23 April 2015
EMA/CHMP/213560/2015 - adopted
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Invega

International non-proprietary name: PALIPERIDONE

Procedure No. EMEA/H/C/000746/II/0043

Note

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

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Table of contents

List of abbreviations

ADR	adverse drug reaction
AE	adverse event
ANCOVA	analysis of covariance
BMI	body mass index
CGI-S-SCA	Clinical Global Impression of Severity for Schizoaffective
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
CSR	Clinical Study Report
C-SSRS	Columbia Suicide Severity Rating Scale
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th Edition
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECG	electrocardiogram
EPS	extrapyramidal symptoms
ER	Extended-release
ESRS-A	Extrapyramidal Symptom Rating Scale-Abbreviated
EU	European Union
HAM-D (-17 and -21)	Hamilton Rating Scale for Depression; -17 indicates use of the first 17 items of the scale and -21 indicates use of all 21-items of the scale
INVEGA	registered trade name of paliperidone (R076477) prolonged-release tablet formulation
ITT	intent-to-treat
J&JPRD	Johnson & Johnson Pharmaceutical Research & Development
JRD	Janssen Research & Development
LAI	long-acting injectable
LOCF	last observation carried forward
LS	mean least squares mean
MedDRA	Medical Dictionary for Regulatory Activitiesmg eq. milligram equivalent
MSQ	Medication Satisfaction Questionnaire
MMRM	Mixed Model Repeated Measures
PANSS	Positive and Negative Syndrome Scale
PI	Product Information
PK	pharmacokinetic(s)
PP1M	Paliperidone palmitate monthly injectable
PR	prolonged release
PSP	Personal and Social Performance Scale
QTc	corrected QT interval
QTcB	QT interval of ECG, corrected by the method of Bazette
QTcF	corrected QT interval according to Fridericia method
QTcLD	linear-derived corrected QT interval
RUQ	Resource Utilization Questionnaire
SAE	serious adverse event
SD	standard deviation
SMQ	Standardised MedDRA Query
TEAE	treatment emergent adverse event
US	United States
XEPLION	registered trade name in the EU for the paliperidone palmitate monthly injectable formulation; see PP1M above
YMRS	Young Mania Rating Scale

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Janssen-Cilag International N.V. submitted to the European Medicines Agency on 28 July 2014 an application for a variation.

This application concerns the following medicinal product:

Centrally authorised Medicinal product(s): **For presentations: See Annex A**	**International non-proprietary name**
Invega	PALIPERIDONE

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I, IIIA and IIIB

The Marketing authorisation holder (MAH) applied for an extension of the indication for the treatment of schizoaffective disorder. Consequently, the MAH proposed the update of sections 4.1, 4.2, and 5.1 of the SmPC to reflect also on the data from the long-term study on paliperidone palmitate effects in the maintenance of symptom control.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the MAH proposed minor editorial changes throughout the PI.

The variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/149/2009 on the granting of a product-specific waiver.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The applicant did not seek scientific advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Filip Josephson

Timetable	Actual dates
Submission date	28 July 2014
Start of procedure:	22 August 2014
CHMP Rapporteur Assessment Report	13 October 2014
PRAC Rapporteur Assessment Report	17 October 2014
PRAC Rapporteur Updated Assessment Report	29 October 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	6 November 2014
Rapporteur Revised Assessment Report	14 November 2014
Request for supplementary information (RSI)	20 November 2014
Clock-stop extension	18 December 2014
MAH submitted responses	20 February 2015
PRAC Rapporteur Assessment Report	26 March 2015
CHMP Rapporteur Assessment Report	26 March 2015
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	10 April 2015
CHMP Rapporteur Updated Assessment Report	17 April 2015
Opinion	23 April 2015

2. Scientific discussion

2.1. Introduction

Invega tablets contain the active substance paliperidone, an antipsychotic substance that is the active 9-hydroxy-metabolite of risperidone. Janssen-Cilag International NV submits a Type II Variation for Invega prolonged release tablets 1.5, 3, 6, 9, and 12 mg concerning a fulfillment of a previously agreed post-authorisation measure (MEA 012.1) with a proposal for a modification of the schizoaffective disorder indication.

2.2. Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.2.1. Ecotoxicity / environmental risk assessment

No updated Environmental Risk Assessment has been submitted. The applicant has argued that no significant increase in drug usage of INVEGA prolonged-release tablets is anticipated in relation to the

broadening of the current schizoaffective disorder indication (psychotic and manic symptoms) to include depressive symptoms. Little is known about the incidence, prevalence, and demographic factors associated with schizoaffective disorders specifically, partially due to the different definitions used in the various studies. As many studies of schizophrenia include patients with schizoaffective disorders, there is a large degree of overlap in the literature. Therefore, some of the epidemiologic data on schizophrenia may be applicable to patients with schizoaffective disorders. As a consequence, it is highly likely that the previous estimates for drug usage in schizophrenia have included usage in schizoaffective disorder. As such, it has been agreed that the approval of this application is not expected to impact the total environmental impact to paliperidone, and no update to the Environmental Risk Assessment dossier has been considered necessary for the product.

2.2.2. Conclusion on the non-clinical aspects

The broadening of the INVEGA schizoaffective indication to include treatment of the depressive symptoms of schizoaffective disorder in addition to the currently approved psychotic and maniac domains is not expected to cause a significant increase in environmental exposure further to the use of Invega.

2.3. Clinical aspects

2.3.1. Introduction

Following the CHMP assessment of the application for the indication schizoaffective disorder approved in April 2011, the MAH committed to provide a long-term maintenance study on paliperidone palmitate and to submit relevant pharmacokinetic data on switching from oral paliperidone to paliperidone palmitate as a post-authorization measure. The applicant submitted to the CHMP a draft protocol for the long-term maintenance study R092670-SCA-3004 (SCA-3004. Following assessment, the protocol was adopted by CHMP (EMEA/H/C/746-MEA-012.1) on 18 August 2011. As there were no pharmacokinetic evaluations in the study SCA-3004, a pharmacokinetic report was requested by the CHMP to evaluate the similarity of the pharmacokinetics of plasma paliperidone after treatment with paliperidone prolonged-release tablets and paliperidone palmitate long-acting injection.
With the current submission of the results of study SCA-3004 and PK data the commitment is considered fulfilled.
The results of study SCA-3004 are also intended to support broadening of the INVEGA schizoaffective indication, to include treatment of the depressive symptoms of schizoaffective disorder, and to update maintenance data on the basis that Study SCA-3004 was a long-term maintenance study including a 15 months double-blind relapse prevention period. Also a summary of the study SCA-3004 is proposed to be added to the PI.

GCP

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

2.3.2. Pharmacokinetics

Methods

In order to support the extrapolation of effect data between formulations a meta-analysis was conducted to compare the plasma paliperidone exposure after administration of paliperidone palmitate LAI (studies PSY-3005 and PSY-3007) with the exposure observed after daily administration of corresponding doses of paliperidone PR (study SCH-201). Population PK modeling techniques were applied to support the comparison.

Figure 1 and Figure 2 illustrates the comparability in exposure following 6 mg OD oral dose and 75 mg IM every 28 days and 12 mg OD oral dose and 150 mg every 28 days respectively. Graphs A and B are VPCs illustrating the model fit. Figure 2 shows the simulated comparability of high and low doses of paliperidone PR vs paliperidone palmitate LAI.

Figure 1 [A] Steady-state exposure after 1 week of dosing with oral paliperidone PR 6 mg from SCH-201 vs. modelbased projection; [B] Exposure for paliperidone palmitate LAI 75 mg eq. from PSY-3005 vs. model-based projections; [C] Simulated projections from Figures A and B are overlaid to verify the equivalence of paliperidone PR 6 mg to paliperidone palmitate 75 mg eq. The lines and the shaded areas represent the model-based medians and 90% prediction intervals, respectively.

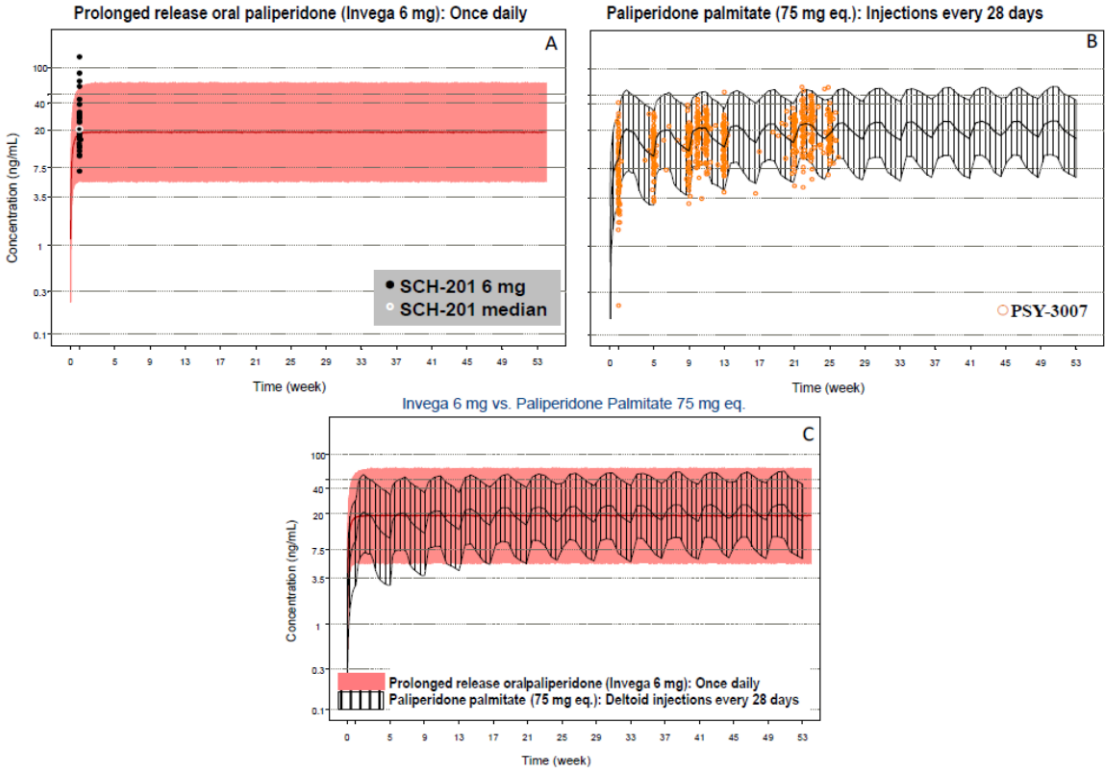


Figure 2 [A] Steady-state exposure after 1 week of dosing with paliperidone PR 12 mg from SCH-201 vs. modelbased projection; [B] Exposure for paliperidone palmitate LAI 150 mg eq. from PSY-3007 vs. model- based projections; [C] The simulated projections from Figures A and B are overlaid to verify the equivalence of paliperidone PR 12 mg to paliperidone palmitate LAI 150 mg eq. The lines and shaded areas are model-based medians and 90% prediction intervals, respectively.

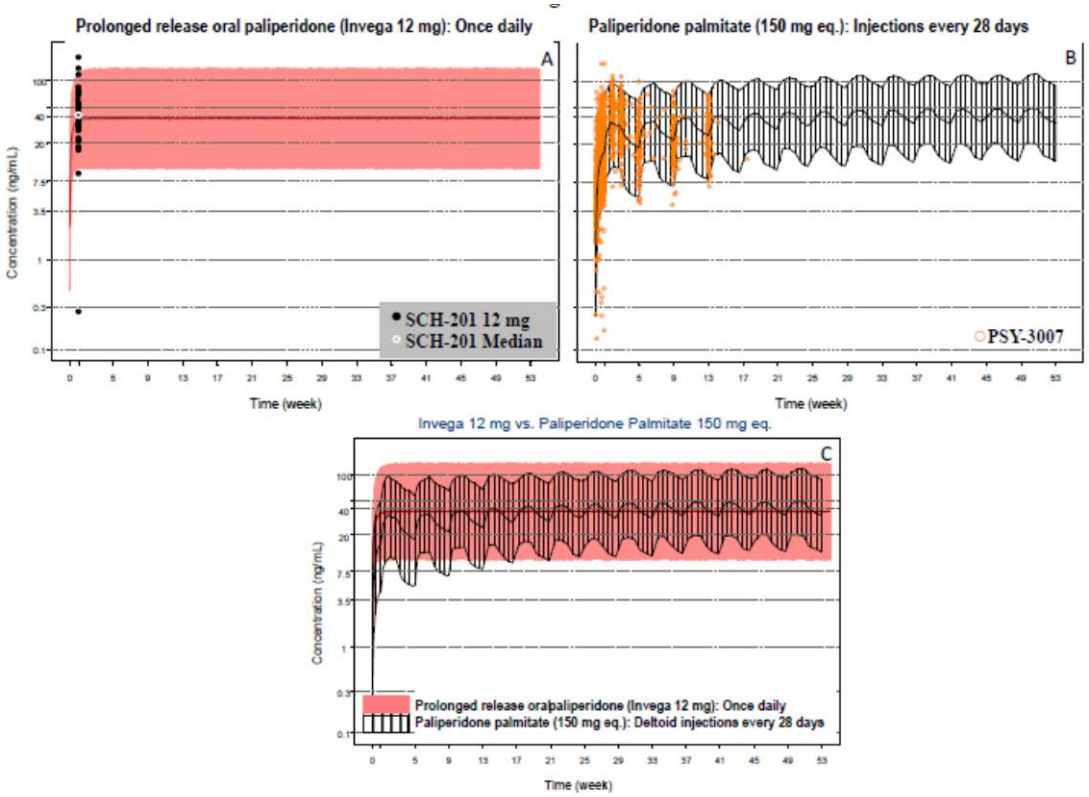
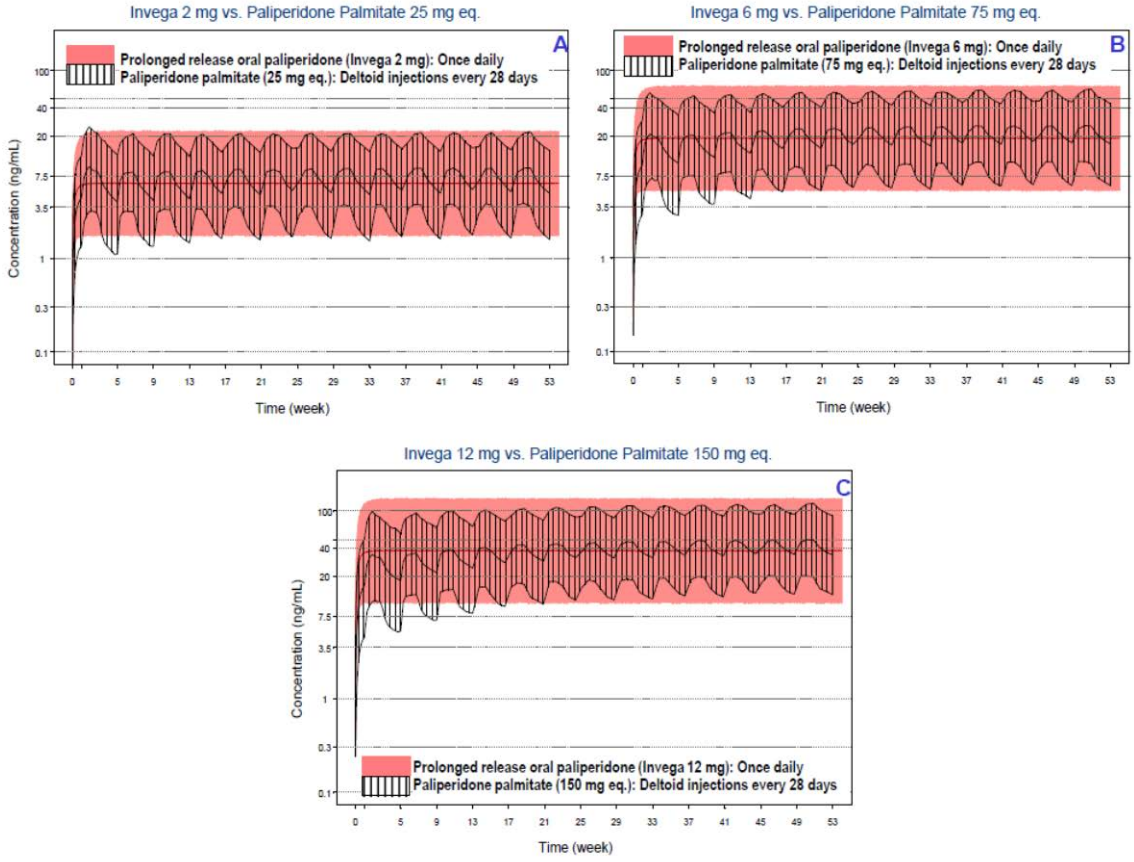
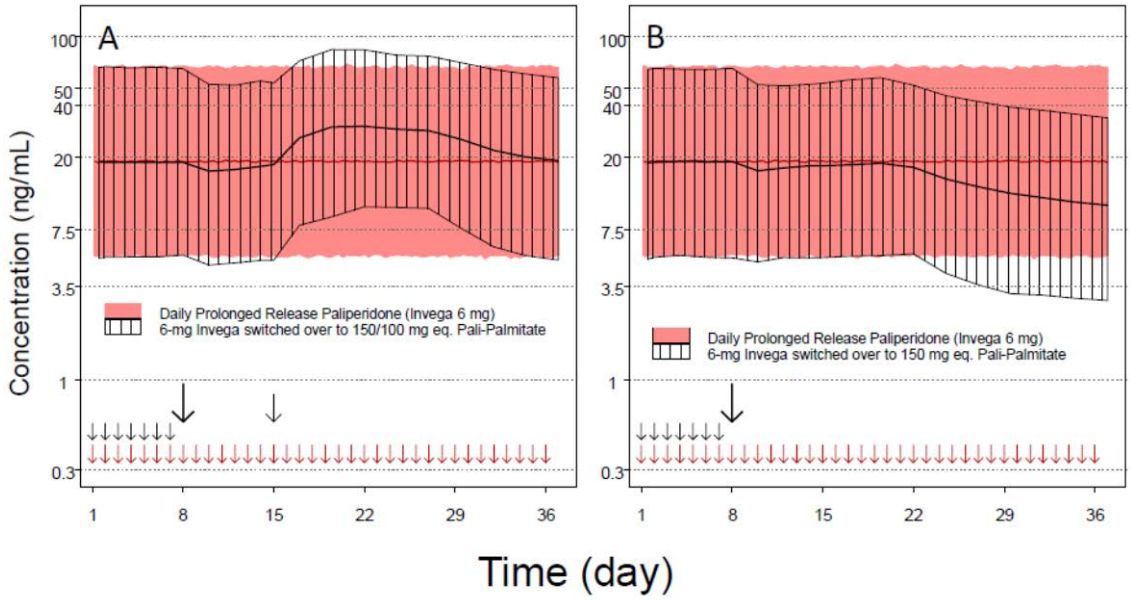


Figure 3 Simulated Comparisons of paliperidone PP vs. paliperidone palmitate LAI



Additional simulations have been performed in which switching from oral paliperidone PR to paliperidone palmitate LAI was addressed. Oral paliperidone PR has a half-life of around 25 hours. During the first week of initiation with paliperidone palmitate LAI, drug concentrations from the oral paliperidone PR will decline within the first week. Therefore, the loading dose of 100 mg eq. paliperidone palmitate LAI on Day 8 would still be needed to maintain the paliperidone concentrations within therapeutic range when switching from oral paliperidone PR. Figure 3 demonstrates that when patients are switched from the recommended 6 mg paliperidone PR dose to paliperidone palmitate LAI using the recommended Day1/Day8 initiation regimen, drug concentrations are maintained during the first week after switching.

Figure 4 Switching from oral paliperidone PR to paliperidone palmitate LAI. Pink shaded areas represent patients stabilized on oral paliperidone PR and continuing oral therapy. (A) Hatched area represents patients switched to paliperidone palmitate LAI on Day -1 using the Day 1/Day 8 initiation. (B) Hatched area represents patients switched to paliperidone palmitate LAI on Day 1 using a single initiation dose alone



2.3.3. Pharmacodynamics

Mechanism of action

Paliperidone is a selective blocking agent of monoamine effects, whose pharmacological properties are different from that of traditional neuroleptics. Paliperidone binds strongly to serotonergic 5-HT2- and dopaminergic D2-receptors. Paliperidone also blocks alfa1-adrenergic receptors and blocks, to a lesser extent, H1-histaminergic and alfa2-adrenergic receptors. The pharmacological activity of the (+)- and (-)-paliperidone enantiomers are qualitatively and quantitatively similar.

2.3.4. Conclusions on clinical pharmacology

The population pharmacokinetic model appears to be adequately validated to use in simulations and the claim that similar steady state exposures are achieved with oral paliperidone PR and paliperidone palmitate LAI is supported. It would have been valuable to see the exposure during a dosing interval for the oral formulation at steady state. However, given the considerable accumulation it appears unlikely that the Cmax/Ctrough ratio at steady state is of clinical significance.

The recommended dosing during a switch between oral paliperidone PR and paliperidone palmitate LAI is also supported by the present model. While the proposed dosing results in temporarily higher exposures for patients switching from a maintenance treatment of 3 mg oral paliperidone PR, the possibility to individualize the dosing, as stated in the current SmPC, appears adequate.

No new data regarding drug-drug interactions for the potentially new patient population has been submitted. Given the known pharmacokinetic and pharmacodynamic profile of paliperidone this appears to be acceptable.

2.4. Clinical efficacy

2.4.1. Dose response study

The main study SCA-3004 was not designed to assess a dose-response of the efficacy of paliperidone palmitate.

2.4.2. Main study

Study R092670-SCA-3004: A randomised, double-blind, placebo-controlled, parallel-group study of paliperidone palmitate evaluating time to relapse in subjects with schizoaffective disorder"

Study SCA-3004 was a Phase 3b, randomized, double-blind, placebo-controlled, parallel-group, international, multicentre study designed to evaluate the efficacy and safety of PP1M (long-acting injectable formulation of paliperidone palmitate), as monotherapy or as an adjunct to mood stabilizers or antidepressants (continue their pre-study stable doses of mood stabilizers or antidepressants), relative to placebo in subjects with schizoaffective disorder. This was the first controlled maintenance study of an atypical long-acting injectable antipsychotic in subjects with schizoaffective disorder.

The study was a post-authorization measure for the approval of the schizoaffective indication for INVEGA tablets (EMEA/H/C/746/II/0023), requested by the CHMP in April 2011. The Company submitted a draft protocol for study R092670-SCA-3004 for assessment and the protocol was adopted by CHMP (EMEA/H/C/746-MEA-012.1). The results of study R092670-SCA-3004 are also intended to support an amendment of the PI for Invega with a broadening of the existing indication for schizoaffective disorder to include both psychotic and manic domains as well as depressive symptoms of schizoaffective disorder.

Methods

Study participants

Patients were enrolled from 31 sites in the United States, 19 sites in Romania, 14 sites in India, 13 sites in the Ukraine, 6 sites in Bulgaria, 3 sites in Malaysia, 4 sites in the Philippines, and 5 sites in the Republic of South Africa. A total of 921 subjects were screened, 667 subjects were enrolled in the open-label Lead-in period, and 432 subjects entered the open-label Stabilization period. Of the 432 subjects who entered the open-label Stabilization period, 334 subjects were randomized to the double-blind Relapse Prevention period (170 subjects to the placebo group and 164 subjects to the paliperidone palmitate group).

To be enrolled the patients should be male or female, above18 years of age and have a lifetime and current diagnosis of schizoaffective disorder (DSM-IV-TR 295.70), as confirmed by the Structured Clinical Interview for DSM-IV Disorders (Clinician's Version) (SCID) at screening. Ninety-five percent of the randomized subjects also met the DSM-5 diagnosis criteria based on investigators' assessments following the release of DSM-5 in May 2013. Subjects must have been experiencing an acute exacerbation of psychotic symptoms no less than 4 days and no more than 4 weeks in duration prior to screening, showing a score of ≥4 on at least 3 of the following 9 items from the PANSS: Delusions, Conceptual Disorganization, Hallucinatory Behaviour, Excitement, Suspiciousness/Persecution, Hostility, Tension,

Uncooperativeness, and Poor Impulse Control. Furthermore, subjects were to have prominent mood symptoms, with a score of ≥16 on the YMRS and/or a score of ≥16 on the HAM-D-21 at screening. To be eligible for randomization to the double-blind Relapse Prevention period, subjects were required to have a PANSS total score ≤70, and YMRS and HAM-D-21 ≤12 at each visit during the 12-week Stabilization period.

Among the exclusion criteria were subjects who met the DSM-IV criteria for major depressive disorder, bipolar disorder, or schizophrenia; had an Axis II diagnosis of Mental Retardation or Borderline Personality Disorder; met the DSM-IV criteria for substance dependence (except for nicotine and caffeine dependence) in the 3 months before the screening visit; or had attempted suicide within 12 months before the screening visit or were at imminent risk of suicide or violent behavior according to the investigator's clinical judgment. For a complete list of exclusion criteria see study protocol.

Treatments

With the exception of study medication and approved rescue medications, no psychotropic medications were to be initiated during the course of the study. Other medications for treatment of emerging illnesses that began after study entry were allowed at the discretion of the investigator.
Continuation of ongoing therapy with either mood stabilizers (lithium, valproate, or lamotrigine) or antidepressants (except monoamine oxidase inhibitors) was permitted. Subjects in the adjunctive therapy group must have been on generally stable doses of mood stabilizers or antidepressants for at least 30 days prior to screening (eg, no more than 5 daily doses differing from the subject's usual dose within 30 days prior to screening). These subjects were to continue on these mood stabilizers or antidepressants throughout the study. Subjects in the study drug monotherapy group must have been essentially free of mood stabilizers or antidepressants for 30 days prior to screening (eg, no more than 5 daily doses of either mood stabilizers or antidepressants within 30 days prior to screening). These subjects were on study drug monotherapy throughout the study.

Subjects receiving therapy with both mood stabilizers and antidepressants were excluded from entering the study. Initiation of new therapy with mood stabilizers or antidepressants was not allowed. The enrollment of subjects who were taking mood stabilizers or antidepressants versus those taking none was monitored. Subjects being treated with lithium and/or valproate had blood samples taken for the assessment of these plasma levels at time points specified in the protocol.
Recommended therapeutic plasma levels are 0.6-1.2 mEq/L for lithium and 50-125 µg/mL for valproate. Subjects who were given stable doses of lithium and/or valproate, but their plasma levels were outside the therapeutic range, were allowed to enter the study. The dose of lithium and valproate may have been adjusted, if necessary, to maintain therapeutic blood levels.

Objectives
The primary objectives of this study were to evaluate the efficacy of paliperidone palmitate compared with placebo in the delay of relapse of the symptoms of schizoaffective disorder and to assess the safety and tolerability of paliperidone palmitate in subjects with schizoaffective disorder.

The key secondary objective of this study was to evaluate change in subject functioning using the Personal and Social Performance Scale (PSP) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo.

The other secondary objectives of this study were:
▪ To evaluate symptom change as measured by the Positive and Negative Syndrome Scale (PANSS) total and PANSS factor scores during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo

▪ To evaluate illness severity change as measured by Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo

▪ To evaluate change in subject medication satisfaction using the Medication Satisfaction Questionnaire during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo

▪ To evaluate change in mood symptoms as measured by Young Mania Rating Scale (YMRS), Hamilton Rating Scale for Depression, 21-item version (HAM-D-21), and HAM-D, 17-item version (HAM-D-17; the first 17 items from the HAM-D-21) during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo

▪ To explore the consistency of treatment effect across subjects receiving paliperidone palmitate as monotherapy and as an adjunct to mood stabilizers or antidepressants during the double-blind Relapse Prevention period

▪ To explore symptom change (ie, PANSS, YMRS, HAM-D-21, HAM-D-17), illness severity (CGI-S-SCA), subject functioning (PSP) and medication satisfaction (MSQ) with paliperidone palmitate during the Lead-in and Stabilization periods

▪ To explore the overall healthcare resource utilization using the Resource Utilization Questionnaire during the double-blind Relapse Prevention period with paliperidone palmitate compared with placebo

▪ To evaluate and explore genetic markers associated with paliperidone efficacy, safety and tolerability

Outcomes/endpoints

Efficacy Criteria (Relapse Criteria)

The primary efficacy end point for the SCA-3004 study was the time between subject randomization to treatment and the first occurrence of a relapse during the Relapse Prevention period.
Relapse was defined as the first occurrence of ANY ONE of the following:

▪ Psychiatric hospitalization due to worsening symptoms (including ER visit ≥23 hours, and not including hospitalizations for social reasons)

▪ Any intervention employed to avert imminent hospitalization due to worsening symptoms (eg, increase in the level of psychiatric care from office visit to day hospitalization [not including increased level of care for social reasons], or need for additional antipsychotic, antidepressants, or mood stabilizing medication) Deliberate self-injury, suicidal or homicidal ideation that is clinically significant as determined by the investigator, or violent behavior resulting in clinically significant injury to another person or property damage

▪ Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (Excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (Poor Impulse Control) to a score of ≥6 after randomization if the score on the corresponding item was ≤4 at randomization
▪ Worsening, as specified below, in any of the following measures at two consecutive visits.

The second confirmation assessment should be made within 7 days of the initial assessment identifying the worsening score.

- An increase of ≥25% in total PANSS score from randomization if the score at randomization was >45
- A ≥10-point increase in total PANSS score from randomization if the score at randomization was≤45
- Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (Excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (Poor Impulse Control) to a score of ≥5 after randomization if the score on the corresponding item was ≤3 at randomization
- Increase in CGI-S-SCA overall score:
  Increase of ≥2 points if the score at randomization was 1 (not ill) to 3 (mildly ill) OR
  Increase of ≥1 point if the score at randomization was ≥4
  (moderately ill or worse)

Key secondary endpoint

Personal and Social Performance Scale (PSP)
The PSP scale was designed to assess the degree of dysfunction a subject exhibits during the month prior to the visit within 4 domains of behavior: a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behavior. The results of the assessment are converted to a numerical score following the PSP scoring guideline. A score lying between 71 and 100 indicates a good functioning; one between 31 and 70 indicates varying degrees of difficulty, and a subject with a score of ≤30 has functioning so poor that he or she requires intensive supervision.

Other secondary endpoints

Positive and Negative Syndrome Scale (PANSS)
The PANSS is a 30-item scale designed to assess various symptoms of schizophrenia including delusions, grandiosity, blunted affect, poor attention, and poor impulse control. The
30 symptoms are rated, at the time of the visit and for the week prior to the visit, on a 7-point scale that ranges from 1 (absent) to 7 (extreme psychopathology). This scale has been shown to be sensitive to medication treatment, provide a balanced representation of positive and negative symptoms, and gauge their relationship to one another and to global psychopathology.

Clinical Global Impression of Severity for Schizoaffective Disorder (CGI-S-SCA)
The CGI-S-SCA is a syndrome-specific 7-point scale (from 1 indicating not ill to 7 indicating very severely ill) that includes an overall severity score as well as scores for the positive, negative, manic, and depressive domains of the illness. The CGI-S-SCA is used to assess the
level of overall impairment, as well as that related to each domain, at the time of the visit and for the week prior to the visit.

Rating Scale for Depression (HAM-D-21)
The HAM-D-21 is a 21-item, clinician-rated scale to evaluate depressed mood as well as the vegetative and cognitive symptoms of depression. The items are rated, at the time of the visit and for the week prior to the visit, on either a 5-point (0 to 4) or a 3-point (0 to 2) scale. The 5-point scale items use a rating of 0 (absent), 1 (doubtful to mild), 2 (mild to moderate), 3 (moderate to severe), and 4 (very severe). A rating of 4 is usually reserved for extreme symptoms. The 3-point scale items use a rating of 0 (absent), 1 (probable), and 2 (definite).

Rating scale for depression (HAM-D-17)
The HAM-D-17 is based on the first 17 items of the HAM-D-21 rating scale.

Young Mania Rating Scale (YMRS)
The YMRS was designed to measure the severity of manic symptoms and to gauge the effect of treatment on mania severity. It can also be used to detect a return of manic symptoms (eg, relapse or recurrence). The YMRS is a checklist of 11 items that are ranked, at the time of the visit and for the week prior to the visit, on a scale of 0 to 4 or 0 to 8. Seven of the items are ranked 0 to 4 and have descriptors associated with each severity level (ie, 0, 1, 2, 3, 4). Four of the items (irritability, speech, content, and disruptive-aggressive behavior) are scored 0 to 8 and have descriptors for every other increment (ie, 0, 2, 4, 6, 8) to allow for the poor cooperation seen in severely ill subjects.

Sample size

The sample size calculations for this study were based on information from previous studies of paliperidone palmitate, paliperidone ER, and Risperdal CONSTA in schizoaffective disorder, schizophrenia, and bipolar disorder (CSR R076477-SCA-3001 2008, CSR R076477-SCA-3002 2008, CSR R076477-SCH-301 2006, CSR R092670-PSY-3001 2009, RIS-BIP-302 2008, RIS-BIM-3003 2008).

With these assumptions, it was planned to randomize 286 subjects in a 1:1 ratio to receive either paliperidone palmitate or placebo to obtain at least 95 relapses (events) to show that paliperidone palmitate was significantly different from placebo at the 2 sided significance level of 0.05, with 90% power to detect a hazard ratio of 0.51 based on an estimated 12-month relapse rate of approximately 50% in the placebo group and 30% in the paliperidone palmitate group.

It was assumed that approximately 45% of the subjects who entered the open-label Lead-in period while being treated with paliperidone palmitate would not meet the stabilization criteria at the end of the Stabilization period for randomization in the double-blind Relapse Prevention period. To meet the expected number of 286 subjects (143 per group) randomized in the double blind Relapse Prevention period, a total of at least 520 subjects were to be enrolled in the open label Lead-in period.

Randomisation

Randomization was not employed in the screening or open-label Lead-in or open-label Stabilization periods. At the start of the double-blind Relapse Prevention period on Day 176, enrolled patients were randomly assigned in a 1:1 ratio to receive placebo or paliperidone palmitate based on a computer-generated stratified randomization schedule prepared at J&JPRD before initiation of the study. The randomization was balanced by using permuted blocks of 4 patients per block and was stratified by study center and by treatment with or without adjunctive mood stabilizers or antidepressants. Central randomization was implemented for this study. An Interactive Voice Response System (IVRS) or Interactive Web Response System (IWRS) were used to randomly assign subjects to study treatment, dispense study drug, and to track subject dose changes.
Medication code numbers were preprinted on the study drug labels and assigned as subjects qualified for the study and were randomly assigned to treatment.

Blinding (masking)
Placebo for every active dose was prepared to matching size pre-filled syringes. The active and placebo drugs differed slightly in appearance. Therefore, to maintain the blind, both paliperidone palmitate and placebo study drug were wrapped so the content was not visible to either the blinded study drug administrator or the subject. Injections were administered by the blinded study drug administrator.

During the double-blind period of the study, prolactin levels were not available to the investigators, site personnel, or the sponsor, as knowledge of these levels could have potentially unblinded the treatment group to which the subject was assigned.

Statistical methods

The primary population for efficacy was the double-blind ITT analysis set which included all randomized subjects who received at least one injection of double-blind study medication.

The primary efficacy null hypothesis was that there is no difference in the distribution of time to relapse between the paliperidone palmitate and placebo groups during the Relapse Prevention period. Treatment differences were compared using a log-rank test stratified by concomitant medication stratum (treatment with mood stabilizers or antidepressants or no such treatment). Subjects who met at least 1 of the criteria for relapse while on double-blind treatment at the time of or before study completion for the primary analysis were considered to have had an event. All other subjects without documentation of relapse for the primary analysis were censored at the time of last study drug administration or the last visit date. This included also subjects who died while on study drug.

The cumulative distribution function of the time to relapse was estimated by the Kaplan-Meier method. The 95% confidence intervals (CIs) for the median relapse rates, as well as the relapse rates at 3 months, 6 months, 9 months, 1 year, and at 15 months were provided. Standard Error (SE) estimates were based on Greenwood's formula. The hazard ratio with a 95% confidence interval was estimated using the Cox proportional hazards model with factor concomitant medication stratum. In addition, time to relapse was examined within each of the two concomitant medication stratum (treatment with MS/AD or no such treatment). In addition, a Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. Test of hypotheses for any difference in risk of relapse in mood event types was examined by the Global Competing Risk test. An additional analysis was carried out for time to early discontinuation for any reason including relapse using a methodology similar to the primary efficacy analysis.

The key secondary endpoint, change from double-blind baseline in PSP score, was analyzed using a mixed model repeated measures (MMRM) Analysis of Covariance (ANCOVA) model. Robustness and consistency of findings at the Month 15 end point was assessed through a number of supportive and sensitivity analyses (pattern mixture model, tipping-point analysis, and pattern mixture modeling with multiple imputation).

The overall type I error rate for testing the primary efficacy endpoint and the key secondary efficacy endpoint was controlled at the 2-sided 0.05 significance level using a fixed sequence gatekeeper approach. Time to first relapse was tested first, followed by change from baseline in PSP. No further adjustments for multiplicity were planned.

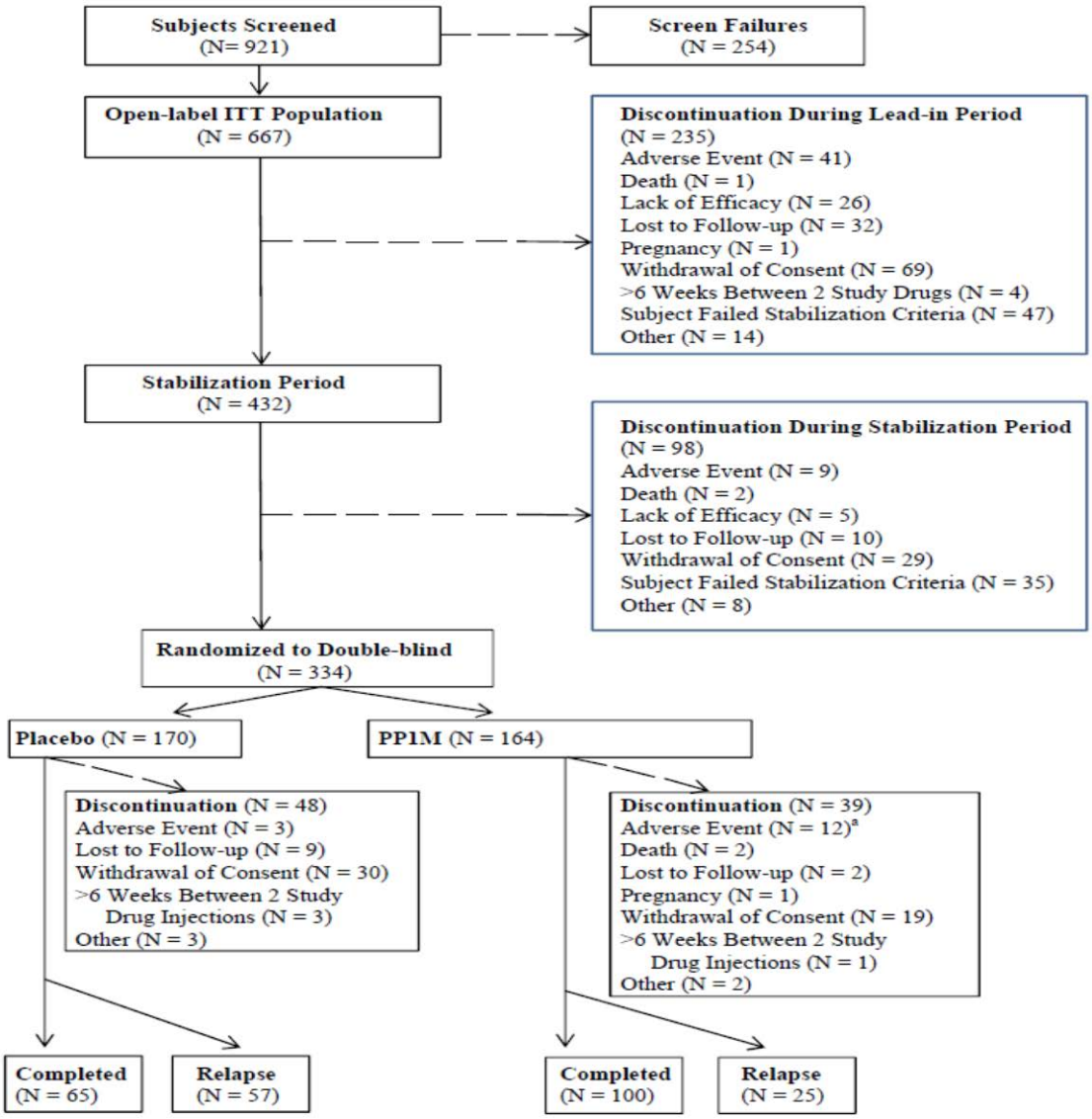
Other secondary efficacy end points (PANSS [total, factor scores, and subscales], HAM-D-21, YMRS, and CGI-S-SCA) were analyzed using an analysis of covariance (ANCOVA) model using both Last Observation Carried Forward (LOCF) and observed cases. The model included treatment, concomitant medication stratum, and country as fixed-effect design factors, and corresponding baseline scale score as a covariate.

Efficacy and safety summaries for the open-label periods were based on the open-label intent to treat (ITT) analysis set, which included all subjects who received at least one injection of open-label study drug. The change from open-label baseline during the open-label treatment period for efficacy variables was summarized descriptively and examined using paired t-tests. These summaries were repeated for those subjects who were on monotherapy and adjunctive therapy.

Results

A total of 667 subjects were enrolled into the open-label period, 347 subjects received paliperidone palmitate as adjunctive therapy to mood stabilizers or antidepressants and 320 subjects received paliperidone palmitate as monotherapy. Of the 667 subjects enrolled, 432 subjects entered the Stabilization period and 334 of these subjects were randomized in a 1:1 ratio to receive either placebo (170 subjects) or to continue receiving paliperidone palmitate (164 subjects) in the double-blind Relapse Prevention period. The majority of subjects enrolled in the open-label period were white (53.1%). There were a higher percentage of male (53.5%) subjects than female (46.5%) subjects and the mean age was 39.5 years (range: 19 to 66 years). The demographic and baseline characteristics of the 334 subjects randomized to the double-blind Relapse Prevention period were similar to those described for subjects enrolled in the open-label period. The most common reason for discontinuation among all open-label subjects was withdrawal of consent (14.7%). Additional reasons for discontinuation in >5% of subjects included adverse events (7.5%), failure of criteria to enter the Stabilization period (7.0%), loss to follow-up (6.3%), and failure of criteria to enter the double-blind Relapse Prevention period (5.2%). During the double-blind period, the most common reason for discontinuation in both the placebo and paliperidone palmitate groups was withdrawal of consent, 17.6% and 11.6%, respectively. A greater proportion of subjects in the paliperidone palmitate group (7.3%) discontinued the study due to an adverse event compared to subjects in the placebo group (1.8%). A diagram of the participant flow is shown below:

Participant flow



More subjects in the paliperidone palmitate, 59.9% (100/164), than in the placebo group 38.2% (65/170) completed the study. The difference in the number of subjects discontinuing early was foremost due to the difference in the number of subjects experiencing a relapse. The most prominent other reasons for early discontinuations were, in both groups, withdrawal of consent besides lost to follow-up in the placebo group and adverse events in the active group. While reason for early withdrawals has been summarized, the CHMP requested the applicant to provide the median follow-up (and range) in the double-blind period of the study.

While both the mean and the median was approximately 9 months in the placebo arm, mean exposure in the paliperidone palmitate arm was 11 months with a median of >14 months mirroring that 61% (100/164) completed the study (i.e. the 15 month treatment period) in the paliperidone palmitate group to be compared to 38.2% (65/170) in the placebo arm. The difference between the groups was, as

already concluded, mainly due to the difference in relapse pattern. Regarding time to withdrawal of consent (the most prominent reason for early discontinuation besides relapse), both the mean and median was similar in both groups but concerned more subjects in the placebo arm, 30/170 (17.6%), than in the active arm, 19/164 (11.6%). The CHMP considered that the median follow-up time for each treatment arm had been clarified.

Recruitment

Conduct of the study

There were 4 amendments to the protocol. The original protocol issued on 24 November 2009.
The first amendment (INT-1; 24 March 2010) included the following changes:

- PANSS component of the stabilization criteria was changed from PANSS total score ≤65 to PANSS total score ≤70);
- Clarify that the timeframe in which subjects must be experiencing an acute exacerbation of psychotic symptoms is in relation to “screening” and not “enrollment”;
- Laboratory tests added to criteria for “subjects must be healthy” to provide consistency between screening procedures and Inclusion Criterion #9;
- Phenylcyclohexylpiperidine (PCP) was added to the list of drugs included in the urine drug screen to be consistent with past paliperidone ER studies of schizoaffective disorder;
- Revised Exclusion Criterion #17 to allow entry of subjects who had previous treatment with low dose clozapine used for treatment of insomnia;
- Revised relapse criteria as follows: “An increase of ≥25% in total PANSS score from randomization if the score at randomization was >45” and “A ≥10 point increase in total PANSS score from randomization if the score at randomization was ≤ 45”;
- Clarified relapse criteria to specify worsening of one or more of the 8 individual PANSS items and increase of ≥ 2 points if the score at randomization was 1 (not ill) to 3 (mildly ill) or Increase of ≥ 1 point if the score at randomization was ≥4 (moderately ill or worse);
- Assessment of tobacco use every 12 weeks was added;
- Clarification that the MSQ will be administered by a study staff member;
- Clarification that Vital sign evaluation will consist of body temperature, sitting systolic and diastolic blood pressure and pulse;
- Added hemoglobin A1C (HbA1c) lab testing to randomization visit and end of study visit;
- Clarification that any subject who becomes pregnant during the study must be promptly withdrawn from the study;
- HAM-D-21 form in Attachment 6 was replaced with the correct HAM-D-21 form;
- Corrections to the anchoring scores of the YMRS Items 1-6, 8 and 9;
- Replaced the RUQ with the correct version;
- and some minor editorial changes.

The protocol changes defined in the second amendment (INT-2; 03 May 2010) included the following changes:

- Change to the dose administration regimen for Day 36 (Week 5). The 117 mg (75 mg eq.) dose was changed to a flexible dose. This allows titration to an optimally efficacious and tolerable dose that will control an acute exacerbation of a subject’s schizoaffective disorder;
- Extension of the window around the second injection (Day 8) of paliperidone palmitate from ±2 days to ±4 days to allow more scheduling flexibility;
- The statement about 13 weeks being needed to reach an upper limit of dose was deleted as it was only applicable when the Day 36 dose was 117 mg and not when the Day 36 dose was made flexible;

- Clarification that serious adverse events will be reported within 30 days after the last visit, whenever that occurs;
- Change made that all sites will now be provided with an electrocardiogram device with required supplies by a central vendor;
- Clarification that data that could be entered directly into the eCRF includes the CGI-S-SCA, HAM-D-21, PANSS, and YMRS data;
- Statement added that backup paper source documents for the scale assessment data should be used and then transcribed into the eDC as soon as the system becomes available.

The protocol changes defined in the third amendment (INT-3; 04 January 2011) included the following:
- Additional analysis of the long-term antidepressants effects of paliperidone palmitate to be performed at the request of the European Regulatory Authority using the HAM-D-17, which is the first 17 items in the currently collected HAM-D-21. In addition, switch-to-depression, worsening of preexisting depression, and de novo depression will be evaluated at the request of the European Regulatory Authority;
- Change in the upper limit of age for inclusion in the study has been removed to allow for evaluation of efficacy and safety in subjects older than 65 years of age made at the request of the European Regulatory Authority;
- Modification of inclusion criterion 6, Added Conceptual Disorganization (P2) and Suspiciousness/Persecution (P6), to increase the generalizability of the study population;
- Clarification of adjunctive therapy including stable dose definition and addition of definition for essentially free of mood stabilizers or antidepressants use to allow for subjects with limited use of mood stabilizers or antidepressants within 30 days prior to screening to be enrolled in the monotherapy group;
- At the request of the European Regulatory Authority, additional analysis were carried out for time to early discontinuation of study medication during the double-blind period for any reason including relapse (not including termination of the study by the sponsor) and for any reason not including relapse;
- minor editorial changes.

The protocol changes defined in the fourth amendment (INT-4; 14 January 2011) were generated to document that after further review of the European Commission's guidance document, it was determined that the changes made in amendment INT-3 should be considered substantial.
A description of the specific changes in applicable sections and rationale for each of the 4 amendments is presented in the protocol amendments section of the protocol (Appendix 1).
In addition, the PSP was declared as a key secondary efficacy variable in the statistical analysis plan (SAP) submitted to the Food and Drug Administration (FDA) on 29 August 2013 (Serial Number 425).

Baseline data

Open label period

Demographic characteristics for subjects in the open-label ITT analysis set are summarized in Table 1 and baseline social demographics are summarized in Table 2.
The majority of all open-label subjects were White (53.1%). There were more male (53.5%) than female (46.5%) subjects in the open-label ITT population, and the mean age was 39.5 years (range: 19 to 66 years). Based on BMI, 34.9% of subjects were classified as having normal body weight, 31.2% of subjects were overweight, and 33.9% were obese.
The majority of all open-label subjects (61.8%) had completed a level of education up to high school or equivalent and were not employed (68.2%) (Table 2). Most subjects (66.4%) were living in a private residence with a spouse, domestic partner, family, or caregiver. In general, the demographic characteristics and the baseline social demographcis were well balanced between the active and placebo groups. A sufficient number of subjects from the SEU were included in Study SCA-3004.

Table 1. Demographic Characteristics - OL ITT Analysis Set (Study R092670-SCA-3004).

	Adjunctive Therapy	Monotherapy	All Open Label
Number of Subjects in OL ITT Population	347	320	667
Age (years)			
N	347	320	667
Mean (SD)	40.1 (10.75)	38.8 (10.63)	39.5 (10.70)
Median	41.0	39.0	40.0
Range	(19; 65)	(19; 66)	(19; 66)
18-25	39 (11.2%)	36 (11.3%)	75 (11.2%)
26-50	239 (68.9%)	234 (73.1%)	473 (70.9%)
51-60	66 (19.0%)	48 (15.0%)	114 (17.1%)
> 60	3 (0.9%)	2 (0.6%)	5 (0.7%)
Gender			
N	347	320	667
Female	163 (47.0%)	147 (45.9%)	310 (46.5%)
Male	184 (53.0%)	173 (54.1%)	357 (53.5%)
Race			
N	347	320	667
White	180 (51.9%)	174 (54.4%)	354 (53.1%)
Black Or African American	95 (27.4%)	100 (31.3%)	195 (29.2%)
Asian	65 (18.7%)	43 (13.4%)	108 (16.2%)
Other	7 (2.0%)	3 (0.9%)	10 (1.5%)

	Adjunctive Therapy	Monotherapy	All Open Label
Ethnicity			
N	347	320	667
Hispanic Or Latino	17 (4.9%)	20 (6.3%)	37 (5.5%)
Not Hispanic Or Latino	323 (93.1%)	298 (93.1%)	621 (93.1%)
Unknown	2 (0.6%)	1 (0.3%)	3 (0.4%)
Not Reported	5 (1.4%)	1 (0.3%)	6 (0.9%)
Height (cm)			
N	347	320	667
Mean (SD)	169.81 (9.980)	169.21 (9.834)	169.52 (9.907)
Median	169.00	169.25	169.00
Range	(142.0; 200.7)	(145.0; 205.7)	(142.0; 205.7)
Baseline Weight (kg)			
N	347	320	667
Mean (SD)	81.60 (20.149)	79.14 (17.248)	80.42 (18.839)
Median	80.00	79.30	79.40
Range	(43.2; 146.1)	(43.5; 145.1)	(43.2; 146.1)
BMI (kg/m^2)			
N	347	320	667
Mean (SD)	28.14 (5.778)	27.59 (5.356)	27.88 (5.582)
Median	27.60	27.35	27.40
Range	(17.3; 42.3)	(18.0; 40.0)	(17.3; 42.3)
normal < 25	122 (35.2%)	111 (34.7%)	233 (34.9%)
overweight >= 25 - < 30	100 (28.8%)	108 (33.8%)	208 (31.2%)
obese >= 30	125 (36.0%)	101 (31.6%)	226 (33.9%)

Note: Percentages are based on the number of subjects in the OL ITT population with a non-missing value for the parameter. One subject was diagnosed Schizoaffective Disorder during screening one day after signing informed consent.

Table 2. Baseline Social Demographics - OL ITT Analysis Set (Study R092670-SCA-3004).

	Adjunctive Therapy	Monotherapy	All Open Label
Number of Subjects in OL ITT Population	347	320	667
Highest Level Of Education Completed			
N	347	320	667
None	18 (5.2%)	17 (5.3%)	35 (5.2%)
Up To High School Or Equivalent	227 (65.4%)	185 (57.8%)	412 (61.8%)
Post-High School Graduate Or Equivalent	102 (29.4%)	118 (36.9%)	220 (33.0%)
Primary Employment Status			
N	347	320	667
Not Employed	229 (66.0%)	226 (70.6%)	455 (68.2%)
Retired	55 (15.9%)	20 (6.3%)	75 (11.2%)
Homemaker	9 (2.6%)	17 (5.3%)	26 (3.9%)
Sheltered Work	2 (0.6%)	3 (0.9%)	5 (0.7%)
Part-Time	18 (5.2%)	23 (7.2%)	41 (6.1%)
Full-Time	34 (9.8%)	31 (9.7%)	65 (9.7%)
Current Living Situation			
N	347	320	667
Private Residence, Alone	42 (12.1%)	38 (11.9%)	80 (12.0%)
Private Residence, With Spouse, Domestic Partner, Family Or Caregiver	225 (64.8%)	218 (68.1%)	443 (66.4%)
Private Residence, With Non-Family Member	16 (4.6%)	9 (2.8%)	25 (3.7%)
Supported Housing/ Community Residence	57 (16.4%)	48 (15.0%)	105 (15.7%)
Homeless – Streets, Parks, Drop-In Center, Or Other Undomiciled	2 (0.6%)	4 (1.3%)	6 (0.9%)
Other	5 (1.4%)	3 (0.9%)	8 (1.2%)

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

The psychiatric history of subjects in the open-label ITT population

For all open-label subjects, the mean age of first psychiatric diagnosis was 26.1 years and mean age of first pharmacological treatment for psychiatric symptoms was 26.6 years. The mean age of first schizoaffective diagnosis was 31.5 years. Most subjects (99.0%) had a pre-existing schizoaffective diagnosis prior to screening. The majority of subjects (64.5%) had a diagnosis of bipolar subtype of schizoaffective disorder confirmed by SCID and 24.3% of subjects had history of prior suicide attempt. The mean number of known psychiatric hospitalizations was 4.8 (median of 3.0) and the mean number of psychiatric hospitalizations in the past 12 months was 0.6. Of the 667 enrolled subjects, 200 subjects were inpatients at the time of screening. At screening, 48.0% of subjects had a depressive mood episode, 26.8% of subjects had a manic mood episode, and 25.2% of subjects had a mixed mood episode. For additional details on the psychiatric history, see Table 6 in the CSR.

Baseline symptoms

The mean and median baseline symptom scores for each scale assessment were similar among subjects in the adjunctive therapy and monotherapy groups (For details see Table 7 in the CSR). At baseline, the mean PANSS total score was 85.8 for all open-label subjects. Based on CGI-S-SCA overall score, most subjects were moderately ill (57.7%) or markedly ill (37.6%) at baseline. The mean baseline PSP score

was 51.4 with 93.3% of subjects classified as variable functioning impairment, 4.5% of subjects classified as poor functioning, and 2.2% of subjects classified as good functioning.

The most common used class of psychotropic medication was the atypical antipsychotics which were used by 73.3 % of all open-label subjects. The psychotropic medications taken by subjects at baseline (taken within 7 days prior to first injection) are summarized in Table 3. At baseline, 104 open-label subjects (15.6 %) were not taking any psychotropic medication. The most commonly used class of psychotropic medication was the atypical antipsychotics (57.1 % of all open-label subjects). Of subjects on mood stabilizers or antiepileptics in the adjunctive therapy stratum, 54.2 % were on mood stabilizers or antiepileptics and 46.7 % were on antidepressants.

Table 3. Baseline psychotropic medications - OL ITT Analysis Set (Study R092670-SCA-3004).

Psychotropic Medication Class Medication Preferred Term	Adjunctive Therapy	Monotherapy	All Open Label
Number of Subjects in OL ITT Population	347	320	667
Number of Subjects Taking:			
0 Baseline Psychotropic Medication	0	104 (32.5%)	104 (15.6%)
1 Baseline Psychotropic Medication	55 (15.9%)	126 (39.4%)	181 (27.1%)
2 Baseline Psychotropic Medications	130 (37.5%)	51 (15.9%)	181 (27.1%)
>2 Baseline Psychotropic Medications	162 (46.7%)	39 (12.2%)	201 (30.1%)
Number of Subjects Taking medications in:			
0 Baseline Psychotropic Medication Class	0	104 (32.5%)	104 (15.6%)
1 Baseline Psychotropic Medication Class	56 (16.1%)	135 (42.2%)	191 (28.6%)
2 Baseline Psychotropic Medication Classes	140 (40.3%)	49 (15.3%)	189 (28.3%)
>2 Baseline Psychotropic Medication Classes	151 (43.5%)	32 (10.0%)	183 (27.4%)
Atypical Antipsychotics	228 (65.7%)	153 (47.8%)	381 (57.1%)
Mood Stabilizers And Antiepileptics	188 (54.2%)	4 (1.3%)	192 (28.8%)
Antidepressants	162 (46.7%)	2 (0.6%)	164 (24.6%)
Benzodiazepines	101 (29.1%)	51 (15.9%)	152 (22.8%)
Non-Benzodiazepines Hypnotics And Anxiolytics	45 (13.0%)	41 (12.8%)	86 (12.9%)
Typical Antipsychotics	50 (14.4%)	34 (10.6%)	84 (12.6%)
Anti-Eps	61 (17.6%)	21 (6.6%)	82 (12.3%)
Beta Blockers	30 (8.6%)	15 (4.7%)	45 (6.7%)
Antihistamines	18 (5.2%)	15 (4.7%)	33 (4.9%)
Stimulants	1 (0.3%)	1 (0.3%)	2 (0.3%)

Note: Percentages are based on the number of subjects in the OL ITT population. Psychotropic medication class is based on SAP defined classes. Medications are coded to generic name using the WHO Drug Dictionary, version 01SEP2012 classic. A subject taking more than one medication in the same class or coding to the same generic name is counted only once within that class. Baseline medications are defined as medications present within 7 days prior to first injection date. Paliperidone taken for oral tolerability testing during screening is not included.

Concomitant psychotropic medications taken during the open-label period are provided in Table 4. With the exception of mood stabilizers and antidepressants taken by the adjunctive therapy group, the most common class of concomitant psychotropic medications taken by subjects was non-benzodiazepines (hypnotic and anxiolytics), 22 % of all open-label subjects. A greater percentage of subjects in the adjunctive therapy group compared to the monotherapy groups were taking benzodiazepines (27.7 % and 15.6 %, respectively) and anti-EPS medications (25.6 % and 13.4 % respectively) during the open-label period.

Table 4. Concomitant Psychotropic Medications - OL ITT Analysis Set (Study R092670-SCA-3004).

	Adjunctive Therapy	Monotherapy	All Open Label
Number of Subjects in OL ITT Population	347	320	667
Number of Subjects Taking:			
0 Psychotropic Medication	2 (0.6%)	184 (57.5%)	186 (27.9%)
1 Psychotropic Medication	147 (42.4%)	69 (21.6%)	216 (32.4%)
2 Psychotropic Medications	90 (25.9%)	34 (10.6%)	124 (18.6%)
>2 Psychotropic Medications	108 (31.1%)	33 (10.3%)	141 (21.1%)
Number of Subjects Taking medications in:			
0 Psychotropic Medication Class	2 (0.6%)	184 (57.5%)	186 (27.9%)
1 Psychotropic Medication Class	152 (43.8%)	73 (22.8%)	225 (33.7%)
2 Psychotropic Medication Classes	90 (25.9%)	37 (11.6%)	127 (19.0%)
>2 Psychotropic Medication Classes	103 (29.7%)	26 (8.1%)	129 (19.3%)
Mood Stabilizers And Antiepileptics	188 (54.2%)	6 (1.9%)	194 (29.1%)
Antidepressants	159 (45.8%)	8 (2.5%)	167 (25.0%)
Non-Benzodiazepines Hypnotics And Anxiolytics	79 (22.8%)	68 (21.3%)	147 (22.0%)
Benzodiazepines	96 (27.7%)	50 (15.6%)	146 (21.9%)
Anti-Eps	89 (25.6%)	43 (13.4%)	132 (19.8%)
Beta Blockers	34 (9.8%)	22 (6.9%)	56 (8.4%)
Atypical Antipsychotics	27 (7.8%)	21 (6.6%)	48 (7.2%)
Antihistamines	15 (4.3%)	24 (7.5%)	39 (5.8%)
Typical Antipsychotics	5 (1.4%)	4 (1.3%)	9 (1.3%)
Stimulants	1 (0.3%)	1 (0.3%)	2 (0.3%)
Anti-Dementia Agents	0	1 (0.3%)	1 (0.1%)

Note: Percentages are based on the number of subjects in the OL ITT population. Medications are coded to ATC Level 4 and generic name using the WHO Drug Dictionary, verion 01SEP2012 classic. A subject taking more than one medication coding to the same ATC code generic name is counted only once within that ATC Level.

Double blind period

Demographic characteristics for subjects in the double-blind ITT analysis set are summarized in Table 5 and baseline social demographics are summarized in Table 6.

The majority of all double-blind subjects were White (54.8%). There was an equivalent proportion of male (50.6%) and female (49.4%) subjects in the double-blind ITT population. The mean age was 38.6 years (range: 19 to 66 years). Based on BMI, 39.5% of subjects were classified as having normal body weight, 29.9% of subjects were overweight, and 30.5% of subjects were obese. A smaller proportion of subjects in the placebo group (28.2%) were classified as obese (BMI ≥30) compared to subjects in the paliperidone palmitate group (32.9%).

Table 5. Demographic characteristics – DB ITT analysis set (Study SCA-3004)

	Placebo	Pali Palmitate	All Double Blind
Number of Subjects in DB ITT Population	170	164	334
Age (years)			
N	170	164	334
Mean (SD)	38.0 (11.05)	39.3 (11.01)	38.6 (11.03)
Median	38.0	39.0	38.5
Range	(19; 66)	(19; 65)	(19; 66)
18-25	26 (15.3%)	21 (12.8%)	47 (14.1%)
26-50	118 (69.4%)	114 (69.5%)	232 (69.5%)
51-60	25 (14.7%)	26 (15.9%)	51 (15.3%)
> 60	1 (0.6%)	3 (1.8%)	4 (1.2%)
Gender			
N	170	164	334
Female	86 (50.6%)	79 (48.2%)	165 (49.4%)
Male	84 (49.4%)	85 (51.8%)	169 (50.6%)
Race			
N	170	164	334
White	88 (51.8%)	95 (57.9%)	183 (54.8%)
Black Or African American	43 (25.3%)	29 (17.7%)	72 (21.6%)
Asian	37 (21.8%)	37 (22.6%)	74 (22.2%)
Other	2 (1.2%)	3 (1.8%)	5 (1.5%)
Ethnicity			
N	170	164	334
Hispanic Or Latino	5 (2.9%)	6 (3.7%)	11 (3.3%)
Not Hispanic Or Latino	163 (95.9%)	158 (96.3%)	321 (96.1%)
Unknown	1 (0.6%)	0	1 (0.3%)
Not Reported	1 (0.6%)	0	1 (0.3%)
Height (cm)			
N	170	164	334
Mean (SD)	168.89 (9.725)	168.37 (9.685)	168.64 (9.694)
Median	169.00	168.00	168.00
Range	(145.0; 198.1)	(142.0; 190.0)	(142.0; 198.1)
Baseline Weight (kg)			
N	170	164	334
Mean (SD)	78.56 (19.122)	77.12 (18.619)	77.85 (18.862)
Median	75.55	76.00	75.85
Range	(43.2; 145.1)	(43.9; 126.6)	(43.2; 145.1)
BMI (kg/m^2)			
N	170	164	334
Mean (SD)	27.38 (5.437)	27.12 (5.859)	27.25 (5.641)
Median	26.50	25.95	26.20
Range	(17.8; 39.5)	(17.6; 42.3)	(17.6; 42.3)
normal < 25	63 (37.1%)	69 (42.1%)	132 (39.5%)
overweight >= 25 - < 30	59 (34.7%)	41 (25.0%)	100 (29.9%)
obese >= 30	48 (28.2%)	54 (32.9%)	102 (30.5%)

Note: Percentages are based on the number of subjects in the DB ITT population with a non-missing value for the parameter.
Note: One subject was diagnosed Schizoaffective Disorder during screening one day after signing informed consent.

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Baseline social demographics are shown in Table 6. The majorities of all double-blind subjects (62.9%) had completed a level of education up to high school or equivalent and were not employed (65.0%). Most subjects (73.7%) were living in a private residence with a spouse, domestic partner, family, or caregiver.

Table 6. Baseline social demographics – DB ITT analysis set (Study SCA-3004)

	Placebo	Pali Palmitate	All Double Blind
Number of Subjects in DB ITT Population	170	164	334
Highest Level Of Education Completed			
N	170	164	334
None	7 (4.1%)	6 (3.7%)	13 (3.9%)
Up To High School Or Equivalent	104 (61.2%)	106 (64.6%)	210 (62.9%)
Post-High School Graduate Or Equivalent	59 (34.7%)	52 (31.7%)	111 (33.2%)
Primary Employment Status			
N	170	164	334
Not Employed	116 (68.2%)	101 (61.6%)	217 (65.0%)
Retired	21 (12.4%)	20 (12.2%)	41 (12.3%)
Homemaker	6 (3.5%)	8 (4.9%)	14 (4.2%)
Sheltered Work	2 (1.2%)	2 (1.2%)	4 (1.2%)
Part-Time	6 (3.5%)	12 (7.3%)	18 (5.4%)
Full-Time	19 (11.2%)	21 (12.8%)	40 (12.0%)
Current Living Situation			
N	170	164	334
Private Residence, Alone	12 (7.1%)	16 (9.8%)	28 (8.4%)
Private Residence, With Spouse, Domestic Partner, Family Or Caregiver	126 (74.1%)	120 (73.2%)	246 (73.7%)
Private Residence, With Non-Family Member	8 (4.7%)	6 (3.7%)	14 (4.2%)
Supported Housing/ Community Residence	23 (13.5%)	17 (10.4%)	40 (12.0%)
Homeless – Streets, Parks, Drop-In Center, Or Other Undomiciled	0	1 (0.6%)	1 (0.3%)
Other	1 (0.6%)	4 (2.4%)	5 (1.5%)

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

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Psychiatric history

The mean age of first psychiatric diagnosis for all double-blind subjects was 26.4 years and mean age of first schizoaffective diagnosis was 30.9 years. The majority of subjects (69.8%) had a diagnosis of bipolar subtype of schizoaffective disorder confirmed by SCID. The mean number of known psychiatric hospitalizations was 3.9 (median of 2.0) and the mean number of psychiatric hospitalizations in the past 12 months was 0.6. Of the 334 randomized subjects, 105 (31.4%) subjects were in-patients at study entry. All double-blind subjects (100%) had a current episode of psychotic symptoms. For the subjects randomized to double-blind treatment, mood symptoms were classified as manic (32.6%), depressive (44.0%), or mixed (23.4%) at screening. A total of 60 subjects (18.0%) had a prior history of suicide attempt. There was a slightly unbalanced distribution of subjects by type of index/current episode at baseline with regard to mood symptoms with 84/170 (49.4 %) and 63/164 (38.4 %) with depressive symptoms in the placebo and paliperidone palmitate group, respectively. It is also noted that there were more subjects in the placebo group than in the paliperidone palmitate group with a diagnosis at baseline of depressive subtype; 59/170 (34.7%) and 42/164 (25.6%). For details on the psychiatric history for the DB ITT Analysis Set, see Table 41 in Study Report. For details on Baseline symptom scores, see Table 42 in CSR.

Concomitant psychotropic medications

A summary of concomitant psychotropic medications started after double-blind Day 1 (first double-blind injection) is provided in Table 7. The majority of subjects in both the adjunctive therapy and monotherapy groups did not start additional psychotropic concomitant medications after double-blind Day 1. After double-blind Day 1, 40 of 170 placebo subjects and 32 of 164 paliperidone palmitate subjects took one or more concomitant psychotropic medications. The most common class of concomitant psychotropic medications started after double-blind Day 1 was non-benzodiazepines (hypnotics and anxiolytics) taken by 6.5% and 6.7% of subjects in the placebo and paliperidone palmitate groups, respectively.

Table 7. Concomitant Psychotropic Medications Started After Day 1 (DB) - DB ITT Analysis Set (Study R092670-SCA-3004)

	Placebo	Pali Palmitate
Number of Subjects in DB ITT Population	170	164
Number Of Subjects Taking At Least One Concomitant Psychotropic Medications	40 (23.5%)	32 (19.5%)
Non-Benzodiazepines Hypnotics And Anxiolytics	11 (6.5%)	11 (6.7%)
Anti-Eps	6 (3.5%)	7 (4.3%)
Beta Blockers	2 (1.2%)	6 (3.7%)
Mood Stabilizers And Antiepileptics	12 (7.1%)	4 (2.4%)
Antidepressants	2 (1.2%)	3 (1.8%)
Antihistamines	3 (1.8%)	3 (1.8%)
Atypical Antipsychotics	8 (4.7%)	3 (1.8%)
Benzodiazepines	6 (3.5%)	3 (1.8%)
Typical Antipsychotics	4 (2.4%)	3 (1.8%)

Note: Percentages are based on the number of subjects in the DB ITT population.
Note: Medications are coded to ATC Level 4 using the WHO Drug Dictionary, version December 2009 classic.
Note: A subject taking more than one medication coding to the same ATC code generic name is counted only once within that ATC Level.

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Numbers analysed

A total of 667 subjects were enrolled into the open-label period, 347 subjects received paliperidone palmitate as adjunctive therapy to mood stabilizers or antidepressants and 320 subjects received paliperidone palmitate as monotherapy. Of the 667 subjects enrolled, 432 subjects entered the Stabilization period and 334 of these subjects were randomized in a 1:1 ratio to receive either placebo (170 subjects) or to continue receiving paliperidone palmitate (164 subjects) in the double-blind Relapse Prevention period.

The most common reason for discontinuation among all open-label subjects was withdrawal of consent (14.7%). Additional reasons for discontinuation in >5% of subjects included adverse events (7.5%), failure of criteria to enter the Stabilization period (7.0%), loss to follow-up (6.3%), and failure of criteria to enter the double-blind Relapse Prevention period (5.2%). During the double-blind period, the most common reason for discontinuation in both the placebo and paliperidone palmitate groups was withdrawal of consent, 17.6% and 11.6%, respectively. A greater proportion of subjects in the paliperidone palmitate group (7.3%) discontinued the study due to an adverse event compared to subjects in the placebo group (1.8%).

Outcomes and estimation

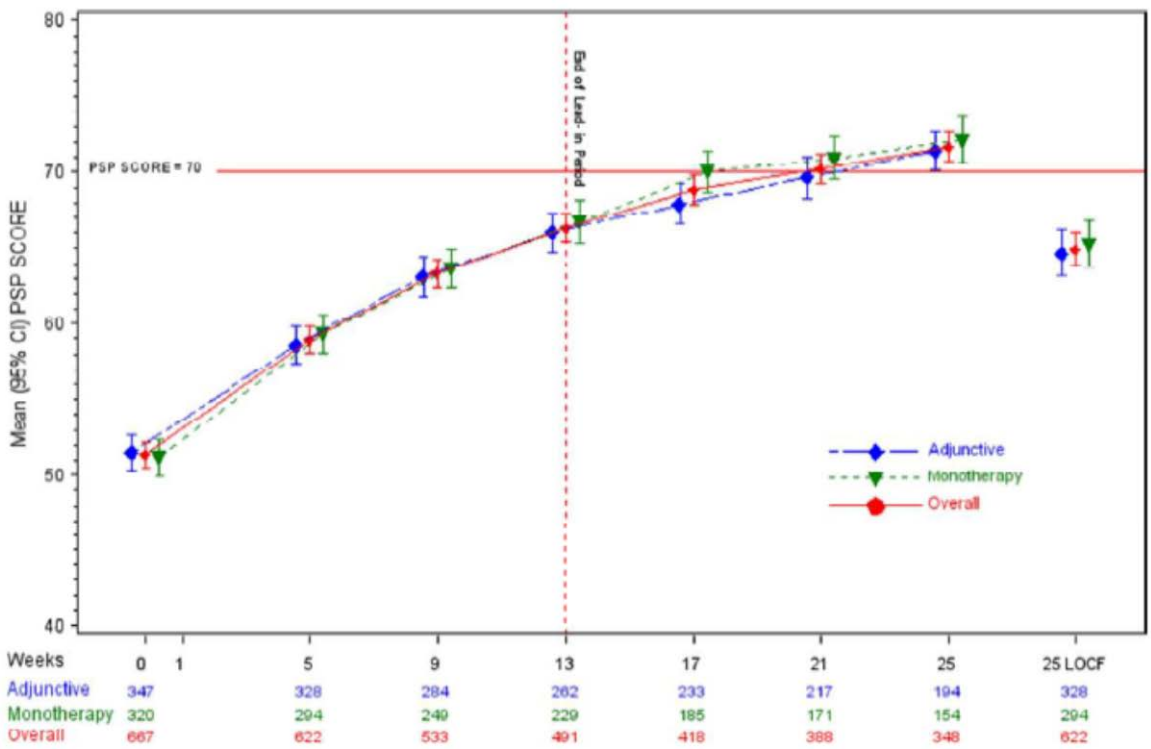
Open label period

The change from open-label baseline during the open-label treatment period for efficacy variables was summarized descriptively and examined using paired t-tests or rank tests. No adjustments were made for multiplicity since this period was used to determine acceptability for entry to the double-blind period.

Personal and social performance scale (PSP)

The mean (standard deviation [SD]) baseline PSP total score for subjects entering the open label period was 51.4 (11.02) suggesting impaired functioning that significantly interfered with role functioning. After subjects had been stabilized during the 6-month open label treatment, the PSP total score for subjects who were randomized improved to 72.0 (8.97. The mean (SD) increase (i.e. improvement) in PSP total score from the open label baseline was 20.8 (13.32). This finding indicates improvement in functioning during the lead-in and stabilization treatment periods for the group of subjects who were randomized. The PSP score change from baseline over time is shown graphically in Figure 5. Based on the mean change in PSP total score, statistically significant improvements (p <0. 001) were observed from baseline to all time points examined. There were only small differences between the adjunctive therapy and monotherapy groups.

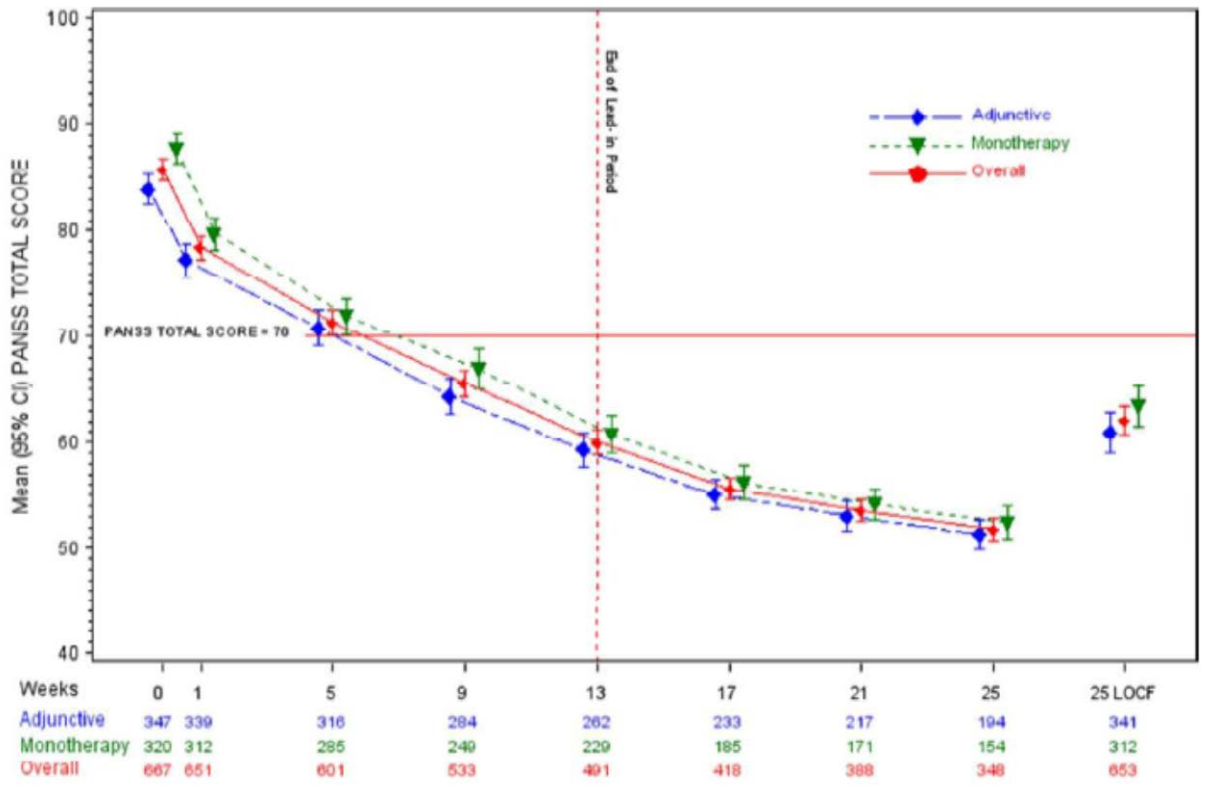
Figure 5. PSP score: change from baseline over time and LOCF in OL period – OL ITT analysis set (Study R092670-SCA-3004)



Positive and negative syndrome scale (PANSS)
Subjects were enrolled in the study with acute exacerbation of their schizoaffective symptoms. The PANSS total scores (based on 30 items) change from baseline over time showed statistically significant improvements ($p<0.001$) from baseline to all time points examined based on the mean change in PANSS total score. The means (95% CI) of PANSS total scores over time showed a decrease (ie, improvement) in the mean PANSS total score over time for the overall open label ITT population as well as the adjunctive therapy and monotherapy groups.

The PANSS total score changes from baseline to Week 13, endpoint Lead-in (last observation carried forward [LOCF]), Week 25, and endpoint open-label (LOCF) show statistically significant improvement ($p<0.001$) in mean PANSS total score at each of the defined endpoints for the overall open-label ITT population as well as the adjunctive therapy and monotherapy groups.
Changes from baseline in the PANSS subscale and factor scores showed that the change from baseline to endpoint open-label (LOCF) was statistically significant ($p<0.001$) for all 3 of the PANSS subscale scores and all 5 of the PANSS factor scores for the all open-label group as well as the adjunctive therapy and monotherapy groups. The means (95% CI) of PANSS total scores over time are presented graphically in Fig. 6. A similar decrease in the mean PANSS total score over time was observed for the overall open-label ITT population as well as the adjunctive therapy and monotherapy groups.

Figure 6. PANSS total score change from baseline over time and end point in OL period – OL ITT analysis set (Study R092670-SCA-3004)



Hamilton rating scale for depression (HAM-D)
Statistically significant improvements ($p<0.001$) were observed from baseline to all time points examined based on HAM-D-21 total score for the all open-label subject population in addition to the adjunctive therapy and monotherapy groups therapy and monotherapy groups. For subjects with a HAM-D-21 score at baseline of 16 or greater, the decrease (i.e., improvement) in mean change of HAM-D-21 at Week 13, endpoint Lead-in (LOCF), Week 25, and end of open-label (LOCF) were all statistically significant.

Statistically significant changes from baseline (p<0.001) were observed at all time points examined based on HAM-D-17 total score for the all open-label subject population in addition to the adjunctive therapy and monotherapy groups.
For subjects with a HAM-D-17 score at baseline of 16 or greater, the decrease in mean change of HAMD-17 at Week 13, endpoint Lead-in (LOCF), Week 25, and end of open-label (LOCF) were all statistically significant.

The MAH examined the direct and indirect effect of treatment based on change in HAM-D-17 total score using a series of regression models in the open-label period. The analysis focused on subjects with prominent depressive symptoms, defined as a HAM-D-17 total score ≥16 at baseline.
The results of these regression analyses indicated that there was a direct treatment effect on depressive symptoms as measured by HAM-D-17 when the effects from potential mediators were accounted for.

Young mania rating scale (YMRS)
Statistically significant decreases (i.e., improvements) from baseline in YMRS total scores (p<0.001) were observed from all the time points analyzed for the all open-label subject population, as well as the adjunctive therapy and monotherapy groups.

CGI-S-SCA, MSQ
Statistically significant changes from baseline in CGI-S-SCA overall scores, and CGI-S-SCA Domain Scores (p<0.001) were observed at all the time points analyzed for the all open-label subject population, as well as the adjunctive therapy and monotherapy groups.

For the MSQ, 38.2% of all open-label subjects at baseline reported being satisfied with their medication, whereas at endpoint open-label (LOCF) the proportion of all open-label subjects satisfied with their study medication increased to 75.4%. A statistically significant (p<0.001) change from baseline in medication satisfaction was reported for subjects in both the adjunctive therapy and monotherapy groups at each study week evaluated.

The results of the efficacy evaluations during the open-label period indicate that treatment with paliperidone palmitate as monotherapy or adjunctive to mood stabilizers or antidepressants improves both functioning and psychotic and manic/depressive mood symptoms in acutely ill subjects with schizoaffective disorder.

Double-blind period

Primary efficacy endpoint

A total of 82 subjects (24.6%) experienced a relapse during the double-blind period. The proportion of subjects who experienced a relapse was greater in the placebo group (57 subjects [33.5%]) compared to the paliperidone palmitate group (25 subjects [15.2%]). Due to the fact that less than 50% of subjects relapsed in each treatment group, median time to relapse could not be computed (Table 8). For the primary efficacy evaluation, the log-rank p-value compared all subjects taking paliperidone palmitate vs. those taking placebo, stratified by concomitant medication stratum. Continued treatment with paliperidone palmitate was associated with a significant delay in time to relapse compared with placebo (p<0.001) using the log-rank test controlling for concomitant medication strata (with or without adjunctive mood stabilizers/antidepressants). A significant delay in time to relapse of schizoaffective symptoms (p<0.001) was observed for subjects in the paliperidone palmitate group compared with subjects in the placebo group using a log rank test without stratification for concomitant medication stratum.
The null hypothesis that there was no difference in the distribution of time to relapse between the 2 treatment groups was rejected.

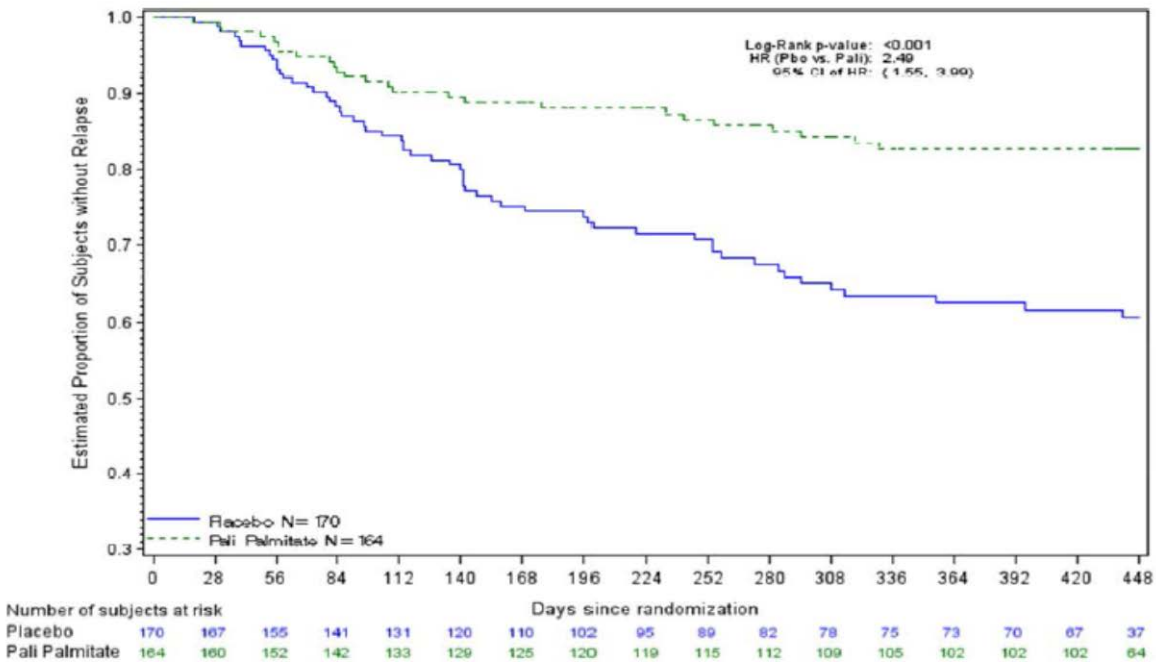
Table 8. Time to Relapse, Days- Double-Blind (DB) ITT Analysis Set (Study R092670-SCA-3004).

	Placebo	Pali Palmitate	All Double Blind
Time to Relapse, Days			
Number assessed	170	164	334
Relapsed	57 (33.5%)	25 (15.2%)	82 (24.6%)
Censored	113 (66.5%)	139 (84.8%)	252 (75.4%)
Kaplan-Meier Median, Days	-	-	-
(95% CI)	(-, -)	(-, -)	(-, -)
Kaplan-Meier 25th Percentile, Days	169	-	294
(95% CI)	(127, 273)	(-, -)	(219, -)
Kaplan-Meier 75th Percentile, Days	-	-	-
(95% CI)	(-, -)	(-, -)	(-, -)
Kaplan-Meier Estimate Probability of Relapse			
Month 3	0.13	0.08	0.10
(95% CI)	(0.08, 0.18)	(0.04, 0.12)	(0.07, 0.14)
Month 6	0.26	0.12	0.19
(95% CI)	(0.19, 0.32)	(0.07, 0.17)	(0.14, 0.23)
Month 9	0.32	0.14	0.23
(95% CI)	(0.24, 0.39)	(0.09, 0.20)	(0.18, 0.28)
Month 12	0.37	0.17	0.27
(95% CI)	(0.29, 0.45)	(0.11, 0.23)	(0.22, 0.33)
Month 15	0.39	0.17	0.28
(95% CI)	(0.31, 0.48)	(0.11, 0.23)	(0.23, 0.34)
Log-Rank p-value[a]	<0.001		
Log-Rank p-value[b]	<0.001		

Abbreviations: CI=confidence interval; ITT=intent-to-treat; Pali=paliperidone
Note: Percentages are based on the number of patients assessed in the DB ITT population.
[a] Primary efficacy evaluation. Log-Rank p-value compares all patients taking paliperidone palmitate vs. those
taking placebo stratified by concomitant medication stratum.
[b] Log-Rank p-value compares all patients taking paliperidone palmitate vs. those taking placebo.

A Kaplan-Meier plot of the time to first relapse for the 2 double-blind treatment groups was significantly longer (p<0.001) for the subjects randomized to continue to receive paliperidone palmitate in the double blind period compared to placebo (Figure 7).

Figure 7. Kaplan-Meier plot of time to relapse, days, DB-ITT analysis set (Study SCA-3004).



The risk of relapse (hazard ratio) was 2.49 (95% CI: 1.55, 3.99; p<0.001) fold higher for a subject who was switched to placebo than for a subject who continued to receive paliperidone palmitate in the double-blind period (Table 9). For patients in monotherapy and adjunctive subgroups the risk of relapse was not statistically significantly different after controlling for treatment (hazard ratio=1.28, 95% CI: 0.82, 1.99; p=0.274).

Table 9. Time to relapse, Cox proportional hazards regression model – double-blind ITT analysis set (Study R092670-SCA-3004).

	Placebo	Pali Palmitate	All Double Blind
Time to Relapse			
Number assessed	170	164	334
Relapsed	57 (33.5%)	25 (15.2%)	82 (24.6%)
Censored	113 (66.5%)	139 (84.8%)	252 (75.4%)
Relative Risk (Hazard Ratio)			
Treatment group, Placebo vs. Pali Palmitate[a]	2.49		
(95% CI)	(1.55, 3.99)		
p-value	<0.001		
Concomitant medication stratum, Adjunctive vs. Monotherapy	1.28		
(95% CI)	(0.82, 1.99)		
p-value	0.274		

Note: Regression analysis of survival data based on a Cox proportional hazards model including effects for treatment and concomitant medication stratum.
[a] The instantaneous risk (hazard) of relapse for a placebo treated subject compared to Paliperidone Palmitate treated subject.

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The most common reasons for relapse for subjects who experienced a relapse in the double-blind period were worsening of clinical scores at 2 consecutive visits, and interventions employed to avert hospitalizations. A higher proportion of subjects in the placebo group (7.1%, 12 subjects) than the paliperidone palmitate group (3.0%, 5 subjects) were hospitalized for decompensating of the subjects' schizoaffective symptoms. A higher proportion of subjects in the placebo group (13.5%, 23 subjects) than in the paliperidone palmitate group (5.5%, 9 subjects) had an intervention employed to avoid their hospitalization. The majority of relapses were with both psychotic and mood symptoms. The frequency distribution of reasons for relapse is shown in Table 10.

Table 10. Frequency distribution of reason for relapse – DB ITT analysis set (Study SCA-3004)

Analysis set: DB ITT	Placebo 170	Pali Palmitate 164	All Double Blind 334
Total number of subjects relapsed	57 (33.5%)	25 (15.2%)	82 (24.6%)
1. Psychiatric hospitalizations	12 (7.1%)	5 (3.0%)	17 (5.1%)
2. Interventions employed to avert hospitalizations	23 (13.5%)	9 (5.5%)	32 (9.6%)
3. Deliberate self-injury, suicidal or homicidal ideation	3 (1.8%)	4 (2.4%)	7 (2.1%)
Self-injury	1 (0.6%)	0	1 (0.3%)
Suicide attempt	0	0	0
Suicidal ideation	3 (1.8%)	4 (2.4%)	7 (2.1%)
Homicidal ideation	1 (0.6%)	1 (0.6%)	2 (0.6%)
Violent behavior resulting in property damage	0	0	0
4. Worsening of PANSS items[a]	10 (5.9%)	3 (1.8%)	13 (3.9%)
5. Worsening of clinical scores at two consecutive visits[b]:	25 (14.7%)	10 (6.1%)	35 (10.5%)
A. >=25% Increase in PANSS Total score	16 (9.4%)	5 (3.0%)	21 (6.3%)
B. >=10 Point increase in PANSS Total Score when the baseline score was <=45	7 (4.1%)	5 (3.0%)	12 (3.6%)
C. Worsening of PANSS items[c]	6 (3.5%)	4 (2.4%)	10 (3.0%)
D. Increase in CGI-S-SCA Overall Score[d]	12 (7.1%)	5 (3.0%)	17 (5.1%)

Note: Percentages are based on the number of patients assessed in the DB ITT population. Reasons for relapse are not mutually exclusive.
[a] Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (poor impulse control) to a score of >=6 after randomization if the score on the corresponding item was <=4 at randomization.
[b] Worsening, as specified below, in any of the following measures at two consecutive visits. The second confirmation assessment was to be made within 7 days of the initial assessment identifying the worsening score.
- An increase of >=25 percent in total PANSS score from randomization if the score at randomization was >45
- A 10-point increase in total PANSS score from randomization if the score at randomization was <=45
[c] Worsening of any one or more of the following PANSS items: P1 (delusions), P2 (conceptual disorganization), P3 (hallucinatory behavior), P4 (excitement), P6 (suspiciousness/persecution), P7 (hostility), G8 (uncooperativeness), or G14 (poor impulse control) to a score of >=5 after randomization if the score on the corresponding item was <=3 at randomization.
[d] Increase in CGI-S-SCA overall score:
- Increase of >=2 points if the score at randomization was 1 (not ill) to 3 (mildly ill) OR
- Increase of >=1 point if the score at randomization was >=4 (moderately ill or worse)

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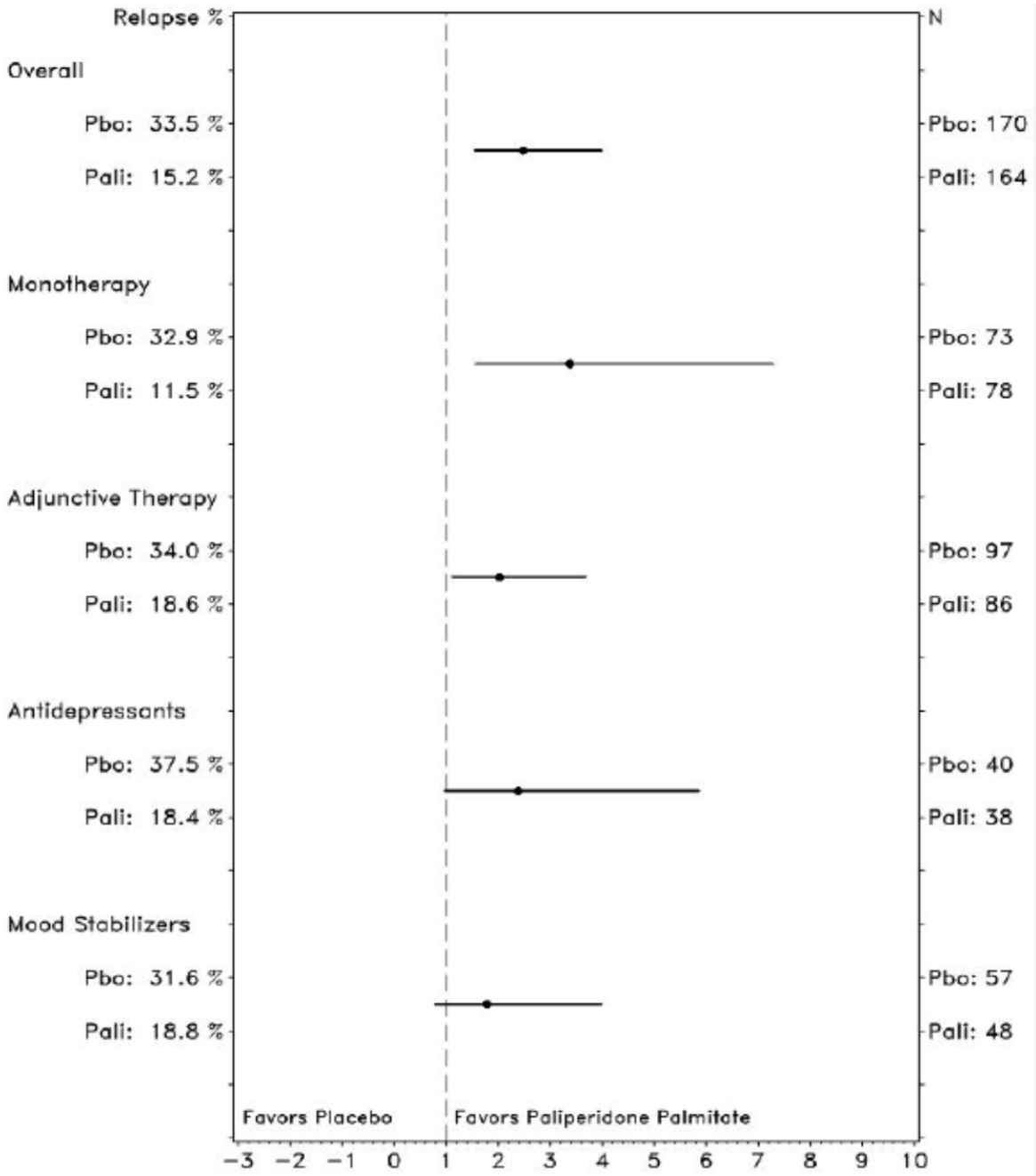
Time to relapse in subjects on monotherapy or adjunctive therapy

For subjects on monotherapy, the proportion who experienced a relapse in the double-blind period was 32.9% (24 subjects) in the placebo group and 11.5 % (9 subjects) in the paliperidone palmitate group. The Kaplan-Meier estimates of time to relapse showed a significantly longer time to relapse for subjects who continued to receive paliperidone palmitate in the double-blind period compared to placebo (p<0.001) The risk of relapse (hazard ratio) was 3.38 (95% CI: 1.57, 7.28; p=0.002) times higher for a subject in the placebo group than for a subject continuing to receive paliperidone palmitate as monotherapy in the double-blind period.

For subjects on
therapy of mood stabilizers or antidepressants, 33 subjects
(34.0%) in the placebo group and 16 subjects (18.6%) in the paliperidone palmitate group experienced a relapse in the double-blind period. The Kaplan-Meier estimates of time to relapse showed a significantly longer time to relapse for subjects who continued to receive paliperidone palmitate in the double-blind period compared to placebo (p=0.018). The risk of relapse (hazard ratio) was 2.03 (95% CI: 1.11, 3.68;

p=0.021) times higher for a subject in the placebo group than for a subject continuing to receive paliperidone palmitate treatment as adjunctive therapy to mood stabilizers or antidepressants.
A summary of overall relapse and relapse by monotherapy and adjunctive therapy stratum with hazard ratios is provided in Fig. 8.

Figure 8. Forest plot of relapse with hazard ratio – DB ITT analysis set (Study SCA-3004)



Time to relapse related to mood symptoms and psychotic symptoms
Mood Symptoms: The risk of relapse due to mood symptoms was higher for subjects in the placebo group than for subjects continuing paliperidone palmitate treatment. Risk of relapse was 2.93 (95% CI: 1.70, 5.04; p<0.001) times higher for relapse due to any mood symptom; 3.62 (95% CI: 1.32, 9.89; p=0.012) times higher for relapse due to manic symptoms; 3.12 (95% CI: 1.39, 6.98; p=0.006) times higher for

relapse due to depressive symptoms; and 1.93 (95% CI: 0.65, 5.78; p=0.238) for relapse due to mixed symptoms (Table 11).

Table 11. Summary of Cox competing risk proportional hazards models on relapse types – DB ITT analysis set (Study SCA-3004)

	Placebo Event/N (%)	Pali Palmitate Event /N (%)	Hazard Ratio (HR)[a]	p-value	95% CI of HR
Mood Symptoms					
1. Any Mood Symptoms	48/170 (28.2%)	18/164 (11.0%)	2.93	<0.001	(1.70, 5.04)
2. Manic	16/170 (9.4%)	5/164 (3.0%)	3.62	0.012	(1.32, 9.89)
3. Depressive	23/170 (13.5%)	8/164 (4.9%)	3.12	0.006	(1.39, 6.98)
4. Mixed	9/170 (5.3%)	5/164 (3.0%)	1.93	0.238	(0.65, 5.78)
Global Competing Risk p-value[b]	0.718				

Note: Percentages are based on the number of patients assessed in the DB ITT population.
[a] Model results are based on Cox proportional hazards models with effects for treatment. Pali Palmitate is the reference cell.
[b] Global test for differences based on the difference in -2 log likelihood for Any Mood Symptoms (First Model) and the sum of the last three models. Competing risk test based on the Wald Chi-Square statistics for difference in the parameters between the specified models. Test the hypothesis that the coefficient treatment for one event type is the same as for another event type.
Pali: Paliperidone

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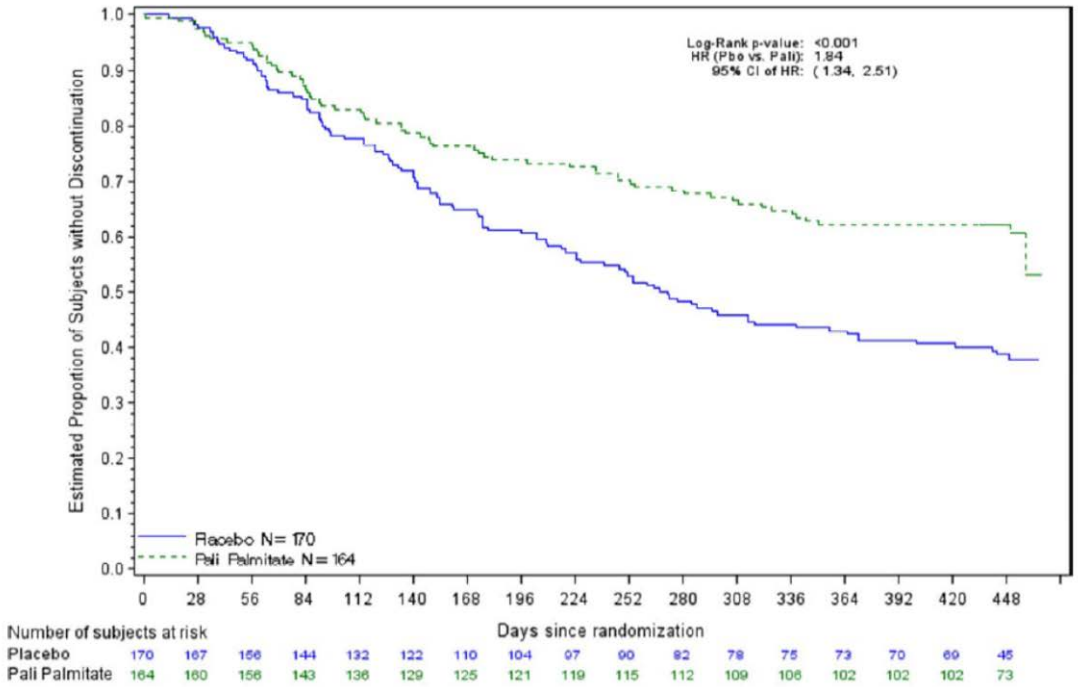
For subjects with manic and depressive type relapses, analysis by type of relapse unadjusted for the presence of competing risks, Kaplan-Meier estimates of time to relapse showed a significantly longer time to relapse for subjects who continued to receive paliperidone palmitate in the double-blind period compared to placebo (p=0.009 and p=0.004, respectively). For subjects with mixed type relapses, the Kaplan-Meier estimates of time to relapse did not show a significant difference between the placebo and paliperidone palmitate groups (p=0.277), however the number of subjects for this category was low.
Psychotic Symptoms: Kaplan-Meier estimates of time to relapse based on psychotic relapses, showed a significantly longer time to relapse for subjects who continued to receive paliperidone palmitate in the double-blind period compared to placebo (p<0.001). The risk of relapse (hazard ratio) was 2.82 (95% CI: 1.70, 4.67; p<0.001) times higher for a subject in the placebo group than for a subject continuing to receive paliperidone palmitate in the double-blind period.

Time to all cause discontinuation (early discontinuation of study medication for any reason, including relapse)

A Kaplan-Meier plot of the time to all cause discontinuation, including relapses for the 2 double-blind treatment groups is presented in Figure 9. The time to all cause discontinuation was significantly longer (p<0.001) for the subjects who were randomized to continue to receive paliperidone palmitate in the double-blind period compared to placebo.

Overall, 169 subjects (50.6%) discontinued from the double-blind period of the study. A greater number of subjects in the placebo group (105 subjects [61.8%]) discontinued the study compared to the paliperidone palmitate group (64 subjects [39.0%]). There was a statistically significant difference in time to discontinuation (p<0.001 based on the long-rank test controlling for concomitant medication strata) between the treatment groups in favor of subjects who were randomized to continue to receive paliperidone palmitate in the double-blind period.

Figure 9. Kaplan-Meier plot of time to all causes discontinuation – DB ITT analysis set (Study SCA-3004)



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Secondary efficacy endpoints

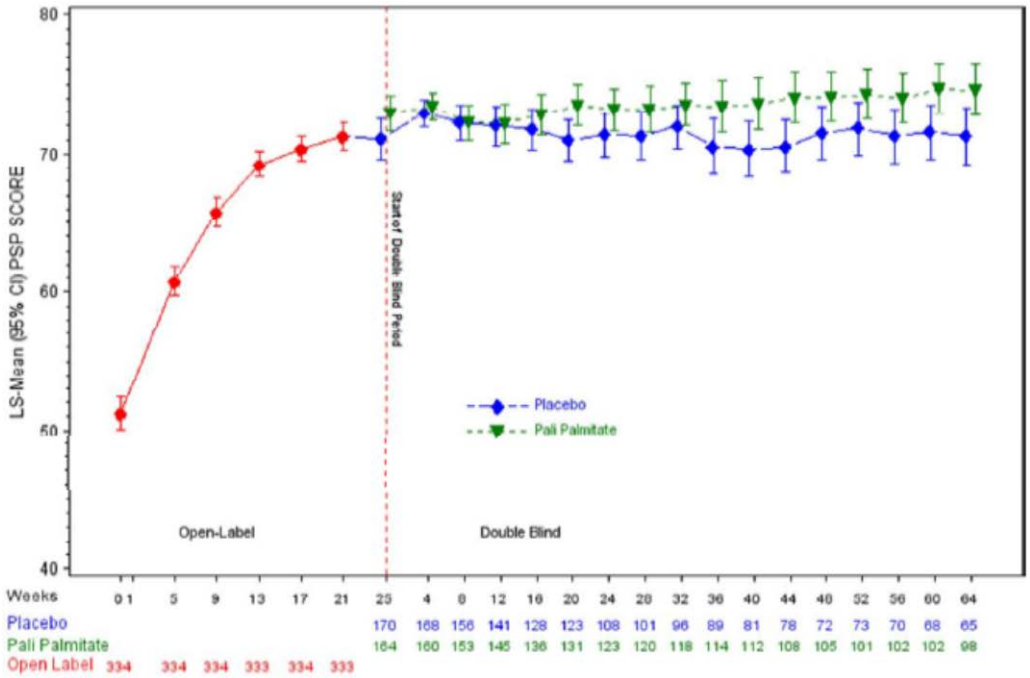
Personal and social performance scale (PSP)

The PSP scale was used to capture information around the degree of dysfunction a subject exhibited during the month prior to the time of examination. Functioning was assessed within 4 domains: a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behavior. The change from double-blind baseline in PSP score was analyzed using a mixed model repeated measures (MMRM) ANCOVA model. The analysis was based on observed data (ie, data collected at each time point without carrying forward previous values). Within-subject repeated measures were modeled using unstructured covariance matrix.

A significant difference (p=0.014) in favor of paliperidone palmitate was demonstrated when comparing the mean change from baseline at Month 15 (Week 64) using the MMRM approach. The least square (LS)-mean (95% CI) difference in change scores between the 2 treatment groups at Month 15 was 3.3 (0.68, 5.95). Thus, the null hypothesis that there was no difference in the mean change from baseline in the PSP score between paliperidone palmitate and placebo at Month 15 end point was rejected.

A summary of observed PSP scores over time in both the open label and double-blind periods is provided graphically in Figure 10.

Figure 10. LS-mean (95 % CI) PSP score over time using MMRM-DB ITT analysis set (Study SCA-3004)



Note: Open Label summaries are based on arithmetic means. LS-Means (95 percent CI) are based on repeated measures mixed effects ANCOVA model with baseline PSP score as covariate; treatment, medication stratum, country, and visit as fixed effect factors; and treatment-by-visit interaction.

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Sensitivity analyses for PSP

To evaluate the validity of the MAR assumption, several sensitivity analyses based on missing not at random (MNAR) were performed to assess the robustness and consistency of findings at the Month 15 end point. These analyses were based on Pattern Mixture Models (PMM), a Tipping-Point Analysis and a Pattern Mixture Model with Multiple Imputation approaches. A summary of LS-mean differences using the sensitivity analyses of PMM, Tipping Point analysis, and PMM with multiple imputation is provided in Table 12.

Table 12. LS-mean differences at study endpoint, sensitivity analyses – DB ITT analysis set (Study SCA-3004)

Method	Time	LS Mean Treatment Difference (SE)	p-value	95% CI
PMM	Week 64	2.14 (1.32)	0.105	-0.44, 4.73
PMM without covariate baseline score	Week 64	3.32 (1.46)	0.023	0.44, 6.16
LOCF, Tipping Point	LOCF	4.5 (1.32)	<0.001	1.94, 7.15
5% worsening of all Pali subjects who relapsed	LOCF	4.1 (1.36)	0.002	1.47, 6.80
10% worsening of all Pali subjects who relapsed	LOCF	3.7 (1.39)	0.008	0.98, 6.45
5% worsening of all Pali subjects who discontinued	LOCF	3.3 (1.36)	0.016	0.63, 5.97
10% worsening of all Pali subjects who discontinued	LOCF	2.0 (1.40)	0.145	-0.71, 4.80
Multiple Imputation	Week 64	3.9 (1.72)	0.027	0.44, 7.29
5% worsening of all Pali subjects who relapsed	Week 64	3.4 (1.72)	0.055	-0.08, 6.79
5% worsening of all Pali subjects who discontinued	Week 64	2.5 (1.71)	0.148	-0.91, 5.92

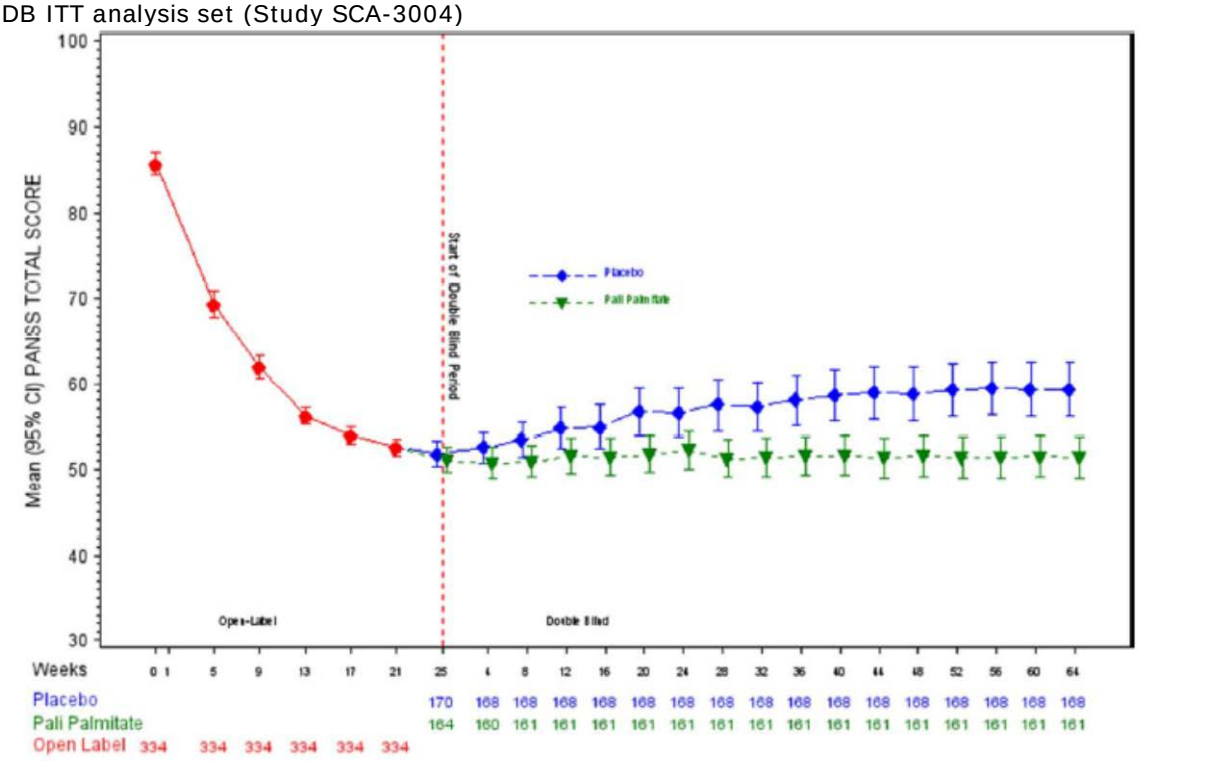
Source: PMM (Attachment TEFPSP16_DB and Attachment TEFPSP16A_DB), LOCF (Table 60, Attachment TEFPSP13A_DB and Attachment TEFPSP13_DB), Multiple Imputation (Attachment TEFPSP17_DB, Attachment TEFPSP18A_DB, and Attachment TEFPSP18_DB)

Positive and negative syndrome scale (PANSS)

Subjects were eligible for randomization into the double-blind Relapse Prevention period if they maintained stabilization criteria throughout the 12-week Stabilization period. One of prospectively defined stabilization criteria was a PANSS total score ≤70. The mean PANSS total score at double-blind baseline was 51.8 for subjects randomized to receive placebo and 51.1 for subjects randomized to continue receiving paliperidone palmitate in the double-blind period (Table 67). Subjects who continued to receive paliperidone palmitate remained stable based on change in PANSS total score from double-blind baseline to end point.

The mean PANSS score for subjects who received placebo worsened by 7.4 points at double-blind end point and this change was significant ($p<0.001$). The difference between the 2 treatment groups was statistically significant ($p<0.001$) in favor of the paliperidone palmitate group. Changes in PANSS total scores over time during the open-label and double-blind phases are presented graphically in Figure 11.

Figure 11. PANSS total score: arithmetic mean (95 % CI) PANSS total score over time using LOCF visits – DB ITT analysis set (Study SCA-3004)



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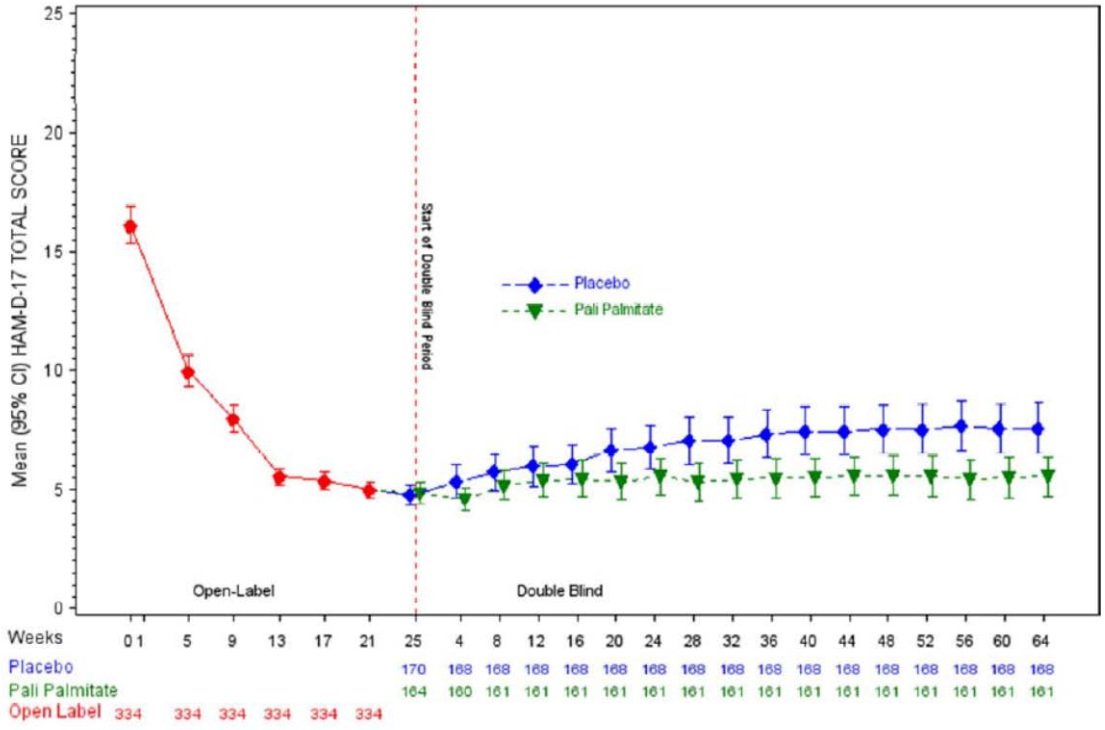
Hamilton rating scale for depression (HAM-D)

Subjects were eligible for randomization into the double-blind Relapse Prevention period if they had a HAM-D-21 rating ≤12. The mean HAM-D-21 total score at double blind baseline was 5.6 for subjects randomized to receive placebo and 5.7 for subjects randomized to continue receiving paliperidone palmitate in the double-blind period. At double-blind end point the mean HAM-D-21 total score had worsened to 6.5 for subjects in the paliperidone palmitate group and to 9.0 for subjects in the placebo group. There was a significant difference ($p<0.001$) between the 2 treatment groups in favor of paliperidone palmitate when comparing the mean change in HAM-D-21 total score from double-blind baseline to end point.

Also for HAM-D-17 there was a significant difference ($p=0.001$) between the 2 treatment groups in favor of paliperidone palmitate when comparing the mean change in HAM-D-17 total score from double-blind baseline to end point (Fig.12).

Figure 12. HAM-D-17 total score: arithmetic mean (95 % CI) HAM-D-17 score over time using LOCF visits – DB ITT analysis set (Study SCA-3004)



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Young mania rating scale (YMRS)

Subjects were eligible for randomization into the double-blind Relapse Prevention period if they had an YMRS rating ≤12. The mean YMRS total score at double-blind baseline was 4.4 for subjects randomized to both the placebo and paliperidone palmitate groups. At double-blind end point the mean YMRS total score for subjects in the paliperidone palmitate group had decreased to 4.3 and for subjects in the placebo group it worsened to 7.5. There was a significant difference ($p<0.001$) between the 2 treatment groups in favor of paliperidone palmitate when comparing the mean change in YMRS total score from double-blind baseline to end point.

Clinical Global Impression of Severity for Schizoaffective Disorder(CGI-S-SCA)

CGI-S-SCA Overall Score
The mean CGI-S-SCA overall score remained relatively stable from double-blind baseline to end point for subjects in the paliperidone palmitate group while a mean increase of 0.4 ($p<0.001$) at double-blind end point was observed for subjects in the placebo group. There was a significant difference ($p<0.001$) between the two treatment groups in favor of paliperidone palmitate when comparing the mean change in CGI-S-SCA overall score from double-blind baseline to end point.

Summary of main study(ies)

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

Table 1. Summary of Efficacy for trial R092670-SCA-3004

Title: Summary of Efficacy for trial R092670-SCA-3004			
Study identifier	SCA-3004		
Design	Randomized, double-blind, placebo-controlled, parallel-group study evaluating the efficacy and safety of paliperidone palmitate, as monotherapy or as an adjunct to mood stabilizers or antidepressants, relative to placebo in delaying the time to relapse in subjects with schizoaffective disorder. Key secondary objective was to evaluate change in subject functioning using the PSP during the DB Period with paliperidone palmitate compared with placebo.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		15 months 25 weeks (13-week lead-in and 12-week stabilization) not applicable
Hypotheses	Superiority: The primary efficacy null hypothesis was that there is no difference in the distribution of time to relapse between the paliperidone palmitate and placebo groups. The key secondary efficacy variable was the mean change from double-blind baseline in PSP score at DB endpoint (Month 15). The corresponding null hypothesis for the key secondary endpoint was that there is no difference in mean change from double-blind baseline in the PSP score between paliperidone palmitate and placebo at endpoint.		
Treatments groups	All enrolled subjects for open-label treatment		Paliperidone palmitate, 25 weeks, 667 enrolled
	Double-blind paliperidone palmitate group		Paliperidone palmitate. 15 months, 164 randomized
	Double-blind placebo group		Placebo. 15 months, 170 randomized
Endpoints and definitions	Primary endpoint	Time to relapse	The primary efficacy endpoint for the study was the time between subject randomization to treatment and the first occurrence of a relapse during the DB Relapse Prevention period. Compare paliperidone palmitate versus placebo on time to relapse and risk of relapse for overall groups; monotherapy group and adjunctive therapy sub-groups; and on psychotic relapses; and mood symptom (manic, depressive, and mixed) relapses
	Key secondary endpoint	PSP	A scale designed to assess the degree of dysfunction that a subject exhibits during the one month prior to the visit within 4 domains of behavior: (a) socially useful activities, (b) personal and social relationships, (c) self-care, and (d) disturbing and aggressive behavior.
	Secondary endpoint	HAMD-17	A 17-item clinician-rated scale to evaluate symptoms of depression.
Database lock	November 25, 2013		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Efficacy and safety summaries for the DB Relapse Prevention Period of the study were based on the double-blind ITT analysis set which included all randomized subjects who received at least one injection of double-blind study drug. The primary population for efficacy was the double-blind ITT analysis set. Difference between treatment groups for the key secondary endpoint, changes in PSP, was evaluated at Month 15.		
Descriptive statistics and estimate variability	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Time to relapse, All Subjects Relapsed Censored	 57 (33.5%) 113 (66.5%)	 25 (15.2%) 139 (84.8%)
Effect estimate per comparison	Time to Relapse All Subjects	Log-Rank Stratified by Concomitant Medication Stratum, P-value	<0.001
		Log-Rank, P-value	<0.001
		Hazard Ratio (HR) 95% CI of HR P-value	2.49 (1.55, 3.99) <0.001
Relapse for Monotherapy subset	Treatment group	Placebo	Pali Palmitate
	Number of subject	73	78
	Relapsed	24 (32.9%)	9 (11.5%)
	Hazard Ratio (HR) 95% CI of HR P-value	3.38 (1.57, 7.28) 0.002	
Relapse for Adjunct to Antidepressants or Mood Stabilizers subset	Treatment group	Placebo	Pali Palmitate
	Number of subject	97	86
	Relapsed	33 (34.0%)	16 (18.6%)
	Hazard Ratio (HR) 95% CI of HR P-value	2.03 (1.11, 3.68) 0.021	
Relapse for Psychotic Symptoms	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Relapsed	53 (31.2%)	21 (12.8%)
	Hazard Ratio (HR) 95% CI of HR P-value	2.82 (1.70, 4.67) <0.001	
Relapse for Any Mood Symptoms	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Relapsed	48 (28.2%)	18 (11.0%)
	Hazard Ratio (HR) 95% CI of HR P-value	2.93 (1.70, 5.04) <0.001	
Relapse for Manic Mood Symptoms	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Relapsed	16 (9.4%)	5 (3.0%)

	Hazard Ratio (HR) 95% CI of HR P-value	3.62 (1.32, 9.89) 0.012	

Relapse for Depressive Symptoms	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Relapsed	23 (13.5%)	8 (4.9%)
	Hazard Ratio (HR) 95% CI of HR P-value	3.12 (1.39, 6.98) 0.006	
Relapse for Mixed Symptoms	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	Relapsed	9 (5.3%)	5 (3.0%)
	Hazard Ratio (HR) 95% CI of HR P-value	1.93 (0.65, 5.78) 0.238	
PSP Score: Mixed Model Repeated Measures (MMRM) ANCOVA, Change from Baseline at Week 64 (Month 15)	Treatment group	Placebo	Pali Palmitate
	Number of subject	170	164
	LS-Mean (SE)	-1.3 (1.03)	2.0 (0.92)
	95% CI of LS-Mean	(-3.31; 0.78)	(0.22; 3.88)
	LS-Mean Difference (SE)	3.3 (1.33)	
	95% CI of LS-Mean Difference	(0.68; 5.95)	
	P-value on LS-Mean Difference	0.014	
HAM-D-17: ANCOVA, Change from Baseline at Week 64 LOCF (Month 15)	Treatment group	Placebo	Pali Palmitate
	Number of subject	168	161
	LS-Mean (SE)	2.7 (0.54)	0.7 (0.55)
	LS-Mean Difference (SE)	-2.1 (0.64)	
	95% CI of LS-Mean Difference	(-3.31; -0.81)	
	P-value on LS-Mean Difference	0.001	

Analysis description	The primary efficacy endpoint for this study was the time between Day 1 of the DB period and the first documentation of a relapse. Treatment differences for time to relapse were compared using a log-rank test stratified by concomitant medication stratum (treatment with mood stabilizers or antidepressants or no such treatment). Time to relapse between treatment groups was also evaluated within each subgroup, treatment with concomitant medications (antidepressants or mood stabilizers) and no concomitant treatment. Risk of relapse for the subgroup of subjects on monotherapy and adjunctive therapy were also examined using Cox proportional hazards models. In addition, a Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. The Cox proportional hazards model was also used to examine differences between treatment groups for psychotic relapses. Test of hypotheses for any difference in risk of relapse in mood event types was examined by the Global Competing Risk test. The key secondary efficacy variable was the mean change from double-blind baseline in PSP score at double-blind endpoint (Month 15). The overall type I error rate for testing paliperidone palmitate versus placebo for both the primary efficacy and key secondary efficacy endpoint was controlled at the 2-sided 0.05 significance level using a fixed sequence gatekeeper approach. Time to first relapse was tested first, followed by change from baseline in PSP. If the null hypothesis corresponding to time to first relapse was rejected, then the PSP would be tested at the 5% level, thus maintaining an overall Type I error rate of 5%. The change from double-blind baseline in PSP score was analyzed using a mixed model repeated measures (MMRM) Analysis of Covariance (ANCOVA) model. The model included baseline PSP score as a fixed-effect covariate; treatment, concomitant medication stratum (treatment with antidepressants or mood stabilizers or no such treatment), country, and time (scheduled assessment visits) as fixed-effect (categorical) factors, and the interaction between time and treatment. Using this model, treatment effects at the Month 15 endpoint were estimated based on differences between least squares (LS) means. Accompanying 95% CIs for the LS mean differences between paliperidone palmitate, and placebo were presented. The change from double-blind baseline in HAM-D-17 score was analyzed using ANCOVA model. The treatment group differences were analyzed using an ANCOVA model. The model will include treatment, concomitant medication stratum, and country as fixed effect design factors, and baseline HAM-D-17 total score as a covariate. Using this model, treatment effects estimated based on differences between LS means. Accompanying 95% CIs for the LS mean differences was presented.

2.4.3. Discussion on clinical efficacy

As requested by the CHMP, the MAH has submitted pharmacokinetic data on switch from oral paliperidone to paliperidone palmitate with the current application. The population pharmacokinetic model is adequately validated and appears to support the claim that the steady state exposures are similar between oral paliperidone PR and paliperidone palmitate LAI. The recommended dosing during a switch between oral paliperidone PR and paliperidone palmitate LAI is also supported by the present model. While the proposed dosing results in temporarily higher exposures for patients switching from a

maintenance treatment of 3 mg oral paliperidone PR, the possibility to individualize the dosing, as stated in the current SmPC, appears adequate.

Study SCA-3004 was a randomized, double-blind, placebo-controlled, parallel-group study to evaluate the efficacy and safety of paliperidone palmitate, as monotherapy or as an adjunct to mood stabilizers or antidepressants, relative to placebo in delaying the time to relapse in subjects with schizoaffective disorder. The study consisted of 4 periods: Screening (up to 7 days), Lead-in (13 weeks), stabilization (12 weeks), and relapse prevention (15 months). A total of 921 subjects were screened, 667 subjects were enrolled in the open-label lead-in period, and 432 subjects entered the open-label stabilization period. Of the 432 subjects who entered the open-label stabilization period, 334 subjects were randomized to the double-blind relapse prevention period (170 subjects to the placebo group and 164 subjects to the paliperidone palmitate group). The randomisation and the measures taken to preserve the blinding seem adequate. Subjects were men and women ≥18 years of age with a lifetime and current diagnosis of schizoaffective disorder.

More subjects in the paliperidone palmitate, 59.9% (100/164), than in the placebo group 38.2% (65/170) completed the study. The difference in the number of subjects discontinuing early was foremost due to the difference in the number of subjects experiencing a relapse. The most prominent other reasons for early discontinuations were, in both groups, withdrawal of consent followed by lost to follow-up in the placebo group and adverse events in the active group respectively. Reasons for early withdrawals have been summarized and median follow-up time (including range) in the double-blind period of the study has been provided by the company after CHMP request (RSI). While both the mean and the median was approximately 9 months in the placebo arm, mean exposure in the paliperidone palmitate arm was 11 months with a median of >14 months mirroring that 61% (100/164) completed the study (i.e. the 15 month treatment period) in the paliperidone palmitate group to be compared to 38.2% (65/170) in the placebo arm. The difference between the groups was, as already concluded, mainly due to the difference in relapse pattern. Regarding time to withdrawal of consent (the most prominent reason for early discontinuation besides relapse), both the mean and median was similar in both groups but concerned more subjects in the placebo arm, 30/170 (17.6%), than in the active arm, 19/164 (11.6%).

The primary efficacy end point for the study was the time between day 1 of the double-blind period and the first documentation of a relapse during the double-blind relapse prevention period.
A greater proportion of subjects in the placebo group (57 subjects [33.5%]) experienced a relapse compared to the paliperidone palmitate group (25 subjects [15.2%]). Continued treatment with paliperidone palmitate was associated with a significant delay in time to relapse compared with placebo ($p<0.001$). The risk (hazard) of relapse was 2.49 (95% confidence interval [CI]: 1.55, 3.99; $p<0.001$) fold higher for a subject who was switched to placebo than for a subject who continued to receive paliperidone palmitate in the double-blind period.

In addition, a Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. For subjects with manic and depressive type relapses, analysis by type of relapse showed a significantly longer time to relapse for subjects who continued on paliperidone palmitate in the double-blind period compared to placebo ($p=0.009$ and $p=0.004$, respectively).

Analysis of the subgroup of subjects on adjunctive therapy and monotherapy demonstrated that the risk of relapse was 2.03 or 3.38 times greater with the placebo group in adjunctive antidepressant/mood stabilizer treatment or in monotherapy, respectively (hazard ratio (HR) 2.03; 95% CI 1.11-3.68; p=0. 021 and HR 3.38; 95% CI 1.57-7.28; $p=0.002$). The difference in efficacy between the two groups was less pronounced in the concomitant medication stratum probably due to a higher relapse rate in this stratum (compared to the monotherapy stratum) in the paliperidone palmitate group. For subjects who received antidepressants as adjunctive therapy, 15 subjects (37.5%) in the placebo group and 7 subjects (18.4%) in the paliperidone palmitate group experienced a relapse in the double-blind period ($p=0.051$).

This is considered to contribute to a conclusion of a benefit of paliperidone palmitate regarding effect on also depressive symptoms.

An analysis of time to early discontinuation for any reason, including relapses, was performed. Median time to all cause discontinuation in the placebo group was less than 9 months while not reached and hence, could not be estimated in the active group. According to the SAP an analysis of early discontinuation not including relapses was also planned but has not been found in the study report. For completeness, and to clarify time to early discontinuations for reason besides relapses, this analysis was requested by the CHMP (RSI). Besides the difference in relapse pattern, there was a difference, although smaller, also in the proportion of subjects discontinuing treatment for other reasons than relapses; in the paliperidone palmitate group 23.8% (39/164) compared to 28.2% (48/170) in the placebo group. The MAH has performed two analyses of time to early discontinuation not including relapses. The analysis not including relapses as event and with subjects experiencing a relapse censored is considered the most appropriate since those with a relapse contribute to the subjects in risk of discontinuing. Looking at the Kaplan-Meier curves, there was a difference between the treatment arms with the survival curves separating after approximately 5 to 6 months of follow-up. The CHMP considered this issue as resolved.

For the key secondary endpoint, Personal and Social Performance Scale (PSP), the change in score from double-blind baseline was analyzed using a MMRM model. The analysis was pre-identified as the primary analysis, and was based on observed data collected at each time point without carrying forward previous values. A significant difference (p=0.014) in favor of paliperidone palmitate was demonstrated when comparing the mean change from baseline at Month 15 (Week 64) using the MMRM approach (treatment difference 3.3; 95% CI: 0.68, 5.95). While the MMRM analysis can be questioned considering the missing at random (MAR) assumption, several sensitivity analyses were performed based on missing not at random (MNAR). Overall, the results were consistent in that the outcome was in favor of paliperidone palmitate although not always statistically significant. The estimated difference between the groups did hence differ depending on analysis with the “worst” outcome in two sensitivity analyses using imputation of worsening LOCF values in the paliperidone palmitate group only. Overall, they are considered to support a difference in favour of paliperidone palmitate, although the size of treatment efficacy could be discussed.

For each of the additional secondary efficacy analyses of PANSS total score, HAM-D-21 score, HAM-D-17 score, YMRS score, and CGI-S-SCA overall score in the DB period there was a statistically significant difference between treatment groups (change from double-blind baseline to end point) in favor of paliperidone palmitate. Analyses were performed with an analysis of covariance (ANCOVA) model using both Last Observation Carried Forward (LOCF) and observed cases. No additional sensitivity analyses were planned. While the results for secondary efficacy endpoints in the analyses based on LOCF all showed statistically significantly differences in favour of paliperidone, the same was not true for the analyses based on completed subjects (observed cases). This concerned foremost PANSS total score, HAM-D-21 and HAM-D-17 respectively. The difference seen may hence to some extent have depended on a difference between groups in withdrawal pattern and, the use of LOCF. While more subjects experiencing a relapse is proof of benefit for paliperidone palmitate, treatment discontinuations for other reasons (than relapses) may have contributed to the differences shown. The difference in proportion of subjects discontinuing was not substantial, 48/170 (28.2%) in the placebo group and 39/164 (23.8%) in the active group but the reasons for early discontinuations differed. The CHMP requested a discussion and additional (sensitivity) analyses for clarification regarding the potential impact on the outcome considering the use of LOCF was requested (RSI). The MAH provided additional sensitivity analyses. While LOCF in this case may have been conservative with subjects in the placebo arm dropping-out earlier, the appropriateness of using LOCF is also depending on the reason for withdrawal. While foremost due to relapse the difference in proportion of subjects discontinuing was considered in support of active treatment in the primary analysis. The additional analyses provided all seem to support that there was a statistically significant difference between paliperidone palmitate and placebo also regarding HAM-D-17 outcomes. While the difference shown may be considered modest, the interpretation may need to take into account the limitations due to the design of study SCA-3004; i.e. of those who were randomised into

the double-blind relapse period, approximately 80% were in remission at baseline and, relapse criteria were designed to identify early indicators of relapse.

There was a statistically significant (p=0.010) difference between treatment groups in favor of paliperidone palmitate also on the patient reported outcome, Medication Satisfaction Questionnaire.

The HAM-D 21 scale has been criticized because it is not validated for schizoaffective disorder and also includes symptoms that could be attributed to psychosis/mania. For that reason, the CHMP recommended in a previous procedure [EMEA/H/C/000746/II/00239] that the HAM-D-17 scale should be used. For the current application, both HAM-D-21 and HAM-D-17 were used, and statistically significant results in favor of the active group were shown for both scales.

In the two 6-week studies submitted in 2009 for the schizoaffective indication, the change in PANSS total score was clearly less pronounced in patients on concomitant treatment with antidepressants/mood stabilizers compared with patients on monotherapy. In the current study SCA-3004, the results for the PANSS in the OL phase were similar for both groups. The MAH did not present a separate analysis for the DB phase regarding PANSS and YMRS, this should be provided. Of note, in the two 6-week studies mentioned above no effect was observed in patients who were treated with both antidepressants and mood stabilizers. These patients were excluded from the current study SCA-3004. For relapse rate, a trend for a more pronounced effect was noted in the monotherapy group (hazard ratio 3.38) vs. the adjunctive therapy group (hazard ratio 2.03) in study SCA-3004 (Fig. 7). The effect on relapse rate was statistically significant vs. placebo for both groups.

2.4.4. Conclusions on the clinical efficacy

The submitted study SCA-3004 has demonstrated that paliperidone palmitate when compared with placebo significantly delays relapse in subjects with schizoaffective disorder which supports maintenance of efficacy for paliperidone palmitate.

Analysis of the subgroup of subjects on adjunctive therapy and monotherapy demonstrated that the risk of relapse was greater with the placebo group in adjunctive antidepressant/mood stabilizer treatment or in monotherapy, respectively. A benefit for paliperidone palmitate compared to placebo was also shown, although borderline (p=0.051), in the subgroup of subjects who received antidepressants as adjunctive therapy. In addition, a Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. For subjects with manic and depressive type relapses, analysis by type of relapse showed a significantly longer time to relapse for subjects who continued on paliperidone palmitate in the double-blind period compared to placebo. Overall, those analyses are considered to contribute to a conclusion of a benefit of paliperidone palmitate regarding effect on also depressive symptoms.

The results for secondary efficacy variables, including PANSS, YMRS and HAM-D, show a statistically significant effect in favour of paliperidone palmitate and seem to support a conclusion of the benefit of paliperidone palmitate as maintenance treatment.

2.5. Clinical safety

Patient exposure

Adverse events
Treatment emergent adverse events

Open-label

In the open-label period, 62.5% of the 667 subjects reported at least 1 treatment-emergent adverse event (TEAE). Moreover, there were 50 subjects (7.5%) who reported TEAEs that resulted in treatment

discontinuation, and 54 subjects (8.1%) who experienced 1 or more serious adverse events (SAEs). Three subjects (0.4%) died during the open-label period (Table 1).

Table 1: Overall Summary of Treatment-Emergent Adverse Events During Open-Label Period ITT Analysis Set (Study SCA-3004)

	Adjunctive Therapy	Monotherapy	All Open-Label
Analysis set: Open-Label ITT	347	320	667
Subjects with TEAE	220 (63.4%)	197 (61.6%)	417 (62.5%)
Possibly related TEAE[a]	159 (45.8%)	162 (50.6%)	321 (48.1%)
TEAE leading to death	2 (0.6%)	1 (0.3%)	3 (0.4%)
1 or more serious TEAE	30 (8.6%)	24 (7.5%)	54 (8.1%)
TEAE leading to treatment discontinuation[b]	29 (8.4%)	21 (6.6%)	50 (7.5%)

[a] Study drug relationship of possible, probable, and very likely are included in this category.
[b] Including subjects who discontinued during Double-Blind Phase with adverse event action taken as DRUG WITHDRAWN, but the onset of adverse event was in the Open-Label Phase.
Percentages calculated with the number of subjects in each group as denominator.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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[TSFAE01.rtf] [JNJ-16977831/SCA3004/DBR_FINAL/RE_CSROL/tsfae01.sas] 10MAR2014, 11:22

Treatment emergent adverse events

Double-blind

The numbers of subjects who reported at least 1 TEAE were 95 subjects (55.9%) and 106 subjects (64.6%) in the placebo group and the paliperidone palmitate group, respectively. Furthermore, subjects in the placebo group reported a higher incidence of SAEs (16 subjects [9.4%]), compared to subjects in the paliperidone palmitate group (9 subjects [5.5%]). In addition, 2 subjects (1.2%) in the paliperidone palmitate group died during the double-blind period (Table 2).

Table 2: Overall Summary of Treatment-Emergent Adverse Events During Double-Blind Period ITT Analysis Set (Study SCA-3004)

	Placebo	PP1M
Analysis set: Double-Blind ITT	170	164
Subjects with TEAE	95 (55.9%)	106 (64.6%)
Possibly related TEAE[a]	38 (22.4%)	64 (39.0%)
TEAE leading to death	0	2 (1.2%)
1 or more serious TEAE	16 (9.4%)	9 (5.5%)
TEAE leading to treatment discontinuation[b]	3 (1.8%)	9 (5.5%)

Note: Percentages calculated based on the ITT population.
[a] Study drug relationship of possible, probable, and very likely are included in this category.
[b] Excludes subjects who discontinued during Double-Blind Phase with adverse event action taken as DRUG WITHDRAWN, but the onset of adverse event was in the Open-Label Phase.
Reported dictionary version: MedDRA 16.1.
Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events.
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Adverse Events

Treatment emergence adverse events

Open-label
The occurrence of common TEAEs (in at least 2% of subjects) is summarized in Table 3. The most frequently observed adverse events were coded to the Nervous System and Psychiatric Disorders system organ classes (SOCs) in 29.8% and 21.9% of subjects, respectively. The most common TEAEs (in ≥5% of subjects) were akathisia (11.1%), injection site pain (10.6%), insomnia (10.0%),

weight increased (8.5%), parkinsonism (6.4%), and headache (5.4%). Most adverse events were mild or moderate in intensity.
There were no notable differences between subjects in the monotherapy groups and adjunctive therapy. In the open-label period, the investigator considered majority of TEAEs (48.1%) to be related to study drug). The TEAEs that were most frequently considered probably related to study drug coded to th SOCs of Nervous System Disorders (47 subjects, 7.0%), and General Disorders and Administration Site Conditions (11 subjects, 1.6%).

Table 3: At Least 2% of Subjects Experiencing Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Open-Label ITT Analysis Set (Study SCA-3004)

	Adjunctive Therapy	Monotherapy	All Open-Label
Number of subjects	347	320	667
Subjects with TEAE	220 (63.4%)	197 (61.6%)	417 (62.5%)
Body system / Preferred term			
Endocrine Disorders	7 (2.0%)	2 (0.6%)	9 (1.3%)
Hyperprolactinaemia	7 (2.0%)	2 (0.6%)	9 (1.3%)
Gastrointestinal Disorders	54 (15.6%)	39 (12.2%)	93 (13.9%)
Constipation	6 (1.7%)	8 (2.5%)	14 (2.1%)
Diarrhoea	11 (3.2%)	9 (2.8%)	20 (3.0%)
Dry Mouth	7 (2.0%)	8 (2.5%)	15 (2.2%)
Nausea	11 (3.2%)	6 (1.9%)	17 (2.5%)
Vomiting	7 (2.0%)	4 (1.3%)	11 (1.6%)
General Disorders And Administration Site Conditions	64 (18.4%)	64 (20.0%)	128 (19.2%)
Fatigue	11 (3.2%)	9 (2.8%)	20 (3.0%)
Injection Site Pain	35 (10.1%)	36 (11.3%)	71 (10.6%)
Infections And Infestations	39 (11.2%)	28 (8.8%)	67 (10.0%)
Upper Respiratory Tract Infection	6 (1.7%)	8 (2.5%)	14 (2.1%)
Investigations	36 (10.4%)	32 (10.0%)	68 (10.2%)
Weight Increased	32 (9.2%)	25 (7.8%)	57 (8.5%)
Metabolism And Nutrition Disorders	25 (7.2%)	17 (5.3%)	42 (6.3%)
Decreased Appetite	7 (2.0%)	3 (0.9%)	10 (1.5%)
Increased Appetite	9 (2.6%)	9 (2.8%)	18 (2.7%)
Musculoskeletal And Connective Tissue Disorders	23 (6.6%)	23 (7.2%)	46 (6.9%)
Arthralgia	8 (2.3%)	6 (1.9%)	14 (2.1%)
Nervous System Disorders	102 (29.4%)	97 (30.3%)	199 (29.8%)
Akathisia	35 (10.1%)	39 (12.2%)	74 (11.1%)
Dyskinesia	5 (1.4%)	9 (2.8%)	14 (2.1%)
Headache	19 (5.5%)	17 (5.3%)	36 (5.4%)
Parkinsonism	25 (7.2%)	18 (5.6%)	43 (6.4%)
Sedation	4 (1.2%)	8 (2.5%)	12 (1.8%)
Somnolence	11 (3.2%)	10 (3.1%)	21 (3.1%)
Tremor	12 (3.5%)	11 (3.4%)	23 (3.4%)
Psychiatric Disorders	76 (21.9%)	70 (21.9%)	146 (21.9%)
Insomnia	39 (11.2%)	28 (8.8%)	67 (10.0%)
Schizoaffective Disorder	10 (2.9%)	10 (3.1%)	20 (3.0%)
Suicidal Ideation	14 (4.0%)	17 (5.3%)	31 (4.6%)
Reproductive System And Breast Disorders	23 (6.6%)	23 (7.2%)	46 (6.9%)
Amenorrhoea	11 (3.2%)	7 (2.2%)	18 (2.7%)
Erectile Dysfunction	2 (0.6%)	7 (2.2%)	9 (1.3%)

Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 16.1.
Incidence is based on number of subjects, not the number of events.

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Double-blind

The prevalence of common TEAEs (in at least 2% of subjects) is described in Table 4. The TEAEs that were reported with a higher frequency in the paliperidone palmitate group than in the placebo group (a 2% difference or more between groups) were: weight increased (8.5% vs. 4.7%), nasopharyngitis (5.5% vs. 3.5%), headache (5.5% vs. 3.5%), hyperprolactinaemia (4.3% vs. 1.2%), and pyrexia (3.7% vs. 1.2%). There was a higher incidence of the following TEAEs in the placebo group than in the paliperidone palmitate group (a 2% difference or more between groups): insomnia (7.1% vs. 4.9%) and schizoaffective disorder (5.9% vs. 3.0%). It should be noted that most adverse events were mild or moderate in intensity. In the placebo group, there were 66 subjects (38.8%) and 43 subjects (25.3%) who reported adverse events that were mild and moderate in intensity, respectively. In the paliperidone palmitate, there were 84 subjects (51.2%) and 52 subjects (31.7%) who reported adverse events that were mild and moderate in intensity, respectively.

In the double-blind period, the investigator identified 69 subjects (42.1%) in the paliperidone palmitate group as having TEAEs considered not related to study drug, and 64 subjects (39.0%) as having TEAEs considered related to study drug. In the placebo group, the investigator determined that the majority of subjects (79 subjects, 46.5%) had TEAEs considered not related to study drug in contrast to 38 subjects (22.4%) who had TEAEs considered related to study drug. Furthermore, TEAEs considered related to study drug with the highest number of subjects in both the placebo and PP1M groups (12 subjects [7.1%] in placebo and 16 subjects [9.8%] in paliperidone palmitate were coded to the SOC of Nervous System Disorders.

Table 4: At Least 2% of Subjects Experiencing Treatment-Emergent Adverse Events by System Organ Class and Preferred Term – Double-Blind ITT Analysis Set (Study SCA-3004)

	Placebo	PP1M
Number of subjects	170	164
Subjects with TEAE	95 (55.9%)	106 (64.6%)
Body system / Preferred term		
Endocrine Disorders	3 (1.8%)	7 (4.3%)
Hyperprolactinaemia	2 (1.2%)	7 (4.3%)
Gastrointestinal Disorders	16 (9.4%)	18 (11.0%)
Diarrhoea	2 (1.2%)	4 (2.4%)
Toothache	2 (1.2%)	5 (3.0%)
General Disorders And Administration Site Conditions	5 (2.9%)	14 (8.5%)
Pyrexia	2 (1.2%)	6 (3.7%)
Infections And Infestations	22 (12.9%)	30 (18.3%)
Nasopharyngitis	6 (3.5%)	9 (5.5%)
Upper Respiratory Tract Infection	4 (2.4%)	7 (4.3%)
Urinary Tract Infection	4 (2.4%)	5 (3.0%)
Investigations	19 (11.2%)	32 (19.5%)
Blood Prolactin Increased	2 (1.2%)	4 (2.4%)
Glycosylated Haemoglobin Increased	4 (2.4%)	2 (1.2%)
Weight Decreased	2 (1.2%)	5 (3.0%)
Weight Increased	8 (4.7%)	14 (8.5%)
Nervous System Disorders	18 (10.6%)	26 (15.9%)
Akathisia	3 (1.8%)	5 (3.0%)
Headache	6 (3.5%)	9 (5.5%)
Tremor	4 (2.4%)	2 (1.2%)
Psychiatric Disorders	38 (22.4%)	29 (17.7%)
Anxiety	4 (2.4%)	3 (1.8%)
Depression	1 (0.6%)	4 (2.4%)
Insomnia	12 (7.1%)	8 (4.9%)
Psychotic Disorder	5 (2.9%)	2 (1.2%)
Schizoaffective Disorder	10 (5.9%)	5 (3.0%)
Suicidal Ideation	4 (2.4%)	5 (3.0%)
Respiratory, Thoracic And Mediastinal Disorders	6 (3.5%)	10 (6.1%)
Cough	2 (1.2%)	5 (3.0%)

Note: Percentages calculated based on the ITT population.
Reported dictionary version: MedDRA 16.1.
Incidence is based on number of subjects, not the number of events.

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Serious adverse event / deaths / other significant events

Deaths

Open-label
During the open-label period of the study, 3 subjects died.

A 55-year-old white woman died as a consequence of cardiogenic shock and coma. It should be noted that the subject had a history of anemia, pneumonia, candidiasis of the esophagus, and chronic nonspecific esophagitis that were ongoing at the time of enrollment. Nine days after the first dose of open-label study drug, the subject became unexpectedly sedated and was hospitalized. She died the following day. The autopsy report determined the cause of death as bilateral pneumonia. This contributed to dystrophic changes in the myocardium and

acute cardiovascular failure. The investigator provided an alternative etiology that *Ascaris lumbricoides* contamination resulted in the inhalation of Ascaris larvae. This led to chronic pneumonia with dystrophic changes in the myocardium. In turn, this contributed to the development of Frederick syndrome and shock condition. Resultantly, the subject lapsed into a coma and died. The investigator considered the cardiogenic shock to be doubtfully related to the study drug whereas the coma was considered not to be related to the study drug.

A 52-year-old white man died from completed suicide. At the time of study entry, the subject displayed symptoms of mania and acute psychosis. Fourteen days after receiving his last dose of study drug, the subject committed suicide. It should be noted that the subject had no prior history of suicidal behavior and C-SSRS was negative for suicidal thoughts and suicidal behavior throughout the study. The investigator considered the event as possibly related to study drug.

A 59-year-old African-American woman died from a myocardial infarction. The subject had a history of osteoarthritis, obesity, hypothyroidism, HIV infection and insomnia that were ongoing at the time of enrollment. She was on concomitant treatment (Viramune® and Trizivir®). The subject died 13 days after her last dose of study drug. The investigator considered the event doubtfully related to study drug.

Double-blind
During the double-blind period of the study, 2 subjects (both in the PP1M group) died.

A 58-year-old African-American man with a history of hypertension and type 2 diabetes mellitus died from coronary artery disease. Following completion of the open label period of the study, the subject was randomized to continue receiving PP1M in the doubleblind period. The death certificate identified the cause of death as coronary artery disease secondary to hypertension. The investigator considered the event not related to study drug.

A 40-year-old African-American man who died due to an unknown event. His death occurred on an unspecified date approximately 4 months after the last injection of study drug (placebo). The investigator considered the event not related to study drug. As the timing of the event fell outside the allocated study window, the death of this subject was not included in the clinical database. The death of the subject is documented in a subject narrative as having experienced a SAE of suicidal ideation before being withdrawn from the study due to missing a scheduled study visit.

In addition, there was another death reported for a subject who had withdrawn from the study. Subject was a 28-year-old white man who died from an overdose of an unknown type of sleeping pill. Having completed the open-label period of the study, the subject was randomized to continue receiving paliperidone palmitate in the double-blind period. The investigator determined the event as not related to study drug.

Serious Adverse Events

Open-label
During the open-label period, there was at least 1 SAE reported in 54 subjects (8.1 %). The majority (77.8%) of reported SAEs belonged to the Psychiatric Disorders SOC. The most frequently occurring events (in ≥2% of open-label subjects) were schizoaffective disorder and suicidal ideation in 16 subjects (2.4%) and 15 subjects (2.2%), respectively (Table 5).

Table 5: Incidence of Serious Treatment-Emergent Adverse Events – Open-Label ITT Analysis Set (Study SCA-3004)

	Adjunctive Therapy	Monotherapy	All Open-Label
Number of subjects	347	320	667
Subjects with Serious TEAE	30 (8.6%)	24 (7.5%)	54 (8.1%)
Body system / Preferred term			
Cardiac Disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Atrioventricular Block Complete	1 (0.3%)	0	1 (0.1%)
Cardiogenic Shock	1 (0.3%)	0	1 (0.1%)
Myocardial Infarction	0	1 (0.3%)	1 (0.1%)
Gastrointestinal Disorders	2 (0.6%)	0	2 (0.3%)
Colitis	1 (0.3%)	0	1 (0.1%)
Vomiting	1 (0.3%)	0	1 (0.1%)
General Disorders And Administration Site Conditions	0	1 (0.3%)	1 (0.1%)
Hyperthermia	0	1 (0.3%)	1 (0.1%)
Hepatobiliary Disorders	1 (0.3%)	0	1 (0.1%)
Cholelithiasis	1 (0.3%)	0	1 (0.1%)
Infections And Infestations	2 (0.6%)	0	2 (0.3%)
Diverticulitis	1 (0.3%)	0	1 (0.1%)
Lobar Pneumonia	1 (0.3%)	0	1 (0.1%)
Injury, Poisoning And Procedural Complications	0	1 (0.3%)	1 (0.1%)
Multiple Injuries	0	1 (0.3%)	1 (0.1%)
Nervous System Disorders	1 (0.3%)	0	1 (0.1%)
Coma	1 (0.3%)	0	1 (0.1%)
Psychiatric Disorders	23 (6.6%)	19 (5.9%)	42 (6.3%)
Completed Suicide	1 (0.3%)	0	1 (0.1%)
Confusional State	0	1 (0.3%)	1 (0.1%)
Depression	1 (0.3%)	0	1 (0.1%)
Depression Suicidal	1 (0.3%)	0	1 (0.1%)
Depressive Symptom	1 (0.3%)	1 (0.3%)	2 (0.3%)
Hallucination, Auditory	1 (0.3%)	0	1 (0.1%)
Homicidal Ideation	1 (0.3%)	0	1 (0.1%)
Mania	1 (0.3%)	2 (0.6%)	3 (0.4%)
Paranoia	1 (0.3%)	0	1 (0.1%)
Psychotic Disorder	2 (0.6%)	2 (0.6%)	4 (0.6%)
Restlessness	1 (0.3%)	0	1 (0.1%)
Schizoaffective Disorder	9 (2.6%)	7 (2.2%)	16 (2.4%)
Suicidal Ideation	7 (2.0%)	8 (2.5%)	15 (2.2%)
Suicide Attempt	1 (0.3%)	1 (0.3%)	2 (0.3%)
Renal And Urinary Disorders	1 (0.3%)	0	1 (0.1%)
Bladder Prolapse	1 (0.3%)	0	1 (0.1%)
Surgical And Medical Procedures	0	1 (0.3%)	1 (0.1%)
Therapy Regimen Changed	0	1 (0.3%)	1 (0.1%)
Vascular Disorders	1 (0.3%)	1 (0.3%)	2 (0.3%)
Deep Vein Thrombosis	1 (0.3%)	1 (0.3%)	2 (0.3%)

Percentages calculated with the number of subjects in each group as denominator.
Reported dictionary version: MedDRA 16.1.

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Double-blind

During the double-blind period, the number of subjects that reported at least 1 SAE in the paliperidone palmitate group and the placebo group was 9 subjects (5.5%) and 16 subjects (9.4%), respectively. In addition, the greater proportion of reported SAEs belonged to the Psychiatric Disorders SOC. Furthermore, schizoaffective disorder was the only SAE that was reported by more than 2 subjects (placebo group, 7 subjects [4.1%]) (Table 6).

Table 6: Incidence of Serious Treatment-Emergent Adverse Events – Double-Blind ITT Analysis Set (Study SCA-3004)

	Placebo	PP1M
Number of subjects	170	164
Subjects with Serious TEAE	16 (9.4%)	9 (5.5%)
Body system / Preferred term		
Cardiac Disorders	0	2 (1.2%)
Cardiac Failure Congestive	0	1 (0.6%)
Congestive Cardiomyopathy	0	1 (0.6%)
Coronary Artery Disease	0	1 (0.6%)
Ear And Labyrinth Disorders	1 (0.6%)	0
Meniere's Disease	1 (0.6%)	0
Gastrointestinal Disorders	0	1 (0.6%)
Gastrooesophageal Reflux Disease	0	1 (0.6%)
General Disorders And Administration Site Conditions	0	1 (0.6%)
Chest Pain	0	1 (0.6%)
Infections And Infestations	0	1 (0.6%)
Bronchitis	0	1 (0.6%)
Injury, Poisoning And Procedural Complications	2 (1.2%)	1 (0.6%)
Brain Contusion	1 (0.6%)	0
Overdose	0	1 (0.6%)
Road Traffic Accident	1 (0.6%)	0
Nervous System Disorders	1 (0.6%)	0
Viith Nerve Paralysis	1 (0.6%)	0
Psychiatric Disorders	12 (7.1%)	5 (3.0%)
Delusion	1 (0.6%)	0
Depression	0	2 (1.2%)
Mania	1 (0.6%)	0
Psychotic Disorder	2 (1.2%)	2 (1.2%)
Schizoaffective Disorder	7 (4.1%)	1 (0.6%)
Suicidal Ideation	2 (1.2%)	0

Note: Percentages calculated based on the ITT population.
Reported dictionary version: MedDRA 16.1.

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Other Adverse Events of Clinical Interest

Open-label

Extrapyramidal Syndrome(EPS)-related Adverse Events

The prevalence of EPS-related TEAEs in subjects during the open-label period was 23.2%. This included a similar percentage of subjects from the monotherapy groups (24.4%) and adjunctive therapy (22.2%). Akathisia (11.1%), parkinsonism (6.4%), tremor (3.4%) and dyskinesia (2.1%) constituted the most frequently reported EPS-related TEAEs (in >2% of open-label subjects). It should be noted that EPS-related TEAEs resulted in discontinuation for 3 subjects (0.4%) with akathisia, 2 subjects (0.3%) with parkinsonism, and subject (0.1%) with dystonia.

Glucose-related Adverse Events

Glucose-related TEAEs were observed in 6 subjects (0.9%). Three subjects (0.4%) reported diabetes mellitus while the remaining events were reported by 1 subject (0.1%) each. None of these events contributed to discontinuation from the study. An adverse event of glycosylated haemoglobin increased was reported in 1 subject (0.3%) from the monotherapy groups. The adverse event was not

serious and did not result in discontinuation from the study. Moreover, the investigator considered the event to be not related to study drug.

Prolactin-related Adverse Events

A prolactin-related adverse event was reported in 31 female subjects (10.0%) and 32 male subjects (9.0%). The most frequently reported prolactin-related adverse events in female subjects were amenorrhoea (5.8%) and galactorrhoea (2.9%). The most commonly reported prolactin-related adverse events in male subjects were libido decreased (2.8%) and erectile dysfunction (2.5%). Prolactin-related TEAEs resulted in discontinuation from the study for: 4 subjects (0.6%) who experienced erectile dysfunction, 2 subjects (0.3%) with hyperprolactinaemia (1 subject also had a TEAE of amenorrhoea), 1 subject (0.1%) with galactorrhoea, 1 subject (0.1%) with sexual dysfunction, and 1 subject (0.1%) with libido decreased. Narratives for the subjects who discontinued from the study as a result of the prolactin-related AE are provided.

Double-blind

EPS-related Adverse Events

Extrapyramidal syndrome-related TEAEs were reported in both the placebo (12 subjects, 7.1%) and paliperidone palmitate groups (14 subjects, 8.5%). The EPS-related TEAEs that were reported at a higher incidence in the placebo than the PP1M group were tremor (2.4% vs. 1.2%, respectively), dyskinesia (1.8% vs. 0.6%, respectively), and restlessness (1.2% and 0.6%, respectively). Moreover, akathisia was reported more frequently in the paliperidone palmitate group than in the placebo group (3.0% vs. 1.8%, respectively). In the paliperidone palmitate group, the following EPS-related TEAEs were reported in 1 subject (0.6%) each: restless leg syndrome, bradykinesia, and musculoskeletal stiffness. In the placebo group, the following EPS-related TEAEs were reported in 1 subject (0.6%) each: dystonia, muscle spasm, and torticolis. Two subjects (1.2%) in the PP1M group discontinued from the study due to EPS-related TEAEs. Narratives for the 2 subjects are provided in.

Glucose-related Adverse Events

Glucose-related TEAEs were reported in both the placebo (4 subjects, 2.4%) and paliperidone palmitate groups (3 subjects, 1.8%). In the paliperidone palmitate group, Type 2 diabetes mellitus was reported by 2 subjects (1.2%). The remaining events were reported by 1 subject (0.6%) per treatment group. Furthermore, 1 subject (0.6%) in the paliperidone palmitate group discontinued the study due to an adverse event of blood glucose increased. Four subjects (2.4%) from the placebo group and 2 subjects (1.2%) from the paliperidone palmitate group reported an adverse event of glycosylated haemoglobin increased, that was considered related to study drug. None of the events was serious, and none led to discontinuation from the study.

Prolactin-related Adverse Events

Prolactin-related TEAEs were reported in the placebo (5 female subjects, 5.8%) and paliperidone palmitate groups (11 female subjects, 13.9%). Blood prolactin increased was the most prevalent prolactin-related TEAE among women, as reported in 5.1% of paliperidone palmitate subjects and 1.2% of placebo subjects. Prolactin-related TEAEs were reported in 1 male subject (1.2%) in the placebo group and 6 male subjects (7.1%) in the paliperidone palmitate group. The most frequently reported prolactin-related TEAE among men was hyperprolactinaemia, reported by 4.7% of subjects in the paliperidone palmitate group only. No other prolactin- related TEAE was reported by more than 1 male subject. The occurrence of a prolactin-related TEAE of galactorrhoea contributed in 1 subject discontinuing from the study.

2.5.1. Discussion on clinical safety

No new safety concerns are identified. The adverse events reported in open-label and double-blind period were similar to previously conducted studies with paliperidone.
During the open-label period the majority of adverse events were related to the Nervous System and Psychiatric Disorders.
During the double-blind period TEAEs that occurred more frequently in the paliperidone palmitate group than the placebo group were weight increased, nasopharyngitis, headache, hyperprolactinaemia, and pyrexia.
There were 5 cases of death described, 3 in the open- label period and 2 in the double blind period. The case reports regarding death were described as not related to the study drug, which is endorsed

2.5.2. Conclusions on clinical safety

There are no new safety concerns.
The current SmPC describes the known safety profile and there is no need for further update of the Product information

2.5.3. PSUR cycle

The PSUR cycle remains unchanged

The annex II related to the PSUR, refers to the EURD list which remains unchanged.

2.6. Risk management plan

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

No new safety concerns have been identified as part of this extension of indication application.

Long-term safety in patients with schizoaffective disorder has now been provided with results of study SCA-3004, therefore “long-term safety in patients with schizoaffective disorder” is no longer listed as missing information.

The PRAC considered that the risk management plan version 6.0 is acceptable. The PRAC endorsed PRAC Rapporteur assessment report is attached.

2.7. Update of the Product information

Following the results obtained in study SCA-3004, the MAH proposes to amend sections 4.1, 4.2 and 5.1 of the SmPC. The Package Leaflet has been updated accordingly. Other minor editorial and formatting corrections are also proposed to be made.

The MAH’s proposed amendments of these sections are shown below.

In section 4.1, the sentence “Effect on depressive symptoms has not been demonstrated” is proposed to be deleted, and also the restriction to treat only “psychotic and manic symptoms” of schizoaffective disorder in adults. In addition, an editorial correction is proposed to be made, since the statement “Invega is indicated for the treatment of schizophrenia in adults” is a duplication error. The first paragraph of the indication already states that Invega is indicated in the treatment of schizophrenia in the adult population. The following changes to section 4.1 are proposed:

“4.1. Therapeutic indications

INVEGA is indicated for the treatment of schizophrenia in adults and in adolescents 15 years and

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

In section 4.2, the statement "Maintenance of effect has not been studied" is proposed to be deleted:

"4.2. Posology and method of administration

Schizoaffective disorder (adults)
The recommended dose of INVEGA for the treatment of schizoaffective disorder in adults is 6 mg once daily, administered in the morning. Initial dose titration is not required. Some patients may benefit from higher doses within the recommended range of 6 mg to 12 mg once daily. Dosage adjustment, if indicated, should occur only after clinical reassessment. When dose increases are indicated, increments of 3 mg/day are recommended and generally should occur at intervals of more than 4 days. ~~Maintenance of effect has not been studied."~~

A summary of the study results of Study SCA-3004 is proposed to be added to section 5.1:

"5.1. Pharmacodynamic properties

~~Effect on depressive symptoms of schizoaffective disorder and maintenance of effect have were not been studied with INVEGA, but have been demonstrated with the long-acting injectable formulation of paliperidone.~~

An effect of INVEGA on depressive symptoms ~~has~~ was not ~~been~~ demonstrated in this study, but has been demonstrated with the long-acting injectable formulation of paliperidone (described further down in this section).

In a long-term trial designed to assess the maintenance of effect, the long-acting injectable formulation of paliperidone was significantly more effective than placebo in maintaining symptom control and delaying relapse of psychotic, manic, and depressive symptoms of schizoaffective disorder. After having been successfully treated for an acute psychotic or mood episode for 13 weeks and stabilised for an additional 12 weeks with the long-acting injectable formulation of paliperidone (doses ranging from 50 to 150 mg) patients were then randomised to a 15-month double-blind relapse prevention period of the study to either continue on the long-acting injectable formulation of paliperidone or on placebo until they experienced a relapse of schizoaffective symptoms. The study showed a significantly longer time to relapse in patients treated with the long-acting injectable formulation of paliperidone compared to placebo ($p<0.001$).
In addition, the list of local representatives in the PL has been revised to amend contact details for the representatives of FR and IS.

Rapporteur's assessment of the update of product information:

The proposed changes by the MAH are considered acceptable. An annotated SmPC is attached.

2.8. Significance or Non-Conformity of paediatric studies

Not applicable.

3. Benefit-Risk Balance

Benefits

Beneficial effects

Invega (paliperidone) was approved in April 2011 for the treatment of psychotic or manic symptoms in schizoaffective disorder in adults based mainly on two 6-week phase III studies in subjects with schizoaffective disorder (type II variation EMEA/H/C/746/II/0023). As part of the approval of the schizoaffective indication, the MAH committed to provide a maintenance study (R092670-SCA-3004) on

paliperidone palmitate in patients with schizoaffective disorders, and relevant pharmacokinetic data on switch from oral paliperidone to paliperidone palmitate. The population pharmacokinetic model suggests that steady state exposures are similar between the two formulations thus supporting the extrapolation of efficacy between formulations.

The MAH has now provided the clinical study report for the relapse-prevention study SCA-3004 and a PK report on switch from oral paliperidone to paliperidone palmitate. The results of study SCA-3004 show that treatment with paliperidone palmitate resulted in a statistically significant delay in the time to relapse in subjects with schizoaffective disorder. The risk of relapse was 2.49 (95 % CI 1.55, 3.99) higher for a subject who switched to placebo than for a subject who continued to receive paliperidone in the double-blind period. Analysis of the subgroups of subjects on adjunctive therapy and monotherapy demonstrated that the risk of relapse was 2.03 or 3.38 times greater with the placebo group in adjunctive antidepressant/mood stabilizer treatment or in monotherapy, respectively (hazard ratio (HR) 2.03; 95% CI 1.11-3.68; p=0. 021 and HR 3.38; 95% CI 1.57-7.28; p=0.002). A Cox proportional hazards model was extended to include 3 types of mood events: manic, depressive and mixed. For subjects with manic and depressive type relapses, analysis by type of relapse showed a significantly longer time to relapse for subjects who continued on paliperidone palmitate in the double-blind period compared to placebo (p=0.009 and p=0.004, respectively).

For the key secondary endpoint, Personal and Social Performance Scale (PSP), a significant difference (p=0.014) in favor of paliperidone palmitate was demonstrated when comparing the mean change from baseline at Month 15 (Week 64) using the MMRM approach. For each of the additional secondary efficacy analyses of PANSS total score, HAM-D-21 score, HAM-D-17 score, YMRS score, and CGI-S-SCA overall score there was a statistically significant difference between treatment groups (change from double-blind baseline to end point) in favor of paliperidone palmitate.

After re-evaluation of acute antidepressant efficacy in subgroup of subjects with prominent depressive symptoms in pooled data from previously submitted short-term, placebo controlled studies, a statistical and clinically significant improvement in HAM-D-17 total score is shown at the group level. Results were based on LOCF and confirmed with sensitivity analyses (tipping point analysis: up to 10% worsening of all paliperidone palmitate patients who discontinued). The difference in reduction in HAM-D-17 total score between active and placebo group was 3.0 (p=0.002), which is a clinical relevant difference in favor for paliperidone which decreased to 2.0 (p=0.048) after sensitivity analyses.

Uncertainty in the knowledge about the beneficial effects

In obese patients there was almost no difference between groups in the proportion of patients with relapse. The MAH clarified the reasons for this result. The pharmacokinetic analysis does not indicate a significant difference in exposure in obese patients.

In the 6-week studies in schizoaffective disorder submitted with Invega type II variation II-23 (SCA-3001, SCA-3002), it was noted that for psychotic symptoms rated with PANSS total score the effect seen in the overall population was entirely attributed to the subgroup with no lithium use. The applicant provided subgroup analysis based on the concomitant antidepressants which suggested that treatment with paliperidone provided additional antidepressant efficacy in short-term (SCA-3001, SCA-3002) as well as long-term (SCA-3004) studies.

Although the remission analysis (HAM-D-17 total score $\leqslant$7) and responder analysis ($\geqslant$50% improvement in HAM-D-17 score at end point) presented differences favouring paliperidone palmitate treatment, 11.1 %-points (p=0.041) and 11.4 (p=0.054), respectively), the differences decreased to 6.8 and 8.5, respectively when discontinuing patients were assumed as non-responders (data not presented).

Risks

Unfavourable effects

The most frequently observed adverse events were coded to the Nervous System and Psychiatric

Disorders system organ classes (SOCs) in 29.8% and 21.9% of subjects, respectively. The most common TEAEs (in ≥5% of subjects) were akathisia (11.1%), injection site pain (10.6%), insomnia (10.0%), weight increased (8.5%), parkinsonism (6.4%), and headache (5.4%).

In the double-blind period compared to placebo weight increased (8.5% vs. 4.7%), nasopharyngitis (5.5% vs. 3.5%), headache (5.5% vs. 3.5%), hyperprolactinaemia (4.3% vs. 1.2%), and pyrexia (3.7% vs. 1.2%) were described.

Regarding serious adverse events (SAE) in the open label period the majority of reported SAEs belonged to psychiatric disorders SOC - schizoaffective disorders and suicidal ideation. In the double blind period the greater proportion of reported SAE were psychiatric disorders SOC- schizoaffective disorders in 2 subjects, compared to 7 subjects in the placebo group.

Other adverse events of clinical interest were extrapyramidal syndrome (akatisia, parkinsonism, tremor and dyskinesia), glucose related adverse events and prolactin-related adverse events.

There are no new safety concerns. Reported adverse events in the study SCA 3004 are relevantly described and labeled in the SmPC.

Uncertainty in the knowledge about the unfavourable effects

There are no known uncertainties about any unfavourable effects.

Benefit-Risk Balance

Importance of favourable and unfavourable effects

The results of study SCA-3004 show that treatment with paliperidone palmitate resulted in a statistically significant delay in the time to relapse in subjects with schizoaffective disorder.
For each of the secondary efficacy analyses of PSP, PANSS total score, HAM-D-21 score, HAM-D-17 score, YMRS score, and CGI-S-SCA overall score there was a statistically significant ($p<0.001$) difference between treatment groups in favor of paliperidone palmitate.

After re-evaluation of acute antidepressant efficacy in subgroup of subjects with prominent depressive symptoms in pooled data from short-term, placebo controlled studies, the difference in reduction in HAM-D-17 total score between active and placebo group was 3.0 ($p=0.002$), is a clinical relevant difference in favor for paliperidone.

There are no new safety concerns. There is no need for any update of the SmPC. The adverse events reported are described in the SmPC.

Benefit-risk balance

Discussion on the Benefit-Risk Balance

For the current application, the MAH has submitted a long-term maintenance study with paliperidone palmitate and relevant pharmacokinetic data on switching from oral paliperidone to paliperidone palmitate as a post-authorization measure. The population pharmacokinetic model suggests that steady

state exposures are similar between the two formulations thus supporting the extrapolation of efficacy and safety between formulations.

The long-term maintenance study SCA-3004 has demonstrated that paliperidone palmitate when compared with placebo significantly delays relapse in subjects with schizoaffective disorder which supports maintenance of efficacy for paliperidone palmitate. An effect on depressive symptoms of schizoaffective disorder is supported by time to relapse analysis (manic and depressive type) which was longer for subjects who continued on paliperidone palmitate in the double-blind period compared to placebo($p=0.009$ and $p=0.004$, respectively, for manic and depressive type). Moreover, a lower risk of relapse has been observed in paliperidone palmitate group than the placebo group during double-blind period and risk of relapse due to depressive symptoms was higher for the patients in the placebo group (relative risk 3,13 (95% CI: 1.39; 6.98). The mean change in HAM-D-17 total score from baseline of the double-blind period was favourable for active treatment as a significant difference of -2.1 ($p=0.001$) has been observed.
Supportive results are also demonstrated with the analysis of CGI-S-SCA Depressive symptom domain. The subgroup analyses based on the concomitant antidepressants also suggested that treatment with paliperidone provided additional antidepressant efficacy.

The pooled subgroup (HAM-D-17>16) analysis of previously submitted studies SCA-3001 and SCA-3002 is crucial for evaluation of antidepressant efficacy efficacy following short-term treatment. A statistical and clinically significant improvement in HAM-D-17 total score is shown at the group level. A clinical relevant difference in reduction of HAM-D-17 total score between active and placebo group was 3.0 ($p=0.002$) in favour for paliperidone, which is comparable with the results presented by antidepressants in placebo-controlled studies in major depression. This key result is more or less supported in the other presented analyses. The remission analysis (HAM-D-17 total score $\leqslant 7$) and responder analysis ($\geqslant 50\%$ improvement in HAM-D-17 score at end point), presented differences favouring paliperidone palmitate treatment, 11.1 %-points ($p=0.041$) and 11.4 ($p=0.054$), respectively. However, when discontinuing patients were assumed as non-responders (data not presented by the MAH) the differences decreased to 6.8 and 8.5, respectively. As a secondary end-point, improvement in CGI-S-SCA Depressive score has also been evaluated in the pooled data from studies SCA-3001 and -3002 that resulted in favour of paliperidone palmitate.

In summary, the totality of the provided data from short-term and long-term studies supports the efficacy of Invega in reduction of depressive symptoms in schizoaffective disorder as a monotherapy or additional to treatment with antidepressants or mood stabilizers. This conclusion is not only based on statistically and clinically significant improvement in HAM D-17 score in patients with prominent depressive symptoms in the SCA-3004 study. The applicant was also requested to demonstrate via a detailed and comprehensive analysis the short and long-term effects on depressive symptoms and discuss their clinical relevance.
The MAH provided indeed additional analyses of data from patients with prominent depressive symptoms that have participated in the short-term studies SCA-3001 and SCA-3002 as well as the long-term study SCA-3004. The HAM D-17 scale includes the first 17 items in the HAM-D-21 and therefore excludes those items that may be attributed to psychosis/mania. The provided additional analyses have shown significant reduction in HAM D-17 score and favorable remission and response rate in Invega treated patients compared to placebo. Moreover, a lower risk of relapse, particularly due to depressive symptoms, has been shown with long-term treatment in study SCA-3004. These findings are supported by the significant improvements in CGI-S-SCA Depressive score and subgroup analyses based on the concomitant antidepressants which overall suggesting antidepressant efficacy of Invega treatment. Having reviewed the available data, the CHMP considered that the proposed removal of caveats on the effect on depressive symptoms in the SmPc is supported.

There are no new safety concerns. There is no need for any update of the safety sections of the SmPC. The adverse events reported are described in the SmPC.

Conclusion
The benefit risk for Invega in treatment of schizoaffective disorder is positive. Efficacy and safety in maintenance therapy has been demonstrated, as effects on depressive symptoms. The variation is considered approvable.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II

Extension of indication for Invega to include depressive symptom domain of schizoaffective disorder; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. Minor editorial changes have been also introduced throughout the PI. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

The variation proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Extension of indication for Invega to include depressive symptom domain of schizoaffective disorder; as a consequence, sections 4.1, 4.2 and 5.1 of the SmPC have been updated. Minor editorial changes have been also introduced throughout the PI. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Summary

This variation extended the indication for Invega to include depressive symptom domain of schizoaffective disorder based on clinical data showing maintenance of symptom control and delay in relapse of psychotic, manic and depressive symptoms for the long acting injectable formulation of paliperidone.

Please refer to Scientific Discussion Invega-H-C-746-II-43