1 April 2016
EMA/CHMP/323556/2016
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Trevicta

International non-proprietary name: paliperidone

Procedure No. EMEA/H/C/004066/X/0007/G

Note

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

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List of abbreviations

ADR	adverse drug reaction
AE	adverse event
AIMS	Abnormal Involuntary Movement Scale
ANCOVA	analysis of covariance
AUC	area under concentration time curve
BARS	Barnes Akathisia Rating Scale
BMI	body mass index
BRAT	Benefit-Risk Action Team
CGI-S	Clinical Global Impression – Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	peak plasma concentration
CSR	clinical study report
C-SSRS	Columbia Suicide Severity Rating Scale
CYP	Cytochrome
D_2	dopamine type 2
DB	double-blind
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision
ECG	Electrocardiogram
EMA	European Medicines Agency
EOS	end of study
EPS	extrapyramidal symptom(s)
ER	extended release
EU	European UnionG
(FT-)IR	(Fourrier Transform) Infrared Spectroscopy
HDL	high density lipoprotein
HOMA-%B	homeostatic model assessment for β-cell function
HOMA-IR	homeostatic model assessment for insulin resistance
HPLC	High performance liquid chromatography
ICH	International Conference on Harmonisation
IDMC	independent data monitoring committee
IM	Intramuscular
IPCs	in-process controls
IR	immediate release
ITT	Intent-to-treat
ITT [DB]	intent to treat for double-blind phase
IVIVC	in vitro – in vivo correlation
K-M	Kaplan-Meier
LAI	long-acting injectable
LDL	low density lipoprotein

LOCF	last observation carried forward
LS	least squares
MAA	Marketing Authorisation Application
MedDRA	Medical Dictionary for Regulatory Activities
mg eq.	milligram equivalent
mITT	modified intent-to-treat
MPA	Medical Products Agency (Sweden)
NLT	Not Less Than
NMS	neuroleptic malignant syndrome
NMT	Not More Than
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
P-gp	P-glycoprotein
Ph. Eur.	European Pharmacopoeia
PIP	Paediatric Investigational Plan
PK	Pharmacokinetic
PP	per protocol
PP1M	paliperidone palmitate 1-month injection
PP3M	paliperidone palmitate 3-month injection
PRF	piston release force
PSP	Personal and Social Performance Scale
PTF	piston travel force
QTc	corrected QT interval
QTcLD	linear-derived corrected QT interval
QTPP	Quality Target Product Profile
RH	Relative Humidity
RMP	Risk Management Plan
SAE	serious adverse event
SAP	statistical analysis plan
SAS	Simpson Angus Rating Scale
SmPC	Summary of Product Characteristics
SOC	system organ class
t½	half-life
t_{max}	time to peak plasma concentration
TEAE	treatment-emergent adverse event
US	United States
WFI	Water For Injection

1. Background information on the procedure

1.1. Submission of the dossier

The Marketing Authorisation Holder (MAH), Janssen-Cilag International NV, submitted to the European Medicines Agency (EMA) on 28 July 2015 an application for a grouping of variations in accordance with Article 7(2) of Commission Regulation (EC) No 1234/2008, consisting of an extension of the marketing authorisation, a Type II C.1.6a variation, a Type IAIN A.2 and a Type IB C.I.7b variation for Trevicta.

The line extension (grouped) application includes:

- The extension application that introduces four new strengths of a once-every-3-month paliperidone injection formulation (175 mg, 263 mg, 350 mg and 525 mg);
- The Type II (C.I.6a) variation that modifies the existing "Paliperidone Janssen" indication, i.e.: Trevicta, a 3-month injection, indicated for the maintenance treatment of schizophrenia in adult patients who have been adequately treated with 1-month paliperidone palmitate injectable product for at least four months;
- The Type IAIN (Code A.2) variation that amends the tradename from "Paliperidone Janssen" to Trevicta.
- The Type IB (code C.I.7) variation that deletes all 6 "Paliperidone Janssen" dosage strengths (ie. Paliperidone Janssen 25 mg, 50 mg, 75 mg, 100 mg, 150 mg, and 100 & 150 mg).

The legal basis for this application refers to:

- Article 19 of Regulation EC/1234/2008 (Annex I, point 2(c)) - Extensions of marketing authorisations
- Article 10 of Commission Regulation (EC) No 1234/2008 – "Prior Approval" procedure for major variation of type II
- Article 7(2)(iii) of Regulation 1234/2008/EC – Group of variations

Information on Paediatric requirements

Not applicable.

Information relating to orphan market exclusivity

Similarity

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

Scientific Advice

The applicant received Scientific Advices from the CHMP on 21/10/2010 and 21/10/2011. The Scientific Advices pertained to non-clinical and clinical aspects.

Licensing status

Paliperidone Janssen has been given a Marketing Authorisation in EU on 05/12/2014.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

- The application was received by the EMA on 28 July 2015.
- The procedure started on 20 August 2015.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 11 November 2015.
- The PRAC Rapporteur Risk Management Plan (RMP) Assessment Report was adopted by PRAC on 3 December 2015.
- During the meeting on 17 December 2015, the CHMP agreed on the consolidated List of Questions to be sent to the MAH. The final consolidated List of Questions was sent to the MAH on 17 December 2015.
- The MAH submitted the responses to the CHMP consolidated List of Questions on 28 January 2016.
- The Rapporteurs circulated the Joint Assessment Report on the MAH's responses to the List of Questions to all CHMP and PRAC members on 3 March 2016.
- The MAH submitted in written the responses to the CHMP List of Outstanding Issues on 11 March 2016 prior to the March 2016 CHMP meeting.
- During the meeting on 1 April 2016, 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 for four new strengths of a once-every-3-month paliperidone injection formulation (175 mg, 263 mg, 350 mg and 525 mg) for Trevicta, and a positive recommendation for the approval to the variations to the Product Information.

2. Scientific discussion

2.1. Introduction

Schizophrenia is a chronic, severe and debilitating form of mental illness. Data suggest that schizophrenia affects, on average, approximately 0.45% of the worldwide population, with an annual incidence of approximately 15 per 100,000. The incidence and morbidity risk of schizophrenia are generally consistent across broad geographic regions, and among diverse ethnic, cultural, and socioeconomic categories. Schizophrenia is characterized by fundamental and characteristic distortions of thinking and perception and by inappropriate or blunted affect. The long-term outcome of schizophrenia varies along a continuum of reasonable recovery to total incapacitation. Antipsychotic medications are the mainstay of treatment, although nondrug therapies provide additional benefit to many patients. Antipsychotic drugs include conventional antipsychotics, typified by haloperidol, and second-generation drugs, such as paliperidone.

Paliperidone palmitate is a pro-drug which is rapidly hydrolysed to the active component paliperidone after intramuscular injection. Paliperidone is a monoaminergic antagonist that exhibits the characteristic effects of antipsychotics on dopamine Type 2 (D2) receptors combined with the predominant serotonin (5 hydroxytryptamine Type 2A) antagonism of second-generation antipsychotic drugs. Paliperidone is the major active metabolite of risperidone.

Paliperidone is available in two formulations, an oral prolonged-release tablet formulation, Invega (paliperidone), also referred to as paliperidone ER and a 1-month LAI formulation, Xeplion (paliperidone palmitate), also referred to as PP1M in the report.

The MAH applies for a marketing authorisation for a new formulation of paliperidone palmitate, Trevicta (formerly Paliperidone Jansen). This is a 3-month long-acting injectable (LAI) formulation, also referred to as PP3M in the report.

The initially proposed indication for Trevicta was maintenance treatment of schizophrenia in adult patients who have been adequately treated with XEPLION for at least four months. The indication as later revised to maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product.

2.2 Quality aspects

2.1.1. Introduction

Trevicta is presented as prolonged release suspension for injection containing 273 mg, 410 mg, 546 mg and 819 mg of paliperidone palmitate as active substance equivalent to 175 mg, 263 mg, 350 mg or 525 mg paliperidone respectively.

Other ingredients are polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide (for pH adjustment) and water for injections, as described in section 6.1 of the SmPC.

The finished product is available as a pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, backstop, and tip cap (bromobutyl rubber) with two (one 1½ inch long and 1 inch long) safety needles, as described in section 6.5 of the SmPC.

2.1.2. Active Substance

The active substance is the same as described in the approved dossier. No new information documentation or changes were proposed for the active substance. The quality of active substance is considered acceptable for the new strength proposed with the present application.

2.1.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Paliperidone palmitate eq. 200 mg/ml extended release suspension for injection will be provided in a prefilled syringe. Dosage strengths ranging from eq. 175 mg to eq. 525 mg are obtained by filling the syringes with different volumes of the eq. 200 mg/ml bulk suspension. A separate overfill has been determined for each dosage strength.

Table 2 presents the different dosage strengths, including the syringe size.

Table 1: Different Dosage Strengths with their Syringe Size		
Dose as paliperidone palmitate (mg)	Dose equivalent as paliperidone (mg)	Syringe Size
273	175	1 mL Long
410	263	2.25 mL
546	350	2.25 mL
819	525	2.8 mL

The aim of the pharmaceutical development was to obtain a prolonged release formulation of paliperidone with an injection interval of 3 months for the treatment of schizophrenia.

The Quality Target Product Profile (QTPP) for the paliperidone palmitate 3-month formulation was defined by the applicant as: a sterile paliperidone palmitate suspension with a 3-month extended release profile, dosage strengths ranging from eq. 175 mg to eq. 525 mg in a pre-filled syringe, minimal injection volume suitable for gluteal or deltoid injection, manually resuspendable and homogeneous suspension, sufficient shelf life in all climatic zones.

The development of the 3-month formulation was based upon the insight gained during the development of the 1-month formulation.

The mechanism of release of the paliperidone palmitate 3-month formulation is the same as the approved 1-month formulation (Xeplion). After intramuscular injection, paliperidone palmitate is slowly dissolved at the injection site and then enzymatically hydrolyzed to paliperidone which is taken up in the systemic circulation.

The rate-limiting factor for the bioavailability is the dissolution of the paliperidone palmitate particles at the site of injection.

The formulation has been optimised in relation to certain aspects so that the performance of the 3 months formulation is ensured.

The 3-month formulation proposed for commercial use has been used during the phase 1 clinical trials as well as in the phase 3 studies without any modification.

Study R096270-PSY-1002, which is described in the approved paliperidone palmitate 1-month dossier, demonstrated that increasing the particle size of the suspension lowers C_{max} and extends T_{max}.

Based on the results from the R092670-PSY1002 study the particle size for the 3-month formulation was established.

It was anticipated that patients switching from the 1-month formulation to a 3-month formulation would require a 3-fold higher dose, relative to the corresponding dose of 1-month formulation (i.e., 50, 75, 100 and 150 mg-eq. were increased to 150, 225, 300 and 450 mg-eq., respectively).

Based on pharmacokinetic simulations, it was decided to develop 3.5-fold higher doses (50, 75, 100 and 150 mg-eq. increased to 175, 263, 350 and 525 mg-eq., respectively).

Hence, the following doses and corresponding fill volumes were selected:

- 175 mg-eq or 0.875 mL filled in 1-mL Long syringe
- 263 mg-eq or 1.315 mL filled in 2.25-mL syringe
- 350 mg-eq or 1.750 mL filled in 2.25-mL syringe
- 525 mg-eq or 2.625 mL filled in 2.8-mL syringe

In order to minimize the injection volume, the active substance concentration was doubled from 156 mg/ml to 312 mg/ml.

An evaluation of the resuspendability behavior was performed on 3 validation batches which had been stored for 9-11 months at room temperature. Based on the results shaking instruction is recommended in the SmPC (section 4.2 Method of administration) to allow an additional safety window to ensure the suspension is resuspended.

An in-use stability study was performed whereby the piston release force (PRF) and piston travel force (PTF) was measured after shaking and compared to samples of the same batch after shaking followed by a holding time (with no additional shaking immediately prior to testing). Based on the results, a 5 minute in-use storage instruction is recommended in the SmPC (section 4.2 Method of administration) as it is good clinical practice to inject the product as soon as reasonably practical after suspension.

In addition the robustness of the formulation for excipient concentration, proposed particle size range and pH was sufficiently demonstrated.

A particle size test method has been developed for quality control of the finished product performance at process, release, and stability, based on the method for the approved 1-month formulation, with some parameters optimised . The method is able to detect minor differences in particle size between different batches, identify changes which occur during stability tests (stability indicating), provide reliable information regarding the particle size ranges, and is discriminative enough to discriminate between actual active substance particles and artifacts (such as air bubbles) and agglomerates.

A second test method used to evaluate the impact of paliperidone palmitate particle size on product performance is the *in vitro* release test. The *in vitro* release method developed has discriminating properties towards the particle size of the paliperidone palmitate particles.

An *in vivo in vitro* correlation between the particle size and the release of the substance has been established. The method has been shown to be discriminatory even for relatively small variations of the particle size and also stability indicating.

Other physicochemical characteristics of the active substance such as purity, crystallinity, and morphology were evaluated for their potential influence on the product performance (i.e. the *in vivo* release profile).

All inactive ingredients used in the manufacturing of the drug product are conventional pharmaceutical excipients. The 3-month formulation contains the same active substance and the same excipients as the 1-month formulation with the minor exception of the removal of disodium hydrogen phosphate from the 3-month formulation. The function of each excipient and the rationale for their selection was satisfactorily presented.

An overfill volume is added to the nominal volume to obtain the targeted effective fill volume of the syringes, and compensates for losses in the syringe tip and needle.

Development of the manufacturing process, and production of phase 3 clinical and primary stability batches, took place at a pilot facility. The manufacturing process was transferred, scaled up, and further characterised at the commercial manufacturing facility. Apart from the difference in scale, the manufacturing equipment used for commercial production is the same regarding design and operating principles, as compared to the equipment used to produce the phase 3 clinical and primary stability batches. Equivalence before and after scale-up was demonstrated by comparing the manufacturing process and the physicochemical characteristics of the product.

Similar to the approved 1-month formulation, the product is manufactured aseptically because terminal sterilization of the final suspension was shown not to be feasible for technical and stability reasons.

The drug product is packaged in an assembled prefilled syringe (with plunger rod and backstop attached) with2 needles for administration: a thin walled 22 G, 1 inch safety needle and a thin walled 22 G, 1½ inch. safety needle. The compatibility and integrity of the proposed packaging materials and the product has been demonstrated. The leachable study showed only a limited amount of leachables after 6 months at 40 °C/75% RH (simulating 24 months at room temperature storage conditions) above the acceptable intake for an individual mutagenic impurity defined by ICH M7. Nevertheless, the toxicological assessment showed that the observed levels do not pose an appreciable extra risk to human safety. Finally the functional suitability of all the packaging components (pre-package, pre-sterilised intramuscular needles) has been assessed and qualified through testing of the pre-filled syringe based on relevant ISO standards.

Manufacture of the product and process controls

The finished product is aseptically manufactured by dispersing the sterile active substance in a sterile buffer solution, wet milling the suspension to a target particle size, dilution of the milled suspension using WFI, and aseptically filling and stoppering of the final suspension into pre-sterilized syringes. The manufacturing process is considered as a non-standard process.

The critical steps were identified as sterile filtration, milling and filling. All the proposed in-process controls (IPCs) established for the manufacturing process are acceptable, justified and are considered suitable to guarantee the intended quality of the product.

The process validation study was conducted with three full scale batches of paliperidone palmitate 3-month formulation. The validation batches were produced at the commercial facility according to the intended 100-L batch formula and manufacturing process. The 3 bulk batches of paliperidone palmitate 3-month formulation were entirely filled in the 4 proposed dosage strengths using the commercial container closure system. All results obtained for the bioburden, bacterial endotoxin, and filter integrity and filler challenge tests meet the acceptance criteria. The manufacturing process is considered validated and capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release and shelf life specifications include appropriate tests and limits for this kind of dosage form including appearance/ resuspendability/ injectability, identification (FTIR, HPLC), assay (HPLC), chromatographic purity (HPLC), pH (Ph. Eur.), particulate matter (light obscuration), uniformity of dosage units (Ph. Eur.), *in vitro* release testing (Ph. Eur.), particle size distribution (laser diffraction), sterility (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The specification and control tests applied for the finished product at time of release and throughout the shelf life of the product are in compliance with general pharmacopoeial standards and ICH guidelines (Q3B and Q6A). The analytical methods used have been adequately described and appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards of active substance and impurities has been presented.

Batch analysis data from 3 validation batches of the finished product manufactured at the proposed commercial facility and scale were presented. Batch analysis results from three characterisation batches manufactured at the commercial scale at the proposed commercial facility and another five batches at the development site were also presented. In addition results from three registration stability batches

manufactured at smaller scale in the pilot plant were presented. Finally batch results from the clinical batches manufactured at various batch sizes were also provided.

All batches meet the specifications active at the time. The analytical results presented demonstrate consistency in manufacturing and conformity with the proposed commercial specifications.

Stability of the product

Stability studies have been performed on three registration pilot batches and a full scale clinical batch of paliperidone palmitate 3-month formulation, stored in proposed packaging in upright and tip down position. The manufacturing process and primary packaging system used to manufacture and package the registration stability batches and the full scale clinical batch are equivalent.

Stability data are available through 12 months of storage at long term conditions (25 °C/40% RH and 30 °C/35% RH), intermediate (30 °C/75% RH) and accelerated conditions (40 °C/ NMT 25% RH).

Samples have been tested for appearance/resuspendability/injectability, particle size distribution, *in vitro* release, pH, assay and chromatographic purity, bacterial endotoxins and sterility as per the release methods. In addition stability samples have been tested for aldehydes content (HPLC), weight loss and container closure integrity by validated methods.

In addition stress testing, photostability study (as per ICH) and freeze thaw testing have been performed on representative batches of all fill volume and packaging configurations.

At long term condition, a limited drop in particle size was observed which flattens out after 6 months storage.

When stored at the stress condition of 50 °C, a clear increase in particle size was observed due to the Ostwald ripening process. This phenomenon was also observed after 6 months storage at 40 °C/NMT 25% RH and is starting after 12 months storage at the 30 °C conditions. When the product was stored at the freeze-thaw conditions or frozen conditions, a more pronounced initial drop in particle size was observed.

At the stress condition of 50 °C a decrease in dissolution rate is observed. This decrease can be explained by Ostwald ripening. This phenomenon is observed at the other conditions, but it is less pronounced conditions and is limited at 5 °C.

For the lowest fill volume (0.875 mL) some weight loss was observed. This phenomenon is also seen after 6 months at 40 °C/NMT 25% RH. For the other fill volumes the weight loss is negligible or not observed.

No other significant stability-related changes were observed. Based on the available stability data, the 3-month formulation stored in the proposed packaging has been demonstrated to be chemically stable, with only limited changes in particle size and *in vitro* release profile being observed.

Based on the overall stability data provided the proposed shelf-life of 24 months without any storage precaution is accepted.

Adventitious agents

None of the excipients are of human or animal origin.

2.1.4. Discussion on chemical, pharmaceutical and biological aspects

No new information or changes were proposed for the active substance with the current application. The quality of active substance is considered acceptable for the new strengths proposed. Information on development, manufacture and control of the finished product has been presented in a satisfactory manner. The manufacturing process has been validated. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.1.5. 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.

2.1.6. Recommendation(s) for future quality development

Not applicable.

2.2. Non-clinical aspects

2.2.1. Introduction

Paliperidone palmitate (R092670) is an aqueous suspension for intramuscular injection. Formulations of paliperidone palmitate provide therapeutic plasma concentrations of paliperidone for 1 month (with the marketed paliperidone palmitate 1-month formulation, PP1M, Xeplion) or 3 months (with the investigational paliperidone palmitate 3-month formulation, PP3M). Plasma concentrations also depend on the particle size, concentration, and volume of the formulation.

The PP3M formulation (also denoted F015) contains the same drug substance and excipients as the PP1M formulation (also denoted F013; with the minor exception of the removal of disodium hydrogen phosphate) and is manufactured using the same equipment and process. The PP3M formulation differs from the PP1M formulation in the particle size and a higher concentration of paliperidone palmitate (PP3M: 312 mg/mL and PP1M: 156 mg/mL, corresponding to paliperidone concentrations of 200 mg/mL and 100 mg/mL, respectively). Additionally, the maximum volume to be injected in patients is increased from 1.5 mL (150 mg eq. paliperidone) for the PP1M formulation to 2.625 mL (525 mg eq. paliperidone) for the highest strength of the PP3M formulation.

The PP3M non-clinical program has been designed to build upon previous toxicology experience with the active ingredient. Because of the higher concentrated formulation of PP3M compared with PP1M, the local tolerability of the PP3M formulation was assessed and compared with the PP1M formulation in the minipig. Since the maximum clinical dose was increased during the clinical development, the first local tolerance study was repeated by a second one at higher dose levels.

2.2.2. Toxicology

Local Tolerance and toxicokinetic data

The non-clinical studies conducted in support of the new PP3M formulation comprise two 12-week local tolerance studies in minipigs with intramuscular administration. The approved PP1M formulation

(Xeplion) was included for comparison of tolerance and toxicokinetics. Intramuscular injection was chosen in order to comply with the human route of administration.

The dose level selection is considered as adequate. The tested PP3M and PP1M formulations were identical to the clinical formulations in composition and concentration. The low doses was set at approximately the maximal recommended human doses of paliperidone (per injection site) and the high doses were set to include the maximal human administration volume (per injection site).

In both studies, central nervous system effects were observed in both formulation groups. At necropsy dose-related local reactions were seen at the injection sites, with no relevant difference between formulations. Histopathologically, similar dose-related inflammatory reactions were observed across formulations, but the cellular reaction patterns and sizes of crystalline material in inflammatory cells were different. However, these microscopic differences are not considered to reflect a meaningful difference in adversity. Exposure, measured as are under the concentration time curve (AUC) after a single dose of the PP3M formulation was similar to that after 3 consecutive (once a month) dose administrations of the PP1M formulation.

In SmPC section 4.8 of Trevictra it is stated that 5.3% of subjects in clinical trials reported mild injection site related adverse reactions. Injection site reactions are also included as an important identified risk in the Risk Management Plan. Hence, the safety concern of local injection side reaction observed in the non-clinical studies was already adequately covered.

No further data regarding systemic exposure with PP3M was considered necessary in light of the available combined nonclinical safety data from PP1M (Xeplion) as well as from the oral paliperidone prolonged-release tablets toxicology programs.

Impurities

There are no new impurities in the paliperiodone palmitate PP3M formulation, compared to that of the approved PP1M formulation. The impurities R206474, R206475, R207919, R208224 and R208225 are considered toxicologically qualified at 2.1%, 0.9%, 0.9%, 1.8%, and 3.0%, respectively.

2.2.3. Ecotoxicity / environmental risk assessment (ERA)

The MAH has submitted an ERA comprising of Phase I assessment and several Phase II Tier A studies. The same study data were used as previously assessed in relation to an oral paliperidone formulation(Invega) and a paliperidone palmitate for injection submission (Xeplion).

In the updated ERA for Trevicta, the MAH presents a refinement (based on sales forecast and EU inhabitants) of the Phase I paliperidone $PEC_{surfacewater}$ of 0.0019 µg/L which is below the threshold value of 0.01 µg/L. Although the refinement strategy in Phase I can be questioned, a similar refinement in phase I was considered acceptable in both previous paliperidone applications. During a previous assessment of a 1-month paliperidone palmitate injection formulation (Xeplion), the $PEC_{surfacewater}$ was estimated at 0.0027 µg/L based on a worst case scenario including sales estimates for both oral and injectable formulations. As the new 3-month injection formulation in Trevicta is intended to replace use of other paliperidone products in the maintenance treatment of schizophrenia and since the maximum daily paliperidone dose of 6.25 mg/day (525 mg every 84 days) for Trevicta is only slightly higher than the maximum daily paliperidone dose for the 1-month injection formulation (Xeplion) of 5.36 mg/day (150 mg every 28 days), no significant increased overall use of paliperidone is expected and no relevant increase in exposure of the environment to the active substance is expected. The CHMP thus concluded that no further testing was required and that introduction of the new paliperidone palmitate 3-month injection formulation is unlikely to represent a risk to the environment following prescribed usage in

patients.

2.2.4. Conclusion on the non-clinical aspects

The non-clinical part of the dossier is considered to be adequate and sufficient to support the present application for the new 3-month formulation of paliperidone palmitate (PP3M).

2.3. Clinical aspects

2.3.1. Introduction

Good Clinical Practice (GCP)

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

2.3.2. Pharmacokinetics

The new 3-month formulation of paliperidone palmitate (PP3M) differs from the already approved 1-month formulation (PP1M) in its suspension strength, particle size, and higher fill volume, leading to a slower release after intramuscular (IM) injection. Given the slow release, it is intended to be used in patients already stabilized on PP1M. The dose conversion from PP1M to PP3M is based on a ratio of 1 to 3.5. The PP3M formulation has been used in the pivotal clinical studies and is identical to the formulation proposed for commercial use.

Objectives of the pharmacokinetic (PK) development program for the PP3M formulation included documentation of its single- and multiple-dose PK across the entire proposed dose range (175 to 525 mg eq.) and identification of the key demographic- and injection site related covariates affecting PP3M PK in order to support label recommendations for PP3M dosing. The PK properties of PP3M were measured from extensive PK sampling in 308 subjects from the Phase 1 study R092670-PSY-1005, and from semi-intensive PK sampling in 397 subjects in the Phase 3 long-term, randomized withdrawal study R092670-PSY-3012 and 504 subjects in the Phase 3 non-inferiority study R092670-PSY-3011. All studies were conducted in the intended patient population.

Population pharmacokinetics

A population PK model for paliperidone palmitate was developed based on both data from the Phase 1 study with rich sampling and the phase 3 study (PSY-3012) with sparse sampling. The model development was in general well performed and reported. Adequate predictive performance was demonstrated by prediction corrected visual predictive checks stratified for important covariates. The model is considered qualified for simulations of different dosing regimens.

Simulations based on the population pharmacokinetic analysis

Administration of PP3M at doses 3.5 times higher than PP1M appears to result in paliperidone plasma exposure within the same range as for PP1M. As observed in study PSY-3011, peak-to-trough fluctuation seems to be somewhat higher for PP3M compared to PP1M. The simulations indicate that plasma concentrations are stable when switching back to PP1M after the fourth PP3M injection.

The simulations support the proposed SmPC recommendation where a ±2 week dosing window is suggested during the switch from PP1M to PP3M. The SmPC recommendations for dosing windows in case of missed doses are also supported by the simulations.

The proposed dosage recommendations for the switch to oral paliperidone ER after termination of PP3M treatment needed to be further justified. The MAH provided satisfactory additional simulations for the transition of subjects from PP3M to oral paliperidone extended-release (ER), including the lower strengths and time until new steady state is reached. The predictive properties of the applied ER model were also adequately demonstrated. Thereby the proposed dosage recommendations for the switch to oral paliperidone ER after termination of PP3M treatment was considered to be well supported by those additional simulations and the dosage table was also made clearer to avoid misinterpretations.

Analytical methods

Plasma samples were analysed for paliperidone, paliperidone enantiomers and/or paliperidone palmitate concentrations using validated liquid chromatography coupled to tandem mass spectroscopy (LC-MS/MS) methods. Some clarifications on the validity of some of the results were requested and were considered satisfactorily addressed by the MAH.

Absorption

After a single-dose administration of PP3M following at least 4 months of treatment with PP1M, paliperidone was slowly absorbed with a median Tmax of 23-31 days. The relative bioavailability after intramuscular injection of paliperidone PP3M compared to an immediate release IM formulation of paliperidone was close to 100%.. Similar to PP1M, low plasma paliperidone palmitate concentrations were detectable in a limited number of samples (1.4%) after single-dose IM injections of PP3M.

The absorption rate of paliperidone was slightly faster after injection in the deltoid muscle compared to the gluteal injection, with similar increase in Cmax (23-28%) after single-dose and at steady-state. There was no difference in AUC after single-dose administration but at steady-state the difference was in the same magnitude as Cmax (23-30%). The estimates from the population PK analysis were less pronounced, with only 11-12% higher Cmax and Cmin after deltoid compared to gluteal injection. The overall results are in accordance with previous observations for the PP1M formulation. For PP1M the day 1 and day 8 initiation doses must each be administered in the deltoid muscle in order to attain therapeutic concentrations rapidly, but the following monthly maintenance doses can be administered in either the deltoid or gluteal muscle. Given that PP3M is only indicated for patients already stabilized on PP1M, no specific recommendation regarding injection site was deemed necessary.

No new *in vitro – in vivo* correlation (IVIVC) has been presented. The IVIVC for PP1M is not relevant for the PP3M formulation, since the particle size of paliperidone in PP3M falls outside the currently validated IVIVC.

Distribution

The one-compartment population PK model estimated an apparent central volume of distribution of 1960 L for paliperidone after administration of PP3M, which is higher than the estimate obtained for PP1M (391 L). The interpretation of the volume parameter is limited given the flip-flop pharmacokinetics of paliperidone depot injection formulations.

Elimination

The population PK model estimated a total body clearance of 3.84 L/h for paliperidone after 3-monthly injection with PP3M, which was in agreement with the estimate after administration of PP1M (4.95 L/h).

Paliperidone exhibits flip-flop kinetics when administered as PP3M, i.e., the apparent half-life is driven by the absorption process. Simulations with the final population PK model estimated median paliperidone t1/2 from the PP3M formulation to be in the range of 84 to 95 days following deltoid injections and 118 to

139 days following gluteal injections of 175 to 525 mg eq. PP3M, which supports a once every 3 months injection cycle.

The mean (+)/(-) ratios of the paliperidone enantiomers were approximately 1.8 and 1.9 for AUC and Cmax, respectively, after deltoid injection of 175 mg eq. PP3M, and 1.7 for both parameters after gluteal injection of 525 mg eq. PP3M. The observed ratios are similar to that observed for the 1-month paliperidone palmitate formulation, i.e., 1.7.

No additional data regarding excretion and metabolism for PP3M was deemed necessary as data obtained with the PP1M formulation and the oral paliperidone ER formulation were considered sufficient.

Dose proportionality and time dependencies

After single dose and multiple dose administration a dose proportional increase in AUC and Cmax within the range of 175-525 mg eq. was demonstrated.

Intra- and inter-individual variability

The inter-individual variability for paliperidone after administration of the PP3M formulation was low to moderate for AUC (22-35%) and moderate to high for Cmax (49-99%). For AUC the inter-individual variability was similar to the PP1M formulation but somewhat higher for Cmax (40-60% reported for PP1M). The applicant was asked to submit data on intra-individual variability of the PP3M formulation in comparison to PP1M. The CHMP concluded that intra-individual variability was comparable between the two formulations.

Pharmacokinetics in target population

All studies with PP3M have been conducted in the intended target population. The steady-state plasma exposure after administration every 3-month with PP3M was roughly similar to administration every 1-month with PP1M, see Table 4.

Table 2: **Pre-dose plasma concentrations of paliperidone after administration of PP1M and PP3M (study PSY-3012).**

Predose Plasma Concentrations Paliperidone	PP1M, 50 mg eq. / PP3M, 175 mg eq.			PP1M, 75 mg eq. / PP3M, 263 mg eq.			PP1M, 100 mg eq. / PP3M, 350 mg eq.			PP1M, 150 mg eq. / PP3M, 525 mg eq.		
	n	mean	SD	n	mean	SD	n	mean	SD	n	mean	SD
PP1M (Transition Phase)												
$C_{Day\ 64,\ Week\ 9}$, ng/mL	9	17.4	10.5	27	21.5	9.06	155	21.6	11.9	145	23.0	14.0
$C_{Day\ 92,\ Week\ 13}$, ng/mL	6	13.9	5.61	28	20.7	8.24	148	21.7	11.0	135	24.6	13.0
$C_{Day\ 120,\ Week\ 17}$, ng/mL	6	15.1	5.75	22	21.0	6.94	142	24.1	12.5	119	31.7	18.1
PP3M (Maintenance and Double Blind Phase)												
$C_{Day\ 204,\ Week\ 29}$, ng/mL	5	10.3	4.29	14	18.8	9.65	62	22.4	11.4	49	27.4	14.0
$C_{Day\ 288,\ Week\ 41}$, ng/mL	4	9.44	2.12	9	20.2	9.33	56	21.5	10.4	39	30.1	15.0
$C_{Day372\ ,\ Week\ 53}$, ng/mL	3	8.23	4.82	6	25.8	11.0	34	24.5	12.8	27	29.7	14.6
$C_{Day456\ ,\ Week\ 65}$, ng/mL	-	-	-	1	-	-	8	26.7	18.4	16	30.7	14.7
$C_{Day540\ ,\ Week\ 77}$, ng/mL	-	-	-	1	-	-	1	-	-	6	36.7	8.74

17-week transition phase: 150 mg eq. PP1M on Day 1, 100 mg eq. PP1M on Day 8, flexible dose on Day 36 and Day 64 (50, 75, 100, or 150 mg eq.), dose of Day 92 is the same as Day 64
12-week maintenance phase: single injection of a fixed dose of PP3M (175, 263, 350 or 525 mg eq.)
Double-blind phase: injection of a fixed dose of PP3M (175, 263, 350 or 525 mg eq.) or placebo every 3 months

Special populations

As for PP1M, specific dosage recommendations for PP3M are only recommended for patients with renal impairment. While use in patients with moderate or severe renal impairment is not recommended, use in patients with mild impairment is possible but subject to dose adjustment. The dosing instructions (choice of needle for injection) are influenced by weight/body mass index (BMI).

Pharmacokinetic interaction studies

No additional data regarding interactions was deemed necessary as data obtained with the PP1M formulation and the oral paliperidone extended release formulation were considered by the CHMP to be sufficient.

2.3.3. Pharmacodynamics

Relationship between plasma concentration and effect

An exposure-response analysis was conducted to describe the relationship between paliperidone plasma concentrations and positive and negative syndrome scale for schizophrenia (PANSS) total scores, time to relapse of symptoms of schizophrenia, and dropout following administration of PP1M and PP3M in study 3012. Additionally, the relationship between paliperidone concentrations and time to relapse of symptoms of schizophrenia as well as dropouts following administration of PP1M and PP3M in study 3011, was described.

No relationship between paliperidone concentrations and PANSS scores could be established and further model development was not needed.

The developed models for relapse and drop-out are not generally applicable and predictive of treatment outcome. It appears that frequency of relapse is sensitive to severity of disease, patient population and drop-out rate which varied between studies.

2.3.4. Discussion on clinical pharmacology

The pharmacokinetics of the new PP3M formulation has been characterized after single-dose administration and at steady-state in the intended patient population. The pharmacokinetic studies have demonstrated the slow release of paliperidone after IM injections of PP3M. The influence of different injection sites has been evaluated. Dose-proportionality has been demonstrated within the therapeutic dose range. The steady-state plasma exposure after administration every 3-month with PP3M has been shown to be roughly similar to administration every 1-month with PP1M. A number of simulations have been presented addressing different dosing scenarios.

The pharmacokinetics in special populations has been sufficiently described. As for PP1M, specific dosage recommendations for PP3M are only recommended for patients with renal impairment.

Additional data regarding excretion, metabolism and drug-drug interactions is not deemed necessary for the PP3M formulation as data obtained with PP1M and paliperidone extended release is considered sufficient.

2.3.5. Conclusions on clinical pharmacology

The pharmacokinetics of the new PP3M formulation has been well characterized. Overall, the clinical pharmacology program was considered sufficient to support the present application.

2.4. Clinical efficacy

2.5.1 Dose response studies and main clinical studies

Summary of main efficacy results

The clinical program sought to investigate the use of the new 3-months paliperidone palmitate injection (PP3M) in the maintenance treatment of schizophrenia in adult patients after adequate treatment with a 1-month paliperidone palmitate injectable product (PP1M) for at least 4 months (Table 5). The dose conversion from PP1M to PP3M is based on a ratio of 1:3.5 and has been studied in a single dose, two periods, parallel, randomized study using different PP3M prototype formulations in schizophrenic patients.

Table 3: Clinical Studies Supporting the Efficacy and/or Safety of Paliperidone Palmitate 3-month Injection for the Treatment of Schizophrenia

Study Type/ Protocol ID	Study Description	Study Treatments	Number of Subjects
Phase 3 Non-inferiority Study			
R092670-PSY-3011	Randomized, DB, parallel group, multicenter non-inferiority study (PP3M versus PP1M) of 48 weeks duration preceded by a 17-week, OL phase[a] with PP1M	PP3M (fixed dose[b]: 175, 263, 350, or 525 mg eq./3 months based on 3.5 times PP1M dose at end of OL phase) PP1M (fixed dose[b]: 50, 75, 100 or 150 mg eq./4 weeks based on PP1M dose at end of OL phase)	OL phase, n=1,429 DB phase: PP3M: 504 PP1M: 512
Phase 3 Long-term, Randomized Withdrawal Study			
R092670-PSY-3012	DB, placebo-controlled, multicenter, long-term, randomized withdrawal study of variable duration preceded by a 17-week, OL Transition phase[c] with PP1M and a 12-week OL Maintenance phase with PP3M	PP3M (fixed dose[d]: 175, 263, 350, or 525 mg eq./3 months based on 3.5 times PP1M dose at end of OL Transition phase) Placebo: (DB phase only)	OL Transition phase: n = 506 OL Maintenance phase, n=379 DB phase: PP3M: 160 Placebo: 145
Completed Phase 1 PK and Safety Study			
R092670-PSY-1005	Randomized, single-dose, open label, parallel group, multicenter study consisting of 4 panels, with each panel including 2 single-dose treatment periods (paliperidone IR in period 1 and PP3M in period 2). In each panel the single dose of PP3M was followed by a 364- to 544-day observation period for PK	PP3M: Panel A: 300 mg eq., gluteus (F015 wet or dry milled) Panel B: 75, 150, 450 mg eq., gluteus, or 300 or 450 mg eq., deltoid (F015 wet milled)	PP3M total: n = 308 Panel A: n = 66 Panel B: n = 120 Panel C: n = 24 Panel D: n = 98

	and safety evaluations.	Panel C: 150 mg eq., gluteus (F016 wet milled] Panel D: 175 or 525 mg eq., deltoid, or 350 or 525 mg eq., gluteus (F015 wet milled)

[a] All subjects in Study PSY-3011 received the first PP1M injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. Injections of PP1M at Weeks 5 and 9 could have been given in the deltoid or gluteus muscle and were flexibly dosed (50 to 150 mg eq.). At Week 13, subjects received the same dose of PP1M as at Week 9.

[b] Treatment in DB phase started at Week 17. Subjects assigned to PP3M received a fixed dose that was a 3.5-fold multiple of the PP1M dose received at Week 9. Subjects assigned to PP1M received the same dose as at Week 9 of the OL phase.

[c] All subjects in Study PSY-3012 (except those continuing PP1M or switching from another LAI antipsychotic) were scheduled to receive the first PP1M injection of 150 mg eq. on Day 1 and the second injection of 100 mg eq. on Day 8, both in the deltoid muscle. Injections of PP1M at Weeks 5 and 9 could have been given in the deltoid or gluteus muscle and were flexibly dosed (50 to 150 mg eq.). At Week 13, subjects received the same dose of PP1M as at Week 9.

[d] Treatment in the DB phase started at Week 29; those assigned to PP3M received the same dose as at Week 17 of the OL Maintenance phase.

Key: DB=double-blind; IR=immediate release; mg eq.=milligram equivalent; OL=open-label; PK=pharmacokinetic; PP1M=paliperidone palmitate 1-month injection; PP3M=paliperidone palmitate 3-month injection.

Source: Mod2.7.4/SCS/Tab1.

Study design

Study PSY-3011 was a randomized, double-blind, parallel group, multicentre non-inferiority study in adults 18 to 70 years of age with schizophrenia. The study consisted of two treatment phases: a 17-week flexible dose open-label stabilization phase (referred to as the Open label Phase) and a 48-week fixed dose, randomized, double-blind controlled phase (referred to as the Double-blind Phase). In the Open-label Phase, all subjects received PP1M. Subjects that entered the Double-blind Phase were randomly assigned, in a 1:1 ratio, to receive either a fixed dose of PP1M or a fixed dose of PP3M. The primary efficacy endpoint was the percentage of subjects who were relapse free at the end of the study who had been adequately treated with PP1M for an acute exacerbation.

Study PSY-3012 was a randomized, double-blind, parallel group, placebo controlled, multicentre study designed to determine the efficacy and safety of PP3M in adults 18 to 70 years of age with schizophrenia. There were three treatment phases: the Transition Phase, the Maintenance Phase, and the Double-blind Phase. Overall, 506 subjects were enrolled into the study and 305 subjects were randomly assigned, in a 1:1 ratio in the Double-blind Phase, to receive either a fixed dose of PP3M or placebo. The primary endpoint in the relapse prevention study was Time to first relapse.

Disposition of patients

In the non-inferiority study (PSY-3011), subjects were grouped into 3 regions, European Union (EU), United States (US) and Non-EU/non US. Overall, 1429 subjects with schizophrenia were enrolled into the study and 1016 subjects with schizophrenia were randomized in the DB phase of the study. A total of 824 subjects (83%) completed the study. The percentage of subjects who completed the Double-blind phase was higher for EU sites (85%) and non-EU/non-US sites (84%) than for US sites (64%).

The number of subjects who discontinued from the study in the PP3M and PP1M groups were 79 subjects [16%] and 92 subjects [18%], respectively. The most common reason (≥5%) to discontinue from the study was withdrawal of consent (49 subjects [10%] in the PP3M group, 53 subjects [10%] in the PP1M group).

In study PSY-3012, 506 subjects with schizophrenia were enrolled into and dosed in the Open-label Phase, and 305 subjects with schizophrenia were randomized into in the Double-blind Phase, as of 09 April 2014, the date of study completion. Of the 305 randomized subjects, a total of 270 subjects (89%) completed the study, while 35 subjects (11%) discontinued from the Double-blind Phase. A higher percentage of subjects in the PP3M group than the Placebo group (93% vs. 84%) completed the study; hence, a higher percentage of subjects in the Placebo group than the PP3M group discontinued the Double-blind Phase (23 subjects [16%] vs. 12 subjects [8%)]). The most common reason for discontinuation in any treatment group were withdrawal of consent (10 subjects [7%] in the Placebo group, 7 subjects [4%] in the PP3M group), and other reasons (8 subjects [6%] in the Placebo group, 2 subjects [1%] in the PP3M group).

Baseline characteristics

Study PSY-3011

No major imbalances between treatment groups with respect to demographic and baseline characteristics were observed. About 55% of the subjects investigated were male and the age ranged from 18 to about 70 years with a mean (SD) age of 38.4 (11.86) years (range: 18 to 70 years). Based on BMI, 44% of subjects were classified as having normal BMI; 32% of subjects were overweight, and 24% were obese. Overall the majority of subjects were recruited at sites outside Europa and US (60%) with the remainder recruited in Europe (30%) and the US (10%).

About 61% of subjects had been hospitalized at least once due to within 24 months prior to enrolment; the mean (SD) duration of hospitalization due to a psychiatric disorder was 94.2 days. The PP3M and PP1M treatment groups were generally similar and well balanced with respect to diagnosis and severity, except for the mean (SD) duration of psychiatric hospitalization, which at study entry was numerically longer in the PP3M group than in the PP1M group (96.4 vs. 88.5 days).

Study PSY-3012

More male (75%) than female (25%) subjects were enrolled in the study and the majority of subjects were white (59%), with a mean (SD) age of 38.4 (11.15) years (range: 18 to 68 years). Based on BMI, 44% of subjects were classified as having normal body weight; 33% of subjects were overweight, and 24% were obese.

At Open-label baseline, the mean (SD) PANSS total score was 74.0 (15.43) (range: 33 to 114).

About 77% of subjects had been hospitalized at least once due to psychosis 24 months prior to enrollment; the median duration of hospitalization due to a psychiatric disorder was 32.0 (range: 1 to 2880) days. At Double-blind baseline, the psychiatric characteristics of subjects in the Placebo and PP3M groups were generally similar, except for the mean (SD) duration of psychiatric hospitalization, which at study entry was numerically higher in the Placebo group than in the PP3M group (106.2 [322.88] vs. 80.7 [161.47]), which should be interpreted with caution because of large and unbalanced standard deviations and the imputation of missing dates/months.

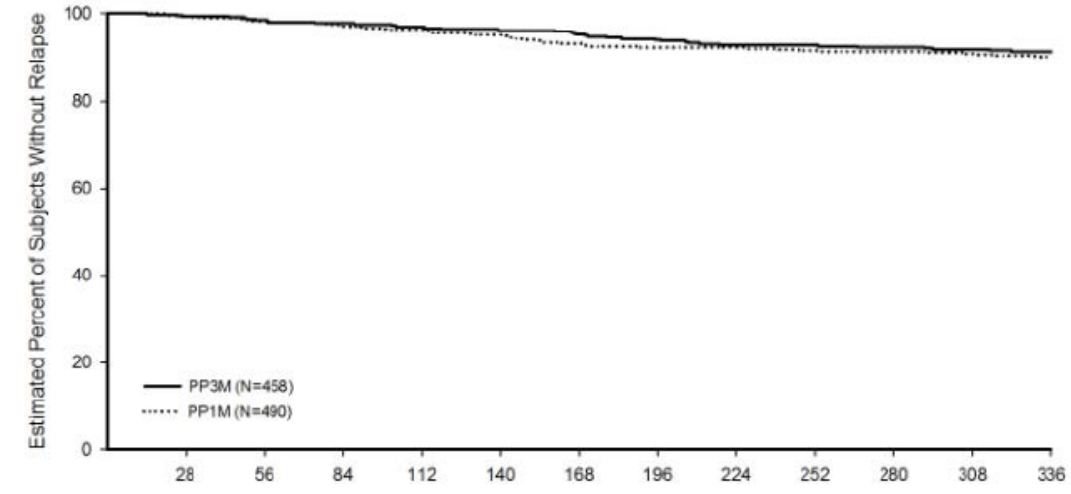
Main results

Primary endpoint

In study PSY-3011, the percentage of subjects who experienced a relapse during the DB phase in both the PP3M and PP1M groups was 8% and 9%, respectively. The estimated difference (95% CI) between the treatment groups (PP3M-PP1M) in percentages of subjects who remained relapse free was 1.2% (-2.7%, 5.1%) demonstrating that PP3M was non-inferior to PP1M.

With regards to time to first relapse for PP3M- and PP1M-treated subjects, no pattern was observed to indicate the occurrence of more relapses around trough levels of PP3M compared to PP1M (Figure 4).

Figure 4: Kaplan-Meier Plot of Time to Relapse During the Double-blind Phase
(Study R092670-PSY-3011: Per-protocol Analysis Set)



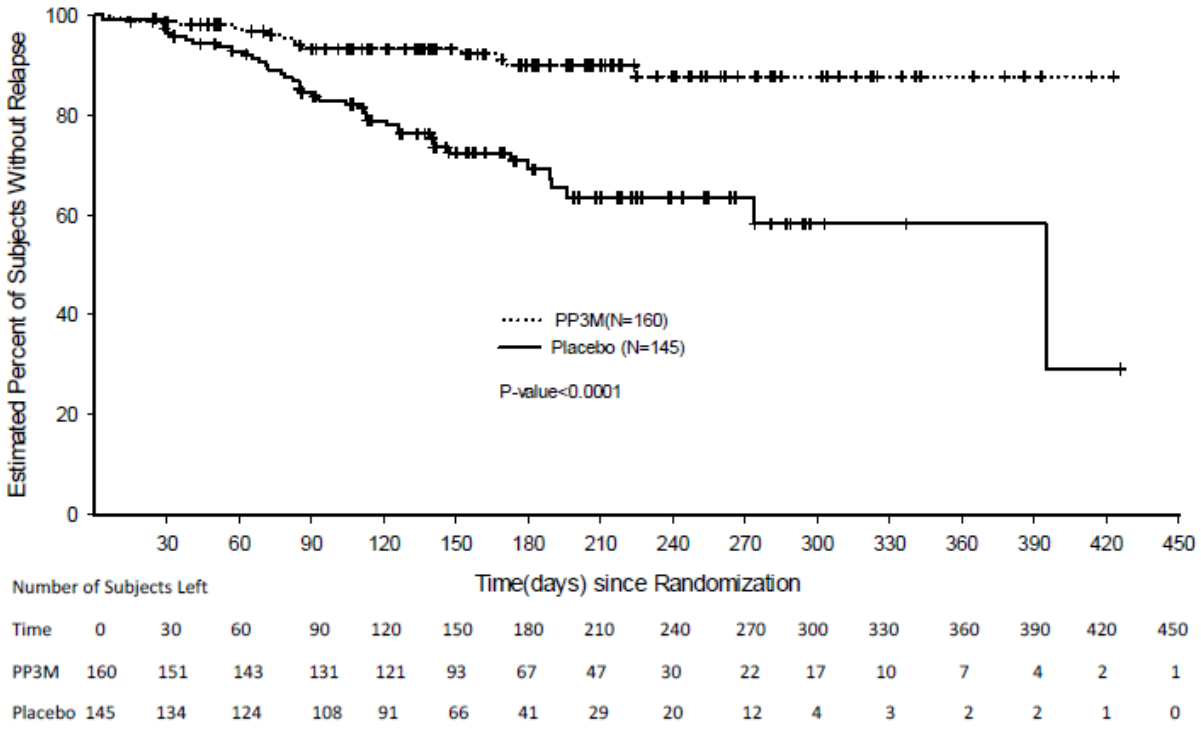
Number of Subjects Left

Time	0	28	56	84	112	140	168	196	224	252	280	308	336
PP3M	458	454	441	425	419	406	394	386	372	368	361	353	244
PP1M	490	483	470	454	442	432	416	405	397	384	376	367	223

The most common reasons for relapses were an increase of ≥25% in total PANSS score (23 subjects [5%] in the PP3M group and 24 subjects [5%] in the PP1M group) and psychiatric hospitalizations (16 subjects [3%] in the PP3M group and 22 subjects [4%] in the PP1M group).

Study PSY-3012 resulted in a statistically significant difference in time to relapse between treatment groups in favour of PP3M ($p<0.0001$) (as presented in Figure 5). Three times as many subjects in the Placebo group (29.0%) as compared to the PP3M group (8.8%) experienced a relapse event. The 25% quantile of time to relapse and median time to relapse were 141 days and 395 days, respectively, for the Placebo group but were not estimable for the PP3M group.

Figure 5: Kaplan-Meier Plot of Time to Relapse During the Double-Blind Phase - Final Analysis
(Study R092670-PSY-3012: ITT (DB) Analysis Set)



Number of Subjects Left

Time	0	30	60	90	120	150	180	210	240	270	300	330	360	390	420	450
PP3M	160	151	143	131	121	93	67	47	30	22	17	10	7	4	2	1
Placebo	145	134	124	108	91	66	41	29	20	12	4	3	2	2	1	0

The most common reasons for relapses were an increase of ≥25% in total PANSS score (34 subjects [23%] in the Placebo group vs. 10 subjects [6%] in the PP3M group) and psychiatric hospitalizations (10 subjects [7%] in the Placebo group vs. 2 subjects [1%] in the PP3M group).

Secondary endpoints

PANSS Total Score

In study PSY-3011, the mean (SD) change from Double-blind baseline to Double-blind endpoint (LOCF) in PANSS total scores was -3.5 (12.50) and -4.3 (11.78) in the PP3M and PP1M groups, respectively. The between the treatment groups (PP3M-PP1M) change in PANSS total score at End Point (DB) was 0.9 (-0.61, 2.34).

The mean PANSS total score in study PSY-3012 increased in the Placebo group from Double-blind baseline to Double-blind end point (Mean [SD]: 6.7 [14.40]) (indicating worsening), while the mean PANSS total score numerically decreased in the PP3M group (Mean [SD]: -0.5 [8.36]). The mean change in Placebo group at Double-blind end point was statistically significantly greater than the PP3M group ($p<0.001$).

CGI-S

The mean (SD) change from Double-blind baseline to Double-blind end point in the CGI-S score in study PSY-3011 was -0.1 (0.84) in the PP3M group and -0.1 (0.75) in the PP1M group, with the LS-Means difference (95% CI) between the treatment groups (PP3M-PP1M) in change scores at Double-blind end point of 0.0 (-0.05, 0.13).

In study PSY-3012, the mean (SD) change during the Double blind period in the CGI-S score was 0.4 (0.87) and 0.1 (0.6) in the Placebo and PP3M group, respectively. The analysis of covariance of change in

CGI-S scores showed a significant difference (p<0.001) between the two groups in favor of the PP3M group.

PSP

The mean (SD) change in the PSP score in study PSY-3011 was 1.3 (10.22) in the PP3M group and 1.9 (9.21) in the PP1M group. The LS means difference (95% CI) between the treatment groups (PP3M-PP1M) in change scores at Double-blind end point was -0.5 (-1.73, 0.64).

In study PSY-3012, a statistically significant difference was observed with treatment (p=0.002), country (p<0.001), and baseline PSP score (p<0.001) using the repeated measures model. At Weeks 24 and 36 (DB), a statistically significant difference (p=0.029, p=0.014 respectively) was noted for the comparison between the PP3M and Placebo groups. At Week 48 (DB), the p-value for comparing PP3M versus Placebo was 0.219. The test results at and beyond Week 48 (DB) should be interpreted with caution due to a limited number of subjects at these time points (n=22 at Week 48 [DB]).

Clinical studies in special populations

N/A

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

N/A

Supportive study(ies)

N/A

2.4.1. Discussion on clinical efficacy

Design and conduct of clinical studies

The two phase 3 studies, Study R092670-PSY-3011 and R092670-PSY-3012, were planned and initiated in parallel.

Study PSY-3011 was a 48-week, double-blind non-inferiority study to compare the efficacy of the new 3-month injectable paliperidone palmitate formulation (PP3M) against the existing 1-month injection formulation (PP1M) in preventing relapse of the symptoms of schizophrenia in subjects who were first stabilized on PP1M for 17 weeks (4 months). The primary efficacy endpoint was the percentage of subjects who had not relapsed at the end of the 48-week Double-blind Phase. This was determined using the Kaplan-Meier 48-week cumulative estimate (i.e., percentage of subjects remaining relapse free). The predefined non-inferiority margin proposed for the study was 15% based on the historical placebo-controlled studies and expert advice, while the CHMP indicated a preference for a non-inferiority margin of 10%.

The CHMP noted some study design characteristics for study PSY-3011, including assay sensitivity that has been inferred using placebo information from other studies, and enrichment strategy as a limiting factor for the indication which should be clearly reflected in the SmPC.

During the Double-blind (DB) Phase of the study, 21 subjects received only approximately 75% of the intended dose due to a manufacturing issue (insertion of a short plunger). This manufacturing defect only affected subjects in the PP3M group. The decision was to maintain these subjects in the study and to maintain the blind. During the study, neither the investigators nor the Sponsor knew which arm of the

study the manufacturing issue impacted; only after database lock was it known to have impacted only the PP3M group. These 21 subjects were excluded from the analysis set. This approach was considered acceptable by the CHMP.

Study PSY-3012 was a multicentre, double-blind, placebo-controlled, long-term, randomised withdrawal study comparing PP3M to placebo. The Double-blind Phase was of variable duration; subjects could remain in the Double-blind Phase until they experienced a relapse event (based on prospectively defined criteria), meet discontinuation/withdrawal criteria, or pre-defined study conclusion criteria were reached. The primary efficacy endpoint was the time between subject randomisation into the Double-blind Phase and the first documentation of a relapse event.

The criteria used to define relapse were identical in both studies and also to those used in the PP1M development program. There were some differences between study PSY-3011 and 3012 including the assumptions made at the planning stage concerning expected withdrawal rates before randomisation (approximately 25% in PSY3011 and 50% in PSY3012) and relapse rates (after 48 weeks/12 months with PP3M; >30% in PSY3011 and approximately 20% in PSY3012). These need to be considered in the light of the added maintenance phase in PSY3012 that implied a further selection of subjects before randomisation and hence, fewer subjects were expected to experience a relapse.

Both randomisation and blinding procedures seem appropriate (both studies). However, placebo injections used for masking in the PP3M treatment group in study PSY-3011 constrained the evaluation of the PP3M treatment that is intended to be given once every 3 months. It is considered that the PP3M treatment effect is mixed with a certain unknown placebo effect due to the monthly placebo injections when active medication is not given. To be randomised into the DB phase in PSY3012, subjects (besides having completed the transition phase) had to meet a number of pre-defined “clinical stability criteria” at three clinic visits (week 4, 8 and 12) during the 12 weeks Maintenance phase (i.e. week 21, 25 and 29 in the study) after having received one injection PP3M at the time of entering the Maintenance phase (i.e. week 17 in the study). Given the randomised withdrawal design in order to assess PP3M as maintenance treatment in the prevention of relapse, the randomisation of subjects meeting a number of pre-defined stabilization criteria is per se appropriate.

In general, the statistical methods used were acceptable in both studies. In PSY-3012, an interim efficacy analysis was conducted and seems to have been appropriately planned and performed; an independent Statistical Supporting Group was used for data handling and analysis with the review of the analysis to be performed by the IDMC.

Overall, 1429 subjects were enrolled into study PSY-3011 and dosed in the open-label (OL) phase, and 1016 subjects were randomized in the DB phase of the study. Of the 995 mITT (DB) subjects, 483 subjects were in the PP3M group and 512 subjects were in the PP1M group. A total of 824 subjects (83%) completed the study. Per the protocol, subjects who had relapses during the DB phase were considered having completed the study. The percentage of subjects who completed the study was similar in the PP3M and PP1M groups. Study PSY-3011 was clearly over-dimensioned. The PP population in the DB phase included additional 188 subjects on the top of the 380 evaluable subjects per treatment arm that were initially planned. While a non-inferiority margin of 15% was assumed in the sample size calculation, it is possible that the intentional over-recruitment allowed for a comparison with a smaller non-inferiority margin. The number of subjects was not well balanced across the treatment groups, probably due to the large block-size and several centres that included only a few subjects. The CHMP noted that the risk for imbalance could have been minimized in the planning stage of the study.

In study PSY-3012, all randomised subjects were included in the ITT (DB) analysis set. The ITT (DB) analysis set for the interim analysis included all subjects who qualified for inclusion into the ITT (DB)

analysis set at the time of the interim analysis data cut-off and comprised 283 subjects (Placebo, n=135; PP3M, n=148). The ITT (DB) analysis set for the final analysis included 305 subjects (Placebo, n=145; PP3M, n=160). The imbalance in treatment assignment seen also in study PSY3012 has been justified by the MAH as due to that a varying number of subjects were recruited at the sites implying that randomisation was not always balanced within centres.

Efficacy data and additional analyses

The results of the primary efficacy endpoint and the secondary efficacy endpoints for Study PSY-3012 demonstrate that PP3M was significantly superior to placebo in delaying the relapse of symptoms of schizophrenia in adult subjects following adequate treatment with the currently marketed PP1M for 4 months. In addition, the first long term efficacy study, PSY-3011, demonstrated that PP3M is non-inferior to PP1M treatment with respect to relapse rate by week 48 following initial treatment with PP1M for 4 consecutive months.

Based on these results, the MAH proposed an indication for use of PP3M in patients suffering from schizophrenia in line with the design of studies PSY-3011 and 3012. However, the population PK simulations provided by the MAH supports the possibility of an earlier switch to PP3M following two initial doses of PP1M at day 1 and day 8 already at week 5. The timing of the initiation of PP3M could be based on the clinical decision of treating physician given the knowledge of other antipsychotics' (risperidone and paliperidone palmitate) systemic exposure, efficacy and safety.

It was furthermore acknowledged that the maintenance dosage with paliperidone palmitate needs to be established and maintenance of safety and efficacy of the treatment during three months with PP3M should not be risked. It should also be considered that treatment with a non-optimised dose may compromise the benefit/risk of the treatment during 3 months after a psychotic episode. On the other hand, the possibility of initiating the PP3M treatment earlier for patients who are stabilized and maintained at the right dose according to the clinical judgment of the treating physician should not be disregarded by restricting the indication with requirement of 4 months of pre-treatment with PP1M. The need for dose adjustment or choice of treatment between PP1M and PP3M could be based on the clinical stability of the patient in terms of safety and efficacy judged by the treating physician. This is also supported by the dosing data over time in study reports (PSY-3011 and 3012) provided by the MAH. During the open-label period of the study PSY-3011, flexible dosing for PP1M was allowed only at week 5 and week 9. At week 13 subjects received the dose of PP1M that was administered at week 9. A change in dose from Week 9 to Week 13 led to withdrawal from the studies. Although the change in dosing groups over time reflects dose adjustments and withdrawal of subjects, there were no substantial shifts in proportion of patients in each dosing group between week 5 and week 9 during this period that flexible dosing was allowed. The proportion of patients in each dosing groups were rather stable between week 5 and 9. This data (although slightly complicated by the withdrawals) points towards the evidence that dose adjustments have not been needed for the majority of the patients who participated in studies PSY-3011 and PSY 3012. The indication for Trevicta should reflect this, i.e. switching to the 3-months injection formulation in patients clinically stable on a 1-month formulation.

The study results in PSY-3011 showed that PP3M treatment was not less effective than PP1M in the limited studied population. The statistical methods were acceptable in general, although a concern was raised regarding the robustness of the primary endpoint analysis, and additional sensitivity analyses have been requested by the CHMP and were provided by the MAH.

Thirty-seven subjects (8.1%) in the PP3M group and 45 subjects (9.2%) subjects in PP1M group experienced a relapse event during the Double-blind Phase. The median time to relapse (median survival time refers to the time at which the cumulative survival function equals 0.5 [or 50%]), was not estimable

for either the PP3M or the PP1M group. The estimated difference (95% CI) between the treatment groups (PP3M-PP1M) in percentages of subjects who remained relapse free was 1.2% (-2.7%, 5.1%). The lower bound of the 95% CI (-2.7%) was larger than the pre-specified non-inferiority margin of -15%, but also -10%, demonstrating that PP3M was non-inferior to PP1M.

The primary analysis was based on a high level of censored data, which resulted in a less reliable estimate of treatment effect. Therefore, robustness of the results was further explored by a responder analysis of relapse-free rates between the treatment groups using Fisher's Exact test and confidence interval based on binomial distribution. Based on this analysis, the lower bound of the 95% confidence interval of the difference between the treatment groups (PP3M-PP1M) in the percentages of subjects who remained relapse free is -2.15%, which is above the CHMP-preferred non-inferiority margin. The result is thus consistent with the results based on the Kaplan Meier analysis.

The percentage of relapse events in the PP3M treatment group was similar in both study PSY3011 and PSY3012. Assay sensitivity has been inferred, relying also on the information from study PSY3001, (52-week study aimed at demonstrating XEPLION's superiority over placebo in preventing schizophrenic relapses), where the relapse rate observed in the PP1M group (~10%) was comparable with the relapse event for PP1M in the PSY3011 study (~9%). Quite few relapse events were registered in PP3M and PP1M treatment group (8% and 9%, respectively, in the PP analysis set), which ultimately indicates that both PP1M and PP3M are effective treatments, but could also mask insufficiency in the definition of relapse event, study duration or conduct. For illustration, it can be noted that nearly 60% of the study population included in the DB phase have had at least one hospitalization for psychosis within the recent 24 months prior to study start, while only 4% of subjects had psychiatric hospitalization during the DB phase. Number of subjects who completed the study without a relapse was 75% and 74%, respectively, in the PP3M and PP1M treatment groups, and the rest of the subjects (17% in each group) withdrew prematurely.

As mentioned, the Kaplan-Meier analysis was based on a high level of censored data (>90%), making the survival curves less reliable. Among the censored data, relatively large percentage of withdrawn subjects could potentially be considered as treatment failure. The censored data were initially not shown as tick marks in the Kaplan-Meier plots, and a discrepancy was noted between the numbers of subjects left in the figures and the completion/withdrawal tables. The figures were updated to illustrate the censored observations and the discrepancy between the numbers in the figures and tables is explained by the fact that the end-of-study visit at Week 48 could have occurred before the last time-point in the Kaplan-Meier figure (Day 336). An additional analysis was also performed of time to withdrawal using Kaplan-Meier methods and showed no apparent difference in time to discontinuation between the PP3M and PP1M treatment, which is in line with the overall efficacy conclusions.

To confirm the primary analysis performed on the Per-protocol analysis set, the mITT (DB) population was analysed, including all subjects who were randomly assigned to treatment during the DB phase, received at least 1 dose of double-blind study drug, and had no errors in the delivery of active treatment due to the manufacturing of the investigational product. This modification of the ITT based on a specific protocol deviation did not allow for an indication of the treatment effect in subsequent practice, which is one of the main purposes of the ITT approach. Similarly, the mITT (DB) Sensitivity analysis set cut the analysis set even further, and was not considered more general than the mITT (DB). A re-run of the primary analysis was therefore performed upon a CHMP requested based on the ITT analysis set that includes all randomized subjects in the DB phase who received at least 1 dose of the study drug. Based on this ITT analysis, the Kaplan-Meier estimate of the difference between the treatment groups (PP3M-PP1M) in the percentages of subjects who remained relapse free is 1.6% with the lower bound of the 95% CI at -2.1%, which is above the CHMP-preferred non-inferiority margin, and consistent with the

results reported in the CSR for the per protocol analysis set and for the mITT (DB) analysis set.

Concerning the primary endpoint and missing values a few clarifications were needed in the definition of the relapse event. One of the conditions used to define a relapse event is psychiatric hospitalization. According to the statistical analysis plan, if the start date was completely missing or if year was missing for hospitalization collected in the Health Resource Utilization Questionnaire, no imputation of dates was performed, and for adverse events, no imputation of partial or completely missing dates was to be done, but handling of missing hospitalisation dates in the Evaluation of Relapse Form was not described. However, the MAH has clarified that there were no missing psychiatric hospitalization dates in the Evaluation of Relapse Form for Study PSY-3011 or Study PSY-3012.

Regarding handling of missing values of the PANSS, it was confirmed that no imputation of missing values was used for the PANSS total score when used to derive the primary endpoint. Last observation carried forward (LOCF) was used for the missing PANSS total scores in the secondary analysis (change from baseline endpoint).

In study PSY-3012 the interim efficacy analysis was performed as planned when 42 relapse events (60% of the projected 70 relapse events) had occurred during the Double-blind Phase at the time the study was stopped based on positive results in favour of PP3M and, in accordance with recommendation of the IDMC. At early termination, more subjects in the PP3M, 83.8% (134/160), than in the placebo group 55.2% (80/145) was still ongoing in the study. Hence, more subjects in the placebo group than in the PP3M group had discontinued with the difference foremost due to the number of subjects experiencing a relapse. The final analysis of the relapse data further confirmed the findings of the interim analysis with a statistically significant difference between treatment groups in favour of PP3M ($p<0.0001$).

The instantaneous risk (hazard ratio) of relapse of schizophrenia symptoms was in the interim analysis 3.45 (95% CI: 1.73, 6.88) times higher for a subject switching to placebo than for a subject continuing to receive PP3M indicating that there was a 71% decrease in relapse risk with continued PP3M treatment. Three times as many subjects in the placebo group (29.0%) as in the PP3M group (8.8%) experienced a relapse event. In the final analysis, the instantaneous risk of relapse was 3.81 (95% CI: 2.08, 6.99) times higher for a subject switching to placebo than for a subject continuing to receive PP3M indicating that there was a 74% decrease in relapse risk with continued PP3M treatment.

There was a high level of censored data also in study PSY-3012, in the PP3M arm of the same magnitude as seen in PSY-3011, here however, more easily accepted considering the difference between groups in the proportion of censored cases and the main reason thereof, i.e. the difference in number of subjects experiencing a relapse. The randomisation of subjects was still ongoing at the time of the interim analysis and the last subject was randomised approximately only one month before the date for study completion. This implied that the analyses included also subjects with limited follow-up and hence, limited time at risk to experience a relapse. Based on the assumption that the randomisation of subjects was similar over time in both arms, this may rather imply that the analysis could have been biased toward futility and hence, of more concern in a non-inferiority than superiority study. However, to further clarify time to early discontinuations for reasons besides relapses, an analysis of early discontinuation not including relapses was requested. In addition, the MAH was asked to also clarify follow-up time in the DB phase for each treatment group respectively (overall and among those who were still in the study at study completion/early termination). A new analysis and clarifications have been provided by the MAH that confirms the differences seen between the treatment arms. The median (minimum; maximum) treatment duration was 146.0 (16; 426) days in the Placebo group and 169.0 (8; 463) days in the PP3M group representing follow-up time for the overall (ITT [DB]) population. The duration of total exposure among those who were still in the study at early termination was shown to be similar between the two groups; the median (minimum; maximum) treatment exposure was 168.0 (29; 426) days in the placebo group

and 176.0 (15; 463) days in the PP3M group.

In addition to the primary analysis of time to relapse, further analyses based on Cox proportional hazards model were conducted showing consistent outcomes irrespective of subgroup although based on a limited number of subjects.

2.4.2. Conclusions on the clinical efficacy

Concerns regarding the primary endpoint analysis and withdrawals (study PSY-3011) are considered solved with the additional analyses and satisfactory clarifications provided by the Applicant. Additional analyses have as requested, also been provided for study PSY-3012 and raises no concerns.

The efficacy of the new 3-month paliperidone palmitate injectable formulation PP3M has been investigated in 2 phase III clinical studies with fixed dosing treatment regimens. The relapse prevention study showed a significant reduction in risk for relapse of schizophrenia symptoms when treated with PP3M compared to placebo. The observed relapse rate for PP3M was comparable with the 1-month paliperidone palmitate injection (PP1M) in the same study or between studies and in good agreement with historical data from other anti-psychotics. Different pop PK switching scenarios from oral paliperidone to PP3M have been performed and did support an earlier switch than 4 months.

Considering the totality of data, the CHMP concluded that maintenance of effect with PP3M has been demonstrated. Based on population PK, safety and efficacy and the clinical experience with risperidone and/or paliperidone, an earlier switch from PP1M to PP3M than 4 months, although not investigated in the Phase III studies, seemed to be possible. Thereby the CHMP considered that the switch from PP1M to PP3M could be based on the clinical stability of the patient in terms of safety and efficacy as judged by the treating physician. This was reflected in the final indication.

Overall, the CHMP concluded that the clinical efficacy data were adequate to support the present application for the new 3-monthly paliperidone palmitate injectable formulation of Trevicta in the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product.

2.5. Clinical safety

The clinical safety is based on results from 3 clinical studies of PP3M in adults with schizophrenia (PSY-3011, PSY-3012, and PSY-1005) or schizoaffective disorder (PSY-1005 only) with differing exposure to PP3M. Subjects in study PSY-1005 received only a single dose of PP3M, while the mean duration of exposure to double-blind treatment with PP3M was longer in study PSY-3011 (295.1 days) and in study PSY-3012 (175.1 days). The study population in long-term studies is considered representative of the patient population for applied PP3M indication.

Patient exposure

The estimated number of adult patients with schizophrenia who have received at least 1 dose of PP3M across the 3 clinical studies is 1,191 (combined exposure of 567.6 patient years).This includes 504 who received exposure to PP3M in Study PSY-3011 (at least 1 dose in DB phase), 379 who received exposure to PP3M in Study PSY-3012 (at least 1 dose in Maintenance phase), and 308 who received a single dose of PP3M in Study PSY-1005. Across Studies PSY-3011 and PSY-3012, a total of 319 subjects (291 from PSY-3011, 28 from PSY-3012) received at least 48 weeks of exposure to PP3M.

Adverse events

The list of adverse events observed during studies is in line with what is already known for the substance paliperidone palmitate and does not differ significantly between PP1M and PP3M. The most frequent adverse events included psychiatric disorders (schizophrenia, anxiety, insomnia), weight gain, injection site reactions, nervous system disorders (headache, akathisia), nasopharyngitis is reflected in the SmPC.

Study PSY3011

A total of 846 (59.2%) subjects reported at least 1 treatment emergent adverse event (TEAE) during treatment with PP1M in the 17-week Open-label phase of Study PSY-3011 (Table 5). The most common TEAEs were psychiatric disorders. During the DB of PSY-3011, the overall rates of TEAEs, rates of TEAEs in all MedDRA system organ classes (SOCs), as well as those of common individual TEAEs were well balanced between the PP3M and PP1M groups. Weight increased was the most frequently reported TEAE in both treatment groups. In both groups, most TEAEs were considered to be mild or moderate in severity, with few individual TEAEs reported as severe in more than 1 subject each. The higher proportion of subjects with abnormal weight gain in the Double-blind Phase of Study PSY-3011 compared with Study PSY-3012 has been discussed and explained by longer duration of exposure in this study with contribution of increased tendency of patients originated from Asia showing a higher tendency of experiencing weight gain. The observed adverse events during both phases of the Study PSY-3011 are line with what is already known for the substance paliperidone palmitate and does not differ significantly between PP1M and PP3M.

Table 5: Treatment-emergent Adverse Events in 5% or More of Subjects During Open-label Phase or in Either Treatment Group of Double-blind Phase (Study R092670-PSY-3011: ITT [OL] and Safety Analysis Sets)

	Open-label Phase	Double-blind Phase	
Body System or Organ Class/ Dictionary-derived Term	PP1M (N=1429)	PP3M (N=504)	PP1M (N=512)
Total subjects with TEAE, n (%)	**846 (59.2)**	**342 (67.9)**	**340 (66.4)**
General disorders and administration site conditions, n (%)	**220 (15.4)**	**51 (10.1)**	**35 (6.8)**
Injection site pain	127 (8.9)	12 (2.4)	14 (2.7)
Infections and infestations, n (%)	**175 (12.2)**	**82 (16.3)**	**81 (15.8)**
Nasopharyngitis	66 (4.6)	36 (7.1)	33 (6.4)
Investigations, n (%)	**137 (9.6)**	**143 (28.4)**	**152 (29.7)**
Weight increased	64 (4.5)	105 (20.8)	109 (21.3)
Nervous system disorders, n (%)	**256 (17.9)**	**66 (13.1)**	**67 (13.1)**
Akathisia	82 (5.7)	20 (4.0)	14 (2.7)
Headache	46 (3.2)	18 (3.6)	26 (5.1)
Psychiatric disorders, n (%)	**328 (23.0)**	**89 (17.7)**	**85 (16.6)**
Anxiety	83 (5.8)	27 (5.4)	24 (4.7)
Insomnia	96 (6.7)	16 (3.2)	24 (4.7)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Key: PP1M=paliperidone palmitate 1-month; PP3M=paliperidone palmitate 3-month; TEAE=treatment-emergent adverse event.

Study PSY-3012

A total of 330 (65.2%) subjects reported at least 1 TEAE during treatment with paliperidone palmitate (PP1M or PP3M) during the 29-week open-label Transition/Maintenance phases of Study PSY-3012. The most common were psychiatric disorders (Table 6). During the DB phase of PSY-3012, TEAEs were reported at rates of 61.9% and 57.9% for the PP3M and placebo groups. Of note, psychiatric disorder TEAEs (eg, anxiety, insomnia, schizophrenia) were more frequent in the placebo group than in the PP3M group during the DB phase, likely related to exacerbation of the underlying psychotic disorder (amounting to a relapse for efficacy analysis) after switching from PP3M to placebo. For most of the other common TEAEs in the DB phase, reporting rates were similar or lower in the PP3M group compared with the placebo group (Table 6). The TEAEs that occurred more frequently in the PP3M group compared to the placebo group (≥3% difference in rates) were increased weight, headache, nasopharyngitis, and akathisia. In both treatment groups, most TEAEs were considered to be mild or moderate in severity.

During the open-label phase of the study PSY-3011 three studies had experienced hypersensitivity reactions with PP1M of which one was considered as an SAE. During the double-blind phase study-3012 of study PSY-3012 one subject is listed to have experienced hypersensitivity reaction with PP3M. According to the narrative provided for the subject listed to have experienced hypersensitivity reaction with PP3M during double-blind phase of study PSY-3012, this reaction was not related to the PP3M treatment.

Table 6: Treatment-emergent Adverse Events in 5% or More of Subjects During Transition/Maintenance Phases or in Either Treatment Group of Double-blind Phase (Study R092670-PSY-3012: ITT [OL] and Safety Analysis Sets)

Body System or Organ Class/ Dictionary-derived Term	Open-label Trans. / Mainten. Phase Paliperidone Palmitate (N=506)	Double-blind Phase Placebo (N=145)	Double-blind Phase PP3M (N=160)
Total subjects with TEAE, n (%)	**330 (65.2)**	**84 (57.9)**	**99 (61.9)**
General disorders and administration site conditions, n (%)	**85 (16.8)**	**6 (4.1)**	**11 (6.9)**
Injection site pain	44 (8.7)	0	2 (1.3)
Infections and infestations, n (%)	**53 (10.5)**	**16 (11.0)**	**28 (17.5)**
Nasopharyngitis	14 (2.8)	2 (1.4)	9 (5.6)
Investigations, n (%)	**72 (14.2)**	**25 (17.2)**	**27 (16.9)**
Weight increased	51 (10.1)	5 (3.4)	14 (8.8)
Weight decreased	8 (1.6)	11 (7.6)	2 (1.3)
Psychiatric disorders, n (%)	**147 (29.1)**	**46 (31.7)**	**30 (18.8)**
Anxiety	44 (8.7)	16 (11.0)	13 (8.1)
Insomnia	50 (9.9)	17 (11.7)	11 (6.9)
Schizophrenia	16 (3.2)	15 (10.3)	2 (1.3)
Nervous system disorders, n (%)	**95 (18.8)**	**10 (6.9)**	**25 (15.6)**
Headache	33 (6.5)	6 (4.1)	14 (8.8)

Note: Incidence is based on the number of subjects experiencing at least 1 adverse event, not the number of events.
Mainten.=maintenance; PP3M=paliperidone palmitate 3-month; TEAE=treatment-emergent adverse event; Trans.=transition.

Study PSY-1005

Among subjects who received a single dose of PP3M in Study PSY-1005, the common TEAEs were consistent with those observed in Studies PSY-3011 and PSY-3012, although the overall rates of TEAEs and rates of TEAEs by MedDRA SOCs were numerically higher in Study PSY-1005. This observation is likely the result of the concomitant use of other antipsychotics among all subjects in PSY-1005 and the extended post-treatment follow-up period after dosing in this Phase 1 study.

A total of 47 adverse drug reactions (ADRs) were identified for PP3M which all have previously been identified as ADRs for paliperidone and/or risperidone (which is metabolised to the primary active metabolite paliperidone) and are listed for the respective centrally approved products.

Infections and infestations: Cystitis, Upper respiratory tract infection, Urinary tract infection

Blood and lymphatic system disorders: Anaemia

Metabolism and nutrition disorders: Blood triglycerides increased, Decreased appetite, Diabetes mellitus, Hyperglycemia, Hypertriglyceridemia, Increased appetite, Weight decreased, Weight increased

Psychiatric disorders: Anxiety, Depression, Insomnia

Nervous system disorders: Akathsia, Dyskinesia, Dystonia, Headache, Parkinsonism, Sedation/somnolence, Tardive dyskinesia, Tremor

Eye disorders: Vision blurred

Cardiac disorders: Bradycardia, Postural orthostatic tachycardia syndrome, Tachycardia

Vascular disorders: Hypertension, Hypotension, Orthostatic hypotension

Gastrointestinal disorders: Constipation, Diarrhea, Nausea, Vomiting

Hepatobiliary disorders: Transaminases increased

Skin and subcutaneous tissue disorders: Eczema, Pruritus, Rash

Musculoskeletal and connective tissue disorders: Back pain

Reproductive system and breast disorders: Amenorrhea, Breast pain, Galactorrhea, Gynaecomastia, Menstrual disorder

General disorders and administration site conditions: Chest discomfort, Fatigue, Injection site reaction

Since PP1M and PP3M both share the same pro-drug and active metabolite as well as the same route of administration and formulation characteristics, the MAH proposed that the calculation of ADR frequencies in the proposed PP3M SmPC be based on the incidence of ADRs in clinical studies for PP1M and PP3M combined which is endorsed by the CHMP.

No new safety concerns have been raised related to adverse events of special interest and no apparent difference between PP3M and PP1M was reported. Adverse events of special interest included suicidality, aggression or agitation, somnolence and sedation, seizures and convulsions, extrapyramidal symptoms, neuroleptic malignant syndrome, adverse events suggestive of proarrhythmic potential, QT prolongation-related adverse Events, other cardiovascular- and cerebrovascular-related adverse events, orthostatic hypotension and tachycardia based on vital sign measurements, electrocardiographic changes, potentially prolactin-related adverse events and laboratory changes, metabolic effects, body weight changes, injection site-related events). The reflection of these ADRs in the SmPC was considered adequate.

Adverse events of special interest

Psychiatric and nervous system-related adverse events

Suicidality

There were no reports of completed suicide among the 1,191 subjects treated with PP3M across the completed clinical studies, PSY-3011, PSY-3012, or PSY-1005. There was 1 death due to suicide attempt (overdose of clozapine) during the DB phase of Study PSY-3011 in the PP1M group; a second death in the PP1M group in this study was a possible suicide attempt (ie, toxicity to ingestion of various agents). Suicidality-related events were not common in the Phase 3 studies with PP3M. During the DB phases, suicidality-related TEAEs were reported for 1.8% of subjects each (n=9 each) in the PP3M and PP1M groups in Study PSY-3011, and for 1.3% (n=2) and 2.1% (n=3) of subjects in the PP3M and placebo groups, respectively, in Study PSY-3012. Most of these events consisted of suicidal ideation. Suicidality-related events led to study drug discontinuation for 1 subject each in the PP3M and PP1M groups in PSY-3011 and for no subject in Study PSY-3012. Further, the C-SSRS assessments yielded no evidence of worsening in suicidal ideation or behaviour over the course of either Phase 3 study.

Seizures and Convulsions

Seizure-related AEs were reported at incidences of less than 1% across the completed Phase 2/3 studies with PP1M. Subjects with significant or unstable neurological disease, including a seizure disorder, were excluded from participating in the clinical studies with PP3M. Across the 3 completed studies with PP3M (PSY-3011, PSY-3012, or PSY-1005), there were no AEs suggestive of a seizure or convulsion-related event among subjects exposed to PP3M.

Extrapyramidal Symptoms

Results from all analyses indicated that the incidence of EPS-related TEAEs was low.

During the DB phase of Study PSY-3011, reporting rates for EPS-related TEAEs were similar for the PP3M (8.3%) and PP1M (7.4%) groups, with the most common events in both treatment groups categorized under hyperkinesia (akathisia 4% in PP3M vs 2.7% in PP1M group) and parkinsonism (3.3% in PP3M vs 3.3). None of the EPS-related TEAEs in subjects exposed to PP3M in Study PSY-3011 were serious. A similar low percentage of subjects in the PP3M (n=3, 0.6%) and PP1M (n=2, 0.4%) groups were discontinued from study treatment due to an EPS-related event.

During the Maintenance phase for Study PSY-3012, 12 (3.2%) subjects had EPS-related events after injection of PP3M, with events under the categories of hyperkinesia (1.6%) and Parkinsonism (1.3%) being the most common. In the DB phase of PSY-3012, the incidence of EPS-related TEAEs in subjects maintained on PP3M (8.1%) was higher than that reported in subjects switched to placebo (3.4%). Again, events under the groups of hyperkinesia (5.0%, consisting mainly of akathisia [4.4%]) and Parkinsonism (3.8%) were the most common events in the PP3M group during the DB phase. None of the EPS-related TEAEs reported following PP3M treatment in the Maintenance or DB phase were serious; 1 subject was discontinued from the Maintenance phase due to an event of restlessness.

An examination of the time to EPS-related TEAEs during the DB phases of PSY-3011 or PSY-3012 showed no clustering of these events at visits that would be expected to correspond to peak median plasma concentrations of paliperidone for subjects randomized to PP3M.

There were no reports of tardive dyskinesia in the completed Studies PSY-3012 or PSY-1005. In Study PSY-3011, tardive dyskinesia was reported during the DB phase in 1 subject receiving PP3M; this event resolved after discontinuation.

The rates of reported EPS-related TEAEs were consistent with the findings based on EPS rating scales, and there was no discernible increase in the use of anticholinergic medications relative to pre-study levels during treatment with PP3M in either Phase 3 study.

Neuroleptic Malignant Syndrome

No subject in any of the 3 completed studies with PP3M had NMS or reported as an AE. None of the identified events suggestive of distinct symptoms that could be part of the NMS presentation in subjects exposed to PP3M were serious, and for only 1 subject was treatment with PP3M withdrawn due to an identified event (extrapyramidal disorder in PSY-3011).

Cardiovascular or Cerebrovascular Safety

Cardiovascular safety data from studies of PP3M are in agreement with the findings from the PP1M clinical development program and do not provide evidence for a new safety signal. There does not appear to be an increased risk of pro-arrhythmic events for PP3M.

In none of the 3 clinical studies was there any report of the AE term ‘sudden death’ and no cases of ventricular tachycardia, ventricular fibrillation or flutter, loss of consciousness, or torsade de pointes. Furthermore, no cases of syncope (serious or non-serious) or cerebrovascular accident were reported in any subject treated with PP3M.

TEAEs related to QT prolongation were infrequent (<1%) during the DB phases of the Phase 3 studies (PSY-3011: 0.4% each in PP3M and PP1M groups; PSY-3012: 0% in DB phase). All reported events related to QT prolongation in the DB phase were non-serious and did not result in study drug discontinuation.

Low rates of tachycardia-related TEAEs were observed with PP3M, and the rates of these events were similar during the DB phase for PP3M and PP1M (2.0% and 1.8%, respectively) in PSY-3011, and for PP3M and placebo (1 subject each, <1%) in PSY-3012. During the DB phase of PSY-3011, TEAEs related to orthostatic hypotension were low and reported in fewer subjects in the PP3M group (0.4%) compared with the PP1M group (1.4%). There were no AE reports of orthostatic hypotension in the PP3M group during the DB phase of Study PSY-3012. Across all 3 studies, none of the reports of tachycardia- or orthostatic hypotension-related TEAEs were serious or resulted in discontinuation. One subject treated with PP3M in Study PSY-3011 had a TEAE of coronary artery disease during the DB phase which was not serious and did not result in treatment discontinuation.

Orthostatic Hypotension

Orthostatic Hypotension was defined as >15 bpm difference in standing minus supine pulse rate and either a decrease in systolic (>20 mmHg) or diastolic (>10 mmHg) blood pressure after standing relative to the supine position.

The incidence of orthostatic hypotension during the DB phase of Study PSY-3011 (relative to DB baseline value) was 5.8% in the PP3M group and 7.2% in the PP1M group. Similarly, orthostatic hypotension during the DB phase of Study PSY-3012 occurred at low and similar rates for the placebo and PP3M groups (<2%).

Endocrine and Metabolic Effects

Prolactin elevation

The incidence of potentially prolactin-related TEAEs during the DB phase of Study PSY-3011 was similar for female subjects in the PP3M and PP1M groups (6.5% and 5.6%, respectively), and was lower among male subjects in both treatment groups (PP3M: 2.3%; PP1M: 0.4%). None of these events during the DB phase were serious; 1 event in the PP3M group (galactorrhea) led to study drug discontinuation (compared with 4 events in the PP1M group).

During the DB phase of Study PSY-3012, there was a single report of a potentially-related prolactin TEAE (amenorrhea) in the PP3M group that was not serious and did not result in treatment discontinuation (no events in placebo group).

Serum glucose concentrations and Insulin Resistance

The proportion of subjects who had a shift from a normal glucose concentration at DB baseline to a high value during the DB phase (<100 to ≥126 mg/dL [<5.551 to ≥6.994 mmol/L]) was low and similar for the PP3M and PP1M groups in Study PSY-3011 (3% and 5%, respectively) and for the PP3M and placebo groups in Study PSY-3012 (4% and 2%, respectively).

In both Phase 3 studies and treatment groups, geometric mean values for HOMA-%B indicated a mild degree of beta-cell dysfunction at open-label baseline, while HOMA-IR geometric mean values at open-label baseline indicated a mild insulin resistance. HOMAHOMA-IR and HOMA-%B evaluations showed small directional changes consistent with normal compensatory pancreatic control, indicating that PP3M had no significant negative impact on beta-cell functioning and insulin resistance.

Hyperglycemia

During the DB phase, the occurrence of hyperglycaemia-related TEAEs was lower for the PP3M group than for the PP1M group (2.6% vs 4.9%) in Study PSY-3011, as well as lower for the PP3M group compared to the placebo group (2.5% vs 5.5%) in Study PSY-3012. One subject in the PP3M group of Study PSY-3011 had an event of diabetes mellitus on Day 1 of the DB phase that resulted in study drug discontinuation and

a second episode that resulted in hospitalization and was classified as serious; both reports of diabetes mellitus were assessed as doubtfully related to study drug.

Lipid Parameters

There were no differences between the PP3M and PP1M groups in Study PSY-3011, or between the PP3M and placebo groups in Study PSY-3012, in the proportion of subjects with treatment-emergent marked abnormalities in fasting lipid levels during the DB phase. Notably, in both studies, ≤1% of subjects in each treatment group had a marked elevation in triglycerides (≥5.7 mmol/L) during the DB phase. A marked elevation in LDL cholesterol (≥4.1 mmol/L) was observed for 8-9% of subjects in the PP3M groups of Study PSY-3011 (versus 9% for PP1M group) and PSY-3012 (vs 12% for placebo).

In Study PSY-3011, the proportion of subjects who had a shift from a normal value at DB baseline to a high value during the DB phase was similar in the PP3M and PP1M groups for total cholesterol (shift from <200 to ≥240 mg/dL [<5.172 to ≥6.206 mmol/l]) (PP3M: 2.1% vs PP1M: 1.7%), LDL cholesterol (shift from <100 to ≥160 mg/dL [<2.586 to ≥4.138 mmol/L]) (0.4% vs 0.6%), and triglycerides (shift from <150 mg/dL to ≥200 mg/dL [<1.694 to ≥2.258 mmol/L]) (11.3% vs 9.1%). HDL cholesterol values tended to decline during the DB phase in both treatment groups, and the proportion with a shift from a normal to a low value (≥40 to <40 mg/dL [≥ to <1.034 mmol/L]) was also similar in the PP3M (17.8%) and PP1M (15.8%) groups.

The proportions of subjects showing the same shifts in plasma lipid values were also similar for the PP3M and placebo in Study PSY-3012: 1.4% and 3.9%, respectively, for an increase in total cholesterol; 0% and 0.8%, respectively, for an increase in LDL cholesterol; and 13.5% and 9.4%, respectively, for a decrease in HDL cholesterol. The percentage of subjects who had a shift from a normal baseline to a high value for triglycerides (<150 to ≥200 mg/dL) during the DB phase of Study PSY-3012 was 8.1% for the PP3M group and 1.6% for placebo.

Body Weight Changes

In Study PSY-3011, the mean increases in body weight and BMI from DB baseline to DB end point in the PP3M group were smaller than those for the PP1M group (1.10 kg and 0.38 kg/m2 vs. 1.46 kg and 0.52 kg/m2).

In Study PSY-3012, the mean changes in body weight and BMI over the 29-week open-label Transition/Maintenance phases of PSY-3012 (ie, at open-label end point) were 1.42 kg and 0.48 kg/m2, respectively. Increases in body weight and BMI, albeit smaller than those seen during the initial 29 weeks of treatment with PP1M/PP3M, were also apparent during the DB phase among subjects who remained on PP3M (mean increase relative to DB baseline of 0.94 kg and 0.30 kg/m2, respectively, over a mean period of follow up of approximately 25 weeks). The weight gain seen with paliperidone palmitate (PP1M/PP3M) by the end of the Open-label phase tended to resolve following discontinuation of treatment, as subjects switched to placebo in the DB phase showed mean reductions in body weight (-1.28 kg and -0.44 kg/m2 over a mean period of follow-up of approximately 21 weeks).

The proportion of subjects with an abnormal weight gain, defined as an increase of at least 7%, occurred at similar rates for the PP3M and PP1M groups from DB baseline to end point (15% and 16%, respectively) in Study PSY-3011. In Study PSY-3012, a weight gain of ≥7% from DB baseline to end point was noted for 10% of subjects in the PP3M group compared with 1% of subjects receiving placebo. The percentages of subjects who experienced a weight decrease of ≥7% from DB baseline to end point were 7% and 4% for the PP3M and PP1M groups, respectively, in Study PSY-3011 and 1% and 8% in the PP3M and placebo groups, respectively, in Study PSY-3012. In study PSY-3011, after adjusting for exposure the event-rate

per patient year in all weight gain related TEAEs (weight increase ≥7%, weight increase related TEAE and weight gain related TEAE) did not differ as markedly during the double-blind phase of the studies.

The percentage of subjects for whom TEAEs related to weight increase were reported was similar during the DB phase for the PP3M and PP1M groups (21.6% and 21.7%, respectively) in Study PSY-3011. In Study PSY-3012, the incidence of weight increase was 8.8% and 3.4% for the PP3M and placebo groups, respectively, during the DB phase.

Most of events of weight increase during the DB phase in both Phase 3 studies were assessed as mild or moderate in severity, and none were serious. In Study PSY-3011, 1 subject (0.2%) in the PP3M group was discontinued from study treatment during the DB phase due to a TEAE of weight increased.

Injection Site-related Events

During the DB phase of Study PSY-3011, injection site-related TEAEs were reported for 7.9% of subjects in the PP3M group and 5.9% of subjects in the PP1M group. None of the injection site-related TEAEs in either treatment group were assessed as serious and none resulted in study drug discontinuation. During the DB phase, TEAEs of injection site induration (2.8%), injection site pain (2.4%), and injection site swelling (1.4%) were the most frequently reported local reactions in the PP3M group (corresponding rates in PP1M group of 1.2%, 2.7%, and 0.4%, respectively). No injection site reactions TEAE was assessed as severe and most were mild in severity. During the DB phase of Study PSY-3012, 6 subjects (3.8%) in the PP3M group, and none in the placebo group, had an injection site-related TEAE (2 reports of injection site pain and single reports of induration, mass, swelling at injection site and pain in extremity). None of these TEAEs were severe in intensity, serious, or resulted in discontinuation.

Following the single PP3M injection in Study PSY-1005, 7.8% of subjects reported an AE related to injection site reaction, the most common of which were injection site pain and pain in extremity. All of these TEAEs were non-serious and did not result in discontinuation.

Serious adverse events and deaths

The types and rates of serious adverse events (SAEs) reported for subjects treated with PP3M in Studies PSY-3011 or PSY-3012 were consistent with the safety profile of PP1M as observed in acute treatment studies as well as in a long-term, randomized withdrawal study. Furthermore, the majority of SAEs in the two Phase 3 studies with PP3M were judged by the investigator as either unrelated or doubtfully related to study treatment. Across studies, most of the reported SAEs were in the psychiatric disorders SOC and were likely related to the natural changes in the course of the underlying disease.

During the DB phase of PSY-3011, treatment-emergent SAEs occurred in 5.2% of subjects in the PP3M group compared with 7.2% of those in the PP1M group. There were no SAEs of possible clinical interest reported after PP3M exposure in this study. In the DB phase of Study PSY-3012, treatment-emergent SAEs occurred at a lower rate in the PP3M group compared with the placebo group (2.5% vs 10.3%). A single SAE event of possible clinical interest (venous thrombosis of limb [right leg]) occurred approximately 75 days after the single PP3M injection (350 mg eq.) in the open-label Maintenance phase. The event resolved and the subject continued in the study (randomized to placebo group). Across all panels in Study PSY-1005, 35 of the 325 treated subjects (10.8%) experienced a SAE, most of which were in the psychiatric disorders SOC and likely related to subjects' underlying disease.

Across the 3 studies included in the PP3M clinical development program, there were 2 deaths in subjects exposed to PP3M (death due to hepatocellular carcinoma in PP3M group of Study PSY-3011; death due to metastatic melanoma in Panel B of Study PSY-1005 that occurred 7 months following a single injection of PP3M). In addition, there were a total of 6 deaths in subjects exposed only to PP1M (toxic megacolon,

arteriosclerotic cardiovascular disease; sudden cardiac arrest; suicide attempt [overdose of clozapine]; bacterial meningitis; toxicity to various agents [drug intoxication]).

Thus, the overall fatality rate in subjects receiving PP3M in these clinical studies (2 of 1,191 subjects, 0.2%) does not appear different from that reported for PP1M (12/3,817, 0.3%) (EMEA/H/C/002105). No new safety signal based on these cases was identified that could be definitely attributed to paliperidone palmitate – either as the PP3M or the PP1M formulation.

Laboratory findings

Based on mean changes from double-blind baseline and the occurrence of treatment-emergent markedly abnormal values and associated TEAEs in Studies PSY-3011 and PSY-3012, the effects of PP3M on the results of chemistry and haematology laboratory tests (including liver and renal function tests, serum lipid levels, and glucose levels) did not show clinically meaningful differences from those of PP1M or placebo.

Safety in special populations

Pregnancy and lactation

One subject in study PSY-3011 who was exposed to PP3M discontinued the study drug due to pregnancy with no further information for follow-up. Based on the available data, paliperidone palmitate should only be used during pregnancy after careful assessment of the benefit-to-risk profile.

Immunological events

During the open-label phase of the study PSY-3011 three studies had experienced hypersensitivity reactions with PP1M of which one was considered as an SAE. During the double-blind phase of study PSY-3012 one subject is listed to have experienced hypersensitivity reaction with PP3M. Hypersensitivity and anaphylactic reactions were already listed in the SmPC. Hypersensitivity reactions have also been observed in studies PSY-3011 and PSY-3012. According to the narrative of the patient in study PSY-3012 the hypersensitivity reaction during double-bling phase of the study was not related to PP3M but other concomitant treatment.

Based on the results of drug interaction studies, paliperidone is not expected to inhibit clearance of drugs that are metabolized by cytochrome P450 (CYP) mediated pathways, or to inhibit P-glycoprotein (P-gp) mediated transport of other drugs, in any clinically meaningful manner. There were no specific drug interaction studies conducted with PP3M as the available data from the studies with PP1M and/or paliperidone extended release formulations were considered relevant to PP3M, and sufficient to characterize the drug interaction potential with this long-acting injectable antipsychotic. It can be anticipated that less intestinal metabolic or transporter mediated drug-drug interactions occur using paliperidone palmitate formulations compared to paliperidone oral tablets.

Discontinuation due to AES

The rates of discontinuation due to TEAEs were low and did not exceed 5% in any phase of either Phase 3 study. In Study PSY-3011, TEAEs leading to discontinuation were reported at rates of 3.0% and 2.5% in the PP3M and PP1M groups, respectively, during the DB phase. By preferred term, no TEAEs leading to study discontinuation during the Double-blind Phase occurred in more than 2 subjects in either treatment group. One event of possible clinical interest led to discontinuation in a PP3M-treated subject during the DB phase (tardive dyskinesia). This event was not considered serious and symptoms resolved by the 3-month follow-up after discontinuation of study medication.

In Study PSY-3012, TEAEs leading to discontinuation were mainly observed in the psychiatric disorders SOC (17 subjects [3.4%]), and the most frequently reported (≥1%) TEAEs were psychotic disorder and schizophrenia (each 1.2%) during the open label phase. No subject assigned to the PP3M group was discontinued during the DB phase due to an AE (vs 1 placebo-treated subject), and 10 subjects (2.6%) were discontinued during the Maintenance phase after a single PP3M injection. These latter 10 subjects were discontinued mostly for psychiatric disorders (eg, psychotic disorder, schizophrenia) or for isolated cases of gastritis erosive and electrocardiogram QT prolonged.

Few subjects in Study PSY-1005 (8/325, 2.5%) were discontinued due to an AE after receiving a single dose of PP3M. All discontinuations in this Phase 1 study occurred during follow-up after administration of a single dose of PP3M.

2.5.1. Discussion on clinical safety

The safety evaluation is based on one single-dose and two long-term studies in a total 1,191 subjects who received at least one dose of PP3M and of whom 319 subjects were exposed to PP3M at the proposed recommended dose range (175 to 525 mg eq.) for at least 48 weeks . The size of the safety population was considered appropriate by the CHMP also taking into account the known safety profile of the substance.

The discontinuation rate due to adverse events in subjects who received PP3M was low. The incidence and type of adverse events leading to study discontinuation were in accordance with the adverse events already known for the substance paliperidone (marketed as extended release formulation, and one month formulation PP1M).

The treatment-emergent adverse events were similar in PP1M and PP3M treatment groups and were mostly mild or moderate in severity.

Similar to PP1M, a risk for new onset or worsening of EPS has been observed over an extended period in the proposed dose range with PP3M. In both Phase 3 studies with PP3M, reports of akathisia was the most common individual EPS-related event following exposure to PP3M (reported at rates of 4% during the DB phase for each study; 3% on PP1M in PSY-3011). For both Phase 3 studies, there was no apparent relationship between PP3M dose and the overall rates of EPS-related events. None of the EPS-related TEAEs in subjects treated with PP3M were serious. The rates of reported EPS-related AEs were consistent with the findings based on EPS rating scales. While the risk of tardive dyskinesia is theoretically higher with prolonged exposure to D2 receptor antagonism, there was only 1 report of treatment-emergent tardive dyskinesia following exposure to PP3M across the completed studies with PP3M, and the symptoms resolved in this case.

Neuroleptic malignant syndrome, rhabdomyolysis, acute kidney injury, seizure, or convulsion related events were not observed in the clinical studies in subjects treated with PP3M. The risk of pro-arrhythmic events was not increased for PP3M, and cardiovascular safety data with PP3M were consistent with findings from the PP1M and paliperidone extended release clinical development programs, including thorough QT/QTc studies. Moreover, QTc interval data in Study PSY-3011 were similar for the PP3M and PP1M treatment groups.

Although elevations in prolactin concentrations were observed during administration of PP3M in Studies PSY-3011 and PSY-3012, these were mostly asymptomatic and infrequently associated with potentially prolactin-related TEAEs. Moreover, the ability of PP3M to elevate prolactin levels was similar in magnitude to findings for PP1M in Study PSY-3011.

Treatment-emergent diabetes mellitus and hyperglycaemia-related AEs were not common in the completed studies with PP3M, consistent with the absence of treatment-emergent marked abnormalities in glucose levels as a laboratory finding. PP3M also had no significant negative impact on beta-cell functioning and insulin resistance, as shown by results for HOMA-IR and HOMA-%B evaluations in the Phase 3 studies. Further, treatment with PP3M was not associated with clinically significant abnormalities in serum lipids.

Weight gain, a known effect of paliperidone, was seen with PP3M. In Study PSY-3011, the mean increase in body weight from baseline over a similar duration of treatment was smaller for PP3M (1.10 kg, corresponding mean increase in BMI of 0.38 kg/m2) than for PP1M (1.46 kg and 0.52 kg/m2). The mean increase in body weight across the mean period of follow-up during the DB phase of ~25 weeks for subjects randomized to PP3M in Study PSY-3012 (0.94 kg and 0.30 kg/m2) was nearly identical to that observed for PP3M in Study PSY-3011. About 15% of subjects treated with PP3M (16% PP1M) in Study PSY-3011 experienced a weight gain of ≥7% from DB baseline. The corresponding proportions in Study PSY-3012 were 10% for PP3M and 1% for placebo.

Overall, PP3M injection in the deltoid or gluteal muscle was well tolerated. Treatment-emergent injection site-related AEs following PP3M injection were not common in both Phase 3 studies, none of the injection site-related TEAEs were assessed as serious in both studies and none resulted in study drug discontinuation during study PSY-3012 while in study PSY-3011, 2 subjects (0.1%) during open-label phase discontinued their treatment due to TEAE of injection site pain.

The types and rates of serious adverse events reported for subjects treated with PP3M in studies PSY-3011, -3012 or -1005 were consistent with those of PP1M. The majority of SAEs were in the psychiatric disorders and were judged as either unrelated or doubtfully related to PP3M. There were no SAEs of possible clinical interest reported after PP3M exposure in study PSY-3011. In study PSY-3012 a lower rate of treatment-emergent SAEs were reported in the PP3M group compared with the placebo group (2.5% vs 10.3%) with a single SAE event of possible clinical interest (venous thrombosis of limb) occurred after PP3M injection (350 mg eq.) which resolved.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics. Overall, the safety information in the SmPC was considered to adequately reflect the safety profile of the new PP3M formulation.

2.5.2. Conclusions on the clinical safety

The provided data did not raise any new safety concerns for the new 3-month paliperidone palmitate injectable formulation concerning the proposed indication when compared to the known safety profile of paliperidone as substance from experience with paliperidone palmitate 1 month formulation. The CHMP considered that the clinical safety data for Trevicta were sufficient to support the present application.

2.6. Risk Management Plan

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

The PRAC considered that the risk management plan version 7.1 is acceptable. The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 7.1 with the following content:

Safety concerns

Important Identified Risks	• Cerebrovascular accident • Injection site reactions (injectable formulations only) • Hypersensitivity reactions (injectable formulations only)
Important Potential Risks	• Carcinogenicity (pituitary adenomas, endocrine pancreas tumours, breast cancer) • Overall increased mortality in elderly patients with dementia • Cerebrovascular adverse events in elderly patients with dementia • Cognitive and motor impairment • Suicidality • Depression in patients with affective disorders (INVEGA only) • Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy bodies • Gastrointestinal obstruction (in patients with pre-existing severe gastrointestinal narrowing [pathologic or iatrogenic] or in patients with dysphagia or significant difficulty in swallowing tablets) (INVEGA only due to non-deformable nature of tablet) • Decreased bone mineral density/osteoporosis • Accidental exposure to product by child (INVEGA only)
Missing Information	• Use in haemodialysis patients • Exposure during pregnancy • Exposure via breastfeeding

Pharmacovigilance plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Planned submission of final report
"Post-Authorization Safety Study of Cardiovascular and Cerebrovascular Adverse Events in Elderly Patients Treated with Paliperidone PR, Paliperidone Palmitate and Other Antipsychotics" [Category 3 for XEPLION] [Category 3 for INVEGA]	To estimate the incidence of cardiovascular and cerebrovascular events among elderly patients treated with XEPLION, INVEGA, and other oral and parenteral antipsychotics. To compare the incidence of cardiovascular and cerebrovascular events among elderly patients treated with paliperidone (stratified according to INVEGA users and XEPLION users) to the incidence among elderly patients treated with other oral and parenteral antipsychotics. To describe the demographic characteristics, comorbidities, and concomitant medications among elderly (age ≥65 years) patients treated with INVEGA, XEPLION, and other oral and parenteral antipsychotics.	Cerebrovascular accident; Overall increased mortality in elderly patients with dementia; Cerebrovascular adverse events in elderly patients with dementia.	Started	December 2016

Risk minimisation measures

Safety Concern	Risk Minimisation Measures	
	Routine	Additional
Important Identified Risks:		
Cerebrovascular accident	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.8 (Undesirable effects) that cerebral ischaemia is a rare ADR. See also below in the Important Potential Risk section of this table, in the row entitled "Cerebrovascular adverse events in elderly patients with dementia."	None proposed
Injection site reactions (injectable formulations only)	The XEPLION and Trevicta SmPCs state in Section 4.8 (Undesirable effects) the following ADRs: injection site reaction (common for both formulations); induration (uncommon for both formulations); injection site abscess, injection site cellulitis, and injection site haematoma (rare for both formulations); injection site cyst (rare postmarketing for XEPLION, rare for Trevicta), and injection site necrosis and injection site ulcer (frequencies not known, postmarketing or based on information from RISPERDAL CONSTA).	None proposed
Hypersensitivity reactions (injectable formulations only)	The XEPLION and Trevicta SmPCs state in Section 4.3 (Contraindications) the contraindication of hypersensitivity to the active substance, to risperidone, or to any of the excipients, which are listed in SmPC Section 6.1 (List of excipients). Section 4.1 (Therapeutic indications) of the XEPLION SmPC states that patients must previously have been stabilised on (or responsive to) oral paliperidone or risperidone, and this section of the Trevicta SmPC states that Trevicta is to be used only after the patient has been adequately treated with 1-month paliperidone palmitate injectable for at least four months. Section 4.4 (Special warnings and precautions for use) of the XEPLION and Trevicta SmPCs states that hypersensitivity reactions can occur even in patients who have previously tolerated oral risperidone or oral paliperidone. Section 4.8 (Undesirable effects) of all 3 SmPCs lists the ADRs of hypersensitivity (rare for INVEGA, uncommon for XEPLION and Trevicta) and anaphylactic reaction (rare for INVEGA, rare postmarketing for XEPLION, frequency not known for Trevicta).	None proposed

Safety Concern	Risk Minimisation Measures	
	Routine	Additional
Important Potential Risks:		
Carcinogenicity (pituitary adenomas, endocrine pancreas tumours, breast cancer)	The INVEGA, XEPLION, and Trevicta SmPCs include in Section 4.4 (Special warnings and precautions for use) a warning under "Hyperprolactinaemia" stating that tissue culture studies suggest that cell growth in human breast tumours may be stimulated by prolactin. Although no clear association with the administration of antipsychotics has so far been demonstrated in clinical and epidemiological studies, caution is recommended in patients with relevant medical history. Paliperidone should be used with caution in patients with possible prolactin-dependent tumours. Section 5.3 (Preclinical safety data) of all 3 SmPCs states that, in oral carcinogenicity trials of risperidone in rats and mice, increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenomas (both species) were seen. This section of the SmPCs for XEPLION and Trevicta also states that the carcinogenic potential of intramuscularly injected paliperidone palmitate was assessed in rats. Female rats showed a statistically significant increase in mammary gland adenocarcinomas at 10, 30, and 60 mg/kg/month. Male rats showed a statistically significant increase in mammary gland adenomas and carcinomas at 30 and 60 mg/kg/month; this is 1.2 and 2.2 times the exposure level of the maximum recommended human dose of 150 mg eq. of XEPLION, or 0.6 and1.2 times the exposure level of the maximum recommended human dose of 525 mg eq. of Trevicta. These tumours can be related to prolonged dopamine receptor type 2 antagonism and hyperprolactinaemia. The relevance of these tumour findings in rodents in terms of human risk is unknown.	None proposed
Overall increased mortality in elderly patients with dementia	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.4 (Special warnings and precautions for use) that these products have not been studied in elderly patients with dementia. As per the Trevicta SmPC, Trevicta is not recommended to treat elderly patients with dementia due to increased risk of overall mortality and cerebrovascular adverse reactions. Hence, until data demonstrate otherwise, the experience from risperidone is considered relevant. In a meta-analysis of 17 controlled clinical trials, elderly patients with dementia treated with other atypical antipsychotics, including risperidone, aripiprazole, olanzapine, and quetiapine had an increased risk of mortality (4%) compared with 3.1% for placebo.	None proposed
Cerebrovascular adverse events in elderly patients with dementia	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.4 (Special warnings and precautions for use) that these products have not been studied in elderly patients with dementia. Hence, until data demonstrate otherwise, the experience from risperidone is considered relevant. An approximately 3-fold increased risk of cerebrovascular adverse reactions has been seen in randomised placebo-controlled clinical trials in the dementia population with some atypical antipsychotics, including risperidone, aripiprazole, and olanzapine. The precise mechanism for this increased risk is not known. The SmPCs for INVEGA and XEPLION also specify that these products should be used with caution in elderly patients with dementia who have risk factors for stroke. As per the Trevicta SmPC, Trevicta is not recommended to treat elderly patients with dementia due to increased risk of overall mortality and cerebrovascular adverse reactions. See also above in the Important Identified Risk section of this table, in the row entitled "Cerebrovascular accident."	None proposed

Safety Concern	Risk Minimisation Measures	
	Routine	Additional
Cognitive and motor impairment	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.5 (Interaction with other medicinal products and other forms of interaction) that, given the primary central nervous system effects of paliperidone, these products should be used with caution in combination with other centrally acting medicines, e.g., anxiolytics, most antipsychotics, hypnotics, opiates, or alcohol. Section 4.7 (Effects on ability to drive and use machines) of all 3 SmPCs states that INVEGA, XEPLION, and Trevicta can have minor or moderate influence on the ability to drive and use machines due to potential nervous system and visual effects. Therefore, patients should be advised not to drive or operate machines until their individual susceptibility to INVEGA, XEPLION, or Trevicta is known. Section 4.8 (Undesirable effects) identifies sedation/somnolence as an ADR (very common for INVEGA, common for XEPLION and Trevicta) reported in trials. Section 4.9 (Overdose) of all 3 SmPCs identifies drowsiness and sedation as risks from overdose.	None proposed
Suicidality	Individuals with psychotic disorders, especially those with first-episode psychosis, are at increased risk of suicidal behaviour compared with the general population. This inherent risk is understood by mental health professionals and is not specified in the INVEGA, XEPLION, or Trevicta SmPCs, as this is the nature of the disease that is being treated. The possibility of suicide attempt is inherent in psychotic illnesses, and close supervision of high risk-patients (such as those with previous attempts or a history of substance abuse) should accompany drug therapy.	None proposed
Depression in patients with affective disorders (INVEGA only)	The INVEGA SmPC Section 4.4 (Special warnings and precautions for use) states that patients with schizoaffective disorder treated with INVEGA should be carefully monitored for a potential switch from manic to depressive symptoms.	None proposed
Increased sensitivity to antipsychotics in patients with Parkinson's disease or dementia with Lewy bodies	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.4 (Special warnings and precautions for use) that physicians should weigh the risks against the benefits when prescribing antipsychotic medicinal products to patients with Parkinson's disease or dementia with Lewy bodies since both groups may be at increased risk of NMS as well as having an increased sensitivity to antipsychotics. Manifestations can include confusion, obtundation, postural instability with frequent falls, in addition to EPS.	None proposed

Safety Concern	Risk Minimisation Measures	
	Routine	Additional
Gastrointestinal obstruction (in patients with preexisting severe gastrointestinal narrowing [pathologic or iatrogenic] or in patients with dysphagia or significant difficulty in swallowing tablets) (INVEGA only due to nondeformable nature of tablet)	The INVEGA SmPC Section 4.4 (Special warnings and precautions for use) states that, because the INVEGA tablet is non-deformable and does not appreciably change shape in the gastrointestinal tract, INVEGA should not ordinarily be administered to patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic) or in patients with dysphagia or significant difficulty in swallowing tablets. There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of medicines in non-deformable controlled-release formulations. Due to the controlled-release design of the dosage form, INVEGA should only be used in patients who are able to swallow the tablet whole. Section 4.8 (Undesirable effects) of the INVEGA lists intestinal obstruction as a rare ADR.	None proposed
Decreased bone mineral density/ osteoporosis	The INVEGA, XEPLION, and Trevicta SmPCs in Section 4.8 (Undesirable effects) identify hyperprolactinaemia and various potentially prolactin-related ADRs that inform the prescriber about hyperprolactinaemia and the possible consequences of hypergonadotropic hypogonadism.	None proposed
Accidental exposure to product by child (INVEGA only)	The outer labelling states that INVEGA should be kept out of the sight and reach of children. The blister packaging meets local requirements regarding opacity, such that children cannot see the tablets. INVEGA packaging in the United States and Canada is child resistant. In the future, INVEGA will be supplied in child resistant packaging for all countries where INVEGA is marketed.	None proposed

Safety Concern	Risk Minimisation Measures	
	Routine	Additional
Missing Information:		
Use in haemodialysis patients	The INVEGA SmPC Section 4.2 (Posology and method of administration) states that INVEGA has not been studied in patients with severe renal impairment (i.e., in patients with creatinine clearance below 10 mL/min, which is a level that could require haemodialysis). The XEPLION and Trevicta SmPCs in Section 4.2 (Posology and method of administration) state that these products are not recommended in patients with moderate or severe renal impairment (creatinine clearance <50 mL/min), which would include levels that could require haemodialysis.	None proposed
Exposure during pregnancy	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.6 (Fertility, pregnancy and lactation) that no adequate data are available from the use of paliperidone during pregnancy. Neonates exposed to (antipsychotics [including paliperidone])[a] during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. Agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder have been reported. Consequently, newborns should be monitored carefully. INVEGA and XEPLION should not be used during pregnancy unless clearly necessary. For the longest-acting formulation (Trevicta), this SmPC section states that paliperidone has been detected in plasma up to 18 months after a single dose, and that consideration should be given to the long-acting nature of Trevicta, since a foetus exposed to Trevicta administered before and during pregnancy may develop adverse reactions in the neonatal period. Section 5.3 (Preclinical safety data) of all 3 SmPCs states that intramuscular paliperidone palmitate and oral paliperidone were not teratogenic in animals. In rat reproduction studies with oral risperidone, which is extensively converted to paliperidone in rats and humans, adverse effects were seen on the birth weight and survival of the offspring. Other dopamine antagonists, when administered to pregnant animals, have caused negative effects on learning and motor development in the offspring.	None proposed
Exposure via breastfeeding	The INVEGA, XEPLION, and Trevicta SmPCs state in Section 4.6 (Fertility, pregnancy and lactation) that paliperidone is excreted in the breast milk to such an extent that effects on the breastfed infant are likely if therapeutic doses are administered to breastfeeding mothers. For the longest-acting formulation (Trevicta), this SmPC also states that paliperidone has been detected in plasma up to 18 months after a single dose, and that consideration should be given to the long-acting nature of Trevicta, since a breastfed infant may be at risk from Trevicta administration long before breastfeeding. INVEGA, XEPLION, and Trevicta should not be used while breastfeeding.	None proposed

[a] The parenthetical phrase is the only part that varies among SmPCs.

2.7. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the MAH fulfils the

requirements of Article 8(3) of Directive 2001/83/EC.

2.8. Product information

2.8.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

The efficacy of the new 3-month paliperidone palmitate injectable formulation, PP3M, has been investigated in 2 phase 3 clinical studies with fixed dosing treatment regimens. Pharmacokinetic studies have demonstrated the slow release of paliperidone after IM injections of PP3M. The steady-state plasma exposure after administration every 3 months with PP3M has been shown to be roughly similar to administration every month with PP1M (1-month injectable paliperidone palmitate formulation). The data support the proposed 3 monthly injection frequency.

The observed relapse rate for PP3M was low (8-10%) and comparable with PP1M in the same study or between studies and in good agreement with historical data from other anti-psychotics. The first long term efficacy study, PSY-3011, demonstrated that PP3M is non-inferior to PP1M treatment with respect to relapse rate at week 48 following the initial monthly treatment with PP1M. The relapse prevention study, PSY-3012, showed a significant reduction in risk for relapse of schizophrenia symptoms when treated with PP3M compared to placebo. In this study, PP3M was significantly superior to placebo in delaying the relapse of symptoms of schizophrenia in adult subjects following adequate treatment with the currently marketed PP1M for 4 months. Having reviewed the available data, the CHMP considered that efficacy of PP3M in the maintenance treatment of adult patients with schizophrenia has been demonstrated.

The possibility of initiating the PP3M treatment in patients who are adequately treated with PP1M earlier than four months of pre-treatment is supported by the population PK simulations following two initial doses of PP1M at day 1 and day 8. The switch between PP1M and PP3M could be based on the clinical stability of the patient in terms of safety and efficacy as judged by the treating physician. The MAH has agreed with this therapeutic approach and has amended the indication for paliperidone palmitate to reflect this.

Uncertainty in the knowledge about the beneficial effects

Uncertainties around missing psychiatric hospitalization dates and handling of missing values of the PANSS were raised during the procedure but were satisfactorily addressed by the MAH.

There was furthermore a high level of censored data in both phase 3 studies. In study PSY-3012, in the PP3M arm censoring was of the same magnitude as seen in PSY-3011, here however, more easily accepted considering the difference between groups in the proportion of censored cases and the main reason thereof, i.e. the difference in number of subjects experiencing a relapse. To further clarify time to early discontinuations for reasons besides relapses, the MAH performed an analysis of early discontinuation not including relapses. In addition, the MAH clarified follow-up time in the DB phase for each treatment group respectively; overall and among those who were still in the study at study completion/early termination. Differences seen between the treatment arms were confirmed. Concerns

were considered solved with the additional analyses and satisfactory clarifications provided by the Applicant.

The percentage of relapse events in the PP3M treatment group was similar in both study PSY3011 and PSY3012. Assay sensitivity has been inferred, relying also on the information from studyPSY3001 (52-week study aimed at demonstrating XEPLION's superiority over placebo in preventing schizophrenic relapses), where the relapse rate observed in the PP1M group (~10%) was comparable with the relapse event in the PSY3011 study (~9%). Quite few relapse events were hence registered in PP3M and PP1M treatment group (8% and 9%, respectively, in the PP analysis set), which ultimately indicates that both PP1M and PP3M are effective treatments, but could also mask insufficiency in the definition of relapse event, study duration or conduct.

Risk

Unfavourable effects

There were a total of 2 deaths in subjects exposed to PP3M and 6 in subjects exposed to PP1M across the 3 completed studies with PP3M. The overall fatality rate in subjects who received PP3M (2/1,191 subjects [0.2%]) is similar to that previously observed with PP1M (0.3%).

A low proportion of subjects discontinued the DB phase due to adverse events in studies PSY-3011 (in PP3M group 3.0% and PP1M 2.5%) and PSY-3012 (no subject in the PP3M group).

Cases of EPS have been observed. Akathisia was the most common individual EPS-related event following exposure to PP3M in both studies (reported at rates of 4% during the DB phase for each study; 3% on PP1M in PSY-3011). A risk for new onset or worsening of EPS has been observed with long term administration of the proposed dose range of PP3M without an apparent relationship between PP3M dose and the overall rates of EPS-related events. There was 1 report of treatment-emergent tardive dyskinesia following exposure to PP3M, and the symptoms resolved in this case. None of the EPS-related TEAEs in subjects treated with PP3M were serious.

The risk of pro-arrhythmic events was not increased for PP3M compared to PP1M, and cardiovascular safety data with PP3M were consistent with findings from the PP1M and paliperidone extended release clinical development programs, including thorough QT/QTc studies. Moreover, QTc interval data in Study PSY-3011 were similar for the PP3M and PP1M treatment groups.

Although elevations in prolactin concentrations were observed during administration of PP3M in Studies PSY-3011 and PSY-3012, these were mostly asymptomatic and infrequently associated with potentially prolactin-related TEAEs. Moreover, the ability of PP3M to elevate prolactin levels was similar in magnitude to findings for PP1M in Study PSY-3011.

Treatment-emergent diabetes mellitus and hyperglycaemia-related AEs were not common in the completed studies with PP3M, consistent with the absence of treatment-emergent marked abnormalities in glucose levels as a laboratory finding. PP3M also had no significant negative impact on beta-cell functioning and insulin resistance, as shown by results for HOMA-IR and HOMA-%B evaluations in the Phase 3 studies. Further, treatment with PP3M was not associated with clinically significant abnormalities in serum lipids.

Weight gain, a known effect of paliperidone, was also seen with PP3M. In Study PSY-3011, the mean increase in body weight from baseline over a similar duration of treatment was smaller for PP3M (1.10 kg, corresponding mean increase in BMI of 0.38 kg/m2) compared to PP1M (1.46 kg and 0.52 kg/m2). The mean increase in body weight across the mean period of follow-up during the DB phase of ~25 weeks for subjects randomized to PP3M in Study PSY-3012 (0.94 kg and 0.30 kg/m2) was nearly identical to that

observed for PP3M in Study PSY-3011. About 15% of subjects treated with PP3M (16% PP1M) in Study PSY-3011 experienced a weight gain of ≥7% from DB baseline. The corresponding proportions in Study PSY-3012 were 10% for PP3M and 1% for placebo. The higher proportion of subjects with abnormal weight gain and TEAEs related to weight gain in the double-blind phase of study PSY-3011 compared with study PSY-3012 can be explained by differences in treatment duration between the 2 studies. The MAH has provided additional data on exposure adjusted risk for weight gain and related TEAEs and data concerning the mean weight changes over time during these 2 studies which showed similar rates for abnormal (≥7%) weight gain and TEAEs related to weight gain/weight increase in PP1M- and PP3M-treated subjects during the double-blind phase between the 2 studies.

Injection site-related adverse events following PP3M injection were not common, severe, or serious or led to treatment discontinuation. In Study PSY-3011 injection site pain was reported with the incidence of 8.9% during open-label phase, while 2.4% in PP3M group and 2.7% in PP1M group during double-blind phase. In Study PSY-3012, injection site pain was reported in 8.7% of the subjects during open-label phase and ion 1% in PP3M group during the double blind phase.

Uncertainty in the knowledge about the unfavourable effects

The safety profile observed for the new 3-month paliperidone palmitate injectable formulation was broadly in line with the known safety profile of the previous 1-month injectable formulation. The Important Potential Risks with Trevicta have been previously discussed. They are reflected in the RMP and remain unchanged.

Benefit-risk balance

Importance of favourable and unfavourable effects

The new 3-month paliperidone palmitate injectable formulation has been shown to be non-inferior to a 1-month formulation in the maintenance treatment of adult patients with schizophrenia who have been stabilized with oral paliperidone treatment. Therefore, patients who benefited from the 2-month formulation are also expected to benefit from treatment with the new 3-month formulation. Furthermore, superiority to placebo in delaying the time to relapse has been shown.

The new formulation offers a benefit to patients as it allows reducing the dosing frequency from 1 monthly to 3 monthly. Currently, there is no other antipsychotic formulation available for this extended dosing interval. The new formulation is thus expected to improve compliance of patients who would not need or prefer frequent visits to clinic, or would like to avoid monthly or more frequent injections with their treatment.

The safety profile and the tolerability of the new 3-month formulation did not differ from the 1-month formulation during the phase 3 studies. No new safety concern specifically related to then new formulation was raised.

Benefit-risk balance

Based on the available data, the CHMP concluded that the benefits of Trevicta in the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product outweigh the risks, thereby the overall benefit-risk balance was considered positive.

Discussion on the benefit-risk balance

This application concerns Trevicta, a new formulation of paliperidone palmitate, a 3-month long-acting injectable, also referred to as PP3M.

The pharmacokinetic studies have demonstrated the slow release of paliperidone after IM injections of PP3M. The steady-state plasma exposure after administration every 3-month with PP3M can be considered as similar to administration every 1-month with PP1M. The clinical results are considered to support a clinically relevant effect of Trevicta and did not raise any new safety concerns compared to the known safety profile of paliperidone. Furthermore, the population PK simulations provided by the MAH supports the possibility of an earlier switch than 4 months from PP1M to PP3M, according to the clinical judgement of the treating physician. This was reflected in the final indication.