EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Assessment report

Invega

International nonproprietary name: paliperidone

Procedure No. EMEA/H/C/000746/II/0023

Variation Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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1. Scientific discussion

1.1. Introduction

Schizoaffective disorder is a common, chronic, and disabling mental illness. Schizoaffective disorder as defined using Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) criteria has features of both schizophrenia—including 2 or more of the following symptoms: hallucinations, delusions, disorganized speech, grossly disorganized or catatonic behaviour, or negative symptoms—and prominent affective symptoms consistent with major depression or mania[1]. According to DSM-IV, a diagnosis of schizoaffective disorder is made when the symptom criteria for schizophrenia are met and during the same continuous period there is a major depressive episode, manic episode, or mixed episode. During that same period, hallucinations or delusions must be present for at least 2 weeks in the absence of prominent mood symptoms.

Schizoaffective disorder includes all the signs and symptoms of a manic episode and/or a major depressive episode, in addition to the presence of symptoms consistent with schizophrenia. Nevertheless, the clinical features of schizoaffective disorder differ from bipolar disorder and schizophrenia in important ways, including prognosis and approaches to treatment. The course of schizoaffective disorder is ill defined, with overall prognosis appearing to be intermediate to that of schizophrenia and affective disorders[2].

The lifetime prevalence of schizoaffective disorder ranges from 0.3% to 0.8%[3]. The incidences of schizoaffective disorder and schizophrenia were approximately 24% and 32%, respectively, among frequent users of mental health services[4].

Schizophrenia and schizoaffective disorder have similarities in terms of symptoms, comorbidities, and genetic risk. Thus, atypical antipsychotics may be particularly useful in the treatment of schizoaffective disorder. However, currently there is no antipsychotic that has been approved for use in this indication in the European Union (EU).

In this type II variation, the MAH initially applied for an extension of indication of Invega as follows:

"Treatment of schizoaffective disorder as monotherapy or in combination with mood stabilisers and/or antidepressants."

Furthermore, the MAH requested consideration of this application under Article 14(11) of Regulation (EC) No 726/2004 and submitted a justification that the application concerns a new therapeutic indication which is claimed to bring a significant clinical benefit in comparison with existing therapies.

Invega prolonged release tablets (Paliperidone ER) are currently approved in the European Union (EU) for the treatment of schizophrenia with recommended dose of 6 mg once daily. Dosage adjustment may be required within the recommended range of 3-12 mg once daily.

Paliperidone (9-hydroxy-risperidone) belongs to the class of atypical antipsychotics and is the major metabolite of risperidone, used for the treatment of schizophrenia.

[1] APA 2000
[2] Marneros 1990, Grossman 1991, Harrow 2000
[3] Perala 2007, Malhi 2008
[4] Kent 1995

1.2. Non clinical aspects

Environmental risk assessment (ERA)

The MAH predicted that based on available epidemiological studies, the approval of the proposed indication will not significantly increase the use of paliperidone in the EU. Taking into account the updated calculation of the PEC refinement based on actual use of the product and that in the studies, both patients with schizoaffective disorder and schizophrenia were included, the ERA was considered acceptable by the CHMP.

1.3. Clinical aspects

The development program completed to support the proposed extension of indication consisted of:

- Two Phase I studies to investigate the possible interactions between divalproex sodium and paliperidone in healthy subjects (R076477-BIM-1003) and in clinically stable patients with schizophrenia, bipolar I disorder or schizoaffective disorder (R076477-BIM-1004), when co-administered;

- Two randomised, double-blind, placebo-controlled, parallel-group, 6 week, Phase III studies, to assess the efficacy and safety with 2 dose levels(R076477-SCA-3001)[5] and flexible doses (R076477-SCA-3002)[6] of paliperidone

Additionally, the MAH also provided some pharmacokinetic (PK) data from patients with schizoaffective disorder and the results from an in vitro induction study (FK5875), previously submitted in the withdrawn application (EMEA/H/C/746/II/19).

A Phase 3b safety and tolerability study (SCH-4005) in subjects with schizophrenia or schizoaffective disorder and with active hepatic disease is also currently ongoing.

In April and May 2009, the MAH sought national scientific advices at the MPA and BfARM, respectively on whether the proposed clinical program could support a claim for an indication in schizoaffective disorder. During the national scientific advices, the main considerations were related to the following requirements: sensitivity analysis related to efficacy (responder analysis); subgroup analyses for 1) the primary endpoint with subjects who had major depression or mania, 2) for co-medication (antidepressants (AD) only, mood stabilizers (MS) only, AD and MS, neither AD or MS); consistency on both PANSS positive and negative symptoms; generalisibility of the data to the EU population and adequate supportive data (e.g dose finding studies) on the proposed dosing regimen.

1.3.1 Pharmacokinetics

- **Pharmacokinetic interaction studies**

1) Study R076477-BIM-1003

This was an open label, 2-treatment, single-sequence study in 24 healthy men (one subject withdrew consent).

The primary objective of the study was to evaluate the effect of divalproex sodium (VPA) at steady state on the PK of a single dose of paliperidone ER (12 mg). The secondary objective was to evaluate the effect of a single dose of 12 mg paliperidone ER on the steady-state PK of divalproex sodium ER.

Divalproex sodium ER (extended release) increased the plasma exposure of paliperidone by an estimated 51% ($C_{max:}$ maximum plasma concentration) and 52% ($AUC_{0-\infty:}$ area under the plasma

[5] hereafter referred to as SCA-3001
[6] hereafter referred to as SCA-3002

concentration-time curve from time 0 to infinite time). Median T_{max} for paliperidone was approximately 24 hours for both treatments. The estimated half-life of paliperidone was not different between the treatments (mean 23.5 hours for paliperidone alone and 24.0 hours for paliperidone + VPA).

VPA steady-state concentrations were similar after administration of divalproex sodium ER alone and after co-administration of paliperidone ER and divalproex sodium ER. The treatment ratios for Cmax,ss (maximum plasma concentration during a dosing interval at steady state) and AUCτ (area under the plasma concentration-time curve during a dosing interval) were close to 100%. The 90% CIs (confidence intervals) for geometric mean ratios of AUCτ and Cmax, ss (maximum plasma concentration during a dosing interval at steady state) fell within 80% and 125%.

The frequency of the adverse events (AEs) were 35 % for the combination (paliperidone+VPA) and 79 % for paliperidone alone.

2) *Study R076477-BIM-1004*

This was an open label, single-sequence, PK drug-drug interaction study of oral paliperidone ER co-administered with oral divalproex sodium ER (DEPAKOTE® ER, Abbott) in clinically stable subjects with schizophrenia, bipolar I disorder or schizoaffective disorder who were on valproate therapy.

The primary objective of this study is to assess the potential effect of multiple doses of paliperidone

ER tablets on the steady-state PK of VPA.

Fourteen of the 17 enrolled subjects completed the study as per the study protocol and three subjects were withdrawn due to an adverse event, withdrawal of consent, and the third due to a positive test for cocaine. One subject did not fast for 10 hours before intake of divalproex sodium on Day 7 and plasma concentrations and PK parameters for VPA were excluded from descriptive statistics and statistical analyses.

Mean VPA steady-state concentration-time profiles were comparable after co-administration of paliperidone ER and divalproex sodium ER and after administration of divalproex sodium ER alone.

Plasma VPA steady-state concentrations were similar after administration of divalproex sodium ER alone and after co-administration with paliperidone ER. Mean AUCτ and Cmax,ss values were similar for both treatments.The VPA treatment ratios for Cmax,ss and AUCτ were close to 100%. The 90% confidence intervals for geometric mean ratios of AUCτ and Cmax,ss fell within 80 and 125%.

The number of subjects who reported treatment-emergent AEs was higher during treatment with paliperidone ER plus divalproex sodium ER than during treatment with divalproex sodium ER alone (63 versus (vs). 18%). One subject experienced a serious adverse event (blood creatinine increased), and one subject was discontinued from study due to a non-serious adverse event (akathisia). The increase in blood creatinine was based on an isolated laboratory finding, without clinical signs of acute renal impairment, and the finding was considered by the laboratory as likely recorded in error.

- **Additional pharmacokinetic analysis**

No specific PK studies have been conducted in patients with schizoaffective disorder and no plasma samples were taken from the Phase III studies included in this variation application. In two schizophrenia studies previously submitted (SCH-102 and SCH-1014), patients with schizoaffective disorder were allowed for inclusion and some PK data were obtained in these studies.

A total of thirteen subjects with schizoaffective disorder (5 from Study SCH- 102 and 8 from Study SCH-1014) and 58 subjects with schizophrenia (27 from Study SCH-102 and 31 from Study SCH-1014) were included in this subgroup analysis.

Results indicated that no pharmacokinetic differences between patients with schizoaffective disorder and those with schizophrenia were observed.

- **In vitro metabolism**

An *in vitro* induction study (Study FK5875) has been performed, to assess the effect of paliperidone on the activity of the cytochrome P450 enzymes CYP1A2, CYP2C19 and CYP3A4 in human hepatocytes.

Omeprazole led to a 13-fold increase in CYP1A2 activity compared to vehicle alone. Rifampicin-mediated induction of CYP2C19 activity, led to a moderate, but significant 2-fold increase compared to vehicle alone. Rifampicin led to a moderate, but significant 2.3-fold increase of CYP3A4 function compared to vehicle alone. Paliperidone did not induce, nor inhibit, CYP1A2, CYP2C19 and/or CYP3A4.

- **Discussion on pharmacokinetic aspects**

A single paliperidone ER dose or multiple dosing with paliperidone ER did not affect VPA steady state concentrations.

In the multiple dose paliperidone ER study (R076477-BIM-1004), different VPA doses (500 to 2000 mg once daily) were administered, but since all subjects remained on a stable dose of VPA throughout the study, this was considered acceptable by the CHMP. Multiple dosing with paliperidone ER 12 mg/day did not affect the pharmacokinetics of VPA. The paliperidone dose used in this study was the highest recommended dosage in both schizophrenia and the schizoaffective disorder indications.

However, in the single dose paliperidone ER study (R076477-BIM-1003), an effect of VPA co-administration was observed with approximately 50% higher exposure to paliperidone. According to the MAH, the most likely mechanism behind the observed increase in exposure an absorption-based interaction: a prolongation of the gastric residence time of the paliperidone ER tablet could have extended the time for paliperidone absorption in the small intestine, and thus, increased the bioavailability. It was also hypothesized that prolongation of the gastric residence time in those subjects who showed the highest treatment ratio of AUC and C_{max} may have been caused by a physical phenomenon such as swelling of the divalproex sodium ER tablets, which might have prevented passage through the pylorus.

In the CHMP's view, Invega is an OROS (oral osmotic system) formulation, and it is known that concomitant intake with a high-fat meal increases the bioavailability by 50-60%, which is also thought to be due to an effect on gastric emptying and consequently a larger time for absorption in the small intestine. Even if both formulations used in this interaction study are ER and the divalproex sodium ER tablet, it seems rather unlikely that the size increase (due to swelling) would be so extensive that it would affect passage through the pylorus. The CHMP therefore considered that the mechanism behind the observed interaction was not completely clear and recommended that information based on the study results could be reflected into the SPC.

In study R076477-BIM-1003, the adverse events (AEs) observed were consistent with the known safety profile of divalproex sodium ER and paliperidone ER tablets and the combined treatment did not result in a higher incidence of AEs due to an increase in plasma concentrations of paliperidone.

No interaction study with lithium has been performed. Although an interaction between paliperidone and lithium does not seem theoretically plausible, the CHMP recommended this information to be reflected into the SPC.

The potential for paliperidone to induce CYPs 1A2, 2C19 and 3A4 was also investigated in an in vitro study (FK5875), including positive controls. No induction was observed with paliperidone. The rifampicin-mediated induction was relatively low, being approximately 2-fold for both CYP 2C19 and 3A4, while omeprazole caused a 13-fold induction of CYP1A2. The small effect observed with rifampicin

indicates that the study may not be very sensitive in detecting an inducing effect. Considering that the rifampicin induction effect was very small, the validity of the study for assessment of CYP2C19 and CYP3A4 induction is questioned and therefore the CHMP still maintained its recommendation for non inclusion of this information into the SPC.

1.3.2 Clinical efficacy

- **Main clinical studies**

Two randomised, double-blind, placebo-controlled, parallel-group, 6 week, Phase III studies were conducted to assess the efficacy and safety with 2 dose levels (SCA-3001) and flexible doses (SCA-3002) of paliperidone.

Studies SCA-3001 and SCA-3002 were multicenter and conducted in the US, India (both SCA-3001 and SCA-3002), Russia and Ukraine (SCA-3001), Asia and Romania (SCA-3002) with a majority of US patients included in these studies. The design was similar in the two studies.

METHODS

Inclusion/ Exclusion Criteria

Patients who enrolled were: male or female, 18 to 65 years of age; fulfilling the DSM-IV criteria for schizoaffective disorder; experiencing an acute exacerbation with a Positive And Negative Syndrome Scale (PANSS) score of at least 60; presenting a score of $\geq$ 4 on at least 2 of the PANSS items (Hostility, Excitement, Tension, Uncooperativeness, and Poor Impulse Control) at screening and randomisation, and presenting a score of $\geq$16 on the Young Mania rating Scale (YMRS) and/or a score of $\geq$16 on the Hamilton Rating Scale for Depression (HAM-D-21) at screening and randomisation.

Key exclusion criteria were: meeting DSM-IV criteria for major depressive disorder, bipolar disorder, schizophrenia, or schizophreniform disorder; currently meeting criteria for any other Axis I diagnosis except substance abuse; meeting the DSM-IV criteria for substance dependence in the 6 months before study entry, an Axis II diagnosis of Mental Retardation or Borderline Personality Disorder; suicide attempt within 12 months or at imminent risk of suicide according to the investigator's clinical judgement, and first episode (no prior history of psychotic symptoms).

Randomisation and Blinding

Randomisation was centralised with randomly permuted blocks and stratified by site and by concomitant treatment with antidepressants and/or mood stabilizers versus no such concomitant treatment.The capsules of study drug, including placebo, were identical in appearance. To further keep the blind, post-baseline prolactin levels were not available to the investigators or the sponsor during the course of the study.

Treatment period

After a screening and wash-out period of 2-5 days, eligible patients were randomised to 6 weeks of double-blind treatment with paliperidone ER or placebo. The patients were hospitalised during the wash-out period and at least for the first 8 days of double-blind treatment.

In study SCA-3001 the patients were assigned to a low or high dose-group of paliperidone ER or placebo in a 1:1:1 ratio, while in study SCA-3002 the patients were assigned to paliperidone ER in a flexible dose regimen or placebo in a 2:1 ratio.

In the low or high dose comparison to placebo (study SCA-3001), paliperidone ER treated patients were started on 12 or 6 mg/day. During the first 15 days the dose could be reduced once to 9 and 3

mg, respectively. After at least 4 days on a reduced dose, the dose could be increased to the original dose.

In the flexible dose study (study SCA-3002), paliperidone ER treated patients were started on 6 mg/day for 4 days, and thereafter the dose could be adjusted between 3 and 12 mg/day until Day 15.

In neither of the studies dose adjustment was allowed after the Day 15 visit.

Primary/Secondary Endpoints

The primary efficacy variable was the change from baseline to Week 6 in PANSS total score.

Secondary efficacy endpoints included: change from baseline to Week 6 in PANSS-24; change from baseline to Week 6 in PANSS subscales and factor scores; actual and change from baseline to Week 6 in Clinical Global Impression of Severity for Schizoaffective disorder (CGI-C-SCA); CGI of Change-SCA (CGI-C-SCA) at week 6; responder rate (defined as the percentage of patients with $\geq$30% reduction from baseline in PANSS total score and a CGI-C-SCA $\leq$2 at week 6); change from baseline to Week 6 in HAM-D-21; change from baseline to Week 6 in YMRS.

Statistical Method

All efficacy analyses were performed with the Intent-To-Treat (ITT) analysis set which included all randomised patients who received at least 1 dose of study medication and had both a baseline and at least 1 post-baseline PANSS assessment.

The primary endpoint and all other variables measuring change from baseline were analysed with an analysis of covariance (ANCOVA) model with treatment, concomitant treatment stratum and country as fixed factors and baseline score as covariate. The treatment effect was estimated with the difference between LS means with accompanying 95% confidence interval.

The responder data were analysed with the Cochran Mantel Haenszel test controlling for concomitant medication stratum and country.

In the three-armed study (SCA-3001) the overall type I error was controlled with the Hochberg step-up procedure. All secondary analyses were considered supportive and no further adjustments for multiplicity were planned.

In all analyses the primary approach for imputation of missing values was the Last Observation Carried Forward (LOCF) method. Alternative analyses were performed with a repeated measures mixed effects model (MMRM), and analyses where increasingly worse (up to 20 %) LOCF values were imputed for missing values in the active treatment group while the originally imputed LOCF value was kept for the placebo group.

RESULTS

1) Study SCA-3001

Patient characteristics

Three hundred and eighty seven patients were enrolled, and of these 316 were randomised to a low or high dose of paliperidone ER, or placebo. Almost all patients were included in the ITT populations. The withdrawal rate was dose-dependent with more discontinuations on placebo (41.1%) and lower doses (33.9%), mainly due to lack of effect and withdrawal of consent.

Demographic characteristics were similar for the three treatment groups with the exception of body weight and body mass index (BMI), which were higher in the placebo group especially compared to the paliperidone ER low dose group.

Baseline ratings and psychiatric history are presented in Tables 1 and 2.

Table 1 Baseline ratings in study SCA-3001

Parameter	Placebo (N=107)	PALI ER Low Dose (N=105)	PALI ER High Dose (N=98)	Overall (N=310)
PANSS Total Score	107	105	98	310
Mean (SD)	91.6 (12.5)	95.9 (13.0)	92.7 (12.6)	93.4 (12.8)
Median (Min;Max)	90.0 (64;126)	95.0 (70; 135)	94.0 (63;121)	93.0 (63;135)
CGI-S-SCA Score, n (%)	107	105	98	310
Mean (SD)	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)
Median (Min;Max)	5.0 (4;6)	5.0 (3;6)	5.0 (3;6)	5.0 (3;6)
Normal Not At All Ill	0	0	0	0
Minimally Ill	0	0	0	0
Mildly Ill	0	2 (1.9)	1 (1.0)	3 (1.0)
Moderately Ill	51 (47.7)	44 (41.9)	39 (39.8)	134 (43.2)
Markedly Ill	50 (46.7)	54 (51.4)	52 (53.1)	156 (50.3)
Severely Ill	6 (5.6)	5 (4.8)	6 (6.1)	17 (5.5)
HAM-D-21 Total Score	107	105	98	310
Mean (SD)	18.8 (8.5)	21.0 (9.1)	20.6 (10.1)	20.1 (9.2)
Median (Min;Max)	18.0 (0;45)	21.0 (4;46)	19.0 (4;42)	19.0 (0;46)
<16	43 (40.2%)	29 (27.6%)	37 (37.8%)	109 (35.2%)
≥16	64 (59.8%)	76 (72.4%)	61 (62.2%)	201 (64.8%)
YMRS Total Score	107	105	98	310
Mean (SD)	25.6 (9.4)	25.4 (9.8)	26.2 (10.7)	25.7 (10.0)
Median (Min;Max)	27.0 (2;47)	25.0 (1;47)	27.0 (5;50)	26.0 (1;50)
<16	17 (15.9%)	17 (16.2%)	19 (19.4%)	53 (17.1%)
≥16	90 (84.1%)	88 (83.8%)	79 (80.6%)	257 (82.9%)
HAM-D-21 and YMRS ≥16, n (%)	47 (43.9)	59 (56.2)	42 (42.9)	148 (47.7)

Note: Percentages are based on the number of subjects in the ITT analysis set with a non-missing value for the parameter.

Table 2 Psychiatric history in study SCA-3001

Parameter	Placebo (N=107)	PALI ER Low Dose (N=105)	PALI ER High Dose (N=98)	Overall (N=310)

Prior Psychiatric Diagnoses, n (%)	104	105	96	305
Schizophrenia	46 (43.0)	56 (53.3)	44 (44.9)	146 (47.1)
Bipolar Disorder	36 (33.6)	29 (27.6)	30 (30.6)	95 (30.6)
Depression	18 (16.8)	19 (18.1)	16 (16.3)	53 (17.1)
Other	56 (52.3)	51 (48.6)	47 (48.0)	154 (49.7)
Schizoaffective Diagnosis Prior To Screening, n (%)				
N	103	105	98	306
Yes	97 (94.2)	91 (86.7)	88 (89.8)	276 (90.2)
No	6 (5.8)	14 (13.3)	10 10.2)	30 (9.8)
Missing	4	0	0	4
Age (Years) at First Schizoaffective Diagnosis				
N	103	105	98	306
Mean (SD)	32.4 (11.3)	32.9 (10.3)	32.1 (10.4)	32.5 (10.7)
Median (Min;Max)	30.0 (6;59)	33.0 (13;61)	30.5 (15;56)	31.0 (6;61)
Current Diagnosis of Schizoaffective Disorder Confirmed by SCID, n (%)				
N	107	104	96	307
Depressive	33 (30.8)	35 (33.7)	27 (28.1)	95 (30.9)
Bipolar	74 (69.2)	69 (66.3)	69 (71.9)	212 (69.1)
Duration (Days) of Current Episode				
N	107	105	96	308
Mean (SD)	20.4 (37.1)	18.3 (7.2)	18.5 (9.9)	19.1 (22.9)
Median (Min;Max)	16.0 (4;394)	19.0 (6;52)	16.5 (5;86)	17.0 (4;394)
Number of Total Psychiatric Hospitalizations				
N	105	104	97	306
Mean (SD)	4.4 (5.9)	4.5 (6.3)	4.2 (5.1)	4.3 (5.8)
Median (Min;Max)	2.0 (0;35)	3.0 (0;44)	2.0 (0;20)	2.0 (0;44)
Attempted Suicide, n (%)				
N	107	105	98	310
Yes	31 (29.0)	30 (28.6)	19 (19.4)	80 (25.8)
No	76 (71.0)	75 (71.4)	79 (80.6)	230 (74.2)
How Many Suicide Attempts, n (%)				
N	31	30	19	80
1	19 (61.3)	16 (53.3)	11 (57.9)	46 (57.5)
2-4	10 (32.3)	12 (40.0)	7 (36.8)	29 (36.3)
>=5	2 (6.5)	2 (6.7)	1 (5.3)	5 (6.3)

There were some differences with respect to psychotropic medication at baseline with more placebo patients treated with antidepressants and more atypical antipsychotics and hypnotics/anxiolytics in the low dose group (Table 3).

Table 3 Baseline psychotropic medication in study SCA-3001

Parameter	Placebo (N=107) n (%)	PALI ER Low Dose (N=105) n (%)	PALI ER High Dose (N=98) n (%)
Anti-EPS	17 (15.9)	21 (20.0)	17 (17.3)
Antidepressants	31 (29.0)	21 (20.0)	19 (19.4)
Atypical Antipsychotics	36 (33.6)	41 (39.0)	35 (35.7)
Typical Antipsychotics	35 (32.7)	37 (35.2)	34 (34.7)

Benzodiazepines	61 (57.0)	64 (61.0)	54 (55.1)
Non-Benzodiazepines Hypnotics and Anxiolytics	42 (39.3)	42 (40.0)	37 (37.8)
Mood Stabilizers and Antiepileptics	30 (28.0)	30 (28.6)	31 (31.6)

More than two thirds of the patients took at least one concomitant psychotropic medication during the study. Benzodiazepines and other anxiolytics were the most common concomitant medication (Table 4).

Table 4 Concomitant psychotropic medication in study SCA-3001

Parameter	Placebo (N=107) n (%)	PALI ER Low Dose (N=105) n (%)	PALI ER High Dose (N=98) n (%)
Number of Subjects Taking:			
0 Psychotropic Medications	33 (30.8)	27 (25.7)	24 (24.5)
1 Psychotropic Medication	14 (13.1)	17 (16.2)	18 (18.4)
2 Psychotropic Medications	19 (17.8)	25 (23.8)	21 (21.4)
>2 Psychotropic Medications	41 (38.3)	36 (34.3)	35 (35.7)
Antidepressants	27 (25.2)	15 (14.3)	20 (20.4)
Atypical Antipsychotics	10 (9.3)	8 (7.6)	8 (8.2)
Typical Antipsychotics	7 (6.5)	5 (4.8)	7 (7.1)
Benzodiazepines	52 (48.6)	55 (52.4)	44 (44.9)
Non-Benzodiazepine Hypnotics and Anxiolytics	47 (43.9)	44 (41.9)	47 (48.0)
Mood Stabilizers and Antiepileptics	27 (25.2)	32 (30.5)	27 (27.6)

Efficacy Results

These are summarised below (see Table 5, Figure 1).

Table 5 Primary, key secondary and responder results in study SCA-3001. ITT-LOCF results.

Endpoint	Placebo (N=107)	PALI ER Low dose (N=105)	PALI ER High dose (N=98)
PANSS, change from baseline (P-value vs placebo)	-21.7	-27.4 (0.187)	-30.6 (0.003)
PANSS-24, change from baseline (P-value vs placebo)	-18.5	-23.0 (0.202)	-26.1 (0.002)
HAM-D-21, change from baseline * (P-value vs placebo)	-9.9	-13.6 (0.013)	-14.5 (0.032)
YMRS, change from baseline * (P-value vs placebo)	-11.5	-14.3 (0.066)	-19.4 (<0.001)
Responders (%) (P-value vs placebo)	40.2	56.7 (0.008)	62.2 (0.001)
CGI-C-SCA: Much or very much improved (%) (P-value vs placebo)	43,9	57.7 (0.013)	68.4 (<0.001)

*) In patients with a baseline score ≥16 on HAM-D-21 and YMRS, respectively.

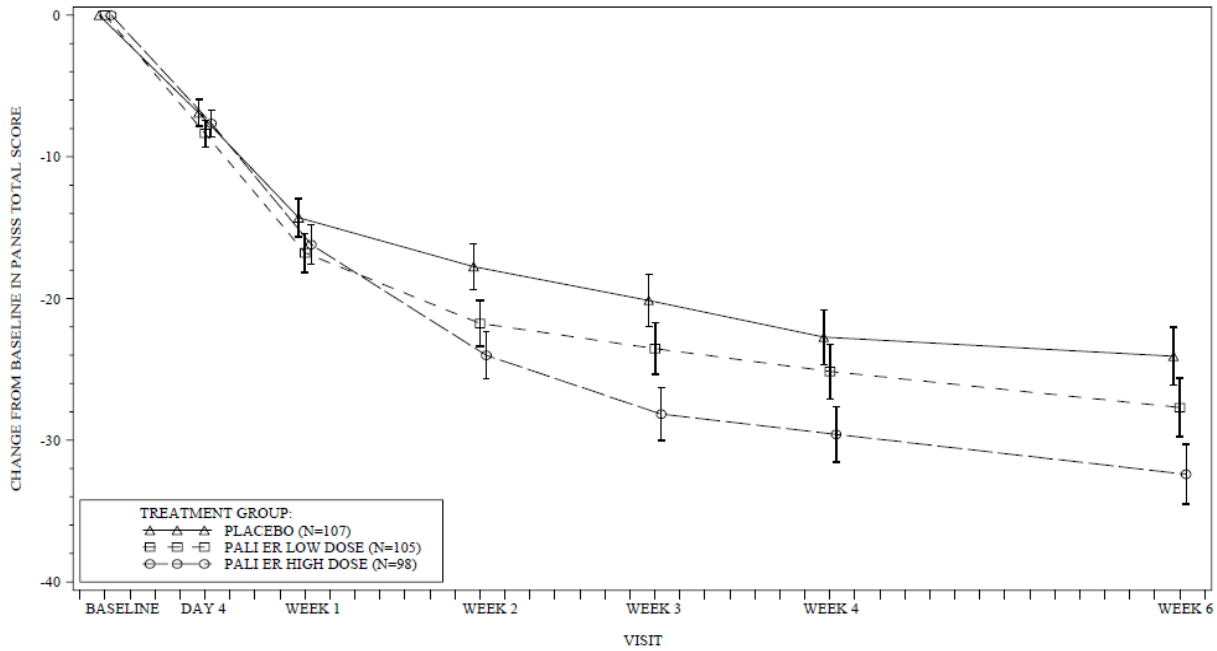


Figure 1 Change from baseline in PANSS Total score in study SCA-3001. ITT-LOCF results

A significant difference versus placebo was observed for the paliperidone ER high dose group for the primary endpoint PANSS Total score while a significant result was not achieved for the low dose group (Table 5 and Figure 1).

For the key secondary variables PANSS-24, HAM-D-21, YMRS, responders and percentage of patient much or very much approved on the CGI-C-SCA scale, there was an overall pattern of significant or nearly significant results in favour of both dose groups versus placebo with a clear tendency of dose response (Table 5).

Although there was no statistical evidence of a differential effect depending on whether the patient was on concomitant treatment with antidepressants and/or mood stabilizers or not (treatment-by-concomitant medication interaction, p-value=0.641), the effect was clearly less pronounced and not reaching statistical significance for patients on concomitant treatment (see Figure 2).

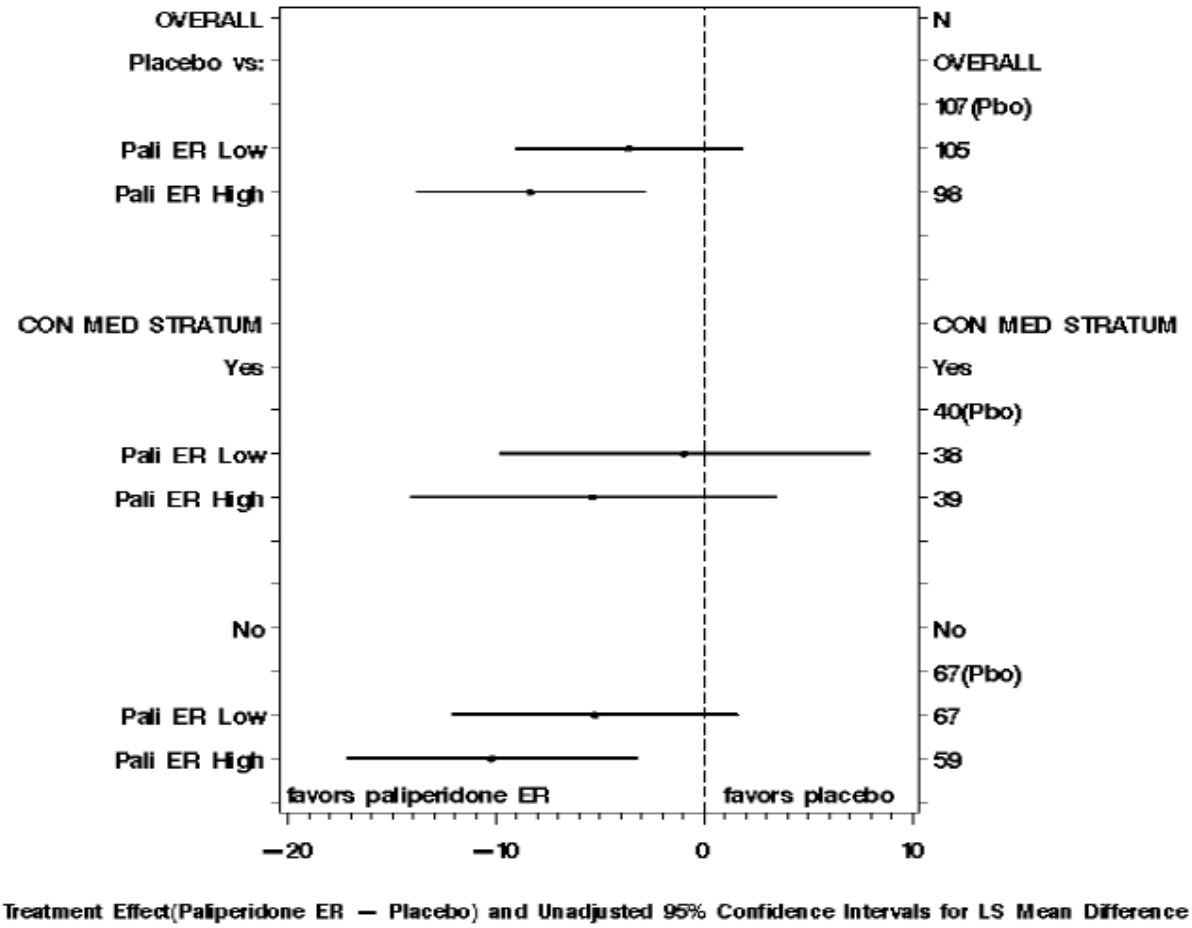


Figure 2 Forest plot of change in PANSS Total score (paliperidone ER vs placebo) by concomitant medication stratum in study SCA-3001. ITT-LOCF results.

Neither was there any statistical evidence of a differential effect with respect to country or geographical region. However there is some tendency of a lower effect in US patients compared to Non-US patients (Table 6).

Table 6 Change in PANSS Total score by country and region (US/Non-US) in study SCA-3001. ITT-LOCF results.

Parameter	Placebo (N=107)		PALI ER Low Dose (N=105)		PALI ER High Dose (N=98)		Interaction
	N	Estimate (SE)	N	Estimate (SE)	N	Estimate (SE)	
P-values:							
Trt * Country							0.706
Trt * Categorized Country							0.855

Treatment by Country:						
India	33	-21.5 (3.4)	34	-23.8 (3.4)	31	-29.5 (3.6)
Russia	12	-27.3 (5.9)	13	-24.9 (5.6)	11	-41.2 (6.1)
Ukraine	23	-27.5 (4.2)	19	-37.9 (4.6)	21	-36.6 (4.4)
United States	39	-19.4 (3.2)	39	-22.7 (3.2)	35	-25.8 (3.3)
Treatment by Categorized Country						
US	39	-19.4 (3.2)	39	-22.7 (3.2)	35	-25.9 (3.4)
Non-US	68	-24.2 (2.5)	66	-27.8 (2.5)	63	-33.6 (2.6)

2) Study SCA-3002

Patient characteristics

Three hundred and ninety one patients were enrolled, and of these 311 were randomised to flexibly dosed paliperidone ER (3-12 mg), or placebo in a 2:1 ratio. The withdrawal rate was higher on placebo (45.3%) versus active treatment (38%,) mainly due to lack of effect.

The treatment groups were well balanced with respect to demographic characteristics as well as with respect to baseline severity.

Baseline ratings and psychiatric history are presented in Tables 7 and 8.

Table 7 Baseline ratings in study SCA-3002

Parameter	Placebo (N=93)	PALI ER (N=211)	Overall (N=304)
PANSS Total Score	93	211	304
Mean (SD)	91.7 (12.1)	92.3 (13.5)	92.1 (13.1)
Median (Min;Max)	89.0 (62;121)	91.0 (63;149)	90.5 (62;149)

CGI-S-SCA Score, n (%)	93	211	304
Mean (SD)	4.6 (0.6)	4.6 (0.7)	4.6 (0.7)
Median (Min;Max)	5.0 (3;6)	5.0 (3;6)	5.0 (3;6)
Normal Not At All Ill	0	0	0
Minimally Ill	0	0	0
Mildly Ill	1 (1.1)	3 (1.4)	4 (1.3)
Moderately Ill	39 (41.9)	91 (43.1)	130 (42.8)
Markedly Ill	47 (50.5)	98 (46.4)	145 (47.7)
Severely Ill	6 (6.5)	19 (9.0)	25 (8.2)
HAM-D-21 Total Score	93	211	304
Mean (SD)	20.4 (7.9)	20.1 (8.5)	20.2 (8.3)
Median (Min;Max)	22.0 (4;38)	20.0 (5;43)	20.0 (4;43)
<16	28 (30.1%)	66 (31.3%)	94 (30.9%)
≥16	65 (69.9%)	145 (68.7%)	210 (69.1%)
YMRS Total Score	93	211	304
Mean (SD)	22.6 (10.6)	23.4 (9.7)	23.1 (10.0)
Median (Min;Max)	22.0 (1;47)	24.0 (0;43)	23.0 (0;47)
<16	23 (24.7%)	50 (23.7%)	73 (24.0%)
≥16	70 (75.3%)	161 (76.3%)	231 (76.0%)
HAM-D-21 and YMRS ≥16, n(%)	42 (45.2)	95 (45.0)	137 (45.1)

Note: Percentages are based on the number of subjects in the ITT analysis set with a non-missing value for the parameter.

Table 8 Psychiatric history in study SCA-3002

Parameter	Placebo (N=93)	PALI ER (N=211)	Overall (N=304)
Prior Psychiatric Diagnoses, n (%)			
Schizophrenia	50 (53.8)	94 (44.5)	144 (47.4)
Bipolar Disorder	35 (37.6)	60 (28.4)	95 (31.3)
Depression	22 (23.7)	37 (17.5)	59 (19.4)
Other	31 (33.3)	77 (36.5)	108 (35.5)
Schizoaffective Diagnosis Prior to Screening, n (%)			
N	92	205	297
Yes	85 (92.4)	187 (91.2)	272 (91.6)
No	7 (7.6)	18 (8.8)	25 (8.4)
Missing	1	6	7
Age (Years) at First Schizoaffective Diagnosis			
N	92	205	297
Mean (SD)	31.6 (9.2)	30.4 (9.7)	30.8 (9.5)
Median (Min;Max)	30.0 (15; 57)	29.0 (3; 54)	30.0 (3; 57)
Current Diagnosis of Schizoaffective Disorder Confirmed by SCID, n (%)			
N	93	211	304
Depressive	34 (36.6)	61 (28.9)	95 (31.3)
Bipolar	59 (63.4)	150 (71.1)	209 (68.8)
Duration (Days) of Current Episode			
N	93	208	301
Mean (SD)	18.6 (7.5)	20.1 (27.4)	19.6 (23.1)
Median (Min;Max)	18.0 (1; 43)	18.0 (1; 389)	18.0 (1; 389)

Number of Total Psychiatric Hospitalizations			
N	91	208	299
Mean (SD)	9.2 (12.6)	8.0 (8.8)	8.4 (10.1)
Median (Min:Max)	5.0 (0; 99)	5.0 (0; 60)	5.0 (0; 99)
Attempted Suicide, n (%)			
Yes	33 (35.9)	79 (37.6)	112 (37.1)
No	59 (64.1)	131 (62.4)	190 (62.9)
How Many Suicide Attempts, n (%)			
1	13 (39.4)	41 (51.9)	54 (48.2)
2-4	14 (42.4)	29 (36.7)	43 (38.4)
>=5	6 (18.2)	9 (11.4)	15 (13.4)

Table 9 Baseline psychotropic medication in study SCA-3002.

Parameter	Placebo (N=93)	PALI ER (N=211)
Anti-EPS	15 (16.1)	28 (13.3)
Antidepressants	25 (26.9)	55 (26.1)
Atypical Antipsychotics	40 (43.0)	117 (55.5)
Typical Antipsychotics	20 (21.5)	47 (22.3)
Benzodiazepines	65 (69.9)	157 (74.4)
Non-Benzodiazepine Hypnotics and Anxiolytics	45 (48.4)	117 (55.5)
Mood Stabilizers and Antiepileptics	35 (37.6)	90 (42.7)

Compared to study SCA-3001, more patients (>90%) were concomitantly treated with at least one psychotropic medication (Table 9).

Efficacy Results

These are summarised below (see Table 10, Figure 3).

Table 10 Primary, key secondary and responder results in study SCA-3002. ITT-LOCF results.

Endpoint	Placebo (N=93)	PALI ER (N=211)
PANSS, change from baseline (P-value vs placebo)	-10.8	-20.0 (<0.001)
PANSS-24, change from baseline (P-value vs placebo)	-9.8	-17.5 (<0.001)
HAM-D-21, change from baseline * (P-value vs placebo)	-6.2	-10.2 (<0.001)
YMRS, change from baseline * (P-value vs placebo)	-5.7	-10.6 (0.001)
Responders (%)	28.0	40.5

(P-value vs placebo)		(0.046)
CGI-C-SCA: Much or very much improved (%) (P-value vs placebo)	32.2	46.2 (0.003)

*) In patients with a baseline score ≥16 on HAM-D-21 and YMRS, respectively.

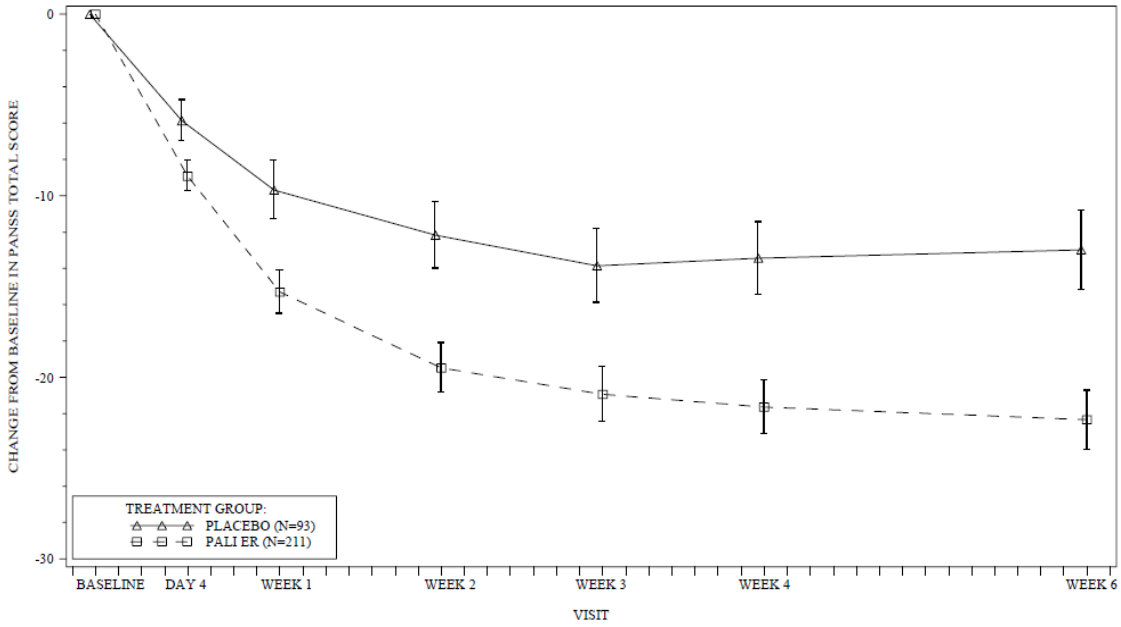


Figure 3 Change from baseline in PANSS Total score in study SCA-3002. ITT-LOCF results.

A significant difference comparable to the difference seen for the high dose in study SCA-3001 was observed for flexibly dose paliperidone ER versus placebo.

All key secondary efficacy variables were statistically significant in favour of paliperidone ER.

There was no statistical evidence of a treatment-by concomitant medication interaction (p=0.486) and the difference versus placebo was statistically significant for both strata (Figure 4).

Neither was there any statistical evidence of country or regional difference but similar to study SCA-3001 the magnitude of effect tended to be lower for US patients compared to Non-US patients (Table 11).

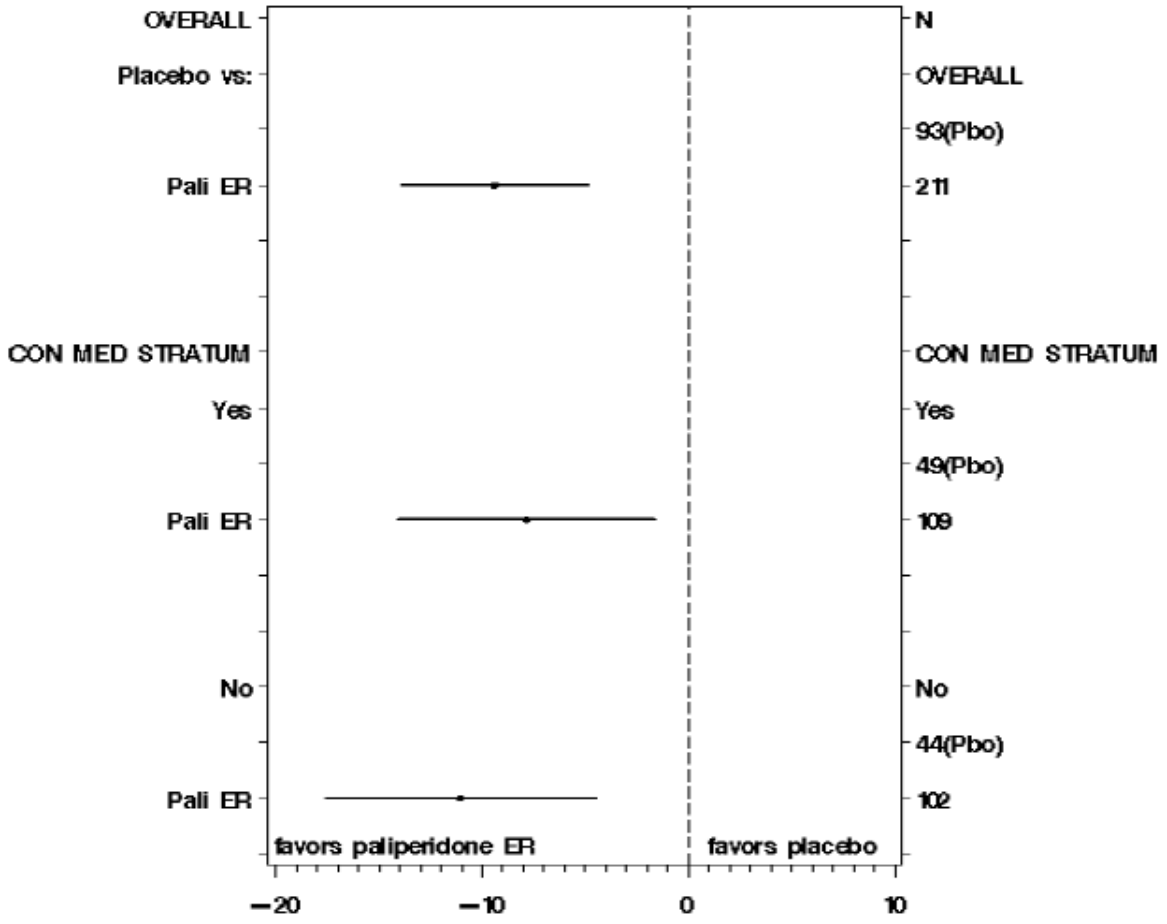


Figure 4 Forest plot of change in PANSS Total score (paliperidone ER vs placebo) by concomitant medication stratum in study SCA-3002. ITT-LOCF results.

Table 11 Change in PANSS Total score by country and region (US/Non-US) in study SCA-3002. ITT-LOCF results.

Parameter	Placebo (N=93)		PALI ER (N=211)		Interaction
	N	Estimate (SE)	N	Estimate (SE)	
P-values:					
Trt * Country					0.235
Trt * Categorized Country					0.560
Treatment by Country:					
India	13	-20.6 (5.1)	26	-22.5 (3.6)	
Korea	2	17.6 (12.9)	10	-16.9 (5.8)	
Malaysia	5	-16.5 (8.2)	10	-30.3 (5.8)	
Philippines	7	-14.4 (6.9)	15	-34.6 (4.8)	
Romania	24	-9.8 (3.7)	57	-19.8 (2.5)	
United States	42	-8.8 (2.8)	93	-16.3 (1.9)	
Treatment by Categorized Country					
US	42	-8.7 (2.9)	93	-16.2 (1.9)	
Non-US	51	-12.9 (2.6)	118	-23.0 (1.7)	

- **Supportive studies**

There are no studies demonstrating an effect beyond 6 weeks of paliperidone ER in schizoaffective disorder. To support the maintenance of the effect, the MAH referred to the data establishing maintenance of effect in the initial CHMP approval of the schizophrenia indication, primarily a relapse prevention study (SCH-301), with some support from open-label extension studies (SCH-701, SCH-703, SCH-704 and SCH-705) conducted in schizophrenia. In study SCH-301, patients responding to 14 weeks open label paliperidone treatment were randomised to continue on active treatment or placebo. Roughly twice as many patients had a relapse on placebo compared with paliperidone (see Figure 5).

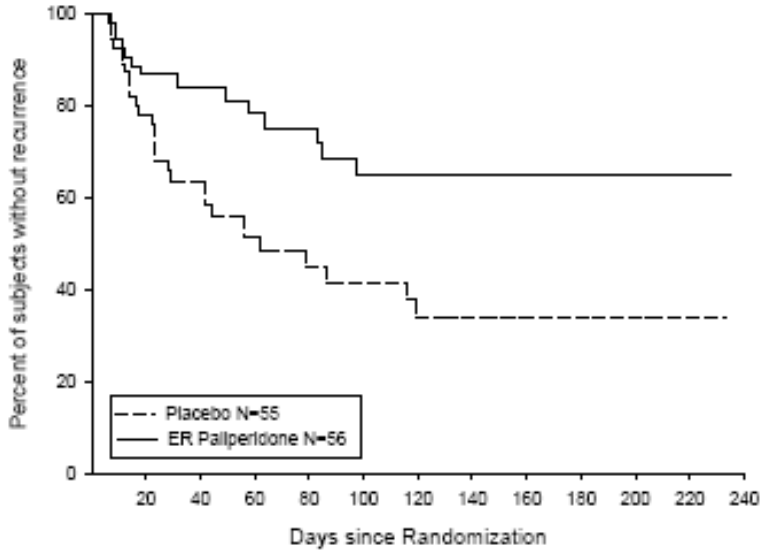


Figure 5

In the 4 open label studies, flexible doses of paliperidone ER were administered covering the range 3 to 15 mg. The combined intent-to-treat analysis sets of the 4 studies included a total of 1,309 subjects, among whom 895 received paliperidone ER for greater than 6 months and 571 received paliperidone ER for more than 1 year. In all studies, the mean PANSS total score decreased from baseline (open-label) to end point.

In study SCH-703, improvement during the open-label treatment phase was more prominent for subjects treated with placebo during the double-blind phase, although incremental improvement was also noted in subjects previously treated with paliperidone ER and olanzapine.

In study SCH-704, subjects entering the open-label phase had previously experienced statistically significant decreases in the mean PANSS total score during double-blind treatment. Despite this improvement already realized at the start of the open-label phase, continued improvement was observed during open-label treatment. Improvement during the open-label phase was most pronounced in subjects previously treated with double-blind placebo, as these subjects had notably higher PANSS scores at open-label baseline.

In study SCH-705, subjects previously treated with double-blind placebo had the most improvement.

In study SCH-701, the largest treatment effect during the open-label extension was observed in subjects treated with double-blind placebo, as these subjects had notably higher PANSS scores at open-label baseline.

The MAH also referred to studies with the mother compound risperidone in which schizophrenia as well as schizoaffective patients have been studied (RIS-USA-79, RSI-SCH-401, RIS-INT-57) and the Vieta et al study (2001). Comparative pharmacokinetic data were also presented to further support this proposed extrapolation.

In study RIS-USA-79 stable outpatients fulfilling the DSM-IV criteria for chronic schizophrenia or schizoaffective disorder were randomised to at least one year double-blind treatment with risperidone 2-8 mg/day (median modal dose 4 mg) or haloperidol 5-20 mg/day (median modal dose 10 mg). Primary endpoint was time to relapse with relapse defined as clinical deterioration, increased level of care, or violence towards self and/or others. Overall the result was in favour of risperidone and the magnitude of effect was similar in patients with schizoaffective disorder and in patients with schizophrenia (Table 12).

Table 12 Relapse rates in the overall population and the two sub-populations in study RIS-USA-79.

Population	*Risperidone*		*Haloperidol*		*P-value*
	N	*% relapse*	*N*	*% relapse*	*(Log rank-test)*
Total	*177*	*25.4*	*188*	*40.0*	*0.001*
Schizoaffective disorder	*32*	*27.3*	*33*	*40.6*	*0.005*
Schizophrenia	*144*	*25.0*	*156*	*39.7*	*0.011*

In a 12 months double-blind study (RSI-SCH-401) comparing two doses of risperidone long-acting injection in subjects with stable schizoaffective disorder (n=66) or stable schizophrenia (n=258) similar relapse rates (15% vs 22%, respectively) were observed.

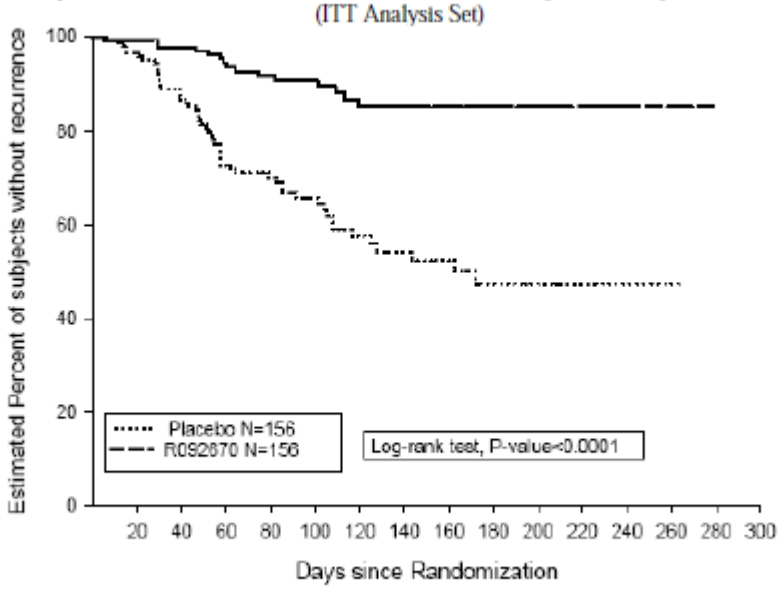
In a 12 months open label study (RSI-INT-57) comparing three doses of risperidone long-acting injection in subjects with schizophrenia or schizoaffective disorder, improvements in PANSS total score were statistically significant ($p \leq 0.004$) at each time point in all 3 dose groups for subjects with schizophrenia Similarly, for subjects with schizoaffective disorder, the improvement in PANSS total score in each dose group was statistically significant ($p \leq 0.029$) at each time point.

In the Vieta et al. study (2001), a long-term (6-month) open-label adjunctive study of risperidone in 541 subjects with bipolar I disorder (55% of subjects), schizoaffective disorder, bipolar subtype (34%), bipolar II disorder (8%), or bipolar disorder not otherwise specified (3%), statistically significant improvements from baseline in all efficacy measures (YMRS, HAM-D, PANSS total score, PANSS subfactors, and Clinical Global Impression) at the 6-month end point were observed. Mean (SD) scores on the YMRS decreased from 25.6 (10.7) at baseline to 2.4 (4.6) at end point ($p<0.0001$) (Figure 10). Mean (SD) HAM-D scores declined from 12.8 (7.9) at baseline to 4.1 (4.8) at 6 months ($p<0.001$).

Further long-term clinical studies with paliperidone ER and other related compounds (paliperidone palmitate, risperdal consta), conducted either in bipolar I disorder, schizophrenia or treatment resistant depression, were referred by the MAH as supportive data. All of these populations had at least one symptom domain of schizoaffective disorder (psychosis, mania and depression).

In the schizophrenia study PSY-3001, subjects were treated with flexible doses of paliperidone palmitate in a 9-week transition phase, followed by a 12-week maintenance phase. The dose of paliperidone palmitate was fixed in a second 12-week period of the maintenance phase. Those subjects who continued to achieve symptom response were then randomly assigned to continue with fixed doses of paliperidone palmitate or were switched to placebo. Results are presented in Figure 6.

Figure 4: Kaplan-Meier Plot of Time to Recurrence (Interim Analysis) in Study R092670-PSY-3001 (ITT Analysis Set)



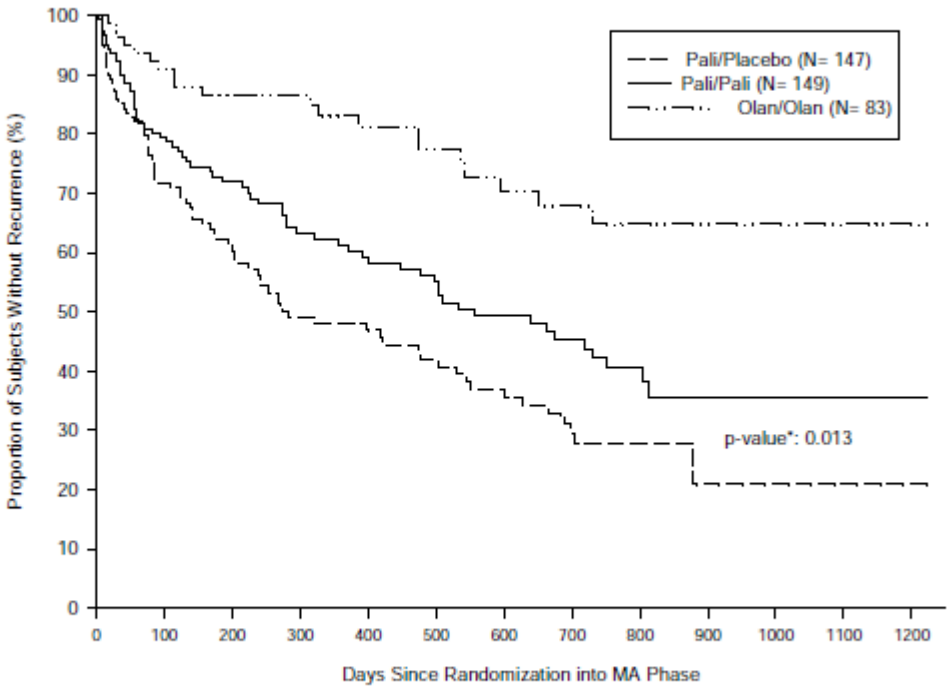
R092670=paliperidone palmitate

Figure 6

In the Bipolar I disorder study BIM-3004, treatment periods consisted of a 3-week double-blind acute treatment phase; a 12-week double-blind continuation phase; a double-blind maintenance phase (lasting until the subject experiences a recurrence); and a follow-up phase. Subjects were randomly assigned in a 4:1 ratio to paliperidone ER or olanzapine (for assay sensitivity) in the double-blind acute treatment phase of the study. Paliperidone ER was dosed once daily in a flexible dosage range of 3 to 12 mg/d to optimize each subject's level of clinical response and tolerability of the study drug. Subjects who achieved a clinical response (i.e., a reduction from baseline [Day 1] in YMRS total score of ≥50%) at the end of the 3- week acute treatment phase entered the double-blind continuation phase. At the end of the 12-week continuation phase, all subjects in the paliperidone ER treatment arm who achieved remission (i.e., YMRS ≤12 and MADRS ≤12) for each of the last 3 weeks of the phase were re-randomly assigned to paliperidone ER or placebo in a 1:1 ratio. Results are presented in Figure 7.

Paliperidone ER: Health Authority Response SCA

Figure 7: Time to Recurrence of Any Mood Symptoms (Final Analysis)
(Study R076477-BIM-3004: Intent-to-Treat (MA) Analysis Set)

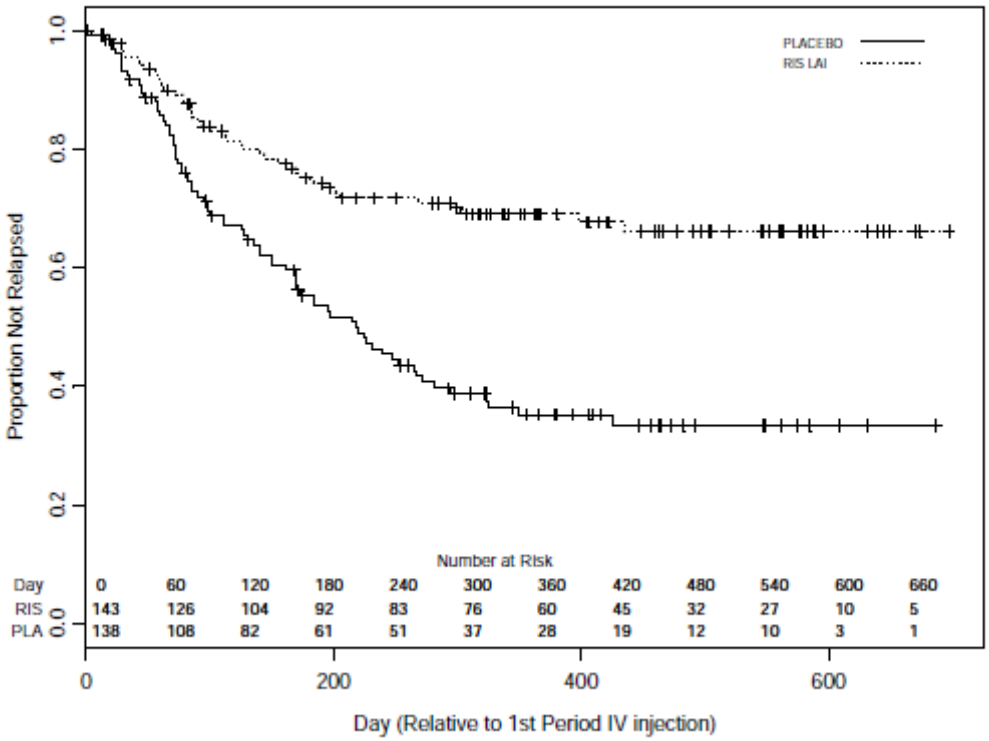


* Weighted z statistic of the comparison of paliperidone PR with placebo; alpha = 0.019 based on the rho-family of alpha spending function at information fraction of 87.1% at the time of interim analysis (rho=2.5) at the 0.025 (1-sided level)

Figure 7

In the Bipolar I disorder study RIS-BIM-3003, treatment periods consisted of 3 weeks of open-label oral risperidone treatment ; 26 weeks of open-label stabilization on risperidal consta; a randomized, double-blind, placebo-controlled period with risperidal consta treatment (up to 24 months); and an 8-week open-label extension with risperidal consta. Subjects who met criteria for an initial response during open-label oral risperidone treatment were eligible to enter the 26-week open-label stabilization on risperidal consta. Subjects who entered double-blind treatment were randomly assigned, in a 1:1 ratio, to a continuation of the dose of risperidal consta (25, 37.5, or 50 mg) they received at the end of the open-label stabilization period or placebo injections every 2 weeks for up to 24 months. Results are presented in Figure 8.

Figure 8: Kaplan-Meier Curves for Primary Endpoint (Time to Relapse of Mood Episodes) in Study RIS-BIM-3003
(Randomized Treated Excluding 2 Sites Analysis Set)

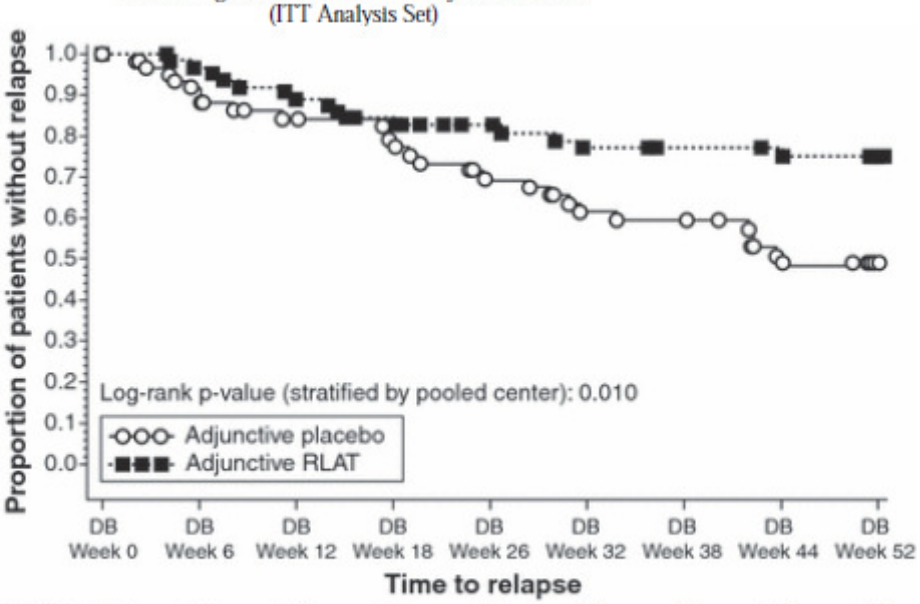


RIS LAI=risperidone long-acting injectable (RISPERDAL CONSTA)

Figure 8

In the Bipolar I disorder study RIS-BIP-302, subjects had 4 or more mood episodes in the 12 months prior the study entry. Following a 16-week, open-label stabilization phase with risperidal consta plus treatment as usual (TAU), remitted subjects entered a 52-week, double-blind, placebo-controlled relapse prevention phase. Randomly assigned subjects continued treatment with adjunctive risperdal consta (25-50 mg every 2 weeks) plus TAU or switched to adjunctive placebo injection plus TAU. Results are presented in Figure 9.

Figure 11: Kaplan-Meier Estimation of the Distribution of Time to Relapse Based on Independent Relapse Monitoring Board Decision in Study RIS-BIP-302 (ITT Analysis Set)



Adjunctive RLAT: n = 65	60	56	51	45	42	40	38	38
Adjunctive placebo: n = 59	51	46	41	36	31	30	22	21

DB=double blind, RLAT=risperidone long-acting therapy (RISPERDAL CONSTA)

Figure 9

In the treatment resistant depression study RIS-INT-93, all subjects entered the first portion of the study in a 4- to 6-week phase to confirm resistance using open-label citalopram treatment. Those subjects with a suboptimal response defined as <50% reduction in 17-item HAM-D score) were eligible to enter the open-label risperidone augmentation phase (0.25-2.0 mg/d) for 4 to 6 weeks. Those subjects who demonstrated a clinical response to risperidone augmentation (defined as HAM-D score ≤7 or CGI-S ≤2) were eligible to enter the 24-week double-blind phase. In the double-blind phase, subjects either continued receiving risperidone plus citalopram or were switched to placebo plus citalopram.Results are presented in Figure 10.

Figure 13: Kaplan-Meier Estimates of Time to Relapse in Study RIS-INT-93: Proportional Hazards Model (ITT Population)

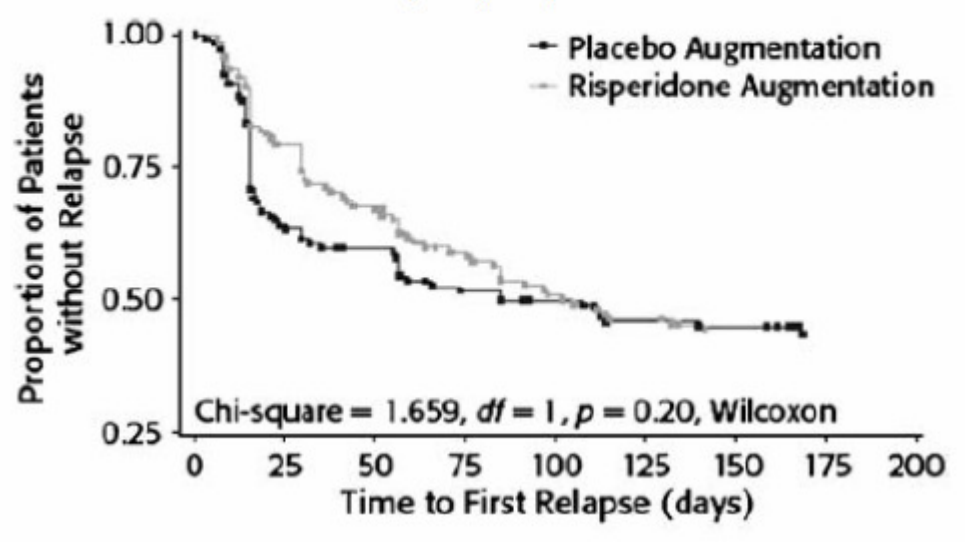


Figure 10

- **Choice of the Dose**

The MAH recommended 6 mg once a day for the treatment of schizoaffective disorder with the possibility to adjust the dose between 3 and 12 mg/day.

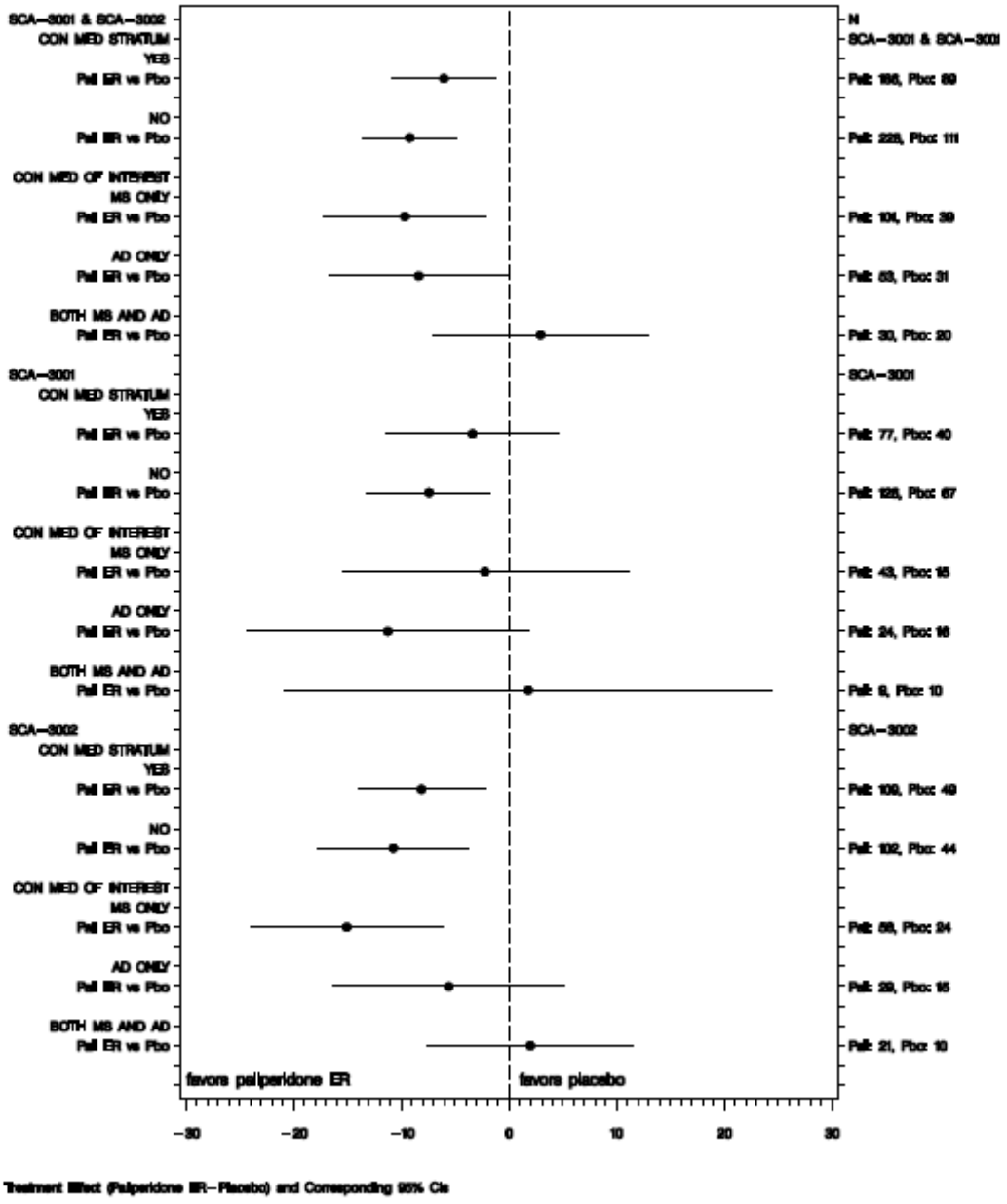
In the CHMP's view, the low dose, particularly 3 mg, is not supported by the clinical studies, as study SCA-3001 clearly favored the high dose group. Also a dose recommendation for 3 mg cannot be deduced from study SCA-3002, as only single cases received 3mg/d and 30-35% patients each received 6mg, 9mg or 12mg/d as final dose.

Following MAH's justifications on dosing recommendation, the CHMP was still of the opinion that the low dose could not be recommended. In study SCA-3001, the low dose (6 mg/d, with option to reduce to 3mg/d) was not efficacious with a mean change in PANSS of -27.4 vs -21.7 (placebo group) (p= 0.187). In the other pivotal study SCA-3002 only 3 out of 304 patients (1%) were treated with the 3 mg dose in study SCA-3002. The CHMP recommended to modify the proposed posology in the SPC accordingly.

- **Additional analyses**

At the CHMP's request, analyses from pivotal studies SCA-3001 and SCA-3002 were performed to compare the efficacy in the sub-groups defined as "antidepressants only" and "mood stabilisers only". Primary endpoint results were presented in Figure 11:

Figure 5: Forest Plot of Change in PANSS Total Score at End Point (LOCF) by Concomitant Medication Stratum and Antidepressant/Mood Stabiliser Use
(Studies R076477-SCA-3001 and -SCA-3002: Intent-to-Treat Analysis Set)



AD=antidepressant; CI=confidence interval; CON MED=concomitant medication; MS=mood stabiliser; Pali=paliperidone; Pbo=placebo

Figure 11

A post-hoc analysis from pooled pivotal studies SCA-3001 and SCA-3002 was also conducted measuring changes from baseline for YMRS and HAM-D and PANSS total scores for 3 subgroups of subjects: with prominent manic symptoms at baseline (defined as YMRS total score ≥16), prominent depressive symptoms at baseline (defined as HAM-D total score ≥16), or mixed symptoms at baseline (defined as both YMRS and HAM-D total scores ≥16). Results are summarised in tables 13-15:

Table 13 Change from baseline (LOCF) in efficacy parameters in subjects with prominent manic symptoms at baseline (SCA-3001 and SCA-3002 ITT analysis set)

	Placebo (N=160)		Paliperidone PR (N=328)	
Parameter	Actual	CFB	Actual	CFB
YMRS Total Score (Endpoint)				
n	160	160	327	327
LS Mean (SE)	18.4 (0.9)	-9.8 (0.9)	13.8 (0.7)	-14.6 (0.7)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-4.8 (1.0)
95% CI	--	--	--	(-6.8, -2.9)
HAM-D Total Score (Endpoint)				
n	160	160	327	327
LS Mean (SE)	12.1 (0.7)	-6.3 (0.7)	9.4 (0.5)	-9.2 (0.5)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-2.9 (0.7)
95% CI	--	--	--	(-4.3, -1.5)
PANSS Total Score (Endpoint)				
n	160	160	328	328
LS Mean (SE)	74.0 (1.8)	-18.3 (1.8)	66.3 (1.4)	-26.5 (1.3)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-8.2 (1.9)
95% CI	--	--	--	(-11.9, -4.5)

The ANCOVA model included treatment, protocol, country-within-protocol, and concomitant medication as fixed effects, and baseline value as a covariate.
CFB=change from baseline; CI=confidence interval

Table 14 Change from baseline (LOCF) in efficacy parameters in subjects with prominent depressive symptoms at baseline (SCA-3001 and SCA-3002 ITT analysis set)

	Placebo (N=129)		Paliperidone PR (N=282)	
Parameter	Actual	CFB	Actual	CFB
YMRS Total Score (Endpoint)				
n	129	129	281	281
LS Mean (SE)	14.8 (0.9)	-7.0 (0.9)	11.9 (0.7)	-10.2 (0.7)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-3.1 (0.9)
95% CI	--	--	--	(-4.9, -1.3)
HAM-D Total Score (Endpoint)				
n	129	129	281	281
LS Mean (SE)	16.0 (0.9)	-8.9 (0.9)	12.4 (0.7)	-12.7 (0.7)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-3.8 (0.9)
95% CI	--	--	--	(-5.5, -2.0)
PANSS Total Score (Endpoint)				
n	129	129	282	282
LS Mean (SE)	76.8 (2.1)	-19.2 (2.1)	69.2 (1.6)	-27.0 (1.6)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-7.9 (2.1)
95% CI	--	--	--	(-11.9, -3.8)

The ANCOVA model included treatment, protocol, country-within-protocol, and concomitant medication as fixed effects, and baseline value as a covariate.
CFB=change from baseline; CI=confidence interval

Table 15 Change from baseline (LOCF) in efficacy parameters in subjects with prominent mixed symptoms at baseline (SCA-3001 and SCA-3002 ITT analysis set)

	Placebo (N=89)		Paliperidone PR (N=196)	
Parameter	Actual	CFB	Actual	CFB
YMRS Total Score (Endpoint)				
n	89	89	195	195
LS Mean (SE)	17.7 (1.4)	-9.0 (1.4)	13.9 (1.1)	-13.2 (1.1)
p value	--	--	--	<0.001
LS Mean Difference	--	--	--	-4.2 (1.2)
95% CI	--	--	--	(-6.6, -1.8)
HAM-D Total Score (Endpoint)				
n	89	89	195	195
LS Mean (SE)	14.9 (1.2)	-9.1 (1.3)	11.8 (1.0)	-12.7 (1.0)
p value	--	--	--	0.001
LS Mean Difference	--	--	--	-3.5 (1.1)
95% CI	--	--	--	(-5.7, -1.4)
PANSS Total Score (Endpoint)				
n	89	89	196	196
LS Mean (SE)	76.1 (2.9)	-20.2 (2.9)	68.3 (2.3)	-28.7 (2.3)
p value	--	--	--	0.001
LS Mean Difference	--	--	--	-8.5 (2.5)
95% CI	--	--	--	(-13.5, -3.4)

The ANCOVA model included treatment, protocol, country-within-protocol, and concomitant medication as fixed effects, and baseline value as a covariate.
CFB=change from baseline; CI=confidence interval

Further analyses were also performed excluding patients on prohibited additional antipsychotics prior to the last PANSS assessment (see Tables 16, 17 and Figure 12).

Table 16

Table 2: PANSS Total Score - Change From Baseline to Week 6 LOCF End Point
(Study R076477-SCA-3001: ITT Analysis Set Without Subjects With Prohibited Concomitant AP)

Parameter	Placebo (N=102)	PALI PR Low Dose (N=101)	PALI PR High Dose (N=90)
Baseline			
N	102	101	90
Mean (SD)	91.9 (12.7)	96.3 (13.1)	92.6 (12.9)
Median (Range)	91.0 (64;126)	95.0 (70;135)	94.0 (63,121)
Week 6 LOCF End Point			
N	102	101	90
Mean (SD)	69.7 (20.7)	68.0 (21.1)	62.0 (20.3)
Median (Range)	72.0 (30;111)	66.0 (32;119)	57.5 (30;143)
LS Mean (SE)	68.4 (2.0)	64.2 (2.1)	60.4 (2.2)
95% CI	(64.4;72.4)	(60.1;68.3)	(56.2;64.6)
Week 6 LOCF End Point Change from Baseline			
N	102	101	90
Mean change (SD)	-22.2 (21.6)	-28.3 (20.8)	-30.7 (19.3)
Median (Range)	-19.5 (-89;15)	-31.0 (-77;13)	-30.5 (-79;22)
LS Mean (SE)	-25.3 (2.0)	-29.5 (2.1)	-33.2 (2.2)
95% CI	(-29.3;-21.2)	(-33.5;-25.4)	(-37.5;-29.0)
p value (vs. placebo)		0.125	0.004[a,b]
LS Mean Diff (SE)		-4.2 (2.7)	-8.0 (2.8)
95% CI		(-9.6;1.2)	(-13.4;-2.5)
Effect Size vs Placebo		0.22	0.42

[a] Significant at 0.01 alpha level
[b] Significant using the Hochberg procedure
Note: p values for between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, concomitant medication stratum, and country, and with baseline value as a covariate.
ANCOVA=analysis of covariance
Cross-reference: Attachment 2.1

Table 17

Table 5: PANSS Total Score - Change From Baseline to Week 6 LOCF End Point (Study R076477-SCA-3002: ITT Analysis Set Without Subjects With Prohibited Concomitant APs)

Parameter	Placebo (N=86)	PALI PR (N=200)
Baseline		
N	86	200
Mean (SD)	92.1 (12.4)	92.5 (13.7)
Median (Range)	90.0 (62;121)	91.5 (63;149)
Week 6 LOCF End Point		
N	86	200
Mean (SD)	80.5 (23.4)	71.6 (20.9)
Median (Range)	78.0 (31; 142)	70.0 (30; 123)
LS Mean (SE)	79.0 (2.2)	69.4 (1.7)
95% CI	(74.6;83.5)	(66.1;72.7)
Week 6 LOCF End Point Change from Baseline		
N	86	200
Mean (SD)	-11.6 (18.2)	-20.9 (18.7)
Median (Range)	-13.5 (-56; 28)	-21.0 (-92; 29)
LS Mean (SE)	-13.4 (2.2)	-23.0 (1.7)
95% CI	(-17.8;-8.9)	(-26.3;-19.7)
p value (vs. placebo)		<0.001**
LS Mean Diff (SE)		-9.6 (2.3)
95% CI		(-14.2;-5.0)
Effect Size vs Placebo		0.53

** = Significant at 0.01 alpha level
Note: p values for between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, concomitant medication stratum, and country, and with baseline value as a covariate.
ANCOVA=analysis of covariance
Cross-reference: Attachment 4.1

Figure 1: Forest Plot of Change in PANSS Total Score at End Point (LOCF) by Concomitant Medication Stratum
(R076477-SCA-3001 and -SCA-3002: ITT Excluding Subjects on Prohibited Additional APs Prior to PANSS Total Score Assessment)

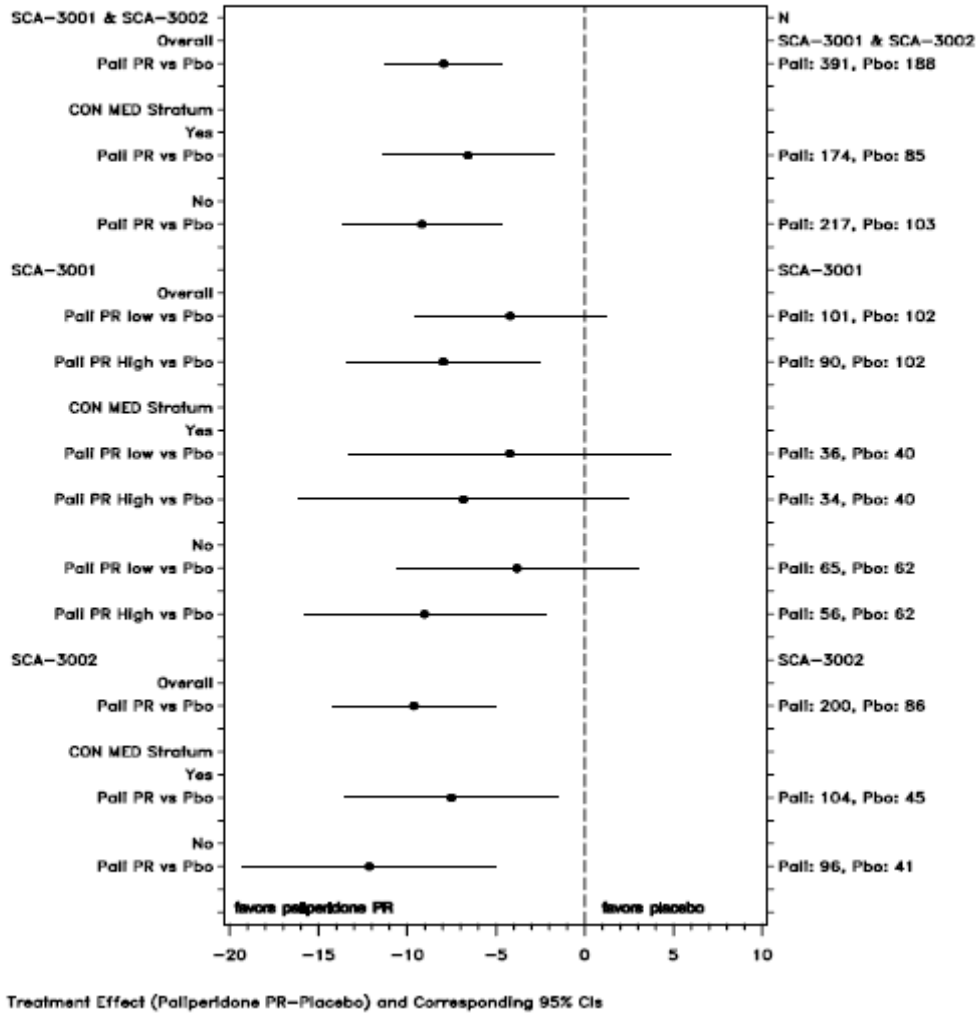


Figure 12

Additionally, post-hoc responder analyses that considered subjects who discontinued from the study as non-responders showed that at week 6, the proportions of subjects who responded to treatment were statistically significantly greater than placebo for studies SCA-3001 and SCA-3002 (34.6% and 23.7%, respectively) in the ER groups (SCA-3001: 55.1%, p=0.002 for the high dose group; SCA-3002: 35.7%, p=0.048 for the flexible dose group). However, the proportion of subjects who responded to treatment was not statistically significant over the placebo in the paliperidone ER low dose group (45.2%; p=0.067) for study SCA-3001. Same analyses excluding subjects receiving prohibited concomitant antipsychotic medication prior to the last PANSS assessment during the study showed similar results.

Analyses comparing sub-groups defined as "concomitant use of lithium" and "no concomitant use of lithium" were performed in subjects with prominent depressive symptoms for HAM-D total score and in subjects with prominent manic symptoms for YRMS total score. Results are summarised in Tables 18 and 19, respectively.

Table 18

Table 9: HAM-D Total Score - Change From Baseline to Week 6 LOCF End Point (Study R076477-SCA-3001 and -SCA-3002: ITT With Baseline HAM-D Total Score ≥16)

Parameter	Placebo	PALI PR
Overall		
N	129	281
Mean (SD)	-8.1 (9.9)	-12.0 (9.1)
Median (Range)	-8.0 (-39; 15)	-12.0 (-38; 15)
LS Mean (SE)	-8.4 (1.2)	-12.1 (1.1)
95% CI	(-10.7; -6.0)	(-14.2; -10.0)
p value (vs. placebo)		<0.001**
LS Mean Diff (SE)		-3.7 (0.9)
95% CI		(-5.5; -2.0)
Interaction between Treatment and Lithium Use		0.439
Subjects with No Concomitant Lithium Use		
N	118	266
Mean (SD)	-8.1 (10.0)	-12.1 (9.1)
Median (Range)	-7.5 (-39; 15)	-12.0 (-38; 15)
LS Mean (SE)	-8.8 (0.9)	-12.7 (0.7)
95% CI	(-10.6; -7.0)	(-14.1; -11.3)
p value (vs. placebo)		<0.001**
LS Mean Diff (SE)		-3.9 (0.9)
95% CI		(-5.7; -2.1)
Subjects with Any Concomitant Lithium Use		
N	11	15
Mean (SD)	-7.6 (7.8)	-10.5 (9.8)
Median (Range)	-8.0 (-24; 3)	-11.0 (-22; 6)
LS Mean (SE)	-7.4 (3.0)	-10.4 (2.7)
95% CI	(-13.7; -1.1)	(-16.1; -4.7)
p value (vs. placebo)		0.477
LS Mean Diff (SE)		-3.0 (4.1)
95% CI		(-11.5; 5.6)

** = Significant at 0.01 alpha level

Note: The p values for between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, lithium use, study identifier, country nested within study identifier, and with baseline value as a covariate.

The p value for interaction is from an ANCOVA model with fixed effects for treatment, lithium use, study identifier, country nested within study identifier, interaction of treatment and lithium use, and with baseline value as a covariate.

ANCOVA=analysis of covariance

Cross-reference: Attachment 6.2

Table 19

Table 10: YMRS Total Score - Change From Baseline to Week 6 LOCF End Point (Study R076477-SCA-3001 and -SCA-3002: ITT With Baseline YMRS Total Score ≥16)

Parameter	Placebo	PALI PR
Overall		
N	160	327
Mean (SD)	-8.9 (11.2)	-13.7 (11.8)
Median (Range)	-7.5 (-47; 20)	-14.0 (-43; 22)
LS Mean (SE)	-9.2 (1.1)	-13.9 (1.0)
95% CI	(-11.4; -7.0)	(-15.9; -12.0)
p value (vs. placebo)		<0.001**
LS Mean Diff (SE)		-4.8 (1.0)
95% CI		(-6.7; -2.8)
Interaction between Treatment and Lithium Use		0.904
Subjects with No Concomitant Lithium Use		
N	142	303
Mean (SD)	-9.0 (11.3)	-13.8 (11.8)
Median (Range)	-7.0 (-47; 20)	-14.0 (-43; 22)
LS Mean (SE)	-10.0 (1.0)	-14.7 (0.7)
95% CI	(-11.9; -8.0)	(-16.1; -13.3)
p value (vs. placebo)		<0.001**
LS Mean Diff (SE)		-4.7 (1.0)
95% CI		(-6.8; -2.7)
Subjects with Any Concomitant Lithium Use		
N	18	24
Mean (SD)	-8.3 (10.3)	-12.5 (11.9)
Median (Range)	-9.5 (-23; 9)	-11.5 (-38; 5)
LS Mean (SE)	-8.1 (3.0)	-14.3 (2.7)
95% CI	(-14.1; -2.0)	(-19.9; -8.7)
p value (vs. placebo)		0.075
LS Mean Diff (SE)		-6.3 (3.4)
95% CI		(-13.2; 0.7)

** = Significant at 0.01 alpha level
Note: The p values for between-treatment-group comparisons are from an ANCOVA model with fixed effects for treatment, lithium use, study identifier, country nested within study identifier, and with baseline value as a covariate.
The p value for interaction is from an ANCOVA model with fixed effects for treatment, lithium use, study identifier, country nested within study identifier, interaction of treatment and lithium use, and with baseline value as a covariate.
ANCOVA=analysis of covariance
Cross-reference: Attachment 6.2

For the subgroup of subjects who used lithium during the study, the mean improvement in the paliperidone ER group was numerically smaller than in the placebo group (-18.1 vs. -18.5), while for the subgroup of subjects who did not receive lithium the numerical differences between paliperidone ER and placebo (-24.8 vs. -16.4) favoured paliperidone ER.

- **Discussion on clinical efficacy**

In two placebo-controlled short-term phase 3 studies, statistically significant effect in favour of paliperidone ER for the primary endpoint PANSS Total score was shown. The clinical relevance of the results is illustrated in responder analyses showing differences versus placebo of 22 and 12.5 %-units for the two studies, respectively. The validity of these effects for schizoaffective patients are substantiated in analyses of secondary endpoints, including PANSS-24 which consist of the PANSS items corresponding to the DSM-IV criteria for schizoaffective disorder, and clinically relevant reductions of depressive and manic symptoms in patients with pronounced affective symptoms at baseline.

In study SCA-3001, an effect of paliperidone ER 9-12 mg/day (high dose group) has been demonstrated for the primary endpoint with consistent support in the analyses of the secondary endpoints.

In study SCA-3002, an effect of flexibly dosed (3-12 mg/day) paliperidone ER has been demonstrated.

The number of EU patients studied was limited (81 patients from Romania).Otherwise the study population is dominated by US patients (with a potentially less pronounced effect), and Asian patients. After a subgroup analysis (EU Caucasians vs US Caucasians) performed by the MAH, the CHMP considered these results to be sufficiently supportive of the external validity of the two short-term studies.

However, the CHMP raised major concerns regarding the comparative efficacy data between mono-therapy and combination with anti-depressives-mood stabilizers, as presented by the MAH. For instance, in study SCA-3001, although no statistical evidence of a differential effect depending on whether the patient was on concomitant treatment with antidepressants and/or mood stabilizers or not (treatment-by-concomitant medication interaction, p-value=0.641) was observed, the change in PANSS Total score was clearly less pronounced not reaching statistical significance for patients on concomitant treatment(see Figure 2). Moreover, apart from PANSS total score, which reflects the schizophrenia component, the CHMP considered that information was required in both settings about the effect on the affective component (mania, depression).

Following the above major concern, the MAH performed a post-hoc analysis pooling the pivotal studies SCA-3001 and SCA-3002. In the pooled analysis, clinically relevant effects on PANSS and YMRS total scores were demonstrated in patients with mood stabilizers only and in patients with antidepressants only. The CHMP noted that no effect is observed in patients on both mood stabilizers and antidepressants. However, this observation is based on 50 patients in total and must be interpreted with caution. In subgroup analyses of the pooled studies, highly significant effects on PANSS and YMRS total scores have been demonstrated for patients with prominent manic symptoms, prominent depressive symptoms, as well as in patients with prominent mixed symptoms. The point estimates of difference in the least-squares (LS) mean changes from baseline for the YMRS and PANSS total scores were respectively : -4.8 and -8.2 (prominent manic symptoms at baseline); -3.1 and -7.9 (prominent depressive symptoms) and -4.2 and -8.5 (prominent mixed symptoms). The magnitude of effect for all endpoints was considered by the CHMP clinically relevant and comparable to other studies of acute treatment in schizophrenia, manic episodes associated with bipolar I disorder and major depressive episodes, respectively. As expected the effect on manic symptoms is less pronounced in patients with prominent depressive symptoms.

Prior to any final conclusions on the above, further analyses were required, excluding patients on prohibited additional antipsychotics prior to PANSS total score assessment. Results (see Figure 12) were consistent with the earlier analyses (Figures 2 and 4) in the "no concomitant medication" stratum. In both studies SCA-3001 and SCA-3002 using the pre-specified and post-hoc responder analyses, paliperidone ER had a statistically favourable effect on the proportion of responders relative to placebo among subjects with schizoaffective disorder. Same analyses excluding subjects receiving prohibited concomitant antipsychotic medication prior to the last PANSS assessment during the study showed similar results.

The overall effect of lithium in the pivotal studies was also questioned by the CHMP and subgroup analyses were performed by the MAH in subjects with prominent depressive symptoms for HAM-D total score and in subjects with prominent manic symptoms for YRMS total score and in all subjects for PANSS total score to address this point. In total, 29 patients on paliperidone ER and 22 on placebo received at least one dose of lithium meaning 11% of subjects in the placebo group and 7% of subjects in the combined paliperidone ER group used lithium during the phase III studies. With respect to affective symptoms rated with HAM-D and YMRS total scores, there were no major numerical differences in magnitude of effect between patients with no concomitant lithium use and patients with any lithium use, and no indication of a treatment by lithium use interaction (see Tables 18 and 19). In contrast, for psychotic symptoms rated with PANSS Total Score, the effect seen in the overall population is entirely attributed to the subgroup with no lithium use. However, due to the limited number of patients, the CHMP considered that no reliable conclusions can be drawn on this issue.

To further support the effect of paliperidone ER as monotherapy or add-on treatment in schizoaffective disorder, indirect comparison of efficacy results between paliperidone ER and other antipsychotics from available clinical studies in this population was also conducted by the MAH. However, the CHMP considered this analysis of limited value. The CHMP noted that only 2 published randomised, double-blind studies comparing an antipsychotic versus an antidepressant or mood stabilizer were identified7 .

The proposed initial extrapolation of available long term data from the schizophrenia studies and from the studies with the mother compound risperidone (performed in schizophrenia and schizoaffective disorder) to support the long-term maintenance of the effect of paliperidone ER in schizoaffective disorder was questioned by the CHMP. The pivotal studies had a maximum length of 6 weeks and longer-term maintenance studies were not included in the development program. Although pharmacokinetic data were presented to support the extrapolation using the mother compound risperidone, all schizophrenia long term studies with paliperidone ER had an open-label design and neither risperidone or comparators used in the proposed supportive long term studies have been authorised in schizoaffective disorder.

In light of the above major concern related to extrapolation of long term data to support the long-term maintenance of the effect of paliperidone ER in schizoaffective disorder and on the basis of the available data to date, the CHMP agreed to convene a Central Nervous System Scientific Advisory Group (SAG-CNS) to discuss the need for long-term efficacy data for paliperidone in the applied indication. The SAG-CNS was held on 13 July 2010 and the main conclusions were the following:

- Ideally, long-term studies in the target population with outcome scales validated for schizoaffective disorder should have been performed. However, in the absence of such studies, it was considered reasonable that there is maintenance of effect on psychotic symptoms during prolonged treatment since the psychotic symptoms of schizoaffective disorder are similar to those in schizophrenia. Thus, this was considered a valid extrapolation.

[7] 1) Brockington *et al.* Trials of lithium, chlorpromazine and amitriptyline in schizoaffective patients. Br J Psychiatry 1978;133:162-8; 2) Okuma et al. A double-blind study of adjunctive carbamazepine versus placebo on excited states of schizophrenic and schizoaffective disorders. Acta Psychiatr Scand 1989;80:250-9.

- The group was convinced that there is good evidence of maintenance of effect on manic symptoms. From the submitted documentation, the SAG-CNS is not convinced that there is a clinically significant effect on depressive symptoms. The HAM-D scale is not validated for measuring depressive symptoms in schizophrenia and related disorders. Other assessment scales which have been validated should have been considered (i.e. the Calgary Depression Scale for Schizophrenia). There was no evidence for a tachyphylactic mechanism.

To further address the above major concern, additional long-term clinical studies with paliperidone ER and other related compounds (paliperidone palmitate, risperdal consta), conducted either in bipolar I disorder, schizophrenia or treatment resistant depression, were referred by the MAH as supportive data. All of these populations had at least one symptom domain of schizoaffective disorder (psychosis, mania and depression).

An oral explanation took place on 20 July 2010. In the MAH's view:

- overlap in symptom presentation according to DSM-IV criteria supports the validity of extrapolation of data in different populations having one of the symptom domains of schizoaffective disorder (psychosis, mania, depression);

- studies RIS-USA-79, RIS-SCH-401 and RIS-INT-57 showed that patients with schizoaffective disorder and schizophrenia responded similarly;

- generally, there is a consistent benefit across acute and maintenance studies in psychotic and mood disorders for paliperidone and risperidone;

- the maintenance of the effect of paliperidone ER has been demonstrated in psychosis (study SCH-301) and in preventing any mood episode in (study BIM-3004). In addition, comparative data from studies with paliperidone ER and risperdal consta showed an effect in preventing manic/mixed episodes.

Having considered the SAG-CNS conclusions and the oral explanation provided by the MAH, the CHMP recommended the following indication:

"INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."

On the basis of the available data, the CHMP also recommended to include in section 4.2 of the SPC related to schizoaffective disorder that "Maintenance of effect has not been studied". The CHMP requested a long-term maintenance study on paliperidone palmitate to be conducted to confirm the maintenance of the effect of paliperidone in this population. Additional pharmacokinetic data on switching from oral paliperidone to paliperidone palmitate should also be provided by the MAH. The request for these data has been included, upon request of the CHMP, in a new version of the risk management plan.

Furthermore, the CHMP has identified that an effect on depressive symptoms has not been demonstrated, which should be clearly reflected in the product information. The HAM-D 21 scale used in the clinical trials is not validated for schizoaffective disorder and also includes symptoms that could be attributed to psychosis/mania. Furthermore, some improvement of depressive symptoms may be expected when treating an acute and distressing psychotic episode even in the absence of a genuine antidepressive effect of the administered drug. On the basis of the maintenance study protocol, as proposed by the MAH, the CHMP recommended the use of HAM-D-17 scale.

1.3.3 Clinical safety

- **Patient exposure**

The number of subjects who received at least one dose, and was part of the overall safety analyses set is shown in each concomitant medication stratum, as continuation of ongoing therapy with mood stabilizers (lithium, valproate, or lamotrigine) and/or antidepressants (except monoamine oxidase inhibitors) was permitted in both studies (see Table 16).

Table 20: Number of Subjects in Each Concomitant Medication Stratum (Studies R076477-SCA-3001 and R076477-SCA-3002: All Randomized Subjects Analysis Set)

Concomitant Medication Stratum	Placebo (N=202) n (%)	Pali ER Low Dose (N=109) n (%)	Pali ER High Dose (N=100) n (%)	Pali ER Flex Dose (N=216) n (%)	Pali ER High/Flex (N=316) n (%)	Total Pali ER (N=425) n (%)	Total (N=627) n (%)
All randomized subjects	202 (100)	109 (100)	100 (100)	216 (100)	316 (100)	425 (100)	627 (100)
No treatment with antidepressants and/or mood stabilizers	112 (55)	69 (63)	59 (59)	104 (48)	163 (52)	232 (55)	344 (55)
Treatment with antidepressants and/or mood stabilizers	90 (45)	40 (37)	41 (41)	112 (52)	153 (48)	193 (45)	283 (45)
Safety	202 (100)	108 (99)	98 (98)	214 (99)	312 (99)	420 (99)	622 (99)
No treatment with antidepressants and/or mood stabilizers	112 (55)	68 (62)	59 (59)	103 (48)	162 (51)	230 (54)	342 (55)
Treatment with antidepressants and/or mood stabilizers	90 (45)	40 (37)	39 (39)	111 (51)	150 (47)	190 (45)	280 (45)
Intent-to-Treat	200 (99)	105 (96)	98 (98)	211 (98)	309 (98)	414 (97)	614 (98)
No treatment with antidepressants and/or mood stabilizers	111 (55)	67 (61)	59 (59)	102 (47)	161 (51)	228 (54)	339 (54)
Treatment with antidepressants and/or mood stabilizers	89 (44)	38 (35)	39 (39)	109 (50)	148 (47)	186 (44)	275 (44)

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Up to 01 May 2009 in the ongoing Phase 3b Study SCH-4005 in patients with schizophrenia or schizoaffective disorder and hepatic disease, 114 subjects were assigned to open-label treatment, and 84 subjects received at least 1 dose of paliperidone ER.

Total duration of study medication and average daily dose during the double-blind phase are summarized in Table 20. Across both completed Phase 3 studies paliperidone ER exposure was calculated to be 39.3 subject-years. ´

Table 20: Exposure to Study Medication (Studies R076477-SCA-3001 and R076477-SCA-3002: Safety Analysis Set)

	Placebo (N=202)	Pali ER Low Dose (N=108)	Pali ER High Dose (N=98)	Pali ER Flex Dose (N=214)	Pali ER High/Flex (N=312)	Total Pali ER (N=420)
Total duration of study med (days)						
N	202	108	98	214	312	420
Category, n (%)						
1	2 (1)	3 (3)	1 (1)	4 (2)	5 (2)	8 (2)
2 - 5	13 (6)	4 (4)	3 (3)	14 (7)	17 (5)	21 (5)
6 - 11	23 (11)	7 (6)	4 (4)	17 (8)	21 (7)	28 (7)
12 - 18	27 (13)	8 (7)	4 (4)	17 (8)	21 (7)	29 (7)
19 - 25	12 (6)	8 (7)	2 (2)	10 (5)	12 (4)	20 (5)
26 - 35	6 (3)	5 (5)	6 (6)	16 (7)	22 (7)	27 (6)
≥ 36	119 (59)	73 (68)	78 (80)	136 (64)	214 (69)	287 (68)
Mean (SD)	30.7 (15.62)	34.0 (14.50)	37.8 (12.22)	32.6 (14.87)	34.3 (14.28)	34.2 (14.32)
Median	42.0	43.0	43.0	42.0	42.0	42.0
Range	(1;48)	(1;51)	(1;50)	(1;48)	(1;50)	(1;51)
Average daily dose (mg)						
N	202	108	98	214	312	420
Mean (SD)	0.0 (0.00)	5.7 (0.77)	11.7 (0.71)	8.0 (2.06)	9.2 (2.46)	8.3 (2.63)
Median	0.0	6.0	12.0	8.0	9.4	8.0
Range	(0;0)	(3;6)	(9;12)	(3;14)*	(3;14)*	(3;14)*

*Three subjects (Subject 211617, Subject 211706, and Subject 211008) had mean daily doses greater than 12 mg/day. The mean daily doses (13.5 mg, 13.44 mg, and 12.065 mg) were calculated as the total dose divided by the treatment duration where total dose is based on the number of capsules taken at each given dose and the duration of treatment is based on the treatment start and stop dates. Since there was not a daily drug administration log, mean daily dose computations were based on calculated treatment duration.

In Study SCH-4005, 114 subjects received conventional or atypical oral antipsychotics for 4 weeks (Phase 1), and 84 subjects cross-titrated from oral antipsychotic treatment to paliperidone ER treatment for 1 week and then received paliperidone ER for 4 weeks (Phase 2, starting dose 6 mg/d, dose range 3 to 12 mg/d). Of the 84 subjects receiving paliperidone ER during Phase 2, the median duration of exposure was 34 days, and the mean (SD) duration was 30 (9.2) days, and the average daily dose was 7.5 mg. This treatment resulted in 6.89 subject-years of paliperidone ER exposure.

- **Adverse events**

Treatment-Emergent Adverse Events (TEAEs) were reported for 65% of 622 subjects during the double-blind phase of the studies. In 44%, AEs were considered possibly, probably, or very likely related to study drug.

All common treatment-emergent adverse events, ie, events that occurred in at least 5% of subjects in any treatment group during the double-blind phase, are presented in Table 21.

Table 21: Treatment-Emergent Adverse Events in ≥ 5% of Subjects in Any Treatment Group by Preferred Term - Double-Blind Phase (Studies R076477-SCA-3001 and R076477-SCA-3002: Safety Analysis Set)

Body System or Organ Class Dictionary-derived Term	Placebo (N=202) n (%)	Pali ER Low Dose (N=108) n (%)	Pali ER High Dose (N=98) n (%)	Pali ER Flex Dose (N=214) n (%)	Pali ER High/Flex (N=312) n (%)	Total Pali ER (N=420) n (%)	Tot (N=6 n (%
Total no. subjects with adverse events	118 (58.4)	78 (72.2)	68 (69.4)	140 (65.4)	208 (66.7)	286 (68.1)	404 (65.0)
Nervous system disorders	56 (27.7)	42 (38.9)	41 (41.8)	84 (39.3)	125 (40.1)	167 (39.8)	223 (35.9)
Headache	30 (14.9)	15 (13.9)	13 (13.3)	32 (15.0)	45 (14.4)	60 (14.3)	90 (14.5)
Tremor	7 (3.5)	13 (12.0)	11 (11.2)	10 (4.7)	21 (6.7)	34 (8.1)	41 (6.6)
Dizziness	12 (5.9)	6 (5.6)	4 (4.1)	18 (8.4)	22 (7.1)	28 (6.7)	40 (6.4)
Akathisia	9 (4.5)	4 (3.7)	6 (6.1)	13 (6.1)	19 (6.1)	23 (5.5)	32 (5.1)
Sedation	7 (3.5)	8 (7.4)	4 (4.1)	9 (4.2)	13 (4.2)	21 (5.0)	28 (4.5)
Hypertonia	4 (2.0)	9 (8.3)	4 (4.1)	10 (4.7)	14 (4.5)	23 (5.5)	27 (4.3)
Somnolence	4 (2.0)	5 (4.6)	8 (8.2)	9 (4.2)	17 (5.4)	22 (5.2)	26 (4.2)
Gastrointestinal disorders	40 (19.8)	26 (24.1)	23 (23.5)	54 (25.2)	77 (24.7)	103 (24.5)	143 (23.0)
Nausea	12 (5.9)	9 (8.3)	8 (8.2)	10 (4.7)	18 (5.8)	27 (6.4)	39 (6.3)
Dyspepsia	5 (2.5)	5 (4.6)	6 (6.1)	12 (5.6)	18 (5.8)	23 (5.5)	28 (4.5)
Dry mouth	8 (4.0)	7 (6.5)	2 (2.0)	9 (4.2)	11 (3.5)	18 (4.3)	26 (4.2)
Constipation	5 (2.5)	4 (3.7)	5 (5.1)	8 (3.7)	13 (4.2)	17 (4.0)	22 (3.5)
Psychiatric disorders	48 (23.8)	20 (18.5)	20 (20.4)	39 (18.2)	59 (18.9)	79 (18.8)	127 (20.4)
Insomnia	14 (6.9)	5 (4.6)	9 (9.2)	14 (6.5)	23 (7.4)	28 (6.7)	42 (6.8)
Agitation	10 (5.0)	7 (6.5)	1 (1.0)	10 (4.7)	11 (3.5)	18 (4.3)	28 (4.5)
Schizoaffective disorder	7 (3.5)	6 (5.6)	0	6 (2.8)	6 (1.9)	12 (2.9)	19 (3.1)
Infections and infestations	17 (8.4)	11 (10.2)	11 (11.2)	26 (12.1)	37 (11.9)	48 (11.4)	65 (10.5)
Nasopharyngitis	3 (1.5)	2 (1.9)	5 (5.1)	7 (3.3)	12 (3.8)	14 (3.3)	17 (2.7)

Events more frequently reported for paliperidone compared with placebo, were in the Nervous system disorders System Organ Class (SOC) with 39.8% vs. 27.7%, respectively and the Gastrointestinal disorders SOC with 24.5% vs. 19.8%, respectively. With respect to common TEAEs, tremor, hypertonia, somnolence, and dyspepsia occurred at higher incidences (more than 3%) in paliperidone ER-treated subjects compared with placebo. Also events such as akathisia, dizziness, sedation dystonia, were among commont reported events, more frequently seen in paliperidone groups.

In subjects receiving concomitant antidepressants and/or mood stabilizers, TEAEs occurred at a greater incidence compared to those subjects not receiving these therapies (70.4% versus 60.5% respectively). Within the strata, those without concomitant antidepressants and/or mood stabilizers, TEAEs occurred in 49% on placebo, and 66% on paliperidone (total), while in the group on concomitant medication, TEAEs occurred in 70% of both placebo and total paliperidone.

- **Serious adverse events (SAEs) and deaths**

In phase III studies, serious TEAEs were reported for 37 subjects (5.9%), and AEs lead to discontinuation of 40 subjects (6.4%). incidence of SAEs was higher for placebo (6.9%) vs. the total paliperidone group (5.5%), and higher for paliperidone ER low dose (9.3%) compared with the high dose (2.0%). Most of the SAEs were related to psychiatric disorders.

There were two cases of suicidal ideation in the placebo group, and one case of suicidal behaviour in the low dose paliperidone group. These SAEs were considered related to the underlying psychiatric disorder. In the paliperidone group there were two cases of serious infection, while all other SAEs were reported as single occurrences across all treatment groups. All SAEs (excepted case related to small intestinal obstruction) were considered unrelated to paliperidone.

There were no deaths reported during any of the studies (BIM-1003, BIM-1004, SCA-3001, and SCA-3002), or up to the cut-off date of 01 May 2009 in study SCH-4005.

- **Discontinuation due to AEs**

Overall, 7% of subjects withdrew due to adverse events in the placebo group as well as in the total paliperidone ER group. Discontinuation due to AEs ranged from 4% of subjects in the paliperidone ER high dose group to 9% of subjects in the low dose group. Consequently, no apparent dose relationship in relation to withdrawal was observed.

- **Laboratory findings and vital signs**

Apart from elevated serum prolactin levels (see below), there were no other clinically relevant mean changes from baseline at any time point across treatment groups for laboratory analytes, including hematology, renal function, liver function, fasting blood glucose, serum lipid, and urinalysis parameters. In the high paliperidone ER group, slight increases in mean changes from baseline to endpoint in ALT and AST values were noted, with no corresponding change in the median values.

There were no clinically noteworthy differences in means or mean changes from baseline to end point in any laboratory analyte for paliperidone ER-treated subjects receiving antidepressants and/or mood stabilizers relative to subjects receiving paliperidone ER alone.

There were no clinically relevant differences in mean changes from baseline for supine and standing pulse rate or systolic and diastolic blood pressure between the placebo and paliperidone ER groups. Review of number of subjects with increases in standing and supine pulse rates above limits defined as clinically important, showed a higher percentage of increases in paliperidone ER-treated subjects compared with placebo (eg 15% and 9% for standing pulse rate in the total paliperidone ER and placebo groups, respectively).

- **Other safety findings**

Extrapyramidal Symptom (EPS)-Related Adverse Events

The overall incidence of EPS-related AEs was higher in paliperidone treated subjects (19.8%) than in placebo-treated subjects (10.9%), corresponding to e.g. parkinsonism, hyperkinesias, tremor and dystonia. All treatment-emergent EPS-related adverse events were considered by the investigator to be mild or moderate in severity, except dystonia (n=1, placebo) and tremor (n=1, paliperidone ER flexible dose group). None was reported as a serious AE.

Suicidality

There were no reports of completed suicide in either study. Suicidality during the double-blind phase was reported by 3% of placebo-treated and 0.5% of paliperidone ER-treated subjects. Six subjects in the placebo group experienced suicidal ideation that was considered mild (n=2), moderate (n=2), or severe (n=2). One subject in the paliperidone ER low dose group experienced suicidal behavior that was considered severe, and 1 subject in the paliperidone ER high dose group experienced suicidal ideation that was moderate in severity.

Depression

The depressed mood and depression experienced by the placebo- and paliperidone ER-treated subjects were mild or moderate in severity.Overview of the AEs are presented in Table 22.

Table 22: Treatment-Emergent Depression-Related Adverse Events - Double-Blind Phase (Studies R076477-SCA-3001 and R076477-SCA-3002: Safety Analysis Set)

MedDRA System Organ Class Term MedDRA Preferred Term	Placebo (N=202) n (%)	Pali ER Low Dose (N=108) n (%)	Pali ER High Dose (N=98) n (%)	Pali ER Flex Dose (N=214) n (%)	Pali ER High/Flex (N=312) n (%)	Total Pali ER (N=420) n (%)	Total (N=622) n (%)
Total no. subjects with depression-related AE	5 (2.5)	2 (1.9)	2 (2.0)	0	2 (0.6)	4 (1.0)	9 (1.4)
Psychiatric disorders	5 (2.5)	2 (1.9)	2 (2.0)	0	2 (0.6)	4 (1.0)	9 (1.4)
Depressed mood	4 (2.0)	2 (1.9)	0	0	0	2 (0.5)	6 (1.0)
Depression	1 (0.5)	0	2 (2.0)	0	2 (0.6)	2 (0.5)	3 (0.5)

Convulsion/Seizures

Overview of the AEs are presented in Table 23.

Table 23: Treatment-Emergent Convulsion/Seizure-Related Adverse Events - Double-Blind Phase

MedDRA System Organ Class Term MedDRA Preferred Term	Placebo (N=202) n (%)	Pali ER Low Dose (N=108) n (%)	Pali ER High Dose (N=98) n (%)	Pali ER Flex Dose (N=214) n (%)	Pali ER High/Flex (N=312) n (%)	Total Pali ER (N=420) n (%)	Total (N=622) n (%)
Total no. subjects with convulsion/seizure-related AE	0	1 (0.9)	0	0	0	1 (0.2)	1 (0.2)
Nervous system disorders	0	1 (0.9)	0	0	0	1 (0.2)	1 (0.2)
Grand mal convulsion	0	1 (0.9)	0	0	0	1 (0.2)	1 (0.2)

Neuroleptic Malignant Syndrome

No cases of neuroleptic malignant syndrome were reported in either study.

Potentially Prolactin-Related Events

Mean changes from baseline in serum prolactin levels were greater in paliperidone ER-treated subjects than placebo and greater in paliperidone ER-treated females than in paliperidone ER-treated males. Prolactin-related adverse events occurred in 2.1 % of paliperidone ER-treated subjects and more frequently in females (6 of 9 cases) than in males. All potentially prolactin-related events were considered mild or moderate in severity. No subject discontinued. Three of the 10 potentially prolactin-related adverse events (ie, erectile dysfunction in 1 male and galactorrhoea in 2 females) were noted as persisting. The remaining 7 adverse events resolved.

Glucose-Related Events

The incidence of treatment-emergent glucose-related adverse events was (<1%) and corresponded with the general lack of clinically significant changes in blood glucose levels. Two subjects in the paliperidone ER flexible dose group experienced blood glucose increased (blood glucose value of 13.9 mmol/L at 6 weeks; normal range of 3.6 to 7.7 mmol/L) and hyperglycaemia (blood glucose value of 17.3 mmol/L at 6 weeks), respectively. Both events were considered to be moderate in severity.

Weight-related events

Weight-related TEAEs were reported for 8.1% of paliperidone ER-treated subjects and 2.5% of placebo-treated subjects. It included weight increased (4.0% of paliperidone vs. 1.5% for placebo), increased appetite (2.4% vs. 0.5%, respectively), neither of which increased in frequency with dose.

Weight decrease was reported as well (1.0% paliperidone vs. none on placebo) ; decreased appetite (1.4% versus 0.5%, respectively). All except one (weight increased in one female subject on paliperidone ER flexible dose) were considered mild or moderate in severity. No subject discontinued study treatment due to a weight-related TEAE.

In addition, paliperidone ER-treated subjects with a screening BMI of 30 kg/m2 or greater (obese) gained more weight at end point than paliperidone ER-treated subjects with a screening BMI less than 25 kg/m2 (normal) or 25 to less than 30 kg/m2 (overweight). A higher percentage of paliperidone ER-treated subjects (5%) had an increase in body weight of 7% or greater than placebo-treated subjects (1%), and the increase in body weight of 7% or more was dose related (3% low dose vs. 7% high dose group); with a 1% incidence in the placebo group.

Cardiovascular Effects: Proarrhythmic Potential

There was 1 subject on paliperidone ER low dose group who experienced a grand mal convulsion that was considered severe. There were no other TEAEs suggestive of proarrhythmic potential.

Electrocardiograms

Increases of 30 to 60 msec from average predose values in corrected QTcLD intervals at endpoint were reported for 2.6% of paliperidone ER-treated subjects compared with 0.6% of subjects in the placebo group. No subject experienced an increase in QTcLD interval greater than 60 msec.

- **Discussion on clinical safety**

Short term safety data from the two Phase 3 studies with paliperidone ER in patients with schizoaffective disorder do not reveal any new safety concerns, compared with what is known from previous studies with paliperidone and from experience with risperidone. Interim data from an ongoing open label Phase 3b study in 114 subjects with schizophrenia or schizoaffective disorder and hepatic disease were also analysed.

In the two phase 3 studies, events more frequently reported for paliperidone compared with placebo, were in the Nervous system disorders SOC (39.8% vs. 27.7%, respectively) and the Gastrointestinal disorders SOC (24.5% vs. 19.8%, respectively). With respect to common TEAEs, tremor, hypertonia, somnolence, and dyspepsia occurred at higher incidences (more than 3%) in paliperidone ER-treated subjects compared with placebo. Also events such as akathisia, dizziness, sedation and dystonia, were among commonly reported events, more frequently seen in paliperidone groups.

The incidence of SAEs was higher for placebo (6.9%) vs. the total paliperidone group (5.5%), and higher for paliperidone ER low dose (9.3%) compared with the high dose (2.0%). Most SAEs appeared in the Psychiatric disorders SOC (19 of 27).

Among events of special interest, the overall incidence of EPS-related AEs was higher in paliperidone treated subjects (19.8%) than in placebo-treated subjects (10.9%), corresponding to e.g. parkinsonism, hyperkinesias, tremor and dystonia. Regarding prolactin, mean changes from baseline in serum prolactin levels were greater in paliperidone ER-treated subjects than placebo and greater in paliperidone ER-treated females than in paliperidone ER-treated males. Prolactin-related adverse events occurred in 2.1 % of paliperidone ER-treated subjects and more frequently in females (6 of 9 cases) than in males. As expected, weight increase occurred more frequently in paliperidone treated subjects, compared with placebo.

When comparing the overall reporting of adverse events across regions, there was a difference between European patients (180 of 622 subjects were from Romania, Russia and Ukraine) and those from the USA and Rest of the World, with lower frequencies reported by EU-patients. This was also

observed for paliperidone ER-treated subjects, since adverse events were reported by a higher percentage of subjects at non-European sites (78.3%) compared with European sites (43.0%).

However, a dose-relationship was found for a significant number of ADRs (e.g . toothache, pharyngolaryngeal pain, galactorrhoea, tremor, akathisia, somnolence, nausea, dyspepsia, constipation, insomnia, asthenia, nasopharyngitis, myalgia, increased appetite).

Additionally, significant effect related to concomitant medication on the rate of ADRs was observed. This information was subsequently reflected in the SPC.

Furthermore, the CHMP required further long-term safety to confirm above findings beyond a six week observation period. To address this major concern, the MAH referred to studies with the mother compound risperidone in which bipolar as well as schizoaffective patients have been studied (RSI-INT-57, RIS-BIP-302), taking into account that categories and dosages of medications used most frequently in these populations are similar.

In Study RIS-INT-57, which included 110 patients with schizoaffective disorder and 561 patients with schizophrenia, long-acting risperdone was administered every second week for 12 months. Concomitant treatment was allowed and among the patients with schizoaffective disorder 48% received antidepressants and 49% received mood stabilizers. No unexpected safety issue was identified and overall the safety profile was comparable for the two diagnoses. There was no tendency of increasing safety problems over time (81 of the patients with schizoaffective disorder remained on treatment for the entire study period).

In 12 months study (RIS-BIP-302) in bipolar depression long-acting risperidone (n=72) was compared to placebo as add-on to treatment as usual, which in the risperidone group included antidepressants (31%) and mood stabilizers (90%). Overall the safety pattern was as expected for risperidone with tremor (24%), insomnia (19%), and muscle rigidity (11%) being the most frequent events. Compared to placebo the total incidence of treatment emergent adverse events was lower and with respect to severity fewer events were moderate or severe.

Overall, the CHMP considered these data reassuring and supportive of the safety profile of paliperidone ER in the proposed indication, taking into account the comparative PK data of paliperidone versus risperidone. More than 100 patients have been treated for 12 months concomitantly with antidepressants and/or mood stabilizers and risperidone in doses comparable to or higher than the recommended dose range for paliperidone in schizoaffective disorder.

No new safety issue has been identified and no major increased incidence of treatment emerging adverse events has been observed. However, the CHMP considered that data on safety and efficacy during long-term treatment with paliperidone was desirable to confirm the findings of the other studies conducted with the mother compound, risperidone. In addition, the CHMP recommended to align the safety information regarding hyperprolactinaemia with the approved SPC for long acting risperidone injection. The CHMP also recommended further revision of the proposed SPC information related to EPS.

During the oral explanation held on 20 July 2010, the MAH provided further data on depressive switches with paliperidone ER. In pivotal studies (SCA-3001 and SCA-3002), the incidence of such event was 6.1% (8/132) versus 11.3% (8/71) in paliperidone ER and placebo groups, respectively. In study BIM-3004, the incidence was 7.2% (44/563) and 6.2% (9/146) in paliperidone ER and olanzapine groups, respectively. The MAH concluded that there was no evidence for increased depressive switches with paliperidone ER.

However, in the absence of comparative data on such event with other antipsychotics, the CHMP recommended to include a warning on possible switch to depression, given the effect on depressive symptom of paliperidone ER has not been established in the intended population.

1.3.4 Risk Management plan (RMP)

An updated RMP (version 7.4) was submitted.

An overall summary is presented in Table 24.

Table 24 Overall summary of RMP

Safety Concern	Proposed Pharmacovigilance Activities (routine and additional)	Proposed Risk Minimisation Activities (routine and additional)
Important identified risks:		
• Prolactin-related adverse events	Routine PV as listed in the current RMP	Labelling as outlined in Section 4.8 of the INVEGA SPC where hyperprolactinaemia and potentially prolactin-related adverse events (eg, amenorrhoea, galactorrhoea, gynaecomastia) are identified as ADRs.
• Increase in QT_cLD	Routine PV as listed in the current RMP	The INVEGA SPC identifies QT prolongation as a special warning/precaution (Section 4.4) and states that caution should be exercised in patients with known cardiovascular disease or family history of QT prolongation or in concomitant use with other medicines thought to prolong the QT interval. Caution is advised when prescribing INVEGA with medicines known to prolong the QT interval (Section 4.5). Electrocardiogram QT prolongation is listed as an ADR with INVEGA, risperidone, and other drugs in the antipsychotic class (Section 4.8) and is identified as a risk from overdose (Section 4.9)
• Orthostatic hypotension	Routine PV as listed in the current RMP	The INVEGA SPC identifies orthostatic hypotension as a special warning/precaution (Section 4.4), stating that INVEGA may induce orthostatic hypotension in some patients based on its α-blocking activity. INVEGA should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions that predispose the patient to hypotension. The potential for an additive effect on orthostatic hypotension when INVEGA is administered with other therapeutic agents that have this potential is also stated (Section 4.5). Orthostatic hypotension is identified as an ADR (Section 4.8).

• EPS/Tardive dyskinesia	Routine PV as listed in the current RMP	The INVEGA SPC identifies tardive dyskinesia as a special warning/precaution (Section 4.4) in the use of medicines with dopamine receptor antagonistic properties, and identifies patients with Parkinson's Disease or Dementia with Lewy Bodies at potentially increased risk for EPS. EPS and tardive dyskinesia are listed as ADRs (Section 4.8). EPS is also identified in overdose (Section 4.9).
• Neuroleptic malignant syndrome	Routine PV as listed in the current RMP	The INVEGA SPC identifies neuroleptic malignant syndrome as a special warning/precaution (Section 4.4), stating that all antipsychotics, including INVEGA, should be discontinued if a patient develops signs or symptoms indicative of NMS. Patients with Parkinson's Disease or Dementia with Lewy Bodies are also identified as being at a potentially increased risk of NMS. NMS is listed in as an ADR (Section 4.8).
• Hyperglycaemia and glucose-related adverse effect	Routine PV as listed in the current RMP	The INVEGA SPC identifies hyperglycaemia as a special warning/precaution (Section 4.4), and states that rare cases of glucose-related ADRs have been reported in clinical trials with INVEGA. Appropriate monitoring is advisable in diabetic patients and in patients with risk factors for the development of diabetes mellitus. Hyperglycaemia is listed as an ADR (Section 4.8).
• Weight gain	Routine PV as listed in the current RMP	The INVEGA SPC identifies weight increased as an ADR, and weight gain is noted as dose-related (Section 4.8).
• Seizures	Routine PV as listed in the current RMP	The INVEGA SPC identifies Seizures as a special warning/precaution (Section 4.4), and states that INVEGA should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold. Caution is advised if INVEGA is combined with other medicines known to lower the seizure threshold (Section 4.5). Convulsion and grand mal convulsion are identified as ADRs (Section 4.8).

• Somnolence	Routine PV as listed in the current RMP	The SPC states that INVEGA should be used with caution in combination with other centrally acting medicines (Section 4.5). Paliperidone can have minor or moderate influence on the ability to drive and use machines, and patients should be advised not to drive or operate machines until their individual susceptibility to INVEGA is known (Section 4.7). Sedation and somnolence are identified as ADRs in clinical trials (Section 4.8). Additionally, drowsiness and sedation are identified in Section 4.9 (Overdose).
• Priapism	Routine PV as listed in the current RMP	The INVEGA SPC identifies Priapism as a special warning/precaution, and states that medicines with α-adrenergic blocking effects have been reported to induce priapism (Section 4.4). Priapism is also listed as an ADR (incidence not known) (Section 4.8). During the postmarketing surveillance, priapism was reported with oral paliperidone.
• Cerebrovascular accident	Routine PV as listed in the current RMP	The INVEGA SPC identifies cerebrovascular accident as an ADR (Section 4.8).
Important potential risks:		
• Pituitary adenomas	Routine PV as listed in the current RMP	The potential risk of pituitary adenomas is addressed in Section 5.3 (Preclinical Safety Data) of the INVEGA SPC.
• Endocrine pancreas tumours	Routine PV as listed in the current RMP	The potential risk of endocrine pancreas tumours is addressed in Section 5.3 (Preclinical Safety Data) of the INVEGA SPC.
• Breast cancer	Routine PV as listed in the current RMP	The potential risk of breast cancer is addressed in Section 5.3 (Preclinical Safety Data) of the INVEGA SPC.
• Increased mortality in elderly patients with dementia	Routine PV as listed in the current RMP	The potential risk of increased mortality in elderly patients with dementia is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC.
• Cerebrovascular adverse events in elderly patients with dementia	Routine PV as listed in the current RMP	The potential risk for cerebrovascular adverse events in elderly patients with dementia is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC.

• Increased risk of neuroleptic malignant syndrome and an increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy Bodies	Routine PV as listed in the current RMP	The increased risk of NMS and increased sensitivity to antipsychotics in patients with Parkinson's disease and dementia with Lewy Bodies are addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC.
• Cognitive and motor impairment	Routine PV as listed in the current RMP	The potential risk for Cognitive and motor impairment is addressed in multiple sections of the INVEGA SPC. Section 4.5 (Interaction With Other Medicinal Products and Other Forms of Interaction) and Section 4.7 (Effects on Ability to Drive and Use Machines) of the INVEGA SPC. Sedation and Somnolence are identified as ADRs (Section 4.8). Additionally, drowsiness and sedation are identified in Section 4.9 (Overdose).
• Antiemetic effect	Routine PV as listed in the current RMP	The potential risk of an Antiemetic effect is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC.
• Risk of gastrointestinal obstruction in patients with pre-existing severe gastrointestinal narrowing	Routine PV as listed in the current RMP	The potential risk of gastrointestinal obstruction in patients with pre-existing severe gastrointestinal narrowing is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC. Small intestinal obstruction is also listed in Section 4.8 (Undesired Effects) as an ADR.
• Venous thromboembolism	Routine PV as listed in the current RMP	The potential risk of venous thromboembolism (VTE) is addressed in Section 4.4 (Special Warnings and Precautions For Use) of the INVEGA SPC. Since patients treated with antipsychotics often present with acquired risk factors for VTE, all possible risk factors for VTE should be identified before and during treatment with INVEGA and preventative measures undertaken.

• Body temperature dysregulation	Routine PV as listed in the current RMP	The INVEGA SPC identifies body temperature dysregulation as a special warning/precaution, and states that disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic medicines (Section 4.4). Care is advised when prescribing INVEGA to patients who will be experiencing conditions which may contribute to an elevation in core body temperature or being subject to dehydration.
• Leukopenia	Routine PV as listed in the current RMP	None
• Neutropenia	Routine PV as listed in the current RMP	None
• Agranulocytosis	Routine PV as listed in the current RMP	None
• In patients with affective disorders	Routine PV as listed in the current RMP	Labelling as outlined in Section 4.4 of the INVEGA SPC where it is stated that patients with schizoaffective disorder treated with paliperidone should be carefully monitored for switch to depression.
Important missing information		
• Use in paediatric patients	Routine PV as listed in the current RMP	Safety has not been established in paediatric patients and this is appropriately indicated in Section 4.2 (Posology and Method of Administration) of the INVEGA SPC.
• Use in haemodialysis patients	Routine PV as listed in the current RMP	Safety has not been established in haemodialysis patients and this is appropriately indicated in Section 4.2 (Posology and Method of Administration) of the INVEGA SPC.
• Use in pregnancy	Routine PV as listed in the current RMP	Safety has not been established in pregnancy and this is appropriately indicated in Section 4.6 (Pregnancy and Lactation) of the INVEGA SPC.
• Use in nursing mothers	Routine PV as listed in the current RMP	Safety has not been established in nursing mothers and this is appropriately indicated in Section 4.6 (Pregnancy and Lactation) of the INVEGA SPC.

• Long term safety and Maintenance of effect in patients with schizoaffective disorder	- Routine PV as listed in the current RMP - registry studies (R076477-SCH-4015 and -SCH-4016) - Study R092670-SCA-3004 in patients with schizoaffective disorder maintained on paliperidone palmitate to establish long term efficacy and safety Final study protocol by 21 January 2011 Final study report*by March 2014	Maintenance of effect has not been studied and this is appropriately indicated in Section 4.2 of the INVEGA SPC.

*****Pharmacokinetic data supporting switching from oral paliperidone to paliperidone palmitate will also be provided in March 2014 to support the long-term efficacy and safety of paliperidone in the treatment of schizoaffective disorder

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.

1.3.5 User Consultation

The MAH referred to the Readability Testing of the paliperidone tablets Package Leaflet (PL) conducted during the assessment of the initial marketing authorisation application.

The MAH considered that minor changes have been proposed in the PL. Since the change mainly relate to the adverse drug reactions listing in the PL and that the layout is not significantly changed, this justification was considered acceptable by the CHMP.

2. BENEFIT RISK ASSESSMENT

2.1 Benefits

Paliperidone ER, the active metabolite of risperidone, has earlier been approved for treatment of schizophrenia based on studies demonstrating efficacy in acute short-term treatment as well as maintenance of effect. To fulfil the regulatory requirements for the additional claim schizoaffective disorder the MAH has performed specific studies in that patient population.

In two placebo-controlled short-term studies statistically significant effect in favour of paliperidone ER for the primary endpoint PANSS Total score was shown. The clinical relevance of the results is illustrated in responder analyses showing differences versus placebo of 22 and 12.5 %-units for the two studies, respectively. The validity of these effects for schizoaffective patients are substantiated in analyses of secondary endpoints, including PANSS-24 which consist of the PANSS items corresponding to the DSM-IV criteria for schizoaffective disorder, and clinically relevant reductions of depressive and manic symptoms in patients with pronounced affective symptoms at baseline.

In the pooled analysis, clinically relevant effects on PANSS and YMRS total scores were demonstrated in patients comedicated with mood stabilizers only and in patients with antidepressants only. In subgroup analyses of the pooled studies, highly significant effects on PANSS and YMRS total scores have been demonstrated for patients with prominent manic symptoms, prominent depressive symptoms, as well as in patients with prominent mixed symptoms. The magnitude of effect for all endpoints was considered by the CHMP clinically relevant and comparable to other studies of acute treatment in schizophrenia, manic episodes associated with bipolar I disorder and major depressive episodes, respectively. As expected the effect on manic symptoms is less pronounced in patients with prominent depressive symptoms.

Maintenance of effect has not been specifically studied with paliperidone ER in patients with schizoaffective disorder. The CHMP has also identified that effects on depressive symptoms has not been demonstrated.

Having considered the SAG conclusions and the oral explanation provided by the MAH, the CHMP recommended the following indication:

"INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."

On the basis of the available data, the CHMP also recommended to include in section 4.2 of the SPC related to schizoaffective disorder that "Maintenance of effect has not been studied".

2.2 Risks

In the clinical program for schizoaffective disorder 420 patients have been treated with paliperdone ER. The safety profile in this indication is as expected from the studies in schizophrenia and acute mania associated with bipolar I disorder as well as from the overall safety database for the mother compound risperidone. No new safety concerns have been identified.

However, the CHMP required further long-term safety to confirm the above findings beyond a six week observation period. To address this major concern, the MAH referred to studies with the mother compound risperidone in which bipolar as well as schizoaffective patients have been studied (RSI-INT-57, RIS-BIP-302), taking into account that categories and dosages of medications used most frequently in these populations are similar.

Overall, the CHMP considered these data reassuring and supportive of the safety profile of paliperidone ER in the proposed indication, taking into account the comparative PK data of paliperidone versus risperidone. More than 100 patients have been treated for 12 months concomitantly with antidepressants and/or mood stabilizers and risperidone in doses comparable to or higher than the recommended dose range for paliperidone in schizoaffective disorder. No new safety issue has been identified and no major increased incidence of treatment emerging adverse events has been observed. However, the CHMP recommended to align the safety information regarding hyperprolactinaemia with the approved SPC for long acting risperidone injection. The CHMP also recommended further revision of the proposed SPC information related to EPS.

A dose-relationship was also found for a significant number of ADRs (e.g .toothache, pharyngolaryngeal pain, galactorrhoea, tremor, akathisia, somnolence, nausea, dyspepsia, constipation, insomnia, asthenia, nasopharyngitis, myalgia, increased appetite).

Additionally, significant effect related to concomitant medication on the rate of ADRs was observed. This information was subsequently reflected in the SPC.

A long-term maintenance study has been agreed to be conducted by the MAH, which will further provide long-term safety data in this population.

2.3 Balance

In the overall study population, clinically relevant effects on psychotic and manic symptoms have been demonstrated in schizoaffective disorder that with respect to severity compares well with schizophrenia and no additional safety concerns have been identified.

However, no specific long-term data on paliperidone are available to confirm the maintenance treatment. In addition, effect on depressive symptoms has not been demonstrated.

A long-term maintenance study has been agreed to be conducted by the MAH, as part of the risk management plan.

3. Conclusion

On 18 November 2010, the CHMP considered this Type II variation to be acceptable and agreed on the amendments to be introduced in the Summary of Product Characteristics, Annex II and Package Leaflet.

Furthermore, the CHMP reviewed the data submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004 and considered the indication to be new

and that it is held to bring a significant clinical benefit in the absence of existing therapies (see appendix).

Appendix

REVISED CHMP ASSESSMENT REPORT ON THE NOVELTY OF THE INDICATION/SIGNIFICANT CLINICAL BENEFIT IN COMPARISON WITH EXISTING THERAPIES

1. Introduction

Paliperidone (R076477) is a monoaminergic antagonist with a high affinity for serotoninergic (5-hydroxytryptamine type 2A) and dopaminergic D2 receptors. Paliperidone (9-hydroxyrisperidone) is the major active metabolite of risperidone. The controlled release of paliperidone from the extended-release formulation results in slower absorption of paliperidone than an immediate-release formulation, steadily rising plasma concentrations on the first day of dosing, and reduced fluctuations in plasma concentrations at steady state.

Invega was first granted a marketing authorisation in the EU on 25 June 2007 for the treatment of schizophrenia in adults.

In September 2009 the Marketing Authorisation Holder (MAH) submitted an application for a Type II variation (EMEA/H/C/746/II/23) to include the new indication "*Treatment of schizoaffective disorder as monotherapy or in combination with mood stabilisers and/or antidepressants"* for Invega.

In the initial assessment of the variation application, the CHMP raised major objections on both efficacy and safety as well as a number of other concerns. Based on the outcome of Central Nervous System Scientific Advisory Group (SAG-CNS) and CHMP assessment, the applicant amended the proposed indication as follows: "INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."

In accordance with the provisions of Article 14(11) of Regulation (EC) No 726/2004, the MAH applied for an extended marketing protection period for Invega in the context of the current Type II variation.

The request is based on the MAH's position that the approval of paliperidone PR in the sought indication will offer significant clinical benefit compared with existing therapies since no other medications are currently approved for the treatment of schizoaffective disorder in the EU.

2. Justification of significant clinical benefit as presented by the applicant

Proposed new indication as compared to already authorised indication

Schizoaffective disorder is a common, chronic, and disabling mental illness associated with significant impairment of functioning. Schizoaffective disorder is recognized in both the Diagnostic and Statistical Manual, 4th edition (DSM-IV) and the International Classification of Disease, 10th Revision (ICD-10) as a distinct diagnostic entity (APA 2000; WHO 1993), with clinical features, course, and outcome differing from schizophrenia (Lake 2007, Cheniaux 2008, Peralta 2008). Schizoaffective disorder includes the signs and symptoms of a manic episode and/or a major depressive episode, in addition to the presence of symptoms consistent with schizophrenia. Nevertheless, the clinical features of schizoaffective disorder differ from bipolar disorder and schizophrenia in important ways, including prognosis and approaches to treatment. Compared with subjects with schizophrenia, subjects with schizoaffective disorder show a higher risk of substance abuse, higher hospitalisation rates, and higher suicide rates (Cheniaux 2008, Olfson 2009, Radomsky, 1999).

According to DSM-IV, a diagnosis of schizoaffective disorder is made when the symptom criteria for schizophrenia are met and during the same continuous period there is a major depressive episode, manic episode, or mixed episode. During that same period, symptoms that meet Criterion A for schizophrenia (ie, 2 or more of the following: hallucinations, delusions, disorganised speech, grossly disorganised or catatonic behavior, or negative symptoms) must be present for at least 2 weeks in the absence of prominent mood symptoms (APA 2000). Diagnostic criteria for schizoaffective disorder according to ICD-10 are slightly more inclusive than DSM-IV criteria, and include persons in whom definite schizophrenic and definite affective symptoms are prominent simultaneously, or within a few days of each other, within the same episode of illness, and for whom the episode does not meet criteria for either schizophrenia or a depressive or manic episode (WHO 1993).

In an analysis of Medicaid claims data from 2 U.S. states focusing on over 55,000 adults treated for schizoaffective disorder or schizophrenia, roughly one-third were treated for schizoaffective disorder (Olfson 2009). In this analysis patients with schizoaffective disorder were significantly more likely to receive cotreatment for substance use or for an anxiety, depressive, bipolar, or other mental disorder during the prestudy period (Olfson 2009). Similar to previous reports, the patients with schizoaffective disorder were also significantly more likely to be treated with mood stabilisers, antidepressants, and/or anxiolytics. Furthermore, patients with schizoaffective disorder were significantly more likely to receive

psychotherapy. This analysis supports the current diagnostic classification that regards schizoaffective disorder and schizophrenia as distinct diagnostic entities and suggests a more complicated clinical course and more complex treatment needs in patients with schizoaffective disorder.

Given the complex medication regimens often utilised in schizoaffective disorder, these patients may be at particularly high risk for cytochrome P450-mediated drug-drug interactions, especially when co-administering certain antipsychotic and antidepressant medications. In addition, it has been suggested that patients with affective symptoms may be more vulnerable to the extrapyramidal side effects associated with antipsychotic medications (Gao 2008).

Details of existing therapies related to the proposed new indication

There are no medications approved for use in schizoaffective disorder in the EU to the applicant's knowledge. Furthermore, no treatments have been systematically studied in patients with schizoaffective disorder nor are there any widely accepted guidelines for the treatment of this condition. Nonetheless, patients with schizoaffective disorder are often prescribed complex pharmacological regimens as clinicians attempt to manage the psychotic and affective symptoms (Malhi 2005).

Therefore, despite the widespread use of antipsychotics alone or in combination with antidepressants and/or mood stabilisers in the treatment of schizoaffective disorder, there are little data (aside from that contained within the current application) that support the safety and efficacy of this practice. While off-label uses are legal and in many instances may be in the best interest of patients, they have not received the same degree of independent scrutiny through randomised clinical trials as agents that have been approved by Regulatory authorities (Pickar 2008).

Significant clinical benefit based on improved efficacy as presented by the applicant

The efficacy and safety of paliperidone PR has been shown in 2 adequately powered and well-controlled Phase 3 clinical studies in subjects with schizoaffective disorder (R076477-SCA-3001 and R076477-SCA-3002; hereafter referred to as SCA-3001 and SCA-3002, respectively). These data were further supported by results from 2 completed Phase 1 drug interaction studies (R076477-BIM-1003 and R076477-BIM-1004; hereafter referred to as BIM-1003 and BIM-1004).

The 2 Phase 3 trials (SCA-3001 and SCA-3002) included adult subjects with a Structured Clinical Interview for DSM-IV Disorders (SCID)-confirmed DSM-IV diagnosis of schizoaffective disorder who were experiencing an acute exacerbation. In SCA-3001, patients were assigned to 1 of 2 dose levels of paliperidone: a low-dose group (6 mg/day with the option to reduce to 3 mg/day) or a high-dose group (12 mg/day with the option to reduce to 9 mg/day). In SCA-3002, patients received flexible doses of paliperidone (3-12 mg/day, starting at 6 mg/day).

In addition to study medication, subjects were permitted to receive concomitant treatment with a mood stabiliser and/or antidepressant, provided these medications had been given at a stable dose within 30 days of screening. Approximately half the subjects enrolled received ongoing treatment with a mood stabiliser and/or antidepressant during the studies. Therefore, the study populations were representative of the patient population likely to be treated with paliperidone PR in clinical practice. Randomisation was stratified by site and by treatment with concomitant medications (antidepressants and/or mood stabilisers) vs. no concomitant treatment with those medications.

Efficacy was evaluated using the positive and negative symptom scale (PANSS), as validated multi-item inventory composed of 5 factors to evaluate positive symptoms, negative symptoms, disorganised thoughts, uncontrolled hostility/excitement, and anxiety/depression. As secondary outcomes, mood symptoms were evaluated using the Hamilton Depression Rating Scale (HAM-D-21) and the Young Mania Rating Scale (YMRS).

The findings of the Phase 3 studies SCA-3001 and SCA-3002 have provided evidence for the efficacy of paliperidone PR in the treatment of schizoaffective disorder

Studies SCA-3001 and SCA-3002 showed superior efficacy of paliperidone PR high dose (12 mg/day, with option to reduce to 9 mg/day) and paliperidone PR in a flexible-dose range of 3 to 12 mg/day (starting dose 6 mg/day) to placebo on the primary efficacy variable (change from baseline to end point in PANSS total score), as well as on other efficacy endpoints including the YMRS and HAM-D-21 in subjects with prominent mania and depression, respectively. In subgroup analyses of the pooled

studies, paliperidone PR was effective when used both as monotherapy and when administered with concomitant antidepressants and/or mood stabilisers. Overall, there was a small mean numerical advantage in patients receiving paliperidone PR monotherapy vs combination therapy.

Efficacy on PANSS, YMRS, and HAM-D-21 scores was demonstrated regardless of baseline mood status. In subgroup analyses of the pooled studies, highly significant effects were demonstrated for patients with prominent manic symptoms (YMRS total score ≥16), prominent depressive symptoms (HAM-D-21 total score ≥16), or mixed symptoms (both YMRS and HAM-D-21 total scores ≥16) at baseline.

These findings were further supported by improvements in other secondary efficacy variables such as the change in the PANSS 24-item score corresponding to DSM-IV criteria for schizoaffective disorder, PANSS subscales and factor scores, and global impressions of illness (CGI-S-SCA and CGI-C-SCA).

The improvement in the PANSS total score and the change in the severity of illness were of significant magnitude to be clinically meaningful. After 6 weeks of treatment, a greater proportion of subjects treated with paliperidone PR than with placebo were treatment responders. The efficacy of paliperidone PR was independent of the demographic characteristics age, sex, race, or geographic location, as well as of baseline affective symptomatology.

Significant clinical benefit based on improved safety as presented by the applicant

Paliperidone PR is an atypical antipsychotic approved for the treatment of schizophrenia, with over 150,000 patient-years of postmarketing exposure worldwide.

The clinical development program of paliperidone PR in the treatment of schizoaffective disorder included 2 completed Phase 3 studies, in which 420 subjects with schizoaffective disorder were exposed to paliperidone PR for a total of 39.3 subject-years; a Phase 1 drug interaction study in healthy men in which 24 subjects were exposed to paliperidone PR for a total of 0.13 subject-years; a Phase 1 drug interaction study in subjects with schizophrenia, bipolar I disorder, or schizoaffective disorder in which 16 subjects were exposed to paliperidone PR for a total of 0.21 subject-years; and an ongoing Phase 3b study in subjects with schizophrenia or schizoaffective disorder and with hepatic disease in which 84 subjects were exposed to paliperidone PR for 6.89 subject-years through the cutoff date.

The comprehensive safety data of 1,107.00 subject-years in 2,054 individual subjects in the Phase 3 clinical development program of paliperidone PR in schizophrenia complements the safety data from clinical studies of paliperidone PR in the new indication.

Paliperidone PR, administered in daily doses ranging from 3 to 12 mg, either as monotherapy or in combination with antidepressants and/or mood stabilisers, was generally well tolerated for a period of 6 weeks in the 2 double-blind placebo-controlled studies SCA-3001 and SCA-3002. There were no deaths in either Phase 3 study, in either Phase 1 study, or in the ongoing Phase 3b study through the cutoff date.

There was no difference between the paliperidone PR and placebo groups with respect to the incidence of suicidality-related adverse events in the completed Phase 3 schizoaffective disorder studies. Adverse events related to depression were infrequent and occurred in numerically fewer paliperidone PR-treated than placebo-treated subjects.

Extrapyramidal symptoms have been associated with atypical antipsychotics in patients with schizoaffective disorder (Janicak 2001, Keck 2001). There were no reports of tardive dyskinesia or neuroleptic malignant syndrome in the 4 completed studies. In the Phase 3 studies, extrapyramidal symptom-related adverse events and concomitant use of anticholinergic medications were reported at higher rates in subjects treated with paliperidone PR compared to placebo. In SCA-3001, anticholinergic medications were used more frequently in the paliperidone PR high dose group compared with the low dose group. The EPS-related adverse events were usually mild and usually did not lead to withdrawal, and none was serious. These findings are consistent with the data from Phase 3 studies of paliperidone PR in the treatment of schizophrenia.

Consistent with the findings of the clinical program in schizophrenia, ECG data did not suggest an increased cardiovascular risk with paliperidone PR in the dose range of 3 to 12 mg. No adverse events of ventricular fibrillation and flutter or torsade de pointes occurred during any of the completed studies.

With the exception of mostly asymptomatic increases in serum prolactin levels, changes in clinical laboratory test values in subjects receiving paliperidone PR for up to 6 weeks were transient, largely asymptomatic, and considered not clinically relevant. Limited weight gain was observed in subjects treated with paliperidone PR; a dose-related trend in weight gain was apparent in SCA-3001.

A greater proportion of subjects receiving paliperidone PR in combination with mood stabilisers and/or antidepressants experienced at least one adverse event as compared to those subjects receiving monotherapy. There was also a higher incidence of adverse events in placebo-treated subjects in the combination therapy stratum compared to placebo-treated subjects receiving monotherapy. This suggests that in subjects treated with combination therapy (paliperidone PR plus antidepressants and/or mood stabilisers), a considerable number of the adverse events observed may be related to the antidepressant and/or mood stabiliser rather than paliperidone PR. There were no other differences of clinical concern in the safety and tolerability profile of paliperidone PR given alone or in combination with antidepressants and/or mood stabilisers.

Psychiatric disorders that were serious or led to discontinuation of study drug occurred more frequently in subjects in the paliperidone PR low dose group receiving concomitant antidepressants and/or mood stabilisers. This may potentially have been due to less effective control of psychiatric disorders in the low dose group compared to the high dose and flexible dose groups, as well as more severe illness in subjects receiving antidepressants and/or mood stabilisers at enrollment.

Significant clinical benefit based on major contribution to patient care as presented by the applicant
As summarised above, paliperidone PR has demonstrated a favorable benefit-risk profile in the treatment of schizoaffective disorder in 2 large, well-controlled Phase 3 studies. The population included in these studies were well-defined using current diagnostic criteria and reflective of the real-world setting, in that they were receiving an atypical antipsychotic alone or in combination with mood stabilisers and/or antidepressants.

These studies represent the first large-scale, placebo-controlled studies conducted in patients with schizoaffective disorder. No other agent has been studied in this population in such a rigorous manner. Therefore, the key benefit paliperidone PR offers over other medications is that it is the only agent that has demonstrated efficacy and safety in schizoaffective disorder according to current standards.

The Sponsor conducted a review of the literature to explore the efficacy of paliperidone PR versus other agents in the treatment of schizoaffective disorder. Consistent with findings of other literature reviews (Levinson 1999, Keck 1999, Jäger 2010), no other large-scale, prospective, well controlled studies were identified during the Sponsor's review of the literature.

Therefore, it is not possible to make meaningful comparisons between paliperidone PR and other agents in the treatment of schizoaffective disorder. Of note, most of the studies identified during the search evaluated the efficacy of antipsychotics and mood stabilisers as monotherapy, which is not reflective of clinical practice. Only 2 double-blind, randomised, controlled studies involving adjunctive treatment of an antipsychotic with an antidepressant or mood stabiliser were identified during the Sponsor's review (Brockington 1978, Okuma 1989).

MAH's overall conclusion supporting significant clinical benefit

Schizoaffective disorder is a serious, disabling, and persistent mental illness associated with significant impairment of functioning and a high lifetime risk of suicide. The loss of life and disability due to severe impairment of functioning in patients with schizoaffective disorder results in a substantial cost-of-illness burden to society. Despite the significance of this condition, current therapies have not been studied in adequate and well-controlled clinical trials and there are no European Agency-approved medications for the treatment of this illness.

There is a need for efficacious treatments of schizoaffective disorder with a favourable benefit-risk balance. As documented in the current application (EMEA/H/C/746/II/23), paliperidone PR has demonstrated a favorable benefit-risk balance in the acute treatment of psychotic and manic episodes of schizoaffective disorder in 2 well-controlled Phase 3 studies. These studies (SCA-3001 and SCA-3002) represent the first large-scale, placebo-controlled studies in the treatment of schizoaffective disorder. As no other agents are approved for schizoaffective disorder, the approval of paliperidone PR in this indication would represent a significant and clinically meaningful contribution to patient care, allowing clinicians to make evidence-based decisions when considering treatment choices.

3. Assessment of the applicant's justification of significant clinical benefit

Proposed new indication

Taking into account the provisions of *the "Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)"*, the CHMP is of the opinion that the proposed new indication: *"INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."* can be considered as a new therapeutic indication.

Details of existing therapies related to the proposed new indication

There are currently no authorised medicinal products for the use in schizoaffective disorder.

Psychotherapy is recognised as a non-pharmacological approach to treatment. However, psychotherapy is generally used in association with pharmacological treatment and therefore does not constitute alone an existing therapeutic alternative.

The CHMP considered therefore that no existing therapies are currently available for this new indication.

Significant clinical benefit based on improved efficacy

In the overall study population, clinically relevant effects on psychotic and manic symptoms have been demonstrated in the new indication for schizoaffective disorder, a disease that with respect to severity compares well with schizophrenia. However, the data provided to support the long-term maintenance of effect were questioned by the CHMP.

In light of the concern related to extrapolation of long term data to support the long-term maintenance of the effect of paliperidone ER in schizoaffective disorder and on the basis of the available data to date, the CHMP agreed to convene a SAG-CNS to discuss the need for long-term efficacy data for paliperidone in the applied indication. The group was convinced that there is good evidence of maintenance of effect on manic symptoms. However, from the submitted documentation, the SAG was not convinced that there is a clinically significant effect on depressive symptoms.

The MAH concluded that there was no evidence for increased depressive switches with paliperidone PR. However, in the absence of comparative data on such event with other antipsychotics, the CHMP recommended to include a warning on possible switch to depression, given the effect on depressive symptom of paliperidone PR has not been established in the intended population.

On the basis of the available data, the CHMP recommended the following indication: "INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."

In the absence of existing therapies for the above-mentioned new indication, the CHMP considered that there is significant clinical benefit on efficacy for Invega in the targeted population.

Significant clinical benefit based on improved safety

In the clinical program for schizoaffective disorder 420 patients have been treated with paliperidone ER. The safety profile in this indication is as expected from the studies in schizophrenia and acute mania associated with bipolar I disorder as well as from the overall safety database for the mother compound risperidone.

Overall, the CHMP considered the data reassuring and supportive of the safety profile of paliperidone ER in the proposed indication, taking into account the comparative pharmacokinetic data of paliperidone versus risperidone.

More than 100 patients have been treated for 12 months concomitantly with antidepressants and/or mood stabilizers and risperidone in doses comparable to or higher than the recommended dose range

for paliperidone in schizoaffective disorder. No new safety issue has been identified and no major increased incidence of treatment emerging adverse events has been observed.

Overall, the CHMP considered that the safety profile for Invega remains unchanged. In the absence existing therapies for the above-mentioned new indication, the CHMP is of the opinion that no significant clinical benefit on safety for Invega can be identified at this present time.

Significant clinical benefit based on major contribution to patient care

The CHMP is of the opinion that Invega is expected to contribute to patient care as an authorised medicinal product.

4. CHMP Conclusion

Following the overall assessment of the efficacy and safety data provided, the CHMP considers that the benefit/risk ratio of Invega is positive for the following indication: "INVEGA is indicated for the treatment of psychotic or manic symptoms of schizoaffective disorder. Effect on depressive symptoms has not been demonstrated."

In the absence of existing therapies, the CHMP considered that the justification for one additional year of marketing protection was valid.

5. Outcome

The CHMP reviewed the data submitted by the applicant taking into account the provisions of Article 14(11) of Regulation (EC) No. 726/2004, and taking into account the provisions of the "*Guidance on elements required to support the significant clinical benefit in comparison with existing therapies of a new therapeutic indication in order to benefit from an extended (11-year) marketing protection period (November 2007)*", considered that the new therapeutic indication is held to bring significant clinical benefit in the absence of existing therapies.