26 April 2019
EMA/CHMP/266482/2019
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Sixmo

International non-proprietary name: buprenorphine

Procedure No. EMEA/H/C/004743/0000

Note

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

AE	Adverse Event
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
API	Active Pharmaceutical Ingredient
AR	Assessment Report
AS	Active substance
ASI	Addiction Severity Index
ASM	Active Substance Manufacturer
AST	Aspartate aminotransferase
BPN	Buprenorphine
CCS	Container Closure System
CDF	Cumulative Distribution Function
CEP	Certificate of Suitability of the EP
CFU	Colony Forming Units
CGI	Clinical Global Impression
CI	Confidence Interval
CMAs	critical material attributes
CNS	Central Nervous System
CoA	Certificate of Analysis
COWS	Clinical Opioid Withdrawal Score
CPP	Critical Process Parameter
CQA	Critical Quality Attribute
CYP	Cytochrome
CRS	Chemical Reference Substance (official standard)
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSMB	Drug Safety Monitoring Board
EC	European Commission
EDQM	European Directorate for the Quality of Medicines
EE	Efficacy evaluable
EMCDDA	European Monitoring Centre for Drugs and Drug Addiction
EOT	(1) End of Trial, (2) End of Treatment

EP	European Pharmacopeia
EVA	Ethylene Vinyl Acetate Polymer
GC	Gas Chromatography
HIV	Human Immunodeficiency Virus
HPLC	High Performance Liquid Chromatography
ICH	International Conference on Harmonisation
INR	International Normalised Ratio
IPC	In-process control
IR	Infrared
ITT	Intention to treat
IVIVC	*in vitro-in vivo* correlation
KF	Karl Fischer
LDPE	low density polyethylene
LOA	Letter of Access
LOD	Limit of Detection
LOQ	(1) Limit of Quantification, (2) List of Questions
LS	Least Squares
MA	Marketing Authorisation
MAH	Marketing Authorisation Holder
MS	Mass Spectrometry
ND	Not detected
NLT	Not less than
NMT	Not more than
NT	Not tested
OOS	Out of Specifications
OUD	Opioid Use Disorder
PET	polyethylene terephthalate
PI	Principal Investigator
PIP	Paediatric Investigation Plan
PK	Pharmacokinetics
PP	Per protocol
PSD	Particle size distribution
PDE	Permitted Daily Exposure

Ph. Eur.	European Pharmacopoeia
PIL	Patient Information Leaflet
QbD	Quality by Design
QOS	Quality Overall Summary
RH	Relative Humidity
RRT	Relative retention time
RSD	Relative standard deviation
SAE	Serious Adverse Event
SD	Standard Deviation
SE	Standard Error
SEM	Standard error of the mean
SL	Sublingual
SmPC	Summary of Product Characteristics
SOWS	Subjective Opioid Withdrawal Score
TLC	Thin Layer Chromatography
ULN	Upper Limit of Normal
UV	Ultraviolet
VAS	Visual Analogue Scale

1. Background information on the procedure

1.1. Submission of the dossier

The applicant L. Molteni & C. dei Fratelli Alitti Società di Esercizio S.p.A. submitted on 6 November 2017 an application for marketing authorisation to the European Medicines Agency (EMA) for Sixmo, 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 23 February 2017. 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:

Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0131/2017on the granting of a (product-specific) waiver.

Scientific advice

The applicant did not seek Scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: Greg Markey

The application was received by the EMA on	6 November 2017
The procedure started on	23 November 2017
The Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	12 February 2018
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	26 February 2018

The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	22 March 2018
The CHMP agreed on a list of outstanding issues in writing and/or in an oral explanation to be sent to the applicant on	15 November 2018
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	8 November 2018
The outstanding issues were addressed by the applicant during an oral explanation before the CHMP during the meeting on	26 February 2019
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 to Sixmo on	26 April 2019

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Opioid use disorder (OUD) can involve the misuse of prescribed opioid medications, use of diverted opioid medications, or use of illicitly obtained opioids such as heroin.

The psychiatric diagnoses in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) opioid abuse and opioid dependence were replaced by one diagnosis, opioid use disorder, in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

2.1.2. Epidemiology

The average prevalence of high-risk opioid use among adults (15–64) is estimated at 0.4% of the EU population, the equivalent of 1.3 million high-risk opioid users in Europe in 2015. 630,000 opioid users received substitution treatment in the European Union in 2015. Many long-term opioid users in Europe, typically with polydrug use histories, are now aged in their 40s and 50s. Between 2006 and 2015, the mean age of those entering treatment for problems related to opioid use increased by 4 years. 80% of heroin users entering treatment are male and entrants have a mean age of 34 years at first treatment entry (European Drug Report 2017).

Information from drug treatment and other sources indicates that the overall long-term trend in injecting as a route of administration continues to be downward. Among heroin users entering specialised drug treatment for the first time in their life, for example, reports of injecting are now at their lowest point for over a decade, although considerable variation exists between countries.

The latest data show that heroin use still accounts for the majority, around 80%, of new opioid-related treatment demands in Europe. Methadone, buprenorphine and fentanyl together make up another 14% of new opioid-related treatment demands. In addition, the overall decline in treatment demand related to heroin, observed since 2007, is no longer evident (European Drug Report 2017).

While North America has experienced considerable morbidity and mortality associated with the misuse of prescription opioids, rising levels of heroin use and, most recently, the emergence of highly potent synthetic opioids, in particular fentanyl derivatives, differing patterns of use are seen in Europe. One difference between the two regions is that in Europe, very few clients presenting for specialised drug treatment do so for addiction to opioid pain medicines. This probably reflects the different regulatory frameworks and approaches to marketing and prescribing that exist between Europe and the North America. However, the possibility of under-reporting cannot be dismissed, as Europeans experiencing problems with prescription medicines may access different services than those used by illicit drug users.

Medicines used for opioid substitution treatment, however, now play a more significant role in treatment demands and health harms in a number of European countries. Overall, non-heroin opioids account for around a fifth of all opioid-related demands to specialised drug services. The role that synthetic opioids, such as methadone, play in overdose deaths is difficult to quantify at EU level, but in many countries these substances are now important, and in a few countries they predominate. Reducing the misuse of medicines, including those used for opioid substitution treatment, is a growing challenge for many European healthcare providers.

2.1.3. Biologic features

DSM-5 diagnostic criteria for OUD are described below.

A problematic pattern of opioid use leading to clinically significant impairment or distress is manifested by two or more of the following within a 12-month period:

- Opioids are often taken in larger amounts or over a longer period than was intended
- A persistent desire or unsuccessful efforts to cut down or control opioid use
- A great deal of time is spent in activities necessary to obtain the opioid, use the opioid, or recover from its effects
- Craving, or a strong desire or urge to use opioids
- Recurrent opioid use resulting in a failure to fulfill major role obligations at work, school, or home
- Continued opioid use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of opioids
- Important social, occupational, or recreational activities are given up or reduced because of opioid use
- Recurrent opioid use in situations in which it is physically hazardous
- Continued opioid use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance
- Tolerance*
- Withdrawal*

* Experiencing these symptoms while taking opioids solely under appropriate medical supervision is an exception to (does not meet) these criteria for OUD.

The severity of OUD at the time of diagnosis can be specified as a subtype based on the number of criteria present:

- Mild – Two to three criteria
- Moderate – Four to five criteria
- Severe – Six or more criteria

A 2002 United States nationally representative survey found that, of people who had any lifetime use of heroin, 53 percent went on to develop a Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) disorder of heroin abuse or dependence. Persons who try heroin may be a select population that is inherently at higher risk for developing an opioid use disorder (OUD).

A 2015 study of a nationally representative (Australia), community-based sample estimated that 10 to 20 percent of patients prescribed opioids for non-cancer pain control developed a pharmaceutical OUD.

2.1.4. Clinical presentation, diagnosis

Opioid Use Disorder is typically a chronic, relapsing and life-threatening disorder. It is characterized by compulsive opioid use causing significant mental, physical, and social effects, including transmission of infectious diseases such as HIV and Hepatitis B/C, unintentional overdose, criminal activity and

incarceration. Patients presenting with an opioid use disorder (OUD) may appear acutely intoxicated, in opioid withdrawal, or show no acute effects related to their opioid use.

In Europe, opioid-related overdose deaths are increasing with current data indicating that opioids are found in 81% of fatal overdoses here. There are also increasing reports of problems associated with new synthetic opioids and opioid substitution medicines. (European Drug Report 2017).

For persons who develop an OUD, relapse following withdrawal appears to be common, particularly if effective maintenance treatment is not established.

2.1.5. Management

Treatment of opioid dependence involves either long-term opioid substitution or detoxification. Successful long-term abstinence is often unachievable and so long-term treatment with an opioid substitute is frequently required. Opioid dependence often follows a remitting and relapsing course and so harm reduction is the main goal of treatment.

A strong evidence base supports the appropriate use of opioid substitution medicines, which has been shown to reduce morbidity, mortality and offending amongst those receiving it (European Drug Report 2017).

Currently available opioid substitution treatments (e.g. methadone and buprenorphine) are administered orally, usually on a daily basis, to minimise opioid cravings. They can be associated with poor adherence, potential for diversion and misuse, risk of overdose and accidental paediatric exposure. Administration also requires periodic observation by a healthcare professional (HCP), with the frequency of observation being dictated by clinical outcome and stability (weekly, twice weekly versus daily HCP observation).

In Europe, methadone is the most commonly prescribed opioid substitution drug, received by around two thirds (63 %) of substitution clients. A further 35 % of clients are treated with buprenorphine-based medications (European Drug Report 2017).

Buprenorphine is an opioid partial agonist/antagonist which is authorised in Europe for opioid use disorder. It is available in sublingual formulations either as monotherapy or in combination with naloxone.

Sixmo is a subcutaneous implant formulation of buprenorphine hydrochloride, dispersed in a solid matrix of ethylene vinyl acetate polymer (EVA), that is intended to provide continuous delivery of buprenorphine for 6 months. The applicant proposes that Sixmo represents a novel abuse- and diversion-deterrent formulation of buprenorphine that ensures adherence and reduces the cost of and patient inconvenience associated with observed dosing.

About the product

Each Sixmo implant contains buprenorphine hydrochloride (equivalent to 74.2 mg of buprenorphine). Buprenorphine is an opioid partial agonist/antagonist with binds to the μ and ƙ receptors of the brain. Its activity in opioid maintenance treatment is attributed to its slowly reversible properties with the μ receptors which, over a prolonged period, minimises opioid cravings.

Type of Application and aspects on development

This is a Centralised Procedure in accordance with Article 8(3) of Directive 2001/83/EC. The applicant has requested consideration under Annex 3(2)(b) of Regulation (EC) No 726/2004 "Significant innovation or interest of patients at EU level".

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as implant containing 80 mg of the active substance (AS) buprenorphine hydrochloride, equivalent to 74.2mg free base. Each implant measures ~26 mm in length and ~2.5 mm in diameter.

The other ingredient is ethylene vinyl acetate copolymer.

Each Sixmo implant is packaged individually into a PET/LDPE/Alu/LDPE-peelable foil laminated sachet and provided with an individually packaged applicator as described in section 6.5 of the SmPC.

2.2.2. Active Substance

General information

The chemical name of buprenorphine hydrochloride is (2S)-2-[17-(Cyclopropylmethyl)-4,5α-epoxy-3-hydroxy-6-methoxy-6α,14-ethano-14α-morphinan-7α-yl]-3,3-dimethylbutan-2-ol hydrochloride corresponding to the molecular formula $C_{29}H_{42}ClNO_4$. It has a relative molecular mass 504.1 and has the structure shown in Figure 1.

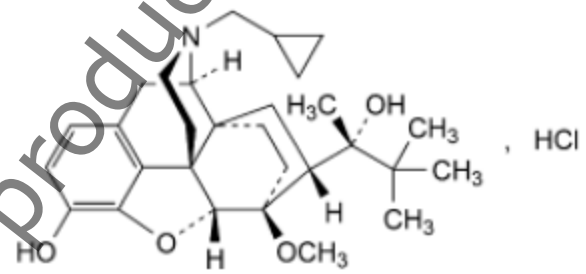


Figure 1 Structure of buprenorphine hydrochloride

As per Ph. Eur. monograph 1181, buprenorphine hydrochloride appears as a white or almost white, crystalline powder, sparingly soluble in water, freely soluble in methanol, soluble in ethanol (96 per cent), practically insoluble in cyclohexane.

Buprenorphine hydrochloride has the 2S configuration and is controlled by specific optical rotation according to the Ph. Eur. monograph. Polymorphism is not referred in the monograph but it is noted from the literature that buprenorphine does not exhibit polymorphism and processing conditions are such that it is unlikely a new polymorph would be formed.

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

Manufacture, characterisation and process controls

The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability.

The CEP specifies storage in a double polyethylene bags placed in either an aluminium can or a multilayer aluminium bag.

Specification

The active substance specification is based on the Ph. Eur. monograph and includes tests for appearance, identification (IR, chloride test), appearance of solution (Ph. Eur.), acidity or alkalinity (Ph. Eur.), specific optical rotation (Ph. Eur.), related substances (HPLC), loss on drying (Ph. Eur.), assay (HPLC), residual solvents (GC). In addition to the tests required by the Ph. Eur., the following tests are included in the specification: sulphated ash (Ph. Eur.), particle size (laser diffraction), microbial enumeration (Ph. Eur.) and endotoxins (Ph. Eur.).

Due to the nature of the substance and its intended use, lower acceptance criteria than those outlined in Ph. Eur. 5.1.4 have been chosen for microbial enumeration. Endotoxin limit has been set considering Ph. Eur. 5.1.10. <85>.

All additional methods have been adequately validated and described according to ICH Q2. The in-house method for determination of related compounds and residual solvents are based on the EP monograph method for chromatographic purity of buprenorphine hydrochloride. The test method is part of the submitted CEP. The particle size distribution method using a laser diffraction instrument has been validated.

Stability

A retest period of 60 months is specified in the CEP.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Sixmo is an implant containing 80 mg of the active substance (AS) buprenorphine hydrochloride, equivalent to 74.2mg free base, in an ethylene vinyl acetate copolymer (EVA) matrix. Each implant measures ~26 mm in length and ~2.5 mm in diameter. The total weight of each implant is 112 mg. Implants are individually packaged into laminated foil sachets. The sachets are terminally sterilized by irradiation with ionising radiation. The composition is simple, consisting of the active substance and excipient/polymer matrix (EVA).

Sixmo was developed to provide a sustained release formulation of buprenorphine hydrochloride (BPN) in an ethylene vinyl acetate (EVA) matrix. The target Sixmo formulation was to meet the following criteria:
• a steady-state delivery of BPN
• stable plasma levels for the entire treatment period
• extended treatment period (target of approximately 6 months per administration)
The development program focused on the target product profile and respective critical quality attributes (CQA) listed in Table 1. The CQA ensure the quality, safety and the efficacy of Sixmo implant.

Table 1 Quality Target Product Profile (QTPP) and Critical Quality Attributes (CQA)

Quality Target Product Profile	Critical Quality Attributes
Ease of Product Identification: Drug Product Dosage Strength	Appearance Identity
Efficacy and In-vivo Performance: Target Probuphine® formulation will exhibit a sustained therapeutic Buprenorphine plasma profile with low fluctuation when dosed six months.	Assay Content Uniformity Dissolution
Safety	Residual Solvents Related Substances(Impurities / Degradants) Sterility Endotoxin level

Implants were designed to be administered subcutaneously and deliver a desired sustained release profile for a period of 6 months; therefore, the following characteristics were considered in the formulation design and development:

• High drug loading to enable minimal number of implant(s) administered.

• Release characteristics that provide continuous steady-state profile for the six-month term of treatment.

• Manufacturing process that is robust, reproducible, and can be easily scaled up to commercial scale.

• Physical attributes and sufficient durability to allow the administration of the implants subcutaneously as well as removal of the implants after the six month treatment period.

• Sufficient stability in the subcutaneous physiological conditions.

• Stable formulation with biocompatible components.

Implants with the above characteristics can be formulated with hot melt extrusion technology in which the drug particles are homogenously distributed in the polymer matrix. EVA was selected as the inert polymer matrix material because it is an excipient which is used in products authorized in the European Union and is also included in the FDA Inactive Ingredient Guide (IIG), it is used widely in controlled and sustained release products and it is non-erodible, allowing easier removal of the implant from the patient at any time during the treatment duration.

The EVA used in Sixmo has been fully characterised for identity, physical properties, and biocompatibility. It is considered that EVA has minimal potential of biological reactivity *in vivo*. Compatibility of the active substance with the excipient is evidenced by finished product stability data.

The excipient is a well-known pharmaceutical ingredient and their quality is compliant with In house standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report

Both the Sixmo and placebo implants have been evaluated for safety and potential adverse effects in preclinical chronic toxicology studies in dogs and in human clinical trials. Long-term animal studies conducted with the implant are considered to have adequately qualified the impurities under conditions which mimic human usage. No information was identified in the scientific literature which indicated that any of the impurities would be toxic at the anticipated exposure levels in patients. To fully assess the

potential exposure to humans from these implants, leachables and extractables studies were also performed.

Drug Release Mechanism

BPN particles are uniformly distributed in the matrix of EVA copolymer within the implant structure. During the extrusion process, the melted EVA entraps the BPN particles. Thus, the size and surface of the pore structure formed is mainly a function of the size and surface area of the BPN particles. The matrix consists of both closed and open pore structures. In the closed pore structure, the BPN particles are trapped/enclosed completely by the EVA, whereas in the open pore structure, the BPN particles are exposed to the fluid media in which the implant is placed. As a result, only the BPN particles in the open pore structure will be released, whereas, the BPN particles in the closed pore structure will not be released unless the EVA matrix is dissolved. Since EVA is insoluble and impermeable in the dissolution media/subcutaneous physiological medium, drug diffusion through the EVA membrane within the implant matrix does not occur. Thus, the EVA serves as an inert excipient that provides rigidity to the implant matrix. The release profile indicates that the release rate is governed initially by surface area of the AS particles exposed to the fluid media in the open pore structure followed by diffusion of the dissolved AS in the open pore structure. Once the implant is exposed to the dissolution media, the AS particles in the pores that are closest to the surface of the implant start dissolving and are released immediately. This is due to the high concentration gradient between the AS particles in the pores closest to the implant surface and the surrounding fluid media outside the implant and results in the initial burst release. The dissolution of AS opens the pore structure further whereby AS particles deep in the pore structure are now accessible to the fluid media. However, due to the narrowness of the pore structure, diffusion of the dissolved AS from deep inside the pore structure to the surface becomes slower after the initial burst release. Once the implants are manufactured an alcohol wash is applied to remove AS on the outside of the implant and to prevent a significant dose dumping effect.

Dissolution method

A discussion on the development of the dissolution parameters has been provided and it has been demonstrated how they were arrived upon. The justification for the choice of dissolution conditions is accepted. The applicant has justified the abbreviated duration of the test by demonstrating that it can discriminate between implants with acceptable and non-acceptable release characteristics.

EMA/CHMP/QWP/428693/2013, which is applicable to oral modified release products but also discusses principles relevant to other modified release dosage forms, notes that adjustments to the properties of a drug product necessitates the development of a dissolution method that can detect changes which may have an effect on the efficacy and safety. This requires a qualitative or quantitative link from pharmacokinetic parameters through *in vivo* drug release to *in vitro* dissolution rate. While the literature suggests that linking *in vitro* dissolution with the *in vivo* release of implants is sometimes possible, in the absence of an IVIVC, the difficulty in establishing a link with the six month implant release profile is acknowledged and there are likely numerous factors beyond simple dissolution involved in the *in vivo* release. The volumes of liquid the implant is exposed to will be greatly reduced in comparison to those volumes in the gastro-intestinal tract (which are relevant to the guideline). In addition, there does not appear to be any advantage in extending the dissolution method timeline. Sampling time points for the QC method were agreed. In conclusion the method is considered suitable for use as a quality control method. Nevertheless since it has not been possible to establish an IVIVC, dissolution testing should be used to control the product's quality and performance but not for future use as justification for significant changes to the product (such as scale-up which may impact the efficacy and safety in ways that the dissolution test will be unable to detect).

Manufacturing process development

The proposed commercial manufacturing process for the implant includes milling of EVA, blending of EVA with the active substance, hot melt extruding of the blend into implants, cutting the implants, weight

sorting, washing, drying, weight sorting, metal detection, packaging, and gamma irradiation. Gamma irradiation was chosen as terminal sterilization method to achieve a sterile product while retaining the product's physio-chemical characteristics.

In order to gain process understanding early in the development program, a phased approach was applied to establish critical material attributes (CMAs) and critical process parameters (CPPs) affecting the process robustness and reproducibility and eventually impact the implant's CQAs. Prior to characterization studies, a risk assessment was conducted based on scientific knowledge and the drug product formulation, measuring the potential impact of key input parameters for each unit operation of the manufacturing process against the proposed CQAs. During process development, high risks for each process were addressed. An initial risk assessment was conducted based on scientific knowledge of the formulation and process, measuring the potential impact of key input parameters for each unit operation of the manufacturing process against the proposed critical quality attributes (CQAs). Using a cause and effects matrix, the relative risk that the process, material attributes, and process parameters was ranked as high, medium, or low. The ranks are assigned according to changes to process step, material attribute, or process parameter impacting CQAs. The CQAs include appearance, implant weight and dimensions, assay, content uniformity, dissolution, related substances, residual solvent, endotoxin and bioburden/sterility. A summary of the risk assessment for each unit operation and associated process parameters was presented. Experimental studies were defined and executed in order to establish additional scientific knowledge and understanding, to allow appropriate controls to be developed and implemented, and to reduce the risk to an acceptable level. After detailed experimentation, the initial manufacturing process risk assessment was updated according with the current process understanding. Based on the different processes selected, the raw material attributes (MAs) that can impact the finished product CQAs have been discussed. Based upon the outcome of product and process understanding studies, including the risk assessment, the control strategy for the manufacturing process was defined. The control strategy may be further refined based on additional experience gained during the commercial lifecycle of the product. No design space is claimed.

The manufacturing process was successfully scaled from small scale initially to pilot scale. Changes in the extrusion equipment and parameters led to a series of improvements in the BPN and EVA blend uniformity, the control of the blend feed rate, the variability in implant weight and thereby the content uniformity, weight and dimensions of the implants. Upscaling to the commercial scale uses the same manufacturing process and equipment to the development and registration/stability batches, except that more material is being processed to complete the batch.

The blending step has been optimised to determine the optimal blend time for an industrial batch. The extrusion process was studied to gain insight on how process variables impact the output material CQAs and interact with each other, and identify potential boundary limits at full scale operation. Finally for the terminal sterilization step, a gamma irradiation study was performed to define the conditions and parameters of the sterilisation step for the routine production. While the gamma process was originally validated as the method of providing the terminally sterilising ionizing radiation, the proposed facility is not available to process Sixmo, therefore all future commercial batches will be processed using the electron beam (e-beam) method at a new site; the relevant GMP documents have been presented. For the e-beam process dose mapping was performed, including packing dimensions and orientation, confirmation of the reference dose and dose ratios, as well as dose range and uniformity. The commercial sterilisation process has been validated. Product batches sterilized by both methods have been evaluated and no significant differences in product characteristics were identified.

The finished product is co-packaged with an applicator sterile medical device for sub-dermal insertion of the implants, intended for single-patient use and forming a single integral product. It consists of 1) a cannula, 2) an insertable stylet (obturator), and 3) a cover (needle guard). The first two components are shown in the figure below. A CE mark has been granted; the provided information is acceptable.

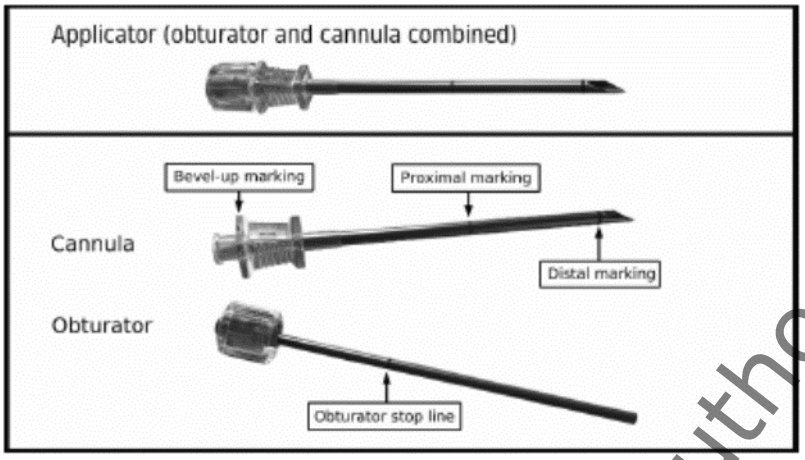


Figure 2 Applicator for sub-dermal insertion:1) a cannula, 2) an insertable stylet (obturator),

Sixmo implants are packaged in a laminated foil pouch which is sealed and then sterilised. The pouch is a laminated foil sachet (pouch) made of the following (from outside to inside): polyethylene terephthalate (PET), low density polyethylene (LDPE), aluminium foil, LDPE, LFP-222 (peelable foil film). Implant kits contain four implants with one applicator. The applied specifications and methods have been provided and are deemed satisfactory. The pouch material complies with Regulations (EC) No 10/201 and (EC) 1935/2004 and with Directive 2002/72/EU. The presented information about the co-packaged applicator is satisfactory (see above).

Manufacture of the product and process controls

Sixmo implants manufacturing process consists of the following main steps includes blending, extrusion, cutting, weight sorting, washing, drying, weight sorting, labelling/pouching, sterilization, final product labelling and secondary packaging. Manufacturing process controls are defined for the process and encompass implant manufacturing, packaging and irradiation. Manufacturing process parameters (both PPs and CPPs) for individual unit operations within the stages implant manufacturing, packaging and irradiation are tabulated, and set-points are defined. The proposed process parameters and CPPs reflect the final control strategy.

The initial process validation data from three batches has been supplemented with respect to the new sterilisation method and re-evaluated in relation to the updated control strategy as per the EMA guideline on Process Validation and it is confirmed that data are valid. Information regarding an engineering qualification batch has been also provided. Three different lots of AS and one lot of EVA were used. Enhanced sampling (statistically justified) and testing was performed during manufacture to ensure product content uniformity and adherence to product specifications. The manufacture process is considered validated.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for appearance (visual), pouch appearance (visual), implant weight, length and diameter, tensile strength (pneumatic grip), content uniformity (Ph. Eur.), identification (HPLC), assay (HPLC), impurities (HPLC), dissolution (apparatus 2, HPLC), ethanol (GC), sterility (Ph. Eur.), endotoxins (Ph. Eur.) and package integrity (dye penetration).

Assay, impurities and endotoxin limits as well as weight and dimensions specification have been satisfactorily justified. The dissolution specification has been justified with reference to the performance of clinical batches. However, as the method cannot be satisfactorily correlated to *in vivo* release, it has been clarified that clinical and/or IVIVC data will be required to justify significant finished product changes in future. The inclusion of a limit for tensile strength at release and stability does provide an additional layer of control for the finished product and further ensures batch-to-batch consistency. An ICH Q3D risk assessment has been provided and no further controls are indicated. Forced degradation studies have been provided in support of the specification. The specification can be considered appropriate to control the quality of the product.

The analytical procedures are presented and have been validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used in the routine analysis of finished product has been presented.

Batch analyses are provided for seven batches at the proposed industrial batch size. All parameters are within the specified limits and consistency among the batches was shown.

Stability of the product

Stability data of six commercial scale batches (including three process validation batches) of Sixmo implants stored in the proposed container closure under long term conditions (25°C±2°C / 60%±5% RH) for up to 60 months and under accelerated conditions (40°C±2°C / 75%±5% RH) for up to 6 months according to the ICH guidelines were provided. These stability batches were sterilised by gamma irradiation procedure.

An additional batch sterilised by the electron-beam intended to be used for all commercial batches has been put into stability. The applicant has provided statistical justification that the mode of sterilisation does not lead to different release characteristics (dissolution and assay). Supporting stability data were used to provide confidence that that there is no statistical difference in assay or dissolution for implants sterilized by electron beam compared to those sterilized by gamma irradiation on stability up to 6 months. In addition, two additional batches sterilised by electron beam will be placed on stability in accordance with the submitted stability protocols.

The following parameters have been investigated: description/appearance, package appearance, assay, dissolution, sterility, endotoxin, package integrity. EVA Impurities Limit Testing has been included at 48 months and 60 months in the stability testing protocol. The methods used were the same as for release testing and are stability indicating. The results of all parameters were within the specifications and no trends were observed. Some variability of the assay was observed but the findings do not appear to be stability-related and it is considered that the introduction of the new assay method and the tightening of the control strategy provide sufficient reassurance.

Photostability studies have been provided on one commercial batch according to ICH Q1B, demonstrating the product is photostable.

In-use studies have not been carried out because they are not applicable considering the nature of the product.

A shelf life of four years with no specified storage conditions, as stated in the SmPC (sections 6.3 and 6.4) is acceptable.

Adventitious agents

The medicinal product does not contain excipients from human or animal origin.

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 applicant has applied QbD principles in the development of the active substance and/or finished product and their manufacturing process. However, no design spaces were claimed for the manufacturing process of the active substance, nor for the finished product. The control strategy of the product has been revised and is considered adequate to ensure consistent quality of the finished product. Given that it has not been possible to establish an IVIVC, any that changes that impact a CQA or the overall control strategy for the finished product will require in vivo studies. The impact of aging on relevant physical properties (such as tensile strength, etc.) has been adequately explored and adequate controls are in place. The applicator, which is co-packaged with the implants, complies with the essential requirements of Directive 93/42/EEC, by provision of a valid CE certificate. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that from a quality perspective 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.

2.2.6. Recommendations for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

Sixmo implants are intended to provide sustained delivery of buprenorphine (BPN) for 6 months for substitution treatment of opioid dependence. The pharmacological characteristics of buprenorphine are well known from non-clinical studies described in the published literature and from clinical experience with other buprenorphine products marketed for the treatment of opioid dependence, and treatment of moderate to severe pain.

Buprenorphine is a derivative of the opioid alkaloid thebaine that is more potent (25 - 40 times) and a longer lasting analgesic than morphine. Buprenorphine possesses mixed agonist-antagonist activity. It appears to act as a partial agonist at mu(μ)-opioid receptors, an antagonist at kappa(κ)-opioid receptors and also as an antagonist at delta(δ)-opioid receptors. The lack of delta-agonist activity has been suggested to account for the observation that buprenorphine tolerance may not develop with chronic use. Buprenorphine binds with high affinity to opioid receptors and has slow rates of opioid receptor association and dissociation, which results in prolonged pharmacodynamic activity and low dependence liability. As a partial μ-receptor agonist with low intrinsic activity at the receptor site, BPN exhibits a “ceiling effect” such that the opioid agonist effects plateau at higher doses, resulting in a low risk of overdose compared with full agonists. Because of its slow onset of action, opioid-dependent patients are less likely to experience sedation or euphoria when taking an appropriate dose. Norbuprenorphine, a dealkylated metabolite of buprenorphine exhibits weak pharmacodynamic activity in vivo owing to low CNS permeability and export from the brain by P-glycoprotein transporter.

The pharmacological profile of BPN is well known and as such no new pharmacodynamics studies have been carried out in respect of this mixed Marketing Authorization Application (MAA). Data from the literature has been presented to demonstrate how BPN is well-suited for the treatment of opioid dependence. The lack of studies to support the pharmacology of buprenorphine is acceptable.

Buprenorphine has a slow rate of receptor association and dissociation, which results in a prolonged pharmacodynamic action and low dependence liability, which is demonstrated in animal models of opioid dependence taken from the published literature. As a partial μ-agonist, the opioid agonist effects of buprenorphine plateau at higher doses, meaning that there is a lower risk of overdose in comparison to full agonists.

Both buprenorphine and norbuprenorphine also exhibit antinociceptive activity, however norbuprenorphine has a weaker effect than buprenorphine as it is a substrate for p-glycoprotein the brain efflux transporter and therefore has a low CNS permeability.

Secondary pharmacodynamic effects on the central nervous, gastrointestinal, cardiovascular, respiratory, and other systems have reported in the literature, and generally exhibit a ceiling effect. As expected for an opioid mixed agonist-antagonist, secondary pharmacodynamic effects include CNS and respiratory depression and decreased intestinal contractility and transit time. Cardiovascular effects include bradycardia or tachycardia, depending on the dose, with minimal hemodynamic changes. Buprenorphine is known to block the hERG channel in vitro with a reported IC50 of 7.5 μM, and was associated with less QTc prolongation than levomethadyl or methadone in a published randomized clinical trial. No new secondary pharmacodynamic effects are expected with Sixmo.

As buprenorphine is a well characterised compound and as such no new safety pharmacology studies were performed in respect of this application. Buprenorphine is a well-known active substance, the implanted dose, even though it is a slow sustained release, is considerably higher than other products currently used clinically. QTc prolongation risks have been demonstrated for other buprenorphine containing products. Safety pharmacology endpoints were not included as part of the chronic toxicity studies performed in Beagle dogs with Sixmo. However, the highest Cmax achieved in animals is 30-fold lower than the IC50 reported for buprenorphine inhibition of the hERG channel (Katchman et al., 2002). Also, the highest Cmax observed in an outlier value from the PK study TTP-400-02-01 was 29 ng/mL. This concentration is over 100-fold lower than the IC50 for buprenorphine. Overall, the risk for QT prolongation with Sixmo appears low.

Pharmacodynamic drug interactions for Sixmo have not been performed and none are deemed necessary. Pharmacodynamic drug interactions of BPN with benzodiazepines have been identified with the co-administration of both drugs having the potential to induce severe respiratory depression and death. The potential for this interaction has been adequately addressed in the SmPC.

Overall, the nonclinical pharmacology package presented is considered acceptable to support this MAA.

2.3.2. Pharmacokinetics

Sixmo implants are designed to deliver a sustained dose of buprenorphine for 6 months for substitution treatment of opioid dependence. The implants are composed of two components, the active ingredient buprenorphine hydrochloride (HCl) (buprenorphine) and the excipient ethylene vinyl acetate (EVA). Treatment with Sixmo also results in lower overall clinical exposure to buprenorphine when compared with the currently marketed daily dose of sublingual tablets over the same treatment period (Study PRO-810). Only one study (Study PRO-NDR-1201) used a clinically relevant formulation of the implants.

To measure buprenorphine and norbuprenorphine levels the Applicant developed and validated an LC-MS/MS method which was conducted with appropriate specificity and sensitivity for dogs. The reproducibility for rats only just met the acceptance criteria and 5 samples had a percentage difference of >50%. One sample in the rabbit assay also had a percentage difference of >50%. Although no discussion of the sensitivities of the methods for 2850 and 2851 have been provided, it is acknowledged that these methods were used to bridge to data from the Suboxone/Subutex label. As the submission in the EU is under the legal basis of 8(3), reference to suboxone/Subutex is not allowed and these bridging studies have not been referenced in the sections for carcinogenicity or reproductive toxicity for this application.

Plasma buprenorphine levels were assessed in dogs following SC insertion of 8, 16, or 24 Sixmo implants (nominal 90 mg/implant) for up to one year in pilot and definitive chronic toxicity studies (PRO-NTR-0214, PRO-NTR- 0215, respectively). Plasma buprenorphine concentrations were maximal within 24 hours post-implantation (Tmax) in most animals, followed by a decrease to a steady-state level that was maintained at >80% of this level through 8.5 months. Maximum plasma concentrations (Cmax) of buprenorphine and area-under-the-plasma-concentration/time-curve (AUC) assessed over the maximum one-year treatment period were approximately linear with dose, and ranged from approximately 22 to 54 ng/mL and 26,000 to 64,000 ng.hr/mL, in the pilot study, and 64 to 80 ng/mL and 19,000 to 76,000 ng.hr/mL in the definitive study, respectively. Post hoc analysis demonstrated that steady-state levels were attained between 3 and 8 weeks after implantation, and that plasma concentrations at steady state (Css) for the 8, 16, and 24 implant groups were 2.3±1.0, 6.3±3.7, and 8.1±2.4 ng/mL, respectively (Kleppner et al, 2006). When implants were removed during steady state 36 weeks post-implantation, terminal half-life (t½) was 8.6 hr. There were no apparent gender differences in TK parameters calculated for buprenorphine. Norbuprenorphine was detected intermittently in most animals for approximately the first two weeks after implantation, with concentrations ranging from approximately 0.6 to 3.8 ng/mL, 1.8-7.9% of buprenorphine Cmax. Sixmo implants were well tolerated at Cmax and AUC0-last levels that were 13 and 15 times, respectively, the exposure levels observed in clinical study PRO-810.

In the pilot study (PRO-NTR-0214) dogs in the test article group had broken implants and none of the control implants were broken. Again, in the definitive study (PRO-NTR-0215) all of the dogs in the 10 month group had broken implants compared to the control group, where there were no broken implants. One dog, in Group B2 of the definitive study, CRIADH, had a very high Cmax, 179 ng/mL, within 3 hours of implantation, as compared to the other seven. The Cmax values in the other seven dogs ranged between 49 ng/mL and 83 ng/mL. Dog CRIADH also had 21/24 implants broken, which raises concerns regarding possible dose dumping. However, other animals such as CRIALH, CRIAKH, CRIAHA and CRIAXH also had 17 to 23 implants broken with no evidence of increased Cmax or AUC values. Therefore, the Cmax in animal CRIADH is considered inadvertent and unlikely to be related to dose dumping. Also, breaking the implant in two would increase the surface area by 4.6% according to the applicant's calculations and should not result in dose dumping. The differences in breakage numbers can be explained as control implants were made of 100% EVA in contrast to the buprenorphine implants which contained 25% EVA and 75% buprenorphine. The 100% EVA implants were demonstrated by the applicant to be relatively unbreakable. In the release characteristic study (PRO-NDR-1202) the data show that the exposure resulting from buprenorphine release from two Sixmo lots, as measured by AUC, are

generally similar over time, and that the manufacturing process change from sieved buprenorphine to nonsieved buprenorphine in the blending step with EVA before extrusion had little effect on the overall Sixmo exposure. Despite the fact that the AUC demonstrated similar exposure over time, there were however, observed differences in Cmax and Tmax. Tmax is 3 hours and Cmax is 22 ng/ml in the un-sieved formulation compared to Tmax of 30h and Cmax of 13.2 ng/ml in the sieved formulation. Toxicology studies used sieved buprenorphine formulation and the animal PK studies were carried out using the un-sieved formulation. However, given that the exposure to buprenorphine from the Sixmo implants is lower compared to that from sublingual buprenorphine, and given that the exposure over time is similar for the two formulations, there are no concerns from a toxicological persective.

Also in this study, the animals in Group 6, had previously been exposed to BPN in Groups 2 and 4, (8 x 70 mg implants). Following a 7 day wash out period they were re-implanted with 8 x 80 mg implants (Report PRO-NDR-0701). The second implant site was distinct from the first, and there was no measurable blood buprenorphine prior to the second implantation.

The effects of external heat application to the pharmacokinetic parameters and characteristics of buprenorphine release from Sixmo implants were evaluated in dogs (Study PRO-NDR-1201). No consistent changes in plasma buprenorphine exposure were observed when external heat was applied for 8 hours directly after implantation or when reapplied for 8 hours at 5 weeks after implantation. Norbuprenorphine plasma concentrations were generally below the limit of quantitation.The objective of Study PRO-NDR-1201 was to elucidate the pharmacokinetics of buprenorphine from Sixmo implants following external application of heat, this study used a clinically relevant formulation of the implants. It is noted that the thermal chips used to monitor the animal's temperature were not fully equilibrated to the skin surface before application of heat. Although the thermal chips were not adequately equilibrated to the dog's skin surface, this was an issue for both groups. The mean skin temperatures were similar at the beginning of the study and increased and decreased by a similar amount in both groups of dogs. Therefore, it is accepted that the lack of full equilibration did not affect the validity of the study. One animal in the control group was hypothermic 4 hours post implantation and was provided with warm-water recirculating blankets and warmed fluid bags. However, given that the affected animal had plasma concentrations of buprenorphine that were consistent throughout the study with plasma buprenorphine concentrations in other animals in the control group, it is accepted that the blankets and warmed fluid did not make a significant difference to the release profile of the implants. Application of external heat immediately following implantation resulted in a slightly lower Cmax and AUC0-48 compared to the control group. When heat was applied at Week 5 no consistent differences in AUC0-24 were observed, when compared to the same group of animals at Week 4 when no heat was applied.

In Study PRO-NDR-1201, 1 animal in Group 2 was noted to have a swollen implantation site at 552 hours post-implantation which persisted throughout the study. Two implants were unable to be located during removal procedures. Three animals in this study were noted to have apparent infection at the implantation sites, however adequate warning regarding the possibility of infection has been included into the proposed SmPC.

A post hoc analysis of the toxicokinetic data from the pilot and definitive chronic toxicity study show that peak plasma concentrations were achieved around 24 hours post-implantation, with steady-state reached between 3 and 8 weeks after implantation, reflecting the results seen in study PRO-NDR-1202. Plasma concentrations were dose proportional.

No changes in the distribution, metabolism, or elimination profiles of systemic buprenorphine are expected to occur from SC implantation of Sixmo compared with marketed medicinal products containing buprenorphine, and utilising different methods of administration. Therefore, no new metabolism, distribution, or elimination studies were performed with Sixmo. The disposition of buprenorphine after

various routes of administration as described in the literature was summarised by the applicant. Buprenorphine is highly protein bound.

The pharmacokinetic drug interactions involving buprenorphine are well known and are described in the literature. Clinically relevant PK interactions are inhibitors of CYP3A4, resulting in enhanced bioavailability of BPN, and similarly, inducers of CYP3A4 may have the potential to reduce buprenorphine plasma concentrations because of increased metabolism of buprenorphine to norbuprenorphine. Section 4.5 of the proposed SmPC has adequately addressed the potential interactions.

All issues have been resolved, the nonclinical pharmacokinetics package presented is considered acceptable to support this MAA.

2.3.3. Toxicology

The applicant has provided toxicology studies conducted to support this mixed marketing authorisation application, single dose toxicity in mice with extracts of the Sixmo implants and two chronic toxicity studies in dogs. Also local and systemic toxicology studies of Sixmo and EVA-only placebo implants, and studies of extracts of Sixmo and EVA-only placebo implants, including studies conducted in accordance with ISO 10993 guidelines for the biological evaluation of medical devices were carried out.

Single dose toxicity

Acute systemic toxicity of extracts from Sixmo implants was evaluated in mice in accordance with ISO 10993, Part 11, systemic toxicity, to estimate the potential harmful effects of potential absorption of toxic leachables and degradation products. Toxicity studies, including LD50 values, were also provided from the literature.

Following IP injection of extracts from Sixmo implants there was no observable acute toxicity associated with Sixmo extracts in this study. However, these tests are designed to allow estimation of hazards that could possibly arise from an acute exposure by the intended clinical route. The clinical route for Sixmo is subcutaneous insertion, IP injection of extracts were administered in this study. However, the use of IP injection instead of SC (the intended clinical route) optimised exposure to buprenorphine and any possible leachables from the EVA matrix.

References from the published literature show that a single dose of buprenorphine can cause CNS effects. Either an increase or decrease in locomotor behaviour dependent on dose and species, respiratory depression, which in animals exhibits a ceiling effect and changes in cardiovascular parameters.

Chronic toxicity studies

The potential for Sixmo implants to induce systemic toxicity was evaluated in a chronic toxicity study in dogs. Prior to this study, a pilot study was conducted to aid in dose selection for the definitive study. Both of these studies included toxicokinetic assessments. The duration of the definitive chronic toxicity study of 10 months was greater than the maximum intended clinical duration of Sixmo implantation of 24 weeks/6 months. Lethargy and a reduction in food consumption was observed on the day of implantation. These transient effects were attributed to known pharmacological effects of buprenorphine, and are probably due to the rapid initial release and absorption of buprenorphine into the systemic circulation, followed by a decline to steady-state levels. Buprenorphine was detectable in plasma during the entire implantation period. Overall Sixmo implants were well tolerated in pilot and definitive chronic toxicity studies in dogs treated for up to 12 and 10 months, respectively, as determined by local and systemic assessments.

At the implantation sites at 1 month there was redness, swelling and abscesses which were characterised microscopically by accumulations of numerous vacuolated macrophages and lesser numbers of

degenerative and viable neutrophils which were encapsulated by a band of fibrous tissue infiltrated by plasma cells and lymphocytes. There was evidence of recovery at the implantation sites by month 10. EVA-only placebo implants elicited similar reactions at implantation sites however invariably had less inflammatory cells. The buprenorphine implants were considered to be more irritant compared with control EVA-only implants based on microscopic evaluation of subcutaneous implantation sites. Fibrosis of the implant site has been observed in these and other studies carried out by the applicant and this has implications for the absorption and pharmacologic action of buprenorphine.

In these studies, the applicant has used buprenorphine implants with a nominal dose of 90 mg per implant that is not wholly representative of the Sixmo implant that is to be marketed. However, the amount of buprenorphine contained in the implants used in the pivotal repeat-dose toxicity in dogs was based on acceptance criteria for assay which was 72% ± 10 % of the weight of the implant rather than mg per implant. During development the weight of the implant changed but the buprenorphine percentage of the weight per implant remained the same. Furthermore, given that the same percentage weight of buprenorphine per implant was used in the pivotal repeat-dose toxicity study as has previously been used clinically and that the doses administered were higher in the animal studies than in the clinic, the difference in formulation can be accepted from a toxicological point of view.

In the pilot study (PRO-NTR-0214) 1 animal was observed to have a firm cutaneous mass on the ventral abdomen, this became ulcerated. On Day 266 the animal developed diarrhoea and appeared thin. On Day 321 the same animal was noted to be lethargic, cold and unresponsive and was euthanised, on autopsy severe lung changes were reported that were consistent with aspiration pneumonia, however no signs of breathing difficulties were noted. The implants in this animal could not be located. Therefore, it is impossible to draw a conclusion as to whether the inability to locate the implants could have impacted the deteriorating condition of the animal. The only signs exhibited by the other animals on this study were lethargy and reduction in food consumption on the day of implantation. Nonetheless, the same number of implants were used in the subsequent definitive study without any problems identified.

In the definitive study, PRO-NTR-0215, the group of dogs that had buprenorphine implanted for 10 months had 24 implants at Day 0 and then received an additional 6 implants at 8.5 months, to maintain the desired systemic exposure conditions. The decision to re-implant the animals was mainly driven by toxicological rather than pharmacokinetic considerations, with the aim of maintaining steady state for a period longer than the intended clinical use.

It is noted that upon removal from the tissue, 70% of the original implants and 8.3% of the re-implanted implants were broken into 2-3 pieces. Given that 1 animal in the pilot study had implants that could not be located and a large amount of implants were broken in the definitive study there are concerns about the robustness of the implants and the implications of this during removal. An overview of the rates of implant breakage will be clearly outlined in the SmPC.

Toxicokinetic assessment revealed that buprenorphine was rapidly released from implants into the systemic circulation, and was detectable in plasma during the entire implantation period. The applicant calculates safety margins based on buprenorphine exposure between the chronic toxicity study and clinical exposure in Study PRO-810. Exposure to buprenorphine from the proposed clinical dose of Sixmo (4 implants, 24 weeks) is approximately 37% of the exposure achieved by Suboxone (16 mg QD, 24 weeks). However, Study PRO-810 was not completed, and was terminated at week 8, with data extrapolated to week 24.

Toxicokinetic parameters were examined as part of the pilot and definitive repeat-dose studies in dogs. In the pilot study lasting up to 12 months, buprenorphine was detectable for the entire duration of the study. Exposures increased approximately proportionally with dose between the groups with 8 and 16 implants, however the exposures from 16 and 24 implants appeared to be similar. Once the buprenorphine implants were removed, plasma concentrations of buprenorphine appear to decline rapidly. Norbuprenorphine

concentrations were generally not detectable after Day 42 with the exception of a few samples in 1 animal. The graphs provided were difficult to interpret as the x-axis of the graph was labelled in thousands of hours and it is stated that the elimination following removal was rapid. Therefore, it is not possible to elucidate over what time period elimination occurred. However, given that there is some discussion provided on the elimination of buprenorphine in a clinical setting, from a non-clinical perspective the lack of data and discussion on elimination can be accepted.

In the definitive study, buprenorphine was detectable for the entire 10-month duration of the study however, additional implants were implanted at 8.5 months so it is difficult to interpret whether this is an accurate representation of what would happen in a clinical setting. The majority of animals achieved Tmax within 24 hours. Following implantation of the additional 6 implants at 8.5 months, Tmax was reached at a median of 56 hours. Norbuprenorphine reached Cmax between 24 hours and 8 days.

The Applicant has calculated the exposure margins using the definitive 10-month chronic dog study in comparison with a 6-month study in humans, Study PRO-810. The design of the non-clinical study included implantation of an additional 6 implants, to the initial implantation of 24 implants, at 8.5 months. Also Study PRO-810 was terminated at week 8 and data extrapolated to week 24 and is therefore not considered to be robust and no definitive conclusions can be drawn from this data. Buprenorphine is in clinical use for substitution treatment of opioid dependence. Therefore, a comparison of the exposure of subjects treated with Sixmo implants with the exposure of subjects treated with the approved medicinal product Suboxone is considered to be more relevant with respect to safety evaluation of Sixmo than a margin calculation based on animal data. Systemic exposure to buprenorphine via the sublingual formulation (Suboxone) in Study PRO-810 was higher than that for Sixmo. Based on these data, the safety risk associated with systemic exposure to buprenorphine is expected to be lower for Sixmo than for sublingual buprenorphine, therefore, from a toxicological point of view the lack of calculation of safety margins is acceptable.

Additional studies from the published literature were provided showing that buprenorphine injected IM into baboons, and IP into mice produced haematological changes associated with an inflammatory response that were similar to those seen in the definitive study in dogs. In rats, buprenorphine given SC for 4 weeks produced a decrease in liver weight and a dose-dependent increase in interstitial pneumonia. There was also an increase in thymus and lymph node weight but this was not associated with any histopathology.

Genotoxicity

In order to satisfy, in part, the requirements for ISO 10993, Part 3, tests for genotoxicity, carcinogenicity and reproductive toxicity, extracts of Sixmo and EVA (placebo) implants were tested for genotoxicity in the bacterial reverse mutation (Ames), in vitro chromosome aberration, and in vivo mouse micronucleus assays. No genotoxic extractables were detected in Sixmo or EVA implant extracts. Literature evidence of the lack of genotoxic potential of buprenorphine was provided. It is accepted that the drug substance BPN is not genotoxic.

Carcinogenicity

No new carcinogenicity studies have been conducted with Sixmo implants. As buprenorphine is a well-known active substance further carcinogenicity studies are not required. No animal studies evaluating the carcinogenic potential of buprenorphine are available in the public domain. However, since the first approval of a buprenorphine product, Temgesic, in the EU in 1977, and in the US since 1985 (Buprenex) there have been no reports indicating any carcinogenic potential of buprenorphine.

Furthermore, additional literature references for related compounds show that there is no indication of potential of carcinogenicity.

Section 5.3 of the SmPC has been updated to state that "There is no suspicion of carcinogenicity based on the clinical use of buprenorphine "

Reproductive and Developmental toxicity

No new reproductive and developmental studies were conducted with Sixmo implants. The potential for buprenorphine to induce reproductive and developmental toxicity is well characterized in animal models, and no change is anticipated with Sixmo. The evaluation of reproductive and developmental toxicity relies on buprenorphine studies described in the literature and clinical data is provided to supplement the animal data.

There is a lack of published information on the effects of buprenorphine on fertility. Buprenorphine is not recommended during pregnancy and in women of childbearing potential not using contraception. Section 4.6 of the SmPC has been updated with the following text:

'No published information is available regarding a potential effect of buprenorphine on male and female fertility'

The lack of published data on potential effects on fertility is acknowledged, as well as the restriction in women of childbearing potential.

The excipient EVA is not novel and is used in other pharmaceutical products with no evidence to suggest that there would be any adverse local or systemic toxicity over an extended time period. An absence of discussion on reproductive and developmental toxicity is acceptable.

Local Tolerance

The local tolerance to Sixmo or Sixmo extracts was evaluated in four studies in accordance with ISO 10993. Sixmo extracts were assessed in a guinea pig sensitization study using the maximization method, and in an acute intracutaneous reactivity study in rabbits, in accordance with ISO 10993, Part 10, Test for Irritation and Sensitization. Sixmo implants were evaluated in 4-week and 26-week subcutaneous implantation studies with histopathology in rabbits in accordance with ISO 10993, Part 6, tests for Local Effects after Implantation.

These studies indicated that extracts of Sixmo and/or EVA-only placebo implants did not induce dermal contact sensitization in guinea pigs, or intracutaneous reactivity or pyrogenicity in rabbits. The Sixmo extract was classified as a slight irritant in 4- and 26-week ISO 10993 subcutaneous implantation studies, whereas the EVA-only placebo implant extract was classified as a slight irritant in the 4-week study but not in the 26-week study. An ISO 10993 in vitro cytotoxicity assay showed that the Sixmo extract did not induce cell lysis or other evidence of cytotoxicity in L-929 fibroblasts.

Sixmo implants and EVA-only implants were both classed as slight irritants when implanted SC for a period of 4 weeks compared to the USP negative control implant. Over a period of 6 months, only the Sixmo implants were classified as slight irritant relative to the EVA-only and USP negative control

implants. Fibrosis was also observed at implantation sites with all treatments, with a higher score in one Sixmo-treated animal, suggesting individual variability in the tissue response between animals.

Toxicological Assessment of Ethylene Vinyl Acetate (EVA)

EVA, the structural foundation and only excipient in Sixmo implants, is contained in several approved products, including Implanon NXT/Nexplanon implant and NuvaRing, and is listed in the FDA Inactive Ingredients for Approved Drug Products database. EVA-only implants were used as controls in different nonclinical studies, and the applicant carried out other studies in line with ISO 10993 examining the effects of Sixmo and EVA-only extracts. Results from these studies indicate that EVA implants and extracts thereof are generally well tolerated.

The potential source of toxicity from polymers is considered to be leachables from the polymer matrix. The most likely leachants are (1) unreacted vinyl acetate and (2) low molecular weight polyvinyl acetate. EVA used in the manufacture of the Sixmo contains 33% w/w vinyl acetate. EVA control implants have been included in definitive toxicity studies, where 24 implants were implanted subcutaneously in dogs for up to 10 months. These were well tolerated. Potential leachable impurities associated with EVA have been characterized in forced extraction studies and evaluated for toxicological risk. Extracts from Sixmo and/or EVA implants did not induce dermal contact sensitization in guinea pigs, or intracutaneous reactivity or pyrogenicity in rabbits. The Sixmo extract was classified as a slight irritant in 4- and 26-week ISO 10993 subcutaneous implantation studies, whereas the EVA-only placebo implant extract was classified as a slight irritant in the 4-week study but not in the 26-week study. An in vitro cytotoxicity assay showed that the Sixmo extract did not induce cell lysis or other evidence of cytotoxicity in L-929 fibroblasts.

Extracts of Sixmo and EVA-only placebo implants were tested for genotoxicity in the bacterial reverse mutation (Ames), in vitro chromosome aberration, and in vivo mouse micronucleus assays. These studies showed that Sixmo extracts were nonmutagenic in the bacterial reverse mutation assay, and that Sixmo and EVA-only placebo implant extracts were nonclastogenic in the in vitro chromosome aberration assay, and were nonclastogenic and did not damage the mitotic apparatus in the in vivo mouse bone marrow micronucleus assay.

Potential leachable impurities associated with EVA have been characterized in forced extraction studies and evaluated for toxicological risk. Potential impurities commonly associated with polymers, such as unreacted or residual monomers and/or their degradation products, such as polyvinyl acetate, polyvinyl alcohol, and vinyl acetate, were not identified in these studies. Three compunds were identified after extraction of EVA placebo implants and ground EVA in boiling IPA for 30 minutes, butylated hydroxytoluene (BHT), 3-5-di-tert-Butyl-4- hydroxybenzaldehyde, and erucamide.

3,5-di-tert-butyl-4-hydroxybenzaldehyde may be weakly clastogenic, however the amount in in 5 Sixmo implants is 1.15 ug /6 months, is less than the TTC levels permitted in M7. The maximum erucamide, and 3,5-di-tert-butyl-4-hydroxybenzaldehyde is less than the virtually safe lifetime dose of 1.5 µg/day.

The results of the extractable and leachable studies described above demonstrate that the maximum potential daily exposure to identified and unidentified IPA-extractable impurities from EVA placebo implants is less than the threshold of toxicological concern of 1.5 µg/day, which is considered to be a virtually safe dose even for exposures over a lifetime. No impurities were detected in aqueous extracts of EVA placebo implants or ground EVA, suggesting a low risk of impurity exposure in physiological environments such as the subdermal compartment. No extractable compounds were detected from the laminated foil pouches used for packaging Sixmo implants. Maximum theoretical levels of exposure to metals extracted from EVA implants, ground EVA, and laminated foil pouches were well below US federal drinking water standards.

Impurities

An updated drug product specification has been supplied which provides a limit for each individual unspecified impurity of NMT 0.2% for release and shelf-life. The proposed limit is in line with that specified by ICH Q3B (R2).

2.3.4. Ecotoxicity / environmental risk assessment

The Applicant has used published literature on the use of opioid substitution treatment in the EU and assumed 100% market share to calculate a revised $PEC_{surface\ water}$ for Buprenorphine which 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, Buprenorphine is not expected to pose a risk to the environment. Buprenorphine hydrochloride is already used in existing marketed products and no significant increase in environmental exposure is anticipated.

2.3.5. Discussion on non-clinical aspects

Pharmacology

The pharmacological profile of BPN is well known and as such no new pharmacodynamics studies have been carried out in respect of this mixed Marketing Authorization Application (MAA). Data from the literature has been presented to demonstrate how BPN is well-suited for the treatment of opioid dependence.

A brief summary on the pharmacology of buprenorphine is provided from the literature, describing the mixed partial agonist activity at µ-opioid receptors and antagonistic activity at κ- and δ-opioid receptors. The major metabolite norbuprenorphine is also active at opioid receptors but has low CNS permeability as it is a substrate for P-glycoprotein.

Secondary pharmacodynamic effects on the central nervous, gastrointestinal, cardiovascular, respiratory, and other systems are well known and generally exhibit a ceiling effect. These include CNS and respiratory depression and decreased intestinal contractility and transit time. Cardiovascular effects include bradycardia or tachycardia, depending on the dose, with minimal hemodynamic changes. Buprenorphine is known to block the hERG channel in vitro with a reported IC50 of 7.5 µM, and was associated with less QTc prolongation than other opioids.

As buprenorphine is a well characterised compound and as such no new safety pharmacology studies were performed in respect of this application. Buprenorphine is a well-known active substance, the implanted dose, even though it is a slow sustained release, is considerably higher than other products currently used clinically. QTc prolongation risks have been demonstrated for other buprenorphine containing products. Safety pharmacology endpoints were also included as part of the chronic toxicity studies performed in Beagle dogs with Sixmo. However, the Cmax observed in toxicology studies was 30-fold lower than the reported IC50 for buprenorphine inhibition of the hERG channel, thus the risk for QT prolongation appears low.

Pharmacokinetics

Sixmo implants are designed to deliver a sustained dose of buprenorphine for 6 months after subcutaneous implantation for the treatment of opioid dependence. The systemic absorption and plasma pharmacokinetics of buprenorphine were evaluated in in vivo studies following subcutaneous implantation of Sixmo implants in dogs. The pharmacokinetic properties of buprenorphine have been well characterized in the literature. No changes in the distribution, metabolism, or elimination profiles of systemic buprenorphine are expected to occur from subcutaneous implantation of Sixmo compared with approved medicinal products. Therefore, no new metabolism, distribution, or elimination studies were performed with Sixmo.

To measure buprenorphine and norbuprenorphine levels the Applicant developed and validated an LC-MS/MS method which was conducted with appropriate specificity and sensitivity for dogs.

Pharmacokinetic studies were carried out in dogs for up to 12 months. Sixmo implants delivered sustained plasma levels of buprenorphine that were maintained for more than 6 months. Peak plasma levels were generally observed within 24 hours of implantation, and steady state was established 3 to 8 weeks later depending on the dose implanted. In the pilot study and the definitive study, all of the dogs in the test article group had broken implants as compared to the control group who had none. One dog had a very high Cmax compared to the rest of the group and 21/24 implants were broken. Despite the fact that 70% of implants were broken in the buprenorphine group there was no evidence of dose dumping. PK studies were carried out to compare the use of sieved vs unsieved buprenorphine in the formulation of the implants. Despite the fact that the AUC demonstrated similar exposure over time, when comparing the two formulations, there were however, observed differences in Cmax and Tmax,. Toxicology studies used sieved buprenorphine formulation and the animal PK studies were carried out using the un-sieved formulation. However, given that the exposure to buprenorphine from the Sixmo implants is lower compared to that from sublingual buprenorphine, and given that the exposure over time is similar for the two formulations, there are no concerns from a toxicological persective.

A clinically relevant formulation of Sixmo implants was used to examine the application of external heat on the absorption of buprenorphine. Two implants in one animal in this study were unable to be located at the time of removal, Three animals included in this study were noted to have signs of infection at the implantation sites, however adequate warning regarding the possibility of infection is included in the proposed SmPC. Overall, the application of external heat to the implant site had no consistent effect on plasma buprenorphine exposure.

Further testing of the PK properties of buprenorphine were conducted in mice, rats and rabbits. Exposures exceeded the highest exposure in humans following SC implantation by at least 13-fold.

Pharmacokinetic drug interactions involving buprenorphine of clinical relevance are well known. Both inhibitors and inducers of CYP3A4 affect buprenorphine bioavailability.

Toxicology

The toxicology studies conducted to support this application included local and systemic toxicology studies of Sixmo and EVA-only placebo implants, and studies of extracts of Sixmo and EVA-only placebo implants, including studies conducted in accordance with ISO 10993 guidelines for the biological evaluation of medical devices.

Acute single dose toxicity studies were carried out in line with ISO 10993, the use of IP injection instead of SC (the intended clinical route) optimised exposure to buprenorphine and any possible leachables from the EVA matrix Sixmo was well tolerated in pilot and definitive chronic toxicity studies in dogs treated for up to 12 and 10 months, respectively, as determined by local and systemic assessments,

In the repeat dose studies, the applicant used buprenorphine implants with a nominal dose of 90 mg per implant, rather than the clinically proposed 80 mg. However, given that the same percentage weight of buprenorphine per implant was used in the pivotal repeat-dose toxicity study as has previously been used clinically and that the doses administered were higher in the animal studies than in the clinic, the difference in formulation can be accepted from a toxicological point of view.

In the definitive repeat dose study the group of dogs that had buprenorphine implanted for 10 months had 24 implants at Day 0 and then received an additional 6 implants at 8.5 months, to maintain the desired systemic exposure conditions. Upon removal from the tissue, 70% of the original implants and 8.3% of the re-implanted implants were broken into 2-3 pieces. Given that 1 animal in the pilot study had implants that could not be located and a large amount of implants were broken in the definitive study there are

concerns about the robustness of the implants and an overview of the rates of implant breakage will be clearly outlined in the SmPC.

Toxicokinetic parameters were examined as part of the pilot and definitive repeat-dose studies in dogs. These studies show that peak plasma concentrations were achieved around 24 hours and that plasma concentrations were approximately dose proportional. Once the buprenorphine implants were removed, plasma concentrations of buprenorphine appear to decline rapidly. The Applicant has calculated the exposure margins using the definitive 10-month chronic dog study in comparison with a 6-month study in humans, PRO-810, additionally the design of the non-clinical study included implantation of an additional 6 implants, to the initial implantation of 24 implants, at 8.5 months. Study PRO-810 was terminated at week 8 and data extrapolated to week 24 and is therefore not considered to be robust and no definitive conclusions can be drawn from this data. A comparison of the exposure of subjects treated with Sixmo implants with the exposure of subjects treated with the approved medicinal product Suboxone is considered to be more relevant with respect to safety evaluation of Sixmo than a margin calculation based on animal data. Systemic exposure to buprenorphine via the sublingual formulation (Suboxone) in Study PRO-810 was higher than that for Sixmo. Based on these data, the safety risk associated with systemic exposure to buprenorphine is expected to be lower for Sixmo than for sublingual buprenorphine, therefore, from a toxicological point of view the lack of calculation of safety margins is acceptable.

The evaluation of genotoxicity, carcinogenicity, and reproductive and developmental toxicity relies on buprenorphine studies described in the literature, and in the case of carcinogenicity and reproductive and developmental toxicity, is supported by data presented in the Suboxone SmPC/EPAR.

No new carcinogenicity studies have been conducted with Sixmo implants. As buprenorphine is a well-known active substance further carcinogenicity studies are not required. No animal studies evaluating the carcinogenic potential of buprenorphine are available in the public domain. However, since the first approval of a buprenorphine product, Temgesic, in the EU in 1977, and in the US since 1985 (Buprenex) there have been no reports indicating any carcinogenic potential of buprenorphine.

The potential for buprenorphine to induce reproductive and developmental toxicity is well characterized in animal models, and no change is anticipated with Sixmo. The evaluation of reproductive and developmental toxicity provided by the applicant relies on buprenorphine studies described in the literature for both animals and humans.

There is a lack of published information on the effects of buprenorphine on fertility. Buprenorphine is not recommended during pregnancy and in women of childbearing potential not using contraception.

The excipient EVA is not novel and is used in other pharmaceutical products with no evidence to suggest that there would be any adverse local or systemic toxicity over an extended time period. An absence of discussion on reproductive and developmental toxicity is acceptable.

Extracts of Sixmo and EVA only placebo extracts were tested for genotoxicity, and were shown to be non-mutagenic and non-clastogenic. Sixmo and/or EVA-only placebo implants, were well tolerated in studies designed to meet ISO 10993 requirements for biological evaluation of medical devices, including acute systemic toxicity in mice, dermal sensitization in guinea pigs, acute intracutaneous reactivity in rabbits, subcutaneous implantation in rabbits, pyrogenicity in rabbits, and in vitro cytotoxicity.

EVA as the structural foundation of the implant was demonstrated to be well tolerated. Potential leachables and impurities were also investigated. Forced extraction studies indicate that potential leachable impurities do not pose a safety risk to patients treated with the maximum recommended number of Sixmo implants.

A drug product specification has been supplied which provides a limit for each individual unspecified impurity of NMT 0.2% for release and shelf-life. The proposed limit is in line with that specified by ICH Q3B (R2).

2.3.6. Conclusion on the non-clinical aspects

From a non-clinical perspective, Sixmo is approvable.

2.4. Clinical aspects

2.4.1. Introduction

GCP

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

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

2.4.2. Pharmacokinetics

Titan Pharmaceuticals has conducted 7 clinical studies which evaluated the safety and efficacy of Sixmo for substitution treatment of opioid dependence. PK data were collected and analyzed in 6 of the 7 studies. These included one open-label PK and safety study (TTP-400-02-01), two Phase 3 placebo-controlled safety and efficacy studies (PRO-805 and PRO-806), two open-label retreatment studies (PRO-807 and PRO-811), and one bioavailability study (PRO-810). Study PRO-814 did not include PK assessments.

Sixmo implants manufactured for the first-in-human study, TTP-400-02-01 had a label claim of nominally 90 mg ± 9 mg buprenorphine, and test results for the lot used in that trial showed the implants contained an average of 83 mg buprenorphine. The manufacturing specifications for Sixmo used in subsequent trials (PRO-805, PRO-806, PRO-807, PRO-811, and PRO-810) were changed to reflect the more accurate label claim of 80 mg ± 8 mg buprenorphine; no changes were made to the actual formulation or manufacturing process apart from scale-up from a 15 g to 400 g process.

2.4.2.1. Population pharmacokinetic analyses

Appropriate methods have been used for the population PK modelling, simulations and exposure-response, especially considering the designs of the clinical studies. Sampling times in the phase 3 studies limited the ability of the model to estimate the quick release phase of the Sixmo implants, however limited data from the bioavailability study (PRO-810) were available. Ultimately, the final population PK model included a linear elimination with a peripheral compartment, plus two depot compartments for Sixmo implant with first order absorption, for the quick- and slow-release and a third depot compartment for SL BPN. WT on CL/F and BMI on KA3 (slow-release phase) were retained in the final model as covariates. While the VPCs indicate some over-prediction of variability, the model appears fit for purpose.

Simulations of plasma BPN for 4 Sixmo Implants, 4+1 Sixmo Implants, 12 mg SL BPN indicated that the median Cavg during the slow-release phase of Sixmo implants and 4-24 weeks after 12 mg SL BPN were 0.638 ng/mL and 1.39 ng/mL, respectively. BMI did not appear to have an impact on exposure levels.

Exposure-response analyses was described by an Emax model without covariates. Values of Emax and EC50 were 40.9 % and 0.181 ng/mL, respectively.

The population model estimates the clearance, Q, volume of distribution (V1 &V2) are estimated to be 45.2 L/h, 100 L/h, 1244 L (96 L for PRO-810) and 1308 L, respectively, and are in-line with literature values. The difference in V1 for the studies is explained by the sampling schemes used in the respective studies.

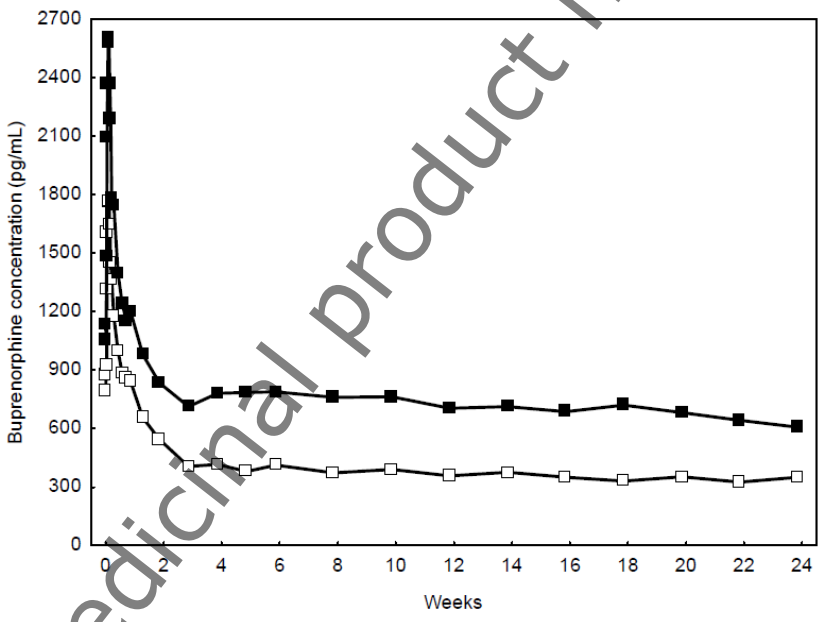
2.4.2.2. Absorption

The Applicant established the following PK parameters (for 4 implants): **Cmax:** 3.23 ± 0.48 ng/mL (TTP-400-02-01 study); 4890 pg/mL (PRO-810 study); **Tmax:** 15.95 ± 4.9 hours (TTP-400-02-01 study);12 hours (PRO-810 study).

At day 24 the following mean buprenorphine concentrations were recorded PRO-805 study:573±243 pg/mL; PRO-806 study:633±300 pg/mL,

In TTP-400-02-01 study average plasma concentration from Day 21 to removal was reported e.g 0.72 ± 0.11 ng/mL for 4 implants group.

Figure 3 Study TTP-400-02-01, Mean Plasma Buprenorphine Concentrations for Dose Groups A and B



Open boxes = Dose Group A (2 Sixmo implants); Closed boxes = Dose Group B (4 Sixmo implants)

Sixmo implants release buprenorphine which produce, around after 21 days of treatment, low (<1 ng/mL) buprenorphine concentration. On the other hand during first 4 weeks significantly higher values were recorded. This “two-phased” buprenorphine release profile may have clinical impactions. Clinical implications of the buprenorphine release profile from Sixmo implant should be further discussed by the Applicant taking into consideration the amended population e.g patients who are stable on 8mg of SLN

buprenorphine in the first initial phase – please see MO in relation to the safety profile of Sixmo in the proposed target population.

AUC0-24 was only investigated in PRO-810 study at two time points (e.g. at day 1 and 28 days after the implantation – please see Table 3 below) on the small number of subjects.

Bioavailability

In PRO-810 study the relative bioavailability as compared to 16 mg sublingual buprenorphine was investigated.

Table 2 Study PRO-810, Overall Mean (±SD) Plasma (Unadjusted) Buprenorphine Pharmacokinetic Parameters Following Treatment with Sublingual Buprenorphine or Sixmo Implants (PK Population)

PK Parameter	SL BPN		Probuphine Implants		
	Day -2 n = 9[b]	Day -1 n = 9[c]	Day 1 n = 9[d]	Day 28 n = 8[d]	Day 57[a] n = 6[d]
C_{max} (pg/mL)	8610 ± 6900	10400 ± 13400	4890 ± 1110	914 ± 157	781 ± 128
T_{max}[e] (hr)	1.5 (0.50, 2.5)	1.5 (1.0, 2.0)	12 (9.0, 36)	10 (0.00, 24)	0.00 (0.00, 12)
AUC_{0-t}[f] (pg·hr/mL)	66251.3 ± 35877.5	62665.6 ± 36396.8	113131 ± 27737.0	19595.8 ± 3371.57	10230.5 ± 2264.24
AUC_{0-24} (pg·hr/mL)	66251.3 ± 35877.5	62665.6 ± 36396.8	75191.1 ± 24443.0	19595.8 ± 3371.57	10230.5 ± 2264.24
$t_{½}$[e] (hr)	11.42 (11.04 – 12.09)	7.63	--	--	--
λ_z (hr^{-1})	0.0604 ± 0.00231	0.0908	--	--	--
ln C_{max}	8.8976 ± 0.52544	8.8840 ± 0.73905	8.4743 ± 0.20560	6.8048 ± 0.16940	6.6485 ± 0.16938
ln AUC_{0-t}	11.003 ± 0.44841	10.937 ± 0.46671	11.613 ± 0.22442	9.8696 ± 0.17730	9.2080 ± 0.25918
ln AUC_{0-24}	11.003 ± 0.44841	10.937 ± 0.46671	11.184 ± 0.30992	9.8696 ± 0.17730	9.2080 ± 0.25918

SL BPN = Treatment A = 16 mg/day QD SL BPN for 5 consecutive days
Probuphine Implants = Treatment B = 4 Probuphine Implants (80 mg BPN HCl/implant) for 24 weeks
[a]Day 57 represents post-removal of the 4 Probuphine implants parameters.
[b]On Day -2, n = 4 for λ_z and $t_{½}$. Apparent terminal λ_z and $t_{½}$ values are missing in 5 patients (Subjects 1001001, 1001007, 1001008, 1001011, and 1001014) due to the absence of apparent terminal phase or due to a resultant too long (relative to the duration of the sampling interval) estimated apparent terminal $t_{½}$ values.
[c]On Day -1, n = 1 for λ_z and $t_{½}$. Apparent terminal λ_z and $t_{½}$ values are missing in 8 patients (Subjects 1001001, 1001007, 1001008, 1001010, 1001011, 1001014, 1001015, and 1001017) due to the absence of an apparent terminal phase or due to a resultant too long (relative to the duration of the sampling interval) estimated apparent terminal $t_{½}$ values.
[d]On Days 1, 28, and 57, n = 0 for λ_z and $t_{½}$. Apparent terminal λ_z and $t_{½}$ values are missing due to the absence of apparent terminal phase or due to a resultant too long (relative to the duration of the sampling interval) estimated apparent terminal $t_{½}$ values in all patients.
[e]Median (min, max) reported for T_{max} and $t_{½}$.
[f]On Days -1 and -2, AUC_{0-t} represents the AUC from Day -1 or Day -2 Hour 0 through Day 1 or Day -2 Hour 12 and on Day 1, AUC_{0-t} represents the AUC from Day 1 Hour 0 through Day 2 Hour 36, relative to the time of implantation.

Study PRO-810 was performed in order to investigate the relative bioavailability of Sixmo versus sublingual (SL) buprenorphine as determined by AUC0-24 at steady state and to investigate the PK profile of Sixmo implants.

The study was halted at week 8 (day 56) and no PK assessments were performed after this time point therefore this study was not providing the PK data for the proposed 6 month implantation period.

The applicant reported AUC0-24 values at day 57. However it needs to be noted that the Blood samples for the determination of plasma concentrations of BPN were collected only just before and after the implant removal.

The relative bioavailability of 4 Sixmo implants versus 16 mg of sublingual buprenorphine tablets as determined by plasma buprenorphine AUC0-24 was assessed at “steady state”. For Sixmo implants “steady state” phase was defined as the latter phase of sustained buprenorphine release e.g 28 days after implantation.

This assessment have shown that at day 28 after implantation, the relative bioavailability of 4 Sixmo implants was approximately 70% lower than that observed after treatment w**ith 16 mg SL

buprenorphine (e.g the mean BPN AUC0-24 value on Day 28 following 4 Sixmo implants was only 29.6% and 31.3% of the mean Day -2 and Day -1 AUC0-24 values for SL BNP).

Similarly, the mean plasma concentrations at Day 28 were approximately 38% to 48% lower than trough concentrations recorded immediately preceding SL dosing with 16 mg tablets on Days -2 and -1.

2.4.2.3. Investigation potential for dose dumping

The risk of dose dumping was investigated in the context of changes to body temperature and as a result of mechanical stress.

The application of external heat to Sixmo implants was studied in implanted dogs (Study PRONDR- 1201) and no dose dumping of buprenorphine was detected in this study.

As claimed by the applicant the dose dumping is also unlikely in case of mechanical stress leading to breakage of implants into two parts. In this case the surface area exposed to the interstitial fluid and where absorption can occur increases only by 4.6%. The residual content in explanted rods after 6-months implantation was similar for implants retrieved in 2 pieces as compared to intact implants.

2.4.2.4. Dose proportionality and time dependency

The dose proportionality was not investigated in the Sixmo development program.

AUCs of buprenorphine were not compared between dose levels.

In TTP-400-02-01 study, mean Cmax and the average plasma concentration from Day 21 to removal was compared for two dose levels e.g 2 implants versus 4 implants

For Dose Group A (2 implants), maximum plasma concentration was 2.00 ± 0.41 ng/mL, time to maximum plasma concentration was 17.34 ± 5.00 hours, and the average plasma concentration from Day 21 to removal was 0.37 ± 0.07 ng/mL. For Dose Group B (4 implants), maximum plasma concentration was 3.23 ± 0.48 ng/mL, time to maximum plasma concentration was 15.95 ± 4.9 hours, and the average plasma concentration from Day 21 to removal was 0.72 ± 0.11 ng/mL.

The applicant claimed that the approximate 2-fold higher steady state concentration for 4 implants over 2 implants suggests dose linearity. The comparison of mean Cmax for 2 implants (2.00ng/ml) and 4 implants (3.23 ng/ml) indicated however less than dose proportional increase in Cmax. No data for fifth implant were provided. In line with the originally proposed SmPC fifth implant could be inserted in patients with insufficient response to the initially inserted 4 implants. The dose proportionality has not been discussed up to the dose level of 5 implants. The applicant has decided to no longer pursue the plan to use the 5th implant.

Table 3 Study TTP-400-02-01, Sixmo Pharmacokinetic Summary

Buprenorphine Pharmacokinetic Parameter	Dose Group A[a] Mean (SD)	Dose Group B[b] Mean (SD)
C_{max} (ng/mL)	2.00 (0.41)	3.23 (0.48)
C_{avg} (ng/mL) (Day 21 through implant removal)	0.37 (0.07)	0.72 (0.11)
T_{max} (hours)	17.34 (5.00)	15.95 (4.9)

2.4.2.5. Intra- and inter-individual variability

The variability in the BPN concentrations in subjects treated with Sixmo implants was lower than the variability reported in the placebo group or following administration of SL buprenorphine.

2.4.2.6. Special populations

No formal studies were conducted to evaluate the PK properties of Sixmo in special populations. Instead the mean values of buprenorphine and norbuprenorphine concentrations from pooled studies (e.g. Studies PRO-805 and PRO-806; Studies PRO-807 and PRO-811; and Studies PRO-TTP-400-02-01 and PRO-810 were pooled together) were compared between different subgroups and presented in the table format. The validity of such comparison is limited. No statistical analysis of the observed effects was performed, confidence intervals were not reported. In addition, the data from patients receiving SL buprenorphine supplementation in the Sixmo treatments groups were pooled together with patients not receiving such supplementation therefore the precise determination of the contribution of Sixmo implants to the observed effects cannot be made. The applicant was requested to re-analyse the data and provide more robust discussion on the PK in different subpopulations treated with Sixmo. As requested the data were re-analysed and only subjects not receiving supplementation were included.

The population PK analysis was performed and provided for assessment.

BMI did not appear to have an impact on exposure levels as per the popPK analysis however the provided data are insufficient to firmly conclude whether there is any correlation between BMI and Cmax during the initial fast absorption phase.

In general higher buprenorphine and norbuprenorphine concentrations were observed in females as compared to males.

Children aged under 18 of age were not enrolled to studies the product is now only recommended for adults.

Patients with age over 65 years of age were not included in studies and therefore the use of Sixmo implants in this population is not recommended

No PK data on the use of Sixmo in patients with impaired renal or hepatic function were provided.

2.4.3. Pharmacodynamics

No additional clinical studies to examine the mechanism of action of Sixmo were conducted given the available data on buprenorphine. Buprenorphine is an opioid partial agonist at the mu opioid receptor and an antagonist at the kappa receptor. Mixed agonist-antagonist activity and slow rates of opioid receptor association and dissociation result in prolonged pharmacodynamics activity and low dependence liability.

As a partial mu receptor agonist with low intrinsic activity, buprenorphine exhibits a “ceiling effect” such that the opioid effects of buprenorphine plateau at higher doses

2.4.4. Discussion on clinical pharmacology

Titan Pharmaceuticals has conducted 7 clinical studies which evaluated the safety and efficacy of Sixmo for substitution treatment of opioid dependence. The PK data were collected and analyzed in 6 of the 7 studies. These included one open-label PK and safety study (TTP-400-02-01), two Phase 3 placebo-controlled safety and efficacy studies (PRO-805 and PRO-806), two open-label retreatment studies (PRO-807 and PRO-811), and one bioavailability study (PRO-810). Study PRO-814 did not include PK assessments.

Studies PRO-810 and TTP-400-02-01 provided the main PK data. In PRO-810 study the relative bioavailability as compared to 16 mg sublingual buprenorphine was investigated and Cmax, Tmax and AUC0-24 on day 1 after impanation and at “steady-state” were recorded.

In TTP-400-02-01 study, concentrations of buprenorphine and norbuprenorphine after implantation of 2 or 4 Sixmo implants were compared to concentrations recorded after treatment with 8 mg or 16 mg of SL buprenorphine. Cmax, Tmax and Cavg (average concentration from Day 21 to the last observation before removal calculated) were reported as well as renal clearance of unchanged buprenorphine and mean terminal half-life after Sixmo removal. In this study the residual content of explanted implants were also investigated. AUC were not compared in this study

In PRO-805, PRO-806, PRO-807 and PRO-811 studies concentrations of buprenorphine and norbuprenorphine were recorded at different time points and compared to those observed in other treatment groups (e.g placebo group in PRO-805 and PRO-806 study or comparator group in PRO-806 study).

It needs to be highlighted that the interpretation of the originally provided data was difficult due to the “as needed” administration of supplemental SL BPN and the variability in the collection time of PK sampling relative to the administration of supplemental SL BPN. The recorded buprenorphine and norbuprenorphine concentration results were significantly confounded by co-administration of SL buprenorphine. The applicant was requested to focus their assessment on the subgroup of subjects not receiving any SL supplementation or when received SL supplementation was unlikely to affect the measured buprenorphine and/or norbuprenorphine concentrations.

As per the guideline (EMA/CPMP/EWP/280/96 Corr1) the following aspects of these modified release formulations need to be investigated: the rate and extent of absorption, fluctuations in drug concentrations at steady state, inter-subject variability in pharmacokinetics arising from the drug formulation, dose proportionality, factors affecting the performance of the modified release formulation and the risk of unexpected release characteristics (e.g. dose dumping).

The absolute bioavailability was not investigated in the Sixmo development program. The relative bioavailability was investigated in PRO-810 study.

The **relative bioavailability** of 4 Sixmo implants versus 16 mg of sublingual buprenorphine tablets as determined by plasma buprenorphine AUC0-24 was compared at “steady state”. For Sixmo implants it was not true steady state as “steady state” phase was defined as the latter phase of sustained buprenorphine release (e.g at day 28 after implantation).

This comparison has shown that at day 28 after implantation, the relative bioavailability of 4 Sixmo implants was approximately 70% lower than that observed after treatment with 16 mg SL buprenorphine (e.g the mean BPN AUC0-24 value on Day 28 following 4 Sixmo implants was only 29.6% and 31.3% of the mean Day -2 and Day -1 AUC0-24 values for SL BNP).

Similarly, the mean plasma concentrations at Day 28 were approximately 38% to 48% lower than trough concentrations recorded immediately preceding SL dosing with 16 mg tablets on Days -2 and -1.

The applicant originally proposed that patients previously treated with sublingual buprenorphine up to the dose of 16 mg per day can be switched to 4 Sixmo implants. This recommendation was not supported by the presented above PK data as the markedly lower exposure was recorded after insertion of 4 Sixmo implants as compared to the exposure recorded during the treatment with 16 mg tablets per day. The proposed indication was amended and now only includes subjects who are stable on 8 mg dose of sublingual buprenorphine.

Markedly lower buprenorphine concentrations as compared to 16 mg tablets were also recorded in other studies. In Study TTP-400-02-01, a comparison between SL BPN and Sixmo in Group B (16 mg tablets versus 4 implants) showed significantly lower concentrations achieved after implantation. Average plasma buprenorphine concentrations from Day 21 to implant removal were lower than those observed 24 hours after the respective SL buprenorphine dosing e.g at day 21 after implantation average concentration was 33% lower in Group B as compared to the trough buprenorphine concentration recoded after treatment with SL Buprenorphine in the same group. AUCs were not compared in this study. Peak plasma buprenorphine concentrations for SL BPN and following Sixmo insertion were also compared showing lower concentrations for implants. In study PRO-806, the overall mean plasma BPN concentrations were lower in subjects who received 4 or 5 Sixmo implants compared with subjects who received 12, 14, or 16 mg/day SL BPN.

The **dose proportionality** was not investigated in the Sixmo development program. AUCs of buprenorphine were not compared between dose levels..

Sixmo implants release buprenorphine which produce, around after 21 days of treatment, low (<1 ng/mL) buprenorphine concentration. On the other hand during first 4 weeks significantly higher values were recorded. This "**two-phased" buprenorphine release profile** may have clinical impactions. The applicant is requested to discuss clinical implications of the buprenorphine release profile from Sixmo implant taking into consideration the amended population e.g patients who are stable on 8mgs of SLN in the first initial phase- **see safety MO.**

Switching from sublingual tablets. In line with the SmPC sublingual buprenorphine should be discontinued 12 to 24 hours prior to insertion of Sixmo implants.The proposed SmPC recommendation is acceptable.

As indicated by the applicant the **variability** in the BPN concentrations in subjects treated with Sixmo implants was lower than the variability reported in the placebo group or following administration of SL buprenorphine. However the assessment of the variability in the Sixmo group originally was based on the data from subjects who received or not received SL supplementation. For phase 3 studies the intra-occasion variability was re-analysed separately for patients with and without SL BPN supplementation and based on these results it was concluded that the intra-occasion variability in plasma buprenorphine concentration by visit was not significantly different between these two groups.

The risk of **dose dumping** was investigated in the context of changes to body temperature and as a result of mechanical stress.

The application of external heat to Sixmo implants was studied in implanted dogs and no dose dumping of buprenorphine was detected in this study.

As claimed by the applicant the dose dumping is also unlikely in case of mechanical stress leading to breakage of implants into two parts. In this case the surface area exposed to the interstitial fluid and where absorption can occur increases only by 4.6%. The residual content in explanted rods after 6-months implantation was similar for implants retrieved in 2 pieces as compared to intact implants.

For Sixmo, the application site is limited to one body area e.g inner side of the upper arm, therefore the assessment of the PK profile after impanation at different application sites were not performed.

No formal studies were conducted to evaluate the PK properties of Sixmo in **special populations**. Instead the mean values of buprenorphine and norbuprenorphine concentrations from pooled studies (e.g. Studies PRO-805 and PRO-806; Studies PRO-807 and PRO-811; and Studies PRO-TTP-400-02-01 and PRO-810 were pooled together) were compared between different subgroups and presented in the table format. The validity of such comparison is limited. No statistical analysis of the observed effects was performed, confidence intervals were not reported. In addition, the data from patients receiving SL buprenorphine supplementation in the Sixmo treatments groups were pooled together with patients not receiving such supplementation therefore the precise determination of the contribution of Sixmo implants to the observed effects cannot be made.

The population PK analysis was performed and provided for assessment.

BMI did not appear to have an impact on exposure levels as per the popPK analysis however the provided data are insufficient to firmly conclude whether there is any correlation between BMI and Cmax during the initial fast absorption phase.

In general, higher buprenorphine and norbuprenorphine concentrations were observed in females as compared to males. Children aged under 18 of age were note enrolled to studies however the product is now recommended for adults only.

Patients with age over 65 years of age were not included in studies and therefore the use of Sixmo implants in this population is not recommended.

No PK data on the use of Sixmo in patients with impaired renal or hepatic function were provided by the Applicant. The proposed SmPC wording is in line with the SmPC for Suboxone. It is noted that BPN concentrations recorded in patients after insertion of 4 Sixmo was relatively low (similar to those observed after treatment with 8 mg tablets) therefore it is considered that the recommendation present in the SmPC for Suboxone in relation to patients with renal impairment is also relevant to Sixmo.

Buprenorphine is contraindicated in patients with severe hepatic impairment. The guidance on use of Sixmo in moderate hepatic impairment has been revised to reflect the context of use of implantable Sixmo since there is no option to down-titrate the buprenorphine dose with this formulation, in comparison to other buprenorphine formulations.

2.4.5. Conclusions on clinical pharmacology

The clinical pharmacology dossier is acceptable.

2.5. Clinical efficacy

2.5.1. Main study(ies)

PRO-814

Randomized, Double-Blind, Double-Dummy, Active-Controlled Multicenter Study of Adult Outpatients With Opioid Dependence Transitioned From a Daily Maintenance Dose of 8 mg or Less of Sublingual Buprenorphine or Buprenorphine/Naloxone to Four Sixmo® Subdermal Implants

Date First Subject Enrolled: 26 June 2014

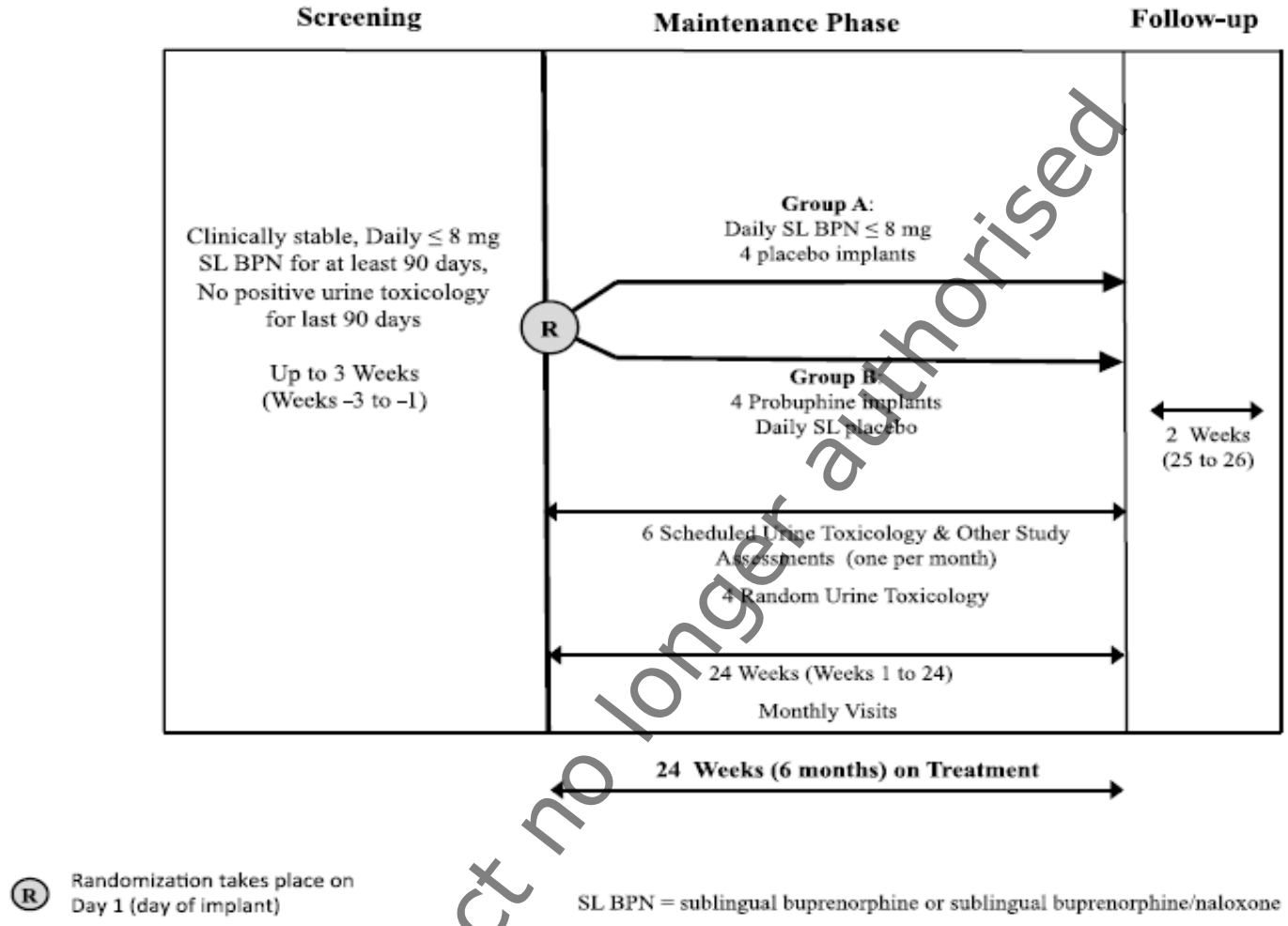
Date Last Subject Completed: 18 May 2015

Methods

This was a randomized, double-blind, double-dummy, active-controlled, multicentre study that evaluated the safety and efficacy of four 80 mg Sixmo implants in adult outpatients with opioid dependence who were clinically stabilized on ≤8 mg SL BPN.

The study consisted of 3 phases: a Screening Phase (up to 3 weeks in duration), a 24-week Maintenance Phase; and a 2-week Follow-Up Phase. The study had a Screening Visit, 12 Maintenance Phase visits, a Post-Treatment Telephone Contact, and a Follow-Up Visit.

Figure 4 Study Design



Sixmo was compared to SL BPN using a non-inferiority analysis. Given the pharmacokinetic data showing that four 80 mg Sixmo implants yield BPN plasma concentrations similar to those observed with a daily SL BPN dose of ≤8 mg, the study design was consistent with other trials in which subjects were transferred to alternative dosage forms yielding similar plasma concentrations of drug (e.g., transfer from once-daily to weekly dosing of anti-diabetics, Gastaldelli, 2014).

Research indicates that for most people with drug dependence, the threshold of significant improvement is reached after approximately 3 months of treatment, with further gains as treatment is continued (WHO, 2004). Therefore, subjects in maintenance treatment for at least 24 weeks were included in the study.

- **Study participants**

Inclusion Criteria (main)

Were male or female, 18-65 years of age, inclusive.

Had a primary diagnosis of opioid dependence (Diagnostic and Statistical Manual – 4th Edition – text revision [DSM-IV-TR]).

Were considered clinically stable by their treating healthcare provider and confirmed by the following at the time of randomization:

a. Had been on SL BPN treatment for 6 months (at least 24 weeks).

b. Had been on a SL BPN dose of ≤8 mg/day for at least the last 90 days.

c. Had no positive urine toxicology results for illicit opioids in the last 90 days.

Were free from significant withdrawal symptoms (score of ≤5 on the Clinical Opiate Withdrawal Scale [COWS]), as measured at Screening.

Exclusion Criteria (main)

Had a current diagnosis of chronic pain syndrome requiring chronic opioid treatment, or conditions associated with acute episodic flares that required opioid treatment.

Had recent scarring or tattoos on their upper arms, or a history of keloid scarring.

Required current use of agents metabolized through CYP3A4 such as azole antifungals

(e.g., ketoconazole), macrolide antibiotics (e.g., erythromycin), or protease inhibitors

(e.g., ritonavir, indinavir, and saquinavir).

Had a history of coagulopathy within the past 90 days, and/or current anti-coagulant therapy such as warfarin.

Had a current DSM-IV-TR diagnosis for substance dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, cocaine).

Had significant symptoms or other factors that in the opinion of the investigator would have precluded compliance with the protocol, subject safety, adequate cooperation in the study, or obtaining informed consent.

Had a current medical condition such as severe respiratory insufficiency, HIV.

Had a clinically significantly low platelet count on the screening laboratory assessment or liver function test abnormalities (high AST, ALT, Bilirubin or creatinine).

- **Treatments**

Eligible subjects were randomized in a 1:1 ratio to 1 of 2 treatment groups and received either:

- Daily SL BPN tablets (containing BPN and naloxone) for 24 weeks at a dose equivalent to their usual single daily dose of BPN (≤8 mg per day) plus 4 placebo implants (surgically implanted on Day 1), or
- Daily SL placebo tablets for 24 weeks plus 4 Sixmo implants (surgically implanted on Day 1); the Sixmo implants were expected to yield BPN plasma concentrations within a range comparable to the average plasma concentrations observed following daily doses of ≤8 mg SL BPN.

Sixmo and placebo implants were implanted and removed by a trained Implant Clinician.

Prior to randomization on Day 1, it was recommended that subjects discontinue their prior SL

BPN and have implants inserted subdermally within 12-24 hours after their last SL BPN dose.

Implantation under the skin of the upper arm was performed using a specialized applicator provided by the sponsor, which was similar in design to commercially-approved applicators used for the insertion of other implantable drugs, such as Implanon®.

Subjects were monitored closely for AEs and vital signs for at least 30 minutes following insertion by medically qualified personnel. Subjects were instructed to place SL BPN or placebo tablets under their tongue until dissolved. For dosages requiring more than one SL tablet, tablets were to be placed in different areas under the tongue at the same time.

Supplemental SL BPN and Other Interventions

The investigator was instructed to treat additional symptoms of opioid dependence as they normally would, including additional counselling sessions, supplemental SL BPN, or other pharmacological interventions. Supplemental SL BPN was allowed at the discretion of the investigator without any limitations. However, subjects were told that while additional counselling and other pharmacological interventions were available, their then-current dose of BPN was expected to be adequate to maintain stability and that they were not expected to need supplemental SL BPN. Any supplemental SL BPN, additional counselling, and other pharmacological interventions provided by the investigator were recorded, along with the reasons for determining the need for supplemental intervention.

PRO-814 utilized LC-MS/MS (liquid chromatography tandem mass spectrometry) for urinalysis of illicit opioids. Urinalysis did not include buprenorphine or its metabolites.

- **Objectives**

Primary Objective

The primary objective of the study was to demonstrate maintenance of treatment efficacy when transferring adult outpatients with opioid dependence who were clinically stabilized on ≤8 mg SL BPN, to 4 Sixmo implants compared to SL BPN.

Secondary Objective

The secondary objective of the study was to confirm the safety of 4 Sixmo implants in adult out patients with opioid dependence who were clinically stabilized on ≤8 mg SL BPN.

- **Outcomes/endpoints**

Primary Efficacy Variable(s)

The primary efficacy variable was responder rate, where a responder was defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use. Evidence of illicit opioid use was defined as a positive opioid urine toxicology result or self-reported illicit opioid use.

The primary analysis of responder rate was based on the ITT population.

To derive the responder rate, the monthly illicit opioid use assessment window had to be determined. The monthly window was defined as the time from the previously scheduled visit window date to the current window date. For example, the first monthly illicit opioid use assessment window was the time between the randomization date and the Week 4 visit date; the second monthly illicit opioid use assessment window was the time between the Week 4 visit date + 1 and the Week 8 visit date. Based on this definition, the monthly window may not have been exactly 4 weeks for all subjects or for all monthly assessment windows within the same subject.

Evidence of illicit opioid use within a monthly window was defined as a positive opioid urine toxicology result or self-reported illicit opioid use within that monthly window, including the results from random urine toxicology samples obtained within that monthly window. Therefore, there was evidence of illicit opioid use, if self-reported illicit opioid use was present, regardless of whether the opioid urine toxicology result was positive or negative. If urine toxicology results were missing, the results were imputed as described in Section 9.7.1.2.

For the primary efficacy variable, a test of non-inferiority of Sixmo (active) versus SL BPN (control) was conducted. A non-inferiority margin of 20% was employed to define non-inferiority.

Secondary Efficacy Analyses

Secondary efficacy variables were evaluated using the ITT population. These variables included the following:

Percentage of subjects with no urine illicit opioid use by month: The percentages for each treatment and between-treatment percentage differences were estimated and presented with 95% CIs of the estimates.

Time to first evidence of urine illicit opioid use: This was defined as the number of days between the randomization day and the day the sample was obtained.

Cumulative percentage of evidence of urine illicit opioid use by month: This was calculated for all scheduled visits from Week 4 through Week 24.

Percentage of subjects with no self-reported use of any illicit drug by month.

Measures of craving (desire to use and need to use VAS): Changes from Baseline in the

VAS measures were derived by subtracting the baseline values from the post-baseline values; thus, negative changes were indicative of improvement.

Measures of withdrawal (COWS and SOWS): Changes from Baseline in COWS and SOWS were derived by subtracting the baseline values from the post-baseline values; thus, negative changes were indicative of improvement.

Other Efficacy Analyses included

Supplemental SL BPN use

Additional unscheduled visits to obtain counselling

Additional unscheduled visits to obtain supplemental pharmacological therapies

Urine toxicology results for other drugs of abuse

Treatment discontinuation and reasons for discontinuation

- **Sample size**

Determination of Sample Size

The sample size of 90 per treatment group (180 subjects overall) was selected to achieve 87.3% power, assuming both groups had a 75% rate of responders. If the responder rates were actually lower but equal in both groups, with a 65% rate of response pre group, the power of the trial to determine non-inferiority was 80.3%. If each treatment group had an 85% rate of response, the power of the trial to determine non-inferiority was 96.4%.

- **Randomisation**

Eligible subjects were randomized to 1 of 2 treatment groups in a 1:1 ratio. Randomisation was accomplished centrally, using an Interactive Voice Response System and/or by an Interactive

Web Response System managed by the sponsor. Subjects who provided written informed consent were assigned a unique number that was used to identify them throughout the study.

Once a subject number was assigned, it could not be reassigned to any other subject.

In the event that a replacement implant kit (implants or SL study medication) was needed, the investigator was to use the Interactive Voice Response System/Interactive Web Response

System and request a replacement kit, which was set up in the system as an unscheduled visit.

An error in configuration of the unscheduled visit functionality of the system resulted in the incorrect dispensing of study drug for 2 subjects (Subjects 001-001 and 007-008).

The subject, who was originally randomized to receive daily SL BPN tablets plus 4 placebo implants, received a replacement kit containing Sixmo implants and was implanted with active implants. As a result, the subject was subsequently reassigned to the Sixmo treatment group; both the sponsor and the subject remained blinded to treatment allocation.

Subject 007-008, who was randomized to receive daily SL placebo tablets plus 4 Sixmo implants, received the correct medication at randomization. Between the Week 4 and Week 8 visits, the site logged an unscheduled visit for the subject and requested a replacement kit (for SL medication). The subject received a replacement kit containing SL BPN tablets instead of placebo tablets. As a result, the subject received Sixmo and SL BPN tablets for a short period of time (approximately 2 weeks).

The site was notified of the misallocation and the subject was notified. At the time of the notification the subject was within their visit window for their Week 8 visit and returned to clinic for the planned visit, at this time the subject received the correct medication. The site's IRB was notified of the misallocation.

In parallel, sites were notified of the issue and an investigation was opened on the Interactive Web Response System. A programing issue was identified and corrected.

- **Blinding (masking)**

The subject, investigational site personnel, sponsor, and sponsor designees directly involved in the conduct and/or monitoring of the study were not aware of the treatment group assignments.

Since the placebo implants had a slightly different appearance than the Sixmo implants, any staff involved in the implant insertion and removal procedures, including the Implanting Clinician, did not participate in the study evaluations or discuss with other study staff any information regarding the implants in reference to the subjects. In addition, the blinded study staff was instructed to not ask the Implanting Clinician or staff involved in the implant insertion and removal procedures for information regarding subject group assignment that might inadvertently result in unblinding. To maintain the subject blind, appropriate steps were taken to ensure that the subject was unable to view the implant insertion or removal procedures at any time.

The SL BPN tablets used in the study had a nearly-matching placebo. To maintain the study blind, subjects were told that clinical supplies of SL BPN had been specifically developed for the study and could have looked or tasted differently than commercially-available products to which they were accustomed. In addition, a different brand of SL BPN was used for any potential supplemental SL BPN needs. Designated unblinded site personnel maintained drug accountability records for all dispensed and returned SL BPN and SL placebo tablets. These unblinded site personnel did not participate in the study evaluations or discuss with other study staff any information regarding the SL tablets in reference to the subjects.

- **Statistical methods**

A Statistical Analysis Plan (SAP), dated 16 November 2014, was finalized before database lock.

All analyses were performed using SAS version 9, and all hypothesis tests were conducted at a 2-sided significance level of 0.05. Continuous (non-survival related) data were summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Frequencies and percentages were used to summarize categorical (discrete) data.

Unless otherwise stated, confidence intervals (CIs), when presented, were constructed at the 2-sided 95% level. For binomial variables, the 95% CIs were constructed using the normal approximation without continuity correction.

Analysis Populations

Four study populations were used in this study:

- Randomized Population: consisted of all subjects who completed the Screening Phase and were randomized to a treatment group.
- Intent-to-Treat (ITT) Population: consisted of all randomized subjects who received study medication and provided some efficacy data. Primary efficacy analyses were based on the ITT population.
- Per-Protocol (PP) Population: included all subjects in the ITT population who had no major protocol violations (see Section 9.7.1.6 for the definition of major protocol violation).
- Safety Population: included all subjects who received study medication. Analyses based on this population grouped subjects according to the treatment they actually received regardless of the treatment they were randomized to receive.

Several sensitivity analyses were also performed, for the primary endpoint as follows:

- Responder rate in which missing urine data were imputed with 10% relative penalty (as described in Section 9.7.1.2) (ITT population)
- Responder rate based on adjusted monthly windows (further described in the SAP), using the primary imputation method for missing urine test results (ITT population).
- Responder rate using the primary imputation method for missing urine test results in a subset of ITT subjects who provided all required samples (completer's analysis)
- Responder rate using the primary imputation method for missing urine test results (PP population).

Handling of Dropouts or Missing Data

To avoid bias, in the primary analyses, missing urine values were replaced by randomly generated binary indicators (1 = opioid positive and 0 = opioid negative) using seed = 1374809352 in SAS.

The primary imputation involved a 20% (non-inferiority margin) relative penalty. With this imputation, missing urine values in the SL BPN group were imputed based on the proportion of "opioid-positive" samples within the treatment group. This proportion was the average of the within-subject proportion of "opioid-positive" sample. Missing urine values in the Sixmo group were imputed based on the proportion equal to 1.2 times the maximum proportion of the 2 proportions from the 2 treatment groups. For example, if the proportions of "opioid-positive" samples were to be 14% for the Sixmo group and 15% for SL BPN group, the imputation for the SL BPN group would be based on 15% and the imputation for the Sixmo group would be based on 18%.

The conclusion of non-inferiority and superiority of the Sixmo group over the SL BPN group, as measured by response rate, was considered robust, even in the presence of missing values, since the conclusion was based on an imputation method in favour of SL BPN.

Table 4 Results

- **Participant flow**

POPULATION	STATUS AT THE END OF TREATMENT PERIOD	SUBLINGUAL BUPRENORPHINE	PROBUPHINE	TOTAL
RANDOMIZED		90 (100.0%)	87 (100.0%)	177 (100.0%)
SAFETY#		89 (98.9%)	87 (100.0%)	176 (99.4%)
	COMPLETED	84 (94.4%)	81 (93.1%)	165 (93.8%)
	DISCONTINUED	5 (5.6%)	6 (6.9%)	11 (6.3%)
ITT#		89 (98.9%)	84 (96.6%)	173 (97.7%)
	COMPLETED	84 (94.4%)	81 (96.4%)	165 (95.4%)
	DISCONTINUED	5 (5.6%)	3 (3.6%)	8 (4.6%)
PER PROTOCOL#		72 (80.0%)	67 (77.0%)	139 (78.5%)
	COMPLETED	69 (95.8%)	65 (97.0%)	134 (96.4%)
	DISCONTINUED	3 (4.2%)	2 (3.0%)	5 (3.6%)

Table 5 Subject Disposition (Safety Population)

Category	SL BPN	Probuphine	Total
Randomized	90	87	177
Safety Population (N)	89	87	176
Completed, n (%)	84 (94.4)	81 (93.1)	165 (93.8)
Discontinued, n (%)	5 (5.6)	6 (6.9)	11 (6.3)
Reason for discontinuation, n (%)			
Adverse event	0	1 (1.1)	1 (0.6)
Request of sponsor or regulatory agency	1 (1.1)	0	1 (0.6)
Lost to follow-up	2 (2.2)	4 (4.6)	6 (3.4)
Other[a]	0	1 (1.1)	1 (0.6)
Subject request	2 (2.2)	0	2 (1.1)

Of the 177 subjects enrolled and randomized into the study, 176 (99.4%) subjects were included the safety population. Subject 007-027 (SL BPN group) did not receive study medication and was excluded from this population.

A total of 173 (97.7%) subjects were included the ITT population. Four subjects, 1 in the SL BPN group (Subject 007-027) and 3 in the Sixmo group (Subjects 001-001, 012-006, 015-012), were excluded from the ITT population. Subject 007-027 did not receive study medication; the other 3 subjects did not have any post-baseline evaluations and therefore did not provide any post-baseline efficacy data.

A total of 139 (78.5%) subjects were included the PP population. Thirty-eight subjects (18, SL BPN; 20 Sixmo) were excluded from the PP population. One subject in the SL BPN group (Subject 007-027) was excluded because no study medication was administered; the other 37 subjects were excluded from the PP population for a major protocol deviation.

Table 6

Category	SL BPN	Probuphine	Total
Randomized (N)	90	87	177
Safety population, n (%)	89 (98.9)	87 (100.0)	176 (99.4)
ITT population, n (%)	89 (98.9)	84 (96.6)	173 (97.7)
PP population, n (%)	72 (80.0)	67 (77.0)	139 (78.5)

Abbreviations: ITT, intent-to-treat; PP, per-protocol; SL BPN, sublingual buprenorphine
Source: Table 14.1.1.1

Protocol deviations

A total of 37 (21.4%) subjects in the ITT population, 17 (19.1%) in the SL BPN group and 20 (23.8%) in the Sixmo group, had a major protocol deviation during the study.

The most common type of major protocol violation was related to incorrect conduct of study procedures/assessments, primarily lack of psychological counselling at 1 or more of the specified visits and missing or unstable samples for illicit drug screen or opiate testing.

Most of the subjects excluded from the PP analyses were due to procedural deviations such as missed psychosocial counselling, out of window visits, and isolated cases of missing urine samples, or unusable samples. These deviations were not expected to increase the safety risk of subjects or impact on the conclusion of the study results.

Table 7

Category[a]	SL BPN N=89	Probuphine N=84	Total N=173
Number of Subjects with at Least 1 Major Protocol Violation	17 (19.1)	20 (23.8)	37 (21.4)
Study Procedures/Assessments	11 (12.4)	16 (19.0)	27 (15.6)
Missing Endpoint Assessments	4 (4.5)	5 (6.0)	9 (5.2)
Other protocol deviation	0	2 (2.4)	2 (1.2)
Study treatment compliance	2 (2.2)	1 (1.2)	3 (1.7)
Study treatment/administration/dispensing	1 (1.1)	0	1 (0.6)
Visit Scheduling	1 (1.1)	0	1 (0.6)

Abbreviations: ITT, intent-to-treat; SL BPN, sublingual buprenorphine
[a] Subjects may have had a major protocol violation in >1 category.
Source: Listing 16.2.3, Listing 16.2.10.14

- **Conduct of the study**

This trial was conducted in accordance with the ethical principles of Good Clinical Practice (GCP), according to the International Conference on Harmonization (ICH) Harmonized Tripartite Guideline, including, where applicable, the Declaration of Helsinki. The study was also conducted in keeping with applicable national and local laws and regulations.

Changes in Study Conduct

The original protocol was dated 14 May 2014. The protocol was amended 3 times: 14 August 2014 (Amendment 1); 24 September 2014 (Amendment 2); and 30 March 2105 (Amendment 3). The main purpose of these amendments was to streamline and add clarity to the text and address administrative needs. They were not expected to change the characteristics of study population or impact the quality and reliability of the safety and efficacy assessments. Therefore, the amendments were not expected to have any impact on the conclusions of the study.

Changes to Planned Analyses

Except for a few items noted below, no changes were made to the planned analysis outlined in the final SAP.

In the SAP, it was stated that craving would be measured with a desire to use VAS, a need to use

VAS, and a craving VAS. This was in error, as no craving VAS was used in the study.

Two post-hoc analyses were added for the primary efficacy variable: by site and by gender. In addition, a post-hoc analysis was added for the cumulative percentage of evidence of urine illicit opioid use by month imputing results with self-reported opioid use.

The SAP stated that in addition to reporting incidence, all AE tables would include the total number of events, counting multiple events per subject. Subsequent to finalization of the SAP, the AE tables were changed to follow a format of reporting incidence only.

- **Baseline data**

Demographic and Other Baseline Characteristics

The demographic and baseline characteristics observed in the ITT population were very similar to those observed in the safety population.

Table 8 Demographics (Safety Population)

Category	SL BPN N=89	Probuphine N=87	Total N=176
Age (years)			
Mean (SD)	39 (10.8)	38 (11.2)	39 (11.0)
Min, max	22, 64.0	21, 63.0	21, 64.0
Gender, n (%)			
Male	52 (58.4)	52 (59.8)	104 (59.1)
Female	37 (41.6)	35 (40.2)	72 (40.9)
Race, n (%)			
White	85 (95.5)	82 (94.3)	167 (94.9)
Black or African American	2 (2.2)	3 (3.4)	5 (2.8)
Asian	0	1 (1.1)	1 (0.6)
American Indian or Alaska native	1 (1.1)	1 (1.1)	2 (1.1)
Other	1 (1.1)	0	1 (0.6)
Ethnicity, n (%)			
Hispanic or Latino	3 (3.4)	3 (3.4)	6 (3.4)
Not Hispanic or Latino	86 (96.6)	84 (96.6)	170 (96.6)
BMI (kg/m^2)			
Mean (SD)	27 (5.92)	28 (6.94)	28 (6.47)
Min, max	19, 50.6	14, 46.4	14, 50.6

Abbreviations: BMI, body mass index; SD, standard deviation; SL BPN, sublingual buprenorphine
Source: Table 14.1.2.1

History of Substance Abuse

The most common primary opioid of abuse was prescription opioid pain relievers (74.4%), followed by heroin (21.0%). Seven (4.0%) subjects had "other" reported as the primary opioid of abuse: heroin and prescription opioid pain reliever (3 subjects), non-prescription opioid use (1 subject), morphine and heroin (1 subject), non-prescription pain reliever (1 subject), and oxycodone off the street (1 subject). Overall, median time since first opioid abuse was 10.5 years (range: 1.4 to 45.6 years). Median time since first diagnosis of opioid abuse was 4.6 years (range: 0.5 to 43.6 years). The history of opioid abuse was comparable between the 2 treatment groups.

Table 9 History of Opioid Abuse (Safety Population)

Category	SL BPN N=89	Probuphine N=87	Total N=176
Met DSM-IV-TR criteria for opioid abuse, n (%)			
Yes	89 (100.0)	86 (98.9)	175 (99.4)
Not reported[a]	0	1 (1.1)	1 (0.6)
Primary opioid of abuse, n (%)			
Prescription opioid pain reliever	65 (73.0)	66 (75.9)	131 (74.4)
Heroin	22 (24.7)	15 (17.2)	37 (21.0)
Other	2 (2.2)	5 (5.7)	7 (4.0)
Not reported	0	1 (1.1)	1 (0.6)
Time since first opioid abuse (years)			
N	89	86	175
Mean (SD)	11.5 (7.68)	11.2 (6.62)	11.3 (7.16)
Median	10.7	10.1	10.5
Min, max	1.6, 45.6	1.4, 36.6	1.4, 45.6
Time since first diagnosis (years)			
N	89	86	175
Mean (SD)	6.2 (6.95)	6.2 (5.93)	6.2 (6.45)
Median	3.9	5.4	4.6
Min, max	0.6, 43.6	0.5, 34.6	0.5, 43.6

Substance Abuse Treatment History

Overall, most of the subjects in the safety population had previously entered BPN treatment either 1 (69.9%) or 2 (22.7%) times.

The median duration of BPN treatment was 2.8 years (range: 0.4 to 10.0 years). The highest mean daily dose of BPN ever taken by subjects prior to study entry was 14 mg/day (range: 2 to 36 mg/day); the most common highest daily doses were 8 mg/day (32.4%) and 16 mg/day (40.9%).

Per protocol, all subjects were receiving a dose of BPN ≤8 mg/day at study entry; the majority of subjects were receiving 8 mg/day BPN (72.7%).

Table 10 Buprenorphine Treatment History (Safety Population)

Category	SL BPN N=89	Probuphine N=87	Total N=176
Buprenorphine Treatment (years)			
Mean (SD)	3.4 (2.54)	3.5 (2.64)	3.5 (2.58)
Median	2.5	3.0	2.8
Min, max	0.4, 10.0	0.5, 10.0	0.4, 10.0
Highest Dose of Buprenorphine Treatment Ever Taken (mg/day)			
Mean (SD)	14 (6.16)	14 (5.85)	14 (6.00)
Min, max	4.0, 36.0	2.0, 32.0	2.0, 36.0
Highest Dose of Buprenorphine Treatment Ever Taken (mg/day), n (%)			
≤4	2 (2.2)	2 (2.3)	4 (2.3)
8	26 (29.2)	31 (35.6)	57 (32.4)
10	2 (2.2)	1 (1.1)	3 (1.7)
11	0	1 (1.1)	1 (0.6)
12	6 (6.7)	8 (9.2)	14 (8.0)
16	41 (46.1)	31 (35.6)	72 (40.9)
20	0	2 (2.3)	2 (1.1)
22	1 (1.1)	0	1 (0.6)
24	8 (9.0)	10 (11.5)	18 (10.2)
32	2 (2.2)	1 (1.1)	3 (1.7)
36	1 (1.1)	0	1 (0.6)
Dose of Buprenorphine at Study Entry (mg/day), n (%)			
2	3 (3.4)	6 (6.9)	9 (5.1)
4	15 (16.9)	12 (13.8)	27 (15.3)
6	4 (4.5)	8 (9.2)	12 (6.8)
8	67 (75.3)	61 (70.1)	128 (72.7)

Abbreviations: SD, standard deviation; SL BPN, sublingual buprenorphine
Source: Table 14.1.3.1

Medical History

Overall, the most common medical conditions at study entry were psychological/psychiatric in nature (64.2%), followed by musculoskeletal (43.2%) and cardiovascular (28.4%) conditions. Medical history results were comparable between the 2 treatment groups.

Psychiatric History

Overall, the proportion of subjects in the safety population who had current, past, or recurrent major depressive episodes was 1.1%, 31.3%, and 15.3%, respectively. Likewise, the proportion of subjects who had current, past, or recurrent major depressive disorder was 1.7%, 27.8%, and 8.5%. The proportion of subjects who had recurrent major depressive episodes was slightly higher in the SL BPN group (19.1%) compared with the Sixmo group (11.5%); similar trends were observed for past major depressive disorder (33.7% vs. 21.8%) and recurrent major depressive disorder (12.4% vs. 4.6%).

Fifteen (8.5%) subjects, 9 (10.1%) in the SL BPN group and 6 (6.9%) in the Sixmo group, were considered by the investigators to be suicidal in the month preceding study entry.

With the exception of lifetime panic disorder (5.6%, SL BPN; 12.6%, Sixmo), no appreciable differences were observed between the 2 treatment groups for the prevalence of other psychiatric disorders.

Prior and Concomitant Medications

Overall, the most common class of prior medications was drugs used in addictive disorders (100.0%), followed by antidepressants (41.5%). The use of prior medications was generally comparable between the 2 treatment groups.

Table 11 Prior Medications Taken by ≥10% of All Subjects by WHO Drug ATC Class (Safety Population)

WHO Drug ATC Class	SL BPN N=89 n (%)	Probuphine N=87 n (%)	Total N=176 n (%)
Drugs used in addictive disorders[a]	89 (100.0)	87 (100.0)	176 (100.0)
Antidepressants	35 (39.3)	38 (43.7)	73 (41.5)
Antiinflammatory and antirheumatic products, non-steroids	12 (13.5)	17 (19.5)	29 (16.5)
Antiepileptics	14 (15.7)	13 (14.9)	27 (15.3)
Anxiolytics	12 (13.5)	11 (12.6)	23 (13.1)
Antipsychotics	11 (12.4)	11 (12.6)	22 (12.5)
Psychostimulants, agents used for ADHD and nootropics	14 (15.7)	8 (9.2)	22 (12.5)
Other analgesics and antipyretics	9 (10.1)	12 (13.8)	21 (11.9)

Measurements of Treatment Compliance

Compliance with study medication was captured through visual inspection and palpation of the insertion site and pill count at each study visit. No evidence of implant removal or attempted removal by the subjects was noted. One case of implant expulsion was reported. Two subjects (1 per treatment group) reporting having their study medication stolen. Subject 007-026, a 31-year-old white male in the SL BPN group, completed 24 weeks of treatment and underwent his Week 24 EOT Visit on Day 175. The investigator reported palpating only 3 implants prior to the removal procedure, as well as visualizing only 3 implants during the procedure. An ultrasound was performed the same day, but the fourth implant could not be located. Subject 015-003, a 45-year-old white male in the SL BPN group, completed 24

weeks of study treatment and underwent his Week 24 EOT Visit on Day 170. Ultrasound was not needed prior to removal, since the implants were palpable. The investigator reported palpating 4 implants prior to the removal procedure. However, only 3 implants were accounted for after removal. On Day 197, the subject underwent an ultrasound of the region of the scar, but the missing implant could not be located.

Urine Toxicology for Other Drugs of Abuse

All urine toxicology samples (scheduled and random) were tested for other drugs of abuse (e.g., cocaine, benzodiazepines, barbiturates, amphetamines, phencyclidine, and tetrahydrocannabinol [THC]) using qualitative (immunoassay) methods. Positive results were not confirmed using quantitative methods.

Supplemental SL BPN and Other Interventions:

The investigator was instructed to treat additional symptoms of opioid dependence as they normally would, including additional counselling sessions, supplemental SL BPN, or other pharmacological interventions. However, subjects were told that while additional counselling and other pharmacological interventions were available, their then-current dose of BPN was expected to be adequate to maintain stability and that they were not expected to need supplemental SL BPN. Any supplemental SL BPN, additional counselling, and other pharmacological interventions provided by the investigator were recorded, along with the reasons for determining the need for supplemental intervention.

Supplemental SL BPN was supplied by the sponsor. For potential supplemental SL BPN needs, a different brand of SL BPN (Actavis) was used to prevent the unblinding of study drug; lot numbers were 1294C141, 2258E141, and 2839G141. The investigator or designee maintained an inventory record of all SL BPN dispensed to subjects for supplemental use.

- **Outcomes and estimation**

The primary efficacy variable was responder rate, where a responder was defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use (based on a composite of both urine results and self-report results). The primary analysis of responder rate was based on the ITT population.

For the primary efficacy variable, a test of non-inferiority of Sixmo (active) versus SL BPN (control) was conducted. A non-inferiority margin of 20% was employed to define non- inferiority.

A CI for the difference in proportions was calculated, and non-inferiority was established if the lower bound of the 95% CI for the difference of proportions (Sixmo – SL BPN) was greater than –0.20.

The proportion of responders was 87.6% in the SL BPN group and 96.4% in the Sixmo group. The 2-sided 95% CI (0.009, 0.167) of the proportion difference (Sixmo – SL BPN) was well above the pre-defined successful margin for non-inferiority.

Furthermore, after establishment of non-inferiority, superiority of Sixmo over SL BPN was tested. The proportion of responders was statistically significantly higher in the Sixmo group (P = 0.034).

Results of the sensitivity analyses were consistent with the primary efficacy results. In each analysis, the proportion of responders was numerically higher in the Sixmo group compared with the SL BPN group, and non-inferiority was demonstrated in each case. The superiority of Sixmo over SL BPN was established for the ITT population, the primary analysis population (P < 0.05). However, the p-value was not significant based on the completer's analysis or the PP population, largely due to smaller sample sizes.

Table 12

Category	SL BPN n (%)	Probuphine n (%)	Proportion Difference (95% CI) Probuphine - SL BPN	*P* Value (2-Sided)[a]
ITT Population (with Primary [20% Relative Penalty] Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non−responder	11 (12.4)	3 (3.6)		
ITT Population (with 10% Relative Penalty Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non−responder	11 (12.4)	3 (3.6)		
ITT Population (Based on Adjusted Monthly Window, Using Treatment Based Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non−responder	11 (12.4)	3 (3.6)		
Completer's Analysis (with within Treatment Based Imputation Method for Missing Urine Testing Results)				
N	79	76		
Responder	70 (88.6)	73 (96.1)	0.074 (−0.008, 0.157)	0.083
Non−responder	9 (11.4)	3 (3.9)		
PP Population (with within Treatment Based Imputation Method for Missing Urine Testing Results)				
N	72	67		
Responder	66 (91.7)	65 (97.0)	0.053 (−0.022, 0.129)	0.176
Non−responder	6 (8.3)	2 (3.0)		

Secondary Efficacy Results

Percentage of Subjects with No Urine Illicit Opioid Use by Month

At each month evaluated (i.e., Month 1 through 6), most (≥85.4%) of the subjects in both treatment groups had no urine illicit opioid use. At each evaluation, the proportion of subjects who had no urine illicit opioid use was numerically higher in the Sixmo group compared with the SL BPN group (No statistically significant differences were observed between treatment groups, except at Month 3, where the proportion of subjects with no urine illicit opioid use was significantly (P = 0.004) higher in the Sixmo group (98.8%) compared with the SL BPN group (87.6%).

Table 13 Percentage of Subjects with No Urine Illicit Opioid Use by Month (ITT Population)

Visit	No Illicit Opioid Use[a]	SL BPN N=89 n (%)	Probuphine N=84 n (%)	Proportion Difference (95% CI) Probuphine - SL BPN	*P* Value[b]
Month 1	Yes	84 (94.4)	80 (95.2)	0.009 (−0.057, 0.075)	0.800
	No	5 (5.6)	4 (4.8)		
Month 2	Yes	79 (88.8)	80 (95.2)	0.065 (−0.015, 0.145)	0.119
	No	10 (11.2)	4 (4.8)		
Month 3	Yes	78 (87.6)	83 (98.8)	0.112 (0.039, 0.184)	0.004
	No	11 (12.4)	1 (1.2)		
Month 4	Yes	80 (89.9)	80 (95.2)	0.054 (−0.024, 0.131)	0.182
	No	9 (10.1)	4 (4.8)		
Month 5	Yes	79 (88.8)	81 (96.4)	0.077 (−0.000, 0.153)	0.056
	No	10 (11.2)	3 (3.6)		
Month 6	Yes	76 (85.4)	76 (90.5)	0.051 (−0.046, 0.147)	0.306
	No	13 (14.6)	8 (9.5)		

Table 14 Responder Rate (ITT and PP Populations and Completer's Analysis)

Category	SL BPN n (%)	Probuphine n (%)	Proportion Difference (95% CI) Probuphine - SL BPN	*P* Value (2-Sided)[a]
ITT Population (with Primary [20% Relative Penalty] Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non–responder	11 (12.4)	3 (3.6)		
ITT Population (with 10% Relative Penalty Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non–responder	11 (12.4)	3 (3.6)		
ITT Population (Based on Adjusted Monthly Window, Using Treatment Based Imputation Method for Missing Urine Testing Results)				
N	89	84		
Responder	78 (87.6)	81 (96.4)	0.088 (0.009, 0.167)	0.034
Non–responder	11 (12.4)	3 (3.6)		
Completer's Analysis (with within Treatment Based Imputation Method for Missing Urine Testing Results)				
N	79	76		
Responder	70 (88.6)	73 (96.1)	0.074 (–0.008, 0.157)	0.083
Non–responder	9 (11.4)	3 (3.9)		
PP Population (with within Treatment Based Imputation Method for Missing Urine Testing Results)				
N	72	67		
Responder	66 (91.7)	65 (97.0)	0.053 (–0.022, 0.129)	0.176
Non–responder	6 (8.3)	2 (3.0)		

Abbreviations: CI, confidence interval; ITT, intent-to-treat; PP, per-protocol; SL BPN, sublingual buprenorphine
[a] Based on the chi-square test for superiority claim.

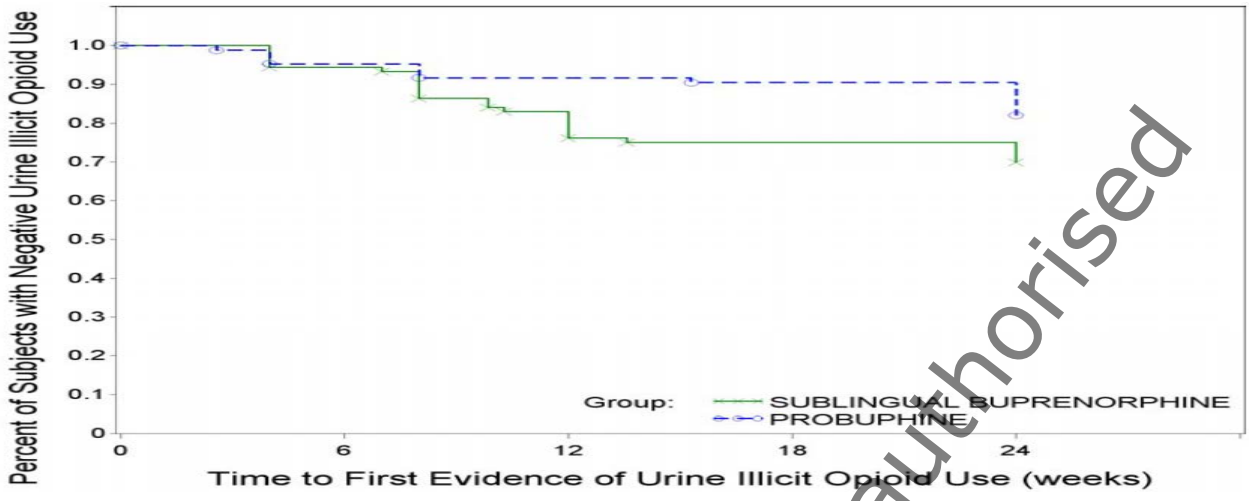
In this analysis, the proportion of responders was 87.6% in the SL BPN group and 96.4% in the Sixmo group. The 2-sided 95% CI (0.009, 0.167) of the proportion difference (Sixmo – SL BPN) was well above the pre-defined successful margin for non-inferiority.

Furthermore, after establishment of non-inferiority, superiority of Sixmo over SL BPN was tested. The proportion of responders was statistically significantly higher in the Sixmo group (*P* = 0.034).

Time to First Evidence of Urine Illicit Opioid Use

The proportion of subjects who showed any evidence of urine illicit opioid use was 28.09% (25/89) and 14.29% (12/84) in the SL BPN and Sixmo groups, respectively. Median time to first evidence of urine illicit opioid use could not be estimated for either treatment group; results of the log-rank test showed a statistically significant (*P* = 0.037) difference between treatment groups for event free distribution of first evidence of urine illicit opioid use.

Figure 5 Time to First Evidence of Urine Illicit Opioid Use



Percentage of Subjects with No Self-Reported Use of Any Illicit Drugs by Month

At each month evaluated (i.e., Month 1 through 6), most (≥79.1%) of the subjects in each treatment group had no self-reported use of any illicit drugs. Except at Week 16, the proportion of subjects who had no self-reported use of any illicit drugs was slightly higher in the Sixmo group compared with the SL BPN group, with differences ranging from 1.4% to 6.3%. The difference between treatment groups was not significant at any time point.

Measures of Craving (Desire to Use and Need to Use VAS)

Changes from Baseline in the VAS measures were derived by subtracting the baseline values from the post-baseline values; thus, negative changes were indicative of improvement. A 100 mm VAS was used for measures of craving. As a supportive analysis, the VAS variable for desire to use was also analyzed via MMRM methods. No statistically significant differences were observed between the 2 treatment groups at any post-baseline time point for changes from Baseline ($P \geq 0.384$). For measure of craving (need to use VAS) No statistically significant differences were observed between the 2 treatment groups at any post baseline time point for changes from Baseline ($P \geq 0.505$)

Measures of Withdrawal (COWS and SOWS)

Withdrawal results were analysed based on the COWS for the ITT population by month of evaluation.

Changes from Baseline in the VAS score for desire to use were very small in each treatment group throughout the study. In the SL BPN group, mean changes in the VAS score ranged from −0.1 at Week 20 and Week 24/EOT to 0.3 at Weeks 4 and 8. In the Sixmo group, mean changes ranged from −0.1 (Week 8, Week 20, Week 24/EOT) to 0.2 (Week 4). No statistically significant differences were observed between the 2 treatment groups at any post-baseline time point for changes from Baseline ($P \geq 0.122$).

Results of the supportive analysis using MMRM methods confirmed the findings of the main analysis.

Table 15 Clinical Opiate Withdrawal Scale (COWS) (ITT Population)

Visit	Statistic	SL BPN N=89	Probuphine N=84	Difference (Probuphine - SL BPN)	*P* Value[a]
Day 1 (BL)	Mean (SD)	1.0 (1.12)	1.0 (1.26)		
Week 4 (Change from BL)	Mean (SD)	0.3 (2.12)	0.2 (1.92)		
	LS Mean (SE)[a]	0.3 (0.21)	0.2 (0.21)	−0.1	0.865
	95% CI[a]	−0.1, 0.7	−0.2, 0.7	−0.6, 0.5	
Week 8 (Change from BL)	Mean (SD)	0.3 (2.50)	−0.1 (1.28)		
	LS Mean (SE)[a]	0.3 (0.20)	−0.1 (0.21)	−0.4	0.122
	95% CI[a]	−0.1, 0.7	−0.5, 0.3	−1.0, 0.1	
Week 12 (Change from BL)	Mean (SD)	0.1 (2.15)	0.0 (1.93)		
	LS Mean (SE)[a]	0.1 (0.21)	0.1 (0.21)	−0.1	0.846
	95% CI[a]	−0.3, 0.5	−0.4, 0.5	−0.6, 0.5	
Week 16 (Change from BL)	Mean (SD)	−0.1 (1.90)	−0.0 (1.81)		
	LS Mean (SE)[a]	−0.1 (0.18)	−0.0 (0.19)	0.1	0.804
	95% CI	−0.4, 0.3	−0.4, 0.4	−0.5, 0.6	
Week 20 (Change from BL)	Mean (SD)	0.2 (2.11)	−0.1 (1.52)		
	LS Mean (SE)[a]	0.2 (0.19)	−0.1 (0.20)	−0.3	0.248
	95% CI[a]	−0.2, 0.6	−0.5, 0.3	−0.9, 0.2	
Week 24/EOT (Change from BL)	Mean (SD)	−0.1 (1.69)	−0.1 (1.51)		
	LS Mean (SE)[a]	−0.1 (0.16)	−0.1 (0.17)	−0.0	0.922
	95% CI[a]	−0.4, 0.3	−0.4, 0.2	−0.5, 0.4	

On Day 1, the mean SOWS score was 2.2 and 2.7 in the SL BPN and Sixmo groups, respectively. With a total possible score of 64, these values indicate that based on subjective assessment, subjects' withdrawal symptoms were well controlled at Baseline.

Changes from Baseline in the VAS score were small in each treatment group throughout the study. In the SL BPN group, mean changes in the VAS score ranged from −0.4 at Week 16 to 0.4 at Week 8. In the Sixmo group, mean changes ranged from −1.1 (Week 8) to 0.3 (Week 4). Except at Week 8, differences between the 2 treatment groups were generally small at each post-baseline time point for changes from Baseline ($P \geq 0.252$). At Week 8, the difference was marginally significant in favour of Sixmo ($P = 0.068$).

Results of the supportive analysis using MMRM methods confirmed the findings of the main analysis.

Table 16 Subjective Opioid Withdrawal Scale (SOWS) (ITT Population)

Visit	Statistic	SL BPN N=89	Probuphine N=84	Difference (Probuphine - SL BPN)	*P* Value[a]
Day 1 (BL)	Mean (SD)	2.2 (3.15)	2.7 (3.84)		
Week 4 (Change from BL)	Mean (SD)	0.3 (5.51)	0.3 (5.56)		
	LS Mean (SE)[a]	0.3 (0.58)	0.3 (0.59)	0.1	0.926
	95% CI[a]	−0.9, 1.4	−0.8, 1.5	−1.6, 1.7	
Week 8 (Change from BL)	Mean (SD)	0.4 (5.63)	−1.1 (3.39)		
	LS Mean (SE)[a]	0.3 (0.47)	−1.0 (0.48)	−1.2	0.068
	95% CI[a]	−0.7, 1.2	−1.9, −0.0	−2.6, 0.1	
Week 12 (Change from BL)	Mean (SD)	−0.1 (4.15)	−0.4 (5.53)		
	LS Mean (SE)[a]	−0.1 (0.51)	−0.4 (0.53)	−0.2	0.772
	95% CI[a]	−1.2, 0.9	−1.4, 0.7	−1.7, 1.2	
Week 16 (Change from BL)	Mean (SD)	−0.4 (4.25)	−0.2 (5.33)		
	LS Mean (SE)[a]	−0.5 (0.50)	−0.2 (0.51)	0.3	0.697
	95% CI[a]	−1.4, 0.5	−1.2, 0.8	−1.1, 1.7	
Week 20 (Change from BL)	Mean (SD)	−0.1 (4.47)	−0.9 (3.48)		
	LS Mean (SE)[a]	−0.1 (0.42)	−0.8 (0.43)	−0.7	0.252
	95% CI[a]	−0.9, 0.7	−1.7, 0.0	−1.9, 0.5	
Week 24/EOT (Change from BL)	Mean (SD)	0.1 (5.26)	−0.6 (4.63)		
	LS Mean (SE)[a]	0.0 (0.52)	−0.6 (0.54)	−0.6	0.425
	95% CI[a]	−1.0, 1.1	−1.6, 0.5	−2.1, 0.9	

Accurate and rapid assessment of opioid withdrawal is important in the clinical management of opioid dependent patients COWS is a valid instrument with sufficient sensitivity to detect mild opiate withdrawal. No statistically significant differences were observed between the 2 treatment groups at any post-baseline time point. The subjective scale SOWS also demonstrated that similar improvement with Sixmo compared to SL BPN no statistical difference was seen between the groups, fluctuations between the groups for both COWS and SOWS was low.

SOWS is a reliable and valid instrument to assess opioid withdrawal during rapid detoxification. As the baseline levels were very low at baseline the population most suitable for treatment is one which is already well controlled with low cravings. Overall there is no difference seen between Sixmo and SL BPN for COWS or SOWs at week 24.

Exploratory Efficacy Results

Supplemental SL BPN Use

A total of 28 (16.2%) subjects, 13 (14.6%) in the SL BPN group and 15 (17.9%) in the Sixmo group, used supplemental SL BPN during the study. The study was designed to allow complete investigator discretion for supplemental SL BPN use without any restrictions. Overall, the number of episodes of supplemental SL BPN use ranged from 1 episode (5 [2.9%] subjects) to 21 episodes (1 [0.6%] subject). The mean dose of supplemental SL BPN dispensed per episode was 27.7 mg (range: 4.0 to 84.0 mg). The use of supplemental SL BPN was also site-specific; 21 of the 28 subjects who used supplemental SL BPN came from 2 sites (Site 007 and Site 011), accounting for 12 of the 13 subjects in the SL BPN group who used supplemental SL BPN and 9 of the 15 subjects in the Sixmo group.

As requested by the FDA, the subjects who received supplemental SL BPN were analyzed after database lock to determine if they had previous history of supplemental SL BPN use 6 months prior to enrollment into the study. Of the 28 subjects who used supplemental SL BPN during the course of the study, it was confirmed with the clinical sites treating these subjects that none of them took supplemental SL BPN during the 6 months leading up to their entry into the study.

Table 17 Use of Supplemental SL BPN by Subject (ITT Population)

Treatment Group	Subject Number	Number of Dispensing Episodes (Tablets Dispensed per Episode)
SL BPN	004-001	2 episodes (1, 5 tablets)
	007-001	4 episodes (22, 12, 9, 15 tablets)
	007-011	2 episodes (5, 5 tablets)
	007-012	3 episodes (5, 8, 5 tablets)
	007-013	2 episodes (10, 10 tablets)
	007-024	6 episodes (5, 7, 5, 7, 7, 10 tablets)
	007-026	4 episodes (10, 10, 4, 13 tablets)
	011-002	4 episodes (7, 10, 11, 28 tablets)
	011-006	4 episodes (10, 15, 15, 15 tablets)
	011-010	5 episodes (10, 10, 10, 28, 28 tablets)
	011-013	7 episodes (10, 10, 28, 28, 10, 28, 6 tablets)
	011-015	3 episodes (10, 10, 25 tablets)
	011-019	5 episodes (10, 18, 28, 28, 28 tablets)
Probuphine	003-001	1 episode (14 tablets)
	005-029	6 episodes (7, 14, 30, 30, 30, 30 tablets)
	007-004	1 episode (11 tablets)
	007-005	2 episodes (7, 7 tablets)
	007-008	2 episodes (6, 3 tablets)
	007-014	1 episode (4 tablets)
	007-016	1 episode (10 tablets)
	007-019	1 episode (5 tablets)
	007-021	6 episodes (6, 10, 8, 10, 15, 12 tablets)
	011-014	4 episodes (10, 28, 28, 28 tablets)
	011-023	5 episodes (15, 28, 28, 28, 28 tablets)
	016-006	7 episodes (4, 15, 28, 30, 28, 29, 26 tablets)

Treatment Group	Subject Number	Number of Dispensing Episodes (Tablets Dispensed per Episode)
	019-008	21 episodes (7, 6, 12, 40, 33, 66, 14, 14, 9, 11, 7, 9, 10, 5, 9, 4, 7, 7, 8, 7, 7 tablets)
	021-007	6 episodes (14, 14, 30, 30, 30, 30 tablets)
	023-008	5 episodes (12, 18, 60, 60, 60 tablets)

Additional Unscheduled Visits to Obtain Counselling

A total of 25 (14.5%) subjects, 13 (14.6%) in the SL BPN group and 12 (14.6%) in the Sixmo group, received supplemental counselling at least once during the study. Of these 25 subjects, most had ≤4 counselling sessions (22 subjects, 88.0%). Use of supplemental counselling was comparable between the 2 treatment groups.

Urine Toxicology Results for Other Drugs of Abuse

For each drug tested, most of the subjects in each treatment group had negative urine toxicology results at the scheduled and random urine toxicology evaluations. The drug with the highest proportion of positive results was cannabinoids. The urine toxicology profile for other drugs of abuse was comparable between the 2 treatment groups.

Treatment Discontinuation

The cumulative proportion of subjects who discontinued the study during the Maintenance Period (i.e., through Month 6) was <5% in each treatment group. During Month 7, all but 8 subjects had completed the Follow-Up Period and were discontinued from the study. All subjects were out of the study by Month 8.

Table 18 Cumulative Proportion of Subjects Discontinued by Month (ITT Population)

Time	SL BPN N=89 n (%)	Probuphine N=84 n (%)	Total N=173 n (%)
Month 1 (Day 28)	0	0	0
Month 2 (Day 56)	1 (1.1)	1 (1.2)	2 (1.2)
Month 3 (Day 84)	1 (1.1)	2 (2.4)	3 (1.7)
Month 4 (Day 112)	1 (1.1)	3 (3.6)	4 (2.3)
Month 5 (Day 140)	2 (2.2)	3 (3.6)	5 (2.9)
Month 6 (Day 168)	4 (4.5)	3 (3.6)	7 (4.0)
Month 7 (Day 196)	84 (94.4)	81 (96.4)	165 (95.4)
Month 8 (Day 224)	89 (100.0)	84 (100.0)	173 (100.0)

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Study PRO-805

Title: A Randomized, Double-Blind, Placebo-Controlled, Multi-Centre Study of Sixmo in Patients with Opioid Dependence			
Study identifier	PRO-805		
Design	This was a randomized, double-blind, placebo-controlled, multicentre US study in adult subjects with untreated opioid dependence.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 10 days 2 week follow up
Hypothesis	Test of superiority to placebo		
Treatment groups	4-5 placebo implants		24 weeks duration, 55 subjects randomized, 17 subjects completed study. Supplemental SL BPN allowed.
	4-5 Sixmo implants		24 weeks duration, 108 subjects randomized, 71 subjects completed study. Supplemental SL BPN allowed.
Endpoints and definitions	Primary endpoint	The cumulative distribution function of the percentage of opioid-negative urine samples for Weeks 1 through 16.	Urine samples were collected thrice weekly throughout the study. Authenticity of urine specimens was verified at the site by measurement of urine temperature. Missing urine samples were imputed as opioid-positive. If a subject withdrew from the study, urine samples from that point onwards were considered positive.

	Key secondary endpoint	The cumulative distribution function of the percentage of opioid-negative urine samples for Weeks 17 through 24.	
	Other endpoints	The proportion of study completers. Weeks abstinent Withdrawal symptoms and cravings (SOWS, COWS, VAS) Physician and subject rated global improvement	
Database lock	Not stated		

Results and Analysis

Analysis description				
Analysis population and time point description	Intent to treat at 16 weeks (Primary endpoint)			
	Treatment group	**Placebo**	**Sixmo**	
	Number of subjects	55	108	(Difference)
	Percentage of opioid-negative urine samples for Weeks 1 through 16.	Median 20.8, mean 28.3 (SE 3.97), minimum 0, maximum 92	Median 40.7, mean 40.4 (SE 3.15), minimum 0, maximum 98	p=0.0361
	Percentage of opioid-negative urine samples for Weeks 17 through 24	Median 0.0, Mean 10.7 (SE 3.19) minimum 0, maximum 92	Median 4.4, Mean 29.0 (SE 3.34), minimum 0, maximum 100	p=0.0004
	Proportion of study completers (Weeks 1-24)	n=17, 30.9%	n=71, 65.7%	p<0.0001
	Total number weeks abstinent (Weeks 1-24)	Median 1.0, mean 2.7 (SE 0.51), minimum 0, maximum 16	Median 2.0, mean 4.3 (SE 0.53), minimum 0, maximum 20	
	Maximum period of continuous abstinence in weeks	Median 1.0, mean 1.3 (SE 0.21), minimum 0, maximum 7	Median 1.0, mean 1.9 (SE 0.25), minimum 0, maximum 17	
	Repeated measures ANCOVA COWS	LS Mean 3.4 (SE 0.29)	LS Mean 2.3 (SE 0.20)	Treatment effect p=0.0004
	Repeated measures ANCOVA SOWS	LS Mean 6.5 (SE 0.73)	LS Mean 4.1 (SE 0.52)	Treatment effect p=0.0039

	Repeated measures ANCOVA VAS	LS Mean 15.8 (SE 1.58)	LS Mean 9.9 (SE 1.09)	Treatment effect p=0.0009
	Self-rated global improvement EOT	Very much improved-37.8% Much improved-40.0% Minimally improved-17.8% No change-4.4% Missing-18%	Very much improved-65.2% Much improved-23.6% Minimally improved-6.7% No change-1.1% Missing-18%	p<0.0009
	Illicit drug use self-report EOT	19 (34.5%)	44 (40.7%)	Heroin, marijuana and cocaine most commonly

Study PRO-806

Title: A Randomized, Placebo and Active-Controlled, Multi-Centre Study of Sixmo in Patients With Opioid Dependence			
Study identifier	PRO-806		
Design	This was a 3 arm, randomized, double-blind, placebo-controlled and active-controlled, multicentre US study of Sixmo in adult subjects with untreated opioid dependence.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		24 weeks 3-16 days SL BPN induction 5 weeks follow-up
Hypothesis	Test of superiority to placebo and non-inferiority to SL BPN		
Treatments groups	Group A (Blinded)		4-5 Sixmo implants for 24 weeks. Supplemental SL BPN allowed. N=114 (ITT). 73 subjects (64%) completed study.
	Group B (Blinded)		4-5 Placebo implants for 24 weeks. Supplemental SL BPN allowed. N=54 (ITT). 14 subjects (26%) completed study.
	Group C (Open label)		12 to 16 mg/day SL BPN for 24 weeks. Supplemental SL BPN allowed. N=119 (ITT). 76 subjects (64%) completed study.
Endpoints and definitions	Co-Primary endpoint	#1	Urine toxicity results for illicit opioids without imputation of positive values based on subject self-reported data in the Sixmo and placebo groups from Weeks 1 through 24. [The cumulative distribution function (CDF) of the percentage of urine samples that were negative for illicit opioids at 24 weeks (from Weeks 1 through 24) in Groups A and B.]
	Co-Primary endpoint	#2	Urine toxicity results for illicit opioids with imputation of positive values based on subject self-reported data in the Sixmo and placebo groups from Weeks 1 through 24. [The CDF of the percentage of urine samples negative for opioids from Weeks 1 through 24 for treatment groups A and B with imputation based on subject self-reported illicit drug use data.]

	Key secondary endpoint	#1	Urine toxicity results for illicit opioids in the Sixmo and placebo groups from Weeks 1 through 16 and Weeks 17 through 24. [The CDF of the percentage of urine samples that were negative for illicit opioids over Weeks 1 through 16 for Sixmo versus placebo and the CDF of the percentage of urine samples that were negative for illicit opioids over Weeks 17 through 24 for Sixmo versus placebo.]
	Key secondary endpoint	#2	Urine toxicity results for illicit opioids in the Sixmo and SL BPN groups from Weeks 1 through 24. [The difference of proportions of urine samples that were negative for illicit opioids over 24 weeks of treatment for Sixmo versus SL BPN (non-inferiority assessment)]
	Other endpoints		The proportion of study completers for Sixmo versus placebo and for Sixmo versus SL BPN.
	Other endpoints		Mean percentage of urine samples that were negative for illicit opioids
	Other endpoints		Mean weeks of abstinence
	Other endpoints		Mean maximal period of continuous abstinence
	Other endpoints		Withdrawal symptoms and cravings (COWS, SOWS, VAS)
	Other endpoints		Subject- and investigator-assessed global impression
Database lock	Not stated		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat at 24 weeks (Primary endpoint)			
Descriptive statistics and estimate variability	Treatment group	**Group A** **Sixmo implants**	**Group B** **Placebo implants**	**Group C** **SL BPN**
	Number of subject	114	54	119
	Percentage negative urines weeks 1-24	Median 20.28, mean 31.21 (SE 2.968), minimum 0.0, maximum 98.6	Median 9.03, mean 13.41 (SE 2.562), minimum 0.0, maximum 97.3	Median 16.33, mean 33.48 (SE 3.103), minimum 0.0, maximum 98.6
	Percentage negative urines weeks 1-16	Median 28.27, mean 34.74 (SE 3.045), minimum 0.0, maximum 97.9	Median 13.39, mean 17.13 (SE 2.658), minimum 0.0, maximum 95.9	Median 18.7, mean 36.21 (SE 3.235), minimum 0.0, maximum 97.9
	Percentage negative urines weeks 17-24	Median 0.0, mean 24.17 (SE 3.238), minimum 0.0, maximum 100	Median 0.0, mean 5.92 (SE 2.793), minimum 0.0, maximum 100	Median 6.34, mean 28.00 (SE 3.229), minimum 0.0, maximum 100

	Proportion of study completers	73 (64%)	14 (25.9%)	76 (63.9%)
	Mean % negative urines weeks 1-24	LS Mean (SE) 35.998 (2.845)	LS Mean (SE) 14.363 (3.780)	LS Mean 35.096 (2.754)
	Total # weeks abstinent (Weeks 1-24)	Median 2.0, mean 4.5 (SE 0.59), minimum 0, maximum 23	Median 0.0, mean 1.6 (SE 0.49), minimum 0, maximum 22	Median 1.0, mean 4.8 (SE 0.59), minimum 0, maximum 23
	Self-rated Clinical Global Improvement at end of treatment	Very much improved 41.2% Much improved 30.7% Minimally improved 8.8% No change 2.6%	Very much improved 25.9% Much improved 33.3% Minimally improved 16.7% No change 9.3%	Very much improved 47.9% Much improved 24.4% Minimally improved 7.6% No change 0
	Physician-rated Clinical Global Improvement at end of treatment	Very much improved 50.0% Much improved 14.9% Minimally improved 13.2% No change 5.3%	Very much improved 22.2% Much improved 14.8% Minimally improved 20.4% No change 18.5%	Very much improved 48.7% Much improved 18.5% Minimally improved 7.6% No change 2.5%

Effect estimate per comparison	Proportion of study completers	**Sixmo vs placebo** Treatment effect detected p=0.0002	**Sixmo vs SL BPN** Significant treatment effect not detected p=0.6211
	Mean % negative urines weeks 1-24	**Sixmo vs placebo** Treatment difference (95% CI) 21.6345 (12.51, 30.75) p<0.0001	**Sixmo vs SL BPN** Treatment difference (95% CI) 0.9017 (-6.36, 8.16) p=0.8070
	Mean total # weeks abstinent (Weeks 1-24)	**Sixmo vs placebo** Treatment difference (95% CI) 3.5751 (1.78, 5.37) p=0.0001	**Sixmo vs SL BPN** Treatment difference (95% CI) 0.2648 (-1.17, 1.70) p=0.7158
	COWS change from baseline	**Sixmo vs placebo**	**Sixmo vs SL BPN**
		Treatment effect demonstrated	Treatment effect demonstrated
		LS Mean Sixmo -0.01, placebo 2.43	LS Mean Sixmo -0.01, SL BPN -0.84
		P-value <0.0001	P-value = 0.0005
	SOWS change from baseline	**Sixmo vs placebo**	**Sixmo vs SL BPN**
		Treatment effect demonstrated	Treatment effect demonstrated
		LS Mean Sixmo 5.58, placebo 10.30	LS Mean Sixmo 5.58, SL BPN 2.89
		P-value <0.0001	P-value = 0.0006
	VAS change from baseline	**Sixmo vs placebo**	**Sixmo vs SL BPN**
		Treatment effect demonstrated	Significant treatment effect not demonstrated

		LS Mean Sixmo 11.17, placebo 28.77	LS Mean Sixmo 11.17, SL BPN 7.59
		P-value <0.0001	P-value = 0.0543

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

Pooled PRO-805/ PRO-806 Results

The curves for the CDF with imputation for subject illicit opioid self-report are shown for the pooled Studies PRO-805 and PRO-806 below

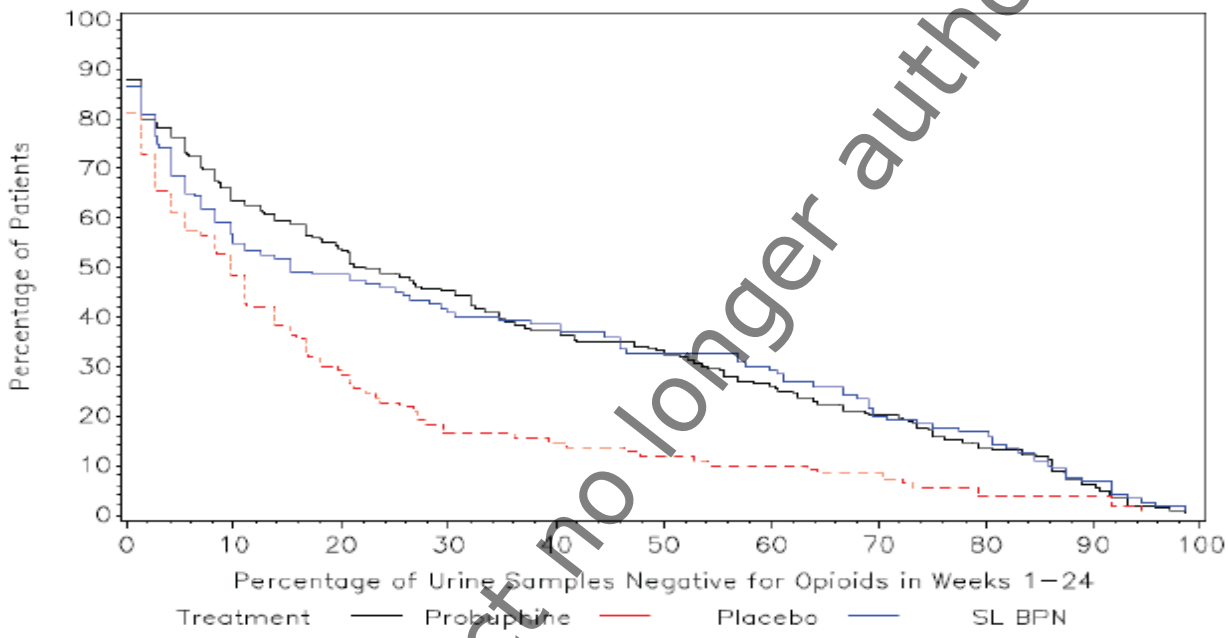
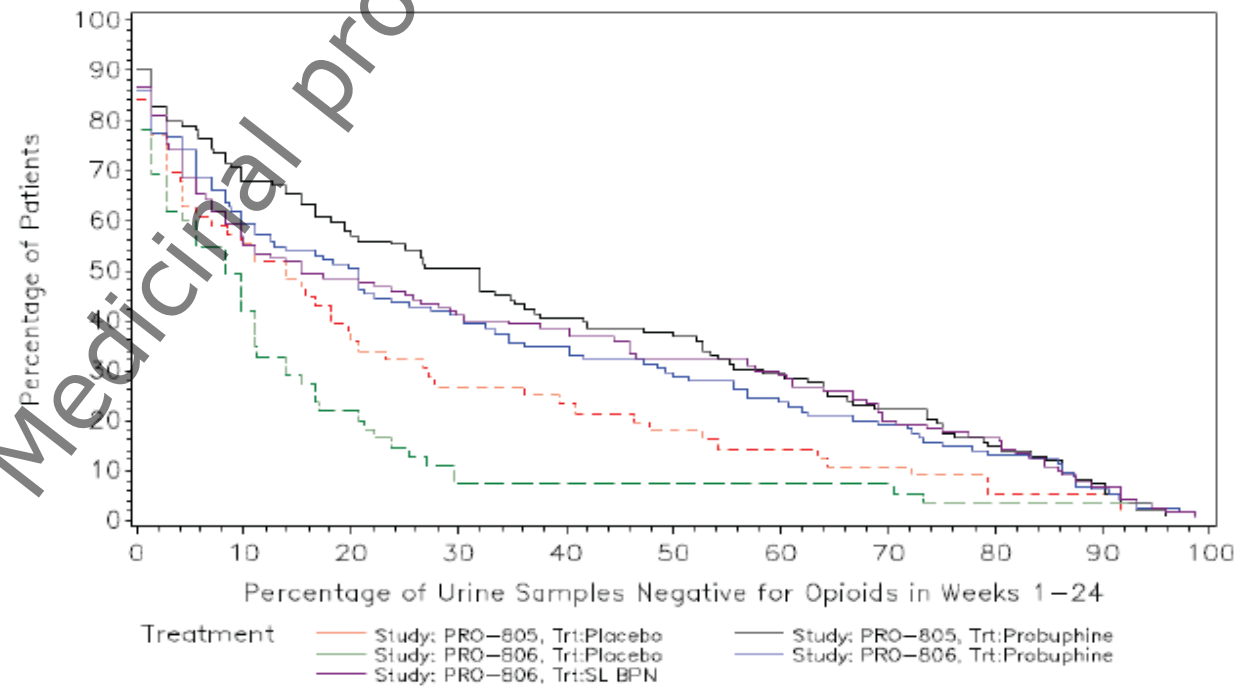


Figure 6 Cumulative Distribution Function of the Percentage of Urine Samples Negative for Opioids in Weeks 1 - 24, with Imputation for Subject Illicit Opioid Self-Report: Studies PRO-805 and PRO-806 Presented Individually (ITT Population)



For the pooled analysis, a statistically significant difference between the Sixmo and placebo groups was observed ($p<0.0001$). There also was a significant shift with the Hodges- Lehmann estimator for percent opioid urine negative values between the Sixmo and placebo groups of 9.2% (CI 4.2, 16.7). Analyses of the data by individual study yielded similar results, which were also individually the same as those previously obtained as post hoc (Study PRO-805) or planned (Study PRO-806) analyses for the individual studies

Summary of the Significance Testing and Sample Sizes of the CDF of Percentage of Negative Urine Results for Opioids by Timeframe, with Imputation for Subject Illicit Opioid Self-Report, Studies PRO-805 and PRO-806 (ITT Population).

Table 19

Timeframe	Probuphine N	Placebo N	p-value[a]
Weeks 1 to 24[b]			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0142
Study PRO-806	114	54	<0.0001
Weeks 1 to 24, excluding self-report			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0142
Study PRO-806	114	54	<0.0001
Weeks 1 to 16			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0305
Study PRO-806	114	54	<0.0001
Weeks 17 to 24			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0004
Study PRO-806	114	54	0.0002
Weeks 5 to 24 [c]			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0024
Study PRO-806	114	54	<0.0001
Weeks 9 to 24 [c]			
Pooled studies	222	109	<0.0001
Study PRO-805	108	55	0.0008
Study PRO-806	114	54	0.0001

Supportive studies

PRO-807 Phase 3	Open-label extension study to PRO-805	Probuphine (4-5 implants)*	N=62	24 weeks
PRO-811 Phase 3	Open-label extension study to PRO-806	Probuphine (4-5 implants)*	N=85	24 weeks

Study PRO-807: An Open-Label, Multi-Center Extension Study of Sixmo in Patients with Opioid Dependence

Objectives: The primary objective was to determine the safety of Sixmo in subjects who had completed 24 weeks of treatment in Study PRO-805 and who were re-treated with Sixmo over an additional 24 weeks. Key secondary objective of the study was to determine the efficacy of Sixmo through PK analyses.

Study conduct: This was a 6-month, open-label extension study of Sixmo in subjects with a history of opioid dependence who had completed 24 weeks of treatment in Study PRO- 805. After removal of the PRO-805 implantation, subjects who enrolled in study PRO-807 underwent an induction period of up to 13 days with SL BPN (Suboxone) tablets at a dose of 12 to 16 mg/day.

Efficacy results (based on safety population): The mean percentage of opioid-negative urine samples was 39.9% over the 24-week period.

The percentage of study completers was 74.2% (46 subjects).

Self-reported illicit drug use was reported for 41.9% of subjects at Baseline and 54.8% of subjects at the end-of-treatment visit (Week 24).

Supplemental SL BPN was provided to 26 (41.9%) subjects during the study. The mean (standard error; SE) days of use per week and weekly dose were, respectively, 0.22 (0.079) days and 2.90 (1.025) mg for the subjects previously in the Study PRO-805 Sixmo group, and 0.32 (0.145) days and 4.39 (2.310) mg for subjects previously in the Study PRO- 805 placebo group. Corresponding median days of use per week and weekly dose were, respectively, 0.00 days and 0.00 mg for the subjects previously in the Study PRO-805 Sixmo group, and 0.12 days and 0.64 mg for subjects previously in the Study PRO-805 placebo group.

Opioid withdrawal symptoms and cravings were well controlled at Baseline and throughout the study. At Baseline, the mean SOWS, COWS, and VAS scores were 5.0 (out of 64), 2.8 (out of 44), and 12.3 (out of 100) respectively. Decreases from baseline to end of treatment were seen for all 3 scores, with mean changes from baseline of -2.4 (SOWS), -0.9 (COWS), and -4.8 (VAS).

Self- and observer-assessed CGI data indicated good control of problems with opioid use. At Visit 7 (Week 8), the proportion of subjects who reported that they had no problems with opioid use was 45.2%, and the proportion of subjects who reported their opioid use and problems as either very much improved or much improved was 72.6%

Study PRO-811: A Phase 3, 6-Month, Open-Label Re-Treatment Study of Sixmo in Opioid Addiction

Objectives: The primary objective was to determine the safety of Sixmo in subjects who had completed 24 weeks of treatment in Study PRO-806 and who were re-treated with Sixmo over an additional 24 weeks. Key secondary objective of the study was to determine the efficacy of Sixmo through PK analyses.

Study conduct: This was a 6-month, open-label extension study of Sixmo in subjects with a history of opioid dependence who had completed 24 weeks of treatment in Study PRO-806. After removal of the PRO-806 implantation, subjects who enrolled in study PRO- 811 underwent an induction period of up to 16 days with SL BPN (Suboxone) tablets at a dose of 12 to 16 mg/day. Subjects were to be maintained on a fixed dose of SL BPN for at least 3 consecutive days prior to implantation.

Efficacy assessments: There were no primary efficacy endpoints in this study. One secondary efficacy endpoint was the PK analysis. Other secondary efficacy endpoints included percentage of study completers (i.e., retention in treatment), subject self-reported illicit drug use, supplemental SL BPN use, subjective and objective withdrawal symptom scores (SOWS and COWS), opioid-craving scores (VAS), Beck Depression Inventory II, subject- and observer-assessed CGI scores and Patient Satisfaction Survey. Urine toxicology was not assessed in this study.

Efficacy results (based on safety population):

The percentage of study completers overall was 78.8% (67 subjects). The percentage of completers was higher in subjects who had previously received Sixmo or placebo in Study PRO-806 (82.5% and 87.5%, respectively) than in those who had received SL BPN in Study PRO-806 (65.0%).

Self-reported illicit drug use was reported for 34.1% of subjects at Baseline and 38.8% of subjects at the end-of-treatment visit (Week 24); there were no significant differences between groups based on previous randomization in Study PRO-806.

Supplemental SL BPN was provided to 17 (20.0%) of the 85 subjects during the study.

Opioid withdrawal symptoms and cravings were well controlled at Baseline and throughout the study. At Baseline, the mean SOWS, COWS, and VAS scores were 3.41 (out of 64), 1.72 (out of 44), and 4.3 (out of 100) respectively; scores on the COWS dropped from Baseline through the study period but increased slightly for the SOWS (mean change from baseline +0.32) and VAS (mean change +2.5).

Overall, these results indicate sustained adequate control of opioid withdrawal symptoms and cravings.

At Week 24, the proportion of subjects who exhibited no symptoms of opioid dependence as assessed by the investigator had increased to 57.9% in the prior Sixmo group, decreased to 37.5% in the prior placebo group, and remained at 60.0% for the former SL BPN group.

2.5.2. Discussion on clinical efficacy

Discussion on clinical efficacy: Design and conduct of clinical studies

Sixmo is a subcutaneous implant formulation of the active ingredient buprenorphine hydrochloride (buprenorphine), dispersed in a solid matrix of ethylene vinyl acetate polymer (EVA), that is intended to provide continuous delivery of buprenorphine for 6 months.

The initial indication sought by the applicant for Sixmo is:

"Substitution treatment for opioid drug dependence, within a framework of medical, social and psychological treatment. Treatment is intended for use in adults and adolescents over 15 years of age who have agreed to be treated for addiction."

This has now been amended to include only stable patients requiring no more than 8mg SL BPN, as follows:

Sixmo is indicated for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.

The Sixmo clinical program comprises 7 studies which evaluated the safety and efficacy of Sixmo for substitution treatment of opioid dependence.

The applicant has submitted three pivotal studies (PRO-814, PRO-805 & PRO 806) to support the application as well as two open label extension studies to 805 and 806 (called PRO-807 and PRO-811 respectively). The applicant has also submitted two open label PK studies in support of this application.

Sixmo is an invasive, extended release product and thus carries greater risk than a sublingual preparation of buprenorphine. These added risks include insertion site reactions, infection, bleeding and potential respiratory depression, also breakage of the implant as well as its local migration have been noted. This is a major safety concern. Respiratory depression is of particular concern in the setting of concomitant use with alcohol or other respiratory depressants. These potential risks may be balanced by the improved convenience of use compared to sublingual formulations.

Studies PRO-805 and PRO-806 were double-blind, placebo controlled studies with a similar design, and were conducted in opioid-dependent adult subjects who were new entrants to buprenorphine treatment. Study PRO-806 contained an open-label, active comparator arm (SL buprenorphine [SL BPN]; Suboxone) in addition to the placebo arm.

In Study PRO-805, the SL BPN induction period was 10 days. After initial titration, subjects were restricted to a fixed daily dose of 12 to 16 mg/day by the end of the induction period. Subjects requiring doses outside this range were excluded from the study. In Study PRO-806, subjects were also restricted to maximum induction doses of 12-16 mg per day after initial titration. In this study, induction was completed within 16 days. It is noted that an induction/stabilisation period of 10 to 16 days may not mirror typical clinical experience with SL BPN, where satisfactory stabilisation could require a longer period of time in this heterogenous patient group.

Study PRO-814 was a double-blind, double-dummy, active (SL BPN)-controlled study in a subpopulation of opioid-dependent adult subjects who had been previously stabilized on SL BPN (at doses of 8 mg/day or less for at least 90 days).

A total of 626 patients were treated in the three pivotal studies.

The applicant chose the dose based on study TTP-400-02-01, PK data from this study suggested that the steady state concentration with 4 Sixmo implants (Day 21) was comparable to trough levels of SL BPN at 8 mg/day. Titan hypothesized that due to continuous receptor stimulation and adequate receptor occupancy at a dose of 4 Sixmo implants, clinically meaningful efficacy could be achieved.

Subjects in all Phase 3 studies were to meet the Diagnostic and Statistical Manual of Mental Disorders Fourth Edition, Text Revision (DSM-IV-TR) definition for current opioid dependence. Subjects meeting the DSM-IV-TR definition for current dependence on any other psychoactive substances other than opioids or nicotine (e.g., alcohol, sedatives) were excluded from the study, although current abuse of other substances was not exclusionary. The phase 3 studies enrolled male and female opioid-dependent subjects, aged between 18 and 65 years.

The studies PRO-805 and PRO-806, enrolled opioid-dependent adult subjects who were starting treatment with opioid substitution therapy and who were new entrants to therapy with buprenorphine. Subjects were not eligible if they had previously received pharmaceutical treatment for opioid dependence within 3 months of study start (e.g., methadone or buprenorphine). The majority of subjects in these studies reported heroin as their primary opioid of abuse. This reflects the current pattern of opioid abuse in Europe.

Study PRO-814 enrolled a clinically stable subpopulation of opioid dependent subjects in the maintenance stage of treatment. Subjects were required to be on SL BPN treatment for at least the previous 6 months, and had received a stable dose of 8 mg/day or less SL BPN for at least 90 days prior to randomisation. In

addition, the treating physician must have considered the subject “clinically stable,” and the determination must have been supported by abstinence from opioid use (assessed by urine toxicology) for the last 90 days and the absence of withdrawal symptoms and opioid craving at study entry. The most common primary opioid of abuse was prescription opioid pain relievers (74.4%), followed by heroin (21.0%). Seven (4.0%) subjects had “other” reported as the primary opioid of abuse. This is in contrast to the opioid abuse pattern in Europe where 80% of opioid-addicted treatment entrants cite heroin as their primary drug of abuse (European Drug Report 2017). However as the indication has been amended to patients who require no more than 8 mg/day of sublingual buprenorphine dose, this would therefore not benefit patients requiring higher maintenance doses of SL BPN.

Specifically, in Studies PRO-805 and PRO-806, approx. 62.5% abused heroin where as 37.5% abused prescription opioid pain relievers. Whereas for study 814, approx. 74% of patients listed prescription opioid pain relievers as the primary opioid of abuse whereas 21% reported heroin use.

The study protocols of 805, 806 and 814 allowed administration of supplemental SL BPN, where clinically indicated, for subjects in all treatment groups. Subjects who required supplemental SL BPN ≥3 days per week for 2 consecutive weeks, or ≥8 days of supplemental SL BPN over 4 consecutive weeks were eligible to receive one additional (5th) implant.

The randomised trials were conducted at a number of sites in the USA and the applicant stated that they were conducted in accordance with Good Clinical Practice.

Study PRO-805 objectives

The primary objective of Study PRO-805 was to determine the efficacy of Sixmo versus placebo in the treatment of subjects with opioid dependence over 16 weeks of treatment. The key secondary objective was to determine the efficacy of Sixmo versus placebo in the treatment of subjects with opioid dependence over treatment Weeks 17 through 24. Other secondary endpoints assessed the proportion of study completers, mean weeks of abstinence and continuous abstinence, withdrawal symptoms and cravings (mean total scores on SOWS, COWS, VAS), physician- and subject-rated global improvement and plasma sample results for buprenorphine and norbuprenorphine levels (Taken 12-24 hours after most recent SL BPN dose).

The endpoints measured in Study PRO-805 were appropriate to the stated objectives of this study and mirror real-world clinical assessment of this condition. They are also similar to the endpoints used in previous sublingual buprenorphine trials which have supported authorisation of this substance.

The sample size calculations took into account the drop-out rates in the published SL BPN trials (30-50%).

Study PRO-806 objectives

The primary objective of study PRO-806 was to confirm the efficacy of Sixmo versus placebo in adult subjects with Diagnostic and Statistical Manual of Mental Disorders IV text revision (DSM-IV-TR) defined opioid dependence over Weeks 1 through 24 of outpatient treatment through the assessment of thrice-weekly urine toxicology results and subject self-reported illicit drug use data.

The key secondary objectives were to evaluate the efficacy of Sixmo versus placebo in adult subjects with DSM-IV-TR-defined opioid dependence over Weeks 1 to 16 and Weeks 17 to 24 of outpatient treatment through the assessment of thrice-weekly urine toxicology results and to demonstrate non-inferiority of Sixmo versus SL BPN in adult subjects with DSM-IV-TR-defined opioid dependence over Weeks 1 through 24 of outpatient treatment through the assessment of thrice-weekly urine toxicology results.

Measuring efficacy up to 16 weeks and from 17 to 24 weeks is considered appropriate to the formulation of this product as well as the condition treated.

The endpoints measured in Study PRO-806 were comprehensive and appropriate to the stated objectives of the study. Withdrawal symptoms and cravings were measured using validated scales (mean total scores on SOWS, COWS, VAS) in both Study PRO-805 & PRO-806.

A potential limitation of the primary outcome measure in Studies PRO-805 and PRO-806 is that urine samples were not directly observed in these studies. Assessment of urine temperature alone is a slightly crude authenticity measurement and cannot control for substitution of samples that have been kept warm by storage close to the body or other methods such as storage in an insulated container. Additionally, urine toxicology assessments detected only "opioids" and could not further delineate between BPN or other opioids.

Slightly more women were enrolled in Study PRO-806 compared to Study PRO-805 (39% versus 31.3%). Additionally, a greater proportion of these women were randomised to placebo than Sixmo or SL BPN. A greater proportion of participants in this trial were white compared to Study PRO-805 (82.6% versus 74.8%). The median age and age range across the two trials is similar.

The baseline characteristics of the participants enrolled in Studies PRO-805 and PRO-806 are similar to those recorded in the 2017 EMCDDA report and therefore, results obtained should be generalizable to the European population of opioid users.

Study PRO-814 objectives

The primary efficacy variable was a test of non-inferiority of Sixmo (active treatment) versus SL BPN (control treatment) was conducted using 20% non-inferiority limit. After the non-inferiority was demonstrated, a chi square test was used to test for superiority.

The choice of non-inferiority margin for the variable, was based on studies indicating rates of continued opioid abstinence following complete withdrawal of about 18 to 31% (Breen et al. 2003, Senay 1977). Although limited data are available on abrupt withdrawal, published survey data indicate an abstinence rate of about 15% (Winstock et al. 2011). In addition, the applicant conducted a survey of addiction experts to estimate the proportion of patients, who have been on a stable dose of 8 mg or less of SL BPN, expected to maintain abstinence after abrupt discontinuation of the SL BPN. The results indicated that clinicians would expect that a median of only 25% of clinically stabilized patients would not relapse (i.e., maintain clinical stability) to illicit opioid use if these patients were taken off their stable dose of 8 mg or less of SL BPN/day. Based on these data, the 20% margin was selected.

The applicant chose a responder as the primary endpoint in study 814, where a responder was defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use (based on a composite of both urine toxicology testing results and self-report results). This endpoint was chosen based on a survey of addiction specialists who considered this level of drug use consistent with patients responding to treatment in clinical practice. The urine sampling scheme in this study included 6 regularly scheduled (monthly) visits during the 24-week treatment phase, plus 4 randomly scheduled visits.

Overall the treatment arms were balanced with respect to demographic factors and proportion of those with heroin and opiate pain prescription drugs dependency. The efficacy showed non inferiority to SL BPN however there several issues required for further clarification.

Efficacy data and additional analyses

Pivotal studies PRO-805 and PRO-806

Primary efficacy was assessed by examining urine toxicology for illicit opioids.

The primary efficacy endpoint in Study PRO805 was the CDF of the percentage of urine samples that were negative for illicit opioids for Weeks 1 through 16. Whereas study 806 had co-primary efficacy endpoints. These were the CDF of the percentage of urine samples that were negative for illicit opioids for Weeks 1

through 24 in the Sixmo and placebo groups (co-primary #1), and the CDF of the percentage of urine samples that were negative for illicit opioids for Weeks 1 through 24 in the Sixmo and placebo groups with imputation based on subject self-reported illicit drug use data.

In Study PRO-805, analysis of the primary endpoint [CDF of the percentage of opioid-negative urine samples (Weeks 1 to 16)] revealed a statistically significant difference between treatments (p=0.0361), which was in favour of Sixmo treatment. The key secondary endpoint was the CDF of the percentage of opioid-negative urine samples for Weeks 17 through 24. Again, there was a statistically significant between-treatment difference (p=0.0004), which was in favour of Sixmo. However, median and mean percentage of opioid negative urine samples were much lower during the week 17 to 24 time-period than they were for weeks 1-16, implying a reduction in efficacy with time. This reduction in efficacy over time was also seen for other endpoints (E.g. total number of weeks abstinent and the maximum period of continuous abstinence) and in Study PRO-806.

In Study PRO-805, 65.7% of participants in the Sixmo group completed the full study compared to 30.9% in the placebo group. This difference was noted to be statistically significant at p<0.0001.

In Study PRO-805, from visit 9 until end of treatment, participants who received Sixmo implants reported higher illicit drug use such as heroin, marijuana and cocaine. 41% of participants in the Sixmo group reported illicit drug use by the end of treatment compared to 35% of participants in the placebo group. It must also be considered that there may be under-reporting of illicit drug use in either arm.

In Study PRO-805 data were missing for a significant number of participants for the stated endpoints Physician-rated CGI, self-rated CGI and supplemental SL BPN use, making assessment of these endpoints difficult. For example, physician-rated CGI data were missing for 64% of placebo-treated participants and 31% of Sixmo-treated participants for visit 12. Self-rated CGI data were missing for 65% of placebo-treated participants and 30% of Sixmo-treated participants for visit 12. The study schedule mandated that CGI be assessed at this visit. Likewise, despite supplemental SL BPN use being a defined endpoint for this study, data are missing for 41% of participants in the Sixmo group (compared to 9% of the placebo group).

In Study PRO-806, analysis of the co-primary endpoint #1 [CDF of the percentage of opioid-negative urine samples (Weeks 1-24)] revealed a statistically significant difference between treatments (p<0.0001), which was in favour of Sixmo treatment. The CDF results for co-primary endpoint #2 were fundamentally the same (p<0.0001), indicating that the majority of self-reported illicit opioid data corroborated the corresponding urine toxicology data. However, as occurred in Study PRO-805 also, median and mean percentage of opioid negative urine samples were much lower during the week 17 to 24 time-period than they were for weeks 1-16, implying a reduction in efficacy with time.

The primary endpoints were supported by various sensitivity analyses.

Non-inferiority of Sixmo versus SL BPN was shown in Study PRO-806 with regard to the difference in proportions of urine samples that were negative for opioids over 24 weeks. The proportion of opioid-negative urine samples was comparable for the two groups, with 31.2% in the Sixmo group and 33.5% in the SL BPN group. The confidence interval for difference of proportions (Sixmo versus SL BPN) was -10.732, 6.197. Therefore, it can be concluded that Sixmo is non-inferior to SL BPN.

The beneficial effects seen with Sixmo are not sustained throughout Study PRO-806 with a falloff in efficacy seen from week 9. A similar trend is seen in the SL BPN group, however. Overall, participants in the SL BPN group responded somewhat better than those in the Sixmo group. Likewise, the margin of benefit of Sixmo over placebo seen in the early weeks of this trial is not maintained in the later weeks of Study PRO-806.

There was a statistically significant difference in the proportion of study completers in the Sixmo (63.9%) versus placebo (25.9%) group in Study PRO-806.

There was also a statistically significant difference between Sixmo and placebo for the mean percentage of urine samples negative for illicit opioids for Weeks 1 through 24 ($p<0.0001$),

Weeks 1 through 16 ($p<0.0001$), and Weeks 17 through 24 ($p<0.0001$) for the ITT population. There were no statistically significant differences observed between Sixmo and SL BPN in the mean percentage of urine samples negative for illicit opioids across all 3 time periods.

At baseline in Study PRO-806 (post induction with SL BPN), all study participants appear to have had their opioid cravings well-controlled based on median COWS, SOWS and VAS scores.

The difference between Sixmo and placebo in the repeated-measures analysis of results of COWS score, SOWS score and VAS score in Study PRO-806 was statistically significant ($p<0.0001$ for all 3 scores). At the end of treatment and at follow-up, the median total COWS score in the SL BPN group and the Sixmo group was the same.

At the end of treatment and at follow-up, the median total SOWS score in the SL BPN group and the Sixmo group was similar. The difference between Sixmo and SL BPN in the repeated-measures analysis of results of COWS and SOWS score was also statistically significant but in favour of SL BPN ($p<0.0005$ and $p<0.0006$, respectively).

At the end of treatment, the median total VAS score in the SL BPN group and the Sixmo group was similar. The difference between Sixmo and SL BPN in the repeated-measures analysis of results of VAS score was not found to be statistically significant ($p=0.543$).

At EOT in Study PRO-806 (Week 24), there was a statistically significant difference between Sixmo and placebo for global severity of opioid dependence ($P=0.0003$) and for global improvement of opioid dependence ($P=0.0002$) on investigator-assessed CGI.

There was no statistically significant difference in self-assessed CGI between Sixmo and SL BPN at EOT (Week 24) in Study PRO-806, with similar proportions of subjects in each category of self-rated opioid use and similar proportions of subjects in each treatment group rating their changes in opioid use as much improved or very much improved.

Likewise, there was also no statistically significant difference in investigator-assessed CGI between Sixmo and SL BPN at EOT (Week 24) in Study PRO-806. The proportion of subjects in each category of severity prior to induction and at Week 24, as well as the proportions of subjects reporting various degrees of improvement at Week 24, were similar between treatment groups.

Despite subject disposition and sample size being similar across the study populations in studies PRO-805 and PRO-806, some differences in efficacy were seen in the comparable arms in these studies. Differences in particular were seen with respect to proportion of opioid-negative urines detected, with Sixmo performing less well in Study PRO-806. This was despite very similar study completion rates for both groups across the 2 studies.

However, the populations enrolled into both studies were not stable at baseline and non-inferiority to sublingual buprenorphine was demonstrated in Study PRO-806.

Study PRO-814

The primary efficacy variable was responder rate, where a responder was defined as a subject with no more than 2 out of the 6 months of treatment evaluation with any evidence of illicit opioid use (based on a composite of both urine toxicology testing results and self-report results).

For the primary efficacy endpoint, a test of non-inferiority of Sixmo versus SL BPN was conducted.

A non-inferiority margin of 20% was employed to define non-inferiority. After non-inferiority was demonstrated, a chi square test was used to test for superiority.

The proportion of responders was 87.6% in the SL BPN group and 96.4% in the Sixmo group which was quite high. The 2-sided 95% confidence interval (CI; 0.009, 0.167) of the proportion difference (Sixmo – SL BPN) was well above the predefined successful margin for non-inferiority. Furthermore, after establishment of non-inferiority, superiority of Sixmo over SL BPN was tested and established (p=0.034) by chi square test. The robustness of results was supported by the completer and PP analyses, and various sensitivity analyses. The 95% CI was well within the pre-set inferiority margin of 20%.

A different primary endpoint analysis would have been preferred (percentage of negative urine samples) to that which was presented (responder rate). Additionally, a more conservative method for missing samples would have been preferred i.e. imputed as positive results. However the endpoint in terms of harm reduction is accepted and the company recalculated missing urine as positive which supported the initial primary analysis.

In the study, patients were allowed to receive supplemental SL BPN and these were dispensed in accordance with clinical practice. The initial data show that more patients were dispensed SL BPN and an overall greater number of tablets of SL BPN in the Sixmo arm compared with placebo, however this was clarified by the applicant and was accepted.

Four subjects, 1 in the SL BPN group (Subject 007-027) and 3 in the Sixmo group (Subjects 001-001, 012-006, 015-012), were excluded from the ITT population. Subject 007-027 did not receive study medication; the other 3 subjects did not have any post-baseline evaluations and therefore did not provide any post-baseline efficacy data.

As these patients were randomised to treatment they should be included in the ITT analysis. This was addressed by the applicant and did not lead to any difference in results.

Percentage urine illicit drug use (805, 806 and 814):

The difference in % urine samples negative for illicit substances was recorded as a secondary endpoint and was found to be similar at weeks 24 across the studies 27.89%, 31.2% (studies 805, 806). Study 806 compared with SL BPN was comparable at 33.5%.

Study 814 reported on proportion of subjects who showed any evidence of urine illicit opioid use was 28.09% and 14.29% in the SL BPN and Sixmo groups, respectively.

Retention within the study was similar in both PRO-805 and PRO-806 studies (65.7% and 64% respectively). It was much higher in study PRO-814; which documented a retention rate of 96.4%. This was comparable to SL BPN arm which was recorded as 94.4%. This is not unexpected given that subjects in Study PRO-814 were on a lower daily dose of SL BPN and were a more stable OUD population.

It is possible that the true figure for treatment failure quoted in the efficacy studies could be much higher than that stated. In this patient population, missing urine collections, missing counselling sessions, incarceration, loss to follow up and patient request could all reflect treatment failure.

Changes from baseline in measures of craving, (desire to use and need to use) and withdrawal (Clinical Opioid Withdrawal Scale, Subjective Opioid Withdrawal Scale and Visual Analog Scale) overall demonstrated a treatment effect for Sixmo. Similarly, the pooled analysis over Weeks 1 to 24 indicated a treatment effect for each parameter ($p<0.0001$ for each parameter). Moreover, for each component time point analysed except Week 26 (2 weeks post-implant removal), the differences between the Sixmo and placebo groups in the pooled analysis were statistically significant.

In Study PRO-814, because subjects were controlled on 8 mg of SL BPN or less, the baseline COWS and SOWS were very low. Consequently, with treatment, the changes observed were also low. However, this is to be expected given the stable population and low overall level of SL BPN use.

Conclusions on clinical efficacy

While abstinence from illicit opioids is considered an ideal outcome of the treatment of opioid dependence, it is often unachievable. No clinical guideline places exclusive focus on abstinence measures. Rather, most published studies, treatment guidelines, and clinicians emphasize reduction in use over abstinence. The difficulties in obtaining total abstinence have been widely acknowledged, and it is understood that "as with other chronic conditions, opioid dependence tends mostly to follow a relapsing and remitting course" and that opioid withdrawal (rather than maintenance treatment) results in poorer outcomes in the long term (World Health Organization [WHO], 2009).

Standard pharmacological treatment of opioid dependence aims at reducing (or ideally ceasing) illicit opioid use. Opioid agonist maintenance treatment, combined with psychosocial assistance, has been found to be the most effective treatment for opioid dependence (WHO, 2009). The most commonly used opioid substitution treatments are methadone and buprenorphine (either as a single agent [Subutex] or in combination with naloxone [Suboxone]).

Current clinical practice in treatment of opioid dependence focuses on reduction in use as a medically important, and realistic treatment goal rather than on complete abstinence. Such reduction in use aims at harm reduction (i.e., to reduce negative consequences of drug use rather than prevent drug use *per se,* Center for Substance Abuse Treatment. Medication- Assisted Treatment for Opioid Addiction in Opioid Treatment Programs, 2005). In line with this, endpoints related to reduction of opioid use (as assessed by urine toxicology) are recognized as suitable to assess the efficacy of new treatments for opioid dependence, and have been used in clinical studies leading to the regulatory approval of e.g., Suboxone (European Public Assessment Report [EPAR] Suboxone 2006).

Sixmo is a fixed dose and is not as flexible as oral dosing regimens therefore will not meet the needs of patients who require higher doses of opioids or when their needs change. The applicant initially proposed that, a fifth rod can be given in patients not controlled with four implants. However, PK for a fifth implant was not studied and the patient population whom would benefit most from receiving a fifth implant was unclear. This proposal has now been withdrawn by the applicant. There was no formal dose finding/dose response study conducted as part of the clinical development programme. Such a study would have been useful to determine the equivalent dose from which to transition patients to a more predictable or specified number of Sixmo implants.

The pivotal studies demonstrated superiority of Sixmo against placebo and non-inferiority compared to SL BPN. However, the almost 1/3 of patients did not continue in studies PRO-805 and PRO-806, this could be due to a number of factors, such as, that patients were not stable on SL BPN, the dose was insufficient to meet their needs or they were transitioned too early to Sixmo. Also the effects appeared to wear off with time in Studies PRO-805 and PRO-806. In contrast, patients who were on stable sublingual doses of 8 mg BPN or less in study PRO-814 had a very high completion rate of 90%.

The clinical benefit to patients for the intended indication for all patients with Opioid Use Disorder was questioned. Based on the data presented and the exposure levels, the proposed medicinal product appears to be more suitable for stable patients with lower requirements for SL BPN (8 mg/day or less). This is now the intended population and the indication has been amended by the applicant.

It is unclear from the data presented whether there was any imbalance in the response rates in patients who used illicit opioids or those with dependence on prescription opioids. In Study PRO-814, only 37 subjects (21%) reported heroin as their main opioid of abuse and only 15 of these subjects were

randomised to receive Sixmo Furthermore, subjects with alcohol dependency and dependency on other substances such as cocaine and sedatives were excluded from the clinical development programme. Therefore, the study results if true may not be generalisable to those who have a concomitant alcohol or moderate to severe dependence on other psychoactive substances such as cocaine or sedatives.

In Studies PRO-805 and PRO-806, a reduction in efficacy was seen over time for the percentage of urine samples negative for illicit opioids, the total number of weeks abstinent and the maximum period of continuous abstinence. An indication in those aged 15 or more and less than 18 years is not supported as no data has been provided for this age-group (although it is acknowledged that opioid dependence can occur at younger age group). Extrapolation from adult data to adolescents over 15 years of age has not been justified and the applicant has withdrawn use in adolescents from the SmPC.

2.6. Clinical safety

Introduction

Buprenorphine is a member of the opioid pharmacological class. It's pharmacological effects are believed to be mediated through partial agonist activity at mu (μ)-opioid receptors in the central nervous system (CNS).

Buprenorphine also acts as an antagonist or partial agonist at kappa (κ)-opioid receptors.

The most commonly reported treatment-emergent adverse events (TEAEs) reported with this pharmacological class include constipation, insomnia, headache, nausea, hyperhidrosis, drug withdrawal syndrome, and pain (Suboxone 16 mg/4 mg sublingual tablets SmPC, 2016; Subutex 8 mg sublingual tablets SmPC, 2016).

As such, certain well-characterised TEAEs were anticipated and monitored closely throughout the course of the Sixmo development program.

The primary evaluation of safety is based on pooled data from the double-blind studies PRO-805, PRO-806, and PRO-814. In addition, safety data from the 2 extension studies, PRO-807 and PRO-811, have been pooled and are presented (supportive data) separately from the 3 pivotal studies.

For the other studies, TTP-400-02-01 and PRO-810, safety is discussed by study.

It is acknowledged that active substance buprenorphine has a clearly established pharmacological profile over several years and the safety profile is adequately characterised. Nevertheless, the proposed use of a novel delivery system to administer the active substance buprenorphine via subdermal implant is noteworthy.

Patient exposure

Patient exposure

The primary evaluation of safety is based on pooled data from the double-blind studies PRO-805, PRO-806, and PRO-814.

The primary safety population comprises 626 subjects who were randomized to receive Sixmo or placebo implants or sublingual buprenorphine (SL BPN) in the pooled double-blind studies.

In addition, safety data from the 2 extension studies, Studies PRO-807 and PRO-811, were pooled and are presented separately from the 3 pivotal studies (supportive data). For the other studies, TTP-400-02-01,

a first-in-man study in heroin-dependent subjects previously maintained on SL BPN, and PRO-810, an open-label single cross-over PK study, safety is presented by study only.

A tabular overview of the clinical program with Sixmo is presented in Table 21.

Table 20 Clinical Program with Probuphine

Study	Study type	Objective	Treatment (Duration)	Patients treated
TTP-400-02-01	PK study vs. SL BPN Open-label, cross-over	To evaluate the PK profile of Probuphine vs. SL BPN (Subutex)	2 or 4 Probuphine implants (24 weeks)	N=12 (patients maintained on SL BPN [8 or 16 mg daily])
PRO-810[a]	PK study vs. SL BPN Open-label, single cross-over	To evaluate the PK profile of Probuphine vs. SL BPN (Suboxone)	Induction with SL BPN (16 mg/day), then transition to 4 Probuphine implants Supplemental SL BPN (56 days maximally)	N=9 (new entrants to BPN)
PRO-805	Efficacy and safety vs placebo Randomized, double-blind	To evaluate efficacy and safety vs placebo	Induction with SL BPN (Subutex or Suboxone), then transition to: 4 Probuphine implants[b] or 4 Placebo implants[b] Supplemental SL BPN (24 weeks)	New entrants to BPN, 12-16 mg/day SL BPN: N=108 in Probuphine group, N=55 in the placebo group
PRO-806	Efficacy and safety vs placebo and vs SL BPN (Suboxone) Randomized, double-blind[c]	To evaluate efficacy and safety vs placebo and vs SL BPN (Suboxone)	Induction with 12-16 mg/day SL BPN (Suboxone), then transition to: 4 Probuphine implants[b] or 4 placebo implants[b] or SL BPN (12-16 mg/day, as open-label active control)[c] Supplemental SL BPN (24 weeks)	New entrants to BPN, 12-16 mg/day SL BPN N=114 in Probuphine group, N=54 in placebo group, N=119 in SL BPN group

PRO-807	Open-label extension study to PRO-805	To evaluate safety of serial 6-month treatment	4 -5 Probuphine implants[b] Supplemental SL BPN (Suboxone) (24 weeks)	N=62
PRO-811	Open-label extension study to PRO-806	To evaluate safety of serial 6-month treatment	4-5 Probuphine implants[b] Supplemental SL BPN (Suboxone) (24 weeks)	N=85
PRO-814	Efficacy and safety vs SL BPN (generic equivalent to Suboxone) Randomized, double-blind, double-dummy	To evaluate the safety and efficacy of Probuphine vs SL BPN (generic equivalent to Suboxone)	4 Probuphine implants and daily SL placebo tablets or 4 placebo implants and daily SL BPN tablets (generic equivalent to Suboxone) ≤ 8 mg Supplemental SL BPN (24 weeks)	Patients stabilized on SL BPN (8 mg/day or less): N=87 in Probuphine, N=89 in SL BPN group

Abbreviations: BPN = buprenorphine, PK = pharmacokinetic, SL= sublingual.

[a] Study duration was planned to be 24 weeks, but was terminated after 8 weeks by the sponsor for administrative reasons.

[b] Study protocols PRO-805, PRO-806, PRO-807, and PRO-811 specified that an additional implant resulting in a total of five implants, could be inserted if the patient met pre-defined criteria. For studies PRO-805 and PRO-806, the additional implant was to be consistent with the randomized treatment for the patient (i.e., either an active or placebo formulation). For the extension studies PRO-807 and PRO-811, the implant was Probuphine.

[c] The SL BPN arm was open-label.

Source: Clinical study reports (CSRs) for Studies TTP-400-02-01, PRO-805, PRO-806, PRO-807, PRO-810, PRO-811, and PRO-814.

The integrated safety analyses were performed on pooled data from the double-blind studies PRO-805, PRO-806, and PRO-814. The 3 double-blind studies were similar in design with regard to study duration (24 weeks), Sixmo dose (4 implants, which could be increased to 5 implants in Studies PRO-805 and PRO-806), and the use of dose adjustments with SL BPN.

All studies enrolled male and female adults with DSM-IV-TR) defined opioid dependence (DSMIV-TR-2000). Subjects differed with regard to disease severity.

The double-blind studies PRO-805 and PRO-806 consisted of subjects newly initiating buprenorphine treatment for opioid dependence while Study PRO-814 consisted of subjects in the maintenance phase of their treatment (stable daily dose of ≤8 mg of buprenorphine). Overall, Sixmo the subjects treated in these double-blind studies are considered representative of the target population for Sixmo in the proposed indication.

The safety datasets include information for 626 subjects who had received Sixmo or placebo implants or SL BPN in the pooled double-blind studies.

The rationale for combining the placebo and SL BPN groups in the statistical analysis was that such a high percentage of subjects in the placebo group received supplemental SL BPN that there ultimately was only

a difference in the degree of exposure to buprenorphine between the SL BPN group and the placebo group for safety issues.

The open-label SL BPN group in Study PRO-806 was not included in analyses of implant site AEs, as these subjects did not receive implants and were therefore not at risk of implant-site adverse events.

The double-blind studies included the following comparisons:

- Study PRO-805: Sixmo implant vs placebo implant
- Study PRO-806: Sixmo implant vs placebo implant vs SL BPN tablets
- Study PRO-814: Sixmo implant + placebo tablets vs placebo implant + SL BPN Tablets Studies PRO-805 and PRO-806 were double-blind, placebo-controlled studies with similar design, and were conducted in opioid-dependent subjects who were new entrants to buprenorphine treatment. Only subjects who achieved a target dose of 12–16 mg/day SL BPN for at least 3 consecutive days were eligible to be randomized.

Study PRO-814 was a double-blind, double-dummy, active (SL BPN)-controlled study in a subpopulation of opioid-dependent subjects. No induction was required in Study PRO-814.

Table 21 Cumulative Exposure to Probuphine (Safety Population)

	TTP-400-02-01	PRO-805/ PRO-807 Continuing Probuphine	PRO-807/ Placebo-> Probuphine	PRO-806/ PRO-811 Continuing Probuphine	PRO-811/ Placebo-> Probuphine	PRO-811/ SL BPN-> Probuphine	PRO-810	PRO-814/ Probuphine	Total
Any Exposure	12	108	12	114	8	20	9	87	370
≥1 month	12	102	12	112	8	18	8	84	356
≥2 months	12	99	12	109	7	17	0	83	339
≥3 months	12	96	11	108	7	16	0	81	331
≥4 months	12	87	11	103	7	14	0	81	315
≥5 months	12	81	10	99	7	14	0	81	304
≥6 months	0	60	3	78	2	7	0	1	151
≥7 months	0	47	0	54	0	0	0	0	101
≥8 months	0	42	0	53	0	0	0	0	95
≥9 months	0	41	0	52	0	0	0	0	93
≥10 months	0	41	0	50	0	0	0	0	91
≥11 months	0	39	0	46	0	0	0	0	85
≥12 months	0	8	0	1	0	0	0	0	9

Abbreviations: CRF = case report form; SL BPN = sublingual buprenorphine

Note: Study drug exposure is calculated as the date of implant removal minus the date of implant insertion plus one. If the removal date is missing, the study discontinuation date from the CRF is used. For PRO-805, PRO-806, PRO-807, and PRO-811, subjects who completed their respective study are assigned 6 months of exposure in that study. Subjects with more than 28 weeks of exposure in a given study are recorded as 28 weeks.

Note: A month is defined as 365.25/12 days.

Source: Pooled safety tables, Table 8.1.2.4

Table 22 Demographic Characteristics for Double-blind Studies: Studies PRO-805, PRO-806 and PRO-814 (Safety population)

	Study PRO-805 N=163		Study PRO-806 N=287			Study PRO-814 N=176	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54	SL BPN N=119	Probuphine N=87	SL BPN N=89
Sex, n (%)							
Male	72 (66.7)	40 (72.7)	72 (63.2)	31 (57.4)	72 (60.5)	52 (59.8)	52 (58.4)
Female	36 (33.3)	15 (27.3)	42 (36.8)	23 (42.6)	47 (39.5)	35 (40.2)	37 (41.6)
Race, n (%)							
White	82 (75.9)	40 (72.7)	95 (83.3)	45 (83.3)	97 (81.5)	82 (94.3)	85 (95.5)
Black	14 (13.0)	6 (10.9)	14 (12.3)	7 (13.0)	16 (13.4)	3 (3.4)	2 (2.2)
Asian	0	1 (1.8)	0	1 (1.9)	1 (0.8)	1 (1.1)	0
American Indian or Alaskan Native	5 (4.6)	0	3 (2.6)	0	0	1 (1.1)	1 (1.1)
Native Hawaiian or Other Pacific Islander	1 (0.9)	0	N/A	N/A	N/A	0	0
Other	6 (5.6)	8 (14.5)	2 (1.8)	1 (1.9)	5 (4.2)	0	1 (1.1)
Ethnicity, n (%)							
Hispanic or Latino	12 (11.1)	12 (21.8)	24 (21.1)	11 (20.4)	17 (14.3)	3 (3.4)	3 (3.4)
Not Hispanic or Latino	96 (88.9)	43 (78.2)	90 (78.9)	43 (79.6)	102 (85.7)	84 (96.6)	86 (96.6)
Age (years)							
Median	33.0	39.0	36.0	33.0	32.0	36	37
Mean	35.8	39.3	36.4	35.2	35.3	38	39
Range	(19, 62)	(20, 61)	(19, 60)	(19, 59)	(18, 60)	(21, 63.0)	(22, 64.0)

Abbreviations: N/A = not applicable; SL BPN = sublingual buprenorphine
Source: CSR PRO-805, Table 4; CSR PRO-806, Table 11-1; and CSR PRO-814, Table 14.1.2.1

Table 23 Substance Abuse History and Abuse Treatment History, Studies PRO-805, PRO-806 and PRO-814 (Safety Population)

	PRO-805		PRO-806			PRO-814	
	Probuphine N=108	Placebo N=55	Probuphine N=114	Placebo N=54	SL BPN N=119	Probuphine N=87	SL BPN N=89
Primary opioid of abuse, n (%)							
Heroin	69 (63.9)	34 (61.8)	76 (66.7)	28 (51.9)	75 (63.0)	15 (17.2)	22 (24.7)
Prescription opioid analgesic	39 (36.1)	21 (38.2)	38 (33.3)	26 (48.1)	43 (36.1)	66 (75.9)	65 (73.0)
Other	0	0	0	0	1 (0.8)	5 (5.7)	2 (2.2)
Not reported	0	0	0	0	0	1 (1.1)	0
Abuse treatment history,[a] n (%)							
Yes	73 (86.9)	36 (90.0)	63 (55.3)	31 (57.4)	68 (57.1)	86 (98.9)	89 (100.0)
No	11 (13.1)	4 (10.0)	51 (44.7)	23 (42.6)	51 (42.9)	0	0
Missing[b]	24	15	0	0	0	1 (1.1)	0
Addiction diagnosis[b], n (%)							
In the last 5 years	78 (72.2)	40 (72.7)	85 (74.6)	42 (77.8)	82 (68.9)	42 (48.3)	50 (56.2)
In the last 10 years	17 (15.7)	4 (7.3)	13 (11.4)	6 (11.1)	16 (13.4)	33 (37.9)	26 (29.2)
Buprenorphine treatment (years)							
Median	N/A	N/A	N/A	N/A	N/A	3.0	2.5
Range (min, max)	N/A	N/A	N/A	N/A	N/A	0.5, 10.0	0.4, 10.0
BPN dose at study entry (mg/day), n (%)							
2	N/A	N/A	N/A	N/A	N/A	6 (6.9)	3 (3.4)
4	N/A	N/A	N/A	N/A	N/A	12 (13.8)	15 (16.9)
6	N/A	N/A	N/A	N/A	N/A	8 (9.2)	4 (4.5)
8	N/A	N/A	N/A	N/A	N/A	61 (70.1)	67 (75.3)

BMI=body mass index, BPN=buprenorphine, max=maximum, min=minimum, N=number of subjects, N/A=not applicable, SL=sublingual.
[a] For study PRO-805, this referred to any drug abuse treatment. For Studies PRO-806 and PRO-814 this referred to opioid abuse treatment.

Limitations of the Clinical Safety Database

The main limitation of the safety database is the comparably high drop out rate of placebo versus Sixmo subjects, and the resulting difference in study duration between the two groups in the placebo-controlled studies PRO-805 and PRO-806.

In studies PRO-805 and PRO-806, 69% and 74% of placebo subjects, respectively, withdrew early from the study. This is contrasted by lower drop out rates of around 34-36% of Sixmo subjects in the two studies. The high drop out rate among placebo subjects was primarily due to treatment failure

As a consequence placebo subjects were exposed to study drug for a shorter duration than Sixmo subjects. However, when comparing the safety profile of the two groups, very similar AE patterns were observed.

Adverse events

Common Adverse Events

Adverse Events in Double-Blind Studies PRO-805, PRO-806 and PRO-814

Overview of Treatment-Emergent Adverse Events by Study

During clinical development of Sixmo, the insertion /removal technique was modified in order to improve the overall safety. Study PRO-805 (and the corresponding extension study PRO-807) used a prototype blunt-tipped applicator, and an implant removal technique originally developed for contraceptive implants where the implants were grasped at one end and pulled out. Implanting physicians received training by way of an instructional video. Starting with Study PRO-810, improved implant insertion and removal techniques were used. In addition, the experience of the PRO-805 and PRO-807 investigators indicated that modifications to the applicator would be beneficial. Starting from study PRO-810 onward, a sharp, bevel-tipped applicator was used for implant insertion. The “U technique” was employed for implant removal, and a modified, commercially available vasectomy clamp was used. The training provided to implanting physicians was enhanced and included face-to-face didactic and hands-on instruction using a meat model. The same techniques were also used in the later studies PRO-806 and PRO-814. These techniques are currently used commercially for administration of Sixmo in the US, and will also be used for administration of the proposed Sixmo implant in the EU.

A by-study comparison of TEAE categories from the three double-blind studies (initial Phase 3 study PRO-805 and the later studies PRO-806 and PRO-814) is presented in Table 25, based on the pooled safety database.

Table 24 Summary of Treatment-Emergent Adverse Events by Study for Studies PRO-805, PRO-806, PRO-814 (Safety Population)

N(%) of patients	Study PRO-805		Study PRO-806			Study PRO-814	
	Probuphine N=108 n (%)	Placebo N=55 n (%)	Probuphine N=114 n (%)	Placebo N=54 n (%)	SL BPN N=119 n (%)	Probuphine N=87 n (%)	SL BPN N=89 n (%)
Any TEAE	90 (83.3)	44 (80.0)	82 (71.9)	36 (66.7)	86 (72.3)	50 (57.5)	50 (56.2)
Any implant site TEAE	63 (58.3)	28 (50.9)	32 (28.1)	14 (25.9)	N/A	20 (23.0)	12 (13.5)
Any non-implant site TEAE	81 (75.0)	39 (70.9)	77 (67.5)	33 (61.1)	86 (72.3)	42 (48.3)	47 (52.8)
Any related TEAE[b]	74 (68.5)	36 (65.5)	50 (43.9)	20 (37.0)	22 (18.5)	24 (27.6)	15 (16.9)
Implant site TEAE	61 (56.5)	28 (50.9)	31 (27.2)	14 (25.9)	N/A	20 (23.0)	12 (13.5)
Non-implant Site TEAE	52 (48.1)	18 (32.7)	34 (29.8)	11 (20.4)	22 (18.5)	10 (11.5)	3 (3.4)
Any severe intensity TEAE	10 (9.3)	3 (5.5)	9 (7.9)	3 (5.6)	14 (11.8)	3 (3.4)	9 (10.1)
Implant site TEAE	1 (0.9)	0	0	1 (1.9)	N/A	0	0
Non-implant site TEAE	9 (8.3)	3 (5.5)	9 (7.9)	3 (5.6)	14 (11.8)	3 (3.4)	9 (10.1)
SAEs	2 (1.9)	4 (7.3)	6 (5.3)	3 (5.6)	7 (5.9)	2 (2.3)	3 (3.4)
TEAEs leading to study discontinu-ation[a]	4 (3.7)	0	2 (1.8)	2 (3.7)	5 (4.2)	1 (1.1)	0
Death	0	0	0	0	1 (0.8)	0	0

BPN = buprenorphine; CRF = case report form, N/A = not applicable; SAE = serious adverse event, SL = sublingual; TEAE = treatment-emergent adverse event

[a] Reflects responses provided on the AE CRF, and not on the disposition CRF.

[b] TEAEs considered by the investigator to be at least possibly related to study drug and/or implant procedure, or for which the relationship was missing.

Source: Pooled safety tables, Table 9.3.17.

In all studies, the majority of subjects experienced at least one TEAE. Generally, the frequencies of TEAEs were similar between treatment groups. As evaluated by study, the incidence of implant site TEAEs was notably higher in Study PRO-805 than in Study PRO-806 or Study PRO-814. The incidences of implant site TEAEs were higher in both treatment groups in Study PRO-805 (Sixmo 58.3%; placebo 50.9%) than

those in Study PRO-806 (Sixmo 28.1%, placebo 25.9%) or in Study PRO-814 (Sixmo 23.0%, SL BPN 13.5%). A similar pattern between original (Study PRO-807) and current (Study PRO-811) techniques was seen for the open-label studies. The lower frequencies of implant site AEs in the later studies can be attributed to the improvements in the insertion/removal techniques between the studies which used the original techniques, PRO-805 and PRO-807, and in the later studies using the current techniques, PRO-806, PRO-811 and PRO-814. Of note, only the current insertion/removal techniques will be used commercially.

In all studies, the types and frequencies of non-implant site TEAEs were generally similar between treatment groups. When comparing the frequencies between studies, Study PRO-814 had the lowest incidences of non-implant site TEAEs. Subjects in Study PRO-814 were exposed to buprenorphine for at least 6 months before study entry, meaning that the study could have preselected for patients who tolerate buprenorphine well and also, once entered, these subjects did not have to go through an adjustment period of taking buprenorphine. In addition, subjects in Study PRO-814 were clinically stable, and had reached a maintenance phase in their treatment. It is possible that these subjects were in better health overall than subjects in Studies PRO-805 and PRO-806, who were just starting treatment with buprenorphine. It should be noted, however, the types of non-implant site TEAEs reported were similar across studies (as presented in individual CSRs).

Comparison of safety for Sixmo versus SL BPN

Studies PRO-806 and PRO-814 provide comparative safety data for Sixmo versus SL BPN. As shown in Table 25, the non-implant site AE frequencies were similar between the Sixmo and the SL BPN groups. Also, no notable differences in the pattern of individual non-implant AEs were observed.

Common Implant Site TEAEs (Pooled Double-Blind Studies)

Common implant site TEAEs reported by ≥2% of subjects in either treatment group are summarized in Table 26 by preferred term (PT).

Table 25 Implant Site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Pooled Double-Blind Studies PRO-805, PRO-806, PRO-814 (Safety Population)

System Organ Class Preferred Term	Probuphine N=309 n (%)	Placebo/SL BPN N=198[a] n (%)	Total N=507 n (%)
Any Implant Site TEAE	**115 (37.2)**	**54 (27.3)**	**169 (33.3)**
General disorders and administration site conditions	**97 (31.4%)**	**46 (23.2%)**	**143 (28.2%)**
Implant site pain	39 (12.6)	18 (9.1)	57 (11.2)
Implant site pruritus	38 (12.3)	15 (7.6)	53 (10.5)
Implant site erythema	32 (10.4)	13 (6.6)	45 (8.9)
Implant site haematoma	20 (6.5)	15 (7.6)	35 (6.9)
Implant site haemorrhage	23 (7.4)	10 (5.1)	33 (6.5)
Implant site oedema	16 (5.2)	5 (2.5)	21 (4.1)
Implant site scar	11 (3.6)	8 (4.0)	19 (3.7)
Implant site reaction	7 (2.3)	3 (1.5)	10 (2.0)

SL BPN = sublingual buprenorphine; TEAE = treatment-emergent adverse event
[a] Note, subjects in the SL BPN group of Study PRO-806 are excluded from the analysis of implant site AEs, as they did not have an implant, and were not at risk for implant site AEs.

A greater percentage of subjects in the Sixmo group than in the placebo/SL BPN group (37.2% versus 27.3%) reported at least one implant site TEAE.

The most frequent implant site TEAEs were implant site pain (11.2% overall) and implant site pruritus (10.5% overall). The frequencies of the individual implant site AEs tended to be higher in the Sixmo than in the placebo/SL BPN group. However, there were no pronounced differences between the two groups.

These data indicate that the implant-site safety profile for Sixmo is principally related to the implant procedure and route of administration rather than to the buprenorphine, or any interaction between buprenorphine and EVA, contained in the Sixmo product.

Related implant site TEAEs

In the vast majority of subjects with implant site TEAEs, these AEs were considered related to study drug and/or implant procedure (Pooled safety tables, Table 8.2.3.3.1).

Implant site TEAEs by intensity

Implant site TEAEs in the pooled double-blind studies are presented by intensity in Pooled safety tables, Table 8.2.3.2.1. In the majority of subjects with implant site TEAEs, implant site AEs were mild. The incidence of moderate implant site TEAEs was similar in the Sixmo and placebo/SL BPN groups (7.4% versus 5.1%), while the incidence of mild implant site TEAEs was slightly higher in the Sixmo compared with the placebo/SL BPN group (29.4% versus 21.7%). Only 1 subject in each treatment group had a severe implant site TEAE. The subject in the Sixmo group had severe implant site pain and implant site infection. The subject in the placebo/SL BPN group had severe implant site pain (Module 2.7.4, Section 2.1.1.1.1).

Safety by Implant Technique (Original versus Current Technique)

The applicator and the implant technique were changed during clinical development, after Studies PRO-805 and PRO-807 had been completed. That means that the double-blind study PRO-805 and the respective open-label extension study both used the previous technique, while Studies PRO-806, PRO-814, and PRO-811 used the current technique. This change led to a substantial reduction in the frequencies of implant site TEAEs. Of note, only the current techniques will be used commercially, thus the implant-site adverse reactions of Sixmo (as presented in the Sixmo SmPC) will be based on the AEs observed with the current techniques only.

Common Non-Implant Site TEAEs (Pooled Double-Blind Studies)

The evaluation of non-implant site TEAEs in the pooled double-blind studies was based on the safety population of 626 subjects treated in the 3 double-blind studies (Sixmo: 309 subjects; placebo/SL BPN: 317 subjects).

Common non-implant site TEAEs reported by ≥2% of all subjects are summarized in Table 27 by system organ class (SOC) and PT.

Table 26 Non-Implant Site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Pooled Double-Blind Studies PRO-805, PRO-806, and PRO-814 (Safety Population)

System Organ Class Preferred Term	Probuphine N=309 n (%)	Placebo/SL BPN N=317 n (%)	Total N=626 n (%)
Any Non-Implant Site TEAE	**200 (64.7)**	**205 (64.7)**	**405 (64.7)**
Infections and infestations	**113 (36.6)**	**113 (35.6)**	**226 (36.1)**
Nasopharyngitis	27 (8.7)	22 (6.9)	49 (7.8)
Upper respiratory tract infection	25 (8.1)	23 (7.3)	48 (7.7)
Gastroenteritis viral	7 (2.3)	9 (2.8)	16 (2.6)
Influenza	7 (2.3)	9 (2.8)	16 (2.6)
Bronchitis	6 (1.9)	9 (2.8)	15 (2.4)
Abscess limb	4 (1.3)	10 (3.2)	14 (2.2)
Tooth abscess	6 (1.9)	8 (2.5)	14 (2.2)
Urinary tract infection	7 (2.3)	6 (1.9)	13 (2.1)

System Organ Class Preferred Term	Probuphine N=309 n (%)	Placebo/SL BPN N=317 n (%)	Total N=626 n (%)
Gastrointestinal disorders	**78 (25.2)**	**61 (19.2)**	**139 (22.2)**
Nausea	20 (6.5)	15 (4.7)	35 (5.6)
Constipation	20 (6.5)	9 (2.8)	29 (4.6)
Vomiting	17 (5.5)	11 (3.5)	28 (4.5)
Toothache	14 (4.5)	10 (3.2)	24 (3.8)
Diarrhoea	10 (3.2)	13 (4.1)	23 (3.7)
Abdominal pain upper	10 (3.2)	7 (2.2)	17 (2.7)
Psychiatric disorders	**64 (20.7)**	**68 (21.5)**	**132 (21.1)**
Insomnia	26 (8.4)	36 (11.4)	62 (9.9)
Anxiety	15 (4.9)	18 (5.7)	33 (5.3)
Depression	20 (6.5)	10 (3.2)	30 (4.8)
Nervous system disorders	**62 (20.1)**	**53 (16.7)**	**115 (18.4)**
Headache	39 (12.6)	32 (10.1)	71 (11.3)
Dizziness	11 (3.6)	7 (2.2)	18 (2.9)
General disorders and administration site conditions	**51 (16.5)**	**29 (9.1)**	**80 (12.8)**
Pain	12 (3.9)	9 (2.8)	21 (3.4)
Fatigue	9 (2.9)	4 (1.3)	13 (2.1)
Musculoskeletal and connective tissue disorders	**41 (13.3)**	**39 (12.3)**	**80 (12.8)**
Back pain	18 (5.8)	15 (4.7)	33 (5.3)
Arthralgia	6 (1.9)	7 (2.2)	13 (2.1)
Injury, poisoning and procedural complications	**35 (11.3)**	**36 (11.4)**	**71 (11.3)**
Contusion	6 (1.9)	8 (2.5)	14 (2.2)
Respiratory, thoracic and mediastinal disorders	**39 (12.6)**	**23 (7.3)**	**62 (9.9)**
Oropharyngeal pain	14 (4.5)	10 (3.2)	24 (3.8)
Cough	10 (3.2)	4 (1.3)	14 (2.2)
Skin and subcutaneous tissue disorders	**27 (8.7)**	**19 (6.0)**	**46 (7.3)**
Hyperhidrosis	8 (2.6)	6 (1.9)	14 (2.2)

SL BPN = sublingual buprenorphine; TEAE = treatment-emergent adverse event
Source: Pooled safety tables, Table 8.2.4.1.1

A total of 405 subjects overall (64.7%) reported at least one non-implant site TEAE, the frequencies in both treatment groups being 64.7%. Most frequent were TEAEs in the SOC of infections and infestations (36.1% of subjects overall), gastrointestinal disorders (22.2% overall), psychiatric disorders (21.1% overall), and nervous system disorders (18.4% overall).

The most frequent non-implant site TEAEs (reported by ≥5% of subjects in any group) by PT were headache (Sixmo 12.6%, placebo 10.1%), insomnia (Sixmo 8.4%, placebo 11.4%), nasopharyngitis (Sixmo 8.7%, placebo 6.9%), upper respiratory tract infection (Sixmo 8.1%, placebo 7.3%), nausea (Sixmo 6.5%, placebo 4.7%), anxiety (Sixmo 4.9%, placebo 5.7%), back pain (Sixmo 5.8%, placebo 4.7%), depression (Sixmo 6.5%, placebo 3.2%), constipation (Sixmo 6.5%, placebo 2.8%), and vomiting (Sixmo 5.5%, placebo 3.5%).

The whole pattern of TEAEs was very similar for the Sixmo and the placebo/SL BPN groups. Frequencies of individual TEAEs tended to be higher in the Sixmo than in the placebo group. However, there were no notable imbalances in the incidence of individual nonimplant site TEAEs between treatment groups.

These data suggest that the non-implant safety profile of Sixmo is largely driven by the buprenorphine released by the implant.

Related non-implant TEAEs

Non-implant site TEAEs considered related to study drug and/or implant procedure in the pooled double-blind studies are presented in Table 28, by SOC and PT.

Table 27 Related Non-Implant Site Treatment-Emergent Adverse Events in Pooled Double-Blind Studies PRO-805, PRO-806, and PRO-814 (Safety Population)

System Organ Class Preferred Term	Probuphine N=309 n (%)	Placebo/SL BPN N=317 n (%)	Total N=626 n (%)
Any related non-implant TEAE	**96 (31.1)**	**54 (17.0)**	**150 (24.0)**
Infections and infestations	**9 (2.9)**	**4 (1.3)**	**13 (2.1)**
Nasopharyngitis	1 (0.3)	1 (0.3)	2 (0.3)
Upper respiratory tract infection	2 (0.6)	0	2 (0.3)
Influenza	0	1 (0.3)	1 (0.2)
Urinary tract infection	1 (0.3)	0	1 (0.2)
Viral infection	4 (1.3)	1 (0.3)	5 (0.8)
Cellulitis	1 (0.3)	0	1 (0.2)
Skin infection	1 (0.3)	0	1 (0.2)
Furuncle	1 (0.3)	0	1 (0.2)
Peritonsillar abscess	1 (0.3)	0	1 (0.2)
Pharyngitis	0	1 (0.3)	1 (0.2)
Rash pustular	1 (0.3)	0	1 (0.2)
Vulvovaginal mycotic infection	1 (0.3)	0	1 (0.2)
Gastrointestinal disorders	**41 (13.3)**	**15 (4.7)**	**56 (8.9)**
Nausea	11 (3.6)	4 (1.3)	15 (2.4)
Constipation	17 (5.5)	5 (1.6)	22 (3.5)
Vomiting	8 (2.6)	2 (0.6)	10 (1.6)
Toothache	1 (0.3)	0	1 (0.2)
Diarrhoea	7 (2.3)	3 (0.9)	10 (1.6)
Abdominal pain upper	4 (1.3)	3 (0.9)	7 (1.1)
Abdominal discomfort	2 (0.6)	1 (0.3)	3 (0.5)
Abdominal pain	1 (0.3)	0	1 (0.2)
Flatulence	1 (0.3)	0	1 (0.2)
Dry mouth	2 (0.6)	0	2 (0.3)

Psychiatric disorders	**26 (8.4)**	**13 (4.1)**	**39 (6.2)**
Insomnia	12 (3.9)	9 (2.8)	21 (3.4)
Anxiety	4 (1.3)	1 (0.3)	5 (0.8)
Depression	2 (0.6)	0	2 (0.3)
Initial insomnia	2 (0.6)	0	2 (0.3)
Restlessness	0	2 (0.6)	2 (0.3)
Drug dependence	0	1 (0.3)	1 (0.2)
Libido decreased	3 (1.0)	0	3 (0.5)
Sleep disorder	3 (1.0)	0	3 (0.5)
Apathy	1 (0.3)	0	1 (0.2)
Disorientation	0	1 (0.3)	1 (0.2)
Euphoric mood	1 (0.3)	0	1 (0.2)
Mood swings	0	1 (0.3)	1 (0.2)
Orgasmic sensation decreased	1 (0.3)	0	1 (0.2)
Nervous system disorders	**35 (11.3)**	**16 (5.0)**	**51 (8.1)**
Headache	18 (5.8)	8 (2.5)	26 (4.2)
Dizziness	9 (2.9)	3 (0.9)	12 (1.9)
Somnolence	6 (1.9)	1 (0.3)	7 (1.1)
Migraine	2 (0.6)	0	2 (0.3)
Hypoaesthesia	0	1 (0.3)	1 (0.2)
Tremor	1 (0.3)	2 (0.6)	3 (0.5)
Lethargy	1 (0.3)	1 (0.3)	2 (0.3)
Restless legs syndrome	0	3 (0.9)	3 (0.5)
Sedation	3 (1.0)	0	3 (0.5)
Hypersomnia	1 (0.3)	0	1 (0.2)
Paraesthesia	1 (0.3)	0	1 (0.2)
Depressed level of consciousness	1 (0.3)	0	1 (0.2)
General disorders and administration site conditions	**21 (6.8)**	**6 (1.9)**	**27 (4.3)**
Pain	4 (1.3)	2 (0.6)	6 (1.0)
Fatigue	9 (2.9)	1 (0.3)	10 (1.6)
Pyrexia	1 (0.3)	0	1 (0.2)
Oedema peripheral	1 (0.3)	1 (0.3)	2 (0.3)
Chills	4 (1.3)	1 (0.3)	5 (0.8)
Asthenia	4 (1.3)	0	4 (0.6)
Influenza like illness	0	1 (0.3)	1 (0.2)
Feeling cold	1 (0.3)	1 (0.3)	2 (0.3)
Discomfort	1 (0.3)	0	1 (0.2)
Drug interaction	1 (0.3)	0	1 (0.2)
Face oedema	1 (0.3)	0	1 (0.2)
Irritability	0	1 (0.3)	1 (0.2)
Malaise	0	1 (0.3)	1 (0.2)
Swelling	1 (0.3)	0	1 (0.2)
Musculoskeletal and connective tissue disorders	**9 (2.9)**	**1 (0.3)**	**10 (1.6)**
Back pain	3 (1.0)	0	3 (0.5)
Pain in extremity	1 (0.3)	0	1 (0.2)
Muscle spasms	3 (1.0)	0	3 (0.5)
Myalgia	0	1 (0.3)	1 (0.2)
Musculoskeletal pain	1 (0.3)	0	1 (0.2)

Injury, poisoning and procedural complications	**4 (1.3)**	**2 (0.6)**	**6 (1.0)**
Muscle strain	0	1 (0.3)	1 (0.2)
Post procedural complication	3 (1.0)	0	3 (0.5)
Hand fracture	1 (0.3)	0	1 (0.2)
Incision site haemorrhage	0	1 (0.3)	1 (0.2
Respiratory, thoracic and mediastinal disorders	**2 (0.6)**	**4 (1.3)**	**6 (1.0)**
Nasal congestion	0	1 (0.3)	1 (0.2)
Rhinorrhoea	0	2 (0.6)	2 (0.3)
Yawning	0	1 (0.3)	1 (0.2)
Pulmonary embolism	1 (0.3)	0	1 (0.2)
Chronic obstructive pulmonary disease	1 (0.3)	0	1 (0.2)
Respiratory depression	1 (0.3)	0	1 (0.2)
Skin and subcutaneous tissue disorders	**9 (2.9)**	**8 (2.5)**	**17 (2.7)**
Hyperhidrosis	6 (1.9)	5 (1.6)	11 (1.8)
Rash	1 (0.3)	1 (0.3)	2 (0.3)
Night sweats	1 (0.3)	1 (0.3)	2 (0.3)
Cold sweat	1 (0.3)	0	1 (0.2)
Dry skin	1 (0.3)	0	1 (0.2)
Piloerection	0	1 (0.3)	1 (0.2)
Investigations	**9 (2.9)**	**6 (1.9)**	**15 (2.4)**
Alanine aminotransferase increased	2 (0.6)	1 (0.3)	3 (0.5)
Aspartate aminotransferase increased	2 (0.6)	2 (0.6)	4 (0.6)
Gamma-glutamyltransferase increased	1 (0.3)	1 (0.3)	2 (0.3)
Weight decreased	3 (1.0)	0	3 (0.5)
Weight increased	2 (0.6)	0	2 (0.3)
Blood alkaline phosphatase increased	0	1 (0.3)	1 (0.2)
Blood lactate dehydrogenase increased	2 (0.6)	0	2 (0.3)
Neutrophil count increased	1 (0.3)	0	1 (0.2)
Hepatic enzyme increased	1 (0.3)	1 (0.3)	2 (0.3)
International normalised ratio increased	0	2 (0.6)	2 (0.3)
Lipase increased	1 (0.3)	0	1 (0.2)
Lymphocyte count decreased	1 (0.3)	0	1 (0.2)
Mean cell volume abnormal	1 (0.3)	0	1 (0.2)
Prothrombin time prolonged	0	2 (0.6)	2 (0.3)
Blood alkaline phosphatase decreased	1 (0.3)	0	1 (0.2)
Blood amylase increased	1 (0.3)	0	1 (0.2)
Blood bicarbonate increased	1 (0.3)	0	1 (0.2)
Blood bilirubin increased	1 (0.3)	0	1 (0.2)
Blood cholesterol decreased	1 (0.3)	0	1 (0.2)
Blood glucose increased	1 (0.3)	0	1 (0.2)
Body temperature fluctuation	1 (0.3)	0	1 (0.2)
Haematocrit decreased	1 (0.3)	0	1 (0.2)
Haemoglobin decreased	1 (0.3)	0	1 (0.2)
Hepatic enzyme abnormal	0	1 (0.3)	1 (0.2)
Mean cell haemoglobin increased	1 (0.3)	0	1 (0.2)
Monocyte count increased	1 (0.3)	0	1 (0.2)
Platelet count decreased	1 (0.3)	0	1 (0.2)

Red blood cell count decreased	1 (0.3)	0	1 (0.2)
Metabolism and nutrition disorders	**7 (2.3)**	**4 (1.3)**	**11 (1.8)**
Decreased appetite	3 (1.0)	2 (0.6)	5 (0.8)
Dehydration	1 (0.3)	0	1 (0.2)
Increased appetite	1 (0.3)	2 (0.6)	3 (0.5)
Abnormal weight gain	1 (0.3)	0	1 (0.2)
Food craving	1 (0.3)	0	1 (0.2)
Vascular disorders	**5 (1.6)**	**3 (0.9)**	**8 (1.3)**
Hot flush	5 (1.6)	3 (0.9)	8 (1.3)
Reproductive system and breast disorders	**2 (0.6)**	**0**	**2 (0.3)**
Dysmenorrhoea	1 (0.3)	0	1 (0.2)
Erectile dysfunction	1 (0.3)	0	1 (0.2)
Eye disorders	**2 (0.6)**	**2 (0.6)**	**4 (0.6)**
Lacrimation increased	0	1 (0.3)	1 (0.2)
Eye discharge	1 (0.3)	0	1 (0.2)
Vision blurred	1 (0.3)	1 (0.3)	2 (0.3)
Cardiac disorders	**1 (0.3)**	**1 (0.3)**	**2 (0.3)**
Bradycardia	1 (0.3)	0	1 (0.2)
Ventricular extrasystoles	0	1 (0.3)	1 (0.2)
Renal and urinary disorders	**3 (1.0)**	**1 (0.3)**	**4 (0.6)**
Urinary hesitation	2 (0.6)	0	2 (0.3)
Micturition urgency	1 (0.3)	0	1 (0.2)
Pollakiuria	1 (0.3)	0	1 (0.2)
Polyuria	0	1 (0.3)	1 (0.2)
Blood and lymphatic system disorders	**1 (0.3)**	**0**	**1 (0.2)**
Lymphadenopathy	1 (0.3)	0	1 (0.2)
Ear and labyrinth disorders	**0**	**3 (0.9)**	**3 (0.5)**
Ear pain	0	1 (0.3)	1 (0.2)
Tinnitus	0	1 (0.3)	1 (0.2)
Vertigo	0	1 (0.3)	1 (0.2)

SL BPN = sublingual buprenorphine; TEAE = treatment-emergent adverse event.
TEAEs considered by the investigator to be at least possibly related to study drug and/or implant procedure, or for which the relationship was missing.

A greater percentage of subjects in the Sixmo treatment group than in the placebo/SL BPN treatment group (31.1% versus 17.0%) reported at least one related non-implant site TEAE. Most frequent related TEAEs were in the SOCs gastrointestinal disorders (8.9% of subjects overall), nervous system disorders (8.1% overall), psychiatric disorders (6.2% overall) and general disorders and administration site conditions (4.3% overall), with higher frequencies being reported for the Sixmo than for the placebo/SL BPN group.

Most frequent related TEAEs by PT (≥2% of subjects in any group) were headache (Sixmo 5.8%, placebo 2.5%), constipation (Sixmo 5.5%, placebo 1.6%), insomnia (Sixmo 3.9%, placebo 2.8%), nausea (Sixmo 3.6%, placebo 1.3%), dizziness (Sixmo 2.9%, placebo 0.9%), fatigue (Sixmo 2.9%, placebo 0.3%), vomiting (Sixmo 2.6%, placebo 0.6%), and diarrhea (Sixmo 2.3%, placebo 0.9%). Although the frequencies of individual related TEAEs were slightly higher in the Sixmo than in the combined placebo/SL BPN Sixmo group, the pattern of related TEAEs was similar between the two groups, which is as expected given the fact that subjects in the placebo/SL BPN groups were also exposed to buprenorphine.

Overall, the data suggest that the non-implant safety profile of Sixmo is largely driven by the buprenorphine released by the implant. Moreover, the pattern of related TEAEs with Sixmo is consistent with the adverse drug profile for approved buprenorphine products, as described in the product labels for Subutex and Suboxone (Subutex 8 mg SL tablets SmPC 2016,

Suboxone 16 mg/4mg SL tablets SmPC 2016). Most frequent adverse drug reactions (10% of subjects or more) with Subutex and/or Suboxone are constipation, headache, insomnia, nausea, hyperhidrosis, drug withdrawal syndrome and pain.

No important new TEAEs attributable to treatment with Sixmo implants were observed.

Based on buprenorphine's known mechanism of action, and considering also the subject population in the Sixmo studies, the following events (which were reported in single subjects in the Sixmo group only) were not considered to be related to study drug: Urinary tract infection, vulvovaginal mycotic infection, toothache, pain in extremity, musculoskeletal pain.

Therefore, the terms described above will not be included as adverse drug reactions in the SmPC for Sixmo.

Non-implant TEAEs by intensity

A total of 50 subjects (8.0%) reported severe non-implant site TEAEs considered related to study treatment. Severe non-implant TEAEs were reported by 21 subjects (6.8%) in the Sixmo group and 29 subjects (9.1%) in the placebo/SL BPN group.

Severe events were most frequent in the SOCs infections and infestations and gastrointestinal disorders.

Adverse Events in Extension Studies PRO-807 and PRO-811

Common Implant Site TEAEs

The evaluation of implant site TEAEs in the pooled open-label studies included 147 subjects who had been previously treated in the double-blind predecessor studies (107 with Sixmo, 40 with placebo or SL BPN). All of these subjects except the subjects receiving SL BPN in Study PRO-806 had received prior implants, either Sixmo or placebo, in the double-blind studies. As for the double-blind studies, it should be noted that insertion and removal equipment, techniques, and training were all refined, improved, and validated during the clinical development program. Study PRO-807 used the previous techniques, while Study PRO-811 used the current techniques.

Common implant site TEAEs (reported in ≥2% of subjects overall) in the open-label studies are presented in Table 29.

Table 28 Implant Site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Extension Studies PRO-807 and PRO-811 (Safety Population)

System Organ Class Preferred Term	PRO-807 [a] N=62	PRO-811 [a] N=85	Total [a] N=147
	n (%)	n (%)	n (%)
Any Implant Site TEAE	**28 (45.2)**	**12 (14.1)**	**40 (27.2)**
General disorders and administration site conditions	**26 (41.9)**	**8 (9.4)**	**34 (23.1)**
Implant site erythema	16 (25.8)	1 (1.2)	17 (11.6)
Implant site haemorrhage	11 (17.7)	3 (3.5)	14 (9.5)
Implant site pruritus	12 (19.4)	1 (1.2)	13 (8.8)
Implant site pain	12 (19.4)	0	12 (8.2)
Implant site haematoma	7 (11.3)	2 (2.4)	9 (6.1)
Implant site oedema	8 (12.9)	0	8 (5.4)
Implant site rash	1 (1.6)	2 (2.4)	3 (2.0)
Infections and infestations	**4 (6.5)**	**4 (4.7)**	**8 (5.4)**
Implant site infection	3 (4.8)	1 (1.2)	4 (2.7)

TEAE=treatment-emergent adverse event.

[a] Note, all subjects in Studies PRO-807 and PRO-811 received Probuphine. Subjects in Studies PRO-807 and PRO-811 who were in the Probuphine groups in the 6-month parent studies had additional exposure to Probuphine compared to subjects who were in the placebo and/or SL BPN groups of the parent studies.

The frequency of implant site AEs was markedly higher in Study PRO-807 (which used the original implant insertion and removal techniques) than in Study PRO-811 (which used the new techniques, 45.2% versus 14.1%).

The most common implant site TEAEs reported in the open-label studies were comparable, with slight differences in rank ordering, to those reported in the double-blind studies (Table 26), confirming that the implant safety profile of Sixmo is consistent over repeated implant events.

Common Non-Implant Site TEAEs

Common non-implant site TEAEs that were reported by ≥2% of all subjects are summarized in Table 30.

Table 29 Non-Implant Site Treatment-Emergent Adverse Events Reported by ≥2% of Subjects in Pooled Extension Studies PRO-807 and PRO-811 (Safety Population)

System Organ Class Preferred Term	PRO-807[a] N=62	PRO-811[a] N=85	Total N=147
	Probuphine n (%)	Probuphine n (%)	Probuphine n (%)
Any non-implant site TEAE	**41 (66.1)**	**54 (63.5)**	**95 (64.6)**
Infections and infestations	**11 (17.7)**	**26 (30.6)**	**37 (25.2)**
Upper respiratory tract infection	2 (3.2)	7 (8.2)	9 (6.1)
Urinary tract infection	1 (1.6)	5 (5.9)	6 (4.1)
Subcutaneous abscess	0 (0.0)	5 (5.9)	5 (3.4)
Nasopharyngitis	2 (3.2)	2 (2.4)	4 (2.7)
Tooth infection	1 (1.6)	2 (2.4)	3 (2.0)
Gastrointestinal disorders	**18 (29.0)**	**16 (18.8)**	**34 (23.1)**
Constipation	8 (12.9)	2 (2.4)	10 (6.8)
Abdominal discomfort	5 (8.1)	1 (1.2)	6 (4.1)
Toothache	3 (4.8)	3 (3.5)	6 (4.1)
Nausea	2 (3.2)	3 (3.5)	5 (3.4)
Abdominal pain upper	2 (3.2)	1 (1.2)	3 (2.0)
Diarrhoea	1 (1.6)	2 (2.4)	3 (2.0)
Nervous system disorders	**14 (22.6)**	**16 (18.8)**	**30 (20.4)**
Headache	10 (16.1)	10 (11.8)	20 (13.6)
Dizziness	2 (3.2)	2 (2.4)	4 (2.7)
Hypoaesthesia	2 (3.2)	2 (2.4)	4 (2.7)

Psychiatric disorders	**11 (17.7)**	**12 (14.1)**	**23 (15.6)**
Insomnia	7 (11.3)	2 (2.4)	9 (6.1)
Depression	1 (1.6)	4 (4.7)	5 (3.4)
Anxiety	1 (1.6)	3 (3.5)	4 (2.7)
General disorders and administration site conditions	**6 (9.7)**	**8 (9.4)**	**14 (9.5)**
Fatigue	1 (1.6)	4 (4.7)	5 (3.4)
Injury, poisoning and procedural complications	**7 (11.3)**	**7 (8.2)**	**14 (9.5)**
Contusion	2 (3.2)	3 (3.5)	5 (3.4)
Excoriation	3 (4.8)	0 (0.0)	3 (2.0)
Musculoskeletal and connective tissue disorders	**6 (9.7)**	**8 (9.4)**	**14 (9.5)**
Back pain	3 (4.8)	5 (5.9)	8 (5.4)
Pain in extremity	0 (0.0)	3 (3.5)	3 (2.0)
Investigations	**10 (16.1)**	**3 (3.5)**	**13 (8.8)**
Gamma-glutamyl transferase increased	3 (4.8)	2 (2.4)	5 (3.4)
ALT increased	3 (4.8)	1 (1.2)	4 (2.7)
AST increased	2 (3.2)	2 (2.4)	4 (2.7)
Skin and subcutaneous tissue disorders	**6 (9.7)**	**5 (5.9)**	**11 (7.5)**
Rash	2 (3.2)	1 (1.2)	3 (2.0)
Respiratory, thoracic and mediastinal disorders	**7 (11.3)**	**2 (2.4)**	**9 (6.1)**
Oropharyngeal pain	3 (4.8)	0 (0.0)	3 (2.0)
Rhinorrhea	2 (3.2)	1 (1.2)	3 (2.0)
Blood and lymphatic system disorders	**3 (4.8)**	**1 (1.2)**	**4 (2.7)**
Immune system disorders	**2 (3.2)**	**2 (2.4)**	**4 (2.7)**
Metabolism and nutrition disorders	**2 (3.2)**	**2 (2.4)**	**4 (2.7)**
Decreased appetite	1 (1.6)	2 (2.4)	3 (2.0)
Reproductive system and breast disorders	**1 (1.6)**	**3 (3.5)**	**4 (2.7)**
Ear and labyrinth disorders	**2 (3.2)**	**1 (1.2)**	**3 (2.0)**
Eye disorders	**3 (4.8)**	**0 (0.0)**	**3 (2.0)**

ALT = alanine aminotransferase; AST = aspartate aminotransferase; BPN = buprenorphine; SL = sublingual;

A total of 95 subjects overall (64.6%) reported at least one non-implant site TEAE, the frequencies in both studies being similar (66.1% in PRO-807 and 63.5% in PRO-811). Most frequent were TEAEs in the SOC of infections and infestations (25.2% of subjects overall), gastrointestinal disorders (23.1% overall), nervous system disorders (20.4% overall), and psychiatric disorders (15.6% overall).

The most frequent non-implant site TEAEs (reported by ≥5% of subjects overall) by PT were headache (PRO-807 16.1%, PRO-811 11.8%), constipation (PRO-807 12.9%, PRO-811 2.4%), insomnia (PRO-807 11.3%, PRO-811 2.4%), upper respiratory tract infection (PRO-807 3.2%, PRO-811 8.2%) and back pain (PRO-807 4.8%, PRO-811 5.9%). There were some imbalances in AE frequencies between the two studies, none of which were considered clinically relevant.

The most common non-implant site TEAEs reported in the open-label studies were comparable, with some differences in rank ordering, to those reported in the double-blind studies confirming that the non-implant safety profile Sixmo is consistent over repeated implant events.

Of note, there were some non-implant site AEs (32 TEAEs in 22 subjects) that occurred during the follow-up of the double-blind studies and during the induction period for the open-label studies. These are

not captured in the double-blind study analysis. Two serious adverse events (SAEs) were reported in this period (Subjects 019-036 and 604-012).

Related non-implant TEAEs

A greater percentage of subjects in the study PRO-807 than in study PRO-811 (27.4% versus 16.5%) reported at least one non-implant site TEAE considered related to study treatment. Most frequent related TEAEs were in the SOCs gastrointestinal disorders (10.2% of subjects overall), nervous system disorders (8.2% overall) and general disorders and administration site conditions (5.4% overall), with higher frequencies being reported in study PRO-807 than in study PRO-811.

Most frequent related non-implant site TEAEs by PT (≥2% of subjects overall) were headache (PRO-807 6.5%, PRO-811 3.5%), constipation (PRO-807 9.7%, PRO-811 1.2%), fatigue (PRO-807 1.6%, PRO-811 4.7%), insomnia (PRO-807 3.2%, PRO-811 1.2%) and abdominal discomfort (PRO-807 3.2%, PRO-811 1.2%, Pooled safety tables, Table 9.3.13). Albeit the frequencies of individual related TEAEs were slightly higher in PRO-807 than PRO-811, the pattern of related TEAEs was similar between the two groups, and also similar to the pattern seen in the double-blind studies.

In the majority of subjects, non-implant site TEAEs in the pooled open-label studies were mild or moderate. Six subjects (4.1%) had severe non-implant site TEAEs. Severe non-implant site TEAEs in the pooled open-label studies included cellulitis, onychomycosis, nausea, insomnia, depression, emotional disorder, orgasmic sensation decreased, suicidal ideation, and back pain.

Adverse Events in PK Studies TTP-400-02-01 and PRO-810

Study TTP-400-02-01

Eleven of the 12 subjects (92%) reported at least one AE. All AEs reported were mild to moderate in severity and no AEs were assessed as severe. No SAEs or deaths were reported. No subjects prematurely discontinued treatment with Sixmo because of an AE. All AEs reported in more than one subject were: implant site reactions in 6 subjects; lethargy and upper respiratory tract infection in 5 subjects each; constipation and dizziness in 3 subjects each; and abdominal pain, anxiety, bradycardia, diarrhea, headache, insomnia, and pain in extremity in 2 subjects each.

Study PRO-810

A total of 6 (66.7%) subjects reported a total of 18 AEs during the study. Each AE was categorized as either “implant site” or “other adverse event.” No implant site AEs and no AEs related to the implant insertion or removal procedure were reported. No AEs were considered related to study treatment, and no deaths were reported.

All AEs were non-implant site AEs. Most frequent AEs by SOC were nervous system disorders (4 subjects, 44.4%) and infections and infestations (3 subjects, 33.3%). The most frequently reported PT was headache (4 subjects, 44.4%). Dyspepsia, upper respiratory tract infection, and hypertension were reported in 2 (22.2%) subjects each. All other AEs were reported in single subjects. A total of 3 SAEs were reported, all in the same subject (Subject 10-01009). The SAEs were 2 events of pancreatic cyst and 1 event of nausea. The subject was hospitalized twice, once due to the SAE of pancreatic cyst and once due to the SAE of nausea. Study drug was discontinued as a result of recurrence of the pancreatic cyst. The events of pancreatic cyst were severe in intensity; all other AEs reported in the study were mild in intensity.

Implant Site TEAEs by Subgroup

Implant site TEAEs are summarized for subgroups of subjects in the pooled double-blind studies stratified by sex, age, BMI, and race in Table 31.

Among subjects who received Sixmo, there were few differences in the incidence of implant site TEAEs between subgroups of subjects based on sex or age. Implant site TEAEs were reported by greater percentages of Black subjects and subjects of other races than White subjects (for the Sixmo group, 51.6% and 47.4% versus 34.7%, respectively). In the Sixmo group, a greater percentage of subjects in the low than high BMI subgroup had implant site TEAEs (Sixmo group, 41.1% versus 33.9%, respectively). However, the number of subjects of Black and other races was low, and differences between subgroups in individual implant site TEAEs were generally small and did not suggest global trends.

Table 30 Implant Site Treatment-Emergent Adverse Events by Subgroup in the Pooled Double-Blind Studies PRO-805, PRO-806, and PRO-814 (Safety Population)

	Probuphine		Placebo/SL BPN	
Subgroup	**N**	**n (%)**	**N**	**n (%)**
Sex				
Male	196	75 (38.3)	123	40 (32.5)
Female	113	40 (35.4)	75	14 (18.7)
Age (years)				
18 to 35	156	59 (37.8)	97	27 (27.8)
36 to 65	153	56 (36.6)	101	27 (26.7)
Race				
White	259	90 (34.7)	170	41 (24.1)
Black	31	16 (51.6)	15	7 (46.7)
Other	19	9 (47.4)	13	6 (46.2)
BMI				
≤ 25 kg/m^2	141	58 (41.1)	97	23 (23.7)
>25 kg/m^2	168	57 (33.9)	101	31 (30.7)

Abbreviations: BMI = body mass index; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SL BPN = sublingual buprenorphine

Note: Subjects in the SL BPN arm in Study PRO-806 are excluded from this display as they were not at risk for implant site adverse events. A subject reporting more than one adverse event for a particular MedDRA PT is counted only once for that MedDRA PT.

Non-Implant Site TEAEs by Subgroup

Non-implant site TEAEs are summarized for subgroups of subjects in the pooled double-blind studies stratified by sex, age, BMI, and race in Table 32.

Among subjects who received Sixmo, there were few differences in the incidence of nonimplant site TEAEs between subgroups of subjects based on age. Non-implant site TEAEs were reported by greater percentages of female than male subjects (69.0% versus 62.2%, respectively), by greater percentages of Black subjects and subjects of other races than White subjects (74.2% and 73.7% versus 62.9%, respectively), and by greater percentages of subjects in the low than high BMI subgroup (68.1% versus 61.9%, respectively). However, the numbers of Black subjects and subjects of other races were low, and differences between subgroups in individual non-implant site TEAEs were generally small and did not suggest global trends.

Table 31 Non-Implant Site Treatment-Emergent Adverse Events by Subgroup in the Pooled Double-Blind Studies PRO-805, PRO-806, and PRO-814 (Safety Population)

	Probuphine		Placebo/SL BPN	
Subgroup	N	n (%)	N	n (%)
Sex				
Male	196	122 (62.2)	195	124 (63.6)
Female	113	78 (69.0)	122	81 (66.4)
Age (years)				
18 to 35	156	102 (65.4)	166	112 (67.5)
36 to 65	153	98 (64.1)	151	93 (61.6)
Race				
White	259	163 (62.9)	267	171 (64.0)
Black	31	23 (74.2)	31	17 (54.8)
Other	19	14 (73.7)	19	17 (89.5)
BMI				
≤25 kg/m^2	141	96 (68.1)	162	108 (66.7)
>25 kg/m^2	168	104 (61.9)	155	97 (62.6)

Abbreviations: BMI = body mass index; MedDRA = medical dictionary for regulatory activities; PT = preferred term; SL BPN = sublingual buprenorphine

Note: SL BPN denotes subjects assigned to the SL BPN arm in Studies PRO-806 and PRO-814. All subjects in all studies took SL BPN during induction and had the option of taking supplemental SL BPN during treatment. A subject reporting more than one adverse event for a particular MedDRA PT is counted only once for that MedDRA PT.

TEAEs by Primary Opioid Dependence Subgroup

Implant site TEAEs in the pooled double-blind studies for subgroups stratified by primary opioid dependence (heroin versus prescription opioid or other pain medication) are discussed below. Across all studies, implant TEAEs were reported by a greater percentage of subjects whose primary dependence was on heroin than subjects whose primary dependence was on prescription opioid or other pain medication. There were no notable differences in the types of TEAEs between the heroin and prescription opioid or other pain medication groups.

Among subjects who received Sixmo, a greater percentage of subjects with heroin dependence (112 subjects [70.0%]) than prescription opioid or other pain medication dependence (88 subjects [59.1%]) reported at least one non-implant site TEAE. However, there were few notable (≥5%) differences in the incidence of individual non-implant site TEAEs between these subgroups.

Of the non-implant site TEAEs reported by ≥2% of the subjects in the Sixmo group, upper respiratory tract infection was reported by a greater percentage of subjects whose primary dependence was on heroin (18 subjects [11.3%]) than prescription opioid pain or other medications (7 subjects [4.7%]) in the Sixmo group.

Important co-morbidities:

Drug use is associated with a wide range of comorbidities, including injury through accidents or violence, mental health disorders, pulmonary diseases, stroke, and cardiovascular problems. Opioid use is additionally closely associated with the transmission of infectious diseases, such as HIV and hepatitis viruses (EMCDDA, 2010; National Institute on Drug Abuse [NIH], 2014) and the use of a secondary drug, often alcohol, cannabis, cocaine, or other stimulants (EMCDDA, 2011).

The average age of high-risk opioid users is increasing in Europe (Pirona et al, 2015). A history of poor health, bad living conditions, tobacco and alcohol use, and age-related deterioration of the immune system make high-risk opioid users susceptible to a range of chronic health problems, including cardiovascular and lung problems resulting from chronic tobacco use and injecting drug use. Long-term

heroin use is often associated with chronic pain conditions and infection with hepatitis viruses which places the patient at increased risk of cirrhosis and over liver problems (EMCDDA, 2015).

Serious adverse events and deaths

Deaths, Serious Adverse Events and Adverse Events of Special Interest

Deaths

There was one death in the SL BPN treatment group in Study PRO-806. This subject had an accidental overdose of heroin, three days following early study discontinuation,that was not related to study drug.

Serious Adverse Events

There were few differences across studies in the incidences or types of SAEs reported in double –blind and open label extension studies. Twenty-six subjects had one or more non-fatal SAEs in the double-blind studies and 4 subjects had one or more non-fatal SAEs during an open-label extension study (note, one of these 4 subjects also had an SAE in the respective double-blind study, and for 2 of the subjects the SAE started before Sixmo was inserted in the extension study). In the pooled double-blind studies, non-fatal SAEs were reported in 10 subjects in the Sixmo group and 16 subjects in the placebo/SL BPN group. Consistent with the design of the open-label studies, all 4 subjects who had non-fatal SAEs during the open-label studies were being treated with Sixmo.

The only implant site SAE reported as related to treatment (cellulitis at the implant site) occurred in a subject in the placebo group (Study PRO-805),that was resolving at the time of last follow-up. One subject in the Sixmo group (Study PRO-805) had 3 non-implant site SAEs (exacerbation of COPD and 2 events of pulmonary embolism).The subject recovered from these events.

Implant Expulsions and Extrusions

A total of 6 (1.0%) of the 626 subjects in the double-blind studies experienced implant expulsion (implants that completely left the insertion site) and/or implant extrusion (implants that were protruding through the skin). This included 3 subjects with implant expulsions (one subject each in Studies PRO-805, PRO-806, and PRO-814) and 3 subjects with implant extrusions (all in Study PRO-805). For 4 of the 6 affected individuals (all in PRO-805), the implant extrusion/expulsion problems were attributed to improper insertion technique; with the implementation of improved implant insertion equipment, techniques, and standardized training, such events did not reoccur in later studies (PRO-806 and PRO-814). The cases in Studies PRO- 806 and PRO-814 were associated with an active implant site infection.

Additionally, 1 subject in the open-label extension studies experienced implant extrusion (Study PRO-807). Another subject in Study PRO-807 experienced implant expulsion; this subject had also experienced implant extrusion in Study PRO-805.

No other cases of implant removal or tampering were reported in clinical studies of Sixmo.

Withdrawal Symptoms Reported as Treatment-emergent Adverse Events

As previously mentioned, the primary analysis of withdrawal symptoms was included as efficacy outcome variables (Subjective Opiate Withdrawal Scale [SOWS], COWS, and VAS).

Laboratory findings

Summary of Clinical Laboratory Evaluations

Overall, the laboratory findings were consistent between studies. There were few changes from baseline in laboratory results. Increases in liver enzymes were seen in some subjects but occurred with equal

incidence in the Sixmo and placebo and/or SL BPN groups. Small increases were observed for both basophiles and eosinophils, but the lack of a strong difference between the Sixmo group and the placebo/SL BPN group suggests the likelihood that these increases were not due to the specific formulation of buprenorphine used in Sixmo.

Hematology

Changes in Observed Values

There were few changes in mean or median observed values or change from baseline values observed for hematology values in any of the treatment groups in the double-blind study. Only minor mean and median changes were observed in evaluations of data from the pooled open-label studies.

Basophils and Eosinophils

Because allergic reactions and hypersensitivity events have been reported for other products containing buprenorphine, and because basophils and eosinophils are possible indicators of allergic reactions and hypersensitivity events, a special examination of these 2 hematology parameters was performed.

Shifts to values above the ULN for basophils and for eosinophils were uncommon and occurred in both the Sixmo and the combined placebo/SL BPN groups for the double-blind studies and in the open-label studies. In the double-blind studies, a greater number of subjects in the Sixmo group compared with the placebo/SL BPN group had shifts in eosinophils from normal at baseline to above the ULN at the highest value observed during treatment. This observation was not sustained through the end of treatment, however; the percentages of subjects with shifts from normal at Baseline to above the ULN at the end of treatment were similar for the

Sixmo group compared with the placebo/SL BPN group. No subjects discontinued due to high basophil or eosinophil counts; no such event was reported as a TEAE. Furthermore, in the double-blind studies, hypersensitivity was reported more frequently in the combined placebo/SL BPN group (2 subjects, 0.6%, both assessed as not related to study drug) than Sixmo group (0 subjects), suggesting no increase in hypersensitivity reactions after treatment with Sixmo compared with other formulations of buprenorphine.

Thus, although shifts from normal at Baseline to above the ULN were observed for both

basophils and eosinophils, the lack of a strong difference between the Sixmo group and the placebo/SL BPN group suggests the likelihood that these shifts were not due to the specific formulation of buprenorphine used in Sixmo but were rather due either to buprenorphine in general (since all groups, including the majority of subjects in the placebo/SL BPN groups, received buprenorphine at least once during the study) or possibly to other events unrelated to buprenorphine use.

Clinical Chemistry Values

Changes in Observed Values

In the clinical studies, there were few changes in mean or median values for any clinical chemistry values.

Liver Enzymes and Bilirubin

Normal-to-high (above the normal range) shifts were observed for liver enzymes and bilirubin values. However, as evaluated in the double-blind studies, the incidence of normal-to-high shifts (based on maximal values and end-of-study values) was similar among the Sixmo and placebo/SL BPN groups.

While the number of subjects with normal-to-high shifts for specific parameters differed between treatment groups, no consistent trends emerged. For example, normal-to-high shifts in ALT were more common in the placebo/SL BPN group than in the Sixmo group, whereas normal-to high shifts in AST and GGT were more common in the Sixmo group than in the placebo/SL BPN group.

In both treatment groups, normal-to-high shifts were less common based on the value at the end of the study than based on the maximal value during the study. This suggests that above normal range values that occurred during the study tended to normalize over time.

The applicant presented a cumulative overview of cases reporting changes in hepatic function in patients treated with Sixmo, including data from post-marketing experience where available.

Buprenorphine is extensively metabolized in the liver and plasma levels were found to be increased in patients with moderate and severe hepatic impairment. Buprenorphine is contraindicated in patients with severe hepatic impairment.

Baseline liver function tests and documentation of viral hepatitis status are recommended prior to commencing therapy with buprenorphine. Patients who are positive for viral hepatitis, on concomitant medicinal products and/or have existing liver dysfunction are at risk of accelerated liver injury. Regular monitoring of liver function is recommended. As buprenorphine pharmacokinetics may be altered in patients with hepatic impairment, lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment are recommended. (Suboxone 16 mg/4 mg sublingual tablets SmPC, 2016).

Recommendations on hepatic monitoring as outlined in the product information for other buprenorphine formulations have now been proposed for Sixmo SmPC.

The guidance on use of Sixmo in moderate hepatic impairment has been revised to reflect the context of use of implantable Sixmo since there is no option to down-titrate the buprenorphine dose with this formulation, in comparison to other buprenorphine formulations which recommend lower initial doses and careful dose titration in patients with mild to moderate hepatic impairment. (Suboxone 16 mg/4 mg sublingual tablets SmPC, 2016)**.**

Electrocardiogram Results (Pooled Double-blind Studies)

Infrequent increases in QTcB and QTcF intervals were observed after treatment with Sixmo as well as with placebo/SL BPN. These results may be expected based on the observation of QTc prolongation after treatment with other products containing buprenorphine.

The comparison between Sixmo and placebo/SL BPN provided for the double-blind studies suggests that Sixmo is not associated with a greater incidence of clinically meaningful QTc prolongation compared to SL BPN. Other than the increases in

QTcB and QTcF, there were few changes in vital signs and ECGs.

Safety in special populations

Pregnancy and lactation

There are no adequate and well-controlled studies of Sixmo (or buprenorphine) in pregnant women. Female subjects who were pregnant or planning to become pregnant during the study were excluded from entering Studies PRO-805, PRO-806, PRO-807, PRO-811 and PRO-814.

Female subjects who became pregnant in PRO-805, PRO-806, PRO-807 and PRO-811 were to be withdrawn from the study. Subjects who became pregnant during PRO-814 could elect to continue the study; this was the case for 2 subjects in PRO-814.

There were a total of 7 pregnancies during the Sixmo clinical development program. The outcome of the pregnancies was a healthy baby for 3 cases, spontaneous abortion for 3 cases, and an elective abortion for the remaining case. No adverse pregnancy outcomes were identified in the clinical program.

The potential for buprenorphine to induce effects on embryo-fetal development and/or effects on pre- and postnatal development is described in the literature.

Published data are consistent with those reported for Suboxone (Suboxone SmPC 2016; Suboxone EPAR 2006) indicating that buprenorphine is embryotoxic at maternal toxic dosages, but is not teratogenic.

Due to the lack of safer alternatives, there is clinical experience on the use of buprenorphine in the treatment of opioid dependence during pregnancy. As reviewed by Farid et al. (2008), clinical retrospective and prospective studies on buprenorphine maintenance for pregnant opioid-dependent women indicated that it is well tolerated and safe. Neonatal outcomes are not conclusive, as studies are limited. Nevertheless, most pregnancies lack complications with neonatal outcomes, including birth weight, APGAR scores, head circumference and body length, being within normal ranges. In addition, mortality is not a major problem, with one stillbirth and one spontaneous abortion being the only reported cases. Notwithstanding the benefits of managing pregnant opioid-dependent women with buprenorphine, caution is needed as adverse effects have been associated with this treatment.

The use of buprenorphine during pregnancy is known to cause neonatal abstinence syndrome in the infant (Johnson et al. 2003).

Overall, buprenorphine should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Buprenorphine and its metabolites are excreted in human breast milk (Lindemalm et al. 2009). Therefore, breastfeeding should be discontinued during treatment with buprenorphine.

Hepatic impairment

Sixmo should not be used in patients with severe hepatic impairment. Patients with moderate hepatic impairment should be monitored for signs and symptoms of toxicity or overdose.

Renal impairment

No dose modifications of Sixmo are required for patients with renal impairment.

Use in adolescents

Oral formulations of buprenorphine are approved for use in adolescents (Subutex: 16 years and over, Suboxone: over 15 years), although the studies of Suboxone have been conducted mainly in adults who were addicted to 5 -10 years or longer (Woody et al. 2008). Literature evidence supports the use of buprenorphine in opioid-dependent adolescents and young adults (Marsch et al. 2005, Woody et al. 2008). In these studies, buprenorphine was shown to be safe and effective.

No evidence of opioid intoxication or psychomotor impairment was observed (Marsch et al. 2005).

Long-Term Safety

A total of 107 subjects were treated with Sixmo over two serial treatment cycles, i.e., enrolled in the Sixmo groups of Studies PRO-805 and PRO-806, and rolled over to the corresponding extension studies. However, not all of the 107 subjects completed the two serial treatments and were exposed for one year. Long-term safety was assessed in the 88 subjects who were at risk (i.e., subjects with more than 365 days at risk, defined as exposure time plus the post-removal follow up period in which AEs were recorded).

A total of 77 of the 88 subjects (87.5%) experienced at least one TEAE. The most common (≥10%) implant site TEAEs were implant site pain (21.6%), implant site pruritus (19.3%), implant site erythema (17.0%), implant site hematoma (17.0%), implant site haemorrhage (13.6%), and implant site edema (13.6%).

The most common (≥10%) non-implant site TEAEs were headache (25.0%), insomnia (18.2%), upper respiratory tract infection (15.9%), back pain

(13.6%), constipation (12.5%), depression (12.5%), nasopharyngitis (10.2%), and vomiting (10.2%), Pooled safety tables, Table 8.2.2.8; Module 2.7.4, Table 43.

The type and frequency of TEAEs reported in subjects who had at least 1 year of exposure to Sixmo were generally similar to that reported for the subjects treated in the 6-month Studies PRO-805 and PRO-806. These data therefore indicate that the overall implant and non-implant safety profiles for Sixmo are maintained through up to at least 1 year's exposure (i.e., 2 implant periods).

In the dosing section 4.2 of the Sixmo SmPC, long term treatment is addressed by the following language: *"If continued treatment is desired at the end of the first six-month treatment cycle, a new set of Sixmo implants may be administered following removal of the old implants."*

This wording is in line with the established use of buprenorphine in clinical practice and in line with approved labelling of approved buprenorphine products (e.g., Suboxone). By nature, buprenorphine is a drug to be given long term as substitution therapy. The safety of buprenorphine in chronic use in the proposed indication and in the targeted patient population is well established. For this reason there is no need to initiate new clinical studies with longer treatment periods than the available 6 months data in order to support the proposed indication and dosing recommendations.

Overdose

Given the nature of the implant, overdose with Sixmo is unlikely.

One case of accidental pediatric exposure occurred in Study PRO-814 in the SL BPN treatment group.

Drug Abuse

On the basis of subjects (from all studies, including the double-blind and the open-label studies) who returned for implant removal and implant-site inspections, no evidence of diversion of Sixmo implants was detected. However, there were 3 cases in which the implants were expelled sufficiently to be finally removed by the subjects themselves. There is no additional evidence that any subject attempted to remove their implants or have their implants removed prior to returning at the end of the study for implant removal. Of the 1958 Sixmo implants that were inserted in the double-blind clinical studies, 167 implants (8.5%) were not accounted for as a result of subjects who failed to return for implant removal, including 16 implants in subjects lost to follow-up due to incarceration or inpatient drug treatment program. If failure to return for implant removal is interpreted as possible diversion, evidence of Sixmo

diversion was minimal based upon data from subjects who failed to return implants following the clinical studies of Sixmo.

Opioid Withdrawal Symptoms

The partial opioid agonist properties of buprenorphine may precipitate opioid withdrawal signs and symptoms in persons who are currently physically dependent on full opioid agonists - such as heroin, morphine, or methadone - before the effects of the full opioid agonist have subsided. *De novo* patients must undergo a medically supervised induction with buprenorphine prior to initiating treatment with Sixmo.

Opioid withdrawal symptoms necessitating SL buprenorphine use at a level warranting a fifth implant were seen in approximately 20% of subjects in Studies PRO-805 and PRO-806. In Study PRO-814, in clinically stable patients and in which a fifth implant was not an option, a smaller percentage of subjects required supplemental SL buprenorphine. Opioid withdrawal symptoms can be managed by a Sixmo dose increase or transferring the patient to another form of buprenorphine following removal of Sixmo.

There was no indication of an increase in withdrawal symptoms in subjects taking Sixmo relative to subjects taking placebo/SL BPN. Efficacy outcomes evaluating withdrawal symptoms indicated that transitioning subjects from daily SL BPN to four 80-mg Sixmo doses was not associated with any meaningful increase in withdrawal or cravings symptoms at Week 1 in Studies PRO-805 and PRO-806, and there was no significant difference in withdrawal or craving symptoms between Sixmo and SL BPN groups at Week 4 in Study PRO-814.

Effects on Ability to Drive or Operate Machinery or Impairment of Mental

Ability

The effects on the ability to drive or operate machinery are expected to be similar to that of other drugs in this class (Suboxone 16 mg/4 mg sublingual tablets SmPC, 2016; Subutex 8 mg sublingual tablets SmPC, 2016; Dagtekin et al, 2007).

Immunological events

Hypersensitivity reactions, including cases of bronchospasm, angioedema, and anaphylactic shock, have been reported in patients taking buprenorphine (Suboxone 16 mg/4 mg sublingual tablets SmPC, 2016; Subutex 8 mg sublingual tablets SmPC, 2016).

In the pooled, double-blind studies in the Sixmo clinical development program, the incidence of possible hypersensitivity reactions was slightly higher in the placebo group (2.5%) than in the Sixmo (1.9%) or SL buprenorphine group (0.8%). There were no allergic reaction and hypersensitivity events that led the subjects to withdraw from the study during the double-blind studies, indicating that all subjects were able to tolerate the possible allergic and hypersensitivity reactions occurring during the study.

Adverse Events Related to the Pharmacological Class Effects of Buprenorphine

Generally, there were few differences between the treatment groups with regard to the occurrence of special interest AEs. Notable differences included a higher incidence of possible allergic reactions in the Sixmo and the placebo implant groups than in the SL BPN group, which was primarily due to the AE implant site pruritus (12.3%, 12.8%, 0.5% with Sixmo, placebo and SL BPN, respectively). There were no allergic reaction and hypersensitivity events that led the subjects to withdraw from the study during the double-blind studies, indicating that all subjects were able to tolerate the possible allergic and hypersensitivity reactions occurring during the study. Hypersensitivity was reported at an incidence of 5.4% in the label for Implanon, a subcutaneously implanted product that also contains EVA

as an inactive ingredient (Implanon US Package Insert 2012), indicating that there are no apparent novel allergic or hypersensitivity reaction signals for Sixmo.

The occurrence of possible drug abuse, dependence, and/or withdrawal syndrome TEAEs was higher in the placebo group (35.8%), and slightly higher in the Sixmo group (30.7%), compared with the SL BPN group (22.6%). Most frequently reported were insomnia (9.9%), nausea (5.6%), anxiety (5.3%), depression (4.8%), dizziness (2.9%), hyperhidrosis (2.2%), and fatigue (2.1%). The placebo group tended to have the highest frequencies of these terms, while frequencies were generally similar for the Sixmo and the SL BPN groups. Also, slightly higher frequencies of gastrointestinal disorders were reported for Sixmo and placebo compared to SL BPN (20.7%, 17.4% versus 14.9%).

Safety related to drug-drug interactions and other interactions

No drug-drug interaction clinical studies have been conducted with Sixmo.

Several reports of buprenorphine-related deaths have been attributed to a pharmacodynamics interaction with benzodiazepines resulting in potentiation of respiratory depression.

The only clinically relevant PK interaction detected during the development of Suboxone is confined to inhibitors of CYP3A, resulting in enhanced bioavailability of buprenorphine.

Therefore, potent inhibitors of CYP3A4 (e.g., protease inhibitors like ritonavir, nelfinavir, or indinavir, or azole antifungals such as ketoconazole or itraconazole) have the potential to increase plasma concentrations of buprenorphine (Suboxone EPAR 2006; Elkader and Sproule 2005).

Similarly, inducers of CYP3A4 (e.g., phenobarbital, carbamazepine, phenytoin, rifampin) may have the potential to reduce buprenorphine plasma concentrations because of increased metabolism of buprenorphine to norbuprenorphine (Suboxone EPAR 2006; Elkader and Sproule 2005).

In an interaction study of buprenorphine with ketoconazole, subjects received 8, 12, or 16 mg/day buprenorphine alone for two weeks, and ketoconazole 400 mg/day was added for six days. Ketoconazole administration resulted in clinically significant, 2-fold increases in both Cmax and AUC of buprenorphine after SL administration of buprenorphine alone (Suboxone EPAR 2006; Elkader and Sproule 2005).

Sixmo should be administered cautiously when co-administered with benzodiazepines, and CYP3A inhibitors and inducers, and this is reflected in the SmPC of Sixmo.

Discontinuation due to AES

Adverse Events Leading to Discontinuation

Treatment-emergent adverse events that led to subject withdrawal from the clinical studies were to be captured in the case report form (CRF) on both the disposition page and on the AE page. Some TEAEs that were captured on the AE page were not also captured on the disposition page. This section focuses on those TEAEs leading to withdrawal that were captured on the AE page of the CRF, as this information was deemed more comprehensive than the TEAEs captured on the disposition page.

Double-blind studies: A total of 14 subjects withdrew from any of the studies due to TEAEs. The incidence was balanced between the Sixmo and the placebo/SL BPN group (7 subjects each, 2.3% and 2.2%, respectively).

In Study PRO-805, 4 subjects withdrew due to TEAEs, 3 of these due to implant site AEs (all in the Sixmo group), and one due to hepatic enzyme increased (Sixmo group).

In Study PRO-806, 9 subjects withdrew due to TEAEs (2, 5, and 2 subjects in the Sixmo, SL BPN and placebo groups, respectively). Of note, none of these was related to implant site events, which reflects

the improvements in implant insertion/ removal procedures between Studies PRO-805 and PRO-806. Most common were withdrawals due to abnormalities in hepatic enzymes (alanine aminotransferase [ALT] increased/aspartate aminotransferase [AST] increased in one SL BPN subject, and liver function test abnormal in one Sixmo subject).

The following TEAEs leading to discontinuation were reported for single subjects only: breast cancer in one Sixmo subject, drug dependence, weight decrease, neck pain and sinus tachycardia in one subject each in the SL BPN group, and overdose and hepatitis C in one subject each in the placebo group.

In Study PRO-814, only one subject (Sixmo group) withdrew due to a TEAE (muscle spasms).

Open-label studies: An additional 3 subjects withdrew from one of the open-label studies (PRO- 807 or PRO-811) due to a TEAE. Two subjects withdrew from Study PRO-807 (which used the same implant technique as Study PRO-805) due to implant-site TEAEs, and one subject in Study PRO-811 withdrew due to a non-implant site TEAE (ALT increased) that started while the subject was receiving SL BPN after completing Study PRO-806 and before commencing the induction period in Study PRO-811.

PK studies: In Study-PRO-810, one subject withdrew from the study for a pancreatic cyst unrelated to treatment. There were no TEAEs leading to withdrawal in Study TTP-400-02-01.

2.6.1. Discussion on clinical safety

The safety profile of Sixmo is dominated by implant site AEs, which were reported in about 33% of subjects overall in the double-blind studies. Implant site pain, implant site pruritus, implant site erythema, implant site hematoma, implant site hemorrhage, and implant site edema were the most commonly reported AEs. A slightly higher percentage of Sixmo subjects than placebo/SL BPN subjects experienced implant site AEs; however, there were no notable differences in the incidence of individual implant site TEAEs between treatment groups.

The non-implant site profile was very similar between Sixmo and placebo/SL BPN treated subjects. Also, in studies allowing a direct comparison to the active comparator SL BPN (PRO-806 and PRO-814), no notable differences were seen for the non-implant site AEs. The safety database was also examined for TEAE terms that might indicate broad safety concerns for respiratory depression, CNS depression, orthostatic effects, hepatic injury, allergic reaction, gastrointestinal disorders, psychiatric disorders, reproductive or neonatal disorders, and drug abuse, dependence and/or withdrawal symptoms. These are categories of interest based on the known pharmacology of buprenorphine and known safety profile of marketed buprenorphine products. In general, the incidence of TEAEs falling into these categories in the Sixmo clinical program was consistent with that observed with other buprenorphine products.

Overall, the data indicate that the safety profile for Sixmo is principally related to the implant procedure and route of administration rather than to the buprenorphine, or any interaction between buprenorphine and EVA, contained in the Sixmo product.

Of note, the applicator and the implant technique were changed during clinical development, after Studies PRO-805 and PRO-807 had been completed. This means that the double-blind study PRO-805 and the respective open-label extension study both used the previous technique, while Studies PRO-806, PRO-814, and PRO-811 used the current technique.

Modifications were made to the equipment, to the design of the applicator, to the general surgical techniques related to the insertion and removal of the implants, and to the training procedures, in order to improve the overall safety. The original applicator in the PRO-805 and PRO-807 studies was blunt-tipped and was associated with more tissue adhesions to the implants, resulting in more implant fractures. The modified sharp applicator mitigated tissue damage and allowed closer placement of implants, thus facilitating easier removals. The incidence of implant-related TEAEs was substantially

lower in the studies conducted after these changes were implemented (PRO-805: 51-58%, PRO-806: 26-28%, PRO-814: 14-23%).

The improvements made in implant insertion equipment, techniques, and standardized training for the later clinical studies also greatly reduced the occurrence of partial or complete implant expulsion.

Sixmo was overall well-tolerated, and most TEAEs were mild to moderate in severity and did not deter the majority of subjects from continued participation in the clinical studies or retreatment with an additional implant.

Of note, only the current implant insertion and removal techniques will be used commercially.

Educational materials and programs will be provided to minimize the risks for improper subcutaneous placement and implantation related complications, and will maximize the ability of clinicians to locate the implants at the time of implant removal.

Because Sixmo is inserted subcutaneously, dose modifications are not made as easily as for other buprenorphine products. However, the ability to prescribe occasional supplemental SL BPN, e.g., in stressor situations, in effect allows a clinician to titrate patients over a continuous dose range before deciding on a dose increase by inserting a fifth implant.

Regarding dose reductions, the implantable formulation presents some challenges in cases where an emergent safety issue, a planned operation requiring opioid anesthesia, pregnancy or other health status changes, or patient preference may require dose reduction.

Emergency or chronic pain control may also be complicated by the presence of Sixmo implants, since buprenorphine can blunt the pain control of other opioids by virtue of its competitive binding and partial agonist properties at opioid receptors. Under ideal conditions, Sixmo implants would be removed to manage acute safety issues and planned surgeries or other health status changes; that this requires a special procedure makes dose management in this context inherently more complicated than with other buprenorphine products. Clear guidance on HCPs involved in prescribing and implanting Sixmo implants is reflected in the SmPC.

Furthermore, in emergency situations, caregivers may not be aware that an unconscious patient has implants inserted, which raises a risk for administration of drugs that will interact dangerously with buprenorphine. This is a particular concern during the initial days and weeks after implantation, when buprenorphine levels are relatively high. Again, this concern will be adequately reflected in the SmPC.

Across Phase 3 studies, a total of 309 subjects were treated with Sixmo in the double-blind studies for 6 months, and 107 of these were treated for up to 12 months. Subjects in Studies PRO-805 and PRO-806 (and their respective extension studies) were exposed to 4 Sixmo implants (total dose of 320 mg). Around 20% of subjects in the Sixmo group of Studies PRO-805 and PRO-806, and around 10% of subjects in the extension studies received a dose increase in the form of a fifth implant, based on pre-defined protocol criteria.

All subjects in Study PRO-814 were treated with 4 implants.

Treatment with buprenorphine implants offers a novel treatment option for patients and physicians by introducing a new route of administration that has the potential to address some of the shortcomings associated with SL BPN treatment (eg.poor patient compliance).

There is a reduced risk for abuse, misuse, and diversion and accidental paediatric exposure to buprenorphine with Sixmo due to the implantable formulation.

The primary evaluation of safety is based on pooled data from the double-blind studies PRO-805, PRO-806, and PRO-814. In addition, safety data from the 2 extension studies, PRO-807 and PRO-811, have been pooled and are presented (supportive data) separately from the 3 pivotal studies.

The safety profile for the active substance buprenorphine is generally well characterised.

The most commonly reported treatment-emergent adverse events (TEAEs) reported with this pharmacological class include constipation, insomnia, headache, nausea, hyperhidrosis, drug withdrawal syndrome, and pain.

A number of serious AEs relating to buprenorphine use have been described. These include severe respiratory failure, hepatitis, hepatic events, dependence, drug withdrawal syndrome, CNS depression; and allergic reactions (hypersensitivity).

In this context, well-characterised TEAEs were anticipated and monitored closely throughout the course of the Sixmo development program.

In addition, buprenorphine is known to affect the QT interval. This is considered significant in the population of patients who may be prescribed Sixmo.

The overall safety profile for Sixmo was considered to be in line with the currently established safety data for the active substance buprenorphine.

Safety evaluation of the clinical studies was divided into Implant site AEs and non-implant site TEs.

Due to the novel delivery system of implantable Sixmo, the special category of product specific implant site AEs relating to procedural complications around the insertion or removal of Sixmo implants and AEs local to the Sixmo implantation site are of interest. Implant site and procedural-related AEs are considered important in the overall context of use of Sixmo. Whilst the modification in the procedural technique during the clinical studies appeared to significantly reduce the number of Implant site AEs, the SmPC will reflect the breakage rates experienced using the new implantation/removal technique. In addition, implant safety is further optimised in that only physicians with experience in minor surgical procedures who have completed the relevant training in probupine insertion/removal will be authorised to insert and remove the implants. This is specified in the SmPC and is also addressed in the RMP.

The applicant will also conduct a post-authorisation study on implant safety in both EU and US patients receiving Sixmo.

There is no longer term data beyond two implant cycles currently available. Data on treatment with Sixmo in a second cycle of six months is limited at this time and this is reflected in the SmPC.

Due to the implantable formulation of buprenorphine, there is a concern around inflexibility with dosage particularly in situations where the dosage of buprenorphine needs to be carefully monitored or titrated. This has been reflected in the SmPC and careful patient selection is required.

Buprenorphine SL can be administered as a rescue medication if the patient experiences withdrawal symptoms while on treatment with Sixmo.

In patients where down-titration or careful monitoring of buprenorphine dosage is recommended, the lack of flexibility with respect to down-titration of buprenorphine dosage is adequately reflected in the SmPC.

In addition, the applicant's responses to PK and safety queries indicated that an initial peak of BPN could pose safety concerns in patients especially in the first week following implantation. However patients may have a higher tolerability and the SPC has been updated to reflect caution and advice to patients in relation to this point.

The potential failure of implant and high observed frequency of implant ADRs is noted, there is approximately a 25% breakage rate, which occurs at the time of removal of the implant although these were not generally considered were not clinically relevant as the implants were safely removed.

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

The safety of Sixmo is considered to be sufficiently demonstrated.

2.7. Risk Management Plan

Safety concerns

Summary table of safety concerns

Important identified risks	**<u>Safety concerns related to the SC implant:</u>** • Protrusion or expulsion of the SC implant • Infection at the insertion or removal site **<u>Safety concerns related to the active substance:</u>** • Respiratory depression / respiratory failure • Hepatitis, hepatic events, use in patients with hepatic failure • Dependence • Precipitation of opioid withdrawal syndrome • Use during pregnancy and lactation (effects on newborn and infant) • CNS depression (including effects on driving ability) • Hypersensitivity • Risk of fatal outcome in patients with a history of polysubstance misuse/dependence who self-administer psychoactive substances while using Sixmo
Important potential risks	**<u>Safety concerns related to the SC implant:</u>** • Damage to nerves or blood vessels during insertion and/or removal procedure • Implant migration and/or missing implant or partial implant **<u>Safety concerns related to the active substance:</u>** • Use in patients with head injury and increased intracranial pressure • Peripheral edema
Missing information	**<u>Safety concerns related to the SC implant:</u>** • Long-term use (>12 months) **<u>Safety concerns related to the active substance:</u>** • Patients >65 years old

Pharmacovigilance plan

Summary table of ongoing and planned additional pharmacovigilance activities in the PV plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate	To evaluate the rate of breakage of Sixmo implants and to evaluate implant site treatment-emergent	Protrusion or expulsion of the SC implant, Infection at the insertion or removal site (important identified	Full study protocol	Provided within 3 months from the date of the marketing authorisation

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in the routine clinical care – MOLTeNI-2019-01 Planned	adverse events.	risks); Damage to nerves or blood vessels during insertion and/or removal procedure; Implant migration and/or missing implant or partial implant (important potential risks); Patients >65 years old (missing information).	Final study report:	granting. Estimated Q2 2024 (3 years after first enrolment plus 6 months for study report completion).
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
Prospective descriptive observational study of insertion-, localization-, and removal-related events and their sequelae associated with the use of Probuphine –PRO-816 Planned	To document and evaluate the safety of Probuphine under real-life conditions.	Protrusion or expulsion of the SC implant; Infection at the insertion or removal site (important identified risks); Damage to nerves or blood vessels during insertion and/or removal procedure, Implant migration and/or missing implant or partial implant (important potential risks); Patients >65 years old (missing information).	Clinical study report Final study report: Progress of Study PRO-816 in the PSURs, in accordance with Sixmo periodic safety update reports (PSURs) periodicity	within 6 months from study completion) Estimated Q2 2024 PSURs, in accordance with Sixmo PSUR periodicity

Risk minimisation measures

Summary table of pharmacovigilance activities and risk minimization activities by safety concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Safety concerns related to the SC implant		
Protrusion or expulsion of the SC implant	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 3 Routine risk minimization activities recommending specific clinical measures to address the risk: Insertion and removal of the Sixmo implants must be	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	performed by a physician or other qualified healthcare professional who is competent in minor surgery and has been trained to conduct the insertion and removal procedure, SmPC, section 4.2 Detailed instructions describing a step by step process for implant insertion / removal are provided in the SmPC, section 4.2 The same removal technique is employed for the removal of protruding or partially expelled implants. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged, SmPC, section 4.2. Recommendation to examine the insertion site one week following implant insertion for signs of any problems with wound healing, including evidence of implant extrusion from the skin is included in the SmPC, section 4. 2 Instructions for the healthcare professional on how to proceed in the case of spontaneous expulsion are included in the SmPC, section 4.4 Recommendation to confirm proper placement by palpation immediately after insertion is included in the SmPC, section 4.4 Instructions for the patient on what to do in the case of spontaneous expulsion are included in the PL, section 2 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment: proper insertion and removal techniques reduce the risk of protrusion or expulsion of the SC implant	**activities:** MOLTeNI-2019-01, PRO-816:
Infection at the insertion or removal site	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation to examine the insertion site one week following implant insertion for signs of infection is included	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	in the SmPC, section 4.2 Recommendation to avoid excessive palpation shortly after insertion of the implants is included in the SmPC, section 4.4 Recommendation to examine the incision site for infection if spontaneous expulsion occurs is included in the SmPC, section 4.4 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	MOLTeNI-2019-01, PRO-816:
Safety concerns related to the active substance		
Respiratory depression / respiratory failure	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.2, 4.3, 4.4, 4.5, 4.8, and 4.9 PL sections 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation to monitor elderly and persons with hepatic impairment for signs and symptoms of toxicity or overdose in the SmPC, section 4.2 Recommendation to monitor all patients receiving Sixmo for conditions indicative of diversion, or progression of opioid dependence and addictive behaviours suggesting the need for more intensive and structured treatment for substance use in the SmPC, section 4.4 Recommendation to warn patients that it is extremely dangerous to self-administer non-prescribed benzodiazepines while taking Sixmo, and should also be cautioned to use benzodiazepines concurrently with Sixmo only as directed by their healthcare professional, in the SmPC, section 4.5 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Additional risk minimization measures: Patient alert card	
Hepatitis, hepatic events, use in patients with hepatic failure	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2, 3, and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations that patients with mild to moderate hepatic impairment should be monitored for signs and symptoms of precipitated opioid withdrawal, toxicity, or overdose caused by increased levels of buprenorphine, in the SmPC, sections 4.2 and 4.4 Recommendation that when a hepatic event is suspected, a liver function evaluation is required, including whether to discontinue treatment with Sixmo and if the treatment is continued, hepatic function should be monitored closely, in the SmPC, section 4.4 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none
Dependence	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.4 and 4.8 PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendations for monitoring and treating patients if Sixmo implants are discontinued in the SmPC, section 4.4 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:**	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	None	
Precipitation of opioid withdrawal syndrome	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: Instructions for the induction of *de novo* patients before Sixmo insertion, SmPC, section 4.2 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none
Use during pregnancy and lactation (effects on newborn and infant)	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.6 and 5.3 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for neonatal monitoring at the end of pregnancy is included in the SmPC, section 4.6 Recommendation that breastfeeding should be discontinued during treatment with Sixmo, SmPC, section 4.6 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: none **Additional pharmacovigilance activities:** none
CNS depression (including effects on driving ability)	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.4, 4.5, 4.7, 4.8, and 4.9 PL sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Patients may experience somnolence, especially in the first week following insertion of the implants and should be cautioned in this respect in the SmPC, section 4.4 Recommendation to prescribe Sixmo with caution to patients taking benzodiazepines or other drugs that act on the CNS in the SmPC, section 4.5 Recommendation to caution patients about driving or operating hazardous machinery until they are reasonably certain that Sixmo does not adversely affect their ability to engage in such activities, in the SmPC, section 4.7 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Additional pharmacovigilance activities:** none
Hypersensitivity	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.3 and 4.8 PL sections 2 and 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none
Risk of fatal outcome in patients with a history of polysubstance misuse/dependence who self-administer psychoactive substances while using Sixmo	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.4 and 4.5 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk:	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection**: none **Additional pharmacovigilance**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Prior to initiating Sixmo therapy, the patient's medical and treatment history, including use of non-opioid psychoactive substances, needs to be reviewed, in order to ensure that Sixmo treatment can be safely initiated. Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**activities:** none
Safety concerns related to the SC implant		
Damage to nerves or blood vessels during insertion and/or removal procedure	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.2, 4.4, and 4.8 Routine risk minimization activities recommending specific clinical measures to address the risk: Insertion and removal of the Sixmo implants must be performed by a physician or other qualified healthcare professional who is competent in minor surgery and has been trained to conduct the insertion and removal procedure, SmPC, section 4.2 Detailed instructions describing a step by step process for implant insertion / removal are provided in the SmPC, section 4.2 The same removal technique is employed for the removal of protruding or partially expelled implants. Exploratory surgery without knowledge of the exact location of all implants is strongly discouraged, SmPC, section 4.2. Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** MOLTeNI-2019-01, PRO-816
Implant migration and/or missing implant or partial implant	**Routine risk minimization measures:** Routine risk communication SmPC sections 4.2, 4.3, 4.4, and 4.8 PL sections 2 and 4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Follow-up

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Ultrasound and MRI facilities need to be available to the clinical site at which the insertion and removal of Sixmo occurs, SmPC, section 4.2 Suitable methods for the location of non-palpable implant(s) or fragment(s) include ultrasound with a high frequency linear array transducer (10 MHz or greater) or magnetic resonance imaging (MRI). Sixmo implants are not radiopaque and cannot be seen by X-ray or CT scan, SmPC, section 4.2 If implant(s) or implant fragment(s) are not removed during a removal attempt, the patient should undergo imaging for localisation as soon as is feasible with the subsequent removal attempt performed on the same day as localisation, SmPC, section 4.2 Patients who have contraindications for MRI should not be allowed to receive Sixmo, SmPC, section 4.3 Recommendation to confirm proper placement by palpation immediately after insertion is included in the SmPC, section 4.4 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** Live training for healthcare professionals, including lecture slides, followed by a knowledge assessment	questionnaire (Annex 4) **Additional pharmacovigilance activities:** MOLTeNI-2019-01, PRO-816
Use in patients with head injury and increased intracranial pressure	**Routine risk minimization measures:** Routine risk communication: SmPC sections 4.4 and 4.8 PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation to use with caution in patients with head injury, intracranial lesions, and other circumstances where cerebrospinal pressure may be increased in the SmPC, section 4.4 Other routine risk minimization measures beyond the Product	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none

Safety concern	Risk minimization measures	Pharmacovigilance activities
	Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** Patient alert card	
Peripheral edema	**Routine risk minimization measures:** Routine risk communication: SmPC section 4.8 PL section 4 Routine risk minimization activities recommending specific clinical measures to address the risk: None Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none
Safety concerns related to the SC implant		
Long-term use (greater than 12 months)	**Routine risk minimization measures:** Routine risk communication: SmPC section 4.2 PL section 3 Routine risk minimization activities recommending specific clinical measures to address the risk: none Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None proposed	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** none **Additional pharmacovigilance activities:** none
Safety concerns related to the active substance		
Patients >65 years old	**Routine risk minimization measures:** Routine risk communication: SmPC section 4.4	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal**

Safety concern	Risk minimization measures	Pharmacovigilance activities
	PL section 2 Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation that opioids should be administered with caution to elderly or debilitated patients in the SmPC, section 4.4 Due to lack of data in this population, use of Sixmo is not recommended in patients over 65 years, SmPC section 4.4 Other routine risk minimization measures beyond the Product Information: Legal status: restricted and special medical prescription **Additional risk minimization measures:** None	**detection:** none **Additional pharmacovigilance activities:** MOLTeNI-2019-01, PRO-816

Conclusion

The CHMP and PRAC considered that the risk management plan version 1.1 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

Based on the safety concerns linked with implant insertion of removal, the CHMP is of the opinion that a separate entry in the EURD list for Sixmo is needed, as it cannot follow the already existing entry for buprenorphine. The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request the alignment of the new PSUR cycle with the international birth date (IBD). The IBD is 26 May 2016. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points.

2.9. Product information

2.9.1. 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.*

Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Sixmo (buprenorphine) is included in the additional monitoring list as it has a PASS imposed at the time of granting the marketing authorisation and measures for ensuring the safe use of the medicinal product included in the risk management system.

Therefore the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

OUD has a prevalence ranging from 0.6 to 0.8% (Bulletin of the World Health Organization [WHO] 2013).

Globally, more users die each year from heroin use than from any other illicit drug. In Europe, 82% of fatal overdoses are due to opioids, and the mortality rate for injection drug users is approximately 5-10 times that for the general population of the same age and gender (EMCDDA, European Drug Report 2016).

The burden of disease is substantial, with high rates of morbidity and mortality, disease transmission, increased health care, crime and law enforcement costs, and less tangible costs of family distress and lost productivity (Cochrane Database Syst Rev. 2005 Jul 20; (3):CD003409.)

The intended indication is Sixmo is indicated for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.

The treatment of opioid dependence is important to reduce its health and social consequences and to improve the well-being and social functioning of people affected. The main objectives of treating and rehabilitating persons with opioid dependence are to reduce dependence on illicit drugs; to reduce the morbidity and mortality caused by the use of illicit opioids, or associated with their use, such as infectious diseases; to improve physical and psychological health; to reduce criminal behaviour; to facilitate reintegration into the workforce and education system and to improve social functioning (WHO).

3.1.2. Available therapies and unmet medical need

There are approximately 1.3 million high-risk opioid users in the EU. Opioids are the principal drug in about 38% of all drug treatment requests in the EU. Approximately 630,000 opioid users received opiate substitution therapy in 2015. Heroin use accounts for about 80%, of new opioid related treatment demands in Europe. Approximately 38% overall inject heroin but this varies considerably across member states. Almost 80% of drug overdoses in the EU involve opioids.

As no single treatment is effective for all individuals with opioid dependence, diverse treatment options are needed, including psychosocial approaches and pharmacological treatment. Both detoxification with subsequent abstinence-oriented treatment and substitution maintenance treatment are essential components of an effective treatment system for people with opioid dependence.

There are two therapeutic treatment pathways, opioid substitution treatment or detoxification. While abstinence from illicit opioids is considered an ideal outcome, it is often unachievable. The difficulties in obtaining total abstinence have been widely acknowledged, and it is understood that “as with other chronic conditions, opioid dependence tends mostly to follow a relapsing and remitting course”.

A primary goal of treatment for opioid dependence is to help patients to reduce or eliminate illicit opioid use as this facilitates achievement of other important goals, including improved physical and mental health, and psychosocial functioning.

Standard pharmacological treatment of opioid dependence therefore aims at reducing (or ideally ceasing) illicit opioid use, and may involve long-term administration of opioid substitution treatment.

There are a number of therapies authorised for use in this condition, therefore there is not high unmet need. In the EU methadone is the most widely prescribed opioid substitution therapy (63%) and a further 35% are treated with buprenorphine-based medications. These are mainly oral or sublingual therapies. Treatment may be supervised in a healthcare setting or users may take the treatment in their own home. The former requires that the user attend a treatment centre daily and the latter risks diversion of the treatment for illicit use or risk of accidental overdose by others in the household such as young children. Psychosocial interventions, including cognitive and behavioural approaches and contingency management techniques, can add to the effectiveness of treatment if combined with agonist maintenance treatment and medications for assisting opioid withdrawal

The proposed treatment is a long acting therapy of 6 months duration which is administered subcutaneously by a health care professional. The applicant proposes that this should reduce the risk of diversion and of accidental overdose in the home.

3.1.3. Main clinical studies

In support of efficacy the applicant has submitted three main studies: a double blind placebo-controlled study (805), a non-inferiority, double-blind, double-dummy randomised controlled trial (806) and a double blind double dummy placebo control study in patients receiving 8mg or less of SL BPN/day (814).

The first two randomized, controlled studies, PRO-805 and PRO-806, enrolled opioid-dependent adults who were starting treatment on opioid substitution and who were new entrants to treatment with buprenorphine. Patients were not eligible if they had previously received pharmacological treatment for opioid dependence within 3 months of study start (e.g. methadone or buprenorphine). The majority of patients in these studies reported heroin as their primary opioid of abuse. Patients were treated for up to 24 weeks on-study. The primary endpoint in both studies was the proportion of urine samples negative for opioids. Secondary endpoints included control of opioid cravings, retention in treatment, global functioning, as well as supplemental SL BPN use. The primary analysis was the CDF of the percentage of urine samples that were negative for illicit opioids from either Week 1 through Week 16 (PRO-805) or Week 1 through Week 24 (PRO-806). In both studies, the pre-specified primary endpoints were met.

Study PRO-814 enrolled a selected “clinically stable” subpopulation of opioid dependent adult patients who were already on maintenance treatment. Clinically stable in this context means that these patients had responded well to buprenorphine treatment for at least 3 months. These patients were required to have been on SL BPN treatment for at least 6 consecutive months prior to study entry, and to have received a stable dose of 8 mg/day or less SL BPN for at least 90 days prior to randomization. The primary endpoint was responder rate, defined as subjects with no more than 2 of 6 months with any evidence of illicit opioid use based on a composite of both urine results and self-report results, at week 24. For the primary efficacy variable, a test of non- inferiority of Sixmo (active) versus SL BPN (control) was conducted. A non-inferiority margin of 20% was employed to define non-inferiority.

In the primary analysis, the proportion of responders was 87.6% in the SL BPN group and 96.4% in the Sixmo group. The proportion of responders was statistically significantly higher in the Sixmo group (P = 0.034). This is the intended population for treatment as proposed by the Applicant.

Two additional studies (807 and 811) which were open label single arm follow-on studies of studies 805 and 806 respectively were submitted primarily as safety studies. However, secondary endpoints included percentage of urine samples negative for illicit opioids over the 24-week treatment period, percentage of study completers (i.e., retention in treatment), subject self-reported illicit drug use, supplemental SL BPN use, subjective and objective withdrawal symptom scores (SOWS and COWS), opioid-craving scores (VAS), quality of life to support longer term efficacy up to 12 months treatment.

3.2. Favourable effects

The active constituent of Sixmo (buprenorphine hydrochloride) is well recognised as a substitution treatment for opioid drug dependence.

The majority of treatments for Opioid Use Disorder require regular interaction with HCP as diversion is a problem. This newly proposed Sixmo formulation provides an alternative treatment modality for opioid dependent patients.

In Study 805, the primary analysis compared the cumulative distribution function (CDF) of the percentage of negative values for Week 1 to Week 16 in the Sixmo group (Group A) and the placebo implant group (Group B), using a stratified Wilcoxon rank sum (van Elteren) test with (pooled) site and gender as stratification variables. Overall the mean percentage of negative samples (per week) for weeks 1-24 was: 22.4% (CI: 15.33-29.48%) for placebo and 36.6% (CI: 30.50-42.64%) for the active treatment group (ITT population). The secondary efficacy results were generally in line with the primary analysis.

There was also a higher response rate seen in the secondary endpoints such as total number of weeks abstinent from illicit opioid use, cravings SOW, COWS and self-reported illicit drug use.

In Study 806, the primary analysis compared the CDF of the percentage of urine samples that were negative for illicit opioids at 24 Weeks (from Weeks 1 through 24) with and without imputation of self-reported opioid use. A statistically significant response over placebo was demonstrated ($p<0.0001$), which was in favour of Sixmo treatment. Non-inferiority to sublingual buprenorophine was also shown. The results were comparable to SL BPN but it appears that this is achieved by a better response rate during weeks 1-16 but diminishes from weeks 17-24. For the secondary endpoints statistically significant better results were demonstrated for Sixmo compared to placebo for completers, mean total weeks abstinent, cravings (COWS and SOWS) and for VAS change from baseline. The results for Sixmo were somewhat better when compared to SL BPN and statistical significance was achieved for COWS and SOWS in favour of Sixmo

Study 814 enrolled a relatively stable patient population on lower doses of SL BPN, and tested for non-inferiority to SL BPN over 24 weeks.

The primary analysis was “a responder” which is defined as a subject with no more than 2 of 6 months with any evidence of illicit opioid use using a non-inferiority margin of 20%. Non inferiority was demonstrated in the study with confidence intervals far from the non-inferiority margin.

Additionally, the proportion of responders was statistically significantly higher in the Sixmo group (*P* = 0.034)

No statistical difference was seen for the secondary endpoints which included Cumulative percentage of evidence of urine illicit opioid use by month and cravings (COWS and SOWS). Both groups had high retention rates.

Overall superiority over placebo was well demonstrated and appears to be non-inferior to SL BPN with occasional superiority to SL BPN was demonstrated.

For the pooled analysis (805, 806), a statistically significant difference between the Sixmo and placebo groups was observed ($p<0.0001$). The Hodges-Lehmann estimator for percent urine negative values also showed a significant shift comparing the Sixmo and placebo groups (9.2%).

3.3. Uncertainties and limitations about favourable effects

There are a number of uncertainties and limitations relating to the efficacy data.

While the goal of therapy is to prevent illicit drug use rather than achieve abstinence from opioid use the needs of patients who are transitioning from illicit or prescription opioids can be variable. The results can be dependent on the quantity of opioid used, use of illicit opioids versus prescription opioids, duration of opioid use, social circumstances, patient age and route of opioid administration.

As the pivotal studies demonstrated, patients required ongoing supplemental SL BPN despite Sixmo treatment. The dose of Sixmo is relatively low and would not be sufficient alone as a maintenance treatment for patients with moderate or severe opioid dependence. This could be more difficult in unstable patients whom are difficult to treat. Although a lower amount of SL BPN would be needed if used in conjunction with Sixmo, it is difficult to see the clinical benefit as a combination treatment in such patients. Sixmo may not achieve better control outcomes for such patients. They will still need to attend a clinic to receive SL BPN and therefore this does not prevent diversion or accidental ingestion by children. Furthermore, clinical experience is limited to 12 only months, this is considered limited for chronic treatment however further studies on this are awaited, to out rule whether efficacy would diminish over time. As a result of these concerns the Applicant amended the population to one not requiring more than 8mg SL BPN in stable patients and there is no experience beyond 12 months treatment (i.e. 2 cycles).

It is unclear whether the effects demonstrated would be equally seen in patients who are prescription opioid users or those using illicit drug such as heroin. It is reported that prescription opioid users have better treatment outcomes than those who use heroin (Nielsen et al., 2013; Potter et al., 2013). On average, they use less total opioid per day, have fewer co-occurring substance use disorders, have better family and social functioning, shorter treatment histories, are less likely to administer by injection, and experience fewer legal consequences (Moore et al., 2007; Rosenblum et al., 2007). Overall, prescription opioid users have better treatment outcomes than those who use heroin (Nielsen et al., 2013; Potter et al., 2013). In the Sixmo clinical development programme, the results seen in Study PRO-814 were more favourable than those seen in Studies PRO-805 and PRO-806. Study PRO-814 had a far smaller proportion of heroin users enrolled (21% of the total population, n=36). Studies PRO-805 and PRO-806 had a higher proportion of heroin users enrolled (63% and 62.4% of subjects respectively). However this is to be expected as illicit opioid users usually have concomitant conditions.

The pivotal and supportive efficacy studies only included subjects aged 18 and over. Currently, there is no data to support use in those aged 15 to 18, this has been taken into account by the applicant. In addition, no persons over the age of 65 years were included in the efficacy studies. While efficacy is not expected to no different in this age group, there are no safety data available either. As a result of these concerns the applicant restricted use to patients over 18 years of age. It is also recommended that the SmPC should be revised to reflect the absence of product specific data in patients >65 years.

There were a number of exclusions for both studies e.g. subjects with concomitant alcohol and other drug dependencies. Polydrug use is an important issue in drug dependency. It is therefore unclear to what extent the results of the studies are generalisable to the wider drug-using population.

The longer term efficacy data is limited to 2 open label single arm studies which were primarily designed as safety studies and therefore have some limitations. Although the study outcomes were generally encouraging at week 24 (end of treatment), some participants switched to riskier behaviours, for example, a higher number of patients using heroin compared to baseline. While this may be a natural progression it requires further consideration

A high proportion of patients required additional sublingual buprenorphine in all studies, in particular in studies PRO-805 and PRO-806. Expectedly, the percentages were higher with those on placebo, but they were also very high in those randomised to receive Sixmo

A major concern relates to the absence of product specific recommendations for Sixmo use in patients where careful monitoring and dose reduction or down-titration may be required. Therefore, careful patient selection is required and monitoring as the Sixmo causes a steep rise in buphrenorphine levels following implantation and the SmPC was amended to caution patients and prescribers.

In order to reflect Sixmo's inflexible posology and absence of an option to down-titrate the dosage, specific recommendations relevant to the implantable delivery system and therefore achievable in clinical practice are provided for HCPs in the product information.

The inflexibility with down-titration of Sixmo dosage is considered relevant in the proposed population where co-morbid medical conditions such as hepatic impairment may co-exist. This major safety concern is also relevant to other patient populations where urgent down-titration of Sixmo dosage may be required to avoid toxicity such as in adolescents, in patients with other medical conditions, in patients with poor nutritional status, immunocompromised patients and patients at increased risk of fatal respiratory depression e.g. those with a history of polysubstance abuse who may self-medicate with non-prescribed psychoactive substances. Therefore, careful patient selection is advised and the Sixmo implants can be removed if necessary.

3.4. Unfavourable effects

The active substance buprenorphine has a clearly established pharmacological profile over several years and the safety profile is adequately characterised. Nevertheless, the proposed use of a novel delivery system to administer the active substance buprenorphine via Sixmo subdermal implant is worthy of special consideration.

In the clinical studies, implant site AEs, were reported in almost 33% of subjects overall in the double-blind studies. Implant site pain, implant site pruritus, implant site erythema, implant site hematoma, implant site haemorrhage, and implant site oedema were the most commonly reported AEs. A slightly higher percentage of Sixmo subjects than placebo/SL BPN subjects experienced implant site AEs; however, there were no notable differences in the incidence of individual implant site TEAEs between treatment groups.

The non-implant site profile was very similar between Sixmo and placebo/SL BPN treated subjects. Also, in studies allowing a direct comparison to the active comparator SL BPN (PRO-806 and PRO-814), no notable differences were seen for the non-implant site AEs. The safety database was also examined for TEAE terms that might indicate broad safety concerns for respiratory depression, CNS depression, orthostatic effects, hepatic injury, allergic reaction, gastrointestinal disorders, psychiatric disorders, reproductive or neonatal disorders, and drug abuse, dependence and/or withdrawal symptoms. These are

categories of interest based on the known pharmacology of buprenorphine and known safety profile of marketed buprenorphine products. In general, the incidence of TEAEs falling into these categories in the Sixmo clinical program was consistent with that observed with other buprenorphine products.

The data indicate that the safety profile for Sixmo is principally related to the implant procedure and route of administration.

Of note, the applicator and the implant technique were changed during clinical development, after Studies PRO-805 and PRO-807 had been completed. This means that the double-blind study PRO-805 and the respective open-label extension study both used the previous technique, while Studies PRO-806, PRO-814, and PRO-811 used the current U technique.

Modifications were made to the equipment, to the design of the applicator, to the general surgical techniques related to the insertion and removal of the implants, and to the training procedures, in order to improve the overall safety.

The incidence of implant-related TEAEs was substantially lower in the studies conducted after these changes were implemented (PRO-805: 51-58%, PRO-806: 26-28%, PRO-814: 14-23%).

The improvements made in implant insertion equipment, techniques, and standardized training for the later clinical studies also greatly reduced the occurrence of partial or complete implant expulsion.

However, there were 6 document cases of Clinically significant implant breakage post marketing, implant migration and difficulty removing the implants.

A patient who was enrolled in Study PRO-807 experienced “implant fragment surfacing” from the PRO-805 implantation (on 03 Jul 2008). This implies that the implants from study PRO-805 were not removed intact, however healthcare professionals will require to be experienced in minor surgery and receive training by the company for insertion and removal of Sixmo.

Sixmo was overall well-tolerated, and most TEAEs were mild to moderate in severity and did not deter the majority of subjects from continued participation in the clinical studies or retreatment with an additional implant.

In the clinical studies, the majority of the subjects were Caucasian. The number of non-Caucasian subjects included in the studies was limited and this has been reflected in the SmPC. However, it is noted that a higher proportional frequency of implant site TEAEs were observed in non-Caucasian groups in the clinical studies, though the number of non-Caucasians studied was low, but a true difference is not expected. In addition, non-implant site TEAEs were observed at a higher frequency in non-Caucasian patients.

There were differences in implant site TEAEs observed between the patients with BMI< 25 and > 25.

A higher frequency of non-implant site TEAEs observed in patients with BMI<25.

TEAEs were also more frequently observed in patients whose primary opioid dependence was on heroin.

There is an absence of product-specific safety data in relation to the use of Sixmo in 15-18 year old adolescents and patients over 65 years, therefore no posology recommendations can be made in the SmPC in relation to these subgroups in view of the absence of data.

In addition, there is no data for use of Sixmo beyond two treatment cycles.

The currently available data from post-marketing experience is limited.

The proposed post-authorisation studies are of special interest in that they will provide further insights into the use of Sixmo from the perspective of the implant/procedural issues, longer term use and cardiac

safety. The planned PRO-816 study which will enrol 1300 patients form US and EU will examine safety of Sixmo further.

3.5. Uncertainties and limitations about unfavourable effects

The overall safety profile for Sixmo was considered to be in line with the currently established data for the active substance buprenorphine.

In addition to the systemic AEs associated with the active substance buprenorphine, it is noted that due to the novel delivery system of Sixmo, that there is a separate category of product specific AEs relating to insertion or removal of Sixmo implants and these are considered important in the overall context of use of the product, especially in view of the risk of implant breakage and the potential for implant fragment migration requiring invasive surgical exploration and removal.

No long term data is currently available in relation to the repeat insertion of Sixmo implants beyond two treatment cycles of six months (one year treatment in total).

Due to the implantable formulation of buprenorphine, there is a concern around inflexibility with dosage particularly in situations where the dosage of buprenorphine needs to be carefully monitored or titrated. In patients where down-titration or careful monitoring of buprenorphine dosage is recommended, the lack of flexibility with respect to down-titration of buprenorphine dosage has been adequately reflected in the SmPC.

The implants should be removed after 6 months. Outpatients addiction care clinics may not have MRI or ultrasound equipment available needed for removal of the implant.

Moreover, adherence in the target population is often poor, and patients may skip the visit to remove the implants, therefore careful patient selection is recommended.

3.6. Effects Table

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Favourable Effects						
CDF	The cumulative distribution function of the percentage of opioid-negative urine samples for Weeks 1 through 16.	%	Median 40.7	Median 20.8	p=0.0361	PRO 805
CDF	The cumulative distribution function of the Percentage of opioid-negative urine samples for Weeks 17 through 24	%	Median 4.4	Median 0.0	p=0.0004	PRO 805
Retention rate	Proportion of study completers (Weeks 1-24)	%	n=71, 65.7%	n=17, 30.9%	p<0.0001	PRO 805

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Study PRO 806			Treatment	Control	SL BPN, comparator	**Uncertainties / Strength of evidence**
CDF	The cumulative distribution function (CDF) of the percentage of urine samples that were negative for illicit opioids at 24 weeks (from Weeks 1 through 24	%	Median 20.28,	Median 9.03,	Median 16.33,	
Retention rate	Proportion of study completers (Weeks 1-24)	N, %	73 (64%)	14 (25.9%)	76 (63.9%)	Low numbers in placebo arm
Abstinence	Total # weeks abstinent (Weeks 1-24)	weeks	Median 2.0,	Median 0.0,	Median 1.0,	
Effect	**Short Description**	**Unit**	**Treatment**	**Control SL BPN**	**Uncertainties / Strength of evidence**	**References**
Responder	No more than 2 of 6 months with any evidence of illicit opioid use.	%	96.4%	87.6%	95% CI (0.009, 0.167) of the proportion difference. (*P* = 0.034).	Study PRO -814
illicit opioid use by month	Percentage of subjects in the ITT population with no urine illicit opioid use by month	%	95.2 (ave)	89.15 (ave)	No statistically significant differences were observed between treatment groups, except at month 3	Study PRO -814
CDF	Cumulative percentage of evidence of no urine illicit opioid use by month;	%	90.8 (ave)	79.9 (ave)	No statistically significant differences were observed between treatment groups, except at month 1	Study PRO -814

Abbreviation: CDF: Cumulated Distribution Function; ave: average, #number.

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Unfavourable Effects						
Implant site AEs		%	45.2 14.1		Incidence of Implant site AEs higher in patients with lower BMI, Non-Caucasian Note: reduction in overall Implant site TEs in Study PRO 811 due to modification in procedural techniques for insertion/removal.	Study PRO-807 Study PRO-811
GGT increased ALT increased AST increased		% % %	3.4 2.7 2.7		increase in incidence of raised LFTs	Integrated data from PRO-807 and 811
Nasopharyngitis		%	8.7	6.9	Increase incidence of common AEs	Pooled safety data
Nausea		%	6.5	4.7	Increase incidence of common AEs	Pooled safety data
Constipation		%	6.5	2.8	Increase incidence of common AEs	Pooled safety data
Vomiting		%	5.5	3.5	Increase incidence of common AEs	Pooled safety data

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Opioid dependence is an important public health problem with widespread impacts on the health and well-being of the individual as well as wider societal effects. Opioid substitution therapy in conjunction with social and psychological support is a mainstay in managing opioid dependence. There are a number of therapeutic options available to patients with OUD therefore there is not a high unmet need for new therapeutic options.

In theory, having a depot slow release formulation would benefit patients as they would be more independent, require less SL BPN and therefore would not need to attend as frequently to clinic.

However the PK profile shows a 2 phase release, the initial high peak which could pose both immediate and longer term management issues for stable patients. The mean buprenorphine AUC0-24 on Day 1 following insertion of Sixmo implants was 13.5% and 20% greater as compared to the mean buprenorphine AUC0-24 values following SL buprenorphine dosing on Days -2 and -1, respectively(16 mg/day). No such comparison is available with 8 mg tablets, but much higher differences would be expected.

In theory this formulation could also reduce risk of diversion and accidental ingestion, especially as the intended population are stable, however, no data were provided on this.

At steady state, the Buphrenorphine plasma levels were too low to meet the needs of patients with moderate to severe opioid addiction as this group would require additional SL BPN to reduce opioid cravings. Therefore the indication has been amended to stable patients requiring no more than 8mg of SL BPN.

There is no direct correlation in regards to improvement in the quality of life for the patients in studies PRO-805 and PRO-806 from the reduction in illicit drug use of 14.2% and 17.8% over the course of 6 months. The definition of the responder in the study PRO-814 is also not based on any evidence in regards to the change in quality of life or any other direct endpoint, however would seem reasonable in the context of the intended population. Therefore, the clinical efficacy is mainly reliant on a single study PRO-814, which mainly consisted mostly of patients using prescription opioids, rather than heroin (the latter accounted for 21% of the study population). However it is accepted that Sixmo was found to be non-inferior to standard of care sublingual Buphrenorphine.

The limited patients and duration of 12 months and lack of safety data beyond 12 months is a concern. Continued use in the same site would likely lead to scarring and fibrotic changes making insertion and removal more difficult. The applicant is planning further studies to examine other anatomical sites and to further examine implant safety in a prospective observational trial of 1300 EU and US patients.

Safety

The primary evaluation of safety is based on pooled data from the double-blind studies PRO-805, PRO-806, and PRO-814. In addition, safety data from the 2 extension studies, PRO-807 and PRO-811, have been pooled and are presented (supportive data) separately from the 3 pivotal studies.

In general, the safety profile for the active substance buprenorphine is well characterised.

The most commonly reported treatment-emergent adverse events (TEAEs) reported with this pharmacological class include constipation, insomnia, headache, nausea, hyperhidrosis, drug withdrawal syndrome, and pain.

A number of serious AEs relating to buprenorphine use have been described. These include severe respiratory failure, hepatitis, hepatic events, dependence, drug withdrawal syndrome, CNS depression; and allergic reactions (hypersensitivity).

In this context, certain well-characterised TEAEs were anticipated and monitored closely throughout the course of the Sixmo development program.

In addition, buprenorphine is known to affect the QT interval. This is considered significant in the population of patients who may be prescribed Sixmo.

The overall safety profile for Sixmo was considered to be in line with the currently established data for the active substance buprenorphine.

In addition to the systemic ADRs associated with the active substance buprenorphine, it is noted that due to the novel delivery system of Sixmo, that there is a separate category of product specific AEs relating to insertion or removal of Sixmo implants and these are considered important in the overall context of use of the product.

No long term data is currently available in relation to the repeat insertion of Sixmo implants beyond two treatment cycles of six months (one year treatment in total) and further clarification was provided by the applicant however only 89 patients have received a second cycle of Sixmo. is

Due to the implantable formulation of buprenorphine, there is concern around inflexibility with dosage particularly in situations where the dosage of buprenorphine needs to be carefully monitored or titrated. Specific warnings and recommendations to optimise safe use have been included in the proposed product information in order to address the concerns around inflexible posology.

In patients where down-titration or careful monitoring of buprenorphine dosage is recommended, the lack of flexibility with respect to down-titration of buprenorphine dosage is acknowledged and information to address this issue has been added to the SmPC. Therefore careful patient selection is required.

Buprenorphine SL can be administered as a rescue medication if the patient experiences withdrawal symptoms while on treatment with Sixmo.

The implant removal procedure may involve significant tissue destruction, including risk of injury to neural and vascular structures. The U technique itself could also precipitate breakage of the implant during the removal. If the clinician cannot localise the implant when the removal is required, the Applicant advocated clinicians to use ultrasound with a high frequency linear array transducer (10 MHz or greater) or MRI, but there is a lack of information on how to use these devices for such purpose. As this product is not radiopaque (and therefore not detectable by X ray) it is recommended that migrated or missing implants are detected by more expensive and less available methods such as MRI or high-resolution ultrasound to facilitate retrieval. This may not be feasible in some many geographical areas and is therefore considered to be more problematic for patients and physicians. However, specific recommendations/restrictions in relation to this issue are provided in the SmPC and careful patient selection is required.

It is noted that cases of missing implants or broken implant fragments have been reported in both clinical studies and post-marketing experience, and in some cases the clinicians had attempted to use ultrasound for implant localisation but without success. In the post marketing setting there were 6 documented cases of implant breakage, implant migration and difficulty removing the implants. The cause of implant breakages is not fully elaborated by the applicant and is therefore not fully understood; furthermore, and because it may be due to multiple factors, such as intrinsic formulation issues, removal technique, inadvertent trauma, deliberate trauma etc) and therefore cannot be adequately mitigated. However the Applicant has provided data which demonstrated a lower breakage rate using the U technique and also in more experience/trained physicians insertion and removal of Sixmo. Although the risk of breakage is not eliminated, the Applicant stated that all fragments were removed and no serious adverse events occurred. The data is presented in section 5.1 of the SPC and the applicant is encouraged to make further manufacturing changes to minimise the risk of breakages further.

It has been demonstrated that there is a higher initial spike of buprenorphine exposure following Sixmo insertion which correlates with a higher degree of dose related adverse events. From week 1 to week 24 there are consistently higher adverse events seen with Sixmo including constipation, headache and somnolence which appear to correlate with higher PK level (spike), particularly in week 1, when compared to SL BPN arm, however there were no serious safety issues reported. Over the 24 weeks there was 2.5 times higher rate of constipation and almost 10 fold higher somnolence rate with Sixmo. The applicant has reflected these product specific PK/safety findings in the SmPC-

It must also be considered that the relative size of the population is small and as higher exposure is seen, this could further translate into higher differences for patients treated with Sixmo and consequently more serious adverse events with larger patient exposure, however the company has proposed a training programme for physicians for insertion and removal of Sixmo. Also, the implantation of Sixmo will be limited to suitably experienced physicians who receive additional training on Sixmo implantation and removal.

A higher proportion of ADRs (both non-implant and implant-related ADRs) was also identified in patients being treated for heroin dependence, compared with patients treated for prescription opioid dependence. The Applicant attributed these findings to poorer health status and co-morbidities in heroin users, which is agreed.

Uncertainties also remain in relation to the potential for higher rates of non-implant related ADRs in underweight patients, which may be of further relevance with real world use of Sixmo, especially given the target population. The SmPC was amended to caution physicians in relation to the higher exposure in the first 1-2 weeks.

In the context of the revised Sixmo indication, the safety profile is considered to have been adequately characterised in a more stable population.

3.7.2. Balance of benefits and risks

It is understood that opioid addiction is a significant public health concern and that additional treatment options could be helpful to increase adherence to treatment and decreased illicit drug use. While all main studies produced statistically significant results in the selected primary and requested additional efficacy measures, the clinical utility of the product has been amended to a stable population requiring no more than 8mg SL BPN. This would probably not meet the needs of many patients with OUD, however in a stable population on 8mg sl BPN per day Sixmo provides an additional therapeutic option for patients and physicians

The applicant committed to conduct a comprehensive training programme. Moreover, insertion and removal of Sixmo rods will be conducted by a physician who is competent in minor surgery and who has received adequate training specific to the procedure of Sixmo insertion and removal.

The Applicant also will conduct a prospective observational study (of approx. 1300 patients) with OUD in EU patients similar to Study PRO-816, but with the aim to evaluate the breakage rate of implants, whether or not clinically significant, and insertion/removal complications implant related safety.

3.8. Conclusions

The overall B/R of Sixmo is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Sixmo is favourable in the following indication:

Sixmo is indicated for substitution treatment for opioid dependence in clinically stable adult patients who require no more than 8 mg/day of sublingual buprenorphine, within a framework of medical, social and psychological treatment.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to special and restricted medical prescription.

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

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.

Additional risk minimisation measures

Prior to the launch of SIXMO in each Member State (MS), the Marketing Authorisation Holder (MAH) must agree the content and format of the educational materials, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority (NCA).

The MAH shall ensure that in each MS where SIXMO is marketed, all physicians expected to insert / remove SIXMO subcutaneous (SC) implant are provided with an educational programme, aiming at

preventing / minimising the important identified risk of implant protrusion / (spontaneous) expulsion, the important potential risks of damage to nerves or blood vessels during insertion / removal procedure, (dislocation and) migration / missing (partial) implant.

The physician educational programme, provided in conjunction with the Summary of Product Characteristics (SmPC), should include lecture slides and a detailed, face to face, step-by step description and live demonstration of the surgical procedure for SIXMO insertion and removal. Physicians should also be informed about risks and complications of this procedure (i.e. implant migration, protrusion, expulsion, and nerve damage).

The MAH shall also ensure that in each MS where SIXMO is marketed, each patient being prescribed this SC implant receives from the treating physician the Patient Information Leaflet (PIL) and a (wallet-sized) patient alert card, to be carried out at all times while on SIXMO treatment, and presented to other health care professionals (HCP) before any medical treatment / intervention is carried out. The patient alert card should mention:

- That the card-holder is using SIXMO (buprenorphine only opioid-dependence treatment via SC implant located at the inner side of the upper arm)
- Implant insertion and six-month removal date(s)
- Name and contact details of the treating physician
- The safety concerns associated with SIXMO therapy (i.e. potential life-threatening interactions with other, concomitant therapies)

Obligation to conduct post-authorisation measures

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
MOLTeNI-2019-01 - A prospective, observational (non-interventional), post-authorisation safety cohort study to evaluate the incidence of the breakages and insertion/removal complications of buprenorphine implants (Sixmo) in the routine clinical care	Q2 2024 (Estimated)

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

Restricted and special medical prescription.