Janssen-Cilag Taiwan, Johnson & Johnson

Clinical Study Report

Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotics to long-acting risperidone microspheres.

Protocol No.: RISC-TWN-MA10; Phase IV

Issue/Report Date: 25 Sep 2009
Prepared by: Janssen-Cilag Taiwan
Department: Medical Affairs
Document No.: RISC-TWN-MA10

1. TITLE PAGE

Indication: Schizophrenia or schizoaffective disorders

Protocol No.: RISC-TWN-MA10

Date of Study Report: 25 Sep 2009

Sponsor: Janssen-Cilag Taiwan, Johnson & Johnson

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Jyoti Arora
Kinapse Ltd
Dec 02, 2013 03:36

2. SYNOPSIS

Name of Sponsor/Company: Janssen-Cilag Taiwan, Johnson & Johnson	
Title of Study:	Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotics to long-acting risperidone microspheres.
Study Centre and Investigators:	中山醫學大學附設醫院 / 賴德仁 教授 成大醫院 / 楊延光 主任 彰化基督教醫院 / 邱南英 主任 天主教聖馬爾定醫院 / 楊志強 主任 臺大醫院 雲林分院 / 黃隆正 醫師 嘉義基督教醫院 / 劉俊宏 醫師
Phase of Development:	Phase IV
Objective:	The primary objective of the trial is to evaluate the maintained efficacy and improvement of overall functionality with two-week interval injections of long acting risperidone microspheres on patients receiving psychiatric home-care treatment with schizophrenia and schizoaffective disorders.
Methodology:	Multicenter, open labeled study
Number of Patients:	31 patients
Duration of Treatment:	6 months
Criteria for Evaluation:	
Efficacy:	• Positive and Negative Syndrome Scale (PANSS) • Personal and Social Performance (PSP) Scale • Clinical Global Impression (CGI) • Quality of Life Questionnaire (SF-36) • Patient Satisfaction • Caregiver's Satisfaction
Safety:	• Simpson-Angus Rating Scale (SAS) • Adverse Events

	• Clinical Laboratory Tests • Vital Signs
Statistical Methods:	• Wilcoxon signed rank test • Paired t test • Descriptive statistics
Summary	
Summary:	The results showed that long acting resperidone does show modest efficacy in treating stable patients with schizophrenia, particularly from caregiver's perspective. These findings were supported by western countries' studies[16, 17]. Regarding the safety, the higher level of triglyceride and increased body weight after switching to long-acting resperidone was noted in this study which the similar results were supported by others[16,17]. Therefore, the adverse effects which related metabolic issues need to be addressed in the future. The results of the present study need be interpreted with caution due to the following limitation. Firstly, this study only recruited a small number of patients. Secondly, this was a relatively short-term (6-month) study. Longer term data are needed to confirm the findings from this study. Thirdly, the high drop-out rate (11/31) weakens the results. Fourthly, this was a single are open-label study that used one switching strategy. Switching antipsychotic agents in common in clinical practice; therefore, it would be beneficial to incorporate a number of switching strategies in a parallel design. Finally, this was a non-randomized study which only in clued clinically stable patients. To validate the results, randomized, double-blinded studies with longer follow-up durations need to be conducted in the future.
Date of the Report:	25 Sep 2009

SIGNATURE PAGE

PRINCIPAL INVESTIGATOR SIGNATURE

Study Title: **Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotics to long-acting risperidone microspheres.**

Date of Study Report: **25-Sep-2009**

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

Principal Investigator:

Signature: _____

Date: _____

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4. ETHICS

4.1 Institutional Review Board (IRB)/Ethics Committee (EC)

The protocol, amendments, informed consent form, and all other forms of patient information related to the study (e.g., case report form [CRF]) were reviewed and approved by a Joint Institutional Review Board (JIRB). Janssen-Cilag Taiwan, Johnson & Johnson received a copy of the written JIRB approval of the protocol and informed consent form prior to authorizing the shipment of the study drug supplies to the site.

4.2 Ethical Conduct of Study

In Taiwan the study was conducted in accordance with the Declaration of Helsinki, Good Clinical Practice (GCP) and applicable regulatory requirements. The investigators assured that the study was conducted in accordance with prevailing local laws and customs and complied with the provisions as stated in the Taiwan guidelines. The investigator was responsible for reporting to the authorities and the JIRB/IRB any modifications, safety updates, amendments and violations of the protocol that impacted patient safety.

4.3 Patient Information and Consent

A voluntary written informed consent form was signed by each patient after the nature of the study was explained and prior to any study-related procedure being performed. The JIRB and local IRBs approved the contents of the informed consent form.

5. INVESTIGATOR AND STUDY ADMINISTRATIVE STRUCTURE

This study was performed at 6 centers in Taiwan. Information on personnel associated with the conduct and evaluation of this study was given as follows. This study was sponsored by Johnson & Johnson Janssen-Cilag Taiwan and monitored by the sponsor's designated representative.

List of Structure

Center and Investigator(s):

中山醫學大學附設醫院 / 賴德仁 教授

成大醫院 / 楊延光 主任

彰化基督教醫院 / 邱南英 主任

天主教聖馬爾定醫院 / 楊志強 主任

臺大醫院 雲林分院 / 黃隆正 醫師

嘉義基督教醫院 / 劉俊宏 醫師

6. INTRODUCTION

Schizophrenia continues to be a devastating and costly disease, despite recent advances in treatment. People with schizophrenia have psychotic episodes characterised by delusions, hallucinations, unusual thought content, aggression and excitement, which often result to hospitalisation. However, other symptoms that may continue during periods of relative wellness create much of the disability associated with the disease. Declining social and occupational functioning are extensions of such symptoms as poor executive functioning, restricted affect, poverty of speech, disorganisation, lack of motivation, cognitive impairment, and poor self-care. These symptoms are often called negative symptoms and are an important focus of new drug development[1].

While classical antipsychotics suppress and control positive symptoms of schizophrenia, there is no clear evidence from controlled studies that they are effective for ameliorating the negative symptoms of schizophrenia, such as alogia, affective flattening, anhedonia/asociality, depressed appearance, avolition/apathy, psychomotor retardation and attentional impairment. The atypical antipsychotics like Risperdal® have been shown not only to be effective for suppressing positive symptoms but have improved efficacy on negative symptoms as well.

Depot antipsychotics were developed in the 1960s as an attempt to improve the long-term treatment of schizophrenia and other disorders benefiting from long-term antipsychotic medication. By maintaining more stable plasma levels, the major advantage of depot antipsychotics over oral medication is the facilitation of compliance in medication taking. Non-compliance is very common among patients with schizophrenia or schizoaffective and is a frequent cause of relapse. Most depot antipsychotics are fatty-acid esters of parent antipsychotic compounds. In general, they are dissolved in a

vegetable oil and injected intramuscularly. Their duration of action is determined by a gradual release of the ester from the depot into the circulation and its subsequent hydrolysis by esterases. In the case of risperidone, however, formation of a fatty-ester compound is not possible since the molecule does not contain a free hydroxyl group.

So far, Risperdal® has been available as a tablet and a liquid formulation. Recently a long acting formulation has been developed. Microspheres of biological polymers have been prepared in which risperidone is incorporated. The long acting risperidone microspheres formulation is an aqueous suspension which contains risperidone in a matrix of glycolic acid-lactate co-polymer. Gradual hydrolysis of the co-polymer at the site of injection ensures the slow and steady release of risperidone over a period of several weeks. The long acting risperidone microspheres formulation combines the advantages of conventional depot antipsychotics (as compliance and stable plasma levels) and the proven efficacy of risperidone on positive and negative symptoms representing an innovative new tool in the long-term treatment of patients.

Single doses (25, 50 and 100 mg risperidone) of the long acting risperidone microspheres have been administered to chronic schizophrenic subjects in five phase I trials[2-10]. The plasma concentration of the active moiety showed an initial burst (about 2% of the dose) within the first 24 hours. A gradual release of the main fraction of the risperidone microspheres started after about 2-3 weeks, peaked at about 4-5 weeks and lasted until 6-7 weeks after the intramuscular injection. The bioavailability was close to complete. There was a dose-proportional increase in peak plasma concentrations and AUC for the active moiety (= risperidone + 9-OH-risperidone) across these studies. Pharmacokinetic modelling based on single dose data indicated the need for injections every two weeks to reach the comparable oral concentration range within the recommended risperidone oral therapy.

The multiple dose (25, 50 and 75 mg risperidone) trials studied the steady state pharmacokinetics of 5 injections every two weeks administered to chronic schizophrenic subjects[11, 12]. In most subjects steady state was reached after 8 weeks (4 injections).

The phase III programme included three trials with over 1700 schizophrenic or schizoaffective patients of whom more than 1300 were treated with long acting risperidone microspheres; one double-blind efficacy trial comparing 3 strengths of long acting risperidone microspheres with placebo and one double-blind equivalence trial comparing long acting risperidone microspheres with risperidone oral tablets[13, 14]. These studies demonstrated that long acting risperidone microspheres were equally efficacious in comparison to oral risperidone. The patients continued to improve after randomisation to either oral or microsphere risperidone. The conclusion was based on total PANSS and positive and negative symptoms on the PANSS rating scale, and was also supported by the CGI evaluations. There was a significant improvement from the baseline for long acting risperidone microspheres compared to placebo (p< 0,001). The third trial, a one-year open-label trial was performed to document the long-term safety and efficacy of long acting risperidone microspheres in a larger patient population. This trial showed that after the beginning of treatment with risperidone microspheres the patients continuously improved on the PANSS scale for 6-9 months and then were stabilised[15]. All trials used a run-in with oral risperidone prior to the subject switching to risperidone microspheres. The 25mg dose was found to be the lowest effective dose and therefore, this will be used as the recommended starting dose for this trial.

For more detailed information, refer to the Investigator's Brochure for Risperdal CONSTA™.

Several Studies[16, 17] have shown that Risperdal CONSTA™ provides great benefits

to chronic psychotic patients even though their psychotic symptoms had been stable for long time. In Taiwan, psychiatric home-care treatment is a unique program for relatively psychotic patients living in the community. Therefore, we purpose this study to evaluate the role of Risperdal CONSTA™ in psychiatric home-care program.

7. OBJECTIVE

7.1 Primary Objective

The primary objective of the trial is to evaluate the maintained efficacy and improvement of overall functionality with two-week interval injections of long acting risperidone microspheres on patients with schizophrenia and schizoaffective disorders.

7.2 Specific Objective

Efficacy

Primary Endpoint

- Compare the change in total PANSS score at endpoint versus the baseline

Secondary Endpoints

- Compare the PSP score at endpoint, versus the baseline and pre-risperidone long-acting period;
- Compare the CGI score at endpoint, versus the baseline and pre-risperidone long-acting period;
- Compare the SF-36 at endpoint, versus the baseline and pre-risperidone long-acting period;
- To compare the 6-month study period of patients taking risperidone long-acting versus the 6-month pre-study (pre-risperidone long-acting) with respect to rates of patient compliance; rate, frequency, and duration of relapse, incidence of adverse events, number of hospitalization days, frequency and cases of ER visits.

Safety

- Compare the change in SAS score at endpoint, versus the baseline;
- Identify the side effect profile of Long Acting Risperidone;

8. INVESTIGATIONAL PLAN

8.1 Study Design

8.1.1 Study Design

This trial was a six-month, non-randomised, single arm, multicenter study aimed to evaluate efficacy and safety in patients with schizophrenia or schizoaffective disorder who are switched from an antipsychotic medication to two-week interval injections of long acting risperidone microspheres. Patients from any antipsychotic medication can be switched to long acting risperidone microspheres without prior oral risperidone run in phase. Patients must be receiving psychiatric home-care treatment. All patients stayed on their previous medication for the first three weeks of risperidone microsphere treatment (see 8.3.2 Dosage Record and Compliance Measurement and Table 1). Thereafter, the previous medication will be tapered off. For patients previously taking anticholinergic medication, continue the anticholinergic medication as long as the antipsychotic associated with EPS is being taken and then taper and discontinue the anticholinergic medication over the first 3 weeks after the antipsychotic is discontinued. Study medication must be administered by intramuscular (gluteal) injection every two weeks. Most patients should be started on 25 mg long acting risperidone microspheres. However, some patients (e.g. who suffer from persistent symptoms and/or are known to respond only to higher dosages of antipsychotics) may require a higher initial dose of long acting risperidone microspheres. Efficacy failure will only be considered for patients who have received the maximum dose of 50 mg long-acting risperidone microspheres and are still symptomatic or have not responded to treatment after at least 2 months on said dose (4 doses). Risperidone microspheres 25, 37.5 and 50 mg will be used for this trial.

Assessments of efficacy and safety were performed at baseline and on months 1, 3, and 6.

8.1.2 Study Design Rationale

Long acting risperidone microspheres have a pharmacokinetic profile that differs from the profiles known from conventional depot antipsychotics. Because of this profile, a 3-week supplementation with antipsychotic medication is necessary when a patient is started on long acting risperidone microspheres. Since in daily practice patients would go from one depot to another, this trial will be conducted to evaluate the efficacy, improvement of overall functionality and safety for the immediate switch from previous depot or oral antipsychotic medication to long acting risperidone microspheres. For the first three weeks of risperidone microsphere treatment, all patients will stay on their previous oral medications, which thereafter were tapered off.

Table 1. Summary of Recommended Dosing and Switching Strategies for Long-acting Risperidone

Issue	Guideline
Prescribing a starting dose for adult with schizophrenia	25 mg/2 wk
Administering a test dose	If the patient has never taken oral risperidone, give a hypersensitivity challenge with 1mg/d of oral risperidone for 2 consecutive d
Switching to long-acting risperidone from oral antipsychotics	Start with 25 mg/2 wk of long-acting risperidone Continue coverage with current oral antipsychotic for 3 wk
Switching to long-acting risperidone from depot conventional antipsychotics	Administer long-acting risperidone instead of the conventional depot antipsychotic at the next scheduled injection date No coverage with an oral antipsychotic is necessary
Achieving steady-state	Occurs after 4 consecutive injections given every 2 wk, i.e., about 8 wk after the first injection
Managing missed doses before steady-state plasma concentration is achieved	If >2 wk have passed since the last injection, administer long-acting risperidone as soon as possible and provide coverage with an oral anti-psychotic for 3 week
Managing missed doses after steady-state plasma concentration is achieved	If 3-6 wk have passed since the last injection, administer a dose of long-acting risperidone as soon as possible and monitor the patient for symptoms If ≥ 6 wk have passed since the last injection, administer long-acting risperidone as soon as possible and provide coverage with an oral antipsychotic for 3 week
Discontinuing concomitant anticholinergic medication	Discontinue only if patients have no extrapyramidal symptoms (EPS) For patients previously taking an oral antipsychotic, continue the anticholinergic medication as long as the oral antipsychotic associated with EPS is being taken and then taper and discontinue the anticholinergic medication over the first 3 wk after the oral antipsychotic is discontinued
Managing breakthrough symptoms	Determine the type of symptoms For anxiety, prescribe a benzodiazepine For depression, prescribe an antidepressant For immediate control of psychosis, prescribe an oral antipsychotic
Considering efficacy failure	For patients who have received the maximum dose of 50 mg long-acting risperidone microspheres and are still symptomatic or have not responded to treatment, should be maintained on the said dose for 2 to 4 months before considering efficacy failure.

Marder, Stephen, et. al. Clinical Guidelines Dosing and Switching Strategies for Long-Acting Risperidone. J Clin Psychiatry 2003; 64 (suppl 0)

8.2 Patient Population

8.2.1 Patient Population

The intention is to construct the homogeneous group of patients receiving psychiatric home-care treatment.

8.2.2 Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

- Male or female
- Meet the diagnostic criteria for schizophrenia or schizoaffective disorder according to DSM-IV-TR;
- Age $\geq$ 18;
- Subject has been given an adequate dose of an appropriate antipsychotic for an adequate period of time prior to enrollment, but previous treatment is considered unsatisfactory due to one or more of the following reasons: lack of efficacy, lack of tolerability or safety, lack of compliance and/or other reasons to switch to another antipsychotic medication;
- Female subjects must be postmenopausal, surgically sterile, or practicing an effective method of birth control (e.g., prescription oral contraceptives, contraceptive injections, intrauterine device, double-barrier method, contraceptive patch, male partner sterilization) before entry and throughout the study; have a negative urine β-HCG pregnancy test at screening; and a negative urine pregnancy test on screening visit.

Subjects or their legally acceptable representatives must have signed an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study.

8.2.3 Exclusion Criteria

Potential subjects who meet any of the following criteria will be excluded from participating in the study:

- A primary, active DSM-IV-TR diagnosis other than schizophrenia and schizoaffective disorder
- Relevant history or current presence of any significant and/or unstable cardiovascular, respiratory, neurological (including seizures or significant cerebrovascular), renal, hepatic, hematologic, endocrine, immunologic or other systemic disease
- Biochemistry, hematology or urinalysis results that are not within the laboratory's normal reference range and are deemed to be clinically significant by the investigator
- History of evidence of clinically significant hepatic disease (including aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 2 times the upper limit of normal) at screening
- History of severe, life-threatening allergic reaction to any drug
- Known hypersensitivity to risperidone
- Subject has been given adequate doses of Risperdal CONSTA for an adequate period of time prior to enrollment, but previous treatment with Risperdal

CONSTA is considered unsatisfactory due to one or more of the following reasons: lack of efficacy, lack of tolerability or safety and/or other reasons;

- History or current symptoms of tardive dyskinesia;
- History of neuroleptic malignant syndrome (NMS)
- Significant risk of suicidal or violent behavior, as clinically assessed by the investigator
- Exposure to an experimental drug, experimental biologic or experimental medical device within 30 days before screening
- Female subject who is pregnant or breastfeeding or planning to become pregnant during the study period
- Treatment with any of the following disallowed therapies:
  - Risperdal CONSTA within 12 weeks before screening
  - Electroconvulsive therapy within 60 days before screening
  - Nonselective/irreversible MAOI antidepressants within 4 weeks before screening
  - Other prescription, over-the-counter, or herbal agents with psychoactive properties within 2 days before baseline

It is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone long acting injectable microspheres in those patients who have no history of risperidone use.

8.3 Visit Schedule and Assessments

Table 2. Visit schedule and assessments

Period	Screening period				Baseline	Run-in period			Treatment period		End of trial
Visit					1				2	3	4
Week						1	2	3	4	12	24
Day	-28	-21	-14	-7	1[a]	8	15	22	29	85	169
Screening/Administrative Procedure											
Informed consent[c]					X						
Medical history					X						
Psychiatric history					X						
Substance abuse history					X						
Psychiatric evaluation					X						
Inc/excl. criteria					X						
Physical examination					X						X
Study Drug Administration											
A. Previous antipsychotic											
a. Oral antipsychotic	X	X	X	X	X	X	X	X			
b. 2-week interval depot			X		X						
c. 3-week interval depot		X			X						
d. 4-week interval depot	X				X						
B. Risperdal CONSTA injection[d]					X		X		X	X	X
Efficacy Procedure											
PANSS					X				X	X	X
PSP					X				X	X	X
CGI					X				X	X	X
SF-36					X						X
Patient's satisfaction					X						X
Caregiver's satisfaction					X						X
Safety Assessment											
Vital signs/Body weight					X				X	X	X
ECG (if applicable)					X						
Clinical lab evaluations					X						X
Pregnancy test in women[e]					X						X
SAS					X				X	X	X
Adverse event monitoring[f]					X				X	X	X
Concomitant medication review					X				X	X	X
Retrospective Data Collection					X						

8.3.1 Dosage Record and Compliance Measurement

8.3.1.1 Drugs, formulations and strengths

The treatment consists of vials containing risperidone in microspheres: 25, 37.5, 50 mg and pre-filled syringes containing a reconstitution vehicle (diluent) for intramuscular injection.

Two 20G needles are provided – one for preparing the suspension (microspheres and diluent) and one for the intramuscular injection.

Both the vial containing risperidone in microspheres and the pre-filled syringes containing the diluent must be stored between +2^{o}C and +8^{o}C.

The medication is packed in containers labelled with description of the trial number and medication number and dosing instructions. Before the trial starts, a Janssen-Pharmaceutica monitor explains the step-by-step procedures for the preparation of the injection admixture with the designated staff member(s) who administer the trial medication.

8.3.1.2 Dosages

Long acting risperidone microspheres must be administered by intramuscular (gluteal) injection every two weeks. Injections should alternate between the two buttocks. Most patients should be started on 25 mg long acting risperidone microspheres. However, some patients (e.g. who suffer from persistent symptoms and/or are known to respond only to higher dosages of antipsychotics) may require a higher initial dose of long acting risperidone microspheres. In this case, patients should be started on 37.5 mg or as much

as 50 mg of the drug. If necessary, dosage should be adjusted according to the patients' symptoms and response to treatment.

Physicians should wait until the drug has achieved steady-state plasma concentration at the present dose, i.e., after about 4 injections or about 8 weeks after the first injection of that dose, before deciding whether the dose should be lowered or increased[18].

For patients who have received the maximum dose of 50 mg long-acting risperidone microspheres and are still symptomatic or have not responded to treatment, there should be maintained on the said dose for 2 to 4 months before considering efficacy failure.

It is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone long acting injectable microspheres in those patients who have no history of risperidone use.

Test dose

It is recommended to establish tolerability with oral risperidone prior to initiating treatment with risperidone long acting injectable microspheres in those patients who have no history of risperidone use.

Those patients should receive 1mg risperidone tablets once daily for 2 days prior to the first risperidone depot microsphere injection.

8.3.2 Efficacy Assessments

8.3.2.1 Positive and Negative Syndrome Scale (PANSS)

The neuropsychiatric symptoms of schizophrenia were assessed using the 30-item PANSS scale, which provides a total score (sum of the scores of all 30 items) and scores for 3 subscales, the positive subscale (7 items), the negative subscale (7 items), the general psychopathology subscale (16 items) and the remission subscale (8 items). Each

scale is rated 1 (absent) to 7 (extreme). The PANSS assessment should be administered by a qualified rater (defined as a trained clinician: Psychiatrist, D.O. or M.D., Psychiatric resident, D.O. or M.D., Psychologist, Ph.D., or masters level mental health professional with a recognized degree licensed to practice psychology or counselling and with recent experience in conducting PANSS and qualification training in performing PANSS and CGI-S assessments). If possible, for a given subject, the same rater should administer this scale at all visits.

Subjects were interviewed at start (visit 1), on week 4 (visit 2), week 12 (visit 3), and week 24 (visit 4/end-point) using the PANSS. The primary parameter is change in total PANSS score at endpoint versus baseline.

8.3.2.2 Clinical Global Impression (CGI)

The CGI-S rating scale is used to rate the severity of a subject's overall clinical condition on a 7-point scale ranging from 1 (not ill) to (extremely severe). This scale permits a global evaluation of the subject's condition at a given time. The CGI-S assessment should be administered by a qualified rater as previously defined. The individual administering the PANSS should also score the CGI-S.

8.3.2.3 Personal and Social Performance (PSP) Scale

The PSP scale assesses the degree of difficulty a subject exhibits over a 7-day period within 4 domains of behaviour: a) socially useful activities, b) personal and social relationships, c) self-care, and d) disturbing and aggressive behaviour. The results of assessment are converted to a numerical score following the PSP scoring guidelines. A mental health professional experienced in the treatment of subjects with schizophrenia

who has received the sponsor's rater training will administer the PSP. If possible, for a given subject, the same person should administer this scale each time it is administered.

8.3.2.4 Quality of Life Questionnaire (SF-36)

The SF-36 Taiwan standard version was developed in 1996 through the collaboration of Drs. Jui-Fen Rachel Lu, Chung-Fu Lan, Shwu-Chong Wu, Wen-Liang Liu, Jwo-Leun Lee, and Chun-Huei Chi. The SF-36 Taiwan version was developed following the protocol by the International Quality of Life Assessment (IQOLA) Project. This rating scale includes 36 items concerning the subject's quality of life.

8.3.2.5 Patient Satisfaction

Subjects were interviewed at start and at the end of the trial (week 24/end-point) to assess their satisfaction with the current treatment on a 5-point scale (very good, good, reasonable, moderate or poor).

8.3.2.6 Caregiver's Satisfaction

Caregivers were interviewed at start and at the end of the trial (week 24/end-point) to assess their satisfaction with the current treatment on a 5-point scale (very good, good, reasonable, moderate or poor).

8.3.3 Safety Assessments

8.3.3.1 Simpson-Angus Rating Scale (SAS)

Extrapyramidal side effects were evaluated using the SAS. A measurement using SAS will be performed at baseline, and at all other times indicated in the Time and Events

Schedule.

8.3.3.2 Adverse Events

Adverse events were reported by the subject (or, when appropriate, by a caregiver, surrogate, or the subject's legally acceptable representative) for the duration of the study. Adverse events were followed by the investigator for a length of time as determined by the sponsor. Specific details on adverse event reporting are provided in Table 11.

8.3.3.3 Clinical Laboratory Tests

Blood samples for serum glucose (A.C.), BUN, creatinine, aspartate aminotransferase, alanine aminotransferase, TG, LDL, total-cholesterol was taken at the start of the study on screening day and at the end of the treatment. For female subjects, a pregnancy test kit was administered at the start of the study, at the second week of a missed menstrual period all throughout the study period and End of trial. The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the adverse event section of the CRF. The following tests were performed:

Serum Chemistry Panel

BUN
Creatinine
Glucose (A.C.)
aspartate aminotransferase (AST)
alanine aminotransferase (ALT)
TG
LDL
Total cholesterol

8.3.3.4 Vital Signs (pulse, temperature, blood pressure, respiration rate, weight)

Blood pressure and heart rate measurements were assessed with a completely automated device consisting of an inflatable cuff and an oscillatory detection system. All values were registered on a built-in recorder so that measurements are observer-independent.

8.3.4 Data Management and Statistical Methods

All subjects who receive at least one injection of risperidone microspheres will be included in the analysis of the safety, demographic, and baseline characteristic data. An analysis of treatment-emergent adverse events will be performed. All subjects who receive at least one injection of risperidone microspheres and provide post-baseline efficacy measurements will be included in efficacy data analyses. This is the intent-to-treat analysis set.

Baseline for all analyses is Visit 1 (start of risperidone long-acting). If there are substantial numbers of protocol violators (e.g., more than 10%), an additional per-protocol analysis may be performed. The main comparison in change of efficacy between long acting risperidone microspheres and previous neuroleptic medication is equivalence (non-inferiority) in mean total PANSS score. The changes from baseline to endpoint were also tested for differences using the Wilcoxon signed rank test or paired t test (ordinal/continuous data).

Statistical tests for differences between endpoint and baseline was interpreted at the 5% significance level (two-tailed).

9. RESULTS

The demographic data of these participants were described in Table 9.1 and Table 9.2.

Table 9.1. Demographic characteristics

Category	Statistics	Results (N=31)	
Age (year)	Mean±SD	37.6 ± 10.1	
	Median	39.0	
	Min – Max	20.0 - 68.0	
Gender	Male	20	(65%)
	Female	11	(35%)

Table 9.2. Disposition of patients

Status	No. of subjects
Subject randomized	31
Safety population	31
Intent-to-treat (ITT) population	31
Completed the Study Treatment	20
Withdrawal/Early Terminated Study Treatment	11

31 patients were recruited and 20 of them completed this study. The reasons of patients withdrawal / early termination were showed in Table 9.3.

Table 9.3. Reason of Subjects Withdrawal/Early Termination

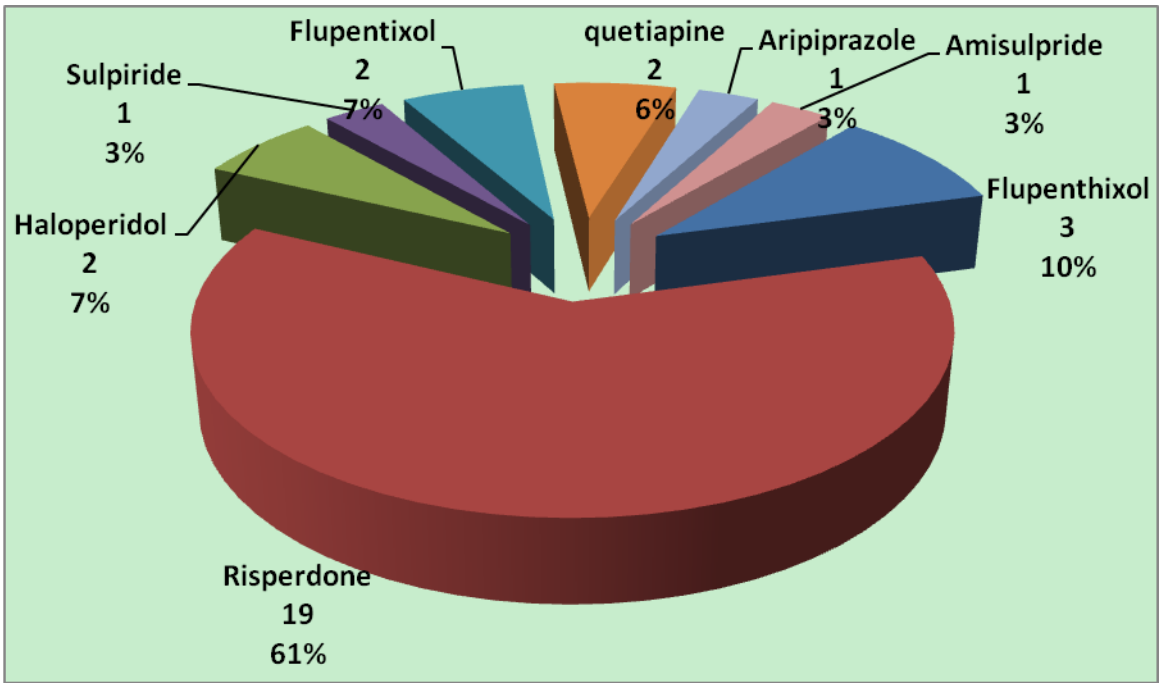
Category	No. of Subject (N=31)	
Withdrawal/Early Terminated Study Treatment	**11**	**(35.5%)**
Adverse Event	1	(3.2%)
Insufficient Response	2	(6.5%)
Patient ineligible to continue the trial	1	(3.2%)
Patient withdrew consent	5	(16.1%)
Patient lost to follow-up	2	(6.5%)

The reasons for switching to long acting risperidone were showed in Table 9.4 (n=27). The previous medication before switching was showed in Fig 9.1. Most of the previous medications before switching are risperidone.

Table 9.4. Reason for Switching to Long Acting Risperidone Microsphere

Category	No. of Subjects (N=27)	
Insufficient efficacy of previous antipsychotic medication	9	(26.5%)
Side effects	6	(17.6%)
Non-compliance	19	(55.9%)

Figure 9.1. Previous Medications



The summarized results of the efficacy assessments were showed in Table 9.5, 9.6, and 9.7. At the 6-month end point, the scores of CGI, caregiver's satisfaction were significant improved. However, the rest of assessments, included PANSS, PSP, SF-36, and patients satisfaction was not statistical different.

Table 9.5. Summarized results of efficacy assessments.

	subscale	Visit	Mean	Std. Deviation	Paired t' / Wilcoxon Signed ranks Test	p
Positive and Negative Syndrome Scale (n=25)	PANSS SUM	1	73.64	25.04	--	--
		2	68.2	24.28	-2.47'	0.02*
		3	66.12	19.86	-1.47'	0.15
		4	65.68	23.42	-1.48'	0.15
	positive symptoms	1	21.44	7.52	--	--
		2	20.32	7.35	-1.19'	0.24
		3	19.24	7.12	-1.28'	0.21
		4	18.72	7.81	-1.8'	0.08
	negative symptoms	1	21.4	8.71	--	--
		2	18.64	8.47	-2.99'	0.01**
		3	18.52	6.59	-1.78'	0.09
		4	18	7.66	-1.9'	0.07
	disorganized thoughts	1	15.84	7.16	--	--
		2	15.32	6.59	-1.03'	0.31
		3	14.68	5.28	-1.07'	0.29
		4	14.48	6.07	-1.12'	0.27
	uncontrolled Hostility / Excitement	1	6.68	3.72	--	--
		2	6.64	3.33	-0.43	0.67
		3	6.6	2.97	-0.18	0.86
		4	6.72	4.18	-0.26	0.79
	anxiety / depression	1	8.08	3.24	--	--
		2	7.28	2.78	-2.48	0.01*
		3	7.04	2.61	-1.65	0.1
		4	7.68	2.88	-0.57	0.57
clinical global impression (n=24)		1	4.29	1	--	--
		2	3.88	1.26	-2.35	0.02*
		3	3.63	1.28	-2.49	0.01*
		4	3.5	1.56	-2.38	0.02*
Personal and Social Performance (n=24)		1	52.67	20.09	--	--
		2	56.96	19.12	-2.42	0.02*
		3	61.08	16.14	-3.5	0.00***
		4	59.29	19.67	-1.76	0.08
SF-36 (n=20)	general health	1	15.05	2.74	--	--
		4	15.6	1.73	-0.41	0.68
	physical function	1	27.2	3.46	--	--
		4	24.75	6.33	-0.78	0.44
	role physical	1	5.75	2	--	--
		4	6.05	1.88	-1.24	0.21
	role emotional	1	4.45	1.36	--	--
		4	4.75	1.45	-1.1	0.27
	social function	1	5.4	1.1	--	--
		4	5.35	0.99	-0.05	0.96
	bodily pain	1	3.8	2.31	--	--
		4	3.35	2.01	-0.98	0.33
	mental health	1	19.9	2.86	--	--
		4	19.65	2.6	-0.22	0.83
	vitality	1	15.4	1.82	--	--
		4	16.05	2.24	-1.49	0.14
patient satisfaction (n=22)		1	3.27	1.03	--	--
		4	3.55	0.51	-1.25	0.21
Caregiver's Satisfaction (n=22)		1	3	0.82	--	--
		4	3.59	0.59	-2.7	0.01**

Table 9.6. Patient Satisfaction

Result	No. of Patient (N=22/31)	
Descent	**4**	(12.9%)
Very good to Moderate	1	(3.2%)
Very good to Good	1	(3.2%)
Good to Moderate	2	(6.5%)
Improvement	**9**	(29.0%)
Moderate to Good	2	(6.5%)
Poor to Good	2	(6.5%)
Poor to Moderate	5	(16.1%)

Table 9.7. Caregiver's Satisfaction

Result	No. of Patient (N=22/31)	
Descent	**2**	(6.5%)
Moderate to Poor	1	(3.2%)
Good to Moderate	1	(3.2%)
Improvement	**12**	(38.7%)
Moderate to Good	5	(16.1%)
Poor to Good	3	(9.7%)
Poor to Moderate	4	(12.9%)

The summarized results of safety assessment were showed in Table 9.8. At the 6-month end point, there were no significant change in the severity of EPS and other biochemical and vital data. However, both triglyceride and body weight increased.

Table 9.8. Summarized results of safety assessments.

	subscale	Visit	Mean	Std. Deviation	Paired t' / Wilcoxon Signed ranks Test	p
Simpson-Angus Rating Scale (n=24)		1	5.88	5.77	--	--
		2	5.04	4.35	-1.3	0.19
		3	3.58	3.68	-2.1	0.04*
		4	3.75	3.22	-1.81	0.07
Clinical Laboratory Tests (n=18)	血中尿素氮(BUN)	1	11.82	3.9	--	--
		4	12.31	3.55	0.34'	0.74
	fasting blood sugar	1	90.06	12.13	--	--
		4	109.33	58.22	-1.76	0.08
	血清肌酸酐 (Creatinine)	1	0.9	0.2	--	--
		4	0.92	0.23	-0.51	0.61
	Aspartate aminotransferase	1	22.11	7.29	--	--
		4	24.83	13.12	-0.57	0.57
	Alanne aminotransferase	1	28	17.1	--	--
		4	32.5	30.82	-0.41	0.68
	三甘油脂(TG)	1	110.5	45.61	--	--
		4	172.11	103.9	-2.18	0.03*
	Low-density lipoprotein (LDL)	1	106.28	42.07	--	--
		4	126.11	37.68	1.83'	0.08
	total cholesterol	1	173.83	54.37	--	--
		4	194.72	48.12	1.1'	0.29
Vital (n=24)	weight	1	67.77	15.48	--	--
		2	69.09	15.87	2.38'	0.03*
		3	71.66	16.15	3.9'	0.00***
		4	71.35	15.53	3.18'	0.00**
	Temperature	1	36.45	0.48	--	--
		2	36.52	0.41	-0.66	0.51
		3	36.47	0.46	-0.2	0.84
		4	36.32	0.41	-1.06	0.29
	PULSE	1	88.13	10.51	--	--
		2	87.79	16.67	-0.07	0.94
		3	87.46	10.74	-0.34	0.73
		4	83.13	9.69	-1.53	0.13
	BPSYS	1	120.08	12.61	--	--
		2	122.71	14.36	0.96'	0.35
		3	122.38	17.21	0.81'	0.43
		4	115.88	22.8	-1.05'	0.3
	BPDIA	1	80.46	9.99	--	--
		2	81.46	10.08	0.55'	0.59
		3	80.75	12.93	0.1'	0.92
		4	80.54	9.32	0.04'	0.97

There were 35 adverse effects, and 4 serious adverse effects (SAE). Those SAE were reported non-drug-related AE (Table 9.9).

Table 9.9. Treatment-emergent Adverse Event

Variable	**Results (N=31)**		
	Number of All Adverse Events	**Number of Subjects with Adverse Events**	
All AEs	35	18	(58.1%)
Drug-related AEs	0	0	(0.0%)
Serious AEs	4	4	(12.9%)
Drug-related serious AEs	0	0	(0.0%)

10. DISCUSSION

The results showed that long acting resperidone does show modest efficacy in treating stable patients with schizophrenia, particularly from caregiver's perspective. These findings were supported by western countries' studies[16, 17]. Regarding the safety, the higher level of triglyceride and increased body weight after switching to long-acting resperidone was noted in this study which the similar results were supported by others[16,17]. Therefore, the adverse effects which related metabolic issues need to be addressed in the future.

The results of the present study need be interpreted with caution due to the following limitation. Firstly, this study only recruited a small number of patients. Secondly, this was a relatively short-term (6-month) study. Longer term data are needed to confirm the findings from this study. Thirdly, the high drop-out rate (11/31) weakens the results. Fourthly, this was a single are open-label study that used one switching strategy. Switching antipsychotic agents in common in clinical practice; therefore, it would be beneficial to incorporate a number of switching strategies in a parallel design. Finally, this was a non-randomized study which only in clued clinically stable patients. To validate the results, randomized, double-blinded studies with longer follow-up durations need to be conducted in the future.

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CIOMS Report for SDE00026747 RISC-TWN-MA10

Run Information

User Name: Goodright, Matthew (83911000)

Run Date: 24-Oct-2013

Parameters

Results: 5 cases selected from 5 matching the following criteria

Status: NOT = Deleted

J&J Cases Only: = (J&J Drug, J&J Device, Gene Therapy)

Last Distributed: = Yes

Protocol Number: = *RISC*TWN*MA10*

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Kinapse Ltd
Dec 02, 2013 03:36

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4.-6. REACTION ONSET		
		DA	MO	YR			DA	MO	YR
CHC	TW	04	OCT	1979	27 Year	M	02	OCT	2007

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [X] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

SUICIDE ATTEMPT(10042464)

This report was received from clinical trial RISC-TWN-MA10: Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotic to long-acting risperidone microspheres, concerns a 27 year old male patient 01001, from Taiwan: SAE2007TW064.

The patient's medical history and concurrent conditions were not reported. The patient's weight was 60.5 kilograms and

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

RISPERDAL CONSTA (RISPERIDONE) Microspheres

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

37.5 mg

16. ROUTE OF ADMINISTRATION

Intra-muscular

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

SCHIZOPHRENIA, PARANOID TYPE

18. THERAPY DATES (from/to)

05-SEP-2007 - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: ALCOHOL USE ??-??-???? - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : RISC-TWN-MA10
Center no :
Patient no : 01001

24b. MFR. CONTROL NO.

TW-JNJFOC-20071001830(2)

24c. DATE RECEIVED BY MFR.

13-DEC-2007

24d. REPORT SOURCE

[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE

[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

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height was 162 centimeters. The patient was treated with risperidone long-acting injection (LAI)(microspheres, intra-muscular, batch 6G554)(microspheres, intra-muscular, batch 6FSK000) 37.5 mg initiated on 25-JUL-2007 and risperidone (formulation unspecified, oral) 2 mg once a day initiated on 05-JUN-2007 for an unspecified indication. Concomitant medications were not reported.

On 02-OCT-2007, the patient had a depressed mood and attempted suicide (burning charcoal). The patient recovered from the event on 02-OCT-2007, however he was admitted to the hospital on 03-OCT-2007. No action was taken regarding risperidone LAI. Action taken with risperidone oral was not specified. The investigator considered the causality between suicide attempt, risperidone LAI, and risperidone oral as doubtful.

This report is serious (life threatening, hospitalization).

Additional information received on 19-OCT-2007.

The patient was treated with risperidone LAI 37.5 mg on 05-SEP-2007 and 25 mg on 25-JUL-2007 to 22-AUG-2007. No action taken regarding study drug.

Additional information received on 13-DEC-2007.

The patient's medical history included acid reflux esophagitis, alcohol use, head injury, mild mental retardation, schizophrenia, paranoid type, and smoker (1 ppd). The patient had had four previous hospitalizations. After the patient had been discharged in 2001, his condition was barely satisfactory under irregular "OPD follow-up" and partial medication compliance. However he began to quit medication in recent weeks. His symptoms became more and more noted recently. Auditory hallucination, presecutory delusion and delusion of reference became vivid again. The patient had been hospitalized on 31-JUL-2007. During the hospitalization, he denied all presecutory delusion and auditory hallucination. He asked for discharge frequently. He had economic stress and he said he needed to leave for work, and had promised to follow-up. However, the patient had admitted persecutory idea prior to discharge.

The patient began feeling light headedness, nausea, and vomiting. He stopped taking his psychiatric medication at night, but took them during the daytime. Gradually he experienced worsened auditory hallucination and delusion of persecution. He also had sleep problems and unexplained fears. He stayed in his room for almost a month, and had worse self care. On 02-OCT-2007, he attempted suicide and began to inhalate the charcoal-burned air. He called his mother, and his sister came home. The patient had attempted suicide due to feeling worthlessness and hopelessness. The patient presented to the hospital with self talking, auditory hallucinations, persecutory delusion, delusion of references, and suicide idea. After admission, the patient was resumed on risperidone 4 mg at night for auditory hallucination. Rivotril 1 mg a day was started for poor impulse control, cymbalta 30 mg for depressed mood, pariet 20 mg, novamin 10 mg, mopride 10 mg a day for reflux esophagitis, and risperidone LAI 25 mg received on 17-OCT-2007 and 31-

Continuation Sheet for CIOMS report **Mfr. Control No.: TW-JNJFOC-20071001830**

OCT-2007. The patient was provided supportive psychotherapy, re-educative psychotherapy, occupational therapy, and family consultation. The symptoms of auditory hallucination and depressed mood improved after the above treatment. Discharge was arranged on 09-NOV-2007.

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	RISPERDAL CONSTA (RISPERIDONE) Microspheres
Daily Dose	2) 25 mg
Therapy Dates/Duration	2) 25-JUL-2007 - Stopped

Causality

1. SUICIDE ATTEMPT [10042464]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Doubtful
Causality as per Mfr.	Doubtful

Seq. No.	2
Drug	RISPERDAL (RISPERIDONE) Unspecified
Daily Dose	1) 2 mg, 1 in 1 Day
Indication	1) SCHIZOPHRENIA, PARANOID TYPE
Route of Admin.	1) Oral
Therapy Dates/Duration	1) 05-JUN-2007 - ??-??-????

Causality

1. SUICIDE ATTEMPT [10042464]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Doubtful
Causality as per Mfr.	Doubtful

Other relevant history (Cont...)

Medical History: GASTROOESOPHAGEAL REFLUX DISEASE ??-??-???? - ??-??-????
Medical History: HEAD INJURY ??-??-???? - ??-??-????
Medical History: MILD MENTAL RETARDATION ??-??-???? - ??-??-????
Medical History: SCHIZOPHRENIA, PARANOID TYPE ??-??-???? - ??-??-????
Medical History: TOBACCO USER ??-??-???? - ??-??-???? : Comments: 1 ppd

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4.-6. REACTION ONSET		
		DA	MO	YR			DA	MO	YR
LHC	TW	09	SEP	1961	47 Year	M	28	JAN	2008

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

ABNORMAL BEHAVIOUR(10061422)

This report was received from clinical trial RISC-TWN-MA10: Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotic, concerns a male patient of unknown age patient 01004, from Taiwan: SAE2008TW008.

The patient's medical history and concurrent conditions included: schizophrenia. The patient's weight was not reported. The patient was treated with risperidone long

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

RISPERDAL CONSTA (RISPERIDONE) Microspheres

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [ ] NA UNK

15. DAILY DOSE

25 mg

16. ROUTE OF ADMINISTRATION

Intramuscular

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [ ] NA UNK

17. INDICATIONS FOR USE

SCHIZOPHRENIA

18. THERAPY DATES (from/to)

26-OCT-2007 - 04-FEB-2008

19. THERAPY DURATION

103 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

RISPERIDAL (RISPERIDONE) Unspecified ??-??-???? - ??-??-????4 mg,1 in 1 Day

23. OTHER RELEVANT HISTORY

Medical History: SCHIZOPHRENIA ??-???-1999 - ??-??-????

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : RISC-TWN-MA10
Center no :
Patient no : 01004

24b. MFR. CONTROL NO.
TW-JNJFOC-20080200234(3)

24c. DATE RECEIVED BY MFR.
02-APR-2008

24d. REPORT SOURCE
[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE
[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

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(Cont.) = Continuation attached sheet(s)

Continuation Sheet for CIOMS report **Mfr. Control No.: TW-JNJFOC-20080200234**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

acting injection (LAI)(microspheres, intramuscular) 25 mg initiated on 21-NOV-2007 for schizophrenia. On 30-JAN-2008, the patient was hospitalized for an unknown reason. Concomitant medications were not reported. The patient outcome and action taken with risperidone LAI was unknown.

The reporter provided no causality assessment. The information currently reported in this case does not meet the ICH E2A standard of "reasonable causal relationship." In the absence of additional information, the Company causality is "doubtful."

This report is serious (hospitalization).

Additional information was received from a physician on 10-MAR-2008:

This report concerns a 47-year-old male. Patient demographics were updated. The patient's medical history and concurrent conditions included hypertension, schizophrenia beginning 1999, weight loss of 10 kilograms (kg) in 5 months, and suicide attempt on 18-APR-2007 (by cutting neck with knife). The patient was noted to have inpatient hospitalizations on 18-APR-2007 (after suicide attempt) and from 10-SEP-2007 to 02-NOV-2007 (when he was found wandering outside late at night trying to buy a house). The patient's weight was 72 kilograms.

The patient was treated with risperidone LAI (microspheres, intramuscular) 25 mg initiated on 26-OCT-2007 (previously reported as 21-NOV-2007) to 04-FEB-2008 and 37.5 mg initiated on 04-FEB-2008 for schizophrenia. Concomitant medications included risperidone (unspecified), estazolam, trazodone, clonazepam, and propranolol hydrochloride.

On 26-JAN-2008, the patient experienced unusual behavior described as refusing to take drug and food, sleep disturbance, and "self-talking." The behavior persisted eight days when the patient was hospitalized on 04-FEB-2008. On 05-FEB-2008, laboratory data also included: glucose of 92, hematocrit of 38.7 %, hemoglobin of 13.8 g/dl, red blood cell/count of 430 mm.3, white blood cell count of 5100 mm.3. Electrocardiograph and chest x-ray results were pending. No information pertaining to treatment or outcome was provided.

The investigator provided no causality assessment. The information currently reported in this case does not meet the ICH E2A standard of "reasonable causal relationship." In the absence of additional information, the Company causality is "doubtful."

Additional information received on 20-MAR-2008.

Clarification of onset date of the SAE was reported as 28-JAN-2008, previously reported as 28-JAN-2007.

Additional information received on 02-APR-2008.

Continuation Sheet for CIOMS report **Mfr. Control No.: TW-JNJFOC-20080200234**

After hospital admission, the patient was resumed on risperidone (oral) 4 mg a day for psychotic symptoms. Estazolam 2 mg a day and trazodone 100 mg a day for sleep, clonazepam 2 mg a day for anxious mood, propranolol hydrochloride 20 mg a day for restlessness, nifedipine 30 mg a day for hypertension, risperidone (oral) dose was increased to 6 mg a day, and the dose of risperidone LAI was increased to 37.5 mg. The patient's symptoms improved.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
GLUCOSE	05-FEB-2008	92		
HAEMATOCRIT	05-FEB-2008	38.7 % (percent)		
HAEMOGLOBIN	18-FEB-2008	13.8 g/dL (grams/deciliter)		
RED BLOOD CELL/COUNT	05-FEB-2008	430 mm.3 (per cubic millimeter)		
WHITE BLOOD CELL COUNT	05-FEB-2008	5100 mm.3 (per cubic millimeter)		

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	RISPERDAL CONSTA (RISPERIDONE) Microspheres
Daily Dose	2) 37.5 mg
Therapy Dates/Duration	2) 04-FEB-2008 - Ongoing

Causality

1. ABNORMAL BEHAVIOUR [10061422]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Provided
Causality as per Mfr.	Doubtful

Other relevant history (Cont...)

Medical History: SUICIDE ATTEMPT 18-APR-2007 - ??-??-???? : Comments: by cutting neck with knife
Other History: no known allergies, previous suicide attempt on 18-APR-2007
Medical History: HYPERTENSION ??-??-???? - ??-??-????
Medical History: WEIGHT DECREASED ??-??-???? - ??-??-???? : Comments: 10 kg in 5 months

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
TWF	TW	25	MAR	1968	39 Year	M	16	FEB	2008

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

PSYCHOTIC DISORDER(10061920)

This report was received from clinical trial RISC-TWN-MA10: Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotic, concerns a 39 year old male from Taiwan: SAE2008TW015.

The patient's medical history and concurrent condition included schizophrenia. The patient's weight was 66 kilograms and height was 169 centimeters. The patient

(Cont.)

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

RISPERDAL CONSTA (RISPERIDONE) Microspheres

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

25 mg, 1 in 2 Week

16. ROUTE OF ADMINISTRATION

Intramuscular

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

PSYCHOTIC DISORDER

18. THERAPY DATES (from/to)

08-OCT-2007 - 13-FEB-2008

19. THERAPY DURATION

130 Day

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Other History: Father, other sister and brothers, two aunts had schizophrenia

(Cont.)

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : RISC-TWN-MA10
Center no :
Patient no : 03002

24b. MFR. CONTROL NO.
TW-JNJFOC-20080204414(2)

24c. DATE RECEIVED BY MFR.
19-MAR-2008

24d. REPORT SOURCE
[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE
[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

(Cont.) = Continuation attached sheet(s)

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received his first injection with risperidone long-acting injectable (LAI)(microspheres, intramuscular) 25 mg on 08-OCT-2007 for an unspecified indication. Concomitant medications were not reported. It was noted that the patient enrolled in the trial on 01-OCT-2007.

On an unknown date, the patient was brought to the emergency room due to dangerous behaviors (such as turning on the stove and forgetting to turn it off, and connecting the electrical circuit) and outside wandering with alcohol drinking. He was later admitted to the hospital on 16-FEB-2008 for risk prevention. No action was taken regarding risperidone LAI. The patient had not recovered from dangerous (abnormal) behavior and outcome was unknown for wandering. The investigator considered the causality between dangerous (abnormal) behavior, wandering, and risperidone LAI as possible.

This report is serious (hospitalization).

Additional information was received from a physician on 27-FEB-2008.

The patient's history included poor academic performance and interpersonal relationships since adolescence. At the age of 27, the patient was noted to have suspicious attitude, persecutory delusion, auditory hallucination, outside wandering, violent behavior toward family, self-care ability regression, and function deterioration; the patient was diagnosed as schizophrenic. At age 30, the patient began medication intervention but due to lack of insight, irregular drug adherence, and poor support system, his psychotic symptoms persisted. The patient was treated with long-acting haloperidol. The patient was hospitalized several times from ages 34 to 36 years, and received home care for three years but the psychotic symptoms never subsided. Risperidone therapy was started in OCT-2007.

The patient was treated with risperidone LAI 25 mg initiated on 08-OCT-2007 to 13-FEB-2008. On 16-FEB-2008, the patient experienced psychotic exacerbation (severe) and was hospitalized. The previously reported events of dangerous abnormal behaviors and wandering were subsumed under the event of psychotic exacerbation. During his hospitalization, risperidone LAI was continued and the dose was increased to 37.5 on an unknown date; risperidone (oral) 3 mg was also added. On 20-FEB-2008, the patient could not sleep and was wandering all night and was treated with trazodone 100 mg. On 24-FEB-2008, the patient experienced a fever (temperature of 38.5 degrees Celsius). Fever work-up revealed leukocytosis (white blood cell count of 10.1) with a pneumonia patch over the left lower lung field, aspiration pneumonia was favored. Treatment included amoxicillin clavulanate 1.2 grams intravenous every eight hours. The patient's physical condition was then considered stable. During this hospitalization, the patient displayed some disturbing behaviors, such as oral intake of his urine and stool secondary to auditory hallucinations. At the time of this report, the patient's psychotic symptoms had not shown improvement. Auditory hallucinations, loosening of association, poverty of thought content, autistic thinking, self-absorbed attention, social isolation, and poor self-care ability were still noted. The plan was to continue hospitalization. Medications during the patients hospitalization included: risperidone, propranolol, flunitrazepam,

Continuation Sheet for CIOMS report **Mfr. Control No.: TW-JNJFOC-20080204414**

clonazepam, amoxicillin clavulnate, "clarinasc", and serrapeptase. The patient had not recovered from psychotic exacerbation. The dose of risperidone LAI had been increased.

The patient was dropped from the study due to the exacerbation of psychotic symptoms and his exposure to tazodone. The investigator considered the event of psychotic exacerbation as possibly related to risperidone LAI.

Additional information received on 19-MAR-2008.

The patient's history included smoker and alcohol use. The patient was admitted into an acute ward on 16-FEB-2008 and received medical care and he became more stable with less disorganized behaviors. The patient was discharged on 17-MAR-2008. The patient continues to receive risperidone LAI 37.5 mg every 2 weeks as of 26-MAR-2008.

Test	Test Date	Result / Unit	Normal Low Range	Normal High Range
TEMPERATURE	24-FEB-2008	38.5 (fever) Celsius		
WHITE BLOOD CELL COUNT	??-???-????	10.1	3.40	9.1

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	RISPERDAL CONSTA (RISPERIDONE) Microspheres
Daily Dose	2) 37.5 mg, 1 in 2 Week
Therapy Dates/Duration	2) ??-??-???? - Ongoing

Causality

1. PSYCHOTIC DISORDER [10061920]

Change in dose	Dose Increased
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Possible
Causality as per Mfr.	Possible

Other relevant history (Cont...)

Medical History: ALCOHOL USE ??-??-???? - ??-??-????
Medical History: SCHIZOPHRENIA ??-??-???? - ??-??-????
Medical History: TOBACCO USER ??-??-???? - ??-??-????

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH DA	MO	YR	2a. AGE	3. SEX	4.-6. REACTION ONSET DA	MO	YR
HYS	TW	15	JUL	1961	46 Year	F	03	MAR	2008

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

CHOLECYSTITIS(10008612)

This report was received from clinical trial RISC-TWN-MA10: LAT risperidone in schizophrenia patients on home-care treatment , concerns a 46 year old female patient 004003, from Taiwan: SAE2008TW030.

The patient's medical history and concurrent conditions included: schizophrenia. The patient's weight was 60 kilograms and height 151 cm. The patient was treated with risperidone long acting injection (LAI)(microspheres, intramuscular) 25 mg initiated on 03-JAN-2008 to 28-JAN-2008 and dose increased to 37.5 mg initiated on 11-FEB-2008 for

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

RISPERDAL CONSTA (RISPERIDONE) Microspheres

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [ ] NA UNK

15. DAILY DOSE

37.5 mg

16. ROUTE OF ADMINISTRATION

Intramuscular

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [ ] NA UNK

17. INDICATIONS FOR USE

SCHIZOPHRENIA

18. THERAPY DATES (from/to)

11-FEB-2008 - ??-??-????

19. THERAPY DURATION

UNK

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: SCHIZOPHRENIA ??-??-???? - ??-??-????

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : RISC-TWN-MA10
Center no :
Patient no : 004003

24b. MFR. CONTROL NO.
TW-JNJFOC-20080402621(0)

24c. DATE RECEIVED BY MFR.
08-APR-2008

24d. REPORT SOURCE
[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE
[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

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Continuation Sheet for CIOMS report **Mfr. Control No.:** **TW-JNJFOC-20080402621**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

schizophrenia. On 03-MAR-2008, the patient experienced gallstones with chronic cholecystitis. The patient had a cholecystectomy done. The patient had recovered without sequelae on 06-MAR-2008. Concomitant medications were not reported. Action taken with risperidone LAI was unknown.

The investigator considered the causality between gallstone cholecystitis and risperidone LAI as not related.

This report is serious (hospitalization).

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	RISPERDAL CONSTA (RISPERIDONE) Microspheres
Daily Dose	2) 25 mg
Therapy Dates/Duration	2) 03-JAN-2008 - Stopped

Causality

1. CHOLECYSTITIS [10008612]

Change in dose	Unknown
Outcome after Change in dose	Unknown
Outcome after Reintro. of dose	Unknown
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. PATIENT	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4.-6. REACTION ONSET		
		DA	MO	YR			DA	MO	YR
LCS	TW	18	SEP	1980	27 Year	M	16	MAY	2008

7.-13. DESCRIBE REACTION(S) (include relevant test/lab data)

SCHIZOPHRENIA(10039626)

This report was received from clinical trial RISC-TWN-MA10: LAT risperidone in schizophrenia patients on home-care treatment, concerns a 27-year-old male patient 02002, from Taiwan: SAE2008TW053.

The patient's medical history and concurrent conditions included: schizophrenia. The patient's weight was 97 kilograms.

The patient was treated with risperidone long acting injection (LAI) (microspheres, intra-muscular) 50 mg

(Cont.)

8.-12. CHECK ALL APPROPRIATE TO ADVERSE REACTION

- [ ] PATIENT DIED
- [X] INVOLVED OR PROLONGED INPATIENT HOSPITALIZATION
- [ ] INVOLVED PERSISTENCE OF SIGNIFICANT DISABILITY OR INCAPACITY
- [ ] LIFE THREATENING

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

RISPERDAL CONSTA (RISPERIDONE) Microspheres

(Cont.)

20. DID EVENT ABATE AFTER STOPPING DRUG?

[ ] YES [ ] NO [X] NA

15. DAILY DOSE

50 mg

16. ROUTE OF ADMINISTRATION

Intra-muscular

21. DID EVENT REAPPEAR AFTER REINTRODUCTION?

[ ] YES [ ] NO [X] NA

17. INDICATIONS FOR USE

SCHIZOPHRENIA

18. THERAPY DATES (from/to)

??-??-???? - Ongoing

19. THERAPY DURATION

Ongoing

III. CONCOMITANT DRUGS AND HISTORY

22. CONCOMITANT DRUGS AND DATES OF ADMINISTRATION (exclude those used to treat event)

No Concomitant Products Reported

23. OTHER RELEVANT HISTORY

Medical History: SCHIZOPHRENIA ??-??-???? - ??-??-????

IV. MANUFACTURER

24a. NAME & ADDRESS OF MANUFACTURER

Study no : RISC-TWN-MA10
Center no :
Patient no : 02002

24b. MFR. CONTROL NO.
TW-JNJFOC-20080604682(0)

24c. DATE RECEIVED BY MFR.
19-JUN-2008

24d. REPORT SOURCE
[X] STUDY [ ] LITERATURE
[X] HEALTH PROFESSIONAL

DATE OF THIS REPORT

25a. REPORT TYPE
[ ] INITIAL [ ] FOLLOWUP [ ] FINAL

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Continuation Sheet for CIOMS report **Mfr. Control No.:** **TW-JNJFOC-20080604682**

Describe Reaction(s) (include relevant test/lab data) (Cont...)

initiated on an unknown date for schizophrenia.

On 16-MAY-2008, the patient experienced worsening schizophrenia and was hospitalized because he could not performed his activities of daily living (ADL). Concomitant medications were not reported.

The patient had not recovered from worsening schizophrenia.

The dose of risperidone LAI was not changed.

The investigator considered the causality between worsening schizophrenia and risperidone LAI as not related.

This report is serious (hospitalization).

No Relevant Test/Laboratory Data Reported

Suspect Drug(s) (Cont...)
Product-Reaction level

Seq. No.	1
Drug	RISPERDAL CONSTA (RISPERIDONE) Microspheres

Causality

1. SCHIZOPHRENIA [10039626]

Change in dose	Dose Not changed
Outcome after Change in dose	Not Applicable
Outcome after Reintro. of dose	Not Applicable
Causality as per reporter	Not Related
Causality as per Mfr.	Not Related

CSR Documentation Form

CSR Documentation Form (Note to File)
to Document Errata/Revision, Document Not Approved per SOP Timeframe, Other

Date of this CSR Documentation Form: 28 October 2013

Document Type: Clinical Study Report

Protocol Number: RISSCH4119 (RISC-TWN-MA10)

Document Title: Evaluation of efficacy and safety of long-acting risperidone microspheres in patients with schizophrenia or schizoaffective disorders, who is receiving psychiatric home-care treatment, when switching from typical depot or oral antipsychotics to long-acting risperidone microspheres

Other Qualifier (if applicable): N/A

Issue Date: NA

Primary Compound ID (generic name if applicable): R064766 (Risperidone)

Legal Entity of Reporting Company: Janssen Taiwan

Document ID No.: N/A

What is the purpose of this Documentation Form (check the relevant box)?

☐ **Document decision for Erratum/Revision to the report**

Reasons for Erratum/Revision:

Participants Involved:

The Erratum or Revision History (templates available on the RegMW portal under Other Document Types) should be available in the electronic repository or appended to this Documentation Form.

☑ **Document that the report was NOT approved/issued according to the timeframe specified in SOP-10107 (chek the box for this)**

Reasons for delay: The study was completed and issued before the implementation of Cross-Pharma SOP-10107 (version 1.0, effective date: 30 Oct 2010), and establishment of Medical Affairs (MAF) and Local Global Clinical Operations-Medical Affairs Operations (GCO-MAO) departments in the management of clinical trials for Janssen Taiwan.

Nevertheless, attempts were made during [Nov-Dec 2012 and Mar 2013] to retrieve any related clinical study documents. A clinical study report dated 25Sep2009 is found. However, raw data of the conducted study was not found.

We contacted the contracted data management vendor, Medica Surf, and

CSR Documentation Form

investigator, Dr Yang Yen-Kuang, to retrieve the database, but to no avail. Dr Yang mentioned that the raw data be returned to company when the study completed.

Hence, we have regrettably resolved to conclude that the information clinical study report is incomplete. We are not able to produce the study exposure data, drug levels or treatment compliance data.

Participants Involved: Pei-Fang Chung (response for missing study investigation)

Was report subject to specific Health Authority timing requirements?	☐ Yes	☑ No	
For a clinical study conducted in adults, was report completed within 1 year of the protocol-defined end of study, as required by EU Directive?	☐ Yes	☐ No	☑ N/A
For a pediatric clinical study, was report completed within 6 months of the protocol-defined end of study, as required by EU Directive?	☐ Yes	☐ No	☑ N/A
Was an SOP deviation memo filed?	☐ Yes	☑ No	

☐ **Document other action taken with regard to this report (including Limitations) (chek this box)**

Describe:

Reasons:

Participants Involved:

☐ **Supplemental information is attached**

CSR Documentation Form

Individual approving this form:

Name: Park Jun Hong

*Title: MD

Signature: [signature] Date: Nov. 1st 2013

* Title: Responsible Medical Officer: The sponsor's physician who attests that the Clinical Study Report, revision or addendum, accurately describes the conduct and results of the clinical study. This function can be performed by the Molecule/Compound Responsible Physician, the Study Responsible Physician., The Medical Leader, the Clinical Leader, the Medical Director, the Safety Physician, or a physician identified to perform this attestation function. (definition from the SOP)

NOTE: Insertion of validated electronic signature or approval by signatory in ERIS is acceptable.

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