EMA/502561/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

BYANNLI

International non-proprietary name: paliperidone

Procedure No. EMEA/H/C/005486/X/0002/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
ANCOVA	analysis of covariance
AS	active substance
AUC	area under concentration-time curve
BARS	Barnes Akathisia Rating Scale
BfArM	Federal Institute for Drugs and Medical Devices
BMI	body mass index
CGI-S	Clinical Global Impression - Severity
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
Cmax	maximum plasma concentration
COC	cyclic-olefin-copolymer
COVID-19	Coronavirus Disease 2019
CQA	Critical Quality Attributes
CSR	clinical study report
C-SSRS	Columbia-Suicide Severity Rating Scale
CYP	cytochrome
D2	dopamine Type 2
DB ITT	double-blind intent-to-treat
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	Electrocardiogram
EMA	European Medicines Agency
EPS	extrapyramidal symptom(s)
ER	extended release
EU	European Union
FDA	Food and Drug Administration
FOIA	Freedom of Information Act
FP	finished product
FTIR	Fourier transform infrared spectroscopy
HDL	high-density lipoprotein
(U)HPLC	(ultra)high performance liquid chromatography
ICH	International Council on Harmonisation
IM	intramuscular
IR	immediate release
ITT	intent-to-treat
IVIVC	in vitro – in vivo correlation
JRD	Janssen Research and Development
LAI	long-acting injectable
LDL	low-density lipoprotein
LOCF	last observation carried forward
MAA	marketing authorisation application
MedDRA	Medical Dictionary for Regulatory Activities
mg eq.	milligram equivalent
MPA	Medical Products Agency
NMS	neuroleptic malignant syndrome
PANSS	Positive and Negative Syndrome Scale for Schizophrenia
P-gp	P-glycoprotein

Ph. Eur.	European Pharmacopoeia
PR	prolonged release
RH	relative humidity
USP (-NF)	United States Pharmacopoeia (National Formulary)
WFI	water for injections

1. Background information on the procedure

1.1. Submission of the dossier

Janssen-Cilag International N.V. submitted on 19 November 2020 a group of variation(s) consisting of an extension of the marketing authorisation to add two new strengths of 700 mg and 1000 mg and of the following variation(s):

Variation(s) requested		**Type**
A.2.a	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	IAin
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
C.I.7.b	C.I.7.b - Deletion of - a strength	IB
A.7	A.7 - Administrative change - Deletion of manufacturing sites	IA

A.2.a - To change the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to BYANNLI
A.7 - To delete Cilag AG (Hochstrasse 201, CH-8200 Schaffhausen) as a site responsible for manufacturing, primary and secondary packaging and release testing of the finished product
C.I.7.b. - To delete the 25 mg, 50 mg, 75 mg, 100 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006).

The MAH applied for the following indication:

BYANNLI, a 6-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products (see section 5.1).

Furthermore, the PI is brought in line with the latest QRD template version.

1.2. Legal basis, dossier content and multiples

The legal basis for this application refers to:

Article 7.2 of Commission Regulation (EC) No 1234/2008 – Group of variations

1.3. Information on Paediatric requirements

Not applicable

1.4. Information relating to orphan market exclusivity

1.4.1. 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.

1.5. Scientific advice

The PP6M product has been developed for the treatment of schizophrenia in adult patients who have been adequately treated with PP1M preferably for four months or more or PP3M for at least one injection cycle. The Phase 3 clinical program was designed so that patients were stabilized on either PP1M or PP3M prior to conversion to PP6M.

Clinical development of PP6M began in 2017. The development program for PP6M in the treatment of schizophrenia is composed of 2 Phase 3 studies: 1 pivotal, non-inferiority study and 1 open-label extension study:

- Study R092670PSY3015 (completed) – multinational, randomized, double-blind, active-controlled, non-inferiority study to compare PP6M with PP3M in adults with schizophrenia previously stabilized on corresponding doses of PP1M or PP3M.
- Study R092670PSY3016 (ongoing) – multinational, single-arm 24-month open-label extension to Study R092670PSY3015 in selected countries intended to provide access to PP6M in subjects with schizophrenia completing the PSY3015 study without relapse and to assess the long-term safety and tolerability of PP6M.

In addition, the objectives of the PK development program for PP6M included:

- Characterize the PK of paliperidone after gluteal injections of PP6M for subjects randomized in Study PSY3015
- Provide individual estimates of the secondary pharmacokinetic parameters (i.e. AUC for the considered dosing interval [AUC_{tau}], AUC for a 6-month dosing period [$AUC_{6months}$], through concentration [$C_{trhough}$] and C_{max})
- Evaluate common clinical questions and dosing scenarios through simulations using the population PK model of PP6M

Consistent with the approach used in the EU registration procedures for PP1M and PP3M, data from elderly PK, drug-drug interaction, renal-impairment and hepatic-impairment studies from the paliperidone ER program (EMEA/H/C/746) are used to support the current application for PP6M given that paliperidone palmitate is completely hydrolysed to circulating paliperidone after IM injection and various intrinsic and extrinsic factors are not expected to differentially affect absorption of paliperidone after it is released in muscle tissue.

The development program for PP6M has been discussed with the European Medicines Agency (EMA) Scientific Advice Working Party (SAWP) over the course of 2 Scientific Advice procedures in September 2016 and September 2017. The PSY3015 study design was discussed within a scientific advice (EMEA/H/SA/1678/2/2016/III) and as a response to the initially proposed non-inferiority margin of -12.5%, a

NI margin of -10% was recommended (FU advice: EMEA/H/SA/1678/2/FU/1/2017/II).

In the September 2016 advice procedure, general agreement was noted for the proposed clinical pharmacology and pharmacometric development plan, the proposed periods of prior exposure to PP1M or PP3M, and that a single clinical study evaluating pharmacokinetics (PK), safety, and efficacy of PP6M in comparison to PP3M could be sufficient to support the registration of PP6M, subject to the study results and assessment of the total data package. The Agency reviewed the proposed study design (PSY3015 Protocol Element Document, dated August 2016) and recommended modifications to the PK sampling and monitoring of injection site reactions.

Based on the scientific advice from the CHMP and following additional feedback from a meeting with the US Food and Drug Administration (FDA) on 19 January 2017 to discuss the revised study design, the Applicant made further revisions to the proposed PSY3015 study design and submitted a draft protocol to the CHMP for scientific advice. During the September 2017 advice procedure, the CHMP endorsed the proposed noninferiority study design (including the non-inferiority margin of -10%) and primary endpoint and recommended that non-inferiority testing be performed in both the intent-to-treat (ITT) and per protocol populations. Additionally, the CHMP noted the acceptability of a PP6M single high dose of 1000 mg eq. (vs. 2 previously proposed high doses of 850 and 1050 mg eq.) *and agreed that a single non-inferiority study is acceptable to support the registration of PP6M*. Since standard of care outside EU countries may be different and socio-cultural and other factors intervene significantly on the risk of relapse of previously stable schizophrenia patients, *the Agency recommended that more than 25% of subject enrollment be from EU countries* to allow for assay sensitivity in determination of relapse rates to show a difference between treatments.

Pre-submission meetings between the Applicant and the CHMP Rapporteur (Medical Products Agency [MPA], Sweden) and Co-rapporteur (Federal Institute for Drugs and Medical Devices [BfArM], Germany) took place on 23 September 2020 and 8 September 2020, respectively. In addition to a discussion of regulatory and procedural matters, the Applicant obtained clarification on specific aspects related to clinical pharmacology, PP6M efficacy and safety data, biostatistics, and the Risk Management Plan.

Summary of questions raised/ issues discussed in the Scientific Advice*

The Applicant received Scientific Advice on the development of Paliperidone palmitate (Paliperidone palmitate IM) from the CHMP on 15 September 2016 (EMEA/H/SA/1678/2/2016/III) and 14 September 2017 (EMEA/H/SA/1678/2/FU/1/2017/II)). The Scientific Advice pertained to the following preclinical and clinical aspects:

Preclinical

- Choice of animal preclinical models and general acceptability of the non-clinical package to support the MAA.

Clinical

- Sufficiency of the assessment of efficacy (noninferiority) of PP6M versus PP3M was a secondary objective for the MAA.

• Choice of patients with schizophrenia who are clinically stable on paliperidone palmitate extended release injection product as adequate population for single registration trial.

• Acceptability of the dosing strength planned to be used, based on population-PK modelling and to keep the PP6M injection volume to a maximum of 5 mL

• Acceptability of the general strategy for the clinical development for the MAA.

* This summary forms the basis for possible future inclusion of information on Scientific Advice in a European public assessment report (EPAR) for the product.

1.6. Steps taken for the assessment of the product

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

Rapporteur: Kristina Dunder

PRAC Rapporteur: Ulla Wändel Liminga

The application was received by the EMA on	19 November 2020
The procedure started on	24 December 2020
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2021
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 March 2021
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	17 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 April 2021
The CHMP agreed on the consolidated List of Questions to be sent to the MAH during the meeting on	22 April 2021
The MAH submitted the responses to the CHMP consolidated List of Questions on	21 May 2021
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	23 June 2021
The CHMP agreed on a list of outstanding issues to be sent to the MAH on	22 July 2021
The MAH submitted the responses to the CHMP List of Outstanding Issues on	17 August 2021
The CHMP Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	23 August 2021 02 September 2021
The CHMP Rapporteurs circulated the updated CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	09 September 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting	16 September 2021

a marketing authorisation to BYANNLI on	

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Schizophrenia is a severe mental illness characterized by psychosis, mood disorders, and cognitive disorders. The clinical signs and symptoms of schizophrenia are very complex and display different patterns which vary widely from patient to patient. The symptoms are commonly divided into several broad clusters (see Section 2.1.4).

2.1.2. Epidemiology

Based on data from 2016, the global mean point prevalence of schizophrenia was estimated to be 0.28%, with an estimated 20.9 million prevalent cases worldwide. The high prevalence is attributed to the fact that it is a lifelong illness that typically has an onset in young adulthood. The long-term outcome of schizophrenia varies along a continuum of reasonable recovery to total incapacitation.

2.1.3. Clinical presentation, diagnosis

The symptoms are commonly divided into several broad clusters:

- The positive symptoms represent an addition to normal behavior that may involve hallucinations (perceptual experiences not shared by others), delusions (e.g., that others can interfere with one's thoughts), thought disorder, bizarre behavior and disorganized speech, movement disorders (repetition of certain motions over and over), and catatonia (no movement or no response to others).
- The negative symptoms comprise elements that are absent from normal behavior, including anhedonia (loss of the ability to experience pleasure), asociality (withdrawal from social contacts), lack of volition, lack of motivation, flat or blunted affect or emotion, and alogia (reduced quantity or content of speech).
- Patients with schizophrenia may also suffer from cognitive impairments such as diminished attention, memory, and executive function (e.g., the ability to plan, initiate, and regulate goal-directed behaviors).
- Behavioral and affective deficits including depression, lethargy, mood swings, and inappropriate and odd presentation are frequently associated with schizophrenia, causing avoidance on the part of others and thereby leading to social isolation.

2.1.4. Management

Antipsychotic drugs are commonly divided into typical (first generation) and atypical (second generation) categories. Clinically effective doses of typical antipsychotic drugs generate a striatal dopamine D_2 receptor occupancy of about 60% to 80%, approaching a level that is associated with a high risk of extrapyramidal side effects. Typical antipsychotic drugs are mostly effective against positive symptoms but have a more limited effect on and may even exacerbate negative and cognitive symptoms. In contrast, atypical antipsychotics have lower affinity for and occupancy of the dopaminergic receptors and a high degree of

occupancy for the 5HT2A serotonin receptors. Compared to typical antipsychotics, atypicals induce fewer extrapyramidal side effects at clinically effective doses and may have greater efficacy in reducing negative symptoms.

In 1984, based on the assumption that $5HT_{2A}$ antagonism might improve efficacy of D_2 blockers (particularly for negative symptoms) and reduce extrapyramidal side effects, Janssen Pharmaceutical developed the atypical antipsychotic risperidone, which combines potent $5HT_{2A}$ and D_2 blockades. Risperidone was launched in 1993 and rapidly incorporated into clinical practice and is currently widely recommended as a first line option for treatment of psychosis. Clinical experience has supported the efficacy and tolerability of both oral and long acting risperidone in several reviews. The drug was first approved in Europe in 1993.

As with other oral antipsychotic drugs, a challenge associated with risperidone is that many patients with schizophrenia are poorly compliant with their medications. In the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study, 74% of patients were found to have discontinued their prescribed drug within 18 months, many due to either poor tolerability or lack of efficacy. Even among those who do not explicitly discontinue drug therapy, non-adherence to long-term oral medication regimes is one of the most significant therapeutic issues in the therapy of schizophrenia and related disorders. As a result, many patients do not experience the full benefit of antipsychotic drug therapy, and suffer frequent relapses or exacerbations, which require re-hospitalization. Missing as few as 1 to 10 days of oral antipsychotic therapy nearly doubles the risk of hospitalization (Keks and Culhane 1999, Byerly, Nakonezny et al. 2007). The use of depot antipsychotics as a maintenance treatment for individuals with a history of non-adherence with oral antipsychotics is well recognized. Thus, adherence to medication can be problematic for patients with schizophrenia.

In contrast to oral formulations, long-acting injectable (LAI) antipsychotics may reduce the risk of relapse and hospitalization and thus improve quality of life. Because LAI antipsychotics are administered by a healthcare provider, LAIs offer transparency with respect to medication adherence, alerting healthcare professionals to nonadherence.
Many LAI antipsychotics are available with treatment intervals of 2 to 4 weeks. The LAI antipsychotic Paliperidone, the active metabolite of risperidone, is available in 3 formulations: an oral prolonged-release (PR) osmotic pump technology (OROS) tablet formulation (also referred to a paliperidone extended-release [ER] tablets, INVEGA) and 2 long-acting injectable (LAI) formulations: paliperidone palmitate 1-month injection (PP1M; XEPLION) and paliperidone palmitate 3-month injection (PP3M; TREVICTA), but there is none longer than 3 months.

A paliperidone palmitate 6-month injection (PP6M) has been developed by the Applicant. The idea is that the 6-month dosing interval with PP6M might work for the most stable schizophrenia patients in cases a longer dosing interval is preferred, and that it might offer benefits to some underserved schizophrenia patients as well. There are patients with limited access to healthcare for various reasons, such as geographic or economic problems with clinic visits for injections, or with limited access to treatment due to problems associated with homelessness.

2.2. About the product

Risperidone is a benzisoxazole derivative and a second-generation antipsychotic agent which combines potent serotonin (5-hydroxytryptamine) 5-HT2 and dopamine D2 receptor antagonism. Paliperidone also blocks alpha 1-adrenergic receptors and slightly less, H1-histaminergic and alpha 2-adrenergic receptors. Paliperidone is not bound to cholinergic receptors.

Pharmacotherapeutic group: Psycholeptics, other antipsychotics. ATC code: N05AX13.

Paliperidone palmitate is an aqueous suspension for intramuscular (IM) injection. Based on its extremely low water solubility, paliperidone palmitate dissolves slowly after injection before being hydrolyzed to paliperidone, which then enters the systemic circulation. By slowly releasing paliperidone from the injection site, the paliperidone palmitate formulation enables a dosing interval that achieves therapeutic plasma

concentrations of paliperidone for 1 month (PP1M), 3 months (PP3M), or 6 months (PP6M) depending on particle size, concentration and dosage. The efficacy and safety of the paliperidone formulations currently available for the treatment of schizophrenia have been well characterized and established.

The oral formulation of paliperidone (INVEGA) was first approved in the European Union (EU) on 27 June 2007 (EMEA/H/C/00746) and is currently approved for the treatment of schizophrenia in adults and adolescents 15 years of age and older and for the treatment of schizoaffective disorder in adults. The PP1M formulation (XEPLION) was approved in the EU on 4 March 2011 (EMEA/H/C/002105) for the maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone. The PP3M formulation (TREVICTA) was approved in the EU on 26 May 2016 (procedure EMEA/H/C/4066/X/007/G) for the maintenance treatment of schizophrenia in adult patients stabilized with PP1M. Paliperidone PR tablets, PP1M, and PP3M are also licensed globally in numerous other countries, including the United States (US).

2.3. Type of Application and aspects on development

2.4. Quality aspects

2.4.1. Introduction

This application concerned a line extension for the addition of two new strengths grouped with a number of type IA and IB variations to change the (invented) name of the medicinal product, to delete a manufacturing site and to delete a number of strengths from the MA.

The long-acting injectable (LAI) formulation of the antipsychotic paliperidone is available in 3 formulations: an oral prolonged-release (PR), osmotic pump technology (OROS), tablet formulation (also referred to a paliperidone extended-release [ER] tablets, INVEGA) and 2 LAI formulations: paliperidone palmitate 1-month injection (PP1M; XEPLION) and paliperidone palmitate 3-month injection (PP3M; TREVICTA), but there was none acting for longer than 3 months. The present LE application concerns the introduction of the 6-month LAI formulation. The PP1M formulation (XEPLION) was approved in the EU on 4 March 2011 (EMEA/H/C/002105); the PP3M formulation (TREVICTA) was approved in the EU on 26 May 2016 (procedure EMEA/H/C/4066/X/007/G).

The finished product is presented as prolonged release suspension for injection containing 700 mg or 1000 mg of paliperidone (as palmitate) as active substance.

Other ingredients are: polysorbate 20, polyethylene glycol 4000, citric acid monohydrate, sodium dihydrogen phosphate monohydrate, sodium hydroxide (for pH adjustment) and water for injections.

The product is available in pre-filled syringe (cyclic-olefin-copolymer) with a plunger stopper, plunger rod, backstop, and tip cap (bromobutyl rubber) with a thin wall 20G 1½ inch (0.9 mm × 38 mm) safety needle.

2.4.2. Active Substance

The active substance (AS) paliperidone palmitate has already been assessed in connection with the marketing authorization of Invega, Xeplion and Trevicta in the centralised procedure. Information provided on the active substance paliperidone palmitate in this application is identical to that approved for Invega, Xeplion and Trevicta.

2.4.3. Finished Medicinal Product

The following variations related to the authorised finished product were applied:

- change the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to BYANNLI; A.2.a - IAIN,

- to delete Cilag AG (Hochstrasse 201, CH-8200 Schaffhausen) as a site responsible for manufacturing, primary and secondary packaging and release testing of the finished product; A.7 – IA,

- to delete the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006); 6 x C.I.7.b - IB.

Revised product information reflecting the new invented name has been provided. The dossier has been updated to delete Cilag AG (Hochstrasse 201, CH-8200 Schaffhausen) as a site responsible for manufacturing, primary and secondary packaging and release testing of the finished product. The revised product information also reflects the deletion of the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 150 mg/100 mg strengths. Since Paliperidone Janssen-Cilag International (BYANNLI) was an informed consent application of Xeplion, the deletion of the above mentioned strengths is to ensure that the present duplicate MA concerns only the two newly introduced strengths intended for biannually (once every 6 months) administration. The other strengths are available in the MAs of Invega, Xeplion and Trevicta.

All the applied variations are accepted and approved.

2.4.3.1. Description of the product and pharmaceutical development

The finished product (FP) is presented as a white to off white prolonged-release suspension for injection in prefilled syringe containing 700 mg or 1000 mg of paliperidone (as palmitate) and is intended for intramuscular injection every 6 months. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.4.1 of this report. The different dosage strengths, including the syringe size and, the nominal fill volume are presented in Table 1.

Table 1. Different Dosage Strengths with their Syringe Size and Fill Volumes

Dose Equivalent as Paliperidone (mg)	Dose as Paliperidone Palmitate (mg)	Syringe Size	Nominal Fill Volume (mL)
700	1092	5 mL	3.5
1000	1560	5 mL	5.0

The AS is the palmitate ester of paliperidone, which is the major active metabolite of risperidone. Paliperidone palmitate is practically insoluble in aqueous media over a broad pH range. This low solubility of the AS makes it possible to formulate it as a suspension with an extended release profile.

Development of the formulation used in the approved 3-month formulation was based on the insight gained during the 1-month formulation, however a quantitative change in the relative amounts of the excipients in the formulation was required due to an increase in the particle size and active substance concentration. In addition, disodium hydrogen phosphate was not required to meet the targeted buffering capacity.

Development work was performed to ensure that the resulting suspension can be easily resuspended and smoothly injected using thin-walled IM needles. Therefore, the development work focused on the optimization of the concentration of the wetting agent and the stabilizing agents:

-the same wetting agent and stabilizing agent as used in the 1-month formulation were used but in different amounts.

-the concentration of the buffer components, sodium hydroxide and citric acid, was modified in order to maintain chemical stability and the targeted pH.

The suspension contains an aqueous buffer solution that easily penetrates into the muscle tissue, after which the undissolved paliperidone palmitate particles are localized at the site of administration as a loose agglomerate. The paliperidone palmitate particles of the FP suspension dissolve very slowly in the fluids at the injection site. The dissolved prodrug, paliperidone palmitate, is then hydrolysed by esterases into its active compound paliperidone and palmitic acid. This is supported by the observation that little or no paliperidone palmitate reaches the systemic circulation. Only paliperidone enters into the systemic circulation. The dissolution rate of paliperidone palmitate in the extracellular fluids is hypothesized to be the release rate limiting step, and is determined by the specific surface area, and thus particle size and morphology, of the paliperidone palmitate particles. The particle size and morphology are discussed further below in this section; particle size is controlled in the FP specification.

When developing the 3-month formulation, the active concentration was increased to 312 mg/mL paliperidone palmitate (eq. 200 mg/mL paliperidone) in order to achieve the desired dose range, reduce the release rate, and minimize the injection volume. A further concentration increase was not feasible as this would negatively impact processability of the suspension. Therefore, the active concentration of the 6-month formulation was not further increased.

The prior knowledge from the 3-month formulation was successfully leveraged to result the 6-month formulation and no additional formulation development studies were performed; this is acceptable.

The following physicochemical characteristics of the AS were evaluated for their potential influence on the finished product performance (i.e., the in vivo release profile): purity, crystallinity and polymorphism, morphology, solubility, and particle size.

The data demonstrated that none of these characteristics have an impact on the performance of the finished product (FP). For purity, crystallinity, and morphology, this is because the same characteristics are consistently obtained after production. For particle size, this is because the FP milling step is robust and independent of the incoming particle size.

To obtain the 6-month release profile, the bulk suspension is filled in 5 mL syringes to the volumes of 3.5 mL (eq. 700 mg dose) and 5.0 mL (eq. 1000 mg dose). The drug release characteristics of PP6M are determined by drug particle size, concentration and injection volume of the suspension. Drug particle size and concentration for the 6-month formulation were derived from the 3-month formulation, while injection volume was increased to the volumes of 3.5 mL (eq. 700 mg dose) and 5.0 mL (eq. 1000 mg dose) in order to obtain the desired release profile of 6 months. Earlier dose-proportionality and human pharmacokinetic (PK) studies with the approved 1-month finished product (also called PP1M) had proven that the release rate decreases with increasing drug particle size and concentration, and injection volume of finished product suspension. Based on PK simulations, 3.5-fold higher doses were developed for the 3-month formulation. The population PK model developed for the 3-month formulation was applied to the dose selection of the 6-month formulation.

The particle size range developed for the formulation was based on the results of the clinical study R092670-PSY1002, which demonstrated that increasing the particle size of AS in the suspension decreases the Cmax and extends the Tmax.

As the *in vivo* dissolution of the AS particles is the release rate limiting step, the solubility and physical characteristics of the AS are important factors in the formulation design.

Since the same crystal structure and morphology are consistently obtained during production of clinical, primary stability, and validation batches, the particle size is considered as the only variable parameter that can influence the drug release rate. The release characteristics of the FP are controlled by 2 test methods: (1) through an *in vitro* release test and (2) by measuring the particle size distribution of the suspension by means of laser diffraction. Both methods are stability indicating and discriminative for the particle size.

All excipients are well characterized and widely used in pharmaceutical preparations. The excipients used in the commercial formulation have detailed monographs in relevant pharmacopoeias (USP/NF or Ph. Eur.) and are generally recognized as safe. There are no novel excipients used in the formulation. The list of excipients is included in section 6.1 of the SmPC and in paragraph 2.1.1 of this report.

With regard to the manufacturing process development the 6-month formulation is manufactured at the same manufacturing site using the approved 3-month formulation product. Therefore, the existing criticality analysis for 3-month formulation was re-assessed to confirm an appropriate control strategy for the Critical Quality Attributes (CQAs) of the 6-month formulation. The criticality of the process steps of the 6-month formulation was established in line with the 3-month formulation No new manufacturing development experiments were conducted for the 6-month formulation on Steps 1-9. After reassessment of criticality of the filling process, the CQAs particulate matter, sterility and bacterial endotoxins are listed as impacted by Step10 – filling of final suspension. The re-assessment of criticality is applicable for both the 3-month and the 6-month formulations.

Similar to the approved 3-month formulation, the 6-month formulation is manufactured aseptically because terminal sterilization of the final suspension is not feasible. In compliance with Guideline on the sterilisation of the medicinal product, active substance, excipient and primary container EMA/CHMP/CVMP/QWP/850374/2015, the FP needs to be manufactured through aseptic processing using sterile active substance as input for the process. Aseptic crystallization of the AS is performed by dissolving the AS in ethyl alcohol and sterilization by filtration before aseptic precipitation and further aseptic processing.

The production of Phase 3 clinical and primary stability/validation 6-month formulation batches occurred at full scale size at the commercial site.

As discussed above, particle size of the AS in the suspension drives the *in vivo* and *in vitro* release. An IVIVC model which links in vitro drug release with *in vivo* release for formulations manufactured with a different particle size has been successfully established for the 1-month formulation formulation with dv50 particle sizes, which encompasses the dv50 particle size range of the 6-month formulation .

The development of the *in vitro* release method for the 6-month formulation was described and shown to be sufficiently discriminative. The IVIVC confirmed that the *in vitro* release method is biorelevant.

The container closure system is pre-filled syringe (cyclic-olefin-copolymer, COC) with a plunger stopper, plunger rod, backstop, and tip cap (bromobutyl rubber) with a thin wall 20G 1½ inch (0.9 mm × 38 mm) safety needle. The syringe barrel complies with Ph. Eur. 3.1.3 and Ph. Eur. 3.1.5 for plastic containers. The tip cap complies with Ph. Eur. 3.2.9 for rubber closures.

Given that compatibility and safety had been proven for PP3M, the same syringe barrel type and bromobutyl rubber tip cap, using the same materials and supplier, were selected for PP6M. Primary stability studies have demonstrated that during storage in the selected container closure system, the chemical and physical quality

of the finished product is maintained throughout the course of the stability studies. The bromobutyl rubber stopper has been assessed as toxicologically safe in presented extractable and leachable studies.

The container closure system integrity has been successfully demonstrated during storage by means of blue dye ingress testing and a bacterial ingress study, during transportation by plunger movement testing, and after transportation by blue dye ingress testing.

Shipping qualification was performed to demonstrate that the PP6M combination product kit is not adversely affected during shipping, both physically and functionally. It was also demonstrated that horizontal shipment of syringes improves re-suspendability of the FP after shaking, leading to lower injectability forces during administration. Thus, section 6.4 of the SmPC includes a recommendation to this effect.

2.4.3.1. Manufacture of the product and process controls

The FP is manufactured at Janssen Pharmaceutica NV, Beerse, Belgium.

The manufacturing process comprises 4 main stages and 10 steps in total, preparation of the suspension concentrate, milling of the suspension concentrate, dilution of the suspension concentrate and filling of final suspension.

The FP is aseptically manufactured by dispersing the sterile AS 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.

Critical steps have been clearly stated and the applied controls are acceptable as are the other in-process controls. The critical steps were identified as sterile filtration, milling and filling.

The process validation activities consisted of the manufacture of three 100-L batches of the validated bulk suspension. Based on the presented validation data for the 6-month formulation, the data previously presented for the 3-month formulation and considering the adequacy of in-process controls and experience gained on 3-month formulation, it is considered that the manufacture of the 6-month formulation is sufficiently robust and the process produces the finished product (paliperidone palmitate 6-month formulation) is of consistent quality, complying with the designated specification.

2.4.3.2. Product specification

The release and shelf-life specifications for the FP include tests and limits for appearance/ resuspendability/ injectability (visual), identification (HPLC, FTIR), assay (HPLC), chromatographic purity (HPLC), pH (Ph. Eur.), particulate matter (laser diffraction), uniformity of dosage units (Ph. Eur.), *in vitro* release testing (Ph. Eur.-UHPLC), particle size distribution (laser diffraction), sterility (Ph. Eur.) and bacterial endotoxin (Ph. Eur.).

The specification provided for the 6-month product is similar as the currently approved 3-month product, with the exception that the acceptance criteria for endotoxins which have been tightened to account for the higher dosage strength. The specifications used for the control of FP are in line with ICH Q6A, ICH Q3B and were selected on the basis of the available manufacturing and testing experience, manufacturing process capabilities, regulatory guidance, scientific knowledge, and the stability characteristics. Appropriate data have been presented to justify the specifications for each quality characteristic that is controlled. The specifications established for control ensure the identity, safety, and purity of FP throughout the proposed shelf life. The specifications for the finished product are considered adequately justified.

A risk-based assessment was conducted in accordance with ICH Q3D, taking into account any potential contributions from the AS, excipients, manufacturing equipment, container closure system (primary packaging), and processing water into the FP. Based on this assessment supplemented with analytical screening, testing of the FP for elemental impurities is not considered necessary as levels of elemental impurities from various sources are not expected to exceed the permitted daily exposure 30% threshold levels.

A risk assessment with regard to the potential presence of nitrosamines in the FP has been conducted based on principles of the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020).Based on the risk assessment conducted, no risk for presence of, or formation of, nitrosamines is identified for the FP. Moreover, formation of nitrosamines during storage is considered negligible and thus, no additional control measures are deemed necessary.

The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with the ICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

The finished product is released onto the market based on the above release specifications, through traditional final product release testing.

Batch analysis data provided for three commercial scale batches of the each strength and three pilot batches of the each strength, all manufactured by the proposed manufacturer. The results were within the proposed specification. The batch analysis data provided indicate the capability of the manufacturing process to produce FP of consistent quality, complying with the designated specification.

2.4.3.3. Stability of the product

Stability data have been presented on three commercial scale batches of each strength stored in the intended container closure system under long term (25 °C/ 40% RH and 30 °C/ 35% RH) for up to 12 months and under accelerated conditions (40 °C/NMT 25% RH) for up to 12 months were provided as per ICH guideline for semi-permeable containers.

Samples were tested for appearance, assay, chromatographic purity, pH*, in vitro* release, particle size distribution weight loss, sterility and bacterial endotoxins. The weight loss method has been sufficiently described. Al results were within the specifications and in line with the observed results for the 3 month formulation.

A stability studies were also performed under a range of stress conditions such as light (ICH conditions), freeze-thaw cycling -15 °C/30 °C (24 h/24 h)) for at least 2 weeks, for at least 1 month at -20 °C, for at least 12 months at 5 °C, and for at least 1 month at 50 °C in the proposed commercial packaging. The available stability data indicate that the FP is chemically and physically stable under the tested conditions.

Based on the overall submitted stability data, the proposed shelf-life of 2 years without any special storage condition, as stated in SmPC 6.3 and 6.4, is acceptable.

2.4.3.4. Adventitious agents

None of the excipients in the manufacture of the FP is of human or animal origin.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

This application concerned a line extension for the addition of two new strengths forms grouped with 8 type IA, IA_{IN} and IB variations to change the (invented) name of the medicinal product, to delete a manufacturing site and to delete a number of strengths from the MA.

The 8 grouped type IA, IA_{IN} and IB variations have been supported by the respective documentations as per the variation classification guideline and are accepted.

The AS has been previously assessed in connection with the marketing authorization applications of Invega, Xeplion and Trevicta in the centralised procedure; no new information on the active substance has been provided with this line extension.

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

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable and consistent. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. The new strengths are approvable from a quality perspective.

In addition, the following variations related to the authorised finished product were applied and are also approved:

- change the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to BYANNLI;

- to delete Cilag AG (Hochstrasse 201, CH-8200 Schaffhausen) as a site responsible for manufacturing, primary and secondary packaging and release testing of the finished product;

- to delete the 25 mg, 50 mg, 75 mg, 100 mg, 150 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006).

2.4.6. Recommendation(s) for future quality development

None.

2.5. Non-clinical aspects

2.5.1. Introduction

PP6M will be administered with a higher dose volume than PP3M.

The PP6M nonclinical program was designed to build upon previous non-clinical experience with the active ingredient. The dossier contains one new study, a 26-week local tolerance study in minipigs with the objective to compare the impact of increasing the administration volume between PP3M (max in clinic 2.6

mL) and PP6M (max in clinic 5.0 mL). Furthermore, the impurity qualification information previously submitted for the paliperidone palmitate products XEPLION (PP1M) and TREVICTA (PP3M) was updated according to the use of the PP6M formulation and the abuse liability potential was discussed.

2.5.2. Pharmacology

Paliperidone is a racemate comprised of enantiomers: paliperidone (+) R078543 and paliperidone (-) R078544. The pharmacological profiles of the racemate and the 2 enantiomers are similar in *in vitro* binding assays, *in vivo* receptor occupancy studies, and *in vivo* functional interaction studies. Paliperidone palmitate is a prodrug of paliperidone (R076477). Following intramuscular administration, paliperidone palmitate is converted to paliperidone, with minimal systemic exposure to paliperidone palmitate in animals as well as in humans. The pharmacological profile of paliperidone was adequately evaluated during the development of oral paliperidone and was accepted for the XEPLION and TREVICTA dossiers.

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT2- and dopaminergic D2-receptors. Paliperidone also blocks alpha 1-adrenergic receptors and slightly less, H1-histaminergic and alpha 2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

Paliperidone is not bound to cholinergic receptors. Even though paliperidone is a strong D2-antagonist, which is believed to relieve the symptoms of schizophrenia, it causes less catalepsy and decreases motor functions less than traditional neuroleptics. Dominating central serotonin antagonism may reduce the tendency of paliperidone to cause extrapyramidal side effects.

No new pharmacology studies were considered needed to support the use of 6-month injections with paliperidone palmitate.

2.5.3. Pharmacokinetics

Any systemic effect following the IM injection of paliperidone palmitate is mediated through paliperidone. The ADME characteristics of paliperidone after IM administered paliperidone palmitate have been adequately evaluated during the development of the 1-month formulation (PP1M) and were accepted for the XEPLION dossier.

The toxicokinetics of the local tolerance study in the minipig are described in the SmPc (Section 3.2.3).

2.5.4. Toxicology

The non-clinical toxicology program in support of the long-acting injectable nanosuspension of paliperidone palmitate builds on the large dataset of non-clinical toxicology studies previously conducted with oral paliperidone to support the marketing authorization of paliperidone prolonged-release tablets (INVEGA). To support the development of paliperidone palmitate as a long-acting once a month injectable aqueous nanosuspension, the toxicology program of PP1M consisted of single- and repeat-dose toxicity studies addressing systemic toxicity as well as local tolerance at the intramuscular (IM) injection site.

To support the approval of the PP3M product (TREVICTA), two 12-week local tolerance studies were performed in male minipigs comparing the local tolerance and toxicokinetics of the 3-month formulation (PP3M) and the 1-month formulation (PP1M). 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 were not considered to reflect a meaningful difference in adversity. The AUC exposure after a single dose of the PP3M formulation was similar to that after 3 consecutive (once a month) dose administrations of the PP1M formulation. Data in support of the 1- and 3-month formulations (PP1M and PP3M, respectively) were assessed in the XEPLION dossier (EMEA/H/C/2105) and TREVICTA dossier (EMEA/H/C/4066), respectively.

Local tolerance

To support the PP6M formulation intended for IM administration once every 6 months, a 26-week local tolerability study in minipigs compared the impact of increasing the volume between PP3M (max in clinic 2.6 mL) and PP6M (max in clinic 5.0 mL). The study was conducted in compliance with GLP. The intramuscular route of administration was selected because this is the intended clinical route.

The maximum anticipated clinical dose of PP6M is 1000 mg eq. paliperidone, while the maximum recommended clinical dose of PP3M is 525 mg eq. paliperidone. The 2-fold higher maximum clinical dose of PP6M is achieved by the IM injection of a 2-fold higher injection volume, which is 5.0 mL for PP6M compared with 2.625 mL for PP3M.

In this 6-month local tolerability study in male minipigs, the animals received a bilateral (Groups 1 to 9) or a unilateral (Group 10) intramuscular injection of the long-acting injectable formulation of paliperidone palmitate either once (PP6M) or twice with a 3-month dosing interval (PP3M). Saline control and vehicle control groups for each treatment modality were included to investigate whether possible effects were due to the vehicle, the compound, or the combination. Intralipid® 20% was considered as a placebo in clinical trials with PP6M and was, therefore, included as well.

The lowest doses of PP3M and PP6M approximated the maximum recommended (PP3M) or anticipated (PP6M) human dose on the basis of the maximum external dose (i.e., 525 and 1000 mg eq. paliperidone, respectively, scaled on a per kg body weight basis). The highest doses of PP3M and PP6M reflected the maximum recommended (PP3M) or anticipated (PP6M) human dose on the basis of the maximum injection volume (i .e., 2.625 and 5.0 mL/injection, respectively, rounded to 2.6 and 5.3 mL/injection, respectively). Consequently, the lowest dose of PP3M was set at approximately 17.5 mg eq. paliperidone/kg body weight (assuming a 15 kg minipig), and the highest dose at approximately 70 mg eq./kg, administered by a bilateral IM injection with a fixed volume of 0.66 and 2.6 mL per injection site, respectively. The lowest dose of PP6M was set at approximately 35 mg eq./kg, and the highest dose at approximately 141 mg eq./kg, administered by a bilateral intramuscular injection with a fixed volume of 1.3 and 5.3 mL per injection site, respectively. An intermediate dose of approximately mg eq./kg of PP6M was administered by a unilateral intramuscular injection with a fixed volume of 5.3 mL.

Saline control and vehicle control groups for each treatment modality were included to investigate whether possible effects were due to the vehicle, the compound, or the combination. Overall, the study design is considered adequate.

Mortality

There was one preterminal mortality during the study that was considered related to treatment. Administration of PP6M at 141 mg eq./kg resulted in early termination of one minipig due to its poor clinical condition (decreased activity, poor appetite over an extended period and tremors) and body weight loss (-6%

from Days 1 to 8). This animal was given meloxicam for pain relief during Days 2 to 7. At necropsy, slight- to moderate-size formulation depots were present within the skeletal muscle in both injection sites and unilaterally also in the subcutis. These depots were surrounded by (sub)chronic inflammation and adjacent myofibers showed slight degeneration/necrosis, mineralization, and regeneration. Infiltration of macrophages and giant cells was noted in the subcutis and interstitium of the skeletal muscle. Prominent granulopoiesis in the bone marrow was in line with the inflammatory response at the injection sites. There were no treatment-related findings noted in remaining organs.

The preterminal animal had the highest paliperidone plasma levels (217 ng/mL on Day 10) of the Group 8 animals but the levels were not substantially different from the other two animals (183 ng/mL on Day 14 and 188 ng/mL on Day 10). The time of the early termination coincided with the estimated time of T_{max}.

Clinical signs, body weight, hematology and clinical chemistry

In all paliperidone palmitate-dosed groups, test article-related systemic clinical signs included decreased activity throughout most of the study, and occasionally repetitive behavior (increased rooting/chewing at the cage or cage materials), abnormal gait (described as clumsy/stumbling), reduced appetite, decreased vocalization, and/or tremors during the study. A higher occurrence (number of observations/group) of CNS-related clinical signs was generally observed in PP6M-treated animals given 70 or 141 mg eq./kg when compared to animals given PP6M at 35 mg eq./kg or PP3M-treated animals.

Transient mean body weight losses for PP6M at 70 and 141 mg eq./kg or reductions in mean body weight gain for PP3M at 70 mg eq./kg were mainly noted at the beginning of the study.

There were no paliperidone palmitate-related changes in hematology or clinical chemistry parameters sampled at Days 90 and 182.

Dermal scores

Treatment-related dermal findings were noted in PP3M- and PP6M-treated animals. In PP3M-treated animals, very slight to slight edema at 17.5 mg eq./kg (Days 8 to 92) and very slight to moderate edema at 70 mg eq./kg (Days 8 to 182). In PP6M-treated animals, very slight to slight edema at 35 mg eq./kg (Days 8 to 85), slight to moderate edema at 141 mg eq./kg (Days 8 to 43) and transient slight to severe (severe initially) edema at 70 mg eq./kg (Days 8 to 182).

Injection site reactions

At terminal necropsy, pale foci and pale to white linear striations in the skeletal muscle were noted upon gross pathology examination in the injection sites of some but not all animals treated with PP3M at 17.5 or 70 mg eq./kg (Groups 3 and 4) and in some but not all animals treated with PP6M at 35 or 70 mg/kg (Groups 7 and 10). There was no clear dose-response relationship for either PP3M or PP6M. At terminal necropsy, no macroscopic findings were noted in the injection sites of the animals treated with PP6M at 141 mg eq./kg (Group 8).

Bilateral injections on Day 1 and Day 91 with PP3M at 17.5 or 70 mg eq./kg (Groups 3 and 4) resulted in time- and dose-related multifocal infiltrations of macrophages and multinucleated giant cells in the subcutis and/or in interstitium of the skeletal muscle. No remaining formulation depots were found within the injection sites at 3 or 6 months after dosing in 5 of 6 minipigs.

Bilateral or unilateral injections with PP6M resulted in remaining formulation depots at 6 months after dosing surrounded by chronic inflammation at 35 and 70 mg/kg (Groups 7 and 10). There was a high individual variation in the injection site reaction, largely related to the subcutaneous or intramuscular location of the

formulation depot. Minimal to moderate multifocal infiltrations of macrophages and multinucleated giant cells in the subcutis and/or in interstitium of the skeletal muscle were noted for all terminal minipigs dosed with PP6M, including those dosed at 141 mg/kg (Group 8). Large subcutaneous depots, surrounded by a limited chronic inflammatory response (with less infiltrating macrophages and a higher fibrous component) were noted at 70 mg/kg (Group 10), while the intramuscular formulation depots were smaller and triggered a more pronounced inflammatory response. Upon administration of PP6M at 141 mg/kg (Group 8) no remaining formulation depots were found in the injection sites 6 months after dosing. Intramuscular and/or subcutaneous depots were only noted in terminal minipigs from Group 4 (PP3M at 70 mg eq./kg), Group 7 (PP6M at 35 mg eq./kg), and Group 10 (PP6M at 70 mg eq./kg). Formulation depots were composed of slightly eosinophilic amorphous material with cholesterol-like clefts and (multi) focal mineralization. These were usually surrounded by a slight to moderate chronic inflammatory reaction, mainly composed of infiltrating macrophages and (young) fibroblasts. The resolution of these depots is dependent on infiltration of macrophages and their phagocytosis of the crystalline particles, as evidenced by the cholesterol-like clefts within macrophages and multinucleated giant cells.

Toxicokinetics

Plasma paliperidone T_{max} was observed between 10 and 27 days for PP3M and between 10 and 14 days for PP6M. Overall, the increase in plasma paliperidone exposure was approximately dose proportional across the studied dose range for both PP3M and PP6M. At 70 mg eq./kg, the mean C_{max}, $AUC_{(0\text{-}90)}$, and $T_{1/2}$ were similar between the PP3M and PP6M groups.

The exposure after a single dose of the PP6M formulation was approximately similar to that after 2 consecutive (once every 3 months) dose administrations of the corresponding PP3M formulation.

While intramuscular and/or subcutaneous depots were noted in terminal minipigs administered PP3M at 70 mg eq./kg, PP6M at 35 mg eq./kg, and PP6M at 70 mg eq./kg, in individual animals from those groups, the systemic paliperidone exposure was not affected by the IM or subcutaneous location of the injection site depots.

Dependence

Based on the pharmacological profile of paliperidone, the risk of abuse and dependence potential of its prodrug paliperidone palmitate is thought to be minimal. Moreover, clinical experience with risperidone (resulting in high exposure to its pharmacologically active metabolite paliperidone), with paliperidone itself, and other typical and atypical neuroleptics does not reveal any risk of abuse or dependence. Therefore, no dedicated abuse liability studies in animals (i.e., drug discrimination, self-administration, and physical dependence) or in humans were conducted to evaluate the abuse and dependence potential of paliperidone or paliperidone palmitate. This was agreed.

Impurities

The non-genotoxic impurities R206474, R206475, R207919, R208224 and R208225 are synthesis impurities that are homologue esters, structurally related to paliperidone palmitate. They originate from coupling of paliperidone with the palmitic acid impurities, dodecanoic acid, tetradecanoic acid, pentadecanoic acid, heptadecanoic acid, and octadecanoic acid, respectively.

The impurity qualification information was previously submitted for the paliperidone palmitate products XEPLION and TREVICTA was updated according to the use of the PP6M formulation. Overall, the strategy is considered acceptable. Thus, the toxicologically qualified concentrations of the non-genotoxic impurities

R206474, R206475, R207919, R208224 and R208225 for PP6M are 1.7%, 0.7%, 0.8%, 1.4%, and 2.3%, respectively.

Regarding non-genotoxic impurities, the argumentation of the Applicant is as follows: PP6M is intended for chronic dosing by intermittent administration. For individual genotoxic impurities, according to ICH M7 (R1) the threshold of toxicological concern of 1.5 µg/day applies for chronic treatment exceeding 10 years of treatment. However, PP6M is administered intermittently either once every 6 months. Over a lifetime of 70 years, PP6M will be administered once every 6 months or in total 140 times. This translates into approximately 4.7 months of consecutive daily dosing. According to ICH M7 (R1) the acceptable intake for an individual impurity is 20 µg/day for >1 to 12 months of daily treatment. At a maximum dose of 1,560 mg paliperidone palmitate/6 months, the concentration limit for individual genotoxic impurities in the final paliperidone palmitate drug substance is 13 ppm (20 x 1,000/1,560 = 13 ppm).

It is not fully agreed that a lifetime administration of PP6M given about 140 times can be translated into approximately 4.7 months of consecutive daily dosing. Given the depot formulation, it seems more likely that the genotoxic impurities, like the active substance, will be released slowly during an extended period of time. However, the reasoning can be viewed as a worst-case scenario and is therefore acceptable.

2.5.5. Ecotoxicity/environmental risk assessment

The API in the medicinal product Paliperidone Palmitate 6 months Prolonged Release Suspension for Injection, paliperidone palmitate (R092670), is completely hydrolysed to paliperidone (R076477) and palmitic acid in the human body. Consequently, paliperidone palmitate is considered as the pro-drug and paliperidone as the drug. Therefore, in the environmental risk assessment of Paliperidone Palmitate Prolonged Release Suspension for Injection, the environmental impact of the paliperidone (R076477) is assessed. This strategy is agreed as paliperidone is considered a pro-drug.

During the assessment, the following final study reports were submitted:

a. Physico-chemical properties of paliperidone (OECD 107 and 105)

b. Terrestrial plant growth study (OECD 208)

c. Acute earthworm toxicity (OECD 207)

d. Micro-organisms toxicity (OECD 216)

The following studies are ongoing and are proposed by the Applicant to be submitted not later than April 2022:

a. Collembola reproduction (OECD 232)

b. Soil degradation (OECD 307)

c. Aerobic degradation study in sediment/water systems (OECD 308)

Given that no complete ERA has been submitted, it was not possible to fully conclude on the potential risk of paliperiodone to the environment. A Letter of Commitment to complete the outstanding studies and the ERA was provided.

Phase I: Estimation of exposure

Screening for persistence (P), bioaccumulation (B) and toxicity (T)

The octanol/water partition coefficient study in accordance with OECD 107 has been performed as part of the following study 'Determination of Physico-Chemical Properties of Paliperidone (JNJ-16232411-AAA)" (CRL Study No. 20259674; 04 May 2021).

For ionizable compounds the distribution coefficient octanol/water (log Dow) should be determined instead of the partition coefficient octanol/water (log Pow). As this is the case for paliperidone, the log Dow as a function of different pH values and at 20°C was determined, resulting in the following values:

log Dow at pH 5: -0.6

log Dow at pH 7: 0.9

log Dow at pH 9: 2.1

The water solubility at 20°C was determined to be 0.0343 g/L.

The results for log Dow are below the value of 4.5 and it is agreed that no further screening for persistence, bioaccumulation and toxicity is required. Moreover, the result of the log Dow (at pH 7) is < 3, show that paliperidone has a low tendency to bioaccumulate in aquatic organisms and no bioconcentration study is required.

Calculation of $PEC_{surfacewater}$

The predicted environmental concentration in surface water ($PEC_{surfacewater}$) was calculated using the formula and the default values according to guideline EMEA/CHMP/SWP/4447/00 (EMA 2006):

$PEC_{surface\ water}$ [mg/L] = (DOSEai x F_{pen}) / ($WASTEW_{inhab}$ x Dilution)

DOSEai	Maximum daily dose applied per inhabitant	12 mg/(inh·d) Maximum daily dose from all formulations with paliperidone/paliperidone palmitate is represented by Invega:

Form	Dosage range
Invega (oral dosage form)	3-12 mg paliperidone/day
Xeplion (1-month injection)	25-150 mg paliperidone/month
Trevicta (3-months injection)	175-525 mg/3 months
PP6M (6-months injection)	700-1000 mg paliperidone/6 months

F_{pen}	Market penetration	0.01 [Default]
$WASTEW_{inhab}$	Amount of wastewater per inhabitant per day	200 L/(inh·d) [Default]
DILUTION	Dilution factor	10 [Default]

The $PEC_{surfacewater}$ of paliperidone in surface water is calculated to 0.06 µg/L using the default parameters.

Refinement of $PEC_{surfacewater}$

The $PEC_{surfacewater}$ can be refined with estimation for the market penetration of the medicinal product in the EU, based on prevalence data for schizophrenia in the EU. The market penetration factor is calculated as follows: $F_{pen,refined}$=0.36% (0.0036) based on prevalence data for schizophrenia in the Netherlands (see below). The refined $PEC_{surfacewater}$ of paliperidone in surface water is 0.022 µg/L.

Table 2

ANNEX 1: PREVALENCE OF SCHIZOPHRENIA IN EU

PREVALENCE OF SCHIZOPHRENIA (TOTAL CASES)
From Incidence and Prevalence Database (Clarivate Analytics)
Note: Numbers/rates reported by the original source appear in bold type.

Region/Country	Age group (years)	Prevalence rate (%)	Prevalence number	Population*
EUROPE				
[11] Czech Republic	all ages	**0.22**	23,510	10,686,269
[12] Denmark	all ages	**0.25**	14,045	5,618,075
[13] England	all ages	**0.25**	see notes	see notes
[14] Finland	all ages	**0.25**	13,843	5,537,364
[15] France	all ages	**0.24**	161,674	67,364,357
[16] Germany	all ages	**0.22**	177,007	80,457,737
[17] Greece	all ages	**0.24**	25,828	10,761,523
[18] Hungary	all ages	**0.22**	21,617	9,825,704
[19] Ireland	all ages	**0.28**	14,191	5,068,050
[20] Italy	all ages	**0.23**	143,167	62,246,674
[21] Netherlands	all ages	**0.36**	61,744	17,151,228
[22] Norway	all ages	**0.25**	13,430	5,372,191
[23] Poland	all ages	**0.22**	84,526	38,420,687
[24] Portugal	all ages	**0.24**	26,022	10,842,647
[25] Romania	all ages	**0.22**	47,206	21,457,116
[26] Russia	all ages	**0.20**	284,246	142,122,776
[27] Scotland	all ages	**0.23**	see notes	see notes
[28] Spain	15 to 64	**0.62**	203,580	32,835,413
[29] Spain	all ages	**0.27**	133,194	49,331,076
[30] Sweden	all ages	**0.27**	27,111	10,040,995
[31] Ukraine	all ages	**0.19**	83,509	43,952,299
[32] Wales	all ages	**0.24**	see notes	see notes

These estimates were tabulated from the following publication: Charlson FJ et al; "Global Epidemiology and Burden of Schizophrenia: Findings from the Global Burden of Disease Study 2016." Schizophrenia Bulletin; 5/12/18; DOI:10.1093/schbul/sby058. They were extracted from the Clarivate Analytics Incidence and Prevalence Database (IPD), which provided population estimates based on matching to the age-specific population for the current year's population. From Janssen, this IPD database is available from: https://www.rightfind.com/vlib/portal/mlportal.aspx?clientid=60

According to guideline EMEA/CHMP/SWP/4447/00 (EMA 2006) and the 'Questions and answers' document to this guideline (EMA 2016), the $PEC_{surfacewater}$ can be refined based on published epidemiological data. The

prevalence data referred to are dated 2016 but published in 2018. Although not fully up to date, the data are considered acceptable. The refined $PEC_{surfacewater}$ of paliperidone is 0.022 µg/L which is above the threshold of 0.01 µg/L and consequently, a Phase II Environmental fate and effect analysis is required.

Calculation of $PEC_{groundwater}$

The $PEC_{groundwater}$ can be derived from the $PEC_{surfacewater}$ using the following formula:

The $PEC_{groundwater}$ = 0.25 × $PEC_{surfacewater}$ = 0.006 µg/L

The $PEC_{groundwater}$ of paliperidone in ground water is 0.006 µg/L.

Phase II: Environmental fate and effects analysis

Aquatic environmental exposure assessment

Table 3: Overview of completed (with result) and ongoing environmental fate studies in the aquatic and terrestrial compartment with paliperidone.

Test, Guideline, GLP-compliance	Species, Study design, Duration	Results
Water solubility OECD No. 105 GLP	At 20°C	0.0343 g/L
Partition coefficient OECD No. 107 or 123 GLP	Shake flask method at 20°C	log Dow at pH 5: -0.6 log Dow at pH 7: 0.9 log Dow at pH 9: 2.1
Adsorption desorption coefficient OECD No. 106 GLP	4 soils (loamy sand, loam, clay loam and silt)	10113 – 113414 mL/g
Ready biodegradability OECD No. 301F GLP	Manometric Respirometry Test 30 days	Not readily biodegradable
Aerobic transformation in aquatic sediment systems OECD No. 308 GLP	*Study in progress*	*To be provided as part of the final ERA Report*

The adsorption coefficients for 4 soils with different organic carbon contents indicate that there is high affinity for paliperidone to bind to sewage sludge in the Sewage Treatment Plant (STP) and to soils and thus further terrestrial testing is required.

The study OECD308 is in progress. If the results show that >10% of parent compound (+NER) shift to sediment in the water: sediment simulation study, effects on a sediment dwelling organism should be further investigated in Phase Tier IIB.

Aquatic environmental effects assessment

Table 4: Overview of the aquatic environmental effect studies.

Test, Guideline, GLP-compliance	Species, Study design, Duration	Results
Activated sludge, respiration inhibition OECD No. 209 GLP	Activated sludge 3 hours	EC_{50} >2000 mg/L NOEC = 2000 mg/L
Acute toxicity to Daphnia magna OECD No. 202 GLP	Daphnia magna Static test 48 hours	EC_{50} (48h) > 23 mg/L NOEC (48h) = 2.1 mg/L

Acute toxicity to fish OECD No. 203 GLP	Zebra fish (Brachydanio rerio) Static test 96 hours	LC_{50} (96h) = 18 mg/L NOEC (96h) = 2.5 mg/L
Algal growth inhibition test OECD No. 201 GLP	Scenedesmus subspicatus Static test 72 hours	E_bC_{50} = 14 mg/L E_rC_{50} > 16 mg/L $NOEC_b$ = 7.0 mg/L $NOEC^r$ = 7.0 mg/L
Daphnia reproduction test OECD No. 211 GLP	Daphnia magna Semi static 21 days	NOEC = 2.5 mg/L LOEC = 7.9 mg/L
Fish early life stage test OECD No. 210 GLP	Zebra fish (Brachydanio rerio)	NOEC = 3.2 mg/L LOEC = 10 mg/L

Calculation of $PNEC_{water}$, $PNEC_{microorganisms}$ and $PNEC_{groundwater}$

The predicted no effect concentration (PNEC) is calculated by applying an assessment factor to the values resulting from tests on environmental organisms from the compartment of concern.

To calculate the PNEC from the long-term toxicity tests and the microbial effect study, an assessment factor of 10 is applied. This assessment factor accounts for inter-species variations of differences in sensitivity, intra-species variability, and laboratory data to field impact extrapolation (additive, synergistic and antagonistic effects from the presence of other substances may also play a role here).

The $PNEC_{water}$ is based on the lowest NOEC result from the long-term toxicity tests. The $PNEC_{microorganism}$ is based on the NOEC result of the microbial effect study. The $PNEC_{groundwater}$ is based on the NOEC result of the acute toxicity test with Daphnia magna.

Figure 1

$$PNEC_{water} = \frac{\text{Lowest NOEC from long - term toxicity}}{\text{Assessment factor}} = \frac{2.5\ mg/L}{10} = 250\ \mu g/L$$

$$PNEC_{microorganisms} = \frac{\text{NOEC from microbial inhibition study}}{\text{Assessment factor}} = \frac{2000\ mg/L}{10} = 200\ mg/L$$

$$PNEC_{groundwater} = \frac{\text{NOEC from long - term toxicity Daphnia magna}}{\text{Assessment factor}} = \frac{2.5\ mg/L}{10} = 250\ \mu g/L$$

Outcome of Phase II TIER A Fate and Effects Analysis

Calculation of the Ratio $PEC_{surfacewater}/PNEC_{water}$

$PEC_{surfacewater}/PNEC_{water}$ = 0.023 µg/L/250 µg/L = 9.2×10^{-5}

Calculation of the Ratio $PEC_{surfacewater}/PNEC_{microorganisms}$

$PEC_{surfacewater}/PNEC_{microorganisms}$ = 0.023 µg/L/200 mg/L = 1.2×10^{-7}

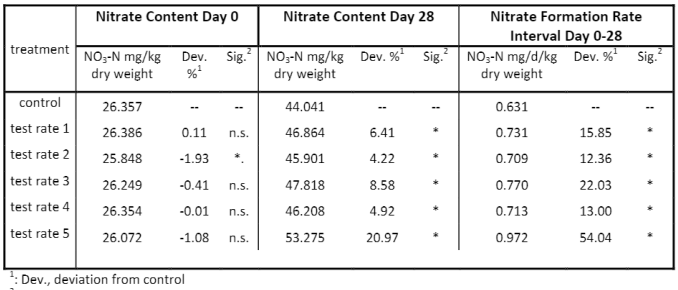
Calculation of the Ratio $PEC_{groundwater}/PNEC_{groundwater}$

$PEC_{groundwater}/PNEC_{groundwater}$ = 0.006 µg/L/250 µg/L = 2.4×10^{-5}

As the ratios $PEC_{surfacewater}/PNEC_{water}$ and $PEC_{groundwater}/PNEC_{groundwater}$ are below 1 and the ratio $PEC_{surfacewater}/PNEC_{microorganisms}$ is below 0.1, no further testing in the aquatic compartment is necessary.

Terrestrial environmental effects assessment

Table 5: Overview of the terrestrial environmental effect studies.

Test, Guideline, GLP-compliance	Species, Study design, Duration	Results
Aerobic degradation in soil OECD No. 307 GLP	Study in progress	To be provided as part of the final ERA Report
Effects on soil microorganisms OECD No. 216 GLP	Biologically active agricultural soil: Loamy sand, 28 days exposure	Effects of paliperidone on nitrate-N content and nitrate-N rate (mean values):  [1]: Dev., deviation from control [2]: sig.: significance according Student-t-test, one-sided smaller, α = 0.05 (* = significant; n. s.: not significant) test rate 1: 10 mg Paliperidone/kg soil dry weight test rate 2: 32 mg Paliperidone/kg soil dry weight test rate 3: 100 mg Paliperidone/kg soil dry weight test rate 4: 320 mg Paliperidone/kg soil dry weight test rate 5: 1000 mg Paliperidone/kg soil dry weight It can be concluded that paliperidone has no negative impact on nitrogen transformation (nitrate-N
Effects on terrestrial plants OECD No. 208 GLP	Oilseed rape (*Brassica napus*) Soybean (*Glycine max*) Sunflower (*Helianthus annuus*) Tomato (*Solanum lycopersicum*) Garden onion (*Allium cepa*)	Summary of effect concentrations (based on fresh weight, emergence, mortality and phytotoxicity):

treatment	Nitrate Content Day 0			Nitrate Content Day 28			Nitrate Formation Rate Interval Day 0-28		
	NO_3-N mg/kg dry weight	Dev. %[1]	Sig.[2]	NO_3-N mg/kg dry weight	Dev. %[1]	Sig.[2]	NO_3-N mg/d/kg dry weight	Dev. %[1]	Sig.[2]
control	26.357	--	--	44.041	--	--	0.631	--	--
test rate 1	26.386	0.11	n.s.	46.864	6.41	*	0.731	15.85	*
test rate 2	25.848	-1.93	*.	45.901	4.22	*	0.709	12.36	*
test rate 3	26.249	-0.41	n.s.	47.818	8.58	*	0.770	22.03	*
test rate 4	26.354	-0.01	n.s.	46.208	4.92	*	0.713	13.00	*
test rate 5	26.072	-1.08	n.s.	53.275	20.97	*	0.972	54.04	*

<table>
<tr>
<td></td>
<td>Perennial ryegrass (Lolium perenne)</td>
<td>
<table>
<tr><th></th><th>NOEC [mg test item/kg dry soil]</th><th>LOEC</th><th>Statistical Analysis</th></tr>
<tr><td>Brassica napus</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
<tr><td>Glycine max</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
<tr><td>Helianthus annuus</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
<tr><td>Solanum lycopersicum</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
<tr><td>Allium cepa</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
<tr><td>Lolium perenne</td><td>≥1000</td><td>>1000</td><td>1, 2, 3</td></tr>
</table>
[1] for fresh weight: two-sample comparison, Student t-test, α = 0.05, one sided smaller
[2] for emergence: two-sample comparison, Fisher's Exact Binomial Test, α = 0.05, one sided greater
[3] for mortality and for phytotoxicity no statistical analysis was performed due to the absence of effects
It can be concluded that a NOEC of ≥1000 mg paliperidone/kg dry soil can be set for all plant species. The emergence rate was not statistically significantly reduced for any species tested. No mortality was observed for any species tested. No phytotoxic effects were observed for any species tested.
</td>
</tr>
<tr>
<td>Acute effects to Earthworm OECD No. 207 GLP</td>
<td>Earthworms (Eisenia fetida)
14-day exposure in treated artificial soil</td>
<td>
Effect of paliperidone on earthworm (Eisenia fetida) mortality and biomass 14 days after treatment:
<table>
<tr><td>Concentration of Paliperidone (JNJ-16232411-AAA) [mg/kg soil dry weight]</td><td>Control</td><td>3.33</td><td>10.0</td><td>33.3</td><td>100.0</td><td>333.0</td><td>999.3</td></tr>
<tr><td>Mortality [%]-14 day</td><td>0.0
–</td><td>0.0
n.s.</td><td>0.0
n.s.</td><td>0.0
n.s.</td><td>0.0
n.s.</td><td>0.0
n.s.</td><td>0.0
n.s.</td></tr>
<tr><td>Weight change [%]</td><td>-9.11
–</td><td>-11.20
n.s.</td><td>-9.48
n.s.</td><td>-6.53
n.s.</td><td>-6.99
n.s.</td><td>-9.71
n.s.</td><td>-12.36
*</td></tr>
<tr><td colspan="8">Endpoints [mg/kg soil dry weight]</td></tr>
<tr><td>NOEC [mg/kg]-14 day related to mortality</td><td colspan="7">> 999.3</td></tr>
<tr><td>NOEC [mg/kg]-14 day related to biomass change</td><td colspan="7">333.0</td></tr>
<tr><td>LC_{50} [mg/kg]-14-day</td><td colspan="7">> 999.3</td></tr>
</table>
n.s.: statistically not significant compared to the control (William's Test, α=0.05)
*: statistically significant compared to the control (William's Test, α=0.05)

It can be concluded that following 14 days exposure with paliperidone to earthworms the LC_{50} was above 999.3 mg/kg soil dry weight. The NOEC related to mortality was 999.3 mg/kg soil dry weight and related to biomass changes was 333.0 mg/kg soil dry weight.
</td>
</tr>
<tr>
<td>Collembola reproduction test OECD No. 232 GLP</td>
<td>Study in progress</td>
<td>To be provided as part of the final ERA Report</td>
</tr>
</table>

The terrestrial risk assessment cannot be concluded until studies OECD 307 and 232 are available.

Table 6: Summary of main study results (some studies are in progress)

Substance (INN/Invented Name): Paliperidone					
CAS-number (if available): 144598-75-4					
PBT screening		Result			**Conclusion**
Bioaccumulation potential- log K_{ow}	OECD107	log K_{ow} at pH 5: -0.6 log K_{ow} at pH 7: 0.9 log K_{ow} at pH 9: 2.1			Potential PBT (N)
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log K_{ow}	-0.6 to 2.1 at pH 5-9			not B
Persistence	DT_{50} or ready biodegradability	Not readily biodegradable (see OECD 301F)			P
Toxicity	NOEC or CMR				T/not T
PBT-statement:	The compound is not considered as PBT. However, a ready biodegradability test showed that it is not biodegradable, and hence should be considered as P.				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surfacewater}$, refined	0.022	µg/L			>0.01 threshold (Y)
Other concerns (e.g. chemical class)	N/A	N/A			N/A
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	4 soils (loamy sand, loam, clay loam and slit) K_{oc} = 10113 – 113414 mL/g			10113 113414 66107 25085 mL/g >10000 thus terrestrial testing is required
Ready Biodegradability Test	OECD 301F	Not readily biodegradable.			Thus OECD 308 is required.
Water solubility	OECD 105	0.0343 g/L at 20ºC			
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50,\ water}$ = $DT_{50,\ sediment}$ = $DT_{50,\ whole\ system}$ = % shifting to sediment =			*Study in progress, to be reported as part of final ERA report*
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test/*Species*	OECD 201	E_bC_{50} E_rC_{50} $NOEC_b$ $LOEC_r$	14 >16 7.0 7.0	mg/L	*Scenedesmus subspicatus*
Acute Toxicity *Daphnia magna*	OECD 202	$EC_{50,48h}$ $NOEC_{48h}$	>23 2.1	mg/L	*Daphnia magna*
Fish, Acute Toxicity	OECD 203	$LC_{50,96h}$ $NOEC_{96h}$	18 2.5	mg/L	*Brachydanio rerio*

Daphnia sp. Reproduction Test (semistatic 21 days)	OECD 211	NOEC LOEC	2.5 7.9	mg/L	*Daphnia magna*
Fish, Early Life Stage Toxicity Test/*Species*	OECD 210	NOEC LOEC	3.2 10	mg/L	*Brachydanio rerio*
Activated Sludge, Respiration Inhibition Test	OECD 209	EC_{50} NOEC	>2000 2000	mg/L	
Phase IIb Studies					
Aerobic and anaerobic transformation in soil	OECD 307	DT50 $\%CO_2$			*Study in progress, to be reported as part of final ERA report*
Soil Microorganisms: Nitrogen Transformation Test	OECD 216	NOEC	≥1000	mg/kg	*Loamy sand* 28 days exposure
Terrestrial Plants, Growth Test/*Species*	OECD 208	NOEC	≥1000 for all species	mg/kg	*Brassica napus, Glycine max, Helianthus annuus, Solanum lycopersicum, Allium cepa, Lolium perenne*
Earthworm, Acute Toxicity Tests	OECD 207	$NOEC_{14d,\ mortality}$ $NOEC_{14d,\ biomass\ change}$	>999.3 333	mg/kg	*Eisenia fetida* 14-day exposure in treated artificial soil
Collembola, Reproduction Test	OECD 232	NOEC		mg/kg	*Study in progress, to be reported as part of final ERA report*

Given that no complete ERA has been submitted, it is not possible to fully conclude on the potential risk of paliperidone to the environment.

The completed studies (i. e. OECD 232, 307 and 308), including an updated ERA, should be provided as a Type II variation. If the results of OECD 308 show >10% of the substance at any time point after or at 14 days is present in sediment, a study in sediment dwelling organisms should be included.

The Applicants committed to complete the 3 remaining studies (OECD 232, OECD 307 and OECD 308) and finalise the Environmental Risk Assessment (ERA) as a post-marketing measure within a variation procedure submitted no later than April 2022. A Letter of Commitment was provided accordingly.

In case a study in sediment dwelling organisms (OECD 218) is warranted, the variation will be delayed to accommodate the completion of this additional study, estimated to be submitted no later than the end of 2023, and an updated Letter of Commitment will be provided once this is known. This was considered acceptable.

The Applicant proposed to file a Type IB variation (code C.I.z) instead of a Type II variation in order to submit the stand-alone ERA studies which seem to be in agreement with the applicable EMA Guidance (EMA 2021). However, it is still preferred that the remaining ERA data are submitted in a Type II variation.

2.5.6. Discussion on non-clinical aspects

In the support of this extension application to seek approval for a new 6-month deport formulation, one new 26-week local tolerance study in minipigs was performed. The new PP6M formulation and the approved PP3M formulation (TREVICTA) was included for comparison of local tolerance and toxicokinetics. This strategy to bridge to the existing toxicology data on systemic toxicity and to address the local safety of the new 6-month formulation was agreed by CHMP (Procedure No.: EMEA/H/SA/1678/2/2016/III). A similar bridging strategy was also performed in support of approval of the 3-month deport formulation (TREVICTA).

In the new 26-week local tolerance study, PP6M was compared to PP3M. Overall, the study design is considered adequate. The low doses were 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). The highest total dose of PP6M at 141 mg eq./kg, exceed the recommended maximum clinical dose.

There was one preterminal mortality during the study that was considered related to treatment. Administration of PP6M at 141 mg eq./kg resulted in early termination of one minipig due to a poor clinical condition (decreased activity, poor appetite over an extended period and tremors) and body weight loss. The moribund condition was likely related to high paliperidone exposure, and potentially injection site pain may have affected the general well-being of the animal. The Applicant is of the opinion that this finding does not represent a new or heightened safety concern for patients. This position can be agreed given the supratherapeutic dose in treatment naïve animals, and the absence of new or unexpected findings at necropsy examination. The total dose of the animals given 141 mg eq./kg is more than twice (2 bilateral injections of 5.3 mL of 200 mg eq./mL formulation) that of the human max dose (1 unilateral injection of 5.0 mL of 200 mg eq./mL formulation). Moreover, the body weight of the minipigs was around 15 kg at study start to be compared with a weight of 50 kg (or above) in adult patients. Thus, the pigs given the highest total dose received a paliperidone dose several folds above the clinical maximum dose. Moreover, the minipigs were treatment-naïve while in the clinical situation, PP6M is intended to be used in patients who have already demonstrated a therapeutic effect and ability to tolerate PP1M preferably for four months or more or PP3M for at least one injection cycle at the time of initiation of PP6M (see SmPC section 4.2).

In all paliperidone palmitate-dosed groups, test article-related systemic clinical signs included decreased activity throughout most of the study, and occasionally repetitive behavior (increased rooting/chewing at the cage or cage materials), abnormal gait, reduced appetite, decreased vocalization, and/or tremors. A higher occurrence (number of observations/group) of these findings was generally observed in PP6M- versus PPM3-dosed animals.

Treatment-related dermal findings mostly noted throughout the study period in PP3M- and PP6M-treated animals generally consisted of very slight to moderate edema at all dose levels and. PP6M-treated animals at 70 mg eq./kg initially showed severe edema, but this reaction became less prominent at later time points. The more notable reaction in these animals may be related to the presence of large subcutaneous depots noted at microscopic evaluation (see below).

Macroscopic evaluation of the injection sites at 3 (PP3M) or 6 months (PP6M) post dose revealed pale foci and pale to white linear striations in the skeletal muscle in some but not all animals treated with PP3M and PP6M with no clear dose-response relationship. Most notably, no macroscopic findings were noted in the injection sites of the animals treated with PP6M at a total dose of 141 mg eq./kg. These macroscopic observations correlated histologically to (multi)focal subcutaneous and intramuscular depots.

Remaining formulation depots were observed at the injection sites in few animals given PP3M and in several animals given PP6M at 35 and 70 mg eq./kg but surprisingly not in animals given the highest total dose of PP6M at 141 mg eq./kg. Formulation depots were composed of slightly eosinophilic amorphous material with cholesterol-like clefts and (multi) focal mineralization. These were usually surrounded by a slight to moderate chronic inflammatory reaction, mainly composed of infiltrating macrophages and (young) fibroblasts.

A local inflammatory response mainly composed of infiltrating macrophages and multinucleated giant cells in the subcutis and/or in interstitium of the skeletal muscle were observed at the injection sites of both PP3M and PP6M-treated animals. There was, however, a high individual variation in the injection site reaction, largely related to the subcutaneous or intramuscular location of the formulation depot. In animals given one unilateral injection of PP6M at 70 mg eq./kg, large subcutaneous depots, surrounded by a limited chronic inflammatory response (with less infiltrating macrophages and a higher fibrous component) were noted. In animals with intramuscular depots, the formulation depots were generally were smaller and triggered a more pronounced inflammatory response. Thus, the inflammatory reaction and its nature were depending on the size and location (subcutaneous versus intramuscular). Variations in location and size of the depot and their associated inflammatory responses played a role in the different outcomes for these injection site reactions, indicating the relevance of a true intramuscular injection for injection site resolution. Considering the small size of the M. biceps femoris in minipigs, it seems likely that the subcutaneous depots could be the result of subcutaneous rather than intramuscular injection rather than migration of test formulation from the skeletal muscle into the subcutaneous tissue.

The systemic exposure generated by PP3M and PP6M is adequately covered by the combined nonclinical safety data from the PP1M as well as from the oral paliperidone and risperidone toxicology programs.

Taken together, the intramuscular administration of PP3M and PP6M resulted in local dermal irritation and an inflammatory response at the injection site. There were no paliperidone palmitate-related changes in hematology or clinical chemistry parameters.

In the clinical trial of BYANNLI, 10.7% of subjects reported injection site related adverse reaction (SmPC section 4.8). None of these events were serious or led to discontinuation. Based on the investigators' ratings, induration, redness, and swelling were absent or mild in ≥ 95% of the assessments. Subject-rated injection site pain based on a visual analogue scale was low and decreased in intensity over time.

2.5.7. Conclusion on the non-clinical aspects

In the new 26-week local tolerance study, intramuscular administration of PP3M and PP6M resulted in local dermal irritation (edema) and an inflammatory response at the injection site. There were large variations in the injection site reactions mainly related to the location of the formulation depots (subcutaneous or intramuscular). Somewhat more pronounced local reactions were observed in some PP6M treated animals and are likely related to the larger administration volume. Apart from this, the nature of the injection site reaction was not apparently different between PP3M and PP6M.

The CHMP considered the following measures necessary to address the non-clinical issues:

Regarding the environmental risk assessment, the ERA studies in progress (i. e. OECD 232, 307 and 308) should be submitted when finalised together with an updated ERA. If the results of OECD 308 show >10% of the substance at any time point after or at 14 days is present in sediment, a study in sediment dwelling

organisms should be included. A Letter of Commitment to complete the outstanding studies and the ERA was provided accordingly.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

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

Table 7: Tabular overview of clinical studies

Protocol ID (Abbreviation)	Study Description	Study Treatments	Number of Subjects
Phase 3 Non-inferiority Study (completed)			
R092670PSY3015 (PSY3015)	Randomized, DB, active-controlled, interventional, parallel-group, multicenter non-inferiority study (PP6M versus PP3M) of 12 months preceded by an OL phase (transition phase of 1 to 4 months and a maintenance phase that included 1 injection cycle with either PP1M or PP3M, yielding a phase duration of 1 or 3 months, accordingly) in subjects with schizophrenia	PP6M DB [a]: fixed dose 700 or 1000 mg eq. (moderate or high) based on PP1M or PP3M dose at the end of maintenance phase/6 months PP3M DB: fixed dose 350 or 525 mg eq. (moderate or high) based on PP1M or PP3M dose at the end of maintenance phase/3 months	OL Phase: n=838 DB Phase: • PP6M: n=478 • PP3M: n=224
Phase 3 OL Extension Study (ongoing)			
R092670PSY3016 (PSY3016)	24-month OL extension study in subjects with schizophrenia who had been previously treated in the DB, randomized, active-controlled study R092670PSY3015	PP6M: flexible dose 700 or 1000 mg eq./6 months	OL: • PP6M: n=178[b]

DB= Double-blind; mg eq.=milligram equivalent; OL=open-label; PP3M=paliperidone palmitate 3-month product; PP6M= paliperidone palmitate 6-month product.

[a] The DB phase included 4 injections for all treatment groups. The PP3M (active control) groups received 1 injection of PP3M every 3 months. The PP6M (investigational drug) groups received 1 injection every 3 months in the following sequence: PP6M → placebo → PP6M → placebo.

[b] As of the cutoff date of 29 May 2020, of 178 subjects, 57 received PP3M in the DB phase of Study PSY3015 and received at least 1 dose of PP6M in PSY3016 and 2 subjects received a second dose; 121 subjects received PP6M in PSY3015 and received 1 additional dose of PP6M in PSY3016, and 4 subjects received 2 additional doses of PP6M.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The PP6M formulation has a higher injection volume than PP3M and PP1M and should only be dosed in the gluteal muscle. PP6M is intended to be used in patients already stabilized on PP3M or PP1M. Patients stabilized with 100 mg eq. or 150 mg eq. PP1M can be transitioned to 700 mg eq. or 1000 mg eq. PP6M respectively. Patients stabilized with 350 mg eq. or 525 mg eq. PP3M can be transitioned to 700 mg eq. or 1000 mg eq. PP6M respectively.

Objectives of the PK development program for the PP6M included characterization of the PK of paliperidone after gluteal injections of PP6M for subjects randomized in Study PSY3015, provision of individual estimates of the secondary pharmacokinetic parameters (i.e. AUC for the considered dosing interval [AUC_{tau}], AUC for a

6-month dosing period [$AUC_{6months}$], through concentration [$C_{through}$] and C_{max}) and evaluation of common clinical questions and dosing scenarios through simulations using the population PK model of PP6M. The pharmacokinetic properties of PP6M were measured from semi-intensive PK sampling in 478 subjects in phase 3 non-inferiority study R092670PSY3015. The study was conducted in the intended patient population.

Methods

Analytical methods

Plasma samples were analysed for paliperidone and paliperidone palmitate concentrations using validated liquid chromatography coupled to tandem mass spectroscopy (LC-MS/MS) methods.

Population pharmacokinetic analysis

The primary objectives of the population PK (popPK) analysis were to characterize the gluteal PK of paliperidone after administration of PP6M, provide individual estimates of exposure parameters and to evaluate covariate effects and to simulate different dosing scenarios.

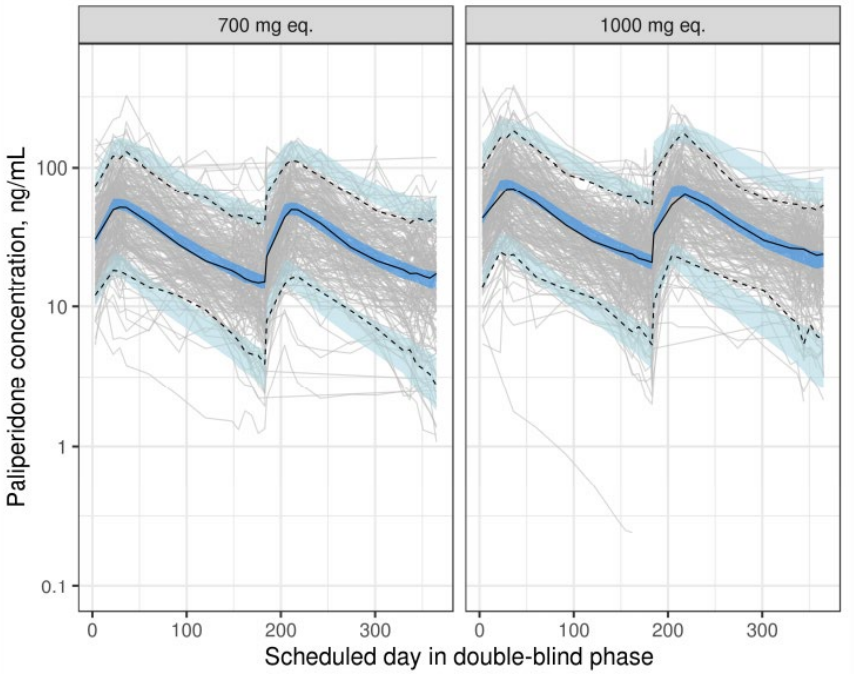
Three intramuscular formulations, PP1M, PP3M and PP6M, were used in study PSY3015. Therefore, the popPK model was based on three sub-models, describing the PK after administration of each of these formulations. The PP1M and the PP3M models have previously been assessed and were considered qualified for simulations. The structural popPK model for PP6M was also considered qualified.

In total, 20,402 paliperidone plasma concentrations from 811 subjects were used in the final popPK dataset for study PSY3015. Of these samples, 15,932 were included in the dataset from 700 subjects in the double-blind phase, of which 68% were in the PP6M treatment arm and 32% in the PP3M treatment arm. Less than 1% of the plasma concentrations were excluded from the analysis, due to co-medication, aberrant data, outliers and BQL values.

The PP6M popPK model was a one-compartment disposition model with first-order elimination. The absorption model included two depot compartments, one with a saturable rapid absorption process and one with a saturable slow absorption process.

For PP3M, the model slightly underpredicted the observed median after the third and fourth doses and there was also a slight overprediction of the variability.

Figure 2: VPC applying the PP6M Poppk Model to PSY3015 Double-Blind Data (External Evaluation), Stratified by the PP6M Doses



Grey lines: Individual observed profiles; Solid back line: Median of observations Dashed black lines: 5th and 95th percentiles of observations; Shaded areas: 95% confidence interval around the median, 5th and 95th percentile of simulations

Absorption

Following IM injection in the multiple dose study, median t_{max} was reached after 28-30 days. Population PK model simulations indicate that the maximum paliperidone concentrations were reached after 33 and 35 days.

The bioavailability of PP6M has not been assessed in a dedicated study.

No bioequivalence study was conducted. The formulation used in PP6M product used in the Phase 3 study PSY3015 will be used in the commercial product without any modifications.

No separate IVIVC was developed for PP6M formulation. The effect of particle size on the in vitro dissolution profile and in vivo PK, and the association between the in vitro release rate and in vivo PK profile, was confirmed in Study R092670-PSY-1002,16 which was submitted as part of the MAA for PP1M (EMEA/H/C/2105). In this study, the range of particle sizes investigated encompassed the particle size used in the PP6M product.
PP6M is restricted to the gluteal muscle and is administered with a 1.5 inch needle only. Thus, effect of injection site and needle length on PP6M PK were not investigated.

The occurrence of measurable prodrug in plasma was infrequently observed in subjects after PP6M dosing (4.5 % and 7.7 % after the 700 and 1000 mg eq. doses). Approximately half of prodrug samples in the double-blind phase of study PSY3015 were within 2-fold of the LLOQ (0.2 ng/ml). Among these, 2 samples had very high concentrations; one subject from PP3M dose had a prodrug concentration of 315 ng/ml and one subject from PP6M dose had a prodrug concentration of 99 ng/ml.

Distribution

Based on the popPK analysis, the apparent central volume of distribution for paliperidone was 1960 L.

Elimination

Based on the popPK analysis, the apparent total clearance for paliperidone was comparable to the 1-month formulation and the 3-month formulation h. The median apparent half-life was estimated to 148 and 159 days after administration of 700 andb 1000 mg PP6M, respectively.

No additional data regarding excretion, metabolism and inter-conversion have been obtained with PP6M.

Dose proportionality

The popPK analysis indicated a dose proportional increase in $AUC_{6months}$, C_{max} and C_{trough} after administration of 700 and 1000 mg eq. PP6M.

Time dependency

The mean C_{trough} value after 700 mg eq. for PP6M was 17.2 ng/ml after the first injection and 17.6 ng/ml after the second injection. The mean C_{trough} value after 1000 mg eq. for PP6M was 23.2 ng/ml after the first injection and 24.3 ng/ml after the second injection.

Intra- and inter-individual variability

The variability in AUC_{6month} after up to two administrations of 700 mg eq. and 1000 mg eq. doses of PP6M ranged from 43 to 48 %. The variability in C_{max} was higher and ranged from 56 to 103 %.

Exposure metrics were derived from the final popPK model's Empirical Bayes estimates (EBE's) of the model parameters. The inter-individual variability (CV%) was 43-44%, 47-50%, and 53-65% for $AUC_{6months}$, C_{max} and C_{trough}, respectively. Inter-occasion variability has not been estimated.

Pharmacokinetics in target population

Study with PP6M have been conducted in the intended target population. The pharmacokinetics of the PP6M formulation has been characterised after multiple-dose in study PSY3015. Dose-normalized mean C_{trough} were lower for PP6M than PP3M. Dose-normalized mean C_{max} was slightly higher for PP6M compared to PP3M. Median t_{max} and dose-normalized AUC_{6month} were comparable for PP6M and PP3M.

Table 8: Pharmacokinetic results of Paliperidone after administration of PP3M at 350 or 525 mg eq. and PP6M at 700 or 1000 mg eq. in the Double-blind phase.

Pharmacokinetics of Paliperidone (mean [SD], t_{max}: median [range])	PP3M 350 mg eq.	PP3M 525 mg eq.	PP6M 700 mg eq.	PP6M 1000 mg eq.
DB 0-6 months				
n	98[a]	112[b]	222[c]	229[d]
t_{max} (h)	670.80 (0.00 - 2256.57)	679.92 (0.00 - 2325.15)	671.09 (0.00 - 4367.42)	674.00 (0.00 - 4366.57)
t_{max} (days)	27.95 (0.00 - 94.02)	28.33 (0.00 - 96.88)	27.96 (0.00 - 181.98)	28.08 (0.00 - 181.94)
C_{trough} (ng/mL)	19.8 (9.82)	34.1 (19.7)	17.2 (11.5)	23.2 (16.2)
C_{max} (ng/mL)	42.5 (23.7)	67.0 (39.1)	68.8 (40.4)	93.6 (61.2)
AUC_{3month} (ng.h/mL)	64357 (31797)	103499 (51173)	-	-
AUC_{6month} (ng.h/mL)	128713 (63593)	206998 (102347)	152555 (73249)	204527 (97213)
DB 6-12 months				
n	87[e]	101[f]	193[g]	197[h]
t_{max} (h)	766.17 (23.67 – 2301.80)	692.33 (44.62 - 2233.83)	717.87 (43.33 - 4367.33)	720.45 (0.00 - 3623.42)
t_{max} (days)	31.92 (0.99 - 95.91)	28.85 (1.86 - 93.08)	29.91 (1.81 - 181.97)	30.02 (0.00 - 150.98)
C_{trough} (ng/mL)	22.7 (10.8)	34.8 (20.6)	17.6 (11.7)	24.3 (12.8)
C_{max} (ng/mL)	44.1 (21.1)	67.2 (55.1)	67.9 (69.8)	84.2 (47.0)
AUC_{3month} (ng.h/mL)	68410 (27774)	103004 (57770)	-	-
AUC_{6month} (ng.h/mL)	136819 (55549)	206009 (115541)	143258 (66364)	191933 (81831)

[a] n=92 for C_{trough}, and n=97 for AUC_{3month} and AUC_{6month}
[b] n=108 for C_{trough}
[c] n=182 for C_{trough} and n=215 for AUC_{6month}
[d] n=181 for C_{trough} and n=222 for AUC_{6month}
[e] n=82 for C_{trough}, and n=84 for AUC_{3month} and AUC_{6month}
[f] n=95 for C_{trough}
[g] n=160 for C_{trough} and n=185 for AUC_{6month}
[h] n=177 for C_{trough} and n=194 for AUC_{6month}

Simulation based on the population pharmacokinetic model

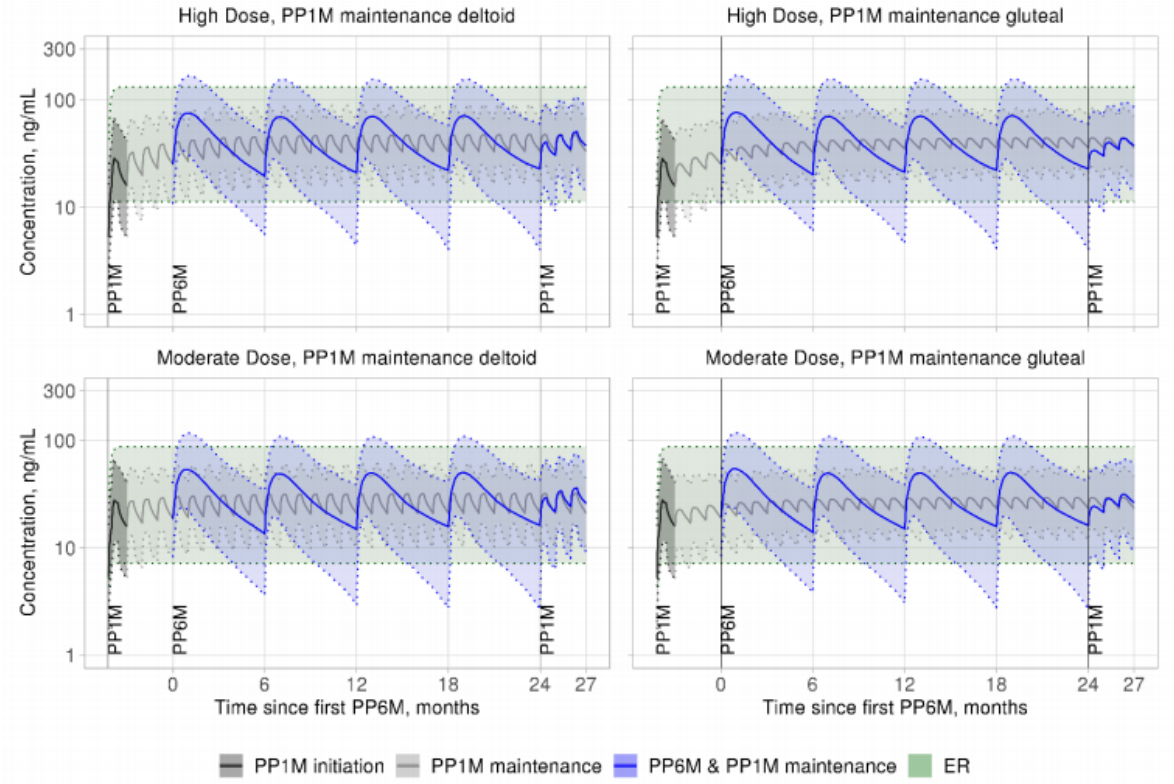
Different scenarios related to PP6M initiation and maintenance dosing, dosing windows and missed doses were simulated based on the final PP1M, PP3M, PP6M and oral paliperidone ER (extended release) models. The PP1M, PP3M and ER models have been assessed in previous PP3M application (EMEA/H/C/4066).

Initiation and Maintenance Regimens

Simulated paliperidone plasma concentration-time profiles after 4 months of standard treatment with PP1M, followed by 4 cycles of PP6M, and thereafter transition to PP1M, are presented in Figure 2. The exposure after repeated oral administration of 8 mg and 12 mg paliperidone was used as comparison in the figures with moderate and high doses respectively. The Applicant claims that steady-state of the PP6M concentration-time profile was attained after the fourth dose, when transitioning from PP1M directly to PP6M. The effect on C_{max} and C_{trough} was less than 2.5% when transitioning from PP1M to PP6M one week later or earlier than the monthly scheduled dose.

Simulations indicate that median paliperidone concentrations can be observed up to 42 months after the administration of 1000 mg eq PP6M.

Figure 3: Simulated Paliperidone Plasma Concentrations Versus Time for the High and Moderate Dose Groups After a 4-month PP1M Treatment, Gluteal PP6M, and Deltoid PP1M (left) vs Gluteal PP1M (right) Maintenance Regimen



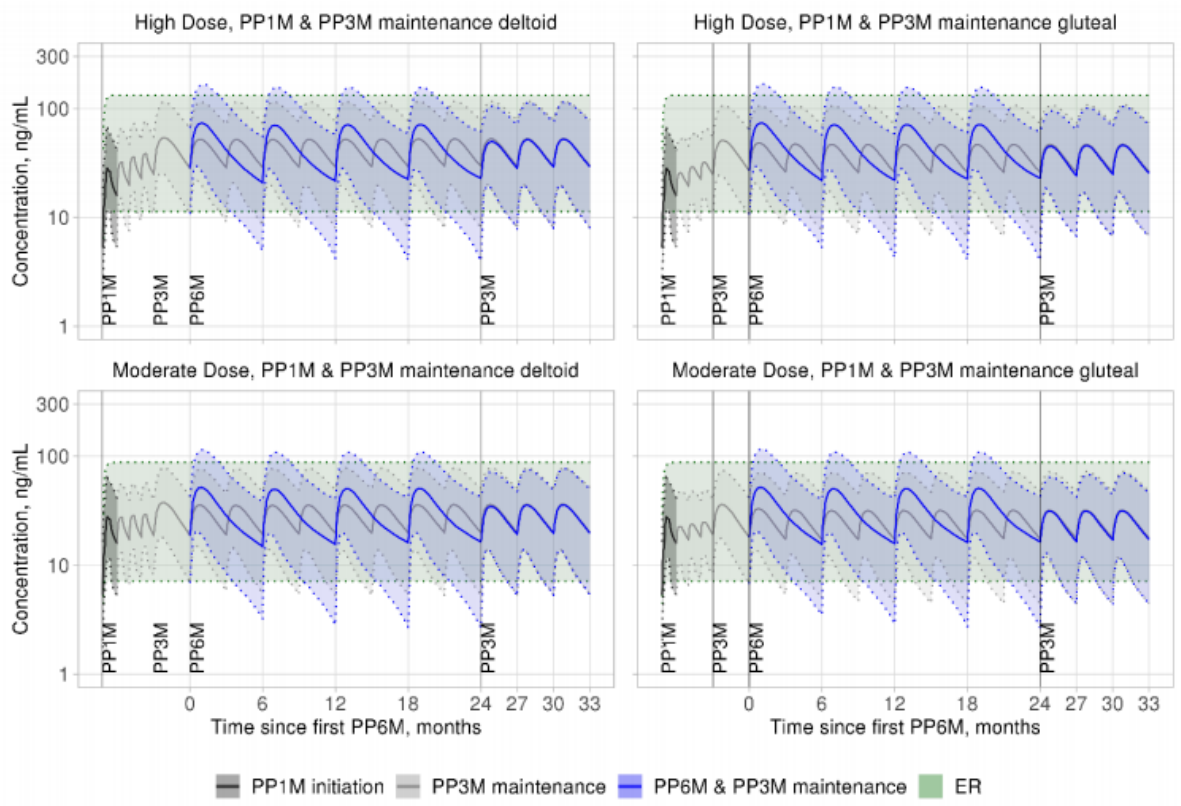
The middle solid line represents the median paliperidone concentration and the shaded area between the bottom and top dotted lines represents the 90% prediction band. Standard PP1M 4-month treatment (initiation doses dark grey followed by maintenance doses light grey) followed by PP6M dosing (blue) in parallel to PP1M (light grey). After 4 doses of PP6M, patients are transitioned again to PP1M. The green shaded band between the dotted lines is the 90% prediction band following treatment with oral paliperidone ER.

In the left panel the PP1M maintenance is given in the deltoid muscle, while in the right panel the PP1M maintenance was dosed in the gluteal muscle. The top row is for the high dose (150 mg eq. PP1M, 1000 mg eq. PP6M), the bottom row for the moderate dose (100 mg eq. PP1M, 700 mg eq. PP6M) level.

PP1M: paliperidone palmitate 1-month product; PP6M: paliperidone palmitate 6-month product; ER: extended-release tablets

Modified from: Mod5.3.3.5/PopulationPKReport/Fig20

Figure 4: Simulated Paliperidone Plasma Concentrations Versus Time profiles for the High and Moderate Dose Groups After 4-Month PP1M Treatment, Followed by One Cycle of Deltoid PP3M (left) vs Gluteal PP3M (right), Gluteal PP6M, and deltoid PP3M (left) vs Gluteal PP3M (right) Maintenance Regimen



The middle solid line represents the median paliperidone concentration and the shaded area between the bottom and top dotted lines represents the 90% prediction band. Standard PP1M 4-month treatment (initiation doses dark grey followed by maintenance doses light grey) followed by PP3M (light grey) and PP6M dosing (blue) in parallel. After 4 doses of PP6M, patients are transitioned again to PP3M. The green shaded band between the dotted lines is the 90% prediction band following treatment with oral paliperidone ER.

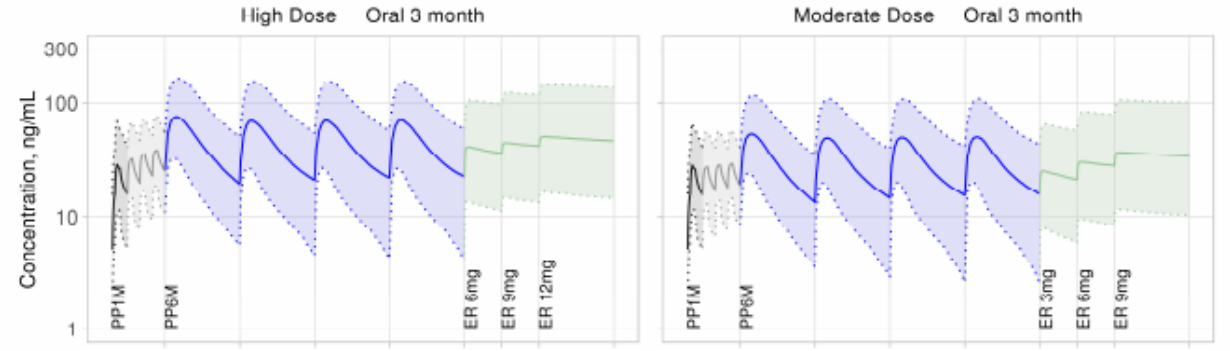
In the left panel the PP1M and PP3M maintenance is given in the deltoid muscle, while in the right panel the PP1M and PP3M maintenance was dosed in the gluteal muscle. The top row is from the high dose (150 mg eq. PP1M, 525 mg eq. PP3M, 1000 mg eq. PP6M), the bottom row from the moderate dose (100 mg eq. PP1M, 350 mg eq. PP3M, 700 mg eq. PP6M) level.

PP1M: paliperidone palmitate 1-month product; PP3M: paliperidone palmitate 3-month product; PP6M: paliperidone palmitate 6-month product; ER: extended-release tablets
Modified from: Mod5.3.3.5/PopulationPKReport/Fig21

Oral paliperidone ER after termination of PP6M treatment

Simulations were performed to provide guidance on how to perform the transition of subjects from PP6M to oral paliperidone ER in the event of PP6M discontinuation. Potential scenarios included oral dosing 180 days after the last steady-state PP6M injection. The oral paliperidone ER tapering schedule proposed by the Applicant included 3 mg / 6 mg daily dosing for 3 months followed by an increase in dose to 6 mg / 9 mg daily dosing for another 3 months, and finally maintenance dosing with 9 mg / 12 mg for the moderate / high PP6M dose levels (Figure 5).

Figure 5: Simulated Paliperidone Plasma Concentrations Versus Time profiles for the High and Moderate Dose Groups Followed By Daily Oral Paliperidone ER in Up-Titration Steps of 3 Months.



The middle solid line represents the median paliperidone concentration and the shaded area between the bottom and top dotted lines represents the 90% prediction band. Standard PP1M 4-month treatment in deltoid (initiation doses dark grey followed by maintenance doses light grey) followed by PP6M dosing (blue), again followed by oral paliperidone ER (green). The left panels are for the high dose (150 mg eq. PP1M, 1000 mg eq. PP6M), the right panels are for the moderate dose (100 mg eq. PP1M, 700 mg eq. PP6M) level.

ER: paliperidone extended-release formulation; PP1M: paliperidone palmitate 1-month formulation; PP6M: paliperidone palmitate 6-month formulation.
Source: Mod5.3.3.5popPK/Sec6.3.2/Fig22

Dosing windows and managing missed doses

Exposure parameters following the simulations of worst-case scenarios of different dosing windows around the regularly scheduled 6-month dosing interval are tabulated in Table 9.

Table 9: Simulated median (5th and 95th percentiles) of C_{max} and C_{trough}, when dosing is performed 1 and 2 weeks earlier and 1, 2, and 3 weeks later.

Dose Level	*Regimen*	*C_{max} (ng/mL)*	*C_{trough} (ng/mL)*
High	base PP6M	76.1 (29.4-163)	
	1 wk earlier	76.3 (29.4-164)	
	2 wk earlier	76.6 (29.6-165)	
Moderate	base PP6M		15.8 (2.64-43.1)
	1 wk later		15.3 (2.38-42.3)
	2 wk later		14.9 (2.08-41.4)
	3 wk later		14.4 (1.79-40.0)

Note: While the impact of earlier dosing on the C_{max} is assessed with reference to PP6M 1000 mg eq., the impact of later dosing on C_{trough} is assessed with reference to PP6M 700 mg eq. This approach allows a comparison of the worst-case for each dose strength (i.e. effect on C_{max} for the highest dose and effect on C_{trough} for the moderate dose).

Simulations were also performed to address the scenarios when the 5th PP6M dose was missed. Criteria were to achieve a quick return to paliperidone plasma concentrations as before the missed dose, without creating an overshoot due the applied re-initiation regimen. If more than 6 months and 3 weeks and up to (not including) 8 months elapsed since the last steady-state PP6M dose, the paliperidone treatment was re-initiated with one deltoid PP1M dose (100 mg for the moderate dose and 150 mg for the high dose) for one month before continuing the regular PP6M 6-month injection schedule. If between 8 and up to (including) 11 months have elapsed after the last steady-state PP6M dose, the paliperidone treatment was re-initiated with a 100 mg PP1M deltoid injection on Day 1 and Day 8, followed by the regular PP6M 6-month injection schedule starting one month after the 2nd PP1M dose. If more than 11 months have elapsed after the last steady-state PP6M dose, the paliperidone treatment was re-initiated with a 4-month PP1M cycle, i.e. PP1M

initiation (150 mg PP1M deltoid injection on Day 1 and 100 mg PP1M deltoid injection on Day 8), followed by PP1M maintenance (three 100 or 150 mg PP1M deltoid/gluteal injections each month for moderate or high dose, respectively) and then a PP6M 6-month regimen.

Special populations

No dedicated study has been performed with PP6M in special populations such as patients with renal and hepatic impairment.

Creatinine clearance (CRCL) was included as a covariate on CL in the popPK model. Simulations indicated a 19-20 % higher median C_{max} and C_{trough} in subjects with mild renal impairment, 50-80 ml/min, as compared to normal subjects after the administration of high PP6M doses. After administration of 700 mg eq. PP6M doses to mild RI subjects (50-80 ml/min), the median C_{max} and C_{trough} was 15-18 % lower relative to those with normal renal function on 1000 mg eq. of PP6M.

Effect on gender, race, age, weight and BMI on the pharmacokinetics of paliperidone was evaluated in study PSY3015, using non-compartmental as well as a population PK approach.

Interactions

No specific drug interaction studies were conducted with PP6M as data from the studies with PP1M and paliperidone ER are considered relevant to PP6M.

Exposure relevant for safety evaluation

With the highest recommended dose of 1000 mg eq., the mean paliperidone concentration (AUC_{6month}) after the second injection were around 191933 ± 81831 ng*h/ml. The highest C_{max} was shown after the first injection in the multiple dose study PSY3015, with mean C_{max} value of 93.6 ± 61.2 ng/ml.

Measurable paliperidone palmitate concentrations have been observed in 4.5 % and 7.7 % after the 700 and 1000 mg eq. doses. The highest observed paliperidone palmitate concentration was 99 ng/ml for PP6M.

2.6.2.2. Pharmacodynamics

No new pharmacodynamics studies have been performed with PP6M. According to the Applicant no absolute individual threshold of paliperidone concentrations been identified that would ensure efficacy.

2.6.3. Discussion on clinical pharmacology

Methods

Analytical methods

The analytical methods are adequately performed. The pre-study validation for paliperidone has previously been assessed in the PP3M application.

Population pharmacokinetic analysis

The final popPK model adequately describes the pharmacokinetics of paliperidone following PP6M administration. The goodness-of-fit plots did not show any major trend in the observed versus individual and population predicted concentrations. The pcVPC for PP6M seemed adequate. Thus, the model is considered acceptable to use for simulations of PP6M.

Due to the relatively high shrinkage for CL, $K_{amt1\ 50}$ and $K_{amt3\ 50}$ the empirical Bayes estimates (EBE) might be biased, and therefore should be interpreted with caution.

Absorption

Even though the bioavailability of PP6M has not been assessed in a dedicated study, data seem to be suggestive of complete bioavailability.

According to the applicant, the changes in clinical status were minimal for those who had detectable levels of paliperidone palmitate and there was no clear association with the peak plasma concentrations.

The clinical pharmacokinetics of paliperidone after a single dose of PP6M (700-1000 mg eq.) in the gluteus has not been studied. The absence of a single dose PK study is considered acceptable.

Distribution

Interpretation of the volume parameter is limited for a formulation with flip-flop kinetics since the disposition parameter is masked by the slow absorption.

Elimination

Paliperidone exhibits flip-flop kinetics when administered as PP6M, i.e. the apparent half-life is driven by the absorption process. The inclusion of half-life in section 5.2 of SmPC is supported by popPK analysis.

No additional data regarding excretion and metabolism for PP6M is deemed necessary as data obtained with the PP1M, PP3M and the oral paliperidone ER formulation are considered appropriate. No additional data regarding inter-conversion for PP6M is deemed necessary

Dose proportionality

There seems to be an approximately dose proportional increase in $AUC_{6months}$ and C_{max} after administration of 700 and 1000 mg eq. PP6M. Inclusion of dose-proportionality in section 5.2 of SmPC is supported.

Time dependency

Based on descriptive statistics there are no indications of a time dependent change in the pharmacokinetics.

Intra- and inter-individual variability

For AUC the inter-individual variability was similar to PP3M formulation but somewhat higher for C_{max} compared to PP3M.

Based on the popPK analysis, the inter-individual variability of $AUC_{6months}$, C_{max} and C_{trough} were moderate to high for PP6M and seemed slightly higher than for PP3M.

Pharmacokinetics in target population

Peak-to-trough fluctuations were higher after administration of PP6M (peak-to-trough ratio 2.71-3.41) compared to after administration of PP3M (peak-to-trough ratio 1.66 to 2.11). AUC_{6month} seemed comparable after the second injection of PP6M when compared to PP3M (PP3M 350 mg eq. vs PP6M 700 mg eq. and PP3M 525 mg eq. vs PP6M 1000 mg eq.).

Simulations based on the population pharmacokinetic model

Initiation and Maintenance Regimens

According to the Applicant is the steady-state plasma concentrations reached after the fourth PP6M injection. However, the simulations indicated only a small difference in C_{max} and C_{trough} between the second and the fourth PP6M dose. Peak-to-trough fluctuations were larger for PP6M compared to PP1M and PP3M. The simulations indicated that plasma concentrations were relatively stable when switching back to PP1M and PP3M from PP6M. The proposed doses for transition between PP1M, PP3M and PP6M is supported by the clinical data in study PSY3015 (since similar doses for transition were used in the clinical study) and also by the popPK simulations.

Oral paliperidone ER after termination of PP6M treatment

The proposed dosage recommendations for the switch to oral paliperidone ER after termination of PP6M treatment is supported. The median $C_{average}$ increased with dose during each of the oral up-titration steps. However, the 90% prediction intervals of the exposure metrics for PP6M and paliperidone ER seemed to overlap. The proposed dosing recommendations are provided as a guide to healthcare professionals. The patients will be treated based on their individual clinical profile.

Dosing windows and managing missed doses

The Applicant suggests a 2 weeks earlier and 3 weeks later dosing window than the scheduled 6-month time point. Only a small increase in median C_{max} was observed when the high PP6M dose was administered 2 weeks earlier than the target date, supporting that PP6M can be administered up to 2 weeks earlier than intended. The median C_{trough} decreased from 15.8 ng/ml to 14.4 ng/ml (8.9%) when PP6M 700 mg was administered 3 weeks later than the scheduled 6-month time point, and the C_{trough} at 5^{th} percentile decreased from 2.64 to 1.79 ng/mL (32% reduction).

The data from the PP6M clinical studies indicated no relationship between low paliperidone concentrations and lack of efficacy. Since a dosing window of only +/- 3 days (a maximal dosing window of approximately 1 week) was allowed for PP6M in the clinical study PSY3015, the study data cannot support the proposed dosing window.

Following the administration of PP6M, PP3M and PP1M at the target dosing intervals (no dosing delays), the median C_{trough} of PP6M (14.4 ng/mL moderate dose) is lower than that for corresponding doses of PP3M (17.6 ng/mL at 350 mg e.q.) and PP1M (21.0 ng/mL at 100 mg e.q.) for which dosing windows of ± 14 days and ± 7 days respectively are recommended. No absolute individual threshold of paliperidone concentrations has been identified that would ensure efficacy.

Even if uncertainties remain regarding the lower boundary of the therapeutic range and an exact time point for when the risk for lack of efficacy becomes unacceptable cannot be determined based on available data, extending the acceptable dosing window beyond the +/- 3 days tested in the clinical study is reasonable given the long half-life of the formulation and the apparently shallow concentration-response relationship. The long half-life observed for PP3M is also expected for PP6M.

In a relapse prevention study for PP3M, the time to the first relapse seemed similar between the placebo group (145 patients) and PP3M group (160 patients) during the first 3-4 weeks. Due to the similarities in PK between PP3M and PP6M (i.e. a similar long half-lifeis also expected for PP6M), these results seem to support a dosing window of +3 weeks.

Overall, considering clinical practical and logistical aspects and based on the information provided by the Applicant, a 2 weeks earlier and 3 weeks later dosing window is supported

Simulations of the re-initiation of treatment with PP1M and also PP6M (a re-initiation treatment not proposed by the Applicant) after a longer interruption with PP6M were provided. The simulations using the proposed PP1M re-initiation regimen following the PP6M dose interruption seemed adequate. In addition, re-initiation of treatment with PP6M after PP6M dose interruptions up to 11 months after the last steady-state PP6M dose indicated similar C_{max} and C_{trough} of paliperidone after the first and subsequent doses as before the dose interruption. The proposed PP1M re-initiation recommendations are similar to the currently approved re-initiation recommendations after a missed dose of either PP1M or PP3M. Although the data support that the similar plasma levels are obtained by a continued 6 months injection even after up to 11 months of delay, the

proposed recommendation to start over again with PP1M after a missed dose could be motivated from some perspectives.

Special populations

Specific dosage recommendations for PP6M are only recommended for patients with renal impairment, which is supported. PP1M and PP3M, PP6M is not recommended for patients with moderate and severe renal impairment. The high dose of PP6M (1000 mg eq.) is not recommended in patients with mild renal impairment.

Interactions

No additional data regarding interactions is deemed necessary as data obtained with the PP1M, PP3M formulation and the oral ER formulation are considered appropriate.

2.6.4. Conclusions on clinical pharmacology

The pharmacokinetics of the new PP6M formulation has been well characterized. The total plasma exposure after PP6M was roughly similar to corresponding doses of PP3M. A number of simulations have been performed addressing different dosing scenarios to support the dosing recommendations in the SmPC.

The application is recommended for approval from a pharmacokinetic point of view.

2.6.5. Clinical efficacy

Dose-response studies and main clinical studies

Main study(ies)

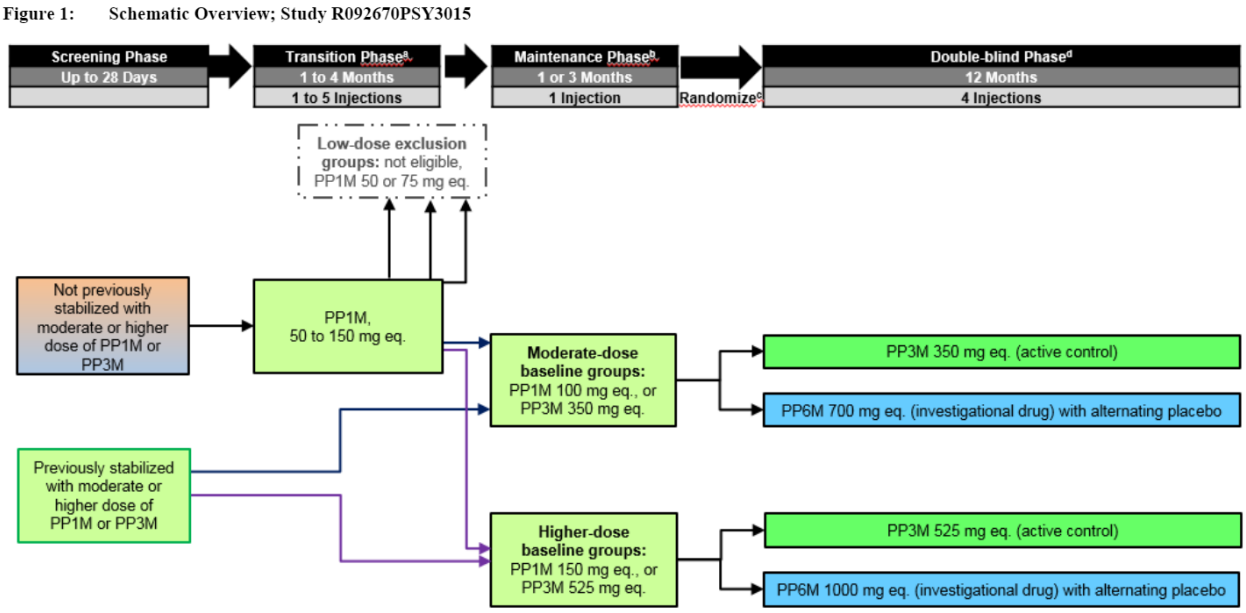
Methods

Main study PSY3015

The main study PSY3015 was a randomized, double-blind, active-controlled, multicenter, interventional, parallel-group study. It was designed to determine if the efficacy of PP6M was non-inferior to the efficacy of PP3M in clinically stable adults with schizophrenia previously treated with PP1M for at least 4 months, or PP3M for at least one 3-month injection cycle.

The study phases shown in Figure 1.

Figure 6: Study Design Study R092670PSY3015



Key: mg eq. = (paliperidone palmitate) milligrams equivalent (to paliperidone); PP1M = paliperidone palmitate 1-month (product); PP3M = paliperidone palmitate 3-month (product); PP6M = paliperidone palmitate 6-month (product).

a During the Transition Phase, the dose levels and the number of injections depended first on a subject's previous treatment and then on his or her individual efficacy and tolerability results.

b Each subject's Maintenance Phase dose was matched by straightforward progression (PP1M to PP1M, or PP3M to PP3M) or by established conversion (PP1M to PP3M) from the same dose that they had been receiving during the Screening Phase or at the end of the Transition Phase, as applicable. See Protocol (Appendix 1) for more details.

c Randomisation occurred on the day of the first double-blind injection (ie, 1 month after the Maintenance Phase injection of PP1M, or 3 months after the Maintenance Phase injection of PP3M).

d The Double-blind Phase included 4 injections for all treatment groups. The active control groups received 1 injection of PP3M every 3 months. The investigational drug groups received 1 injection every 3 months in the following sequence: PP6M → placebo → PP6M → placebo.

Screening phase

The screening phase included discontinuation of disallowed psychotropic medications and completion of an oral tolerability test for subjects without documented exposure to risperidone or paliperidone. Eligible subjects enrolled in Study PSY3015 entered either the transition phase or the maintenance phase, depending on their previous antipsychotic treatment.

Stability was defined as at least 3 months of injections with the last 2 doses being the same strength. Subjects who entered the screening phase on an oral antipsychotic, injectable risperidone, or PP1M previously initiated but not yet stabilized entered a transition phase with 1 to 5 injections of PP1M over 1 to 4 months. The number of injections depended on the subject's previous treatment as well as individual efficacy and tolerability results. Subjects who completed the transition phase and met the predefined criteria of receiving 100 or 150 mg eq. of PP1M and PANSS total score <70 proceeded to the maintenance phase.

Also subjects who entered the screening phase with previous PP1M stability as defined above at the 100 or 150 mg eq. dose, or PP3M stability defined as at least one 3-month injection cycle at 350 or 525 mg eq. dose, and for all a PANSS total score of <70 points, proceeded to the maintenance phase.

Maintenance phase

During the maintenance phase subjects received either 1 dose of PP1M (100 or 150 mg eq.) or PP3M (350 or 525 mg eq.) for 1 or 3 months. The maintenance phase dose was matched by straightforward progression

(PP1M to PP1M, or PP3M to PP3M) or by established conversion (PP1M to PP3M) from the dose they had during screening phase or at the end of transition phase, as applicable. The transition and maintenance phases are referred to as the *open-label phase.*

Subjects who completed the maintenance phase and met the predefined criteria for stability, PANSS total score <70 for the 2 previous assessments, proceeded to the double-blind phase.

Treatments in double-blind phase

Randomised phase
The double-blind phase was 12 months in duration and included 2 injection cycles of PP6M (investigational drug with alternating placebo) or 4 injection cycles of PP3M. Subjects were randomized in a 2:1 ratio to treatment with PP6M or PP3M as follows:

- PP6M treatment group:

  - The open-label 100 mg eq. PP1M and 350 mg eq. PP3M doses were converted to doubleblind 700 mg eq. doses.

  - The open-label 150 mg eq. PP1M and 525 mg eq. PP3M doses were converted to doubleblind 1000 mg eq. doses.

- PP3M treatment group:

  - The open-label PP1M doses (100 or 150 mg eq.) were converted to double-blind PP3M doses (350 or 525 mg eq.).

  - The open-label PP3M doses (350 or 525 mg eq.) were continued at the same double-blind dose level.

Dose adjustment was not permitted during the double-blind phase. Subjects remained in this phase until they experienced a relapse event based on prospectively defined criteria, until they met discontinuation/withdrawal criteria, or until predefined study conclusion criteria were reached.

To note, study PSY3015 was not designed to evaluate the efficacy of distinct doses of PP6M. Consistent with the anticipated use of PP6M in clinical practice, the selection of the PP6M dose for individual subjects was based on the dose of PP1M or PP3M previously optimized for the individual's treatment during the open-label treatment phase.

Objectives

The objective of study PSY3015 is considered relevant to the Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia EMA/CHMP/40072/2010 Rev. 1. The primary hypothesis non-inferiority is in accordance to the study protocol for PSY3015 and is considered adequate to address the objectives.

Outcomes/endpoints

The primary efficacy endpoint was the time to relapse during the double-blind phase. The primary endpoint was based on the difference in the Kaplan-Meier 12 month estimate of survival (i.e., percentage of subjects remaining relapse free) between PP6M and PP3M.

The date of relapse for an individual subject was defined as the date of the first positive findings from a PANSS assessment for symptoms of relapse.

Protocol-specified relapse criteria involved 1 or more of the following:

- sustained worsening in the PANSS total score (an increase from randomization of 25% if the score at randomization was >40, or an increase by 10 points if the score at randomization was ≤40 on 2 consecutive visits separated by 3 to 7 days);
- clinically significant, overt symptomatology manifested by psychiatric hospitalization, suicidal/homicidal ideation or aggressive behavior, or deliberate self-injury and/or violent behavior resulting in injury;
- sustained worsening of individual PANSS items of delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/ persecution, hostility, or uncooperativeness (score of ≥5 if maximum score at randomization was ≤3, or score of ≥6 if maximum score at randomization was 4, on 2 consecutive visits separated by 3 to 7 days).

Secondary efficacy endpoints included the *mean changes from baseline during the 12-month double-blind phase* in the following scales:

- PANSS total score on the 30-item PANSS,[38]
- PANSS subscales (positive, negative, general psychopathology)
- PANSS Marder factors (positive symptoms, negative symptoms, disorganized thoughts, uncontrolled hostility/excitement, anxiety/depression)[51]
- CGI-S scale
- Personal and Social Performance (PSP) scale.
- Proportion of subjects during the double-blind phase who met criteria for symptomatic remission, based on Andreasen criteria[3] and defined as a simultaneous score of mild or less on all selected PANSS items (P1, P2, P3, N1, N4, N6, G5, and G9).
- PANSS responder rates

The validity and reliability of the PANSS has been demonstrated in studies of schizophrenia.[5,47] The full 30-item PANSS was administered at screening, prior to the first dose of PP1M in the transition phase (if applicable), prior to the first dose in the maintenance phase, at the end of the maintenance phase, prior to the first dose of PP3M or PP6M in the double-blind phase, and at 3-month intervals during the double-blind phase. The abbreviated PANSS was used at selected visits when the full PANSS was not administered. It consisted of the PANSS items required for assessment of relapse (P1, P2, P3, P6, P7, and G8).

The CGI-S was conducted at the same time points as the full or abbreviated PANSS, providing investigator ratings on the present severity of psychotic disorder, by a 7-point scale ranging from 1 to 7.[25]

The PSP was administered at screening, at the start of the transition (if applicable), maintenance and double-blind phases, and at 3-month intervals during the double-blind phase. The PSP assessed the degree of difficulty a subject exhibits over a 7-day period within 4 domains: (1) socially useful activities, (2) personal and social relationships, (3) self-care and (4) disturbing and aggressive behavior.[58] The PSP has been shown to have good validity and test-retest reliability with stable schizophrenia[60] and with acute symptoms,[64] and to show a good correlation with the PANSS.[35]

The criteria for determining relapse in Study PSY3015 are in accordance to the study protocol and is considered adequate to address the objectives. According to the applicant, criteria for relapse in Study PSY3015 were identical to previous clinical studies for the approval of PP3M. Further the applicant has

described the secondary endpoints as being similar to those assessed to support approval of PP3M and PP1M. This is agreed and facilitates that outcomes between the different studies can be compared.

Randomisation and blinding (masking)

Eligible subjects were randomised at Day 1 of the DB phase (visit 7b in the study). To be eligible, subjects were required to be clinically stable prior to randomisation according to pre-defined criteria. These have been stated to be identical with the corresponding criteria for randomisation in study R092670PSY3011, a non-inferiority study comparing PP3M with PP1M and the key registration study of PP3M.

The randomisation used a 2:1 ratio, PP6M:PP3M. Balance was achieved by using randomly permuted blocks and was stratified by study site and by moderate or high dose in the Maintenance Phase. Central randomisation was implemented by the use of an Interactive Web Response System (IWRS).

Stratification by moderate or high dose in the maintenance phase is agreed. Stratification by site may have been for administrative reasons. By study design, subjects could switch to PP6M from either PP1M or PP3M, hence, stratification by PP1M or PP3M could in addition have been considered.

The sponsor and all study-site personnel except for the study drug administrator were to be blinded to the administration of the study drug during the Double-blind Phase. Due to differences in syringe sizes for PP3M versus PP6M, the study drug administrator was allowed only to prepare and administer injections, contact IWRS to receive subject medication kit numbers, and to keep drug administration and accountability information. The subject and study staff, other than the study drug administrator, were not allowed to view the syringe or needle or to observe the injection. The subject was instructed to look away during the injection and related steps before and after.

To maintain the blind, the subjects who were assigned to treatment with PP6M received injections of placebo at the 3-month time points between their 6-month doses of investigational drug.

The investigator/sub investigator who assessed the injection site for tenderness, erythema/redness, and induration/swelling was not allowed to review the subject's visual analogue scale (VAS) rating of the injection site pain. In addition, the sponsor and all study-site personnel were to be blinded to the results of PK measurements and prolactin measurements until the time of database lock and unblinding.

During the double-blind phase all administrations were in the gluteal muscles only. Although the blinding procedure is not considered optimal in that the subject was instructed to look away, this should have been facilitated by the site of the injection.

Statistical methods

The statistical analysis plan (SAP) for Study PSY3015: version 4.0 was dated 26 May 2020 and includes an amendment history. Added with version 2 (5 April 2019) was the definition of the primary estimand, supplementary estimands and corresponding analyses with reference to a draft of the ICH E9 addendum available in early 2019. The changes made were not to affect the detailed analyses specified in the previous version of the SAP finalized on 16 Mar 2018 (version 1.0).

The double-blind intent-to-treat analysis population (DB ITT) included all subjects who were randomly assigned to either PP6M or PP3M during the Double-blind Phase and received at least 1 dose of double-blind study drug. This was the primary analysis population for the primary efficacy endpoint.

The per-protocol analysis population included subjects who were randomised (to PP6M or PP3M) during the Double-blind Phase and received at least 1 dose of double-blind study drug excluding subjects with major protocol violations/deviations. Subjects with a major deviation and/or a major protocol violation were

identified prior to database lock and unblinding. Same main analysis, sensitivity analyses and supplementary analyses as defined for the DB ITT population were repeated based on the PP population.

If a subject had received at least one dose of double-blind study drug but then relapsed or had met other relevant conditions for withdrawal or discontinuation, then the subject was to enter a Follow-up Phase. The Follow-up Phase ended 12 months after the subject's first double-blind injection and was meant to collect supplementary poststudy data in terms of minimum safety information (i.e., adverse events) and minimum efficacy information (i.e., relapse status).

The primary efficacy estimand was defined as follows:

The population was restricted to those who were stabilized on either PP1M or PP3M during the Maintenance Phase and meet the inclusion/exclusion criteria.

The variable was time to first occurrence of a relapse event during the Double-blind Phase.

The intercurrent events and corresponding strategies were the following:

• Treatment discontinuation – Hypothetical Strategy: After treatment discontinuation, assume similar efficacy for subjects who discontinued as those subjects from the same treatment group who did not discontinue the treatment.

• Major protocol violations – Treatment Policy Strategy: use all relapse events, regardless of whether or not major protocol violations had occurred.

The population-level summary was the difference in Kaplan-Meier estimate at Month 12 of relapse-free proportions between the two treatment groups.

Subjects who met at least one of the pre-defined criteria for a relapse during the Double-blind Phase before DB Month 12 date were considered to have had a relapse event. Under the primary estimand only the relapse events occurring during the Double-blind Phase prior to treatment discontinuation were counted as events in the primary analysis.

Subjects still in the DB phase up to the date of DB Month 12 without a relapse event, were censored at the date of the DB Month 12 whether the date was before or after Day 365. Subjects who discontinued treatment (and therefore the Double-blind Phase) before Day 365 without a relapse event, were censored at the day of discontinuation.

For the main analysis, the Kaplan-Meier method was used to estimate the Month 12 cumulative estimate of survival (i.e., percentage of subjects remaining relapse-free). Standard Error (SE) estimates were based upon Greenwood’s formula. Non-inferiority of PP6M to PP3M was to be concluded if the lower limit of the 2-sided 95% confidence interval of the difference in the relapse-free rates between PP6M and PP3M exceeded -10%.

As a sensitivity analysis a Tipping Point analysis has been performed based on the assumption that subjects on PP6M who discontinued prematurely had a higher relapse hazard starting from the discontinuation time, compared with similar subjects who remained in the DB phase. For the PP3M group, the ignorable censoring assumption was maintained.

Three supplementary estimands were defined to support the primary estimand. The only component that changed from the definition of the primary estimand was how the strategy for treatment discontinuation was defined. For subjects who discontinued treatment during the Double-blind phase and entered the Follow up phase, their last day of the Follow up phase was recorded as the trial disposition date.

To evaluate the consistency of the results in various subgroups, the Kaplan-Meier estimate of time to relapse was used for the analysis of a number of pre-defined subgroups. The treatment difference between PP6M and PP3M groups at Month 12 and its 95% confidence interval were reported and a forest plot was used for graphical display.

There was no adjustment for multiple testing for the secondary efficacy analyses.

Results

Numbers analysed

A total of 702 subjects were randomised and were included in the ITT (DB). Consistent with previous scientific advice from CHMP, more than 25% of subjects were enrolled and treated at sites in the EU during the double-blind phase (n=193, 28%).

Table 10: Number of Subjects in Each Analysis Set by Study Phase; OL ITT (Study R092670PSY3015)

	OL Transition	OL Maintenance			-Combined OL-	Double-Blind		
	OL PP1M (N=568)	OL PP1M (N=362)	OL PP3M (N=405)	Total Maintenance (N=767)	OL PP1M/PP3M (N=838)	PP3M (N=224)	PP6M (N=478)	Total Double-Blind (N=702)
Intent-to-Treat(OL)	568 (100.0%)	362 (100.0%)	405 (100.0%)	767 (100.0%)	838 (100.0%)	224 (100.0%)	478 (100.0%)	702 (100.0%)
All randomized subjects	463 (81.5%)	342 (94.5%)	360 (88.9%)	702 (91.5%)	702 (83.8%)	224 (100.0%)	478 (100.0%)	702 (100.0%)
Intent-to-Treat(DB)	463 (81.5%)	342 (94.5%)	360 (88.9%)	702 (91.5%)	702 (83.8%)	224 (100.0%)	478 (100.0%)	702 (100.0%)
Per-protocol	456 (80.3%)	333 (92.0%)	346 (85.4%)	679 (88.5%)	679 (81.0%)	217 (96.9%)	462 (96.7%)	679 (96.7%)

Note: Percentages calculated with the number of subjects in each group as denominator.
Note: All enrolled subjects were included in the Intent-to-Treat (OL) analysis set.

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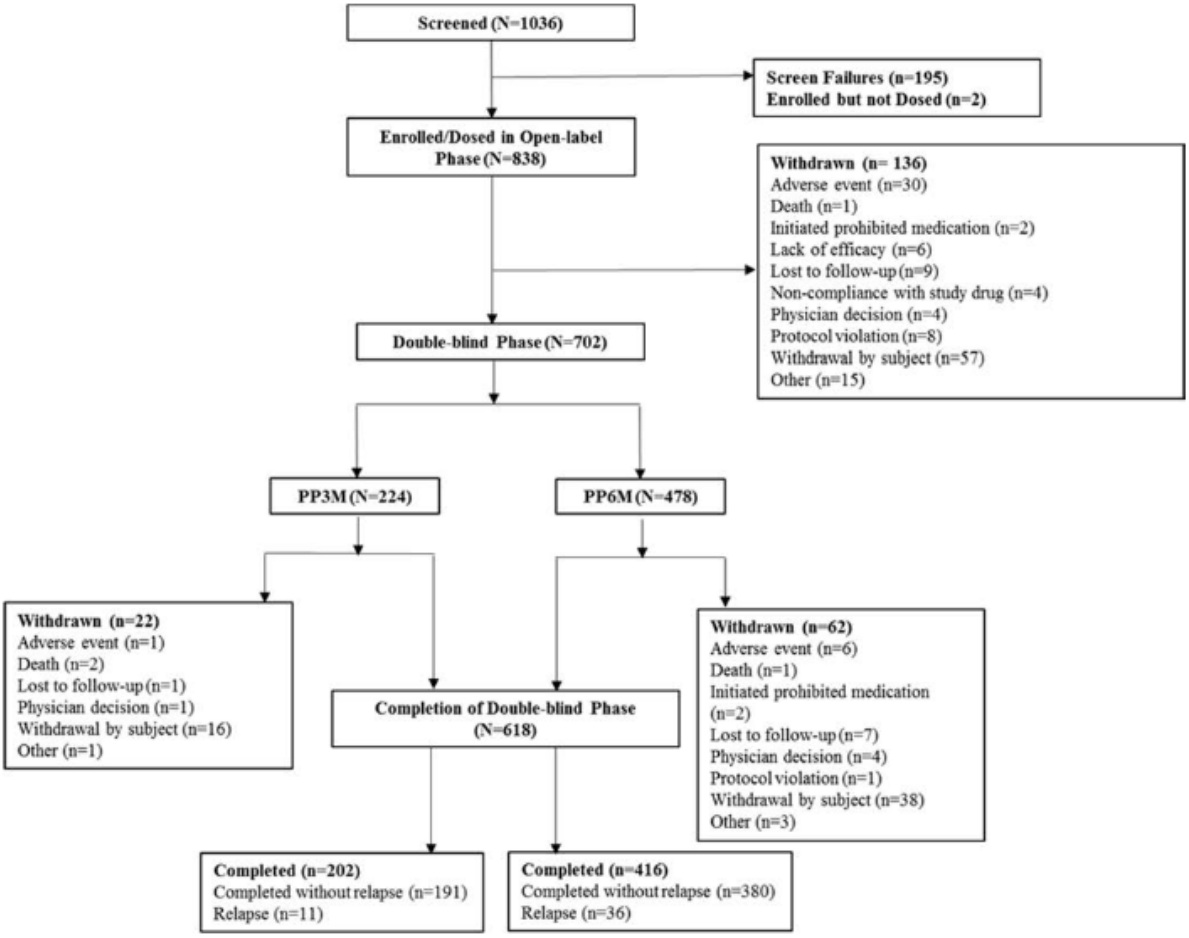
Participant flow

Figure 7

Figure 2: Study Completion and Withdrawal Information (Study R092670PSY3015)



Cross-reference: Mod5.3.5.1/PSY3015/Fig2

Baseline data

Table 11

TSIDEM01B: Demographic and Baseline (OL) Characteristics;DB ITT (Study R092670PSY3015)			
	PP3M (N=224)	PP6M (N=478)	Total (N=702)
Age (years) [a]			
N	224	478	702
Mean (SD)	40.0 (10.98)	41.2 (11.77)	40.8 (11.53)
Median	39.0	40.5	40.0
Range	(19; 68)	(18; 69)	(18; 69)
Age category (years) [a], n (%)			
N	224	478	702
18-25	22 (9.8%)	44 (9.2%)	66 (9.4%)
26-50	163 (72.8%)	330 (69.0%)	493 (70.2%)
51-65	36 (16.1%)	96 (20.1%)	132 (18.8%)
>65	3 (1.3%)	8 (1.7%)	11 (1.6%)
Sex, n (%)			
N	224	478	702
Male	154 (68.8%)	326 (68.2%)	480 (68.4%)
Female	70 (31.3%)	152 (31.8%)	222 (31.6%)
Undifferentiated	0	0	0
Unknown	0	0	0
Race, n (%)			
N	224	478	702
American Indian or Alaska Native	0	0	0
Asian(include Asian subcategories) [b]	30 (13.4%)	66 (13.8%)	96 (13.7%)
Black or African American	23 (10.3%)	49 (10.3%)	72 (10.3%)
Native Hawaiian or Other Pacific Islander	0	3 (0.6%)	3 (0.4%)
White	168 (75.0%)	353 (73.8%)	521 (74.2%)
Other	0	0	0
Multiple[c]	2 (0.9%)	3 (0.6%)	5 (0.7%)
Not reported	1 (0.4%)	4 (0.8%)	5 (0.7%)
Ethnicity, n (%)			
N	224	478	702
Hispanic or Latino	25 (11.2%)	75 (15.7%)	100 (14.2%)
Not Hispanic or Latino	197 (87.9%)	397 (83.1%)	594 (84.6%)
Not reported	2 (0.9%)	6 (1.3%)	8 (1.1%)
Country, n (%)			
N	224	478	702
Argentina	15 (6.7%)	33 (6.9%)	48 (6.8%)
Australia	1 (0.4%)	3 (0.6%)	4 (0.6%)
Brazil	23 (10.3%)	50 (10.5%)	73 (10.4%)
Bulgaria	13 (5.8%)	29 (6.1%)	42 (6.0%)
Czech Republic	11 (4.9%)	28 (5.9%)	39 (5.6%)
France	2 (0.9%)	5 (1.0%)	7 (1.0%)
Hong Kong	1 (0.4%)	3 (0.6%)	4 (0.6%)
Hungary	8 (3.6%)	11 (2.3%)	19 (2.7%)
India	12 (5.4%)	22 (4.6%)	34 (4.8%)
Italy	3 (1.3%)	5 (1.0%)	8 (1.1%)
Korea, Republic of	0	3 (0.6%)	3 (0.4%)
Malaysia	6 (2.7%)	13 (2.7%)	19 (2.7%)
Mexico	6 (2.7%)	17 (3.6%)	23 (3.3%)

TSIDEM01B: Demographic and Baseline (OL) Characteristics;DB ITT (Study R092670PSY3015)			
	PP3M (N=224)	PP6M (N=478)	Total (N=702)
Poland	17 (7.6%)	38 (7.9%)	55 (7.8%)
Russian Federation	40 (17.9%)	83 (17.4%)	123 (17.5%)
Spain	9 (4.0%)	14 (2.9%)	23 (3.3%)
Taiwan	9 (4.0%)	21 (4.4%)	30 (4.3%)
Turkey	6 (2.7%)	14 (2.9%)	20 (2.8%)
Ukraine	15 (6.7%)	33 (6.9%)	48 (6.8%)
United States	27 (12.1%)	53 (11.1%)	80 (11.4%)
Region, n (%)			
N	224	478	702
European Union	63 (28.1%)	130 (27.2%)	193 (27.5%)
US	27 (12.1%)	53 (11.1%)	80 (11.4%)
Non-EU/Non-US	134 (59.8%)	295 (61.7%)	429 (61.1%)
Baseline (OL) weight (kg)			
N	224	478	702
Mean (SD)	80.8 (17.01)	81.9 (16.86)	81.5 (16.90)
Median	81.5	80.0	80.1
Range	(48; 128)	(47; 140)	(47; 140)
Baseline (OL) height (cm)			
N	224	478	702
Mean (SD)	171.2 (9.98)	171.3 (9.82)	171.3 (9.86)
Median	172.0	172.0	172.0
Range	(140; 196)	(144; 196)	(140; 196)
Baseline (OL) BMI (kg/m2)			
N	224	478	702
Mean (SD)	27.5 (4.96)	27.9 (4.96)	27.7 (4.96)
Median	27.0	27.4	27.2
Range	(17; 40)	(17; 40)	(17; 40)
Baseline (OL) BMI category (kg/m2), n (%)			
N	224	478	702
Normal <25	76 (33.9%)	139 (29.1%)	215 (30.6%)
Overweight 25-<30	82 (36.6%)	192 (40.2%)	274 (39.0%)
Obese >= 30	66 (29.5%)	147 (30.8%)	213 (30.3%)
Baseline (OL) waist circumference (cm)			
N	224	476	700
Mean (SD)	95.7 (14.41)	95.7 (15.30)	95.7 (15.01)
Median	95.0	94.0	94.5
Range	(61; 139)	(61; 140)	(61; 140)
Nicotine use, n (%)			
N	224	478	702
Current	90 (40.2%)	188 (39.3%)	278 (39.6%)
Former	15 (6.7%)	32 (6.7%)	47 (6.7%)
Never	119 (53.1%)	258 (54.0%)	377 (53.7%)

a) Age at Screening visit.
b) Asian subcategories include Chinese, Korean, Japanese, Filipino, Asian Indian, Thai, Malaysian, and Asian (other).
c) If multiple race categories are indicated, then Race is recorded as "Multiple".

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As shown below in the analysis of the primary endpoint, more subjects in the PP3M arm than in the PP6M remained relapse free. Based on subgroup analyses, there was a numerical difference among those on a high

dose level during maintenance with an estimated percentage of 91.7% of subjects being relapse free in the PP6M arm compared to 96.6% in the PP3M arm.

Summary of main efficacy results

The following table summarise the efficacy results from the main study supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 12: Summary of efficacy for trial PSY3015

Title: A Double-blind, Randomized, Active-controlled, Parallel-group Study of Paliperidone Palmitate 6-Month Formulation			
Study identifier	Protocol R092670PSY3015; Phase 3 EudraCT Number: 2017-001941-28 EDMS-ERI-130495167, 5.0		
Design	Double-blind, Randomized, Active-control, Parallel group, Multi-centres, 20-countries, Clinical Study of Paliperidone Palmitate 6-Month versus 3.month formulas, in Schizophrenia patients stabilised on Paliperidone before randomisation		
	Duration of main phase Run-in phase: Duration of Extension phase:		12 months <time> <not applicable> 24 months OL Study PSY3016
Hypothesis	Non-inferiority of PP6M to PP3M		
Treatments groups	PP6M		Paliperidon 6 months injection. 12 months duration, n=478
	PP3M		Paliperidon 3 months injection. 12 months, n=224
Endpoints and definitions	Primary endpoint	RF	Time to relapse during the Double-blind Phase; percentage relapse free subjects at Month 12. -Non-inferiority of PP6M to PP3M if the lower limit of the 2-sided 95% CI of the difference in the relapse-free rates exceeded -10%. -PP6M superior to PP3M if the lower limit of the 2-sided 95% CI of the difference in the relapse-free rates exceeded
	Secondary endpoint	PANSS*,**	*PANSS total score, on the 30-item PANSS. **PANSS subscales (pos, neg, general and Marder factors) Mean changes from baseline at Month 12.
	Co-Secondary endpoint	CGI-S	CGI-S scale Mean change from baseline at Month 12.
Database lock	<date>		
Results and Analysis- see ITT analysis below. Also PP primary analysis showed non-inferiority of PP6M to PP3M, by RF difference of -3.2% [95% CI: -7.1%; 0.7%].			
Analysis description	Primary Analysis		

Analysis population and time point description	Intent to treat, schizophrenia, randomised cohorts At 12 months			
Descriptive statistics and estimate variability	Treatment group	PP6M	PP3M	Difference (95% confidence interval) PP6M-PP3M
	Number of subject	478	224	
	Estimated Relapse Rate based on Kaplan Meier model	8.1%	5.2%	2.9% (-1.1%, 6.8%)
	(RF) Relapse rate Observed	7,5% (n=36)	4,9% (n=11)	2,6%

Secondary Efficacy Endpoints

Table 13: Secondary Efficacy Endpoints: Change from Double-blind Baseline to End of 12 Month (Study R092670PSY3015: DB ITT Analysis Set)

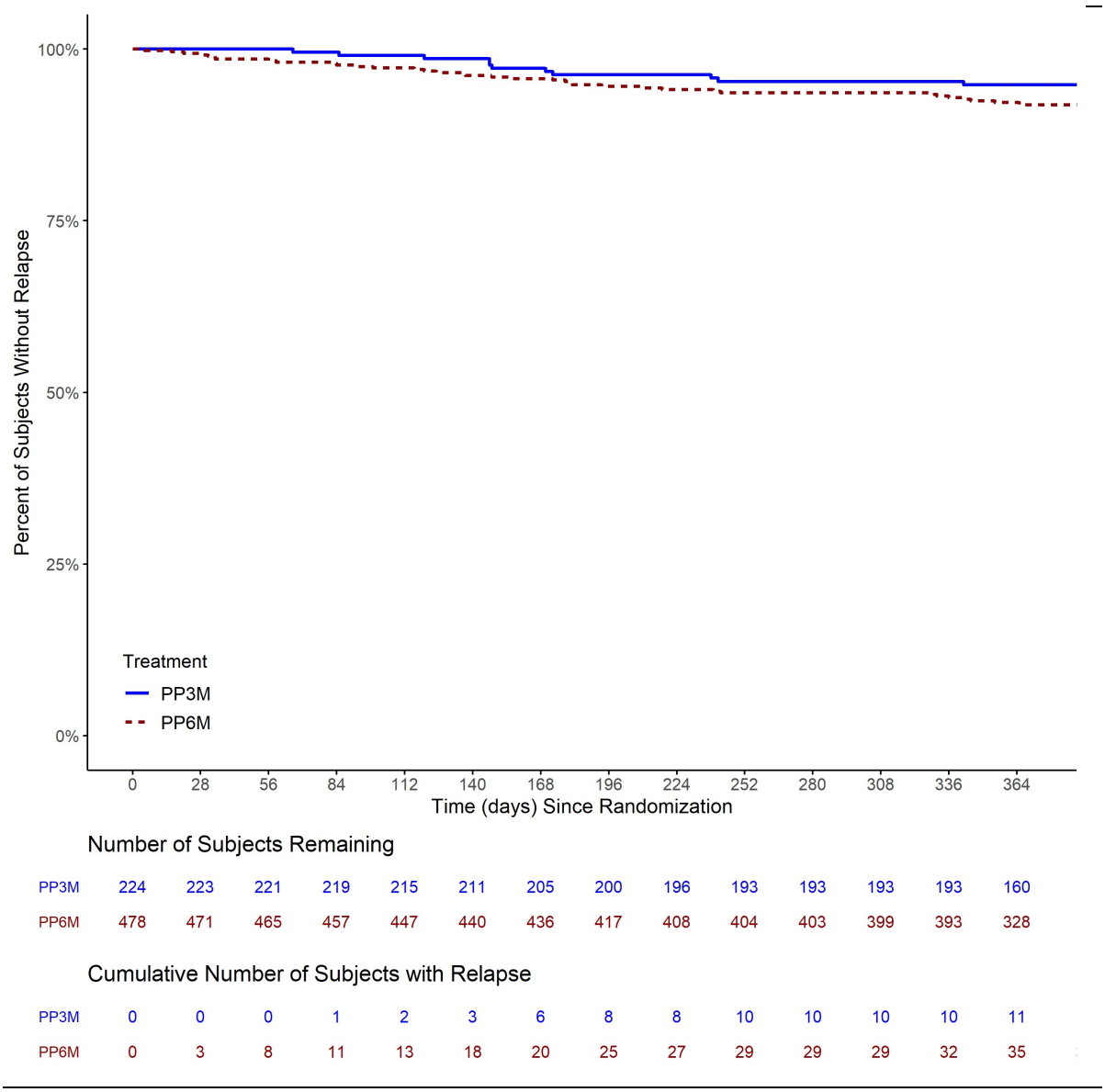
	Mean (SD) Change: DB Baseline to End of 12 Month		Difference in LS Means
Secondary Endpoint	PP6M (N=478)	PP3M (N=224)	(95% CI)
PANSS Total Score	-1.8 (8.92)	-1.6 (7.40)	-0.1 (-1.44; 1.19)
PANSS Factor Scores			
Positive symptoms	-0.4 (3.65)	-0.4 (3.19)	0.0 (-0.50; 0.56)
Negative symptom	-0.8 (2.82)	-0.7 (2.61)	-0.0 (-0.45; 0.38)
Disorganized thoughts	-0.4 (2.35)	-0.2 (2.56)	-0.2 (-0.59; 0.16)
Uncontrolled hostility/excitement	0.1 (1.71)	0.0 (1.31)	0.1 (-0.14; 0.32)
Anxiety/depression	-0.3 (2.24)	-0.3 (2.17)	0.0 (-0.28; 0.34)

PANSS Subscale Scores			
Positive	-0.1 (3.30)	-0.1 (2.82)	0.0 (-0.46; 0.51)
Negative	-0.7 (2.70)	-0.6 (2.61)	-0.1 (-0.48; 0.35)
General psychopathology	-1.0 (4.86)	-0.9 (4.18)	-0.0 (-0.76; 0.66)
CGI-S Score	0.0 (0.70)	0.0 (0.63)	-0.0 (-0.11, 0.09)
PSP Total Score	1.0 (7.12)	1.1 (8.11)	-0.2 (-1.27, 0.97)

Based on analysis of covariance (ANCOVA) model with treatment (PP6M vs PP3M) and country as factors, and baseline value as a covariate. Difference is for change from baseline, PP6M – PP3M.

Key: ANCOVA=analysis of covariance; CI=confidence interval; DB=double-blind; LS=least squares; PP3M=paliperidone palmitate 3-month product; PP6M=paliperidone palmitate 6-month product.

Figure 8: Kaplan-Meier Plot of Time to Relapse During the Double-blind Phase Up to Month 12; DB ITT (Study R092670PSY3015)



Also the per-protocol analysis demonstrated non-inferiority of PP6M to PP3M (K-M difference of -3.2% [95% CI: -7.1%; 0.7%]).

The results across prespecified population subgroups (sex, age, race, baseline BMI, region, dose level in maintenance phase, dose regimen in maintenance phase) were generally consistent with the results of the primary endpoint analysis:

Figure 9

Figure 6: Forest Plot of Estimated Percentage (95% CI) of Subjects that Remained Relapse Free at the End of Month 12 of Double-blind by Various Subgroups; DB ITT (Study R092670PSY3015)

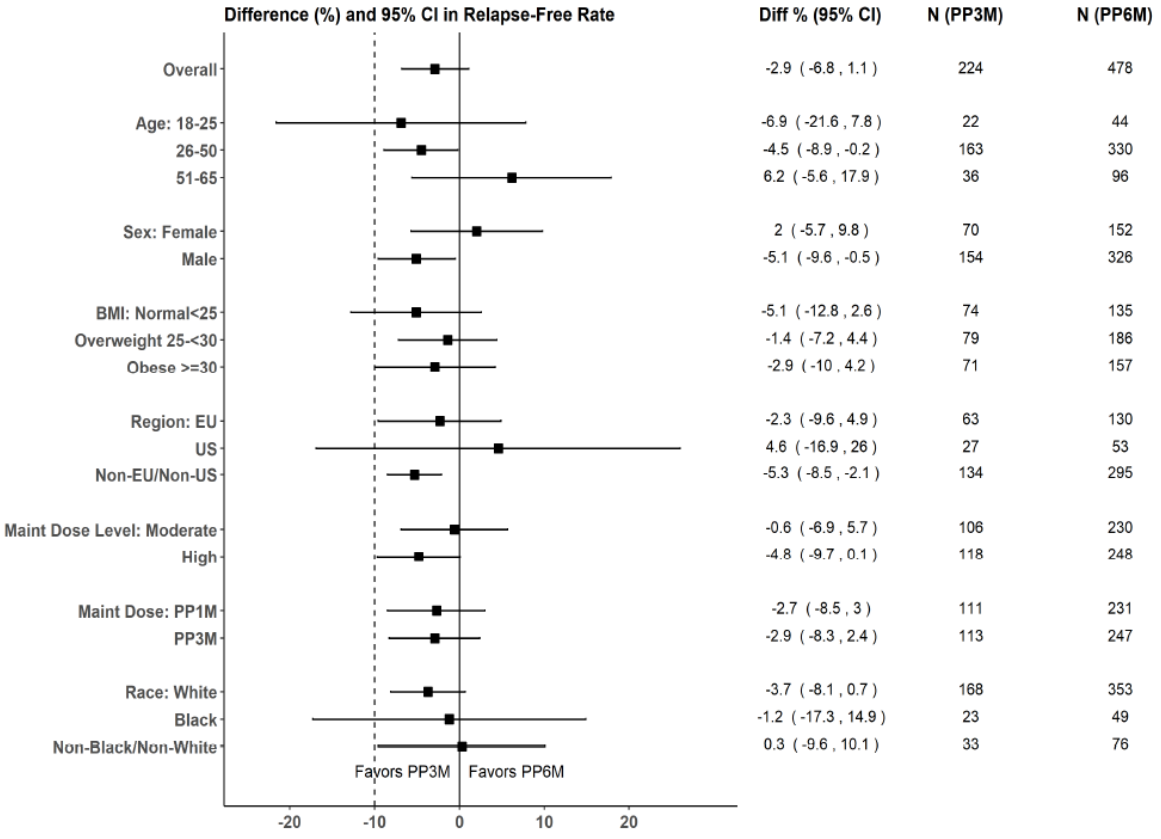


Table 14: Show numbers of PP3M vs PP6M subjects assessed, censored and with a relapse, with respect to the maintenance phase dosage levels "moderate" and "high" respectively.

TEFRELP01B_MADL: Time to Relapse at the End of 12 Months in the Double-blind Phase and Number (%) of Subjects that Remained Relapse Free by Dose Level in Maintenance: High and Moderate;DB ITT (Study R092670PSY3015)

	PP3M (N=224)		PP6M (N=478)	Total (N=702)
Dose level in Maintenance Phase: Moderate				
Number assessed	106		230	336
Number censored (%)	99 (93.4%)		213 (92.6%)	312 (92.9%)
Number of relapse (%)	7 (6.6%)		17 (7.4%)	24 (7.1%)
Time to Relapse (days) (a)				
25% quantile (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
Median (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
75% quantile (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
Relapse Free (a)				
End of 12 Months (day 365 (DB))				
Percentage Relapse Free	92.8		92.1	
Difference (PP6M-PP3M)		-0.6		
95% CI		(-6.9; 5.7)		
Dose level in Maintenance Phase: High				
Number assessed	118		248	366
Number censored (%)	114 (96.6%)		229 (92.3%)	343 (93.7%)
Number of relapse (%)	4 (3.4%)		19 (7.7%)	23 (6.3%)
Time to Relapse (days) (a)				
25% quantile (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
Median (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
75% quantile (95% CI)	NE (NE ; NE)		NE (NE ; NE)	NE (NE ; NE)
Relapse Free (a)				
End of 12 Months (day 365 (DB))				
Percentage Relapse Free	96.6		91.7	
Difference (PP6M-PP3M)		-4.8		
95% CI		(-9.7; 0.1)		

(a) Based on Kaplan-Meier product limit estimates.
Note: NE stands for Not Estimable.
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2.6.5.1. Clinical studies in special populations

N/A

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

N/A

2.6.5.3. Supportive study(ies)

N/A

2.6.6. Discussion on clinical efficacy

Design and conduct of clinical studies

Efficacy data and additional analyses

The rates of relapse during the double-blind phase were 7.5% (n=36) of subjects in the PP6M group and 4.9% (n=11) of subjects in the PP3M. However, study PSY3015 did not identify an association between lower PP6M paliperidone trough levels and increased relapse rate as compared to PP3M. The relapses in the PP6M group was considered not to cluster near visits corresponding to trough plasma paliperidone concentrations. Visual exploration of individually predicted plasma paliperidone concentration-time profiles in subjects who relapsed indicated relapse events being distributed throughout the dosing cycles. The distribution of concentrations at the time of relapse appeared to cover the entire 90% prediction interval range of the population simulations.

Given the small reported numbers, the Applicant in round 2 has added preliminary data from the extension study PSY3016 for relapse events. The 5 clinically defined relapse events were distributed across the dosing interval (day 4, 20, 105, 122, 156 after last PP6M dose). However, in PSY3016 clinical criteria only are used for relapse, and not the additional PANSS scoring used in PSY3015.

Design and conduct of clinical studies

The study design of PSY3015 is relevant to Guideline on clinical investigation of medicinal products, including depot preparations in the treatment of schizophrenia EMA/CHMP/40072/2010 Rev. 1, and in agreement with previous SA with CHMP. The PSY3015 study design was discussed within a scientific advices (EMEA/H/SA/1678/2/2016/III), as a response to the initially proposed non-inferiority margin of -12.5%, a NI margin of -10% was recommended (FU advice: EMEA/H/SA/1678/2/FU/1/2017/II).

Also, the dose selection for PP6M and PP3M was agreed to by CHMP prior to the start of Study PSY3015. The inclusion of patients for randomisation and dosage after randomisation are in accordance to the study protocol for PSY3015 and are considered adequate to address the objectives.
The methods for randomisation are in accordance to the study protocol and considered adequate to address the objectives. To be eligible, subjects were required to be clinically stable prior to randomisation according to pre-defined criteria. These have been stated to be identical with the corresponding criteria for randomisation in study PSY3011, a non-inferiority study comparing PP1M with PP3M and the key registration study of PP3M.

Overall the baseline characteristics are considered adequate to address the objectives, being balanced between PP6M and PP3M treatment groups in the randomised phase of Study PSY3015, in accordance to the study protocol. Consistent with scientific advice from CHMP, more than 25% of subjects were enrolled and treated at sites in the EU during the double-blind phase (n=193 [28%]).

Stratification by moderate or high dose in the maintenance phase is agreed. Stratification by site may have been for administrative reasons. It is nonetheless acknowledged that none of the stratification variables were accounted for in the primary analysis of the primary endpoint. By study design, subjects could switch to PP6M from either PP1M or PP3M, hence, the applicant could in addition have considered stratification by PP1M or PP3M.

In line with the sought indication it was considered important to have adequate numbers of subjects treated with either PP1M or PP3M in the Maintenance Phase for randomisation to the Double-blind Phase. Based on low expected enrolment of subjects previously treated with PP3M, some subjects (after appropriate treatment with PP1M) were to be switched to PP3M during the Maintenance Phase. This was to occur early in the course of the study and until the target of approximately one-half of the total Maintenance Phase sample was treated with PP3M. The distribution of the in total 767 subjects in the maintenance phase between PP1M and PP3M respectively ended up being 362 (47.2%) and 405 (52.8%). The proportion of subjects

subsequently randomised were high albeit slightly lower among those having been treated with open-label PP3M (88.9%) than among those treated with open-label PP1M (94.5%).

What implications, if any, an invoked switch from PP1M to PP3M could have had on the outcome in the randomised part of the study is not clear. However, this switch occurred pre-randomisation and despite not being a stratification factor, the proportion of subjects switching from PP1M and PP3M to randomised treatment was balanced between randomised arms.

The applicant has concluded on assay sensitivity and refers to that study PSY3015 shared several design elements with the placebo-controlled, randomised withdrawal study with PP3M (PSY3012) as well as with PSY3011, used to demonstrate non-inferiority of PP3M versus PP1M. The criteria used to define relapse was identical across the three studies. Further, all three studies have been stated to have shared similar eligibility criteria, with the exception PANSS total score at study entry. According to the Applicant the latter implied that the PSY3015 study population could be considered overall more stable with regard to schizophrenia symptoms. At the double-blind phase baseline, the patient populations were nonetheless very similar: for PSY3015 the mean (median) total PANSS score 52 (53) and 3.0 (3) for CGI-S; for PSY3011 the mean (median) total PANSS score 58 (60) and 2.9 (3) for CGI-S; for PSY3012 mean (median) total PANSS score 55 (56) and 2.7 (3) for CGI-S.

Given shared characteristics, comparisons between studies could be considered relevant. According to the Applicant, the assay sensitivity of PSY3015 can be clinically inferred as the results of study PSY3012 demonstrated efficacy of PP3M compared with placebo, and since the results of PSY3015 has shown that PP6M is non-inferior to PP3M. While the leap from the comparison between PP3M and placebo in study PSY3012 may seem somewhat farfetched given differences in study design and study objective, it is agreed that the percentage of relapse events in the PP3M arm (4.9%) appear similar as in study PSY3011 (7.9%) .

The scope of the 6-monthly injection is stated to be in order to further improve adherence and convenience. Albeit a double-blind design is mandatory given the disease setting and study objective, nor adherence or convenience could be assessed given the study design.

During the double-blind phase, the subject and all study-site personnel except for the study drug administrator were to be blinded. Due to differences in syringe sizes for PP3M versus PP6M, the study drug administrator was allowed only to e.g. prepare and administer injections. Although the blinding procedure is not considered to have been optimal in that the subject was instructed to look away, this should have been facilitated by the injection site being the gluteal muscle due to the larger volume associated with a PP6M dose. One concern is whether it was not possible for a subject randomised to switch to PP6M to feel a difference since already familiar with PP1M and/or PP3M injections. More subjects in the PP6M, 59/478 (12.3%) than in the PP3M 11/224 (4.9%) arm reported injection site related AEs, the most common in both arms, being injection site pain. However, treatment compliance was similar in the two treatment arms. To maintain the blind, subjects randomised to PP6M received placebo injections at the 3-month time points between their 6-month doses of investigational drug.

The randomisation used a 2:1 ratio, PP6M:PP3M, and was stratified by study site and dose level in the maintenance phase. Stratification by moderate or high dose level at baseline is agreed. Being in line with the sought indication, subjects could switch to PP6M from either PP1M or PP3M, hence, stratification by PP1M or PP3M could in addition have been considered. The targeted sample size was 549 subjects. Due to a much lower dropout rate than expected in the open-label phase, the total number of randomised subjects was 702 (478:PP6M, 224:PP3M).

The scope with the PP6M is to allow longer time periods between administrations and the primary objective was to show non-inferiority between administrations every 6-month compared with administrations every 3-month. To be randomised subjects had to be stable on treatment with either PP3M or PP1M. As a comment regarding the study design it had been preferred if subjects randomised to the control arm could have remained on their maintenance treatment regimen to avoid to also have subjects in the control arm switching to a treatment regimen implying longer intervals between administrations. In this respect it is found

reassuring that the subgroup analyses on the primary endpoint based on maintenance dose regimen (PP1M/PP3M) showed consistent outcomes. In line with what had been planned, half of randomised subjects were on PP1M and despite not being a stratification factor, the proportion of subjects switching from PP1M and PP3M to randomised treatment was balanced between randomised arms.

Further, the concept of bio-creep may be worth considering: the claimed efficacy of PP6M is based on a non-inferiority exercise versus PP3M while in turn, the claimed efficacy of PP3M is based on non-inferiority versus PP1M. In this respect, it is recognised that a more stringent NI margin was used in study PSY3015 (-10%) than in study R092670PSY3011 (-15%), a non-inferiority study comparing PP3M with PP1M and the key registration study of PP3M.

Previous discussion regarding the design characteristics of study R092670PSY3011 is applicable also here and concern assay sensitivity and the need to consider that the PP6M treatment effect is mixed with a certain unknown placebo effect due to the placebo injections month 3 and month 9 to maintain study blind.

The criteria used to define relapse was identical across these two studies and regarding assay sensitivity, the percentage of relapse events in the PP3M arm (4.9%) appear similar as in study PSY3011 (7.9%) Of some reassurance regarding study design and conduct is that the percentage of relapse events was higher in the PP6M arm than in the PP3M arm. Overall, there were few relapse events observed during the 12 months double-blind phase offering support to the efficacy of both treatments.

In the primary analysis, the censoring rate was high (>92%). For the majority this was due to study completion/end of study. The percentage of subjects who discontinued (study/treatment) is acceptable and was in total 12.0% (84/702): in the PP6M arm this concerned 13.0% (62/478) and in the PP3M arm 9.8% (22/224). The most common reason irrespective of treatment arm was withdrawal by subject. However, the completion rate is considered adequate to address the objectives in PSY3015. All randomised subjects were included in the ITT set. The PP set included 96.9% (PP3M) and 96.7% (PP6M) of the subjects in the ITT. While this may imply a well conducted study it could also imply that the criteria used to define the PP population were too generous. It is noted that the proportion of subjects with protocol deviations was slightly higher in the PP6M treatment arm, 10.5% (50/478) than in the PP3M arm, 7.6% (17/224).

Study completion was 08 May 2020, which included a period during which the COVID-19 pandemic was occurring globally. The applicant has described that when disruption to the pandemic started, the trial was already fully enrolled, and all subjects had received all injections of study drug, with most subjects having completed the study, and has concluded that the impact was minimal. This is agreed based on the pre-defined supplementary analysis performed to evaluate the potential impact of COVID-19 that was included in the SAP that was finalized before database lock (10 June 2020). The submitted statistical analysis plan (SAP) version 4.0 was dated 26 May 2020.

The original analysis plan was in accordance with scientific advice received and at the time, the ICH E9(R1) was not yet implemented. Added with SAP version 2 was the definition of the primary estimand, supplementary estimands and corresponding analyses with reference to a draft of the ICH E9 addendum available in early 2019. According to the applicant, the changes made were not to affect the analyses specified in the SAP version 1.0 (finalized on 16 Mar 2018).

Primary analyses were performed based on the ITT (all randomised) and the PP population from which very few were excluded and thereby was the ITT and PP outcomes respectively very similar. The PP set included 96.9% (PP3M) and 96.7% (PP6M) of the subjects in the ITT. This may imply either a well conducted study or a too generously defined PP population. Considering all protocol violations/deviation there were a higher percentage of subjects concerned in the PP6M treatment arm, 10.5% (50/478) than in the PP3M arm, 7.6% (17/224).

The added primary and supplementary estimands is per se appreciated. The primary estimand implied the use of a hypothetical strategy in case of treatment/study discontinuation and hence assumed similar efficacy for subjects who discontinued as those subjects from the same treatment group who did not discontinue

treatment. This is not agreed why the performed supplementary analyses are endorsed in that they included follow-up data collected during an optional follow-up phase meant to collect poststudy data in terms of minimum safety information (i.e., adverse events) and minimum efficacy information (i.e., relapse status). Of the in total 84 subjects who withdrew early, 43 continued in the follow-up phase. No relapse events were observed during the follow-up phase and the results from the analysis of the supplementary estimands (S1-S3) were shown to be very similar compared with the primary efficacy analysis. Information revealing the distribution across randomised arms of the 43 subjects who continued in the FU phase was lacking and the MAH has now confirmed both the total and the number per randomised arm. Of those 43 subjects who provided follow-up data, 7 had been randomised to the PP3M arm and 36 had been randomised to PP6M arm.

There were no adjustments for multiple testing for analysis of secondary efficacy endpoints. Considered to have implications for the data to be presented in the SmPC it is acknowledged that the only outcome proposed in section 5.1 is for the primary endpoint. This is hence agreed.

Subjects in the randomised phase were subject to frequent study contacts. All were plasma sampled by 2 weeks intervals or more, in addition PP6M received placebo injections after 3 + 9 months. All subjects also frequently completed symptom scales at least at monthly visits, being actively screened for symptoms in progress and potential relapse.

The magnitude of the placebo effect on psychiatric symptoms from these frequent active care contacts was not discussed by the MAH but those activities presumably has contributed to rather high relapse-free rates for both products. The Applicant has added in the SmPC 5.1, the wording …injection every 3 months with regular scheduled visits between injections... to clarify that efficacy of PP6M without continuous care contacts in between the PP6M injections has not been studied.

Efficacy data and additional analyses

Subgroups

The results across prespecified population subgroups sex, age, race, baseline BMI, region, dose level in maintenance phase, dose regimen in maintenance phase were generally consistent with the results of the primary endpoint analysis. The lower bound of the 95% CI for a few subgroups (eg, 18 to 25- year old age group, US region, Black race) was lower than -10% due to the small size of the subgroups that led to very wide confidence intervals.

Efficacy by Dose Level (700 or 1000 mg eq.)

To note, the choice of dose regimen during the maintenance phase (PP1M or PP3M) was not based on randomization, but on the subject's pre-study status. Likewise, the choice of eq. dose (700 mg. eq. or 1000 mg) was not based on randomization but determined at the beginning of the maintenance phase. The study was not designed to evaluate the efficacy of individual dose levels.

The relapse-free rates at Month 12 in the double-blind phase were similar for the PP6M dose levels 700 mg. eq. (92.1%) and 1000 mg. eq (91.7%), and the number of subjects were also similar (700 mg. eq.: 230 subjects; 1000 mg. eq.: 248 subjects). The results of a subgroup analysis of the relapse-free rate at Month 12 by maintenance phase dose level showed comparable efficacy for the moderate and high dose levels.

Efficacy by Maintenance Dose Regimen (PP1M or PP3M)

The relapse-free rates at Month 12 during the double-blind phase were similar for PP6M subjects who were transitioned from PP1M in the maintenance phase (91.6%) and those who were transitioned from PP3M in the maintenance phase (92.3%). The number of subjects in each subgroup were also similar (PP1M: 231 subjects and PP3M: 247 subjects). The results of a subgroup analysis of the relapse-free rate at Month 12 by maintenance phase dose level showed comparable efficacy for the PP1M and PP3M maintenance phase dose regimens.

2.6.7. Conclusions on the clinical efficacy

Overall, consistent data from study PSY3015 demonstrate non-inferior efficacy of PP6M comparable to that of PP3M, in the treatment of stabilised adult patients with schizophrenia who have been adequately treated with either PP1M for 4 months or PP3M for one 3-month injection cycle. In turn, the efficacy of PP3M is based on non-inferiority previously shown versus PP1M. There was no evidence that the efficacy of PP6M fluctuated during the 6-month dose interval.

The potential for unblinding from minor differences in between injection methods, and of reported injection-related TEAEs, is considered to have had no significant impact on the efficacy results. The primary efficacy data appear consistent with subgroups. Overall, the efficacy data for PP6M are considered to be robust.

2.6.8. Clinical safety

2.6.8.1. Patient exposure

In the Open-label phase before the double-blind phase of Study PSY3015, 838 subjects with schizophrenia received at least 1 dose of PP1M or PP3M. In the double-blind phase, a total of 702 subjects were randomized of which 224 received PP3M and 478 received PP6M. As of the cutoff date of 29 May 2020, the mean (SD) duration of exposure was 96.3 (37.87) days in the PP6M group during the Open-label Phase. The mean (SD) dose of PP6M was 888.8 (145.31) mg eq. during the study.

There were pronounced differences in disease severity at the OL baseline between subjects treated with PP3M in the DB phase of studies PSY3011 and PSY3015.

All injections in the DB phase of Study PSY3015 were administered in glutea, since PP6M is required to be administered in the glutea due to the high injection volume.

PP6M is only available in two different strength (ie 700 mg and 1000 mg), whereas PP1M and PP3M is available in equipotent strengths as well as additional strengths. The consequences are that PP6M will not be an alternative for some patients.

The risperidone metabolite 9OH-risperidone is paliperidone. According to the SmPC, transition from risperidone to PP6M or from PP6M to risperidone is not an alternative.

Based on the plasma concentration curves and Pop PK simulations, there is a potential increased risk for ADRs the period directly after injection of PP6M and a potential risk for lack of effect during the end of the dosing interval.

The amount of active substance in PP6M is high, and equivalent to extensive overdose. However, according to AE data as well as data on plasma concentrations vs AE/safety, there are no indications of dose dumping or medication error.

To avoid a missed dose of PP6M, patients may be given the injection up to 2 weeks before or 3 weeks after the scheduled 6-month time point, according to the SmPC. (A dosing window of ± 14 days is recommended for the approved PP3M product). The 5-weeks window for PP6M is based on pharmacokinetic and clinical data as well as clinical practical considerations.

2.6.8.2. Adverse events

During the double-blind phase, the overall rates of TEAEs and rates of TEAEs in all MedDRA system organ classes (SOCs), as well as those of common individual TEAEs were well balanced between the PP6M and PP3M groups.

The TEAE reported more frequently in the PP6M group (at least 3% difference) were injection site related, as in the PP6M group 12.3% reported injection site-related TEAEs as compared to in the PP3M group 4.9%. No injection site-related TEAEs were assessed as serious and none resulted in study drug discontinuation.

The total incidence of injection site-related TEAEs was almost identical between the PP6M 700 mg eq. and PP6M 1000 mg eq. groups (12.1% and 12.6%, respectively).

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 intensity, with few individual TEAEs in the psychiatric disorders SOC reported as severe in more than 1 subject each.

Overall, the types and rates of clinically significant AEs of special interest in subjects treated with PP6M were consistent with the safety profile of PP3M and PP1M. There were no cases of NMS, rhabdomyolysis, or acute kidney injury among subjects treated with PP6M in Study PSY3015, nor were there any cases of overdose in the PP6M group of Study PSY3015. During the double-blind phase, TEAEs related to somnolence and sedation occurred in a low percentage of subjects in the PP6M (1.9%) and PP3M (1.3%) groups. The potential for overdose with PP6M is limited because it is administered by a healthcare professional; the product is not intended to be self-administered by patients. There were 2 non-fatal, non-serious cases of overdose or accidental overdose in the PP3M group during the double-blind phase of Study PSY3015; both cases have been confirmed as dosing errors by the site staff.

The frequency of EPS-related TEAEs during the double-blind phase was low and consistent for the PP6M (9.6%) and PP3M (8.5%) groups. None of the EPS-related TEAEs in subjects treated with PP6M were serious; 1 subject treated with PP6M experienced an EPS-related TEAE of Parkinsonism which led to study drug discontinuation. Changes in EPS rating scale scores and use of anticholinergic medications during the double-blind phase were similar in both PP6M and PP3M groups.

Overall, the types and rates of clinically significant AEs of special interest in subjects treated with PP6M were consistent with the safety profile of PP3M and PP1M.

A total of 42 ADRs were identified for PP6M which included 29 grouped terms and 13 individual preferred terms and comprised 94 distinct preferred terms No new ADRs were identified for PP6M compared with other approved paliperidone or risperidone products.

See also results regarding serum prolactin, injections site reactions and body weight presented below.

Injection Site

Injection Site-related Events

Concerns regarding injection site reactions as well as pain at the injection site have been raised in the previous use of LAI antipsychotics by some health care professionals. The PP6M product differs from PP3M and other LAI antipsychotics by the large injection volumes, up to 5.0 ml.

Injection Site Evaluations by Subjects

- Subjects were asked about the pain associated with the injection by means of a 100-mm VAS, scaled from "no pain at all" to "unbearably painful." The VAS-Acute assessed pain once within 30 minutes after each injection. The VAS-Residual assessed pain at the time points days or weeks later as indicated in the Time and Events Schedules in the protocol Appendix 1.

Injection Site Evaluations and Follow-up by Investigators

- Investigators or subinvestigators evaluated the injection sites for tenderness, erythema/redness, and induration/swelling, at the same time points as the VASs completed by the subject, plus at the End-of-Study Visit or at the time of early withdrawal. The characteristics were scored as 0 = absent, 1 = mild, 2 = moderate, or 3 = severe. The scales and anchors are a hybrid from the Sponsor's previous studies of PP3M and from a US FDA guidance.
- The results were recorded on the eCRF. Every effort was made to have the same individual perform all injection site evaluations for a particular subject. The investigator/subinvestigator completed these assessments within 30 minutes after the injection and at all visits marked in the Time and Events Schedules (Appendix1) thereafter; for any characteristic still rated mild, moderate, or severe at the last marked visit, the investigator/subinvestigator added assessments at subsequent visits until all of the characteristics were rated absent.
- The investigator followed any clinically significant abnormalities persisting at the end of the study until resolution or until reaching a clinically stable endpoint.

During the double-blind phase, a greater percentage of subjects in the PP6M group reported injection site-related TEAEs (12.3%) compared with the PP3M group (4.5%). TEAEs of injection site pain were the most frequently reported local reactions in both treatment groups (PP6M: 7.7% and PP3M: 4.0%). None of the injection site-related TEAEs observed during the Double-blind Phase were reported as serious or severe, lead to "dose interruption" or resulted in study drug discontinuation.

The total incidence of injection site-related TEAEs was almost identical between the PP6M 700 mg eq. and PP6M 1000 mg eq. groups (12.1% and 12.6%, respectively). To note, the TEAE of injection site pain was reported for a greater percentage of subjects receiving the high dose of PP6M (9.1%) compared with those receiving the moderate dose (6.5%).

Among the 27 events reported as “moderate” or “severe” intensity, 3.6% of subjects in the PP6M group and 1.3% of subjects in the PP3M group reported at least one injection site-related TEAE of "moderate" intensity, with no "severe" event.

Also for the placebo doses given in between PP6M doses, injection site-related TEAEs were reported; e.g. for placebo high dose 7 events of “Injection site pain”, “Very likely related to study Agent”, and for placebo moderate dose, 5 events of “Injection site pain”, “Very likely related to study Agent”.

While most injection site-related TEAEs were reported on the day of the injection, median time to onset ranged from 1.0 to 3.0 days across the different injections. The TEAE median durations varied from 3.0 days [placebo moderate dose] to 22.5 days [PP3M 525 mg eq. dose], however no clear overall pattern was observed for different injection volumes.

Injection Site Ratings

In Study PSY3015, mean subject ratings of injection site pain were similar for PP6M and PP3M throughout the double-blind phase, and decreased in intensity over the course of the study (ie, improved tolerability). Subjects' evaluations of the intensity of the pain showed similar decreases for the moderate and high dose level in the PP6M group.

Based on the investigators' assessments, the injection was well tolerated. Induration, redness and swelling in both groups were mild in intensity during the double-blind phase. The rates of reported induration, redness and swelling were similar between the PP6M and PP3M groups over time. Investigator evaluation of tenderness was higher for subjects in the PP6M group versus the PP3M group, although the majority were mild.

There is no further data reported from at least 8 cases which should have been referred to further examinations according to the study protocol and the Scientific Advice EMA/CHMP/SAWP/601629/2016. In no case such data from dermatological specialists, biopsies or radiological examination were available. Only one case had been referred to specialist, and that specialist report had not been collected.

Based on the investigators' clinical assessments, the Applicant concludes "across the Open-label and Double-blind Phases, none of the moderate or severe injection site-related TEAEs reported were suggestive of suspected cellulitis or abscess, nodule, fibroma, furuncle or other noninfectious reaction which would have required referral to a dermatologist or surgeon for consideration of fine needle aspiration and/or tissue biopsy or for incision or drainage procedures".

Furthermore, subgroup analyses of TEAEs by age and BMI did not show any clear differences in the incidences of injection site-related TEAEs according to age group (18-25, 26-50, 51-65, or >65 years) or BMI category (<25, 25-30, or >30 kg/m^2 in the PP6M or PP3M groups. However, the sample size in the subgroup aged >65 years was small (n=3 for PP3M; n=8 for PP6M).

Additional subgroup analyses of the investigator's evaluation of the injection site by age group and by baseline BMI showed a similar pattern of injection related TEAEs across the various age groups and BMI categories.

Prolactin

Prolactin-related Adverse Events and Laboratory Changes

After randomization to PP6M or PP3M in Study PSY3015, the mean change in serum prolactin from double-blind baseline to double-blind end point was -2.190 µg/L for males and -4.828 µg/L for females in the PP6M group and 1.555 µg/L for males and 9.029 µg/L for females in the PP3M group. In males, median prolactin levels remained relatively stable throughout the maintenance and double-blind phases in both treatment groups, whereas in female subjects, median prolactin levels increased from maintenance phase baseline to double-blind baseline in both treatment groups. During the double-blind phase, median prolactin levels for female subjects continued to increase from double-blind baseline through Week 3 in both groups and then returned to the double-blind baseline level at Month 6. Median prolactin levels again increased through Month 7 and returned to the double-blind baseline level at Month 12, the end of the double-blind phase.

High prolactin levels relative to the maintenance phase baseline were noted in a similar percentage of subjects in the PP6M and PP3M groups in both males (approximately 35%) and females (approximately 30%).

Although elevations in prolactin concentrations were observed in some subjects, most of those were asymptomatic in both men and women. The incidence of potentially prolactin-related TEAEs during the double-blind phase of Study PSY3015 was similar for female subjects in the PP6M and PP3M groups (9.2% and 8.6%, respectively), and was lower among male subjects in both treatment groups (PP6M: 1.2%; PP3M: 0.6%). None of these events during the double-blind phase were serious or led to study drug discontinuation.

Overall, the patterns of Prolactin-related Adverse Events and of prolactin level variations in PSY3015 are in line with data from the previous study PSY3011 (comparing PP3M to PP1M). No clinically significant differences between PP3M and PP6M were identified.

Body weight

Weight gain, a known effect of paliperidone, was seen with PP6M. The mean [SD] increase in body weight over a similar duration of treatment (double-blind baseline to double-blind end point) was smaller in the PP6M group (0.10 [4.959] kg, corresponding mean increase in BMI of 0.0 [1.72] kg/m2) than the PP3M group (0.96 [5.103] kg and 0.3 [1.78] kg/m2).

The percentage of subjects who had ≥7% weight gain at the double-blind endpoint compared to the double-blind baseline was 10.6% in the PP6M group and 13.2% in the PP3M group. The percentage of subjects who had ≥7% weight gain at any time during the double-blind phase compared to the double-blind baseline was 12.8% in the PP6M group and 17.0% in the PP3M group. The incidence of TEAEs related to weight gain was similar across both treatment groups (PP6M: 9.2% and PP3M: 8.0%). The percentages of subjects who experienced a weight decrease of ≥7% from double-blind baseline to end point were 9.1% and 6.8% for the PP6M and PP3M groups. The most frequently reported TEAE related to weight gain was weight increased in both the PP6M (8.4%) and PP3M (7.6%) groups.

Metabolic Effects

Treatment-emergent diabetes mellitus and hyperglycemia-related events were not common in Study PSY3015, consistent with the absence of treatment-emergent marked abnormalities in glucose levels. Treatment with PP6M also was not associated with any clinically significant increase in lipid abnormalities.

2.6.8.3. Serious adverse event/deaths/other significant events

In the 2 studies included in the PP6M clinical development program, there were a total of 4 deaths in subjects treated with paliperidone palmitate (PP6M, PP3M or PP1M, up to the clinical cutoff of 29 May 2020), including 1 death in the open-label transition phase of Study PSY3015 on PP1M (completed suicide); 3 deaths during the double-blind phase of Study PSY3015 (1 on PP6M [death by undetermined cause] and 2 on PP3M [sudden death, cause unknown; pulmonary embolism]). There were no deaths in PSY3016 as of the cutoff date. Each of the 4 deaths in the PP6M program (Studies PSY3015 and PSY3016) as of the clinical cutoff date for this submission was judged by the investigator to be not related to study drug.

In Study PSY3011 from the PP3M clinical program, there were a total 6 deaths in subjects treated with paliperidone palmitate (PP3M or PP1M), including 2 deaths during the open-label phase on PP1M (arteriosclerotic cardiovascular disease; sudden cardiac arrest); and 4 deaths during double-blind phase (1 on PP3M [hepatocellular carcinoma] and 3 on PP1M [suicide attempt; acute bacterial meningitis; drug intoxication]).

The types and rates of SAEs reported for subjects treated with PP6M in Study PSY3015 were consistent with the safety profile of PP3M and PP1M as observed in acute treatment studies as well as in long-term, randomized withdrawal studies. Furthermore, the majority of SAEs in Study PSY3015 were judged by the investigator as either not related or doubtfully related to study treatment. 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. Treatment-emergent SAEs other than psychiatric disorders were reported in isolated cases in Study PSY3015. During the double-blind phase of Study PSY3015, treatment-emergent SAEs occurred in 5.0% of subjects in the PP6M group compared with 6.7% of those in the PP3M group. Other than psychiatric disorders, there were no SAEs of possible clinical interest reported after PP6M exposure in this study.

As of the clinical cutoff date of 29 May 2020, one SAE of nephrotic syndrome was reported in 1 subject treated with PP6M in the ongoing Study PSY3016. The SAE was judged by the investigator to be not related to study drug; the subject recovered, and the event was considered to be resolved.

In pooled safety data from the double-blind phases of PSY3015 and PSY3011, treatment-emergent SAEs occurred in 7.2% in the PP1M group of Study PSY3011; 5.6% in the pooled PP3M group [studies PSY3015 and PSY3011] and 5.0% in the PP6M group of study PSY3015. Most of the reported SAEs were in the psychiatric disorders SOC.

2.6.8.4. Laboratory findings

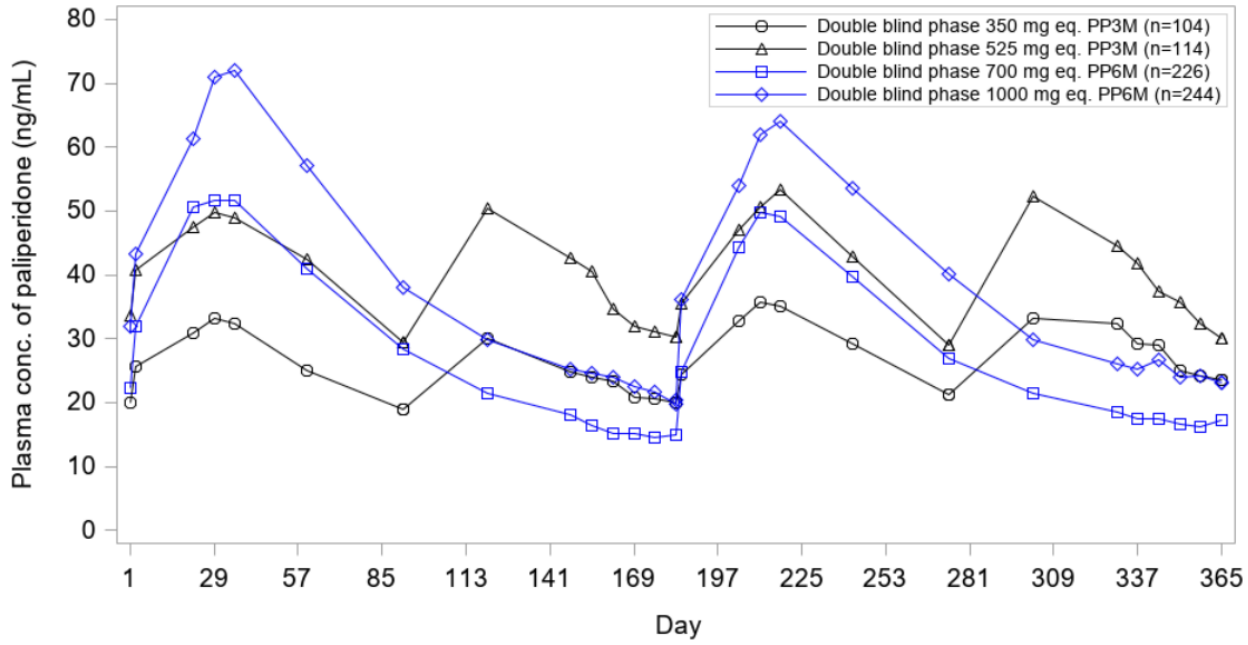
In Study PSY3015, PP6M showed no clinically meaningful mean changes from double-blind baseline to end point on the results of chemistry and hematology laboratory tests for any of the laboratory analytes. Based on the occurrence of treatment-emergent markedly abnormal laboratory values and associated TEAEs, the effects of PP6M on the results laboratory tests did not show clinically meaningful differences from those of PP3M.

Cases of potential clinical significance were identified based on individual plasma concentration time profiles according to the following criteria: high paliperidone plasma levels (n=35) and high paliperidone palmitate plasma levels (n=2). Subjects who had detectable levels of paliperidone palmitate (n=79). According to the Applicant, the changes in clinical status were minimal, and there was no clear association with the peak plasma concentrations.

For serum prolactin, see above.

A total of 20,402 paliperidone plasma concentrations from 811 subjects were used in the final popPK dataset for study PSY3015, of which 15,932 samples were from 700 subjects in the double-blind phase of which 68% were in the PP6M treatment arm and 32% in the PP3M treatment arm.

Figure 10: Linear median plasma concentration-time profiles of paliperidone after administration of paliperidone palmitate at 350 or 525 mg eq. PP3M and 700 or 1000 mg eq. PP6M in the Double-Blind Phase.



Vital signs

Consistent with findings observed for PP1M and PP3M, treatment with PP6M in Study PSY3015 was associated with a significant increase in standing pulse rate in a small percentage of subjects. Two percent or fewer subjects in the PP6M group experienced a clinically notable increase or decrease in standing or supine systolic or diastolic blood pressure during the double-blind phase.

Most of the AEs associated with vital sign abnormalities, including cases of orthostatic hypotension as an AE, were reported at incidences of 2% or less and were mild or moderate in intensity. Vital sign measurements were similar for the PP6M and PP3M groups during the double-blind phase. Orthostatic changes were observed in 1.3% of patients in the PP6M group and 0.5% of patients in the PP3M group.

Abnormal increases in heart rate occurred in 7.7% of subjects in the PP6M group and 11.2% of subjects in the PP3M group during double-blind treatment. Abnormal decreases in heart rate occurred in 3.8% of subjects in the PP6M group and 1.8% of subjects in the PP3M group.

The QTc interval data in Study PSY3015 were similar for the PP6M and PP3M treatment groups. In the PP6M group, 2 subjects and 1 subject (<1%) had increases in QTcF and QTcLD values >60 msec. In the PP3M group none of the subjects had increases in QTcF and QTcLD values >60 msec. In Study PSY3015, the incidence of treatment-emergent abnormal ECG parameters (PR, QRS, and QT intervals) was low (<2%) during the double-blind phase in the PP6M group. Administration of PP6M was not associated with clinically significant mean increases in QTc intervals during the double-blind phase. The mean change in QTcLD during the double-blind phase was similar for the PP6M and PP3M groups in Study PSY3015.

Consistent with the approach taken for the PP1M MAA and the PP3M line extension, the Applicant did not conduct a separate thorough QT study with PP6M.

Critical Evaluation of Relevant Body Systems

Overall, the types and rates of clinically significant AEs of special interest in subjects treated with PP6M were consistent with the safety profile of PP3M and PP1M.

2.6.8.5. Safety in special populations

Although some subgroup associated differences in rates of TEAEs were observed, the results did not suggest that administration of PP6M was associated with a clinically relevant increased risk in any of the subgroups evaluated.

Evaluation of TEAEs by dose regimen in the maintenance phase (PP1M or PP3M) indicated that the types (preferred terms) and incidences of TEAEs , as well as TEAEs leading to treatment discontinuation, were similar for subjects who transitioned to PP6M from PP1M and for those who transitioned to PP6M from PP3M. Therefore, a transition from either PP1M or PP3M to PP6M would be acceptable if clinically indicated.

In addition, the total rate of TEAEs in the double-blind phase was similar for the moderate (700 mg eq.) and high (1000 mg eq.) dose level subgroups within the PP6M treatment arm (moderate: 67.8%; high: 56.9%).

2.6.8.6. Immunological events

See Sections on AEs.

2.6.8.7. Safety related to drug-drug interactions and other interactions

A total of 5 drug interaction studies were conducted as part of the clinical pharmacology programs for oral paliperidone ER and PP1M. These studies investigated the effects of paroxetine (potent CYP2D6 inhibitor), carbamazepine (potent inducer of CYP-enzymes and P-glycoprotein [P-gp]), trimethoprim (organic cation inhibitor) on the PK of oral paliperidone. Furthermore, the interactions between valproic acid and paliperidone ER were evaluated. All of these drug interactions were considered relevant to PP6M as well. It can be anticipated that less intestinal metabolic or transporter-mediated drug-drug interactions occur using paliperidone palmitate formulations as compared to paliperidone oral tablets.

2.6.8.8. Discontinuation due to adverse events

Discontinuation due to TEAEs were reported at low rates during the double-blind phase in Study PSY3015 (3.3% and 2.7% in the PP6M and PP3M groups). One event of possible clinical interest led to discontinuation in a PP6M-treated subject during the double-blind phase (Parkinsonism). This event was not considered serious and symptoms resolved after 127 days. Among subjects treated with PP6M in the double-blind phase, the rate of discontinuation due to TEAEs was similar in subjects treated with moderate (700 mg eq.; 3.0%) and high (100 mg eq.; 3.6%) doses of PP6M. The rate of discontinuation due to TEAEs was similar for subjects in the PP6M group who were transitioned from PP1M to PP6M (2.6%) and those who were transitioned from PP3M to PP6M (4.0%).

As of the cutoff date of 29 May 2020, 1 subject receiving PP6M experienced TEAEs of intrusive thoughts, schizophrenia, and suicidal ideation leading to study drug discontinuation.

In pooled safety data from the double-blind phases of PSY3015 and PSY3011, TEAEs leading to study discontinuation were reported at low rates across all treatment groups: 2.5% in the PP1M group of study PSY3011, 2.9% in the PP3M group of pooled studies PSY3011/3015, and 3.3% in the PP6M group of study PSY3015. In the pooled PP3M group, 1 event of possible clinical interest led to discontinuation in a PP3M-treated subject during the double-blind phase of PSY3011 (tardive dyskinesia). This event was not considered

serious and symptoms resolved by the 3-month follow-up after discontinuation of study medication. As described above 1 event of possible clinical interest led to discontinuation in a PP6M-treated subject during the double-blind phase of PSY3015 (Parkinsonism).

According to the Applicant, this assessment indicated that the types (preferred terms) and incidences of TEAEs, as well as TEAEs leading to treatment discontinuation, were similar for subjects who transitioned to PP6M from PP1M and for those who transitioned to PP6M from PP3M. Therefore, a transition from either PP1M or PP3M to PP6M would be safe if clinically indicated.

Long-term Safety

In the present Phase 3 study, PSY3015, the overall data confirm that the PP6M product (administered at doses of 700 and 1000 mg eq.) is safe in adults with schizophrenia treated for periods of up to 12 months. Data previously obtained during studies to evaluate the safety of PP3M and PP1M in patients with schizophrenia did not identify any safety concerns during long-term therapy with doses of PP3M as high as 525 mg eq. or PP1M as high as 150 mg eq. Pending the assessment of the ongoing application, it might be possible to extrapolate to 48-month safety data in long term studies on PP1M and PP3M.

2.6.8.9. Post marketing experience

This review of postmarketing cumulative data for paliperidone palmitate injectable products from product approvals through 30 June 2020 is consistent with the established safety profiles of PP1M and PP3M. No new significant safety issues or signals were identified.

Literature

The data presented in the publications selected from this period confirmed that the benefit-to-risk ratios for the use of paliperidone ER in the treatment of schizophrenia and schizoaffective disorder, PP1M in the treatment of schizophrenia and schizoaffective disorder, and PP3M in the treatment of schizophrenia, remain favourable. No new clinically significant safety issues were identified.

In summary

Overall, the data regarding the types and incidences of adverse events and ADRs, adverse events of clinical interest for the class of atypical antipsychotics, laboratory findings, vital sign measurements, and injection-site reactions reported were generally similar for PP6M and PP3M in Study PSY3015, and in agreement with the findings from the PP3M and PP1M clinical development programs, and did not provide evidence for a new safety signal. The safety findings were similar for subjects who transitioned to PP6M from PP1M and for those who transitioned to PP6M from PP3M. Thus the use of PP6M at the proposed dose levels of 700 and 1000 mg eq. in the maintenance treatment of schizophrenia patients who have previously received PP1M preferably for four months or PP3M for at least one injection cycle, is supported by the findings presented in this safety summary.

The review of postmarketing cumulative data for paliperidone palmitate injectable products from product approvals through 30 June 2020 is consistent with the established safety profiles of PP1M and PP3M. No new significant safety issues or signals were identified.

2.6.9. Discussion on clinical safety

The extent of exposure in numbers of patients exposed to PP6M and duration of treatment is in general adequate and long-term data is sin general sufficient based on studies PSY3015 and PSY3016. In addition, the extensive exposure data for the PP3M, PP1M, and paliperidone ER products in earlier studies is in general supportive for PP6M, pending the current assessment adequacy for extrapolation.

During the double-blind phase in study PSY3015, the overall rates of TEAEs as well as those of common individual TEAEs were balanced between the PP6M and PP3M groups. The only TEAEs reported more frequently in the PP6M group than in the PP3M group was injection site pain. Weight increased was the most frequently reported TEAE in both treatment groups. The types and rates of clinically significant AEs of special interest in subjects treated with PP6M were consistent with the safety profile of PP3M and PP1M. In both groups, most TEAEs were considered to be mild or moderate in intensity, with few individual TEAEs in the psychiatric disorders SOC reported as severe in more than 1 subject each.

Although the injection with PP6M was well tolerated based on investigator assessments of the injection site and subjects' visual analog scale ratings (intensity of perceived injection pain, and of pain in the area of the injection), some differences were noted. A tendency for increases in tenderness was observed by investigators in the PP6M group.

The frequency for TEAEs of injection site reactions, including injection site pain, was higher in the PP6M group compared to the PP3M group. No clear relation to age or BMI was found, and the time relations of injection related TEAEs did not show a clearly different pattern with PP6M injections as compared to PP3M or placebo.

Although a potential relation of higher TEAE frequencies to the higher injection volumes with PP6M (up to 5 ml) is noted, the overall data suggest acceptable tolerability of PP6M at the injection site across the range of ages and BMI categories enrolled in study PSY3015. The administration recommendations are considered applicable to all subjects provided an appropriately longer time is advised for the injections of larger volumes.

No new safety signal-based deaths were identified and the types and rates of SAEs reported for subjects treated with PP6M in Study PSY3015 were consistent with the safety profile of PP3M and PP1M. A similar, low percentage of subjects in the PP6M and PP3M groups discontinued the double-blind phase due to an AE(s).

The incidence of diabetes mellitus and hyperglycemia-related TEAEs was in general consistent with the low incidence of treatment-emergent markedly abnormal glucose levels in individual subjects. Treatment with PP6M also was not associated with any clinically significant increase in lipid abnormalities.

The increase in body weight over a similar duration of treatment was smaller in the PP6M group compared to the PP3M group. The percentages of subjects who experienced a weight decrease were lower for the PP6M than the PP3M group. The percentage of subjects for whom TEAEs related to weight gain were reported was similar during the double-blind phase for the PP6M and PP3M groups in Study PSY3015. These results taken together, PP6M does not appear to be an issue regarding body weight.

Vital sign measurements were similar for the PP6M and PP3M groups during the double-blind phase.

PopPK modelling of PP6M demonstrated elevated median (±SD) plasma concentrations of paliperidone (between 100 and 300 ng/mL) directly after PP6M injection. Furthermore, the amount of active substance in the two strengths of PP6M is high (700 and 1000 mg paliperidone eq. respectively). Based on safety results, there are no indications of dose dumping, medication error or increased adverse events or other safety issues directly after PP6M injections.

Missed doses and dosing window of 2 weeks before up to 3 weeks after scheduled dose. Safety aspects and data. The highest PP6M dose strength (1000 mg eq.) was used to simulate the worst case scenario where shortening the dosing interval results in the highest Cmax for injections administered 1 week earlier and 2 weeks earlier relative to the scheduled 6-month injection after reaching PP6M steady state on 1000 mg eq., the median Cmax increased from 76.1 ng/mL to 76.3 (+0.3%) and to 76.6 (+0.7%), respectively. According to the Clinical Study Protocol for PSY3015, the time window was ±3 or ±7 days for dosing, and according to the Clinical Study Report no protocol deviations regarding time window was detected.

High prolactin levels relative to the maintenance phase baseline were noted in a similar percentage of subjects in the PP6M and PP3M groups in both males (approximately 35%) and females (approximately 30%). Overall patterns of prolactin level variations and of Prolactin-related Adverse Events in PSY3015 are in line with data from the previous study PSY3011 comparing PP3M to PP1M.

In additional simulations provided by the Applicant, paliperidone is estimated to remain in plasma up to medians of 38-42 months (depending on dose level) after a single dose of PP6M. SmPC section 4.6 (Women of child-bearing potential, Pregnancy and Breast-feeding) and 5.2 (Pharmacokinetic properties) were updated accordingly with also the agreement for the wording in section 4.6 that "BYANNLI should only be used in women planning to become pregnant if clearly necessary".

The last review of postmarketing cumulative data for paliperidone palmitate injectable products from product approvals through 30 June 2020 is consistent with the established safety profiles of PP1M and PP3M. No new significant safety issues or signals were identified

The issues previously considered by the PRAC Rapp to be included in the RMP have been resolved.

In the SmPC, information on section 4.6 on Pregnancy and Breast-feeding has been agreed.

The RMP has been updated throughout to add "BYANNLI" (PP6M).

The remaining key findings to be part of the benefit-risk assessment are results on injection site reactions.

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

2.6.10. Conclusions on the clinical safety

Safety of PP6M is similar to PP3M and in line with the known safety profile of paliperidone and no new safety issues were identified. PP6M differ to PP3M in dose, strength, volume, and duration of treatment.

- The TEAE reported more frequently in the PP6M group than in the PP3M group (at least 3% difference between groups) was injection site reactions, including injection site pain.
- 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 intensity, with few individual TEAEs in the psychiatric disorders SOC reported as severe in more than 1 subject each.
- Prolactin levels varied during Study PSY3015 for both PP6M and PP3M in line with data from the previous PSY3011 study of PP1M and PP3M.

2.7. Risk Management Plan

2.7.1. Safety concerns

Summary of Safety Concerns

Important Identified Risks	None
Important Potential Risks	None
Missing Information	Exposure during pregnancy

2.7.2. Pharmacovigilance plan

Routine pharmacovigilance is considered sufficient to identify and characterise the risks of the product and to monitor the effectiveness of the risk minimisation measures (RMMs).

2.7.3. Risk minimisation measures

Table 15: Summary Table of Risk Minimization Activities and Pharmacovigilance Activities by Safety Concern

Safety Concern	Risk Minimization Measures	Pharmacovigilance Activities
Missing information: Exposure during pregnancy	**Routine risk minimization measures:** INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs Section 4.6, Fertility, pregnancy and lactation Section 5.3, Preclinical safety data **Additional risk minimization measures:** None	**Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:** Cumulative review of pregnancies in the PBRER/PSUR. **Additional pharmacovigilance activities:** None

Key: PBRER/PSUR = Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report; SmPC = Summary of Product Characteristics.

2.7.4. Conclusion

The CHMP considered that the risk management plan version 10.1 is acceptable.

2.8. Pharmacovigilance

2.8.1. 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.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.9. Product information

2.9.1. User consultation

A user consultation with target patient groups on the package information leaflet (PIL) has been performed based on a bridging report making reference to XEPLION.

The bridging report submitted by the applicant has been found acceptable in a previous assessment report.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Schizophrenia is a chronic and debilitating mental disorder with a heterogeneous combination of symptoms. Symptoms of schizophrenia can be divided into "positive" (behaviors and thoughts that are not normally present, such as delusions and hallucinations), "negative" (social withdrawal, flat affect, anhedonia), and "cognitive" (a broad set of cognitive dysfunctions) categories.

Schizophrenia follows a fluctuating course marked by acute exacerbation of psychotic crises superimposed upon a background of poorly controlled negative, neurocognitive, and social cognitive symptoms, with adverse environmental events triggering crises.
The proposed indication for Byannli is;
BYANNLI, a 6-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products (see section 5.1).

3.1.2. Available therapies and unmet medical need

Antipsychotic medication is essential in schizophrenia treatment. Atypical, or second generation (SGA), antipsychotics such as risperidone, paliperidone, aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone are usually preferred over first-generation antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, and perphenazine) because of their lower risk of neurological side effects.

Oral atypical antipsychotics are usually used as first-line treatment options, with the exception of clozapine, which is reserved for treatment resistant disease.

However, nonadherence to oral antipsychotic drugs among patients with schizophrenia is common, with the frequency estimated to be about 50%. Nonadherence has a negative impact on the course of schizophrenia and leads to relapse, rehospitalization, and attempted suicide.

Without antipsychotic treatment, schizophrenia can result in severe problems that affect functioning in everyday life, such as the inability to work or attend school, other health and medical problems, and being victimized.

Several atypical antipsychotics are available as LAI formulations (eg, risperidone, PP1M, PP3M, and aripiprazole), with potential benefits in patients nonadherent to oral therapy. The use of LAI antipsychotics has been increasing gradually over the last decade. LAI antipsychotics containing paliperidone palmitate are approved with a maximum interval between injections of 3 months (PP3M).

The PP6M is intended for the treatment of schizophrenia only in adults who have been adequately treated with PP1M preferably for four months or more, or with PP3M for at least one injection cycle. PP6M is not intended for treatment without prior exposure to PP1M or PP3M.

The claimed 6-months indication is intended for patients who remained stable on LAI treatment with a shorter injection interval, in case a substantially longer dosing interval is preferred. According to the Applicant this might offer benefits also to those with limited access to healthcare, such as geographic or economic problems with clinic visits, or else limited access to treatment due to problems associated with e g homelessness.

The PP6M formulation has a higher injection volume than PP3M and PP1M and should only be dosed in the gluteal muscle.

3.1.3. Main clinical studies

The main clinical study PSY3015 was a well-designed international randomized, double-blind, active-controlled, multicenter, interventional, parallel-group study with the aim to demonstrate that the effect of PP6M is non-inferior to PP3M in adults with schizophrenia, previously treated with PP1M for at least 4 months or PP3M for at least one 3-month injection cycle. In addition, the pharmacokinetic properties of PP6M were measured from semi-intensive PK sampling.

The study design and the numbers completing/entering the study are considered adequate to reach this conclusion; 416/478 (87.0%) in the PP6M arm and 202/224 (90.2%) in the PP3M arm. Consistent with previous scientific advice from CHMP, more than 25% of subjects were enrolled and treated at sites in the EU during the double-blind phase (n=193, 28%).

3.2. Favourable effects

The efficacy of PP6M was based on the demonstration of non-inferiority versus PP3M, for the documented difference of relapse rate in Kaplan-Meier estimate -2,9% (95% CI -6.8 , 1.1) in ITT analysis (10% pre-defined lower margin of CI). The results were consistent in the pre-defined subgroups age, sex, BMI, region, dose and race.

Efficacy of PP3M previously has been based on non-inferiority versus PP1M, which was assessed in study PSY3011. Thus, the favourable effects of paliperidone are well known from PP1M and PP3M. The pharmacokinetics of PP6M has been well characterized. The total plasma exposure after PP6M was roughly similar to corresponding doses of PP3M. A number of simulations have been performed addressing different dosing scenarios to support the dosing recommendations in the SmPC.

3.3. Uncertainties and limitations about favourable effects

Some additional clarifications from a pharmacokinetic perspective were performed as requested with respect to switching between formulations, dosing windows and re-initiation of PP6M.

3.4. Unfavourable effects

The unfavourable effects of paliperidone are known from PP1M and PP3M.
There is no indication of any new safety signal with PP6M. During the double-blind phase, a higher percentage of subjects in the PP6M group reported injection site-related TEAEs (12.3%) compared to the PP3M group (4.9%). TEAEs of injection site pain were the most frequently reported local reactions in both treatment groups (PP6M: 7.7% and PP3M: 4.0%). No injection site reaction TEAE was reported as severe, and most were mild.
Further safety assessment is pending data from the ongoing study OLE PSY3016.

3.5. Uncertainties and limitations about unfavourable effects

Some additional information has been added concerning the more frequent injection site reactions for PP6M, the potential risk of dose dumping, and the longstanding serum concentrations with regard to pregnancy and breast-feeding.

Though the amount of active substance in PP6M is high, the potential risk of dose dumping is considered to be low, primarily due the extremely low water solubility of the prodrug paliperidone palmitate. Overall, the physico-chemical and biological properties indicate that PP6M is a predictable and robust formulation with a very low potential for unexpected drug release after intramuscular administration.

The estimated long-standing serum concentrations up to 4 years after a single PP6M dose require clinical consideration about pregnancy and breast-feeding, this was discussed with the company and clarified in the SmPC 4.6 and 5.2 as well as in the Package leaflet.

The Applicant has provided simulation data on the 5^{th} and 95^{th} percentiles of C_{max} and C_{trough} at the different dosing-windows, i.e. PP6M administration 1 and 2 weeks earlier, and later than the scheduled 6-month time point, up to a delay of 11 months. The simulation data per se provide no support for the recommended extra dosing of PP1M after a missed dose of PP6M, even up to a delay of 11 months. The Applicant has provided additional information in support of the recommendation for extra dosing of PP1M after a missed dose, e.g. a clinical need to evaluate the stability of treatment in such cases should be considered.

Based on the plasma concentration curves and Pop PK simulations, there might be a potentially increased risk for ADRs the period directly after injection of PP6M and a potential risk for insufficient effect or relapse during the end of the dosing interval. From PSY3015 there are no clear clinical indications of such unfavourable effects, neither from limited preliminary data from PSY3016 (ongoing).

3.6. Effects Table

Table 16: Effects Table for BYANNLI (PP6M, paliperidone 6-months injectable) in the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1 monthly or 3 monthly paliperidone palmitate injectable products (data cut-off: 08 May 2020).

Effect	Short Description	Unit	PP6M	PP3M active control	Uncertainties/ Strength of evidence	References
Favourable Effects						
Relapse free rate	No relapse in 12 months RCT	%	92,5	95,1	Upper bound (6.8) of CI for the difference within pre-defined 10% margin	PSY3015
Unfavourable Effects						
Injection site TEAE		%	12.3	4.9		PSY3015
injection site pain TEAE		%	7.7	4.0		PSY3015

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

This application concerns a new formulation of paliperidone palmitate allowing dosing every 6th month for the treatment of patients with schizophrenia. Previously, long acting products with 1- and 3-months dosing intervals are approved. The PP6M is intended for the treatment of schizophrenia in adults who have been adequately treated with PP1M preferably for four months or more, or with PP3M for at least one injection cycle. PP6M is not intended for treatment without prior exposure to PP1M or PP3M.

The claimed 6-months indication is intended for patients who remained stable on LAI treatment with a shorter injection interval, in case a substantially longer dosing interval is preferred. According to the Applicant this might offer benefits also to those with limited access to healthcare, such as geographic or economic problems with clinic visits, or else limited access to treatment due to problems associated with e g homelessness. This is acknowledged, but it should also be considered that the longer dosing interval may lead to less frequent contacts with health care providers. However, it is assumed that the prescriber can judge which patients the PP6M would be suitable.

The non-inferiority finding for PP6M supports a clinical benefit similar to the PP3M and PP1M.
Efficacy data are considered clinically significant and robust based on the primary endpoint analysis in study PSY3015 and consistent subgroup analyses.

The PP6M formulation has a higher injection volume than PP3M and PP1M and should only be dosed in the gluteal muscle.

As the higher volume is most likely the explanation to the higher incidence of injections site reactions compared to PP3M, a minor clarification concerning advisable injection speed is requested. In addition, concerning estimated serum concentrations up to 4 years after a single PP6M dose, further clarification were provided concerning pregnancy and breast-feeding. Section 4.6 and 5.2 and the package leaflet were updated satisfactorily accordingly with notably agreed wording in section 4.6 that "BYANNLI should only be used in women planning to become pregnant if clearly necessary.

The data regarding adverse events and ADRs, adverse events of clinical interest for the class of atypical antipsychotics, laboratory findings and vital sign measurements reported were generally similar for PP6M and PP3M in Study PSY3015.

3.7.2. Balance of benefits and risks

Considering that the effect of the PP6M is noninferior to the PP3M and that no new serious adverse events have been documented, the benefits are considered to outweigh the risks.

3.8. Conclusions

The overall benefit/risk balance of BYANNLI is positive.

4. Recommendations

Based on the CHMP review of data on quality and safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of, BYANNLI Prolonged-release suspension for injection, 700 mg, 1000 mg is favourable in the following indication:

BYANNLI, a 6-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly or 3-monthly paliperidone palmitate injectable products.

The CHMP therefore recommends the extension(s) of the marketing authorisation for BYANNLI subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription.

Conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

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

- **Risk Management Plan (RMP)**

The Marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

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

  Not applicable

- **Obligation to conduct post-authorisation measures**

  Not applicable

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

Not applicable

In addition, CHMP recommends the variation(s) to the terms of the marketing authorisation concerning the following change(s):

Variations requested		**Type**	**Annexes affected**
X.02.III	Annex I_2.(c) Change or addition of a new strength/potency	Line Extension	I, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
C.I.7.b	C.I.7.b - Deletion of - a strength	Type IB	I, IIIA, IIIB and A
A.2.a	A.2.a - Administrative change - Change in the (invented) name of the medicinal product for CAPs	Type IAin	I, IIIA, IIIB and A
A.7	A.7 - Administrative change - Deletion of manufacturing sites	Type IA	None

A.2.a - To change the (invented) name of the medicinal product from Paliperidone Janssen-Cilag International to BYANNLI
A.7 - To delete Cilag AG (Hochstrasse 201, CH-8200 Schaffhausen) as a site responsible for manufacturing, primary and secondary packaging and release testing of the finished product
C.I.7.b. - To delete the 25 mg, 50 mg, 75 mg, 100 mg and 150 mg/100 mg strengths from the Paliperidone Janssen-Cilag marketing authorisation (EU/1/20/1453/001-006).