19 September 2013
EMA/685541/2013
Committee for Medicinal Products for Human Use (CHMP)

CHMP assessment report

Lidocaine/Prilocaine Plethora

International non-proprietary name: lidocaine / prilocaine

Procedure No. EMEA/H/C/002693/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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An agency of the European Union

Product information

Name of the medicinal product:	Lidocaine/Prilocaine Plethora
Applicant:	Plethora Solutions Ltd. Hampden House, Monument Business Park, Chalgrove, OX44 7RW, UK
Active substance:	lidocaine / prilocaine
International Nonproprietary Name/Common Name:	lidocaine / prilocaine
Pharmaco-therapeutic group (ATC Code):	Anaesthetics, local (N01BB20)
Therapeutic indication:	Lidocaine/Prilocaine Plethora is indicated for the treatment of primary premature ejaculation in adult men.
Pharmaceutical form:	Cutaneous spray, solution
Strength:	150 mg/ml + 50 mg/ml
Route of administration:	Cutaneous use
Packaging:	Sprayer (alu)
Package size:	1 spray

Executive summary

Premature ejaculation (PE), also referred to as early (EE) or rapid ejaculation (RE), is generally defined by three essential criteria: brief ejaculatory latency; loss of control; and psychological distress in the patients and/or partner (Althof et al. 2010). According to the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, version IV (DSM-IV TR), PE is described as 'the persistent or recurrent onset of ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The disturbance must cause marked distress or interpersonal difficulty. The premature ejaculation is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids)'. PE has two subtypes: lifelong and acquired PE. Lifelong PE is characterised by early ejaculation at every/or nearly every intercourse with every or nearly every sexual partner from the first sexual encounter onwards, whereas men with acquired PE develop early ejaculation at some point in their life having previously had normal ejaculation experiences (Wespes E et al. 2006).

The approaches to the management of PE have been primarily based on behavioural techniques and pharmacological treatment with selective serotonin reuptake inhibitors (SSRIs). The latter is based on increasing the time it takes to ejaculate by preventing the neurotransmitter 5-hydroxytryptamine (serotonin) from being taken back up into nerve cells in the brain and spinal cord.

In September 2013, the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) recommended the authorisation of Lidocaine/Prilocaine Plethora (lidocaine/prilocaine) for the treatment of premature ejaculation in adult men. Lidocaine/Prilocaine Plethora (also called PSD502, TEMPE) contains the active substances lidocaine and prilocaine, local anaesthetics that act by blocking the transmission of nerve impulses, reducing sensory stimulation. The medicine has been developed as a cutaneous spray solution able to provide rapid-onset topical anaesthesia to the glans penis mucosal surface for the treatment of primary premature ejaculation in adult men. The recommended dose is 3 actuations applied to cover the glans penis. Each such dose supplies a total of 22.5 mg lidocaine and 7.5 mg prilocaine. A maximum of 3 doses can be used within 24 hours with at least 4 hours between doses.

Clinical efficacy of lidocaine/prilocaine in males with PE was demonstrated in two multi-centre, multinational, randomised, double-blind, placebo controlled studies, both followed by an open-label phase. In the general population of patients with PE, lidocaine/prilocaine was shown to increase the time to achieve ejaculation after penetration (intra-vaginal ejaculatory latency time or IELT, an indicator of pharmacological activity); it also increased control over ejaculation and reduced the feelings of distress in patients with premature ejaculation as measured by the Index of Premature Ejaculation (IPE). During the 3 months of the double-blind treatment phase, the average IELT increased from 0.58 to 3.17 minutes in the Lidocaine/Prilocaine Plethora group and from 0.56 to 0.94 minutes in the placebo group. The clinically significant increases in IELT were paralleled by significant differences in the IPE scores ($p < 0.0001$).

The most common side effects were hypoaesthesia (reduced sensation) and genital burning in both men and women, plus erectile dysfunction in men and headache, influenza, nasopharyngitis and vulvovaginal discomfort in female sexual partners.

Although the lidocaine/prilocaine clinical development program allowed inclusion of males with no upper age limit, due to the low number of elderly subjects enrolled, there are limited data on the efficacy and safety of Lidocaine/Prilocaine Plethora in patients 65 years and over.

The metabolism of lidocaine and prilocaine results in the formation of 2,6-xylidine and *o*-toluidine, respectively, amongst other metabolites. Therefore prilocaine in high doses may cause an increase in

methaemoglobin level. Caution should therefore be raised in patients with anaemia, congenital or acquired methaemoglobinaemia or patients on concomitant therapy known to produce such conditions.

In an *ex-vivo* study in rats, Lidocaine/Prilocaine Plethora was shown to reduce sperm motility and therefore the potential for reduction of sperm motility following clinical use of the medicinal product cannot be excluded.

A pharmacovigilance plan for Lidocaine/Prilocaine Plethora will be implemented as part of the marketing authorisation. The risk management plan includes an updated drug-utilisation study aimed to characterise real clinical practice and the patients who are prescribed the product.

Lidocaine/Prilocaine is not expected to pose a risk to the environment. The Applicant should provide the study reports of the experimental determination of the log Kow value for both lidocaine and prilocaine.

Overall, the efficacy of lidocaine/prilocaine over placebo has been demonstrated. The adverse effect profile of lidocaine/prilocaine for both male subjects and their female partners appears to be benign and manageable and no new safety signals have been observed with lidocaine/prilocaine. Therefore the benefit/risk balance of lidocaine/prilocaine in the treatment of premature ejaculation in adult men is considered positive.

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LIST OF ABBREVIATIONS

ALT:	Alanine aminotransferase
ASA:	American Society of Anaesthesiologists
AST:	Aspartate aminotransferase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area under the concentration curve
BLD:	Below Limits of Detection
BMI:	Body mass index
BMS:	Biomedical Systems
BW:	Body Weight
BWG:	Body Weight Gain
CFR:	Code of Federal Regulations
CHMP:	Committee of Human Medicinal Products
CIL :	Central Imaging Lab
CIN :	Cervical intraepithelial neoplasia
cm :	Centimeter
Cmax:	Maximum plasma concentration
CNS:	Central Nervous System
CPMP:	Committee for Proprietary Medicinal Products
CRF:	Case report form
CSR:	Clinical study report
CT:	Computed tomography
CTD:	Common Technical Dossier
CU:	Clinical unit
CVS:	Cardiovascular System
DB:	Double-blind
dd:	daily dose
DDD:	Defined Daily Dose
DNA:	Deoxyribonucleic acid
DVD:	Digital Versatile Disk
DSM-IV TR:	Diagnostic and Statistical Manual of Mental Disorders, version IV
EC:	European Community
ECG:	Electrocardiogram
eCRF:	Electronic case report form
EE:	Early Ejaculation
EMA:	European Medicines Agency
ERCP:	Endoscopic retrograde cholangiopancreatography
EU:	European Union
EUS:	Endoscopic ultrasound
FDA:	Food and Drug Administration
Fpen:	Penetration Factor
GGT:	Gamma-glutamyl transferase
GLP:	Good Laboratory Practice
h:	Hour
Hb:	Haemoglobin
HIV:	Human immunodeficiency virus
HPLC:	HIGH Pressure Liquid Chromatography
Hr:	Hour
i.e.:	id est
i.v.:	Intravenous/ly
IARC:	International Agency for Research on Cancer
ICH:	International Conference on Harmonisation
ID:	Identification
IELT:	Intravaginal Ejaculatory Latency Time
IIEF-5:	International Index of Erectile Function 5
IPE:	Index of Premature Ejaculation
IPMN:	Intraductal papillary mucinous neoplasm
IRC:	Independent Review Charter
ISE:	Integrated Summary of Efficacy
ITT:	Intention-to-treat
IU:	Indiana University

IUDB:	Indiana University Database
IV:	Intravenous use
kg:	Kilogram
KUB:	Kidney, Ureter and Bladder
L:	Liter
LC-MS/MS:	Liquid Chromatography-tandem Mass Spectrometry.
LDL:	Low-density lipoprotein
LLOQ:	Lower Limit of Quantification
LLQ:	Limit of quantification
LOD:	Limit of detection
ma:	maximal annual amount of drug substance
MAOIs:	Monoamine oxidase inhibitors
MedDRA:	Medical Dictionary for Regulatory Activities
mg:	Milligram
MHRA:	Medicines and Healthcare Products Regulatory Agency
mL:	Milliliter
mm:	Millimeter
MPD:	Main pancreatic duct
MRCP:	Magnetic resonance cholangiopancreatography
MRI:	Magnetic resonance imaging
MTD:	Maximum Tolerated Dose
N:	Number of subjects with non-missing value of the variable
NA:	Not applicable
NCI:	National Cancer Institute
ND:	No Data
ng:	Nano-gram
NIH:	National Institutes of Health
NOAEL:	No Observed Adverse Effect Level
NOEL:	No observed effect level
OL:	Open-label
Pap:	Papanicolaou [smear]
PBT:	Persistence, Bioaccumulation and Toxicity
PCA:	Patient-controlled analgesia
PD:	Pharmacodynamics
PE:	Premature ejaculation
PEC:	Predicted Environmental Concentration
PECsw:	PECsurfacewater
pH:	Potential of hydrogen
PIP:	Paediatric Investigation Plan
ppm:	parts per million
QC:	Quality Control
r:	Correlation coefficient
RE:	Rapid Ejaculation
SAE:	Serious adverse events
SAP:	Statistical analysis plan
SD:	Standard deviation
S-D:	Sprague Dawley
SME:	Small and Medium-sized Enterprise
S-MRCP:	Secretin-stimulated magnetic resonance cholangiopancreatography
SOC:	System organ class
SOP:	Standard Operating Procedure
SPC:	Summary of Product Characteristics
SSRI:	Selective serotonin reuptake inhibitor
STD:	Sexually-transmitted disease
SWP:	Safety Working Party
T:	Tesla
T½:	Apparent half-life
T½el:	Terminal Elimination half-life
TEAE:	Treatment-emergent adverse event
Tmax:	Time of maximum concentration
UK:	United Kingdom
UV:	Ultraviolet
WHO:	World Health Organisation
µg:	Microgram

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Plethora Solutions Ltd. submitted on 1 June 2012 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Lidocaine/Prilocaine Plethora, through the centralised procedure under Article 3 (2) (b) of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 16 February 2012. The eligibility to the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004 was based on demonstration of significant therapeutic innovation.

The applicant applied for the following indication: Treatment of primary premature ejaculation in adult men.

The legal basis for this application refers to:

Article 10(b) of Directive 2001/83/EC – relating to applications for new fixed combination products.

The application submitted is a new fixed combination medicinal product.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/79/2008 on the granting of a (product-specific) waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

New active Substance status

Not applicable.

Scientific Advice

The applicant did not seek scientific advice at the CHMP.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Catalent Pharma Solutions
Blagrove
Frankland Road
Swindon

SN5 8YG
United Kingdom

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Concepcion Prieto Yerro Co-Rapporteur: Greg Markey

- The application was received by the EMA on 1 June 2012.
- The procedure started on 20 June 2012.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 21 September 2012. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 18 September 2012.
- During the meeting on 18 October 2012, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 19 October 2012.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 26 April 2013.
- The summary report of the inspection between 24-25 April 2013 was issued on 6 June 2013. The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 27 May 2013.
- During the meeting on 13 June 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the CHMP meeting on 27 June 2013, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 19 August 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Outstanding Issues to all CHMP members on 27 August 2013.
- During the meeting on 5 September 2013 the Pharmacovigilance Risk Assessment Committee (PRAC) adopted the PRAC Advice on the submitted Risk Management Plan.
- During the meeting on 19 September 2013, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation Lidocaine/Prilocaine Plethora on 19 September 2013.

2. Scientific discussion

2.1. Introduction

Problem statement

Although there is no clear consensus on the definition of Premature ejaculation (PE), also referred to as early (EE) or rapid ejaculation (RE), it is generally accepted it consists of three essential criteria: brief ejaculatory latency; loss of control; and psychological distress in the patients and/or partner (Althof et al. 2010). According to the American Psychiatric Association's Diagnostic and Statistical Manual of

Mental Disorders, version IV (DSM-IV TR), rapid (premature) ejaculation is defined as 'the persistent or recurrent onset and ejaculation with minimal sexual stimulation before, on, or shortly after penetration and before the person wishes it. The disturbance must cause marked distress or interpersonal difficulty. The premature ejaculation is not due exclusively to the direct effects of a substance (e.g., withdrawal from opioids)'.

PE is the commonest sexual complaint, affecting 30% of sexually active men (Lauman, 1999) to as high as 66% in Germany (Aschka et al., 2001). Also PE is self-reported and the obvious stigma associated with it is likely to lead to it being underreported. Furthermore it is important to clearly distinguish between PE and Erectile Dysfunction (ED) as they may coexist.

Ejaculation generally occurs because of reflex mechanism initially triggered by stimulation of the penis via pudendal sensory nerves, with communication to the spinal cord and the sensory cortex. The secondary reflex is completed after activation of the efferent somatic fibers to the ischiocavernosus and other perineal muscles. The aetiology of PE is however not well understood, with little data to support suggested biological and psychological hypotheses (Rowland et al., 1993), including anxiety, penile hypersensitivity (Xin et al., 1997) and serotonin receptor dysfunction.

PE comprises several subtypes; lifelong or acquired PE. Lifelong PE is characterised by early ejaculation at every/or nearly every intercourse with every or nearly every sexual partner from the first sexual encounter onwards. Men with acquired PE develop early ejaculation at some point in their life having previously had normal ejaculation experiences (Wespes E et al. 2006). In 2008 the International Society for Sexual Medicine defined lifelong PE as a male sexual dysfunction characterised by "….ejaculation which always or nearly always occurs prior to or within about one minute of vaginal penetration, the inability to delay ejaculation on all or nearly all vaginal penetrations, and the presence of negative personal consequences, such as distress, bother, frustration and/or the avoidance of sexual intimacy" (McMahon et al. 2000).

Acquired PE may be due to sexual performance anxiety, psychological or relationship problems, erectile dysfunction, prostatitis or hyperthyroidism among other causes. Several psychoactive drugs can cause delayed or retarded ejaculation.

A detailed and complete sexual history should be obtained for all patients for the correct diagnosis to be established. This should be accompanied with a questioning of the patients about frequency and duration of activity required for ejaculation, as well as whether the problem exists with certain types of sexual stimulation versus others. New devices that can stimulate patients to ejaculation may be useful (O'Leary et al., 2001).

The approaches to the management of PE have been primarily based on behavioural techniques and pharmacological treatment (selective serotonin reuptake inhibitors (SSRIs)).

The current available pharmacological treatment for PE is based on increasing the time it takes to ejaculate by preventing the neurotransmitter 5-hydroxytryptamine (serotonin) from being taken back up into nerve cells in the brain and spinal cord, thereby increasing the amount of serotonin between nerve cells. At the present time, no CHMP scientific guidelines specific for PE are available.

About the product

Lidocaine/Prilocaine Plethora also called as PSD502, TEMPE, cutaneous spray, solution is a formulation developed by the applicant to provide rapid onset topical anaesthesia to the glans penis mucosal surface for the treatment of primary premature ejaculation in adult men.

The pharmacological mode of action of lidocaine and prilocaine is well established. Like other local anaesthetics, they act directly on nerve cells to block their ability to transmit impulses down their axons. Lidocaine and prilocaine have similar anaesthetic potency. The molecular targets of both are the voltage-dependent sodium channels of neurons. The drugs bind selectively to the intracellular surface of sodium channels and block the entry of sodium into the cell. The blocking of sodium influx prevents the depolarisation necessary for action potential propagation and at sufficient concentrations block impulse conduction. Since binding of lidocaine and prilocaine to sodium channels is completely reversible, when drug administration is stopped the drug diffuses away. Restoration of active sodium pumping and continued leakage of potassium restores the membrane potential to its polarised state. The membrane potential remains deactivated and refractory to further stimulation for a short period. Eventually nerve function is completely restored (Lagan and McLure, 2004; Becker and Reed, 2006).

Lidocaine has a rapid onset of action and anaesthesia is obtained within a few minutes, with an intermediate duration of action. Prilocaine has a slower onset of action with slightly longer duration of action (Martindale Lidocaine 2012, Martindale Prilocaine 2012). The combination of lidocaine and prilocaine in PSD502 provides a rapid onset of action. So, application of lidocaine and prilocaine in their base forms at a pH of 8.0, optimises penetration, maximising the depth of neural blockade and minimising time to onset of numbness (Henry et al., 2008). Lidocaine and prilocaine, are well known substances that have been used extensively for many years in various formulations, including creams, gels and solutions, which are available over-the-counter or on 'prescription only' depending on their concentration and use. Lidocaine and prilocaine have been used in anaesthesia for many years, and as such there is considerable experience with these drugs in the healthcare industry. In addition to anaesthesia, lidocaine has been widely used in treatment of ventricular arrhythmias.

Lidocaine/prilocaine cutaneous spray, solution incorporates a combination of two active substances, lidocaine and prilocaine at concentrations of 150 mg/ml and 50 mg/ml respectively.

The combination of lidocaine and prilocaine results in a lowering of the melting point of the mixture in comparison to the melting point of the individual components. As such they co-exist in an appropriate ratio in liquid form at standard temperature and pressure. Both drug substances are readily absorbed through mucous membranes such as the glans penis, but not through normal keratinised skin. The only other constituent of the spray is the propellant 1,1,1,2-tetrafluoroethane (also referred to as HFA-134a and norflurane), which is a commonly used propellant in pharmaceutical products within the EU.

Lidocaine/Prilocaine Plethora cutaneous spray is presented as a 6.5 ml filled in an aluminium spray container with metered valve. Each spray dispenses 50 µL of solution (PSD502 delivers 7.5 mg lidocaine and 2.5 mg prilocaine per metered-dose spray (actuation)) and each dose consists of three spray actuations. After application, the propellant evaporates, leaving a thin layer of the drugs on the glans penis.

Type of Application and aspects on development

This application is submitted under Article 10b of Directive 2001/83/EC (i.e. fixed combination).

The proposed indication for Lidocaine/Prilocaine Plethora 150 mg/mL + 50 mg/mL cutaneous spray, solution is treatment of primary premature ejaculation in adult men.

No formal scientific advice was given by the EMA for this medicinal product.

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as a cutaneous spray containing 150 mg/ml of lidocaine and 50 mg/ml of prilocaine as active substances.

Other ingredients are: 1,1,1,2-tetrafluoroethane.

The product is available in an aluminium spray container with metering valve.

The product is presented in an aluminium metered-spray-can with valve.

2.2.2. Active Substance

Lidocaine

The chemical name of lidocaine is 2-(diethylamino)-N-(2, 6-dimethylphenyl) acetamide and has the following structural formula:

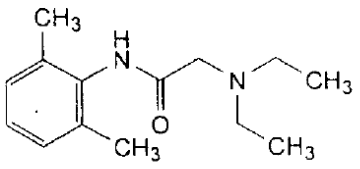

Figure 1: Lidocaine

Lidocaine is a white or almost white, crystalline powder, practically insoluble in water and very soluble in alcohol and in methylene chloride.

As there is a monograph of lidocaine in the European Pharmacopoeia, the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for lidocaine which has been provided within the current Marketing Authorisation Application.

Manufacture

A Certificate of Suitability (CEP) has been granted for the active substance. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of lidocaine.

Stability

The CEP of the active substance manufacturer includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

Prilocaine

The chemical name of prilocaine is N-(2-methylphenyl)-2-propylamino-propanamide and has the following structural formula:

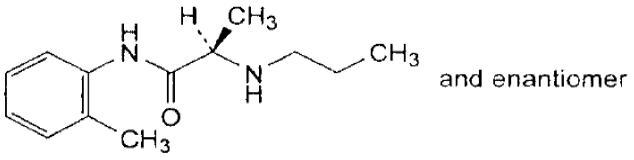

Figure 2: Prilocaine

Prilocaine is a white or almost white, crystalline powder, slightly soluble in water and very soluble in acetone and in ethanol (96 per cent).

The active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for prilocaine which has been provided within the current Marketing Authorisation Application.

Manufacture

A Certificate of Suitability (CEP) has been granted for the active substance. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

Specification

The active substance will be tested and assessed by the finished product manufacturer applying the methods and specifications laid down in the Ph. Eur. monograph and CEP of prilocaine.

Stability

The CEP of the active substance manufacturer includes a suitably validated re-test period in a defined container closure system, supported by the available stability data.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

The objective of the pharmaceutical development was to develop a cutaneous spray to provide rapid onset of topical anaesthesia to the glans penis mucosal surface for the treatment of premature ejaculation in adult men.

The medicinal product is a metered-dose aerosol spray that delivers a mixture of lidocaine and prilocaine. It provides a film of local anaesthetic when delivered at the site of application.

Each actuation dispenses 7.5 mg lidocaine and 2.5 mg prilocaine in their base forms. The active substances are mixed in a 3:1 ratio and have a pKa that is favourable for the absorption through mucous membranes.

The only excipient present in the formulation is the propellant 1,1,1,2-tetrafluoroethane, which evaporates at the site of application following actuation. Tetrafluoroethane is a well-established, commercially available, non-flammable, non-CFC propellant. This excipient is used as both a propellant and solvent, eliminating the requirement for additional surfactants or vehicles.

The formulation used during clinical studies is the same that the used for marketing.

The primary packaging is an aerosol can with a valve, dip tube, button actuator collar and dust cap. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Compatibility studies were performed with a wide range of materials that are used in contraceptive devices currently on the EU market (male condom, cervical cap, the diaphragm and the female condom). Deterioriation was observed when Lidocaine/Prilocaine Plethora was used with polyurethane-based female and male condoms. A statement is included in the package leaflet that polyurethane-based barrier contraceptives do not provide effective contraception when lidocaine/prilocaine cutaneous spray is used.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of four main steps: (1) mixing, (2) filling, (3) additional filling with tetrafluoroethane and (4) packaging. The process is considered to be a standard manufacturing process.

The major steps of the manufacturing process have been validated by a number of studies. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this cutaneous spray.

Product specification

The finished product release specifications include include tests for appearance (visual inspection), identification of lidocaine (HPLC, TLC), identification of prilocaine (HPLC, TLC), assay of lidocaine and of prilocaine (HPLC), dose content uniformity (HPLC), uniformity of delivered dose (HPLC), impurities (HPLC), mean content delivered per dose (HPLC), number of expelled actuations (shot counting), moisture (Karl Fisher), leakage rate (weight check) and microbial contamination (Ph. Eur.).

Batch analysis results are provided for five production batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability of the product

Stability data of four production scale batches stored under long term conditions for 36 months at 25ºC/60%RH and for up to 6 months under accelerated conditions at 40ºC/75%RH according to the ICH guidelines were provided. The batches of lidocaine/prilocaine cutaneous spray are identical to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested for all parameters as stated in the finished product specification.

Testing was performed with the finished product in the upright position with reduced testing performed in an inverted position to provide information on the effect of the orientation. The analytical methods

used in stability study are identical to those used in the release of drug product and therefore no further validation studies were necessary. The analytical procedures used are stability indicating.

In addition, a freeze/thaw study was conducted on two batches and a temperature excursion study was performed on one batch of lidocaine/prilocaine cutaneous spray. Forced degradation studies were also performed on one batch and in-use stability studies were performed on two batches of lidocaine/prilocaine cutaneous spray. The temperature excursion study was performed to evaluate the effect of storage in extreme temperature conditions (60°C) for 7 days. The significant change was in the leakage rate, however, as a worst-case scenario, if the drug product was stored at 60°C for 3 weeks, approximately 161 mg will be lost, which is less than 3 actuations. If the drug product is inadvertently exposed to temperatures up to 60°C for two days, no adverse effects are anticipated. The forced degradation study demonstrated that oxidation is the only stressed condition that results in significant degradation of the drug product and drug substances. The results of the in-use study support an in-use shelf life of 12 weeks.

Based on available stability data, the shelf-life and storage conditions as stated in the SmPC are acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.3. Non-clinical aspects

2.3.1. Introduction

The majority of the studies have been conducted in accordance with Good Laboratory Practice (GLP). The non-GLP studies generally were conducted in a GLP compliant facility and the practices and procedures adopted during their conduct were consistent with the OECD Principles of Good Laboratory Practice. In this assessment report, CHMP/ICH Non-clinical Guidelines have been considered, and mainly ICH Topic M3 (R2): Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals (CPMP/ICH/286/95), Note for guidance on safety pharmacology studies for human pharmaceuticals CPMP/ICH/539/00 (ICH topic S7A), ICH M 4S, common technical document for the registration of pharmaceuticals for human use – Safety (CPMP/ICH/2887/99-Safety), Note for Guidance on the detection of toxicity to reproduction for medicinal products & Toxicology to male fertility (CPMP/ICH/386/95), Note for Guidance on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95 (ICH topic S1A)), Non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/05), Non-clinical documentation for mixed marketing authorisation applications (EMEA/CHMP/SWP/799/95) and Environmental risk assessment of medicinal products for human use (CHMP/SWP/4447/00).

2.3.2. Pharmacology

Lidocaine/Prilocaine Plethora, also called PSD502, TEMPE, is a cutaneous spray formulation developed by Plethora Solutions Ltd. to provide rapid onset topical anaesthesia to the glans penis mucosal surface for the treatment of primary premature ejaculation in adult men. The local anaesthetic effects reduce penile sensitivity and so increase ejaculatory latency time. PSD502 contains the drug substances lidocaine and prilocaine at concentrations of 150 mg/ml and 50 mg/ml respectively, dissolved in 1,1,1,2-tetrafluoroethane. This, also referred to as HFA-134a and norflurane, is a commonly used propellant in pharmaceutical products within the EU.

The pharmacological mode of action of lidocaine and prilocaine is well established. Like other local anaesthetics, they act directly on nerve cells to block their ability to transmit impulses down their axons. Lidocaine and prilocaine have similar anaesthetic potency. The molecular targets of both are the voltage-dependent sodium channels of neurons. The drugs bind selectively to the intracellular surface of sodium channels and block the entry of sodium into the cell. The blocking of sodium influx prevents the depolarisation necessary for action potential propagation and at sufficient concentrations block impulse conduction. Since binding of lidocaine and prilocaine to sodium channels is completely reversible, when drug administration is stopped the drug diffuses away. Restoration of active sodium pumping and continued leakage of potassium restores the membrane potential to its polarised state. The membrane potential remains deactivated and refractory to further stimulation for a short period. Eventually nerve function is completely restored (Lagan and McLure, 2004; Becker and Reed, 2006).

Lidocaine has a rapid onset of action and anaesthesia is obtained within a few minutes, with an intermediate duration of action. Prilocaine has a slower onset of action with slightly longer duration of action (Martindale Lidocaine 2012, Martindale Prilocaine 2012). The combination of lidocaine and prilocaine in PSD502 provides a rapid onset of action. So, application of lidocaine and prilocaine in their base forms at a pH of 8.0, optimises penetration, maximising the depth of neural blockade and minimising time to onset of numbness (Henry *et al*., 2008).

Non-clinical evaluation of the pharmacology of PSD502 has not been submitted; however, the Applicant has made reference to the clinical data which demonstrate that use of Lidocaine/Prilocaine Plethora increases the latency time to ejaculation.

Likewise, the Applicant has not submitted a detailed secondary pharmacodynamics assessment. However, the nonclinical overview indicates that lidocaine is a class 1b antiarrhythmic agent used in the treatment of ventricular arrhythmias, while prilocaine is used for infiltration anaesthesia and nerve block in dental procedures and that carbonated solutions of prilocaine have been tried in epidural and brachial plexus nerve blocks (Hardman *et al*. 1996; Martindale Prilocaine 2012, respectively).

Similarly, the pharmacodynamics written summary states that Safety pharmacology is not applicable but the nonclinical overview summarized the effects of prilocaine and lidocaine on the central nervous and cardiovascular systems, as they are reported in the literature (Martindale Lidocaine, 2012; Gold *et al.*, 1998; Kanai *et al*., 1998; Cousins and Mather, 1980; Conklin, 1987; Copeland *et al.,* 2008; Hardman *et al*., 1996; Martindale Prilocaine 2012; EMLA Product Monograph 2010.).

Likewise, pharmacodynamic drug interactions studies have not been submitted.

In the absence of non-clinical data, the Applicant has provided clinical data in order to support efficacy (and demonstrate the pharmacological properties) of the proposed product. Application of PSD502 was shown to increase the intravaginal ejaculatory latency time and also improve a number of other indices for premature ejaculation such as Patient Reported Outcome.

Primary pharmacodynamic studies

No new pharmacology studies have been conducted because the drug substances, lidocaine and prilocaine, are well established. This is agreed by the CHMP.

Secondary pharmacodynamic studies

No secondary pharmacodynamics studies have been submitted. This is agreed by the CHMP.

Safety pharmacology programme

No safety pharmacology studies have been submitted. This is agreed by the CHMP.

Pharmacodynamic drug interactions

No pharmacodynamic drug interactions studies have been submitted. This is agreed by the CHMP.

2.3.3. Pharmacokinetics

No non-clinical pharmacokinetic studies have been conducted with PSD502 by the Applicant. However, the analytical methods used to determine plasma levels of lidocaine, prilocaine and their respective metabolites, 2,6-xylidine and ó-toluidine in the toxicokinetic studies have been established and validated by five analytical methods, using HPLC/UV and LC-MS/MS techniques. These analyses were performed using plasma samples of mice and rats, and were validated in the range of 0.50-500 ng/mL for lidocaine and prilocaine and in the range of 1-1000 ng/mL for 2,6-xylidine and for ó-toluidine in rat plasma, and in the range 10-10000 ng/mL for ó-toluidine in mouse plasma.

Distribution, metabolism and excretion as well as pharmacokinetic drug studies have not been performed with PSD502. The pharmacokinetics of lidocaine and prilocaine has been reported in the literature (Fransson et al., 2002; Weiland et al., 2006; Ko et al., 2007; Ko et al., 2008; Rolsted et al., 2009; Wei et al., 2007; Gazarian et al., 1995; Akerman et al., 1966; Integrated Laboratory Systems 2000) and product package inserts (EMLA, 1999)).

Absorption parameters for PSD502, after topical application in rats, have been presented by the Applicant in the Study Report Nº 459135(29516) and 459140(30745). Also plasma levels of lidocaine and prilocaine and their metabolites were determined in a vaginal application study in which the maximum feasible dose of PSD502 was applied (Study Report Nº 519010(32378). The results of these pharmacokinetics studies of absorption indicate that all analytes were presented in all treated animals, with a concentration of lidocaine about 3 times higher than prilocaine, and similar levels of both metabolites across the treated groups. Systemic exposure to lidocaine, prilocaine and 2,6-xylidine increased in a dose- proportional manner while the increases in systemic exposure to ó-toluidine were slightly supra-proportional.

Sex-related differences in systemic exposure to 2,6-xylidine and ó-toluidine were observed when the metabolites were assayed alone after oral treatment, whereby the exposure was greater in males compared with females, indicating possible physiological and/or metabolic differences between the sexes. However, in the study where the systemic exposure of lidocaine, prilocaine, 2, 6-xylidine and ó-toluidine was evaluated after topical administration, no clear sex differences were apparent.

For lidocaine, the primary route of metabolism in the rat is via hydroxylation, with preferential hydroxylation at the 3-carbon. The metabolism of prilocaine is primarily due to the hydrolysis of the amide bond forming o toluidine instead of 2,6 xylidine and in man, the primary urinary metabolite is p-hydroxytoluidine (34% of dose), followed by o-hydroxytoluidine (2.7%) and ó-toluidine. The metabolism of both of the active substances does not appear to be different when administered in combination. It is noted that the lidocaine metabolite 2,6 xylidine and the prilocaine metabolite, ó-

toluidine which present safety concerns such as the formation of methaemoglobin, have not been classified as major metabolites in man.

2.3.4. Toxicology

The toxicology of both lidocaine and prilocaine, as well as their metabolites, is well known and it is well documented in the scientific literature (de Jong and Bonin, 1980; Akerman et al., 1966; Rosenberg et al., 1993; Hofman et al., 1977; Feldman et al., 1989; Munson et al., 1975; Martindale Lidocaine Martindale Prilocaine, 2012; Vasters et al., 2006; EMLA® Product Monograph 2010, EMLA SPC 2011). Also the toxicity of lidocaine has been tested in Hazardous Substances Data Bank, 2012, in which there are not acute toxicity values for prilocaine.

It is known that the topical application of both lidocaine and prilocaine is associated with irritation, conjunctival hyperaemia, swelling, fluid and exudate discharge and iris reaction. The lidocaine can have serious effects on the central nervous and cardiovascular systems. An overdosage of lidocaine can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Meanwhile prilocaine has a low systemic toxicity mainly because of high absorption in the lung and a large volume of distribution and thus is associated with a lower risk of neurological or cardiac side-effects, although its major disadvantage is the formation of methaemoglobin by two of its metabolites, 4-hydroxy-2-methylaniline and 2-methylaniline (ó-toluidine). Methaemoglobinaemia has been noted after i.v. administration of lidocaine.

Single dose toxicity

No studies on the single-dose toxicity of PSD502 have been conducted. The lack of single dose toxicity studies is not a concern to the CHMP. Moreover, the Applicant has provided several bibliographical references to explain the acute toxicity in both lidocaine and prilocaine, and their respectively metabolites, 2,6-xylidine and σ-toluidine, intraperitoneal and intravenously administered and after topical application (de Jong and Bonin, 1980; Akerman et al., 1966; Rosenberg et al., 1993; Hofman et al., 1977; Feldman et al., 1989; Munson et al., 1975; Martindale Lidocaine Martindale Prilocaine, 2012; Vasters et al., 2006; EMLA Product Monograph 2010, EMLA SPC 2011). As well the acute toxicity of lidocaine has been tested in Hazardous Substances Data Bank, 2012, in which there are not acute toxicity values for prilocaine.

Table 1:

Acute Toxicity Values for Lidocaine (Hazardous Substances Data Bank, 2012)	
Mouse LD_{50} oral	292 mg/kg
Mouse LD_{50} intraperitoneal	105 mg/kg
Mouse LD_{50} subcutaneous	238 mg/kg
Mouse LD_{50}intravenous	19.5 mg/kg
Rat LD_{50} oral	317 mg/kg
Rat LD_{50} intraperitoneal	133 mg/kg
Rat LD_{50} subcutaneous	335 mg/kg
Rat LD_{50} intravenous	25 mg/kg

Acute toxicity values for prilocaine are not available from the Hazardous Substances Data Bank, 2012. Median convulsant (CD50) and median lethal (LD50) doses of lidocaine following intraperitoneal

injection were determined in adult mice; the CD50 was 111.0 mg/kg and the LD50 1331.1 mg/kg (de Jong and Bonin 1980).

In studies in mice, twice the dose of intraperitoneal prilocaine was required than with lidocaine (200 mg/kg prilocaine vs. 100 mg/kg lidocaine) to cause convulsions (Akerman et al. 1966). The prilocaine concentration in the brain was about three times higher than that for lidocaine when the convulsions appeared (prilocaine 115.6 ± 14.6 µg/g and lidocaine 43.1 ± 2.8 µg/g). The convulsions following prilocaine injection lasted 5 minutes less than those for lidocaine, starting later and ending earlier than those following lidocaine injections.

The CNS and CVS toxicity of intravenously administered 0.5% prilocaine was investigated in slightly anaesthetized rats. Arterial blood pressure, ECG and EEG were continuously monitored. The mean dose of prilocaine producing asystole was 166 mg/kg, arrhythmias did not appear until just before asystole. Seizure activity on the EEG occurred at a prilocaine dose of 53 mg/kg (Rosenberg et al. 1993).

Threshold convulsive doses following intermittently infused lidocaine hydrochloride were established in mongrel dogs for each of three distinct and predictable seizure patterns. The first seizure activity was tonic extension which occurred at an infused lidocaine dose of 12.2 ± 0.6 mg/kg, followed by running activity after 22.7 ± 0.9 mg/kg lidocaine. The threshold for intermittent tonic-clonic seizures occurred at an infused dose of 33.3 ± 1.5 mg/kg (Hofman et al. 1977).

In another study in dogs, lidocaine was infused intravenously at a rate of 8 mg/kg/min until seizures occurred. The average dose at seizure onset was 20.8 ± 4.0 mg/kg and with an arterial plasma concentration of 47.2 ± 5.4 µg/mL (Feldman et al. 1989).

The CNS toxicity of lidocaine and prilocaine was studied during constant rate intravenous infusion in rhesus monkeys. Drug effects were compared by determination of drug dosage and arterial plasma concentration that induced behavioural and electrical seizure activity. Mean (± SD) seizure dosages were: lidocaine 14.2 ± 3.2 mg/kg and prilocaine 18.1 ± 3.2 mg/kg and corresponding plasma levels were lidocaine 24.5 ± 4.4 µg/mL and prilocaine 20.5 ± 4.2 µg/mL (Munson et al. 1975).

Repeat dose toxicity

The Applicant has submitted several repeat-dose toxicity studies conducted in rats with the combination as required by the Guideline on the non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/2005). Also 3 repeat-dose oral toxicity studies with the metabolites of lidocaine and prilocaine, 2,6-xylidine and σ -toluidine hydrochloride, respectively, have been done.

In most of these studies, the Applicant has provided the exposures to the metabolites 2,6-xylidine and σ -toluidine (which are considered to be carcinogenic in rats and most likely carcinogenic in human), and has discussed how the exposure compare to that observed in humans.

Table 2. Repeat-dose toxicity studies performed with PSD502, and with the metabolites of lidocaine and prilocaine, *2,6-xylidine and σ-toluidine , respectively.*

*: dose reduced on day 3 for practical reasons; ↓: Decrease; ↑: Increase; +: slight; ++: mild; +++: moderate; ++++: marked/severe

Study ID / GLP Compliance	Species / Sex / Number / Group	Dose / Route	Duration	NOEL / NOAEL (mg/kg/day)	Major findings
459114 / Yes	Mice (B6C3F1/Crl) / M-F / 52 / 3	300, 1000, 3000 ppm / Oral	14 days	ND	At 1000: areas of sparse hair (2F)
459109 / Yes	Rats (Fischer F344) / M-F / 24 /	1000, 3000 6000 ppm / Oral	14 days	ND	At 6000: ↓BW at the start of treatment; + ↓BW (M); ↓ food consumption At 3000: ↓BW at the start of treatment (F). + ↓BW (M); ↓ food consumption
454093 / Yes	Rats (S-D) / M-F / 30 / 3	300, 1000, 3000 ppm / Oral	14 days	ND	At 3000: ↓BW both M and F, ↓ food consumption both M and F At 1000: ↓BW both M and F, ↓ food consumption both M and F; scabs on the dorsal thorax (1M) At 300: ↓BW in F; scabs on the dorsal thorax (3M)
459135 / No	Rats (Fischer F344) / M-F / 24 / 4	0, 6, 60, 600/400 mg/day / Topical	7 days (6 hours/day)	**NOAEL:** 6 mg/day **MTD:** 60 mg/day	At 600/400: Deaths (2F); ↓ BW; +++ desquamation (3M); ++++ desquamation (1F); ++++ erythema to + eschar (1F); scab on dorsal area (4F); corrugated skin; irregular respiration, subdued behaviour, eyes partially closed, walking on tiptoes, and stained fur (1F); + erythema (3M) At 60: ++ desquamation (1M & 3F); ++ erythema (1F);
459140 / Yes	Rats (Fischer F344) / M-F / 48 / 4	0, 1, 4, 40 mg/day / Topical	28 days (6 hours/day)	ND	At 40: ++/+++ desquamation (2M&3F); ++ desquamation (2M&1F); + erythema (1F&2F); At 4: ++/+++ desquamation (1F); ↑ uterus weight; At 1: ++ desquamation (4F); + erythema (2F); ↑ uterus weight

518457 / No	Rats (Fischer F344) / F / 12 / 4	0.9, 3.5, 40, 60, 80, 134 mg/day / Intravaginal	14 days	NOAEL no defined. A dosage of no more than 60 mg/day of PSD502 would be considered suitable.	At 134: 3 Deaths; cold to touch, clear discharge from nose and vagina, crackling, slow or gasping breathing, swollen head and staggering (3) At 80: 1 Death; staggering, rolling gait and hunched appearance (2); dark liver, reddened fat and blood vessels attached to the uterus (euthanized F) At 60: hunched appearance (3); rolling gait (1); reddened vaginal mucosa (1); stained skin
519010 / Yes	Rats (Fischer F344) / F / 54 / 3	0, 30 and 60 mg/day / Intravaginal	28 days	NOEL and NOAEL no established	At 60: hunched appearance and subdued behaviour, irregular breathing; ↓ BWG; ↑ vaginal weight; diffuse epithelial hyperplasia in vagina and cervix; DNA adducts in uterus, cervix and vagina; ↑ oestrous At 30: 1 Death; hunched appearance and subdued behaviour; ↑ vaginal weight; diffuse epithelial hyperplasia in vagina and cervix; DNA adducts in uterus, cervix and vagina; ↑ oestrous
521983 /Yes	Rats (Fischer F344) / F / 32 / 4	0, 0.2, 0.6 and 2 mg/day / Intravaginal	28 days	ND	None

In the **study 459135**, male and female rats were dosed with PSD502 by topical administration during 7 days. Clinical signs and general appearance were checked twice daily; body weights were recorded pre-trial and daily and food consumption was recorded pre-trial and three times during the treatment period. Also, necropsy for each animal was performed on day 7 and selected tissues collected and fixed in 10% neutral buffered solution.

On day 3, the group 4 dose level had to be reduced from 600 to 480 mg/day since the treatment had exceeded the maximum possible dose due the amount of solution on the dose site. Two females in high dose group died on Day 5 of treatment; necropsy did not demonstrate any effects due to treatment. However the remaining females in this group showed many brown scabs on the dorsal area of the skin.

Males and females rats were also treated with PSD502 daily for 28 days in other pivotal study, **study 459140**. Clinical signs, bodyweight, food consumption and skin assessments were monitored. Also, all animals were subjected to a necropsy examination after completion of the 28 day treatment period and tissues were evaluated histologically. Although the uterus weight in females treated at 1 and 4 mg/day were noted to be statistically significant higher when compared with their control, due to the lack of a dose related response and no histological findings this was considered not to be related to treatment with PSD502. In the same way the brain weight in females treated at 1 mg/day was noted to be moderately statistically significant but as this was not seen in the absolute values or the higher dose levels, and no histological findings were noted, this was also considered to be incidental to treatment with PSD502.

In addition, samples of the dermal application site (skin), liver, urinary bladder and nasal mucosa at termination were taken for DNA adducts analyses which were not conducted under GLP conditions, but these analyses at The New York Medical Center was approved by the UK MHRA. The results are shown in the following table 3.

Table 3. DNA adducts in 10^9 normal nucleotides. * Standard Deviation

Dose mg/day	Male	Female
Initial analysis		
Control	BLD	BLD
1	8.55 ± 2.49*	3.77 ± 0.29
4	12.53 ± 4.48	20.22 ± 10.33
40	23.4 ± 2.9	15.9 ± 0.4
Repeat analysis		
Control	BLD	BLD
1	6.16 ± 5.34	9.23 ± 5.25
4	16.04 ± 5.62	28.69 ± 6.34
40	35.36 ± 24.63	39.14 ± 17.40

As is shown in table 3, only samples taken from the nasal mucosa had detectable DNA adducts, seen also at the 1 and 4 mg/day groups, and demonstrated that DNA adducts derived from lidocaine can be detected following topical application of relatively high doses of PSD502 to the rat. DNA adducts derived from prilocaine could not be detected under identical conditions.

Also, haemoglobin was extracted from red cell fraction samples and analysed for 2,6-xylidine and *o*-toluidine adduct formation.

Table 4. Haemoglobin adducts (mg/day).

	Dose mg/day	Sex (Male / Female)	Pretrial	Day 28
			ng/g Haemoglobin	
2,6-xylidine	Control	M	< LLOQ	0.092
		F	< LLOQ	0.205
	1	M	< LLOQ	27.0
		F	< LLOQ	29.0
	4	M	< LLOQ	103.85
		F	< LLOQ	105.37
	40	M	< LLOQ	253.83
		F	< LLOQ	300.67
o-toluidine	Control	M	1.906	0.952
		F	8.71	3.34
	1	M	1.56	66.1
		F	4.8	114.9
	4	M	1.63	237.17
		F	5.08	500
	40	M	1.44	641.67
		F	4.05	1315

As it is seen in the table 4, dose related increases in 2,6-xylidine and σ-toluidine haemoglobin adducts in all groups, and the increases in the lower doses, 1 and 4 mg/day, were approximately proportional to their doses. Low levels of σ-toluidine adducts were present in the pre-dosing haemoglobin samples.

In the repeat dose toxicity study **518457** also performed in rats during 14 days, the animals were treated with 100 µL/dose of PSD502 into the vagina as 0.9, 3.5, 40 and 134 mg/day. No adverse signs were noted for animals that received 0.9 or 3.5 mg/day of PSD502 and these animals were re-assigned and treated as 80 and 60 mg/day, respectively. There were 4 unscheduled deaths: 1 animal at 80 mg/day group and all 3 animals at 134 mg/day group on the first day of treatment. Adverse signs in these animals included cold to touch, a clear discharge from the nose and vagina, crackling, slow or gasping breathing, a swollen head and staggering, but no abnormal necropsy findings were noted in

the 3 animals that received 134 mg. However, dark liver and reddened fat and blood vessels attached to the uterus were observed in the euthanized animal of 80 mg/day group, and 1 animal that received 60 mg/day for 14 days had reddened vaginal mucosa. So, for a 28 day dosing period to the vaginal tissue of rats, a dosage of no more than 60 mg/day of PSD502 would be considered suitable.

In the other toxicity study in rats with vaginal administration for 28 consecutive days, study **519010**, female rats were administered with 100 µL/dose of PSD502 as 0, 30 and 60 mg/day. All animals were examined for reaction to treatment, and food consumption and body weights were recorded twice weekly. Also, following dosing on Day 1 and Day 28, blood samples were collected for toxicokinetic analysis for lidocaine, prilocaine, and their respective metabolites. At the end of the treatment, a necropsy was performed and the vagina, uterus and ovaries were examined histologically.

Also in this study, tissues were collected to perform DNA adducts analysis. The analyses indicated that very low levels of 2,6-xylidine and *o*–toluidine DNA adducts, in the order of <2 in 10^8 normal nucleotides, were noted in all groups. There was evidence of a dose-relationship with increasing levels of adducts with increasing dosages. The average value expressed as DNA adducts in 10^9 is shown in table 5.

Table 5. DNA adducts analysis in study Nº 519010

Dosage (mg/day)	Cervix	Uterus	Vagina
0	0.10	0.63	0.42
30	6.45	8.08	6.93
60	15.71	17.29	15.04

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In the tolerance study **521983**, also performed during 28 day in rats with vaginal administration of PSD502, the animals were treated at doses of 0, 0.2, 0.6 and 2 mg/day. Clinical observations, body weights and food consumption were recorded. Gross necropsy findings, organ weights and histopathological examinations were also evaluated.

No unscheduled deaths and no evidence of systemic toxicity were found in this study. No gross necropsy or histological findings were considered to be related to treatment with PSD502.

The toxicity of 2,6-xylidine and of σ-toluidine hydrochloride were addressed in three studies performed in rats and mice. In the study **459114**, males and females mice were fed with diets containing σ-toluidine hydrochloride for a period of up to 14 days. The dietary route of administration was selected for this study as this was the route used in a previously published study conducted by the National Cancer Institute (NCI-CG-TR-153) and the doses were calculated to be 300 ppm (56.9 mg/kg/day), 1000 ppm (239.6 mg/kg/day) and 3000 ppm (668.6 mg/kg/day). In this study, no adverse effects were reported.

In the some way, the toxicology of σ-toluidine hydrochloride was also evaluated during 14 days in rats (study **459109)**, where the dietary route of administration was also selected taking into account the previously published study (NCI-CG-TR-153). The treatment of σ -toluidine hydrochloride at 1000, 3000 and 6000 ppm resulted in the likely intake of 92.6, 264.7 and 501.3 mg σ-toluidine hydrochloride/kg/day for males, and 84.7, 231.1 and 438.9 mg σ -toluidine hydrochloride/kg/day for females. No adverse clinical observations were reported in this study.

On the other hand, in the study **459093**, male and female rats were fed with diet containing 2,6-xylidine for a period of up to 14 days. The dose levels were chosen to be the same as those used in a previous carcinogenicity study conducted by the National Toxicology Program (NIH Publication No. 90-2534) and they were calculated to be 300 ppm (25 mg/kg/day), 1000 ppm (75.5 mg/kg/day) and 3000 ppm (228.5 mg/kg/day). The observed effects were reduced body weight gain and food consumption except in the 300 ppm group males. No adverse clinical observations were reported.

According to the literature studies provided, the topical application of both lidocaine and prilocaine is related with irritation, conjunctival hyperaemia, swelling, fluid and exudate discharge and iris reaction.

The most serious effects of lidocaine intoxication are on the CNS and cardiovascular system and overdosage can result in severe hypotension, asystole, bradycardia, apnoea, seizures, coma, cardiac arrest, respiratory arrest, and death. Also it is reported that prilocaine has a low systemic toxicity mainly because of a high absorption in the lung and a large volume of distribution and thus is associated with a lower risk of neurological or cardiac side-effects, although its major disadvantage is the formation of methaemoglobin by 2 of its metabolites, 4-hydroxy-2-methylaniline and 2-methylaniline (σ-toluidine). Methaemoglobinaemia has been noted after i.v. administration of lidocaine.

Genotoxicity

The genotoxic potential of PSD502 was not studied but no special concerns were identified with the individual molecules (lidocaine and prilocaine separately). However, there is evidence to suggest that the metabolites σ-toluidine is considered as a mutagen and 2,6-xylidine has genotoxic effects in mammalian cells, in mouse lymphoma cells, Chinese hamster ovary cells and BALB/c-3T3 cells.

Carcinogenicity

As the carcinogenic potential of 2,6-xylidine and σ-toluidine is well-known, the Applicant has performed additional studies, which aim to bridge the existing carcinogenic data.

Long-term studies

No long-term studies on the carcinogenicity of PSD502 have been conducted. The lack of long-term studies on the carcinogenicity of PSD502 is acceptable, since any potential carcinogenicity is due to the formation of the metabolites of lidocaine and prilocaine respectively; 2,6-xylidine and σ-toluidine which are classified by the IARC as probably carcinogenic for humans and are addressed in bibliographic references provided (Studies NTP TR 278 and NCI-CG-TR-153), performed during 104 weeks. So, at high dose (3000 ppm) of 2,6-xylidine, a significant increase of the incidences of papillomas and carcinomas of the nasal cavity was found in both male and female rats, and malignant mesenchymal tumours, rhabdomyosarcoma, were also observed in the nasal cavity. In addition, the increased incidences of subcutaneous fibromas and fibrosarcomas in male and female rats and of neoplastic nodules of the liver in female rats may have been related to the administration of 2,6-xylidine. In the other study, the rats dosed at 3000 and 6000 ppm with σ-toluidine showed several types of sarcomas of the spleen and other organs in both males and females, mesotheliomas of the abdominal cavity or scrotum in males, transitional-cell carcinomas of the urinary bladder in females and an increased incidence of fibromas of the subcutaneous tissue in the males and fibroadenomas or adenomas of the mammary gland in the females. Also in this study, mice administered with 1000 and 3000 ppm with σ-toluidine presented haemangiosarcomas at various sites in males, and hepatocellular carcinomas or adenomas were induced in females.

Short or medium-term studies

The potential for vaginal and cervical carcinogenicity of PSD502 was investigated by histological examination and DNA adducts formation in vaginal and cervical tissue in the 28 days repeat-dose toxicity study (Study No 519010) performed in female rats. The results of this study are shown in table 5.

Since the published studies on carcinogenicity of 2,6-xylidine and σ-toluidine have no toxicokinetic data, three studies have been performed: 14 day dietary toxicokinetic study with 2,6-xylidine in the rat.(Study Number 459093), 14 day dietary toxicokinetic study with o-toluidine in the rat (Study

Number 459109) and 14 day dietary toxicokinetic study with o-toluidine in the mouse (Study Number 459114).

The three studies, studies number 459114, 459093 and 459109, performed by the Applicant complete the published carcinogenic data of 2,6-xylidine and σ-toluidine.

The results from the repeat-dose study 519010 show that DNA adducts are formed in all three genital tract tissues (uterus, cervix and vagina), in a dose proportional manner, when PSD502 was dosed at 30 and 60 mg/day for 28 days. Although the presence of DNA adducts are markers of DNA exposure to metabolites and the Applicant states that the generation of DNA adducts from the topical application of PSD502 in clinical use will be limited, it can be not discarded an increased in the formation of DNA adducts since PSD502 will be used in an intermittent but chronic clinical use.

Other studies

No other carcinogenicity studies have been submitted, there is not a concern of the lack of other carcinogenicity studies.

Reproduction toxicity

Since both lidocaine and prilocaine are well established products, aspects with respect to potential effects on reproduction and embryofoetal development are based upon data from the literature. In line with the "Guideline on Non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/05)" and "Guideline on Non-clinical documentation for mixed marketing authorisation applications (EMEA/CHMP/SWP/799/95)" no reproductive and developmental toxicity study has been conducted with PSD502. Besides, no major findings in reproductive organs have been observed in the repeat-dose toxicity studies. The reproductive and teratogenic effects of both lidocaine and prilocaine have been studied in mice, rats and rabbits dosed subcutaneous, intraperitoneal and with osmotic mini-pumps (EMEA, 1999; Fujinaga, 1998; Martin and Jurand, 1992; Xylocaine, 2004; Wiedling, 1965; Fujinaga and Mazze, 1986). It is known that a 1:1 w/w mixture of lidocaine HCl/prilocaine HCl in doses up to 40 + 40 mg/kg after subcutaneous administration in rats does not affect organogenesis or early foetal development (EMLA® Product Monograph, 2010). Also it is known that both lidocaine and prilocaine cross the placenta and blood-brain barrier and they are distributed into breast milk (Naguib *et al.,* 1998; Martindale Lidocaine, 2012; Martindale Prilocaine, 2012).

Ex vivo study have been performed in order to determine the effects of the proposed product on rat sperm motility (study number 495000). In this study, the sperm of 5 sexually mature rats was collected from the epididymis and suspended in 0.2% BSA in Medium 199. PSD502 was sprayed into microcentrifuge tubes from preformulated spray canisters which delivered 7.5 mg lidocaine and 2.5 mg prilocaine per actuation and, after the evaporation of the HFA 134a propellant, 400 µL of 0.2% BSA in Medium 199 was added. This mixed was added to 100 ml of the suspension of the sperm and then was evaluated for motility using a computerised sperm motility analyser. The results are shown below, in table 6.

Table 6. Treatment and effect of PSD502 on sperm motility.

Rat	Sample	Source	Test Drug Sprayed into Vial	% Motility	% Rapid Cells
A	A1	Right epididymis	Blank	90	53
	A2	Right	Blank	85	52

		epididymis			
	A3	Left epididymis	Blank	94	57
	A4	Left epididymis	Blank	70	54
B	B1 (1)	One epididymis	Blank	89	55
	B2	One epididymis	1 actuation of PSD502	52	23
	B2	One epididymis	1 actuation of PSD502 (repat of above>)	34	20
	B3	One epididymis	2 actuations of PSD502	71	47
	B4	One epididymis	5 actuations of PSD502	22	0
	B1 (2)	One epididymis	Blank	76	46
C	C1	One epididymis	4 actuations of PSD502	1	0
	C2	One epididymis	2 actuations of PSD502	17	2
	C3	One epididymis	1 actuation of PSD502	22	0
	C4	One epididymis	Blank	86	52
D	D1	One epididymis	Blank	97	61
	D2	One epididymis	4 actuations of PSD502	0	0
	D3	One epididymis	3 actuations of PSD502	13	0
	D4	One epididymis	2 actuations of PSD502	0	0
	D5	One epididymis	1 actuation of PSD502	0	0
	D6	One epididymis	Blank	77	0
E	E1	One epididymis	Blank	98	68
	E2	One	1 actuation of PSD502	10	1

		epididymis			
	E3	One epididymis	1 control actuation	96	61
	E4	One epididymis	Blank	92	55
	E5	One epididymis	2 control actuations	90	50

The results shown PSD502 has a negative effect on sperm motility but at concentrations far higher than in clinical use.

With regards to the adverse effects on pregnancy rate, the Applicant elaborated that the sperm after the ejaculation could be exposed to a maximum of approximately 10.5 mg lidocaine and 3.5 mg prilocaine (14 mg PSD502). Besides, after the ejaculation, the sperm is propelled towards the cervix, away from the area of the glans penis where any remaining PSD502 is likely to be concentrated in vaginal secretions. Therefore, it is suggested that sperm involved in fertilisation may not interact with lidocaine or prilocaine in the vaginal cavity following clinical use of PSD502.

In the same way, the applicant has submitted bibliographic references which have reported that no adverse effects on human sperm motility were observed (Bennett et al. 1992,).

Also, in the clinical trials in female partners, the ejaculated sperm has not been exposed to lidocaine and prilocaine metabolites in the vagina, and effects on the sperm that could subsequently affect the embryo or offspring should not occur.

Toxicokinetic data

The toxicokinetic studies have been conducted as part of the repeat dose toxicity studies in rats and mice to assess the systemic exposure to the lidocaine, prilocaine and their metabolites, 2,6-xylidine and σ-toluidine.

Two female rats were found dead in the group dosed at 600/480 mg/day with PSD502 topically administered in the study Nº 459135 and one female rat in the group dosed at 30 mg/day with PSD502 administered by intravaginal route in the study Nº 519010. According to the results of study Nº 459135, the company considered that the dose of 40 mg/day was appropriate for the main dermal study, 28 Day local tolerance dermal study (Nº 30745), and that this dose was 427 times the proposed clinical dose to male patients on an mg/kg basis.

On other hand, in the two repeated-dose toxicity studies following the topical administration (Nº 518457 and Nº 519010), a maximum volume of PSD502 was introduced into the vaginas of the rats to investigate the formation of DNA adducts in the vagina and cervix. Thus the PSD502 doses were very large both on mg/kg basis and based on the local concentration of PSD502 and the observed mortality, these findings are not relevant to female partners of treated patients.

Local tolerance

The local tolerance of PSD502 (at 4 to 160 mg/kg/day) has been assessed in a 28 day repeated dose toxicity study after the dermal application of the drug to rats (study Nº 459140).

The topical use of the product was associated with mild/moderate desquamation, signs of erythema and eschar; however, the applied doses were higher than those proposed clinically and there were no

signs of antigenicity or immunotoxicity. No further studies to address the local tolerance of PSD502 were needed.

Other toxicity studies

No other toxicity studies have been realized with PSD502, and this is not regarded as of concern by the CHMP.

Antigenicity

No antigenicity studies with PSD502 have been conducted in experimental animals, this is regarded as acceptable and supported by the fact that no signs of antigenicity have been found in the repeat-dose toxicity studies.

Immunotoxicity

Immunotoxicity studies have not been performed with PSD502 because of the previous clinical experience with the PSD502 drug substances individually; this is regarded as acceptable and supported by the fact that no signs of immunotoxicity have been found in the repeat-dose toxicity studies.

Dependence

No studies on dependence have been carried out with PSD502 because of the previous clinical experience with the PSD502 drug substances individually, this was accepted.

Metabolites

The metabolites of toxicological relevance, 2,6-xylidine and *o*-toluidine have been addressed, and no further studies are needed to characterise the metabolites.

Studies on impurities

Only one impurity, named PGAK-1, was present at 25 ºC in the PDS502 formulation and it has been further characterised. There are no further concerns to be raised from the nonclinical viewpoint.

Other studies

No other studies have been realized with PSD502, and this is not regarded as of concern by the CHMP.

2.3.5. Ecotoxicity / environmental risk assessment

In accordance with the EMEA "Guideline on the environmental risk assessment of medicinal products for human use (EMEA/CHMP/SWP/4447/00)", an environmental risk assessment has been performed for PSD502. The octanol/water partition coefficient, log Kow, is 2.26 for lidocaine and 2.11 for prilocaine, according to Hansch 1995. Since both values are below 4.5, an assessment for Persistence, Bioaccumulation and Toxicity, in accordance with the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH) "Guidance on information requirements and chemical safety assessment" (ECHA, 2008) is not required. In line with the Guideline "Questions and answer on Guideline on the environmental risk assessment of medicinal products for human use (EMA/CHMP/SWP/44609/2010)" a calculated value of Log Kow is generally not acceptable and has to be determined experimentally.

Also, the predicted environmental concentration in the surface water (PECsw) has been calculated roughly according to the applicable guideline. So, the PECsw for lidocaine was 0.0052 microg/L and for prilocaine was 0.0017 microg/L. The Applicant has used a refine Fpen that is acceptable in accordance with the EMEA/CHMP/SWP/4447/00 and EMA/CHMP/SWP/44609/2010 guidelines. As the PECsw values are below of 0.01 microg/L, a phase II assessment has not to be performed.

Table 7: Summary of main study results

Substance (INN/Invented Name):			
CAS-number (if available):			
PBT screening		Result	**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107 or …	Lidocaine: 2.26 Prilocaine: 2.11	Potential PBT NA
PBT-assessment			
Parameter	**Result relevant for conclusion**		**Conclusion**
Bioaccumulation	log K_{ow}	Lidocaine: 2.26 Prilocaine: 2.11	
Phase I			
Calculation	**Value**	**Unit**	**Conclusion**
PEC $_{surfacewater}$, default or refined (e.g. prevalence, literature)	Lidocaine = 0.0052 Prilocaine: 0.0017	µg/L	> 0.01 threshold NO

Lidocaine/Prilocaine PEC $_{surfacewater}$ value is below the action limit of 0.01 µg/L. and is not a PBT substance as log K_{ow} does not exceed 4.5.

Therefore Lidocaine/Prilocaine is not expected to pose a risk to the environment.

The applicant should provide the study reports of the experimental determination of the log Kow value for both lidocaine and prilocaine.

2.3.6. Discussion on non-clinical aspects

The lack of secondary pharmacodynamics and pharmacodynamic drug interactions studies is not an issue, however a justification for the absence of such data should have been provided. Although no new safety pharmacology studies have been performed and bibliographical references have been submitted, a summary of the effects in the central nervous, cardiovascular and respiratory system should have been provided in the pharmacodynamics written summary as it is written in the nonclinical overview.

The Applicant has not performed any distribution, metabolism and excretion or pharmacokinetic drug studies with PSD502 and the majority of the pharmacokinetic aspects of this application were therefore based upon data from the literature. On the other hand, the Applicant has discussed the potential for pharmacokinetic drug interactions when administered with other locally or systemically applied medicinal products.

The Applicant has submitted repeat-dose toxicity studies conducted with PSD502 which is in line with the Guideline on the non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/2005). In one of these studies, study 459135, a pilot study, 2 females treated with 600/480 mg/day of PSD502 by dermal route were found dead on day 5 of treatment. Another 2 deaths have also occurred in two intravaginal studies following the topical application of PSD502.

The Applicant states that in this dermal study, the appropriate dose is 40 mg/kg which is estimated to be 427 times the proposed clinical dose. In the same way, in the intravaginal studies, a maximum volume of PSD502 was introduced into the vaginas of the rats to investigate the formation of DNA adducts in the vagina and cervix. Thus the PSD502 doses were very large both on mg/kg basis and a local concentration basis and the deaths in the studies do not have clinical relevance to female partners of treated patients.

Lidocaine was not considered to be mutagenic in a wide range of genotoxicity studies and prilocaine was not considered to be mutagenic but induced homologous recombination in a very sensitive assay

and this was considered to be the result of an aberrant genetic repair mechanism. Overall, the data available suggest that the active substances could be genotoxic by way of their metabolites. Exposure to 2,6-xylidine and ó-toluidine following the proposed clinical use of PSD502 in men and female partners will be very low and intermittent allowing normal genetic repair mechanisms to operate and preventing the formation of permanent genetic defects.

The data generated in order to bridge the pre-existing carcinogenicity studies from the literature suggest that the exposures of 2,6 xylidine causing nasal adenomas in a 2-year rat study were 200-fold higher than that observed clinically following exaggerated clinical use. In addition, the no–effect exposures in a mouse study conducted with ó-toluidine was substantially higher than that proposed clinically. A no-effect dose was not established in the 2-year rat carcinogenicity conducted with ó-toluidine; however, the doses administered were extremely high and it is worthwhile to note that in the clinical situation, this metabolite was only detected in one subject following exaggerated use.

As the experience of long-term use in the intended indication is limited to one year, concerns regarding the potential systemic risks (e.g. methaemoglobinaemia, systemic malignancies) and carcinogenicity potential were raised. These concerns were adequately addressed by the Applicant. Overall, the potential occurrence of methaemoglobinaemia from prilocaine and carcinogenicity risk from *o*-toluidine is extremely unlikely based upon the clinical and non-clinical information provided by the Applicant.

The presence of DNA adducts and haemoglobin adducts are also relevant to the potential for carcinogenicity. It is noted that in the rat dermal study, metabolite haemoglobin adduct levels at 1 mg/day which is ~10 fold higher than the proposed clinical dose were approximately 15 times the level of 2,6-xylidine and approximately 29 times the level of o-toluidine adduct levels in a clinical trial over an 8 month period. At 1 mg/day, 2,6-xylidine DNA adduct levels were very low and only detected in the nasal mucosa and not in liver and bladder and o-toluidine levels were not detected. These data suggest that DNA adducts of 2,6-xylidine and ó-toluidine following the prescribed use of PSD502 would not be detectable in man.

Data from the literature suggest that lidocaine or prilocaine do not have the potential to cause foetal abnormalities. In accordance with the “Guideline on Non-clinical development of fixed combination of medicinal products (EMEA/CHMP/SWP/258498/05)” and “Guideline on Non-clinical documentation for mixed marketing authorisation applications (EMEA/CHMP/SWP/799/95)”, studies to evaluate the effects on reproduction or embryofoetal development have not been conducted with PSD502. It is noted that no major findings concerning the reproductive organs have been observed in the repeated-dose toxicity studies. The results of an ex-vivo study conducted by the Applicant show that the product reduces the sperm motility; hence PSD502 may adversely affect the pregnancy rate at the intended clinical use. However, bibliographic references submitted by the applicant reported that no adverse effects on human sperm motility were identified during incubation with lidocaine. Nonetheless, the effects on sperm motility have been included within the SmPC, Section 4.6.

No signs of antigenicity or immunotoxicity have been observed during the repeat-dose toxicity studies, and no further evaluations are needed.

Regarding with the log Kow, both lidocaine and prilocaine have a log Kow which are below 4.5, according to a bibliographic reference (Hansch, 1995) that has been provided by the Applicant.

Given the observed systemic exposure to lidocaine and prilocaine following the administration of PSD502 the potential for pharmacokinetic interactions with drugs which reduce the clearance of lidocaine/prilocaine (e.g. beta-blockers and cimetidine) is considered to be low; however, relevant warnings have been included within the SmPC section 4.5, which is acceptable.

The effect of PSD502 on locally applied agents, such as spermicides would have been quite relevant to the proposed indication; however, given the fact that PSD502 affects sperm motility, the potential for

pharmacodynamic interaction could not be tested. The effects on sperm motility have been included within the SmPC Section 4.6 as follows: “A study in rats showed that Lidocaine/Prilocaine Plethora caused a reduction in sperm mobility”.

The CHMP recommends the following point to be addressed:

- The Applicant should provide all the study reports of the experimental determination of the log Kow value for both lidocaine and prilocaine.

2.3.7. Conclusion on the non-clinical aspects

Overall the non-clinical program conducted by the Applicant meets the requirements and the data are acceptable From the pharmacodynamic and pharmacokinetic point of view; both lidocaine and prilocaine, as well as their metabolites 2,6-xylidine and o-toluidine, are well characterized.

Overall, the majority of the non-clinical issues have been satisfactorily addressed in the SmPC. Animal studies do not indicate reproductive toxicity, this information is adequately reflected in section 5.3 in the SmPC). As a precautionary measure, it is preferable to avoid the use of Lidocaine/Prilocaine Plethora during pregnancy unless effective male barrier contraceptive measures are taken in order to avoid potential foetal exposure.

No teratogenic effects of lidocaine were observed in studies of embryonic/foetal development in rats and rabbits receiving doses during organogenesis. Embryotoxicity was observed in rabbits at doses toxic to the mother. The postnatal survival time of the offspring of rats treated during pregnancy and lactation with a dose toxic to the mother was shown to be reduced.

In a study of pregnant rats receiving a combination of lidocaine and prilocaine during organogenesis, no effects on embryonic/foetal development were observed. There are however no systemic exposure data available for comparison with clinical exposure.

Lidocaine was not genotoxic and the carcinogenic potential of lidocaine has not been studied. The lidocaine metabolite 2,6-xylidine has genotoxic potential *in vitro*. In a carcinogenicity study of rats exposed to 2,6-xylidine *in utero*, postnatally and throughout their lifetime, tumours in the nasal cavity, subcutaneous tumours and liver tumours were observed. The clinical relevance of tumour findings in relation to short-term/intermittent use of lidocaine in humans is unknown. Human exposure from Lidocaine/Prilocaine Plethora is 20-30 fold less than the minimum dose that did not result in tumours and 200 fold less than the minimum dose that did result in tumours.

Prilocaine was not genotoxic and the carcinogenic potential of prilocaine has not been studied. The prilocaine metabolite *o*-toluidine has genotoxic potential *in vitro*. In carcinogenicity studies of *o*-toluidine in rats, mice and hamsters, tumours were observed in several organs. The clinical relevance of tumour findings in respect of short-term/intermittent use of prilocaine in humans is unknown. Human exposure is 1000 fold less than than the minimum dose studied. This dose did result in tumours

There are no adequate data from the use of lidocaine and prilocaine on fertility in humans. In an *in vitro* study of rats Lidocaine/Prilocaine Plethora has shown a reduction in sperm motility when 22.5 mg lidocaine and 7.5 mg prilocaine (i.e. the amount in 1 human dose) was in direct contact with rat sperm. However this study did not reproduce the circumstances of clinical use, as the concentration of Lidocaine/Prilocaine Plethora in direct contact with the sperm would be many fold lower. The potential for reduction of sperm motility following the clinical use of the medicinal product cannot be excluded; therefore it is not possible to state whether Lidocaine/Prilocaine Plethora would prevent pregnancy. This medicinal product may reduce the possibility of pregnancy, but should not be used as a contraceptive.

The Applicant will provide the results of additional studies to further characterise the environmental risk assessment .

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

- Tabular overview of clinical studies

Table 8:

Tabular Display of Premature Ejaculation Studies					
	PSD502-PE-002	PSD502-PE-004	PSD502-PE-001	PSD502-PE-005	ANAE-059-00
Phase	IIb	III	II	II	II
Indication	PE	PE	PE	PE	PE
Study design	Multi-centre, double-blind, placebo-controlled, parallel group followed by open-label phase	Multi-centre, double-blind, placebo-controlled, parallel group followed by open-label phases	Multi-centre, double-blind, placebo-controlled, parallel group	Multi-centre, doubleblind, Placebo-controlled, 4 way crossover	Proof-of-concept), single centre, open-label
PE eligibility	Subjects with baseline IELT ≤ 1 minute in at least 2 of the first 3 sexual encounters, lifelong PE* according to ISSM definition* and DSMIV criteria	Subjects with baseline IELT ≤ 1 minute in at least 2 of the first 3 sexual encounters, lifelong PE* according to ISSM definition* and DSMIV criteria	History of primary PE of at least 6 months duration as defined according to DSMIV criteria	Subjects with baseline IELT ≤ 1 minute in at least 1 sexual encounter, lifelong PE according to ISSM definition	Self-reported sexual dissatisfaction due to PE and referral to a urology clinic
Number of subjects entered	256 randomized in doubleblind phase (2 PSD502: 1	300 randomized in doubleblind phase (2 PSD502:1	55 randomized	35 randomized	16 enrolled

Tabular Display of Premature Ejaculation Studies					
	placebo) 223 entered open-label phase	placebo) 274 entered open-label phases			
Number of treated subjects	249 (167 PSD502:82 placebo) during double-blind phase 213 during open-label phase	290 (191 PSD502:99 placebo) during double-blind phase 268 during open-label phases	54 (26 PSD502:28 placebo)	35	14
Dosing regimen	Double-blind phase: PSD502 (30 mg) or placebo applied up to one dose per 24 hours for 3 months Open-label phase: PSD502 (30 mg) applied up to 3 doses per 24 hours (separated by ≥4 hours) for 5 months	Double-blind phase: PSD503 (30 mg) applied as desired up to one dose per day for 3 months Open-label phase 1: PSD502 (30 mg) applied as desired up to 3 doses per 24 hours for 5 months Open-label phase 2: PSD502 (30 mg) applied as desired up to 3 dose per 24 hours for 4 months	PSD502 (30 mg) applied for 4 consecutive sexual encounters	PSD502 (3, 30, and 53 mg) or placebo applied as desired up to one dose per 24 hours each week for a total 4 week period	3 to 5 sprays (30 to 50 mg) applied for 5 consecutive sexual encounters
Location	USA, Canada, and Poland	UK, Czech Republic, Hungary, and	UK and the Netherlands	Czech Republic and Poland	Canada

Tabular Display of Premature Ejaculation Studies					
		Poland			
Primary Objective	To determine the effect of PSD502 on the IPE and IELT	To determine the effect of PSD502 on the IPE and IELT	To evaluate the efficacy of PSD502 compared with placebo treating subjects with PE	To evaluate the effect of 3 different doses (3, 30, and 53 mg) of PSD502 on IELT	To measure IELT in men with PE before and after the application of PSD502 spray to the glans penis

Abbreviations: DSM-IV = Diagnostic and Statistical Manual of Mental Disorders; IELT = intravaginal ejaculatory latency time; IPE: Index of Premature Ejaculation; ISSM = International Society for Sexual Medicine; PE = premature ejaculation; UK = United Kingdom; USA = United States of America

* Additional inclusion criteria added in protocol amendments 4 and 5, for the USA and Canada respectively in PSD502-PE-002 and protocol amendment 3 for all study locations in PSD502-PE-004, in response to the release of the ISSM evidence-based definition of PE. In PSD502-PE-002 these inclusion criteria were present in the protocol in use at the outset in Poland. Subjects who were already enrolled who did not meet the criteria for lifelong PE and/or the ISSM definition were excluded from the per-protocol populations.

2.4.2. Pharmacokinetics

Absorption

- **Male**

In **study PSD502-PE-003**, one dose (30 mg) of PSD502 or placebo was applied once daily to the glans penis of 16 healthy male volunteers for 21 days, except for dosing days 7 and 14, when 3 doses (3 sprays each dose, 9 sprays in total) of PSD502 or placebo were applied, each dose 4 ± 0.25 hours apart. On Dosing Days 1 and 21, plasma samples were taken before dosing (0 hours), and at 1, 2, 4, and 8 hours after dosing to determine levels of PSD502 (lidocaine and prilocaine) and metabolites 2,6-xylidine and o-toluidine. On Dosing Days 7 and 14, a single plasma sample was taken 1.5 hours after the third dose of PSD502.

Each 30 mg dose (3 sprays) of PSD502 provided 22.5 mg lidocaine base plus 7,5 mg prilocaine base in a eutectic-like combination.

Single dose

Lidocaine and prilocaine were quantifiable in plasma 1 hour post dose. The maximum concentrations for lidocaine and prilocaine in an individual male subject were 96 ng/mL and 13 ng/mL, respectively, occurring 2 hours post-dose.

Table 9: Mean (SD) Pharmacokinetic Parameters for Lidocaine and Prilocaine Following a Single Dose (Day 1) and 21 Daily Doses of PSD502 (30 mg) Applied to the Glans Penis: PSD502-PE-003

	Parameter (Unit)	Day 1		Day 21	
Lidocaine	AUC(0-t) (hr*ng/mL)	164.2 (104.76)	n=12	282.8 (160.44)	n=12
	C_{max} (ng/mL)	34.49 (22.269)	n=12	56.11 (33.519)	n=12
	t_{max} (hr)	2.583 (1.0836)	n=12	2.694 (1.0256)	n=12
	$t_{1/2}$ (hr)	2.847 (0.4303)	n=6	3.667 (0.5267)	n=3
Prilocaine	AUC(0-t) (hr*ng/mL)	24.67 (23.135)	n=4	29.43 (12.517)	n=8
	C_{max} (ng/mL)	6.880 (4.4445)	n=4	7.179 (2.4566)	n=8
	t_{max} (hr)	1.750 (0.5000)	n=4	2.521 (0.9642)	n=8
	$t_{1/2}$ (hr)	2.402 (N/A)	n=1	2.858 (0.0790)	n=3

Abbreviations: CSR = clinical study report; N/A = not applicable; SD = standard deviation. See also Pharmacokinetic terms and definitions list.
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.

Multiple doses on a single day

The maximum concentrations of lidocaine and prilocaine measured in any one individual on either of these days was 171.47 ng/mL for lidocaine on Day 14 and 19.39 ng/mL for prilocaine on Day 7.

The maximum plasma concentrations of lidocaine and prilocaine following 3 applications of PSD502 at 4-hourly intervals to healthy male volunteers were therefore well below the plasma concentrations associated with systemic toxicity (>5,000 ng/mL for lidocaine and prilocaine): Approximately 29-fold lower for lidocaine and almost 258-fold lower for prilocaine.

Table 10: Mean (SD) Plasma Concentrations of Lidocaine and Prilocaine Following 3 Doses of PSD502 (each 30 mg) Applied to the Glans Penis 4 Hours Apart (All Subjects): PSD502-PE-003

Sampling Time	Statistic	Lidocaine	Prilocaine
Day 7 1.5 Hours Post-3rd Dose	N Mean (SD) ng/mL CV% Median Min, Max	12 84.306 (54.0226) 64.08 54.110 32.64, 169.63	12 10.5051 (5.4523) 54.25 8.400 3.26, 19.39
Day 14 1.5 Hours Post-3rd Dose	N Mean (SD) ng/mL CV% Median Min, Max	12 88.958 (46.4304) 52.19 78.485 31.82, 171.47	12 9.990 4.3161 43.20 3.73, 16.30

Abbreviations: CSR = clinical study report; Max = maximum; Min = minimum; N/A = not applicable; SD = standard deviation. See also Pharmacokinetic terms and definitions list.
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.

Repeat dosing for 21 Days

Lidocaine and prilocaine plasma concentrations tended to be higher on Day 21 than on Day 1 (see Table 10). The mean (SD) Cmax of lidocaine in the population overall after repeat daily dosing (Day 21) was 56.11 (33.519) ng/mL, reached at a mean (SD) tmax of 2.69 (1.026) hours. For prilocaine on Day 21 in the population overall, the mean (SD) Cmax was 7.18 (2.457) ng/mL, reached at a mean (SD) tmax of 2.52 (0.964) hours.

The mean Cmax for lidocaine and prilocaine following repeat applications of PSD502 for 21 days to healthy male volunteers were therefore well below the plasma concentrations associated with systemic toxicity (>5,000 ng/mL for lidocaine and prilocaine): Approximately 90-fold lower for lidocaine and almost 700-fold lower for prilocaine.

- **Female**

Two studies of PSD502 were carried out in healthy female volunteers. In PSD502-PE-006 3 different single doses of PSD502 (3 mg, 30 mg and 150 mg) or placebo were applied once daily for 7 days to the cervix and vaginal fornices of 21 healthy female volunteers.

The study was terminated early, and thus study PSD502-PE-007 was undertaken to provide supplementary information in female volunteers. In PSD502-PE-007 60 mg PSD502 or placebo was applied once daily for 7 days to the cervix and vaginal fornices of 30 healthy female volunteers. No firm conclusions can be drawn for exposure to lidocaine and prilocaine regarding dose dependency because of the small number of observations and variability.

Single dose

For lidocaine, there appeared to be a dose-proportional trend in exposure to lidocaine across the two studies (see Table 11), with the exception of the post-menopausal 30 mg dose group (n=2) for which the mean Cmax did not fit this pattern. The Cmax was attained up to 2.0 hours after single-dose drug application. For prilocaine there was an increased exposure with increasing dose, but the increase was less than proportional to dose.

The highest mean Cmax for lidocaine and prilocaine (215.54 ng/mL and 28.79 ng/mL, respectively) followed a single 150 mg dose of PSD502 in the pre-menopausal subjects in PSD502-PE-006. This dose

represents a supra-maximal exposure to PSD502 as it is far higher than would be anticipated to occur by transference from a male partner during sexual intercourse. Even so, the maximum concentrations were well below the plasma concentrations associated with systemic toxicity.

Table 11:

Lidocaine and Prilocaine C_{max} and T_{max} Following a Single Dose of PSD502 (3 mg, 30 mg, 60 mg and 150 mg) Applied to the Cervix and Vaginal Fornices of Healthy Female Volunteers: PSD502-PE-006 and PSD502-PE-007

Drug Dose of PSD502	Pre-menopausal subjects		Post-menopausal subjects		Total	
	Mean C_{max} (SD), ng/mL	Median T_{max} (range), hours [a]	Mean C_{max} (SD), ng/mL	Median T_{max} (range), hours [a]	Mean C_{max} (SD), ng/mL	Mean T_{max} (SD), hours
Lidocaine						
3 mg	1.54 (0.837), n=3	1.0 (0.5-1.0), n=3	8.12 (5.855), n=2	0.75 (0.5-1.0), n=2	NR	NR
30 mg	25.53 (17.514), n=3	1.0 (1.0-2.0), n=3	101.04 (40.51), n=2	0.75 (0.5-1.0), n=2	NR	NR
60 mg	35.3 (29.0), n=12	1.83 (1.17) [a], n=12	49.0 (23.1), n=12	0.92 (0.56) [a], n=12	42.2 (26.6), n=24	1.38 (1.01), n=24
150 mg	215.54 (120.683), n=3	1.0 (1.0-2.0), n=3	133.96 (NA), n=1	2.0 (NA), n=1	NR	NR
Prilocaine						
3 mg	NA, n=0	NA, n=0	1.26 (1.110), n=2	0.75 (0.5-1.0), n=2	NR	NR
30 mg	2.69 (1.707), n=3	1.0 (0.5-1.0), n=3	15.59 (6.894), n=2	0.75 (0.5-1.0), n=2	NR	NR
60 mg	4.00 (3.26), n=12	1.46 (0.58) [a], n=12	6.37 (2.93), n=12	0.92 (0.42) [a], n=12	5.19 (3.26), n=24	1.19 (0.57), n=24
150 mg	28.79 (19.706), n=3	1.0 (1.0-2.0), n=3	16.46 (NA), n=1	2.0 (NA), n=1	NR	NR

Abbreviations: CSR = clinical study report; NA = not applicable; NR = not reported. See also Pharmacokinetic terms and definitions list.
Note: 60 mg dose group was in study PSD502-PE-007, all other dose groups were in study PSD502-PE-006
a) T_{max} reported as mean (standard deviation) for PSD502 60 mg dose (PSD502-PE-007 study)
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.

Repeat dosing for 7 Days

As with the PK parameters derived following a single dose, the mean PK parameters for lidocaine and prilocaine at all 3 dose levels in study PSD502-PE-006 for Day 7 for pre and post-menopausal women were comprised of 3 or fewer subjects and were characterised by high variability.

In PSD502-PE-007, there was no, or minimal, meaningful accumulation of lidocaine or prilocaine observed following topical application of multiple doses of 60 mg PSD502 spray to the cervix and vaginal fornices for all female subjects for 7 consecutive days.

- **Bioavailability**

PSD502 has been formulated for topical administration with low systemic absorption as demonstrated in studies PSD502-PE-003, PSD502-PE-006, PSD502-PE-007 and PSD502-PM-001; hence a bioavailability study has not been conducted.

- **Bioequivalence**

There have been two formulations of PSD502 aerosol dosage form used during the clinical development program, both containing lidocaine and prilocaine in a 3:1 ratio with tetrafluoroethane serving as a solvent and propellant. An ethanol-containing formulation was used in an early clinical study PSD502-PE-001, instigated by Medpharma Plc prior to the transfer of PSD502 intellectual property to Plethora Solutions Plc on 9th December 2003. Following completion of study PSD502-PE-001, Plethora removed ethanol as an excipient and the subsequent formulation of lidocaine, prilocaine and tetrafluoroethane has been used in all other clinical studies presented in this Marketing Authorization Application (MAA), and is the one intended for use as the commercial product.

Study PSD502-PE-001 is used as supportive evidence in this application and is not used as sole justification for any efficacy or safety statements hence a bioequivalence study for the two formulations has not been conducted.

Data from food-interaction studies

This was regarded as not applicable as the product is for topical use.

Distribution

The distribution of lidocaine and/or prilocaine following the application of PSD502 to the genital mucosa of male or female healthy volunteers has not been evaluated. However, the distribution of lidocaine and prilocaine following i.v. administration is well documented.

Following an i.v. dose, lidocaine is widely and rapidly distributed into highly perfused tissues followed by redistribution into skeletal muscle and adipose tissue. The steady-state volume of distribution is 1.1 to 2.1 L/kg (mean 1.5 ± 0.3 standard deviation [SD]). Once in the body, lidocaine is bound by plasma proteins, including AAG. The extent of binding is variable, dependent in part on the concentrations of both lidocaine and AAG, but is approximately 66% to 70%. Lidocaine can cross the blood brain barrier and the placenta, presumably by passive diffusion and is distributed in breast milk. The milk: plasma ratio of lidocaine is 0.4.

Following i.v. administration, the steady state volume of distribution of prilocaine is 0.7 to 4.4 L/kg (mean 2.6 ± 1.3 SD). The distribution volume is larger than that for lidocaine, and results in lower plasma concentrations for prilocaine when equal amounts of lidocaine and prilocaine are administered. Once in the body, prilocaine is reported to be 55% bound to plasma proteins. Prilocaine crosses the blood-brain barrier and also crosses the placenta, presumably by passive diffusion, and during prolonged epidural anaesthesia may produce methaemoglobinaemia in the foetus. Prilocaine is also distributed in breast milk, although the milk:plasma ratio for prilocaine is not determined as data are not available.

Elimination

- **Excretion**

PSD502 healthy male volunteer studies

In PSD502-PE-003, following single doses of PSD502 (30 mg) to the glans penis of healthy male volunteers, lidocaine was eliminated with a mean terminal phase half-life (t½) of 2.85 (0.4303) hours (n=6; all subjects). Insufficient data were available to permit the estimation of t½ for prilocaine, 2,6-xylidine and o-toluidine.

PSD502 healthy female volunteer studies

In PSD502-PE-006, the mean t½ values for lidocaine at all 3 dose levels for Days 1 and 7 for pre- and postmenopausal women were in a range between 2.5 - 10.6 hours and the mean t½ values for prilocaine at the 3 mg dose level were 4.1 hours (Day 1, post-menopause) and 55.2 hours (Day 7, pre-menopause). The mean t½ values for prilocaine at the two highest doses were in a range between 2.0 – 3.3 hours.

The mean t½ values for 2,6-xylidine at the 2 highest dose levels for Days 1 and 7 for pre and post-menopausal women were in a range between 5.3 – 23.0 hours. The mean t½ values for o-toluidine at the 2 highest dose levels for Days 1 and 7 for pre- and postmenopausal women were in a range between 3.1 - 17.3 hours. The half-life for metabolites that form after the administration of the parent drug reflect the rate of formation of the metabolite.

In PSD502-PE-007, following a 60 mg daily dose of PSD502, the mean apparent terminal elimination rates (Kel Day 1) for lidocaine and prilocaine were 0.132 and 0.188 (1/hour), respectively; mean t½ values were 5.42 and 3.99 hours, respectively.

- **Metabolism**

The metabolism of lidocaine and/or prilocaine following the application of PSD502 to the genital mucosa of male or female healthy volunteers has been evaluated in studies PSD502-PE-003 (healthy male volunteers) and PSD502-PE-006 and PSD502-PE-007 (healthy female volunteers).

PSD502 healthy male volunteer studies

Single dose

Following the administration of a single 30 mg dose of PSD502 to the glans penis of 12 healthy male volunteers, 2,6-xylidine concentrations were not detected or not quantifiable until 4 hours post-dose. The mean (SD) 2,6-xylidine plasma concentration 4-hours post-dose on Day 1 is depicted in Table 12 below. At 8 hours post-dose, 2,6-xylidine concentrations were not detected or not quantifiable. o-toluidine was not detected or not quantifiable in any subject on Day 1.

Table 12: Mean (SD) Pharmacokinetic Parameters for 2,6-Xylidine Following a Single Dose (Day 1) and 21 Daily Doses of PSD502 (30 mg) Applied to the Glans Penis: PSD502-PE-003

Dosing	Circumcision Status	2,6-Xylidine (SD)	
		C_{max} ng/mL	T_{max} hr
Single dose (Day 1)	Uncircumcised	NA	NA
	Circumcised	NA	NA
	Total	NA	NA
Multiple dose (Day 21)	Uncircumcised	7.84 (0.948), n=2	2.54 (2.180), n=2
	Circumcised	4.36 (NA), n=1	8.0 (NA), n=1
	Total	6.68 (2.118), n=3	4.36 (3.508), n=3

Abbreviations: SD = standard deviation; NA = not applicable/not available; NR = not reported. See also Pharmacokinetic terms and definitions list.
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.
Source: PSD502-PE-003 CSR, Section 14, Table 14.2.3.2

Multiple doses on a single day

Following the administration of 3 x 30 mg doses of PSD502 to the glans penis at 4 hourly intervals on Day 7 and Day 14, the mean (SD) 2,6-xylidine concentration detected at 1.5 hours post-third-dose was 2.24 (3.076) ng/mL on Day 7 (range 0 to 7.9 ng/mL) and 3.71 (3.823) ng/mL on Day 14 (range 0 to 10.60 ng/mL). o-Toluidine was only detectable in a single subject on and Day 14, 1.5 hours after the third dose (2.03 ng/mL) and was just above the lower level of quantification.

Repeat dosing for 21 Days

On Day 21, following 21 daily doses of PSD502 (30 mg) 2,6-xylidine was only quantifiable in 3 subjects. The maximum concentration recorded for any subject was 8.51 ng/mL at 4-hours post-dose. o-toluidine was only detected in a single subject, just above the lower level of quantification 4 hours after dosing on Day 21. All other subjects had concentrations of o-toluidine below the lower limit of quantification at all time-points.

PSD502 healthy female volunteer studies

Single dose

Systemic exposure of the subjects to the metabolites 2,6-xylidine and o-toluidine was low and variable (see Table 13). o-Toluidine was detectable in plasma on Day 1 for a single subject in the 3 mg dose group and for small numbers of subjects in the higher dose groups.

Table 13:

2,6-Xylidine and *o*-Toluidine C_{max} and T_{max} Following a Single Dose of PSD502 (3 mg, 30 mg, 60 mg and 150 mg) Applied to the Cervix and Vaginal Fornices of Healthy Female Volunteers: PSD502-PE-006 and PSD502-PE-007

Dose (mg)	Menopausal Status	2,6-Xylidine (SD)		*o*-Toluidine (SD)	
		C_{max} ng/mL	T_{max} hr	C_{max} ng/mL	T_{max} hr
3	Pre-menopause (n=0)	NA	NA	NA	NA
	Post-menopause (n=1)	NA (n=0)	NA	1.28 (NA)	0.5 (NA)
30	Pre-menopause (n=1)	0.72 (NA)	4.0 (NA) [a]	NA (n=0)	NA
	Post-menopause (n=2)	3.43 (1.011)	2.5 (1.0-4.0) [a]	2.25 (0.41)	2.0 (2.0-2.0) [a]
60	Pre-menopause (n=6)	2.65 (1.39)	3.50 (2.51)	1.27 (0.276), n=2	3.00 (1.41), n=2
	Post-menopause (n=8)	2.37 (0.802)	3.63 (2.13)	2.31 (NA), n=1	2.03 (NA), n=1
150	Pre-menopause (n=3)	6.14 (3.374)	2.0 (2.0-4.0) [a]	2.39 (0.753)	2.0 (1.0-2.0) [a]
	Post-menopause (n=1)	6.33 (NA)	4.0 (NA) [a]	3.49 (NA)	2.0 (NA) [a]

Abbreviations: NA = not applicable; NR = not reported. See also Pharmacokinetic terms and definitions list.
Note: 60 mg dose group was in study PSD502-PE-007, all other dose groups were in study PSD502-PE-006
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.
Source: PSD502-PE-006, Table 11-6 and Table 11-7; PSD502-PE-007 CSR, Table 11-1 and Table 11-2

Repeat dosing for 7 Days

Plasma levels of 2,6-xylidine and o-toluidine in these subjects were low or absent, even following repeat dosing with PSD502 150 mg (see Table 14). No 2,6-xylidine was detectable in plasma after 7 daily administrations of the 3-mg dose.

o-Toluidine was detected in the plasma of 2 or fewer pre- and post-menopausal women in any dose group on Day 7 (including one subject for whom o-toluidine was detectable in plasma on Days 1 and 7 after administration of the 3 mg dose).

Table 14:

2,6-Xylidine and *o*-Toluidine C_{max} and T_{max} Following a 7 Daily Doses of PSD502 (3 mg, 30 mg, 60 mg and 150 mg) Applied to the Cervix and Vaginal Fornices of Healthy Female Volunteers: PSD502-PE-006 and PSD502-PE-007

Dose (mg)	Menopausal Status	2,6-Xylidine (SD)		*o*-Toluidine (SD)	
		C_{max} ng/mL	T_{max} hr	C_{max} ng/mL	T_{max} hr
3	Pre-menopause (n=0)	NA	NA	NA	NA
	Post-menopause (n=1)	NA	NA	1.35 (NA)	1.0 (NA)
30	Pre-menopause (n=2)	1.95 (1.230)	3.0 (2.0-4.0) [a]	1.88 (NA), n=1	2.0 (NA) [a], n=1
	Post-menopause (n=2)	1.05 (0.071)	3.5 (1.0-6.0) [a]	1.31 (0.438)	6.5 (1.0-12.0) [a]
60	Pre-menopause (n=9)	2.40 (1.32)	3.89 (2.37)	1.23 (0.361), n=2	7.01 (7.06), n=2
	Post-menopause (n=9)	2.81 (1.52)	2.33 (1.32)	6.00 (6.23), n=2	1.50 (0.71) [a], n=2
150	Pre-menopause (n=3)	3.58 (3.287)	2.0 (2.0-4.0) [a]	2.05 (1.038)	2.0 (2.0-2.0) [a], n=2
	Post-menopause (n=1)	2.96 (NA)	4.0 (NA) [a]	1.37 (NA)	4.0 (NA) [a]

Abbreviations: NA = not applicable; NR = not reported. See also Pharmacokinetic terms and definitions list.
Note: 60 mg dose group was in study PSD502-PE-007, all other dose groups were in study PSD502-PE-006
The number of subjects (n) reported represents those subjects for whom pharmacokinetic parameters were calculated. In some cases, all or most of the concentration values for a subject were below the quantification limit, and parameters could not be calculated.
Source: PSD502-PE-006, Table 11-6 and Table 11-7; PSD502-PE-007 CSR, Table 11-1 and Table 11-2

Vaginal metabolism of PSD502

Lidocaine and prilocaine were detected in vaginal fluids of subjects following all 3 dose levels in increasing amounts relative to dose. The appearance of lidocaine and prilocaine in the vaginal fluid was from the fluids washing away the administered dose that was sprayed on the vaginal and cervical surfaces. Relative to the doses applied the amount of lidocaine and prilocaine detectable in vaginal

fluids 2 hours post-dose was small. The maximum amount of lidocaine and prilocaine present on the tampon at 2 hours post dose was 7.6% of the administered dose.

As expected, metabolites were not detected in vaginal fluid at any of the dose levels in any subject. These metabolites are principally formed in the liver and excreted in urine as conjugates of further metabolic products. There are no known drug metabolising capabilities or excretory processes in the inner vagina that could result in the presence of 2,6-xylidine or o-toluidine.

Reports in the literature

There is some preliminary evidence that lidocaine is metabolised to a minor extent in the skin, but lidocaine is largely metabolised in the liver by cytochrome P450 (CYP450) isoenzymes CYP1A2 and CYP3A4 to its two major pharmacologically active metabolites, first to MEGX and then to glycinexylidine (GX), and 2,6-xylidine both of which have pharmacologic activity similar to, but less potent than that of lidocaine. Lidocaine has a high hepatic extraction ratio and any impairment of liver function or hepatic blood flow can significantly affect the PK.

First pass metabolism is extensive and bioavailability is about 35% after oral doses. Metabolism in the liver is rapid and approximately 90% of a given dose is dealkylated to form MEGX and GX. These two metabolites have longer half-lives than lidocaine and accumulation, particularly of GGX may occur during prolonged infusions and may contribute to the therapeutic and toxic effects of the drug. The pharmacological activity of 2,6-xylidine is unknown, but it has been shown to be carcinogenic in rats.

Following intravenous administration, MEGX and GX concentrations in serum range from 11 to 36%, and from 5 to 11% of lidocaine concentrations, respectively [1].

Prilocaine is rapidly metabolised in both the liver, also via CYP450 isoenzymes and in the kidneys by amidases, to various metabolites including ortho- (o-)toluidine and N-npropylalanine [1, 23].

The o-toluidine metabolite has been shown to be carcinogenic in several animal models and can produce methaemoglobinaemia following systemic doses of prilocaine approximating 8 mg/kg. Very young patients, patients with glucose-6-phosphate dehydrogenase deficiencies and patients taking oxidizing drugs such as antimalarials and sulfonamides are more susceptible to methemoglobinemia.

Oral application of Oraqix periodontal gel

Serum concentrations of 2,6-xylidine and o-toluidine were also evaluated in patients following application of Oraqix periodontal gel (a eutectic mixture of 2.5% lidocaine and 2.5% prilocaine) to periodontal pockets around all the teeth in the mouthThe ratio for Cmax 2,6-xylidine/Cmax lidocaine was in the range 0.01 to 0.15 and the ratio of Cmax o-toluidine/Cmax prilocaine was between 0.12 and 0.48.

Application of EMLA cream to leg ulcers

The plasma concentrations of lidocaine and prilocaine and their main metabolites were evaluated in 36 patients undergoing debridement of venous leg ulcers following the application of EMLA cream (1 to 2 g/cm2; maximum 10 g) for 30 to 45 minutes under an occlusive dressing. The lidocaine metabolite monoethylglycinexylidide was below the limit of quantification in all samples, whereas 2,6-xylidine was quantifiable in 6 of the samples, but did not exceed 12 ng/mL in any of the samples. Maximum plasma levels of prilocaine were 77 ng/mL and the prilocaine metabolite o-toluidine was quantifiable in 62/136 samples bud did not exceed 11 ng/mL. There was a significant correlation ($p<0.05$) between the plasma levels of lidocaine, prilocaine, and otoluidine and the dose of EMLA cream applied and the leg ulcer area. No apparent sign of accumulation of lidocaine or prilocaine or their main metabolites was observed.

Dose proportionality and time dependencies

No data was presented on this sub-heading.

Special populations

No specific PK studies in special populations were conducted.

Circumcision and menopause

Absorption of lidocaine, prilocaine and appearance of the metabolites 2,6-xylidine and *o*-toluidine is slightly higher in the uncircumcised group. The three possible reasons proposed for this are; firstly, the presence of the foreskin may act as an occlusive barrier, increasing absorption of PSD502, secondly PSD502, may also be absorbed from the inside of the foreskin which thus provides a larger surface area for absorption compared to circumcised subjects. Finally, the mucosa of the glans penis is non-keratinised or poorly keratinised in uncircumcised men, but tends to become keratinised following circumcision. PSD502 is not expected to readily penetrate keratinised skin and it would therefore be expected that the increase in keratinisation following circumcision would reduce the rate of absorption of PSD502.

For the premenopausal subjects, there was a trend to a greater amount of drug collected into the tampon, relative to that for the post-menopausal women, A plausible explanation was that vaginal fluids are greatly reduced after menopause. Metabolites were not detected in vaginal fluid of pre- or post-menopausal subjects.

Pharmacokinetic interaction studies

Anti-infectives

As PSD502 is to be applied to the genitalia, and could potentially also spread to the genital area of the sexual partner, a number of ***in vitro*** studies were performed to study potential interactions with other topical drugs for genital use, and also contraceptive devices, which may be in contact with PSD502.

PSD502 interaction with the following agents was tested:

1. Antifungal agents: Clotrimazole, Econazole, Imidazole, Nystatin, Miconazole and Ketoconazole
2. Antibiotics: Clindamycin and Metronidazole
3. Antiviral agent: Ayclovir (due to cytotoxicity at full strengths, 1/5 strength PSD502 and 1/125 strength Acyclovir were tested).

There was no interference by PSD502 with the antimicrobial activity of any of the antimicrobial agents tested, and this information is included in the SPC. Despite the inability to test interaction with Acyclovir at clinical strengths, it would seem reasonable to assume that there would be no interaction in clinical practice.

Other drugs

According to The EMLA® Product Monograph and EMLA SPC, interaction with Class I anti-arrhythmics, drugs that reduce the clearance of lidocaine (eg, cimetidine or betablockers) and induction of Methaemoglobinaemia due to benzocaine is possible.

Contraceptive devices

Four studies were conducted to evaluate the effect of PSD502 on condoms (Study 48580 Smithers Rapra Technology Ltd, Shropshire, UK), the cervical cap (Study 50686 Smithers Rapra Technology Ltd), the contraceptive diaphragm (Study 50687 Smithers Rapra Technology Ltd), and the female condom (Study 50841 Smithers Rapra Technology Ltd). The various contraceptive devices were exposed to the

30 mg clinical dose of PSD502, and subjected to tensile strength and elongation break tests. In addition, the male and female condoms were also subjected to burst pressure and burst volume testing. It was found that the integrity of the male condom, the cervical cap, and diaphragm were not affected by exposure to PSD502. However, the female condom showed an effect on tensile strength and elongation of break testing following exposure to PSD502, and an increased incidence of punctured devices. The female condom tested was polyurethane based, rather than latex rubber.

Pharmacokinetics using human biomaterials

In vitro studies of microsomes isolated from human skin have identified that the enzymes involved in metabolism of lidocaine are also expressed in low levels in human skin. However literature searches did not reveal any relevant biomaterials studies carried out on genital mucosa.

The effect of PSD502 on the motility of human sperm has not been evaluated. Effect of PSD502 on spermicidal agents could not be tested for technical reasons, due to the inherent effect of PSD502 on sperm mobility and viability.

2.4.3. Pharmacodynamics

Mechanism of action

Lidocaine

Lidocaine base is readily soluble in propellant. However, once the propellant evaporates lidocaine will quickly crystallise on the surface of the skin, rendering it inactive as it is inaccessible to the mucous membrane. Therefore, the presence of prilocaine is an absolute necessity in the formulation as it is required for solubilising lidocaine and maintaining it in its liquid state once the propellant has evaporated.

Prilocaine

By mixing a small amount of prilocaine with lidocaine (ratio 1:3), a mixture is formed which is slightly oily in texture, requires no excipients other than the propellant, and importantly, has a pKa that is favourable for absorption through mucous membranes. In contrast to lidocaine base, prilocaine alone is not particularly soluble in the propellant, but once mixed with lidocaine, it becomes readily soluble and the melting point is lowered so that it remains in a stable liquid form even when dispensed from a pressurized canister, using a metered dose valve.

Primary and Secondary pharmacology

The primary pharmacological activity of the combination product is essentially the same as for the individual active ingredients. Lidocaine has a rapid onset of action and anaesthesia is obtained rapidly while prilocaine has slower onset of action but a slightly longer duration of action. The combination of lidocaine and prilocaine provides rapid onset of action. PSD502 delivers lidocaine and prilocaine in their base forms increasing the speed of onset of anaesthesia.

Both Lidocaine and Prilocaine act on the CNS and cardiac tissues at higher concentrations. As systemic absorption with PSD502 use is very minimal, adverse effects on these tissues is unlikely. Literature references are provided to show the absorption of the actives through a number of different tissues such as the respiratory tract, anorectal mucosa and skin. Most of these are based on the use of EMLA cream.

2.4.4. Discussion on clinical pharmacology

The PD effects and interactions are unlikely to result in any adverse effects.

The acute toxic plasma levels of both prilocaine and lidocaine are well established at approximately 5000 ng/ml. The highest maximum plasma concentrations of lidocaine and prilocaine following application of PSD502 to the glans penis of healthy male volunteers on multiple dosing days (1.5 hours after 3 4-hourly 30 mg doses), were 171.47 ng/mL and 19.39 ng/mL for lidocaine and prilocaine, respectively, which are 29-fold and 258-fold below minimum toxic levels. PSD502 will be dosed intermittently over potentially long periods of time for PE, therefore, the safety of chronic dosing is particularly important for this indication. After 21 daily doses of PSD502 to the glans penis of healthy volunteers, the mean C_{max} of lidocaine in the population overall was 56.11 ng/mL and for prilocaine was 7.18 (2.457) ng/mL; approximately 90-fold and 700-fold below the plasma concentrations associated with systemic toxicity for lidocaine and prilocaine, respectively.
Although lidocaine and prilocaine are not carcinogenic, there is evidence that the major metabolites (2,6-xylidine and *o*-toluidine respectively) or potentially, sub-metabolites of these, may be carcinogenic. Plasma levels of 2,6-xylidine were only detected at low levels, in approximately two thirds of healthy male volunteers in study PSD502-PE-003, where supranormal dosing was tested, and then only at some time-points. In the same study *o*-toluidine was only detected at one time point in 1 of the 12 patients who received active drug. Haemoglobin adducts (along with DNA adducts) are considered biomarkers of exposure to metabolites. Although there were small rises in both *o*-toluidine and 2,6-xylidine Hb adduct levels in the sub-group of subjects tested in the pivotal PSD502-PE-002 study, the rises do not appear to be excessive compared to background levels in the literature and therefore, whilst it is not possible to confirm that these rises do not indicate potential harm, there is no obvious safety signal from these results.

With regard to sexual partners of patients using PSD502, drug transfer to partners during intercourse is minimal (1/4 to 1/8 that of the patient), and no (or minimal) accumulation was seen following daily doses. The lack of spermicide interaction study is also noted in the SmPC/PIL. The systemic exposure following PSD502 dosing is so low this is extremely unlikely. However, as a precautionary measure, a warning is included in the SmPC/PIL. Therefore, the latex-based male condom, the cervical cap, and the diaphragm can be used as effective contraceptives in the presence of PSD502, but not polyurethane-based barrier contraceptives. Deterioriation was observed when Lidocaine/Prilocaine Plethora was used with polyurethane-based female and male condoms.

2.4.5. Conclusions on clinical pharmacology

The Applicant has presented a comprehensive clinical pharmacology program. There are no outstanding issues on clinical pharmacology.
The clinical pharmacology development of PSD502 comprises four pK studies, three studies conducted in healthy volunteers and one in patients undergoing skin grafts. These studies provide limited information on the pK and pD behaviour of the product. The Applicant has completed the missing information with that available for EMLA cream, a eutectic mixture of lidocaine 2.5% and prilocaine 2.5% to be administered topically. The Applicant has justified it through the similar composition and topical administration of both products and the extensive use and the well-known pharmacology of the components. Admittedly, lidocaine and prilocaine are present in a number of formulations. However, EMLA and PSD502 cannot be considered identical formulations. It is uncertain to what extent the data can be extrapolated although given the low expected systemic exposure it does not seem to be an issue. A relative bioavailability study with EMLA would have been useful in order to confirm the

acceptability of the provided data, however the lack of this study was not considered major by the CHMP.

PSD502 acts locally in the glans penis. PK studies have shown that after the administration of single and multiple doses to healthy male volunteers systemic absorption of lidocaine and prilocaine is minimal. Repeated daily dosing increases the exposure although a safety margin of 29 for lidocaine and 258 for prilocaine has been estimated. Similarly, when potential transfer to females partners was investigated the application to cervix and vaginal fornices of doses up to 150 mg (5-fold the dose to be administered to the male) rendered plasma concentrations well below the toxicity limits. Lidocaine and prilocaine plasma concentrations tended to be higher on Day 21, but again, plasma concentrations were well below the limits of toxicity. Slightly greater amount of the actives were recovered from the vaginal fluid of premenopausal women compared to post-menopausal women. It has been explained due to decreased vaginal fluid secretion in the latter group although it is more likely that this is due to increased systemic absorption in the postmenopausal women as seen by slightly higher plasma levels of the actives.

Although the mechanism is not clear, there is no safety concern due to the low levels of the actives, both in plasma and in vaginal fluid.

Concentrations of both lidocaine and prilocaine in uncircumcised subjects appeared to be higher than in the circumcised group, remarkably after repeated dosing. Whereas the stability studies conducted to evaluate the effect of PSD502 on condoms and other devices do not raise any concern about the integrity of these devices except for polyurethane-based condoms the differences in exposure to lidocaine and prilocaine when they (particularly male condoms) are used are not determined. The information has been included in the PI.

2.5. Clinical efficacy

The efficacy of PSD502 in the treatment of primary premature ejaculation in adult men was evaluated in five studies:

- 1 proof of concept phase 2 study (ANAE-059-00)
- 1 dose-range finding study (PSD502-PE-005)
- 2 pivotal studies (PSD502-PE-002 and PSD502-PE-004)
- 1 supportive phase 2 study (PSD502-PE-001)

2.5.1. Dose response study

- **Study PSD502-PE-005**

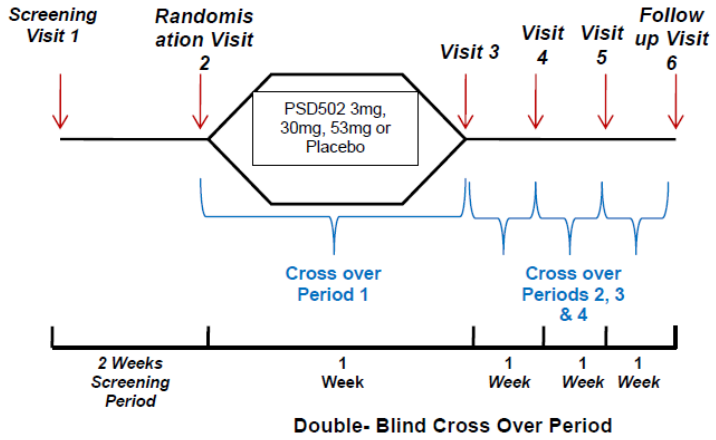
Study PE-005 was primarily aimed to evaluate the effect of 3 doses (3 mg, 30 mg, and 53 mg) of PSD502 on IELT. The study followed a multi-centre, double-blind, placebo-controlled, 4-way crossover design.

After the initial screening assessments subjects underwent a baseline evaluation period of 2 weeks during which they were required to document at least one sexual encounter using a stopwatch with a recorded IELT $\leq$1 minute. Subjects who were eligible to continue in the study were assigned a

randomization number corresponding to pre-determined sequences of PSD502 doses or placebo. The treatment period was 4 weeks (1 week for placebo and 1 week for each of the 3 doses).

The three doses chosen to be tested were 30 mg (3 sprays, each containing 7.5 mg lidocaine and 2.5 mg prilocaine); 3 mg, low dose (3 sprays, each containing 0.75 mg lidocaine and 0.25 mg prilocaine) and 53 mg, high dose (3 sprays, each containing 13.28 mg lidocaine and 4.45 mg prilocaine).

Subject Study Flow



PE-005 included subjects aged ≥18 years, satisfying ISSM criteria for PE with a baseline IELT ≤1 minute in at least one sexual encounter were eligible to enrol in this study. Subjects must have been in a stable heterosexual and monogamous relationship of at least 3 months duration. Subjects were excluded if:

- they had erectile dysfunction, defined as an IIEF-5 score of ≤21 (unless the low score was entirely related to PE symptoms in the opinion of the Investigator),
- they or their partner had any physical or psychological condition that would prevent them from undertaking the study procedures, or had a current history of alcohol or drug abuse, had an increased susceptibility to methemoglobinemia or used class I or III anti-arrhythmic drugs.
- they had received treatment with anti-depressant therapy for PE, local anesthetic spray, intra-cavernosal injection or psychotherapy for PE within 4 weeks of screening. Subjects were able to take tricyclic antidepressants, MAOIs or SSRIs, for indications other than PE, as long as the dose remained unchanged within 4 weeks of screening and continued to remain unchanged throughout the treatment period

The primary efficacy variable was the change in mean IELT from baseline.

The secondary efficacy variables were the proportion of subjects with mean IELT >1 minute and >2 minutes, and the proportion of subjects with at least a two-fold increase in mean IELT compared with baseline

Based on data from PSD502-PE-001, 24 subjects were sufficient to ensure at least 90% power to demonstrate a significant dose response. This assumed that the underlying dose response was such that there is at least a doubling of IELT in the higher doses of PSD502 compared with placebo. There was also at least 80% power to detect at least a 2-fold increase in IELT versus placebo for each individual PSD502 dose.

The primary efficacy variable was to be analysed using a linear random effects model with dose, period and centre as fixed effects, mean baseline IELT as a covariate and subject as a random effect. The mean IELT was to be log-transformed prior to the analysis. Evidence of dose-response was to be

assessed using linear contrast test. Differences between the different doses of PSD502 were also to be assessed but without adjustments for multiplicity. Modelling of the dose-response relationship was also to be undertaken. All randomised subjects receiving at least one dose of study medication were to be used in the analysis. The secondary efficacy variables were to be analysed using a generalised linear mixed model with dose, treatment period and centre as fixed effects, mean baseline IELT as a covariate and subject as a random effect.

All randomised subjects that received the study drug were to be included in the Intent-to-Treat (ITT) population. The ITT population was to be used for the analysis of all baseline characteristics and primary analysis of efficacy data. The per protocol population was to be a subset of the ITT population and was to be formed by excluding subjects with major protocol deviations that could have affected the efficacy assessments. All subjects that received the study drug were to be included in the safety population. The safety population was to be used for the analysis of all safety data.

Efficacy results

A total of 35 subjects were treated. The study population was 100% Caucasian with a mean age of 40 years. Approximately a third of the male subjects in the ITT population were less than 35 years of age. The median age was 39 years (range 21 years to 66 years). The BMI ranged from 19.5 kg/m2 to 35.4 kg/m2, with a mean BMI of 26.49 kg/m2. Approximately 15% of subjects in the ITT population had a BMI of 30 kg/m2 or over.

Table 15:

ITT, Safety and PP populations – Randomised Subjects

Population	Treatment Period (N=35)				
	Overall	Period 1	Period 2	Period 3	Period 4
ITT	35 (100%)	35 (100%)	35 (100%)	34 (97%)	34 (97%)
PP	31 (89%)	31 (89%)	30 (86%)	30 (86%)	29 (83%)
Safety	35 (100%)	35 (100%)	35 (100%)	34 (97%)	34 (97%)

Source: Table 3, Section 14

All subjects had life-long PE. The median time since diagnosis of PE was 1 year (range 0 years to 26 years). Ten (29%) subjects had previously received one or more treatments for PE. The most common type of treatment for PE was SSRIs or other antidepressants, followed by local anaesthetic. There were no circumcised subjects.

Table 16:

Sexual Encounter Data – ITT Population

	Placebo (N=34)	PSD502 3mg (N=35)	PSD502 30mg (N=35)	PSD502 53mg (N=34)
Number of Sexual Encounters	82	83	81	76
Number of Sexual Encounters with Spray	80 (98%)	80 (96%)	81 (100%)	76 (100%)
Proportion of Penetrations	81 (99%)	82 (99%)	77 (95%)	70 (92%)
Proportion of Ejaculation	81 (99%)	82 (99%)	77 (95%)	65 (86%)
Proportion of Penetrations without Ejaculation	0 (%)	0 (%)	0 (%)	5 (7%)

Source: Table 10, Section 14

The number of sexual encounters with the spray was similar for each dose group including placebo. For the 53mg dose, in five (7%) encounters where penetration occurred, the subjects did not achieve ejaculation, whereas all penetrations at the two lower doses resulted in successful ejaculation.

Two subjects did not achieve penetration or ejaculation on any occasion following the 53mg dose, and both these subjects reported difficulty maintaining an erection, and one also complained of local

numbness. Two other subjects were able to achieve penetration but did not ejaculate on each occasion following the 53mg dose.

- Primary Efficacy Variable

When compared with placebo, only treatment with the 30 mg dose significantly delayed ejaculation (geometric mean ratio to placebo 1.7-fold, lower 95% CL 1.19; p = 0.008). The proportion of subjects with at least a 2-fold increase in mean IELT was 32.4%, 57.1%, 65.7% and 47.1% for placebo, 3 mg PSD502, 30 mg PSD502, and 53 mg PSD502, respectively. In part, this was due to the fact that a significant percentage (12%; 4 of 34 subjects) of subjects experienced hypoesthesia with the 53 mg dose, resulting in ejaculation failure (baseline IELT data were carried forward where all IELT data for an individual period were missing).

Table 17:

Summary of Mean IELT (secs) - ITT Population

		Placebo (N=34)	PSD502 3mg (N=35)	PSD502 30mg (N=35)	PSD502 53mg (N=34)
Baseline Mean IELT (secs)	n	34	35	35	34
	Geometric Mean	48.1	48.2	48.2	48.1
	Mean (SD)	63.0 (64.9)	62.7 (64.0)	62.7 (64.0)	63.0 (64.9)
	Median	46	47	47	46
	Range	9 – 350	9 – 350	9 – 350	9 – 350
Mean IELT (secs)	n	34	35	35	29
	Geometric Mean	84.8	107.3	148.5	110.6
	Mean (SD)	116.8 (108.6)	154.1 (111.0)	243.1 (246.9)	164.2 (154.1)
	Median	75	123	147	135
	Range	11 – 484	1 - 451	18 - 980	18 - 778
Ratio to Baseline in Mean IELT	n	34	35	35	29
	Geometric Mean	1.8	2.2	3.1	2.4
	Mean (SD)	2.5 (2.9)	3.2 (2.9)	5.2 (7.2)	3.1 (2.1)
	Median	2	2	3	2
	Range	0 – 16	0 – 15	0 – 37	1 - 8

Source: Table 11, Section 14

The primary efficacy analysis performed on the PP population was very similar to that for the ITT population.

- Secondary Efficacy Variables

A greater proportion of subjects receiving the PSD502 30mg dose attained an IELT > 1 minute and > 2 minutes in comparison to all other doses.

Table 18:
Summary of Mean IELT > 1 min, > 2 mins and 2-fold increase over Baseline (Observed Data) – ITT Population

	Placebo (N=34)	PSD502 3mg (N=35)	PSD502 30mg (N=35)	PSD502 53mg (N=34)
Mean IELT > 1 min	24 (70.6%)	26 (74.3%)	28 (80.0%)	21 (61.8%)
Mean IELT > 2 mins	9 (26.5%)	18 (51.4%)	20 (57.1%)	17 (50%)
Mean IELT ≥ 2 fold increase over Baseline	11 (32.4%)	20 (57.1%)	23 (65.7%)	16 (47.1%)

Source: Table 14, Section 14

- Safety Results

Subjects: In total 23 treatment emergent AEs (TEAEs) were reported by six (17%) subjects: 2 (6%) with 3mg, 4 (11%) with 30mg and 6 (18%) with 53mg.

The most common TEAE were hypoaesthesia of male genitalia (n=5; 14%; 4 reported with 53 mg dose), erectile dysfunction (n=2; 6%), genital burning sensation (n=1; 53mg dose).

Two TEAEs (penile numbness and penile burn) reported by subject 407 during the PSD502 53mg treatment period were reported to be severe. All other TEAEs were either reported as mild or moderate in severity.

Partner: In total 11 TEAEs were reported by four (11%) partners. Overall, two (6%) partners for the subjects treated with PSD502 53mg, two (6%) partners for the subjects treated with PSD502 30mg, three (9%) partners for the subjects treated with PSD502 3mg and no partners for the subjects treated with placebo reported TEAEs. The most common TEAE was hypoaesthesia (vaginal numbness), this was reported five times in total, by one (3%) partner for the PSD502 3mg dose and by two (6%) partners for the PSD502 30mg dose. The second most common TEAE was vulvovaginal burning sensation, this was reported four times in total, by one (3%) partner for the PSD502 30mg dose and by two (6%) partners for the PSD502 53mg dose.

There were no severe TEAEs reported in partners. The severity profile for partners was very similar across the three PSD502 treatment periods.

2.5.2. Main studies (phase III = therapeutic confirmatory trials)

Primary evidence for the efficacy of PSD502 in the treatment of patients with premature ejaculation comes from the individual primary Studies PSD502-PE-002 and PSD502-PE-004. These pivotal studies were phase III, multi-centre, randomised, double-blind, placebo-controlled study, with open-label follow-up in 240-300 subjects with lifelong PE and their sexual partners.

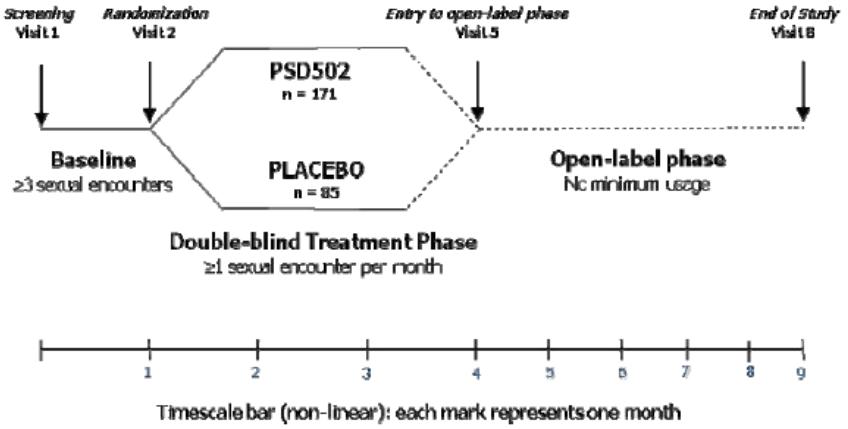
Table 19:

Summary of the Pivotal studies conducted with PSD502 in premature ejaculation

Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product; Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment
PSD502-PE-002	5.3.5.1	Efficacy and safety of PSD502 + PK of PSD502 (drug metabolites)	Double-blind, randomised, placebo-controlled followed by open-label phase	PSD502 (30 mg) cutaneous spray, or placebo cutaneous spray (double-blind phase), applied to the glans penis 5 minutes prior to sexual intercourse , up to one dose per day. Open label : maximum 3 doses per 24 hours, each dose separated by at least 4 hours.	256 (double-blind); 223 continued into open-label phase	Male patients with premature ejaculation	3 months (double-blind) + 5 months (open-label)
PSD502-PE-004	5.3.5.1	Efficacy, safety and tolerability of PSD502	Double-blind, randomised, placebo-controlled followed by open-label phase	PSD502 (30 mg) cutaneous spray, or placebo cutaneous spray (double-blind phase), applied to the glans penis 5 minutes prior to sexual intercourse , up to one dose per day. Open label : maximum 3 doses per 24 hours, each dose separated by at least 4 hours.	300 (double-blind); 274 continued into open-label phase	Male patients with premature ejaculation	3 months (double-blind) + up to 9 months (open label)

The overall design for the studies is shown in Figure 3.

Figure 3: Overall design of study (PSD502-PE-002)



Methods

Two pivotal randomised, double-blind, placebo-controlled, 12-week, parallel-design, multinational studies were performed to evaluate the efficacy and safety of PSD502 on demand dosing (prior to sexual intercourse) in men with premature ejaculation. Only the 30 mg dose was tested.

The demonstration of efficacy in the proposed indication is primarily based on the comparison with placebo. The Applicant states that no products were approved for the treatment of PE at the time of initiation of the studies. Dapoxetine is currently the only approved oral medicinal product for the treatment of PE but several products have been used to cover this need. The justification of the Applicant is acceptable.

The duration of the studies is 12 weeks for the DB phase (dapoxetine efficacy trials were of similar duration). Open label extension to up to 9 months provide a total exposure of 12 month. Long term

efficacy is based on a primarily aimed safety extension of the pivotal studies. No controlled data further to 12 weeks to support efficacy are available.

Study Participants

Inclusion criteria

Male subjects aged 18 years and over with lifelong PE were to be considered suitable for the study if they satisfied the DSM-IV and the ISSM criteria.

Subjects were eligible to enrol in the study if they had documented an IELT ≤ 1 minute in at least 2 of the first 3 sexual encounters in the Baseline period and had a response to Screening PEP to perceived control over ejaculation and satisfaction with sexual intercourse of 'Poor' or 'Very poor', and to personal distress and interpersonal difficulty related to ejaculation of 'Quite a bit' or 'Extremely'.

Subjects were required to be in a stable heterosexual and monogamous relationship and the partner was willing to comply with the study procedures.

Exclusion criteria

Subjects were excluded if they had erectile dysfunction (defined as an IIEF5 score of ≤21) unless the low score was entirely related to PE symptoms in the opinion of the Investigator, or he, or his sexual partner, had a physical or psychological condition that would prevent them from undertaking the study procedures, or had a current history of alcohol or drug abuse or had an increased susceptibility to methaemoglobinaemia or known drug sensitivity to amide-type local anaesthetics or used class I or III anti-arrhythmic drugs.

Subjects also were excluded if they had a pregnant partner or of child-bearing potential and not using appropriate contraception [hormonal contraception or intra-uterine device (IUD) during double-blind part of study; hormonal contraception or IUD or condom during open-label part of study].

Subjects were not to be permitted to have received any treatment for PE (e.g. anti-depressant therapy, local anaesthetic spray, intra-cavernosal injection or psychotherapy for PE) within 4 weeks of Screening until the end of the study. Subjects who were taking tricyclic antidepressants, MAOIs or SSRIs, for indications other than PE, were to be permitted to participate as long as the dose had remained unchanged within 4 weeks of Screening and was planned to remain unchanged throughout the double-blind treatment period.

Treatments

The active test product was PSD502, a metered dose aerosol spray delivering a eutectic-like mixture of lidocaine and prilocaine for topical anaesthesia. A single dose of IP was to consist of 3 sprays applied to the glans penis. Each actuation dispensed lidocaine 7.5 mg and prilocaine 2.5 mg in their base forms (a total dose of 22.5mg lidocaine and 7.5mg prilocaine). The propellant used in this spray was tetrafluoroethane (HFA-134a), which also served as a solvent. Once HFA-134a evaporated, the liquid formulation of lidocaine and prilocaine was to form a slightly oily thin layer of drug at the site of application.

The placebo was a metered dose aerosol spray that was identical in appearance to the PSD502 spray and contained the same propellant HFC gas.

Both pivotal studies were controlled with placebo. No active control was included. The inclusion of dapoxetine as active control (the only approved treatment for this condition) has been discussed by the Applicant. It is acknowledged the additional difficulties of adding a third arm by a different route of administration (and the derived double dummy for masking), mainly when both treatments are

administered in the preambles of the sexual intercourse and at different stages (dapoxetine 1-3 hours before, PSD502 five minutes before). The controlled placebo design is acceptable.

Objectives

The primary objective of the studies was to determine the effect of PSD502 on Index of Premature Ejaculation and Intravaginal Ejaculatory Latency Time.

- The secondary objective of the studies was to evaluate the safety and tolerability of PSD502 in subjects with PE, and their sexual partners and to evaluate the effect of PSD502 on the subject and partner Premature Ejaculation Profile (PEP)

.

Study PE-002 had also the following secondary objectives:

- to determine the minimally important difference in IPE domains;
- to evaluate the relationship between IELT and IPE;

Outcomes/endpoints

Outcomes

Efficacy was primarily assessed by quantitative measures based on time to ejaculation (IELT) and qualitative evaluation of the personal impact as patient reported outcomes (Index of Premature Ejaculation). This is welcome since PE is considered a multidimensional condition. Besides, it reflects the relevant aspects included in the definition of the condition. Both IELT and IPE questionnaire can be considered standard methods of measurement and have been widely used in PE clinical research.

IELT was measured with a stopwatch. As the stopwatch could be operated by the subject or the partner (always the same subject during the trial) some differences in the measures could result from it. It can be relevant in those outcomes (secondary endpoints) in which absolute means instead of changes with respect to baseline are considered in the estimation (e.g. % subjects with mean IELT > 1 or 2 minutes).

Response was also measured in terms of responder rates: IELT > 1 minute (according the ISSM definition) and IELT > 2 minutes. Although important, “normalisation” of the time to ejaculation does not result as significant as the perceived improvement by the subject.

With respect to PRO (Patient-reported outcomes), control over ejaculation and satisfaction were considered the two most relevant measures. Control has been described as the key outcome of the impact of the condition.

The PEP has been validated in subjects with PE satisfying the DSM-IV criteria (without restrictions on IELT) and it has been widely used as PRO in published studies on PE. Relevantly, this outcome also monitors the partner’s perception.

Efficacy endpoints

Intravaginal ejaculatory latency time: Subjects were instructed to start timing at the time of vaginal penetration and to stop at the start of ejaculation. Subjects (or their sexual partner) were to be provided with a stopwatch, and were to record the stopwatch recorded IELT in the diary card for each sexual encounter when IP was used. When ejaculation happened before penetration, then the IELT was set to zero, and if the subject was unable to ejaculate, then the IELT was recorded as missing.

During the double-blind treatment phase of the study, the person recording the IELT (subject or his partner) was to remain the same.

Index of premature ejaculation: The IPE is a 10-item questionnaire with three domains: ejaculatory control (4 questions), distress (2 questions) and sexual satisfaction (4 questions). The 10 items were individually scored as follows:

- Items 1-8 scored 5 to 1 in descending order with the 'No sexual intercourse, not applicable category' set to missing.
- Items 9-10 scored 1 to 5 in ascending order with the 'No sexual intercourse, not applicable category' set to missing.

Control scores range from 4 to 20 with a higher score indicating greater control. Satisfaction scores range from 4 to 20 with a higher score indicating greater satisfaction. Distress scores range from 2 to 10 with a higher score indicating less distress.

Premature Ejaculation Profile: The PEP is a 4 item questionnaire validated for use in PE. Questions were related to perceived control over ejaculation, satisfaction with sexual intercourse, personal distress related to ejaculation, and interpersonal difficulty related to ejaculation, each answered on a 5-point scale, with a maximum score of 5 points for each question, and higher scores representing better functioning. Subjects' sexual partners were to complete a 4 point PEP questionnaire. The questions to be answered by the female sexual partners were identical to those of the subjects' questionnaire except that the females were asked to consider their partners' ejaculation when giving responses.

Global ratings: The study PSD502-PE-002 incorporated global ratings of the quality of orgasm (change from baseline), of distress, control and satisfaction and the opinion of the study medication answering the following questions:

- "In general, how do you rate the orgasm you experience during sexual intercourse?" with a 5-point scale ranging from "Very poor" to "Very Good".
- "What was your opinion of the study medication?" with a 4-point scale from "Poor" to "Excellent".
- "Compared to when you started this study, how do you rate
    - the distress you experience during sexual intercourse?"
    - your ability to control your time to ejaculation during sexual intercourse?"
    - your satisfaction with sexual intercourse?"

The subjects were to provide their answers using a 4-point scale of "no change/worse", "small improvement", "moderate improvement" and "large improvement". These questions were to serve as 'anchor' questions in the estimation of the minimum clinically important difference (MCID) of the IPE domains.

The primary measures of efficacy were the:

- change in mean IELT from Baseline to during the 3 months of double-blind treatment
- change in the IPE domain of ejaculatory control from Baseline to month 3
- change in the IPE domain of sexual satisfaction from Baseline to month 3
- change in the IPE domain of distress from Baseline to month 3 (in study PE-004 it was measured as secondary variable)

The secondary measures of efficacy were the:

- proportion of subjects with mean IELT > 1 minute and > 2 minutes during the 3 months of double-blind treatment
- change in mean IELT from Baseline to each month of double-blind treatment
- change in the IPE domains of ejaculatory control, distress and sexual satisfaction from Baseline to months 1 and 2 separately
- scores for perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse and interpersonal difficulty related to ejaculation based on the subject PEP and the partner at months 1, 2 and 3.

Sample size

Due to the co-primary variables in this study, a fixed sequence Bonferroni procedure was to be used to maintain the overall level of significance at no greater than 5%. Based on data from a previous Phase II study of PSD502 in PE (PSD502-PE-001), it was calculated that with 240 to 300 subjects this procedure would provide in excess of 95% power to detect a statistically significant treatment effect on at least one of the endpoints. Unconditionally, there was to be an excess of 95% power to detect a statistically significant 2-fold increase in mean IELT for PSD502 versus placebo at the 5% level of significance and at least 95% power to detect a statistically significant moderate effect size (Cohen's effect size of 0.55) difference for PSD502 versus placebo in the IPE domains of ejaculatory control and sexual satisfaction individually.

Randomisation

Patients who met the inclusion criteria and did not meet the exclusion criteria at the end of the screening period, were randomized to 1 of the treatment groups in a 2:1 ratio using a computer-generated randomization scheme. Randomization was stratified by study site.

Blinding (masking)

The study design incorporated both a double-blind treatment phase and an optional open label treatment phase. The first three months of the treatment phase of the studies was a double-blind phase (PSD502 and placebo). The cold sensation caused by the latent heat of evaporation from the placebo spray sufficiently mimicked the numbing effect of the PSD502 spray and therefore supported blinding.

The open-label design allowed all study subjects an opportunity for treatment with active treatment.

Statistical methods

All randomised subjects that received the study drug were to be included in the Intent-to- Treat (ITT) population. The ITT population was to be used for the summary of all Baseline characteristics and primary analysis of efficacy data. The PP population was a subset of the ITT population and was to be formed by excluding subjects with major protocol deviations that could have affected the efficacy assessments. All subjects that received the study drug were to be included in the safety population.

For each study the statistical analysis plan (SAP) (and the SAP for the interim analysis of Study PSD502-PE-002) were finalised before the respective database locks.
Eligible subjects were randomised to either PSD502 or placebo in a 2:1 ratio with stratification by centre. Centres that contained less than 12 subjects were pooled with similar centres within the same country such that pooled centres were similarly sized and contained no more than 24 subjects.
Analysis of mean IELT over the 3-month treatment period was conducted on log-transformed data using an analysis of covariance (ANCOVA) model including factors for pooled centre and treatment and with the baseline value as a covariate. The treatment effect of PSD502 compared to placebo was estimated together with the associated 95% confidence interval which was transformed back to show the estimate ratio of treatment effects. A similar ANCOVA model was used to analyse the domains of the IPE without first log-transforming the data. A multiple testing procedure was pre-defined in order to control the Type I error. All tests were two-sided.
Missing data were handled as follows. For subjects who withdrew, the IELT was based on available data within the month that withdrawal occurred. For subjects with no IELT data during a particular period, the mean IELT was set to the mean IELT from the baseline period, baseline observation carried forward (BOCF). For subjects withdrawing during the double-blind phase, the IPE questionnaire was to be completed at the time of withdrawal. For nominal visits after withdrawal, the IPE scores were carried forward from the last visit, last observation carried forward (LOCF). If a subject attended a visit but did not complete the IPE questionnaire or only provided partially completed information, the domains scores were considered to be missing. Subjects withdrawing before completing any questionnaire would have the domain scores set to the baseline values.
Various sensitivity analyses were to be performed to examine the robustness of the results of the analysis of the primary efficacy variables for the ITT population. These were to include an analysis using the observed data and an analysis based on the PP population.

Changes in the planned statistical analyses

The following changes to the protocol-planned analyses were described in the SAPs, which were approved prior to database lock and unblinding.
The 'interim' analysis conducted in Study PSD502-PE-002 to estimate the MCID and investigate the sensitivity to change of the IPE, undertaken after approximately half of the enrolled subjects had completed the double-blind phase of the study, was repeated at the end of the study to utilise the full study data to provide a more powerful analysis.
The protocol stated that the relationship of the IPE domains with IELT was to be investigated. However, emerging data showed that there was significant number of subjects with IPE domain scores at the minimum or maximum values potentially masking such a relationship. Consequently, this analysis was not undertaken.
An additional summary of the incidence of treatment-related AEs starting on the same day or the day after use of the study spray was also performed to provide additional information on AEs commencing immediately following treatment.

In Studies PSD502-PE-002 and PSD502-PE-004 data from the double-blind part of the study were analysed following database lock after all subjects had completed the double-blind treatment phase.

Following the re-opening of the database to enter and clean accumulating data from the open-label phase, a small amount of data from the double-blind phase was further cleaned. Consequently all affected analyses were re-run following database lock after all subjects had completed each study as a whole and the results were compared against the original analyses. They were found to be not significantly affected

Results

Study PE-002

Of the 256 patients enrolled a total of 29 randomised subjects (21 to receive PSD502 and 8 subjects to receive Placebo) withdrew during the double-blind treatment phase. Seven of the withdrawals (4 in PSD502/3 in Placebo) were by subjects prior to them using the assigned treatment.

For the remaining 17 subjects who withdrew following commencement of PSD502 treatment, 7 subjects withdrew due to withdrawal of consent by the subject, 5 subjects were lost to follow-up, 3 subjects (withdrew due to intolerable AEs and 1 subject (1303) withdrew as a result of Sponsor's decision.

In the Placebo group, 2 subjects withdrew due to withdrawal of consent by the subject and 3 subjects were lost to follow-up.

Table 20: Study PE-002 - Subject disposition

	Double-blind (DB) phase						Open-label (OL) phase					
	PSD502		Placebo		All		OL PSD502 /DB PSD502		OL PSD502 /DB placebo		All OL	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Screened					444							
Randomised	171	(100.0)	85	(100.0)	256	(100.0)						
Treated DB phase	167	(97.7)	82	(96.5)	249	(97.3)						
Completed DB phase	150	(87.7)	77	(90.6)	227	(88.7)						
Elected to enter OL phase							146		77		223	
Treated OL phase							142	(97.3)	71	(92.2)	213	(95.5)
Completed OL phase							132	(90.4)	67	(87.0)	199	(89.2)
Withdrawn	21	(12.3)	8	(9.4)	29	(11.3)	14	(9.6)	10	(13.0)	24	(10.8)

Study PE-004

A total of 335 subjects provided written informed consent and were screened. Of these, 35 subjects failed screening. The most common reason for failing screening was failure of the subject to meet the study entry criteria.

A total of 31 study sites across 4 European countries randomised 300 study subjects (PSD502: 200 subjects; Placebo: 100 subjects). Of these, 22 subjects withdrew during the double-blind treatment phase (PSD502: 18 subjects; Placebo: 4 subjects). Half of the withdrawals in the PSD502 treatment group were by subjects prior to them using PSD502 (5 withdrawals of consent by the subject, 3 subjects lost to follow-up and 1 withdrawal of consent by subject's sexual partner). For the remaining 9 subjects who withdrew following commencement of PSD502 treatment, 4 subjects withdrew due to withdrawal of consent by the subject or the subject's sexual partner, 2 subjects withdrew due to

intolerable AEs, 2 subjects were lost to follow-up and 1 subject withdrew as a result of Sponsor's decision.

In the Placebo group, a total of 4 subjects who were randomised to receive placebo discontinued the study during the double blind phase. Of these, 1 subject withdrew consent prior to commencing treatment. Of the remaining 3 subjects who withdrew after receiving at least a single dose of Placebo, 2 subjects withdrew due to withdrawal of consent by the subject and the remaining subject was lost to follow-up.

Table 21: Study PE-004 - Subject disposition

	Double-blind (DB) phase						Open-label (OL) phase					
	PSD502		Placebo		All		OL PSD502 / DB PSD502		OL PSD502 / DB placebo		All OL	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Screened					335							
Randomised	200	(100.0)	100	(100.0)	300	(100.0)						
Treated DB phase	191	(95.5)	99	(99.0)	290	(96.7)						
Completed DB phase	182	(91.0)	96	(96.0)	278	(92.7)						
Elected to enter OL phase							180	(100.0)	94	(100.0)	274	(100.0)
Treated OL phase							174	(96.7)	94	(100.0)	268	(97.8)
Completed at end of first OL phase							25	(13.9)	9	(9.6)	34	(12.4)
Completed at end of second OL phase							143	(79.4)	73	(77.7)	216	(78.8)
Withdrawn	18	(9.0)	4	(4.0)	22	(7.3)	12	(6.7)	12	(12.8)	24	(8.8)

Recruitment

A total of 22 subjects treated with PSD502 in the double-blind phase had acquired PE (6.1% of the population), 19 of whom were recruited in study PSD502-PE-002 in the USA and Canada as these were the only countries where recruitment started before the implementation of the protocol amendment requiring subjects to have lifelong PE. There appears to be no evidence that men with acquired PE respond differently to PSD502 than to men with lifelong PE.

Conduct of the study

A number of amendments were approved to exclude patients with HIV, HBV and HCV, update definition of PE according to the ISSM criteria, clarify the use of condoms in the open label phase clarification of data collection etc.

Baseline data

In Study PE-002 male subjects in the ITT population were 18 to 68 years of age and had a mean age of 38.7 years. Over 80% of the subjects were of white ethnic origin, with Afro-Caribbean being the next represented ethnic group (8.4%). The BMI ranged from 17.9 kg/m2 to 52.1 kg/m2, with a mean BMI of 27.29 kg/m2.

Approximately half of the ITT population had been circumcised (USA: circumcised 87.5%, uncircumcised 12.5%; Canada: circumcised 61.9%, uncircumcised 38.1%; Poland: circumcised 5.0%, uncircumcised 95.5%).

In Study PE-004 male subjects in the ITT population were 19 to 65 years of age and had a mean age of 34.8 years. All but 3 of the 290 subjects (99%) were white. The BMI ranged from 17.9 kg/m^2 to 43.3 kg/m^2, with a mean BMI of 26.22 kg/m^2. Less than 7% of the ITT population had been circumcised.

Numbers analysed

Totals of 249 and 290 subjects comprised the ITT populations for the PSD502-PE-002 and PSD502-PE-004 studies, respectively, which was 97% of the randomized population in both cases. Totals of 193 and 237 subjects comprised the Per Protocol populations, representing 75% and 79% of the randomized populations in PSD502-PE-002 and PSD502-PE-004 studies, respectively.

Outcomes and estimation

Baseline PE measures for the ITT population for both studies are summarised in Table 22.

Table 22: Baseline Premature Ejaculation Measures: ITT Population (PSD502-PE-002 and PSD502-PE-004 Individually)

	PSD502-PE-002			PSD502-PE-004		
Baseline PE Measure	**PSD502 N=167**	**Placebo N=82**	**Total N=249**	**PSD502 N=191**	**Placebo N=99**	**Total N=290**
Mean IELT (minutes)						
Geometric mean	0.562	0.531	0.552	0.599	0.576	0.591
Mean	0.636	0.621	0.631	0.679	0.702	0.687
SD	0.2523	0.2685	0.2573	0.3052	0.3832	0.3334
Range	0.02 – 1.35	0.04 – 1.51	0.02 – 1.51	0.03 – 2.35	0.00 – 3.33	0.00 – 3.33
Median	0.646	0.669	0.650	0.692	0.704	0.696
IPE control domain score						
Mean	4.5	4.3	4.4	5.2	5.1	5.2
SD	1.41	0.73	1.23	2.04	1.79	1.96
Range	4 - 13	4 - 8	4 - 13	4 - 14	4 - 12	4 - 14
Median	4.0	4.0	4.0	4.0	4.0	4.0
IPE satisfaction domain score						
Mean	6.8	6.5	6.7	7.0	7.3	7.1
SD	3.17	2.44	2.94	2.89	2.91	2.89
Range	4 - 20	4 - 13	4 - 20	4 - 19	4 - 17	4 - 19
Median	6.0	6.0	6.0	6.0	7.0	7.0
IPE distress domain score						
Mean	2.7	2.8	2.7	3.3	3.1	3.2
SD	0.95	1.07	0.99	1.73	1.41	1.62
Range	2 - 6	2 - 6	2 - 6	2 - 10	2 - 7	2 - 10
Median	2.0	2.0	2.0	2.0	2.0	2.0

Abbreviations: IELT = intravaginal ejaculatory latency time; IPE = index of premature ejaculation; ITT = intention-to-treat; PE = premature ejaculation; SD = standard deviation

Baseline IELT was the mean of all IELTs recorded on subject diary cards in the period between the start of screening (visit 1) and randomization (visit 2). IELT data are reported in the CSRs in seconds, but are presented here in minutes for consistency with other presentations.

Baseline IPE domain scores were collected at the end of the screening period (visit 2).

Control domain scores range from 4 to 20 with a higher score indicating greater control.

Satisfaction domain scores range from 4 to 20 with a higher score indicating greater satisfaction.

Distress domain scores range from 2 to 10 with a higher score indicating less distress.

In Study PE-002 a median of 13 doses of PSD502 and 12 doses of placebo were administered in the double-blind phase.

In Study PE-004 a median of 15.0 doses of PSD502 and placebo were administered in the double-blind phase.

Primary endpoint

The effectiveness of PSD502 in treating PE was assessed by measuring IELT and the co-primary endpoints of ejaculatory control, sexual satisfaction and distress using the IPE.

- *IELT*

Over the 3 month double-blind treatment phase, the geometric mean IELT for subjects in the ITT population of PSD502-PE-002 had increased to 2.59 minutes in the PSD502 group and to 0.80 minutes in the placebo group, and in PSD502-PE-004, had increased to 3.79 minutes in the PSD502 group and 1.07 minutes in the placebo group.

Subjects who received PSD502 had a 4.66-fold increase in their adjusted geometric mean IELT in PSD502-PE-002 and a 6.30-fold increase in their adjusted mean IELT in PSD502-PE-004, whereas those who received placebo demonstrated a 1.53-fold increase in PSD502-PE-002 and a 1.74-fold increase in PSD502-PE-004. The analysis of the ratio to baseline over the 3 month treatment phase for PSD502/Placebo demonstrated a statistically significant 3.05-fold (95%CI: 2.29, 4.06) treatment benefit in favour of PSD502 ($p<0.0001$; significance level=0.0125) in PSD502-PE-002 and a

statistically significant 3.62 fold (95%CI: 2.80, 4.67) treatment benefit in favour of PSD502 (p<0.0001; significance level=0.0167) in PSD502-PE-004 (Table 23).

Table 23: Mean IELT (minutes) during the 3 Months of Double-blind Treatment for Baseline Carried Forward Analysis: ITT Population (PSD502-PE-002 and PSD502-PE-004 Individually)

Mean IELT	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=167	Placebo N=82	PSD502 N=191	Placebo N=99
Baseline				
n	167	82	191	99
Geometric mean	0.562	0.531	0.599	0.576
Mean	0.636	0.621	0.679	0.702
SD	0.2523	0.2685	0.3052	0.3832
Range	0.02 – 1.35	0.04 – 1.51	0.03 – 2.35	0.00 – 3.33
Median	0.646	0.669	0.692	0.704
Over 3 months				
n	167	82	191	99
Geometric mean	2.590	0.798	3.785	1.069
Mean	5.190	1.173	6.055	1.567
SD	6.7432	1.1833	6.9051	1.7953
Range	0.00 - 40.34	0.02 – 8.05	0.31 – 57.76	0.04 – 15.03
Median	2.682	0.888	3.839	1.067
Ratio (over 3 months/baseline)				
n	167	82	191	99
Geometric mean	4.607	1.505	6.323	1.855
Mean	12.808	1.896	16.950	4.816
SD	45.0498	1.7599	90.3964	23.5010
Median	3.982	1.207	5.822	1.655
Range	0.01 – 559.78	0.27 – 12.58	0.43 – 1243.50	0.24 – 234.78
Adjusted geometric mean ratio	4.66	1.53	6.30	1.74
Treatment effect: PSD502/placebo (95% CI)	3.05 (2.29, 4.06)		3.62 (2.80, 4.67)	
p-value	<0.0001		<0.0001	

Abbreviations: CI = confidence interval; CSR = clinical study report; IELT = intravaginal ejaculation latency time; ITT = intention-to-treat; SD = standard deviation

Note: Analysis of covariance of log-transformed values was performed with factors for treatment and pooled centre with log (baseline IELT) as a covariate. Two-sided test performed at the 1.25% significance level in PSD502-PE-002 and 0.0167% in PSD502-PE-004. IELT data are reported in the CSRs in seconds, but have been converted to minutes for consistency of presentation within this module.

Results of the observed cases analysis (ITT population) were similar to those of the baseline carried forward analysis.

- *IPE: Change from baseline in IPE domain scores at month 3*

For the ITT population, substantial improvement was observed in all 3 domains at month 3 in the PSD502 groups of both studies compared with the placebo groups. The improvements in the scores for all 3 domains were slightly higher in the PE-004 study than in the PE-002 study, even though the baseline scores for all 3 domains were also higher in PE-004 (Table 24).

Table 24: Analysis of Change from Baseline in IPE Domain Scores at Month 3 for Last Observation Carried Forward: ITT Population (PSD502-PE-002 and PSD502-PE-004 Individually)

IPE domain	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=167	Placebo N=82	PSD502 N=191	Placebo N=99
Ejaculatory control				
n	165	82	188	99
Mean	7.2	2.2	9.0	2.3
SD	5.99	3.79	5.35	4.49
Median	6.0	0.0	9.5	0.0
Range	-3 - 16	-1 - 14	-8 - 16	-5 - 16
Adjusted mean (SE) [a]	7.3 (0.40)	2.3 (0.57)	9.2 (0.35)	2.2 (0.48)
Treatment effect (95% CI) [a,b]	5.0 (3.61, 6.34)		7.0 (5.87, 8.18)	
p-value [a,b]	<0.0001		<0.0001	
Sexual satisfaction				
n	167	82	191	99
Mean	6.6	2.1	7.8	1.8
SD	5.96	4.14	5.03	4.93
Median	7.0	1.0	8.3	0.7
Range	-8 - 16	-4 - 14	-7 - 16	-8 - 15
Adjusted mean (SE) [a]	6.7 (0.37)	2.2 (0.53)	7.8 (0.34)	1.9 (0.47)
Treatment effect (95% CI) [a,b]	4.6 (3.30, 5.84)		5.9 (4.78, 7.04)	
p-value [a,b]	<0.0001		<0.0001	
Distress				
n	165	82	188	99
Mean	3.5	0.9	3.9	1.3
SD	2.83	2.04	2.53	2.57
Median	3.0	0.0	4.0	1.0
Range	-2 - 8	-2 - 6	-2 - 8	-4 - 8
Adjusted mean (SE) [a]	3.5 (0.20)	1.0 (0.28)	4.0 (0.17)	1.2 (0.23)
Treatment effect (95% CI) [a,b]	2.5 (1.86, 3.20)		2.8 (2.21, 3.31)	
p-value [a,b]	<0.0001		<0.0001	

Abbreviations: CI = confidence interval; IPE = index of premature ejaculation; ITT = intention-to-treat; LS = least square; SD = standard deviation; SE = standard error

Note: Calculations were made using the number of subjects with non-missing IPEs at baseline and at month 3 in each treatment group. Change was defined as visit - baseline. Control scores range from 4 to 20 with a higher score indicating greater control. Satisfaction scores range from 4 to 20 with a higher score indicating greater satisfaction. Distress scores range from 2 to 10 with a higher score indicating less distress. In order to control the overall level of significance at no greater than 5%, a fixed sequence Bonferroni procedure was implemented for each study. The significance level was 0.033 for control, 0.05 for satisfaction, and distress. For PSD502-PE-004, distress (secondary endpoint) was not included in the testing procedure.

a) Analysis of covariance was performed with factors for treatment and pooled centre with baseline as a covariate.

b) Calculated using the difference of PSD502 minus placebo.

Results of the observed cases analysis (ITT population) on IPE domains of ejaculatory control, sexual satisfaction, and distress were similar to those of the baseline carried forward analysis.

Results observed with the Per Protocol populations were consistent with results observed with the ITT populations.

Table 25:

Mean IELT (minutes) During the 3 Months of Double-blind Treatment for Baseline Carried Forward Analysis: Per Protocol Population (Combined PSD502-PE-002 and PSD502-PE-004)

IELT	PSD502 N=284	Placebo N=146
Baseline (minutes)		
Geometric mean	0.592	0.554
Mean	0.653	0.661
SD	0.2535	0.3365
Range	0.02-2.34	0.00-3.33
Median	0.669	0.673
During 3 months of treatment (minutes)		
Geometric mean	3.558	0.971
Mean	6.095	1.433
SD	7.2197	1.6360
Range	0.14-57.76	0.02-15.03
Median	3.652	0.979
Ratio (during 3 months of treatment/baseline)		
Geometric mean ratio	6.010	1.753
Mean ratio	16.556	3.903
SD	81.1562	19.4007
Range	0.55-1243.50	0.27-234.78
Median	5.225	1.487
Adjusted geometric mean ratio (95% CI)	6.15 (5.50, 6.88)	1.72 (1.47, 2.01)
Treatment effect: PSD502/placebo (95% CI)	3.58 (2.97, 4.33)	
p-value	<0.0001	

Abbreviations: CI = confidence interval; IELT = intravaginal ejaculatory latency time; SD = standard deviation

Note: Analysis of covariance of log-transformed values was performed with factors for treatment and pooled centre with log (baseline IELT) as a covariate. Anti-log calculations were performed to present results in the original scale.

Table 26:

Analysis of Change from Baseline in IPE Domain Scores at Month 3 for Last Observation Carried Forward: Per Protocol Population (PSD502-PE-002 and PSD502-PE-004 Individually)

IPE domain	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=127	Placebo N=66	PSD502 N=157	Placebo N=80
Ejaculatory control				
n	127	66	157	80
Mean	7.6	2.3	9.1	2.5
SD	6.11	3.85	5.31	4.80
Median	8.0	0.0	10.0	0.0
Range	-3 - 16	-1 - 14	-8 - 16	-5 - 16
Adjusted mean (SE) [a]	7.5 (0.48)	2.3 (0.66)	9.2 (0.40)	2.4 (0.55)
Treatment effect (95% CI) [a,b]	5.2 (3.55, 6.77)		6.8 (5.49, 8.13)	
p-value [a,b]	<0.0001		<0.0001	
Sexual satisfaction				
n	127	66	157	80
Mean	7.2	2.3	8.0	2.3
SD	5.90	4.21	5.02	5.07
Median	8.0	1.0	9.0	1.0
Range	-8 - 16	-4 - 14	-7 - 16	-8 - 15
Adjusted mean (SE) [a]	7.1 (0.44)	2.3 (0.61)	8.0 (0.39)	1.9 (2.2)
Treatment effect (95% CI) [a,b]	4.8 (3.29, 6.23)		5.8 (4.53, 7.08)	
p-value [a,b]	<0.0001		<0.0001	
Distress				
n	127	66	157	80
Mean	3.6	1.0	3.8	1.5
SD	2.84	2.15	2.57	2.66
Median	4.0	0.0	4.0	1.0
Range	-1 - 8	-2 - 6	-2 - 8	-4 - 8
Adjusted mean (SE) [a]	3.6 (0.23)	1.0 (0.32)	3.9 (0.19)	1.3 (0.26)
Treatment effect (95% CI) [a,b]	2.6 (1.82, 3.35)		2.6 (2.00, 3.25)	
p-value [a,b]	<0.0001		<0.0001	

Abbreviations: CI = confidence interval; IPE = index of premature ejaculation; LS = least square; SD = standard deviation; SE = standard error

Note: Calculations were made using the number of subjects with non-missing IPEs at baseline and at month 3 in each treatment group. Change was defined as visit - baseline. Control scores range from 4 to 20 with a higher score indicating greater control. Satisfaction scores range from 4 to 20 with a higher score indicating greater satisfaction. Distress scores range from 2 to 10 with a higher score indicating less distress.

a) Analysis of covariance was performed with factors for treatment and pooled centre with baseline as a covariate.

b) Calculated using the difference of PSD502 minus placebo.

Secondary endpoints

- *Mean IELT response of >1 and >2 minutes during months 1-3*

At the end of each month of study treatment, a greater proportion of subjects who received PSD502 than placebo attained a mean IELT >1 minute and >2 minutes in both of the pivotal studies. A higher proportion of subjects in the PSD502-PE-004 study attained a mean IELT >1 minute and >2 minutes (PSD502 and placebo groups) than in the PSD502-PE-002 study.

Table 27:

Summary of Subjects with Mean Categorical IELT at months 1, 2 and 3 and over 3 months of the Double-blind Treatment, for Baseline Carried Forward Analysis: ITT Population (PSD502-PE-002 and PSD502-PE-004 Individually)

Mean IELT	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=167	Placebo N=82	PSD502 N=191	Placebo N=99
Month 1				
n	167	82	191	99
IELT >1 minute	113 (67.7%)	25 (30.5%)	159 (83.2%)	46 (46.5%)
IELT >2 minutes	77 (46.1%)	8 (9.8%)	116 (60.7%)	13 (13.1%)
Month 2				
n	167	82	191	99
IELT >1 minute	123 (73.7%)	30 (36.6%)	169 (88.5%)	48 (48.5%)
IELT >2 minutes	89 (53.3%)	10 (12.2%)	133 (69.6%)	18 (18.2%)
Month 3				
n	167	82	191	99
IELT >1 minute	124 (74.3%)	30 (36.6%)	162 (84.8%)	49 (49.5%)
IELT >2 minutes	96 (57.5%)	10 (12.2%)	137 (71.7%)	26 (26.3%)
Over 3 months				
n	167	82	191	99
IELT >1 minute	134 (80.2%)	31 (37.8%)	171 (89.5%)	53 (53.5%)
IELT >2 minutes	96 (57.5%)	12 (14.6%)	141 (73.8%)	22 (22.2%)

Abbreviations: IELT = intravaginal ejaculatory latency time; ITT = intention-to-treat
Note: For categorical analysis subjects may be counted in more than one category. Percentages are based on the number of subjects in each treatment group

- *Change from baseline to each month of double blind treatment*

At the end of each month of the double-blind treatment phase, the geometric mean IELT for all subjects in the ITT population had increased more from baseline in the PSD502 treatment groups of both pivotal studies and smaller improvements were seen in the placebo groups.

At the end of months 1 and 2, subjects treated with PSD502 had larger changes (representing an improvement) in their adjusted mean change from baseline scores for each of the IPE domains than subjects who received placebo. The changes from baseline were generally slightly larger in the PSD502-PE-004 than the PSD502-PE-002 study for all domains at both months 1 and 2.

- *PEP: subjects and partners (Change from baseline in PEP domain scores)*

In both studies, the PEP scores for subjects and partners followed a similar pattern of improvement to the IELT and IPE scores

At the end of each of months 1, 2 and 3, more subjects treated with PSD502 than Placebo had at least a 1 point category improvement in each of the PEP domains of perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse and interpersonal difficulty related to ejaculation.

In PSD502-PE-002 at month 3, the proportion of PSD502-treated subjects who indicated a response of 'very good' or 'good' was 33.4% for control and 41.0% for satisfaction compared with 2.5% and 10.1%, respectively, of placebo-treated subjects. The proportion of PSD502-treated subjects with a response of 'not at all' or 'a little bit' was 43.6% for distress and 59.0% for interpersonal difficulty compared with 13.9% and 31.6%, respectively, for placebo-treated subjects.

In PSD502-PE-004 at month 3, the proportion of PSD502-treated subjects who indicated a response of 'very good' or 'good' was 40.7% for control and 51.1% for satisfaction compared with 8.4% and 9.4%, respectively, of placebo-treated subjects. The proportion of PSD502-treated subjects with a response of 'not at all' or 'a little bit' was 55.4% for distress and 69.5% for interpersonal difficulty compared with 18.8% and 32.3%, respectively, for placebo-treated subjects.

Table 28: Subject PEP by Visit for Observed Cases: ITT Population (Combined PSD502-PE-002 and PSD502-PE-004)

Domain	Baseline		Month 1		Month 2		Month 3	
	PSD502 N=358	Placebo N=181	PSD502 N=358	Placebo N=181	PSD502 N=358	Placebo N=181	PSD502 N=358	Placebo N=181
Control								
n	327	160	350	180	342	174	340	175
Very good	0	0	17 (4.9%)	1 (0.6%)	31 (9.1%)	2 (1.1%)	47 (13.8%)	4 (2.3%)
Good	0	0	77 (22.0%)	4 (2.2%)	78 (22.8%)	7 (4.0%)	80 (23.5%)	6 (3.4%)
Fair	1 (0.3%)	0	80 (22.9%)	19 (10.6%)	92 (26.9%)	13 (7.5%)	86 (25.3%)	23 (13.1%)
Poor	46 (14.1%)	26 (16.3%)	85 (24.3%)	51 (28.3%)	72 (21.1%)	37 (21.3%)	68 (20.0%)	33 (18.9%)
Very poor	280 (85.6%)	134 (83.8%)	91 (26.0%)	105 (58.3%)	69 (20.2%)	115 (66.1%)	59 (17.4%)	109 (62.3%)
p-value	NA		<0.0001		<0.0001		<00001	
Satisfaction								
n	327	160	350	180	341	174	340	175
Very good	0	0	30 (8.6%)	2 (1.1%)	48 (14.1%)	2 (1.1%)	52 (15.3%)	3 (1.7%)
Good	1 (0.3%)	0	84 (24.0%)	6 (3.3%)	86 (25.2%)	12 (6.9%)	106 (31.2%)	14 (8.0%)
Fair	5 (1.5%)	2 (1.3%)	93 (26.6%)	27 (15.0%)	89 (26.1%)	21 (12.1%)	86 (25.3%)	25 (14.3%)
Poor	97 (29.7%)	51 (31.9%)	76 (21.7%)	66 (36.7%)	69 (20.2%)	52 (29.9%)	55 (16.2%)	58 (33.1%)
Very poor	224 (68.5%)	107 (68.5%)	67 (19.1%)	79 (43.9%)	49 (14.4%)	87 (50.0%)	41 (12.1%)	75 (42.9%)
p-value	NA		<0.0001		<0.0001		<0.0001	
Distress								
n	327	160	350	180	342	174	340	175
Not at all	0	0	47 (13.4%)	3 (1.7%)	69 (20.2%)	3 (1.7%)	85 (25.0%)	4 (2.3%)
A little bit	1 (0.3%)	0	80 (22.9%)	15 (8.3%)	85 (24.9%)	12 (6.9%)	85 (25.0%)	25 (14.3%)
Moderately	1 (0.3%)	0	78 (22.3%)	24 (13.3%)	80 (23.4%)	26 (14.9%)	70 (20.6%)	16 (9.1%)
Quite a bit	100 (30.6%)	57 (35.6%)	85 (24.3%)	62 (34.4%)	60 (17.5%)	62 (35.6%)	60 (17.6%)	54 (30.9%)
Extremely	225 (68.8%)	103 (64.4%)	60 (17.1%)	76 (42.2%)	48 (14.0%)	71 (40.8%)	40 (11.8%)	76 (43.4%)
p-value	NA		<0.0001		<0.0001		<0.0001	
Interpersonal difficulty								
n	327	160	350	180	342	174	340	175
Not at all	1 (0.3%)	1 (0.6%)	102 (29.1%)	13 (7.2%)	126 (36.8%)	19 (10.9%)	151 (44.4%)	21 (12.0%)
A little bit	8 (2.4%)	4 (2.5%)	84 (24.0%)	17 (9.4%)	71 (20.8%)	19 (10.9%)	69 (20.3%)	35 (20.0%)
Moderately	12 (3.7%)	8 (5.0%)	72 (20.6%)	51 (28.3%)	75 (21.9%)	36 (20.7%)	58 (17.1%)	37 (21.1%)
Quite a bit	193 (59.0%)	87 (54.4%)	63 (18.0%)	70 (38.9%)	41 (12.0%)	58 (33.3%)	36 (10.6%)	51 (29.1%)
Extremely	113 (34.6%)	60 (34.6%)	29 (8.3%)	29 (16.1%)	29 (8.5%)	42 (24.1%)	26 (7.6%)	31 (17.7%)
p-value	NA		<0.0001		<0.0001		<0.0001	

At the end of month 3, more partners in the PSD502 group than in the Placebo group had at least a 1 point category improvement in each of the PEP domains of perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse and interpersonal difficulty related to ejaculation.

Table 29:

Partner PEP at Month 3 for Observed Cases: ITT Population (PSD502-PE-002 and PSD502-PE-004 Individually)

Partner PEP Domain	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=167	Placebo N=82	PSD502 N=191	Placebo N=99
Control				
n	148	76	180	94
Very good	9 (6.1%)	1 (1.3%)	20 (11.1%)	4 (4.3%)
Good	37 (25.0%)	7 (9.2%)	52 (28.9%)	6 (6.4%)
Fair	47 (31.8%)	11 (14.5%)	68 (37.8%)	22 (23.4%)
Poor	33 (22.3%)	27 (35.5%)	25 (13.9%)	27 (28.7%)
Very poor	22 (14.9%)	30 (39.5%)	15 (8.3%)	35 (37.2%)
p-value	p <0.0001		p <0.0001	
Satisfaction				
n	148	76	180	94
Very good	14 (9.5%)	2 (2.6%)	25 (13.9%)	6 (6.4%)
Good	38 (25.7%)	11 (14.5%)	64 (35.6%)	9 (9.6%)
Fair	58 (39.2%)	10 (13.2%)	55 (30.6%)	21 (22.3%)
Poor	20 (13.5%)	33 (43.4%)	25 (13.9%)	31 (33.0%)
Very poor	18 (12.2%)	20 (26.3%)	11 (6.1%)	27 (28.7%)
p-value	p <0.0001		p <0.0001	
Distress				
n	148	76	180	94
Not at all	33 (22.3%)	9 (11.8%)	64 (35.6%)	13 (13.8%)
A little bit	47 (31.8%)	11 (14.5%)	47 (26.1%)	21 (22.3%)
Moderately	38 (25.7%)	17 (22.4%)	34 (18.9%)	24 (25.5%)
Quite a bit	15 (10.1%)	20 (26.3%)	26 (14.4%)	20 (21.3%)
Extremely	15 (10.1%)	19 (25.0%)	9 (5.0%)	16 (17.0%)
p-value	p <0.0001		p <0.0001	
Interpersonal difficulty				
n	148	76	180	94
Not at all	70 (47.3%)	17 (22.4%)	81 (45.0%)	22 (23.4%)
A little bit	39 (26.4%)	15 (19.7%)	41 (22.8%)	21 (22.3%)
Moderately	18 (12.2%)	15 (19.7%)	38 (21.1%)	21 (22.3%)
Quite a bit	15 (10.1%)	21 (27.6%)	13 (7.2%)	19 (20.2%)
Extremely	6 (4.1%)	8 (10.5%)	7 (3.9%)	11 (11.7%)
p-value	p <0.0001		p <0.0001	

Abbreviations: Abbreviations: ITT = intention-to-treat; PEP = premature ejaculation profile
Percentages were calculated using the number of non-missing responses in each treatment group.
p-values were calculated using a chi-squared test for trend (Cochran-Armitage Test).

Additional endpoints

In Study PE-002 the minimal clinically important difference (MCID) for the change from baseline in the IPE domains was estimated to be 2.9 to 4.3 points for ejaculatory control, 2.9 to 4.6 points for sexual satisfaction, and 1.4 to 1.5 points for distress. The MCID for the ratio to baseline mean IELT was estimated to be 2 to 3-fold. As the treatment effects for the primary endpoints exceed these estimates, the clinical significance of the results is further demonstrated.
The relationship between the IPE domains and IELT was not undertaken because data showed that a large number of subjects had IPE domain scores at the minimum or maximum values, potentially masking any relationship with IELT.

Other measures of treatment effectiveness also demonstrated significant improvements:

• At the end of the 3 month double-blind treatment phase, the proportion of subjects rating the quality of their orgasm 'Poor' or 'Very poor' reduced by approximately 3-fold from baseline in subjects receiving PSD502 (baseline: 59.3%; month 3: 20.1%) in PSD502-PE-002 and over 3-fold from baseline in subjects receiving PSD502 (baseline: 57.5%; month 3: 16.2%) in PSD502-PE-004. This contrasted with findings in the placebo-treated subjects where the proportion of subjects rating the

quality of their orgasm 'Poor' or 'Very poor' at the end of month 3 was lower by approximately 10% (baseline: 60.0%; month 3: 48.7%) in PSD502-PE-002 and unchanged (baseline: 57.1%; month 3: 51.5%) in PSD502-PE-004.

• At the end of the 3 month double-blind treatment phase, more PSD502 subjects than Placebo subjects rated the study medication as 'Excellent'. In contrast, the worst rating of 'Poor' was assigned by more Placebo subjects than PSD502 subjects.

Table 30:

Summary of Rating of Study Medication at Month 3 of the Double-blind Treatment Phase: ITT population (PSD502-PE-002 and PSD502-PE-004 Individually)

Rating	PSD502-PE-002		PSD502-PE-004	
	PSD502 N=167	Placebo N=82	PSD502 N=191	Placebo N=99
n	155	79	182	96
Excellent	30 (19.4%)	1 (1.3%)	55 (30.2%)	5 (5.2%)
Good	57 (36.8%)	6 (7.6%)	65 (35.7%)	9 (9.4%)
Fair	38 (24.5%)	12 (15.2%)	37 (20.3%)	19 (19.8%)
Poor	30 (19.4%)	60 (75.9%)	25 (13.7%)	63 (65.6%)

Abbreviations: ITT = intention-to-treat

Open-label extension

At the end of the double-blind treatment phase in pivotal studies PSD502-PE-002 and PSD502-PE-004 subjects had the option to participate in the open-label treatment phase in which all subjects received treatment with PSD502. The duration of the open-label phase was 5 months in PSD502-PE-002 and 9 months in PSD502-PE-004.

A total of 497 subjects (98.4% of those completing the double-blind phase) entered the open-label phase of the studies. Most (90.3%) of the subjects completed the open label phase. The most common reasons for discontinuing early were subject/partner request and lost to follow-up (each 4.4%), followed by investigator's decision (0.6%), and adverse event, protocol violation, and sponsor's decision (each 0.2%).

Table 31: Subject Disposition: Randomized Population (Combined PSD502-PE-002 and PSD502-PE-004)

Disposition	PSD502 N=371	Placebo N=185	Total N=556
Double-blind phase			
Randomized	371	185	556
Treated	358 (96.5%)	181 (97.8%)	539 (96.9%)
Completed	332 (89.5%)	173 (93.5%)	505 (90.8%)
Early discontinuation	39 (10.5%)	12 (6.5%)	51 (9.2%)
Subject/partner request	20 (5.4%)	5 (2.7%)	25 (4.5%)
Lost to follow-up	12 (3.2%)	7 (3.8%)	19 (3.4%)
Adverse event	5 (1.3%)	0	5 (0.9%)
Sponsor decision	2 (0.5%)	0	2 (0.4%)
Inclusion/exclusion	1 (0.3%)	0	1 (0.2%)
Open-label phase [a]			
Entered open-label phase	326	171	497
Completed	300 (92.0%)	149 (87.1%)	449 (90.3%)
Early discontinuation	26 (8.0%)	22 (12.9%)	48 (9.7%)
Subject/partner request	9 (2.8%)	13 (7.6%)	22 (4.4%)
Lost to follow-up	14 (4.3%)	8 (4.7%)	22 (4.4%)
Investigator decision	2 (0.6%)	1 (0.6%)	3 (0.6%)
Adverse event	0	1 (0.6%)	1 (0.2%)
Protocol violation	1 (0.3%)	0	1 (0.2%)
Sponsor decision	1 (0.3%)	0	1 (0.2%)

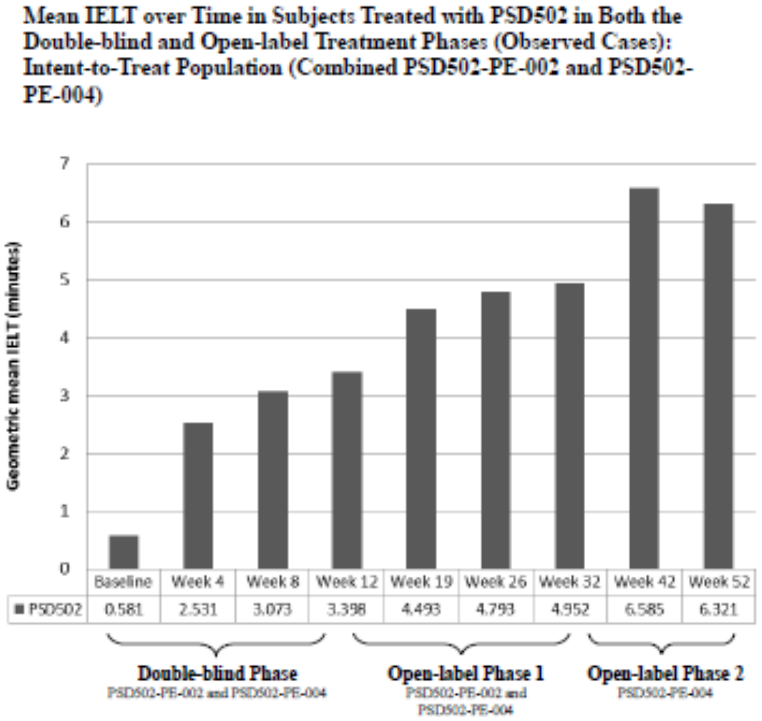
Note: Percentages for the double-blind phase were calculated using the number of subjects randomly assigned to each treatment group. Percentages calculated for the open-label phase were calculated using the number of subjects who entered the open-label phase in each treatment group. Subjects may have had more than one reason for discontinuation, so percentages may add to more than 100%.
a) All subjects received PSD502 in the open-label phase.

- *Change in mean IELT and IPE domain scores over time*

For all subjects in the open-label treatment phase, the ratio to baseline geometric mean IELT ranged from 5.62 (Visit 6) to 6.73 (Visit 7) in PSD502-PE-002, and from 8.39 (Visit 6) to 10.39 (Visit 10) in the PSD502-PE- 004 study. This trend was consistent for the groups who had received PSD502 or placebo in the double-blind phase as well as for all subjects in each open label phase.

For those subjects who received placebo during the double-blind phase and switched to PSD502 during the open-label phase, marked improvements in IELT were observed at the first assessment after initiating treatment with PSD502. Subjects who received PSD502 in the double-blind treatment phases of the both studies had slightly higher ratio to baseline geometric mean IELTs at Visits 6-8 in the open-label treatment phase than those subjects who had previously received placebo during the double-blind treatment phase of the study. However, at Visit 10 in PSD502-PE-004 (following a full 9 months open-label treatment with PSD502), this difference was no longer apparent.

Figure 4:



- *Change from baseline in IPE domain scores*

Improvement was also observed in IPE domain scores from the end of the double-blind treatment phase to the end of the open-label phase. The mean change from baseline for ejaculatory control, sexual satisfaction, and distress score was 12.3, 10.9, and 5.3 points, respectively at the end of the open-label phase. These results demonstrate that PSD502 was as effective in delaying ejaculation, improving ejaculatory control and sexual satisfaction, and reducing distress at the end of the open-label treatment period (month 12) as at the end of double-blind treatment period (month 3).

Ancillary analyses

A subgroup analyses was carried out on the controlled PE Studies population which included subjects from PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg level of PSD502-PE-005.

Hepatic and Renal Impairment

The effect of chronic renal failure on the pharmacokinetics of lidocaine has been investigated in a literature-based study. Lidocaine (1 mg/kg) was administered as an intravenous injection to healthy subjects, subjects with moderate renal insufficiency, subjects with severe renal insufficiency, and functionally anephric patients undergoing long-term haemodialysis. Results of this study showed that clearance in subjects with severe renal insufficiency was approximately half that of the healthy volunteers (6.01 ± 2.54 mL/minute x kg vs. 11.87 ± 2.97 mL/minute x kg; p <0.001), and the half-life was approximately doubled (4.55 ± 1.71 hours vs. 2.24 ± 0.55 hours, p <0.001). No such changes were observed in subjects undergoing regular haemodialysis, whose values were similar to those of the healthy volunteers.

Incidence of Adverse Events by Age Group

When TEAEs were analysed by age group for the Controlled PE Studies population, the most common TEAEs across all age groups were the genital complaints of erectile dysfunction and hypoaesthesia, as observed in the full PSD502 Glanspenis-treated Subjects population. Taking into consideration the variable number of subjects in each age group (i.e., 149 subjects in the 25 to <35 years group and 6 subjects in the ≥65 years group), the frequencies of these events across the age groups were generally comparable. All the events of erectile dysfunction and hypoaesthesia were considered to be related to treatment with PSD502. Severe TEAEs and TEAEs leading to early discontinuation were also analysed by subject age group. No obvious trends were identified in these analyses.

More than 90% of patients included in the controlled trials were younger than 55 years, the number of patients older than 65 years old were limited. Although PE is more common in the younger age group this has been addressed in the PI and RMP as missing information from the safety perspective.

ED is also more frequent in the older population and it is a known AE for this combination of lidocaine and prilocaine. So, at present, it cannot be ruled out that this limited participation of patients older than 65 years of age have an impact on the safety profile of PSD502. This has been addressed in the RMP.

Table 32:

TEAEs by Age Group (in ≥2 total PSD502-treated subjects in any age group): Controlled PE Studies

Preferred Term	18 to <25 years N=46	25 to <35 years N=149	35 to <45 years N=113	45 to <55 years N=80	55 to <65 years N=25	≥65 years N=6
At least one TEAE	5 (10.9%)	14 (9.4%)	22 (19.5%)	21 (26.3%)	4 (16.0%)	2 (33.3%)
Erectile dysfunction	0	6 (4.0%)	2 (1.8%)	4 (5.0%)	1 (4.0%)	1 (16.7%)
Hypoaesthesia of genital male	0	2 (1.3%)	4 (3.5%)	3 (3.8%)	2 (8.0%)	0
Seasonal allergy	1 (2.2%)	0	2 (1.8%)	0	0	0
Acute tonsillitis	0	0	2 (1.8%)	0	0	0
Nasopharyngitis	0	0	6 (5.3%)	0	0	0
Back pain	0	0	2 (1.8%)	1 (1.3%)	0	0
Herpes zoster	0	0	0	2 (2.5%)	0	0
Influenza	1 (2.2%)	1 (0.7%)	0	2 (2.5%)	1 (4.0%)	0
Arthralgia	0	0	1 (0.9%)	2 (2.5%)	0	0
Headache	1 (2.2%)	0	1 (0.9%)	2 (2.5%)	0	0
Hypertension	0	0	0	2 (2.5%)	0	0

Abbreviations: PE = premature ejaculation; TEAE = treatment-emergent adverse event
Note: Percentages were calculated using the number of subjects in each treatment group. Subjects were counted once within each category.
Subjects were included from studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg dose level for PSD502-PE-005.
Source: Section 2.7.4.7, Table 159

Incidence of Adverse Events by Body Weight

The frequency of these events was comparable in the BMI subgroups. The frequency of drug-related vulvovaginal burning sensation was comparable in the partners of subjects in both BMI subgroups.

Severe TEAEs and TEAEs leading to early discontinuation were also analysed by baseline BMI. No obvious trends were identified in these analyses.

Incidence of Adverse Events by Circumcision Status

In the Controlled PE Studies population, the events of erectile dysfunction and hypoaesthesia occurred more frequently in uncircumcised subjects than in circumcised subjects. The proportion of uncircumcised subjects who experienced erectile dysfunction and hypoaesthesia were 3.8% and 2.4%, respectively. In contrast, in circumcised subjects the proportions were 2.0% and 1.0%, respectively. The events of ejaculation failure (0.7%) and genital erythema (0.7%) were only observed in uncircumcised subjects. One possible explanation for this difference is that the mucosa of the glans penis tends to become keratinised following circumcision, and PSD502 is less readily absorbed by keratinised skin than mucosa. The frequency of vulvovaginal burning sensation was greater in the partners of circumcised subjects than in partners of uncircumcised subjects (9.0% vs. 3.4%, respectively. This may be due to the fact that the drug is absorbed better through the poorly-

keratinised mucosa of the uncircumcised subjects, thus leaving less available on the surface for transfer to a partner. Severe TEAEs and TEAEs leading to early discontinuation were also analysed by circumcision status. No obvious trends were identified in these analyses.

Table 33:

TEAEs (in at least 2 subjects in any treatment group) by Circumcision Status: Controlled PE Studies

	Circumcised		Uncircumcised	
Preferred Term	PSD502 N=100	Placebo N=48	PSD502 N=293	Placebo N=166
At least one TEAE	26 (26.0%)	15 (31.3%)	37 (12.6%)	14 (8.4%)
Erectile dysfunction	2 (2.0%)	0	11 (3.8%)	0
Hypoaesthesia of genital male	1 (1.0%)	0	7 (2.4%)	0
Nasopharyngitis	3 (3.0%)	2 (4.2%)	3 (0.3%)	0
Influenza	2 (2.0%)	1 (2.1%)	2 (0.7%)	0
Headache	2 (2.0%)	4 (8.3%)	2 (0.7%)	2 (1.2%)
Seasonal allergy	1 (1.0%)	2 (4.2%)	2 (0.7%)	2 (1.2%)
Arthralgia	1 (1.0%)	0	2 (0.7%)	0
Back pain	1 (1.0%)	1 (2.1%)	2 (0.7%)	0
Genital erythema	0	0	2 (0.7%)	0
Ejaculation failure	0	0	2 (0.7%)	
Hypercholesterolaemia	2 (2.0%)	0	0	0
Upper respiratory tract infection	2 (2.0%)	0	0	1 (0.6%)
Hypertension	2 (2.0%)	0	0	0
Acute tonsillitis	0	0	2 (0.7%)	0
Myalgia	0	2 (4.2%)		
Contusion	0	0	0	2 (1.2%)
Nasal congestion	0	0	2 (0.7%)	0

Abbreviations: PE = premature ejaculation; TEAE = treatment-emergent adverse event
Note: Percentages were calculated using the number of subjects in each treatment group. Subjects were counted once within each category.
Subjects were included from studies PSD502-PE-002, PSD502-PE-004, and the 30 mg level for PSD502-PE-005. Circumcision status was not recorded for subjects in PSD502-PE-001; therefore, these subjects were not included in this table.
Source: Section 2.7.4.7, Table 162

Incidence of Adverse Events by Race

The Controlled PE Studies population was predominantly Caucasian (approximately 90%). No obvious trends were observed for the subject racial subgroups, but interpretations should be made with caution since the majority of subjects were Caucasian.

Incidence of Adverse Events by Lifelong/Acquired PE

In the Controlled PE Studies population, subjects with lifelong PE had events of erectile dysfunction (3.5%) and hypoaesthesia (2.2%). There were no reports of these events in subjects with acquired PE. However, since the majority of subjects (approximately 85%) in the Controlled PE Studies population had a diagnosis of lifelong PE, interpretations of the lifelong/acquired PE analyses should be made with caution.

Incidence of Adverse Events by Categorical Ratio to Baseline IELT

The number of PSD502-treated subjects with ratio to baseline IELT <1, 1 to <2, and ≥2 was 12, 56, and 290, respectively. Given that the number of subjects was not comparable in each subgroup, interpretations of this analysis should be made with caution. The proportion of subjects with erectile dysfunction and hypoaesthesia was 5.4% and 1.8%, respectively, in the 1 to <2 subgroup, and 2.8% and 1.7%, respectively, in the ≥2 subgroup. These events were not observed in the <1 subgroup.

Summary of main efficacy results

A statistically significant and clinically meaningful effect has been shown by this medicinal product in the treatment of lifelong premature ejaculation. It has been observed in objective measures as intravaginal latency time and also perceived as a psychological benefit by the subjects and their partners.

Analysis performed across trials (pooled analyses and meta-analysis)

Data from studies that characterise the efficacy of PSD502 are summarised by combining data from the two pivotal studies PSD502-PE-002 and PSD502-PE-004 using similar statistical methods to those described for each study. The IPE domain of distress was treated as a secondary endpoint in PSD502-PE-004 and as a co-primary endpoint (changed through a protocol amendment) in PSD502-PE-002. For the combined analysis, the IPE domain score of distress was treated as a co-primary efficacy endpoint.

Table 34:

Subject Disposition: Randomized Population (Combined PSD502-PE-002 and PSD502-PE-004)

Disposition	PSD502 N=371	Placebo N=185	Total N=556
Double-blind phase			
Randomized	371	185	556
Treated	358 (96.5%)	181 (97.8%)	539 (96.9%)
Completed	332 (89.5%)	173 (93.5%)	505 (90.8%)
Early discontinuation	39 (10.5%)	12 (6.5%)	51 (9.2%)
Subject/partner request	20 (5.4%)	5 (2.7%)	25 (4.5%)
Lost to follow-up	12 (3.2%)	7 (3.8%)	19 (3.4%)
Adverse event	5 (1.3%)	0	5 (0.9%)
Sponsor decision	2 (0.5%)	0	2 (0.4%)
Inclusion/exclusion	1 (0.3%)	0	1 (0.2%)
Open-label phase [a]			
Entered open-label phase	326	171	497
Completed	300 (92.0%)	149 (87.1%)	449 (90.3%)
Early discontinuation	26 (8.0%)	22 (12.9%)	48 (9.7%)
Subject/partner request	9 (2.8%)	13 (7.6%)	22 (4.4%)
Lost to follow-up	14 (4.3%)	8 (4.7%)	22 (4.4%)
Investigator decision	2 (0.6%)	1 (0.6%)	3 (0.6%)
Adverse event	0	1 (0.6%)	1 (0.2%)
Protocol violation	1 (0.3%)	0	1 (0.2%)
Sponsor decision	1 (0.3%)	0	1 (0.2%)

Note: Percentages for the double-blind phase were calculated using the number of subjects randomly assigned to each treatment group. Percentages calculated for the open-label phase were calculated using the number of subjects who entered the open-label phase in each treatment group. Subjects may have had more than one reason for discontinuation, so percentages may add to more than 100%.

a) All subjects received PSD502 in the open-label phase.

- *IELT*

When IELT values of PSD502-treated subjects were compared with those of the placebo-treated subjects, a 3.3-fold (95% CI: 2.78, 4.01) delay in ejaculation that was statistically ($p < 0.0001$; significance level = 0.0125) and clinically significant was observed.

Table 35:

Mean IELT (minutes) During the 3 Months of Double-blind Treatment for Baseline Carried Forward Analysis: ITT Population (Combined PSD502-PE-002 and PSD502-PE-004)

IELT	PSD502 N=358	Placebo N=181
Baseline (minutes)		
Geometric mean	0.581	0.555
Mean	0.659	0.665
SD	0.2822	0.3377
Range	0.02 to 2.35	0.00 to 3.33
Median	0.672	0.678
During 3 months of treatment (minutes)		
Geometric mean	3.171	0.936
Mean	5.651	1.389
SD	6.8342	1.5568
Range	0.00 to 57.76	0.02 to 15.03
Median	3.339	0.941
Ratio (during 3 months of treatment/baseline)		
Geometric mean ratio	5.455	1.687
Mean ratio	15.018	3.493
SD	72.7801	17.4417
Range	0.01 to 1243.50	0.24 to 234.78
Median	4.932	1.418
Adjusted geometric mean ratio (95% CI)	5.57 (5.00, 6.22)	1.67 (1.44, 1.94)
Treatment effect: PSD502/placebo (95% CI)	3.34 (2.78, 4.01)	
p-value	<0.0001	

Abbreviations: CI = confidence interval; IELT = intravaginal ejaculation latency time; ITT = intention-to-treat; SD = standard deviation

Note: Calculations are based on the number of subjects in each treatment group. In order to control the overall significance at no greater than 5%, a fixed sequence Bonferroni procedure was implemented for each study. The significance level for this analysis was 0.0125.

Analysis of covariance of log-transformed values was performed with factors for treatment and pooled centre with log (baseline IELT) as a covariate. Anti-log calculations were performed to present results in the original scale.

Consistent with results observed in the ITT population, subjects in the Per Protocol population had clinically significant improvement in IELT.

- *IPE domain scores*

Substantial improvement was observed at month 3 in the PSD502 group compared with the placebo group on IPE domains of ejaculatory control, sexual satisfaction, and distress. Results of the observed cases analysis (ITT population) were similar to those of the baseline carried forward analysis.

Table 36:

Analysis of Change from Baseline in IPE Domain Scores at Month 3 for Last Observation Carried Forward: ITT Population (Combined PSD502-PE-002 and PSD502-PE-004)

IPE Domain Score (Points)	PSD502 N=358	Placebo N=181
Ejaculatory control score: Month 3 change		
n	353	181
Mean (SD)	8.2 (5.73)	2.2 (4.18)
Range	-8 to 16	-5 to 16
Median	8.0	0
Missing	5	0
Adjusted mean (SE) [a]	8.2 (0.28)	2.1 (0.38)
LS mean difference (SE) [a,b]	6.1 (0.47)	
95% CI [a,b]	5.2, 7.0	
p-value [a,b]	<0.0001	
Sexual satisfaction score: Month 3 change		
n	358	181
Mean (SD)	7.2 (5.51)	1.9 (4.58)
Range	-8 to 16	-8 to 15
Median	8.0	1.0
Adjusted mean (SE) [a]	7.2 (0.26)	1.9 (0.36)
LS mean difference(SE) [a,b]	5.3 (0.44)	
95% CI [a,b]	4.5, 6.2	
p-value [a,b]	<0.0001	
Distress score: Month 3 change		
n	353	181
Mean (SD)	3.7 (2.68)	1.1 (2.35)
Range	-2 to 8	-4 to 8
Median	4.0	0
Missing	5	0
Adjusted mean (SE) [a]	3.7 (0.13)	1.1 (0.18)
LS mean difference (SE) [a,b]	2.6 (0.22)	
95% CI [a,b]	2.2, 3.0	
p-value [a,b]	<0.0001	

Abbreviations: CI = confidence interval; IPE = index of premature ejaculation; LS = least square; SD = standard deviation; SE = standard error

Note: Calculations were made using the number of subjects with non-missing IPEs at baseline and at month 3 in each treatment group. Change was defined as visit - baseline.

Control scores range from 4 to 20 with a higher score indicating greater control. Satisfaction scores range from 4 to 20 with a higher score indicating greater satisfaction. Distress scores range from 2 to 10 with a higher score indicating less distress.

In order to control the overall level of significance at no greater than 5%, a fixed sequence Bonferroni procedure was implemented for each study. The significance level was 0.0250 for control, 0.0375 for satisfaction, and 0.050 for distress.

a) Analysis of covariance was performed with factors for treatment and pooled centre with baseline as a covariate.

b) Calculated using the difference of PSD502 minus placebo.

Consistent with results observed in the ITT population, subjects in the Per Protocol population had clinically significant improvement in IPE domain scores.

- *Proportion of subjects with mean IELT >1 minute or >2 minutes during the 3 months of double-blind treatment*

Most subjects (85.2%) in the PSD502 group achieved a mean IELT of >1 minute over the course of 3 months of treatment with PSD502. Even though there was a highly significant difference between PSD502 and placebo treated subjects, 46.4% of the placebo subjects had a mean IELT of >1 minute.

Table 37:

Summary of Subjects with Mean Categorical IELT During the 3 Months of Double-blind Treatment, for Baseline Carried Forward Analysis: ITT Population (Combined PSD502-PE-002 and PSD502-PE-004)

Mean IELT	PSD502 N=358	Placebo N=181
IELT > 1 minute	305 (85.2%)	84 (46.4%)
IELT > 2 minutes	237 (66.2%)	34 (18.8%)
IELT > 3 minutes	193 (53.9%)	18 (9.9%)
IELT > 4 minutes	159 (44.4%)	8 (4.4%)

Abbreviations: IELT = intravaginal ejaculation latency time; ITT = intention-to-treat
Note: For categorical analysis subjects may be counted in more than one category. Percentages are based on the number of subjects in each treatment group

- *Ratio to baseline of mean IELT during double-blind treatment by month*

Marked improvement in IELT was observed at the first assessment (month 1). The geometric mean IELT increased from 0.581 minutes to 2.463 minutes in the PSD502 group and from 0.555 minutes to 0.852 minutes in the placebo group. Analysis of covariance of the log-transformed values revealed that ejaculation was delayed 4.4-fold and 1.5-fold compared with baseline in PSD502 and placebo groups, respectively. Similar results (PSD502 vs. placebo) were observed at month 2 (5.0-fold vs. 1.6-fold) and month 3 (5.3-fold vs. 1.7-fold). More than half of the PSD502- treated subjects had a mean IELT of >2 minutes at the end of months 1, 2 and 3 (53.9%, 62.0%, and 65.1% respectively).

When compared with placebo, treatment with PSD502 resulted in a highly statistically significant delay in ejaculation of 2.9-fold (95% CI: 2.36, 3.44) at month 1; 3.2-fold (95% CI: 2.66, 3.88) at month 2 and 3.2-fold (95% CI: 2.55, 3.92) at month 3; p <0.0001 for each month's assessment.

Change was observed in the IPE domains of ejaculatory control, distress and sexual satisfaction from baseline to months 1 and 2 separately.

At month 1, the adjusted mean change (PSD502 vs. placebo) was 6.4 vs. 1.6 for ejaculatory control, 5.9 vs. 1.7 for satisfaction, and 2.9 vs. 0.9 for distress. A similar result was observed at month 2.

Table 38:

Analysis of Change from Baseline in IPE Domain Scores by Visit During the Double-blind Treatment Phase: Last Observation Carried Forward Analysis: ITT Population (Combined PSD502-PE-002 and PSD502-PE-004)

	Change from Baseline to Month 1		Change from Baseline to Month 2	
IPE domain (Points)	PSD502 N=358	Placebo N=181	PSD502 N=358	Placebo N=181
Ejaculatory control				
n	355	181	356	181
Adjusted mean (SE)*	6.4 (0.26)	1.6 (0.36)	7.5 (0.27)	1.7 (0.37)
Sexual satisfaction				
n	356	181	357	181
Adjusted mean (SE)*	5.9 (0.26)	1.7 (0.35)	6.7 (0.26)	1.5 (0.36)
Distress				
n	354	181	355	181
Adjusted mean (SE)*	2.9 (0.13)	0.9 (0.17)	3.4 (0.13)	1.0 (0.18)

Abbreviations: IPE = index of premature ejaculation; ITT = intention-to-treat; SE = standard error
Note: Calculations were made using the number of subjects with non-missing IPEs at baseline and visit in each treatment group.
Control scores range from 4 to 20 with a higher score indicating greater control. Satisfaction scores range from 4 to 20 with a higher score indicating greater satisfaction. Distress scores range from 2 to 10 with a higher score indicating less distress.
a) Analysis of covariance was performed with factors for treatment and pooled centre with baseline as a covariate.

Analysis of covariance revealed a statistically significant improvement for all three IPE domain scores when the PSD502 group was compared with the placebo group at month 1: ejaculatory control: 4.9 points (95% CI: 4.0, 5.8; p <0.0001), sexual satisfaction: 4.2 points (95% CI: 3.4, 5.1; p <0.0001), and distress: 2.1 points (95% CI: 1.6, 2.5; p < 0.0001). A significant improvement was also observed at month 2. An improvement of 5.9 points (95% CI: 5.0, 6.7) for ejaculatory control, 5.2 points (95% CI: 4.3, 6.1) for sexual satisfaction, and 2.4 points (95% CI: 2.0, 2.8) for distress at month 2; all were significant at the p <0.0001 level.

- *Subject PEP: Change from baseline in scores based on the subject PEP at months 1, 2 and 3*

The chi-squared test for trend revealed a statistically significant difference in the subjects' PEP responses in favour of PSD502 (p <0.0001 for each parameter) for all three monthly assessments. At month 3, the proportion of PSD502-treated subjects who indicated a response of 'very good' or 'good' was 37.3% for control and 46.5% for satisfaction compared with 5.7% and 9.7%, respectively, of placebo-treated subjects. The proportion of PSD502-treated subjects with a response of 'not at all' or 'a little bit' was 50.0% for distress and 64.7% for interpersonal difficulty compared with 16.6% and 32.0%, respectively, for placebo-treated subjects.

- *Partner PEP: Change from baseline in scores based on the partner PEP at month 3*

A statistically significant difference in favour of PSD502 was also observed for partner PEP responses (p <0.0001 for each parameter). The proportion of PSD502-treated subjects' partners who indicated a response of 'very good' or 'good' was 35.9% for control and 43.0% for satisfaction compared with 10.5% and 16.5%, respectively, for placebo-treated subjects' partners.

The proportion of PSD502-treated subjects' partners with a response of 'not at all' or 'a little bit' was 58.3% for distress and 70.4% for interpersonal difficulty compared with 31.7% and 44.1%, respectively, for placebo-treated subjects' partners.

Clinical studies in special populations

No studies were performed on special population.

Supportive studies

- ANAE-059-00

ANAE-059-00 was a single-centre, open-label, uncontrolled, proof-of-concept investigator-led study.

The primary objective of ANAE-059-00 was to measure IELT in men with PE before and after the application of PSD502 to the penis. The subjects eligible for enrolment into ANAE-059-00 were men aged 21 to 70 years inclusive, with self-reported sexual dissatisfaction due to PE, and referral to a urology clinic. Subjects were instructed to use the spray on five consecutive encounters and to record the number of sprays and duration of use in each case. Subjects were instructed to apply between 3 and 5 sprays of PSD502 to the glans penis (depending on the size of the glans), approximately 15 to 30 minutes before intercourse.

A sample size of 15 subjects was chosen as it would provide statistical significance if the IELT times increased from two minutes to over 10 minutes.

A total of 14 subjects were treated. Of these, 3 subjects withdrew. The population had a mean age of 41 years and experienced PE for a mean of 10.2 years. Subjects reported a mean IELT of 55 seconds (range, 5 to 120 seconds). Eleven subjects used PSD502 on at least one occasion and recorded at least one quantitative efficacy measurement. The mean duration for which TEMPE was applied prior to initiating intercourse was 17.8 minutes (range from 5 to 45 minutes per encounter).

The mean (SD) IELT increased from 1.4 minutes (± 1.1 minute) to 11.35 minutes (± 10.7 minutes; p = 0.008) after treatment, representing a 9-fold increase of the mean. No subject experienced a decrease in IELT. The mean sexual satisfaction scores after treatment for both subjects and partners were +1, on a scale where -1 was worse, 0 the same, +1 better, and +2 much better. The duration of PSD502 application (5 to 45 minutes) did not appear to affect either the change in IELT or the sexual satisfaction scores.

Four subjects and three partners reported genital numbness on at least one occasion, one subject reported a burning sensation on the first application one subject reported itching scrotum with red spots after the first application, four subjects reported difficulty achieving or maintaining an erection / ejaculating on at least once occasion.

This study mainly contributed to safety data provision of PSD502. No sound conclusions on efficacy can be drawn.

- PSD502-PE-001

PSD502-PE-001 was a multicentre, double-blind, placebo-controlled, parallel-group study which included subjects who fulfilled the DSM-IV criteria, in which a time limit for IELT is not included. This Phase II pilot study was the first controlled study evaluating the efficacy of PSD502 in the treatment of PE. A treatment regimen of 3 sprays of PSD502 (delivering a total of 22.5 mg lidocaine and 7.5 mg prilocaine in a eutectic like combination) was chosen. Each actuation of the PSD502 spray also contained 7.4 mg ethanol as an excipient. Subjects were told to apply 3 sprays to the glans penis approximately 15 minutes before sexual intercourse and to wipe off excess spray before penetration. Subjects were instructed to use the spray for a total of 4 occasions during the 1-month treatment period but not more than once in any 24-hour period.

The primary objective of PSD502-PE-001 was to evaluate the efficacy of PSD502 compared with placebo in treating subjects with PE. The study had a one-month baseline period in which subjects recorded baseline IELT on three separate occasions and completed baseline questionnaires.

The primary endpoint was defined as the proportion of patients who had at least two sexual encounters where the IELT was ≥4 minutes following treatment. Change from baseline of IELT was promoted from a secondary to a co-primary variable in a protocol amendment. The secondary efficacy variables were IELT response (a response was defined as ≥2 IELT recordings of ≥2 minutes or ≥3 minutes in Month 2), the change in IEC score and the change in SQoL score.

The sample size was based on data from the pilot study ANAE-059-00. A sample size of 25 patients per treatment group provides between 70% and 80% power to detect a difference of 40% between PSD502 and placebo, at the α=0.05 level of significance (two-sided). To take account of missing or incomplete data the sample size was increased by approximately 30% and hence 35 patients per group were to be entered into the study.

A total of 54 subjects (26 PSD502 and 28 placebo subjects) were treated in this study. The study population was predominantly Caucasian 80% with a mean age of 40 years. The observed mean change from baseline to the end of the treatment period was 3.8 minutes in the PSD502 group compared with 0.7 minutes in the placebo group. The estimated geometric means for the IELT during month 2, derived from the analysis of the log-transformed data, were 2.50 and 1.04 minutes for PSD502 and placebo respectively representing a 2.4-fold (95% CI: 1.3 to 4.4; p<0.01) difference in favour of PSD502. Twenty-five percent of PSD502-treated subjects were considered responders (at least two sexual encounters where the IELT was ≥4 minutes) compared with 13% of placebo.

The effectiveness of PSD502 in treating PE was supported by positive trends in the IEC completed by subjects and SQoL questionnaires completed separately by subjects and their partners at the end of month 2.

Differences in the selection criteria of the patients and the formulation used (containing ethanol as excipient) with respect to the pivotal studies prevent from considering it for efficacy.

The Applicant has provided a comparison with Dapoxetine to offer information on the relative efficacy of PSD502. This comparison can only be made from the Dapoxetine literature and the PAR since a head-to-head comparison has not been performed in a clinical trial. Pooled IELTs from the Dapoxetine pivotal studies are summarized in the report issued by the Swedish Medicines Product Agency. After 12 weeks DB treatment, mean IELTs increased from an average Baseline of 0.9 minutes, to 1.9 minutes (Placebo); 3.1 minutes (Dapoxetine 30 mg) and 3.6 minutes (Dapoxetine 60 mg). In comparison, mean IELTs increased from a Baseline of 0.659 minutes (PSD502) and 0.665 (Placebo) to 5.651 and 1.389 minutes respectively in the pooled pivotal studies for PSD502.

Despite the limitations of comparing results across studies, these data suggest that the PSD502-treated patients had shorter IELTs at Baseline, and yet showed a much greater rise, to a final higher IELT value, with a greater differential from placebo than either of the Dapoxetine doses. It is interesting to note that only 58% of patients in the Dapoxetine Pivotal studies had an average Baseline IELT of ≤1 minute and would, therefore have fulfilled the ISSM definition of PE.

The main PRO used in the Dapoxetine studies was the PEP and the report only presented a composite responder endpoint, which was not used in the PSD502 studies. However, McMahon et al. published an integrated analysis of the results from five Dapoxetine Phase III Studies [54]. The PEP data from this publication, together with the corresponding data from the PSD502 Pivotal studies is summarized in Table 39.

Table 39: Subject PEP Results – PSD502 Combined Pivotal Studies and Dapoxetine Integrated Analysis

	Baseline		Month 3		Baseline			Month 3		
	PSD502	Placebo	PSD502	Placebo	Dapoxetine		Placebo	Dapoxetine		Placebo
					30mg	60mg		30mg	60mg	
Ejaculatory Control †										
Very good, Good	0%	0%	37.3%	5.7%	0.6%	0.5%	0.3%	26.2%	30.2%	11.2%
Sexual Satisfaction†										
Very good, Good	0.3%	0%	46.5%	9.7%	14.7%	15.5%	15.5%	37.9%	42.8%	24.4%
Distress††										
Quite a bit or Extremely	99.4%	100%	29.4%	74.3%	71.3%	69.7%	73.5%	28.2%	22.2%	41.9%
Interpersonal Difficulty††										
Quite a bit or Extremely	93.6%	89.0%	18.2%	46.8%	38.8%*	36.1%	38.5%	16.0%	12.3%	23.8%

Source: Table 36 Clinical Summary of Efficacy Section 2.7.3.3.2.4.1 and Publication [54]

*Publication states 3.8% but N=288 out of total N of 742, therefore assumed typographical error and should state 38.8%

† Based on pooled data from 4 studies (International, Asia-Pacific and USA)

†† Based on pooled data from 2 studies (International and Asia-Pacific)

It can be seen that the patients who received PSD502 in the PSD502 pivotal studies generally had more severe (lower) PEP scores at baseline and these improved to a greater degree than the patients in the Dapoxetine studies, regardless of Dapoxetine dose.

2.5.3. Discussion on clinical efficacy

Currently, there is no consensus as to what level of IELT constitutes a meaningful improvement in PE. While IELT may be viewed as an indicator of pharmacologic activity, the clinical relevance of achieving a given level of IELT or a given level of change in IELT is likely to differ from individual to individual. Therefore, to understand the improvement in IELT, it is also necessary to examine the relationships between IELT and responses to participant and partner outcome measures.

A statistically significant and clinically meaningful effect has been shown by this medicinal product in the treatment of lifelong premature ejaculation. It has been observed in objective measures as intravaginal latency time and also perceived as a psychological benefit by the subjects and their partners.

Design and conduct of clinical studies

The primary efficacy evaluation for PSD502 in the treatment of premature ejaculation (PE) is based on 2 pivotal trials (with open-label extensions), 1 dose-range finding study and 2 supportive phase 2 studies.

Two additional studies (one conducted in patients with burns undergoing skin graft and one conducted in female patients undergoing hysteroscopy) have been submitted. They only have been considered for safety.

Two pivotal randomized, double blind, placebo controlled, parallel group, 12-week studies support the use of PSD502 in the treatment of subjects with premature ejaculation (studies PE-002 and PE-004). Data from these two studies were integrated for pooled-analyses.

The population of subjects participating in these trials is adequate and representative for patients with lifelong PE. The studies enrolled adult male subjects (18 to 67 years of age) according to the two hallmarks of the condition: a reduced latency time for ejaculation (< 1 minute) and the negative impact on the individual. These criteria correspond to the definition of PE published by the

International Society for Sexual Medicine in 2008, when the pivotal trials were on-going. At that time a small proportion of subjects with acquired PE had been enrolled (6% of the total population). Since the new definition of PE only refers to lifelong PE the recruitment of those patients was stopped. However, the primary efficacy analysis (ITT population) considered both groups of subjects. Given the differences between both syndromes (mainly related to the gradual onset of the symptoms and a more prolonged time to ejaculation in acquired PE) it is uncertain that the results obtained in lifelong PE can be extrapolated to acquired PE. The inclusion of the PRO and control over ejaculation and satisfaction variables in the primary endpoint is acceptable.

Subjects reported an ejaculatory latency time of 0.6 minutes. In addition a minimum of severity in the subjective perception was required. According to the lack of control over ejaculation, the reported level of distress and dissatisfaction with the sexual relationships the patients recruited in the pivotal studies mostly suffered from a severe condition.

These results demonstrate that PSD502 was as effective in delaying ejaculation, improving ejaculatory control and sexual satisfaction, and reducing distress at the end of the open-label treatment period (month 12) as at the end of double-blind treatment period (month 3).

Demographic and baseline characteristics were comparable between the two groups. Most of the subjects randomised were adults (only 6 patients were older than 65 years and 49 older than 55 years) and Caucasian subjects (>90%). The median duration of symptoms since diagnosis was 1 to 1.5 years and most of subjects (70%) had not been previously treated for PE.

Subjects were treated for 12 weeks. Only the comparison with placebo is available. The justification provided by the Applicant about the lack of availability of dapoxetine (the only approved treatment for this condition) at the start of the studies is acknowledged. The additional difficulties of adding a third arm by a different route of administration, mainly when most of treatments are administered before sexual intercourse as on-demand basis are recognised.

Only the 30 mg dose was formally studied. A dose-range finding study was conducted (Study PE-005) in which 3 mg and 53 mg were also tested. Taking into account that it was started when the pivotal studies were already ongoing the study does not appear to provide relevant information apart from confirming the selection of the dose. Important information related to the minimal and maximal effective dose, the optimum dose range or the dose adjustment in case of reporting insufficient effect or adverse events has not been established. Efficacy was primarily based on the effect on IELT and the improvement of the control over ejaculation, sexual satisfaction and the reduction of the distress related to ejaculation (IPE domains). This is welcome since it addresses the multidimensional profile of the condition.

IELT was measured with a stopwatch. Although it is not required for the clinical management of the condition it is recommended for the monitoring of IELT response in clinical research. As the stopwatch could be operated by the subject or the partner (always the same subject during the trial) some differences in the measures could result from it. It can be relevant in those outcomes (secondary endpoints) in which absolute means instead of changes with respect to baseline are considered in the estimation (e.g. % subjects with mean IELT > 1 or 2 minutes). The Applicant has clarified during the procedure the lack of potential differences in patient's response according to the person dealing with the stopwatch. In addition, only one secondary endpoint could have been affected by this fact and their results were consistent with all the other endpoint results.

Efficacy data and additional analyses

Over the 3 month double-blind treatment phase, the geometric mean IELT for subjects in the ITT population of PSD502-PE-002 had increased to 2.59 minutes in the PSD502 group and to 0.80 minutes

in the placebo group, and in PSD502-PE-004, had increased to 3.79 minutes in the PSD502 group and 1.07 minutes in the placebo group, demonstrating a 4.66-fold and a 6.30-fold increase respectively for PSD502. The analysis of the ratio to baseline over the 3 month treatment phase for PSD502/Placebo demonstrated a statistically significant 3.05-fold (95%CI: 2.29, 4.06) treatment benefit in favour of PSD502 ($p<0.0001$; significance level=0.0125) in PSD502-PE-002 and a statistically significant 3.62 fold (95%CI: 2.80, 4.67) treatment benefit in favour of PSD502 ($p<0.0001$; significance level=0.0167) in PSD502-PE-004.

This effect was also perceived as a meaningful change by the patient when the Index of Premature Ejaculation (IPE) domains were measured.

For the IPE domains in the ITT population, substantial improvement was observed in all 3 domains at month 3 in the PSD502 groups of both studies compared with the placebo groups. Changes in adjusted mean scores (PSD502 vs. placebo) at month 3 for the ejaculatory control score were 7.3 vs. 2.3 in PSD502-PE-002, and 9.2 vs. 2.2 in PSD502-PE-004, representing 5.0 point (95% CI: 3.61, 6.34) and 7.0 point (95% CI: 5.87, 8.18) statistically significant treatment benefits in favour of PSD502. Changes in adjusted mean scores (PSD502 vs. placebo) at month 3 for the sexual satisfaction score were 6.7 vs. 2.2 in PSD502-PE-002, and 7.8 vs. 1.9 in PSD502-PE-004, representing a 4.6 point (95% CI: 3.30, 5.84) and 5.9 (95% CI: 4.78, 7.04) statistically significant treatment benefits in favour of PSD502 between the two study treatments. Changes in adjusted mean scores (PSD502 vs. placebo) at month 3 for the distress score were 3.5 vs. 1.0 in PSD502-PE-002, and 4.0 vs. 1.2 in PSD502-PE-004, representing a 2.5 point (95% CI: 1.86, 3.20) and 2.8 (95% CI: 2.21, 3.31) statistically significant treatment benefits in favour of PSD502.
Outcomes related to secondary variables also showed a statistically significant difference with respect to placebo after 12 weeks of treatment:

- When the effect on IELT is expressed as responder rate 85% of subjects treated with PSD502 vs 46% of those treated with Placebo did not formally qualify as PE (IELT lasting > 1 minute). These differences were remarkable when more stringent definitions of responses were analysed (44% of PSD502 subjects reaching IELT longer than 4 minutes compared with 4% of those receiving Placebo)
- Changes in scores based on Premature Ejaculation Profile (PEP) were also significantly superior for PSD502. Subjects treated with PSD502 and their partners reported higher levels of control over ejaculation and sexual satisfaction and lower distress and interpersonal difficulties related to ejaculation than those treated with placebo.

The Applicant has performed an indirect contrast with the available published results from dapoxetine studies. Bearing in mind relevant differences between populations (inclusion criteria, severity of the condition) PSD502 could be comparable to Dapoxetine high dose, performing better than 30 mg dose. These results are comparable to the clinical results obtained in clinical trials with Dapoxetine with the IELT as primary endpoints, the only product approved for this indication. In the Dapoxetine trials, treatment resulted in significant improvement in mean (SD) IELT at the endpoint of 12 weeks [1.66 (2.087), 2.86 (3.588), and 3.36 (3.973) min for placebo, dapoxetine 30 and 60 mg, respectively for the first pivotal study and 1.84 (2.335), 2.70 (3.386) and 3.28 (3.404) min in the second study]. The control over ejaculation and satisfaction with sexual intercourse also improved. In both Dapoxetine studies, improvement in IELT was noted from the first dose and sustained over 12 weeks. Subgroup analyses using baseline average IELT≤1min and >1min showed similar results.

The screening of the subjects was determined by the self-reported reduced ejaculation latency and the qualification of the impact by mean of IPE and PEP questionnaire. IELT was not part of this selection in

order to avoid the training effect on the IELT derived from the frequent use of the stopwatch. This "learning" effect has already been described in the clinical investigation of other conditions (e.g. use of diaries in urinary incontinence trials) and its main consequence is a remarkable placebo effect. This was described in dapoxetine clinical trials, where placebo subjects doubled their IELT with respect to baseline measurement at the end of the treatment period. This finding has not been so remarkable in clinical trials with PSD502. At the end of the double blind phase Placebo treated patients achieved a mean IELT below 1 minute (1.6 ratio with respect to baseline).

Also noteworthy is the similar number of encounters (and the doses of the product) reported in subjects on PSD502 and on placebo. Unless the couples did not report the sexual relationships in which spray was not used some differences would be expected between subjects experiencing improvement of the condition and satisfaction with the results and those without changes in the level of bother reported at baseline. These two features (the modest placebo effect and the lack of discrepancy in the on-demand use between placebo and active group) pose doubts regarding the maintenance of blinding during the trial. The Applicant has explained that the sexual encounter frequency was not collected at baseline as an efficacy measure. Whereas it appears difficult to adequately assess the effect of treatment on this outcome the differences in satisfaction with sexual intercourse between both PSD502 and placebo reported by patients and partners can be considered sufficiently supportive.

Circumcised subjects showed lower benefit than uncircumcised males. The Applicant has explained it due to the keratinisation of the mucosa of the glans penis in circumcised men and the consequent reduction in penetration of the product. Admittedly, some relevant differences in the response were also observed between countries, showing the subjects recruited in USA the lowest IELT and IPE values. The Applicant has attributed this finding to the differences in circumcision status between countries and it has been further supported by additional analyses in the Response document provided by the Applicant.

Other demographic characteristics do not appear to influence in the response except for the age, younger subjects reporting greater benefit than older patients. However, the limited number of subjects older than 65 years and even 55 years included in clinical trials does not allow to determine if such differences in fact exist.

Long-term efficacy data of PSD502 come from the open-label phases of the two pivotal trials. No controlled data further to 12 weeks to support efficacy are available. Although the results obtained at 12 months do not suggest loss of efficacy it provides limited evidence regarding the maintenance of the effect of PSD502. In this phase the use of condoms was permitted and according to the Applicant's responses no relevant differences were observed on efficacy or safety profile of the product. However, the lack of a placebo arm and of the precise number of condom users prevent from reaching valid conclusions on this issue. Data from literature (mainly related to the use of EMLA on the genital mucosa of male patients) are reassuring although a higher rate of local numbness and loss of erection could be reasonably expected. This advice is included in the Product Information.

2.5.4. Conclusions on the clinical efficacy

The efficacy of Lidocaine/Prilocaine Plethora was demonstrated in two multi-centre, multinational, randomised, double-blind, placebo controlled studies, both followed by an open-label phase. Men satisfying the International Society for Sexual Medicine (ISSM) criteria for premature ejaculation (PE) who had a baseline IELT ≤ 1 minute in at least 2 of the first 3 sexual encounters during screening were eligible to enrol.

Clinical trials have shown Lidocaine/Prilocaine Plethora to increase the intra-vaginal ejaculatory latency time (IELT), increase control over ejaculation and reduce the feelings of distress in patients with premature ejaculation as measured by the Index of Premature Ejaculation (IPE). The medicinal product has a rapid onset of action and is effective within 5 minutes of application. The effectiveness of the medicinal product has been demonstrated to persist on repeat use over time.

The effectiveness of Lidocaine/Prilocaine Plethora in treating PE was assessed by measuring IELT and the co primary endpoints of ejaculatory control, sexual satisfaction, and distress using the IPE. During the 3 months of the double-blind treatment phase, the geometric mean IELT increased from 0.58 to 3.17 minutes in the Lidocaine/Prilocaine Plethora group and from 0.56 to 0.94 minutes in the placebo group. 85.2% of subjects in the Lidocaine/Prilocaine Plethora group achieved a mean IELT of > 1 minute over the course of 3 months of treatment with it, whereas 46.4% of the placebo subjects had a mean IELT of > 1 minute. 66.2% of Lidocaine/Prilocaine Plethora-treated subjects and 18.8% of placebo-treated subjects achieved a mean IELT > 2 minutes.

The clinically significant increases in IELT were paralleled by significant differences in the IPE scores ($p < 0.0001$). Adjusted mean change scores (Lidocaine/Prilocaine Plethora vs. placebo) at Month 3 were 8.2 vs. 2.2 for the ejaculatory control score, 7.2 vs. 1.9 for the sexual satisfaction score, and 3.7 vs. 1.1 for the distress score.

In Lidocaine/Prilocaine Plethora-treated subjects, IELT and IPE scores increased at the first measured timepoint. Both IELT and IPE scores continued to increase slightly more throughout the remainder of the double-blind phase. The positive changes in IELT and IPE domain scores were maintained during the open-label treatment phase.

At each of the three monthly assessments all subjects completed a Premature Ejaculation Profile (PEP) questionnaire relating to perceived control over ejaculation, personal distress related to ejaculation, satisfaction with sexual intercourse, and interpersonal difficulty relating to ejaculation. The PEP scores followed a similar pattern of improvement to the IELT and IPE scores. For all of the three monthly assessments completed by the subjects, there was a significant difference between Lidocaine/Prilocaine Plethora and placebo ($p < 0.0001$). Partners completed the PEP questionnaire at month three. There was also a significant difference over placebo in all domains for the responses from the partners ($p < 0.0001$).

2.6. Clinical safety

The clinical safety analysis of the use of 30 mg PSD502 in subjects with premature ejaculation (PE) and their sexual partners is based on ten studies, including:

- four controlled PE studies (PSD502-PE-001 – pilot study, PSD502-PE-002 - pivotal study + PK, PSD502-004 - pivotal study, and PSD502-PE-005 – Dose ranging study)
- one uncontrolled PE study (ANAE-059-00 - open-label pilot)
- three studies in healthy volunteers (PSD502-PE-003 in healthy male volunteers and PSD502-PE-006 and PSD502-PE-007 in healthy female volunteers)
- two non-PE studies in pain management (PSD502-PM-001 in patients undergoing skin grafts as treatment for burns and PSD502-UP-001 in patients undergoing hysteroscopy).

For the integrated safety analysis, the following analysis populations were used: PSD502 Glans-penis-treated Subjects, Controlled PE Studies, Uncontrolled Long-term PE Studies, other studies (dose-

ranging study, healthy male and female volunteer studies, pilot PE study ANAE-059-00 and non-PE studies).

The PSD502 Glans-penis-treated Subjects population (subjects who received repeated doses of PSD502 to the glans penis), and their female sexual partners were the primary safety analysis population. Data from "other studies" are considered as supportive only.

Safety analysis has been provided both for the primary safety analysis population and for those patients included in the controlled trials. In addition, safety analysis for the long-term studies and the dose-ranging study is provided.

The safety profile of PSD502 was established by assessing:

- the incidence of adverse events in subjects and their female sexual partners
- the effects of PSD502 on vital sign assessments, clinical laboratory results, and electrocardiogram (ECG) results for subjects enrolled in the ten studies
- haemoglobin (Hb) adduct levels in a subset of subjects in study PSD502-PE-002 to evaluate potential toxicity of lidocaine/prilocaine metabolites.

Patient exposure

Overall patient exposure

In the pivotal studies, nearly 332 men were exposed to 30mg PSD502 for 3 months in the double blind phase, with 182 being exposed for 12 months in the open-label phase.

A total of **658 subjects** received at least one dose of PSD502 across the 8 studies providing safety data in the integrated analysis. Of the 658 subjects who received PSD502:

- 596 (90.6%) were in the PSD502 Glans-penis-treated Subjects population
- 419 (63.7%) were in the Controlled PE Studies population
- 497 (75.5%) were in the Uncontrolled Long Term PE Studies population
- 35 (5.3%) were in the dose-ranging study
- 12 (1.8%) were healthy male volunteers
- 39 (5.9%) were healthy female volunteers
- 17 (2.6%) were in the single dose non-PE studies.

Most of the glans-penis treated subjects (91.7%) received at least 4 doses of the product and around 50% of them were given at least 32 doses. The mean duration of exposure was 203 days (approximately 7 months).

The total number of female sexual partners in the PSD502 Glans-penis-subjects population is 584.

- *Extent of exposure*

In the PSD502 Glans-penis-treated Subjects population, **91.7%** of subjects received at least 4 doses and 50.5% received at least 32 doses of PSD502 30 mg. The mean number of doses was 40 (median: 33 doses) with a maximum of 197 doses administered. The proportion of subjects who participated in the studies for at least 2 months was 81.4% and those who participated for at least 5 months was 66.1%. The mean length of time PSD502 Glans-penis-treated subjects participated in the studies was 203 days (approximately 7 months) with a median of 216 days.

In the Controlled PE Studies population, **89.3%** of subjects received more than 4 doses and 57.6% received more than 12 doses of PSD502 30 mg. The mean number of doses was 14.9 (median: 14 doses) with a maximum of 31 doses administered. The proportion of subjects who participated in the studies for more than 2 months was 84.4%. The mean length of time subjects participated in the studies was 70.7 days with a median of 78 days.

Adverse events

- **Overall analysis of Adverse Events/common adverse events**

- **PSD502 Glans-penis-treated Subjects population**:

A total of **138 (23.2%)** subjects had at least one TEAE.

The commonest TEAEs for the primary safety analysis population were hypoaesthesia (4.5%), erectile dysfunction (4.4%), nasopharyngitis (2.7%), headache (2.3%), influenza (1.3%), and genital burning sensation (1.0%), genital erythema (0.5%) and ejaculation failure (0.3%). The most commonly reported TEAEs affected 55 subjects (9.2%) and were related to the reproductive system and breast disorders system organ class.

Table 40:

TEAEs (in at least 2 subjects in PSD502 Glans-penis-treated Subjects population) by Decreasing Frequency: PSD502 Glans-penis-treated Subjects, Controlled and Uncontrolled PE Studies

Preferred Term	PSD502 Glans-penis-treated Subjects	Controlled PE Studies		Uncontrolled Long Term PE Studies
	PSD502 [a] N=596	PSD502 [b] N=419	Placebo [b] N=243	PSD502 N=497
Hypoaesthesia of genital male	27 (4.5%)	11 (2.6%)	0	6 (1.2%)
Erectile dysfunction	26 (4.4%)	14 (3.3%)	0	14 (2.8%)
Nasopharyngitis	16 (2.7%)	6 (1.4%)	2 (0.8%)	11 (2.2%)
Headache	14 (2.3%)	4 (1.0%)	7 (2.9%)	8 (1.6%)
Influenza	8 (1.3%)	5 (1.2%)	3 (1.2%)	3 (0.6%)
Genital burning sensation	6 (1.0%)	1 (0.2%)	1 (0.4%)	1 (0.2%)
Back pain	5 (0.8%)	3 (0.7%)	1 (0.4%)	3 (0.6%)
Pharyngolaryngeal pain	4 (0.7%)	1 (0.2%)	0	3 (0.6%)
Upper respiratory tract infection	4 (0.7%)	2 (0.5%)	1 (0.4%)	2 (0.4%)
Arthralgia	3 (0.5%)	3 (0.7%)	0	0
Bronchitis	3 (0.5%)	0	0	2 (0.4%)
Genital erythema	3 (0.5%)	2 (0.5%)	0	1 (0.2%)
Liver function test abnormal	3 (0.5%)	0	0	3 (0.6%)
Pyrexia	3 (0.5%)	0	0	3 (0.6%)
Seasonal allergy	3 (0.5%)	3 (0.7%)	4 (1.6%)	0
Acute tonsillitis	2 (0.3%)	2 (0.5%)	0	0

Abbreviations: DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label; PE = premature ejaculation; TEAE = treatment-emergent adverse event

Note: Percentages were calculated using the number of subjects in each treatment group. All investigator adverse event terms were coded using MedDRA dictionary 11.0. Subjects were counted once within each category.

a) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002 (DB + OL), PSD502-PE-003, PSD502-PE-004 (DB + OL), and all dose levels for study PSD502-PE-005.

b) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg dose level for study PSD502-PE-005.

Source: Section 2.7.4.7, Tables 89, 92, and 93

- **Controlled PE Studies population**

In the controlled PE studies population less patients (16.2%) reported at least one TEAE. The TEAEs distribution was similar or slightly lower to the previously mentioned: erectile dysfunction (3.3% vs 0 in placebo group), hypoaesthesia (2.6% vs 0), genital erythema (0.5% vs 0), ejaculation failure (0.5% vs 0) and genital burning sensation (0.2% vs 0.4%). Slightly lower incidence of TEAEs was observed for the long-term studies population.

Data for the **dose ranging trial** show a dose-related increase of adverse events, being all TEAEs more frequent with the dose of 53 mg.

Given the mechanism of action of the components (lidocaine and prilocaine) of PSD502 and the topical route of administration, these local TEAEs reported are not unexpected.

Additionally, some systemic adverse events were also observed in the PSD502 Glans-penis-treated Subjects population such as nasopharyngitis (2.7%), headache (2.3%) and influenza (1.3%).

- **Female partners**

A total of 83 of the 584 (**14.2%**) female sexual partners in the PSD502 Glans-penis treated Subjects population had at least one TEAE during the studies. The most common (≥1.0%) partner TEAEs in the PSD502 Glans-penis-treated Subjects population were vulvovaginal burning sensation (3.9%), headache (1.9%), influenza (1.2%), nasopharyngitis (1.2%), hypoaesthesia (1.0%), and vulvovaginal discomfort (1.0%).

In the controlled studies, similar incidences were reported for patients treated with PSD502 included in the controlled trials. The most common sexual partner TEAE was vulvovaginal burning sensation (4.5% in the PSD502 group vs. 0.8% in placebo group).

Table 41:

Common (≥2 Partners in PSD502 Glans-penis-treated Subjects Population) Sexual Partner TEAEs by Decreasing Frequency: PSD502 Glans-penis-treated Subjects, Controlled and Uncontrolled PE Studies

Preferred Term	PSD502 Glans-penis-treated Subjects	Controlled PE Studies		Uncontrolled Long Term PE Studies
	PSD502 [a] N=584	PSD502 [b] N=419	Placebo N=243	PSD502 N=497
Vulvovaginal burning sensation	23 (3.9%)	19 (4.5%)	2 (0.8%)	4 (0.8%)
Headache	11 (1.9%)	7 (1.7%)	4 (1.6%)	4 (0.8%)
Influenza	7 (1.2%)	3 (0.7%)	3 (1.2%)	4 (0.8%)
Nasopharyngitis	7 (1.2%)	6 (1.4%)	0	1 (0.2%)
Hypoaesthesia	6 (1.0%)	4 (1.0%)	0	2 (0.4%)
Vulvovaginal discomfort	6 (1.0%)	4 (1.0%)	1 (0.4%)	2 (0.4%)
Pharyngolaryngeal pain	4 (0.7%)	4 (1.0%)	0	0
Back pain	3 (0.5%)	0	0	2 (0.4%)
Diarrhoea	3 (0.5%)	1 (0.2%)	0	2 (0.4%)
Migraine	3 (0.5%)	2 (0.5%)	2 (0.8%)	1 (0.2%)
Seasonal allergy	3 (0.5%)	3 (0.7%)	0	0
Anorectal discomfort	2 (0.3%)	1 (0.2%)	0	1 (0.2%)
Cough	2 (0.3%)	1 (0.2%)	0	1 (0.2%)
Sinus congestion	2 (0.3%)	2 (0.5%)	0	0
Vaginal candidiasis	2 (0.3%)	0	0	1 (0.2%)
Vaginal haemorrhage	2 (0.3%)	0	0	2 (0.4%)
Vaginal pain	2 (0.3%)	2 (0.5%)	0	0
Vulvovaginal pruritus	2 (0.3%)	2 (0.5%)	0	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PE = premature ejaculation; TEAE = treatment-emergent adverse event

Note: Percentages were calculated using the number of subjects in each treatment group. All investigator adverse event terms were coded using MedDRA dictionary 11.0. Subjects were counted once within each category.

a) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and all dose levels for study PSD502-PE-005.

b) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg dose level for study PSD502-PE-005.

Source: Section 2.7.4.7, Tables 131, 132, and 133

- **TEAEs by Relationship to Study Drug**

Fifty-seven subjects (**9.6%**) in the glans-penis-treated population had a TEAE that was considered to be drug-related. The most common (≥1%) were: hypoaesthesia (4.5%), erectile dysfunction (4.4%) and genital burning sensation (1.0%).

Table 42:

Likely Drug-related TEAEs: PSD502 Glans-penis-treated Subjects, Controlled and Uncontrolled PE Studies

Preferred Term	PSD502 Glans-penis-treated Subjects	Controlled PE Studies		Uncontrolled Long Term PE Studies
	PSD502 [a] N=596	PSD502 [b] N=419	Placebo N=243	PSD502 N=497
At least one drug-related TEAE	**57 (9.6%)**	**30 (7.2%)**	**2 (0.8%)**	**24 (4.8%)**
Hypoaesthesia of genital male	27 (4.5%)	11 (2.6%)	0	6 (1.2%)
Erectile dysfunction	26 (4.4%)	14 (3.3%)	0	14 (2.8%)
Genital burning sensation	6 (1.0%)	1 (0.2%)	1 (0.4%)	1 (0.2%)
Ejaculation failure	2 (0.3%)	2 (0.5%)	0	0
Genital erythema	2 (0.3%)	2 (0.5%)	0	0
Headache	2 (0.3%)	2 (0.5%)	1 (0.4%)	0
Pyrexia	1 (0.2%)	0	0	1 (0.2%)
Glucose tolerance impaired	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Hypercholesterolaemia	1 (0.2%)	1 (0.2%)	0	1 (0.2%)
Orgasm abnormal	1 (0.2%)	1 (0.2%)	0	0
Paraesthesia of genital male	1 (0.2%)	0	0	0
Penile pain	1 (0.2%)	0	0	1 (0.2%)
Penis disorder	1 (0.2%)	0	0	0
Pruritus genital	1 (0.2%)	0	0	0
Throat irritation	1 (0.2%)	0	0	1 (0.2%)
Skin irritation	1 (0.2%)	1 (0.2%)	0	0
Hypertension	1 (0.2%)	1 (0.2%)	0	1 (0.2%)

Abbreviations: DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label; PE = premature ejaculation; TEAE = treatment-emergent adverse event

Note: Percentages were calculated using the number of subjects in each treatment group. All investigator adverse event terms were coded using MedDRA dictionary 11.0. Subjects were counted once within each category.

a) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002 (DB + OL), PSD502-PE-003, PSD502-PE-004 (DB + OL), and all dose levels for study PSD502-PE-005.

b) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg dose level for study PSD502-PE-005.

Source: Section 2.7.4.7, Tables 96, 99, and 100

In general, most of the drug-related events occurred immediately, or within 24 hours, following treatment with PSD502.

In the dose-ranging Study, higher incidences were again seen, mainly with the 53 mg dose for which 17.6% of patients reported drug-related TEAEs in comparison to 11.4% with 30 mg PSD502 dose.

Table 43: Likely Drug-related TEAEs in Dose-Ranging Study PSD502-PE-005

System Organ Class Preferred Term	PSD502 3 mg N=35	PSD502 30 mg N=35	PSD502 53 mg N=34	Total PSD502 N=35	Placebo N=34
At least one drug-related TEAE	2 (5.7%)	4 (11.4%)	6 (17.6%)	6 (17.1%)	0
Erectile dysfunction	0	2 (5.7%)	2 (5.9%)	4 (11.4%)	0
Genital burning sensation	0	0	1 (2.9%)	1 (2.9%)	0
Hypoaesthesia of genital male	2 (5.7%)	2 (5.7%)	4 (11.8%)	5 (14.3%)	0

Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities; PE = premature ejaculation; TEAE = treatment-emergent adverse event

Note: Percentages were calculated using the number of subjects in each treatment group. All investigator adverse event terms were coded using MedDRA dictionary 11.0. Subjects were counted once within each category.

Source: Section 2.7.4.7, Table 101

Most of TEAEs were mild or moderate. Seven subjects (1.2%) in the Glans-penis-treated subject population had at least one severe TEAE. Erectile dysfunction occurred in 3 patients (0.5%) and was considered related to treatment. Other severe TEAEs related to study drug were impaired glucose tolerance, hypercholesterolaemia, hyperlipidaemia and hypertension. One case of hypoaesthesia was reported in the dose-ranging trial with the 53 mg dose, a higher dose that the one recommended for this intended indication.

The following AEs were considered severe but unrelated to study drug: myocardial infarction, toothache, tooth infection and back pain.

- **Female partners**

Vulvovaginal burning sensation was the commonest likely drug-related TEAE (8.6%) this is not unexpected considering the topical administration of the drug.

Table 44:

Likely Drug-related Sexual Partner TEAEs: PSD502 Glans-penis-treated Subjects, Controlled and Uncontrolled PE Studies

Preferred Term	PSD502 Glans-penis-treated Subjects	Controlled PE Studies		Uncontrolled Long Term PE Studies
	PSD502 [a] N=584	PSD502 [b] N=419	Placebo N=243	PSD502 N=497
At least one drug-related TEAE	35 (6.0%)	27 (6.4%)	3 (1.2%)	10 (2.0%)
Vulvovaginal burning sensation	23 (3.9%)	19 (4.5%)	2 (0.8%)	3 (0.6%)
Hypoaesthesia	6 (1.0%)	4 (1.0%)	0	2 (0.4%)
Vulvovaginal discomfort	5 (0.9%)	3 (0.7%)	1(0.4%)	2 (0.4%)
Headache	2 (0.3%)	1 (0.2%)	0	1 (0.2%)
Genital burning sensation	1 (0.2%)	1 (0.2%)	0	0
Vaginal pain	1 (0.2%)	1 (0.2%)	0	0
Vulvovaginal pruritus	1 (0.2%)	1 (0.2%)	0	0
Anorectal discomfort	1 (0.2%)	1 (0.2%)	0	0
Paraesthesia oral	1 (0.2%)	1 (0.2%)	0	0
Vaginal candidiasis	1 (0.2%)	0	0	1 (0.2%)
Dysuria	1 (0.2%)	1 (0.2%)	0	0
Throat irritation	1 (0.2%)	0	0	1 (0.2%)
Urinary tract infection	0	0	1 (0.4%)	0

Abbreviations: DB = double-blind; MedDRA = Medical Dictionary for Regulatory Activities; OL = open-label; PE = premature ejaculation; TEAE = treatment-emergent adverse event

Note: Percentages were calculated using the number of subjects in each treatment group. All investigator adverse event terms were coded using MedDRA dictionary 11.0. Subjects were counted once within each category.

a) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002 (DB + OL), PSD502-PE-003, PSD502-PE-004 (DB + OL), and all dose levels for study PSD502-PE-005.

b) TEAEs were included for studies PSD502-PE-001, PSD502-PE-002, PSD502-PE-004, and the 30 mg dose level for study PSD502-PE-005.

Source: Section 2.7.4.7, Tables 139, 140, and 141

Overall, the safety of Lidocaine/Prilocaine Plethora was evaluated based on 596 male patients who applied it during clinical trials. Safety has also been evaluated in 584 female partners of these subjects.

Adverse reactions considered related to study drug occurred in 9.6% of male subjects and 6.0% of female partners. Most cases were classed as mild or moderate.

The most frequent adverse reactions reported with the use of this medicinal product in male patients were local effects of genital hypoaesthesia (4.5%) and erectile dysfunction (4.4%). These adverse reactions caused discontinuation of treatment in 0.2% and 0.5% of patients, respectively.

The most frequent adverse reactions reported with the use of this medicinal product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects.

The adverse events are incorporated in section 4.8 in the SmPC in a tabulated list of adverse reactions.

Serious adverse event / deaths / other significant events

Deaths

No subjects or sexual partners died while participating in the studies of the PSD502 clinical program.

Other serious adverse events

A total of 8 subjects experienced serious adverse events; 6 subjects in PSD502-PE-002, 1 subject in PSD502-PE-004, and 1 subject in PSD502-PM-001. All of the serious adverse events were considered by the investigators to be unrelated to treatment with study drug.

Table 45: List of Subjects Who Had a Treatment-emergent Serious Adverse Event

Subject Identifier	Treatment When Event Started	Onset Study Day / Duration	Preferred Term	Severity	Relationship	Outcome
PSD502-PE-002						
002/08-019	OL / PSD502 30 mg	Day 129 / 1 day	Myocardial infarction	Severe	Unrelated	Recovered
		Day 129 / 8 days	Coronary artery disease	Moderate	Unrelated	Recovered
002/35-021	OL / PSD502 30 mg	Day 147 / 4 days	Cholelithiasis	Moderate	Unrelated	Recovered
002/53-019	DB / placebo	Day 10 / 4 days	Contusion	Mild	Unrelated	Recovered
002/53-021	OL / PSD502 30 mg	Day 221	Blood albumin decreased	Moderate	Unrelated	Unresolved
		Day 221	Haematocrit decreased	Moderate	Unrelated	Unresolved
		Day 221	Platelet count decreased	Moderate	Unrelated	Unresolved
		Day 221	Protein total decreased	Moderate	Unrelated	Unresolved
		Day 221	Red blood cell count decreased	Moderate	Unrelated	Unresolved
002/54-005	OL / PSD502 30 mg	Day 186 / 14 days	Concussion	Moderate	Unrelated	Recovered
002/56-013	DB / PSD502 30 mg	Day 86 / 27 days	Burns second degree	Moderate	Unrelated	Recovered
PSD502-PE-004						
004/14-009	OL / PSD502 30 mg	Day 223 / 104 days	Psychosomatic disease	Moderate	Unrelated	Recovered
PSD502-PM-001						
PM001/01-004	PSD502 30 mg	Day 13 / 128 days	Pulmonary embolism	Mild	Unrelated	Recovered

Abbreviations: DB = double-blind; OL = open-label
Note: Study day was calculated relative to first use of study spray.
Source: Section 2.7.4.7, Table 113

TEAEs were also collected for female sexual partners. The most common were vulvovaginal burning sensation (3.9%), headache (1.9%), influenza (1.2%), nasopharyngitis (1.2%), hypoaesthesia (1.0%), and vulvovaginal discomfort (1.0%). Similar incidences were reported for patients treated with PSD502 included in the controlled trials.

Vulvovaginal burning sensation was the commonest likely drug-related TEAE (8.6%) what is not unexpected considering the topical administration of the drug. Six patients (1%) reported at least one severe TEAE.

Only 3 female sexual partners experienced serious adverse events, which were not considered treatment-related (cardiac failure secondary to desmopressin, pneumotorax and ovarian cyst) what is reassuring.

Laboratory findings

No meaningful changes in any laboratory parameter were observed.

Clinical Laboratory Evaluation

Haematology and chemistry laboratory tests were performed at baseline and at the end of each study. Only single cases of abnormal determinations of laboratory results (bicarbonate and hematocrit levels) were reported for all the studies (controlled, uncontrolled, healthy female/male volunteer studies).

Vital Signs and ECG findings

In the primary safety analysis population two subjects reported elevations of blood pressure during the study and one patient had a shift to abnormal ECG results and the end of study. In the controlled study population the shift from normal to abnormal ECG was comparable in the group treated with PSD502 (3.3%) and placebo (4.1%).

Safety in special populations

No specific in special populations were conducted.

Safety related to drug-drug interactions and other interactions

No *in vivo* drug interaction studies have been carried out with PSD502. However, although PSD502 is a novel spray, the components lidocaine and prilocaine, have been used extensively in both topical and systemic formulations.

Based on reports in the literature from experience with lidocaine and prilocaine:

- Lidocaine may interact with anti-arrhythmic compounds; generally, toxic effects of anti-arrhythmic drugs are additive and potentially synergistic so should be avoided.

- Prilocaine given concomitantly with drugs such as sulfonamides or anti-malarial drugs may result in a predisposition to methaemoglobinaemia.

Four studies were conducted to evaluate the effect of PSD502 on condoms, the cervical cap, the contraceptive diaphragm, and the female condom. Briefly, it was found that the integrity of the male condom, the cervical cap, and diaphragm (all latex rubber-based) were not affected by exposure to PSD502. However, the female condom (polyurethane based) showed an effect on tensile strength and elongation of break testing following exposure to PSD502, and an increased incidence of punctured devices. Therefore, the latex-based male condom, the cervical cap, and the diaphragm can be used as effective contraceptives in the presence of PSD502, but not polyurethane-based barrier contraceptives.

Discontinuation due to adverse events

A total of 5 subjects discontinued from a study early due to TEAEs; 2 subjects from PSD502-PE-002, 2 subjects from PSD502-PE-004, and 1 subject from PSD502-UP-001. Three of the subjects discontinued early because of erectile dysfunction. These 3 events were considered related to the study drug. One of these patients also had hypoaesthesia.

Table 46: List of Subjects Who Had a TEAE Leading to Early Discontinuation

Subject Identifier	Treatment When Event Started	Onset Study Day / Duration (days)	Preferred Term	Severity	Relationship	Outcome
PSD502-PE-002						
002/35-009	DB PSD502 30 mg	Day 4 / 44 days	Erectile dysfunction	Moderate	Possible	Resolved
		Day 4 / 44 days	Hypoaesthesia of genital male	Moderate	Possible	Resolved
002/56-013	DB PSD502 30 mg	Day 86 / 27 days	Burns second degree	Moderate	Unrelated	Resolved
PSD502-PE-004						
004/02-004	DB PSD502 30 mg	Day 57 / 1 day	Erectile dysfunction	Mild	Definite	Resolved
004/26-003	DB PSD502 30 mg	Day 30 / 21 days	Erectile dysfunction	Moderate	Definite	Resolved
PSD502-UP-001						
UP001/01-112	Placebo	Day 1 / 1 day	Procedural pain	Moderate	Unrelated	Resolved

Abbreviations: DB = double-blind
Note: Study day was calculated relative to first use of study spray.
Source: Section 2.7.4.7, Table 120

- **Female sexual partners leading to early discontinuation**

Two subjects discontinued early because of TEAEs experienced by their sexual partners; one partner from PSD502-PE-002 and one from PSD502-PE-004. Partner events leading to early discontinuation were both genital complaints (vulvovaginal discomfort and vulvovaginal burning sensation) and were considered by the investigators to be related to treatment with study drug.

Table 47: List of Sexual Partners Who Had a TEAE Leading to Early Discontinuation

Subject Identifier	Treatment When Event Started	Onset Study Day / Duration	Preferred Term	Severity	Relationship	Outcome
PSD502-PE-002 002/36-001	DB / PSD502 30 mg	Day 3 / 1 day	Vulvovaginal discomfort	Mild	Probable	Recovered
PSD502-PE-004 004/07-002	OL / PSD502 30 mg	Day 115 / 1 day	Vulvovaginal burning sensation	Severe	Definite	Recovered

Abbreviations: DB = double-blind; OL = open-label
Note: Study day was calculated relative to first use of study spray.
Source: Section 2.7.4.7, Table 153

Post marketing experience

No post-marketing experience exists to date as PSD502 spray is not on the market. However, lidocaine and prilocaine are marketed worldwide in various topical formulations, including creams, gels and solutions, which are available over-the-counter or by prescription only depending on their concentration and use. A eutectic mixture of lidocaine and prilocaine is marketed as EMLA cream and EMLA anaesthetic disc (a patch formulation).

As PSD502 is a mixture of lidocaine and prilocaine for topical use, one would expect a toxicity profile similar to that of EMLA cream (a mixture of lidocaine and prilocaine, although in different proportions to PSD502). EMLA cream contains 2.5% lidocaine w/w (25 mg/g) and 2.5% prilocaine (25 mg/g), and it is approved as a local anaesthetic for topical use to produce surface anaesthesia of the skin, and for topical use on the genital mucosa to facilitate the removal of warts in adults.
The most commonly reported events (>1%) with the use of EMLA cream on genital mucosa have been transient local reactions such as erythema, oedema, paleness, and an initial, usually mild, burning sensation, itch, or warmth at the application site. Local paraesthesia such as tingling at the application site has been reported as an uncommon event (>0.1% and <1%), and allergic reactions have been reported as rare events (<0.1%). Allergic reactions to the amide group of local anaesthetics are rare. Occasional reports of contact sensitivity to lidocaine have been reported, and cross reactivity between lidocaine and prilocaine has also been described.
Metabolites of lidocaine and prilocaine include anilines such as 2,6-xylidine and *o*-toluidine, respectively, which are toxic at high levels. Symptoms of aniline poisoning include methaemoglobinaemia, headache, paraesthesia, hyperalgesia, poly neuritis, cardiac arrhythmias, dizziness, hypotension, convulsion, muscle weakness, and/or digestive derangement.

A contraindication of the use of Lidocaine has been introduced in the PI in individuals with hypovolaemia, heart block or other conduction disturbances, and hepatic impairment (may lead to increased plasma levels and known hypersensitivity to amide-type local anaesthetics). A contraindication of the use of Prilocaine is also added in PI in individuals with anaemia or methaemoglobinaemia (congenital or idiopathic) and known hypersensitivity to amide-type local anaesthetics. A warning has been added in the SmpC for individuals with glucose-6-phosphate dehydrogenase deficiency who are more susceptible to drug-induced methaemoglobinaemia.

2.6.1. Discussion on clinical safety

The primary safety analysis population was the glans-penis treated subjects (n=658) that included all patients enrolled in PE studies plus the studies in healthy volunteers. All those patients received at least one dose of PSD502. Most of them (91.7%) received at least 4 doses of the product and around 50% of them were given 32 doses. The mean duration of exposure was 203 days (approximately 7 months). The size of the safety database and the duration of exposure are considered sufficient, although not very extensive enough for the evaluation of the safety profile of the medicinal product.

Safety analysis has been also provided for the controlled trial populations, the long-term studies and the dose-ranging study.

About a quarter of patients (n=138, 23.2%) of the primary safety analysis population reported at least one TEAE. The commonest TEAEs were hypoaesthesia (4.5%), erectile dysfunction (4.4%), nasopharyngitis (2.7%), headache (2.3%), influenza (1.3%), and genital burning sensation (1.0%). Incidences were a bit lower in the controlled trials and the long-term studies. The adverse events are incorporated in section 4.8 in the SmPC.

In 55 subjects (9.2%) of the primary safety analysis population TEAEs were related to the reproductive system and breast disorders system organ class, what is expected given the mechanism of action and the topical administration of PSD502. The most frequent TEAEs were hypoaesthesia (4.5%), erectile dysfunction (4.4%), genital burning sensation (1.0%), genital erythema (0.5%) and ejaculation failure (0.3%). In the controlled PE studies population less patients (16.2%) reported at least one TEAE but a similar incidence was observed. Slightly lower incidence of TEAEs was observed for in the long-term studies. Data for the dose ranging trial show a dose-related increase of adverse events, being all TEAEs more frequent with the dose of 53 mg.

Fifty-seven subjects (9.6%) in the primary safety analysis population had a TEAE that was considered to be drug-related and they were in relation to the local administration of the product and its mechanism of action: hypoaesthesia (4.5%), erectile dysfunction (4.4%) and genital burning sensation (1.0%). Most of the drug-related events occurred immediately, or within 24 hours, following treatment with PSD502. A clear dose-related incidence of TEAEs was observed in the dose-ranging study with higher incidences seen mainly with the 53 mg dose for which 17.6% of patients reported drug-related TEAEs in comparison to 11.4% with 30 mg PSD502 dose.

Most of TEAEs were mild or moderate. Seven subjects (1.2%) had at least one severe TEAE. Erectile dysfunction occurred in 3 patients (0.5%) and was considered related to treatment. Other severe TEAEs related to study drug were impaired glucose tolerance, hypercholesterolaemia, hyperlipidaemia and hypertension. One case of hypoaesthesia was reported in the dose-ranging trial with the 53 mg dose, a higher dose that the one recommended for this intended indication. The following AEs were considered severe but unrelated to study drug: myocardial infarction, toothache, tooth infection and back pain.

There were no relevant differences regarding the nature of the TEAEs observed in healthy volunteers.

TEAEs were also collected for female sexual partners. The commonest were vulvovaginal burning sensation (3.9%), headache (1.9%), influenza (1.2%), nasopharyngitis (1.2%), hypoaesthesia (1.0%), and vulvovaginal discomfort (1.0%). Similar incidences were reported for patients treated with PSD502 included in the controlled trials. Vulvovaginal burning sensation was the commonest likely drug-related TEAE (8.6%) what is not unexpected considering the topical administration of the drug. Six patients (1%) reported at least one severe TEAE. Only 3 sexual partners experienced serious adverse events and these were not considered treatment-related (cardiac failure secondary to desmopressin, pneumothorax and ovarian cyst) what is reassuring. There is no data if inadvertent dosing to other sites (or used in other mucoses) occur although no differences regarding adverse events in genital mucosa are to be expected. This is adequately addressed in the RMP.

Only single cases of abnormal determinations of laboratory results (bicarbonate and hematocrit levels) were reported for all the studies what is considered reassuring.

In the primary safety analysis population two subjects reported elevations of blood pressure during the study and one patient had a shift to abnormal ECG results at the end of study. In the controlled study population the shift from normal to abnormal ECG was comparable in the group treated with PSD502 (3.3%) and placebo (4.1%) what is reassuring.

Overall, 90% of patients included in the controlled trials were younger than 55 years, and a limited number of patients were older than 65 years. The younger age group representation is relevant as PE is more common. However, it cannot be ruled out that the limited participation of patients older than 65 years of age have an impact on the safety profile of PSD502 as ED is also more frequent in the older population and it is a known AE for this combination of lidocaine and prilocaine. This issue is properly addressed in the RMP as missing information.

ED and hypoaesthesia occurred more frequently in uncircumcised subjects. Ejaculation failure (0.7%) and genital erythema (0.7%) were only observed in uncircumcised subjects too. The Applicant's justification of these differences with respect to circumcised patients is supported.

Five subjects discontinued early due to TEAEs; 3 male subjects due to ED and 2 female sexual partners due to genital complaints.

Although the lidocaine/prilocine spray is not available on the market anywhere, there is an authorised product for topical use containing a mixture of lidocaine and proilocaine (EMLA®) in different indication and concentrations. Similar local reactions (erytema, burning sensation, paresthesia) have been reported post-marketing, all of them linked to the mechanism of action of both active substances and the topical use. However, whereas EMLA is going to be used in specific occasions, i.e. minor interventions or surgical interventions, Lidocaine/Prilocaine Plethora is expected to be used for chronic and intermittent use and indicated for the treatment of PE. As it is known that the use of prilocaine may result in a predisposition to methaemoglobinaemia and there is carcinogenicity potential from *o*-toluidine metabolite in humans, a prolonged exposure and the possible accumulation of lidocaine/prilocaine following repeated doses could lead to a higher incidence of these potentially negative events. This concern has been adequately justified by the Applicant. Data provided revealed that the potential occurrence of methaemoglobinaemia from prilocaine and the carcinogenicity risk from o-toluidine following PSD502 administration seem to be negligible. No cases were reported during clinical studies and no considerable accumulation of prilocaine or *o* -toluidine seems to be expected following repeated administrations of PSD502. However, since these risks cannot be ruled out in the intended population, it has been reflected in the RMP and a warning and additional information is included in the PI.

Of note, a concern related to the potential risks for the foetus in pregnant women was also raised. After the assessment of further information provided by the Applicant, this risk seems to be negligible. However, there are limited data in pregnant women and therefore this concern is considered at present unknown. This has been reflected the RMP as well as the PI.

Known interactions of lidocaine and prilocaine have already been included in the proposed SmPC as well as warnings related to these interactions.

The Applicant was requested to include some additional amendments in the proposed SmPC:

- Information related to the compatibility of PSD502 and latex rubber-based contraceptives or polyurethane based contraceptives under section 4.4. It is considered that this information is relevant for a safe use of PSD502 cutaneous spray.

- Information on pregnancy taking into account that there is limited information that offers a reassuring safety profile during pregnancy and lactation in humans.

The above requirements have been adequately addressed in the corresponding sections of the SmPC.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

No relevant concerns seem to have been identified in the clinical development of PSD502 for premature ejaculation. Most of adverse events reported were mild or moderate in intensity and mainly localized reactions related to the local administration and mechanism of action of the product (hypoaesthesia, erectile dysfunction (ED), genital burning sensation, genital erythema and ejaculation failure). Given the mechanism of action of lidocaine and prilocaine and the topical route of administration, these local TEAEs reported are not unexpected.
Few cases were considered severe (3 cases of ED, impaired glucose tolerance, hypercholesterolaemia, hyperlipidaemia and hypertension) all of them considered related to the studied medicinal product. Some systemic adverse events were also observed such as nasopharyngitis, headache and influenza.

Overall, the female sexual partners also had TEAEs, some localised and related to the local administration of the product (vulvovaginal burning sensation, vulvovaginal discomfort and hypoaesthesia) and other systemic (headache, influenza, nasopharyngitis). There is no data in male sexual partners although no differences regarding adverse events in genital mucosa are to be expected. This is properly addressed in the RMP as important potential risk.

Overall, PSD502 has an apparently benign and manageable safety profile. Furthermore, it is known that the use of prilocaine may result in a predisposition to methaemoglobinaemia and there is carcinogenicity potential from *o*-toluidine metabolite in humans, a prolonged exposure could lead to a higher incidence of these potentially negative events. The potential occurrence of these risks seem to be negligible although cannot be ruled out. A specific wording is included to reflect these risks in product information and RMP. Similarly, a concern related to the potential risks for the foetus in pregnant women was also raised. Given the limited data available, some recommendations are provided in the product information.

In addition, the fact that very few patients older than 65 years (less than 10%) were included in the controlled trials raises a concern regarding the efficacy and safety of this product in this specific population. This is reflected in the RMP as missing information.

Finally, there are some additional risks that have been reflected in the updated PI such as the possible effect on male fertility (sperm mobility), the inadvertent dosing to other sites and the potential for off-label use that are adequately reflected in the RMP.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

PRAC Advice

Based on the PRAC review of the Risk Management Plan version 1.0 the PRAC considers by consensus that the risk management system for Lidocaine/Prilocaine (Lidocaine/Prilocaine Plethora) in the of primary premature ejaculation in adult men could be acceptable provided an updated risk management plan and satisfactory responses to the List of Questions are submitted.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

The applicant identified the following safety concerns in the RMP:

Table 2.1 Summary of the Safety Concerns

Summary of safety concerns	
Important identified risks	Erectile dysfunction
Important potential risks	Inadvertent trauma secondary to hypoaesthesia (including application to unintended sites including eyes, oral cavity and anus)
	Partner exposure (leading to application site reactions, hypersensitivity reactions, trauma secondary to hypoaesthesia)
	Effect on fertility (includes potential risk of “Sperm motility”)
	Interference with contraception
	Hypersensitivity
	Carcinogenicity at the application site
	Systemic exposure leading to systemic reactions (e.g. methaemoglobinaemia, systemic malignancies – includes potential risk of carcinogenic potential of 2, 6-xylidine and *o*-toluidine)
	Potential for off label use
Missing information	Use in men whose sexual partner may be pregnant
	Long term clinical safety
	Patients older than 65 years

The PRAC agreed.

- **Pharmacovigilance plans**

Table 2.2: Ongoing and planned studies in the PhV development plan

Activity/Study title (category 1-3)*	Objectives	Safety concerns addressed	Status	Date for submission of interim or final reports (planned or actual)
Drug utilisation study (non-interventional)	Characterise real clinical practice and the patients who are prescribed the product. Study will investigate off label use and other parameters	Potential for off label use	Planned	

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are specific obligations
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

The PRAC, having considered the data submitted, was of the opinion that the proposed post-authorisation PhV development plan is not sufficient to identify and characterise the risks of the product and the MAA should perform as an additional PV measure detailed in the RMP an updated Drug utilisation study aimed to characterise real clinical practice and the patients who are prescribed the product. This study should take into account the following:

- The sample should be representative of the prescription patterns of the product in real life conditions. The proposed sample size should be stated.

- The potential bias introduced by a selection of investigators should be specifically addressed and prevented in the study design.

- A design including a full retrospective collection of data using existing data sources would be a valid approach.

- The detailed description of the information that will be collected will depend on the data source and amended as appropriate.

Further minor amendments to the PhV plan are detailed in section 4.

The PRAC also considered that routine PhV is sufficient to monitor the effectiveness of the risk minimisation measures.

- **Risk minimisation measures**

Table 2.4: Summary table of Risk Minimisation Measures

Safety concern	**Erectile Dysfunction**
Objective(s) of the risk minimisation measures	To inform prescriber and patient of level of risk.
Routine risk minimisation measures	(Proposed) text in SmPC: • Increased risk with condom use highlighted in section 4.4: Precautions for use A higher rate of erectile dysfunction and male genital hypoaesthesia may be experienced when using Lidocaine/Prilocaine Plethora with male condoms. • Described as one of most frequent of ADRs in male patients in section 4.8: Summary of the safety profile The most frequent adverse reactions reported with the use of this medicinal product in male patients were local effects of genital hypoaesthesia (4.5%) and erectile dysfunction (4.4%). These adverse reactions caused discontinuation of treatment in 0.2% and 0.5% of patients, respectively. • Listed in section 4.8 under frequency category of "Common". (Proposed) text in Package Leaflet: • Increased incidence with condom use highlighted in section 2: **Other medicines and Lidocaine/Prilocaine Plethora** If you use Lidocaine/Prilocaine Plethora with condoms, you may be more likely to be unable to develop or maintain an erection. • Listed as "Common" side-effect as "Inability to develop or maintain an erection" in section 4.
	Comment (e.g. on any differences between SmPCs): Not applicable.

	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s)	Objective and justification of why needed.

Safety concern	**Erectile Dysfunction**
(repeat as necessary): None	
	Proposed actions/components and rationale

Safety concern	**Inadvertent trauma secondary to hypoaesthesia (including application to unintended sites including eyes, oral cavity and anus)**
Objective(s) of the risk minimisation measures	To ensure prescriber and patient/sexual partner are aware of risk and are informed of precautions that will minimise the risk.

Routine risk minimisation measures	(Proposed) text in SmPC • Precautions for use included in section 4.4: Care should be taken not to allow Lidocaine/Prilocaine Plethora to come in contact with the eye, as it may cause eye irritation. Also the loss of protective reflexes can permit corneal irritation and potential abrasion. Absorption of Lidocaine/Prilocaine Plethora in conjunctival tissues has not been determined. If contact with the eye occurs, immediately rinse the eye with water or sodium chloride solution and protect it until sensation returns. Lidocaine/Prilocaine Plethora sprayed onto mucous membranes of the patient or their partner, such as the mouth, nose and throat, or transferred onto female genitalia or anal lining, could be absorbed and temporary local numbness/anaesthesia is likely to result. This hypoaesthesia may mask normal pain sensations and, therefore, increase the dangers of localised injury. A higher rate of erectile dysfunction and male genital hypoaesthesia may be experienced when using Lidocaine/Prilocaine Plethora with male condoms. • Described as one of most frequent of ADRs in male patients and female partners in section 4.8: Summary of the safety profile The most frequent adverse reactions reported with the use of this medicinal product in male patients were local effects of genital hypoaesthesia (4.5%) and erectile dysfunction (4.4%). These adverse reactions caused discontinuation of treatment in 0.2% and 0.5% of patients, respectively. The most frequent adverse reactions reported

Safety concern	**Inadvertent trauma secondary to hypoaesthesia (including application to unintended sites including eyes, oral cavity and anus)**

	with the use of this medicianl product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects. • Listed in section 4.8 under frequency category of “Common”. (Proposed) text in Package Leaflet: • Warnings and precautions included in section 2: When you use this medicine, particularly during priming of the container, aim the container away from the face to avoid accidental contact with ears, eyes, nose and mouth. If some medicine accidentally gets into your eyes or your partner’s eyes, rinse them immediately with cold water or saline solution and cover them gently until any effects, such as numbness, wear off. Be aware that normal protective mechanisms, such as blinking, or sensation of a foreign body in the eye, may not occur until the numbness has worn off. Lidocaine/Prilocaine Plethora may also come into contact with other mucous membranes such as your, or your partner’s, mouth, nose and throat, causing them to feel slightly numb for a short while. As this will reduce the ability to feel pain in these areas, extra care should be taken not to injure them until the numbness has worn off. During sexual intercourse, a small amount of this medicine may be transferred e.g. to the vagina or the anus. Therefore, both partners may feel slight numbness for a short while and should take care not to injure themselves, particularly during sexual activity. • Increased incidence of hypoaesthesia with condom use highlighted in section 2: **Other medicines and Lidocaine/Prilocaine Plethora** If you use Lidocaine/Prilocaine Plethora with condoms, you may be more likely to be unable to develop or maintain an erection. You may also be more likely to have reduced feeling in and around the penis. • Listed in section 4 as “Common” side-

Safety concern	**Inadvertent trauma secondary to hypoaesthesia (including application to unintended sites including eyes, oral cavity and anus)**
	effects of: o "Reduced feeling in and around the penis" in male patients. o "Reduced feeling in and around the vagina" in female patients.
	Comment (e.g. on any differences between SmPCs); Not applicable.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary): None	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Partner exposure (leading to application site reactions, hypersensitivity reactions, trauma secondary to hypoaesthesia)**
Objective(s) of the risk minimisation measures	(i) To prevent use of PSD502 by patients/sexual partners who are hypersensitive to any of the ingredients in PSD502 or who have a known hypersensitivity to amide local anaesthetics (ii) To inform prescriber and patient/sexual partner of the risks (and inform of precautions that will minimise the risk of secondary trauma)
Routine risk minimisation measures	(Proposed) text in <u>SmPC</u> • Section 4.3 lists the following contraindications: o Hypersensitivity of the patient or their partner to the active substances or to any of the excipients listed in section 6.1; o Patients or their partner with a known history of sensitivity to local anaesthetics of the amide type. • Section 4.4 contains the following warning: <u>Hypersensitivities</u> Patients allergic to paraaminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine; however, Lidocaine/Prilocaine Plethora should be used with caution in patients with a history (or partner with a history) of

Safety concern	Partner exposure (leading to application site reactions, hypersensitivity reactions, trauma secondary to hypoaesthesia)
	sensitivities to medicinal products, especially if the aetiologic agent is uncertain. • Vulvovaginal burning sensation described as one of most frequent of ADRs in female partners in section 4.8: <u>Summary of the safety profile</u> The most frequent adverse reactions reported with the use of this medicinal product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects. • Listed in section 4.8 under frequency category of "Common". (Proposed) text in <u>Package Leaflet</u> • The following information is included in section 2: **Do not use Lidocaine / Prilocaine Plethora** o if you or your sexual partner are allergic to lidocaine or prilocaine or any of the other ingredients of this medicine (listed in section 6); o if you or your sexual partner have a history of allergy or sensitivity to other local anaesthetics with a similar structure (known as amide-type local anaesthetics). **Warnings and precautions** Talk to your doctor or pharmacist before using Lidocaine/Prilocaine Plethora o if you have a history of medicine sensitivities, especially if you are not certain which medicine causes sensitivity; • Section 4 lists "Common" side-effect of "Feeling of burning in and around the vagina" For "trauma secondary to hypoaesthesia", please see table, above.
	Comment (e.g. on any differences between SmPCs): Not applicable

	Other routine risk minimisation measures: Prescription only medicine

Safety concern	**Partner exposure (leading to application site reactions, hypersensitivity reactions, trauma secondary to hypoaesthesia)**
Additional risk minimisation measure(s) (repeat as necessary): None	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Effect on fertility**
Objective(s) of the risk minimisation measures	To inform prescriber and patient/sexual partner, so that PSD502 is not used, unless necessary for penetration, in those planning to conceive.

Routine risk minimisation measures	(Proposed) text in SmPC • The following information is included in section 4.6: Women of childbearing potential / contraception in male and females Patients hoping to achieve conception should either avoid using Lidocaine/Prilocaine Plethora, or, if it is essential to achieve penetration, should wash the glans penis as thoroughly as possible prior to intercourse. Fertility There are no adequate data from the use of lidocaine and prilocaine on fertility in humans. A study in rats showed that Lidocaine/Prilocaine Plethora caused a reduction in sperm motility. This medicinal product may reduce the possibility of pregnancy, but should not be used as a contraceptive. • The following information is included in section 5.3: Effect on fertility In an *in vitro* study of rats Lidocaine/Prilocaine Plethora has shown a reduction in sperm motility when 22.5 mg lidocaine and 7.5 mg prilocaine (i.e. the amount of 1 human dose) was in direct contact with rat sperm. However this study did not reproduce the circumstances of clinical use, as the concentration of Lidocaine/Prilocaine Plethora in direct contact with the sperm would be many fold lower. The potential for reduction of sperm motility following the clinical use of Lidocaine/Prilocaine the medicinal product cannot be excluded; therefore it is not possible to state whether Lidocaine/Prilocaine Plethora would prevent pregnancy. (Proposed) text in Package Leaflet • The following information is included in section 2:

Safety concern	**Effect on fertility**
	Pregnancy, breast-feeding and fertility Fertility Lidocaine/Prilocaine Plethora may reduce the possibility of pregnancy, but is not a reliable contraceptive. Therefore patients hoping to achieve conception should either avoid using Lidocaine/Prilocaine Plethora, or, if this medicine is essential to achieve penetration, should wash the penis as thoroughly as possible five minutes after Lidoacine/Prilocaine Plethora has been applied, but prior to intercourse.

	Comment (e.g. on any differences between SmPCs): Not applicable.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary): None	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Interference with contraception**
Objective(s) of the risk minimisation measures	To prevent use of PSD502 with polyurethane based barrier contraceptives by patients/sexual partners.
Routine risk minimisation measures	(Proposed) text in SmPC: The following information is provided in section 4.4: Deterioration was observed when Lidocaine/Prilocaine Plethora was used with polyurethane-based female and male condoms. The medicinal product has been tested with the following forms of barrier contraceptives (samples of each type have been specifically tested) and no damage to the contraceptive was detected (list provided). (Proposed) text in Package Leaflet: The following wording is contained in section 2: **Warnings and precautions** Any barrier contraceptives (e.g. male or female condom), which are made from polyurethane-based material cannot be guaranteed to protect against disease or pregnancy when you are also using Lidocaine/Prilocaine Plethora.

Safety concern	**Interference with contraception**
	Lidocaine/Prilocaine Plethora had no damaging effect on the following types of barrier contraceptives during testing (list provided). Check the material that your contraceptive or your partner's contraceptive is made of. Ask your pharmacist if you are unsure.
	Comment (e.g. on any differences between SmPCs): Not applicable

	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary): None	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Hypersensitivity**
Objective(s) of the risk minimisation measures	To prevent use of PSD502 by patients/sexual partners who are hypersensitive to any of the ingredients in PSD502 or who have a known hypersensitivity to amide local anaesthetics.
Routine risk minimisation measures	See table above on “Partner exposure”
	Comment (e.g. on any differences between SmPCs): Not applicable.
	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s): None (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Carcinogenicity at the application site**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	(Proposed) text in SmPC <E.g. Dose reduction for ……. in section 4.2 of the SPC…….. Warning in section 4.4 to…… Listed in section 4.8>
	Comment (e.g. on any differences between

Safety concern	**Carcinogenicity at the application site**
	SmPCs)
	Other routine risk minimisation measures Prescription only medicine
Additional risk minimisation measure(s): None (repeat as necessary)	Objective and justification of why needed.

	Proposed actions/components and rationale

Safety concern	**Systemic exposure leading to systemic reactions (e.g. methaemoglobinaemia, systemic malignancies)**
Objective(s) of the risk minimisation measures	(i) None proposed for "systemic exposure"; (ii) Warnings on potential risk of methaemoglobinaemia and other known systemic toxicities (including drug interactions), is provided for prescriber and user to minimise use in patients and their sexual partners who may be at risk. Symptoms of potential systemic toxicities and treatments are outlined to promote prompt treatment, if reactions should occur.
Routine risk minimisation measures	(Proposed) text in SmPC: Warnings included in following sections: • section 4.4: Anaemia related conditions Patients or their partner with glucose-6-phosphate dehydrogenase deficiency or congenital or idiopathic methaemoglobinaemia are more susceptible to medicinal product-induced methaemoglobinaemia (see section 4.5). Although the systemic availability of prilocaine by cutaneous absorption of Lidocaine/Prilocaine Plethora is low, caution should be exercised in patients with anaemia, congenital or acquired methaemoglobinaemia or patients on concomitant therapy known to produce such conditions. Patients with severe hepatic impairment Patients with severe hepatic disease, because of their inability to metabolise local anaesthetics normally, are at greater risk of developing toxic

Safety concern	**Systemic exposure leading to systemic reactions (e.g. methaemoglobinaemia, systemic malignancies)**

	• section 4.5: Methaemoglobinaemia may be accentuated in patients already taking medicinal products known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, metoclopramide, naphthalene, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, pamaquine, para-aminosalicylic acid, phenobarbital, phenytoin, primaquine and quinine (see section 4.4). The risk of additional systemic toxicity should be considered when large doses of Lidocaine/Prilocaine Plethora are applied to patients already using other local anaesthetics or structurally related medicinal products e.g. class I anti-arrhythmics such as mexiletine. Specific interaction studies with lidocaine/prilocaine and anti-arrhythmic medicinal products class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4). Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given intravenously in repeated high doses over a long time period (30 hours). • Symptoms of systemic toxicities and treatments are included in section 4.9: Prilocaine in high doses may cause an increase in the methaemoglobin level particularly in conjunction with methaemoglobin-inducing agents (e.g. sulphonamides). Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylthioninium chloride. Should other symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression. Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive medicinal products. (Proposed) text in <u>Package Leaflet:</u>

Safety concern	Systemic exposure leading to systemic reactions (e.g. methaemoglobinaemia, systemic malignancies)
	• Warnings and precautions are provided in section 2: Talk to your doctor or pharmacist before using Lidocaine/Prilocaine Plethora - if you, or your sexual partner, have been diagnosed with a genetic disease or other condition affecting your red blood cells (glucose-6-phosphate deficiency, anaemia or methaemoglobinaemia) - if you have a history of medicine sensitivities, especially if you are not certain which medicine causes sensitivity - if you suffer from severe liver problems • Other medicines which may interact with PSD502 or increase the risk of methaemoglobinaemia are listed in section 2 under heading **Other medicines and Lidocaine/Prilocaine Plethora** • Symptoms of systemic toxicity are provided in section 3: **If you use more Lidocaine/Prilocaine than you should** Symptoms of using too much Lidocaine/Prilocaine Plethora are listed below. Contact your doctor or pharmacist if you experience any of these. They are very unlikely to happen if it is used as instructed: • Feeling light-headed or dizzy • Tingling of the skin around the mouth and numbness of the tongue • Abnormal taste • Blurred vision • Ringing in the ears • There is also a risk of a disorder reducing the amount of oxygen in the blood (methaemoglobinaemia). This is more likely when certain medicines have been taken at the same time. If this happens, the skin becomes bluish-grey due to a lack of oxygen. In serious cases of overdose, symptoms may include fits, low blood pressure, slowed breathing, stopped breathing and altered heart beat. These effects may be life-threatening.
	Comment (e.g. on any differences between SmPCs): Not applicable.
	Other routine risk minimisation measures: Prescription only medicine

Safety concern	**Systemic exposure leading to systemic reactions (e.g. methaemoglobinaemia, systemic malignancies)**
Additional risk minimisation measure(s) (repeat as necessary): None	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Potential for off label use**
Objective(s) of the risk minimisation measures	To prevent PSD502 being prescribed or used off-label
Routine risk minimisation measures	(Proposed) text in SmPC: The indication is clearly stated in the SPC in: • section 4.1: Lidocaine/Prilocaine Plethora is indicated for the treatment of primary premature ejaculation in adult men. • section 4.2 *Paediatric population* There is no relevant use of Lidocaine/Prilocaine Plethora in the paediatric population in the indication: treatment of primary premature ejaculation in adult men. (Proposed) text in Package Leaflet • The indication is clearly stated in section 1: Lidocaine/Prilocaine Plethora is indicated for the treatment of lifelong premature ejaculation in adult men. • The following warning is provided in section 2: **Children and adolescents** Do not give this medicine to children or adolescents under 18 years of age.
	Comment (e.g. on any differences between SmPCs): Not applicable
	Other routine risk minimisation measures: Prescription only medicine

Additional risk minimisation measure(s): None	Objective and justification of why needed.

Safety concern	**Potential for off label use**
(repeat as necessary)	
	Proposed actions/components and rationale

Safety concern	**Use in men whose partner may be pregnant**
Objective(s) of the risk minimisation measures	To prevent use in men with pregnant partners.

Routine risk minimisation measures	(Proposed) text in SmPC The following information is provided to the prescriber: • section 4.6: Pregnancy There are no or limited amount of data from the use of lidocaine and prilocaine in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Lidocaine/Prilocaine Plethora during pregnancy unless effective male barrier contraceptive measures are taken in order to avoid potential foetal exposure.. • Section 5.3: Reproductive toxicity *Lidocaine* No teratogenic effects were observed in studies of embryonic/foetal development in rats and rabbits receiving doses during organogenesis. Embryotoxicity was observed in rabbits at doses toxic to the mother. The postnatal survival time of the offspring of rats treated during pregnancy and lactation with a dose toxic to the mother was shown to be reduced. *Prilocaine* In a study of pregnant rats receiving a combination of lidocaine and prilocaine during organogenesis, no effects on embryonic/foetal development were observed. There are however no systemic exposure data available for comparison with clinical exposure. (Proposed) text in Package Leaflet: The following information is provided to the patient in section 2: Pregnancy Lidocaine/Prilocaine Plethora is not recommended for use whilst your partner is pregnant, unless you

Safety concern	**Use in men whose partner may be pregnant**
	exposure of the unborn child.
	Comment (e.g. on any differences between SmPCs): Not applicable

	Other routine risk minimisation measures: Prescription only medicine
Additional risk minimisation measure(s): None (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale

Safety concern	**Long term clinical safety**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	(Proposed) text in SmPC <E.g. Dose reduction for ……. in section 4.2 of the SPC…….. Warning in section 4.4 to…… Listed in section 4.8>
	Comment (e.g. on any differences between SmPCs)
	Other routine risk minimisation measures Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale
	Proposed actions/components and rationale

Safety concern	**Patients older than 65 years**
Objective(s) of the risk minimisation measures	None proposed
Routine risk minimisation measures	(Proposed) text in SmPC <E.g. Dose reduction for ……. in section 4.2 of the SPC…….. Warning in section 4.4 to…… Listed in section 4.8>
	Comment (e.g. on any differences between SmPCs)

Safety concern	Patients older than 65 years
	Other routine risk minimisation measures Prescription only medicine
Additional risk minimisation measure(s) (repeat as necessary)	Objective and justification of why needed.
	Proposed actions/components and rationale
	Proposed actions/components and rationale

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	The most frequent adverse reactions reported with the use of this medicinal product in male patients were local effects of genital hypoaesthesia (4.5%) and erectile dysfunction (4.4%). These adverse reactions caused discontinuation of treatment in 0.2% and 0.5% of patients, respectively. The most frequent adverse reactions reported with the use of this medicianl product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects. • Listed in section 4.8 under frequency category of "Common". (Proposed) text in Package Leaflet: • Warnings and precautions included in section 2: When you use this medicine, if some accidentally gets into your eyes or your partner's eyes, rinse them immediately with cold water or saline solution and cover them gently until any effects, such as numbness, wear off. Be aware that normal protective mechanisms, such as blinking, or awareness of a foreign body in the eye, may not occur until the numbness has worn off. Lidocaine/Prilocaine Plethora may also come into contact with other mucous membranes such as your, or your partner's, mouth, nose and throat, causing them to feel slightly numb for a short while. As this will reduce the ability to feel pain in these areas, extra care should be taken not to injure them until the numbness has worn off. During sexual intercourse, a small amount of this medicine may be transferred e.g. to the vagina or the anus. Therefore, both partners may feel slight numbness for a short while and should take care not to injure themselves, particularly during sexual activity. • Increased incidence of hypoaesthesia with condom use highlighted in section 2:	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Other medicines and Lidocaine/Prilocaine Plethora If you use Lidocaine/Prilocaine Plethora with condoms, you may be more likely to be unable to develop or maintain an erection. You may also be more likely to have reduced feeling in and around the penis. • Listed in section 4 as "Common" side-effects of: o "Reduced feeling in and around the penis" in male patients. o "Reduced feeling in and around the vagina" in female patients. Other routine risk minimisation measures: Prescription only medicine	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Partner exposure (leading to application site reactions, hypersensitivity reactions, trauma secondary to hypoaesthesia)	(Proposed) text in SmPC • Section 4.3 lists the following contraindications: ○ Hypersensitivity of the patient or their partner to the active substances or to any of the excipients listed in section 6.1; ○ Patients or their partner with a known history of sensitivity to local anaesthetics of the amide type. • Section 4.4 contains the following warning: Hypersensitivities Patients allergic to paraaminobenzoic acid derivatives (procaine, tetracaine, benzocaine, etc.) have not shown cross sensitivity to lidocaine and/or prilocaine; however, Lidocaine/Prilocaine Plethora should be used with caution in patients with a history (or partner with a history) of sensitivities to medicinal products, especially if the aetiologic agent is uncertain. • Vulvovaginal burning sensation described as one of most frequent of ADRs in female partners in section 4.8: Summary of the safety profile The most frequent adverse reactions reported with the use of this medicinal product in female partners were vulvovaginal burning sensation (3.9%), and genital hypoaesthesia (1.0%). Vulvovaginal discomfort or burning sensation caused discontinuation of treatment in 0.3% of subjects. • Listed in section 4.8 under frequency category of "Common". (Proposed) text in Package Leaflet • The following information is included in section 2: **Do not use Lidocaine/Prilocaine Plethora** ○ If you or your sexual partner are allergic to lidocaine or prilocaine or any of the other ingredients of	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	this medicine (listed in section 6). ○ If you or your sexual partner have a known history of allergy or sensitivity to local, amide-type anaesthetics. **Warnings and precautions** Talk to your doctor or pharmacist before using Lidocaine/Prilocaine Plethora ○ if you have a known history of medicine sensitivities, especially if you are not certain which medicine causes sensitivities, especially if you are not certain which medicine causes sensitivity • Section 4 lists "Common" side-effect of "Feeling of burning in and around the vagina" For "trauma secondary to hypoaesthesia", please see column, above. Other routine risk minimisation measures: Prescription only medicine	
Effect on fertility	(Proposed) text in <u>SmPC</u> • The following information is included in section 4.6: <u>Women of childbearing potential / contraception in male and females</u> Patients hoping to achieve conception should either avoid using Lidocaine/Prilocaine Plethora, or, if it is essential to achieve penetration, should wash the glans penis as thoroughly as possible prior to intercourse. <u>Fertility</u> There are no adequate data from the use of lidocaine and prilocaine on fertility in humans. A study in rats showed that Lidocaine/Prilocaine Plethora caused a reduction in sperm motility. This medicinal product may reduce the possibility of pregnancy, but should not be used as a contraceptive. • The following information is included in section 5.3: <u>Effect on fertility</u> In an *in vitro* study of rats	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medicinal products known to induce the condition, e.g. sulphonamides, acetanilid, aniline dyes, benzocaine, chloroquine, dapsone, metoclopramide, nitrates and nitrites, nitrofurantoin, nitroglycerin, nitroprusside, para-aminosalicylic acid, phenacetin, phenobarbital, phenytoin, primaquine, quinine (see section 4.4). The risk of additional systemic toxicity should be considered when large doses of Lidocaine/Prilocaine Plethora are applied to patients already using other local anaesthetics or structurally related medicinal products e.g. class I anti-arrhythmics such as mexiletine. Specific interaction studies with lidocaine/prilocaine and anti-arrhythmic medicinal products class III (e.g. amiodarone) have not been performed, but caution is advised (see also section 4.4). Medicinal products that reduce the clearance of lidocaine (e.g. cimetidine or betablockers) may cause potentially toxic plasma concentrations when lidocaine is given intravenously in repeated high doses over a long time period (30 hours). • Symptoms of systemic toxicities and treatments are included in section 4.9: Prilocaine in high doses may cause an increase in the methaemoglobin level particularly in conjunction with methaemoglobin-inducing agents (e.g. sulphonamides). Clinically significant methaemoglobinaemia should be treated with a slow intravenous injection of methylthioninium chloride. Should other symptoms of systemic toxicity occur, the signs are anticipated to be similar in nature to those following the administration of local anaesthetics by other routes. Local anaesthetic toxicity is manifested by symptoms of nervous system excitation and, in severe cases, central nervous and cardiovascular depression. Severe neurological symptoms (convulsions, CNS depression) must be treated symptomatically by respiratory support and the administration of anticonvulsive medicinal products.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	(Proposed) text in Package Leaflet: • Warnings and precautions are provided in section 2: Talk to your doctor or pharmacist before using Lidocaine/Prilocaine Plethora - if you, or your sexual partner, have been diagnosed with a genetic disease or other condition affecting your red blood cells (glucose-6-phosphate deficiency, anaemia or methemoglobinaemia) - if you have a known history of medicine sensitivities, especially if you are not certain which medicine causes sensitivity - if you suffer from severe liver problems • Other medicines which may interact with PSD502 or increase the risk of methaemoglobinaemia are listed in section 2 under heading **Other medicines and Lidocaine/Prilocaine Plethora** • Symptoms of systemic toxicity are provided in section 3: **If you use more Lidocaine/Prilocaine than you should** Symptoms of using too much Lidocaine/Prilocaine Plethora are listed below. Contact your doctor or pharmacist if you experience any of these. They are very unlikely to happen if it is used as instructed: • Feeling light-headed or dizzy • Tingling of the skin around the mouth and numbness of the tongue • Abnormal taste • Blurred vision • Ringing in the ears • There is also a risk of a disorder reducing the amount of oxygen in the blood (methaemoglobinaemia). This is more likely when certain medicines have been taken at the same time. If this happens, the skin becomes bluish-grey due to a lack of oxygen. In serious cases of overdose, symptoms may include fits, low blood pressure,	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	slowed breathing, stopped breathing and altered heart beat. These effects may be life-threatening. Other routine risk minimisation measures: Prescription only medicine	
Potential for off label use	(Proposed) text in SmPC: The indication is clearly stated in the SPC in: • section 4.1: Lidocaine/Prilocaine Plethora is indicated for the treatment of primary premature ejaculation in adult men. • section 4.2 *Paediatric population* There is no relevant use of Lidocaine/Prilocaine Plethora in the paediatric population in the indication: treatment of primary premature ejaculation in adult men. (Proposed) text in Package Leaflet • The indication is clearly stated in section 1: Lidocaine/Prilocaine Plethora is indicated for the treatment of lifelong premature ejaculation in adult men. • The following warning is provided in section 2: **Children and adolescents** Do not give this medicine to children or adolescents under 18 years of age. Other routine risk minimisation measures: Prescription only medicine	None proposed
Use in men whose partner may be pregnant	(Proposed) text in SmPC The following information is provided to the prescriber: • section 4.6: Pregnancy There are no or limited amount of data	None proposed

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	from the use of lidocaine and prilocaine in pregnant women. Animal studies do not indicate reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Lidocaine/Prilocaine Plethora during pregnancy unless effective male barrier contraceptive measures are taken in order to avoid potential foetal exposure.. • Section 5.3: <u>Reproductive toxicity</u> *Lidocaine* No teratogenic effects were observed in studies of embryonic/foetal development in rats and rabbits receiving doses during organogenesis. Embryotoxicity was observed in rabbits at doses toxic to the mother. The postnatal survival time of the offspring of rats treated during pregnancy and lactation with a dose toxic to the mother was shown to be reduced. *Prilocaine* In a study of pregnant rats receiving a combination of lidocaine and prilocaine during organogenesis, no effects on embryonic/foetal development were observed. There are however no systemic exposure data available for comparison with clinical exposure. (Proposed) text in <u>Package Leaflet:</u> The following information is provided to the patient in section 2: <u>Pregnancy</u> Lidocaine/Prilocaine Plethora is not recommended for use whilst your partner is pregnant, unless you use a male condom, as listed above, to prevent exposure of the unborn child. Other routine risk minimisation measures: Prescription only medicine	
Long term clinical safety	None proposed	None proposed
Patients older than 65 years	None proposed	None proposed

The PRAC, having considered the data submitted, was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication.

The CHMP endorsed this advice without changes.

In addition, the CHMP considered that the applicant should take the following minor points into consideration when an update of the Risk management Plan is submitted:

1. The DUS study should not be classified as category 2 and should be categorised as category 3 study. In the milestones a planned date for the submission of the final report should be also provided

2. Table III.5.1 should be a complete overview of all on-going and planed studies in categories 1-3. Routine pharmacovigilance activities should not be included. Therefore, in this case, the only additional PhV activity planned by the MAH that should be included in this table is the Drug Utilization Study.

2.9. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant 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.

3. Benefit-risk balance

Benefits

Beneficial effects

Premature Ejaculation is a sexual dysfunction in men with a significant negative psychological impact leading to distress and reduced sexual satisfaction in both the patient and their partners. Limited therapeutic alternatives are currently available in the EU for this condition. PSD502 is a mixture of two local anaesthetics – lidocaine and prilocaine for the topical treatment of PE.

Two pivotal trials have been provided to support the efficacy and safety of the product. In both trials efficacy was primarily based on the effect on as intravaginal ejaculatory latency time (IELT) and the improvement of the control over ejaculation during sexual intercourse, sexual satisfaction and the reduction of the distress related to ejaculation (IPE domains) addressing the multidimensional profile of the condition. Results showed a statistically significant and clinically relevant effect of PSD502 in objective measures as intravaginal latency time and also perceived as a benefit by the subjects and their partners.

Long-term efficacy data of PSD502 are available coming from the open-label phases of the two pivotal trials and results do not suggest loss of efficacy.

The ease and convenience of application just 5 minutes prior to intercourse would result in increased spontaneity and therefore greater sexual satisfaction.

Uncertainty in the knowledge about the beneficial effects

The pivotal studies have been carried out in heterosexual men who were in a monogamous relationship for at least 3 months prior to study entry. The effect of PSD502 in homosexual men (with single/ multiple partners), and heterosexual men with multiple partners has not been studied. As in the latter case, a psychological element may also be involved, the effect of PSD502 alone may not be sufficient. However based on the results of the studies presented here, there is no reason to believe that PSD502 may not show similar effects in these groups too.

The risk derived from an increased absorption through damaged mucosa or when a condom is used could be of concern. Condoms are widely used as contraceptive measure and/or with casual partners and the lack of information on the effect of condoms on the absorption of PSD502 is of concern. In this respect, the clarifications submitted by the Applicant do not suggest a negative effect on the efficacy or safety profile of the product. However, the limitations of the data provided prevent from reaching valid conclusions on this issue. Given that a higher rate of local numbness and loss of erection could be reasonably expected when condoms are concomitantly used, patients are warned in the Product Information.

Although there are some data on the use of PSD502 at 12 months that do not suggest loss of efficacy the evidence regarding the maintenance of the effect of PSD502 is considered limited. Additionally, only 30 mg dose has been sufficiently studied. No posology recommendation based on clinical data can be offered to subjects requiring dose adjustment in case of reporting insufficient effect or if adverse (tolerability) events occur.

Demographic characteristics do not appear to influence on the response except for the age, younger subjects reporting greater benefit than older patients. However, the limited number of subjects older than 65 years and even 55 years included in clinical trials does not allow to determine if such differences in fact exist. This limitation is reflected in the SmPC.

Risks

Unfavourable effects

The safety profile of Lidocaine/Prilocaine Plethora for both male glans-penis-treated subjects and female partners appears to be benign and manageable since adverse events observed during the clinical trials seem to be expected considering the mechanism of action of both anaesthetics (lidocaine and prilocaine) and the topical administration of this cutaneous solution.

Regarding the safety data presented, the majority of adverse events were local adverse events in the glans penis: hypoaesthesia (4.5%), erectile dysfunction (4.4%), genital burning sensation (1.0%), genital erythema (0.5%) and ejaculation failure (0.3%). Hypoaesthesia, erectile dysfunction and genital burning sensation were considered to be drug-related. In addition, some systemic adverse events such as nasopharyngitis (2.7%), headache (2.3%) and influenza (1.3%) were also observed.

With regards to TEAEs reported for female sexual partners, the commonest were vulvovaginal burning sensation (3.9%), headache (1.9%), influenza (1.2%), nasopharyngitis (1.2%), hypoaesthesia (1.0%), and vulvovaginal discomfort (1.0%). Vulvovaginal burning sensation was the commonest likely drug-related TEAE.

With respect to the SmPC, there are potential risks caused by both anaesthetics that are adequately addressed in the SmPC (sections 4.4 and 4.5). In addition, an appropriate warning related to the compatibility of PSD502 and latex rubber-based contraceptives or polyurethane based contraceptives has been also included in section 4.4 and section 2 of the package leaflet. Moreover, appropriate information regarding fertility, pregnancy and breast-feeding has been implemented by the Applicant in section 4.6 of the SmPC and section 2 of the package leaflet.

Uncertainty in the knowledge about the unfavourable effects

Some uncertainties were detected following Lidocaine/Prilocaine Plethora safety assessment. Despite the reported adverse events that were considered expected taking into account the mechanism of action of both anaesthetics and the topical administration of this cutaneous solution, some issues

related to the prolonged use of PSD502 were requested to be further clarified. Overall, the potential occurrence of methaemoglobinaemia from prilocaine and carcinogenicity risk from *o*-toluidine is extremely unlikely based upon the clinical and non-clinical information provided by the Applicant. Although no cases were reported during clinical trials, these risks cannot be ruled out and is reflected in the RMP. A specific wording is included in product information.
Similarly, a concern related to the potential risks for the foetus in pregnant women was also raised. Given the limited data available, some recommendations are provided in the product information.

Finally, concerns related to the possible effect on male fertility, the inadvertent dosing to other sites (or used in other mucosas) and the potential for off-label use are already included in the RMP. Information concerning the limited number of patients older than 65 years is included in the RMP as missing information. This limitation is adequately reflected in the Product Information.

Benefit-risk balance

Importance of favourable and unfavourable effects

Lidocaine-prilocaine well-established drug combination, with moderate side effects, with a therapeutic innovative local action through spray application that produces “on demand” patient and partner clinical benefits as defined by objective measures (IELT) and domains from patient reported outcomes in the treatment of PE, which is the commonest sexual complaint in men. The innovative local route of administration compared to currently authorised medicinal product for the treatment of PE mean minimises the systemic drug exposure and possibility of systemic side effects.

Benefit-risk balance

A statistically significant and clinically meaningful effect has been shown by PSD502 in the treatment of lifelong PE. It has been observed in objective measures as intravaginal latency time and also perceived as a benefit by the subjects and their partners. Also, indirect comparison to dapoxetine provides supportive results. The lack of sufficient information regarding the efficacy on elderly subjects and the potential risk associated to the concomitant use of condoms is reflected in the Product Information.
Overall, the safety profile of Lidocaine/Prilocaine Plethora for both male glans-penis-treated subjects and female partners appears to be benign and manageable. The local identified risks reported in this dossier were not unexpected. Concerns initially raised regarding metahaemoglobinemia and carcinogenicity potential have been solved and are adequately addressed in the RMP. Concerning the potential risks for the foetus in pregnant women, more detailed recommendations have been provided in the product information. The possible effect on male fertility, the inadvertent dosing to other sites (or used in other mucoses) and the potential for off-label use are included in the RMP. Moreover, the limited number of patients older than 65 years is reflected in the RMP as missing information.

Discussion on the benefit-risk balance

The advantages of this topical formulation in the treatment of PE, including the positive psychological outcomes in the patient and their partners are considered to be much higher than the disadvantages of PSD502 in terms of local adverse effects which are generally manageable. The two active substances in PSD502, Lidocaine/Prilocaine, are well known. The availability of a discrete spray formulation is considered as of added value.

The overall B/R of Lidocaine/Prilocaine Plethora 150 mg/ml + 50 mg/ml cutaneous spray, solution is positive and the application is approvable as the Applicant submitted satisfactory responses to the list of outstanding issues.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Lidocaine/Prilocaine Plethora in the treatment of primary premature ejaculation in adult men is favourable and therefore recommends the granting of the marketing authorisation. Subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.

These conditions fully reflect the advice received from the PRAC.