Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

Decentralised Procedure

Sayanaject 104 mg suspension for injection

(Medroxyprogesterone acetate)

Procedure No: UK/H/5497/001/DC

UK Licence No: PL 00057/1498

Pfizer Limited

LAY SUMMARY

Sayanaject 104 mg suspension for injection
(medroxyprogesterone acetate, suspension for injection, 104 mg)

This is a summary of the Public Assessment Report (PAR) for Sayanaject 104 mg suspension for injection (PL 00057/1498; UK/H/5497/001/DC). It explains how Sayanaject 104 mg 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 Sayanaject 104 mg suspension for injection.

For practical information about using Sayanaject 104 mg suspension for injection, patients should read the package leaflet or contact their doctor or pharmacist.

What is Sayanaject 104 mg suspension for injection and what is it used for?
Sayanaject 104 mg suspension for injection contains the same known active ingredient as a product that is currently licensed called Sayana 104mg/0.65ml suspension for injection (a single-use pre-filled syringe) but it has a different container closure system (a single-use pre-filled injection system) to this currently licensed product.

Sayanaject 104 mg suspension for injection is used:

- For long-term contraception where the patient and the person who provides the patient's contraception (e.g. their doctor, nurse or healthcare provider) have decided that this method is the most suitable for the patient. It is important to be aware that as a long-acting contraceptive its effects last at least 12 weeks. If the patient wishes to use this medicine for more than 2 years, the patient's health professional/doctor/nurse may wish to re-evaluate the risks and benefits of using this medicine to make sure that it is still the best option for them.
- By teenagers, but only after other methods of contraception have been discussed with the person who provides their contraception and are considered unsuitable or unacceptable.

How does Sayanaject 104 mg suspension for injection work?
The active ingredient in Sayanaject 104 mg suspension for injection is medroxyprogesterone acetate (MPA), which is similar to (but not the same as) the natural hormone progesterone that is produced in the ovaries during the second half of a woman's menstrual cycle. This medicine acts by preventing an egg from fully developing and being released from the ovaries during a woman's menstrual cycle. If an egg is not released it cannot become fertilised by sperm and result in pregnancy.

How is Sayanaject 104 mg suspension for injection used?
Sayanaject 104 mg is a suspension for injection and the route of administration is under the skin (subcutaneous) into the front upper thigh or abdomen.

The injection should be administered by the patient's doctor, nurse, or healthcare provider. The detailed instructions on the injection procedure are provided at the end of the package leaflet. The patient should continue to receive Sayanaject 104 mg suspension for injection for as long as instructed by their doctor.

First injection
A dose of 104 mg of this product is given subcutaneously (under the skin), into the front upper thigh or abdomen every 3 months (12 to 13 weeks). Sayanaject 104 mg suspension for injection will only be effective if the patient receives their injection at the proper time. To ensure that the patient is not pregnant at the time of their first injection, it is essential that the patient's first injection be given ONLY

during the first 5 days of their normal menstrual cycle.

After childbirth: If the patient uses Sayanaject 104 mg suspension for injection after having a baby and the patient is not breastfeeding, the first injection MUST be given within 5 days of the birth.

There is evidence that women prescribed Sayanaject 104 mg suspension for injection immediately after childbirth or termination of pregnancy can experience prolonged and heavy bleeding. Because of this, Sayanaject 104 mg suspension for injection should be used with caution at this time.

Further injections
Further doses of Sayanaject 104 mg suspension for injection will then be given every 12 to 13 weeks, (but no later than 14 weeks past the patient's last injection), regardless of when and how much menstrual bleeding the patient has.
It is important that the patient receives their next injections at the right time.

Please read section 3 of the package leaflet for detailed information on dosing recommendations, the route of administration, and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Sayanaject 104 mg suspension for injection have been shown in studies?
Pfizer Limited provided its own data on efficacy and safety studies.

These studies have shown that Sayanaject 104 mg suspension for injection is effective in the use of long-term female contraception.

What are the possible side effects of Sayanaject 104 mg suspension for injection?
The most common side effects with Sayanaject 104 mg suspension for injection (which may affect more than 1 in 10 people are) weight decrease and weight increase.

Common side effects with Sayanaject 104 mg suspension for injection (which may affect up to 1 in 10 people) are:
- Abdominal pain (cramps)
- Nausea
- Acne
- Amenorrhea (very light or no period)
- Heavy, frequent and/or unexpected bleeding
- Irregular periods
- Period pains
- Breast pain/tenderness
- Depression
- Weakness or tiredness
- Headache
- Injection site reactions (including pain, tenderness, lump, persistent skin indentation/dimpling)
- Irritability
- Anxiety
- Decreased sexual feeling
- Vaginal irritation or itching
- Mood changes
- Dizziness
- Back pain

- Pain in limbs
- Abnormal cervical smear

For the full list of all side effects reported with Sayanaject 104 mg suspension for injection, see section 4 of the package leaflet available on the MHRA website.

Why was Sayanaject 104 mg suspension for injection approved?
The MHRA decided that the benefits of Sayanaject 104 mg suspension for injection are greater than its risks and recommended that it be approved for use.

What measures are being taken to ensure the safe and effective use of Sayanaject 104 mg suspension for injection?
A risk management plan (RMP) has been developed to ensure that Sayanaject 104 mg 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 Sayanaject 104 mg suspension for injection including the appropriate precautions to be followed by healthcare professionals and patients.

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

Other information about Sayanaject 104 mg suspension for injection
Denmark, Spain, Finland, France, Italy, Romania, Sweden and the UK agreed to grant a Marketing Authorisation for Sayanaject 104 mg suspension for injection on 08 October 2014. A Marketing Authorisation was granted in the UK on 23 December 2014.

The full PAR for Sayanaject 104 mg suspension for injection follows this summary.

For more information about treatment with Sayanaject 104 mg suspension for injection, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in August 2016.

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I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Member States considered that the application for Sayanaject 104 mg suspension for injection (PL 00057/1498; UK/H/5497/001/DC) could be approved. The product is a prescription-only medicine (POM) and is indicated for long-term female contraception. Each subcutaneous injection prevents ovulation and provides contraception for at least 13 weeks (+/- 1 week). However, it should be taken into consideration that the return to fertility (ovulation) may be delayed for up to one year (see section 4.4 of the Summary of Product Characteristics [SmPC]).

Since loss of bone mineral density (BMD) may occur in females of all ages who use Sayanaject 104 mg suspension for injection long-term (see section 4.4 of the SmPC), a risk/benefit assessment, which also takes into consideration the decrease in BMD that occurs during pregnancy and/or lactation, should be performed before administration of this product.

It is also important that the patient is informed about the long-term nature of this product's effects, including a delayed return to fertility (see section 4.4 of the SmPC).

The application was submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS), and Denmark, Spain, Finland, France, Italy, Romania and Sweden as Concerned Member State (CMS). The application was submitted under Article 8.3 of Directive 2001/83/EC, as amended, for a new product with a known active substance. This application is a line-extension to Sayana 104mg/0.65ml suspension for injection pre-filled syringes (PL 00057/0589; UK/H/0960/001/MR) which was first authorised in the EU to Pfizer Limited on 26 October 2005.

In this line extension application, the only change in the product is the introduction of a new injection system; the proposed product has an injection system that is based on Uniject® technology.

Medroxyprogesterone acetate (MPA) is an analogue of 17 α-hydroxyprogesterone with anti-estrogenic, anti-androgenic and antigonadotrophic effects. MPA belongs to the progestagen pharmaceutical class of drugs (ATC code: G03AC). It acts by inhibiting the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation. The primary mechanism of ovulation suppression also results in endometrial thinning, and these actions produce its contraceptive effect.

No new non-clinical studies were conducted, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

One clinical study was submitted in support of this application. The clinical study was conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place 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 or satisfactory inspection summary reports as certification that acceptable standards of GMP are in place at those non-Community sites.

The RMS and CMS considered that the application could be approved at the end of procedure (Day 210) on 08 October 2014. After a subsequent national phase, a licence was granted in the UK on 23 December 2014.

II QUALITY ASPECTS

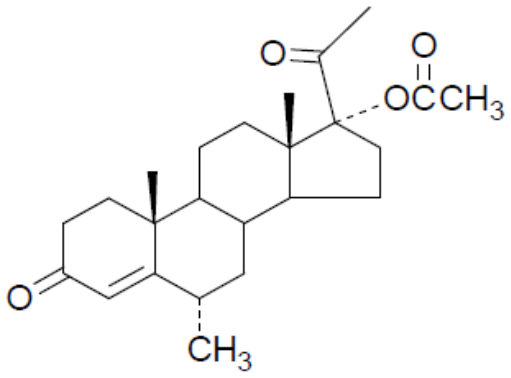
II.1 Introduction

Each single-dose container of finished product contains 104 mg medroxyprogesterone acetate in 0.65 ml suspension for injection. Each pre-filled injector contains 104 mg medroxyprogesterone acetate. Other ingredients consist of the pharmaceutical 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. The finished product is supplied as a single-dose container in the form of a pre-filled injector containing 0.65 ml. 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. Satisfactory specifications and Certificates of Analysis have been provided for all packaging components.

II.2. Drug Substance

INN: Medroxyprogesterone acetate
Chemical name: Medroxyprogesterone acetate – 17-alpha-acetoxy-6-alpha-methylprogesterone

Structural formula:



Molecular formula: $C_{24}H_{34}O_4$
Molecular mass: 386.53
Appearance: A white or almost white powder.
Solubility: Practically insoluble in water, freely soluble in methylene chloride, soluble in acetone and sparing soluble in ethanol (96 percent).

Medrooxyprogesterone acetate is the subject of a European Pharmacopoeia monograph.

Synthesis of the active substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant Certificates of Analysis.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Appropriate proof-of-structure data have been supplied for the active substance. All potential known impurities have been identified and characterised. Satisfactory Certificates of Analysis have been provided for all working standards. Batch analyses data are provided that comply with the proposed specification.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Appropriate stability data have been generated supporting a suitable retest period when stored in the proposed packaging.

II.3. Medicinal Product

Pharmaceutical Development

The objective of the development programme was to formulate a safe, efficacious, single-use injection system based on Uniject® technology with each pre-filled injector containing 104 mg medroxyprogesterone acetate in 0.65 ml suspension for injection.

Suitable pharmaceutical development data have been provided for this application.

All excipients comply with their respective European Pharmacopoeia monographs with the exception of monobasic sodium phosphate monohydrate which complies with the United States Pharmacopoeia (USP). Satisfactory Certificates of Analysis have been provided for all excipients. Suitable batch analysis data have been provided for each excipient.

None of the excipients contain materials of animal or human origin.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Manufacture of the product

A satisfactory batch formula has 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 batch size and shown satisfactory results.

Finished Product Specification

The finished product specification proposed is acceptable. Test methods have been described that have been adequately validated. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Product

Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf-life of 5 years for the unopened product with the storage conditions ‘Do not refrigerate or freeze.’ Once opened the product must be used immediately. Any unused portion must be discarded.

Suitable post approval stability commitments have been provided to continue stability testing on batches of finished product.

II.4 Discussion on chemical, pharmaceutical and biological aspects

There are no objections to the approval of this application from a pharmaceutical viewpoint.

II.5 Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The following text is the approved label text for Sayanaject 104 mg suspension for injection. No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Carton

1. NAME OF THE MEDICINAL PRODUCT

SAYANAJECT 104 mg suspension for injection.
medroxyprogesterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each pre-filled injector contains 104 mg medroxyprogesterone acetate

3. LIST OF EXCIPIENTS

Contains methylparahydroxybenzoate, (E218), propylparahydroxybenzoate (E216) and sodium. See leaflet for further information .Also contains: macrogol, 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.

4. PHARMACEUTICAL FORM AND CONTENTS

0.65 ml suspension for injection
1 x Single-dose container

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
To be used immediately after opening the foil pouch.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

For single use only. Any unused product should be disposed of safely after use, in accordance with local guidance for the disposal of sharps.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited
Ramsgate Road
Sandwich, CT13 9NJ - UK
Tel: + 44 (0) 1304 616161

12. MARKETING AUTHORISATION NUMBER(S)

PL 00057/1498

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Foil Pouch

1. NAME OF THE MEDICINAL PRODUCT

SAYANAJECT ® 104 mg suspension for injection.
medroxyprogesterone acetate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

104 mg medroxyprogesterone acetate

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

0.65 ml suspension for injection

1 x Single-dose container

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Subcutaneous use.
To be used immediately after opening the foil pouch.
Read the package leaflet before use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP:

9. SPECIAL STORAGE CONDITIONS

Do not refrigerate or freeze.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Limited

12. MARKETING AUTHORISATION NUMBER(S)

PL 00057/1498

13. BATCH NUMBER

BN:

14. GENERAL CLASSIFICATION FOR SUPPLY

POM

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

III NON-CLINICAL ASPECTS

III.1 Introduction

As the pharmacodynamic, pharmacokinetic and toxicological properties of medroxyprogesterone acetate are well-known, no new non-clinical studies are required and none have been provided. An overview based on the literature review is, thus, appropriate.

The applicant's non-clinical expert report has been written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

The applicant has identified the volatile leachables recovered in the accelerated stability study. A discussion of the safety of the leachable compounds has been provided. No non-clinical issues were identified.

III.2 Pharmacology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.3 Pharmacokinetics

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.4 Toxicology

Not applicable for this product type. Refer to section 'III.1; Introduction' detailed above.

III.5 Ecotoxicity/environmental risk assessment (ERA)

In accordance with the Guideline on the Environmental Risk Assessment of Medicinal Products for Human use [EMEA/CHMP/SWP4447/00], a justification for the absence of an environmental risk assessment (ERA) has been provided. The applicant states that Sayanaject 104 mg suspension for injection provides an alternative delivery system and would replace the currently marketed medicinal product, and hence the exposure of the environment to medroxyprogesterone acetate is not likely to increase. This is acceptable and an ERA is therefore not deemed necessary.

III.6 Discussion on the non-clinical aspects

No new non-clinical studies were conducted and none are required for this application. A review of the literature is provided and is acceptable. There are no objections to the approval of this application from a non-clinical viewpoint.

IV CLINICAL ASPECTS

IV.1 Introduction

The clinical pharmacology of medroxyprogesterone acetate is well-known. With the exception of data from the pharmacokinetic study detailed below, no new pharmacodynamics or pharmacokinetic data are provided or are required for this application.

No new efficacy or safety studies have been performed and none are required for this type of application. A comprehensive review of the published literature has been provided by the applicant, citing the well-established clinical pharmacology, efficacy and safety of medroxyprogesterone acetate.

IV.2 Pharmacokinetics

The applicant submitted the following study:

A randomised, open-label, parallel group study of the pharmacokinetics (PK) of medroxyprogesterone acetate (MPA) in 68 healthy volunteers to compare the pharmacokinetics of MPA following

subcutaneous (SC) administration using the Uniject™ delivery system or pre-filled syringe (depo-subQ provera 104).

The study participants were pre-menopausal women aged 18-45 years with confirmed ovulatory cycles who were at low risk for 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 subcutaneous administration of DMPA using the Uniject delivery system or pre-filled syringe (PFS);
- To compare the pharmacodynamic 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

Pharmacokinetic 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, four PFS subjects had cyclic ovarian activity prior to Day 92; three 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 hundredmilligrammes. No subjects randomised 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**.**

The pharmacokinetic characteristics of MPA after subcutaneous administration of 104mg/65ml using the Uniject delivery system or PFS showed that Cmax was higher in the pre-filled group and the time to maximum concentration was significantly shorter in the Uniject group (70.9 hours compared with 163 hours. The peak exposure was also higher in the Uniject group). However the AUC ratios [AUC (0-150) and AUC (0-90)] showed that similar amounts of MPA were absorbed from the two injection systems (1.02 and 1.04, respectively- see Table 8).

Although, the standard bioequivalence criteria has not been met, as the 90% CI for AUC (0-150), AUC (0-90) and Cmax lie outside of the accepted criteria of 80 -125%; this is considered acceptable as the primary objective of the study was to demonstrate similar pharmacokinetic criteria and not bioequivalence. Furthermore, the trend towards a higher Cmax in the Uniject group should not have any impact on efficacy and safety.

Also, strictly speaking a bioequivalence study is not required for subcutaneous routes when the test product contains the same concentration of the active substance and the same excipients in similar amounts as the approved medicinal product.

The serum MPA levels on day 92 for the Uniject group were also found to be above 0.1 ng/mL(a biomarker for contraceptive efficacy); suggesting that administration of MPA with the Uniject system confer the ability to provide adequate contraceptive cover for up to three months.

Overall, the pharmacokinetic characteristics of MPA after subcutaneous administration of 104mg/65ml using the Uniject delivery system has been demonstrated to be similar to that of the PFS.

IV.3 Pharmacodynamics

No new pharmacodynamic data were submitted and none were required for an application of this type.

IV.4 Clinical efficacy

No new efficacy data were submitted and none were required for an application of this type.

IV.5 Clinical safety

No new safety data were submitted and none were required for this application.

IV.6 Risk Management Plan (RMP)

The marketing authorisation holder (MAH) has submitted a risk management plan (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 Sayanaject 104 mg suspension for injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:

Summary of safety concerns:

Summary of safety concerns	
Important identified risks	Change in bone mineral density Defective injection system Needle stick injury Persistent subcutaneous injection site reactions
Important potential risks	Incorrect dosage administration Non-sterile Product
Important missing information	N/A

Summary of safety concerns and planned risk minimisation activities:

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Change in Bone Mineral density	The risk of change in bone mineral density following use of SAYANA/DMPA is described in the product labelling and Patient Information Leaflet. As described in the Pharmacovigilance System (EU MAA Module 1, Section 1.8 Additional Information) the MPA Risk Management Committee will continue to monitor and evaluate reports of BMD and fracture-like events on a periodic basis including at time of preparation of PSURs. MPA has a well-known pharmacologic profile and a wide therapeutic safety margin and the above activities are considered to be adequate to minimize risk.	N/A
Defective injection system	Product labelling and Patient Information Leaflet. Monitor	N/A
Needle stick injury	Product labelling and Patient Information Leaflet	N/A
Persistent subcutaneous injection site reactions	Product labelling and Patient Information Leaflet	N/A
Incorrect dosage administration	Product labelling and Patient Information Leaflet	N/A
Non-sterile Product	Product labelling and Patient Information Leaflet	N/A

The RMP for Sayanaject 104 mg suspension for injection adequately documents the safety concerns for the product. Routine pharmacovigilance and risk minimisation are sufficient for the safety concerns in the RMP, given the established benefit-risk profile of medroxyprogesterone acetate and the information available to inform decisions on the balance of benefits and risks when it is used in clinical practice.

IV.7 Discussion on the clinical aspects

With the exception of the pharmacokinetic study, no new clinical studies were conducted, which is acceptable given that the product is a line-extension of an approved product licence containing a well-known active substance.

The study submitted in support of this application demonstrated that the pharmacokinetic characteristics of MPA after subcutaneous administration of 104mg/65ml using the Uniject delivery system were similar to that of the PFS.

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

V User consultation

The package leaflet has been evaluated via a user consultation study, in accordance with the

requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability, as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use*.

VI Overall conclusion, benefit/risk assessment and recommendation

The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with medroxyprogesterone acetate is considered to have demonstrated the therapeutic value of the compound. The benefit-risk is, therefore, considered to be positive.

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 numbers	Product information affected	Date of start of the procedure	Date of end of procedure	Approval/ non approval	Assessment report attached Y/N (version)
To update section 5.1 of SmPC to update the Mode of Action statement to clarify the primary contraceptive mode of action of MPA and to delete a sentence concerning pharmacological effects on the endometrium.	UK/H/5497/001/II/002	SmPC	17/12/2015	28/07/2016	Approved	Yes
To update section 4.2 of the SPC to introduce the option of self injection by patients. In addition, to update the Risk Management Plan. Consequently, the PIL has been updated.	UK/H/5497/001/II/003/G	SmPC, PIL and RMP	17/12/2015	28/07/2016	Approved	Yes

Annex 1

Reference: PL 00057/1498-0004
Product: SAYANAJECT 104 mg suspension for injection
Marketing Authorisation Holder: Pfizer Limited
Active Ingredient: Medroxyprogesterone acetate

Reason:
To update section 5.1 of the SmPC to update the Mode of Action statement to clarify the primary contraceptive mode of action of MPA and to delete a sentence concerning pharmacological effects on the endometrium.

Supporting evidence
The applicant has submitted updated section of the SmPC.

Evaluation
The amended section of the SmPC is satisfactory.

Conclusion
The grant of this variation is recommended.

Decision: Granted
Date: 28 July 2016

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

Type II variation
Final updted variation Assessment Report

Sayanaject 104 mg suspension for injection
(Medroxyprogesterone acetate)

UK/H/5497/001/II/002

Marketing Authorisation Holder: Pfizer Limited

I. RECOMMENDATION

Based on the review of the data on clinical pharmacology the RMS considers that the variation for Sayanaject indicated for contraception, for the proposed changes to section 5.1 of the Summary of Product Characteristics is approvable.

II. EXECUTIVE SUMMARY

II.1 Scope of the variation

This Type II CI.4 variation concerns changes to section 5.1 of the Summary of Product Characteristics. The change proposed is to update the Mode of Action statement to clarify the primary contraceptive mode of action of medroxyprogesterone acetate (MPA) and to delete a sentence concerning pharmacological effects on the endometrium.

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

MPA is a synthetic analogue of 17-hydroxyprogesterone, which has anti-estrogenic, anti-androgenic, and anti-gonadotropic effects. Progestins inhibit ovulation and cause changes in the cervical mucus that inhibit sperm mobility through cervical mucus and therefore entry into the uterine cavity. Clinical data are consistent in indicating that progestins, which include MPA, do not induce abortion.

III.3.1 Clinical pharmacology

Contraceptive Mechanism of Action of MPA

The proven mechanisms of action for depot medroxyprogesterone acetate (DMPA) contraception are to prevent ovulation principally through effects on the hypothalamic-pituitary-ovarian (HPO) axis to prevent sperm from entering the endometrial cavity by making the cervical mucus thick, tenacious and impenetrable to sperm between 6 and 24 hours after injection for most patients. The thinning of the endometrium is not proven to contribute to the contraceptive effect of MPA.

Evidence Showing that Medroxyprogesterone Acetate Does Not Prevent a Fertilized Ovum to Reach and be Implanted in the Mother's Womb

The proven mechanisms of action for DMPA contraception are to prevent ovulation principally through effects on the hypothalamic-pituitary-ovarian (HPO) axis and to prevent sperm from entering the endometrial cavity by making the cervical mucus thick, tenacious and impenetrable to sperm between 6 and 24 hours after injection for most patients. The female reproductive hormones including estrogens and progestins have physiologic effects on the endometrium particularly in terms of making it receptive for implantation around the 6^{th} to 7^{th} days following ovulation. With steady levels of estrogens and progestins, alone or in combination, the woman is anovulatory and does not experience the orchestrated hormonal events that lead to the development of a receptive secretory endometrium. Put another way, women using DMPA as labeled are very unlikely to ovulate, have intrauterine sperm and conceive, regardless of the status of the endometrium. Consistent with that concept, no DMPA clinical data that directly address the question on post-fertilization transport and implantation of the fertilized ovum in the womb were identified.

Non-Clinical Data

In-vitro:

Embryo implantation is a dynamic process of co-ordinated cell-to-cell contact and cell-to-extracellular matrix adherence which is modulated by female steroid hormones. MPA is the progestin used in tissue culture models for the study of endometrial receptivity and embryo implantation. The addition of MPA to estrogen primed endometrial tissue culture resulted in receptive endometrial tissue with a 70% rate of stable mouse embryo blastocyst attachment. This model is used to study blastocyst/embryo apposition and adhesion stages, endometrial invasion and hormonal signaling between embryo and endometrium. To better understand the complex network of molecular signaling modulated by endocrine and paracrine pathways, a three dimensional endometrial tissue culture system, a more clinically relevant model, is utilized by Wang. This system relies on MPA as the progestin to prepare the estrogen primed endometrial tissue for trophoblast invasion (a model for blastocyst endometrial attachment and invasion). The authors concluded that this 3D model, which uses MPA, allows for molecular and cellular events leading to implantation. These in-vitro data strongly suggest that DMPA would not prevent a fertilized ovum from reaching and implanting in the mother's womb.

In-vivo:

Effects of MPA on the genital tissues of the developing fetus have been demonstrated in non-clinical studies and are consistent with known effects of progestins.

Clinical Data

When used as directed DMPA is highly effective because the MPA inhibits ovulation by suppressing gonadotropin releasing hormone by the hypothalamus which suppresses the release of luteinizing hormone from the pituitary and thereby disrupts ovulation. With perfect use DMPA has a contraceptive failure rate per year of 0.2% and the typical use rate is 7%. For a contraceptive failure to occur, a user’s plasma level of MPA must fall low enough to allow for a series of carefully orchestrated physiologic hormonal changes to occur and to allow ovulation once the HPO suppression abates and cervical mucus changes to allow sperm penetration. Those changes including progesterone release from the corpus luteum progress to create the endocrine milieu for the tubal apparatus to be functioning properly, thus allowing fertilization of the oocyte in the ampulla and transport of the ovum to the endometrial cavity. These ovulatory events also induce postovulatory (secretory) endometrial changes to make the endometrium receptive and allow implantation of the blastocyst. The fact that pregnancies occurs with typical use of DMPA confirms that DMPA does not prevent the fertilized ovum from reaching and being implanted in the mother's womb.

Over the course of the normal menstrual cycle, the endometrium undergoes histologic changes which have been well documented, including the pattern at approximately 6-7 days post ovulation when attachment and invasion would occur if conception happened. It has been observed that established DMPA use is associated with deviations in which some, but not all, of the parameters typically seen at the time of implantation are absent. Thus it has been postulated that this may, theoretically, prevent implantation. No available data support prevention of implantation as a contraceptive action of MPA. The typical use contraceptive failure rate of 7% argues against endometrial change prevention of implantation hypothesis.

Progestins, natural and synthetic, have the progestagenic effect of inducing the estrogen-primed endometrium to the secretory endometrium necessary to support gestation. Synthetic progestins are designed to be potent, high-affinity progesterone receptor (PR) agonists that mimic the actions of progesterone but with better bioavailability.

The members of the class of progestins differ in relative receptor binding affinities which help to account for some of the other biologic differences observed in patients; however, it should be noted that, as shown in

Table **1**, MPA and levonorgestrel (LNG) have similar sex steroid relative binding receptor affinities, which supports the premise that they are similar with regards to their actions in the uterus.

Table 1. Receptor Binding Activities of Medroxyprogesterone Acetate (MPA) and Levonorgestrel (LNG)

Receptor	Relative Binding Affinity (%)	
	Medroxyprogesterone Acetate (MPA)	Levonorgestrel (LNG)
Progesterone Receptor (PR)	298	323
Androgen Receptor (AR)	36	58
Estrogen Receptor (ER)	<0.02	<0.02
Glucocorticoid Receptor (GR)	58	7.5
Mineralocorticoid Receptor (MR)	3.1	17

Abbreviations: MPA = medroxyprogesterone acetate; LNG = levonorgestrel

In addition to the similarities in PR, AR and ER receptor binding affinities, there are multiple studies which suggest that the effects on the uterus with LNG and MPA do not differ significantly. A study of the influence of progestins on uterine vascularity showed that there was no significant difference in pulsatility index and resistance index of the uterine artery on comparing the effects of LNG-releasing intrauterine system (Mirena®) and DMPA. A randomized controlled study to assess Mirena® and DMPA as long-term maintenance therapy for patients with moderate and severe endometriosis showed that the symptoms and recurrence of endometriosis were controlled by both therapies. An in vitro study evaluated the modulation of endometrial matrix metalloproteinase-1 (MMP-1) and matrix metalloproteinase-3 (MMP-3) and their inhibition for long-term contraceptive effects using progestins. The results demonstrated that all progestins (including DMPA and LNG) tested, both natural and synthetic, decreased the production of both MMP-1 and MMP-3. Although the relative degree of inhibition varied between different groups of progestins, in each group inhibition by all progestins, compared with the estradiol-only control, was substantial. Similarly, a comparison of altered expression of genes regulating immune activation and cell death in the upper reproductive tract of females using the DMPA and the LNG Intrauterine System (LNG-IUS) suggested similar alterations of gene expression (146 common genes), and endometrial upregulation of IGFBP1 and PRL, biomarkers of progesterone action in both DMPA and LNG-IUS group.

The potency of progestins is demonstrated in the rabbit endometrial model and clinical studies assessing progestogenic effects in estrogen-primed endometria. The clinical data show that relative to norethindrone the potency of LNG was 8-fold greater, whereas the potency of MPA was 10 times lower. The progestin doses for endometrial protection based on these potencies are 0.15mg–0.5mg for LNG and 2.5mg–10mg for MPA. The average steady-state AUC for DMPA 150 mg is 1.66 ng.hr/mL for a 24 hour period and the daily steady-state AUC_{24} for MPA 10 mg is 6.01 ng.hr/mL, which are sufficiently similar to suggest that the effect on the endometrium would be similar to that of LNG 0.15mg–0.5mg.

Therefore, on the basis of clinical effects, anatomical site of action, comparable affinity to progesterone and estrogen receptors within endometrium, and on uterine microcirculation, relative thickness of endometrium, and alteration in gene expressions, there are relevant similarities between LNG and DMPA.

LNG emergency contraception (EC) can provide insight on the periovulatory and potential peri-implantation effect through studies of the pre-ovulation and post-ovulation and/or post-fertilization periods. The current standard of EC, LNG-only, has an extensive and contemporaneous body of literature on the mechanism of action which is relevant to the Agency's request. Those data are well summarized in the The Norvelo® public assessment report which concludes language on implantation or endometrial effect should no longer be included in Norlevo® (levonorgestrel) EC products labelling. We believe that the aforementioned similarities between LNG and MPA support the concept that the following LNG data may be applicable to DMPA.

The Norvelo® public assessment report extensively reviewed the LNG EC mechanism of action literature as follows:

"Several clinical studies have evaluated the mechanism of action of high-dose LNG used for emergency contraception. The primary mechanism of action has been shown to involve blockade and/or delay of ovulation via suppression of the luteinizing hormone (LH) peak.

Studies conducted more recently to evaluate additional potential mechanisms (in particular, post-ovulation and/or post-fertilization effects) consistently conclude that the contraceptive efficacy of LNG for EC is not related to endometrial effects;

In vitro studies have shown that LNG treatment does not prevent the attachment of human embryos to a simulated endometrial environment nor does it alter the relevant endometrial receptivity markers studied. Animal studies in the rat and the monkey also clearly demonstrated that EC dose LNG did not disrupt post-fertilization events.

Clinical studies in women have also evaluated whether LNG EC alters the histological and biochemical characteristics of the endometrium. In multiple studies, LNG in EC doses was administered at mid-cycle followed by endometrial biopsy at the expected time of implantation. No significant endometrial alterations were observed. One study found a single altered endometrial parameter only when LNG was administered prior to the LH surge, the time when EC has been shown to inhibit ovulation.

No changes were seen in the two groups who received the medication later at the time of LH rise or 48 hours after the LH peak. In another study evaluating double the standard dose of LNG EC, none or minor alterations in endometrial receptivity were observed. Furthermore, in two clinical studies, the effectiveness of LNG EC was studied when the cycle day was determined by hormonal analysis (while other studies have used less precise self-reported cycle dates). In these studies, no pregnancy occurred in women who took EC before ovulation, while pregnancies occurred only in women who took EC on or after the day of ovulation, providing evidence that EC were unable to prevent implantation.

In conclusion, multiple studies have demonstrated the primary mechanism of LNG EC to block or delay of ovulation. Review of the evidence suggests that LNG EC cannot prevent implantation of a fertilized egg.

Overall, the results obtained from both recent studies sustain that efficacy of emergency contraception with levonorgestrel can be expected only if treatment is taken before ovulation and not later than the day of ovulation. This excludes effect on implantation.

Based on this assessment, it was agreed that language on implantation or endometrial effect should no longer be included in Norlevo® products labelling. Such mentions were subsequently removed from the product information.

Conclusion

There is no evidence that Depo-Provera® and Sayana Press® prevent a fertilized ovum from reaching and implanting in the mother's womb. This concept is supported, first and foremost, by the notable proportion of pregnancies observed with typical DMPA use and, also by the interpretation of the in-vitro non-clinical and clinical literature for MPA, as well as the LNG EC literature.

Contraceptive failure provides a natural experiment to assess tubal transport, endometrial receptivity and implantation of the fertilized ovum. Pregnancy demonstrates Depo-Provera® or Sayana Press® absence of preventing the transport and implantation of the ovum. This cannot be done in a relevant experimental setting. If this contraceptive product prevented the fertilized ovum from reaching the womb and from being implanted there would not be the up to a 7% failure rate seen with typical use of a product that effectively prevents ovulation and the entry of sperm into the uterus. Additionally, in the laboratory, MPA is the progestin used to prepare the estrogen primed endometrial tissue for trophoblast invasion (a model for blastocyst endometrial attachment and invasion) in 2 and 3 dimensional tissue culture systems. The similarities between DMPA and LNG further suggest that the rigorous contemporary preclinical and clinical studies supporting LNGs inability to prevent implantation of a fertilized egg which lead to the EMA PRAC's decision to remove language on implantation or endometrial effect from labelling for Norlevo® (LNG) products in Europe may be relevant for DMPA**.**

The intention of this variation is to modify the statement on the mechanism of action of Depot Medroxyprogesterone Acetate (DMPA) that is presently included in section 5.1 of the SmPC.

Medroxyprogesterone Acetate mode of action has been investigated in a number of studies. It appears to act primarily by inhibiting the secretion of gonadotropins thereby preventing follicular maturation and inhibiting ovulation. According to a study, DMPA appears to act primarily from its action at the pituitary and hypothalamic levels. It prevents the mid-cycle surge of LH necessary for ovulation i.e. suppression of ovulation. In addition, DMPA has an effect on the cervical mucus making it scanty and thick and thus preventing sperm penetration. However, DMPA also decreases the proliferation of the endometrium which is secondary to it inhibiting ovulation. There is no suggestion however that DMPA acts primarily to prevent implantation.
Overall, the rationale provided to support the mechanism of action of DMPA is considered to be adequate.
The proposal not to include endometrial thinning as part of the mode of action in line with other progestins including levonorgestrel containing emergency contraception is considered acceptable as:

- *Thinning of the endometrium is not the primary mode of action of DMPA*
- *There is no evidence to suggest that DMPA prevents implantation (the 7% failure rate seen with typical use of DMPA mitigates against this notion)*

In conclusion, the proposed changes to section 5.1 of the SmPC are considered acceptable.

III.3.2 Clinical efficacy

N/A

Product information

III.4.1 Summary of Product Characteristics

The MAH is proposing to update Section 5.1 Pharmacodynamic properties as follows:

DMPA subcutaneous injection inhibits the secretion of gonadotropins which, in turn, prevents follicular maturation and ovulation and causes thickening of cervical mucus which inhibits sperm entry into the uterus. These actions produce its contraceptive effect.

Assessor's comment
The proposed change is acceptable.

III.4.2 Package leaflet and user test

N/A

III.4.3 Labelling

N/A

IV. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Based on a review of the supporting documentation submitted by the company, the variation application to update section 5.1 (Pharmacodynamics) of the SmPC is considered approvable. The benefit risk of Sayanaject suspension for injection remains unchanged.

Annex 2

Reference: PL 00057/1498-0005
Product: SAYANAJECT 104 mg suspension for injection
Marketing Authorisation Holder: Pfizer Limited
Active Ingredient: Medroxyprogesterone acetate
Reason: To update section 4.2 of the Summary of Product Characteristics (SmPC) and Patient Information Leaflet (PIL) to introduce the option of self injection by patients. In addition, to update the Risk Management Plan.

Background
SAYANAJECT 104 mg suspension for injection (DMPA-SC in Uniject) was initially approved for use as an injectable contraceptive when administered by a Healthcare professional (HCP) and requires 3-monthly clinic visits by patients. The Marketing Authorisation Holder (MAH) proposes the self-injection of Sayanaject, 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.

Evaluation
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: 28 July 2016

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

Type II variation
Final Variation Assessment Report

Sayanaject suspension for injection 104 mg suspension for injection
Medroxyprogesterone acetate

UK/H/5497/001/II/003/G

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 Sayanaject 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

III. Scope of the variation

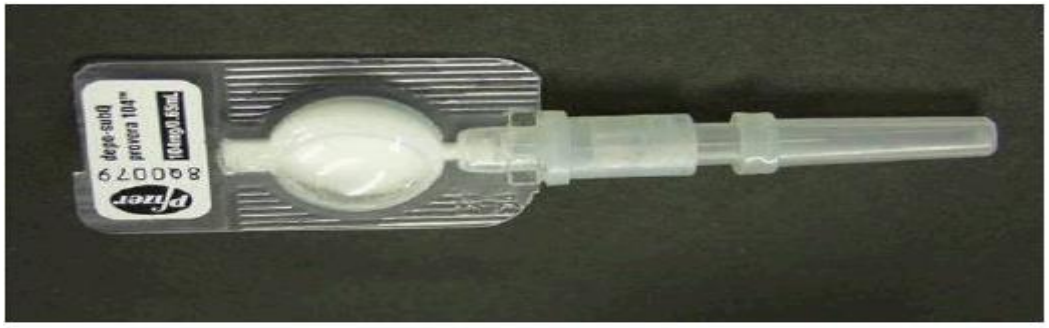
This Type II C.I.4 variation concerns changes to section 4.2 of the Summary of Product Characteristics with consequential changes to the Patient Information and Instructions for Use for Sayanaject (medroxyprogesterone acetate 104mg/0.65ml) to introduce the option of self-injection by patients.

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

III. SCIENTIFIC DISCUSSION

III.1 Clinical aspects

Sayanaject (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 Sayanaject, as an option to women who according to the MAH can independently perform the procedure reliably and safely. The container closure system for Sayanaject utilises a prefilled plastic reservoir with needle attached, designed for single use and immediate disposal.



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 III, 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 questionnaire (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 visit at which it was administered. With the response to each item rated on a scale from 1 to 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.

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.

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.

From the information provided it would appear that no pregnancies occurred at all in the study as a whole.

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.

Conclusion

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 Sayanaject consists of a prefilled plastic reservoir with a needle already attached i.e. the uniject system.

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 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 sayanaject 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 of the subjects 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.

Most of the subjects were satisfied with the method.

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 Sayanaject 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 the uniject system 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)
According 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 provided data from four studies to support the application to allow self-administration of sayanaject 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) in 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 is apparent 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 sayanaject 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 would also appear that errors can occur during the use of the delivery system. It is however crucial to note that the participants in this study did not self-inject.

It is clear 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 applicant considered that the results of Study GA67815 provided evidence that women were 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.

It is accepted that 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 therefore 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 available in the PIL.

Overall, taking into consideration that the DMPA-SC suspension in the uniject is identical to the suspension used in the PFS; the results of studies 267, 269 and GA67815 demonstrated that women were able to self-inject and the results of the usability study showed that women were to follow instructions after training the proposal by the MAH for women to self-inject using sayanaject is considered acceptable.

IV. III.3.3 Clinical safety

The safety profile of DMPA-SC injection was demonstrated in three Phase III 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), inter-menstrual 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), inter-menstrual 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 III 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

Conclusion on Safety
The safety of DMPA-SC has previously been characterised and there are no particular issues. The occurrence of local injection site reaction has previously been noted; in study A67815 the incidence was approximately 10%. There were no adverse events of note reported that are considered to be related to self-administration.

Product information

III.4.1 Summary of Product Characteristics

Suitable changes have been made to the SmPC fragment.

III.4.2 Package leaflet 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 provided 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 depot medroxyprogesterone acetate, intramuscular (DMPA-IM) 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 Sayanaject 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. In addition, The MAH has also provided details of the training proposed for women. This included guidance for Healthcare Practitioners to aid training, educational videos, pamphlets, a website and reminder aids. The proposals were considered to be appropriate and acceptable subject to appropriate vetting to ensure that promotional material is not included.

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

The applicant considered that the results of Study GA67815 provided evidence that women were 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.

It is accepted that 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 therefore 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 available in the PIL.

Overall, taking into consideration that the DMPA-SC suspension in the uniject is identical to the suspension used in the PFS; the results of studies267, 269 and GA67815 demonstrate that women are able to self-inject and the results of the usability study showed that women were to follow instructions after training the proposal by the MAH for women to self-inject using sayanaject is considered acceptable and the benefit risk for Sayanaject remains unchanged.

In conclusion the variation application to allow self-injection is considered approvable.

V. REQUEST FOR SUPPLEMENTARY INFORMATION AS PROPOSED BY THE RMS

V.1 Potential serious risks to public health

None

V.2 Points for clarification

None