European Union Risk Management Plan:

INVEGA® (Paliperidone Prolonged-Release Tablets)

XEPLION® (Paliperidone Palmitate 1-Monthly Formulation [PP1M])

TREVICTA® (Paliperidone Palmitate 3-Monthly Formulation [PP3M])

BYANNLI® (Paliperidone Palmitate 6-Monthly Formulation [PP6M])

Data lock point for current RMP	30 June 2020	Version number	10.1

Final for Procedure EMEA/H/C/005486/X/0002/G – HA approval date (EC decision) 22 November 2021

QPPV Sign-off Date: 30 November 2021
RMP Version Number: 10.1
Supersedes Version: 9.1
EDMS Number: EDMS-RIM-103153, 2.0

Qualified Person for Pharmacovigilance (QPPV) Name:	Dr. Laurence Oster-Gozet, PharmD, PhD
QPPV Signature:	The MAH QPPV has either reviewed and approved this RMP, or approved with an electronic signature appended to this RMP, as applicable.

Details of This RMP Submission:	
Version Number	10.1
Rationale for submitting an updated RMP	To add the paliperidone palmitate 6-monthly (PP6M) product to the RMP in support of the extension application.
Summary of significant changes in this RMP:	Updated RMP throughout to add "BYANNLI" (PP6M), and to remove "Paliperidone Janssen-Cilag International" (a copy of paliperidone palmitate 1-monthly). Updated Part II Module SIII (Clinical Trial Exposure) with Study R092670PSY3015 data. Updated Part II Module SV (Postauthorization Experience) with postauthorization exposure data with data cut-off of 30 June 2020.

Other RMP Versions Under Evaluation:		
RMP Version Number	**Submitted on**	**Procedure Number**
Not applicable		

Details of the Currently Approved RMP:	
Version number of last agreed RMP:	9.1
Approved within procedure	EMEA/H/C/0005486/0000
Date of approval (competent authority opinion date)	18 June 2020

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PART I: PRODUCTS OVERVIEW

Active substance(s) **(International nonproprietary name [INN] or common name)**	Paliperidone
Pharmacotherapeutic group(s) (Anatomical Therapeutic Chemical [ATC] Code)	Other antipsychotics (N05AX13)
Marketing Authorization Holder (MAH)	Janssen-Cilag International, NV
Medicinal products to which the RMP refers	Paliperidone prolonged-release (PR) tablets (paliperidone PR; also termed extended-release [ER]), paliperidone palmitate 1-monthly formulation (PP1M), paliperidone palmitate 3-monthly formulation (PP3M), and paliperidone palmitate 6-monthly formulation (PP6M).
Invented name(s) in the European Economic Area (EEA)	INVEGA, XEPLION, TREVICTA, and BYANNLI.
Marketing authorization procedure	Centralized
Brief description of the product	Paliperidone (9-hydroxy-risperidone, R076477) is a monoaminergic antagonist that exhibits the characteristic dopamine Type 2 (receptor) (D_2) and serotonin 5-hydroxy-tryptamine antagonism of the newer, or second generation, antipsychotic drugs. Paliperidone, the major active metabolite of risperidone (R064766), is a racemic mixture of enantiomers R078543 (+) and R078544 (-) and has similar pharmacological activity to the parent drug. Paliperidone has been developed as a PR formulation utilizing osmotic-controlled release oral delivery system (OROS) technology (INVEGA). The controlled rate of release of paliperidone from the PR OROS formulation results in a pharmacokinetic (PK) profile with a slower rate of absorption than an immediate-release (IR) formulation, an ascending profile on Day 1 of dosing, and reduced fluctuations in plasma concentrations on subsequent days of treatment. Paliperidone palmitate (R092670) is the palmitate ester of paliperidone and has been developed as a long-acting, intramuscular (IM) injectable aqueous suspension with a release profile and dosing regimen that result in sustained therapeutic concentrations as a 1-monthly (PP1M) formulation (XEPLION), 3-monthly (PP3M) formulation (TREVICTA), or 6-monthly (PP6M) formulation (BYANNLI).

Reference to the Product Information	• **INVEGA**, Module 1.3.1, Summary of Product Characteristics (SmPC), Labelling, and Package Leaflet (PL) • **XEPLION**, Module 1.3.1, SmPC, Labelling, and PL • **TREVICTA**, Module 1.3.1, SmPC, Labelling, and PL • **BYANNLI,** Module 1.3.1, SmPC, Labelling, and PL
Indication(s) in the EEA	**Current:** • **INVEGA** is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older. • **INVEGA** is indicated for the treatment of schizoaffective disorder in adults. • **XEPLION** is indicated for maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone. In selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone, XEPLION may be used without prior stabilization with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed. • **TREVICTA**, a 3-monthly injection, is indicated for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product. • **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. **Proposed:** Not applicable
Dosage in the EEA	**Current, INVEGA**: *Schizophrenia (adults)* The recommended dose of INVEGA for the treatment of schizophrenia in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from lower or higher doses within the recommended range of 3 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 5 days. *Schizoaffective disorder (adults)* The recommended dose of INVEGA for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from higher doses within the recommended range of 6 to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days.

<table>
<tr><td>Dosage in the EEA, continued</td><td>Posology also is described in the SmPC for the following: switching to other antipsychotic medicinal products, elderly, hepatic impairment, renal impairment, pediatric population, and other special populations.</td></tr>
<tr><td></td><td>Current, XEPLION: Recommended initiation of XEPLION is a dose of 150 mg on treatment Day 1 and 100 mg 1 week later (Day 8), both administered in the deltoid muscle in order to attain therapeutic concentrations rapidly. The third dose should be administered 1 month after the second initiation dose. The recommended monthly maintenance dose is 75 mg; some patients may benefit from lower or higher doses within the range of 25 to 150 mg based on individual patient tolerability and/or efficacy. Patients who are overweight or obese may require doses in the upper range. Following the second dose, monthly maintenance doses can be administered in either the deltoid or gluteal muscle.

Posology also is described in the SmPC for the following: adjustment of maintenance dose, switching from oral paliperidone or risperidone, switching from risperidone long-acting injection, missed doses, special populations (elderly, renal impairment, hepatic impairment, and pediatric populations), and method of IM administration.</td></tr>
<tr><td></td><td>Current, TREVICTA: Patients who are adequately treated with 1-monthly paliperidone palmitate injectable (preferably for 4 months or more) and do not require dose adjustment may be switched to 3-monthly paliperidone palmitate injection.

TREVICTA should be initiated in place of the next scheduled dose of 1-monthly paliperidone palmitate injectable (±7 days). The TREVICTA dose should be based on the previous 1-monthly paliperidone palmitate injectable dose using a 3.5-fold higher dose as follows:

<table>
<tr><th>If the last dose of 1-monthly paliperidone palmitate injectable is:</th><th>Initiate TREVICTA at the following dose:</th></tr>
<tr><td>50 mg</td><td>175 mg</td></tr>
<tr><td>75 mg</td><td>263 mg</td></tr>
<tr><td>100 mg</td><td>350 mg</td></tr>
<tr><td>150 mg</td><td>525 mg</td></tr>
</table>
There is no equivalent dose of TREVICTA for the 25 mg dose of 1-monthly paliperidone palmitate injectable, which was not studied.

Following the initial TREVICTA dose, TREVICTA should be administered by IM injection once every 3 months (±2 weeks).

Posology also is described in the SmPC for the following: adjustment of maintenance dose, switching from oral paliperidone or risperidone, switching from risperidone long-acting injection, switching from TREVICTA to other antipsychotic medicinal products; missed doses, special populations (elderly, renal impairment, hepatic impairment, and pediatric populations), and method of IM administration.</td></tr>
</table>

Dosage in the EEA, continued

Current, BYANNLI: Patients who are adequately treated with 1-monthly paliperidone palmitate injection at doses of 100 or 150 mg (preferably for 4 months or more) or 3-monthly paliperidone palmitate injection at doses of 350 or 525 mg (for at least 1 injection cycle) and do not require dose adjustment may be transitioned to 6-monthly paliperidone palmitate injection.

BYANNLI for patients adequately treated with 1-monthly paliperidone palmitate injection

BYANNLI should be initiated in place of the next scheduled dose of 1-monthly paliperidone palmitate injection (± 7 days). To establish a consistent maintenance dose, it is recommended that the last 2 doses of 1-monthly paliperidone palmitate injection be the same dosage strength before starting BYANNLI. The BYANNLI dose should be based on the previous 1-monthly paliperidone palmitate injectable dose shown in the following table:

Transitioning to BYANNLI for patients adequately treated with 1-monthly paliperidone palmitate injection

If the last dose of 1-monthly paliperidone injection is	Initiate BYANNLI at the following dose*
100 mg	700 mg
150 mg	1,000 mg

*There are no equivalent doses of BYANNLI for the 25, 50, or 75 mg doses of 1-monthly paliperidone palmitate injection, which were not studied.

BYANNLI for patients adequately treated with 3-monthly paliperidone palmitate injection

BYANNLI should be initiated in place of the next scheduled dose of 3-monthly paliperidone palmitate injection (± 14 days). The BYANNLI dose should be based on the previous 3-monthly paliperidone palmitate injectable dose shown in the following table:

Transitioning to BYANNLI for patients adequately treated with 3-monthly paliperidone palmitate injection

If the last dose of 3-monthly paliperidone injection is	Initiate BYANNLI at the following dose*
350 mg	700 mg
525 mg	1,000 mg

*There are no equivalent doses of BYANNLI for the 175 or 263 mg doses of 3-monthly paliperidone palmitate injection, which were not studied.

Following the initial BYANNLI dose, BYANNLI should be administered once every 6 months. If necessary, patients may be given the injection 2 weeks before or 3 weeks after the 6-month scheduled timepoint.

Posology is also described in the SmPC for the following: adjustment of maintenance dose, switching from oral paliperidone or risperidone, switching from risperidone long-acting injection, switching from BYANNLI to other antipsychotic medicinal products; missed doses, special populations (elderly, renal impairment, hepatic impairment, and pediatric populations), and method of IM administration.

Dosage in the EEA, continued	**Proposed:** Not applicable	
Pharmaceutical form(s) and strengths	**Current**: • **INVEGA**: Prolonged-release tablet: 3, 6, 9, and 12 mg. • **XEPLION**: Prolonged-release suspension for IM injection in prefilled syringes containing 39, 78, 117, 156, or 234 mg of XEPLION, which is equivalent to 25, 50, 75, 100, or 150 mg, respectively, of paliperidone. • **TREVICTA**: Prolonged-release suspension for injection in prefilled syringes containing 273, 410, 546, or 819 mg of TREVICTA; which is equivalent to 175, 263, 350, or 525 mg, respectively, of paliperidone. • **BYANNLI**: Prolonged-release suspension for injection in prefilled syringes containing 1,092 or 1,560 mg of BYANNLI; which is equivalent to 700 or 1,000 mg, respectively, of paliperidone. **Proposed:** Not applicable	
Is/will the product be subject to additional monitoring in the European Union (EU)?	☐ **Yes**	☑ **No**

PART II: SAFETY SPECIFICATION

Module SI: Epidemiology of the Indication(s) and Target Population(s)

Indications: Schizophrenia in adults and adolescents (INVEGA); schizoaffective disorder in adults (INVEGA); maintenance treatment of schizophrenia in adults (XEPLION, TREVICTA, and BYANNLI)

The epidemiology of schizophrenia disorders has been investigated in numerous studies to date and estimates of incidence and prevalence vary significantly across studies. These variations are difficult to assess due to differences in study design, disease definitions used, and different geographic regions (McGrath 2005). As many studies of schizophrenia include patients with schizoaffective disorder, the literature has a large degree of overlap. Therefore, some of the epidemiologic data on schizophrenia may be applicable to patients with schizoaffective disorder. Where information specific to schizoaffective disorder is available, it is included below.

Incidence:

According to the Global Burden of Disease (GBD) Study, there were an estimated 1.14 million incident cases of schizophrenia worldwide in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). A systematic review of the incidence of schizophrenia, which included data from 43 studies drawn from 33 countries spanning 35 years, estimated a pooled median incidence rate for schizophrenia of 18.3 per 100,000 person-years (interquartile range [IQR]: 10.9-28.9) (van der Werf 2014). Another systematic review of the incidence in England over a 60-year period (1950-2009) among persons 16 to 64 years of age was conducted and reported a pooled incidence for schizophrenia of 15.2 per 100,000 person-years (95% confidence interval [CI]: 11.9-19.5) (Kirkbride 2012). In the Netherlands, one study conducted from 1996 to 2006 reported an incidence of the broad definition "schizophrenia spectrum disorders" and narrow definition "schizophrenia" to be 22 per 100,000 person-years and 12 per 100,000 person-years, respectively (Sutterland 2013).

Prevalence:

Although the incidence of schizophrenia is low relative to other mental health disorders, the prevalence is relatively high due to the chronicity of the disease. According to the GBD Study, there were an estimated 20.88 million prevalent cases of schizophrenia worldwide in 2016 (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators 2017). A systematic review of prevalence studies published from 1990 to 2013 reported that for studies reporting a 12-month prevalence, the median estimate was 0.33% with an IQR of 0.26% to 0.51%. Prevalence varied by study design, geographic region, time of assessment, and study quality. The use of a broader definition of "schizophrenia spectrum disorders" increases case identification. For European studies, there were 13 studies that reported lifetime prevalence with a median of 0.52% (IQR: 0.39%-0.87%) (Simeone 2015).

The prevalence of schizoaffective disorder has been estimated to be <1% (0.5%-0.8%) in the general population (Malhi 2008). Other European investigators report a lifetime prevalence for schizoaffective disorder of approximately 0.32% (Pagel 2013; Perälä 2007).

Demographics of the Population in the Authorized Indication - [Age, Sex, Racial and/or Ethnic Origin] and Risk Factors for the Disease:

Age and Sex

Schizophrenia is usually initially diagnosed in young adults, and usually with "first episode of psychosis" (Millan 2016). The peak incidence for schizophrenia has been observed in the late teens and early twenties and is more pronounced among men than women (Laursen 2014). The National Institute of Mental Health (NIMH) reports that symptoms of schizophrenia usually appear between the ages of late teens to early thirties and that men tend to experience symptoms slightly earlier than women (NIMH 2018). Data have suggested that for every 3 men with schizophrenia, 2 women have the disease (Owen 2016). Women may have a more favorable disease course compared with men. One possible explanation for the difference in disease prognosis is that men more often present with deficit schizophrenia, which tends to have a longer chronicity and a poorer functional outcome (Ochoa 2012).

Schizophrenia in patients with an onset of psychotic symptoms before the age of 18 years is known as Early-Onset Schizophrenia (EOS). If the patient develops symptoms before the age of 13 years it is considered Child-Onset Schizophrenia (COS), or Very Early-Onset Schizophrenia (VEOS) (Carlisle 2011; Masi 2006). Schizophrenia is very rare in prepuberty children, and limited epidemiological knowledge is available on this early-onset disorder. The estimated prevalence of COS has been reported to be 1 in 10,000 before the age of 12 years, but the prevalence increases remarkably around puberty and early adolescence (Carlisle 2011; Remschmidt 2002). It is estimated that COS is approximately 50 times less frequent than adult-onset schizophrenia (Remschmidt 2002). Schizophrenia in young people tends to be a more disabling and persistent disorder (Hollis 2000), bringing with it greater vulnerability to physical harm from both the disease and its treatments.

The majority of studies indicate little difference between sexes in the lifetime incidence of schizophrenia and that the risk is approximately equal in men and women within the populations followed clinically (Kendler 1996; McGrath 2006). The available data on EOS and COS are mixed with regard to distribution by sex. In a review (Masi 2006), the authors found that patients diagnosed with VEOS were predominantly boys. Similarly, Carlisle (2011) reported that EOS, particularly COS, presents more often in boys, as age increases, sex ratios tend to even out. A study by Kravariti (2003) involving 42 patients with EOS (aged 12-18 years) found that the male-to-female ratio was 26:16. In contrast, an earlier review article stated that in child- and adolescent-onset schizophrenia, the sex ratio is nearly equal, with no difference in age at onset between boys and girls. This is in contrast to adult-onset schizophrenia, for which it is assumed that estrogens can delay the onset in women by raising the threshold of vulnerability (Remschmidt 2002).

Schizoaffective disorder appears to occur more often in women than in men, particularly in married women. The age of onset for women is later than for men and depressive symptoms are more prevalent in women (Malhi 2008).

Race and/or Ethnic Origin

The distribution of schizophrenia does not appear to be influenced by race. Where differences in race have been observed, biases in diagnostic practice are likely explanations for the observed differences (Neighbors 2003; McGrath 2006). Few epidemiological studies provide information regarding racial distribution of EOS and COS. The study by Kravariti (2003) found that of the 42 EOS cases evaluated, 31 were white, 7 were black, 3 were Asian, and 1 was of mixed race.

A study in England evaluated 568 people aged 16 to 64 years who presented to secondary services with a first psychotic symptom from 1997 to 1999. The authors observed high incidence rate ratios (IRRs) for schizophrenia in both African-Caribbean (IRR: 9.1) and black Africans (IRR: 5.8) in both sexes and in all age groups compared with a white British cohort (Fearon 2006).

Geography

There have been several studies demonstrating that schizophrenia is more common in urban than rural areas (Kahn 2015).

Risk Factors for the Disease

There is a significant amount of research suggesting that there are several risk factors that contribute to schizophrenia, particularly those that affect early neurodevelopment (Owen 2016). The Mayo Clinic identified the following potential risk factors for developing schizophrenia: family history of schizophrenia; exposure to viruses or toxins during prenatal development; poor nutrition during prenatal development; increased immune system activation, such as from inflammation or autoimmune diseases; older paternal age; and use of psychoactive drugs during adolescence (Mayo Clinic 2018). Season of birth has also been consistently established as a risk factor for schizophrenia. There is a small but significant increase in schizophrenia for individuals born in late winter and spring (Kahn 2015). Other factors associated with an increased risk of schizophrenia are childhood adversities, such as parental loss or separation, child abuse, and bullying, and adult adversities, such as stressful life events and social isolation (Stilo 2010).

Main Existing Treatment Options:

Antipsychotic medications are the mainstay of schizophrenia treatment. Atypical, or second generation, antipsychotics (eg, risperidone, paliperidone, aripiprazole, clozapine, olanzapine, quetiapine, and ziprasidone) are usually preferred over typical, or first generation, antipsychotics (eg, chlorpromazine, fluphenazine, haloperidol, and perphenazine) because of their lower propensity to cause neurological side effects. Oral atypical antipsychotics are usually used as first-line treatment options (Barnes 2011), with the exception of clozapine, which is reserved for treatment-resistant disease. Several atypical antipsychotics are available as a long-acting injectable formulation (eg, risperidone [RISPERDAL CONSTA®], paliperidone palmitate [XEPLION], and

aripiprazole [ABILIFY MAINTENA®]) (RISPERDAL CONSTA SmPC; ABILIFY MAINTENA SmPC; see also XEPLION SmPC), which have potential benefits in patients who are nonadherent to oral therapy.

Although medications are the cornerstone of schizophrenia treatment, effective management also requires that the pharmacotherapy be used within a framework of psychological and social support aimed at improving adherence and include vocational and educational support; the National Institute for Health and Care Excellence (NICE) guidelines recommend that all patients with schizophrenia be offered cognitive behavioral therapy and family intervention (Owen 2016).

Despite a much smaller evidence base, there is general consensus that schizophrenia in young people should be treated with the same interventions that are effective in adults (NICE 2013; Mayo Clinic 2014). Oral atypical antipsychotic drugs are typically used as first-line therapy for the treatment of schizophrenia in adolescents; however, only a few blinded, controlled trials have been conducted in this population (Carlisle 2011; NICE 2013). Treatment options are currently limited, with aripiprazole (ABILIFY®) (ABILIFY SmPC) and paliperidone (INVEGA) (see INVEGA SmPC) being the only atypical antipsychotics centrally approved in the EU for the treatment of schizophrenia in adolescents aged 15 years and older.

Patients with schizoaffective disorder are often prescribed complex pharmacological regimens as clinicians attempt to manage the psychotic and affective symptoms. Mood stabilizers, antidepressants, and antipsychotic medications all have a role in the management of schizoaffective disorder as well as psychotherapy and life skills training (Mayo Clinic 2017), with atypical antipsychotics being the cornerstone of treatment (Malhi 2008).

Natural History of the Indicated Condition in the Untreated Population, Including Mortality and Morbidity:

Schizophrenia is a complex syndrome 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. The onset of psychotic symptoms is often preceded by the emergence of subtle changes in belief, thought, and perception that seem to represent forms of delusions, thought disorders, and hallucinations. This is referred to as the prodromal phase and is frequently not recognized. Approximately 80% to 90% of patients with schizophrenia have such a prodrome, which has a median duration of about 52 weeks; psychotic symptoms emerge without an appreciable prodrome in the remaining 10% to 20% of patients (Kahn 2015). Once diagnosed, 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 (Millan 2016). Without 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 (Mayo Clinic 2018).

Patients are typically not referred for consultation until psychosis presents in late adolescence or early adulthood. The outcome of schizophrenia can range from complete recovery to chronic need of care. Patients with schizophrenia generally experience serious impairments in multiple domains of everyday life, including the ability to maintain social relationships, sustain employment, and live independently. These deficits typically persist after patients achieve remission from psychotic symptoms. For patients with schizophrenia, the ability to live independently can be achieved for the vast majority of patients using a combination of antipsychotic medication and psychosocial interventions, which increases quality of life but has little effect on social and professional functioning (Kahn 2015).

Schizophrenia has been associated with a decreased life expectancy with a standardized mortality ratio (standardized for age, sex, race/ethnicity, and geographic region) of 3.7 for all causes of mortality compared to the general population, according to one United States study conducted from 2001 to 2007 (Olfson 2015). There is evidence that the mortality rates are declining, as a recent study conducted in the United Kingdom from 2000 to 2014 reported an all-cause mortality rate of 248.57 per person-years at risk (95% CI: 238.06-259.53) and a mortality rate that decreased during that time with an annual percent change of -2.0%. Compared to the general population, the risk of all-cause mortality was significantly higher (hazard ratio [HR]: 2.08; 95% CI: 1.98-2.19). The suicide rate was also higher for people with schizophrenia than the general population, with rates of 5.98-per-person-years at risk (95% CI: 4.31-8.29) and 0.51 per person-years at risk (95% CI: 0.36-0.72), respectively (Hayes 2017). Natural causes accounted for most of the known causes of death, with cardiovascular disease having the highest mortality rate (403.2 per 100,000 person-years), followed by cancer (200.5 per 100,000 person-years) (Olfson 2015).

The use of antipsychotics is an important factor in reducing mortality in schizophrenia. A nationwide study in Finland of antipsychotics after first hospitalization for schizophrenia found that the use of any antipsychotic compared with no antipsychotic was associated with significantly lower mortality (adjusted HR: 0.45; 95% CI: 0.31-0.67). All-cause mortality risk was found to be significantly lower in patients on long-term antipsychotic treatment (ie, for 7-11 years) than in patients who had not used any antipsychotic drugs during follow-up (HR: 0.81; 95% CI: 0.77-0.84; $p<0.0001$) (Beary 2012; Tiihonen 2009).

Important Comorbidities:

- Psychiatric disorders (Kirkpatrick 2014)
- Metabolic syndrome, diabetes mellitus, impaired glucose tolerance, or obesity (Azad 2016)
- Cardiovascular disease (Azad 2016; Olfson 2015)
- Smoking (Beck 2015)
- Substance use or abuse (Cantor-Graae 2001; Kirkpatrick 2014)
- Cancer (Chou 2016; Olfson 2015)
- Pneumonia (Kuo 2013)
- Falls, fractures, or osteoporosis (Tsai 2014)

PART II: SAFETY SPECIFICATION

Module SII: Nonclinical Part of the Safety Specification

Key Safety Findings	Relevance to Human Usage
Toxicity	
Repeat-dose toxicity	
As with other drugs that antagonize D_2 receptors, paliperidone elevated serum prolactin levels in repeat-dose toxicity studies.	Hyperprolactinemia and potentially prolactin-related adverse events was included as an important identified risk for paliperidone but was subsequently removed at the request of the PRAC during the registration procedure for TREVICTA (EMEA/H/C/004066/X/0007/G) on the basis that routine risk minimization measures have been taken for a considerable period and because the risk is adequately reflected in the Product Information.
In animals treated with paliperidone palmitate (PP1M, PP3M, PP6M), an inflammatory reaction was seen at the IM injection site. Occasionally abscess formation occurred.	Injection site reactions were considered an important potential risk based on nonclinical findings. Although these reactions have also occurred with the use of XEPLION, TREVICTA, and BYANNLI in humans, the impact to the individual is less than anticipated. Injection site reactions are no longer considered an important risk.
Administration of risperidone long-acting injection to male and female rats for 12 and 24 months produced osteodystrophy at a dose of 40 mg/kg/2 weeks. The effect dose for osteodystrophy in rats was on a mg/m^2 basis 8 times the MRHD for risperidone and is associated with a plasma exposure 2 times the maximum anticipated plasma exposure (ie, AUC) in humans at the MRHD. No osteodystrophy was observed in dogs treated for 12 months with risperidone long-acting injection up to 20 mg/kg/2 weeks yielding plasma exposures up to 14 times the MRHD.	No risk for humans is suggested based on findings from animal studies, as osteodystrophy was observed at doses well above the MRHD.
Reproductive toxicity	
In a male fertility study in rats, paliperidone (0.16, 0.63, and 2.5 mg/kg) showed paternal toxicity at the highest dose, without an effect on male fertility.	No male fertility risk for humans is suggested.

Key Safety Findings	Relevance to Human Usage
In a female fertility study with paliperidone (0.16, 0.63, 2.5 mg/kg), prolactin-mediated pseudopregnancies and a prolongation of the precoital interval at all dose levels were observed. At the maternally toxic top dose, there was a slight increase in preimplantation loss resulting in fewer implantations and a lower number of live fetuses. There were no effects on ovulation as assessed by normal numbers of corpora lutea of pregnancy.	Because the increase in preimplantation loss only occurred in the presence of maternal toxicity, this effect is of little relevance to humans.
In animal studies, paliperidone was excreted in the milk.	Paliperidone is also excreted in human breast milk in small quantities. Paliperidone ER, PP1M, PP3M, and PP6M have not been studied in lactating women. Paliperidone should not be used while breastfeeding.
Developmental toxicity	
No teratogenic effects were noted during embryofetal development following oral paliperidone administration in rats (0.63, 2.5, 10 mg/kg) or rabbits (0.31, 1.25, 5 mg/kg) or following a single dose of PP1M in rats (20, 80, and 160 mg equivalents per kg). Even at maternally toxic dose levels in the embryofetal development toxicity study in rats, there were no treatment-related changes at external, visceral, or skeletal examination of the unborn offspring. The embryofetal developmental toxicity study with paliperidone in rabbits showed maternal toxicity at medium and high doses associated with a slight increase in total postimplantation loss at the highest dose. This implantation loss was associated with a slight increase in the number of embryonic/fetal resorptions and fetal death. There have also been studies using risperidone that are considered relevant to paliperidone: • In pregnant mice, oral risperidone during organogenesis caused cleft palate at 10 mg/kg/day, which is 3 times the MRHD for risperidone of 16 mg/day based on mg/m^2 body surface area. Maternal toxicity occurred at 4 times the MRHD for risperidone. • In rats, offspring were studied after dams were dosed with oral risperidone throughout pregnancy. Findings included:	Signs of embryofetal toxicity in the paliperidone rabbit study were seen at a maternally toxic dose level only and at exposures considerably higher than those attained in humans at the MRHD. However, the relevance to humans of these effects of paliperidone is unknown. Exposure during pregnancy is considered missing information.

Key Safety Findings	Relevance to Human Usage
– At 1 mg/kg/day, which is 0.6 times the MRHD for risperidone, neuronal cell death was increased in fetal brains. – At 1 and 2 mg/kg/day, which are respectively 0.6 and 1.2 times the MRHD for risperidone, postnatal development and growth of the offspring were delayed.	
Genotoxicity	
Paliperidone was tested in a full battery of genotoxicity studies and showed no genotoxic properties.	No risk for humans is suggested.
Carcinogenicity	
Risperidone is extensively converted to paliperidone in mice, rats, and humans. Therefore, the carcinogenic potential of paliperidone was assessed in studies with risperidone conducted in Swiss albino mice and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. There were statistically significant increases in pituitary gland adenomas (mouse), endocrine pancreas adenomas (rat), and mammary gland adenocarcinomas (both species). Mammary gland adenomas and adenocarcinomas were also observed in a carcinogenicity study with intramuscularly injected paliperidone in rats.	Carcinogenicity (pituitary adenomas, endocrine pancreas tumors, breast cancer) was included as an important potential risk based on tumor findings in rodents. However, cumulative evidence (clinical, epidemiological, and postmarketing) suggests that tumorigenesis is not a safety concern for paliperidone use in humans.
Safety pharmacology	
Cardiovascular system (including potential for QT interval prolongation)	
In the 3-month repeat-dose toxicity studies in dogs with paliperidone prolonged-release tablets and paliperidone bulk powder, corrected Q-T interval (QTc) van de Water's prolongation exceeding 10% against baseline was observed in dogs.	QT prolongation was included as an important identified risk for paliperidone but was subsequently removed at the request of the PRAC during the registration procedure for TREVICTA (EMEA/H/C/004066/X/0007/G) on the basis that routine risk minimization measures have been taken for a considerable period and because the risk is adequately reflected in the Product Information.

Key Safety Findings	Relevance to Human Usage
Other toxicity-related information or data	
Juvenile toxicity	
In a 7-week juvenile toxicity study in rats with oral doses of paliperidone of 0.16, 0.63, and 2.5 mg/kg (which are 0.12, 0.5, and 1.8 times the MRHD for oral paliperidone of 12 mg/day for adolescents on a mg/m^2 basis), no relevant effects on growth, sexual maturation, or reproductive performance were observed. Doses up to 2.5 mg/kg/day did not impair neurobehavioral development in males or females, except for an effect on learning and memory in female rats treated at 2.5 mg/kg/day. This effect was not observed after discontinuation of treatment. In a 40-week study with juvenile dogs treated with oral risperidone (which is extensively converted to paliperidone), sexual maturation was delayed. Effects on sexual maturation were observed at 15 times the maximum human oral exposure in adolescents. Long bone growth was not affected in dogs at 3.6 times the maximum human oral exposure in adolescents (1.5 mg/day), but effects were observed at 15 times the maximum human oral exposure.	Because effects in paliperidone juvenile toxicity studies in rats and dogs were observed at doses above the MRHD for adolescents, these effects are considered to be of minimal relevance to humans.

Key: AUC = area under the concentration-time curve; D_2 = dopamine Type 2 (receptor); ER = extended-release; IM = intramuscular; MRHD = maximum recommended human dose; PP1M = paliperidone palmitate 1-monthly formulation; PP3M = paliperidone palmitate 3-monthly formulation; PP6M = paliperidone palmitate 6-monthly formulation; PRAC = Pharmacovigilance Risk Assessment Committee; QTc = corrected QT interval.

Summary of Nonclinical Safety Concerns

Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

PART II: SAFETY SPECIFICATION

Module SIII: Clinical Trial Exposure

SIII.1. Brief Overview of Development

Paliperidone (9-hydroxy-risperidone, R076477) is a monoaminergic antagonist that exhibits the characteristic D_2 and serotonin type 2A antagonism of the newer, or second-generation, antipsychotic drugs. Paliperidone has been developed as a psychotropic agent for the treatment of psychiatric disorders.

Four presentations of paliperidone have been authorized in the EU. An ER tablet that utilizes OROS pump technology (INVEGA, also referred to as paliperidone PR) was initially authorized for the treatment of schizophrenia in adults, followed by schizoaffective disorder in adults and schizophrenia in adolescents aged 15 years and older. A PP1M long-acting aqueous suspension for injection (XEPLION) was authorized for the maintenance treatment of schizophrenia in adults, followed by a PP3M long-acting aqueous suspension for injection (TREVICTA) and a PP6M long-acting aqueous suspension for injection (BYANNLI) for the same indication.

SIII.2. Clinical Trial Exposure

Exposure data are provided below from completed clinical trials of paliperidone ER, PP1M, PP3M, and PP6M. These data are derived from clinical trials sponsored by the MAH for registration purposes. In general, data were derived from pivotal Phase 2/3 randomized, double-blind, placebo-controlled efficacy trials. Long-term open-label extensions from the pivotal Phase 3 double-blind trials are also included. Selected Phase 4 trials conducted by the MAH for postapproval commitments or special populations are included herein. Short-term, single-dose Phase 1 trials were not included and, similarly, Phase 4 trials conducted in subjects for an approved indication are not included. (Because of these exclusions, the clinical trial exposure data presented in this RMP are not the same as the clinical trial exposure data presented in the most recent Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report [PBRER/PSUR]). Investigator-initiated and other studies not sponsored by the MAH are also not included in these tables.

This section includes clinical trial exposure in the following patient populations:

- Paliperidone ER: for the EU-approved indications of schizophrenia in adults, schizoaffective disorder in adults, and schizophrenia in adolescents 15 years of age and older.
- PP1M: for the EU-approved indication of schizophrenia in adults, plus the EU-investigational treatment of schizoaffective disorder in adults.
- PP3M: for the EU-approved indication of maintenance treatment of schizophrenia in adults.
- PP6M: for the EU-investigational treatment of schizophrenia in adults.

The use of paliperidone ER has also been evaluated in subjects with bipolar I disorder, but the MAH did not obtain approval for this indication in the EU. The safety profile of paliperidone ER

in clinical trials in subjects with bipolar I disorder is consistent with the observed safety profile of paliperidone ER in clinical trials in subjects with schizophrenia and schizoaffective disorder; thus, these clinical trials are considered supportive. Summaries of clinical trial exposure in clinical trials of paliperidone ER in subjects with bipolar I disorder are provided in Annex 7.4.

Pregnant and lactating women were excluded from the paliperidone ER, PP1M, PP3M, and PP6M clinical trials discussed in this section, as were subjects with a relevant history or evidence of significant and/or unstable cardiovascular, respiratory, neurological (including seizures or significant cerebrovascular disorders), renal, hepatic, endocrine, or immunological diseases. Therefore, no exposure information is presented for these special populations. Separate trials have been conducted outside of the Phase 2/3 clinical trial program with paliperidone in patients with hepatic or renal disease. These trials are discussed in Module SIV. There have also been isolated reports of subjects who became pregnant or female partners of male subjects who became pregnant during paliperidone ER, PP1M, PP3M, and PP6M clinical trials; due to the isolated nature of these reports, details regarding these subjects are provided in Module SIV.

Exposure in Randomized Clinical Trials

The Randomized Clinical Trials population for paliperidone ER includes 10 trials:

Schizophrenia

- R076477-SCH-301
- R076477-SCH-302
- R076477-SCH-303
- R076477-SCH-304
- R076477-SCH-305
- R076477PSZ3001
- R076477PSZ3003
- R076477SCH4012

Schizoaffective Disorder

- R076477SCA3001
- R076477SCA3002

Exposure to paliperidone ER in randomized, blinded trials for the treatment of schizophrenia in adults, schizoaffective disorder in adults, and schizophrenia in adolescents by duration, by age group and sex, by dose, and by race is summarized in Tables SIII.1 through SIII.4. Total exposure for each summary is provided in the corresponding tables.

Table SIII.1: Duration of Exposure of INVEGA: Randomized Clinical Trials Population

Cumulative for all indications: Trials R076477-SCH-301[a], -SCH-302, -SCH-303, -SCH-304, -SCH-305, -SCA3001, -SCA3002, -PSZ3001[b], -PSZ3003[b], and -SCH4012; N=1,962[b]		
Duration of exposure	**Patients**	**Person-years**
Cumulative up to 42 days	1,318 (67)	106.8
Cumulative up to 182 days	1,909 (97)	202.0
Cumulative up to 294 days	1,959 (>99)	228.3
Total person time	1,962 (100)	230.9
INDICATION: Schizophrenia (Adolescents), Trials R076477PSZ3001 and -PSZ3003; N=263[a]		
Cumulative up to 42 days	118 (45)	11.0
Cumulative up to 182 days	224 (85)	43.4
Cumulative overall	263 (100)	63.1
INDICATION: Schizophrenia (Adolescents), Trials R076477PSZ3001 and -PSZ3003; N=263[a]		
Cumulative up to 42 days	985 (77)	81.1
Cumulative up to 182 days	1,265 (99)	119.3
Cumulative up to 294 days	1,276 (>99)	125.9
Cumulative overall	1,279 (100)	128.5
INDICATION: Schizoaffective Disorder, Trials R076477SCA3001 and -SCA3002; N=420		
Cumulative up to 42 days	215 (51)	14.7
Cumulative overall	420 (100)	39.3

[a] Includes adolescents aged 12 to 14 years (N=## or ##% of total pooled exposure in adolescents).
[b] Includes duration of double-blind phase only.
Note: The duration of exposure includes days on which subjects did not actually take trial medication.

Table SIII.2: Exposure of INVEGA by Age Group and Sex: Randomized Clinical Trials Population

Cumulative for all Indications: Trials R076477-SCH-301[a], -SCH-302, -SCH-303, -SCH-304, -SCH-305, -SCA3001, -SCA3002, -PSZ3001, -PSZ3003 and -SCH4012				
Age group	**Patients**		**Person-years**	
	M	**F**	**M**	**F**
12 to 14 years	56 (5)	22 (3)	13.2	4.5
15 to 17 years	113 (10)	72 (9)	28.5	16.9
18 to 25 years	159 (13)	70 (9)	15.4	7.3
26 to 50 years	714 (60)	467 (60)	65.2	49.6
51 to 65 years	133 (11)	94 (12)	14.2	9.7
>65 years	14 (1)	48 (6)	1.5	5.0
Total	1,189 (100)	773 (100)	137.9	93.0
INDICATION: Schizophrenia (Adolescents), Trials R076477PSZ3001 and -PSZ3003; N=263				
	(N=169)	**(N=94)**		
12 to 14 years	56 (33)	22 (23)	13.2	4.5
15 to 17 years	113 (67)	72 (77)	28.5	16.9
INDICATION: Schizophrenia (Adults), Trials R076477-SCH-301[a], -SCH-302, -SCH-303, -SCH-304, -SCH-305, and -SCH4012; N=1,279				
	(N=766)	**(N=513)**		
18 to 25 years	122 (16)	52 (10)	11.9	5.5
26 to 50 years	523 (68)	332 (65)	47.7	36.8
51 to 65 years	107 (14)	81 (16)	11.8	8.3
>65 years[b]	14 (2)	48 (9)	1.5	5.0
INDICATION: Schizoaffective Disorder, Trials R076477SCA3001 and -SCA3002; N=420				
	(N=254)	**(N=166)**		
18 to 25 years	37 (15)	18 (11)	3.5	1.8
26 to 50 years	191 (75)	135 (81)	17.5	12.8
51 to 65 years	26 (10)	13 (8)	2.3	1.4

[a] Includes adolescents aged 12 to 14 years (N=## or ##% of total pooled exposure in adolescents).
[b] Includes duration of double-blind phase only.

Table SIII.3: Exposure of INVEGA by Dose: Randomized Clinical Trials Population

Cumulative for all indications: Trials R076477-SCH-303, -SCH-304, -SCH-305, -PSZ3001[a], and -SCH4012		
Dose of exposure	**Patients**	**Person-years**
1.5 mg (N=120)		
Cumulative up to 42 days	92 (77)	7.1
Overall	120 (100)	10.5
3 mg (N=143)		
Cumulative up to 42 days	115 (80)	9.4
Overall	143 (100)	12.8
6 mg (N=350)		
Cumulative up to 42 days	269 (77)	21.5
Overall	350 (100)	31.2
INVEGA 9 mg (N=246)		
Cumulative up to 42 days	194 (79)	17.0
Overall	246 (100)	23.2
12 mg (N=277)		
Cumulative up to 42 days	229 (83)	19.8
Overall	277 (100)	25.7

Table SIII.3: Exposure of INVEGA by Dose: Randomized Clinical Trials Population

Cumulative for all indications: Trials R076477-SCH-303, -SCH-304, -SCH-305, -PSZ3001[a], and -SCH4012		
15 mg (N=113)		
Cumulative up to 42 days	87 (77)	8.1
Overall	113 (100)	11.2
INDICATION: Schizophrenia (Adolescents)[b,c], Trial R076477PSZ3001; N=150		
1.5 mg (N=54)		
Cumulative up to 42 days	44 (81)	4.0
Cumulative overall	54 (100)	5.2
3 mg (N=16)		
Cumulative up to 42 days	10 (63)	0.9
Cumulative overall	16 (100)	1.7
6 mg (N=45)		
Cumulative up to 42 days	30 (67)	3.1
Cumulative overall	45 (100)	4.8
12 mg (N=35)		
Cumulative up to 42 days	25 (71)	2.4
Cumulative overall	35 (100)	3.6
INDICATION: Schizophrenia (Adults)[c], Trials R076477-SCH-303, -SCH-304, -SCH-305, and -SCH4012; N=1,175		
1.5 mg (N=66)		
Cumulative up to 42 days	48 (73)	3.1
Cumulative overall	66 (100)	5.3
3 mg (N=127)		
Cumulative up to 42 days	105 (83)	8.5
Cumulative overall	127 (100)	11.1
6 mg (N=305)		
Cumulative up to 42 days	239 (78)	18.4
Cumulative overall	305 (100)	26.4
9 mg (N=246)		
Cumulative up to 42 days	194 (79)	17.0
Cumulative overall	246 (100)	23.2
12 mg (N=242)		
Cumulative up to 42 days	204 (84)	17.4
Cumulative overall	242 (100)	22.1
15 mg (N=113)		
Cumulative up to 42 days	87 (77)	8.1
Cumulative overall	113 (100)	11.2
INDICATION: Schizoaffective Disorder[b], Trial R076477SCA3001; N=206		
Low dose[d] (N=108)		
Cumulative up to 42 days	52 (48)	3.3
Cumulative overall	108 (100)	10.1
High dose[d] (N=98)		
Cumulative up to 42 days	38 (39)	2.9
Cumulative overall	98 (100)	10.1

[a] Includes adolescents aged 12 to 14 years (N=45 or 30% of exposure in adolescents).
[b] Includes adolescents aged 12 to 14 years (N=45 or 30% of exposure in adolescents).
[c] Trials R076477PSZ3003, -SCH-302, and -SCA3002 had flexible-dose designs and so were excluded from the analysis.
[d] INVEGA low dose group: initial dose 6 mg/d, with the option to reduce to 3 mg/d; INVEGA high dose group: initial dose 12 mg/d, with the option to reduce to 9 mg/d.

Note: Only fixed-dose trials are included in this table. The randomized flexible-dose trials R076477-SCH-301, -SCH-302, -SCA3001, -SCA3002, and -PSZ3003 were excluded from the analysis.

Table SIII.4: Exposure of INVEGA by Special Populations: Randomized Clinical Trials Population (Race/Ethnic Origin)

Cumulative for all indications: Trials R076477-SCH-301, -SCH-302, -SCH-303, -SCH-304, -SCH-305, -SCA3001, -SCA3002, -PSZ3001, -PSZ3003 and -SCH4012[a]		
	Patients	**Person-years**
White	1,137	147.7
Black	357	31.1
Asian	351	41.1
Other	117	11.0
Total	1,962	230.9
INDICATION: Schizophrenia (Adolescents); Trials R076477PSZ3001 and -PSZ3003; N=263 [a]		
White	186 (71)	47.4
Black	20 (8)	2.8
Asian	55 (21)	12.3
Other	2 (1)	0.6
Total	263 (100)	63.1
INDICATION: Schizophrenia (Adults); Trials R076477-SCH-301[b], -SCH-302, -SCH-303, -SCH-304, -SCH-305, and -SCH4012; N=1,279		
White	748 (58)	82.2
Black	255 (20)	21.0
Asian	165 (13)	15.1
Other	111 (9)	10.2
Total	1,279 (100)	128.5
INDICATION: Schizoaffective Disorder; Trials R076477SCA3001 and -SCA3002; N=420		
White	203 (48)	18.2
Black	82 (20)	7.2
Asian	131 (31)	13.7
Other	4 (1)	0.2
Total	420 (100)	39.3

[a] Includes adolescents aged 12 to 14 years (N=78 or 30% of total pooled exposure in adolescents).
[b] Includes double-blind phase only.

The Randomized Clinical Trials population for PP1M, PP3M, and PP6M includes 13 trials:

Schizophrenia

- R092670-SCH-201
- R092670PSY3001
- R092670PSY3002
- R092670PSY3003
- R092670PSY3004
- R092670PSY3006
- R092670PSY3007
- R092670PSY3008
- PALM-JPN-4
- R092670PSY3011
- R092670PSY3012
- R092670PSY3015

Schizoaffective Disorder

- R092670SCA3004

Exposure to PP1M, PP3M, and PP6M in randomized, blinded trials for the treatment of schizophrenia in adults, schizoaffective disorder in adults, and schizophrenia in adolescents by duration, by age group and sex, by dose, and by race is summarized in Tables SIII.5 through SIII.8. Total exposure for each indication is provided in the corresponding tables.

Table SIII.5: Duration of Exposure of XEPLION, TREVICTA, and BYANNLI: Randomized, Clinical Trials Population

Schizophrenia		
INDICATION: XEPLION; Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, and PALM-JPN-4; N=2,871		
Duration of exposure	**Patients**	**Person-years**
Cumulative up to 98 days	2,394 (83)	445.1
Cumulative up to 196 days	2,572 (90)	511.2
Cumulative up to 364 days	2,712 (94)	608.4
Cumulative up to 392 days	2,868 (>99)	767.6
Total person time	2,871 (100)	770.9
INDICATION: TREVICTA[a] Approved indication; Trials R092670-PSY3011 and -PSY3012; N=883		
Cumulative up to 98 days	254 (29)	51.3
Cumulative up to 196 days	331 (37)	81.5
Cumulative up to 364 days	862 (98)	542.2
Cumulative up to 392 days	868 (98)	548.4
Total person time	883 (100)	566.8
INDICATION: BYANNLI[b]; Trial R092670PSY3015; N=478		
Cumulative up to 98 days	23 (4.8)	3.3
Cumulative up to 196 days	59 (12.3)	19.1
Cumulative up to 364 days	192 (40.2)	143.5
Cumulative up to 392 days	474 (99.2)	426.7
Total person time	478 (100.0)	431.7
Total (XEPLION, TREVICTA, and BYANNLI);[b] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=4,749[c]		
Cumulative up to 98 days	2,547 (53.6)	468.6
Cumulative up to 196 days	2,924 (61.6)	616.5
Cumulative up to 364 days	4,151 (87.4)	1688.3
Cumulative up to 392 days	4,735 (99.7)	2277.5
Cumulative overall	4,749 (100.0)	2294.1
Schizoaffective Disorder		
INDICATION: XEPLION; Trial R092670SCA3004; N=164		
Cumulative up to 98 days	31 (19)	3.4
Cumulative up to 196 days	46 (28)	9.1
Cumulative up to 364 days	62 (38)	21.0
Cumulative up to 392 days	62 (38)	21.0
Cumulative overall	164 (100)	138.7

[a] Includes adolescents aged 12 to 14 years (N=78 or 30% of total pooled exposure in adolescents).
[b] Includes duration of double-blind phase only.
[c] Previous total included data from the 3-month maintenance phase in error. Revised total includes data from the double-blind phase only. Maintenance phase exposure is included in the All Clinical Trials population tables.

Note: The duration of exposure includes days on which subjects did not actually take trial medication.

Table SIII.6: Exposure of XEPLION, TREVICTA, and BYANNLI by Age Group and Sex: Randomized Clinical Trials Population

Schizophrenia

INDICATION: XEPLION: Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, and PALM-JPN-4; N=2,871

Age group	Patients		Person-years	
	M	F	M	F
18 to 25 years	270 (15)	147 (13)	70.5	37.2
26 to 50 years	1,215 (69)	723 (65)	306.3	204.4
51 to 65 years	256 (15)	225 (20)	69.7	73.8
>65 years[a]	13 (1)	22 (2)	3.2	5.8
Total	1,754 (100)	1,117 (100)	449.7	321.3
INDICATION: TREVICTA[b]; Trials R092670PSY3011 and -PSY3012; N=883				
18 to 25 years	411 (16)	222 (13)	166.0	96.0
26 to 50 years	1,759 (68)	1,097 (65)	666.6	471.8
51 to 65 years	388 (15)	344 (20)	159.3	165.0
>65 years[a]	20 (1)	25 (1)	7.2	7.7
Total	2,578	1,688	999.1	740.4
INDICATION: BYANNLI[b]; Trial R092670PSY3015; N=478				
18 to 25 years	38 (11.7)	6 (3.9)	34.7	5.3
26 to 50 years	233 (71.5)	97 (63.8)	206.9	92.1
51 to 65 years	52 (16.0)	44 (28.9)	45.1	39.9
>65 years	3 (0.9)	5 (3.3)	2.6	5.2
Total	326 (100)	152 (100)	289.2	142.4

Total (XEPLION, TREVICTA, and BYANNLI);[b] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=4,749[d]

Age group	Patients, n (%)		Person-years	
	M	F	M	F
18 to 25 years	444 (15.4)	228 (12.3)	206.2	103.5
26 to 50 years	1,990 (68.8)	1,203 (64.7)	939.8	590.8
51 to 65 years	435 (15.0)	395 (21.3)	214.3	214.5
>65 years[a]	22 (0.8)	32 (1.7)	10.5	14.5
Total	2,891 (100)	1,858 (100)	1,370.8	923.3

Schizoaffective Disorder

INDICATION: XEPLION; Trial R092670SCA3004; N=164

Age group	Patients, n (%)		Person-years	
	M	F	M	F
18 to 25 years	8 (9)	13 (16)	8.2	10.1
26 to 50 years	57 (67)	57 (72)	52.6	44.4
51 to 65 years	20 (24)	9 (11)	16.0	7.4
Total	85	79	76.8	61.9

[a] Additional categorization of ages older than 65 years was not performed due to the small number of subjects in this age range.

[b] Does not include subjects who were randomized to XEPLION as a comparator in the double-blind phase of the TREVICTA Trial R092670PSY3011.

[c] Includes subjects who were randomized to XEPLION as a comparator in the double-blind phase of the TREVICTA Trial R092670PSY3011.

[d] Previous total included data from the 3-month maintenance phase in error. Revised total includes data from the double-blind phase only. Maintenance phase exposure is included in the All Clinical Trials population tables.

Note: The duration of exposure includes days on which subjects did not actually take trial medication.

Table SIII.7: Exposure of XEPLION, TREVICTA, and BYANNLI by Dose: Randomized Clinical Trials Population[a]

Schizophrenia		
INDICATION: XEPLION; Trials R092670-SCH-201, -PSY3003, -PSY3004, -PSY3007, and PALM-JPN-4; N=1,452		
Dose of exposure	**Patients**	**Person-years**
25 mg eq. (N=290)		
Cumulative up to 98 days	286 (99)	50.4
Cumulative overall	290 (100)	51.5
50 mg eq. (N=302)		
Cumulative up to 98 days	295 (98)	48.4
Cumulative overall	302 (100)	50.7
75 mg eq. (N=159)		
Cumulative up to 98 days	156 (98)	27.2
Cumulative overall	159 (100)	28.0
100 mg eq. (N=477)		
Cumulative up to 98 days	462 (97)	79.6
Cumulative overall	477 (100)	84.2
150 mg eq. (N=193)		
Cumulative up to 98 days	188 (97)	32.8
Cumulative overall	193 (100)	34.3
150 mg eq. / placebo (N=31)		
Cumulative up to 98 days	31 (100)	7.1
INDICATION: TREVICTA; Trials R092670PSY3011 and -PSY3012; N=883[b]		
175 mg eq. (N=22)		
Cumulative up to 98 days	5 (23)	0.9
Cumulative up to 196 days	5 (23)	0.9
Cumulative up to 364 days	22 (100)	15.3
Cumulative up to 392 days	22 (100)	15.3
Cumulative overall	22 (100)	15.3
263 mg eq. (N=88)		
Cumulative up to 98 days	24 (27)	5.0
Cumulative up to 196 days	35 (40)	9.2
Cumulative up to 364 days	85 (97)	51.5
Cumulative up to 392 days	85 (97)	51.5
Cumulative overall	88 (100)	54.9
350 mg eq. (N=385)		
Cumulative up to 98 days	122 (32)	24.8
Cumulative up to 196 days	153 (40)	37.1
Cumulative up to 364 days	378 (98)	232.1
Cumulative up to 392 days	382 (99)	236.2
Cumulative overall	385 (100)	239.6
525 mg eq. (N=388)		
Cumulative up to 98 days	103 (27)	20.6
Cumulative up to 196 days	138 (36)	34.3
Cumulative up to 364 days	377 (97)	243.4
Cumulative up to 392 days	379 (98)	245.4
Cumulative overall	388 (100)	256.9

Table SIII.7: Exposure of XEPLION, TREVICTA, and BYANNLI by Dose: Randomized Clinical Trials Population[a]

INDICATION: BYANNLI[c]; Trial R092670PSY3015; N=478		
700 mg eq. (N=230)		
Cumulative up to 98 days	10 (4.3)	1.5
Cumulative up to 196 days	26 (11.3)	8.4
Cumulative up to 364 days	93 (40.4)	70.8
Cumulative up to 392 days	227 (98.7)	205.2
Cumulative overall	230 (100.0)	208.8
1,000 mg eq. (N=248)		
Cumulative up to 98 days	13 (5.2)	1.8
Cumulative up to 196 days	33 (13.3)	10.7
Cumulative up to 364 days	99 (39.9)	72.8
Cumulative up to 392 days	247 (99.6)	221.5
Cumulative overall	248 (100.0)	222.8

[a] Only fixed-dose trials are included in this table. The data do not include Trials R092670PSY3001, -PSY3002, -PSY3006, and -PSY3008 or Trial R092670SCA3004 because those trials allowed flexible dosing.

[b] In these trials, subjects were not randomized to the TREVICTA dose levels shown in this table. Instead, open-label flexible dosing of XEPLION was permitted at 2 time points before TREVICTA was initiated; the dose of XEPLION that had been selected for each subject's efficacy and tolerability then was converted to a TREVICTA dose per a 3.5-fold conversion scheme (see SmPC for the conversion scheme). The dose of TREVICTA then remained stable (at the levels shown in this table) for the remainder of the trials.

[c] Participants were randomized to either TREVICTA or BYANNLI. The dose level (moderate or high) was determined by the XEPLION or TREVICTA dose at the end of the maintenance phase. For BYANNLI, the moderate dose level was 700 mg eq. and the high dose level was 1000 mg eq.

Table SIII.8: Exposure of XEPLION, TREVICTA, and BYANNLI by Special Populations: Randomized Clinical Trials Population (Race/Ethnic Origin)

	Patients	Person-years
Schizophrenia		
INDICATION: XEPLION; Approved indication; Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, and PALM-JPN-4; N=2,871		
White	1,691 (59)	521.1
Black	549 (19)	116.6
Asian	599 (21)	127.1
Other	32 (1)	6.2
Total	2871	770.9
INDICATION: TREVICTA[a] Approved indication; Trials R092670PSY3011 and -PSY3012; N=883		
White	529 (60)	344.7
Black	92 (10)	49.4
Asian	205 (23)	150.2
Other	57 (6)	22.5
Total	883	566.8
INDICATION: BYANNLI; Trial R092670PSY3015; N=478		
White	353 (73.8)	320.6
Black	49 (10.3)	42.2
Asian	66 (13.8)	60.2
Other	10 (2.1)	8.7
Total	478 (100.0)	431.7
Total (XEPLION, TREVICTA, and BYANNLI);[b] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=4,749[c]		
White	2,908 (61.2)	1,530.3
Black	709 (14.9)	239.0
Asian	1,056 (22.2)	493.2
Other	76 (1.6)	31.6
Total	4,749 (100.0)	2,294.1
Schizoaffective Disorder		
INDICATION: XEPLION, Investigational indication; Trial R092670SCA3004; N=164		
White	95 (58)	76.2
Black	29 (18)	23.1
Asian	37 (23)	36.8
Other	3 (2)	2.6
Total	164	138.7

[a] Does not include subjects who were randomized to XEPLION as a comparator in the double-blind phase of the TREVICTA Trial R092670PSY3011.

[b] Includes subjects who were randomized to XEPLION as a comparator in the double-blind phase of the TREVICTA Trial R092670PSY3011.

[c] Previous total included data from the 3-month maintenance phase in error. Revised total includes data from the double-blind phase only. Maintenance phase exposure is included in the All Clinical Trials population tables.

Note: The duration of exposure includes days on which subjects did not actually take study medication.

Exposure in All Clinical Trials

The All Clinical Trials population for paliperidone ER includes final data from the 6 randomized, double-blind trials in adult subjects with schizophrenia and their open-label extensions (R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, and -SCH4012); 2 randomized, double-blind trials in adult subjects with schizoaffective disorder (R076477SCA3001 and -SCA3002); and 2 randomized, double-blind trials and 1 long-term open-label safety trial in adolescent subjects (aged 12-17 years, inclusive) with schizophrenia (R076477PSZ3001, -PSZ3002, and -PSZ3003).

Schizophrenia

- R076477-SCH-301/701
- R076477-SCH-302/702
- R076477-SCH-303/703
- R076477-SCH-304/704
- R076477-SCH-305/705
- R076477PSZ3001
- R076477PSZ3002
- R076477PSZ3003
- R076477SCH4012

Schizoaffective Disorder

- R076477SCA3001
- R076477SCA3002

Exposure to paliperidone ER is summarized by duration, by age group and sex, and by race in Tables SIII.9 through SIII.11. Note that exposure for all clinical trials of paliperidone ER is not summarized by dose because the All Clinical Trials population for each indication includes flexible-dose trials or flexible-dose open-label extensions.

Table SIII.9: Duration of Exposure to INVEGA: All Clinical Trials Population

Cumulative for all indications: Trials R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, -SCA3001, -SCA3002, -PSZ3001, -PSZ3002, -PSZ3003, and -SCH4012; N=3,155[a]		
Duration of exposure	**Patients**	**Person-years**
Cumulative up to 42 days	962 (30)	56.6
Cumulative up to 182 days	1,893 (60)	277.5
Cumulative up to 294 days	2,172 (69)	446.7
Cumulative up to 364 days	2,345 (74)	612.1
Cumulative up to 546 days	2,926 (93)	1,273.3
Total person time	3,155 (100)	1,727.2
INDICATION: Schizophrenia (Adolescents); Trials R076477-PSZ3001, -PSZ3002, and -PSZ3003; N=545[a]		
Cumulative up to 42 days	66 (12)	4.2
Cumulative up to 182 days	212 (39)	55.6
Cumulative up to 364 days	306 (56)	110.3
Cumulative up to 728 days	398 (73)	267.7
Total person time for indication	545 (100)	569.5
INDICATION: Schizophrenia (Adults); Trials R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, and -SCH4012; N=2,190		
Cumulative up to 182 days	1,261 (58)	182.6
Cumulative up to 364 days	1,619 (74)	462.4
Cumulative up to 546 days	2,174 (99)	1,090.4
Total person time for indication	2,190 (100)	1,118.4
INDICATION: Schizoaffective Disorder; Trials R076477SCA3001 and -SCA3002; N=420		
Cumulative up to 42 days	215 (51)	14.7
Total person time for indication	420 (100)	39.3

[a] Includes adolescents aged 12 to 14 years (N=149 or 27% of total pooled exposure in adolescents).
Note: The duration of exposure includes days on which subjects did not actually take trial medication.
Note: Includes duration of double-blind and open-label phases.

Table SIII.10: Exposure of INVEGA by Age Group and Sex: All Clinical Trials Population

Cumulative for all Indications: R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, -SCA3001, -SCA3002, -PSZ3001, -PSZ3002, -PSZ3003 and -SCH4012; N=3,155				
Age group	**Patients**		**Person-years**	
	M	**F**	**M**	**F**
12 to 14 years	95 (5)	54 (5)	110.6	55.3
15 to 17 years	242 (12)	153 (13)	259.5	144.0
18 to 25 years	258 (13)	102 (9)	127.4	50.3
26 to 50 years	1,138 (58)	679 (57)	457.4	341.0
51 to 65 years	202 (10)	139 (12)	80.6	67.2
>65 years	23 (1)	70 (6)	8.5	25.5
Total	1,958 (100)	1,197 (100)	1,044.0	683.2
INDICATION: Schizophrenia (Adolescents); Trials R076477-PSZ3001, -PSZ3002, and -PSZ3003; N=545				
	(N=338)	**(N=207)**		
12 to 14 years	95 (28)	54 (26)	110.6	55.3
15 to 17 years	242 (72)	153 (74)	259.5	144.0
>17 years	1 (0)	0	0.1	0
INDICATION: Schizophrenia (Adults); Trials R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, and -SCH4012; N=2,190				
	(N=1,366)	**(N=824)**		
18 to 25 years	220 (16)	84 (10)	123.8	48.6
26 to 50 years	947 (69)	544 (66)	439.9	328.1
51 to 65 years	176 (13)	126 (15)	78.3	65.8
>65 years[a]	23 (2)	70 (8)	8.5	25.5
INDICATION: Schizoaffective Disorder; Trials R076477SCA3001 and -SCA3002; N=420				
	(N=254)	**(N=166)**		
18 to 25 years	37 (15)	18 (11)	3.5	1.8
26 to 50 years	191 (75)	135 (81)	17.5	12.8
51 to 65 years	26 (10)	13 (8)	2.3	1.4

[a] Additional categorization of ages above 65 years was not performed due to the small number of subjects in this age range.

Table SIII.11: Exposure of INVEGA by Special Populations: All Clinical Trials Population (Race/Ethnic Origin)

	Patients	Person-years
Cumulative for all indications: Trials R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, -SCA3001, -SCA3002, -PSZ3001, -PSZ3002, -PSZ3003, and -SCH4012; N=3,155[a]		
White	1,865 (59)	1,173.6
Black	528 (17)	146.0
Asian	474 (15)	217.7
Other	288 (9)	190.0
Total	3,155 (100)	1,727.2
INDICATION: Schizophrenia (Adolescents); Trials R076477-PSZ3001, -PSZ3002, and -PSZ3003; N=545[b]		
White	365 (67)	410.7
Black	39 (7)	27.8
Asian	137 (25)	129.9
Other	4 (1)	1.1
Total	545 (100)	569.5
INDICATION: Schizophrenia (Adults); Trials R076477-SCH-301/701, -SCH-302/702, -SCH-303/703, -SCH-304/704, -SCH-305/705, and -SCH4012; N=2,190		
White	1,297 (59)	744.8
Black	407 (19)	110.9
Asian	206 (9)	74.1
Other	280 (13)	188.6
Total	2,190 (100)	1,118.4
INDICATION: Schizoaffective Disorder; Trials R076477SCA3001 and -SCA3002; N=420		
White	203 (48)	18.2
Black	82 (20)	7.2
Asian	131 (31)	13.7
Other	4 (1)	0.2
Total	420 (100)	39.3

[a] Includes adolescents aged 12 to 14 years (N=149 or 5% of total pooled exposure).
[b] Includes adolescents aged 12 to 14 years (N=149 or 27% of total pooled exposure in adolescents).

The All Clinical Trials population for PP1M includes final data from 1 long-term, open-label Phase 1 trial (R092670PSY1008); 6 double-blind, placebo-controlled trials (R092670-SCH-201, -PSY3003, -PSY3004, -PSY3007, -SCA3004, and PALM-JPN-4); 3 active-controlled trials (R092670PSY3002 [long-term, double-blind], R092670PSY3006 [double-blind], and R092670PSY3008 [open-label]); 1 crossover trial (R092670PSY3005); and 1 trial that had open-label phases before and after a double-blind, randomized withdrawal phase (R092670PSY3001).

The All Clinical Trials population for PP3M includes final data from 1 open-label, single-dose Phase 1 trial (R092670PSY1005); 1 double-blind, placebo-controlled Phase 3 trial (R092670PSY3012); and 1 double-blind, active-controlled Phase 3 trial (R092670PSY3011).

The All Clinical Trials population for PP6M includes final data from 1 double-blind, randomized, active-controlled, parallel-group trial (R092670PSY3015).

Schizophrenia

- R092670PSY1005
- R092670PSY1008
- R092670SCH201
- R092670PSY3001
- R092670PSY3002
- R092670PSY3003
- R092670PSY3004
- R092670PSY3005
- R092670PSY3006
- R092670PSY3007
- R092670PSY3008
- R092670PSY3011
- R092670PSY3012
- PALM-JPN-4
- R092670PSY3015

Schizoaffective Disorder

- R092670SCA3004

Exposure to XEPLION, TREVICTA, and BYANNLI in all clinical trials is summarized in Tables SIII.12 through SIII.14 for all subjects by duration, by age group and sex, and by ethnic or racial origin, respectively. Note that exposure for all clinical trials of XEPLION, TREVICTA, and BYANNLI is not summarized by dose because the All Clinical Trials population includes flexible-dose trials or flexible-dose open-label extensions.

Table SIII.12: Duration of Exposure to XEPLION, TREVICTA, and BYANNLI: All Clinical Trials Population

Schizophrenia		
INDICATION: XEPLION; Trials R092670PSY1008,[a] -SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3005, -PSY3006, -PSY3007, -PSY3008, and PALM-JPN-4; N=3,976		
Duration of exposure	**Patients**	**Person-years**
Cumulative up to 98 days	2,656 (67)	482.6
Cumulative up to 196 days	3,094 (78)	663.9
Cumulative up to 364 days	3,329 (84)	829.9
Cumulative up to 392 days	3,608 (91)	1,114.7
Cumulative up to 728 days	3,899 (98)	1,561.8
Cumulative up to 980 days	3,975 (>99)	1,730.0
Total person time	3,976 (100)	1,732.8
INDICATION: TREVICTA[b]; Trials R092670PSY1005,[a] -PSY3011 and -PSY3012; N=2,243		
Cumulative up to 98 days	672 (30)	49.9
Cumulative up to 196 days	961 (43)	156.6

Table SIII.12: Duration of Exposure to XEPLION, TREVICTA, and BYANNLI: All Clinical Trials Population

Schizophrenia		
Cumulative up to 364 days	1,346 (60)	419.0
Cumulative up to 392 days	1,388 (62)	462.3
Cumulative up to 728 days	2,243 (100)	1,530.9
Cumulative up to 980 days	2,243 (100)	1,530.9
Total person time	2,243 (100)	1,530.9
INDICATION: BYANNLI[c]; Trial R092670PSY3015; N=838		
Cumulative up to 98 days	75 (8.9)	10.6
Cumulative up to 196 days	144 (17.2)	38.6
Cumulative up to 364 days	230 (27.4)	103.4
Cumulative up to 392 days	247 (29.5)	121.5
Cumulative up to 728 days	838 (100.0)	925.8
Cumulative up to 980 days	838 (100.0)	925.8
Total person time	838 (100.0)	925.8
Total (XEPLION, TREVICTA, and BYANNLI);[d] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=7,057		
Cumulative up to 98 days	3,403 (48.2)	543.1
Cumulative up to 196 days	4,199 (59.5)	859.0
Cumulative up to 364 days	4,905 (69.5)	1,352.4
Cumulative up to 392 days	5,243 (74.3)	1,698.5
Cumulative up to 728 days	6,980 (98.9)	4,018.5
Cumulative up to 980 days	7,056 (>99.9)	4,186.7
Total	7,057 (100.0)	4,189.4
Schizoaffective Disorder		
INDICATION: XEPLION; Trial R092670SCA3004; N=667		
Cumulative up to 98 days	265 (40)	28.5
Cumulative up to 196 days	519 (78)	130.2
Cumulative up to 364 days	550 (82)	151.8
Cumulative up to 392 days	554 (83)	155.9
Cumulative overall	667 (100)	328.7

[a] Phase 1 trials included a minority of subjects with conditions other than schizophrenia, but these trials are shown grouped under the indication they were designed to support.

[b] Includes exposure to XEPLION in the TREVICTA Trials R092670PSY3011 and -PSY3012.

[c] Includes exposure to XEPLION and TREVICTA in the transition and maintenance phases as well as exposure to TREVICTA and BYANNLI in the double-blind phase of Trial R092670PSY3015.

[d] Includes exposure to XEPLION and TREVICTA in transition and maintenance phases as well as exposure to XEPLION, TREVICTA and BYANNLI in double-blind phases.

Note: The duration of exposure includes days on which subjects did not actually take trial medication.

Note: Trial R092670PSY1005 was a single-dose trial and contributed 1 day of exposure to this table, although the single injection was intended for 3 months of therapeutic exposure.

Table SIII.13: Exposure of XEPLION, TREVICTA, and BYANNLI by Age Group and Sex: All Clinical Trials Population

Age group	Patients		Person-years	
	M	F	M	F
Schizophrenia				
INDICATION: XEPLION, Approved indication; Trials R092670-PSY1008,[a] -SCH-201, -PSY3001, -PSY3002, -PSY3003,-PSY3004, -PSY3005, -PSY3006, -PSY3007, -PSY3008, and PALM-JPN-4; N=3,976				
18 to 25 Years	354 (15)	185 (12)	146.1	87.3
26 to 50 Years	1,709 (70)	1,025 (66)	710.9	486.6
51 to 65 Years	350 (14)	306 (20)	147.4	139.4
>65 Years[b]	18 (1)	29 (2)	5.1	9.9
Total	2,431 (100)	1,545 (100)	1,009.6	723.2
INDICATION: TREVICTA[c]; Trials R092670PSY1005,[a] -PSY3011 and -PSY3012; N=2,243				
18 to 25 Years	200 (15)	104 (12)	151.6	88.8
26 to 50 Years	937 (69)	600 (68)	584.3	419.8
51 to 65 Years	218 (16)	170 (19)	140.9	136.1
>65 Years[b]	8 (1)	6 (1)	6.4	3.1
Total	1363	880	883.1	647.8
INDICATION: BYANNLI[d]; Trial R092670PSY3015; N=838				
18 to 25 Years	63 (11.4)	17 (6.0)	69.8	14.8
26 to 50 Years	399 (72.2)	182 (63.9)	451.4	197.8
51 to 65 Years	87 (15.7)	78 (27.4)	95.4	81.5
>65 Years[b]	4 (0.7)	8 (2.8)	5.3	9.6
Total	553 (100.0)	285 (100.0)	622.0	303.7
Total (XEPLION, TREVICTA, and BYANNLI);[e] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=7,057				
18 to 25 years	617 (14.2)	306 (11.3)	367.5	190.9
26 to 50 years	3,045 (70.0)	1,807 (66.7)	1,746.7	1,104.2
51 to 65 years	655 (15.1)	554 (20.4)	383.7	357.0
>65 years[b]	30 (0.7)	43 (1.6)	16.9	22.6
Total	4,347 (100.0)	2,710 (100.0)	2,514.8	1,674.7
Schizoaffective Disorder				
INDICATION: XEPLION, Investigational indication; Trial R092670SCA3004, N=667				
18 to 25 Years	37 (10)	38 (12)	19.5	22.6
26 to 50 Years	251 (70)	222 (72)	122.2	107.1
51 to 65 Years	69 (19)	49 (16)	34.5	22.5
>65 Years[b]	0	1 (<1)	0.0	0.4
Total	357	310	176.1	152.6

[a] Phase 1 trials included a minority of subjects with disorders other than schizophrenia, but these trials are shown grouped under the indication they were designed to support.

[b] Additional categorization of ages older than 65 years was not performed due to the small number of subjects in this age range.

[c] Includes exposure to XEPLION during any phase of the TREVICTA trials R092670PSY3011 and -PSY3012.

[d] Includes exposure to XEPLION and TREVICTA in the transition and maintenance phases as well as exposure to TREVICTA and BYANNLI in the double-blind phase of Trial R092670PSY3015.

[e] Includes exposure to XEPLION and TREVICTA in the transition and maintenance phases as well as exposure to XEPLION, TREVICTA and BYANNLI in the double-blind phases.

Note: The duration of exposure includes days on which subjects did not actually take trial medication.

Note: Trial R092670PSY1005 was a single-dose trial and contributed 1 day of exposure to this table, although the single injection of TREVICTA was intended for 3 months of therapeutic exposure.

Table SIII.14: Exposure of XEPLION, TREVICTA, and BYANNLI by Special Populations: All Clinical Trials Population (Race/Ethnic Origin)

	Patients	Person-years
Schizophrenia		
INDICATION: XEPLION; Trials R092670-PSY1008,[a] -SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, PSY3005, -PSY3006, -PSY3007, -PSY3008, PALM-JPN-4; N=3,976		
White	2,377	1,135.7
Black	753	263.4
Asian	787	309.1
Other	59	24.6
Total	3,976	1,732.8
INDICATION: TREVICTA[b]; Trials R092670-PSY1005,[a] -PSY3011 and -PSY3012; N=2,243		
White	1,252	904.7
Black	281	136.7
Asian	618	440.8
Other	92	48.7
Total	2,243	1,530.9
INDICATION: BYANNLI[c]; Trial R092670PSY3015; N=838		
White	606	685.5
Black	106	103.0
Asian	111	120.6
Other	15	16.7
Total	838	925.8
Total (XEPLION, TREVICTA, and BYANNLI);[d] Trials R092670-SCH-201, -PSY3001, -PSY3002, -PSY3003, -PSY3004, -PSY3006, -PSY3007, -PSY3008, -PSY3011, -PSY3012, PALM-JPN-4, and -PSY3015; N=7,057		
White	4235	2,725.9
Black	1,140	503.0
Asian	1,516	870.5
Other	166	90.0
Total	7,057	4,189.4
Schizoaffective Disorder		
INDICATION: XEPLION; Trial R092670SCA3004; N=667		
White	354	178.9
Black	195	71.7
Asian	108	73.0
Other	10	5.1
Total	667	328.7

[a] Phase 1 trials included a minority of subjects with disorders other than schizophrenia, but these trials are shown grouped under the indication they were designed to support.

[b] Includes exposure to XEPLION during any phase of the TREVICTA trials R092670PSY3011 and -PSY3012.

[c] Includes exposure to XEPLION and TREVICTA in the transition and maintenance phases as well as exposure to TREVICTA and BYANNLI in the double-blind phase of Trial R092670PSY3015.

[d] Includes exposure to XEPLION and TREVICTA in the transition and maintenance phases as well as exposure to XEPLION, TREVICTA and BYANNLI in the double-blind phases.

Note: The duration of exposure includes days on which subjects did not actually take study medication.

Note: Trial R092670PSY1005 was a single-dose trial and contributed 1 day of exposure to this table, although the single injection of TREVICTA was intended for 3 months of therapeutic exposure.

PART II: SAFETY SPECIFICATION

Module SIV: Populations Not Studied in Clinical Trials

SIV.1. Exclusion Criteria in Pivotal Clinical Studies Within the Development Program

The key exclusion criteria that were common across the pivotal paliperidone ER, PP1M, PP3M, and PP6M clinical trials and thus represent populations not studied in the Phase 2/3 clinical trial programs are summarized in the tables below.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 1	**Hypersensitivity to the active substance, to risperidone, or to any of the excipients**
Reason for being an exclusion criterion	Subjects with known hypersensitivity to the active substance or to any of the excipients of the test compound were excluded from clinical trials to avoid possible severe and life-threatening hypersensitivity reactions.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Hypersensitivity to the active substance, to risperidone or to any of the excipients of INVEGA, XEPLION, TREVICTA, or BYANNLI is a contraindication to product use (SmPC Section 4.3 [Contraindications]).

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 2	**Pediatric subjects (aged <18 years)**
Reason for being an exclusion criterion	The safety and efficacy of paliperidone ER, PP1M, PP3M, and PP6M were first established in the adult population. It is standard practice to develop a drug in the adult population before the pediatric population unless the target disease is exclusively pediatric.
Considered to be included as missing information	No
Rationale (if not included as missing information)	For paliperidone ER, safety and efficacy in the pediatric population (aged 15 years and older) were established in the agreed Phase 3 PIP trials. The SmPC states that INVEGA is indicated for the treatment of schizophrenia in adults and in adolescents aged 15 years and older and that the safety and efficacy of paliperidone ER have not been established in patients with schizophrenia aged <15 years or in patients with schizoaffective disorder aged <18 years (Section 4.2 [Posology and method of administration]). For XEPLION, TREVICTA, and BYANNLI, the SmPCs specify that the indication is limited to adults with schizophrenia (Section 4.1 [Therapeutic indications]), and that safety and efficacy have not been established for populations aged <18 years (Section 4.2 [Posology and method of administration]).

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 3	**Elderly patients (aged >65 years or >70 years)**
Reason for being an exclusion criterion	Elderly patients aged >65 years were excluded from several of the clinical trials with paliperidone ER and PP1M based on the potential for cerebrovascular events and for comorbid dementia in this population. For the same reasons, the maximum age limit in the PP3M, and PP6M trials was 65 years (for the Phase 1 trial) or 70 years (for the Phase 3 trials).
Considered to be included as missing information	No
Rationale (if not included as missing information)	For paliperidone ER, use in elderly patients was addressed in a Phase 3 trial (R076477-SCH-302). Results indicated that the safety profile of paliperidone ER in elderly subjects (aged ≥65 years) with schizophrenia was similar to the safety profile of paliperidone ER in nonelderly subjects in other trials. As stated in SmPC Section 4.2 (Posology and method of administration), the safety and efficacy of INVEGA have not been studied in patients aged >65 years with schizoaffective disorder. For PP1M, PP3M, and PP6M, patients over 65 years (or over 70 years for the PP3M and PP6M Phase 3 trials) were excluded from the clinical trials. For XEPLION, TREVICTA, and BYANNLI, SmPC Section 4.2 (Posology and method of administration) states that safety and efficacy have not been established in elderly patients aged >65 years.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 4	**Use of prohibited concomitant medications (including other antipsychotics, drugs with the potential to influence paliperidone levels, and recent clozapine use)**
Reason for being an exclusion criterion	Drugs that influence paliperidone plasma concentrations were prohibited to minimize fluctuations in paliperidone plasma levels. Use of other antipsychotic medications was not permitted so that safety and efficacy signals could be appropriately detected.
Considered to be included as missing information	No
Rationale (if not included as missing information)	There is no evidence that combining antipsychotics increases efficacy, and doing so may exaggerate paliperidone's known pharmacological effects, eg, drowsiness, sedation, tachycardia, hypotension, QT prolongation, and extrapyramidal symptoms (SmPC Section 4.9 [Overdose]). Given the primary central nervous system effects of paliperidone, INVEGA, XEPLION, TREVICTA, and BYANNLI should be used with caution in combination with other centrally acting medicinal products, including most antipsychotics (SmPC Section 4.5 [Interaction with other medicinal products and other forms of interaction]). Clozapine is an atypical antipsychotic indicated for treatment-resistant schizophrenia (ie, resistant to non-clozapine antipsychotics). Treatment-resistant schizophrenia is outside of the approved indications for INVEGA, XEPLION, TREVICTA, and BYANNLI.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 5	**Concurrent/recent drug or alcohol abuse or dependence**
Reason for being an exclusion criterion	Substance abuse or dependence may interfere with the ability to detect safety and efficacy signals. Antipsychotics are known to interact with alcohol and many other abused substances; therefore, subjects with recent or concurrent use were excluded from clinical trials. Alcohol withdrawal can lead to seizures and other symptoms. Antipsychotics can lower the seizure threshold and may exacerbate alcohol withdrawal. Withdrawal of other substances of abuse, such as diamorphine, can lead to an acute syndrome that would preclude participation in any clinical study.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Section 4.5 (Interactions with other medicinal products and other forms of interaction) of the INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs advises caution when other centrally acting substances (eg, anxiolytics, most antipsychotics, hypnotics, opiates, alcohol) are used concomitantly.
Criterion 6	**Pregnant women**
Reason for being an exclusion criterion	Per International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) E8 guidelines, pregnant women were excluded from paliperidone ER, PP1M, PP3M, and PP6M clinical trials.
Considered to be included as missing information	Yes Exposure during pregnancy is considered missing information for INVEGA, XEPLION, TREVICTA, and BYANNLI.
Rationale (if not included as missing information)	Not applicable.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 7	**Breastfeeding women**
Reason for being an exclusion criterion	Paliperidone is excreted in breast milk. Breastfeeding women were excluded from the clinical trials.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Section 4.6 (Fertility, pregnancy and lactation) of the INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs states that paliperidone is excreted in the breast milk to such an extent that the effects on breast-fed infants are likely if therapeutic doses are administered to breastfeeding women. Paliperidone should not be used while breastfeeding.
Criterion 8	**History of preexisting gastrointestinal narrowing (paliperidone ER only)**
Reason for being an exclusion criterion	To prevent gastrointestinal obstruction due to the nondeformable OROS tablet.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Section 4.4 (Special warnings and precautions for use) of the INVEGA SmPC includes a warning regarding the potential for gastrointestinal obstruction in patients with a history of preexisting gastrointestinal narrowing.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 9	**Subjects with significant or unstable systemic disease (cardiovascular, respiratory, neurological, hematological, endocrine, obesity, immunological, or other systemic disease).**
Reason for being an exclusion criterion	The Phase 2/3 trials were designed to assess safety and efficacy in the target population and to minimize potential confounding background diseases/disorders. Underlying illness may lead to trial discontinuation, thereby reducing the ability to assess both safety and efficacy.
Considered to be included as missing information	No
Rationale (if not included as missing information)	There are no specific data available regarding the use of paliperidone in patients with significant medical or neurological conditions. Section 4.4 (Special Warnings and Precautions for Use) of the INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs states that physicians should weigh the risks versus the benefits of paliperidone treatment when prescribing to patients with Parkinson's disease or dementia with Lewy bodies since both groups may be at increased risk of NMS as well as have an increased sensitivity to antipsychotics. Manifestation of this increased sensitivity can include confusion, obtundation, and postural instability with frequent falls, in addition to extrapyramidal symptoms.
Criterion 10	**Subjects with history of neuroleptic malignant syndrome or tardive dyskinesia**
Reason for being an exclusion criterion	History of previous NMS or tardive dyskinesia with any antipsychotic increases the risk of recurrence with the introduction of a new antipsychotic. D_2 receptor antagonists, which include paliperidone, have been linked to NMS and tardive dyskinesia, which are serious and sometimes irreversible conditions. Deliberately exposing subjects with a history of NMS or tardive dyskinesia to paliperidone would be unethical.
Considered to be included as missing information	No
Rationale (if not included as missing information)	There are no specific data available regarding the use of paliperidone in patients with these conditions. The treating physician would be expected to weigh the risks versus the benefits of paliperidone treatment for each individual patient.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 11	**History of attempted suicide in the previous 6 months, current suicidal ideation, or at risk of violent behavior against others**
Reason for being an exclusion criterion	It would be unethical to expose high-risk patients in a prospective, randomized clinical trial with a placebo arm and an endpoint of attempted or completed suicide.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Suicidal thoughts and behavior are common in patients with schizophrenia and schizoaffective disorder and were assessed throughout the clinical trial programs for paliperidone ER, PP1M, PP3M, and PP6M. The treating physician would be expected to weigh the risks versus the benefits of paliperidone treatment for each individual patient.
Criterion 12	**Carcinoma during the last 5 years**
Reason for being an exclusion criterion	Subjects with disseminated malignant disease would most likely require other treatments (chemotherapy, radiation treatments, etc.) with unknown effects on the target symptoms. Interactions between chemotherapeutic drugs and paliperidone are unknown. Furthermore, patients with malignancies within the last 5 years are at risk for cancer recurrence, which may increase the risk for early withdrawal from the trial, thereby reducing the ability to detect safety and efficacy signals. It would be of questionable value and doubtful ethics to deliberately enroll patients with a potentially shortened lifespan.
Considered to be included as missing information	No
Rationale (if not included as missing information)	No specific risks have been identified in patients with a history of malignancy. The treating physician would be expected to weigh the risks versus the benefits of paliperidone treatment for each individual patient.

Important Exclusion Criteria in Pivotal Clinical Trials Across the Development Program

Criterion 13	**Patients at risk for developing QT interval prolongation**
Reason for being an exclusion criterion	Subjects at increased risk for developing cardiac arrhythmias or other cardiovascular diseases may require additional evaluation/assessments outside the scope of a clinical trial. Although QT prolongation is very rarely reported with therapeutic doses of paliperidone, it would be unethical to expose a patient with a long QT interval in a clinical trial.
Considered to be included as missing information	No
Rationale (if not included as missing information)	Section 4.4 (Special warnings and precautions for use) of the INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs includes a warning regarding use in patients with known cardiovascular disease or family history of QT prolongation, and in concomitant use with medicines thought to prolong the QT interval.

Key: D_2 = dopamine Type 2 (receptor); ER = extended-release; ICH = International Council on Harmonization; NMS = neuroleptic malignant syndrome; OROS = osmotic-controlled release oral delivery system; PIP = Pediatric Investigation Plan; PP1M = paliperidone palmitate 1-monthly formulation; PP3M = paliperidone palmitate 3-monthly formulation; PP6M = paliperidone palmitate 6-monthly formulation; SmPC = Summary of Product Characteristics.

SIV.2. Limitations to Detect Adverse Reactions in Clinical Trial Development Programs

The clinical development program is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

SIV.3. Limitations in Respect to Populations Typically Under-represented in Clinical Trial Development Program(s)

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Pediatrics	The pediatric development of paliperidone has been limited to 3 Phase 3 trials with paliperidone ER in adolescents aged 12 to 17 years with schizophrenia (see Module SIII.2). Additionally, an open-label, single- and multiple-dose Phase 1 PK trial in pediatric and adolescent subjects (aged 10 to 17 years) was conducted to assess the PK properties of paliperidone ER in adolescents. The majority of paliperidone ER-treated subjects in the clinical trials in adolescents with schizophrenia were aged 15 to 17 years, inclusive (n=395 [72%]); a smaller number were aged 12 to 14 years (n=149 [27%]). All PP1M, PP3M, and PP6M trials were conducted in subjects who were 18 years of age or older, given the limited use of long-acting injectable antipsychotics in adolescents with schizophrenia.
Elderly	Across all clinical trials conducted with paliperidone ER in adults with schizophrenia (N=2,190), 93 patients were over 65 years of age (see Module SIII.2). No elderly patients were included in the paliperidone ER schizoaffective disorder trials. Of the 3,976 subjects with schizophrenia exposed to PP1M in the 10 Phase 2/3 trials and the 1 long-term Phase 1 trial, 47 subjects were over 65 years of age. Only 1 of the 667 subjects with schizoaffective disorder exposed to PP1M was older than age 65 years (see Module SIII.2). Of the 2,243 subjects in the PP3M trials designed to support the schizophrenia indication (2 Phase 3 trials and 1 Phase 1 trial), 14 subjects were over 65 years of age. Of the 838 subjects in the PP6M Phase 3 trial designed to support the schizophrenia indication, 12 subjects were over 65 years of age. The maximum age limit in the PP3M and PP6M trials was 65 years for the Phase 1 trial and 70 years for the Phase 3 trials. Due to the small number of subjects aged >65 years in the paliperidone ER, PP1M, PP3M, and PP6M trials, additional categorization of ages older than 65 years (eg, 65-74 years, 75-84 years) was not performed.
Pregnant women	Fourteen subjects discontinued PP1M studies and 5 subjects discontinued PP3M studies due to pregnancy. No subjects discontinued paliperidone ER or PP6M studies due to pregnancy.
Breastfeeding women	Not included in the clinical development program.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Population with relevant different ethnic origin	For paliperidone ER, including all EU-approved indications (schizophrenia in adults, schizoaffective disorder in adults, and schizophrenia in adolescents), the 3,155 paliperidone ER-treated subjects had the following racial demographics: 1,865 (59%) white, 528 (17%) black, 474 (15%) Asian, and 288 (9%) other racial origin. In the PP1M All Clinical Trials population to support the schizophrenia indication, the 3,976 PP1M-treated subjects had the following racial demographics: 2,377 (60%) white, 753 (19%) black, 787 (20%) Asian, and 59 (1%) other racial origin. In the PP1M All Clinical Trials population to support the schizoaffective disorder indication (Trial R092670SCA3004), the 667 PP1M-treated subjects had the following racial demographics: 354 (53%) white, 195 (29%) black, 108 (16%) Asian, and 10 (1%) other. In the PP3M All Clinical Trials population to support the schizophrenia indication, the 2,243 subjects who were treated with PP3M, PP1M, or both had the following racial demographics: 1,252 (56%) white, 281 (13%) black, 618 (28%) Asian, and 92 (4%) other. In the PP6M All Clinical Trials population to support the schizophrenia indication, the 838 subjects who were treated with PP1M, PP3M, or PP6M had the following racial demographics: 606 (72%) white, 106 (13%) black, 111 (13%) Asian, and 15 (2%) other.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Patients with relevant comorbidities:	
Patients with hepatic impairment	Trial R076477SCH1008 characterized the impact of hepatic impairment on the single-dose PK profile of paliperidone IR in 10 subjects with normal hepatic function and in 10 subjects with moderately impaired hepatic function (Child-Pugh Class B). Trial R076477SCH4005 evaluated the safety, tolerability, and efficacy of flexibly dosed paliperidone ER in 84 paliperidone ER-treated subjects with schizophrenia or schizoaffective disorder and stable hepatic disease (64 Child-Pugh Class A and 14 Class B). Patients with severe hepatic impairment (Child-Pugh Class C) were not included in the clinical development program for paliperidone ER, PP1M, PP3M, or PP6M. As subjects with hepatic impairment were generally excluded from clinical trials, exposure in subjects with any degree of hepatic impairment across the clinical development programs for paliperidone ER, PP1M, PP3M, and PP6M is unknown but assumed to be none outside of the specified trials.

Table SIV.2: Exposure of Special Populations Included or Not in Clinical Trial Development Programs

Type of Special Population	Exposure
Patients with renal impairment	The safety, tolerability, and PK profile of a single oral dose of paliperidone ER 3 mg were evaluated in a pharmacology trial (Trial R076477REI1001) that included 47 subjects in 4 different renal function groups classified by their creatinine clearance (CrCL) values, as predicted by the Cockcroft-Gault formula: normal renal function (CrCL ≥80 mL/min), n=12; mild renal impairment (50 mL/min to <80 mL/min), n=12; moderate renal impairment (30 mL/min to <50 mL/min), n=12; severe renal impairment (CrCL <30 mL/min), n=11. As subjects with renal impairment were generally excluded from clinical trials, exposure in subjects with any degree of renal impairment across the clinical development programs for paliperidone ER, PP1M, PP3M, and PP6M is unknown but assumed to be none outside of the specified trial.
Patients with cardiovascular impairment	Not included in the clinical development program.
Immunocompromised patients	Not included in the clinical development program.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.

Summary of Missing Information Due to Limitations of the Clinical Trial Program

Missing Information: Exposure during pregnancy.

PART II: SAFETY SPECIFICATION

Module SV: Postauthorization Experience

SV.1. Postauthorization Exposure

SV.1.1. Method Used to Calculate Exposure

Reporting frequencies calculated using exposure data do not reflect occurrence rates. Multiple factors influence the reporting of spontaneous experiences and therefore, caution must be exercised in the analysis and evaluation of spontaneous reports. In addition, product exposure is estimated at the time of distribution, not at the time of usage. There is a delay between the times a medication is distributed until it is used by a patient.

Patient exposure was estimated by calculation from distribution data. Estimates of exposure are based upon finished product. The recommended dose for INVEGA is 6 mg once daily, with or without food. Therefore, 180 mg equals 1 person-month of exposure. For XEPLION, the recommended initial dose is 150 mg equivalence on treatment Day 1 and 100 mg equivalence 1 week later, both administered in the deltoid muscle. The recommended subsequent monthly dose is 75 mg equivalence; this can be increased or decreased in the range of 25 to 150 mg equivalence based on individual patient tolerability and/or efficacy. In order to provide an estimate in person-years, it is assumed that on average, a single 87.5 mg equivalence dose corresponds to 1 person-month, and 12 of these doses correspond to 1 person-year. TREVICTA should be administered every 3 months. If needed, dose adjustment can be made every 3 months in increments within the range of 175 to 525 mg based on individual patient tolerability and/or efficacy.

SV.1.2. Exposure

Worldwide cumulative exposure to INVEGA, XEPLION, TREVICTA, and oral generic paliperidone from launch to 30 June 2020 is summarized in Tables SV.1, SV.2, SV.3, and SV.4, respectively.

Table SV.1: Cumulative Exposure to INVEGA (Paliperidone ER) (Launch to 30 June 2020)

Region	Strength	Total Grams	Person-Months	Person-Years
EU	1.5 mg	-	-	-
	12 mg	-	-	-
	3 mg	301,997.0	1,677,761	139,813
	6 mg	773,532.2	4,297,400	358,117
	9 mg	679,446.0	3,774,700	314,559
EU Subtotal		***1,754,975.2***	***9,749,861***	***812,489***
NA	1.5 mg	11,125.5	61,808	5,152
	12 mg	-	-	-
	3 mg	275,398.8	1,529,994	127,499
	6 mg	873,727.3	4,854,041	404,503
	9 mg	541,582.5	3,008,792	250,733
NA Subtotal		***1,701,834.1***	***9,454,635***	***787,887***
ROW	1.5 mg	-	-	-
	12 mg	534.9	2,972	248
	3 mg	677,918.3	3,766,213	313,852
	6 mg	1,450,061.8	8,055,898	671,325
	9 mg	586,052.3	3,255,846	271,321
ROW Subtotal		***2,714,567.3***	***15,080,929***	***1,256,746***
Worldwide Total		**6,171,376.6**	**34,285,425**	**2,857,122**

Key: ER = extended-release; EU = European Union; NA = North America; ROW = rest of world.

Based on the 6,171,376.6 grams of INVEGA distributed worldwide from launch to 30 June 2020, the estimated exposure is 34,285,425 person-months or 2,857,122 person-years.

Table SV.2: Cumulative Exposure to XEPLION (PP1M) (Launch to 30 June 2020)

Region	Strength	Number of Prefilled Syringes	Mg Equivalence	Person-Months	Person-Years
EU	117.000 (75 mg equivalence)	2,071,604	155,370,300	1,775,660	147,971
	156.000 (100 mg equivalence)	4,510,912	451,091,200	5,155,327	429,610
	234.000 (150 mg equivalence)	3,965,023	594,753,450	6,797,182	566,432
	39.000 (25 mg equivalence)	202,573	5,064,325	57,878	4,823
	390.000 (250 mg equivalence)[a]	83,471	20,867,750	238,488	19,875
	78.000 (50 mg equivalence)	1,380,661	69,033,050	788,949	65,745
EU Subtotal		***12,214,244***	***1,296,180,075***	***14,813,484***	***1,234,456***
NA	117.000 (75 mg equivalence)	1,617,293	121,296,975	1,386,251	115,521
	156.000 (100 mg equivalence)	4,365,139	436,513,900	4,988,731	415,728
	234.000 (150 mg equivalence)	5,670,721	850,608,150	9,721,236	810,103
	39.000 (25 mg equivalence)	56,544	1,413,600	16,156	1,346
	390.000 (250 mg equivalence)[a]	-	-	-	-
	78.000 (50 mg equivalence)	366,420	18,321,000	209,383	17,449
NA Subtotal		***12,076,117***	***1,428,153,625***	***16,321,757***	***1,360,147***
ROW	117.000 (75 mg equivalence)	1,173,725	88,029,375	1,006,050	83,838
	156.000 (100 mg equivalence)	2,864,123	286,412,300	3,273,283	272,774
	234.000 (150 mg equivalence)	2,367,194	355,079,100	4,058,048	338,171
	39.000 (25 mg equivalence)	85,316	2,132,900	24,377	2,032
	390.000 (250 mg equivalence)[a]	-	-	-	-
	78.000 (50 mg equivalence)	468,899	23,444,950	267,943	22,328
ROW Subtotal		***6,959,257***	***755,098,625***	***8,629,701***	***719,143***
Worldwide Total[b]		**31,249,618**	**3,479,432,325**	**39,764,942**	**3,313,746**

Key: EU = European Union; NA = North America; PP1M = Paliperidone Palmitate 1-Monthly Formulation; ROW = rest of world.

[a] Starter packs in Belgium, Germany, Netherlands, and Sweden have a 100 mg eq. plus a separate 150 mg eq. unit. A single dose of 250 mg eq. is not available.

[b] Product is being distributed under both XEPLION and INVEGA SUSTENNA® brand names.

Based on the 31,249,618 syringes of XEPLION distributed worldwide from launch to 30 June 2020, the estimated exposure is 39,764,942 person-months or 3,313,746 person-years.

Table SV.3: Cumulative Exposure to TREVICTA (PP3M) (Launch to 30 June 2020)

Region	Strength	Number of Prefilled Syringes	Treatment Course	Person-Years
EU	273.000 (175 mg equivalence)	96,400	96,400	24,101
	410.000 (263 mg equivalence)	117,945	117,945	29,487
	546.000 (350 mg equivalence)	228,812	228,812	57,203
	819.000 (525 mg equivalence)	248,349	248,349	62,087
EU Subtotal		***691,506***	***691,506***	***172,878***
NA	273.000 (175 mg equivalence)	20,869	20,869	5,218
	410.000 (263 mg equivalence)	65,780	65,780	16,445
	546.000 (350 mg equivalence)	146,315	146,315	36,579
	819.000 (525 mg equivalence)	246,054	246,054	61,513
NA Subtotal		***479,018***	***479,018***	***119,755***
ROW	273.000 (175 mg equivalence)	13,642	13,642	3,410
	410.000 (263 mg equivalence)	27,352	27,352	6,839
	546.000 (350 mg equivalence)	65,326	65,326	16,332
	819.000 (525 mg equivalence)	64,282	64,282	16,071
ROW Subtotal		***170,602***	***170,602***	***42,652***
Worldwide Total[a]		**1,341,126**	**1,341,126**	**335,285**

Key: EU = European Union; NA = North America; PP3M = Paliperidone Palmitate 3-Monthly Formulation; ROW = rest of world.

[a] Distribution was firstly observed in June 2015.

Based on the 1,341,126 syringes of TREVICTA distributed worldwide from launch to 30 June 2020, the estimated exposure is 335,285 person-years.

Table SV.4: Cumulative Exposure to Oral Generic Paliperidone (Launch to 30 June 2020)

Region	Strength	Total Grams	Person-Months	Person-Years
NA	1.5 mg	5,611.8	31,177	2,598
	3 mg	45,805.7	254,476	21,207
	6 mg	159,852.3	888,068	74,006
	9 mg	94,276.5	523,759	43,646
NA Subtotal		***305,546.3***	***1,697,480***	***141,457***
Worldwide Total[a]		**305,546.3**	**1,697,480**	**141,457**

Key: EU = European Union; NA = North America; ROW = rest of world.

[a] There were no sales reported in EU and ROW region for the cumulative period.

Based on the 305,546.3 grams of oral generic paliperidone distributed worldwide from launch to 30 June 2020, the estimated exposure is 1,697,480 person-months or 141,457 person-years.

The estimated exposure to INVEGA, XEPLION, TREVICTA, and oral generic paliperidone from launch to 30 June 2020 is 75,747,847 person-months or 6,647,610 person-years.

Exposure by Age and Sex

Prescription sales stratified by age and sex available from IQVIA (formerly IMS Health) are presented (as a percentage of total prescriptions) for INVEGA in Tables SV.5, SV.6, and SV.7, for XEPLION in Tables SV.8, SV.9, and SV.10, and for TREVICTA in Tables SV.11, SV.12, and

SV.13. Data are available for the 3-year-period from 01 January 2017 to 31 December 2019. Prescription units are reported as absolute values.

Table SV.5: Postmarketing (Non-study) INVEGA (Paliperidone ER) Exposure by Age Group in Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	EU[b] (2,442,620 Rx[c])
0 to 17	3.0%
18 to 35	26.5%
36 to 64	60.8%
≥65	9.7%

Key: ER = Extended-Release; EU = European Union; Rx = prescription
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are only available in Germany, Italy, Spain, and the United Kingdom.
[c] Includes retail channels.

Table SV.6: Postmarketing (Non-study) INVEGA (Paliperidone ER) Exposure by Age Group Outside Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	Non-EU[b] (9,492,915 Rx[c])
0 to 17	1.1%
18 to 35	21.4%
36 to 64	60.6%
≥65	16.0%
Age Unspecified	0.9%

Key: ER = Extended-Release; EU = European Union; Rx = Prescription
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are only available in Canada, Japan, and the United States.
[c] Includes retail channels.

Table SV.7: Postmarketing (Non-study) INVEGA (Paliperidone ER) Exposure by Gender (01 January 2017 to 31 December 2019)

Country	Females[a]	Males[a]	Patient Gender Unidentified[a]
Canada [redacted] Rx[b])	67.1%	32.9%	0.0%
Germany [redacted] Rx[b])	23.3%	76.7%	0.0%
Italy ([redacted] Rx[b])	36.1%	63.9%	0.0%
Japan [redacted] Rx[b])	44.4%	54.6%	1.0%
Spain [redacted] Rx[b])	31.9%	68.1%	0.0%
United Kingdom [redacted] Rx[b])	100.0%	0.0%	0.0%
United States ([redacted] Rx[b])	38.5%	61.5%	0.0%

Key: ER = Extended-Release; Rx = Prescription
[a] Regional Rx data by gender are only available for the last 3 years ending December 2019. Data are only available for Canada, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.
[b] Includes retail channels.

Table SV.8: Postmarketing (Non-study) XEPLION (PP1M) Exposure by Age Group in Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	EU[b] (3,445,020 Rx[c])
0 to 17	0.9%
18 to 35	24.1%
36 to 64	69.9%
≥65	5.1%

Key: EU = European Union; PP1M = Paliperidone Palmitate 1-Monthly Formulation; Rx = Prescription.
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are only available in France, Germany, Italy, Spain, and the United Kingdom.
[c] Includes retail channels.

Table SV.9: Postmarketing (Non-study) XEPLION (PP1M) Exposure by Age Group Outside Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	Non-EU[b] (5,468,624 Rx[c])
0 to 17	0.2%
18 to 35	30.3%
36 to 64	62.6%
≥65	6.8%
Age Unspecified	0.1%

Key: EU = European Union; PP1M = Paliperidone Palmitate 1-Monthly Formulation; Rx = Prescription
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are only available in Canada, Japan, and the United States.
[c] Includes retail channels.

Table SV.10: Postmarketing (Non-study) XEPLION (PP1M) Exposure by Gender (01 January 2017 to 31 December 2019)

Country	Females[a]	Males[a]	Patient Gender Unidentified[a]
Canada [redacted] Rx[b])	35.2%	64.1%	0.7%
France [redacted] Rx[b])	34.5%	65.5%	0.0%
Germany [redacted] Rx[b])	44.1%	55.9%	0.0%
Italy ([redacted] Rx[b])	25.7%	74.3%	0.0%
Japan [redacted] Rx[b])	41.5%	58.0%	0.5%
Spain [redacted] Rx[b])	25.9%	74.1%	0.0%
United Kingdom [redacted] Rx[b])	0.0%	100.0%	0.0%
United States [redacted] Rx[b])	32.6%	67.4%	0.0%

Key: PP1M = Paliperidone Palmitate 1-Monthly Formulation; Rx = Prescription
[a] Regional Rx data by gender are only available for the last 3 years ending December 2019. Data are only available for Canada, France, Germany, Italy, Japan, Spain, the United Kingdom, and the United States.
[b] Includes retail channels.

Table SV.11: Postmarketing (Non-study) TREVICTA (PP3M) Exposure by Age Group in Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	EU[b] (638,221 Rx[c])
0 to 17	0.2%
18 to 35	20.3%
36 to 64	76.7%
≥65	2.8%

Key: EU = European Union; PP3M = Paliperidone Palmitate 3-Monthly Formulation; Rx = Prescription.
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are available for France, Germany, Spain, and the United Kingdom.
[c] Includes retail channels.

Table SV.12: Postmarketing (Non-study) TREVICTA (PP3M) Exposure by Age Group Outside Europe (01 January 2017 to 31 December 2019)

Age Groups (Years)[a]	Non-EU[b] (504,703 Rx[c])
18 to 35	54.4%
36 to 64	39.8%
≥65	5.8%

Key: EU = European Union; PP3M = Paliperidone Palmitate 3-Monthly Formulation; Rx = Prescription.
[a] Regional Rx data by age are only available for the last 3 years ending December 2019.
[b] Data stratified by age are available for Canada, and the United States.
[c] Includes retail channels.

Table SV.13: Postmarketing (Non-study) TREVICTA (PP3M) Exposure by Gender (01 January 2017 to 31 December 2019)

Country	Females[a]	Males[a]
Canada [redacted] Rx[b])	46.1%	53.9%
France [redacted] Rx[b])	17.5%	82.5%
Germany [redacted] Rx[b])	44.4%	55.6%
Spain [redacted] Rx[b])	22.9%	77.1%
United Kingdom [redacted] Rx[b])	30.6%	69.4%
United States [redacted] Rx[b])	4.4%	95.6%

Key: PP3M = Paliperidone Palmitate 3-Monthly Formulation; Rx = Prescription.
[a] Regional Rx data by gender are only available for the last 3 years ending December 2019. Data are available for Canada, France, Germany, Spain, the United Kingdom, and the United States.
[b] Includes retail channels.

PART II: SAFETY SPECIFICATION

Module SVI: Additional EU Requirements for the Safety Specification

Potential for Misuse for Illegal Purposes

Drug abuse and dependence are thought to be associated with full or partial dopamine agonists that increase dopamine release in the central nervous system (Di Chiara 2004). Given the pharmacological profile of paliperidone as a full D_2 receptor antagonist, the risk of abuse and dependence is considered minimal.

PART II: SAFETY SPECIFICATION

Module SVII: Identified and Potential Risks

SVII.1. Identification of Safety Concerns in the Initial RMP Submission

Not applicable.

SVII.1.1. Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

Reason for Not Including an Identified or Potential Risk in the List of Safety Concerns in the RMP:

Not applicable.

SVII.1.2. Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Not applicable.

SVII.2. New Safety Concerns and Reclassification With Submission of an Updated RMP

Not applicable.

SVII.3. Details of Important Identified Risks, Important Potential Risks, and Missing Information

Important identified risks: None.

Important potential risks: None.

Missing information: Exposure during pregnancy.

SVII.3.1. Presentation of Important Identified Risks and Important Potential Risks

Not applicable.

SVII.3.2. Presentation of the Missing Information

Missing information: Exposure during pregnancy
Evidence source: INVEGA, XEPLION, TREVICTA, and BYANNLI have not been studied in pregnant women. Information regarding the effects of paliperidone on the pregnant mother and resulting offspring is limited.
Anticipated risk/consequence of the missing information: Since paliperidone has been detected in plasma up to 18 months after a single dose of the 3-monthly paliperidone palmitate injectable, consideration should be given to the long-acting nature of TREVICTA and BYANNLI, as maternal exposure to TREVICTA and BYANNLI before and during pregnancy may lead to adverse reactions in the newborn child. Neonates exposed to antipsychotics (including paliperidone) during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. Intramuscularly injected paliperidone palmitate and orally administered paliperidone were not teratogenic in animal studies. Overall, the nonclinical studies suggest no risk of teratogenicity or congenital malformations with paliperidone at recommended dose levels in humans.

PART II: SAFETY SPECIFICATION

Module SVIII: Summary of the Safety Concerns

Table SVIII.1: Summary of Safety Concerns

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

PART III: PHARMACOVIGILANCE PLAN (Including Postauthorization Safety Studies)

III.1. Routine Pharmacovigilance Activities Beyond Adverse Reaction Reporting and Signal Detection

Specific Adverse Reaction Follow-up Questionnaires	
Safety Concern	**Purpose/Description**
Not applicable	

Other Forms of Routine Pharmacovigilance Activities		
Activity	**Objective/Description**	**Milestones**
Cumulative review of pregnancies in the PBRER/PSUR.	To monitor for risks associated with exposure to INVEGA, XEPLION, TREVICTA, or BYANNLI during pregnancy.	Cumulative reviews will be conducted to align with the EU PSUR reporting interval.

Key: EU = European Union; PBRER/PSUR = Periodic Benefit Risk Evaluation Report/Periodic Safety Update Report.

III.2. Additional Pharmacovigilance Activities

Not applicable.

III.3. Summary Table of Additional Pharmacovigilance Activities

Table Part III.1: Ongoing and Planned Additional Pharmacovigilance Activities

Study Status	**Summary of Objectives**	**Safety Concerns Addressed**	**Milestones**	**Due Dates**
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
Not applicable.				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable.				
Category 3 - Required additional pharmacovigilance activities				
Not applicable.				

PART IV: PLANS FOR POSTAUTHORIZATION EFFICACY STUDIES

Table Part IV.1: Planned and Ongoing Postauthorization Efficacy Studies That Are Conditions of the Marketing Authorization or That Are Specific Obligations

Study Status	Summary of Objectives	Efficacy Uncertainties Addressed	Milestones	Due Dates
Efficacy studies which are conditions of the marketing authorization				
Not applicable				
Efficacy studies which are specific obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
Not applicable				

PART V: RISK MINIMIZATION MEASURES (Including Evaluation of the Effectiveness of Risk Minimization Activities)

Risk Minimization Plan

V.1. Routine Risk Minimization Measures

Table Part V.1: Description of Routine Risk Minimization Measures by Safety Concern

Safety Concern	Routine Risk Minimization Activities
Missing information: Exposure during pregnancy	**Routine risk communication:** INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs Section 4.6, Fertility, pregnancy and lactation Section 5.3, Preclinical safety data **Routine risk minimization activities recommending specific clinical measures to address the risk:** INVEGA, XEPLION, TREVICTA, and BYANNLI SmPCs (Section 4.6, Fertility, pregnancy and lactation) Neonates exposed to [paliperidone] [antipsychotics (including paliperidone)] during the third trimester of pregnancy are at risk of adverse reactions including extrapyramidal and/or withdrawal symptoms that may vary in severity and duration following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, or feeding disorder. Consequently, newborns should be monitored carefully. [Paliperidone] should not be used during pregnancy unless clearly necessary. **Other routine risk minimization measures beyond the Product Information:** Legal status: INVEGA, XEPLION, TREVICTA, and BYANNLI have Prescription Only Medicine legal status.

Key: SmPC = Summary of Product Characteristics.

V.2. Additional Risk Minimization Measures

Not applicable.

V.2.1. Removal of Additional Risk Minimization Activities

Not applicable

V.3. Summary of Risk Minimization Measures and Pharmacovigilance Activities

Table Part V.3: 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.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of Risk Management Plan for INVEGA (Paliperidone Prolonged-Release Tablets)

This is a summary of the risk management plan (RMP) for INVEGA. The RMP details important risks of INVEGA, how these risks can be minimized, and how more information will be obtained about INVEGA's risks and uncertainties (missing information).

INVEGA's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how INVEGA should be used.

This summary of the RMP for INVEGA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of INVEGA's RMP.

I. The Medicine and What It Is Used For

INVEGA is authorized for the treatment of schizophrenia in adults and in adolescents aged 15 years and older and schizoaffective disorder in adults (see SmPC for the full indication). It contains paliperidone as the active substance and it is given by mouth as a prolonged-release tablet (available as 3, 6, 9, or 12-mg tablets).

Further information about the evaluation of INVEGA's benefits can be found in INVEGA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/invega.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of INVEGA, together with measures to minimize such risks and the proposed studies for learning more about INVEGA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of INVEGA is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of INVEGA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of INVEGA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

II.B. Summary of Important Risks

Missing Information: Exposure During Pregnancy	
Risk minimization measures	**Routine risk minimization measures:** SmPCs for INVEGA, XEPLION, TREVICTA, and BYANNLI: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data **Additional risk minimization measures:** None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligation for INVEGA.

II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for INVEGA.

Summary of Risk Management Plan for XEPLION (Paliperidone Palmitate 1-Monthly Injection)

This is a summary of the risk management plan (RMP) for XEPLION. The RMP details important risks of XEPLION, how these risks can be minimized, and how more information will be obtained about XEPLION's risks and uncertainties (missing information).

XEPLION's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how XEPLION should be used.

This summary of the RMP for XEPLION should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of XEPLION's RMP.

I. The Medicine and What It Is Used For

XEPLION is authorized for maintenance treatment of schizophrenia in adult patients stabilized with paliperidone or risperidone and in selected adult patients with schizophrenia and previous responsiveness to oral paliperidone or risperidone.

XEPLION may be used without prior stabilization with oral treatment if psychotic symptoms are mild to moderate and a long-acting injectable treatment is needed (see SmPC for the full indication).

It contains paliperidone as the active substance and it is administered by intramuscular (IM) injection as a prolonged-release suspension in prefilled syringes containing 39, 78, 117, 156, or 234 mg of XEPLION; which is equivalent to 25, 50, 75, 100, or 150 mg, respectively, of paliperidone. XEPLION is administered by a health care professional.

Further information about the evaluation of XEPLION's benefits can be found in XEPLION's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/xeplion.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of XEPLION, together with measures to minimize such risks and the proposed studies for learning more about XEPLION's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of XEPLION is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of XEPLION are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of XEPLION. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

II.B. Summary of Important Risks

Missing Information: Exposure During Pregnancy	
Risk minimization measures	**Routine risk minimization measures:** SmPCs for INVEGA, XEPLION, TREVICTA, and BYANNLI: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data **Additional risk minimization measures:** None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligation for XEPLION.

II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for XEPLION.

Summary of Risk Management Plan for TREVICTA (Paliperidone Palmitate 3-Monthly Injection)

This is a summary of the risk management plan (RMP) for TREVICTA. The RMP details important risks of TREVICTA, how these risks can be minimized, and how more information will be obtained about TREVICTA's risks and uncertainties (missing information).

TREVICTA's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how TREVICTA should be used.

This summary of the RMP for TREVICTA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of TREVICTA's RMP.

I. The Medicine and What It Is Used For

TREVICTA is authorized for the maintenance treatment of schizophrenia in adult patients who are clinically stable on 1-monthly paliperidone palmitate injectable product (see SmPC for the full indication). It contains paliperidone as the active substance and it is administered by injection as a prolonged-release suspension in prefilled syringes containing 273, 410, 546, or 819 mg of TREVICTA; which is equivalent to 175, 263, 350, or 525 mg, respectively, of paliperidone. TREVICTA is administered by a healthcare professional.

Further information about the evaluation of TREVICTA's benefits can be found in TREVICTA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/trevicta.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of TREVICTA, together with measures to minimize such risks and the proposed studies for learning more about TREVICTA's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of TREVICTA is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of TREVICTA are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of TREVICTA. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

II.B. Summary of Important Risks

Missing Information: Exposure During Pregnancy	
Risk minimization measures	**Routine risk minimization measures:** SmPCs for INVEGA, XEPLION, TREVICTA, and BYANNLI: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data **Additional risk minimization measures:** None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligation for TREVICTA.

II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for TREVICTA.

Summary of Risk Management Plan for BYANNLI (Paliperidone Palmitate 6-Monthly Injection)

This is a summary of the risk management plan (RMP) for BYANNLI. The RMP details important risks of BYANNLI, how these risks can be minimized, and how more information will be obtained about BYANNLI's risks and uncertainties (missing information).

BYANNLI's Summary of Product Characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how BYANNLI should be used.

This summary of the RMP for BYANNLI should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of BYANNLI's RMP.

I. The Medicine and What It Is Used For

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

It contains paliperidone as the active substance and it is administered by intramuscular (IM) injection as a prolonged-release suspension in prefilled syringes containing 1,092 or 1,560 mg of BYANNLI, which is equivalent to 700 or 1,000 mg, respectively, of paliperidone. BYANNLI is administered by a health care professional.

Further information about the evaluation of BYANNLI's benefits can be found in BYANNLI's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/XXXXX.

II. Risks Associated With the Medicine and Activities to Minimize or Further Characterize the Risks

Important risks of BYANNLI, together with measures to minimize such risks and the proposed studies for learning more about BYANNLI's risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the PL and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorized pack size - the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without prescription) can help to minimize its risks.

Together, these measures constitute routine risk minimization measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analyzed including Periodic Safety Update Report (PSUR) assessment so that immediate action can be taken as necessary. These measures constitute routine pharmacovigilance activities.

If important information that may affect the safe use of BYANNLI is not yet available, it is listed under "missing information" below.

II.A. List of Important Risks and Missing Information

Important risks of BYANNLI are risks that need special risk management activities to further investigate or minimize the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of BYANNLI. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of Important Risks and Missing Information	
Important identified risks	None
Important potential risks	None
Missing information	Exposure during pregnancy

II.B. Summary of Important Risks

Missing Information: Exposure During Pregnancy	
Risk minimization measures	**Routine risk minimization measures:** SmPCs for INVEGA, XEPLION, TREVICTA, and BYANNLI: • Section 4.6, Fertility, pregnancy and lactation • Section 5.3, Preclinical safety data **Additional risk minimization measures:** None

II.C. Postauthorization Development Plan

II.C.1. Studies Which Are Conditions of the Marketing Authorization

No studies are conditions of the marketing authorization or specific obligation for BYANNLI.

II.C.2. Other Studies in Postauthorization Development Plan

No studies are required for BYANNLI.

Annex 4: Specific Adverse Drug Reaction Follow-up Forms

Not applicable.

Annex 6: Details of Proposed Additional Risk Minimization Activities

Not applicable.