that there is difference in the incidence of adverse events between DMPA-SC and DMPA-IM in view of the safety results observed in the other studies. For this study also injection site reactions, pain and atrophy occurred in approximately 6.% of the subjects.

Table 36. Study 839-FEH-0012-267BMD (Study 267BMD) – Adverse Events Reported by 1% or More Subjects in Either Group

	DMPA-SC		DMPA-IM	
	n	%	n	%
Total Subjects Reported	263†	100	266†	100
Subjects with at least 1 adverse event	214	81.4	207	77.8
Gastrointestinal Disorders				
Abdominal Distension	6	2.3	6	2.3
Abdominal Pain NOS	6	2.3	16	6
Diarrhea NOS	2	0.8	8	3
Dyspepsia	3	1.1	8	3
Flatulence	3	1.1	2	0.8
Nausea	15	5.7	24	9
Oral Pain	3	1.1	1	0.4
Sore Throat NOS	6	2.3	9	3.4
Vomiting NOS	0	0	7	2.6
General Disorders and Administration Site Conditions				
Chest Pain NEC	3	1.1	1	0.4
Fatigue	9	3.4	4	1.5
Influenza-like Illness	2	0.8	3	1.1
Injection Site Atrophy	7	2.7	0	0
Injection Site Pain	4	1.5	0	0
Injection Site Reaction NOS	6	2.3	0	0
Pyrexia	3	1.1	4	1.5
Immune System Disorders				
Hypersensitivity NOS	10	3.8	2	0.8
Infections and Infestations				
Bronchitis NOS	10	3.8	10	3.8
Ear Infection NOS	3	1.1	2	0.8
Fungal Infection NOS	3	1.1	4	1.5
Helminthic Infection NOS	2	0.8	4	1.5
Herpes Simplex	3	1.1	3	1.1
Influenza	7	2.7	8	3
Kidney Infection NOS	3	1.1	0	0
Nasopharyngitis	25	9.5	34	12.8
Pharyngitis Streptococcal	11	4.2	7	2.6
Sinusitis NOS	19	7.2	14	5.3
Tonsillitis NOS	1	0.4	5	1.9
Upper Respiratory Tract Infection NOS	13	4.9	9	3.4
Urinary Tract Infection NOS	20	7.6	6	2.3
Vaginal Candidiasis	5	1.9	2	0.8
Vaginitis	11	4.2	11	4.1
Vaginitis Bacterial NOS	9	3.4	7	2.6
Vaginosis Fungal NOS	4	1.5	1	0.4

Serious adverse events and deaths

Study 269

Serious adverse events were reported in 1.4% (15/1060) of the subjects.

Study 267

Serious adverse events occurred in 1.3% (9/720) of the subjects. One (1) subject died during the study period as the result of injuries sustained in a motor vehicle accident; unrelated to the study drug.

Laboratory findings

Study 269 and 267

No noteworthy changes were found over the study period in the hematology, chemistry, or urinalysis laboratory assays. Blood pressure (both systolic and diastolic) did not change significantly over the study period.

Safety in special populations
N/A

Assessor's overall conclusion on safety
The safety of DMPA-SC has previously been characterised are there are no particular issues. The occurrence of local injection site reaction has previously been noted and in study A67815 the incidence was approximately 10%. In terms of self-injection, there were no adverse events of note reported.

Product information

III.4.1 Summary of Product Characteristics(SmPC)

Suitable changes have been made to the SmPC, based on the points for clarification made by the member states.

III.4.2 Package leaflet (PIL) and user test

Suitable changes have been made to the PIL, based on the points for clarification made by the member states.

III.4.3 Readability user testing

Suitable results from user testing of the revised PIL have been provided such that they show that users understand the PIL and can act on the information that it contains.

III.4.4 Labelling

Not applicable

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

The MAH has submitted a type II variation to introduce the option of home self-injection by patients in section 4.2 of the summary of product characteristics (SmPC) and the PIL. In support of this application, the MAH provides data from four studies (267, 269, GA67815 and A6791035).

Studies 267 and 269 (both have been used previously to demonstrate the efficacy of DMPA-SC. However, the option to self-administer at home was available to a proportion of subjects due to a study protocol amendment). In these two studies home self-injection was performed at least once by 15.6% (278/1787) of subjects. Self-injection was obtained from 6,279 woman-cycles however most of the women who self-administered did so in the clinic and approximate to 5,442 woman cycles. The experience with at-home self-injection totalled 837 woman-cycles and it would appear that nearly all the subjects who self-injected at home did so for only one injection.

Study (GA67815) which compared self-injection of DMPA-SC in prefilled syringes with administration of DMPA-IM (depot medroxyprogesterone acetate, intramuscular) by a healthcare professional in the clinic 128 subjects participated in this study with 64 randomised to DMPA-SC and 64 to DMPA-IM, the results of the study showed that in the DMPA-SC group, the discontinuation rate was 13.8% as compared to the DMPA-IM group were the rate of discontinuation was 25% attributable to 10 subjects being lost to follow up in this group). A total of 171 self-injections were independently attempted, at the post-baseline time-points (3 months, 6 months, 9 months) for the

subjects in the DMPA-S group. This small study provides the bulk of evidence that women are able to self-inject repeatedly on schedule.

Unfortunately Sayana Press which utilises the Uniject system (the subject of this variation) was not used in any of the studies. However, the results of a usability study (A6791035 which assessed the ability of users to correctly operate the Uniject injection delivery suggest that with prior and adequate training women are able to use the Uniject system but using the instructions for use (IFU) alone did not appear to be adequate in preparing women on how to use the system.

Although it would appear that women are able to self-inject when trained appropriately as indicated by the results from studies 267, 269 and GA67815 and in addition, the results from study GA67815 suggest that women can self-inject on repeated occasions on schedule. Unfortunately Sayana Press which utilises the Uniject system and comes with a needle already attached was not used in any of the studies apart from the usability study in which participants did not actually self-inject but the results of the usability study provides some evidence that women are able to inject with adequate training and use of the IFU. Therefore it will be necessary for the MAH to adequately justify that women will be able to self-inject on themselves with the Uniject system. In addition the small numbers of women who have actually self-injected in clinical studies to date is a cause for concern and the MAH should adequately justify that the results obtained will translate into real-life situations.

In terms of safety, the only significant issue to note is the occurrence of local injection reactions with the administration of DMPA-SC.

The benefit risk for Sayana Press remains unchanged and proposal to allow women to self-administer could be approvable if the MAH provides a satisfactory response to the points for clarification and reassurance is provided that women will be adequately trained and counselled.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Potential serious risks to public health

None

V.2 Points for clarification

1. Given that Sayana Press was not used in any of the clinical studies and women did not self-inject in the usability study A6791035, the MAH should adequately justify that women will be able to self-inject on themselves with the Uniject system.

2. Only a small number of women have self-injected on multiple occasions to date in clinical studies. The MAH should adequately justify that the results obtained in these studies will translate into real-life situations.

3. The results of the usability study A6791035 suggest that a certain amount of training is needed and reading the IFU alone might not be sufficient for women. The MAH should provide a detailed discussion of the training proposed for women.

4. It is proposed that women self-inject on a regular basis. The MAH should provide a detailed discussion on how women will be followed-up to ensure they don't miss injections. It should also be clarified whether women will have regular medical check-ups and how frequently this will be.

5. An in-depth discussion should be provided on the disposal of Sayana Press after self-administration. In addition the product information should also be updated.

ASSESSMENT OF THE RESPONSES TO THE MEMBER STATE(S) REQUEST FOR SUPPLEMENTARY INFORMATION

Potential serious risks to public health

None

Points for clarification

1. **Given that Sayana Press was not used in any of the clinical studies and women did not self-inject in the usability study A6791035, the MAH should adequately justify that women will be able to self-inject on themselves with the Uniject system.**

MAH's response

This was the central issue that the MAH posed to MHRA when we sought Scientific Advice in September 2012 in order to take a decision about progressing this project. That is, the purpose of the meeting was to determine whether or not the results of the independent Cameron study (Study GA67815), which used only the DMPA-SC pre-filled syringe (PFS), plus the results of the proposed A6791035 device usability study (using DMPA-SC in Uniject) could, together, serve as adequate primary evidence for approval of self-injection labeling for DMPA-SC in Uniject (Sayana Press). At that meeting it was agreed that this approach would be acceptable (as this replicated the original basis of registration of the Sayana Press injector for Healthcare Professionals) and that no additional clinical study would be required at the time of submission if certain required modifications to the proposed approach were implemented. Specifically:

1. While MHRA accepted that the independently-conducted Cameron study could provide acceptable primary evidence that women could successfully self-inject DMPA-SC unsupervised, at home, MHRA stated that the published report of the Cameron study contained insufficient detail regarding the safety of the study participants. MHRA requested that the MAH work with the study's Principal Investigators in order to collect, from patient records, full details of the safety events that occurred during the study and to prepare a final clinical study report (CSR) that would be suitable for in-depth regulatory review. This requirement was accomplished and the CSR for the Cameron study has been included in the submission.

2. In addition, MHRA stated that the originally proposed design for the A6791035 device usability study was inadequate because it only assessed the participants on a single occasion (Day 1), which would be the day that the 'trained' participants would receive their training on the device. While single assessment is standard practice for device usability studies, it was recognized that DMPA-SC is somewhat unusual in that it is administered at a very widely spaced interval (q3 months) and, therefore, it would be important to demonstrate that women retain the ability to correctly operate the device after 3 months had passed. The MAH agreed to incorporate a follow-up testing visit (Day 90) and to re-assess participants at this visit with no additional (i.e., refresher) training to be provided at that visit.

The results of the Cameron study demonstrated that most participants were able to satisfactorily perform subcutaneous self-injection with DMPA-SC at home, over a 1-year period, when they were instructed and knew how to operate the particular injection device they had been given – which in this case was a pre-filled syringe. However, that clinical experience cannot be immediately extrapolated to DMPA-SC in Uniject because the operation of the Uniject device is different to that of a syringe. While all other aspects of the Cameron study are translatable to women who will self-inject with DMPA-SC in Uniject (e.g., general willingness and ability to perform a subcutaneous self-injection; ability to inject on a prescribed schedule; the safety and efficacy profile of subcutaneous DMPA 104 mg), it was agreed that the MAH must provide evidence that women can correctly interpret the Instructions for Use (IFU) for the Uniject, and, as a result, can correctly operate the device from a mechanical perspective, on the day of training and again, at the 90-day follow-up point. If it can be shown that most women can correctly operate the Uniject device, as they were able to correctly operate the PFS in the Cameron study, then the one key difference between the Cameron study and an

otherwise identical study using DMPA-SC in Uniject will have been bridged since the results of the Cameron study are based on the fact that the women could mechanically operate the injection device.

Providing this linkage is very important, in our view, because the fact that women were able to independently operate a PFS 90 days after training, as they did in the Cameron study, does not necessarily mean that they can do the same with Uniject. The operation of a PFS is essentially self-evident. The patient sees the needle and the plunger and intuitively knows that the needle must be inserted into the skin and, even if she has never personally used a syringe, she will have seen one used and it will be obvious that the plunger must be depressed to deliver the medicine. Furthermore, these points will be just as obvious on Day 90 as they were on Day 1. The one critical requirement of the DMPA-SC PFS, however, is the need to depress the plunger slowly because any attempt to rapidly (i.e., with increased force) deliver a solid-in-liquid suspension (such as DMPA-SC) will increase the viscosity of the suspension and make it difficult to deliver through a fine needle; pure solutions do not have this non-Newtonian property, but solid-in-liquid suspensions do have it. Several participants in the Cameron study did report that the syringe required considerable force to inject and they may not have realized that increasing the force on the plunger would only worsen the problem. Although not explicitly reported to have occurred in the Cameron study, excessive force on the plunger can cause the needle hub to detach from the syringe body since it has a friction-fit interface.

In contrast, the Uniject device might be less intuitive than the PFS, at least on the surface, and it is therefore necessary to assess the ability of typical users to successfully operate the device, both initially and after a time gap. Like the PFS, the needle end of the Uniject is self-evident and the need to insert the needle into the skin will be obvious to the patient. However, instead of a plunger, there is a bubble/reservoir that must be pinched in order to expel the medicine. This simple action requires only thumb and forefinger to perform while the PFS requires a somewhat more complex action: the index and middle fingers must hold the syringe body while the thumb simultaneously depresses the plunger.

There are two particular issues for Uniject that users must consider in order to successfully deliver the dose:

1. The DMPA-SC suspension in the Uniject is identical to the suspension used in the PFS, so the injection must be done slowly over 5-7 seconds and excess pressure will decrease the flow of the suspension through the needle, with either device. The problem could, in theory, be slightly less acute with the Uniject since the needle diameter is slightly larger, which decreases pressure, and because a bubble held between two fingers does not allow the patient to develop quite the same mechanical advantage as she would get with a thumb on a plunger, which also lessens the applied force a little. In the A6791035 usability study, >95% of subjects gave Uniject an overall rating of 'somewhat easy' or 'very easy' to use. However, when questioned about specific steps in the procedure, 20% to 30% (depending on cohort and visit) reported that they felt, subjectively, that they had at least some degree of difficulty squeezing the bubble, including comments that they had to squeeze it firmly or repeatedly in order to ensure that the drug was fully delivered. In fact, despite their expressed concerns on the survey, the participants were actually quite successful in delivering the full dose: the median weight of drug delivered was at or above the nominal weight of the prescribed dose (0.65 mL = 0.677 mg) for both trained and untrained participants, at both the Day 1 and the Day 90 Visits. It appears that the subjects' expressed concern was a reflection of their diligence and their initial unfamiliarity with the injector.

2. The Uniject does have one feature that clearly sets it apart from the PFS: it must be mechanically 'activated' in order to operate. With the needle still capped, the user must hold the two ends of the device and push them together along the central axis. When a 'click' is felt (or heard), the activation step is complete: the proximal end of the needle has punctured the internal septum and is now in contact with the suspension in the bubble reservoir. This step is very simple to perform when you know what to do, but it is not at all self-evident how one would activate the device nor even that activation should be needed; the user must be instructed on the need for activation and how to perform the step through the IFU or the training. In Study A6791035, most of the participants who did not receive any hands-on training (they had the IFU available but with no

demonstration, practice or opportunity to ask questions) were able to perform this step successfully (86.4% on Day 1; 95.0% on Day 90). The trained cohort was provided with the IFU plus a demonstration and an opportunity to practice and ask clarifying questions; in this cohort the activation step was performed successfully by 96.6% on Day 1 and by 100% on Day 90. While the differences between the trained and untrained cohorts fell just shy of statistical significance, it is still reasonable to recommend that women who intend to self-inject with DMPA-SC in Uniject should be given a hands-on demonstration of the device, have clarifying questions answered, and have an opportunity to perform the technique under supervision. Given the simplicity of the device, such training should be relatively quick to accomplish and should not be overly burdensome to the clinic staff.

The Cameron study (GA67815) showed that women who are willing to self-inject and have been instructed in the operation of the subcutaneous injection device can successfully self-administer DMPA-SC at home using the device for which they have received instruction (IFU, demonstration, etc.). In order to reasonably conclude that women can successfully self-inject DMPA-SC using an alternative subcutaneous injection device, and to conclude that the clinical outcomes reported in the Cameron study can reasonably be extrapolated to another subcutaneous injection device, we need evidence showing that the alternative device has essentially similar usability to the PFS. More specifically, we need evidence that the alternative device is 'usable' by a very high proportion of women in the same way that the PFS is usable by a very high proportion of women, which then puts the alternative device on a par with the device used in the Cameron study since all other factors remain constant: drug, dose, formulation, site of injection, timing of injections and so forth. Ideally, we would like to be able to directly compare formal usability data for the PFS and for the Uniject (% successful simulated injections based on use error analysis), but, because the Sayana PFS is a common syringe and not a new device, formal usability testing and use error analysis were not required. While the Cameron study did not collect usability data per se on the PFS, Table 16.2.6.1 (GA67815 CSR) shows that 4 (of 64) subjects had difficulty expelling the suspension from the PFS, which can occur since the plunger can generate quite high applied force against the suspension, increasing viscosity. Another common use error with the PFS is the needle hub becoming disconnected from the syringe body, probably again related to the higher pressures that are possible with a syringe plunger. Therefore, even in the absence of formal usability testing and use error analysis for the PFS, we believe it is reasonable to expect that the usability of the PFS is very good and one could anticipate that the PFS used in the Cameron study would generate overall scores at or above the 95% level in a formal usability study, similar to the scores achieved by the Uniject device.

Therefore, the MAH believes that study A6791035 shows that most women are able to successfully use the Uniject device, when given appropriate instruction, and that this demonstration establishes the Uniject device as having essentially similar usability to the PFS that was deployed in the Cameron study, from the perspective of the patient. Hence, if the two devices are similar in this respect, and if all other factors are not different (drug, dose, formulation, route of administration, site of injection, timing of injections, etc.), then we believe that the clinical experience from the Cameron study (GA67815) is relevant and translatable to the clinical experience that is likely to occur if healthcare professionals are afforded the opportunity to select certain of their Sayana Press patients for self-injection, when they and the patient decide that self-injection is a suitable option for the patient. Should any woman experience significant difficulty in performing their initial injections in the home setting, the PIL is explicit in instructing them to return to their Healthcare professional for advice. This would give the opportunity for re-training or re-assessment regarding suitability for continuing with self-injection.

Assessment of response

The applicant considers that the results of Study GA67815) provide evidence that women are able to successfully self-inject DMPA-SC with the pre-filled syringe (PFS) unsupervised and on repeated occasions at home and these results can be extrapolated to the Uniject system since the results of the usability study for the Uniject system (A6791035) showed that approximately 86% of the women who did not receive hands on training were able to follow the instructions for use and correctly inject on day 1 and on day 90, 95% of the women were able to follow the instructions for use.

This is considered acceptable since the objectives of the usability study were met. Even though the ladies did not self-inject it appears that they were able to follow instructions adequately (with or without training). It is reasonable to assume that if women understand the instructions, have been adequately trained and are willing to self-inject they are likely to succeed. If they encounter problems at home there are clear instructions in the PIL.

Overall, taking into consideration that the DMPA-SC suspension in the Uniject is identical to the suspension used in the PFS and the results of the usability study show that women are to follow instructions after training the proposal by the MAH for women to self-inject using Sayana Press is therefore considered acceptable.

Point resolved

2. Only a small number of women have self-injected on multiple occasions to date in clinical studies. The MAH should adequately justify that the results obtained in these studies will translate into real-life situations.

MAH's response
This is, of course, the essential question for any drug product seeking approval for use in the general population – will the results of carefully controlled clinical trials, large or small, accurately predict what will happen in practice? There are several aspects to consider:

1. Study Design: Typically, trial participants must fulfil a long list of inclusion/exclusion criteria, some of which are medically based. Patients may be excluded on the basis of factors related to concurrent medical conditions, baseline laboratory values, physical or psychological status and other factors. Some of these trial restrictions may become part of clinical practice regarding the use of the drug, but many will not, which will create differences between the study population and the general patient population who will use the drug product. Another study design parameter is the duration of study: will a 1- or 2-year study predict the effects that will be seen after a patient has taken a drug for 11 years? These can be characterized as objective or measurable parameters that could create differences in outcomes between trial participants and real patients.

2. Study Participants: Other differences will not be so easily measurable, particularly those related to behaviour and motivation on the part of the participants, which are important considerations for a topic like self-administration since it has a strong behavioural component. Trial participants typically were willing to give up their personal time for study-required testing and for additional clinic appointments that they would not otherwise have needed. Many patients in the general population are not willing to do this, which means that they are different to those who are willing to adhere to the demands of an investigational study, but in ways that are hard to quantify. As an example, one could imagine that these undefined behavioural differences could lead to different rates of adherence to therapy between trial participants and other patients, which could lead to differences in efficacy or safety between the clinical trial results and 'real life' outcomes.

3. Study Investigators: Study subjects are managed by experienced clinical study investigators. There are many very experienced physicians who do not participate in clinical trials, but there are also physicians in practice who may not have the expertise or experience that would qualify them to be a clinical trial investigator. The way in which a prescriber selects a patient for therapy and how that patient is subsequently managed could influence efficacy and safety outcomes and, therefore, create differences between clinical trial results and results achieved in general practice.

We will now examine how these factors are relevant to the Cameron study (GA67815) and to the Usability study (A6791035) and to what extent the results of these studies might not be predictive of real-world experience.

Study Design (Cameron Study)
The inclusion criteria for the Cameron study (GA67815) are listed below, in full:

1. Women aged 18 to 40 years.
2. Currently using DMPA-IM for at least the previous 9 months.
3. Wishing to continue using DMPA for at least 1 more year.
4. No contraindications to DMPA (World Health Organization [WHO] Medical Eligibility Criteria – category 3 or 4).
5. Not wishing to conceive within the next 2 years.
6. Not planning to move out of the area for at least 12 months.
7. Willing to be contacted at work or at home.
8. Willing and able to give informed consent.
9. Without significant preexisting medical conditions.

The exclusion criteria for the Cameron study are also shown below, but they present no additional restrictions because they are simply the inverse of specific inclusion criteria:

1. Contraindications to DMPA (WHO Medical Eligibility Criteria - category 3 and 4 conditions).
2. Wishing to conceive within the next 2 years.
3. Unable to give informed consent to participation.
4. Likely to move out of the area in the next year.
5. Unwilling to be contacted at home or at work.

Overall, the study entry criteria describe a population that is quite close to the general patient population who might perform self-injection. Most will be current DMPA users, either DMPA-IM or DMPA-SC, and most will be intending to practice long-term contraception, as evidenced by their choice of a depot method. While some patients in the general population will have some significant pre-existing medical condition, these would be varied, making it difficult to assess what, if any, impact the condition might have on the ability to self-inject.

The one study requirement that does differentiate study participants from the general population of patients would be the age requirement for the study: 18 to 40 years. In terms of objective medical/clinical factors, the 18 to 40 years study cohort should be representative of typical DMPA users who are under 18 or over 40 since we are primarily dealing with healthy women. Thus, we will examine the behavioural implications of self-injection by women who fall outside the study-defined age range.

Firstly, it is unlikely that women over 40 (up to the peri-menopause) would be unable to successfully self-inject if it is determined that adult women under 40 can do so. With respect to adolescents, the injection technique is simple, and while there should be little doubt that adolescents should be able to learn and physically perform the technique, there is a responsibility that must be assumed by the adolescent to adhere to the 3-monthly schedule, and this deserves some comment.

In a report on compliance with oral contraceptives (OCPs) [Hillard PJ; 1992;], adolescents using oral pills had an annual contraceptive failure rate as high as 18% due to inconsistent adherence to the unsupervised daily dosing regimen they must follow. Therefore, adequate adherence to a 3-monthly unsupervised regimen cannot necessarily be assumed for all adolescents, particularly for adolescents who are unreliable. However, there is an important difference between OCPs and self-injection of DMPA-SC. With OCPs there is no alternative except to require the adolescent to adhere to the unsupervised daily regimen. But, for DMPASC in Uniject, the HCP can decide that a particular patient would be best served by having the product administered in the clinic if they feel that the patient is unlikely to independently adhere to the prescribed regimen at home. The decision to permit self-injection is entirely under the control of the prescriber and the maturity and reliability of the patient will necessarily be important factors for the prescriber to consider when making that decision for each patient.

Study Participants (Cameron Study)
The focus of this section is to examine whether the study population in the Cameron Study differed from typical DMPA users in ways that may be more subtle and may not be readily apparent simply by reviewing the study entry criteria.

As mentioned above, the DMPA patients at the NHS Lothian clinic who self-administered in the Cameron study (GA67815) were approached by the Investigator when she thought the patient might be suitable for self-injection. Those who participated voluntarily agreed to take part, while other patients declined the opportunity. The demands of the study were minimal from the participant's perspective (no additional visits or tests, etc.), so those who declined most likely did so for reasons other than excessive demands on their time. Study participation enabled the participant to self-inject at home, and if the patient perceived value in being allowed to self-inject (e.g., convenience), then this was presumably the motivating factor that led the patient to agree to participate in the study, since self-injection was not available outside of the study.

In general clinical practice, the situation would not be substantially different to that described above. The HCP would approach only those DMPA patients who, in the opinion of the HCP, would be suitable for self-injection. Those patients who find the option interesting would agree to receive the training and attempt self-injection at home, while those who are uninterested for whatever reason (e.g., fear of handling a needle) would decline the offer. Since the dynamics at play here would be very similar to the dynamics that took place during the recruitment of the Cameron study, we conclude that the study population is probably predictive of the patients who would be attempting self-injection in clinical practice. In both situations the decision made by the patient (to try self-administration in the Cameron study, or not; or to try self-administration in general practice, or not) would not affect the treatment the patient received since DMPA treatment could continue regardless, whether self-injected or HCP-injected.

Study Investigators (Cameron Study)
The principal investigators are recognized experts in the field of reproductive health and are highly qualified clinical study investigators and, therefore, it is legitimate to consider whether their expertise might have led them obtain more favourable results in their study than typical practitioners might achieve in medical practice. Such a situation could certainly arise if the disease under study, or the therapy being tested, was very complex and/or required especially skilled management of the patient. But that does not appear to be the case here. For the most part, these are normal healthy women requiring only routine care. The investigator (or the practitioner) who introduces DMPA self-injection into their practice needs to pay attention to a few key points**:**

- Select appropriate patients: among women who use DMPA, there will be those whom the physician judges to be potentially suitable for home self-administration, assuming they can demonstrate competence during the training session, and others who are probably not suitable for various reasons. It is important for any physician to know their patient, which is a skill shared by reproductive health experts and by general practitioners alike.
- Assist the self-injecting patient to keep to the 3-monthly schedule: in most practices it is routine for DMPA patients to receive some type of reminder to ensure they attend their next 3-monthly clinic visit. It is typically an appointment card, a text or voice-mail message or an email. Whatever method is currently used in a practice, the same method can be very simply adapted to remind the patient of her 'at-home appointment' when she will self-inject DMPA-SC in Uniject. This would pose no additional burden on the practice.

- Provide proper follow-up: the physician needs to query the woman about any problems encountered and assess whether self-injection remains a viable option for the patient, going forward. If not, she can revert to getting the injection at the clinic or switch to another contraceptive method.

These requirements on the part of the prescriber were no different in the Cameron study than they would be in general practice. Moreover, expertise in the field, such as that possessed by the principal investigators, is not necessary to fulfil these basic responsibilities of patient care. Thus, we would

expect that the results obtained by the Investigators in their study will be translatable to general medical practice.

With respect to the Cameron study and for the reasons outlined above (study design; patients, investigators), we conclude that the study results should generally be quite predictive of clinical outcomes in general medical practice. We will now examine the Usability study (A6791035) from the same 3 perspectives.

Study Design (A6791035)
As a usability study, the study design is not intended to mirror clinical practice and involves no actual administration of drug to the participants. A usability study is focused solely on the delivery system. The specific purposes of a delivery system usability study are:

- Enrol participants who are appropriately representative of the intended users of the delivery system and provide them with information (about the delivery system) that closely approximates the information that will be made available to actual patients;

- Identify the 'use errors' that occur, including the frequency of the errors and the consequences of the errors; and

- Identify the underlying causes of the identified 'use errors': mistakes made by the participants, misunderstanding of the instructions by participants, design faults of the delivery system itself, lack of clarity in the instructional materials, manufacturing defects in the delivery system, or other.

Therefore, to the extent that the usability study participants are representative of actual patients, and to the extent that the instructions for use (IFU) and/or training represent what would be used in clinical practice, then the errors observed in the study (and their frequency) should be predictive of the use errors that will occur in clinical practice. The instructional materials used in the A6791035 study are appended to the A6791035 CSR and are the basis for the materials to be used in practice. In terms of the study participants, their relevance to actual patients is discussed in the following section.

Study Participants (A6791035)
The Usability was designed to recruit women who are demographically similar to DMPA users. Subjects were included based on gender (female only), age (18-45 years) and the ability to read. Subjects were excluded if they had a severe or chronic condition that would, in the opinion of the investigator, preclude them from successfully participating in the study; one example would be someone with impairment of the hands that would preclude them from operating a small mechanical device. In clinical practice, DMPA subjects are not required to be literate, but the nature of the assessments in the usability study made that requirement necessary. Therefore, in terms of demographics, the study participants were not dissimilar to DMPA patients. However, not all DMPA patients will be deemed suitable for independent self-injection and the study participants were not selected on the basis of their suitability for self-injection, as would happen in clinical practice. While the criteria that physicians may use to select 'suitable' self-injectors from among all their DMPA patients would necessarily be subjective, that additional screen was not applied to the participants in the usability study.

There may be another difference that is also not readily apparent. The study participants were healthy volunteers who were compensated monetarily for their time whether they were successful or not in operating the Uniject; they did not know the purpose of the drug and their primary motivation was to complete the testing. In contrast, a patient self-injecting DMPA-SC in Uniject has a very strong motivation to learn and perform the task correctly because contraceptive efficacy depends on correct injection. In addition, the patient will be trained and will need to demonstrate her proficiency in the clinic, prior to being allowed to attempt unsupervised injection at home. Those patients who are unable to demonstrate proficiency would not be permitted to self-inject at home. Therefore, given the focus and motivation that the patient will have, in addition to the need for the actual patient to

demonstrate proficiency prior to leaving the clinic, we believe it is unlikely that patients self-injecting at home will make errors at a rate higher than that observed with volunteers in the Usability study.

Study Investigators (A6791035)
This study was conducted in a dedicated Phase 1 unit in Brussels and the investigator did not clinically manage the participants. Therefore, the expertise of the investigator would not be relevant to this discussion in the same way that the expertise of the investigators for the Cameron study was relevant to the translatability of their study findings to clinical practice**.**

Conclusions
We believe that these two studies (GA67815 and A6791035) each provide important information that is directly relevant to the ability of patients to self-inject DMPA-SC in Uniject at home, without direct supervision. The usability study carefully assessed each step in the injection process in detail and determined that most women can successfully operate the Uniject device, even when those women had not been pre-selected by a physician as someone who would be 'suitable' for self-injection, as will happen in clinical practice.

The Uniject is a fairly simply device to operate, as shown in the usability study (A6701035), so the central issue will be the ability of women to remember to inject every 3 months, within the 2-week window that is specified in the SmPC. It is important for the self-injecting patient to know that she can contact the clinic if there is a problem. If a woman attempts to inject but cannot activate the device, or encounters some other issue that prevents a proper injection, that situation will be immediately apparent to the patient; it will not go unnoticed. Therefore, the patient would make an appointment to come in and have the injection performed by the nurse, or other, as needed.

The patient would be encouraged to attend to any injection issue promptly, so that the injection occurs within the 2-week window (12-14 weeks after the previous injection). However, it is reassuring that for most women there would be no immediate risk of pregnancy if an injection was to be delayed. The results from study 839 FEH-0012-272 (Jain et al. 2004) showed that subcutaneous DMPA prevented ovulation for a median time of 212 days (30 weeks). While the shortest effective time was observed to be only 15 weeks in this study, hence necessitating a 3-month interval if all women are to be properly protected, the vast majority of women will have a very considerable margin for error in terms of the timing of injections. This property of DMPA largely explains the reason behind there being no contraceptive failures among the >1700 women in the Sayana Phase 3 programme (Studies 839-FEH-0012-267, 839-FEH-0012-267BMD, 839-FEH-0012-269); the method is quite robust.

We anticipate the results of the two studies discussed above to be confirmed in the Phase IV study proposed by the MAH in response to the request for further evidence of efficacy and safety of Sayana Press in a 'real world 'setting as part of the assessment of the Risk Management Plan (please see the accompanying response to RMP Request 9 for further details).

Assessment of response
The applicant's detailed response is noted. However, the crucial issue is whether efficacy is maintained in real-life situations when women self-inject and if efficacy will be comparable to results obtained in clinical studies. It would appear that the MAH intends to address this issue as it is noted from the responses provided to the RMP the intention to conduct a Phase IV interventional, safety and efficacy study of self-injection with Sayana Press.

Point considered resolved

3. The results of the usability study A6791035 suggest that a certain amount of training is needed and reading the IFU alone might not be sufficient for women. The MAH should provide a detailed discussion of the training proposed for women.

MAH's response
We agree with the conclusion stated in the body of this Question. While the difference in the 'proportion of successful injections' between trained and untrained participants in Study A6791035 fell just shy of statistical significance, the result certainly suggests that it is appropriate that women who intend to self-inject at home with Sayana Press should be trained; they should be given a demonstration of the device, have their questions answered, and be asked to perform supervised self-injection at the clinic in order to demonstrate that they are proficient.

The MAH intends to support the Healthcare Professional's (HCP's) efforts by providing, apart from the IFU itself, written and electronic materials that will be directed to the HCP.

The educational plan recognizes that the HCP has two essential tasks: (i) to use their best judgement in selecting patients who are likely to be successful with self-injection and (ii) to properly train the patient to be proficient in the injection technique. The HCP-directed materials will include practical guidance and a demonstration video.

- The guidance will be available to the HCP electronically and can be printed for easy reference.

    - The guidance will first focus the HCP's attention to the matter of selecting appropriate patients for self-injection. It will recommend that appropriate patients should, first, be suitable for treatment with DMPA (desiring long-term contraception; no contraindications; etc.). Secondly, it will advise that the patient should clearly express a desire to attempt self-injection; there is no requirement to self-inject in order to use Sayana Press since clinic injection is available. Finally, the HCP should assess factors which, in their judgment, may bear upon the patient's reliability and make a determination that the patient is likely to be successful (i.e. no physical, social or psychological impediments that would suggest any inability to successfully self-inject at home).

    - The guidance will then provide support to the HCP who will train the women. It will recommend that the Trainer should be someone who

        - has thoroughly read the IFU in detail,
        - has viewed the training video and understands it,
        - has become proficient in operating the Uniject injector, and, importantly,
        - has first-hand experience administering Sayana Press injections to patients in the clinic.

    - The steps to be covered when training a patient are, briefly:

        - Before sitting with the patient, ask her to read the IFU thoroughly.
        - Sit with the patient. Confirm that the patient understands that self-injection is voluntary/optional (injection in the clinic is still available)
        - Confirm that the patient understands that she must commit to keep to the
        - 3-monthly schedule (+/-1 week) or risk a contraceptive failure.
        - Confirm that the patient understands that if she encounters a problem when injecting (failed injection), she must contact the clinic as soon as possible for advice and/or a clinic appointment, as needed.
        - Show her the device, and allow her to hold it. Point out the components of the injection device, such as the needle cap, the reservoir, etc.). Demonstrate in principle how to activate the device, but without actually doing it (the patient will do this later); strongly emphasize that a 'click' must be heard or felt to ensure the device has been properly activated – or the medicine will not come out of the needle.

- Explain how to give a SC injection. Show the patient how to: (a) choose the injection site; (b) grab a good skin fold to ensure an SC injection; (c) insert the needle straight into the skin fold to full depth; and (d) squeeze the reservoir firmly but slowly for 5-7 seconds, until injection is complete.
- Allow the patient to view the brief Sayana Press video, as a review of the process (the video is described below).
- Invite the patient to perform self-injection. Observe that the patient has properly activated the injector, and confirm that the patient did, indeed, feel/hear a 'click'. Observe her as she performs each step and correct any potential or pending errors.
- Based on the HCP's observations, decide if the patient is suitable to perform self-administration. If yes, review the patient-directed materials (described below) with the patient and answer any questions she may have.
- If the clinic will normally provide a 3-month reminder (by post, email, other), inform the patient of this. Also inform the patient of the reminder techniques available the patient-directed materials.
- Ensure that the patient understands that she can decide, at any time, to get her next injection at the clinic if she is not comfortable doing self-injection, and, that she must call the clinic if an attempted self-injection cannot be completed successfully (injection difficulties during the attempt; or any other reason).

The patient-directed materials would typically be available to the patient after she has been trained. These materials are intended to support the 'hands-on' training received from the HCP and are proposed to consist of:

Sayana Press Responsive Website
The Sayana Press website will be the most important resource for patients. The website will provide access to the patient video as described below and this can also be accessed and played on smartphones as well as computer/laptop due to the responsive design. Patients will be able to subscribe to a reminder service (see below). Frequently asked questions may also be added to the website.

Self-injection Training Video
The training video will be a few minutes long and will use simple animation to illustrate the steps in the injection process using information, graphics and language consistent with the IFU. The video could be first used during the training provided by the HCP, and then used at home as a means to reinforce steps that have already been explained and demonstrated to the patient by the HCP. It is expected that the video will increase patients' confidence by providing them with a visual representation of the IFU in a series of small steps.

Reminders
Women who receive the product for self-administration at home will be solely responsible for maintaining compliance with the schedule of administration. As an alternative to traditional manual methods (e.g., use of calendar, diary) and the reminder aide proposed as Step 8 of the revised IFU (see also response to RMP Request 12), the website will provide instruction for patients on how to add calendar reminders on their own electronic calendar, which is a functionality of smartphones. In addition, it will have an option for patients to receive SMS text reminders. Patients will only receive these reminders if they enrol for the service.

Printed materials
It is proposed to supplement the website/video with a printed patient pamphlet in a question and answer format which will reinforce key messages on the following topics:

How to inject Sayana Press and helpful hints for injecting Sayana Press

The pamphlet will give advice on the importance of properly activating the injector, performing the injection slowly over 5-7 seconds and how best to squeeze the reservoir to expel all the medicine. Also we propose to provide a visual representation (e.g. photographs) of what the injector looks like

before use and once the medicine has been expelled. This will help to show the traces of suspension left in the injector reservoir due to the overage and to reassure patients who may be unsure if they have given themselves a full dose.

Messages regarding contacting their HCP if they experience any problems during administration will be reinforced.

Remembering when to inject Sayana Press

Practical advice on alternative methods of remembering when to give the next injection will be given for patients not enrolling in the reminder service.

The importance of injecting at 13 weeks +/-1 week will be emphasized and will reinforce advice in the PIL regarding what action to take if an injection is administered late or missed.

Summary
Taken together, the HCP- and patient-directed educational materials are intended to ensure that the proper patients are selected for this option, that they are properly trained, and that they have the support they need to be successful and minimize the risks of incorrect administration and non-adherence to the injection schedule. Nevertheless, since self-injection is an option and not a requirement for use of the product, women who are not inclined to self-inject, or are not proficient at the technique, may continue to use Sayana Press administered by the HCP at the clinic.

Assessment of response
The MAH has provided details of the training proposed for women. This include guidance for Healthcare Practitioners to aid training, educational videos, pamphlets, a website and reminder aids. The proposals are considered to be appropriate and acceptable subject to appropriate vetting to ensure that promotional material is not included.

Point considered resolved

4. It is proposed that women self-inject on a regular basis. The MAH should provide a detailed discussion on how women will be followed-up to ensure they don't miss injections. It should also be clarified whether women will have regular medical check-ups and how frequently this will be.

MAH's response
The Phase 3 clinical studies for DMPA-SC showed that this product is highly effective. No contraceptive failures occurred amongst 1779 women during 16,023 woman-cycles (excluding cycles during which a barrier method was used and/or no intercourse occurred). But it only works if women use it and are able to inject competently. Since the first dose would take place under supervision, we need to look at compliance after the first dose, which would be 'adherence' to therapy.

We will first examine the various factors that influence how well, or how poorly, patients adhere to a prescribed regimen and then focus on how those factors come into play for Sayana Press. In particular, we will look at the roles of the patient, the physician/HCP and the MAH/manufacturer, and consider how each can contribute to good adherence to the Sayana Press self-injection schedule. At the end of this Response we will address the topic of medical appointments for these women.

For any drug, adherence to an outpatient therapy depends on three things: (i) the degree of difficulty the patient may have in administering the drug properly; (ii) the administration schedule; and (iii) the patient's motivation to adhere to that schedule. In terms of difficulty of administration, an oral pill is certainly very simple (swallow it with water), while an inhaled agent or a subcutaneous injectable requires some basic training on the delivery device in order to insure that the drug is delivered properly. Improper operation of a dry powder inhaler, for example, results in the powder remaining

largely in the patient's mouth, rather than reaching the lungs. In contrast, IV and IM injectables are generally not suitable for self-administration, for various reasons. We would characterise Sayana Press as being of moderate difficulty to administer in that appropriate instruction is required in order to operate the device properly, but suitable for patient administration when the physician has provided training and determined that the patient is proficient in the technique.

The administration schedule is a major determinant of adherence. A 14-day course of antibiotics for an outpatient infection frequently has incomplete adherence even with a once daily drug, but even more so with a more demanding regimen that requires 3 or 4 doses per day [Sorenson, 2009; Pechere, 2007]. Taking a daily oral contraceptive pill (OCP) is certainly not difficult. However, taking a pill every single day without missing any pills over a 1 year period is actually quite demanding. Consequently, unintended pregnancies are not uncommon with OCPs and are reported to be as high as 18% per year in high-risk adolescents [Hillard PJ; 1992;]. In contrast, the Sayana Press regimen requires 4 doses per year. Presuming that the patient knows how to operate the injector and can note the four scheduled dates on their electronic or paper calendar, this regimen is not very demanding of the patient's time and attention compared to a daily regimen, and this feature would tend to promote better adherence.

However, the most important factor for adherence to therapy is really the motivation of the patient to follow the schedule, irrespective of the route of administration or the dosing schedule itself. Oncology patients and other patients with very serious diseases often have quite complex regimens of numerous daily pills, some with on-treatment and off-treatment periods at semi-irregular intervals. However, oncology patients are typically motivated to take steps to ensure proper adherence (e.g., setting up compartmented pill boxes) because they know that poor adherence can have serious consequences. In contrast, an outpatient with a bothersome but non-serious infection is oftentimes less highly motivated because no similar, severe consequence is perceived by the patient. Patients sometimes stop their antibiotic after a few days as symptoms begin to improve, saving the remaining pills for the next time they need them; this would be poor adherence essentially by intention.

Women using contraception, however, are generally quite motivated to adhere to their regimen since they recognize the seriousness of an unintended pregnancy. Unfortunately, it is easy for a patient to think that she took the pill this morning, since she takes it every morning, but sometimes it didn't actually happen. Or, she unintentionally leaves the pill pack at home when travelling for a few days. Or, a gastrointestinal illness causes the pill to not be absorbed properly.

As suggested by these examples, a key factor to consider is the sensitivity of a drug regimen to transient non-adherence, where the patient has not stopped the regimen by intent, but has not perfectly adhered to the schedule. Missing a few days of a cholesterol-lowering pill will not, in all likelihood, acutely precipitate a myocardial infarction nor is it likely that missing one or two doses of a 14-day BID antibiotic regimen, or taking those doses early or late, will lead to a treatment failure.

Oral contraceptive regimens, however, are notoriously sensitive to missed doses and demand consistent adherence, day after day. It is that need for perfect consistency that is makes a once-a-day contraceptive regimen much more demanding than a once-a-day antihypertensive regimen. In contrast, the 3-monthly Sayana Press regimen is relatively insensitive to transient schedule errors. Per the SmPC, there is a 2-week window for the patient to perform the self-injection. This is useful if the woman is away from home, for a few days or a week, on the scheduled injection date; she can do the injection when she returns without any concern for loss of efficacy. If the injection is done later than the allowed window, then there is a possibility that ovulation could occur.

In one study of 39 women receiving a single dose of DMPA-SC [Jain J, et al. 2004], pharmacokinetics, ovulation suppression and return to ovulation were assessed following a single injection of subcutaneous DMPA. The shortest observed interval for ovulation suppression (serum progesterone <4.7 ng/mL) was 15 weeks in that study. However, the mean time for ovulation suppression was 31 weeks (median = 30 weeks; range = 15 weeks to 51 weeks), which represents 18 weeks beyond the recommended 13-week injection interval. Therefore, even if a woman misses the

dosing window by several weeks, there is relatively little chance of contraceptive failure. In that regard, the method is quite robust.

Therefore, the Sayana Press regimen is reasonably forgiving of common circumstances that could cause a patient to be unable to inject precisely on the target date. For example, the patient who goes abroad for two weeks and forgets to bring her Sayana Press can inject when she returns with little chance that a contraceptive failure would occur.

As noted, the motivation of the patient to comply with the schedule is critical, and the physician can enhance that in several ways. The most important way, and the most obvious, is to ensure that only highly motivated patients are selected for self-injection. Self-injection is not required to use Sayana Press, so there should never be an attempt to persuade a woman to try self-injection if she is not comfortable with the concept. The best patients for self-injection should be those who are eager to try – not just those who are willing. Those patients will take the measures needed to ensure that injections are done in a timely manner (marking a calendar; putting an alert into her mobile phone; etc.) – none of which are difficult to do.

Secondly, the physician can ensure that the training is done thoroughly with each patient. Part of the training is how to activate the device and insert the needle, etc. But another part is education about the responsibility that she is taking on – ensuring that the patient understands that she will bear the responsibility to perform the injection every 3 months (+/-1 week), and that she needs to put an alert or reminder in place to ensure that the date is not missed. And, of course, the patient needs to know that she must call the clinic if she runs into any problems with the injection.

Thirdly, the physician can deploy a system for providing reminders to the patients. That is, most clinics already provide appointment cards and/or telephone contact prior to scheduled DMPA appointments, and this simple system generally works well for patients who intend to continue receiving DMPA. The physician can easily adapt the existing system to provide the same reminder to the self-injecting patient – essentially a reminder for her to perform her 'at home injection appointment'.

While encouraging an individual woman to adhere to a prescribed therapy is largely the province of the healthcare provider who knows her and is managing her, the MAH can assist by providing complete and correct information about the product (SmPC, IFU, PIL) along with complementary tools for conducting and supporting the training (such as the aide in Step 8 of the IFU and the electronic reminder system described in the Response to Question #3).

The MAH can also support the patient. In this case, we are fortunate to be dealing with a selected subgroup of motivated patients who have chosen to self-inject of their own accord.
Many DMPA patients will reject this option out of hand because they do not want to handle the needle or other reasons, but those who do attempt it will be those who genuinely want to do this because they have determined that, in their case, it offers an advantage. The primary support the MAH can offer these women is clear and complete information about the dosing schedule: *it is every 13 weeks and there is a 1 week window either side of that date. You need to keep to that schedule because injections beyond that window may not be effective. If your injection will fall outside of that window you should contact your physician for instructions.*

To conclude, self-injection will necessarily take place in a self-selected group of women who have volunteered to try this approach. Given effective training in how to mechanically operate the device and some simple support measures (e.g. appointment reminders), it would be anticipated that they should be quite successful.

Finally, regarding clinical follow-up of otherwise healthy women using a hormonal contraceptive regimen, it is our view that Healthcare professionals will be led by local clinical or contraceptive guidelines available in their country. Although the Czech Republic have withdrawn from this procedure, the CZ assessor revealed in their query that all women using prescribed contraception in CZ visit their physician every 3 months for routine care. In the US, the practice is an annual follow-up

visit. We are also aware that longer follow-up intervals are used in other EU countries, but in light of the CZ practice, we must recognize that there exists wide variation across the EU. That being the case, the MAH would not be best-placed to recommend, in any formal sense, either the interval or the nature of such follow-up because this is the province of those who guide medical practice in each local country. It is important to note that there is no specific rationale by which DMPA use, per se, should require a change in a physician's standard follow-up interval for women using hormonal contraception.

We therefore propose to modify the PIL to remove reference to any specific time interval for routine follow up.
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Assessment of response
The MAH proposes that follow-up and medical check-up should be based on locally applicable guidelines. It is acceptable but Section 3 of the PIL should remain as it was originally and the section 4.2 of the SmPC should be modified to reflect this information.

Point considered resolvable with SmPC and PIL changes

5. An in-depth discussion should be provided on the disposal of Sayana Press after self-administration. In addition the product information should also be updated.

MAH's response
Precise arrangements for provision and collection of containers for disposal of needles and sharps by a patient injecting at home differs across the EU.

In the UK for example, patients are well provided for in that they may obtain a sharps container on prescription, however arrangements for return of full containers may differ from local authority to local authority, although commonly, full sharps bins are either collected from the patient's home or returned to the pharmacy. Additionally needle clippers to remove the needle may also be available on prescription or for a small charge. However sharps bins collected from home on the local government collection scheme are typically collected when full or every three months, whichever is the soonest. Although this arrangement is suitable for a patient using daily injections (e.g., diabetic) this would not be beneficial for Sayana Press given the one injection every 3 months injection schedule.

A similar arrangement for provision of sharps bins is common in Ireland and the Netherlands

In other EU countries the provision of sharps bins to patients may or may not be common practice and patients are typically expected to return used needles/injectors to the pharmacy. The most pragmatic general practice to adopt would therefore be for patients to return either their sharps containers (if available) or used injectors to their local pharmacy for disposal as this seems to be consistent with practice across all countries surveyed, whereas returning the sharps to a GP/Clinic may or may not be allowed.

We acknowledge that in line with current regulations we wish to discourage the disposal of sharps into household waste and to reinforce messages around prevention of inadvertent injury by reiterating the advice not to attempt to recap the needle once the needle shield has been removed.

A review of Patient Information Leaflets/IFUs for recently approved injectable medicines that may be home administered reveals that there is no set standard text for sharps disposal advice (presumably because of the observed variation in local practice across the EU).

Accordingly, we propose to update the Common PL/IFU text which we believe is consistent with current practices.

Advice on not recapping the needle is already adequately covered in the preceding Step 6 of the IFU.

Assessment of response
The information has been provided.
Point considered resolved

OVERALL CONCLUSIONAND BENEFIT-RISK ASSESSMENT

The benefit risk for SAYANA PRESS remains unchanged and proposal to allow women to self-administer is considered approvable.