Clinical Study Report

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Name of Sponsor/Company	Janssen-Cilag Australia Pty Ltd
Name of Finished Product	INVEGA®
Name of Active Ingredient(s)	Paliperidone Extended Release (ER)

Protocol No.: CR013213

Title of Study: An open label multicentre study to determine the dose distribution of Paliperidone ER OROS® in patients with schizophrenia

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(Note: italicised investigators symbolise either prior principal investigators or joint/assistant principal investigators)

Publication (Reference): None

Study Period: The first patient consented to participate in the study on 18APR2007 and the last patient visit occurred on 04AUG2009. Database lock occurred on 14DEC2009.

Phase of Development: IIIb

OBJECTIVES:

The primary objective of this trial was to determine the dose distribution of paliperidone ER OROS® (from here on in to be referred to as paliperidone ER) in patients with schizophrenia. The primary endpoint was the mean modal prescribed daily dose of paliperidone ER from Day 1 to 84 inclusive. Other measures of prescribed dose distribution such as median modal prescribed daily dosage, overall average daily-prescribed dose from week 0 to 12 and mean and median modal doses for days 57 to 84 inclusive were also calculated.

The secondary study objectives are to:

- Assess clinical efficacy (CGI and GAF) of paliperidone ER;
- Evaluate the safety of paliperidone ER;
- Assess long-term treatment outcomes of paliperidone ER for all patients that enter Phase B.

METHODS:

This was a non-randomised, single-arm, open label, multicentre study aimed to evaluate the dose distribution, efficacy and safety in patients with schizophrenia who were switched from an oral atypical antipsychotic to paliperidone ER. Newly diagnosed patients were also included in the study. The recommended paliperidone ER dose was 6 mg once daily, a flexible dosing regime was utilised for this study, which enabled the initial recommended dose (and subsequent doses) to range from 3 to 12 mg once daily. The study duration was split into two phases:- Phase A was 12 weeks (days 0 to 84); and Phase B, which was an optional follow up phase, was 40 weeks (days 85 to 365).

An interim analysis was planned for the first 50 patients who completed 12 weeks of study (completed or withdrawn) to determine the dose distribution in a time early enough for anticipated reimbursement submissions. However, this interim analysis was not conducted.

Number of Subjects (planned and analyzed):

The planned total sample size for this study of 100 patients was not met. There were 64 patients enrolled. Of these 64 enrolled patients, 59 patients completed Phase A and 32 patients completed Phase B.

Due to the number of enrolled patients being substantially less than the number planned it was decided that further reducing the number of patients to conduct the Per Protocol (PP) analyses would not be worthwhile.

Diagnosis and Main Criteria for Inclusion:

Male or female patients aged between 18 and 65 years (inclusive); with a diagnosis of schizophrenia (assessed using DSM-IV); who required initiation or change in antipsychotic therapy due to lack of efficacy/tolerability; who were out-patients or in-patients (with expected discharge within 8 weeks); and who provided informed consent were eligible to enroll in this study.

Patients were excluded if they had had a CGI-S score of 6 or 7; had taken clozapine during the last 3 months; had a history or current symptoms of tardive dyskinesia; had a serious unstable medical condition; had received a long acting injectable antipsychotic medication within a period equal to or less than the injection's specified treatment interval; or, in the opinion of the investigator, were resistant to antipsychotic treatment. Patients were also excluded if they were in-patients who had been hospitalized for longer than 8 continuous weeks during the past 6 months.

Revisions to the inclusion/exclusion criteria were made in the 1st and 3rd (dated: 29th August 2007) protocol amendments.
Revisions and additions are shown in bold and deletions by a strikethrough.
Inclusion Criteria (Amendment INT-1)
• Patients who require initiation, or a change in antipsychotic therapy due to lack of efficacy or tolerability
Exclusion Criteria (Amendment INT-3)
~~• On a long acting injectable antipsychotic medication during the last 3 months~~
• Have received a long acting injectable antipsychotic medication within a period equal to or less than the injection's specified treatment interval
• In-patients who have been hospitalized **for an index psychotic episode** for longer than 8 continuous weeks during the past 6 months

The addition of the inclusion criterion was to ensure clarification of patient population. The exclusion criteria also changed to ensure clarification of patient population as well as to adapt to treatment intervals for long acting injectable antipsychotic medication that differ from a period of 3 months.

Test Product, Dose and Mode of Administration, Batch No.:

The test product was paliperidone ER tablets in 3-, 6-, 9-mg strengths. Doses ranged from 3mg to 12 mg orally once daily. Batch numbers for tablets in 3-, 6-, 9-mg strengths were 0620766, 0617714 and 0602601 respectively.

Reference Therapy, Dose and Mode of Administration, Batch No.:

Not Applicable, this was an open-label, single-arm study.

Duration of Treatment:

The duration of treatment, consisting of a once daily dose of paliperidone ER (recommended range of 3 to 12mg), depended on whether the patient chose to participate in the optional follow up phase. The study duration was split into two phases. Phase A was 12 weeks and Phase B, which was an optional follow up phase, was 40 weeks.

A patient was to discontinue study treatment if the patient became pregnant, or, the investigator believed that for safety reasons (e.g., adverse event) it is in the best interest of the patient to stop treatment. The investigator discontinued one patient, although the reason for this decision was not specified. If a patient discontinued treatment before the end of the trial final assessments were obtained where possible.

A patient was withdrawn from the study for any of the following reasons:
• lost to follow-up
• withdrawal of consent
• discontinuation of study treatment
• Dose of paliperidone ER exceeded 12mg.

In the situation where a patient is lost-to-follow-up, every possible effort was made by the study site personnel to contact the patient and determine the reason for discontinuation. The measures taken to follow up were documented. When a patient withdrew before completing the study, the reason for withdrawal was documented in the source document. Study drug assigned to the withdrawn patient was not assigned to another patient.

CRITERIA FOR EVALUATION:

Assessments of efficacy and safety were performed in Phase A at baseline, 2, 4, 6, 9 and 12 weeks, and in Phase B at 20, 28, 36, 44 and 52 weeks (see Time and Events schedule, Table X, below). The primary endpoint was the mean modal prescribed daily dose of paliperidone ER from Day 1 to Day 84 (inclusive). Other key primary outcomes included the median modal prescribed daily dose, the overall average daily-prescribed dose from Week 0 to 12, the mean and median modal prescribed doses for Days 57 – 84 inclusive, the mean and median prescribed doses by week of the study from Days 1 – 84 (PP analysis only), and the mean and median consumed daily dose of paliperidone ER from Days 1 – 84.

The secondary outcomes were tabulated by visit and include CGI-S (scores ranging from 1 (not ill) to 7 (extremely severe)), GAF (a 100 point scale rated with respect only to psychological, social, and occupational functioning), clinical deterioration events (hospitalisations, suicidal ideation, violent behaviour, self injury and care increase), and the number and length of hospitalisations.

The safety assessments included the regular monitoring and recording of all adverse events (AEs) and serious AEs (SAEs), discontinuations, exposure to study treatments, physical examination and concomitant and prior medications.

Other assessments including community treatment order (CTO) status, employment status and psychiatric status are in the schedule below (Table 1).

Table 1 Schedule of events

TIME AND EVENTS SCHEDULE

	Phase A Visit window +/- 3 days						Optional follow up - Phase B Visit window +/- 5 days				
	Baseline (Day 0)	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
Informed Consent	X										
First dose of Paliperidone ER	X										
Demographic data including employment status	X										
Physical examination including height and weight	X					X					X
Pregnancy Test	X										
Diagnosis and Psychiatric history	X										
Previous antipsychotic treatments	X										
Psychiatric hospitalisations in prior 30 days	X										
Reason for initiating Paliperidone ER	X										
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X
Hospitalisations for psychiatric reasons	X	X	X	X	X	X	X	X	X	X	X
Clinical deterioration	X	X	X	X	X	X	X	X	X	X	X
CGI-S	X	X	X	X	X	X	X	X	X	X	X
GAF	X	X	X	X	X	X	X	X	X	X	X
CTO status	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
Compliance		X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X

STATISTICAL METHODS:

1. SAMPLE SIZE CALCULATION

The sample size calculation for this study was determined on the basis of yielding a level of precision around the estimate of the Day 1 to 84 mean modal dose of less than 0.75 mg/pt/day. Based upon a series of simulations of mean dose of 3, 6, 9 and 12 mg/day, with a standard deviation (SD) of 2.9 mg/day, the 95% confidence interval (CI) around the mean modal daily dose was from ±0.38 to ±0.57 mg. The desired precision was ±0.50 to ±0.75 mg/day with a sample size of 100.

2. STATISTICAL METHODS

All analyses were conducted on an Intention to Treat basis, including all data for any patient who was enrolled.

The primary endpoint was the mean modal prescribed daily dose of paliperidone ER from Day 1 to 84 (inclusive). Each patient had his or her modal (most frequent) prescribed dose calculated from the prescribing data in the CRF. The mean of all patients' modal prescribed doses over 12 weeks of study comprised the primary endpoint statistic. This is presented as a mean with two tailed 95% confidence interval calculated on a normal distribution.

Other key primary measures of prescribed dose distribution included the median modal prescribed daily dose, the overall average daily-prescribed dose from Week 0 to 12, the mean and median modal prescribed doses for Days 57 – 84 inclusive, the mean and median prescribed doses by week of the study from Days 1 – 84 (PP analysis only). While a PP analysis was planned, it was not conducted as the number of patients enrolled into the study was less than anticipated.

The actual daily doses consumed were also calculated via returned medication count. The mean consumed daily dose was calculated by the total amount (mg) consumed, determined by return meds count, divided by the number of days the patient was in the study (i.e. to withdrawal or 84 days), up to and including the day of withdrawal. The median was also calculated. Both statistics are presented with 95% confidence intervals.

The primary endpoint and the other key primary measures are all continuous outcomes and were summarised using descriptive statistics: number (n), mean, median, mode, standard deviation (SD), minimum (min), maximum (max) and 95% CIs. Categorical data were summarised with frequency tabulations (n(%)).

The visit windows for Phases A and B (described in section above) were ± 3 days and ± 5 days respectively. No values were imputed in the case of missing data. Extreme outlying values were investigated and, where necessary, key analyses were repeated with and without the questionable values.

Medical history and AEs were coded using The Medical Dictionary for Regulatory Activities (medDRA) version 10 (by System Organ Class and Preferred Term). The percentage of patients with specific treatment-emergent adverse events were summarized for each treatment group.

Special attention was given to those patients who had discontinued treatment due to an adverse event or who experienced a severe or a serious adverse event.

3. ANALYSIS POPULATIONS

The Intent-To-Treat (ITT) population included all patients who enrolled and proceeded to randomisation. The primary analysis was based upon ITT principles. The PP population was to include all patients who were enrolled, randomised and completed 12 weeks of the study. PP analyses were to be conducted on all endpoints, however, the PP analyses were not conducted (details provided in Results section).

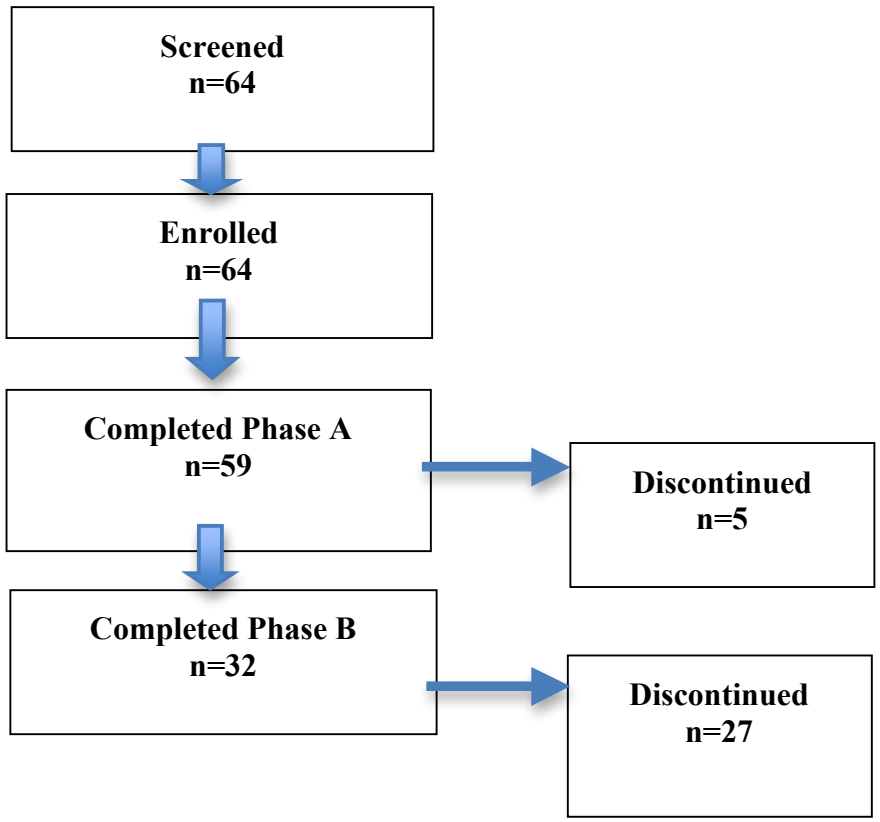
RESULTS:

The interim analysis was not conducted due to patient numbers being substantially lower than originally estimated (see Figure 1).

Due to the number of enrolled patients (n=64) being substantially less than the number planned (n=100) it was decided that further reducing the number of patients to conduct the PP analyses would not be worthwhile. The potential benefit thought to have been gained by conducting a PP analyses was outweighed by possible power issues due to planned sample size not being met.

There were no protocol deviations reported.

Figure 1 Subject flow chart



Of the 64 patients with demographic and baseline characteristics recorded (Table 1), 56% were female and the mean age was approximately 37 (10.4) years. Almost half the patients (43.6%)

were unemployed with the next most common baseline employment category being 'long-term sick leave' (29%). The duration of psychiatric diagnosis ranged from 5 to 51 years with a mean of 27(9.4) years.

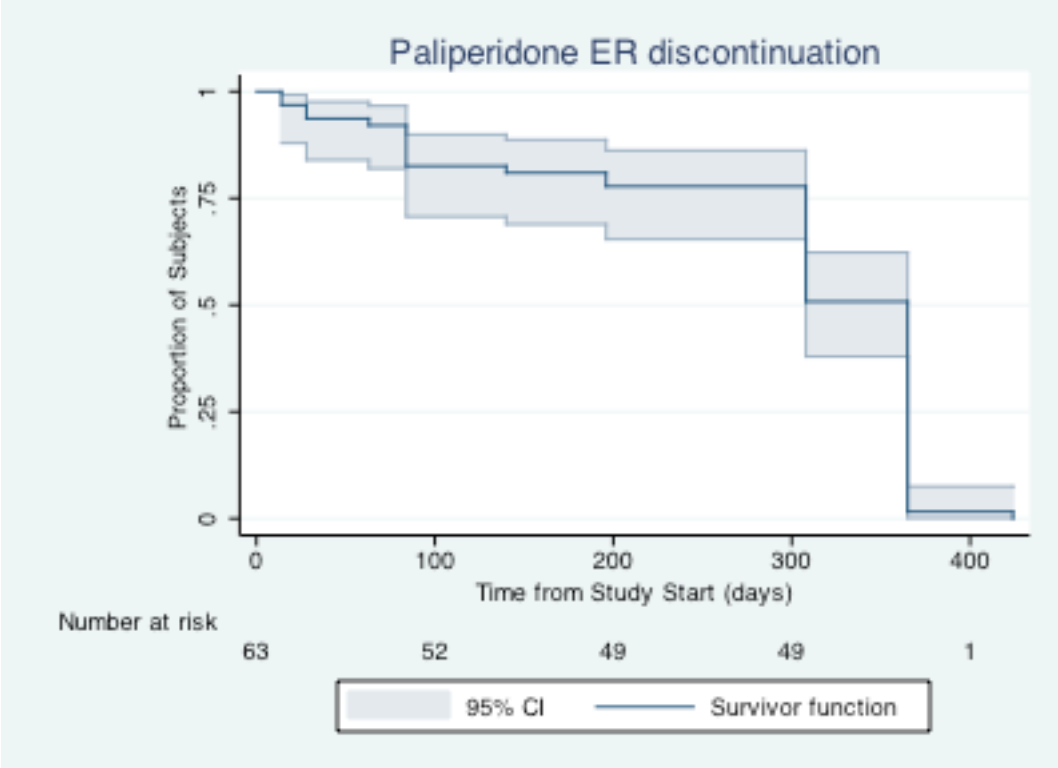
Table 2 Demographic and baseline characteristics

Demographic And Baseline Characteristics (Intent-to-Treat Analysis Set)	Paliperidone (N=64)
Sex, n (%)	
N	64
Male	28 (44)
Female	36 (56)
Age,years	
N	63
Mean (SD)	37.0 (10.4)
Median	35.8
Range	(19.7;64.8)
95% confidence interval	(23.7 to 54.8)
Employment Status, n (%)	
Full time	3 (4.8)
Part time	9 (14.5)
Unemployed	27 (43.6)
Student	1 (1.6)
Housewife/Dependent	4 (6.5)
Long-term Sick Leave	18 (29.0)
Voluntary Work	0
CTO Status (baseline),n(%)	
Not on CTO	50 (78)
On CTO	14 (22)
Psychiatric Diagnosis,n(%)	
Schizophrenia	62 (97)
Disorganised	1 (1.6)
Paranoid	40 (62.5)
Undifferentiated	12 (18.8)
Schizoaffective	1 (1.6)
Missing	1 (1.6)
Length of Diagnosis (yrs)	
N	63
Mean (SD)	27 (9.4)
Median	24
Range	(5;51)
95% confidence interval	(17 to 47)
Height, m	
N	63
Mean (SD)	1.7 (0.10)
Median	1.7
Range	(1.42;1.92)
95% confidence interval	(1.54 to 1.85)
Weight, kg	
N	63
Mean (SD)	86.3 (19.8)
Median	83.9
Range	(19.7;64.8)
95% confidence interval	(61.9 to 117)

The Kaplan-Meier estimate for discontinuation over the whole study is shown in Figure 2. The median time to discontinuation was 365 days (95% CI 308 to 365). The restricted mean time to

discontinuation (restricted to the longest follow-up) was 288 days (95% CI 260 to 317 days). The earliest discontinuation occurred at 14 days, whilst the latest discontinuation occurred at 424 days.

Figure 2 Kaplan-Meier estimate of time to discontinuation of Paliperidone ER



The primary reason for discontinuation was 'other' (11 (34.4%)) followed by 'patient choice' (6 (18.8%)) and 'reason not specified' (6(18.8%)) [Table 3].

Table 3 Reason for discontinuation

Primary reason for discontinuation	Number
Tolerability	3 (9.4%)
Response	3 (9.4%)
Ease	0 (0.0%)
Compliance	3 (9.4%)
Patient Choice	6 (18.8%)
Other	11 (34.4%)
	1
Patient discontinued antipsychotic treatment as per direction of treating team	1
Pt discontinued all treatment with antipsychotic, as per treating team decision	1
Participant was selling trial medication to others	1
Patient thought his schizpohrenia was only a temporary condition	1
patient simply preferred to go back onto previous medication. No real reason	1
Patient preference to discontinue and try a different anti-psychotic	1
Graded downward titration & ceased in favour of Paliperidone	1
Doctor's decision	1
Switching to trial medication	1
Patients mental state improved no longer required	1
Safety evaluation	
Reason not specified	6 (18.8%)
TOTAL	32 (100%)

In the 12-month antipsychotic history, in which patients may have received more than one antipsychotic, 123 oral antipsychotic medications were reported, 31 long-acting medications were reported and there were 2 cases of patients taking paliperidone ER. See Table 4 for the 12-month antipsychotic history by drug name.

Table 4 12-month antipsychotic history by drug name

Drug Name	No. of antipsychotic medications taken in the past 12 months (% of total no. of medications)
Oral	n=123
Amisulpride	8 (12.7%)
Aripiprazole	6 (9.5%)
Chlorpromazine	2 (3.2%)
Clozapine	3 (4.8%)
Haloperidol	7 (11.1%)
Olanzapine	27 (42.9%)
Paliperidone ER	2 (3.2%)
Quetiapine	17 (27.0%)
Risperidone	50 (79.4%)
Trifluoperazine	1 (1.6%)
Ziprasidone	1 (1.6%)
Zuclopenthixol	1 (1.6%)
Long-Acting	
Flupentixol	4 (6.3%)
Fluphenazine	2 (3.2%)
Haloperidol	2 (3.2%)
Risperidone long acting	19 (30.2%)
Zuclopenthixol	4 (6.3%)

EFFICACY RESULTS:

The primary endpoint (the mean modal prescribed daily dose of paliperidone ER (mg) from Day 1 to Day 84 (inclusive)) was 6.9 (2.3), median (range) 6 (3-12) and 95% CI 3 to 12 (n= 63) as shown in Table 5. Similar results were found for the mean modal prescribed daily dose of paliperidone ER (mg) for days 57 to 84 (n=53) although the mean was higher [7.5 (2.4) mg].

Table 5 Modal prescribed and overall average daily dose summary

Mean and median modal prescribed daily dose from day 1 to 84 (ITT)	
N	63
Mean	**6.9**
SD	2.3
Median	**6**
Min	3
Max	12
95% CI	3 to 12
Mean and median modal prescribed daily dose from days 57 to 84 (ITT)	
N	53
Mean	**7.5**
SD	2.4
Median	**6**
Min	3
Max	12
95% CI	3 to 12
Overall average daily-prescribed dose from week 0 to 12 (ITT)	
N	63
Mean	**6.8**
SD	1.8
Median	**6**
Min	3
Max	11.8
95% CI	3.6 to 10.3

The mean modal prescribed dose (mg) by week (ITT) ranged from 5.7 ± 1.6 at week 1 to 7.4 ± 2.4 at week 12 with a median modal prescribed dose of 6 mg each week.

The mean and median consumed daily dose of paliperidone ER from week 0 to 12 was not able to be determined for this study as full drug accountability was not performed. Instead, adherence data by visit is given in Table 6).

Table 6 Adherence to study medication

	Visit 2 Week 2 n=38	Visit 3 Week 4 n=36	Visit 4 Week 6 n=34	Visit 5 Week 9 n=28	Visit 6 Week 12 n=31	Visit 7 Week 20 n=27	Visit 8 Week 28 n=14	Visit 9 Week 36 n=14	Visit 10 Week 44 n=17	Visit 11 Week 52 n=16
Always	36 (94.7%)	34 (94.4%)	33 (97.1%)	27 (96.4%)	28 (90.3%)	22 (81.5%)	13 (92.9%)	14 (100%)	15 (88.2%)	14 (87.5%)
Quite Often	0 (0%)	2 (5.6%)	1 (2.9%)	1 (3.6%)	2 (6.5%0	4 (14.8%)	0 (0)%)	0 (0)%)	0 (0)%)	1 (6.3%)
Some-times	1 (2.6%)	0 (0%)	0 (0)%)	0 (0)%)	1 (3.2%)	1 (3.7%)	1 (7.1%)	0 (0)%)	0 (0)%)	0 (0)%)
Very Infreq-uently	0 (0%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	1 (5.9%)	1 (6.3%)
Never	1 (2.63%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	0 (0)%)	1 (5.9%)	0 (0)%)

The most common CGI-S experienced by 106 (33%) patients was 'Mild' (Table 8). The mean CGI-S and GAF by visit are provided in Table 7 . Overall, improvements were seen as the CGI-S scores tended to decrease over the duration of the study and GAF scores tended to increase until week 36 and then seemed to decrease although the results are based on 17 and 16 patients respectively for weeks 44 and 52.

Table 7 CGI-S (Clinical Global Impression of Severity) and GAF (Global Assessment of Functioning)

	Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
n	63	38	36	34	28	31	27	14	14	17	16
CGI-S	3.7 ± 1.2	3.3 ± 1.1	3.2 ± 1.0	3.1 ± 1.1	2.8 ± 1.0	2.8 ± 1.0	2.9 ± 1.1	2.7 ± 1.1	2.7 ± 0.8	2.9 ± 1.2	2.7 ± 0.8
GAF	54.6 ± 14.7	58.9 ± 15.0	63.9 ± 15.3	63.9 ± 15.6	66.3 ± 13.8	65.4 ± 14.6	65.1 ± 14.7	71.1 ± 13.3	71.6 ± 14.9	69.0 ± 17.2	63.3 ± 15.7

Table 8 CGI-S by visit

Key
frequency
column percentage

	TimePeriod						
CGI-S	0	2	3	4	5	6	Total
Not ill	2	2	1	1	2	2	16
	3.17	5.26	2.78	2.94	7.14	6.45	5.03
Very mild	9	6	9	9	10	11	85
	14.29	15.79	25.00	26.47	35.71	35.48	26.73
Mild	16	14	13	13	11	9	106
	25.40	36.84	36.11	38.24	39.29	29.03	33.33
Moderate	14	9	9	8	3	8	68
	22.22	23.68	25.00	23.53	10.71	25.81	21.38
Marked	22	7	4	2	2	1	42
	34.92	18.42	11.11	5.88	7.14	3.23	13.21
Severe	0	0	0	1	0	0	1
	0.00	0.00	0.00	2.94	0.00	0.00	0.31
Total	63	38	36	34	28	31	318
	100.00	100.00	100.00	100.00	100.00	100.00	100.00

	TimePeriod					
CGI-S	7	8	9	10	11	Total
Not ill	2	1	0	2	1	16
	7.41	7.14	0.00	11.76	6.25	5.03
Very mild	8	6	7	5	5	85
	29.63	42.86	50.00	29.41	31.25	26.73
Mild	10	4	4	4	8	106
	37.04	28.57	28.57	23.53	50.00	33.33
Moderate	5	2	3	5	2	68
	18.52	14.29	21.43	29.41	12.50	21.38
Marked	2	1	0	1	0	42
	7.41	7.14	0.00	5.88	0.00	13.21
Severe	0	0	0	0	0	1
	0.00	0.00	0.00	0.00	0.00	0.31
Total	27	14	14	17	16	318
	100.00	100.00	100.00	100.00	100.00	100.00

Weight and BMI remain fairly constant throughout the study visits as shown in Table 9.

Table 9 Weight and BMI

		Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
Weight												
	n	63	38	36	34	28	31	27	14	14	17	16
	mean	86.3	88.1	89.6	87.6	87.9	83.2	86.1	90.5	90.5	84.2	86.5
	SD	19.8	21.9	21.6	20.0	20.7	17.9	21.1	23.9	23.9	19.7	18.3
	median	83.9	83.8	86.8	85.5	85.5	78.6	84	86	86	86	85
	min	54.9	56	56	55.1	55	55.1	54.8	53.7	53.7	51.6	54.7
	max	150	150	150	150	150	124.8	142	142	142	121.3	119.8
	95% CI	61.9 to 117	61.4 to 144	61.6 to 144	60.3 to 122	58.3 to 122.6	59.8 to 121.6	58.3 to 118.6	53.7 to 142	53.7 to 142	55.4 to 121.3	54.7 to 119.8
BMI												
	n	63	38	36	34	28	31	27	14	14	17	16
	mean	29.9	29.9	30.9	30.4	30.5	29.5	29.7	30.6	30.2	29.5	30.4
	SD	5.9	6.1	6.1	6.1	6.1	6.0	6.2	6.6	6.0	6.8	6.8
	median	29.7	29.4	29.8	29.6	29.4	27.9	28.9	30.1	30.6	30.0	30.5
	min	20.4	20.7	20.8	20.5	20.4	20.0	19.7	20.0	20.6	20.4	20.3
	max	42.4	42.1	42.1	42.0	42.0	43.6	42.5	44.2	40.0	45.1	44.5
	95% CI	22.1 to 40.3	20.8 to 41.6	21.0 to 41.9	21.3 to 42.0	23.1 to 41.6	20.4 to 42.2	20.4 to 40.1	20.0 to 44.2	20.6 to 40.0	20.4 to 45.1	20.3 to 44.5

At each visit, the maintenance of treatment effect was documented by the time to significant deterioration of the psychotic condition. If signs of significant deterioration occurred more than once between visits, this was recorded. Overall there was a decrease in suicidal ideation and no reported incidences of violent behavior resulting in significant injury. There were no hospitalizations for clinical deterioration at baseline. The post-baseline results showed between 0% and 13.5% of patients required hospitalizations due to clinical deterioration with the highest count (5(13.5%)) occurring at Week 4. There were a few incidences of increased care required and one report of self injury at week 12 (Table 10).

Table 10 Clinical Deterioration

	Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
Hospitalised											
Yes	0 (0%)	2 (5.3%)	5 (13.5%)	2 (5.9%)	2 (7.1%)	1 (3.2%)	1 (3.7%)	0 (0%)	0 (0%)	0 (0%)	2 (12.5%)
No	63 (100%)	36 (94.7%)	32 (86.5%)	32 (94.1%)	26 (92.9%)	30 (96.8%)	26 (96.3%)	14 (100%)	14 (100%)	17 (100%)	14 (87.5%)
Care Increase											
Yes	0 (0%)	0 (0%)	2 (5.4%)	1 (2.9%)	1 (3.6%)	1 (3.2%)	2 (7.4%)	0 (0%)	0 (0%)	1 (5.9%)	2 (12.5%)
Multiple						*1 (3.2%*	*1 (3.7%)*				
No	63 (100%)	38 (100%)	35 (94.6%)	33 (97.1%)	27 (96.4%)	30 (96.8%)	25 (92.6%)	14 (100%)	14 (100%)	16 (94.1%)	14 (87.5%)
Suicidal											
Yes	3 (4.8%)	2 (5.3%)	3 (8.1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0(0%)	0(0%)	0 (0%)	0 (0%)
Multiple		*1 (2.6%)*									
No	60 (95.2%)	36 (94.7%)	34 (91.9%)	34 (100%)	28 (100%)	31 (100%)	31 (100%)	14 (100%)	14 (100%)	17 (100%)	16 (100%)
Violent											
No	63 (100%)	38 (100%)	37 (100%)	34 (100%)	28 (100%)	31 (100%)	27 (100%)	14 (100%)	14 (100%)	17 (100%)	16 (100%)
Self Injury											
Yes	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (3.2%)	0(0%)	0(0%)	0(0%)	0(0%)	0(0%)
No	63 (100%)	38 (100%)	37 (100%)	34 (100%)	28 (100%)	30 (96.8%)	27 (100%)	14 (100%)	14 (100%)	17 (100%)	16 (100%)

At baseline 10 patients had CTOs (which enable some hospital order patients to receive involuntary treatment while living in the community). The number of patients with CTOs dropped to 2 or less at each subsequent visit. There were no restricted CTOs (RCTOs) during the study as shown in Table 11.

Table 11 CTO

	Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
CTO	10	2	0	0	0	1	1	0	0	0	1
RCTO	0	0	0	0	0	0	0	0	0	0	0
TOTAL											

There was an increase in part time employment (20.7%) and long-term sick leave (43.8%) and a decrease in percentage of subjects unemployed (13.7%) overall post-baseline visits compared to baseline (Table 12).

Table 12 Employment status by visit

Key frequency column percentage	TimePeriod						
EmploymentStatus	2	3	4	5	6	7	Total
Full time	4	3	2	1	1	1	15
	10.53	8.11	5.88	3.57	3.23	3.70	5.86
Part time	6	8	6	5	4	5	53
	15.79	21.62	17.65	17.86	12.90	18.52	20.70
Unemployed	5	2	5	1	5	7	35
	13.16	5.41	14.71	3.57	16.13	25.93	13.67
Retired	2	1	0	0	0	0	3
	5.26	2.70	0.00	0.00	0.00	0.00	1.17
Student	0	0	0	0	2	0	3
	0.00	0.00	0.00	0.00	6.45	0.00	1.17
Housewife / Dependant	3	5	4	4	4	2	29
	7.89	13.51	11.76	14.29	12.90	7.41	11.33
Long-term Sick Leave	16	18	16	16	14	11	112
	42.11	48.65	47.06	57.14	45.16	40.74	43.75
Voluntary Work	2	0	1	1	1	1	6
	5.26	0.00	2.94	3.57	3.23	3.70	2.34
Total	38	37	34	28	31	27	256
	100.00	100.00	100.00	100.00	100.00	100.00	100.00

	TimePeriod				
EmploymentStatus	8	9	10	11	Total
Full time	1	1	0	1	15
	7.14	7.14	0.00	6.25	5.86
Part time	5	3	6	5	53
	35.71	21.43	35.29	31.25	20.70
Unemployed	3	2	3	2	35
	21.43	14.29	17.65	12.50	13.67
Retired	0	0	0	0	3
	0.00	0.00	0.00	0.00	1.17
Student	0	0	0	1	3
	0.00	0.00	0.00	6.25	1.17
Housewife / Dependant	3	2	1	1	29
	21.43	14.29	5.88	6.25	11.33
Long-term Sick Leave	2	6	7	6	112
	14.29	42.86	41.18	37.50	43.75
Voluntary Work	0	0	0	0	6
	0.00	0.00	0.00	0.00	2.34
Total	14	14	17	16	256
	100.00	100.00	100.00	100.00	100.00

SAFETY RESULTS:

Concomitant medications were categorized into the following groups: anticholinergic use (Table 13), antidepressant use (Table 14), mood stabilizer use (Table 15), benzodiazepine use (Table 16) and somatic medication use (

Table 17). There were no noteworthy changes found across visits for anticholinergic use, antidepressant use or somatic medication use. Benzodiazepine use tended to decrease over time with 25% of patients using benzodiazepine at baseline (n=63) compared to 6% at week 11 (n=16). Approximately 30% of patients used mood stabilizers until Week 10 (n=17) and 11 (n=16) where mood stabilizer use dropped to 18% and 13% respectively. The low number of patients with information available from Week 8 until the end of the study needs to be taken into consideration when interpreting results.

Table 13 Anticholinergic use by visit (ITT)

Key
frequency
column percentage

Anticholinergics	TimePeriod 0	2	3	4	5	6	7	Total
Yes	6	3	4	5	1	4	2	31
	9.52	7.89	10.81	14.71	3.57	12.90	7.41	9.72
No	57	35	33	29	27	27	25	288
	90.48	92.11	89.19	85.29	96.43	87.10	92.59	90.28
Total	63	38	37	34	28	31	27	319
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Anticholinergics	TimePeriod 8	9	10	11	Total
Yes	1	1	2	2	31
	7.14	7.14	11.76	12.50	9.72
No	13	13	15	14	288
	92.86	92.86	88.24	87.50	90.28
Total	14	14	17	16	319
	100.00	100.00	100.00	100.00	100.00

Table 14 Antidepressant use by visit (ITT)

Key
frequency
column percentage

Antidepressants	TimePeriod 0	2	3	4	5	6	7	Total
Yes	14	8	8	7	5	6	4	66
	22.22	21.05	21.62	20.59	17.86	19.35	14.81	20.69
No	49	30	29	27	23	25	23	253
	77.78	78.95	78.38	79.41	82.14	80.65	85.19	79.31
Total	63	38	37	34	28	31	27	319
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Antidepressants	TimePeriod 8	9	10	11	Total
Yes	2	2	5	5	66
	14.29	14.29	29.41	31.25	20.69
No	12	12	12	11	253
	85.71	85.71	70.59	68.75	79.31
Total	14	14	17	16	319
	100.00	100.00	100.00	100.00	100.00

Table 15 Mood stabiliser use by visit (ITT)

MoodStabilisers	TimePeriod 0	2	3	4	5	6	7	Total
Yes	18	14	11	10	9	10	8	92
	28.57	36.84	29.73	29.41	32.14	32.26	29.63	28.84
No	45	24	26	24	19	21	19	227
	71.43	63.16	70.27	70.59	67.86	67.74	70.37	71.16
Total	63	38	37	34	28	31	27	319
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

MoodStabilisers	TimePeriod 8	9	10	11	Total
Yes	3	4	3	2	92
	21.43	28.57	17.65	12.50	28.84
No	11	10	14	14	227
	78.57	71.43	82.35	87.50	71.16
Total	14	14	17	16	319
	100.00	100.00	100.00	100.00	100.00

Table 16 Benzodiazepine use by visit (ITT)

Key
frequency
column percentage

Benzodiazepines	TimePeriod 0	2	3	4	5	6	7	Total
Yes	16	10	11	7	7	4	2	61
	25.40	26.32	29.73	20.59	25.00	12.90	7.41	19.12
No	47	28	26	27	21	27	25	258
	74.60	73.68	70.27	79.41	75.00	87.10	92.59	80.88
Total	63	38	37	34	28	31	27	319
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

Benzodiazepines	TimePeriod 8	9	10	11	Total
Yes	1	1	1	1	61
	7.14	7.14	5.88	6.25	19.12
No	13	13	16	15	258
	92.86	92.86	94.12	93.75	80.88
Total	14	14	17	16	319
	100.00	100.00	100.00	100.00	100.00

Table 17 Somatic medication use by visit (ITT)

```
+-------------------+
| Key               |
|-------------------|
|     frequency     |
| column percentage |
+-------------------+
```

SomaticMed	TimePeriod 0	2	3	4	5	6	7	Total
Yes	23	14	16	13	11	11	8	113
	36.51	36.84	43.24	38.24	39.29	35.48	29.63	35.42
No	40	24	21	21	17	20	19	206
	63.49	63.16	56.76	61.76	60.71	64.52	70.37	64.58
Total	63	38	37	34	28	31	27	319
	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00

SomaticMed	TimePeriod 8	9	10	11	Total
Yes	4	4	5	4	113
	28.57	28.57	29.41	25.00	35.42
No	10	10	12	12	206
	71.43	71.43	70.59	75.00	64.58
Total	14	14	17	16	319
	100.00	100.00	100.00	100.00	100.00

There were 3 patients who had hospitalisations ongoing at the time of reporting. Patient 9860 had an ongoing hospitalisation at Visit 4, Patient 11135 had an ongoing hospitalisation at Visit 5, and Patient 11074 had an ongoing hospitalisation at visit 6. For these patients, the end-date of hospitalisation was entered as the date of data entry into the system. Of the 15 patients hospitalized at baseline, the mean length of hospitalization was 12.4 (11.5) days with a 95% CI of 1 to 45. The number of patients hospitalized post-baseline ranged from 0 to 3 patients across visits as shown in Table 18.

Table 18 Hospitalisations by visit

	Baseline	Visit 2 Week 2	Visit 3 Week 4	Visit 4 Week 6	Visit 5 Week 9	Visit 6 Week 12	Visit 7 Week 20	Visit 8 Week 28	Visit 9 Week 36	Visit 10 Week 44	Visit 11 Week 52
Hospitalised	15	1	3	2	2	1	1	0	0	1	2
Length of Hospitalisation (days)								-	-		
mean ± SD	12.4 ± 11.5	66	7.3 ± 6.0	28.0 ± 5.7	179.0 ± 220.6	34	19			4	20.5 ± 10.6
median	10	66	8	28	179	34	19			4	
min	1	66	1	24	23	34	19			4	20.5
max	45	66	13	32	335	34	19			4	13
95% CI	1 to 45	66 to 66	1 to 13	24 to 32	23 to 335	34 to 34	19 to 19			4 to 4	28 13 to 28

The 3 most frequent adverse events by number of events experienced were psychiatric disorders (74 events), nervous system disorders (46 events) and gastrointestinal disorders (32 events). Of the psychiatric disorders, the most common preferred terms were insomnia (11 events) and akathisia (7 events). Table 19 shows other frequently experienced preferred terms included headaches (9 events) and nausea (7 events). Results were similar for adverse events by number of patients experiencing events (Table 20). Common AEs (occurring in ≥10% of patients) included insomnia (15.9%) and headaches (11.1%) A listing of all adverse events by patient is provided in Appendix 1 (Listing 1).

Table 19 Adverse events by number of events

MedDRA SOC	MedDRA PT	Total Number of Events
Cardiac disorders	Dizziness	5
	Dizziness postural	1
	Palpitations	1
Cardiac disorders Total		7
Endocrine disorders	Amenorrhoea	1
	Galactorrhoea	3
	Menstruation irregular	1
Endocrine disorders Total		5
Eye disorder	Blepharospasm	1
	Night blindness	1
Eye disorder Total		2
Gastrointestinal disorders	Abdominal distension	1
	Abdominal pain	2
	Abdominal pain upper	2
	Constipation	2
	Diarrhoea	2
	Dry mouth	4
	Dysphagia	1
	Nausea	7
	Salivary hypersecretion	4
	Toothache	3
	Vomiting	4
Gastrointestinal disorders Total		32
General disorders and administration site conditions	Chest pain	3
	Fatigue	2
	Feeling abnormal	1
	Influenza like illness	1
	Lethargy	1
	Oedema peripheral	1
General disorders and administration site conditions Total		9
Immune system disorders	Rheumatoid arthritis	1
Immune system disorders Total		1
Infections and infestations	Encephalitis viral	1
Infections and infestations Total		1
Injury, poisoning and procedural complications	Fall	1

MedDRA SOC	MedDRA PT	Total Number of Events
	Intentional overdose	1
	Overdose	1
	Periorbital haematoma	1
Injury, poisoning and procedural complications Total		4
Investigations	Weight increased	2
Investigations Total		2
Metabolism and nutrition disorders	Decreased appetite	1
	Increased appetite	2
	Polydipsia	1
	Thirst	1
Metabolism and nutrition disorders Total		5
Musculoskeletal and connective tissue disorders	Arthralgia	2
	Back pain	3
	Bone pain	1
	Chills	1
	Cogwheel rigidity	2
	Fracture	1
	Joint sprain	1
	Muscle spasms	2
	Muscle tightness	1
	Muscle twitching	1
	Musculoskeletal pain	2
	Musculoskeletal stiffness	4
	Myalgia	1
	Pain in extremity	2
	Restless legs syndrome	2
	Synovial cyst	1
Musculoskeletal and connective tissue disorders Total		27
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-Hodgkin's lymphoma	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Total		1
Nervous system disorders	Abnormal dreams	1
	Dystonia	2
	Epilepsy	2
	Extrapyramidal disorder	3
	Eye movement disorder	1
	Headache	9
	Hypoaesthesia	1
	Migraine	1
	Muscular weakness	1
	Paraesthesia	1
	Psychomotor hyperactivity	1
	Sedation	5
	Sinus headache	1
	Somnolence	2
	Speech disorder	1
	Tardive dyskinesia	2

MedDRA SOC	MedDRA PT	Total Number of Events
	Thinking abnormal NOS	1
	Tremor	6
	VIIth nerve paralysis	1
	Vision blurred	4
Nervous system disorders Total		46
Psychiatric disorders	Abnormal behaviour	1
	Aggression	1
	Agitation	1
	Akathisia	7
	Amnesia	1
	Anxiety	3
	Confusional state	1
	Deliberate self-harm	1
	Depressed mood	1
	Depression	3
	Hallucination	2
	Hallucination, auditory	3
	Hypersomnia	2
	Insomnia	11
	Intentional self-injury	1
	Memory impairment	2
	Mental disorders	3
	Mood altered	1
	Mood swings	1
	Nightmare	1
	Panick attack	1
	Paranoia	3
	Psychotic disorder	1
	Restlessness	2
	Schizoaffective disorder	2
	Schizophrenia	4
	Schizophrenia exacerbated	4
	Sleep disorders	4
	Social phobia	1
	Suicidal ideation	5
Psychiatric disorders Total		74
Renal and urinary disorders	Cystitis	1
	Pollakiuria	1
	Renal pain	1
Renal and urinary disorders Total		3
Reproductive system and breast disorders	Breast inflammation	1
	Erectile dysfunction	1
	Menorrhagia	1
	Metrorrhagia	1
	Orchitis	1
	Testicular swelling	1

MedDRA SOC	MedDRA PT	Total Number of Events
	Uterine prolapse	1
Reproductive system and breast disorders Total		7
Respiratory, thoracic and mediastinal disorders	Common cold	1
	Productive cough	1
	Rhinitis	1
	Upper respiratory tract infection	2
	Wheezing	2
Respiratory, thoracic and mediastinal disorders Total		7
Skin and subcutaneous tissue disorders	Eyelid disorder	1
	Pruritus	3
	Rash	4
Skin and subcutaneous tissue disorders Total		8
Surgical and medical procedures	Tooth extraction	1
Surgical and medical procedures Total		1
Vascular disorders	Hypertension	1
	Orthostatic hypotension	2
Vascular disorders Total		3
Grand Total		245

Table 20 Adverse events by number of patients experiencing event

MedDRA SOC	MedDRA PT	Total Number of Patients Experiencing Event
Cardiac disorders	Dizziness	4
	Dizziness postural	1
	Palpitations	1
Endocrine disorders	Amenorrhoea	1
	Galactorrhoea	3
	Menstruation irregular	1
Eye disorder	Blepharospasm	1
	Night blindness	1
Gastrointestinal disorders	Abdominal distension	1
	Abdominal pain	2
	Abdominal pain upper	2
	Constipation	2
	Diarrhoea	2
	Dry mouth	3
	Dysphagia	1
	Nausea	6
	Salivary hypersecretion	3
	Toothache	2
	Vomiting	3
General disorders and administration site conditions	Chest pain	3
	Fatigue	2

MedDRA SOC	MedDRA PT	Total Number of Patients Experiencing Event
	Feeling abnormal	1
	Influenza like illness	1
	Lethargy	1
	Oedema peripheral	1
Immune system disorders	Rheumatoid arthritis	1
Infections and infestations	Encephalitis viral	1
Injury, poisoning and procedural complications	Fall	1
	Intentional overdose	1
	Overdose	1
	Periorbital haematoma	1
Investigations	Weight increased	2
Metabolism and nutrition disorders	Decreased appetite	1
	Increased appetite	1
	Polydipsia	1
	Thirst	1
Musculoskeletal and connective tissue disorders	Arthralgia	2
	Back pain	3
	Bone pain	1
	Chills	1
	Cogwheel rigidity	2
	Fracture	1
	Joint sprain	1
	Muscle spasms	2
	Muscle tightness	1
	Muscle twitching	1
	Musculoskeletal pain	2
	Musculoskeletal stiffness	2
	Myalgia	1
	Pain in extremity	2
	Restless legs syndrome	2
	Synovial cyst	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-Hodgkin's lymphoma	1
Nervous system disorders	Abnormal dreams	1
	Dystonia	2
	Epilepsy	1
	Extrapyramidal disorder	3
	Eye movement disorder	1
	Headache	7
	Hypoaesthesia	1
	Migraine	1
	Muscular weakness	1
	Paraesthesia	1
	Psychomotor hyperactivity	1
	Sedation	4
	Sinus headache	1

MedDRA SOC	MedDRA PT	Total Number of Patients Experiencing Event
	Somnolence	2
	Speech disorder	1
	Tardive dyskinesia	2
	Thinking abnormal NOS	1
	Tremor	6
	VIIth nerve paralysis	1
	Vision blurred	4
Psychiatric disorders	Abnormal behaviour	1
	Aggression	1
	Agitation	1
	Akathisia	6
	Amnesia	1
	Anxiety	2
	Confusional state	1
	Deliberate self-harm	1
	Depressed mood	1
	Depression	2
	Hallucination	2
	Hallucination, auditory	2
	Hypersomnia	2
	Insomnia	10
	Intentional self-injury	1
	Memory impairment	2
	Mental disorders	3
	Mood altered	1
	Mood swings	1
	Nightmare	1
	Panick attack	1
	Paranoia	3
	Psychotic disorder	1
	Restlessness	2
	Schizoaffective disorder	2
	Schizophrenia	4
	Schizophrenia exacerbated	3
	Sleep disorders	3
	Social phobia	1
	Suicidal ideation	5
Renal and urinary disorders	Cystitis	1
	Pollakiuria	1
	Renal pain	1
Reproductive system and breast disorders	Breast inflammation	1
	Erectile dysfunction	1
	Menorrhagia	1
	Metrorrhagia	1
	Orchitis	1
	Testicular swelling	1
	Uterine prolapse	1

MedDRA SOC	MedDRA PT	Total Number of Patients Experiencing Event
Respiratory, thoracic and mediastinal disorders	Common cold	1
	Productive cough	1
	Rhinitis	1
	Upper respiratory tract infection	2
	Wheezing	2
Skin and subcutaneous tissue disorders	Eyelid disorder	1
	Pruritus	3
	Rash	4
Surgical and medical procedures	Tooth extraction	1
Surgical and medical procedures Total		1
Vascular disorders	Hypertension	1
	Orthostatic hypotension	2

No deaths occurred in this study. There were 28 SAEs that occurred in 16 patients that were reported in this study (one patient had 2 episodes of depression). The most common SAE was suicidal ideation (experienced by 5 patients), followed by schizophrenia (experienced by 3 patients). SAEs by number of patients experiencing the event is summarised in Table 21.

Table 21 SAEs by number of patients experiencing event

MedDRA SOC	MedDRA PT	Total Number of Patients Experiencing Event
Gastrointestinal disorders	Abdominal pain	1
General disorders and administration site conditions	Lethargy	1
Infections and infestations	Encephalitis viral	1
Injury, poisoning and procedural complications	Intentional overdose	1
	Overdose	1
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Non-Hodgkin's lymphoma	1
Nervous system disorders	Dystonia	1
	Extrapyramidal disorder	1
Psychiatric disorders	Depression	2
	Hallucination, auditory	1
	Mental disorders	2
	Paranoia	2
	Psychotic disorder	1
	Schizoaffective disorder	2
	Schizophrenia	3
	Schizophrenia exacerbated	1
	Suicidal ideation	5

STUDY LIMITATIONS:

The planned total sample size for this study of 100 patients was not met. There were 64 patients enrolled.

The interim analysis was not conducted due to patient numbers being substantially lower than originally estimated (see Figure 1). The PP analysis was also not conducted as it was decided that further reducing the number of patients to conduct the PP analyses would not be worthwhile.

Not all planned analyses were performed because the data was not collected in a manner that allowed this. The following were not performed:

- The mean and median consumed daily dose of paliperidone ER from week 0 to 84, calculated by summing the total amount (mg) of paliperidone ER consumed divided by the number of days the patient was in the study, up to and including the day of withdrawal. The total amount (mg) of paliperidone ER consumed will be determined by returned medication counts.

- Previous and concomitant medications were to be classified using The World Health Organisation Anatomical Therapeutic Chemical (WHO ATC) (by Therapeutic Area and Drug Classification), however, drug names were not collected in this study therefore these classifications were not done.

Changes were made to the inclusion/exclusion criteria in the 1st and 3rd protocol amendments. The changes made were to ensure clarification of patient population as well as to adjust to different lengths of treatment intervals for long acting injectable antipsychotic medication.

A large proportion of post-baseline data for patients were not included in the summaries/analyses due to the restrictions imposed by the visit windows.

No other notable study limitations were identified by the Sponsor.

CONCLUSION:

Numerous studies have performed randomized controlled trials investigating the efficacy, safety and tolerability of paliperidone ER at set dose groups ranging from 3-15 mg per day (Davidson, Emsley et al. 2007; Kane, Canas et al. 2007; Marder, Kramer et al. 2007). All doses significantly reduced schizophrenia symptomatology, with an onset of effect as early as day 4. The FDA-approved dose range is 3–12 mg/day with a recommended starting dose of 6 mg/day.

This study utilized the FDA-approved dose range as well as recommended starting dose and took on a flexible dosing strategy for each patient. The mean (SD) modal prescribed daily dose of paliperidone ER from Day 1 to Day 84 (inclusive)), for the 63 patients with dosing data, was 6.9 (2.3) mg with a range of 3-12 mg and a median modal prescribed daily dose of 6 mg. Similar results were found for the mean modal prescribed daily dose of paliperidone ER (mg) for days 57 to 84 (n=53) although the mean (SD) was higher [7.5 (2.4) mg]. In a similar paliperidone ER flexible dosing study (Canuso, Lindenmayer et al. 2010), with a starting dose of 6 mg/day and flexible dosing till day 15, the mean (SD) modal dose of paliperidone ER was 8.6 (2.5) mg/d.

The mean modal prescribed dose (mg) by week (ITT) ranged from 5.7 ± 1.6 at week 1 to 7.4 ± 2.4 at week 12 with a median modal prescribed dose of 6 mg each week.

Common AEs (occurring in ≥10% of patients) included insomnia (15.9%) and headaches (11.1%) which are consistent with findings in another recent paliperidone ER flexible dosing study (Canuso, Schooler et al. 2010).

By using a flexible dosing regimen for paliperidone ER (to best mimic actual clinical practice), the mean modal prescribed daily dose for the first 12 weeks of the study was found to be 6.9 (2.3) mg; improvements were seen in CGI-S and GAF scores; and overall, there was a drop in

concomitant medication use. No new safety findings were observed in this population.

The major study limitations were the number of patients being lower than anticipated, which triggered the interim and PP analyses not to be conducted, and the other major study limitation was that not all data was collected in a manner that allowed all planned analyses to be performed.

REFERENCES:

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I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

SIGNATURE: _____

DATE: 24 NOVEMBER 2010

APPENDIX 1:

Listing 1 Listing of adverse events by patient

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
9158	Anxiety	Anxiety	Psychiatric disorders	23/04/07	8/06/07	Moderate	No
9158	Restlessness	Restlessness	Psychiatric disorders	23/04/07	8/06/07	Moderate	No
9158	Suicidal Ideation	Suicidal ideation	Psychiatric disorders	16/05/07	8/06/07	Severe	Yes
9158	Relapse of illness	Schizophrenia	Psychiatric disorders	16/05/07	8/06/07	Severe	Yes
9208	Blurry vision	Vision blurred	Nervous system disorders	26/04/07	24/05/07	Mild	No
9208	Akathisia	Akathisia	Psychiatric disorders	30/04/07	1/05/07	Moderate	No
9208	Uterine prolapse	Uterine prolapse	Reproductive system and breast disorders	1/05/07	5/12/07	Moderate	No
9208	Dry mouth	Dry mouth	Gastrointestinal disorders	11/05/07	13/05/07	Mild	No
9208	Sleeplessness	Insomnia	Psychiatric disorders	19/05/07	22/05/07	Moderate	No
9208	Dry mouth	Dry mouth	Gastrointestinal disorders	3/06/07	17/09/07	Moderate	No
9208	Speech difficulties	Speech disorder	Nervous system disorders	5/06/07	15/06/07	Mild	No
9208	Disturbed sleep	Sleep disorders	Psychiatric disorders	7/06/07	15/06/07	Moderate	No
9208	Akathisia	Akathisia	Psychiatric disorders	7/06/07	15/06/07	Severe	No
9208	Severe EPS - upper limbs/face/neck	Extrapyramidal disorder	Nervous system disorders	7/06/07	15/06/07	Severe	Yes
9209	Sleeplessness	Insomnia	Psychiatric disorders	18/05/07	23/05/07	Moderate	No
9209	Depressed mood	Depressed mood	Psychiatric disorders	18/05/07	31/05/07	Mild	No
9209	Chest pain	Chest pain	General disorders and administration site conditions	24/05/07	24/05/07	Moderate	No
9209	Worsening of intermittent stomach pain	Abdominal pain upper	Gastrointestinal disorders	25/05/07	28/05/07	Mild	No
9209	Suicidal ideation	Suicidal ideation	Psychiatric disorders	25/05/07	31/05/07	Severe	Yes
9210	Heart palpitations	Palpitations	Cardiac disorders	6/06/07	20/07/07	Mild	No
9344	Sleeplessness	Insomnia	Psychiatric disorders	4/06/07	8/06/07	Moderate	No
9344	Increased appetite	Increased appetite	Metabolism and nutrition disorders	8/06/07	27/06/07	Mild	No
9344	Dystonic Reaction	Dystonia	Nervous system disorders	3/07/07	4/07/07	Severe	Yes
9344	Increased appetite	Increased appetite	Metabolism and nutrition disorders	14/08/07	30/08/07	Mild	No
9344	Sedation	Sedation	Nervous system disorders	14/08/07	30/08/07	Mild	No
9344	Facial Twitching	Muscle twitching	Musculoskeletal and connective tissue disorders	3/10/07	5/10/07	Moderate	No
9344	Increase in visual and auditory hallucinations	Hallucination	Psychiatric disorders	13/11/07	6/12/07	Moderate	No
9615	Intermittent Back Pain	Back pain	Musculoskeletal and connective tissue disorders	28/04/07	Ongoing	Mild	No
9615	Agitation	Agitation	Psychiatric disorders	3/07/07	5/07/07	Mild	No
9615	Drowsiness	Somnolence	Nervous system disorders	5/07/07	5/07/07	Mild	No
9615	Blurry vision	Vision blurred	Nervous system disorders	10/07/07	30/08/07	Mild	No
9615	Dizziness	Dizziness	Cardiac disorders	24/07/07	26/07/07	Mild	No
9615	Wdight gain	Weight increased	Investigations	30/08/07	16/11/07	Moderate	No
9615	Sleeping disturbances	Sleep disorders	Psychiatric disorders	16/10/07	30/10/07	Mild	No
9615	Bladder infection	Cystitis	Renal and urinary disorders	16/10/07	30/10/07	Moderate	No
9615	Disrupted Sleep	Sleep disorders	Psychiatric disorders	3/02/08	28/04/08	Mild	No
9615	Spontaneous menstrual bleeding	Menorrhagia	Reproductive system and breast disorders	23/04/08	5/05/08	Moderate	No
9860	Sleeplessness	Insomnia	Psychiatric disorders	4/07/07	7/07/07	Mild	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
9860	Exacerbation of Schizophrenia	Schizophrenia	Psychiatric disorders	6/07/07	Ongoing	Severe	Yes
9860	Constipation	Constipation	Gastrointestinal disorders	10/07/07	20/07/07	Moderate	No
9860	Sore leg secondary to fall (x2)	Pain in extremity	Musculoskeletal and connective tissue disorders	20/07/07	20/07/07	Mild	No
9860	Fall x 2	Fall	Injury, poisoning and procedural complications	20/07/07	20/07/07	Mild	No
9860	Polydipsia	Polydipsia	Metabolism and nutrition disorders	25/07/07	25/07/07	Mild	No
9860	Sedation	Sedation	Nervous system disorders	25/07/07	25/07/07	Mild	No
9860	Sedation	Sedation	Nervous system disorders	6/08/07	24/08/07	Mild	No
10026	Extrapyramidal side effects	Extrapyramidal disorder	Nervous system disorders	19/07/07	15/08/07	Moderate	No
10026	Increased anxiety	Anxiety	Psychiatric disorders	26/07/07	2/08/07	Moderate	No
10026	Suicidal ideation	Suicidal ideation	Psychiatric disorders	26/07/07	3/08/07	Severe	Yes
10026	Deterioration in mental state	Mental disorders	Psychiatric disorders	26/07/07	3/08/07	Severe	Yes
10026	Suspected diazepam overdose	Overdose	Injury, poisoning and procedural complications	26/07/07	3/08/07	Severe	Yes
10026	Sedation	Sedation	Nervous system disorders	26/07/07	15/08/07	Moderate	No
10026	Dizziness	Dizziness	Cardiac disorders	27/07/07	27/07/07	Mild	No
10026	Insomnia	Insomnia	Psychiatric disorders	27/07/07	1/08/07	Moderate	No
10026	Flat mood	Mood altered	Psychiatric disorders	29/07/07	31/07/07	Mild	No
10026	Dry mouth	Dry mouth	Gastrointestinal disorders	30/07/07	30/07/07	Mild	No
10026	Anxiety	Anxiety	Psychiatric disorders	31/08/07	25/10/07	Mild	No
10026	Cogwheel rigidity	Cogwheel rigidity	Musculoskeletal and connective tissue disorders	31/08/07	25/10/07	Moderate	No
10062	vomitting three times in the space of an hour	Vomiting	Gastrointestinal disorders	17/08/07	17/08/07	Moderate	No
10062	continuing nausea and intermittent vomitting	Nausea	Gastrointestinal disorders	17/08/07	1/09/07	Moderate	No
10062	auditory hallucinations increased and family and neighbours reported she didn't appear 'well'	Hallucination, auditory	Psychiatric disorders	18/08/07	18/08/07	Moderate	No
10062	eye twitch	Blepharospasm	Eye disorder	19/08/07	19/08/07	Moderate	No
10062	hand tremors	Tremor	Nervous system disorders	31/08/07	31/08/07	Moderate	No
10062	reappearance of dermatitic type rash on upper chest and speading to right side of face	Rash	Skin and subcutaneous tissue disorders	2/09/07	9/09/07	Mild	No
10062	auditory hallucinations are cycling every 3-4 days	Hallucination, auditory	Psychiatric disorders	17/09/07	6/12/07	Moderate	No
10062	diarrhoea and vomitting	Diarrhoea	Gastrointestinal disorders	5/10/07	5/10/07	Moderate	No
10062	hip pain - ?muscular/joint pain - on walking - gradual onset	Arthralgia	Musculoskeletal and connective tissue disorders	15/10/07	13/12/07	Moderate	No
10062	vomitting straight after taking tablets and again at night	Vomiting	Gastrointestinal disorders	7/12/07	9/12/07	Moderate	No
10062	nausea from hernia	Nausea	Gastrointestinal disorders	30/01/08	Ongoing	Mild	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
10451	sleep disturbance & breathing difficulty	Sleep disorders	Psychiatric disorders	10/10/07	17/10/07	Moderate	No
10451	hypersomnia	Hypersomnia	Psychiatric disorders	18/10/07	7/08/08	Mild	No
10451	migraine	Migraine	Nervous system disorders	31/10/07	1/11/07	Moderate	No
10451	memory problems	Memory impairment	Psychiatric disorders	18/02/08	Ongoing	Moderate	No
10451	tremor	Tremor	Nervous system disorders	7/08/08	Ongoing	Mild	No
10506	dull ache and stomach cramps for about 2 hours a day	Abdominal pain upper	Gastrointestinal disorders	19/10/07	20/10/07	Mild	No
10506	sharp pain in left shoulder	Musculoskeletal pain	Musculoskeletal and connective tissue disorders	20/11/07	21/11/07	Moderate	No
10506	intermittent abdominal pain and feeling bloated	Abdominal pain	Gastrointestinal disorders	13/12/07	5/02/08	Mild	No
10506	clinical exacerbation	Schizophrenia	Psychiatric disorders	5/06/08	26/08/08	Severe	No
10506	itchy arms and legs occasionally - maybe weekly	Pruritus	Skin and subcutaneous tissue disorders	18/11/08	Ongoing	Mild	No
10506	excessive saliva at night	Salivary hypersecretion	Gastrointestinal disorders	4/12/08	Ongoing	Mild	No
10534	diarrheoa	Diarrhoea	Gastrointestinal disorders	26/10/07	27/10/07	Mild	No
10534	headache	Headache	Nervous system disorders	7/11/07	8/11/07	Mild	No
10534	rhinitis	Rhinitis	Respiratory, thoracic and mediastinal disorders	9/03/08	20/03/08	Mild	No
10559	increase in insomnia	Insomnia	Psychiatric disorders	31/10/07	23/11/07	Mild	No
10559	toothache	Toothache	Gastrointestinal disorders	11/11/07	12/11/07	Mild	No
10559	self-harm, fractured left thumb	Deliberate self-harm	Psychiatric disorders	30/11/07	25/01/08	Mild	No
10559	toothache	Toothache	Gastrointestinal disorders	4/12/07	4/12/07	Mild	No
10559	nightmares	Nightmare	Psychiatric disorders	22/12/07	25/01/08	Mild	No
10559	self inflicted small cut to left arm	Intentional self-injury	Psychiatric disorders	6/03/08	6/03/08	Mild	No
10559	teeth extraction	Tooth extraction	Surgical and medical procedures	1/05/08	15/05/08	Mild	No
10560	increased paranoia, agitation and presence of visual disturbances	Paranoia	Psychiatric disorders	15/11/07	Ongoing	Moderate	No
10566	tremor	Tremor	Nervous system disorders	1/11/07	Ongoing	Mild	No
10566	nausea	Nausea	Gastrointestinal disorders	1/11/07	7/11/07	Mild	No
10566	headache	Headache	Nervous system disorders	1/11/07	7/11/07	Mild	No
10566	vomitted	Vomiting	Gastrointestinal disorders	3/11/07	3/11/07	Mild	No
10566	akathesia	Akathisia	Psychiatric disorders	14/11/07	28/11/07	Mild	No
10566	dry mouth	Dry mouth	Gastrointestinal disorders	15/11/07	28/11/07	Mild	No
10566	blurred vision	Vision blurred	Nervous system disorders	15/11/07	28/11/07	Mild	No
10570	headache	Headache	Nervous system disorders	7/11/07	8/11/07	Mild	No
10570	exacerbation of schizo-affective disorder	Schizoaffective disorder	Psychiatric disorders	23/11/07	17/12/07	Moderate	Yes
10570	depression	Depression	Psychiatric disorders	23/11/07	29/12/07	Moderate	Yes
10570	akathesia	Akathisia	Psychiatric disorders	5/12/07	29/12/07	Mild	No
10570	toothache	Toothache	Gastrointestinal disorders	23/12/07	1/03/08	Mild	No
10570	depression	Depression	Psychiatric disorders	8/07/08	10/09/08	Mild	Yes
10570	auditory hallucinations	Hallucination, auditory	Psychiatric disorders	8/07/08	10/09/08	Mild	Yes
10570	paranoia	Paranoia	Psychiatric disorders	8/07/08	10/09/08	Mild	Yes

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
10570	fleeting suicidal thoughts	Suicidal ideation	Psychiatric disorders	8/07/08	10/09/08	Mild	Yes
10630	testicular infection	Orchitis	Reproductive system and breast disorders	28/11/07	13/12/07	Mild	No
10630	sprained ankle falling down some steps	Joint sprain	Musculoskeletal and connective tissue disorders	15/12/07	27/02/08	Moderate	No
10632	experienced nausea in the afternoon after a meal	Nausea	Gastrointestinal disorders	11/12/07	11/12/07	Moderate	No
10632	feelings of being overwhelmed by everything	Feeling abnormal	General disorders and administration site conditions	11/12/07	11/12/07	Moderate	No
10632	woke up with a blocked nose - son has a cold currently	Common cold	Respiratory, thoracic and mediastinal disorders	12/12/07	12/12/07	Mild	No
10632	pt felt she was becoming unwell as the voices got louder and more annoying	Schizophrenia exacerbated	Psychiatric disorders	22/12/07	22/12/07	Mild	No
10632	again voices became louder and more intrusive - resolved with one dose of clopixol	Schizophrenia exacerbated	Psychiatric disorders	26/12/07	26/12/07	Mild	No
10632	headache - resolved with 2 panadol	Headache	Nervous system disorders	28/12/07	28/12/07	Moderate	No
10632	headache	Headache	Nervous system disorders	22/01/08	22/01/08	Mild	No
10632	increasing vagueness and confusion	Confusional state	Psychiatric disorders	20/02/08	Ongoing	Moderate	No
10648	difficulty falling asleep and staying asleep	Insomnia	Psychiatric disorders	12/12/07	Ongoing	Moderate	No
10648	restlessness	Restlessness	Psychiatric disorders	15/12/07	Ongoing	Mild	No
10648	urinary frequency	Pollakiuria	Renal and urinary disorders	15/12/07	27/12/07	Mild	No
10657	social phobias-worsening	Social phobia	Psychiatric disorders	4/12/07	Ongoing	Moderate	No
10657	worsening of hallucinations	Hallucination	Psychiatric disorders	6/12/07	28/12/07	Moderate	No
10657	thinking too much	Thinking abnormal NOS	Nervous system disorders	6/12/07	28/12/07	Moderate	No
10657	muscle jolts	Muscle spasms	Musculoskeletal and connective tissue disorders	6/12/07	28/12/07	Moderate	No
10657	tiredness	Fatigue	General disorders and administration site conditions	10/12/07	28/12/07	Moderate	No
10657	decrease in appetite	Decreased appetite	Metabolism and nutrition disorders	4/01/08	Ongoing	Moderate	No
10657	headaches-increased frequency	Headache	Nervous system disorders	4/01/08	Ongoing	Moderate	No
10657	mood swings-weird emotions	Mood swings	Psychiatric disorders	4/01/08	Ongoing	Moderate	No
10657	problems sleeping	Insomnia	Psychiatric disorders	4/01/08	Ongoing	Moderate	No
10657	pain in arms and legs	Pain in extremity	Musculoskeletal and connective tissue disorders	4/01/08	Ongoing	Mild	No
10657	nausea	Nausea	Gastrointestinal disorders	4/01/08	Ongoing	Mild	No
10662	sinus pressure and 'thick throat'	Sinus headache	Nervous system disorders	28/12/07	Ongoing	Moderate	No
10662	blurred vision and discomfort behind the right eye	Vision blurred	Nervous system disorders	28/12/07	28/12/07	Mild	No
10662	irritating itchy fingers	Pruritus	Skin and subcutaneous tissue disorders	28/12/07	28/12/07	Severe	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
10662	excessive tongue movement and watery saliva	Tremor	Nervous system disorders	28/12/07	28/12/07	Moderate	No
10662	dysphagia due to swollen tongue	Dysphagia	Gastrointestinal disorders	28/12/07	23/01/08	Mild	No
10662	postural hypotension	Orthostatic hypotension	Vascular disorders	28/12/07	23/01/08	Mild	No
10662	short term memory loss and problems concentrating	Amnesia	Psychiatric disorders	28/12/07	23/01/08	Moderate	No
10662	wheezing	Wheezing	Respiratory, thoracic and mediastinal disorders	28/12/07	23/01/08	Mild	No
10662	tightness at back of neck	Muscle tightness	Musculoskeletal and connective tissue disorders	28/12/07	23/01/08	Mild	No
10662	inflammation around nipple rings	Breast inflammation	Reproductive system and breast disorders	29/12/07	29/12/07	Mild	No
10662	discomfort in lower back (around kidneys)	Back pain	Musculoskeletal and connective tissue disorders	29/12/07	29/12/07	Mild	No
10662	weakness in legs - lasting a few minutes	Muscular weakness	Nervous system disorders	29/12/07	31/12/07	Mild	No
10662	swollen left testicle or gland in left testicle	Testicular swelling	Reproductive system and breast disorders	29/12/07	3/01/08	Mild	No
10662	abdominal bloating	Abdominal distension	Gastrointestinal disorders	29/12/07	23/01/08	Mild	No
10662	problems with memory and goal setting	Memory impairment	Psychiatric disorders	29/12/07	23/01/08	Moderate	No
10662	reduced night vision	Night blindness	Eye disorder	30/12/07	1/01/08	Mild	No
10662	vivid dreams	Abnormal dreams	Nervous system disorders	30/12/07	15/02/08	Moderate	No
10662	intermittent joint pain in right wrist and left shoulder	Arthralgia	Musculoskeletal and connective tissue disorders	7/01/08	23/01/08	Mild	No
10662	headache (eye strain) off and on	Headache	Nervous system disorders	15/02/08	15/02/08	Mild	No
10689	patient's father reported patient complained of chest and arm pain, nausea and vomitting and was examined at Casey emergency dept	Chest pain	General disorders and administration site conditions	12/01/08	12/01/08	Moderate	No
10689	patient's father reports increased aggression and agitation	Aggression	Psychiatric disorders	18/01/08	Ongoing	Moderate	No
10689	skin rash	Rash	Skin and subcutaneous tissue disorders	15/02/08	6/03/08	Mild	No
10690	light headedness on standing and nausea	Dizziness	Cardiac disorders	18/01/08	18/01/08	Mild	No
10711	breakthrough bleeding	Metrorrhagia	Reproductive system and breast disorders	19/01/08	21/01/08	Mild	No
10712	restlessness / akathesia	Akathisia	Psychiatric disorders	5/02/08	25/03/08	Mild	No
10712	hypersalivation	Salivary hypersecretion	Gastrointestinal disorders	1/03/08	11/04/08	Mild	No
10712	insomnia	Insomnia	Psychiatric disorders	10/09/08	1/10/08	Mild	No
10714	Intentional Overdose	Intentional overdose	Injury, poisoning and procedural complications	18/03/08	22/03/08	Moderate	Yes
10718	Irregular menstrual cycle	Menstruation irregular	Endocrine disorders	1/03/08	19/06/08	Mild	No
10718	Sore shoulders, chest and breasts	Musculoskeletal pain	Musculoskeletal and connective tissue disorders	7/11/08	23/01/09	Mild	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
10747	Worsening extra-pyramidal tremor	Extrapyramidal disorder	Nervous system disorders	13/08/08	15/10/08	Moderate	No
10747	viral encephalitis	Encephalitis viral	Infections and infestations	22/11/08	26/11/08	Severe	Yes
10782	akathesia	Akathisia	Psychiatric disorders	29/03/08	30/04/08	Mild	No
10784	Fine tremor, although improving on Paliperidone	Tremor	Nervous system disorders	22/04/08	2/09/08	Mild	No
10785	Slight tremor of hand.	Tremor	Nervous system disorders	20/03/08	3/04/08	Mild	No
10790	occular dystonia	Dystonia	Nervous system disorders	3/03/08	5/03/08	Mild	No
10790	abscence-like complex partial epileptic activity	Epilepsy	Nervous system disorders	14/05/08	21/06/08	Mild	No
10790	weight gain	Weight increased	Investigations	26/05/08	15/09/08	Mild	No
10790	simple partial epileptic phenomena	Epilepsy	Nervous system disorders	24/06/08	29/10/08	Mild	No
10790	overwhelmed with hearing voices	Schizophrenia exacerbated	Psychiatric disorders	13/10/08	11/11/08	Moderate	No
10790	mild sedation	Sedation	Nervous system disorders	13/10/08	18/12/08	Mild	No
10796	undisplaced oblique tibula fracture left ankle	Fracture	Musculoskeletal and connective tissue disorders	1/04/08	15/07/08	Moderate	No
10815	Depression	Depression	Psychiatric disorders	14/04/08	23/04/08	Moderate	Yes
10815	Suicidial Ideation	Suicidal ideation	Psychiatric disorders	14/04/08	23/04/08	Moderate	Yes
10908	Subjective feeling of restless legs	Restless legs syndrome	Musculoskeletal and connective tissue disorders	8/04/08	23/04/08	Mild	No
10955	muscular pain in upper arms bilaterally.	Myalgia	Musculoskeletal and connective tissue disorders	21/10/08	30/10/08	Mild	No
10955	Ganglion at back of right wrist	Synovial cyst	Musculoskeletal and connective tissue disorders	21/10/08	17/02/09	Mild	No
10955	Rheumatoid Arthritis	Rheumatoid arthritis	Immune system disorders	1/12/08	Ongoing	Moderate	No
10967	Dizziness, head ache and dry mouth.	Dizziness	Cardiac disorders	1/05/08	11/06/08	Mild	No
10967	Dizziness, head ache and dry mouth.	Dizziness	Cardiac disorders	1/05/08	11/06/08	Mild	No
10968	excessive thirst and dry mouth	Thirst	Metabolism and nutrition disorders	16/04/08	2/05/08	Mild	No
10968	droopy eyelid (left eye)	Eyelid disorder	Skin and subcutaneous tissue disorders	22/04/08	29/04/08	Moderate	No
10968	itchy rash	Rash	Skin and subcutaneous tissue disorders	28/06/08	Ongoing	Moderate	No
10969	tingling in hands and feet - floating sensation	Paraesthesia	Nervous system disorders	23/04/08	6/05/08	Mild	No
10969	restless leg - increasing since starting pali	Restless legs syndrome	Musculoskeletal and connective tissue disorders	23/04/08	6/05/08	Mild	No
10970	postural hypotension	Orthostatic hypotension	Vascular disorders	23/04/08	25/04/08	Mild	No
10970	flu-like illness	Influenza like illness	General disorders and administration site conditions	26/05/08	2/06/08	Moderate	No
10970	impotence (gains erections cannot ejaculate)	Erectile dysfunction	Reproductive system and breast disorders	17/06/08	Ongoing	Moderate	No
10971	gets 'the shakes' (shivers) when cold	Chills	Musculoskeletal and connective tissue disorders	7/05/08	11/06/08	Mild	No
10971	nausea and vomitting	Nausea	Gastrointestinal disorders	20/05/08	9/06/08	Mild	No
10971	constipation off and on	Constipation	Gastrointestinal disorders	4/06/08	21/11/08	Mild	No
10996	Lactation	Galactorrhoea	Endocrine disorders	4/07/08	2/11/08	Mild	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
10996	Amenorrhoea	Amenorrhoea	Endocrine disorders	4/09/08	2/11/08	Mild	No
11002	Upper respiratory tract infection	Upper respiratory tract infection	Respiratory, thoracic and mediastinal disorders	7/06/08	11/06/08	Moderate	No
11003	Exacerbation of non-Hodgkins lymphoma	Non-Hodgkin's lymphoma	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2/07/08	Ongoing	Severe	Yes
11003	Oedema in lower legs and soft crepitations in bases of both lungs	Oedema peripheral	General disorders and administration site conditions	24/07/08	Ongoing	Moderate	No
11003	Psychotic relapse	Psychotic disorder	Psychiatric disorders	28/08/08	15/09/08	Severe	Yes
11004	akathisia	Akathisia	Psychiatric disorders	16/05/08	3/06/08	Mild	No
11004	lactation	Galactorrhoea	Endocrine disorders	16/05/08	9/07/08	Mild	No
11004	eyes looking up involuntary	Eye movement disorder	Nervous system disorders	1/02/09	Ongoing	Mild	No
11007	stiffness of muscles	Musculoskeletal stiffness	Musculoskeletal and connective tissue disorders	15/05/08	5/06/08	Mild	No
11007	mild tiredness	Fatigue	General disorders and administration site conditions	15/05/08	5/06/08	Mild	No
11007	muscle stiffness	Musculoskeletal stiffness	Musculoskeletal and connective tissue disorders	7/06/08	19/01/09	Mild	No
11007	mild muscle stiffness	Musculoskeletal stiffness	Musculoskeletal and connective tissue disorders	1/02/09	Ongoing	Mild	No
11008	insomnia	Insomnia	Psychiatric disorders	19/05/08	7/07/08	Mild	No
11008	insomnia	Insomnia	Psychiatric disorders	9/07/08	Ongoing	Mild	No
11010	ache at base of spine	Bone pain	Musculoskeletal and connective tissue disorders	13/05/08	13/05/08	Mild	No
11010	increased saliva	Salivary hypersecretion	Gastrointestinal disorders	13/05/08	19/05/08	Mild	No
11010	headaches - afternoon and night	Headache	Nervous system disorders	13/05/08	6/06/08	Mild	No
11010	finger numbness	Hypoaesthesia	Nervous system disorders	13/05/08	6/06/08	Mild	No
11010	drowsiness	Somnolence	Nervous system disorders	13/05/08	24/07/08	Moderate	No
11010	heavy eyes and headaches with alcohol	Headache	Nervous system disorders	17/05/08	17/05/08	Mild	No
11010	thin red lines under each arm pit	Rash	Skin and subcutaneous tissue disorders	17/06/08	25/09/08	Mild	No
11010	itchy skin	Pruritus	Skin and subcutaneous tissue disorders	25/09/08	28/11/08	Mild	No
11010	increased saliva at night	Salivary hypersecretion	Gastrointestinal disorders	25/09/08	28/11/08	Mild	No
11010	black eye & bleeding lip from an unprovoked attack outside a pub (unconfirmed by RA)	Periorbital haematoma	Injury, poisoning and procedural complications	14/04/09	14/05/09	Mild	No
11035	Increased sleep	Hypersomnia	Psychiatric disorders	20/05/08	4/07/08	Mild	No
11035	Right side facial nerve palsy	VIIth nerve paralysis	Nervous system disorders	30/06/08	2/09/08	Moderate	No
11035	Lethargy, nause and constipation	Lethargy	General disorders and administration site conditions	30/03/09	2/04/09	Severe	Yes
11035	Abdominal Pain	Abdominal pain	Gastrointestinal disorders	30/03/09	2/04/09	Severe	Yes
11035	Deterioration in mental state	Mental disorders	Psychiatric disorders	2/04/09	30/04/09	Severe	Yes
11074	Relapse of Schizoaffective Disorder	Schizoaffective disorder	Psychiatric disorders	19/07/08	10/09/08	Severe	Yes
11079	dizziness when lying down	Dizziness postural	Cardiac disorders	7/06/08	Ongoing	Mild	No
11079	increased incidence of leg cramps	Muscle spasms	Musculoskeletal and connective tissue disorders	7/06/08	26/06/08	Mild	No

Patient	AE Verbatim	MedDRA PT	MedDRA SOC	Start Date	End Date	Severity	Serious?
11079	kidney pain and dysuria (?UTI)	Renal pain	Renal and urinary disorders	7/06/08	8/07/08	Moderate	No
11079	intermittent chest pains	Chest pain	General disorders and administration site conditions	1/07/08	Ongoing	Mild	No
11079	panic/anxiety attack	Panick attack	Psychiatric disorders	4/07/08	4/07/08	Moderate	No
11079	sore back and muscle aches	Back pain	Musculoskeletal and connective tissue disorders	21/07/08	Ongoing	Mild	No
11080	significant clinical deterioration and behavioural change	Abnormal behaviour	Psychiatric disorders	6/06/08	Ongoing	Severe	No
11081	phlegmy cough	Productive cough	Respiratory, thoracic and mediastinal disorders	4/01/09	6/02/09	Mild	No
11081	wheeze	Wheezing	Respiratory, thoracic and mediastinal disorders	3/06/09	Ongoing	Mild	No
11082	One episode of vomitting	Vomiting	Gastrointestinal disorders	4/07/08	4/07/08	Mild	No
11082	Lip movements - possibly tardive dyskinesis	Tardive dyskinesia	Nervous system disorders	4/03/09	1/04/09	Mild	No
11083	Muscle stiffness in soleus muscles (lower leg)	Musculoskeletal stiffness	Musculoskeletal and connective tissue disorders	7/08/08	28/08/08	Mild	No
11090	tardive dyskinesia (pill rolling and foot tapping)	Tardive dyskinesia	Nervous system disorders	7/08/08	Ongoing	Moderate	No
11097	Galactorrhea	Galactorrhoea	Endocrine disorders	7/09/08	31/10/08	Mild	No
11097	Paranoid thoughts, lowered mood.	Paranoia	Psychiatric disorders	2/10/08	31/10/08	Moderate	Yes
11135	Upper Respiratory Tract Infection	Upper respiratory tract infection	Respiratory, thoracic and mediastinal disorders	26/08/08	16/09/08	Mild	No
11135	Psychomoter restlessness	Psychomotor hyperactivity	Nervous system disorders	16/09/08	Ongoing	Mild	No
11135	Hypertension, 165/114	Hypertension	Vascular disorders	16/09/08	Ongoing	Mild	No
11135	Nausea and gastro symptoms	Nausea	Gastrointestinal disorders	26/09/08	10/10/08	Mild	No
11135	Exacerbation of positive symptoms of schizophrenia.	Schizophrenia	Psychiatric disorders	10/10/08	Ongoing	Severe	Yes
11218	exacerbation of schizophrenia requiring hospitalisation on 04/07/08	Schizophrenia exacerbated	Psychiatric disorders	4/07/08	8/08/08	Severe	Yes
11251	Cogwheel rigidity	Cogwheel rigidity	Musculoskeletal and connective tissue disorders	8/09/08	Ongoing	Mild	No
11251	Deterioration in mental state	Mental disorders	Psychiatric disorders	31/10/08	6/11/08	Mild	No

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