SCIENTIFIC DISCUSSION

1 Introduction

This is a complete, Article 8(3) application for Invega prolonged release tablets containing the new active substance paliperidone, belonging to the class of atypical antipsychotics.
The claimed indication for Invega tablets, available in strengths of 3 mg, 6 mg, 9 mg and 12 mg, is the treatment of schizophrenia.
Paliperidone (9-hydroxy-risperidone) is the major metabolite of risperidone, which is approved for treatment of schizophrenia since 1994. Paliperidone shares the characteristic serotonin ($5HT_{2A}$) and dopamine (D_2) antagonism and receptor binding profile of its parent risperidone. It binds also to a_1-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and a_2-adrenergic receptors, which may explain some of the other effects of paliperidone.
The goals of treatment of schizophrenia are to rapidly eliminate symptoms, reduce the number of relapses, and reduce the severity of the illness. Improving the level of social function and relationships are also important.
Antipsychotics are the mainstay of treatment of schizophrenia. Conventional antipsychotics, typified by haloperidol, have a proven track record over the last half-century in the treatment of schizophrenia. While these drugs are highly effective against the positive, psychotic symptoms of schizophrenia, they show little benefit in alleviating negative symptoms or the cognitive impairment associated with the disease.
Second generation, also called atypical antipsychotics, differ considerably in their chemical, pharmacological, and clinical profiles and are generally characterised by effectiveness against both the positive and negative symptoms associated with schizophrenia and with enhanced safety profile with respect to extrapyramidal symptoms.
Although a number of products in this class are currently available, treatment challenges and consequently goals for the development of a new second generation antipsychotic continue to exist such as the need for titration, twice daily dosing, slow onset of action necessitating the use of acute intramuscular treatment, and high treatment discontinuation rates due to lack of compliance or other reasons.
Paliperidone is presented as a prolonged-release formulation. The goal of the development program was to identify an extended-release formulation that would enhance the initial tolerability and permit initiation of treatment at an effective dose without the need for initial dose titration. Invega prolonged release tablets are based on the patented OROS® (ORal Osmotic System) Push-Pull™ technology delivery system, designed to deliver the paliperidone active substance in a controlled manner over 24 hours, thereby achieving an effective once-a-day treatment for schizophrenia. The system deploys an osmotic gradient across a semi-permeable membrane for the delivery of the active substance. In addition, paliperidone has been developed as a racemate, since the R- and S-enantiomers have similar pharmacological activity and interconvert *in vivo*.

2 Quality aspects

Introduction
Invega 3, 6, 9, and 12 mg prolonged release tablets contain paliperidone as the only active ingredient. Paliperidone is a new chemical entity belonging to the atypical antipsychotic class of psychotropic drugs. The dosage forms described in this registration dossier are prolonged release tablets using OROS® Push-Pull™ technology to deliver the active substance in a controlled rate over 24 hours.
Invega is administered orally once daily for the treatment for schizophrenia. The proposed indication is: “Treatment of schizophrenia”.
They are supplied in four different packaging materials:

- White high-density polyethylene (HDPE) bottle with induction sealing, and polypropylene (PP) child-resistant closure and two 1-g desiccant silica gel pouches.
- Oriented polyamide (OPA)-aluminum (AL)-polyvinyl chloride (PVC)/AL push-through blister.

- PVC laminated with polychloro trifluoroethylene (PCTFE)/AL push-through blister.
- White PVC laminated with PCTFE/paper-AL push-through blister.

Active substance

Paliperidone is a white to yellow non-hygroscopic powder. It corresponds to the molecular formula: $C_{23}H_{27}FN_4O_3$ and its relative molecular mass is 426.49. Its chemical name is (±)-3-[2-[4-(6-fluoro-1, 2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6, 7, 8, 9-tetrahydro-9-hydroxy-2-methyl-4*H*pyrido[1, 2-*a*] pyrimidin-4-one.
Paliperidone's dissociation constants are pKa1 = 8.2 (piperidine moiety) and pKa2 = 2.6 (pyrimidine moiety). Its solubility in water is 0.003 g/100 ml, rising to to 2.3 g/100 ml in 0.1 N HCl, whereas in ethanol it is 0.076 g/100 ml. The logP of the substance as a neutral molecule in a 1-octanol/aqueous buffered solution (pH 11.9) is 2.39, while the logP of the substance regardless of its form in phosphate solution of pH 7.0 is 1.02.
Paliperidone has one chiral centre and is synthesised as a racemic mixture. Two polymorphs were observed, polymorph I and II, in addition to a hydrate and a solvate. In the final active substance only polymorph I is present, which is the thermodynamically stable crystal form. It has been shown that all investigated active substance batches are of the same crystalline form I.

- Manufacture

Paliperidone is manufactured by a three-step process followed by a purification and a milling step. Acceptable specification for the catalysts used in the process has been presented. The description of the route of synthesis of the starting materials is also regarded sufficient.
During the development of paliperidone active substance, the manufacturing process has been optimised, however the general pathway, including key starting materials and intermediates, remained unchanged. The synthesis changes that were made throughout development lead to three versions of the manufacturing process, but are considered minor and resulted in comparable active substance quality.
A study on the crystallization parameters consistently showed polymorph I is produced, demonstrating that the crystallization step is under control. Moreover, the hydrate and polymorph II can only be obtained by a process which is completely different from the current manufacturing process.

- Specification

The specification for the control of the active substance includes tests for appearance (visual examination), identification (IR (Ph. Eur) and HPLC), heavy metals (USP), residue on ignition and sulphated ash (USP at only release), water content (Karl-Fischer), assay (HPLC), related substances (HPLC), residual solvents (GC) and particle size (laser diffraction).
In humans, the AUC ratio of R/S enantiomers is similar for the different racemic formulations. Furthermore, it has been demonstrated that both enantiomers interconvert into each other after oral administration of the separate enantiomers. Therefore, no specific optical rotation testing will be performed for release of paliperidone.
Intrinsic dissolution profiles of polymorph I, II and the hydrate are identical. Based on these data and the stability studies, which show that polymorph I is the most stable and that only this configuration is present at the different time points and conditions, a specification for polymorphism is not deemed necessary.
The specifications for paliperidone are based on analyses of 38 batches of active substance, prepared by the commercial process, and on toxicological and stability data. The provided batch analyses, confirm the suitability of the specifications.

- Stability

Paliperidone active substance has been subjected to several stability studies, including stress conditions and studies under long-term, intermediate and accelerated conditions
Stability data for four production batches have been submitted stored at 25°C/60% RH (normal conditions) and at 30°C/65% RH for up to 24 months and at 40°C/75% RH (accelerated) for up to 6 months. The parameters studied are appearance, assay, impurities, water content, polymorphism, transition temperature, optical purity, particle size and microbiological purity. The testing methods used are the same as those used at release testing.

The stability data provided indicate that the active substance remains stable at different storage conditions. In addition, no difference has been observed for the stability behaviour of the paliperidone active substance synthesised by the different versions of the current manufacturing method. The stability data provided support the proposed retest period without any labelling instructions.

Medicinal Product

Janssen-Cilag International NV has applied for the 3, 6, 9, and 12 mg strength tablets. However, for the sake of completeness, the 15 mg tablet was also included in the Quality documentation, a strength which was used in clinical and stability studies. Nevertheless, the Applicant is not seeking authorisation for this additional strength, but because the bracketing approach of the stability studies is very much based on stability data from the 15 mg strength, this strength has also been taken into account during the assessment.

- Pharmaceutical Development

Invega utilises the tri-layer core OROS® Push-Pull™ technology system developed by Alza. This osmotic delivery system consists of 2 drug layers and a push layer. Drug layer 1 contains a lower drug concentration than drug layer 2, which provides the drug concentration gradient necessary to achieve an ascending release rate pattern. Additionally, the expandable push layer consists of hydrophilic polymers and osmotic excipients and it contributes to the drug delivery. The tablet core is surrounded by a lubricating subcoat, which enhances robustness of the drug release pattern. The semi-permeable membrane acts as a rate controlling membrane and provides to the tablet mechanical durability. Drug release from the tablet is inversely related to the membrane weight applied to the tablets.
Two orifices are laser drilled through the membrane and subcoat on the first drug layer side of the elongated core of the tablet to provide exit ports for the drug. The presence of the orifices is vital to meet the specified release profile. The colour overcoat and the print applied on the colour allow differentiation between the different strengths.
The water-dispersible colour overcoat erodes quickly in the GI tract. Water is then absorbed through the semi-permeable, rate-controlling membrane at a consistent rate into the core as a result of the osmotic activity gradient established across the membrane by the osmotic excipients. As the drug layers hydrate, a gel-like suspension of paliperidone is formed *in situ*. Similarly, the push layer imbibes water and the hydrophilic polymers hydrate and begin to expand. Delivery of the active substance begins when the volumetric expansion of the osmotic push layer begins to "push" the gel-like drug suspension through the orifices.
The osmotic gradient controls the flux of water through the membrane and into the core, which in turn controls the rate of drug delivered from the tablet. Because water is absorbed at a consistent rate and the volume of the tablet remains essentially the same the delivery rate of drug is proportional to the rate at which water permeates the membrane and the drug concentration at the orifice. Since rate control resides within the semi-permeable membrane, the active substance release is essentially independent from environmental pH, agitation, and other conditions encountered in the gastrointestinal tract. Moreover, drug is expelled from the core continuously as the tablet travels along the gastrointestinal tract.
Only the particle size was specified as the key property of the active substance during Invega development. The tablet functionality was shown to be independent of the active substance particle size within a certain the D50 range. The mean particle size of the active substance is controlled by milling.
Finally, all inactive ingredients of Invega are conventional pharmaceutical excipients used are at the typical levels for a prolonged release tablet formulations. The compatibility of excipient with the active substance was established by appropriate compatibility studies.
Initial PK and PD evaluation focused on the optimal release rate and was conducted with tablets containing 2 mg of paliperidone. Two formulations, differing only in the amount (thickness) of the rate controlling membrane, were tested to provide distinct drug delivery durations with nominal t_{90} of 10 hours ("fast") and nominal t_{90} of 20 hours ("slow"). The bioavailability of the "fast" and "slow" tablets under fasted conditions was 45% and 32%, respectively, relative to the immediate release oral solution. In addition, the incidence of orthostatic hypotension was lower for the "slow" tablets compared with the other two formulations. An alternative formulation was developed to increase bioavailability without compromising the favourable effect on the orthostatic hypotension. 2 mg drug overcoated tablets were developed and tested to explore the impact of increased amount of drug

delivered in the upper GI tract. The bioavailability of the overcoated formulation was improved to 45% but did not outweigh the "slow" formulation advantage in the tolerability profile. Therefore, the "slow" formulation was selected for further testing in Phase 3 clinical trials. The 3 and 9 mg tablets finally chosen for the Phase 3 efficacy studies were similar to the "slow" tablets.
An in vitro-in vivo correlation (IVIVC) was demonstrated for Invega tablets and a Level A IVIVC model was shown and validated by establishing internal and external predictability.
Ultimately, during the development of the commercial formulation the core layer weight was optimised and in a number of studies, the effect of subcoat on release functionality, the effect of membrane weight on release and the effect of orifice size and placement on release functionality were investigated. Moreover the relationship between the key properties of cellulose acetate (the principal component of the rate controlling membrane) and the release functionality of Invega tablets was defined allowing a target membrane weight to be set for each lot of cellulose acetate in order to achieve the target release profile. The target coating weight can be modified based upon excipient lot behaviour affording an important control feature of the process that assures consistent release behaviour of the product from lot to lot.
To ensure that each Invega tablet has two orifices, the laser drilling system is equipped with an automated verification system that detects the laser activation for every tablet. If the laser is not activated, the system ejects the tablet. In addition to the in-process controls, an in vitro evaluation was performed to determine the effect of the lack of orifice on the performance of the dosage form from a safety point of view. Tablets without any orifice were intentionally manufactured and the results were evaluated. It could be demonstrated that there is no risk for dose dumping for the "no orifice" tablets. Considering all this, it can be assumed that the proposed measures to control the drilling process are sufficient and suitable.

- Adventitious Agents

With the exception of lactose monohydrate and stearic acid, none of the excipients used in the manufacturing of Invega are from animal origin. Lactose does not contain and is not derived from specified risk materials, as defined in the EU Regulation (EC) No 999/2001 of 22 May 2001. A TSE certificate for stearic acid has been provided.

- Manufacture of the Product

The process for the manufacture of paliperidone ER tablets consists of the following major operating steps: Granulation (Drug Layer 1, Drug Layer 2, Push Layer), Blending (Drug Layer 1, Drug Layer 2, Push Layer), Core Compression, Subcoating, Membrane Coating, Laser Drilling, Drying, Colour Overcoat and Packaging. A bioequivalence study was performed to compare the in vivo performance of the product manufactured at the two different manufacturing sites. The study showed that the in vivo profiles are similar, demonstrating that the batches are bioequivalent, regardless of the manufacturing site.

- Product Specification

The specification for batch release and shelf-life include the following tests: Appearance (Visual), Identification (HPLC, FTIR), Assay (HPLC), Degradation products (HPLC), Uniformity of Content (Ph.Eur.), Water content (Karl Fischer), Residual Solvent (GC), Dissolution (Ph.Eur.) and Microbial Limits (Ph.Eur.). Dissolution profile is controlled at the time points of 2, 8, 14 and 24 h.
Batch analysis data were provided for three batches of Invega 3 mg tablets, three batches 15 mg tablets and for one batch of each of the 6, 9 and 12 mg tablets. These batches were manufactured at both sites, according to the proposed commercial manufacturing process. The batch analysis data provided indicate the capability of the manufacturing process to produce Invega prolonged release tablets of consistent quality, complying with the designed specification.

- Stability of the Product

Each strength of Invega has been packaged in the proposed four different packaging materials. A bracketing approach was applied and three batches of the highest and lowest strengths (i.e. 3 and 15 mg) were packaged in each of the four different packaging configurations. One batch of each of the intermediate strengths (i.e., 6, 9, and 12 mg) was also packaged in the 4 packaging configurations and placed on stability using the ICH recommended storage conditions.
Up to 12 months of stability data (studies are on-going) at 25 °C/60% RH, 30 °C/65% RH and 5 °C and up to 6 months at accelerated conditions (40 °C/75% RH) demonstrate that tablets of all strengths

of Invega are stable for the attributes of appearance, assay, degradation products, drug release and water content in all four proposed packaging materials. Annual microbial testing was included in the protocols of one batch each of 3 and 15 mg tablets in all four packages. The testing methods used were the same as those used at release. In addition, one batch of each strength was subjected to confirmatory photostability studies as per the ICH conditions. These batches were packaged in that material of the four providing the least protection to light. Results demonstrated satisfactory resistance to photo-degradation.
Finally, in-use stability studies were performed on bottled tablets of one batch of 3- and 15-mg tablets, at 9 months, and will be performed again at 23 months each. Results at 9 months showed that Invega tablets are stable during use in a multi-dose container.
In conclusion, based upon the overall stability data presented, the proposed shelf life and storage conditions Invega tablets as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

The quality of Invega prolonged-release tablets is adequately established. In general, sufficient chemical and pharmaceutical documentation relating to development, manufacture and control of the active substance and drug product has been presented. There are no major deviations from EU and ICH requirements. The results of tests carried out indicate satisfactory consistency and uniformity of all the important product quality characteristics. It can be safely concluded that the product should have a satisfactory and uniform performance in the clinic.
Stability tests indicate that the product under ICH guidelines conditions is chemically stable for the proposed shelf life.

3 Non-clinical aspects

Introduction

Paliperidone is 9-hydroxy-risperidone, which is the major metabolite of risperidone. Paliperidone and risperidone have similar pharmacological profiles. The pharmacokinetic profile of paliperidone is also similar to the active fraction (paliperidone and risperidone) of risperidone. Thus, similar effects of paliperidone as for risperidone should be expected.

Most of the nonclinical pharmacology and the absorption, distribution, metabolism and excretion (ADME) studies on paliperidone were performed at the time when studies were conducted to support the marketing application of risperidone (Risperdal®). However, some ADME studies have also been conducted with oral paliperidone. Some of the repeat-dose toxicity studies have also included risperidone. Studies addressing the gastrointestinal tolerability of paliperidone ER tablets, and the toxicity of impurities in forced degraded paliperidone ER tablets were also conducted.

GLP aspects
All non-clinical pharmacology studies are non-GLP studies. Pivotal studies on pharmacokinetics and on toxicology were GLP-compliant.

Pharmacology
Paliperidone (R076477 or 9-OH-risperidone) is a receptor monoaminergic antagonist that exhibits the characteristic dopamine type 2 (D2) and serotonin (5-hydroxytryptamine [5-HT] type 2A [5-HT2A]) antagonism of antipsychotic drugs. Paliperidone is the major active metabolite of risperidone (Risperdal®) which is a widely used atypical antipsychotic approved for the treatment of schizophrenia and other psychiatric disorders.

The binding profiles for paliperidone, its enantiomers R078543(+) and R078544(−) and risperidone are comparable. Paliperidone is also an antagonist at α1- and α2-adrenergic receptors and the histamine H1-receptor *in vitro* and *in vivo*. In similarity with risperidone, cardiovascular safety issues with clinical relevance have been identified at paliperidone treatment. These are discussed in the clinical safety section of this report.

- Primary pharmacodynamics

Paliperidone displays high affinity for 5-HT2A (Ki 0.22-0.25 nM) and D2 (Ki 4.6 nM) receptors, and is also active as an antagonist at the α1-and α2-adrenergic receptors and the H1-receptor. Binding affinities and profiles for all investigated receptor sites are similar for paliperidone, its enantiomers and risperidone. Several *in vivo* studies were performed in rats and dogs. In rats, paliperidone was slightly less potent than risperidone at early time intervals, but became equipotent at later time intervals, probably reflecting a slower rate of brain penetration. In dogs, paliperidone, its enantiomers and risperidone were roughly equipotent against apomorphine-induced emesis.
Overall, paliperidone induced the expected effects (activity in functional pharmacology models) and the investigated *in vivo* effects were qualitatively and quantitatively similar for paliperidone and risperidone.

- Secondary pharmacodynamics

Dopamine secreted in the portal hypophyseal circulation inhibits prolactin release. By antagonizing this tonic inhibitory action of endogenous dopamine, D2 receptor antagonists elevate prolactin release. The suppressive effect of dopamine on prolactin release in rat anterior pituitary cells was dose-dependently antagonized by paliperidone, risperidone and haloperidol. Both paliperidone and risperidone were less potent than haloperidol in this *in vitro* assay, (2 and 3 times less potent, respectively). Paliperidone was equipotent to risperidone in reversing the dopamine-induced suppression of prolactin release from anterior pituitary cells. Both compounds provoked more pronounced plasma prolactin levels than haloperidol when measured 1 h after identical i.p. or oral doses.

Secondary pharmacodynamic effects and side effect (pre-clinical) profile of paliperidone are very similar to those of risperidone. Anti-adrenergic and anti-histaminergic effects are suspect to elicit hypotensive and sedative effects. Hyperprolactinemia is expected due to the D_2-receptor antagonism.

- Safety pharmacology programme

In in-vitro studies paliperidone at concentrations of $\geq$ 1 μM inhibited both HERG currents and native I_{Kr}, prolonged the APD, occasionally induced EADs, instability, triangulation and Torsade de Pointes (TdP) arrhythmias, which are all markers for a torsadogenic potential. Therefore, the slight inhibitory effects of paliperidone on both I_{Na} and $I_{Ca,L}$, which were observed at a concentration of 10 μM, do not seem to be protective against the induction of TdP arrhythmias by paliperidone at micromolar concentrations. Therapeutically effective free plasma concentrations of paliperidone in humans are about 20 nM. A 30-fold margin between free therapeutic plasma concentrations and IC_{50} values for the block of HERG currents appears to be a line of demarcation between the majority of drugs associated with TdP arrhythmias and those which are not. Therefore, when the paliperidone concentrations effective in in-vitro electrophysiological studies are compared to therapeutically effective free plasma concentrations, paliperidone seems to have a low torsadogenic potential. Nevertheless, since Torsade de pointes may occur with antipsychotics, the torsadogenic potential of paliperidone has been included in section 4.8 of the SPC.
In-vivo studies performed in guinea-pigs and dogs did not show marked effects of paliperidone on QT_c at micromolar plasma concentrations, which might question the relevance of these in-vivo models. However, in the Carlsson model, paliperidone did demonstrate effects on the QT_c.

- Pharmacodynamic drug interactions

No studies were performed. The CHMP considered this acceptable since the extensive clinical and nonclinical experience with risperidone and also taking into account that administration of risperidone results in significant paliperidone exposure.

Pharmacokinetics

Enantiomers
The chemical structure of paliperidone contains a chiral center, and paliperidone can therefore exist racemate of the two enantiomers R078543(+) or R078544(-). Interconversion occurs in aqueous solution under acidic and alkaline conditions. *In vivo* interconversion is also observed resulting in a particular ratio that is slightly different across species. Following paliperidone administration to laboratory animals, there is a systemic abundance of R078544(-) over R078543(+). In humans however, R078543(+) is slightly more abundant in plasma following administration of the ER OROS formulation. Nevertheless, the pharmacological and PK profiles of paliperidone and the two enantiomers are comparable both *in vitro* and *in vivo* and furthermore also closely resemble that of risperidone.

Absorption – Bioavailability
Paliperidone was well absorbed in dog and rats after oral administration of a paliperidone solution. The absolute p.o. bioavailability was estimated at 94.4% in dogs, 78 % in female rats and 46% in male rats. The gender difference observed in the rat species is consistent with a higher rate of metabolism in the male rat. Plasma concentrations obtained after the administration of the OROS ER system never exceeded those seen after dosing with the p.o. solution and resulted in longer time to maximum plasma concentrations and lower Cmax and bioavailability (15.1% compared to paliperidone solution).

Tissue distribution
Paliperidone related radioactivity was widely distributed, the highest concentrations in terms of AUC were found in liver, small intestinal tissue and salivary gland in rats, with T/P AUC ratios for these tissues ranging from 21 to 24. The peak concentration in the liver represented 17 % of the dose radioactivity. Lowest concentrations of total radioactivity were measured in brain, muscle, white fat and testis, with T/P AUC ratios of less than 1. In dogs, the highest tissue concentrations were seen in the liver, lung and kidney, with average levels 5 to 7 times higher than the corresponding plasma levels. Paliperidone was rapidly and widely distributed and crossed the blood-brain barrier; in brain, it was preferentially distributed to the frontal cortex and striatum. In plasma protein binding studies it was shown that in all species tested, including human, paliperidone is bound to a maximum of 85 %.
No study on placental transfer was performed with paliperidone but available data for risperidone in rats indicate that placental transfer is limited. Paliperidone and/or its metabolites were excreted into milk in rats. Tissue radioactivity levels declined rapidly, with no retention observed in any of the investigated tissues of these albino rats.

Protein binding
In plasma protein binding studies it was shown that in all species tested, including human, paliperidone is bound to a maximum of 85 %. Plasma protein binding of the enantiomers exhibited species-dependent stereoselectivity, with higher protein binding seen with R078543(+) than with R078544(-) in dog and human plasma. In human plasma, paliperidone was predominately bound to the α1-acid glycoprotein.

***In vitro* metabolism**
The *in vitro* metabolism of ^{14}C -paliperidone and its separate enantiomers was studied in subcellular liver fractions from male and female Swiss albino mice and Wistar and Sprague Dawley rats, female NZW rabbits, male Beagle dogs, and humans. Paliperidone was metabolized to a very limited extent in human liver matrices as well as in mouse, rabbit and dog liver matrices, whereas it was extensively metabolized in Wistar rat liver matrices and Sprague-Dawley rat hepatocyte suspensions. *In vitro*, a total of eight metabolites were identified, with pathways of primary importance including *N*-dealkylation and alicyclic hydroxylation. The major compound observed in primary hepatocyte cultures was paliperidone (20-90%). Based on the metabolism rate alone, there were no major quantitative differences observed between enantiomers (with the exception of mice and rabbits), and all metabolites observed with paliperidone were also seen with the individual enantiomers. Since metabolism was very limited in the non-rodent species and man, any possible impact of gender-related differences and stereoselectivity in metabolism may be negligible.

***In vivo* metabolism**

In rats, paliperidone was extensively metabolized and the excretion of unchanged paliperidone accounted for 3.19 (male) and 6.42% (female) of the dose. The urine and faeces obtained from rats contained unchanged paliperidone and seven metabolites, M1, M6, M7, M8, M9, M10, M11, (each accounting for more than 1% of the dose), and four minor metabolites (each accounting for less than 1% of the dose). In rat plasma, paliperidone was the major compound (50-68%). In rats, paliperidone was mostly metabolized by alicyclic hydroxylation, oxidative *N*-dealkylation and benzisoxazole scission.
In dogs, the excretion of total radioactivity in urine and faeces were slower than in the rat: at 168 hours after dosing, 59.8% the dose was excreted in urine and 32.4% of the dose was excreted in faeces. Metabolism was limited and after 48 hours the unchanged paliperidone accounted for 32.4% in the urine and none in faeces. The urine and faeces obtained from dogs contained also five metabolites, M8, M9, M10, M11, M12, M16 (accounting each for 1.2-6.5% of the total radioactivity). Unchanged paliperidone accounted for 82% of the total radioactivity in plasma (0-24h sample). In dog plasma only paliperidone and the M9 metabolite were detected (M9 accounting for up to 5% of plasma total radioactivity). In the excreta of dogs, biotransformation products resulted from oxidative *N*-dealkylation, alcohol dehydrogenation and benzisoxazole scission, whether or not in combination with glucuronidation, alicyclic mono-hydroxylation or di-hydroxylation.

In conclusion, the major biotransformation pathways were similar across species. Paliperidone was the major compound in plasma (50-97%) in man, rat and dog and the major compound (32-59%) in urine in man and dog. Overall, the species chosen for toxicity studies are considered relevant.
The metabolites observed following administration of paliperidone have also been observed following risperidone administration. Thus, no new metabolites were identified after the p.o. administration of paliperidone as compared to risperidone.

Excretion
Excretion was examined after single p.o. administration of ^{14}C-paliperidone at a dose of 0.63 mg/kg bw in male and female Wistar rats, in male Beagle dogs and in healthy male subjects one week after receiving a 1-mg dose.
Mass balance data was obtained from rats and dogs and compared to human data (Table 1). Biliary excretion was not determined.

Table 1. Excretion of radioactivity (% of dose) in rats and dogs after administration of [^{14}C]-paliperidone

Species (Study ID)	N	Dose (mg/kg)	Route	Urine (% dose)	Faeces (% dose)	Cage wash (% dose)	Recovery (% dose)	Time (h)
Rat (fasted),	5M	0.63	oral	15.7	86.3	0.35	102	96
	5F	0.63	oral	15.2	86.7	0.42	102	96
Dog (fasted),	3M	0.63	oral	59.8	32.4	0.97	93.1	168
Human (fasted),	5M	1mg/ subject	oral	79.6	11.4	NA	91.1	168

In rats, most of the paliperidone-related radioactivity (86%) was excreted with the faeces. In dogs and humans, the most important excretion route was urine. In humans the cumulative excretion in the urine amounted to 79.6% of the dose.

Pharmacokinetic drug interactions
Due to the very limited metabolism of 14C-paliperidone, the involvement of cytochrome P450-specific forms in paliperidone metabolism was studied using membrane preparations of heterologous systems expressing cytochrome P450 isoforms CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP3A5, and CYP3A4 in combination with cytochrome P450 reductase. *In vitro* results revealed the possible involvement of CYP3A4 and CYP2D6 in the overall metabolism of paliperidone, and in the formation of M11via benzisoxazole scission. No *ex vivo* induction and inhibition studies have been performed. However, the effect of risperidone on hepatic enzyme activity was examined in an *ex vivo* study, in which male Wistar rats were administered risperidone as repeated daily p.o. doses for 1 week. Risperidone exhibited no effects *in vivo* on any of the cytochrome P450 isoenzyme activities measured, or on UDP-glucuronosyltransferase activity. *In vitro* studies with Caco-2 cells indicated that paliperidone appears to have a weak P-gp inhibitory effect. No *in vivo* studies were performed and the clinical relevance is unknown.

Toxicology

- Single dose toxicity

The toxicity of single doses of paliperidone has been investigated in mice and rats via oral and intravenous routes. In single dose toxicity studies, paliperidone was of moderate acute toxicity with approximate non-lethal doses of more than 80 mg/kg (p.o.) in mice and more than 20-40 mg/kg (p.o.) in rats. Upon single intravenous (i.v.) bolus administration of paliperidone, no test-article related mortalities were seen at dose levels up to 10 mg/kg in mice and 40 mg/kg in rats, respectively. Sedation and ptosis were consistently noted across rodent species and routes of administration.

- Repeat dose toxicity (with toxicokinetics)

Paliperidone has been extensively tested in oral repeat-dose toxicity studies in mouse (3 months), rat (up to 6 months), dog (paliperidone up to 3- months and risperidone administered for 12 months). In studies ≥ 3 months, mice, rats and dogs were exposed to paliperidone doses (oral solution or dietary administration) up to 10, 20 and 5 mg/kg/day, respectively. Dogs in a 3-month study were administered an ER formulation up to 90 mg/day.

Toxicity findings related to exaggerated pharmacology, especially due to the dopamine D2 antagonist activity, were numerous. Treatment-related sedation and (palpebral) ptosis were consistently observed in the repeat-dose toxicity studies with paliperidone or risperidone in mice, rats, rabbits, and dogs. In addition, enhanced prolactin release was associated with changes in the following tissues: pituitary gland, mammary gland, endocrine pancreas, female genital tract, male accessory sex organs and adrenal glands in repeat dose toxicity and carcinogenicity studies. Changes in body weight, body weight gain and food consumption were also noted. Treatment related changes related to the anti-adrenergic activity were also seen in the red pulp of the spleen in paliperidone and risperidone treated rats and dogs. Furthermore, QTc prolongation and testes effects, probably unrelated to exaggerated pharmacology, were observed in dogs.

The observed toxicities were seen at systemic exposures in rats and mice below the human exposure (12 mg paliperidone). In dogs, the systemic exposure was approximately at or slightly above the clinical exposure. Similar toxicity profiles were seen after administration of paliperidone and risperidone (see also Genotoxicity).

Genotoxicity

The genotoxicity of paliperidone has been studied with respect to gene mutations in bacteria, mutations in TK locus *in vitro* in Mouse Lymphoma L5178Y cells and *in vivo* in the rat micronucleus test in bone marrow. In similarity with risperidone, no genotoxic potential was evident in any test system when tested up to appropriate concentrations and dose levels according to guidelines.

- Carcinogenicity

In dietary carcinogenicity studies, mice and rats were p.o. treated with risperidone at dose levels of 0, 0.63, 2.5, or 10 mg/kg bw/day. In mice, predominantly at the highest dose level, non neoplastic histopathological changes were observed in the pituitary gland, male endocrine pancreas, male accessory sex organs, female genital tract, and female mammary glands. An increased incidence of splenic red pulp hyperplasia was observed in both sexes. No treatment-related tumour response was observed in male mice. In females, the incidence of mammary adenocarcinomas was increased at all dose levels, particularly at 2.5 and 10 mg/kg. A dose-dependent increase in the incidence of pituitary gland adenomas was found in females at 2.5 and 10 mg/kg. In rats, non neoplastic changes in the pituitary gland, male and female mammary glands, and male and female genital tract were seen at all dose levels. At 10 mg/kg, the testes showed an increased incidence of degeneration and mineralization. Mineralization of the renal pelvis was enhanced in males and females at all dose levels. The incidence of mammary gland adenocarcinoma was increased in males at 10 mg/kg, as well as in females at all dose levels. Male rats also showed a slight increase in the incidence of endocrine pancreas adenoma at 2.5 and 10 mg/kg.
In conclusion, treatment-related tumour findings in mice and rats treated with risperidone occur in the mammary glands and endocrine pancreas, probably due to enhanced prolactin levels. In addition, an increased incidence of pituitary tumours is observed in female mice; this is thought to be due to

prolonged loss of dopamine signaling. The doses used in the carcinogenicity studies did provide exposures to active fraction that were only slightly higher than those determined at clinical exposure.

- Reproduction Toxicity

In the male rat fertility study with doses up to 2.5 mg/kg/day no effects on male fertility were observed but paternal toxicity was noted at the highest dose. In the female rat fertility study, prolactin-mediated pseudopregnancies and a prolongation of the pre-coital interval were observed at all tested doses (0.16-2.5 mg/kg/day). This response is considered to be secondary to prolactin-mediated estrus delay. At the maternally toxic top dose level of 2.5 mg/kg/day, there was a slight increase in pre-implantation loss resulting in fewer implantations and a lower number of live fetuses. Similar effects have been seen with risperidone.
In the rat embryo foetal development study with doses up to 10 mg/kg/day, even at maternally toxic dose levels, no treatment-related changes at external, visceral or skeletal examination in the fetuses were observed. In the rabbit embryo-foetal development study with doses up to 5 mg/kg/day, maternal toxicity was noted at 1.25 and 5 mg/kg. Total post-implantation loss was slightly increased at 5 mg/kg/day. This implantation loss was associated with a slight increase in the number of embryonic/fetal resorptions and fetal death.
No test article-related teratogenicity was found. Risperidone was not teratogenic either.
In a combined pre- and postnatal developmental toxicity and juvenile toxicity DRF study in rats, treatment with paliperidone took place from GD 6 to Day 7 of lactation (doses up to 2.5 mg/kg/day). This study indirectly established the excretion of paliperidone in the milk by the presence of paliperidone in the suckling pups. Maternal treatment at 2.5 mg/kg/day resulted in a reduction in the mean litter viability index on Day 7 of lactation. The main study was conducted in pregnant rats following administration of paliperidone at dose levels up to 1.25 mg/kg/day from GD 6 through Day 20 of lactation. Even at maternally toxic dose levels, there were no effects on gestation or parturition. Maternal necropsy showed no treatment-related abnormalities. Maternal dosing had no adverse effects on pup growth and performance, or on the offspring's reproductive performance.

- Toxicokinetic data

All toxicology studies were accompanied by an adequate toxicokinetic examination. Of special interest are a) the data from the pivotal studies performed in mice, rats and dogs comparing paliperidone and risperidone administration, b) data from studies with i.v. administration, c) data from the oral application of an ER-preparation with a powder preparation (immediate release) and d) the occurrence of paliperidone in the 12 month toxicity study with risperidone.

Table 2: Mean C_{max}- and AUC_{0-24h}-Values of Paliperidone, Risperidone and Active Fraction on Day 178 of the 6-Month Repeat-Dose p.o. Gavage Toxicity Study in Sprague-Dawley Rats

		Paliperidone			Risperidone		
Males (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	212	812	3717	1863	1572	3435
AUC_{0-24h}	(ng.h/mL)	512	1948	8476	5479	2128	7066[a]
Females (n = 6/dose level)							
Dose (mg/kg bw/day)		**0.63**	**2.5**	**10**		**10**	
Analyte		**PALI**	**PALI**	**PALI**	**PALI**	**RIS**	**AF**
C_{max}	(ng/mL)	251	1387	5303	1279	1795	3074
AUC_{0-24h}	(ng.h/mL)	965	5115	23291	8584	4315[e]	10978[e]

[a] AUC_{0-8h} (AUC_{0-24h} could not be estimated accurately)

bw = body weight; PALI = paliperidone; RIS = risperidone; AF = active fraction

Table 3: Mean C_{max}- and AUC_{0-24h}-Values of Risperidone and Metabolically Formed Paliperidone on Day 366 of the 12-Month Repeat-Dose p.o. Toxicity Study in Beagle Dogs

Dose (mg/kg bw/day)		**0.31**	**1.25**	**5**	**0.31**	**1.25**	**5**
Analyte		**RIS**	**RIS**	**RIS**	**PALI**	**PALI**	**PALI**
C_{max}	(ng/mL)	117	325	726	251	766	2236
AUC_{0-24h}	(ng.h/mL)	205	761	1954	3252	10704	30421

bw = body weight; RIS = risperidone; PAL = paliperidone

Interspecies comparison

Comparison of exposure in the tested species at LOAEL in the repeat dose toxicity studies and human exposures are shown in Table 31. The pharmacokinetic human data used for comparison are based on the following from patients 12 mg daily (0.24 mg/kg): $AUC_{(0\text{-}24h)}$ of 896 ng.h/ml and C_{max} of 46 ng/ml (PAL-SCH-101). A number of toxicities in animals were observed after subchronic or chronic administration (see table below).

Table 4. Comparisons of the exposure in tested species (at LOAEL) and human exposure.

Study Type	Route	Sex	Dose (mg/kg/ day)	Dose (mg/m2/ day)	Mean AUC	Exposure margin (AUC)	Mean Cmax	Exposure margin (Cmax)
Mouse, 3-months,	p.o. gavage	M	0.63	1.19	354	0.4	89	1.9
		F	0.63	1.19	284	0.3	52	1.1
Rat [a], 3-months,	p.o. diet	M	1.25	7.5	556	0.6	33	0.7
		F	1.25	7.5	874	1.0	52	1.1
Rat [b], 3-monts	p.o. gavage	M	0.63	3.8	595	0.7	136	3.0
		F	0.63	3.8	346	0.4	93	2.0
Rat [a], 6-months	p.o. gavage	M	0.63	3.8	512	0.6	212	4.6
		F	0.63	3.8	965	1.1	251	5.5
Dog, 3-months	p.o. gavage	M	0.31	6.2	1747 [d]	1.9	153 [d]	3.3
		F	0.31	6.2	2336 [d]	2.6	213 [d]	4.6
Dog, 3-months	p.o. ER tablets in capsule	M	30	37		0.2, 11 [f]		0.3, 12 [f]
		F	30	37		6.3, 14 [f]		11, 19 [f]
Dog, 12-months, RIS[c]	p.o.	M+ F	0.31		3457 [e]	3.9	3.9 [e]	8.0

[a] Sprague Dawley rats; [b] Wistar rats; [c] Risperidone (RIS) administered; [d] means of individual values; [e] active fraction; [f] individual values in dogs.

- Local tolerance

The local tolerability of the paliperidone ER tablets was evaluated in the GI tract. In a 3-month repeat-dose toxicity study in beagle dogs the animals were treated p.o. with 15-mg paliperidone ER tablets at dose levels of 30 and 90 mg/day, and paliperidone bulk powder at 90/60 mg/day. There were no treatment-related clinical signs or histopathological changes that would indicate gastrointestinal injury upon administration of paliperidone in the two formulations. No evidence of gastrointestinal lesions was encountered in any of the dosed groups. In single dose toxicity studies in rats, local toxicity was noted when high doses of paliperidone were administered by the oral and intravenous routes.

- **Other toxicity studies**

- Immunotoxicity

There is no indication of an effect of paliperidone on the functionality of the primary T-cell-dependent antibody response in the spleen, and the repeat-dose toxicity studies performed do not suggest any immunotoxicological properties. No signs of potential immunotoxicity were observed in the repeat-dose toxicity studies with risperidone previously conducted to support registration of Risperdal®.

- Impurities

R125239 (metabolite M12) is considered toxicologically qualified up to 0.62%, which is above the specification level of 0.5% for the active substance, and below the suggested specification for the medicinal product (0.80%).

- Photosafety

Paliperidone was tested for absorption of UV and visible light with wavelengths of 290 to 700 nm. A marginal absorption was seen at 290 nm (absorbance: 1.5) and it gradually declined with increasing wavelengths up to 320 nm. No absorption occurred at wavelengths exceeding 320 nm. The distribution of paliperidone derived radioactivity was extensive to the distinct melanin-rich structures, such as eye-pigment and pigmented parts of the skin and fur in pigmented rats. The retention was also extensive up to the last time point measured (336 h). Since paliperidone absorbs light at the wavelengths from 290 to 329 nm and reaches the eyes following systemic exposure, photosafety

concerns must be taken into account for paliperidone. In accordance to the CHMP/SWP/398/01 guideline "Note for guidance of photosafety testing", a photoxicity study was performed. Results showed that at the concentrations tested, paliperidone was not photoxic in this study. In addition, and in vitro photomutagenicity test will be submitted as a FUM.

Ecotoxicity/environmental risk assessment
The Applicant had initially submitted an Environmental Risk Assessment Report for paliperidone consisting of a number of aquatic ecotoxicity studies and Predicted Environmental Concentration (PEC) / PNEC calculations. From these data, it was concluded that paliperidone is not a PBT substance and that it is unlikely to represent a risk to the sewage micro-organisms. Additional PEC data were provided following the CHMP request; based on these new data no further studies were deemed necessary for the evaluation of the environmental impact of paliperidone.

Discussion on the non-clinical aspects
Paliperidone has been extensively tested to characterise its toxicological and toxicokinetic profiles. All pivotal studies constituting the toxicology program were conducted according to GLP standards. Since paliperidone is the major metabolite of risperidone, comparative repeat-dose toxicity studies with paliperidone and risperidone were carried out. In line with the scientific advice, no 12-month repeat-dose toxicity study in dogs or carcinogenicity studies in rats and mice were performed with paliperidone. These studies were bridged to studies previously conducted with risperidone in support of the marketing application for Risperdal®. Similar toxicity profiles were seen after administration of paliperidone and risperidone. No unexpected findings were noted after paliperidone treatment. Toxicity findings were numerous and included treatment-related sedation and (palpebral) ptosis (observed in repeat-dose toxicity studies in mice, rats, rabbits, and dogs). In carcinogenicity studies performed with risperidone in mice and rats, treatment related tumour findings were noted in the mammary gland, endocrine pancreas and in the pituitary gland. Changes in body weight, body weight gain and food consumption were also noted. Treatment related changes were seen in the red pulp of the spleen in paliperidone and risperidone treated rats and dogs, and QTc prolongation and testes effects were observed in dogs. In similarity to risperidone no genotoxic potential was observed. Paliperidone was not teratogenic in rat and rabbit, but showed embryotoxicity at a maternally toxic dose in rats. Since paliperidone absorbs light in the wavelength from 290 up 329 nm and reaches the eyes following systemic exposure, an in vitro phototoxicity test on paliperidone was performed. This test was found negative, and the Applicant provided acceptable justification for the lack of the additional photosafety studies required by the CPMP/SWP/398/01 guideline "Note for guidance of photosafety testing". However, the submission of an *in vitro* photomutagenicity test was requested as a Follow Up Measure. In addition, an ERA was initially submitted and, following the CHMP request, this was supplemented with an additional PEC value, recalculated using updated source data. Based on the ERA and the new data provided, no environmental testing was deemed necessary by the Applicant. This was considered acceptable by the CHMP.

4 Clinical aspects

Introduction
Paliperidone is a new active substance, belonging to the class of atypical antipsychotics, and is the active metabolite of a well-known active substance, risperidone. Risperidone is extensively metabolised to 9-hydroxy-risperidone (i.e. paliperidone) via CYP2D6 and the exposure after administration of risperidone is often presented in terms of "active moiety", which is the sum of risperidone and 9-hydroxy-risperidone plasma levels.
The product is available in strengths of 3 mg, 6 mg, 9 mg and 12 mg, and the proposed indication is "Treatment of schizophrenia".

Scientific advice for this product was given by the CHMP 2003 on the quality, preclinical and clinical development programmes (EMEA/CPMP/SAWG/3572/03). The CPMP stated that both pivotal short-term studies should be positive in order to obtain a marketing authorisation for the indications of treatment of schizophrenia and the prevention of recurrence of schizophrenic symptoms over the complete dosage regime (3, 6, 9, 12, 15 and 18 mg). Further on the CPMP also agreed on the choice of olanzapine as active comparator.

The applicant has performed an extensive clinical pharmacology program for PK and PD characterisation, comprising 15 clinical pharmacology and 13 biopharmaceutical studies in healthy volunteers, schizophrenic patients and special populations. In addition, population pharmacokinetic analyses and *in vitro* studies have been performed. IR formulations of paliperidone were used in the initial studies. Subsequently, the development was focused on ER formulations leading to the development of ER OROS paliperidone, the formulation used in Phase 3 efficacy studies. In the Phase 3 studies, sparse PK sampling was included and used for a population PK evaluation.

The Invega clinical program for treatment of schizophrenia consisted of three short-term phase III pivotal studies (SCH-303, SCH-304, and SCH-305) evaluating the efficacy and safety of fixed dosages of ER OROS Paliperidone, compared with placebo and the active comparator olanzapine, in schizophrenic adults. Across these studies, a total of 1982 subjects were screened, from which 1692 subjects were enrolled and randomised to double-blind treatment. A total of 972 subjects completed the studies. Subjects who completed the 6-week double-blind phase, or who discontinued due to lack of efficacy after a minimum of 21 days, were eligible to enter the 52-week open-label extension phase.
An additional phase III study (SCH-301) was performed to demonstrate the effectiveness of paliperidone in the prevention of recurrence of symptoms of schizophrenia. A total of 530 subjects were enrolled in the open-label (8 weeks) run-in phase (with flexible doses of paliperidone 3-15 mg), 312 (59%) subjects entered the open-label (6 weeks) stabilisation phase, and 207 (39%) subjects were randomized to double-blind treatment (placebo, n=102; ER OROS Paliperidone, n=105).
Finally, a Phase III short-term study (SCH-302) was performed on a total of 114 elderly (65 years of age or older) patients with schizophrenia in order to evaluate, compared with placebo, the safety and efficacy of flexibly dosed Invega administered once daily for 6 weeks.

The table below (table 5) gives an overview of the Phase III studies contributing to the efficacy profile of ER OROS Paliperidone.

Table 5.

Study ID	No. of study centres / locations	Design	Study Posology	Study Objective	Subjs by arm entered/ compl.	Duration	Gender M/F Median Age	Diagnosis Incl. criteria	Primary Endpoint
SCH-303	53 centers from 11 countries (Europe, India)	multicentre, randomised, double-blind, placebo- and active-controlled, parallel group, dose-response	paliperidone ER OROS - 6 mg/day - 9 mg/day - 12 mg day or olanzapine - 10 mg/day or placebo	to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER OROS (6, 9, 12 mg/day) compared with placebo in adults with schizophrenia	paliperidone ER OROS - 6 mg/day 123/80 - 9 mg/day 122/86 - 12 mg/day 130/101 olanzapine 128/90 placebo 127/58	6 weeks double-blind period	329 males/ 300 females 35 years	diagnosis of schizophrenia (DSM-IV criteria) for at least 1 year; active symptoms at enrollment and PANSS total score between 70 and 120	change in the PANSS total score
SCH-304	45 centers in the USA	multicentre, randomised, double-blind, placebo- and active-controlled, parallel group, dose-response	paliperidone ER OROS - 6 mg/day - 12 mg/day or olanzapine - 10 mg/day or placebo	to evaluate the efficacy and safety of 2 fixed dosages of paliperidone ER OROS (6 and 12 mg/day) compared with placebo in adults with schizophrenia	paliperidone ER OROS - 6 mg/day 112/51 - 12 mg/day 112/54 olanzapine 110/50 placebo 110/37	6 weeks double-blind period	325 males/ 114 females 43 years	diagnosis of schizophrenia (DSM-IV criteria) for at least 1 year; active symptoms at enrollment and PANSS total score between 70 and 120	change in the PANSS total score
SCH-305	74 centers from 14 countries (USA, Canada, Mexico, Eastern Europe, Israel, Asia, South Africa)	multicentre, randomised, double-blind, placebo- and active-controlled, parallel group, dose-response	paliperidone ER OROS - 3 mg/day - 9 mg/day - 15 mg/day or olanzapine - 10 mg/day or placebo	to evaluate the efficacy and safety of 3 fixed dosages of paliperidone ER OROS (3, 9, 15 mg/day) compared with placebo in adults with schizophrenia	paliperidone ER OROS - 3 mg/day 127/70 - 9 mg/day 125/78 - 15 mg/day 115/82 olanzapine 128/88 placebo 123/47	6 weeks double-blind period	417 males/ 197 females 36 years	diagnosis of schizophrenia (DSM-IV criteria) for at least 1 year; active symptoms at enrollment and PANSS total score between 70 and 120	change in the PANSS total score
SCH-302	21 centers from 6 countries (Europe, South Africa)	multicentre, randomised, double-blind, placebo-controlled	paliperidone ER OROS (first week 6 mg/day, thereafter 3 to 12 mg/day depending on tolerability) or placebo	to evaluate the safety and efficacy of flexibly dosed paliperidone ER OROS (3, 6, 9, or 12 mg/day) compared with placebo in geriatric subjects with schizophrenia	paliperidone ER OROS flexible dosing (3, 6, 9, 12 mg/day) 76/64 placebo 38/26	6 weeks double-blind period	31 males/ 83 females 68 years	diagnosis of schizophrenia (DSM-IV criteria) for at least 1 year; age 65 years or older; active symptoms at enrollment and PANSS total score between 70 and 120	safety and efficacy of flexibly dosed paliperidone ER OROS (3, 6, 9, or 12 mg/day) compared with placebo in geriatric subjects with schizophrenia
SCH-301	41 centers from 6 countries (Europe, USA, India)	multicentre, randomised, double-blind, placebo-controlled	paliperidone ER OROS flexible dosing (3 to 15 mg/day) or placebo	to evaluate the efficacy of paliperidone ER OROS compared with placebo in the prevention of recurrence of symptoms of schizophrenia	run-in: 530/347; stabilisation: 312/263; double-blind phase: - paliperidone ER OROS 105/85 - placebo 102/94	8 weeks open-label (OL) run-in; 6 weeks OL stabilisation; double-blind phase of variable duration; flexible dosing in all phases	362 males 168 females 38 years	diagnosis of schizophrenia (DSM-IV criteria) for at least 1 year; active symptoms at enrollment and PANSS total score between 70 and 120	time to the first recurrence event in the double-blind phase

GCP

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

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

Pharmacokinetics

The main objectives of the biopharmaceutics studies with paliperidone were to investigate absolute and relative bioavailability, characterize prolonged release properties, evaluate dose proportionality, and explore the effect of food on the PK of ER OROS paliperidone. The biopharmaceutics studies were mainly (in particular all phase 1 key studies) conducted in healthy subjects. Each of the studies was designed and conducted in accordance with the CPMP guidelines concerning bioavailability and bioequivalence (bridging study) and evaluation of food effect.
Overall 28 Phase 1 and 2a studies were performed including also data from different formulations. Data from 4 key Phase 1 studies (R076477-P01-1008, PALIOROS-P01-1012, R076477-P01-1010 and R076477-P01-1007) provide information on the biopharmaceutical characteristics of paliperidone.

- **Methods**

Analytical methods
In the key studies, analyses of paliperidone (and risperidone, when necessary) were conducted using validated liquid chromatography-tandem mass spectrometry (LC-MS/MS) assays. The LC-MS/MS assay quantifies paliperidone and risperidone individually. If needed, plasma concentrations of the active moiety can be calculated as the sum of the corresponding plasma risperidone and paliperidone concentrations. The analytical methods used showed a satisfactory performance.

Pharmacokinetic data analysis
Non-compartmental methods were used in most studies, mainly by the use of WinNonlin. A compartmental analysis was performed on the i.v. data obtained in Study R076477-P01-1007. An *in vitro-in vivo* correlation (IVIC) was performed using a population approach (NONMEM). A population pharmacokinetic analysis on Phase 1 and Phase 3 data was performed using NONMEM.
AUC was estimated from the time of dosing (t=0) to the time of the last assayed sample. Thereafter AUC estimated was extrapolated from the time of the last assayed sample to infinity. The estimated part never exceeded 20%.
The peak plasma concentration was taken as the concentration in the plasma sample with the highest concentration. $t_{1/2}$ was calculated as the terminal slope of the semilogarithmic drug concentration-time curve.

Statistical analysis
Pharmacokinetic parameters of paliperidone were determined from plasma concentration-time profiles. Statistical analyses were performed using the SAS Statistical Analysis System program in two of the key studies to compare treatments by analysis of variance (ANOVA).

- **Absorption**

The ER OROS tablets have been designed to deliver paliperidone over a 24-hour period. Paliperidone showed some preference for the secretory direction, and the efflux ratio (secretory/absorptive P_{app}) decreased with increasing concentration, indicating involvement of an efflux transporter, e.g. P-gp. When apical pH increased from 6.0 to 8.0, there was a gradual increase in absorptive permeation. P-gp inhibitors (quinidine, verapamil, imipramine) had a limited effect on the transport of paliperidone, with increased absorptive and decreased secretory transport, while inhibitors of other transporters had no effect. Paliperidone inhibited ^{3}H-taxol transport to some extent at the highest concentration tested (100 μM) from an excretion ratio of 18 to 10. The positive control verapamil gave an excretion ratio of 3. Since paliperidone has an absolute bioavailability of more than 90% after administration as an oral solution (Study R076477-P01-1007, see below) and results of the *in vitro* Caco-2 study support that paliperidone can be classified as a highly permeable compound, paliperidone meets the criteria of a Class 2 compound (low solubility, high permeability) in the Biopharmaceutical Classification System.

- Bioavailability

The absolute bioavailability is 28% for the ER OROS formulation and is 106% (complete) for the oral solution. The lower bioavailability for the ER OROS formulation is probably due to a higher fraction of paliperidone released in the colon, where the absorption is lower.

The median T_{max} for an oral solution occurs at 1.5 hours, whereas the median T_{max} of the ER OROS tablet observed in various studies is in the range of 20-25 hours, clearly indicating the extended release characteristics of the formulation. The half-life was similar for all formulations, indicating no absorption-rate limitation in the PK of ER OROS paliperidone. No difference in T_{max} is observed for different doses.

Bioequivalence

Mean PK parameter estimates of the several formulations used across the clinical development of Invega are presented in Table 6. PK parameters were studied only for the 15 mg strength, and for this strength bioequivalence between the different formulations used across the clinical studies has been demonstrated.

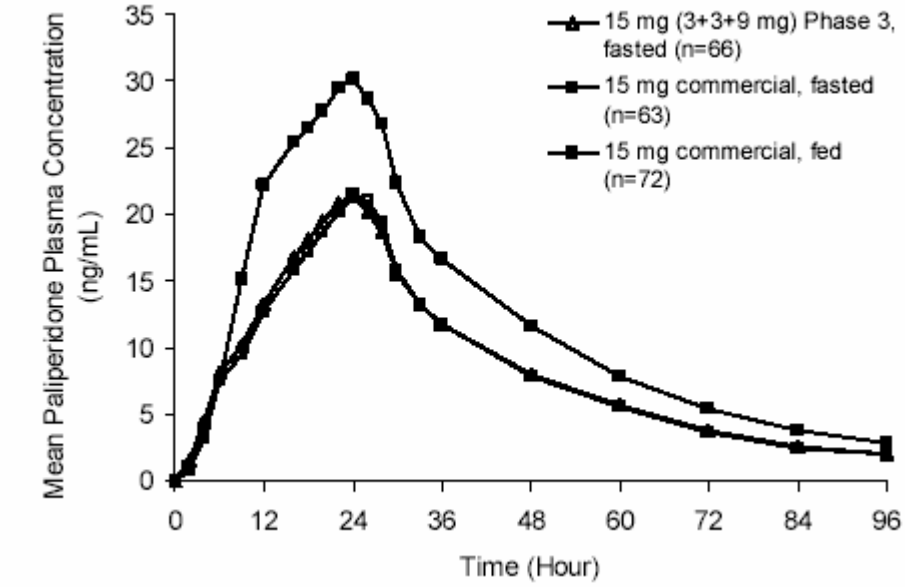

Figure 1: Mean Paliperidone Plasma Concentration-Time Profiles After Single-Dose Administration of ER OROS Commercial (Fasted and Fed) and ER OROS Phase 3 (Fasted) Formulations (Study R076477-P01-1008)

Table 6: Paliperidone PK Parameters (Mean ± SD) After Single-Dose Administration of Invega Commercial (Fed and Fasted) and Phase 3 Tablets (Study R076477-P01-1008)

Parameter	15 mg ER OROS Phase 3 (Fasted) (MV0301019, MV0301025) (n=66)	15 mg ER OROS Commercial (Fasted) (0406659) (n=63)	15 mg ER OROS Commercial (Fed) (0406659) (n=72)	Commercial/ Phase 3 Ratio, % (90%CI) (n=58)	Commercial Fed / Fasted Ratio,% (90%CI) (n=58)
C_{max}, ng/mL	22.1 ± 8.16	22.8 ± 9.84	32.1 ± 15.6 [a]	100.68 (91.62-110.63)	142.26 (129.41-156.39)
AUC_{last}, ng.h/mL	815 ± 294	799 ± 320	1162 ± 533 [b]	96.10 (88.42-104.46)	145.62 (133.92-158.33)
AUC_{∞}, ng.h/mL	886 ± 329	867 ± 349	1262 ± 598 [c]	96.00 (88.21-104.48) [d]	145.78 % (133.91-158.68) [d]
t_{max}, h	22.1 (16.0-28.1)	24.0 (12.0-28.0)	22.0 (12.0-33.5) [a]		
$t_{1/2}$, h	22.9 ± 3.6	22.7 ± 3.8	23.0 ± 3.4 [c]		

t_{max}: median (range); [a] n=71; [b] n= 70; [c] n=69; [d] n=57.

Under fasted conditions, the ER OROS commercial formulation was bioequivalent to the ER OROS Phase 3 formulation at the 15 mg dose, based on the CIs for the ratio commercial tablet/Phase 3 tablet for C_{max}, AUC_{last} and $AUC_{0-\infty}$. Food increased the systemic exposure of paliperidone administered as ER OROS commercial tablet by approximately 45%.

Bioequivalence has been demonstrated between the commercial formulation and the Phase 3 formulation, although not using the same tablet strengths. The bioequivalence was established for the strength of 15 mg, while in the MAA, the highest strength applied for is 12 mg and not 15 mg. In the Phase 3 studies, tablets strengths of 3 and 9 mg were used and therefore the approach to use different strengths is acceptable. The different strengths are of the same tablet size and dose proportionality is demonstrated over the dose range 3-15 mg. Based on this, it is considered that bioequivalence between the Phase 3 and the commercial formulation has been sufficiently established. Considering the minor difference of formulation and the fact that dose linearity has been established over all strengths with the commercial product (except for 3 mg) this proceeding is deemed tolerable.

- Food interaction

The effect of concomitant food intake on the pharmacokinetics of paliperidone has been evaluated in four pilot studies, using early formulations, and in two pivotal studies, in which the commercial ER OROS tablets were used.

Table 7: The Effect of Food on PK Parameters of Paliperidone From Different Formulations (Studies R076477-BEL-1; R076477-P01-1006; R076477-P01-1008; PALIOROS-P01-1012;C-2002-034, C-2004-006).

Dose/Formulation	N[a]	Restrictions	Type of meal	Parameter	%CV fed	%CV fasted	Fed/Fasted Ratio (%) (90%CI)	Study Number
Pilot Studies								
0.5 mg IR tablet	12	no restrictions	standard breakfast	C_{max} AUC_{∞}	28 27	24 25	93 (83-105) 97 (88-107)	R076477-BEL-1
4 mg (2+2 mg) SLOW OROS tablet	27	remain in bed until 4h after dosing	high-fat breakfast	C_{max} AUC_{∞}	61 54	53 50	115 (93-143) 111 (89-139)	C-2002-034
3 mg ER OROS Phase 3 tablet	18	remain in bed until 4h after dosing	standard Japanese breakfast	C_{max} AUC_{∞}	84 83	59 60	136 (100-184) 137 (104-180)	R076477-P01-1006
15 mg (9+3+3 mg) ER OROS Phase 3 tablet	19	sitting or supine for 48h after dosing	high-fat breakfast	C_{max} AUC_{48h}	46 45	32 32	90 (73-110) [b] 92 (74-115) [b]	C-2004-006
Key Food Effect Studies								
15 mg ER OROS commercial tablet	58	supine (i.e., remain in bed until 36h after dosing	high-fat breakfast	C_{max} AUC_{∞}	48 47	43 40	142 (129-156) 146 (134-159)	R076477-P01-1008
12 mg ER OROS commercial tablet	57	ambulant	high-fat breakfast	C_{max} AUC_{∞}	54 51	42 45	160 (144-177) 154 (139-170)	PALIOROS-P01-1012

[a] number of subjects used in inferential statistics
[b] pilot study with sequential study design and limited PK sampling; n = 57
C_{max} in ng/mL; AUC in ng.h/mL
CV = coefficient of variation

Food (standard breakfast) does not affect the pharmacokinetics of paliperidone when administered as an IR tablet. However, an increased exposure is observed with the ER OROS formulation, which is likely to be a formulation effect and not a substance effect. In all studies except one (C-2004-006), food increased the exposure to paliperidone up to 50-60%. Food also increases the variability in C_{max} and $AUC_{0-\infty}$ whereas the T_{max} and the half-life are not altered to a large extent. The observed food effect was likely to be due to a delay in the transit of the ER OROS formulation in the upper part of the GI tract, resulting in increased absorption.

During the evaluation the CHMP was concerned because in the key phase 3 studies paliperidone was administered in the morning, without specific recommendations of administration in relation to food intake. Considering the large increase in exposure and the relatively steep concentration vs. effect relationship for EPS, the CHMP recommended to standardise the administration of paliperidone ER OROS in relation to food intake, in order to reduce variability and avoid unnecessarily high exposures. This recommendation was then introduced in the SPC.

Other factors (e.g. increased GI motility caused by e.g. diarrhoea or certain diets (e.g. vegetarians) or certain medicinal product) potentially affecting the absorption from the ER OROS tablets have been discussed and appropriate information has been included in the SPC.

- **Distribution**

Paliperidone was rapidly distributed into tissues, with a volume of distribution of 487 L (based on population PK modelling). Paliperidone distributed well into the brain, as evidenced by displacement of 11C-racloprine measured using PET imaging in healthy subjects. Within therapeutically relevant concentrations of 50 to 250 ng/mL, the plasma protein binding was 74% for paliperidone, 82% for (+)-paliperidone and 65% for (-)-paliperidone, and was not influenced by sex, age, or renal function. Paliperidone and its enantiomers were predominately bound to α1-acid glycoprotein and albumin. In patients with moderate hepatic impairment, plasma protein binding was reduced, mainly because of a reduction in α1-acid glycoprotein and albumin plasma concentrations.

- **Elimination**

The plasma clearance of paliperidone (about 80 ml/min) is low relative to hepatic plasma flow (about 700 ml/min), and therefore paliperidone can be considered as a drug with a low hepatic extraction ratio. The half-life of paliperidone is 20-25 hours and is independent of dose, route of administration and formulation, indicating no absorption-rate limitation in the pharmacokinetics of ER OROS paliperidone.

- Excretion

Paliperidone was mainly excreted in urine (80% of a radiolabelled dose), while only a small part was excreted in faeces (11%). Almost 60% of the dose was excreted as unchanged drug in urine. Renal clearance of unchanged paliperidone was on average 53 ml/min. About 50% of the renal clearance of unchanged paliperidone was by means of filtration (average CL_{GFR}: 25.9 ml/min), the other half occurred by active processes (average CL_{act}: 27.2 ml/min).

- Metabolism

Paliperidone is not metabolised to a large extent. Almost 60% of the dose was identified as unchanged paliperidone in urine. Four metabolites were identified in urine, each of which accounted for up to a maximum of 6.5% of the dose, while 7% of the urinary radioactivity remained unidentified. Two small metabolites were identified in faeces.
Metabolite profiling was not possible in plasma, due to low radioactivity levels. Based on the AUC_{0-24h} values, unchanged paliperidone represented approximately 97% of the total radioactivity in plasma and therefore the lack of information regarding metabolites in plasma may be accepted.
In vitro results also indicate limited metabolism, with some involvement of CYP2D6 and CYP3A4: paliperidone is metabolised to some extent by CYP2D6 and mean C_{max} and AUC values for poor metabolisers (PMs) are somewhat higher compared with extensive metabolisers (EMs), but with overlapping individual values. Special dose recommendations or precautions are not warranted for patients who are CYP2D6 PMs.

- Inter-conversion

In vivo interconversion between the (+)-enantiomer and the (-)-enantiomer is comparable (about 40%) in both directions after oral administration of the separate enantiomers. Since the pharmacological profiles of the racemate and the 2 enantiomers are qualitatively and quantitatively similar, and pronounced racemization occurs *in vitro* with a constant enantiomeric ratio, the applicant decided to develop the racemate. The CHMP considered this acceptable.

- Comparisons with IR risperidone

After administration of both paliperidone and risperidone as IR dosage forms, the exposure to paliperidone vs. active moiety was similar, while administration of paliperidone in the ER OROS dosage form results in a lower bioavailability, lower C_{max} and AUC compared with IR paliperidone.
From a safety perspective, it can be concluded that the exposure to paliperidone is lower with administration of paliperidone ER OROS at the normal and highest recommended doses compared with administration of IR risperidone at recommended dose levels. Thus, extrapolations of safety data can be made from the previous, extensive use of IR risperidone.

- Pharmacokinetics of metabolites

Paliperidone is mainly excreted unchanged, consequently the PK of metabolites is deemed negligible.

- Consequences of possible genetic polymorphism

Many subjects in the Phase 1 studies underwent cytochrome P450 genotyping to assess the potential impact of genetic polymorphisms on the pharmacokinetics of paliperidone and its enantiomers. In general, the noncompartmental PK parameters of paliperidone for poor metabolizers (PMs) of the CYP2D6 substrate were within the range of values obtained for extensive metabolizers (EMs). Results of a population analysis using data from Phase 1 and Phase 3 studies confirmed that genetic polymorphism for the CYP2D6 isozyme had no discernable impact on the systemic clearance of paliperidone, therefore special dose recommendations or precautions are not warranted for patients who are CYP2D6 PMs.

- **Dose proportionality and time dependencies**

Dose proportionality at the dose levels 3 mg (Phase 3 ER OROS paliperidone tablet, F016), 6 mg, 9 mg, 12 mg and 15 mg (commercial Invega tablets, F047, F048, F049 and F050) was evaluated in Study R076477-P01-1010. This was an open-label, randomized, 5-treatment 5-period crossover study in healthy males. Fifty subjects received study medication and 45 completed all treatments.

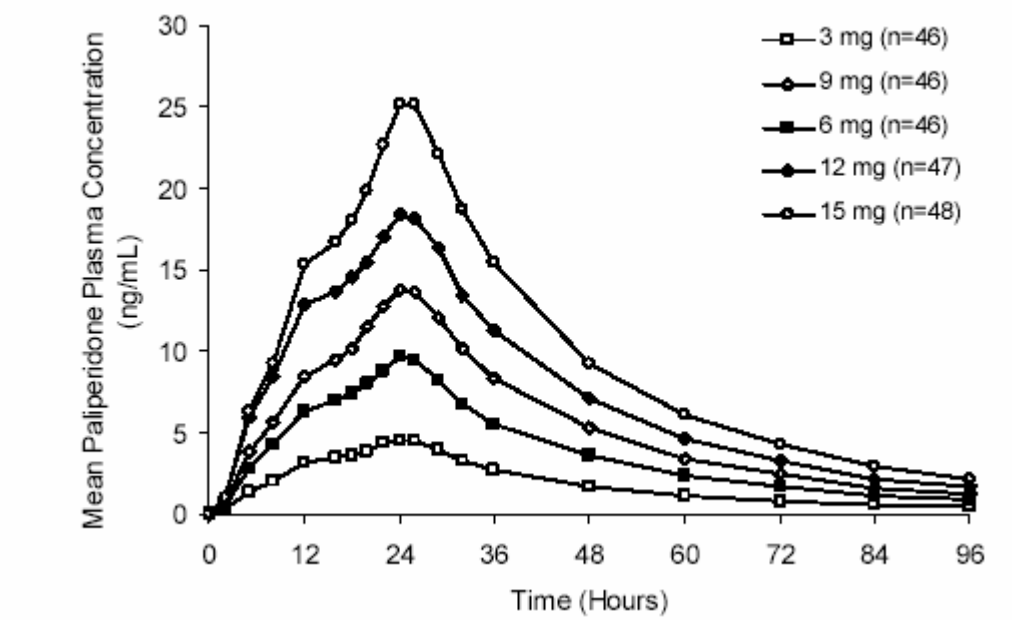

Figure 2: Mean Paliperidone Plasma Concentration-Time Profiles After Single-Dose Administration of ER OROS Paliperidone Tablet (3-15 mg)

Table 8: Paliperidone Plasma PK Parameters (Mean ± SD) After Single-Dose Administration of ER OROS Paliperidone Tablet. (Study R076477-P01-1010).

Parameter	3 mg [a] (MV0301019) (n=46)	6 mg (0406837) (n=46)	9 mg (0406836) (n=46)	12 mg (0406838) (n=47)	15 mg (0406659) (n=48)
C_{max}, ng/mL	4.85 ± 2.16	10.2 ± 3.90	14.8 ± 6.90	19.6 ± 8.01	26.6 ± 11.8
AUC_{last}, ng.h/mL	176 ± 76.2	368 ± 146	525 ± 243	720 ± 327	938 ± 410
AUC_{∞}, ng.h/mL	192 ± 85.0	401 ± 167	567 ± 269	778 ± 370	1014 ± 454
t_{max}, h	24.0 (12.0-29.0)	24.0 (12.0-29.0)	24.0 (8.0-32.0)	24.0 (12.0-29.0)	24.0 (12.0-29.1)
$t_{1/2}$, h	23.5 ± 5.2	23.4 ± 4.5	22.0 ± 3.4	22.1 ± 4.5	22.3 ± 4.4
DN C_{max}, ng/mL	24.3 ± 10.8	25.4 ± 9.74	24.6 ± 11.5	24.5 ± 10.0	26.6 ± 11.8
DN AUC_{last}, ng.h/mL	882 ± 381	919 ± 366	875 ± 404	901 ± 409	938 ± 410
DN AUC_{∞}, ng.h/mL	962 ± 425	1003 ± 418	945 ± 448	973 ± 463	1014 ± 454

[a] 3 mg Phase 3 ER OROS Phase 3 tablet; t_{max}: median (range); DN: dose-normalized to 15 mg.

Linear regression analysis of C_{max}, AUC_{last}, and $AUC_{0-\infty}$ over all dose levels (parameters dose-normalised to 15 mg) demonstrated dose-proportionality. Dose-proportionality was confirmed for 3, 6, 9, 12 and 15 mg ER OROS paliperidone tablets based on the pair-wise comparisons with respect to C_{max}, AUC_{last} and $AUC_{0-\infty}$. All 90%CI of the pair-wise comparisons are within the 80-125%. Thus, the 3, 6, 9, 12 and 15 mg tablets are bioequivalent after dose-normalisation.
Median t_{max} was approximately 24 hours for all dose levels, indicating that the prolonged release properties of the commercial Invega tablet were independent of tablet strength. The elimination half-life was approximately 23 hours and independent of tablet strength.

The steady state PK of paliperidone has been investigated in schizophrenic patients and the studies and the results are described in the section "Pharmacokinetics in target population" below. Steady state has generally been reached within 3-6 days of once daily dosing in the multiple dose studies. An accumulation ratio of 3.8 was estimated in Study PAL-SCH-101 based on AUC_{0-24h} values Days 1 and 6. No comparison of $AUC_{0-\infty}$ after a single dose vs. $AUC_{\tau ss}$ was available. In Phase 3 studies, the plasma concentrations after weeks 2 and 5 respectively were similar and indicated no accumulation of paliperidone over time. No differences in plasma concentrations between the predose (24 hours after drug intake, i.e. near-peak concentrations), 1 to 2 hours postdose and more than 4 hours postdose samples were observed for all visits and all dosing groups. Thus, a low peak to trough variation was observed with ER OROS paliperidone.

- Intra- and Inter-individual variability

The inter-individual variability in PK parameters for the ER OROS formulation (C_{max} and AUC values) is moderate to high (40-50%) with a somewhat increased variability with concomitant food intake. No data on intra-individual variability have been presented.

- **Pharmacokinetics in target population**

PK phase 1 studies revealed a delayed C_{max} at 24 h for paliperidone extended release tablets, which is in line with its *in vitro* characteristics. The terminal half-life has been found of approximately 23 hours on average. To benefit from the 24-hour release profile of ER OROS paliperidone, morning dosing is recommended, and all studies in the clinical development program for this product were consistent with this recommendation.
Steady-state paliperidone concentrations were attained within 4 to 5 days of dosing with ER OROS paliperidone in most subjects. The fluctuation index (peak-to-trough fluctuation) observed with once daily administration of ER OROS paliperidone (38% to 52%) is much lower than with risperidone, dosed once daily (125%) or twice daily (74%).
The low peak-to-trough fluctuation observed with ER OROS paliperidone in the Phase 1 studies was confirmed by data from the Phase 3, 6-week double-blind studies (SCH-302, SCH-303, SCH-304, and SCH-305). In these studies, there were no apparent differences in paliperidone plasma concentrations between predose (i.e., 24 hours after drug intake; equivalent to near-peak concentrations), 1 to 2 hours postdose, and more than 4 hours postdose values. Furthermore, plasma drug concentrations measured after 2 and 5 weeks of fixed dose paliperidone administration were consistent over time, indicating that no further accumulation of paliperidone occurred.

- Population pharmacokinetics

A population PK analysis was performed with the primary objectives to model the PK of paliperidone after oral administration of ER OROS formulation and to estimate the basic PK parameters in healthy subjects and patients; to quantify variability of the PK parameters and to evaluate the impact of patient and other covariates as potential sources of PK variability of paliperidone.
A single CL/F parameter described elimination of paliperidone by all routes, including renal and non-renal pathways. The typical total apparent CL amounted 13.8 l/h (230 ml/min) with a between-subject variability estimated to 52%. In the co-variate analysis, lean body mass (LBM) and CL_{CR} explained the intersubject variability in CL to a statistically significant extent in schizophrenic and schizoaffective patients. Thus, subjects with the lowest LBM and lowest creatinine clearance levels were predicted to exhibit the highest paliperidone exposure. None of the other covariates could explain the intersubject variability in any of the PK parameters to a statistically significant extent. Initially, the covariate effects were only explored graphically and an additional covariate analysis was performed, as requested by the CHMP, to confirm the results from the graphical analysis.

- **Special populations**

Renal impairment
The effect of renal impairment was investigated in a single dose study in subjects with varying degrees of renal impairment (mild, moderate, and severe) as compared with subjects with normal renal function. Since no subjects with CL_{CR} below 10 ml/min have been studied it is suggested to limit the use of paliperidone to patients with a CL_{CR} above 10 ml/min. The exposure to paliperidone is increased on average 2.1-3.4-fold [2.1 (C_{max}) and 3.4 (AUC_{inf})-fold in patients with severe renal impairment compared with healthy subjects and the mean half-life is increased to over 50 hours. In the SPC initially proposed by the Applicant a daily dose of 6 mg was recommended for patients with mild renal impairment (creatinine CL 50-80 ml/min) and a daily dose of 3 mg was recommended in moderate to severe renal impairment (creatinine CL <50 ml/min).
The CHMP suggested that a lower dose in patients with severe renal impairment compared with patients with moderate renal impairment could be more appropriate than the proposed recommendation. To further establish the doses to be recommended in patients with renal impairment, the Applicant used modelling and simulation for prediction of the exposure to paliperidone at steady state with different dosing schedules. The population PK model was used, but the results were inconsistent with results from the Phase I study in renal impairment, since no difference in exposure between severe and moderate renal impairment was detected in this analysis. The CHMP requested to perform a reanalysis, based on the Phase I results. Additional nonparametric superposition and compartmental PK analysis at the defined cut-offs points of CLcr values of 10, 29 (severe), 30, 49 (moderate), 50, 79 (mild), 80 and 120 (normal) mL/min were performed. According to the Sponsor, these analyses supported the dose regime initially proposed (3 mg once-a-day in severe and moderate renal impairment and 6 mg once-a-day in mild renal impairment). The CHMP view was that, based on simulations of steady state plasma levels, the exposure with the proposed doses was predicted to be higher in patients with severe and mild renal impairment compared to patients with normal renal function. The following dose recommendations were therefore applied and included in the final SPC: a dose of 3 mg every other day (with the possibility to increase the dose to 3 mg/day) for patients with severe renal impairment, and a single daily dose of 3 mg for patients with moderate or mild renal impairment, with a possibility to increase the dose to 6 mg once daily in patients with mild renal impairment.

Hepatic impairment
Based on total plasma levels, the exposure to paliperidone was decreased in patients with moderate hepatic impairment (Child Pugh class B) compared with healthy subjects. However, the protein levels were lower and the unbound fraction higher in the hepatically impaired group and the unbound exposure was similar in both groups. As severe hepatic impairment has not been studied, caution should be recommended in such patients. No dose adjustment is required in patients with mild or moderate hepatic impairment. This information has been included in the SPC.

Other special populations
Females had lower CL of paliperidone compared with males, but after correction for body weight and plasma protein binding, the unbound CL was comparable between men and women.

In the population PK analysis, no effect of gender, race or smoking status was observed.

Elderly
Study PALIOROS-SCH-1011
The PK of ER OROS paliperidone have been explored in a specific PK study (PALIOROS-SCH-1011) including healthy young (18-45 years) and elderly (>65 years) subjects. Exposure was examined after both single and multiple dose administration of 3 mg ER OROS paliperidone. The 3 mg dose level was used to ensure safety.
Steady-state pharmacokinetics in this study were predictable from single dose data, indicating linear and time independent pharmacokinetics in the elderly. Elderly subjects had a 20-25% lower clearance as compared to young subjects, resulting in higher C_{max}, longer half-life and larger AUC. The modest increase in paliperidone concentration in elderly subjects indicate that no dosage adjustment is needed for ER OROS paliperidone in elderly subjects, and dose adjustments solely on the basis of age have not been recommended in the SPC. However, apparent plasma clearance, renal clearance and apparent non-renal clearance were affected. Within renal clearance, most of the difference with the young subject group after single dosing was accounted for by a decrease in glomerular filtration for the subjects aged from 65 to 74 years, and to both a decrease in active renal clearance and in glomerular filtration in subjects aged ≥75 years. Results for each enantiomer were similar to results for the racemate except that the differences in PK parameters between young and elderly subjects were larger for R078543 than for R078544. As a consequence, because elderly patients may have diminished renal function, dose adjustments may be required according to their renal function status and doses should be reduced in elderly patients with a creatinine clearance of <50 mL/min.

Study R076477-SCH-302
This was a double blind, randomised, placebo controlled, parallel group study that evaluated the safety and tolerability of flexible doses of ER OROS paliperidone (3 to 12 mg/day) in geriatric subjects with schizophrenia (>65 years of age). Blood samples to measure paliperidone plasma concentrations were collected at limited time points at Visits 6 and 9 (weeks 2 and 5, respectively) of the double blind treatment phase (predose, 1 to 2 hours after dosing, and at least 4 hours post dosing). There were no notable differences in dose-normalised plasma concentrations for the different age groups, although the number of subjects in the older age groups was rather small for definite conclusions. The correlation of paliperidone plasma concentrations with safety parameters (EPS rating scales: AIMS, BARS and SAS, and cardiovascular safety parameters: QTcLD) was explored graphically. There was no apparent relationship between plasma concentration and any of the EPS and cardiovascular safety parameters or their respective shifts from baseline.

Children
No pharmacokinetic data for paliperidone have been presented in children and the product is not intended for use in patients aged below 18 years and this is reflected in the SPC.

- **Pharmacokinetic interaction studies**

Two *in vitro* metabolism studies and two *in vivo* interaction studies (with trimethoprim and paroxetine) have been submitted. On the basis of the *in vitro* results, no *in vivo* studies addressing metabolic interactions were considered necessary. No induction studies have been performed *in vitro* or *in vivo* and were not deemed necessary.

- ***In vitro***

Two *in vitro* studies in human liver microsomes showed that paliperidone does not substantially inhibit the metabolism of drugs metabolized by CYP isozymes, including CYP1A2, CYP2A6, CYP2C8/9/10, CYP2D6, CYP2E1, CYP3A4 and CYP3A5. Therefore, paliperidone is not expected to inhibit clearance of drugs that are metabolized by these metabolic pathways in a clinically relevant manner. The effect of paliperidone on induction of metabolic enzymes has not been investigated. In line with observations in clinical studies where paliperidone displayed time-independent pharmacokinetics, paliperidone is not expected to cause enzyme induction or inhibition. As such, paliperidone is not expected to inhibit P-glycoprotein-(P-gp)-mediated transport of other drugs in a

clinically meaningful manner. An *in vitro* study showed that paliperidone may be a substrate and a weak inhibitor of P-gp. No *in vivo* studies have been performed and the clinical relevance is unknown.

Paliperidone binds primarily to α1-acid glycoprotein and albumin. *In vitro*, high therapeutic concentrations of diazepam (3 μg/mL), sulfamethazine (100 μg/mL), warfarin (10 μg/mL) and carbamazepine (10 μg/mL) (all bound to albumin) caused a slight, though statistically significant increase in the free fraction of paliperidone (at 50 ng/mL), with a maximum increase of 12% (by carbamazepine, from 22.9 to 25.7%). Based upon these data, drug interaction at the level of protein binding is considered unlikely.

- ***In vivo***

The main elimination route of paliperidone is renal excretion and about half of this is through active secretion in the renal tubule. Only one *in vivo* interaction study was performed with paliperidone, addressing the potential interaction with trimethoprim on the renal, secretory level. Trimethoprim, which was chosen due to its inhibitory effect on the organic cation transporter, had only small effects on the PK of paliperidone, e.g. an increase in C_{max} and decreased AUC of total paliperidone, and unbound CL/F and AUC were not different. In the Caco-2 study described above, trimethoprim had no effect on the transport of paliperidone either. Furthermore, there was no indication that paliperidone affected the PK of trimethoprim at steady state, and a drug interaction at the level of renal secretion is considered unlikely.
In the Day 120 response, a new interaction study with paroxetine was included. Multiple dosing with paroxetine caused increases in C_{max} and AUC of a single dose of paliperidone by 10-15%. This increase is not considered clinically relevant.
In a published study, the effect of the P-gp inhibitor verapamil on the PK of risperidone was evaluated in Japanese subjects, and the exposure to risperidone and paliperidone increased 61% and 30%, respectively, while the half-lives were not affected. Effects of P-gp inhibitors directly on paliperidone are difficult to predict based on these data.
Following the CHMP request, the Applicant has discussed the potential for P-gp inhibitors to affect paliperidone. Results from in vitro data suggest that the potential for interactions may be low, but firm conclusions are difficult to make in the absence of human in vivo data. As a result, following the CHMP request, the potential for an interaction has been addressed in the SPC.
Results from a population PK analysis showed that concomitant administration of drugs with P-gp inducing/inhibiting properties during Phase 3 efficacy and safety studies had no significant impact on systemic exposure to paliperidone.
Derived by the presented PK data no severe interactions can be anticipated for paliperidone with other drugs. However, due to the limitations of the analysis described above, no definite conclusions can be drawn.

Pharmacodynamics

- Mechanism of action

Paliperidone is a monoaminergic antagonist with a high affinity for serotoninergic (5-hydroxytryptamine [5-HT] type 2A [$5HT_{2A}$]) and dopaminergic D_2 receptors. Paliperidone binds also to α_1-adrenergic receptors, and, with lower affinity, to H_1-histaminergic and α_2-adrenergic receptors. It has no affinity for cholinergic, muscarinic, or β_1- and β_2-adrenergic receptors.

- Primary and Secondary pharmacology

Paliperidone is the main metabolite of risperidone and its pharmacological profile is very similar to that of risperidone. No essential new pharmacodynamics effects are expected.

Effects on sleep/wake cycle
Results of a multicenter, randomized, double-blind, placebo-controlled, fixed dose, 2-week polysomnography study of ER OROS paliperidone 9 mg once daily in subjects with schizophrenia-related insomnia indicated that treatment was associated with a statistically significant improvement in sleep architecture and sleep continuity. Specifically, among subjects treated with ER OROS paliperidone, the following mean improvements relative to placebo were observed: reduced latency to persistent sleep of 41.0 minutes, decreased sleep onset latency by 35.2 minutes, decreased number of awakenings after sleep onset by 7.0 events, increased total sleep time by 52.8 minutes, increased sleep

period time by 41.7 minutes, and increased sleep efficiency index by 11%. Treatment with ER OROS paliperidone was also associated with a statistically significant decrease (relative to placebo) in Stage 1 sleep of 11.9 minutes and increase in Stage 2 Sleep of 50.7 minutes. No clinically relevant effect on REM sleep was observed.

- **Secondary pharmacology**

Orthostatic hypotension

One of the reasons for developing an ER formulation was to allow treatment initiation with an efficacious dose without having to start at a lower dose in order to reduce the possibility of orthostatic side effects. Reduction of the occurrence of orthostatic hypotension at the start of therapy was the outcome used in the selection of the most desirable extended release profile. However, there was no clear apparent relationship between the paliperidone plasma concentrations and the change in orthostatic systolic blood pressure in study PAL-SCH-101 based on a non-inferiority comparison.

Prolactin

Serum prolactin concentrations have been evaluated. After single or multiple dose administration of IR paliperidone in healthy subjects and subjects with schizophrenia, prolactin concentrations increased and peaked approximately 1-2 hour after dosing and decreased thereafter. An ascending plasma profile, due to extended release, resulted in lower prolactin C_{max} and AUC as compared to a lower dose of IR paliperidone or risperidone (Studies C-2001-039 and C-2002-019).

Effect on QT/QTc

The effect of paliperidone on cardiovascular safety, particularly on QT/QTc prolongation, was assessed in a thorough cardiovascular safety Study (R076477-SCH-1009; see table below). The PK/PD analysis suggests that effects of paliperidone on QTcLD are complex and cannot be explained by plasma concentrations only. Although plasma concentrations measured around C_{max} coincide with the maximum effect on QTcLD change baseline, the PK/PD relationship seems to be more complex.

Table 9: Day-Averaged QTcLD: Least Square Mean Differences From Day 1 (Study R076477-SCH-1009: Pharmacodynamic Analysis Set)

Treatment Arm	Visit	Treatment Group	LSMean (SE)	LSMean Difference (SE)	90% CI on LSMean Difference[a,b]
IR Paliperidone (N=44)	Day 1	Placebo	387.6 (2.22)		
	Day 2	4 mg IR q.d.	390.6 (2.23)	3.0 (1.10)	(1.18; 4.79)
	Day 3	6 mg IR q.d.	388.1 (2.22)	0.6 (1.09)	(-1.23; 2.36)
	Day 4	8 mg IR q.d.	390.5 (2.23)	2.9 (1.10)	(1.13; 4.75)
	Day 8	8 mg IR q.d.	393.0 (2.22)	5.5 (1.09)	(3.66; 7.25)
	Day 9	Posttreatment	390.5 (2.22)	3.0 (1.09)	(1.18; 4.77)
	Day 10	Posttreatment	389.8 (2.22)	2.2 (1.09)	(0.45; 4.05)
Moxifloxacin (N=58)	Day 1	Placebo	391.8 (1.87)		
	Day 2	Placebo	391.8 (1.87)	-0.0 (0.84)	(-1.40; 1.36)
	Day 3	Placebo	390.6 (1.87)	-1.2 (0.84)	(-2.59; 0.17)
	Day 4	Placebo	391.1 (1.87)	-0.7 (0.84)	(-2.09; 0.67)
	Day 8	400 mg q.d.	396.1 (1.87)	4.3 (0.84)	(2.88; 5.64)
	Day 9	Posttreatment	393.1 (1.87)	1.3 (0.84)	(-0.10; 2.65)
	Day 10	Posttreatment	390.8 (1.87)	-1.0 (0.84)	(-2.38; 0.38)

[a] The 2-sided 90% confidence intervals around the mean difference in day-averaged QTcLD during and after paliperidone treatment compared with day-averaged QTcLD on during placebo treatment (Day 1) was constructed using the estimated least-squares means and variances from the mixed models with treatment as a fixed effect and subject as a random effect.

[b] The mean effect of IR paliperidone 8 mg at steady-state (Day 8) on QTc interval was considered "negative" if the 2-sided 90% confidence interval excluded 10 ms. Assay sensitivity was confirmed, i.e., moxifloxacin 400 mg had a positive effect on QTc interval if the 2-sided 90% confidence interval excluded 0 ms.

In conclusion, the risk of QTcLD prolongation seems to be similar to risperidone, which is reflected in the SPC.

The complete discussion of the thorough QT/Qc study and the Phase 3 results concerning the effects of paliperidone on the QT interval are presented in the Clinical Safety section of this report.

Extrapyramidal symptoms (EPS)

The effect of paliperidone on the incidence of EPS was analysed using a hazard model, which related the EPS-incidence to average steady state paliperidone plasma concentrations. EPS-incidence

increased gradually between 5 mg and 10 mg. Below 5 mg (steady state plasma concentrations up to 20 ng/ml) there was no additional EPS-risk compared to placebo, while at doses above 10 mg the risk quickly reached its plateau of approximately 30% compared to about 10% for placebo.
The EC_{50} was estimated to be 24 ng/ml, which corresponds to a D2-receptor occupancy of about 83% (KD app: 4.9±0.53 ng/mL). This is consistent with other reports in the literature that suggest that increased risk to develop EPS is associated with D2-receptor occupancies of > 80%.

The PK/PD EPS model was also used to assess the impact of food intake on the probability to develop EPS during paliperidone administration. There is a relatively steep rise in EPS incidence between concentrations of 20 and 40 ng/ml. The relationship seems less steep when doses are viewed, but considering the placebo incidence of 10% and a maximum incidence of 30%, the incidence with food compared with administration in the fasting state appears to result in an approximately doubled EPS incidence. In order to reduce variability in exposure, the CHMP proposed to recommend standardisation of paliperidone ER OROS administration in relation to food intake. As a result, the Applicant introduced this recommendation in the SPC.

- **Relationship Between Plasma Concentration And Effect**

Based on data from PET studies, a relationship between paliperidone plasma concentrations and D_2 receptor occupancy was found, and plasma concentrations needed to achieve an effect on schizophrenic symptoms were fairly well defined. A dose range for ER OROS paliperidone that would lead to a receptor occupancy of 70-80%, which is likely to be efficacious, was estimated to be between 4.5 and 9 mg (10-20 ng/ml), using the Emax-model, while doses resulting in plasma concentrations above 19.6 ng/ml (>80% receptor occupancy) could be associated with a higher incidence of adverse events associated with central D2 receptor antagonism. Based on this, the dose range of 3 to 15 mg ER OROS paliperidone was evaluated for efficacy and safety in the pivotal Phase 3 studies.

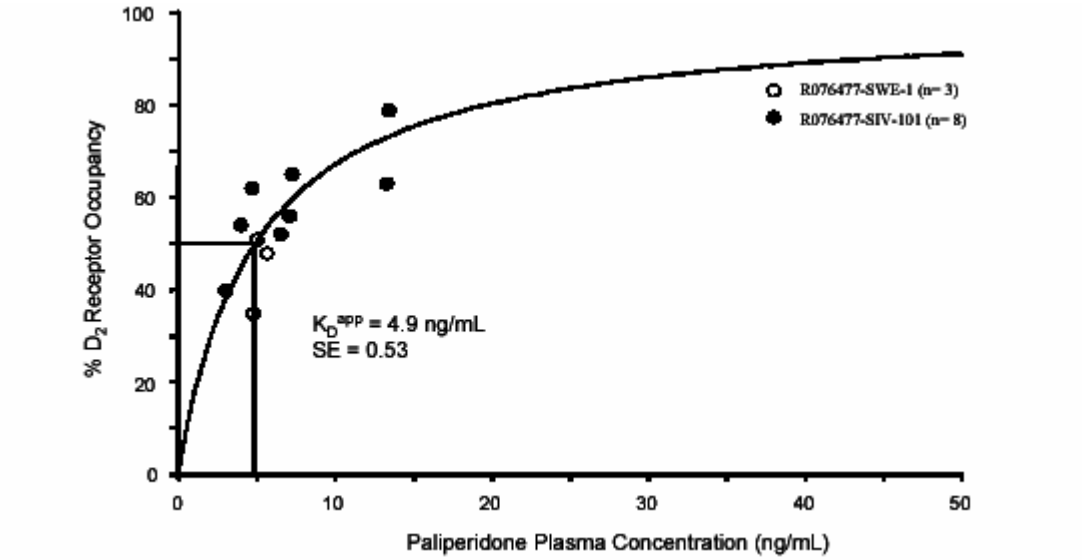

Figure 3: D_2-Receptor Occupancy *vs.* Paliperidone Plasma Concentration (Studies R076477-SIV-101 and R076477-SWE-1)

PK/PD analyses were performed with respect to dose/exposure and PANSS (Positive and Negative Syndrome Scale for Schizophrenia) and EPS (Extrapyramidal Symptoms) relationships. The effect of paliperidone on the endpoint PANSS and responder rates could be described by an E_{max} model. An ED_{50} of approximately 2.45 mg was estimated, with a high uncertainty, though. Replacing dose by concentration did not improve the precision of the model parameters. Dose-response modelling suggested that 3 mg is close to the minimal effective dose and located on the linear part of the dose response curve, whereas it is uncertain whether 2 mg would yield a relevant response rate. A dose of 1 mg is likely to be an ineffective dose.
The correlation of plasma concentrations of paliperidone with safety parameters (EPS rating scales: AIMS, BARS and SAS, and cardiovascular safety parameters: QTcLD) was explored graphically for four Phase 3 studies. The scatterplots showed no apparent relationship between plasma concentration and any of the assessed EPS and cardiovascular safety parameters.

- **Pharmacodynamic interactions with other medicinal products or substances**

No specific studies are available. Based on the *in vitro* and *in vivo* PK properties of paliperidone, the probability of drug-drug interactions is low. Considering the drug's primary effects on the CNS, paliperidone should be administered with caution in combination with other centrally active drugs. Paliperidone may antagonize the effects of levodopa and other dopamine agonists. Due to its alpha>-adrenergic receptor antagonism, paliperidone has the potential to enhance the effect of certain antihypertensive agents. Appropriate information has been included in the SPC.

- **Genetic differences in PD response**

No data is available. A review of publications on paliperidone (as metabolite of risperidone) indicated that exposure to paliperidone in diverse groups of subjects that included subjects with genetic polymorphisms was generally tolerated.

Clinical efficacy

- Dose response study(ies)

No specific dose response studies were performed prior to the main clinical studies. The selection of doses for these studies was based on the pharmacological relationship with risperidone for which a dose between 2 mg and 6 mg is usually recommended, corresponding to 6-18 mg ER OROS paliperdone. Furthermore, from the receptor occupancy studies it was estimated that 4.5-9 mg would result in the desired D_2-receptor occupancy of 70-80%.

- Main study(ies)

The pivotal studies were designed to determine both short-term efficacy and maintenance of effect.

Short-term efficacy

Short-term efficacy has been studied in three placebo-controlled, dose-response, fixed dose studies (SCH-303, SCH-304 and SCH-305) as well as in a flexible dose study in elderly patients (study SCH-302). The fixed dose studies also included olanzapine as an active comparator (Table 10).

Table 10: Treatment assignments in the four short-term phase III studies.

	Treatment Group						
		ER OROS Paliperidone (mg/day)					Olanzapine
	Placebo	3 mg	6 mg	9 mg	12 mg	15 mg	10mg/day
Key Efficacy Studies in Subjects at Least 18 years of age with Schizophrenia							
R076477-SCH-303	X		X	X	X		X
R076477-SCH-304	X		X		X		X
R076477-SCH-305	X	X		X		X	X
Safety and Tolerability Study in Elderly Subjects with Schizophrenia							
R076477-SCH-302	X	3 mg to 12 mg/day					Not Included

Methods (studies SCH-303, SCH-304 and SCH-305)

The studies SCH-303, SCH-304, and SCH-305 were randomised, double-blind, placebo- and active-controlled, parallel-group, dose-response phase III trials. These three main studies used the same methodology, which is therefore presented collectively in the present report.

- **Study Participants**

To be enrolled in the studies the patients should be male or female, 18 years of age or older, fulfil the DSM-IV criteria for schizophrenia at least one year before screening, and experiencing an acute episode, with a total PANSS score at screening between 70 and 120. Patients with any other DSM-IV axis I diagnosis as well as patients treated with depot antipsychotics, antidepressants (unless on a stable dose for at least three months) or mood stabilizers within different specified time limits were excluded. A documented history of lack of response to risperidone was another exclusion criterion.

Finally, patients who experienced a ≥25% decrease in PANSS total score between screening and baseline were not eligible to continue in the study.

- **Design and treatments**

After a screening phase of up to five days the patients were randomized to six weeks double-blind treatment with pre-selected fixed doses of paliperidone (see Table 10 above), placebo or olanzapine 10 mg. There was no titration except in Study SCH-305 where patients randomised to 15 mg were given 12 mg for one week. Patients were hospitalized from the first day of double-blind treatment for a minimum of 14 days.

- **Endpoints**

Primary endpoint was the change from baseline in total score of the Positive and Negative Syndrome Scale (PANSS; Kay *et al*. 1987). The PANSS is a 30-item rating scale for the psychopathology of schizophrenia and related disorders and includes a positive scale, a negative scale and a general psychopathology scale. Secondary endpoints included responders (at least 30% reduction from baseline PANSS total score), change from baseline in the Personal and Social Performance (PSP) scale, Clinical Global Impression of Severity (CGI-S), the Symptoms and Quality of Life in Schizophrenia (SQLS) scale and a Visual Analogue Scale (VAS) for sleep. All scales but PSP are recognised and commonly used in the evaluation of drugs for treatment of schizophrenia.
PSP is intended to reflect the patients functioning and measure the degree of difficulties a subject exhibits over a one month period within four domains of behaviour: socially useful activities, personal and social relationships, self-care, and disturbing and aggressive behaviour. The total score ranges from 1 to 100, Subjects with scores 71 to 100 have mild degree of difficulties; from 31 to 70, varying degrees of disability; and 30 or less, functioning so poorly that intensive supervision is required.

- **Randomisation and blinding**

The randomisation was centralised, balanced by using permuted blocks, and was stratified by study centre. During the double-blind phase all study medications were over-encapsulated to preserve the blind.

- **Statistical methods**

The primary analysis population was the intent-to-treat (ITT) population defined as all randomised patients who received at least one dose of study medication and had at least one post-baseline efficacy assessment. For missing values the last observation carried forward (LOCF) approach was used. In alternative analyses the observed cases (OC) approach was used.
Adjustment for multiplicity was applied at two levels. First, for the primary analysis of the PANSS total score and for the secondary variable PSP score Dunnett's method was used to adjust for the multiple paliperidone dosing group comparisons against placebo. Second, for each dosing group shown to be significant in the primary analysis, the family wise type I error for the analyses of the secondary variables PSP, CGI-S and SQLS scores was controlled at 0.05.
Change from baseline was analysed with analysis of covariance (ANCOVA) with treatment and analysis centre as factors and baseline score as covariate. Categorical data, e.g. percentage of responders, were analysed with the Cochran-Mantel-Haenszel test, controlling for analysis centre.

RESULTS

Study SCH-303

- **Participant flow and withdrawal information**

Six hundred and thirty patients were randomised and only one and two patients were excluded from the safety and ITT-efficacy populations, respectively. The number of withdrawals was fairly similar in the paliperidone and olanzapine groups and differed from the placebo group where there was an excess of withdrawals due to lack of effect (Figure 4).

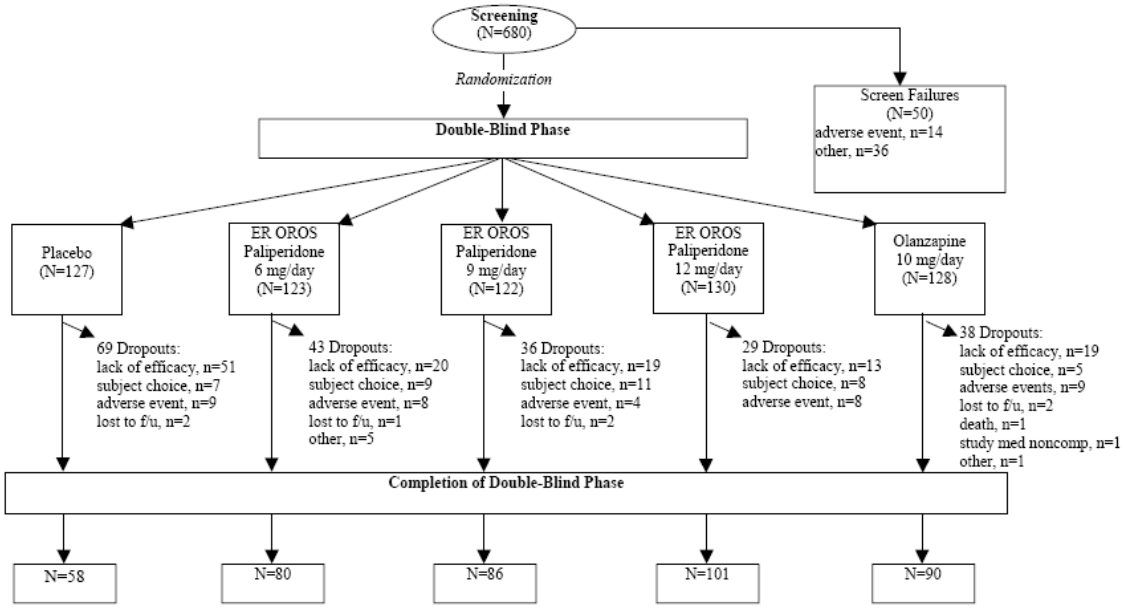

Figure 4: Withdrawal information for Study SCH-303.

The time pattern for total number of withdrawals was similar for all groups up to Day 21 when the higher withdrawal rate in the placebo group became apparent (Figure 5).

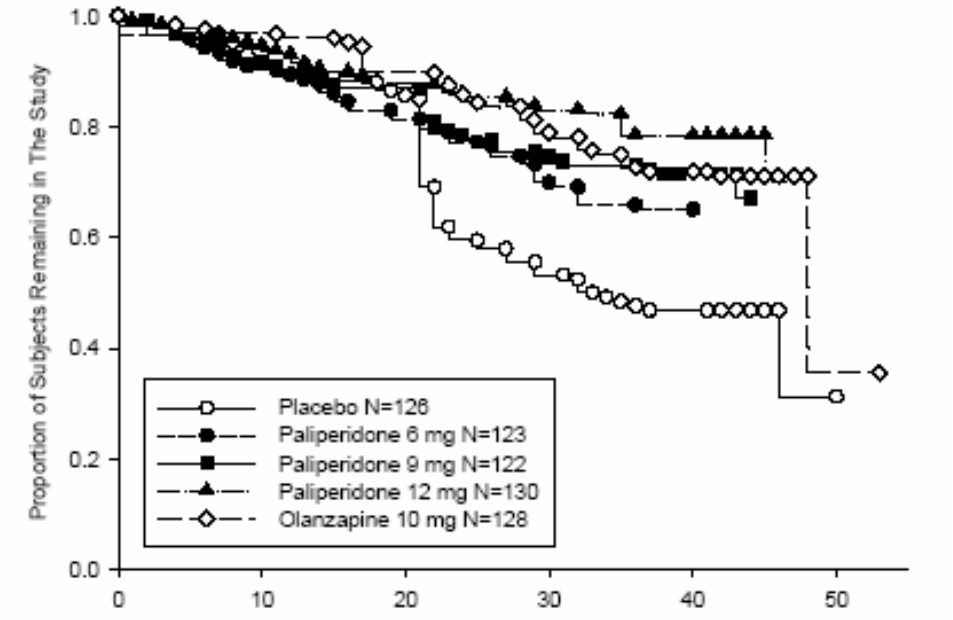

Figure 5: Time to withdrawal in Study SCH-303.

- **Baseline data**

There were no pronounced imbalances between the treatment groups with respect to demographic data, concomitant diseases or psychiatric history. Eighty-eight % of the patients were between 18 and 50 years of age. Females were well represented (48%). Patients of white race dominated (86%). The schizophrenia type was paranoid in 83% of the cases and 87% of the patients had at least one prior hospitalization for psychosis. The CGI-S score was "marked" or worse for 62% of the patients.

- **Outcomes and estimation**

In the analysis of the primary endpoint, change from baseline in PANSS total score, effects statistically significantly superior to placebo (all $p<0.001$) were demonstrated for all paliperidone doses (Table 11). The magnitude of effect was comparable to the effect of olanzapine. The difference

from placebo in the LS mean change was larger in the 12 mg group (-18.9) than either the 6 mg (-13.7) or 9 mg (-13.5) groups.

Table 11: Primary results for Study SCH-303. Mean change from baseline in PANSS total score, ITT-LOCF analysis.

	Placebo N=126	**Paliperidone**			**Olanzapine** 10 mg, N=128
		6 mg, N=123	9 mg, N=122	12 mg, N=129	
Baseline score	94.1	94.3	93.2	94.6	93.0
Change from baseline	-4.1	-17.9	-17.2	-23.3	-19.9
Diff. vs placebo P-value*, 95% CI		-13.7 <0.001, (-19.9;-7.5)	-13.5 <0.001, (-19.7;-7.3)	-18.9 <0.001, (-25.1;-12.8)	
Diff. vs Olanzapine 95% CI		2.4 (-2.5; 7.4)	2.7 (-2.3; 7.6)	-2.9 (-7.8; 2.0)	

*) Adjusted for multiplicity

In the primary ITT-LOCF analysis the effect size relative to placebo increased over time (Figure 6) in contrast to the ITT-OC analysis where the effect size relative to placebo decreased after three weeks (Figure 7). This is explained by the large number of withdrawals due to lack of effect after three weeks in the placebo group (Figure 8).

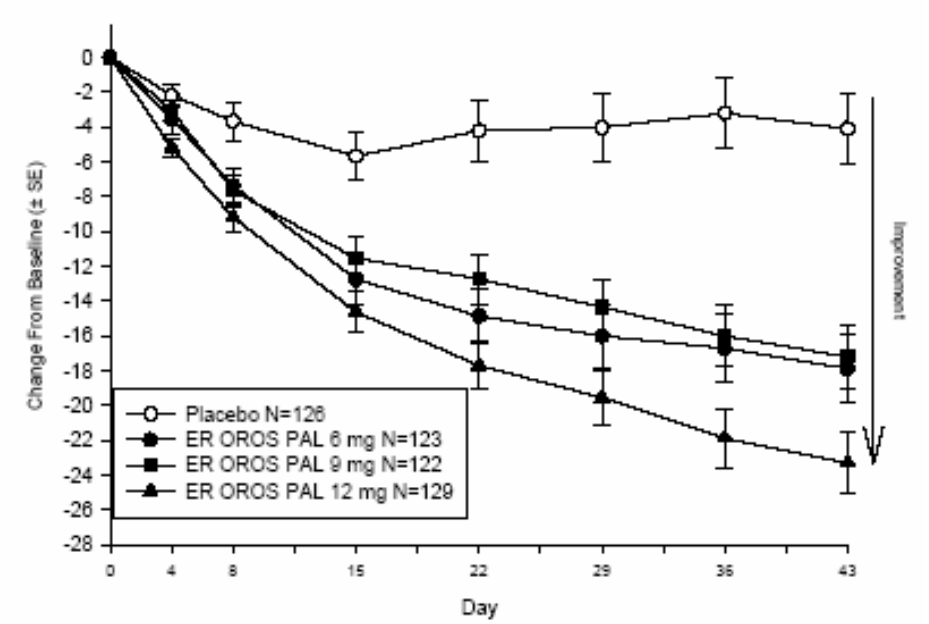

Figure 6: Change from baseline in PANSS total score in Study SCH-303. ITT-LOCF analysis.

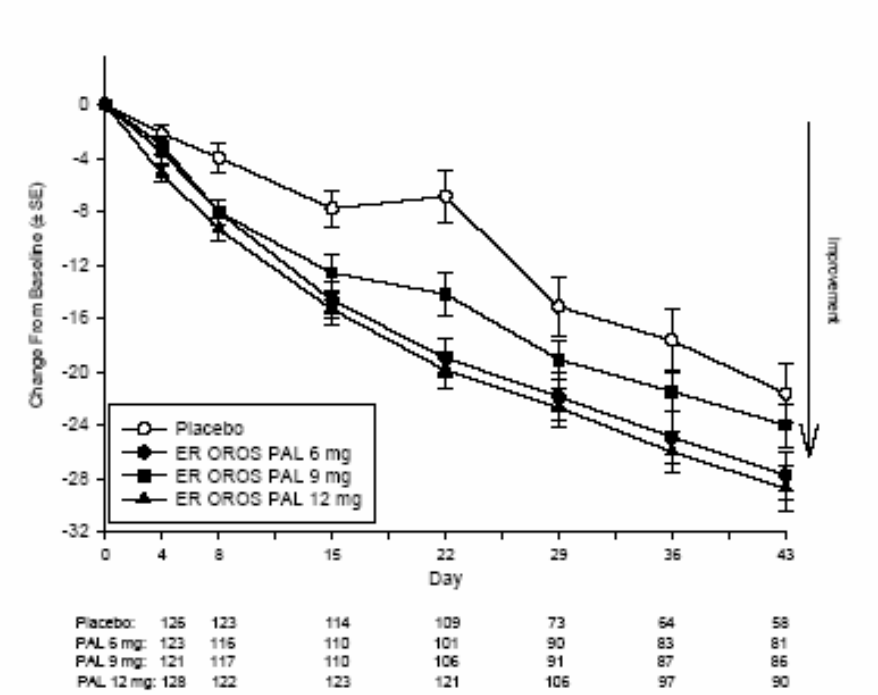

Figure 7: Change from baseline in PANSS total score in Study SCH-303. ITT-OC analysis.

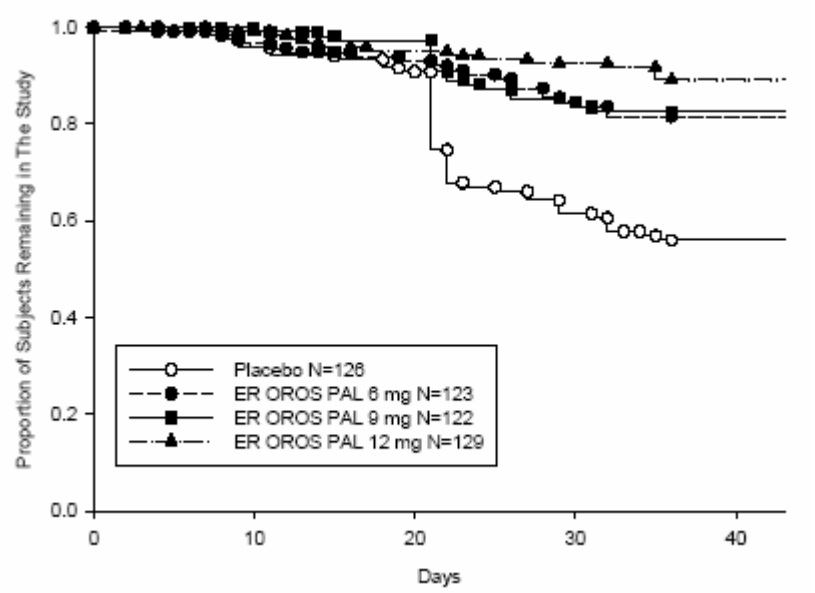

Figure 8: Time to discontinuation due to lack of effect in Study SCH-303.

In the responder analyses significantly more responders were observed in all paliperidone groups (56%, 51% and 61% in the 6 mg, 9 mg and 12 mg groups, respectively, $p<0.001$ for all doses) compared to the placebo group (30%).
The results for other secondary variables are given in Table 12. An effect comparable to the effect of olanzapine and significantly different from placebo was generally demonstrated. Quality of sleep was improved without an increase in daytime drowsiness.

Table 12: Mean (median for CGI-S) change from baseline for secondary variables in Study SCH-303.

Variable	Placebo	Paliperidone			Olanzapine 10 mg
		6 mg	9 mg	12 mg	
PSP P-value vs placebo	0.5	9.1 <0.001	8.1 <0.001	11.5 <0.001	10.3
CGI-S P-value vs placebo	0.0	-1.0 <0.001	-1.0 <0.001	-1.0 <0.001	-1.0
SQLS P-value vs placebo	-4.9	-8.3 0.063	-12.9 0.003	-13.4 <0.001	-10.0
PANSS, Pos. symp. P-value vs placebo	-2.1	-6.6 <0.001	-6.2 <0.001	-8.2 <0.001	-6.1
PANSS, Neg. symp. P-value vs placebo	-1.0	-4.2 <0.001	-3.5 <0.001	-5.0 <0.001	-5.1
PANSS, Disorg. thoughts P-value vs placebo	-0.9	-3.5 <0.001	-3.1 <0.001	-4.6 <0.001	-4.2
PANSS, Host./excitem. P-value vs placebo	0.5	-1.4 <0.001	-1.8 -<0.001	-2.4 <0.001	-1.9
PANSS, Anx./Depr. P-value vs placebo	-0.6	-2.1 <0.001	-2.6 <0.001	-3.0 <0.001	-2.6
Quality of sleep P-value vs placebo	1.0	13.5 <0.001	10.5 <0.001	12.2 <0.001	7.8
Daytime Drowsiness P-value vs placebo	-5.8	-2.4 0.606	-7.2 0.232	-6.4 0.503	-1.6

Study SCH-304

- **Participant flow and withdrawal information**

Four hundred and forty-four patients were randomised and five and twelve patients were excluded from the safety and ITT-efficacy populations, respectively. The withdrawal pattern in Study SCH-304 is similar to the pattern in Study SCH-303, although the excess withdrawal in the placebo group after three weeks is less pronounced (Figure 9).

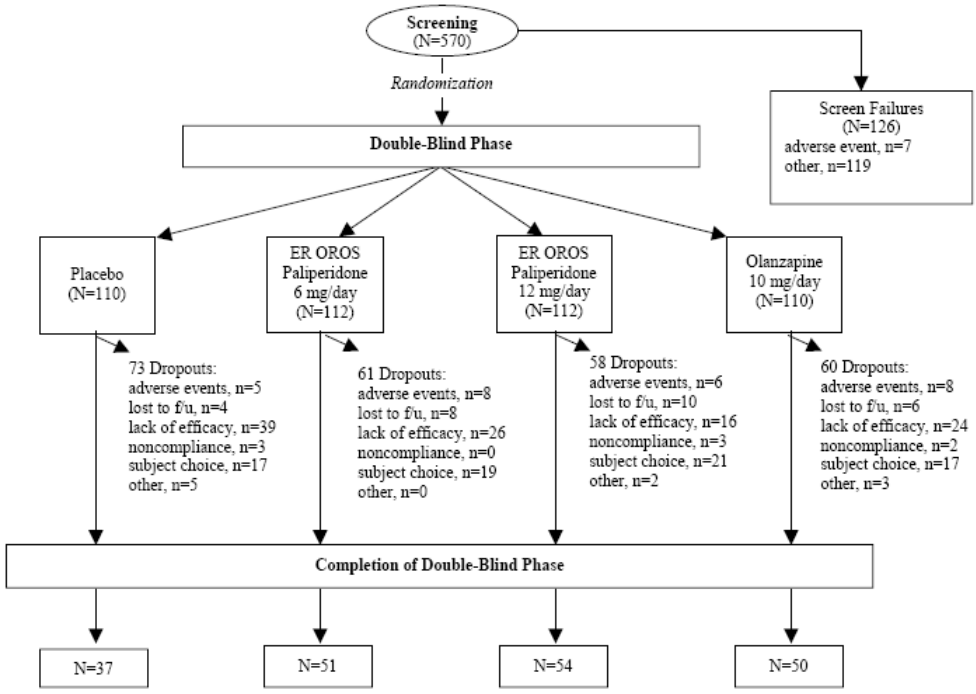

Figure 9: Withdrawal information for Study SCH-304.

- **Baseline data**

The patients differed from Study SCH-303 with respect to gender distribution (26% females) and race (43% white, 55% black). Otherwise baseline characteristics were similar to Studies SCH-303 and SCH-305. There were no pronounced imbalances between the treatment groups with respect to demographic data, concomitant diseases or psychiatric history.

- **Outcomes and estimation**

In the analysis of the primary endpoint, change from baseline in PANSS total score, effects statistically significantly superior to placebo (p=0.006 for 6 mg and p<0.001 for 12 mg) were demonstrated for both paliperidone doses (Table 13). The magnitude of effect was comparable to the effect of olanzapine. The difference from placebo in the LS mean change was slightly larger in the 12 mg group (-8.5) than the 6 mg (-7.0) group.

Table 13: Primary results for Study SCH-304. Mean change from baseline in PANSS total score, ITT-LOCF analysis.

	Placebo N=105	**Paliperidone**		**Olanzapine** 10 mg, N=105
		6 mg, N=111	12 mg, N=111	
Baseline score	93.6	92.3	94.1	94.9
Change from baseline	-8.0	-15.7	-17.5	-18.4
Diff. vs placebo P-value* 95% CI		-7.0 0.006, (-12.3; -1.8)	-8.5 <0.001, (-13.8; -3.3)	
Diff. vs Olanzapine 95% CI		1.6 (-3.2; 6.4)	0.3 (-4.5; 5.0)	

*) Adjusted for multiplicity

In the ITT-OC analysis, similar to study SCH-303, the effect size relative to placebo peaked at three weeks. Again, this is probably explained by the larger number of withdrawals due to lack of effect after three weeks in the placebo group.
In the responder analyses significantly more responders were observed in both paliperidone groups (50%, p=0.025 and 51.4%, p=0.012 in the 6 mg and 12 mg groups, respectively) compared to the placebo group (34.3%).
The results for other secondary variables are given in Table 14. The overall pattern is consistent with results of Study SCH-303, although the effect sizes are smaller and some occasional significances are lacking.

Table 14: Mean (median for CGI-S) change from baseline for secondary variables in Study SCH-304.

Variable	**Placebo**	**Paliperidone**		**Olanzapine** 10 mg
		6 mg	12 mg	
PSP P-value vs placebo	2.9	8.8 0.007	6.6 0.311	7.6
CGI-S P-value vs placebo	0.0	-1.0 0.009	-1.0 <0.001	-1.0
SQLS P-value vs placebo	-3.3	-6.7 0.226	-5.7 0.492	-7.3
PANSS, Pos. symp. P-value vs placebo	-2.9	-5.2 0.005	-6.0 <0.001	-6.3
PANSS, Neg. symp. P-value vs placebo	-2.2	-4.4 0.007	-3.9 0.025	-4.4
PANSS, Disorg. thoughts P-value vs placebo	-1.7	-2.7 0.062	-3.7 <0.001	-3.8
PANSS, Host./excitem. P-value vs placebo	0.3	-1.2 0.025	-1.5 0.007	-0.9
PANSS, Anx./Depr. P-value vs placebo	-1.5	-2.3 0.078	-2.4 0.070	-2.9

Quality of sleep P-value vs placebo	-3.3	8.3 0.009	6.8 0.016	14.0
Daytime Drowsiness P-value vs placebo	-2.6	0.9 0.851	1.2 0.644	2.9

Study SCH-305

- **Participant flow and withdrawal information**

Six hundred and eighteen patients were randomised and four and thirteen patients were excluded from the safety and ITT-efficacy populations, respectively. The withdrawal was dose-dependent with most withdrawals on placebo and fewest on the highest paliperidone dose. The withdrawal differences were mostly due to discontinuations because of lack of effect (Figure 10).

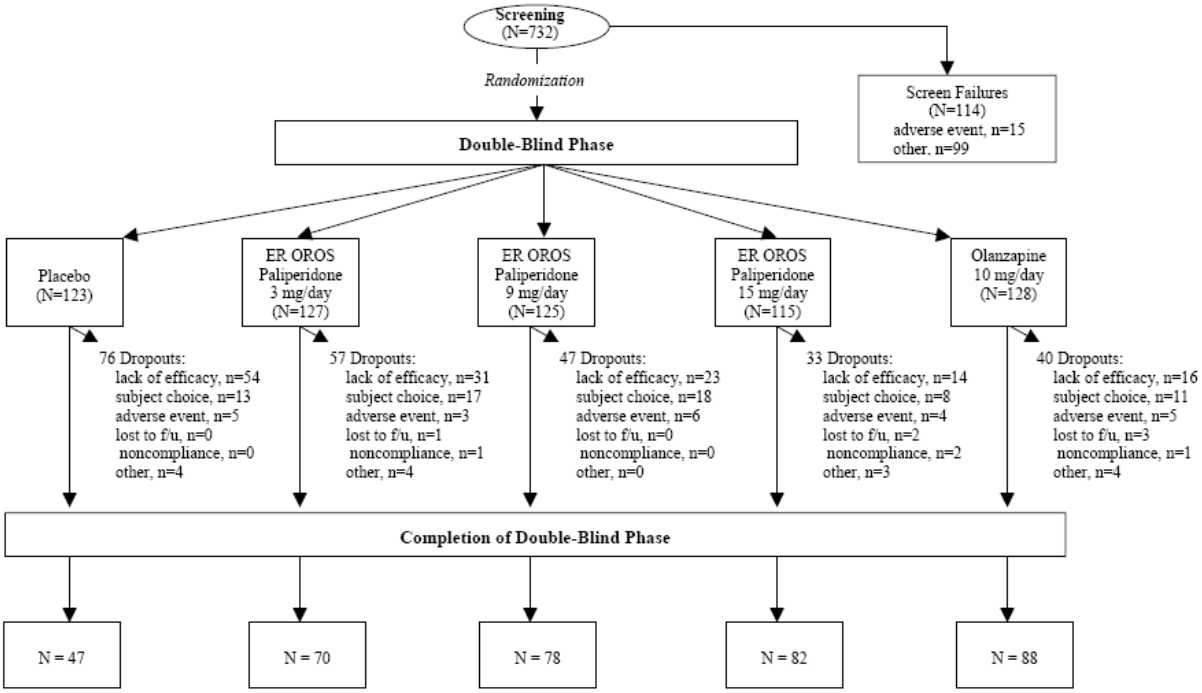

Figure 10: Withdrawal information for Study SCH-305.

- **Baseline data**

The patients differed from Study SCH-303 and SCH-304 with respect to gender distribution (32% females versus 26% in SCH-304) and ethnic appearance 49% white, 21% black, 24% asian). Otherwise baseline characteristics were similar for the three studies. There were no pronounced imbalances between the treatment groups with respect to demographic data, concomitant diseases or psychiatric history.

- **Outcomes and estimation**

In the analysis of the primary endpoint, change from baseline in PANSS total score, statistically significant effects compared to placebo ($p<0.001$) were demonstrated for all paliperidone doses (Table 15). The magnitude of effect was comparable to the effect of olanzapine. The difference from placebo in the LS mean change was larger in the 15 mg group (-17.2) than in either the 3 mg (-11.6) or 9 mg (-12.9) groups.

Table 15: Primary results for Study SCH-305 Mean change from baseline in PANSS total score, ITT-LOCF analysis.

	Placebo N=120	**Paliperidone**			**Olanzapine** 10 mg, N=126
		3 mg, N=123	9 mg, N=123	15 mg, N=113	
Baseline score	93.9	91.6	93.9	92.4	93.3
Change from baseline	-2.8	-15.0	-16.3	-19.9	-18.1
Diff. vs placebo P-value* 95% CI		-11.6 <0.001, (-17.2;-6.1)	-12.9 <0.001, (-18.4;-7.4)	-17.2 <0.001, (-22.8;-11.5)	
Diff. vs Olanzapine 95% CI		2.6 (-1.8;7.0)	1.2 (-3.2;5.6)	-3.1 (-7.6;1.5)	

*) Adjusted for multiplicity

While the effect size tended to increase with time in the ITT-LOCF analysis it was more or less constant from two weeks in the ITT-OC analysis.
In the responder analyses significantly more responders were observed in all paliperidone groups (40%, 46% and 53% in the 3 mg, 9 mg and 15 mg groups, respectively, p<=0.001 for all doses) compared to the placebo group (18%).
The results for other secondary variables are given in Table 16. The results are consistent with the results of the other two short-term studies.

Table 16: Mean (median for CGI-S) change from baseline for secondary variables in Study SCH-305.

Variable	**Placebo**	**Paliperidone**			**Olanzapine** 10 mg
		3 mg	9 mg	15 mg	
PSP P-value vs placebo	-1.5	8.3 <0.001	7.6 <0.001	12.2 <0.001	7.8
CGI-S P-value vs placebo	0.0	-1.0 <0.001	-1.0 <0.001	-1.0 <0.001	-1.0
SQLS P-value vs placebo	-3.8	-7.4 0.034	-6.7 0.296	-7.5 0.147	-7.9
PANSS, Pos. symp. P-value vs placebo	-2.1	-5.0 <0.001	-6.0 <0.001	-6.9 <0.001	-6.1
PANSS, Neg. symp. P-value vs placebo	-1.0	-3.8 <0.001	-3.9 <0.001	-4.2 <0.001	-4.2
PANSS, Disorg. thoughts P-value vs placebo	-0.2	-3.4 <0.001	-3.4 <0.001	-3.9 <0.001	-3.9
PANSS, Host./excitem. P-value vs placebo	1.2	-1.1 <0.001	-1.2 <0.001	-2.3 <0.001	-1.7
PANSS, Anx./Depr. P-value vs placebo	-0.7	-1.8 0.005	-1.9 0.002	-2.6 <0.001	-2.2
Quality of sleep P-value vs placebo	3.6	9.0 0.059	12.3 0.016	11.3 0.075	15.5
Daytime Drowsiness P-value vs placebo	-0.5	-2.9 0.715	-0.9 0.401	-3.8 0.199	-6.8

Maintenance of effect
Maintenance of effect has been investigated in a relapse prevention study (study SCH-301) and in open label extensions of the short-term studies.

Study SCH-301

Methods

- **Study Participants**

To be enrolled in this study the patients should be male or female, 18 to 65 years of age, fulfil the DSM-IV criteria for schizophrenia at least one year before screening, and experiencing an acute episode, with a total PANSS score at screening between 70 and 120. Patients with any other DSM-IV

axis I diagnosis were excluded. A documented history of lack of response to risperidone was another exclusion criterion.

- **Design and treatments**

After a 5-day screening phase eligible patients were treated in an open label 8-week run-in phase with flexible doses of paliperidone (3 to 15 mg). Patients who tolerated the paliperdone treatment, were on a stable paliperidone dose during the last two weeks of the run-in phases and experienced control of acute symptoms defined as PANSS total score of ≤70; PANSS scores on individual items (P1 [delusions], P2 [conceptual disorganization], P3 [hallucinatory behavior], P6 [suspiciousness/ persecution], P7 [hostility] and G8 [uncooperativeness]) of ≤4 (moderate or less), and a CGI-S score of ≤4 (moderately ill or better), were eligible for a 6-week open label stabilization phase. Finally patients remaining on a stable dose and still fulfilling the symptom control criteria were randomly assigned, in a 1:1 ratio, to placebo or flexibly dosed paliperidone (3 to 15 mg).

- **Endpoints**

The primary efficacy variable was time to the first recurrence event. Recurrence was defined as any of the following criteria:

- Psychiatric hospitalization (involuntary or voluntary admission to a psychiatric hospital for decompensation of the subject's schizophrenic symptoms), or
- For PANSS:
  - Increase of 25% in the total PANSS score from randomization for 2 consecutive days if the score at randomization was >40, or
  - A 10-point increase in the total PANSS score from randomization for 2 consecutive days if the score at randomization was ≤40, or
- Deliberate self-injury and/or violent behaviour resulting in clinically significant injury to the subject or another person or property damage, or
- Suicidal or homicidal ideation and aggressive behaviour that was clinically significant (in frequency and severity) in the investigator's judgment, or
- For CGI-S:
  - A score of ≥4 after randomisation for 2 consecutive days if CGI-S score was ≤ 3 at randomization, or
  - A score of ≥5 after randomisation for 2 consecutive days if CGI-S was 4 at randomization, or
- For PANSS items P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behaviour), P6 (suspiciousness/persecution), P7 (hostility) or G8 (uncooperativeness):
  - A score ≥5 after randomisation for 2 consecutive days on any of the above PANSS items if the maximum score for the above PANSS items was ≤ 3 at randomization, or
  - A score ≥6 after randomisation for 2 consecutive days on any of the above PANSS items if the maximum score for the above PANSS items was 4 at randomisation.

Results

- **Participant flow and withdrawal information**

Five hundred and thirty patients were included in the run-in phase, 312 continued into the stabilization phase and 207 were finally randomised. There were more dropouts in the paliperidone group, mainly due to subject choice (Figure 11).

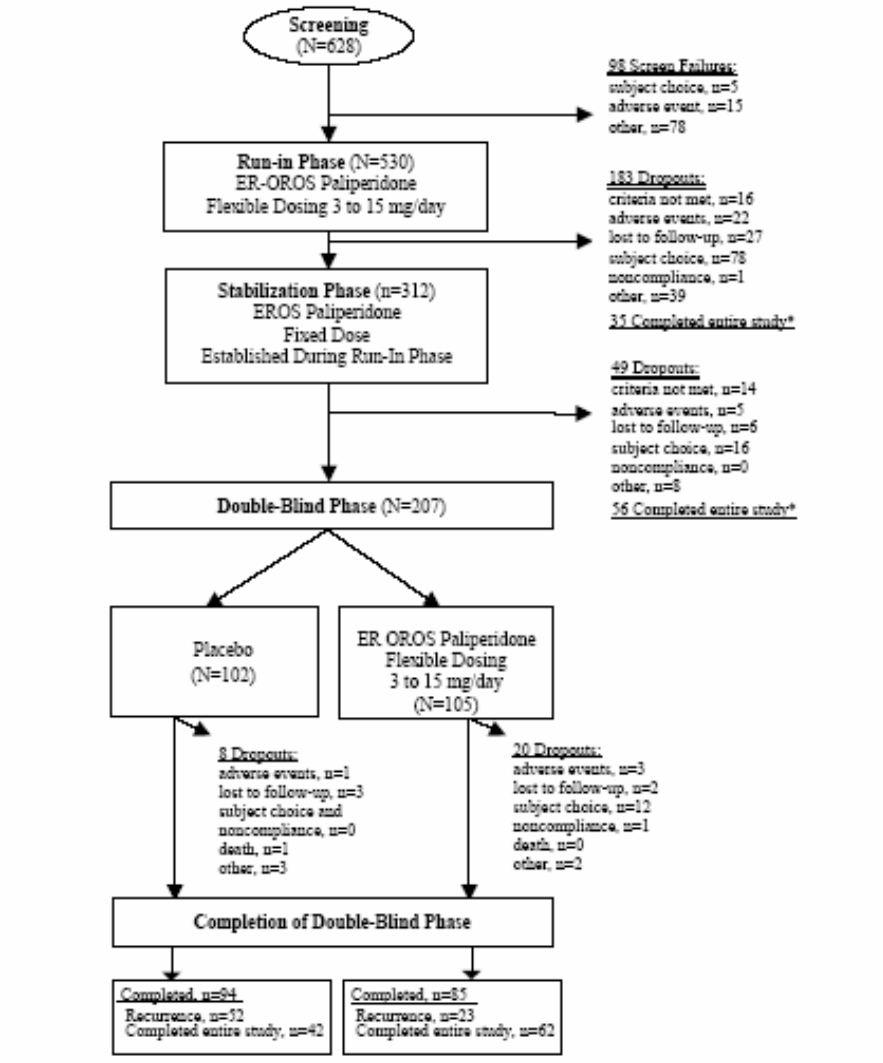

Figure 11: Withdrawal information for Study SCH-301.

- **Baseline data**

In the all treated population 86% of the patients were between 18 and 50 years of age. One patient was 17 years old. A majority of the patients were of white ethnic appearance (53%) and 10% were of Hispanic origin. Seventy-two % had had at least one hospitalization for psychosis prior to the study. The baseline characteristics were similar for the patients actually randomised and there were no major imbalances between the two treatment groups.

- **Outcomes and estimation**

The study was terminated early due a significant effect in a predefined interim analyses (p=0.0053, less than the predefined stopping criterion of 0.0102). Roughly twice as many patients had a recurrence on placebo compared with paliperidone (Figure 12). In a final analysis including patients randomised after the cut-off date for the interim analysis the treatment difference was more pronounced (p<0.001).

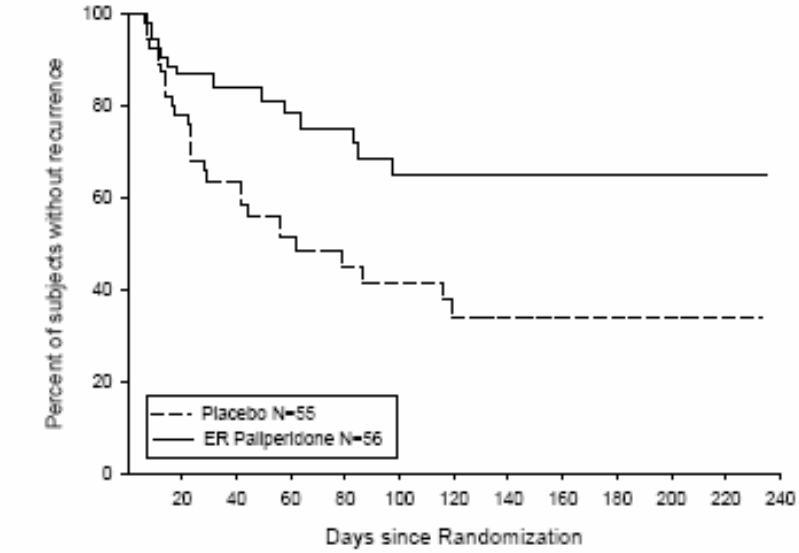

Figure 12: Time to recurrence in Study SCH-301. ITT population, interim analysis.

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

A pooled analysis of the efficacy data of the phase III studies was performed. This analysis is a mixture of randomised comparisons and between study comparisons, e.g. there is no randomised comparison between paliperidone 12 mg and 15 mg. The analysis confirmed that higher doses were more effective than lower doses (as seen in the individual studies). However, in the pooled analysis there was no indication that 15 mg should be more effective than 12 mg. In addition, a dose relationship for safety has been observed with several of the common adverse events being more frequent on the 15 mg dose, indicating that a flexible dosage of 3-12 mg is a reasonable recommendation.

Pooled analyses of subpopulations

Pooled analyses of studies SCH-303, SCH-304 and SCH-305 have been performed to investigate the impact of age (18-25 years of age, 26-50 years of age, and older than 50 years of age), gender (the female representation in the clinical studies ranged from 26 to 48%) and ethnic origin. The magnitude of effect was similar in all age groups, as well as for white, black and patients of Asian origin. Similar effects were demonstrated also for both genders.

- Clinical studies in special populations

Study SCH-302 in geriatric subjects with schizophrenia

This study was designed to determine short-term safety and efficacy of flexibly dosed ER OROS paliperidone (3, 6, 9 and 12 mg) in the elderly population. This trial was a randomized (2:1 ratio paliperidone ER OROS:placebo), 6-week, double-blind, placebo-controlled, multicenter study. Male and female patients aged 65 years or older with a DSM-IV diagnosis of schizophrenia for at least one year were included.

- **Participant flow and withdrawal information**

A total of 114 patients were randomised and no patient was excluded from the safety and ITT-efficacy populations. The withdrawal rate was twice as high in the placebo group, mostly due more withdrawals because of lack of effect (Figure 13).

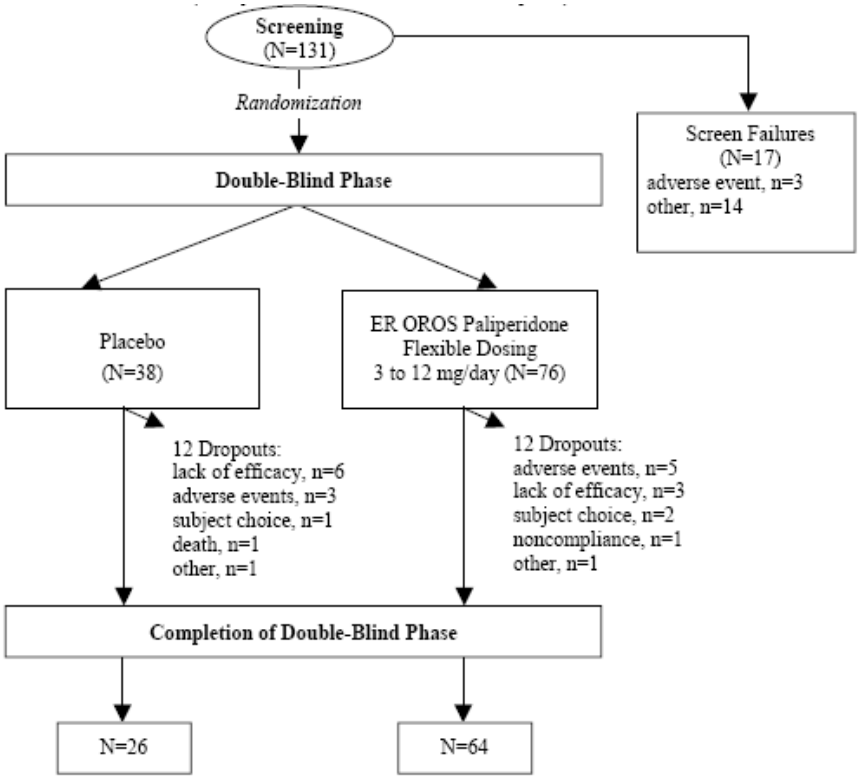

Figure 13: Participant flow in study SCH-302.

- **Baseline data**

More than half of the patients were between 64 and 69 years of age (paliperidone 57%, placebo 61%). The paliperidone group had a lower proportion of patients between 70 and 75 years of age (25% vs 34%), and a higher proportion of patients older than 75 years (18% vs 5%). Apart from this imbalance the baseline characteristics, concomitant diseases and psychiatric history were generally similar between the two treatment groups. 58% of the patients had a CGI-S rating of "marked" or worse, and 89% had been hospitalized at least twice prior to the study; 62% were hospitalized for psychosis at least four times prior to the study.

- **Outcomes and estimation**

In the analysis of the primary endpoint, change from baseline in PANSS total score, a fairly high placebo response was noted. Despite this, there was a significant difference in favour of paliperidone (Table 17). The difference was statistically significant ($p<0.05$) from two weeks and the magnitude of effect tended to increase over time.

Table 17: Primary results for Study SCH-302 Mean change from baseline in PANSS total score, ITT-LOCF analysis.

	Placebo N=38	**Paliperidone 3-12 mg** N= 76
Baseline score	94.3	91.8
Change from baseline	-9.9	-14.6
Diff. vs placebo 95% CI		-5.5 (-9.9; -1.1)

While the effect size tended to increase with time in the ITT-LOCF analysis, it was more or less constant from two weeks in the ITT-OC analysis.

In the responder analysis, 38% of subjects in the ER OROS paliperidone group demonstrated a 30% or greater reduction from baseline in PANSS total score, compared to 29% in the placebo group. This difference was not significant.

The results for other variables are given in Table 18. Apart from the PANSS subscales for positive symptoms, negative symptoms and anxiety/depression, there were no significant differences between the treatments.

Table 18: Mean (median for CGI-S) change from baseline for secondary variables in Study SCH-302.

Variable	Placebo	Paliperidone 3-12 mg
PSP Diff. vs placebo (95% CI)	4.7	4.8 -0.3 (-4.1; 3.5)
CGI-S Diff. vs placebo (95% CI)	0.0	-0.5 0.0 (-1.0; 0.0)
SQLS Diff. vs placebo (95% CI)	-6.0	-9.0 -1.6 (-7.2; 4.0)
PANSS, Pos. symp. Diff. vs placebo (95% CI)	-2.8	-4.7 -2.2 (-3.7; -0.6)
PANSS, Neg. symp. Diff. vs placebo (95% CI)	-2.4	-4.0 -1.7 (-3.3; -0.1)
PANSS, Disorg. thoughts Diff. vs placebo (95% CI)	-2.5	-2.6 -0.3 (-1.4; 0.8)
PANSS, Host./excitem. Diff. vs placebo (95% CI)	-1.3	-1.4 -0.4 (-1.5; 0.6)
PANSS, Anx./Depr. Diff. vs placebo (95% CI)	-0.8	-1.8 -1.2 (-1.9; -0.4)
Quality of sleep Diff. vs placebo (95% CI)	3.8	6.2 0.6 (-9.6; 10.8)
Daytime Drowsiness Diff. vs placebo (95% CI)	2.6	-5.8 -4.5 (-12.5; 3.4)

- **Discussion on clinical efficacy**

The CHMP considered the clinical program for paliperidone in schizophrenia adequate with respect to experimental design, diagnostic criteria and study endpoints. In three phase III studies the short-term effect of different doses of paliperidone in the treatment of an acute episode of schizophrenia has been compared to placebo with olanzapine as an active reference. The outcome of the short-term studies compares well with what has been demonstrated for other drugs for the treatment of an acute episode of schizophrenia. A consistent effect for all doses relative to placebo has been demonstrated and the magnitude of effect is similar to the effect of olanzapine. The difference compared to placebo in change from baseline in PANSS total score ranges between -7 and -19, with most of the comparisons between -13 and -19. There were 15 to 35% more responders in the active groups compared to placebo. Both with respect to PANSS total score and responders there was a trend for better effect with higher doses and there were some significant differences between doses in the individual studies. There was no direct comparison between 12 and 15 mg, and within the recommended dose range there were two direct comparisons between 6 and 12 mg. Some differences in change from baseline in PANSS total score were observed, however, the clinical relevance of these differences is questionable. However, several adverse events were reported more frequently for 15 mg, therefore the recommended dose range (3-12 mg) seems reasonable. Within the recommended dose range there were more adverse events on the higher dose, in particular 26% experienced EPS-related adverse events on 12 mg compared to 10% on 6 mg. Thus, the recommended starting dose (6 mg) seems reasonable as well. A significant, but less pronounced effect has been demonstrated in elderly patients (65 years of age or older). The female representation in the clinical studies ranged from 26 to 48%. Similar effects were demonstrated for both sexes.

Controlled data on maintenance of effect consist of a so called recurrence prevention study. However, since patients were included during an acute episode and most of the separation of the recurrence-free curves occurred during the first weeks after randomisation, the CHMP objected that relapse rather than recurrence prevention had been demonstrated. Nevertheless, relapse prevention provides support for maintenance of effect, and the Sponsor suggested to include maintenance treatment in the therapeutic indication, and proposed the following text for Section 4.1. of the SPC: "INVEGA is indicated for schizophrenia, including acute treatment and maintenance treatment in patients who have shown an initial treatment response". The CHMP was of the view that, for a drug to be approved for treatment of schizophrenia, acute treatment as well as maintenance treatment have to be demonstrated, and that for a recently approved drug with similar documentation Section 4.1. of the SPC reads "Invega is indicated for the treatment of schizophrenia". As a result, the "treatment of schizophrenia" has been agreed upon as the indication for Invega, and this is reflected in the SPC.

Clinical safety

The clinical safety database of Invega comprises the results of 5 completed Phase 3 trials and their (on-going) open-label extensions during which 2054 subjects with schizophrenia were exposed to ER OROS paliperidone, along with data from 28 Phase 1/2a studies involving more than 1100 healthy subjects or subjects with schizophrenia, most of whom received an IR or ER formulation of paliperidone.

Subjects with significant or unstable cardiovascular or endocrine disease were excluded from participation in the Phase 3 efficacy and safety studies. Diabetes, dyslipidemia, and cardiovascular disease were reported as comorbid conditions at study entry for between 2 and 5% of adult subjects with schizophrenia comprising the Pooled Double-blind, Study SCH-301, or Pooled Open-label Safety Analysis Sets. Rates of comorbid diabetes and cardiovascular disease were higher among the elderly subjects with schizophrenia enrolled in Study SCH-302 (12% and 43%, respectively).

- Patient exposure

Patient exposure in phase 3 studies

A total of 2326 subjects with schizophrenia are included in the safety analyses of the phase 3 double-blind studies (see Table 19), including 1682 adults in the 3 studies SCH-303, SCH-304, and SCH-305 and 114 elderly adults in study SCH-302. Of the 1796 subjects in these 4 studies, 1039 received double-blind ER OROS paliperidone, 393 received placebo, and 364 received olanzapine. A total of 530 subjects received at least 1 dose of ER OROS paliperidone in the open-label, run-in phase of Study SCH-301. Two hundred seven of these subjects were randomly assigned to receive placebo (N=102) or ER OROS paliperidone (N=105) during the double-blind phase of the study.

A total of 1170 subjects had received open-label ER OROS paliperidone in the 4 studies SCH-702, -703, -704, and -705 as of 1 November 2005. 235 subjects were enrolled in Study SCH-701 as of 1 November 2005.

Overall, in the combined double-blind and open-label phases of SCH-301/701, -302/702, -303/703, -304/704, and -305/705, 2054 subjects had received ER OROS paliperidone treatment through the 1 November 2005 cut-off date.

Following the CHMP request, the Applicant submitted updated long-term safety data information, summarized with a cut-off date of 26 June 2006 (31 August 2006 for deaths and serious adverse events): the combined exposure to paliperidone ER in Phase 3 clinical trials in 2054 adults and elderly subjects with schizophrenia was 1092.88 subject-years. This represents an increase of 171.57 patient-years. Across all Phase 3 studies, 562 subjects were treated for more than 1 year (>52 weeks), including 415 (27%) subjects in the pooled Phase 3 studies (R076477-SCH-302, -303, -304, -305, -702, -703, -704 and –705) and 147 (28%) subjects in studies (R076477-SCH-301/701).

Protocol Number	Study Design/Number of Subjects
PHASE 3 DOUBLE-BLIND STUDIES IN SUBJECTS WITH SCHIZOPHRENIA	
R076477-SCH-303	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of ER OROS paliperidone (6, 9, and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 629 Treated with Paliperidone: 375
R076477-SCH-304	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 2 fixed dosages of ER OROS paliperidone (6 and 12 mg/day) and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 439 Treated with Paliperidone: 224
R076477-SCH-305	A randomized, 6-week double-blind, placebo- and active-controlled, parallel-group, dose-response study to evaluate the efficacy and safety of 3 fixed dosages of ER OROS paliperidone (3, 9, and 15 mg/day)[a] and olanzapine (10 mg/day) in the treatment of subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 614 Treated with Paliperidone: 364
R076477-SCH-302	A randomized, 6-week double-blind, placebo-controlled study to evaluate the safety and tolerability of flexible doses of ER OROS paliperidone in the treatment of geriatric subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 114 Treated with Paliperidone: 76
R076477-SCH-301	A randomized, double-blind, placebo-controlled, parallel-group study of variable duration preceded by an initial 14-week open-label run-in/stabilization phase evaluating ER OROS paliperidone in the prevention of recurrence in subjects with schizophrenia. Double-blind: Completed No. Subjects Evaluable for Safety: 530 Treated with paliperidone: 530

Key: AC = active-controlled; BA = bioavailability; BE = bioequivalence; b.i.d. = twice daily; CO = crossover; DB = double-blind; ECG = electrocardiogram; ER = extended release; F = female(s); IR = immediate release; i.v.= intravenous; M = male(s); MD = multiple dose; OL = open-label; PAL = paliperidone; PC = placebo-controlled; PD = pharmacodynamics; PET = positron emission tomography; PK = pharmacokinetics; PPB = plasma protein binding; q.d. = once daily; RIS = risperidone; SD = single dose.

[a] Subjects in the 15 mg/day group received 12 mg/day on Days 1-7 and 15 mg/day for the rest of the double-blind phase.

Table 19: Phase 3 double-blind studies contributing to clinical safety data.

Patient exposure in phase 1/2a studies

In the 28 phase 1/2a studies, 1122 subjects were enrolled, including 383 subjects with schizophrenia and 739 non-schizophrenic subjects. Of these, 132 subjects with schizophrenia and 534 non-schizophrenic subjects received 1 or more doses of ER OROS paliperidone.

In the 17 studies that comprise the phase 1/2a studies in healthy adult subjects, 448 subjects received 1 or more single doses of study medication, including 275 subjects who received ER OROS paliperidone, 219 who received IR or other (non-ER OROS) paliperidone formulations, 62 who received placebo, and 52 who received risperidone.

In the 3 studies that comprise the phase 1/2a studies in subjects with schizophrenia, study treatments included up to 2 weeks of daily IR paliperidone (INT-1) and up to 6 days (SCH-101) or 2 weeks (SCH-102) of treatment with ER OROS paliperidone high doses or risperidone. A total of 200 subjects participated in these studies, including 111 who received high doses of ER OROS paliperidone, 34 who received IR paliperidone, and 55 who received risperidone.

The other 8 phase 1/2a studies (P01-1004, P01-1005, REI-1001, SCH-1008, SCH-1009, SCH-1010, PALIOROS-SCH-1011, and PALIOROS-P01-1012) included 474 subjects, 183 of whom had a diagnosis of schizophrenia or schizoaffective disorder. In these 8 studies, 372 subjects, including 93 with schizophrenia or schizoaffective disorder, received 1 or more doses of a paliperidone formulation (IR or ER OROS).

- **Adverse events**

Adverse events in Phase 3 pivotal Double-Blind studies pooled data (SCH-303, SCH-304 and SCH-305)

In these studies adult patients with schizophrenia were treated with daily doses of ER OROS paliperidone ranging from 3 mg to 15 mg (6-week, double-blind, placebo-controlled, fixed-dose trials in adult subjects). Adverse events occurred in a higher percentage of subjects administered ER OROS paliperidone (72%) versus placebo (66%) or versus the olanzapine 10 mg/day group (69%). Table 20 lists those adverse events that were reported with an incidence of ≥5% in any treatment group for the Pooled Double-blind Safety Analysis Set.

Table 20 : Treatment-Emergent Adverse Events With at Least 5% Incidence in Any Treatment Group by MedDRA Preferred Term - Double-Blind Phase
(Studies R076477-SCH-303, R076477-SCH-304, and R076477-SCH-305: Safety Analysis Set)

		ER OROS Paliperidone						Olanzapine
Body System or Organ Class / Dictionary-derived Term	Placebo (N=355) n (%)	3 mg (N=127) n (%)	6 mg (N=235) n (%)	9 mg (N=246) n (%)	12 mg (N=242) n (%)	15 mg (N=113) n (%)	Total (N=963) n (%)	10 mg (N=364) n (%)
Total no. subjects with adverse events	235 (66)	91 (72)	156 (66)	171 (70)	184 (76)	87 (77)	689 (72)	252 (69)
Nervous system disorders	97 (27)	34 (27)	68 (29)	99 (40)	110 (45)	47 (42)	358 (37)	123 (34)
Headache	42 (12)	14 (11)	29 (12)	34 (14)	35 (14)	20 (18)	132 (14)	35 (10)
Akathisia	14 (4)	5 (4)	7 (3)	20 (8)	23 (10)	11 (10)	66 (7)	7 (2)
Extrapyramidal disorder	8 (2)	6 (5)	5 (2)	17 (7)	18 (7)	9 (8)	55 (6)	6 (2)
Somnolence	12 (3)	6 (5)	8 (3)	17 (7)	11 (5)	7 (6)	49 (5)	47 (13)
Dizziness	14 (4)	7 (6)	11 (5)	11 (4)	12 (5)	7 (6)	48 (5)	19 (5)
Sedation	13 (4)	1 (1)	12 (5)	8 (3)	15 (6)	2 (2)	38 (4)	24 (7)
Psychiatric disorders	111 (31)	33 (26)	59 (25)	61 (25)	57 (24)	33 (29)	243 (25)	96 (26)
Insomnia	51 (14)	14 (11)	29 (12)	35 (14)	26 (11)	14 (12)	118 (12)	42 (12)
Anxiety	29 (8)	12 (9)	16 (7)	14 (6)	11 (5)	9 (8)	62 (6)	21 (6)
Agitation	28 (8)	7 (6)	17 (7)	13 (5)	13 (5)	3 (3)	53 (6)	25 (7)
Psychotic disorder	16 (5)	5 (4)	6 (3)	7 (3)	4 (2)	4 (4)	26 (3)	12 (3)
Gastrointestinal disorders	58 (16)	25 (20)	47 (20)	44 (18)	62 (26)	28 (25)	206 (21)	62 (17)
Nausea	19 (5)	8 (6)	9 (4)	10 (4)	10 (4)	2 (2)	39 (4)	8 (2)
Vomiting	17 (5)	2 (2)	6 (3)	9 (4)	12 (5)	8 (7)	37 (4)	5 (1)
Constipation	20 (6)	7 (6)	8 (3)	7 (3)	7 (3)	4 (4)	33 (3)	14 (4)
Dyspepsia	14 (4)	3 (2)	6 (3)	5 (2)	12 (5)	6 (5)	32 (3)	13 (4)
Cardiac disorders	43 (12)	22 (17)	37 (16)	45 (18)	41 (17)	15 (13)	160 (17)	52 (14)
Tachycardia	10 (3)	3 (2)	17 (7)	18 (7)	18 (7)	2 (2)	58 (6)	13 (4)
Sinus tachycardia	15 (4)	11 (9)	9 (4)	10 (4)	17 (7)	8 (7)	55 (6)	20 (5)
Investigations	42 (12)	22 (17)	31 (13)	32 (13)	34 (14)	18 (16)	137 (14)	75 (21)
Electrocardiogram QTc prolonged	9 (3)	4 (3)	9 (4)	7 (3)	12 (5)	4 (4)	36 (4)	10 (3)

The most frequent ADRs (≥2% of subjects receiving ER OROS paliperidone) were headache (13.2%), tachycardia (6.6%), akathisia (6.5%), sinus tachycardia (5.5%), extrapyramidal disorder (5.4%), somnolence (4.9%), dizziness (4.8%), sedation (4.2%), tremor (3.4%), hypertonia (2.8%), dystonia (2.6%), orthostatic hypotension (2.5%), and dry mouth (2.4%).
Those ADRs which appeared to be dose-related included weight increased, headache, salivary hypersecretion, vomiting, dyskinesia, akathisia, dystonia, extrapyramidal disorder, hypertonia, and Parkinsonism. The only clinically relevant difference in reporting rates for common adverse events between the ER OROS paliperidone and olanzapine groups was for somnolence, which was more frequent with olanzapine.

The following represent all ADRs that were reported in the Invega-treated subjects in clinical trials.
Very common (≥10%): headache;
Common (≥1% to <10%)*:* abdominal pain upper, akathisia, asthenia, atrioventricular block first degree, bradycardia, bundle branch block, dizziness, dry mouth, dystonia, extrapyramidal disorder, fatigue, hypertonia, orthostatic hypotension, Parkinsonism, salivary hypersecretion, sedation, sinus tachycardia, somnolence, tachycardia, tremor, vomiting, and weight increased.
Uncommon (≥0.1% to <1%)*:* amenorrhea, anaphylactic reaction, breast discharge, dizziness postural, dyskinesia, edema, electrocardiogram abnormal, erectile dysfunction, galactorrhea, gynecomastia, grand mal convulsion, hypotension, increased appetite, ischemia, menstruation irregular, muscle rigidity, nightmare, oculogyration, palpitations, sinus arrhythmia and syncope;
Rare (≥0.01% to <0.1%) or *Very rare* (<0.01%): none.

In addition, in accordance with the CHMP request, a complete list of ADRs (coded using MedDRA terminology) reported with risperidone and not yet reported with paliperidone has been added to Section 4.8 of the SPC.

Adverse events in Double-Blind Study in elderly subjects (SCH-302)

Among elderly subjects with schizophrenia in Study SCH-302 (6-week, double-blind, placebo-controlled, flexible-dose study), treatment-emergent adverse events occurred at similar rates in the ER OROS paliperidone (67%) and placebo (71%) groups. Common adverse events that were more frequently (≥4% between-group difference in incidence) reported in subjects who received ER OROS paliperidone versus placebo were somnolence (9% vs 5% placebo), dizziness (7% vs 0 placebo), hypotension (5% vs 0 placebo), sinus tachycardia (add %), tachycardia (16% vs 0 placebo), and electrocardiogram QT corrected interval prolonged (7% vs 3% placebo). In the paliperidone group, ADRs judged to be severe included 1 case each of hypertonia, acute coronary syndrome, mania, hypotension, and ECG QT corrected interval prolonged. Of patients who experienced QT-prolongation, almost all had a prior history of cardiovascular disorders and/or cardiovascular adverse events or QTc prolongation reported before initiation of treatment.

Overall, the types and frequencies of ADRs reported in the elderly subjects (64 to 81 years) in this study were similar to those reported in the younger population of adult subjects with schizophrenia in Studies SCH-303, SCH-304, and SCH-305. However, based on the limited data and consistent with general clinical practice, a greater sensitivity of older individuals to ADRs cannot be ruled out, and this is reflected in the SPC. Of note are the cases of QT interval prolonged. Overall, cardiac events (including tachycardia) associated with paliperidone were observed in a higher frequency in this patient group compared with non-elderly.

Adverse events in Double-Blind recurrence Study (SCH-301)

Due to the design of this study (long-term, recurrence/relapse prevention study in adult subjects), only adverse events that newly appeared or worsened in severity after initiation of double-blind medication were considered treatment-emergent in the double-blind phase. The results of this study suggest that subjects who continue to receive ER OROS paliperidone following a period of stabilization may have a lower incidence of new treatment-emergent adverse events after the period of stabilization compared with those for whom treatment is newly initiated. TEAEs were reported at similar rates during the double-blind period for the ER OROS paliperidone (35%) and placebo (40%) groups. Only 4 adverse events occurred in at least 5% of subjects in either treatment group during the double-blind period, all of which were more frequent in the placebo group (schizophrenia, 15% vs 7%; psychotic disorder, 8% vs 0%; aggression, 5% vs 0%; insomnia, 6% vs 5%). The majority of these events were likely related to exacerbation of the underlying psychotic disorder after switching from open-label ER OROS paliperidone to placebo in the double-blind phase. There was no evidence of acute withdrawal symptoms in subjects abruptly withdrawn from ER OROS paliperidone treatment (i.e., switched to placebo).

Adverse events in Open-Label Extension Studies (pooled data)

For the Pooled Open-label Safety Analysis Set, 1 or more adverse events were reported during open-label treatment for 875 (75%) of the 1170 subjects treated with flexibly dosed, open-label ER OROS paliperidone (3-15 mg), including 67% of the 416 subjects who received open-label treatment for ≤6 months and 79% of the 754 subjects who received open-label treatment for >6 months as of the clinical cut-off date (1 November 2005). This small increase suggests an absence of direct proportionality between longer exposure and increased incidence of adverse events. Across all subjects who received open-label ER OROS paliperidone, the most common adverse events were insomnia (14%), headache (12%), and akathisia (10%). Most of the common adverse events were reported at higher rates among subjects who received open-label ER OROS paliperidone for >6 months compared to those who received treatment for ≤6 months; adverse events reported at a lower rate in subjects treated for >6 months included psychotic disorder (12% vs 6% for ≤6 vs >6 months, respectively) and schizophrenia (9% vs 5%). Since these events represent worsening of the underlying psychotic disorder, they most likely led to earlier treatment discontinuation, thereby explaining the shorter duration.

In general, there were no noteworthy differences in the reporting rates for most of the common adverse events as a function of previous double-blind treatment for the Pooled Open-label Safety Analysis Set. Exceptions included extrapyramidal disorder, dystonia, and sinus tachycardia, all of which were reported at rates during the open-label treatment period at least 2-fold higher among subjects who had previously received placebo compared with those who received prior treatment with ER OROS paliperidone. Rates for these 3 adverse events in the placebo/paliperidone group were generally consistent with those observed with ER OROS paliperidone for the Pooled Double-blind Safety Analysis Set. Most adverse event reports of EPS-related events, somnolence, and tachycardia occurred during the first 4 weeks of treatment with ER OROS paliperidone in the extension studies; incidence rates for these adverse events were lower at later time points.
Overall no particular safety issue was noted with long-term compared with short-term treatment.

Specific safety issues

Extrapyramidal symptoms (EPS)
A higher proportion of subjects who received 9, 12, and 15 mg of ER OROS paliperidone versus placebo or lower ER OROS paliperidone doses (3 or 6 mg) experienced EPS-related adverse events categorized as dystonia, dyskinesia, Parkinsonism, and hyperkinesias in the Pooled Double-blind Safety Analysis Set (table 21).

Table 21 : Treatment-Emergent Extrapyramidal Symptom (EPS) Related Adverse Events[a]
(Pooled Double-Blind Studies R076477-SCH-303, 304, 305: Safety Analysis Set)

		ER OROS Paliperidone					Olanzapine
EPS Group[a]	Placebo (N=355)	3 mg (N=127)	6 mg (N=235)	9 mg (N=246)	12 mg (N=242)	15 mg (N=113)	10 mg (N=364)
Dictionary-derived term	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Total no. with any EPS-related adverse event	**39 (11)**	**16 (13)**	**24 (10)**	**62 (25)**	**63 (26)**	**27 (24)**	**31 (9)**
Dyskinesia[b]	12 (3)	6 (5)	6 (3)	19 (8)	21 (9)	10 (9)	7 (2)
Dyskinesia	3 (1)	0	1 (<1)	1 (<1)	4 (2)	1 (1)	1 (<1)
Extrapyramidal disorder	8 (2)	6 (5)	5 (2)	17 (7)	18 (7)	9 (8)	6 (2)
Dystonia[b]	4 (1)	1 (1)	3 (1)	13 (5)	11 (5)	2 (2)	3 (1)
Dystonia	2 (1)	1 (1)	3 (1)	9 (4)	9 (4)	1 (1)	1 (<1)
Muscle spasms	1 (<1)	0	0	1 (<1)	2 (1)	1 (1)	1 (<1)
Oculogyration	0	0	0	5 (2)	0	0	0
Hyperkinesia[b]	14 (4)	5 (4)	7 (3)	20 (8)	24 (10)	11 (10)	8 (2)
Akathisia	14 (4)	5 (4)	7 (3)	20 (8)	23 (10)	11 (10)	7 (2)
Parkinsonism[b]	8 (2)	4 (3)	6 (3)	18 (7)	15 (6)	7 (6)	8 (2)
Drooling	1 (<1)	0	2 (1)	1 (<1)	0	2 (2)	1 (<1)
Hypertonia	4 (1)	3 (2)	3 (1)	10 (4)	8 (3)	4 (4)	5 (1)
Muscle rigidity	0	1 (1)	0	3 (1)	1 (<1)	0	0
Parkinsonism	0	0	1 (<1)	5 (2)	3 (1)	2 (2)	2 (1)
Tremor	12 (3)	4 (3)	6 (3)	11 (4)	8 (3)	3 (3)	8 (2)

[a] Only EPS-related adverse events reported in at least 5 (0.5%) of total subjects receiving ER OROS paliperidone are shown on this table.

[b] Dyskinesia includes MedDRA preferred terms of dyskinesia, extrapyramidal disorder, muscle twitching, tardive dyskinesia.
Dystonia includes MedDRA preferred terms of dystonia, muscle spasms, oculogyration, trismus.
Hyperkinesia includes MedDRA preferred terms of akathisia, hyperkinesia, restless legs syndrome.
Parkinsonism includes MedDRA preferred terms of bradykinesia, cogwheel rigidity, drooling, hypertonia, hypokinesia, muscle rigidity, musculoskeletal stiffness, parkinsonism.

EPS-related adverse events were reported for 33% of subjects receiving open-label ER OROS paliperidone during the run-in/stabilization phase of Study SCH-301; among these, 3 subjects experienced EPS-related adverse events (dyskinesia, akathisia, tremor) that resulted in the discontinuation of open-label ER OROS paliperidone. No subjects had a serious EPS-related adverse event or withdrew for these events during the double-blind phase of Study SCH-301. Dosing was initiated at 9 mg in Study SCH-301, and the higher rate of EPS-related adverse events during the run-in/stabilization phase is consistent with the higher rates of these events seen with doses of 9 mg to 15 mg in the Pooled Double-blind Safety Analysis Set (24%-26%), where 2 EPS-related adverse events were serious among ER OROS paliperidone-treated subjects (akathisia and dystonia), and ER OROS paliperidone treatment was discontinued due to an EPS-related adverse event in 0.6% of subjects.

There was no indication that EPS-related adverse events occurred more often in elderly subjects receiving ER OROS paliperidone compared with placebo in Study SCH-302.
In the Pooled Open-label Safety Analysis Set, the EPS-profile (incidence of EPS-related adverse events: 24%) was almost identical to the one seen in the Pooled Double-blind Safety Analysis Set for doses of 9 mg or higher, and in this Analysis Set, 1% of subjects were withdrawn for EPS-related adverse events, while 3 reports of akathisia and 2 reports of dystonia were considered serious.
Among subjects treated in Study SCH-701, no EPS-related adverse event was serious; 1 subject was discontinued for tremor and dyskinesia within 6 months of switching from double-blind placebo to paliperidone.
Across all of the Phase 3 studies (completed and ongoing), 2 subjects were reported to have tardive dyskinesia. Oculogyration was reported in 5 (<1%) subjects receiving ER OROS paliperidone in the completed Phase 3 double-blind studies, for 3 (0.3%) subjects receiving open-label ER OROS paliperidone treatment, and for 2 subjects treated with ER OROS paliperidone in Study R076477-SCH-1010. None of these reported events were serious or resulted in treatment discontinuation.
In conclusion, extrapyramidal symptoms were dose-related and occurred predominantly with doses of 9 mg/day or more, and this information is reflected in the SPC.

Suicidality
As of 28 February 2006, there were a total of 4 reports (3 in subjects receiving ER OROS paliperidone) of completed suicide among subjects participating in the completed Phase 1/2a studies or completed or ongoing Phase 3 clinical studies. These include 1 report of a completed suicide the day following discontinuation of open-label ER OROS paliperidone in a subject participating in Study SCH-301, 2 reports of completed suicide in subjects receiving open-label ER OROS paliperidone during extension Study SCH-703, and 1 report of a completed suicide in a placebo-treated subject in Study SCH-301.
In the Pooled Double-blind Safety Analysis Set, the percentage of adult subjects with schizophrenia who reported a suicidality adverse event (suicidal ideation or attempt) are similar for the ER OROS paliperidone (n=10, 1%), placebo (n=5, 1%), and olanzapine (n=5, 1%) groups. An estimate of the incidence of these events based on subject-exposure years indicated that the risk of suicidality adverse events was greater for placebo-treated subjects than for subjects treated with ER OROS paliperidone. The rates of suicidal ideation and suicide attempts per subject-years of exposure were 14.5 and 3.6, respectively, for the placebo group compared with 10.3 and 1.1, respectively, for the pooled ER OROS paliperidone group.
No elderly subject in Study SCH-302 had a suicide-related event.
In Study SCH-301, adverse events related to suicide were reported for 5 (1%) subjects during the run-in/stabilization phase on open-label ER OROS paliperidone, and for 5 subjects during the double-blind phase (4 in the placebo group and 1 in the ER OROS paliperidone group).
Adverse events related to suicidality were reported for 26 (2%) subjects in the Pooled Open-label Safety Analysis Set, were more frequent in those treated for ≤6 months than for those treated for >6 months, and most involved suicidal ideation.
In conclusion, there is no signal of an increased risk of suicidality based on the data presented.

Somnolence
In the Pooled Double-blind Safety Analysis Set, the percentage of subjects reporting somnolence, sedation, lethargy, or hypersomnia was similar among subjects receiving ER OROS paliperidone (9%) compared with placebo (7%). The rate of these events was similar at ER OROS paliperidone doses of 6 to 15 mg (9 to 11%), and was lower (6%) for the 3 mg dose group. Somnolence-related adverse events were reported for 19% of subjects treated with olanzapine in these studies.
In Study SCH-301, the frequency of somnolence-related adverse events was 6% for the run-in/stabilization phase and 2% for the double-blind phase (vs 0% for placebo). In Study SCH-302 in elderly subjects, the rate of somnolence-related adverse events for ER OROS paliperidone (9%) was similar to that observed in the double-blind studies in generally younger subjects, but higher than the rate of these events observed for elderly subjects treated with placebo (5%). A life table analysis for the Pooled Double-blind Safety Analysis Set indicated that most reports of somnolence-related adverse events occurred during the first week of treatment, regardless of treatment group.
For the Pooled Open-label Safety Analysis Set, somnolence-related adverse events were reported for 8% of subjects, and most occurred in the first month of treatment with open-label ER OROS paliperidone.

Across all completed double-blind studies, none of the reports of somnolence-related adverse events were serious, and 4 subjects discontinued ER OROS paliperidone as a result of this type of adverse event. For the open-label extension studies, 2 reports of somnolence-related adverse events were serious, and 2 resulted in discontinuation.
In conclusion, somnolence is an expected ADR, but appears to be less common than for the reference compound. Elderly subjects may be at higher risk, as was the case in Study SCH-302.

Effects on Serum Prolactin Levels
Median increases in prolactin levels from baseline were observed for adult subjects with schizophrenia of both sexes receiving ER OROS paliperidone, with median increases at end point larger among female subjects (81.14 ng/mL) than among male subjects (23.75 ng/mL) for the Pooled Double-blind Safety Analysis Set (all dose levels combined). There appeared to be a dose-relationship. The incidence of subjects of both sexes with treatment-emergent elevations in prolactin levels was higher in the ER OROS paliperidone group (70% and 62% for males and females, respectively) versus placebo (13% and 12% for males and females, respectively) or olanzapine (20% and 32% for males and females, respectively). Although a median increase in prolactin levels was also seen among elderly subjects and was more pronounced in female subjects, none of the elderly subjects experienced a potentially prolactin-related adverse event.

No noteworthy differences between paliperidone and IR risperidone were observed in 3 Phase 1 studies with regard to their effect on prolactin levels.

Across all the studies, the proportion of subjects who experienced potentially prolactin-related adverse events (amenorrhoea, gynaecomastia and galactorrhoea) remained below 4% for all dose groups (3mg, 6mg, 9mg and 12mg). None of these events was considered serious, and only one (anorgasmia) was rated as severe by the investigator.

Metabolic-Related Effects

GLUCOSE-RELATED ADVERSE EVENTS
In the Pooled Double-blind Safety Analysis Set, the percentage of subjects with glucose-related adverse events was comparable for the placebo (1%), ER OROS paliperidone (1%), and olanzapine (1%) groups. There was no indication of a dose-related trend in the occurrence of glucose-related adverse events with ER OROS paliperidone. The most common of these events was blood glucose increased, reported for 4 subjects receiving ER OROS paliperidone and 1 subject each receiving placebo or olanzapine. Glucose-related adverse events were considered serious for 2 subjects. Blood glucose increased occurred in a subject with no history of diabetes mellitus treated with ER OROS paliperidone 15 mg; this subject was withdrawn as a result of this adverse event, which resolved after discontinuation. In the second subject, who had a history of diabetes, hypoglycemia and diabetes mellitus were reported during treatment with ER OROS paliperidone 9 mg and were considered serious, but were not treatment limiting.
None of the elderly subjects with schizophrenia in Study SCH-302 had a glucose-related adverse event.

CHANGES IN SERUM GLUCOSE LEVELS
Mean changes from baseline to end point in serum glucose associated with ER OROS paliperidone treatment in all Phase 3 safety analysis sets were similar to that observed with placebo in the Pooled Double-blind Safety Analysis Set. Across the 5 completed double-blind studies, markedly abnormal elevations in serum glucose were reported for 4 subjects receiving ER OROS paliperidone, including 3 subjects who had such abnormalities in the run-in/stabilization phase of Study SCH-301 and for 3 subjects treated with open-label ER OROS paliperidone in the extension studies. Of the 7 subjects with markedly abnormal glucose levels (high or low) while receiving double-blind or open-label ER OROS paliperidone, 3 had adverse events associated with the markedly low (1 in a subject with a history of diabetes mellitus) or markedly high (2 subjects) glucose levels.
In conclusion, in these datasets, the frequency of glucose related ADRs were similar to placebo and appeared not to be dose-related.

CHANGES IN SERUM LIPID LEVELS

Mean changes in serum levels of total cholesterol, LDL cholesterol, HDL cholesterol, or triglycerides were small and not clinically noteworthy in the completed and ongoing Phase 3 studies.

CHANGES IN BODY WEIGHT AND BODY MASS INDEX

In the Pooled Double-blind Safety Analysis Set, the mean body weight and BMI increases in the ER OROS paliperidone 15 mg group (1.9 kg and 0.6 kg/m^2) were similar to those in the olanzapine group (2.0 kg and 0.7 kg/m^2), whereas the mean changes in the ER OROS paliperidone 3 mg to 12 mg groups (0.6 to 1.1 kg and 0.2 to 0.4 kg/m^2) were approximately half those seen in these other 2 groups. Similarly, weight increases from baseline of ≥7% were more common among subjects in the olanzapine and ER OROS paliperidone 15 mg groups (18% for each) compared to the placebo group (5%) or ER OROS paliperidone 3 to 12 mg dose groups (6 to 9%).

No noteworthy mean changes in body weight or BMI were seen among elderly subjects treated with a median modal dose of 9 mg/day (Study SCH-302).

Adverse events of weight increase were infrequent during the open-label extension studies with ER OROS paliperidone (3% and 5% for those treated for ≤6 or >6 months, respectively). None of these events were reported as serious; 2 subjects discontinued open-label ER OROS paliperidone due to weight increase, while 1 subject was withdrawn for an adverse event of weight decrease.

Overall, paliperidone is associated with an increase in BMI in an apparent dose-dependent manner, and this is reflected in the SPC. However, paliperidone appears not to be associated with lipid changes. The effect appears to be lower than for olanzapine, which is expected for a drug similar to risperidone.

Cardiovascular Effects

ORTHOSTATIC HYPOTENSION

In the Phase 3 studies, orthostatic hypotension was not reported as serious or treatment limiting in any subject treated with ER OROS paliperidone. In the Pooled Double-blind Safety Analysis Set, the incidence of orthostatic hypotension as an adverse event was comparable for ER OROS paliperidone doses of 3 mg (2%), 6 mg (1%) and 9 mg (2%) to that for placebo (1%), while higher reporting rates were seen for doses of 12 mg (4%) or 15 mg (3%). In Study SCH-301, the incidence of orthostatic hypotension as an adverse event was 1% during the run-in and stabilization phases; each of these events was mild and occurred early, between Days 1 and 25. Among the elderly subjects with schizophrenia in Study SCH-302, there were no reports of adverse events of orthostatic hypotension with ER OROS paliperidone (flexible dose range of 3 to 12 mg) or placebo.

Overall, paliperidone causes dose-dependent orthostatic hypotension as expected and in the SPC caution is recommended when INVEGA is to be administered in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension.

QT

A thorough QT study (Study SCH-1009) was performed: it was a double-blind, active-controlled, multicenter trial that evaluated the effects of IR paliperidone (8 mg/day dose, which generated supratherapeutic plasma levels on the QT interval) in 141 adults with schizophrenia and schizoaffective disorder. As required by the ICH E14 Guideline, the peak plasma concentration achieved in this study at steady-state with 8 mg IR paliperidone (113 ng/mL) was more than twice as high as that achieved by the highest dose of ER OROS paliperidone to be marketed (12 mg: 45 ng/mL; data from PAL-SCH-101). The primary ECG variable was the difference in day-averaged QTcLD between IR paliperidone 8 mg at steady state (Day 8) and placebo (Day 1). Moxifloxacin was included in the study as a positive control to evaluate assay sensitivity for the primary variable.

The 8 mg dose of IR paliperidone was associated with a small, albeit statistically significant, LS mean increase in the model-adjusted, day-averaged QTcLD of 5.5 msec (90% CI: 3.66, 7.25) relative to placebo (Day 1). Moxifloxacin 400 mg (Day 8) resulted in a LSM (SE) difference in QTcLD versus Day 1 (placebo) of 4.3 msec (90% CI: 2.88, 5.64). While the increase in the mean QTcLD interval in this study exceeded the 5 msec threshold for regulatory concern, it was less than a mean QTc interval increase of >20 msec that is generally accepted as the level of change that signals a substantial increase in the risk of arrhythmias. In addition, since the upper limit of the 90% confidence interval (7.25 msec) was below the predefined limit of 10.0 msec as described in ICH E14, the mean effect of

IR paliperidone 8 mg at steady-state (Day 8) on QTcLD was considered not to exceed the threshold level for regulatory concern. However, it is interesting to note that the upper limit of the 90% confidence interval exceeded the 10 msec value for the 1.5-hour observations on Days 2 and 4, and between 1 and 3 hours on Day 8 (≤13.62ms), and more patients in the paliperidone group (26%) compared with moxifloxacin (17%) had a QTc increase of 30-60 ms.

T_{max} was about 2 hours, both on Day 2 (single 4-mg dose) and on Day 8 (steady-state 8-mg dose). Further data explorations did not demonstrate a correlation between plasma concentration and effect on the mean changes from baseline QTcLD values, suggesting that the effects of paliperidone on QTcLD cannot be explained by plasma concentrations only.

The elderly may be more sensitive, as was suggested in Study SCH-302, and discontinuation due to QT-prolongation among the elderly is of note.

In accordance to what was agreed during the PhVWP May 2006 meeting, the SPC for paliperidone (as recommended for all neuroleptics) include appropriate warnings about the potential to prolong the QT and the potential for causing arrhythmias.

Following the CHMP request, the Applicant presented additional data clarifying that there were no gender-based differences concerning QT prolongation.

Study R076477 SCH-1009 was performed administering IR paliperidone formulation. However, the CHMP objected that the use of the modified-release paliperidone would have been more appropriate, since the effect on QTcLD cannot be explained by plasma concentrations only and a formulation influence cannot be excluded. The Sponsor performed an additional thorough QT study (Study R076477-SCH-1014) to confirm and extend the cardiovascular safety profile of paliperidone ER in subjects with schizophrenia or schizoaffective disorder. This was a non-inferiority study comparing the effects on QTcLD of steady state paliperidone ER at 12 mg and the supratherapeutic dose of 18 mg with steady state quetiapine (a marketed antipsychotic that is considered to have an acceptable cardiovascular safety profile) at 400 mg twice daily. The observed QTcLD prolongation was numerically less with the supratherapeutic dose of 18 mg of paliperidone ER than with quetiapine, and overall, these data further confirmed the cardiovascular safety of the ER formulation of paliperidone at the maximum recommended dose of once daily 12 mg, and at a dose of once daily 18 mg, which is 50% above this recommendation. No evidence of clinically relevant QTcLD prolongation with paliperidone ER in comparison to quetiapine or placebo was observed, so the risk of QTcLD prolongation seems to be similar to paliperidone IR and risperidone.

CHANGES IN RECORDED ECG PARAMETERS

Beside observed increases in heart rate, the incidence of ECG parameters outside clinically important limits during the double-blind period was similar in the placebo and ER OROS paliperidone treatment groups for the Pooled Double-blind Safety Analysis Set and for double-blind Studies SCH-302 and SCH-301. Compared with placebo (23%), a higher percentage of subjects treated with ER OROS paliperidone (36%) or olanzapine (31%) had high heart rate values (>=100 bpm). This finding is consistent with pulse rate results. Similarly, high heart rate values were more common for the ER OROS paliperidone group compared to the placebo group among elderly subjects with schizophrenia in Study SCH-302 (25% vs 5%) and during the double-blind phase of Study SCH-301 (7% vs 2%). The lower incidence of high heart rate values during double-blind treatment with ER OROS paliperidone in Study SCH-301 relative to the other double-blind studies may suggest an attenuation of this effect over time; 32% of subjects had increases in heart rate during open-label ER OROS paliperidone treatment during the run-in/stabilization phase of Study SCH-301.
Multiple ECGs were recorded during the open-label extension studies, and the incidence of an elevation in heart rate to >= 100 bpm was 23%.
Overall, paliperidone causes an increase of heart rate as expected, similar to risperidone.

CHANGES IN CORRECTED QT INTERVALS

In the Pooled Double-blind Safety Analysis Set, LS mean differences in QTcLD from placebo treatment were < 4 ms with all doses of ER OROS paliperidone. None of the adult subjects with schizophrenia receiving ER OROS paliperidone or placebo in these studies had a QTcLD of 480 msec

or higher at any time during double-blind treatment, although a QTcLD value of >480 msec (508 msec) was recorded for one subject (67-year-old woman) on the day following study completion. This subject entered the open-label extension and the QTcLD did not worsen. She did not experience a cardiovascular adverse event and no abnormal vital sign values were recorded. One subject receiving olanzapine had a QTcLD value of ≥480 msec (531 msec) during double-blind treatment and was hospitalized for QTc interval prolongation and hypokalemia; the average predose QTcLD value for this subject was normal (421 msec) and he was withdrawn from study treatment.
The incidence of increases in QTcLD of 30-60 msec was comparable for the placebo and ER OROS paliperidone 3 to 12 mg groups (9% and 5-8%, respectively) but was higher for the 15 mg dose group (12%). One subject each in the ER OROS paliperidone 12 mg and olanzapine groups had a change exceeding 60 msec at one time-point (changes of 62 and 110 msec, respectively).

Similar results were observed in Study SCH-302 among elderly subjects with schizophrenia and in Study SCH-301 among adult subjects with schizophrenia.

Overall, the frequency of QT-prolongation was higher in the 15 mg groups in the double-blind trials. Discontinuation due to QT-prolongation among the elderly is of note. It should be remembered that patients with significant cardiovascular disease were excluded.

ADVERSE EVENTS SUGGESTIVE OF PROARRHYTHMIC POTENTIAL
No safety signal of a proarrhythmic potential emerged from the data provided.

CHANGES IN BLOOD PRESSURE AND HEART RATE
There were no clinically relevant differences between ER OROS paliperidone groups and placebo group with regard to mean changes from baseline in standing or supine systolic and diastolic blood pressure in the Pooled Double-blind Safety Analysis Set, for Study SCH-302, or for Study SCH-301.

Results from the completed double-blind studies and open-label extensions of double-blind studies were consistent in showing that ER OROS paliperidone treatment is associated with increased pulse rate. The percentages of subjects with standing or supine pulse rates of >100 bpm with an increase from baseline of ≥15 bpm were higher in the pooled ER OROS paliperidone dose group (31% and 17%, respectively) than with placebo (22% and 10%, respectively) for the Pooled Double-blind Safety Analysis Set. The highest incidence of elevated pulse rate was observed in the 15 mg dose group (39% and 22%), and there was no consistent relationship between ER OROS paliperidone dose and the occurrence of elevated pulse rates among subjects who received lower doses. The percentages of ER OROS paliperidone-treated subjects with adverse events of tachycardia and sinus tachycardia (6% for each) were lower than the percentages with abnormally high pulse rates. Few reports of tachycardia (2 of 58 cases) and sinus tachycardia (2 of 55 cases) in ER OROS paliperidone-treated subjects were assessed as severe in severity and only 5 cases in total were reported as serious or were treatment limiting.

While more elderly subjects with schizophrenia receiving ER OROS paliperidone compared with placebo had elevated standing or supine pulse rates of >100 bpm with an increase of ≥15 bpm in Study SCH-302, the rates (12% and 7%, respectively) were less than that observed in the other double-blind Phase 3 studies. Among the elderly population studied in Study SCH-302, there was a closer correspondence between reported rates for sinus tachycardia (9%) and tachycardia (7%) in the ER OROS paliperidone group and the observed percentages of subjects with abnormal elevations in pulse rate. No elderly subject was withdrawn from ER OROS paliperidone therapy due to sinus tachycardia or tachycardia, and none of these reported adverse events were considered serious.

Results for Study SCH-301 were consistent with those reported for the other double-blind studies.
In conclusion, in similarity with risperidone paliperidone causes a dose-dependent increase of heart rate, which is expected.

Other Adverse Events of Clinical Interest

NEUROLEPTIC MALIGNANT SYNDROME
Neuroleptic malignant syndrome (NMS) characterised by hyperthermia, muscle rigidity, autonomic

instability, altered consciousness, and elevated serum creatine phosphokinase levels has been reported to occur with antipsychotics, including paliperidone. Therefore, special warnings concerning NMS have been included in the SPC.

OVERDOSE
Experience from overdose is very limited. Three cases were reported during the 5 phase 3 studies and their open-label extension studies, all of which recovered within 5 days (with no treatment in the first case, and after treatment with ziprasidone or with infusions of Ringers, saline, levulose and furosemide in the second and third case respectively). Exhaustive information regarding overdose is included in section 4.9 of the SPC.

Dose Relationships for Safety
The placebo-controlled, fixed dose design of Phase 3 Studies SCH-303, SCH-304, and SCH-305 allow examination of dose relationships for ER OROS paliperidone with respect to safety-related findings. While a dose relationship was not observed for the rates of treatment limiting or serious adverse events, certain safety-related findings were more common with the highest doses of ER OROS paliperidone tested, namely 12 and 15 mg:

- higher reporting rates for headache, salivary hypersecretion, vomiting, and certain EPS-related adverse events (dyskinesia, akathisia, dystonia, extrapyramidal disorder, hypertonia, and Parkinsonism) that were generally not serious or treatment limiting;
- increases in body weight and BMI (largest with 15 mg dose);
- increases in serum prolactin levels that were not accompanied by a similar dose-related trend in reporting rates of potentially prolactin-related adverse events;
- a higher reporting rate for orthostatic hypotension as well as changes in pulse and blood pressure consistent with orthostatic hypotension (seen mainly with 15 mg dose);
- greater percentage with elevated pulse rate (seen for 15 mg dose); and
- mean increases of <5 msec in QTcLD and higher rate of QTcLD increases of 30-60 msec (seen mainly with 15 mg dose).

These findings are expected. Of note is the observation of a possible dose-relationship regarding QT-prolongation.

- **Serious adverse event/deaths/other significant events**

Serious adverse events and deaths
Serious adverse events
In the Pooled Double-blind Safety Analysis Set, the percentage of subjects with serious adverse events was the same for the ER OROS paliperidone (n=55, 6%), placebo (n=23, 6%), and olanzapine groups (n=22, 6%). Psychotic disorder and schizophrenia were the adverse events most commonly reported as serious, and most of these events, as well as other serious psychiatric disorders, occurred in subjects hospitalized due to exacerbation of psychotic symptoms. Serious adverse events other than psychiatric disorders were uncommon (incidence <1% in total ER OROS paliperidone group) and showed no apparent differences in incidence between the treatment groups. There was no apparent dose relationship in the incidence of any serious adverse event among subjects who received ER OROS paliperidone.

In Study SCH-302, a higher proportion of elderly subjects treated with placebo (n=3, 8%) experienced adverse events considered serious compared with those receiving ER OROS paliperidone (n=2, 3%).

During the run-in/stabilization phase of Study SCH-301, 30 (6%) subjects receiving open-label ER OROS paliperidone experienced a serious adverse event, and the rate of serious adverse events during the double-blind phase was higher for the placebo group (16%) than for the ER OROS paliperidone group (8%). As in the other studies, most of the serious adverse events in SCH-301 represented exacerbations of psychiatric conditions.

Up to 1 November 2005, adverse events were reported as serious for 172 (15%) subjects who received open-label ER OROS paliperidone in the Pooled Open-label Safety Analysis Set. Consistent with the observations for the completed double-blind studies, hospitalizations for psychotic disorder (5%),

schizophrenia (4%), and agitation (1.2%) were the only serious events reported for >1.0% of the 1170 subjects in this analysis set.

6 (3%) subjects in the Study SCH-701 Safety Analysis Set had a serious adverse event while receiving open-label ER OROS paliperidone, including 5 who had previously received double-blind placebo (schizophrenia, paranoia, suicide attempt, tibia fracture, syncope) and 1 previously treated with ER OROS paliperidone (schizophrenia).

Between 2 November 2005 and 28 February 2006, serious adverse events were reported for 21 subjects in the ongoing open-label extension studies, 1 of which was a death from unknown causes, 1 was a suicide attempt, 1 was an overdose, 1 was a hospitalization for seizure events, and the remainder mainly involved hospitalizations for exacerbations of psychotic symptoms/condition.

Overall, there was no indication of an increased frequency of SAE for paliperidone compared with placebo.

Deaths
Across all completed and ongoing clinical studies with ER OROS paliperidone, a total of 10 deaths have been reported as of 28 February 2006, including 5 deaths among subjects treated with ER OROS paliperidone, 4 among those receiving placebo, and 1 in an olanzapine-treated subject. The overall fatality rate in the clinical studies with ER OROS paliperidone is not different from that for placebo or olanzapine in these studies. One death was reported among the subjects receiving paliperidone in completed clinical studies: a 36-year-old male receiving ER OROS paliperidone in Study SCH-301 committed suicide. As of 28 February 2006, 4 deaths were reported among subjects treated with ER OROS paliperidone in the ongoing extension studies: 2 fatalities were the result of completed suicides (both in Study SCH-703), one was due to bronchopneumonia (SCH-702), and for one information concerning the cause of death is not known (Study SCH-701). The 4 deaths reported among placebo-treated subjects were the result of coma, cardiac arrest, completed suicide, and gun shot wound, and the death in the olanzapine-treated subject was due to cardio-pulmonary arrest.

Overall, there is no signal of an increased risk of death from any cause based on the data presented.

Subject number (Study number)	Age (Years) Sex	Dictionary-derived Term Reported Term	Day of AE Onset[a]	Action Taken with Treatment	Relationship to Study Drug[b]
Phase 3 Double-Blind Studies					
Treatment Group: ER OROS paliperidone (post run-in phase)					
(R076477-SCH-301)	36 Male	Completed suicide death (suicide - strangulation by hanging)	72	None	Very likely
Treatment Group: Placebo					
(R076477-SCH-302)	75 Female	Coma Coma	21	None	Not related
		Subdural hygroma subdural collection	19	None	Not related
(R076477-SCH-302)	73 Male	Cardiac arrest cardiopulmonary decompensation (due to lung cancer)	42	None	Not related
		Lung neoplasm malignant lung cancer	42	None	Not related
		Respiratory arrest cardiopulmonary decompensation (due to lung cancer)	42	None	Not related
(R076477-SCH-301)	47 Male	Gun shot wound multiple gunshot wounds	174	None	Not related
(R076477-SCH-301)	50 Male	Completed suicide suicide	152	None	Not related
Treatment Group: Olanzapine 10 mg					
(R076477-SCH-303)	32 Male	Cardio-respiratory arrest cardio-respiratory arrest	16	None	Not related
Phase 3 Open-Label Studies					
Treatment Group: Pla/Pali, ≤6 months					
(R076477-SCH-702)	70 Male	Bronchopneumonia Bronchopneumonia	157[c]	None	Not related
Treatment Group: Pali/Pali, >6 months					
(R076477-SCH-703)	42 Female	Completed suicide fall from 3rd floor	283	None	Not related
Treatment Group: Olan/Pali, >6 months					
(R076477-SCH-703)	31 Female	Completed suicide suicide with medication[d]	238	None	Not related

[a] Study day is in reference to the start of double-blind medication, except for **the fisr subject (36 year old male; start of run-in phase)**

[b] Relationship based on assessment of investigator.

[c] Subject was withdrawn from the study due to a serious adverse event (electrocardiogram QT corrected interval prolonged) and died of non-treatment-emergent bronchopneumonia 4 days after receiving the last dose of study medication.

[d] Subject ingested venlafaxine and lorazepam.

Table 22.

- **Laboratory findings**

The overall clinical laboratory test results in the completed and ongoing Phase 3 studies included in this submission did not suggest any safety concerns associated with the use of paliperidone ER OROS in the treatment of schizophrenia. Overall, changes in laboratory test values for individual subjects other than prolactin were transient, of limited severity, and not considered clinically relevant.

- **Safety in special populations**

Pregnancy and lactation
The safety of paliperidone for use in women who are pregnant or lactating has not been established. All clinical studies specifically excluded women who were pregnant or lactating, and women who became pregnant were to be discontinued from the study. No pregnancies occurred during the ER OROS paliperidone clinical trials. Based on the available data, ER OROS paliperidone should only be used in pregnancy if the benefits outweigh the risks or unless clearly necessary, and it should not be used while breast feeding. This is reflected in the SPC (section 4.6).

Children and adolescents
The safety and effectiveness of ER OROS paliperidone in patients <18 years of age have not been studied, and this is reflected in the SPC.

Age, gender, race
There were no noteworthy differences in adverse events reported with respect to gender, age, or racial group for the Pooled Double-blind Safety Analysis Set. In the SPC no dose adjustment for INVEGA is recommended based on gender, race or smoking status.

Immunological events
Immunological events were not commented by the MAH, but paliperidone is not expected to be associated with immunological events.

Elderly
The safety profile of paliperidone is similar for elderly and non-elderly subjects. However, elderly patients are more likely to have decreased creatinine clearance compared with younger patients. Based on the limited data available and consistent with general clinical practice, a greater sensitivity of older individuals to ADRs cannot be ruled out, and this is reflected in the SPC (section 4.8). Discontinuation of paliperidone treatment due to QT prolongation among elderly is of note.
Elderly patients with dementia were excluded from clinical trials with paliperidone and thus this risk could not be assessed. Warnings and precautions regarding the use in elderly patients with dementia are included in section 4.4 of the SPC.

- Safety related to drug-drug interactions and other interactions

No safety issues in this respect can be identified from the submitted clinical data. However, as already mentioned, the SPC has included certain key elements regarding cardiotoxicity, in accordance with the "Pharmacovigilance Working Party Public Assessment Report on Neuroleptics and Cardiac safety, in particular QT prolongation, cardiac arrhythmias, ventricular tachycardia and torsades de pointes".

- Discontinuation due to adverse events

In the Pooled Double-blind Safety Analysis Set, the proportion of subjects that reported adverse events leading to study discontinuation was the same across the Invega (5%), placebo (5%), and olanzapine groups (5%). The most common adverse events that led to discontinuation were psychotic disorder and agitation, and their incidence events showed no clinically relevant difference between treatments. Other treatment-limiting events occurred infrequently and showed no pattern related to treatment or to Invega dose. Discontinuation due to QT-prolongation among the elderly is of note.

- Post marketing experience

Invega has not been marketed in any country at the time of the submission. There is no post marketing experience. The MAH has submitted a risk management plan and a pharmacovigilance plan, apart from routine pharmacovigilance practices, is not deemed necessary. The pharmacovigilance system as described by the applicant is considered acceptable.

1.1 Pharmacovigilance

Detailed description of the Pharmacovigilance system
The CHMP considered that the Pharmacovigilance system as described by the Applicant fulfils the legislative requirements.

In the data submitted the Applicant has provided information which ensures that the necessary resources and systems are in place to support routine pharmacovigilance activities that meet the needs for this product.

Risk Management Plan
The MAA submitted a risk management plan. The CHMP, having considered the data submitted, was of the opinion that

- routine pharmacovigilance was adequate to monitor the safety of the product

and

- no additional risk minimisation activities were required beyond those included in the product information.

The Applicant has provided a good and thorough discussion about potential risks.
Following request by the CHMP, the MAH submitted a document detailing the assessment of the development of breast cancer, which was not originally included in the application.
It has been demonstrated by the applicant that the drilling process is acceptably controlled by the 'automated current draw verification system'. However, in-process controls conducted during the manufacturing process allow a relatively high percentage of tablets which do not have an orifice.
The CHMP envisaged the possibility to address the safety/efficacy implications of this quality issue in the RMP. As a response, the Applicant proposed to include in the INVEGA Risk Management Plan the warning of a potential risk for patients to be exposed to paliperidone ER tablets without an orifice and a detailed description of the risk assessment performed. According to the Applicant, the potential risk of such an exposure can be managed with quality controls during the manufacturing process, postmarketing surveillance for product quality reports of "no orifice" tablets, and monitoring of postmarketing reports of lack of efficacy (e.g. Periodic Safety Update Reports, and no additional risk management activities are required to minimize this risk. The CHMP accepted the Sponsor proposal; as a result, the inclusion of the proposed statement in the RMP was regarded sufficient, and no further activities were deemed necessary.
Based on the identified risks, potential risks, and pharmacological class effects, and the vast postmarketing experience with risperidone, routine pharmacovigilance is considered sufficient for post-authorisation safety monitoring. Overall, no specific pharmacovigilance plan or risk minimisation steps apart from routine pharmacovigilance practices are considered indicated.

Routine pharmacovigilance would include: AE collection and single case processing, drafting and review of aggregate reports (Health Authority Specific Reports including ad hoc reports requested from Health Authorities, Periodic Safety Update Reports, Annual Safety Reports), and surveillance and signal detection (both intra-product and inter-product signaling utilising using various databases such as SCEPTRE, FDA/AERS Database, WHO Vigibase Database, review of lot-related adverse events or product quality/technical complaints).

Table Summary of the **risk management plan (table 23).**

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Identified Risks		
ECG QT corrected interval	Appropriate product labelling and routine pharmacovigilance	None
Orthostatic hypotension	Appropriate product labelling and routine pharmacovigilance	None
Extrapyramidal disorders/Tardive dyskinesia	Appropriate product labelling and routine pharmacovigilance	None
Seizures (Convulsions)	Appropriate product labelling and routine pharmacovigilance	None

Hyperprolactinaemia and related adverse events	Appropriate product labelling and routine pharmacovigilance	None
Hyperglycaemia and related events	Appropriate product labelling and routine pharmacovigilance	None
Weight gain	Appropriate product labelling and routine pharmacovigilance	None
Somnolence	Appropriate product labelling and routine pharmacovigilance	None
Patients with renal disease	Appropriate product labelling and routine pharmacovigilance	None
Dysphagia	Appropriate product labelling and routine pharmacovigilance	None
Body temperature dysregulation	Appropriate product labelling and routine pharmacovigilance	None
Potential for Overdose	Appropriate product labelling and routine pharmacovigilance	None
Neuroleptic Malignant Syndrome	Appropriate product labelling and routine pharmacovigilance	None
Potential Risks		
Off label use in Paediatric Patients	Appropriate product labelling and routine pharmacovigilance	None
Off label Use	Appropriate product labelling and routine pharmacovigilance	None
Patients with Parkinson's Disease or Dementia with Lewy Bodies	Appropriate product labelling and routine pharmacovigilance	None
Increased Risk of Overall Mortality in Elderly Patients with Dementia	Appropriate product labelling and routine pharmacovigilance	None
Increased Risk of Cerebrovascular Adverse Events in Elderly Patients with Dementia	Appropriate product labelling and routine pharmacovigilance	None
Priapism	Appropriate product labelling and routine pharmacovigilance	None
Antiemetic effect	Appropriate product labelling and routine pharmacovigilance	None
Potential for Cognitive and Motor Impairment	Appropriate product labelling and routine pharmacovigilance	None
Misuse and Abuse	Appropriate product labelling and routine pharmacovigilance	None
Gastrointestinal obstruction secondary to formulation	Appropriate product labelling and routine pharmacovigilance	None
Medication Errors	Appropriate product labelling and routine pharmacovigilance	None
Pituitary Tumors/Mammary Tumors and Endocrine Pancreas tumors	Appropriate product labelling and routine pharmacovigilance	None
Abnormal Embryofetal development	Appropriate product labelling and routine pharmacovigilance	None
Potential for Patients to Be Exposed to Paliperidone ER OROS tablets without orifices	Routine pharmacovigilance	None
Potential for Transmission of Infectious Agents	Paliperidone ER OROS tablets are in compliance with the "Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMEA/410/01-Rev.2)	None

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

5 Overall conclusions, risk/benefit assessment and recommendation

Quality
The quality of the product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. There are no unresolved quality issues, which have a negative impact on the Benefit Risk balance of the product.

Non-clinical pharmacology and toxicology
Non-clinical pharmacology and toxicology were sufficiently documented in the non clinical studies program for paliperidone. Since paliperidone is the major metabolite of risperidone, comparative repeat-dose toxicity studies with paliperidone and risperidone were carried out. In line with given scientific advice, no 12-month repeat-dose toxicity study in dogs or carcinogenicity studies in rats and mice were performed with paliperidone. These studies were bridged to studies previously conducted with risperidone in support of the marketing application for Risperdal®.
Toxicity findings related to exaggerated pharmacology, particularly due to dopamine D2 antagonism, were numerous and included treatment-related sedation and (palpebral) ptosis, enhanced prolactin release was associated with changes in the pituitary gland, mammary gland, endocrine pancreas, female genital tract, male accessory sex organs and adrenal glands, changes in body weight and QTc prolongation and testes effects, probably unrelated to exaggerated pharmacology.
In similarity to risperidone, paliperidone showed no genotoxic potential. However, in carcinogenicity studies performed with risperidone in mice and rats, treatment related tumour findings in the mammary gland, endocrine pancreas and pituitary were noted. Paliperidone was not teratogenic in rat and rabbit, but showed embryotoxicity at a maternally toxic dose in rats.
In conclusion, similar toxicity profiles were seen after administration of paliperidone and risperidone. No unexpected findings were noted after paliperidone treatment. Since photogenotoxicity cannot be adequately evaluated using clinical safety data the Applicant is requested to submit an in vitro photomutagenicity test as a follow-up measure.

Efficacy
In total 1982 subjects were screened across the 3 short-term phase 3 pivotal studies (SCH-303, SCH-304, and SCH-305) constituting the clinical development program for paliperidone ER OROS in schizophrenia, from which 1692 subjects were enrolled and randomised to double-blind treatment. A total of 972 subjects completed these studies. Overall, the clinical program is adequate with respect to experimental design, diagnostic criteria and study endpoints.
The three phase III short-term studies performed are of adequate design and demonstrate short-term efficacy of different fixed doses (3-15 mg) of paliperidone ER OROS in patients experiencing an acute episode of schizophrenia. In these studies, a consistent effect for all doses relative to placebo has been demonstrated and the effect size is as expected for an anti-psychotic drug, and indeed it is comparable to olanzapine, the active comparator in the studies.

Controlled data on maintenance of effect consists of a study (SCH-301) designed to demonstrate recurrence prevention. A total of 530 subjects were enrolled in the open-label run-in phase, of which 312 entered the open-label stabilisation phase, and 207 were randomized to double-blind treatment. However, patients were included during an acute episode and despite 14 weeks of open label active treatment prior to randomisation most of the separation between the recurrence-free curves occurred during the first weeks after randomisation. This indicates that relapse rather than recurrence prevention has been demonstrated, and the study is not sufficient to support a recurrence prevention claim. Nevertheless, the results are supportive of a maintained effect for patients who initially respond.

An additional phase 3 short-term study (SCH-302) was performed on a total of 114 elderly (65 years of age or older) schizophrenic patients to determine, compared to placebo, the safety and efficacy of flexibly dosed Invega administered once daily for 6 weeks. A significant, but less pronounced effect has been demonstrated in elderly patients.

Safety
At the time of MAA submission, the combined exposure to paliperidone ER across all Phase 3 studies (completed and ongoing) was 921.31 subject-years for the 2,054 subjects with schizophrenia who received at least 1 dose of paliperidone ER across the dose range of 3 mg to 15 mg. Based on the cumulative safety results presented, the combined exposure to paliperidone ER in Phase 3 clinical trials in 2,054 adults and elderly subjects with schizophrenia is 1092.88 subject-years. This represents an increase of 171.57 patient-years.

Across all Phase 3 studies, 562 subjects were treated for more than 1 year (>52 weeks), including 415 subjects in the pooled Phase 3 studies (Studies R076477-SCH-302, -303, -304, -305, -702, -703, -704, and -705) and 147 subjects in Studies R076477-SCH-301/701.

Through the cut-off date of 26 June 2006 (31 August for deaths and other serious adverse events), there were a total of 10 deaths in all completed and ongoing studies of paliperidone ER.

The most common ADRs observed with Invega that were treatment related were headache, weight increase, tachycardia, bradycardia, akathisia, sinus tachycardia, extrapyramidal symptoms, somnolence, dizziness, sedation, tremor, hypertonia, dystonia, orthostatic hypotension, dry mouth and QTc prolonged. Asymptomatic increase of serum prolactin levels is very frequent.
Overall, discontinuation rate due to adverse events was similar for placebo and Invega across all studies.

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

Having considered the safety concerns in the risk management plan, the CHMP considered that the proposed activities described in section 3.5 adequately addressed these.

Overall, the safety profile is as expected for an active metabolite of risperidone. Thus, the available information indicates that the risks associated with use of paliperidone in adults with schizophrenia are acceptable and similar to risperidone at recommended doses.

- User consultation

User testing has been performed on the Patient Information Leaflet and from the results it can be concluded that the relevant information is accessible and understandable for the patients.

Risk-benefit assessment
Efficacy of paliperidone in the treatment of schizophrenia has been demonstrated relative to placebo and with a magnitude of effect similar to the active comparator olanzapine and to what have been observed for other drugs for treatment of schizophrenia. In addition, studies of sufficient duration according to guidelines have demonstrated maintenance of effect in patients initially responding to treatment.

The extended release formulation may enhance initial tolerability and permits initiation of treatment without the need for dose titration, and this may represent an advantage compared to IR risperidone.

Human pharmacokinetic studies have shown a food interaction, which may increase the variability in exposure. Standardised administration of paliperidone in relation to food intake is therefore recommended.

In non-clinical studies, similar pharmacological and toxicological profiles after administration of paliperidone and risperidone were demonstrated. Since photogenotoxicity cannot be adequately evaluated using clinical safety data, the Applicant is requested to submit an *in vitro* photomutagenicity test as a follow-up measure.

The clinical safety profile is as expected for an active metabolite of risperidone and appears similar to that of risperidone. The available information indicates that the risks associated with the use of paliperidone in adults with schizophrenia are acceptable and similar to risperidone at recommended doses.

The most common ADRs observed with Invega that were treatment related were headache, weight increase, tachycardia, bradycardia, akathisia, sinus tachycardia, extrapyramidal symptoms, somnolence, dizziness, sedation, tremor, hypertonia, dystonia, orthostatic hypotension, dry mouth and QTc prolonged. Asymptomatic increase of serum prolactin levels is very frequent.

Overall, discontinuation rate due to adverse events was similar for placebo and Invega across all studies.

The overall benefit/risk of paliperidone ER OROS tablets is positive.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that

- routine pharmacovigilance was adequate to monitor the safety of the product

and

- no additional risk minimisation activities were required beyond those included in the product information.

Similarity with authorised orphan medicinal products

Not applicable

Market exclusivity

Not applicable

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Invega prolonged release tablets in the treatment of schizophrenia was favourable and therefore recommended the granting of the marketing authorisation.