

Briefing Book
April 7, 2009 PDAC
Serdolect (sertindole) Tablets

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**MEMORANDUM DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: March 10, 2009

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: April 7, 2009 Meeting of the Psychopharmacologic Drugs Advisory Committee
(PDAC)

TO: Members, PDAC

This one-day PDAC meeting will focus on safety and efficacy issues for a new drug application [NDA 20-644, sertindole (Serdolect) tablets, Lundbeck USA], for the treatment of schizophrenia. Sertindole is an atypical antipsychotic drug. The sponsor has conducted acute and longer-term trials to support a claim for sertindole in the treatment of schizophrenia. As part of the background package, we have provided various FDA review documents for this application (team leader memo and primary statistical review for an original application that was withdrawn, primary medical officer and statistical reviews for the currently active application, and a cardiorenal consultative review for the current application). Prior to the April 7th meeting, an additional FDA clinical review of the suicidality data for sertindole in schizophrenia will be provided to the committee. The sponsor's background package will also provide data to support the safety and efficacy for sertindole in the treatment of schizophrenia. The sponsor has, in the Division's view, submitted sufficient data to support the conclusion that sertindole is effective for the acute treatment of schizophrenia. The Division has also concluded that the overall safety profile for this drug, with the exception of a potential to prolong the QTc interval, appears to be similar to that observed with other atypical antipsychotic drugs.

There remains, however, a concern about a possible risk of sudden cardiac death with this drug related to its potential for QTc prolongation. To address this question, the sponsor has conducted a large simple trial, the Sertindole Cohort Prospective (SCoP) Study, comparing sertindole to risperidone, another atypical antipsychotic drug, on all-cause mortality. In addition to examining mortality, this study has also compared these two drugs on suicidality, since there are observational data suggesting a possible advantage for sertindole over other antipsychotic drugs on suicidality, an important aspect of schizophrenia and a common cause of death in this population. The sponsor seeks a claim for sertindole not only as a treatment for schizophrenia in general, but also a claim focused specifically on suicidality in schizophrenia.

Formal presentations at the meeting will include a summary of the safety and efficacy data for this drug by the sponsor. FDA's presentations will focus more specifically on the cardiovascular

risks for sertindole, including both the QTc data and the mortality data from the SCoP Study, and also the data pertinent to the claim for suicidality.

The Division of Psychiatry Products has not yet reached a final conclusion on this application, and seeks the advice of the PDAC before reaching a conclusion.

After you have heard all the findings and arguments, we will ask you, first of all, to discuss and comment on several questions of particular concern regarding the safety and efficacy of sertindole. Then we will ask you to vote on two questions.

The questions for discussion and comment are as follows:

1. Has the cardiovascular risk for sertindole been adequately characterized, and if so, does this risk pose an obstacle to the use of this drug in the treatment of schizophrenia?
2. Has sertindole been shown to have an advantage over other antipsychotic drugs with regard to reducing the risk of suicidality in the schizophrenic population?

The questions for a vote by the committee are as follows:

1. Has sertindole been shown to be effective for the treatment of schizophrenia?
2. Has sertindole been shown to be effective for the treatment of suicidality in schizophrenia?
3. Has sertindole been shown to be acceptably safe for the treatment of schizophrenia?

cc:

HFD-130/TLaughren/MMathis/NKhin/PKronstein/KKeidrow

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/s/

Thomas Laughren
3/10/2009 08:26:15 AM
MEDICAL OFFICER

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	20-644
Priority or Standard	Standard
Submit Date(s)	July 2, 2008
Received Date(s)	July 15, 2008
PDUFA Goal Date	May 15, 2009
Division / Office	Division of Psychiatry Products Office of Drug Evaluation 1
Reviewer Name(s)	Phillip Kronstein, M.D.
Review Completion Date	March 10, 2009
Established Name	Sertindole
(Proposed) Trade Name	SERDOLECT
Therapeutic Class	Atypical Antipsychotics
Applicant	Lundbeck USA, Inc.
Formulation(s)	Oral Tablets; 4 mg, 12 mg, 16 mg and 20 mg
Dosing Regimen	12 to 20 mg/day
Proposed Indication(s)	Schizophrenia; Reduction of the Risk of Fatal and Non-fatal Suicide Attempts in Schizophrenia
Intended Population(s)	Adults

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Following the meeting of the Psychopharmacologic Drug Advisory Committee (PDAC), an addendum will be written, which will include recommendations on regulatory action.

1.2 Risk Benefit Assessment

At the PDAC meeting, the efficacy and safety data for sertindole will be presented and the risks/benefits discussed. Further evaluation of the risk/benefit profile of sertindole will occur after the meeting.

1.3 Recommendations for Postmarketing Risk Evaluation and Mitigation Strategies

The Division has consulted the Office of Surveillance and Epidemiology (OSE) regarding postmarketing risk management activities. They will provide their recommendations, if needed, after the PDAC meeting.

2 Introduction and Regulatory Background

2.1 Product Information

Sertindole (SERDOLECT) is a new molecular entity in the class of atypical antipsychotics. The sponsor is seeking indications for:

- the treatment of schizophrenia
- the reduction in the risk of fatal and non-fatal suicide attempts in patients with schizophrenia

The proposed dosing schedule is once a day, with or without meals, beginning with 4 mg/day and increasing by 4 mg/day every 2-3 days until the recommended target dose of 16 mg is reached. The sponsor states that, depending on individual response, the dose may be increased to 20 mg/day or decreased to 12 mg/day.

2.2 Tables of Currently Available Treatments for Proposed Indications

The 23 moieties approved in the U.S. for the treatment of schizophrenia are: chlorpromazine, promazine, prochlorperazine, perphenazine, trifluoperazine, thioridazine, acetophenazine, propiomazine, fluphenazine, piperacetazine, haloperidol, chlorprothixine, thiothixine, mesoridazine, molindone, loxapine, clozapine, risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, and paliperidone. In addition,

clozapine is indicated for the reduction in the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

2.3 Availability of Proposed Active Ingredient in the United States

Sertindole is not currently marketed in this country.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no recent labeling changes or new safety/efficacy concerns in other members of this drug class. Class labeling is in place that addresses various safety issues, including the increased risk of mortality in elderly patients with dementia as well as increased risk of hyperglycemia, and diabetes mellitus. Other important issues with consideration to related drugs (other atypical antipsychotics) include hyperprolactinemia, neuroleptic malignant syndrome (NMS), seizures, and tardive dyskinesia.

In 2008, the Division asked the sponsors of atypical antipsychotic agents to conduct further analyses of clinical trial data regarding weight as well as glucose and lipid profiles. These metabolic submissions are currently under review, and further labeling changes will be made as needed upon the completion of our review of the data for each individual drug.

Finally, the issue of possible cardiac risk with atypical antipsychotics has received more attention recently with the publication of an article by Wayne Ray, titled: "Atypical antipsychotic drugs and the risk of sudden cardiac death." (N Engl J Med. 2009 Jan 15;360(3):225-35).

2.5 Summary of Presubmission Regulatory Activity Related to Submission

IND 38,373 for sertindole was originally submitted on 11/27/1991. Several key meetings were held during the development of sertindole. (Information on the first three meetings was excerpted from the Group Leader Memo by Thomas Laughren, M.D., dated 8/22/1996)

End-of-Phase 2 Meeting (10/21/1993)

The progress of development so far and the plans for phase 3 were discussed. In particular, the sponsor noted an interest in comparisons with haloperidol, and the Division advised of the need for a fair comparison (i.e. a design in which haloperidol is given in an optimal manner). The Division suggested the desirability of a dose comparison trial (i.e. one that compared the dose response for the two drugs). The Division also encouraged the sponsor to conduct an adequate relapse prevention trial

(i.e. one that randomized responders on open sertindole to continuation on sertindole or a switch to placebo.

The sponsor responded to the advice regarding an adequate comparative trial with a protocol for study M93-098, comparing three different doses each of haloperidol and sertindole with placebo. Despite this improvement in design, the sponsor was cautioned regarding the lack of consensus about how to fairly compare the two drugs, in particular with respect to the population studied (e.g. it would not be acceptable to compare sertindole and haloperidol in patients who already had failed haloperidol) and the adequate use of anticholinergic drugs to control EPS with haloperidol.

Pre-NDA Meeting (7/27/1995)

This was a general discussion of the progress of the development program and the plans for the NDA submission, including possible claims. The Division again cautioned the sponsor about the difficulties in making claims for comparative advantages of their drug over haloperidol. Regarding the issue of long-term efficacy data, the Division made it clear that the sponsor had not accepted its advice to conduct an adequate and well controlled study to address this issue. Most of this meeting was focused on technical issues regarding the format and content of the NDA.

The original NDA for sertindole was submitted on 9/29/1995.

Sertindole was the subject of a 7/15/1996 meeting of the PDAC, and the Committee voted unanimously in favor of its efficacy (6 vs. 0). The response was more mixed for safety (4 in favor, two opposed).

Approvable Letter (10/2/1996)

Many issues were addressed in this letter, but most important was the concern about QT prolongation and the risk of sudden death. The sponsor was asked to propose a system of registration, distribution, and follow up that would permit identification of deaths and an estimate of the risk of sudden death with sertindole. The Division also attached its proposal for labeling, including a requirement for a black box warning regarding QT prolongation and a second-line status.

Approvable Letter (6/16/1997)

Again, this letter addressed numerous issues. One of the most important was the Division's concern that, in lieu of a US registry, the sponsor had proposed to conduct epidemiologic studies utilizing two UK databases and one in the US. The Division did not believe that these studies would result in a sufficiently rapid and interpretable estimate of any excess mortality that may be associated with sertindole use.

Clinical Review
Phillip Kronstein, M.D.
NDA 20-644
SERDOLECT (Sertindole)

On 1/13/1998, the sponsor withdrew the NDA from further consideration, based on events in Europe.

Foreign Marketing History (1996-2008)

Sertindole was authorized in the United Kingdom in May 1996 and subsequently in other European member states through the Mutual Recognition Procedure.

A potential safety signal regarding death rates during sertindole treatment was detected in the United Kingdom Medicines Control Agency's (MCA) Adverse Drug Reaction On-Line Information Tracking (ADROIT) database. Due to sertindole's known effect on the QT interval, there was concern that this possible signal was a reflection of an increased risk of serious and fatal arrhythmias. On 11/2/1998, the Netherlands initiated the marketing suspension of sertindole in the EU. On 6/23/1999, the European Committee for Medicinal Products for Human Use (CHMP) decided to suspend the marketing authorization in the EU until further data could be presented.

As a result, the sponsor conducted several retrospective epidemiological studies to investigate the safety signal. Based on the results of these studies, the CHMP, on 10/18/2001, recommended lifting the marketing suspension for sertindole. A condition for the re-introduction of sertindole in the EU was that the sponsor commit to accounting for all patients treated with sertindole for at least the first year after the re-introduction of the drug to the market by enrolling them in studies. The sponsor agreed to conduct the Sertindole Cohort Prospective (SCoP) Study (a large, randomized, parallel group, active-controlled study comparing the safety of sertindole and risperidone under normal conditions of use) and a post-marketing surveillance study (Study 99823).

In October 2004, the sponsor requested the CHMP to review the conditions stated in its decision to re-introduce sertindole in the EU. Following review of preliminary data from SCoP, which did not appear to show an increase in all-cause mortality for sertindole compared with risperidone, the CHMP, in April 2005, recommended lifting the restrictions on marketing and launch activities.

In September 2007, the CHMP agreed to terminate the SCoP Study after the enrollment of nearly 10,000 patients. Following the submission of the final study report, the CHMP concluded, in September 2008, that the sponsor's commitment regarding the SCoP study had been fulfilled.

Pre-NDA Meeting for Resubmission (1/20/2006)

The sponsor sought to re-submit the NDA in light of the SCoP data and had various questions prior to doing so. In response to one of the questions, the Division expressed continuing concern about substantial QTc prolongation with sertindole and what it believed was a significant risk of excess cardiac deaths with this drug. Although the

preliminary results from SCoP suggested no difference between sertindole and risperidone in overall mortality, there did appear to be an excess risk of cardiac deaths with sertindole. The Division noted that it would not necessarily be expected that an excess risk of cardiac deaths for sertindole compared with risperidone would be reflected in a higher overall mortality for sertindole, given the relatively higher mortality in this population from multiple causes. Given what the Division believed to be an unacceptable risk associated with this drug, it was suggested that the sponsor do additional work to establish a benefit that could overcome this risk (e.g. efficacy in patients shown to be refractory to standard antipsychotics or reduction in suicidality). It was noted that the SCoP Study was trending in favor of sertindole in regard to completed suicides. In response to another question, the Division agreed that a comparative thorough QT study would likely not generate any additional safety information.

Pediatric Written Requests

A pediatric drug development plan was not submitted with this NDA. On September 18, 2008, the sponsor submitted a written request that the requirement for pediatric data be waived for this application. The Division generally grants a waiver for 0-12 years of age and a deferral for 13-17 years of age in schizophrenia.

If the decision is made for approval, a Pediatric Review Committee (PeRC) meeting will be scheduled to review the pediatric deferrals and waivers as well as any plans for clinical trials for pediatric schizophrenic populations with sertindole. Currently, no written requests have been initiated for pediatric trials in schizophrenic populations with sertindole.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This was a paper submission, consisting of hundreds of volumes. Many of the safety analyses were not present, but the sponsor was responded to our requests for them in a timely manner.

3.2 Compliance with Good Clinical Practices

In order to audit the sponsor's compliance with good clinical practices, a Division of Scientific Investigations (DSI) inspection for two sites in the SCoP Study was requested, one in the Philippines with 350 subjects (Site #PH001; investigator: Dino S C Peña), and one in Malaysia with 120 subjects (Site #MY001; investigator: Ahmad Hatim

Sulaiman). These sites were selected because they were large enrollers. The DSI inspection summary report is still pending.

Of note, in a memo signed June 26, 2008, Lundbeck certified “that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.”

3.3 Financial Disclosures

The pivotal efficacy studies were all completed before the Guidance on Financial Disclosure by Clinical Investigators became effective, on February 2, 1999. The Sertindole Cohort Prospective (SCoP) Study was not conducted under the US IND.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Shastri Bhamidipati, Ph.D. is the chemistry reviewer. There are reportedly no aspects of the CMC review important to clinical interpretation of the data.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Sonia Tabacova, Ph.D. is the pharmacology/toxicology reviewer. There are reportedly no new toxicological findings that affect the human safety evaluation, but her final review is not yet available. Of note, in the original NDA, there were pathological fractures observed in a mouse carcinogenicity study. This led to a discussion of a phase 4 commitment to do further preclinical studies to address this issue.

4.4 Clinical Pharmacology

The current Office of Clinical Pharmacology (OCP) reviewer is Andre Jackson, Ph.D, who is looking at four new bioavailability and two new pharmacokinetic studies. However, the original review was performed by Raman Baweja, Ph.D. (review dated 6/19/1996).

4.4.1 Mechanism of Action

Sertindole appears to selectively inhibit mesolimbic dopaminergic neurons. In other words, it has been shown to inhibit spontaneously active dopamine neurons in the mesolimbic ventral tegmental area without affecting dopamine neurons in the substantia nigra compacta. It is believed that this occurs through balanced inhibitory effects on central dopamine (D₂) and serotonin (5HT₂) receptors as well as on alpha-1-adrenergic receptors.

4.4.2 Pharmacodynamics

Sertindole displays high receptor binding affinity in vitro (K_i's in the low nanomolar range) at the following receptor sites: 5HT_{2A/C}, D₂, and alpha-1-adrenergic. Sertindole has moderate affinity (K_i's in the mid-nanomolar range) for D₁ and sigma type 2 receptors, and low affinity (K_i's in the low micromolar range) for alpha-2-adrenergic, H₁, and sigma type 1 receptors. Sertindole has almost no affinity for 5HT_{1A}, 5HT₃, muscarinic cholinergic, β-adrenergic, and PCP receptors. Of note, sertindole is also a potent blocker of the hERG channel current, which is the likely reason for the significant QT prolongation seen with this drug.

4.4.3 Pharmacokinetics

The following section was primarily excerpted from the Group Leader Memo by Thomas Laughren, M.D., dated 8/22/1996.

Sertindole is slowly absorbed after oral administration, reaching the peak concentration at about 10 hours. Food does not significantly affect the rate or extent of sertindole absorption. Sertindole is extensively distributed and highly protein bound (i.e. 99% for a concentration range of 1 to 1000 ng/mL). Sertindole has time dependent kinetics, with clearance decreasing with multiple dosing. However, at steady state, clearance is dose independent and concentrations are proportional to dose for a range of 4-24 mg/day. Sertindole has an elimination half-life of approximately three days, and reaches steady state in about 3-4 weeks.

CYP2D6 and CYP3A contribute to the formation of the major metabolites, dehydrosertindole and norsertindole, both of which appear to be pharmacologically inactive in vivo. 2D6 appears to be the principle pathway; however, in 2D6 poor metabolizers or those converted to poor metabolizer status by concomitant drug use (e.g. fluoxetine), the 3A pathway may take on a greater role.

Single dose studies revealed little effect on renal impairment or age on sertindole pharmacokinetics. A study in patients with liver disease revealed about a 70% decrease in clearance in patients with compromised liver function. Sertindole's

clearance is on average 20% lower in females compared to males. Blacks have 20% lower mean sertindole clearances than Caucasians.

Population pharmacokinetic studies revealed that the clearance of sertindole is reduced by about 50% in patients co-administered fluoxetine or paroxetine, but no effect on clearance was seen with concomitant use of three other 2D6 substrates (sertraline, tricyclic antidepressants, or propranolol). Smaller reductions in clearance (<25%) were observed with concomitant use of macrolide antibiotics (e.g. erythromycin, a 3A inhibitor) and calcium channel antagonists (diltiazem, verapamil, and nifedipine). There is an approximate doubling of the clearance of sertindole with co-administration of carbamazepine or phenytoin, both CYP inducers, and a lesser effect with tobacco use (15% increase in clearance).

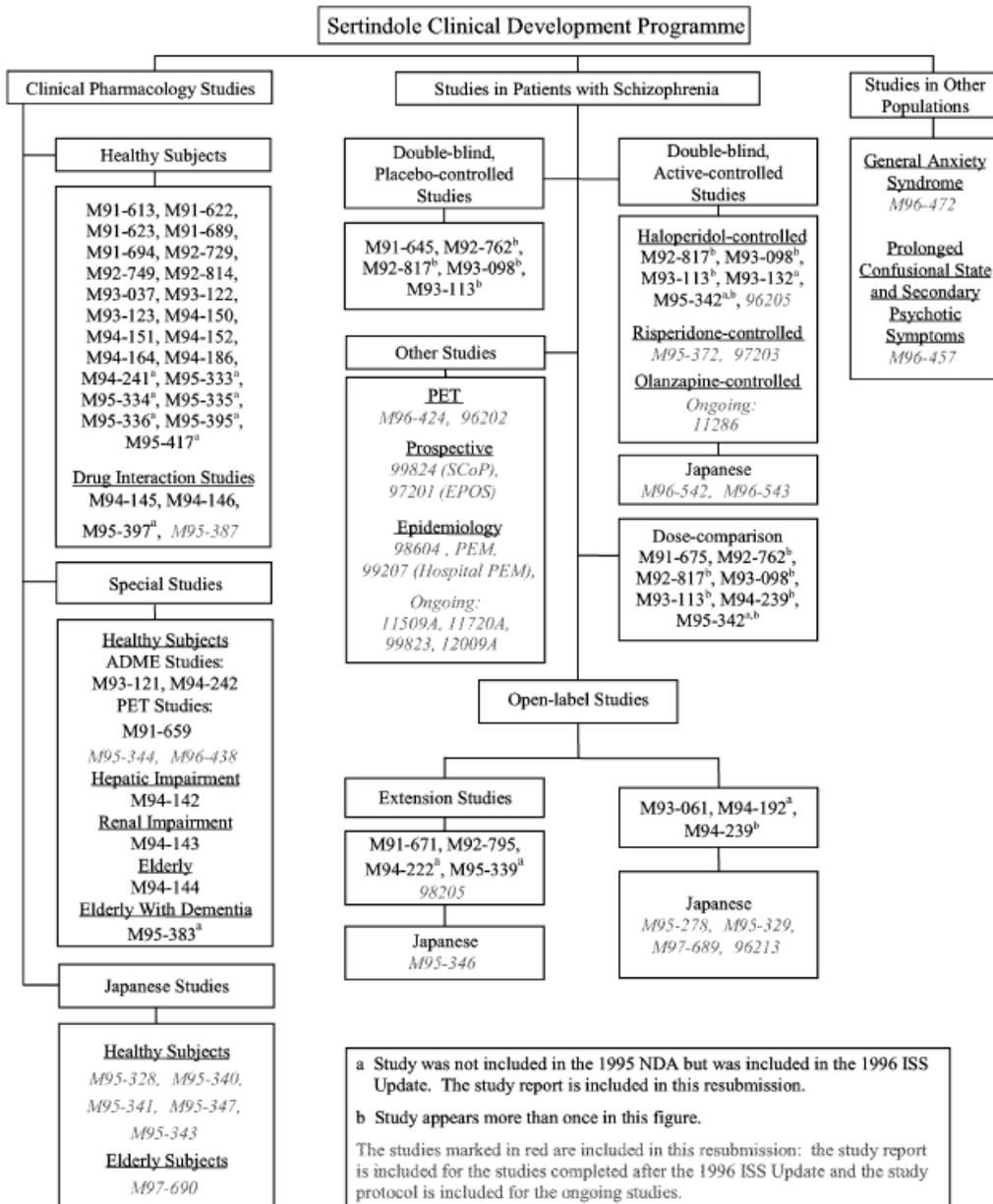
An in vivo study of sertindole (multiple dose) and terfenadine (single dose) revealed a 28% increase in terfenadine's AUC as well as a slight increase in QTc.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

For a table of all studies, please refer to Appendix A. The figure 1 below summarizes the sertindole clinical development program:

Figure 1 The Sertindole Clinical Development Program



5.2 Review Strategy

This is a resubmission of the NDA for sertindole. As such, the efficacy information from the last review will be summarized and updated as needed. The main focus of this review will be the SCoP Study and the Integrated Review of Safety.

6 Review of Efficacy

6.1 Acute Treatment of Schizophrenia

The sponsor's efficacy analysis in schizophrenia was based on the results from four short-term, placebo-controlled studies:

Table 1 List of Four Pivotal Short-Term Placebo-Controlled Studies: Study Design and Overall Result¹

Study	Duration	Population Studied	Sertindole Dose	Active Control (Dose)	Primary Efficacy Measure	Result (vs. Placebo)
M93-113	8 weeks	Schizophrenia	3 Fixed Doses 12 mg/day 20 mg/day 24 mg/day	Haloperidol (4, 8, 16 mg/day)	PANSS Total Score	Positive
M93-098	8 weeks	Schizophrenia	2 Fixed Doses 20 mg/day 24 mg/day	Haloperidol (16 mg/day)	PANSS Total Score	Positive
M92-762	6 weeks	Schizophrenia	3 Fixed Doses 8 mg/day 12 mg/day 20 mg/day	None	PANSS Total Score	Negative (high placebo response)
M91-645	7 weeks	Schizophrenia Schizoaffective Disorder	Flexible Dose 4-20 mg/day (mean dose 17 mg/day)	None	BPRS Total Score	Supportive (Small sample; low completion rate)

¹ Extracted from Team Leader Draft Memo by Ni Khin

During the original NDA review cycle, these studies were reviewed by Earl Hearst, M.D. in his clinical review dated 7/17/96. Dr. Thomas Laughren, the Group Leader at that time, also evaluated efficacy data from these studies according to his Group Leader memo dated 8/22/1996. It should be noted that the Division found positive efficacy results for studies M93-113 and M93-098. The Division also found results from study M91-645 to be supportive of sertindole's efficacy in schizophrenia. This clinical review will summarize study design and efficacy findings from each of these studies.

In addition, the sponsor proposes to describe three other short-term, active-controlled only schizophrenia studies in the label (M95-342, 97203, and 96205). However, the Division has decided that these three additional studies are inadequate in their design and, as such, do not warrant further review.

Of note, this section summarizes information contained in the Group Leader memo by Dr. Thomas Laughren, dated 8/22/1996, from which many of the tables have also been extracted.

Study M93-113

This was a randomized, 43-center (US), double-blind, parallel group, 8-week, fixed-dose study comparing sertindole at three fixed doses (12, 20 or 24 mg/day, given once daily), haloperidol at three fixed doses (4, 8 or 16 mg/day, given once daily), and placebo for the treatment of psychosis in adult inpatients meeting DSM-III-R or DSM-IV criteria for schizophrenia. Patients had to have scores on any two of the Brief Psychiatric Rating Scale (BPRS) positive symptom items (conceptual disorganization, suspiciousness, hallucinatory behaviors, and unusual thought content) summing to at least 8 and could not have had a decrease of more than 20% on the BPRS total score during the placebo lead-in period.

During the 2-week double-blind titration period, the initial dose for both sertindole and haloperidol was 4 mg once daily in the morning. The sertindole was titrated to the assigned dose at the rate of 4 mg every four days, while the haloperidol was increased (for the 8 and 16 mg/day group) to 8 mg/day after three days and (for the 16 mg/day group) to 16 mg/day after an additional three days. Following the titration period was a 6-week double-blind fixed-dose treatment period. Benzotropine mesylate was permitted for extrapyramidal symptoms (EPS) but only on an as needed basis and for limited periods (seven days); it could be continued with repeat evaluation.

The efficacy measures included the Positive and Negative Syndrome Scale (PANSS), the BPRS, and the Clinical Global Impressions Scale (CGI; both the Severity of Illness and Global Improvement subscales), all administered weekly during the 8-week trial. Of note, although the PANSS is a 30-item scale, in which is embedded the 18 items of the BPRS, in this program, the BPRS was administered separately.

The primary efficacy variable was the PANSS total score, which can range from 0 to 180 (based on 0-6 scaling for each of the individual items). Secondary efficacy variables included the PANSS negative subscale (which can range from 0 to 42), the BPRS positive symptom score (which can range from 0 to 24), and the CGI-severity score (where 1 = "normal, not at all ill" and 7 = "among the most extremely ill patients"). The review focused on the intent-to-treat sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up time. The LOCF analysis (using Dunnett's criteria) was considered primary, but OC was also done. The statistical model was ANOVA, or ANCOVA when appropriate, focusing on change from baseline for the efficacy variables and including treatment, investigator, and treatment-by-investigator terms. The exception was the CGI, which was analyzed using the Cochran-Mantel-Haenzel statistic, with centers as strata.

Study Results

Patients in the intent-to-treat dataset (total N=477) were between the ages of 18 and 67 years old, inclusive, with a mean age of 39 years. Fifty-nine percent (59%) were Caucasian, 31% were African-American, 10% were classified as other, and <1% were Asian. Seventy-seven percent (77%) of the patients were male. Treatment groups were comparable at baseline on the demographic variables. However, there were some differences on certain efficacy variables, and ANCOVAs were done in those instances. For the PANSS, the sertindole 20 mg, haloperidol 4 mg, and placebo groups had mean baseline scores of 70.5, 69.0, and 62.0, respectively. The p-values for sertindole 20 mg vs. placebo and haloperidol vs. placebo were 0.012 and 0.013, respectively.

Table 2 Completion Rates to 8 Weeks in Study M93-113¹

Treatment Group	Number of Patients Completed/Randomized (%)
Placebo	36/71 (51%)
Sertindole 12 mg/day	33/72 (46%)
Sertindole 20 mg/day	31/65 (48%)
Sertindole 24 mg/day	33/70 (47%)
Haloperidol 4 mg/day	32/68 (47%)
Haloperidol 8 mg/day	34/63 (54%)
Haloperidol 16 mg/day	33/68 (49%)

¹based on intent-to-treat dataset

Table 3 Summary of Significance Levels for Pairwise Comparisons (Sertindole vs. Placebo) In Study M93-113

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole 12, 20, and 24 mg/day vs Placebo) in Study M93-113																								
Key Outcome Variables	Sertindole 12 vs Pbo								Sertindole 20 vs Pbo								Sertindole 24 vs Pbo							
	Week ²								Week ²								Week ²							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
PANSS Total	-	-	-	t	*	*	*	*	-	*	t	*	*	*	*	*	-	t	-	*	*	t	*	*
LOCF	-	-	-	-	-	-	-	-	-	*	-	*	*	*	*	t	-	-	-	*	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	*	-	*	*	*	*	t	-	-	-	*	-	-	-	-
BPRS Pos	-	-	-	-	-	-	t	*	-	-	-	-	-	t	*	*	-	-	-	t	-	-	t	*
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	t	*	*	-	-	-	t	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	t	*	*	-	-	-	t	-	-	-	-
PANSS Neg	t	-	-	-	t	-	-	t	-	*	-	t	*	*	t	*	-	-	-	-	-	-	-	-
LOCF	t	-	-	-	-	-	-	-	-	t	-	*	-	-	-	-	-	-	-	-	-	-	-	-
OC	t	-	-	-	-	-	-	-	-	t	-	*	-	-	-	-	-	-	-	-	-	-	-	-
CGI Severity	-	-	-	-	t	-	*	t	-	-	t	*	*	*	*	-	-	-	*	*	*	*	*	
LOCF	-	-	-	-	t	-	*	t	-	-	-	*	*	*	*	-	-	-	*	*	*	*	*	
OC	-	-	-	-	t	-	*	t	-	-	-	*	*	*	*	-	-	-	*	*	*	*	t	

1 Based on ANOVA
 * = p ≤ 0.05
 t = p ≤ 0.10
 - = p > 0.10
 ■ = p ≤ 0.021 (critical p-value for Dunnett's Test)

2 End of weeks 1-8

Table 4 Summary of Significance Levels for Pairwise Comparisons (Haloperidol vs. Placebo) In Study M93-113

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Haloperidol 4, 8, and 16 mg/day vs Placebo) in Study M93-113																								
Key Outcome Variables	Haloperidol 4 vs Pbo				Haloperidol 8 vs Pbo				Haloperidol 16 vs Pbo															
	Week ²								Week ²															
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8								
PANSS Total																t	t	-	t	*	*	*	*	█
LOCF																t	-	t	-	*	-	-	-	-
OC																t	t	t	-	-	-	-	-	-
BPRS Pos																*	*	*	*	*	*	*	*	*
LOCF																*	*	*	*	*	*	*	*	*
OC																t	-	-	-	-	-	-	-	-
PANSS Neg																-	-	-	-	-	-	-	-	-
LOCF																-	-	-	-	-	-	-	-	-
OC																t	-	-	t	*	-	t	t	-
CGI Severity																*	*	*	*	*	*	*	*	*
LOCF																*	*	*	*	*	*	*	*	*
OC																t	-	t	-	*	-	t	-	-

1 Based on ANOVA
 * = p ≤ 0.05
 t = p ≤ 0.10
 - = p > 0.10
 █ = p ≤ 0.021 (critical p-value for Dunnett's Test)

2 End of weeks 1-8

Table 5 Baseline and Change in CGI Severity Scores in Study M93-113

CGI Severity Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	4.7	0.0	
Sertindole 12	4.7	- 0.4	0.4
Sertindole 20	4.9	- 0.7	0.7
Sertindole 24	4.6	- 0.5	0.5
Haloperidol 4	4.9	- 0.4	0.4
Haloperidol 8	4.7	- 0.7	0.7
Haloperidol 16	4.9	- 0.6	0.6

1 Mean score at baseline
 2 Mean change from baseline to week 8 (LOCF)
 3 Difference in mean change from baseline to week 8 (LOCF) between active drug groups and placebo

Table 6 Size of Treatment Effect in Study M93-113

Size of Treatment Effect in Study M93-113			
PANSS Total Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	62.0	+ 0.7	
Sertindole 12	63.2	- 9.9	10.6
Sertindole 20	70.5	- 17.6	18.3
Sertindole 24	65.2	- 10.7	11.4
Haloperidol 4	69.0	- 11.8	12.5
Haloperidol 8	64.8	- 16.5	17.2
Haloperidol 16	67.1	- 11.9	12.6
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	12.1	- 1.0	
Sertindole 12	12.3	- 3.0	2.0
Sertindole 20	12.4	- 3.4	2.4
Sertindole 24	12.0	- 3.0	2.0
Haloperidol 4	12.7	- 2.6	1.6
Haloperidol 8	12.4	- 4.3	3.3
Haloperidol 16	12.7	- 3.7	2.7
PANSS Negative Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	17.0	- 0.7	
Sertindole 12	17.2	- 2.8	2.1
Sertindole 20	18.8	- 4.4	3.7
Sertindole 24	17.8	- 2.3	1.6
Haloperidol 4	17.7	- 2.7	2.0
Haloperidol 8	17.0	- 3.3	2.6
Haloperidol 16	17.3	- 2.4	1.7

- 1 Mean score at baseline
- 2 Mean change from baseline to week 8 (LOCF)
- 3 Difference in mean change from baseline to week 8 (LOCF) between active drug groups and placebo

Discussion

The impression was that although there was some evidence for superiority of sertindole over placebo at all three doses, the evidence was most persuasive at the middle (20 mg/day) dose. Using Dunnett's criterion, both the 20 and 24 mg/day doses were superior to placebo in the LOCF analyses at the 8-week endpoint for the PANSS total and CGI severity scores. In the OC analyses, none of the key variables reached statistical significance at the 8-week endpoint using Dunnett's criterion; however, for the 20 mg/day doses, most variables met criteria for either $p < 0.05$ or a positive trend at the 8-week endpoint. It was felt that the poorer outcome in the OC analyses may have resulted from the substantial attrition almost always observed in placebo-controlled schizophrenia trials. In addition, visual inspection of the plots of scores for the various dropout cohorts reportedly revealed that for all the dropout cohorts the 20 mg/day patients were doing better than placebo at the point of dropout. Of note, it is also reassuring that for the PANSS score, the OC and LOCF differences in mean change from baseline to week 8 between active drug groups and placebo are in the same direction and of a similar magnitude. The final conclusion was that although statistically this was not a strikingly positive study, the effect size, as measured by difference between drug and placebo in change in baseline was impressive, especially for the 20 mg/day group (18 PANSS units). Overall, it was felt to be a positive study for the 20 and 24 mg/day doses, with some evidence for 12 mg/day dose as well.

Study M93-098

This was a randomized, 30-center (US), double-blind, parallel group, 8-week, fixed-dose study comparing sertindole at two fixed doses (20 and 24 mg/day, given once daily), haloperidol at one fixed dose (16 mg/day, given once daily), and placebo for the treatment of psychosis in adult inpatients meeting DSM-III-R or DSM-IV criteria for schizophrenia. Patients had to have scores on any two of the positive BPRS items summing to at least 8 and could not have had a decrease of more than 20% on the BPRS total score during the placebo lead-in period.

During the 2-week double-blind titration period, the initial dose for both sertindole and haloperidol was 4 mg once daily. The sertindole was titrated to the assigned dose at a rate of 4 mg every four days, while the haloperidol was increased by 4 mg every four days until reaching 16 mg/day. Following the titration period was a 6-week double-blind fixed dose treatment period. Benztropine mesylate was permitted for EPS but only on an as needed basis and for limited periods (three days); it could be continued with repeat evaluation and documentation.

The efficacy measures included the PANSS, the BPRS, and the CGI, all administered weekly during the 8-week trial. The primary efficacy variable was the PANSS total score. Secondary efficacy variables included the PANSS negative subscale, the BPRS positive symptom score, and the CGI-severity score. The review focused on the intent-

to-treat sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up time. The LOCF analysis (using Dunnett's criteria) was considered primary, but OC analysis was also done. The statistical model used was ANOVA, focusing on change in baseline for the efficacy variables and including treatment, investigator, and treatment-by-investigator terms. The exception was the CGI, which was analyzed using the Cochran-Mantel-Haenzel statistic, with centers as strata.

Study Results

Patients in the intent-to-treat dataset were between 18 and 67 years old, inclusive, with a mean age of 38 years. Sixty-three percent (63%) were Caucasian, 25% were African-American, and 12% were classified as other by the sponsor. Seventy-six percent (76%) of the patients were male. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

Table 7 Completion Rates to 8 Weeks in Study M93-098¹

Treatment Group	Number of Patients Completed/Randomized (%)
Placebo	43/106 (41%)
Sertindole 20 mg/day	44/111 (40%)
Sertindole 24 mg/day	49/108 (45%)
Haloperidol 16 mg/day	54/113 (48%)

¹based on intent-to-treat dataset

Table 8 Summary of Significance Levels for Pairwise Comparisons (Sertindole, Haloperidol, and Placebo) In Study M93-098

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole 20 & 24, and Haloperidol 16 mg/day, vs Placebo) in Study M93-098																									
Key Outcome Variables	Sertindole 20 vs Pbo				Sertindole 24 vs Pbo				Haloperidol 16 vs Pbo																
	Week ²								Week ²																
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	
PANSS Total	-	-	t	*	*	*	*	*	-	-	t	*	*	*	*	*	*	*	*	*	*	*	*	*	*
LOCF	-	-	-	-	-	-	-	-	-	-	t	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	t	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BPRS Pos	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
LOCF	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
OC	*	*	*	*	*	*	*	*	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
PANSS Neg	-	-	-	*	t	t	-	t	-	-	-	*	*	*	*	*	*	*	*	*	*	*	*	*	
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
CGI Severity	-	*	-	*	*	*	*	*	-	t	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
LOCF	-	*	-	*	*	*	*	*	-	t	*	*	*	*	*	*	*	*	*	*	*	*	*	*	
OC	-	*	-	*	*	t	t	t	*	-	t	t	-	*	-	-	*	-	-	*	-	-	-	*	

1 Based on ANOVA
 * = p ≤ 0.05
 t = p ≤ 0.10
 - = p > 0.10

2 End of weeks 1-8

Table 9 Size of Treatment Effect in Study M93-098

Size of Treatment Effect in Study M93-098			
PANSS Total Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	64.4	- 1.2	
Sert. 20	60.6	- 7.5	6.3
Sert. 24	62.8	- 10.3	9.1
Hlprdl. 16	65.1	- 13.3	12.1
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	12.2	- 1.2	
Sert. 20	12.0	- 3.0	1.8
Sert. 24	12.1	- 2.8	1.6
Hlprdl. 16	13.1	- 4.3	3.1
PANSS Negative Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	17.4	- 0.5	
Sert. 20	16.0	- 1.3	0.8
Sert. 24	17.5	- 2.5	2.0
Hlprdl. 16	16.4	- 1.3	0.8
CGI Severity Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	4.7	- 0.1	
Sert. 20	4.7	- 0.4	0.3
Sert. 24	4.8	- 0.4	0.3
Hlprdl. 16	4.9	- 0.7	0.6

1 Mean score at baseline

2 Mean change from baseline to week 8 (LOCF)

3 Difference in mean change from baseline to week 8 (LOCF) between active drug groups and placebo

Discussion

The impression was that both the 20 and 24 mg/day sertindole dose groups were generally superior to placebo in the LOCF analyses at the 8-week endpoint, with or without a correction for multiple comparisons. The evidence for these dose groups was seen as less persuasive in the OC analyses, but it was felt that this was likely due to the substantial attrition almost always observed in placebo-controlled schizophrenia trials. Of note, visual inspection of the plots of the scores for the various dropout cohorts reportedly revealed that for most of the dropout cohorts, the sertindole patients were doing better than placebo at the point of dropout. The effect size, as measured by the difference between drug and placebo on change from baseline, was considered less impressive for this study than for Study M93-113 but still clinically meaningful. Overall, it was felt to be a positive study for both the 20 and 24 mg/day doses but without any great advantage for the higher 24 mg/day dose group.

Study M92-762

This was a randomized, 16-center (US), double-blind, parallel group, 40-day, fixed-dose study comparing sertindole at three fixed doses (8, 12, or 20 mg/day, given once daily) and placebo for the treatment of psychosis in adult inpatients meeting DSM-III-R criteria for schizophrenia. During the 12-day, double-blind titration period, the initial dose of sertindole was 4 mg once daily, with titration to the assigned dose at the rate of 4 mg every 4 days. Benztropine mesylate could be given in single doses for EPS.

The efficacy measures included the PANSS, the BPRS, and the CGI, all administered weekly during the 40-day trial. The primary efficacy variable was the PANSS total score. Secondary efficacy variables included the PANSS negative subscale, the BPRS positive symptom score, and the CGI-severity score. The review focused on the intent-to-treat sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one follow-up time. The statistical model used was ANOVA, focusing on change in baseline for the efficacy variables and including treatment, investigator, and treatment-by-investigator terms. The exception was the CGI, which was analyzed using the Cochran-Mantel-Haenzel statistic, with centers as strata.

Study Results

Patients in the intent-to-treat dataset were between 18 and 66 years old, inclusive, with a mean age of 38 years. Fifty-six percent (56%) were Caucasian, 36% were African-American, and 8% were classified as other by the sponsor. Ninety-six percent (96%) of the patients were male. The treatment groups were comparable at baseline on the demographic and key efficacy variables.

Table 10 Completion Rates to Day 40 in Study M92-762¹

Treatment Group	Number of Patients (%)
Placebo	24/47 (51%)
Sertindole 8 mg/day	20/50 (40%)
Sertindole 12 mg/day	29/50 (58%)
Sertindole 20 mg/day	27/51 (53%)

¹based on intent-to-treat dataset

Table 11 Size of Treatment Effect in Study M92-762

Size of Treatment Effect in Study M92-762			
PANSS Total Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	56.6	- 5.0	
Sert. 8	60.1	- 3.5	1.5
Sert. 12	60.3	- 8.6	3.6
Sert. 20	60.0	- 12.6	7.6
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	12.0	- 1.8	
Sert. 8	12.5	- 1.8	0
Sert. 12	12.7	- 2.3	0.5
Sert. 20	11.9	- 3.1	1.3
PANSS Negative Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	15.0	- 1.3	
Sert. 8	15.1	- 0.2	- 1.1
Sert. 12	15.3	- 2.1	+ 0.8
Sert. 20	17.6	- 23.0	+ 22.0

- 1 Mean score at baseline
- 2 Mean change from baseline to week 7 (LOCF)
- 3 Difference in mean change from baseline to week 7 (LOCF) between active drug groups and placebo

Table 12 Summary of Significance Levels for Pairwise Comparisons (Sertindole vs. Placebo) in Study M92-762

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole 8, 12, and 20 vs Placebo) in Study M92-762																		
Key Outcome Variables	Sertindole 8 vs Pbo						Sertindole 12 vs Pbo						Sertindole 20 vs Pbo					
	Day ²						Day ²						Day ²					
	6	12	19	26	33	40	6	12	19	26	33	40	6	12	19	26	33	40
PANSS Total	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	t
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	*	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BPRS Pos	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS Neg	-	-	-	-	-	-	t	t	-	-	-	-	-	-	-	t	-	-
LOCF	-	-	-	-	-	-	t	-	-	-	-	-	-	-	t	*	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1 Based on ANOVA
* = $p \leq 0.05$
t = $p \leq 0.10$
- = $p > 0.10$

2 End of days 6-40

Discussion

The impression was that this was a negative study, with virtually no statistically significant differences between sertindole and placebo. It was noted that although the change from baseline in the PANSS total score for the 20 mg/day sertindole group was roughly the same in this study as it was for M93-098, the change in the placebo group was so prominent as to preclude any between group differences. There was no active control group to assess the sensitivity of this study to detect a drug effect.

Study M91-645

This was a randomized, 6-center (US), double-blind, parallel group, 7-week, titration study comparing sertindole (4-20 mg/day, given once daily) and placebo for the treatment of psychosis in adult inpatients meeting DSM-III-R criteria for schizophrenia or schizoaffective disorder. Benzotropine mesylate was permitted transiently for moderate-to-severe EPS.

The efficacy measures included the BPRS and the CGI, both administered weekly during the 7-week trial. The protocol specified that the BPRS positive symptom score would be the primary efficacy variable. However, in order to provide consistency with subsequent protocols, the total score was presented as the primary efficacy variable, with the positive symptom score as a supportive variable. The CGI-improvement score, which will not be further discussed, was another supportive efficacy variable. The review focused on the intent-to-treat sample, that is all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments

were available at baseline and at least one follow-up time. The statistical model was ANOVA, or ANCOVA when appropriate, focusing on change from baseline for the BPRS variables and including treatment, investigator, and treatment-by-investigator terms.

Study Results

Patients in the intent-to treat dataset were between 19 and 53 years old, inclusive, with a sponsor calculated mean age of 34. Fifty-eight (58%) were Caucasian and 42% were African-American. Ninety-two percent (92%) of the patients were male. Their diagnoses were the following:

Table 13 Psychiatric Diagnoses of Patients In Study M91-645

Diagnosis ¹	Placebo (N = 11)	Sertindole (N = 23)	Overall (N = 34)
Schizophrenia	9 (81.8%)	17 (73.9%)	26 (76.5%)
Schizoaffective	1 (9.1%)	3 (13.0%)	4 (11.8%)
Unspecified	1 (9.1%)	3 (13.0%)	4 (11.8%)

¹DSM-III-R

The treatment groups were comparable at baseline for the demographic variables. However, there were some differences on efficacy variables, and ANCOVAs were done in those instances. The mean dose of sertindole for completers at 40 days was 17 mg/day.

**Table 14 Completion Rates to 7 Weeks
In Study M91-645¹**

Treatment Group	Number of Patients (%)
Placebo	3/11 (27%)
Sertindole	11/23 (48%)

¹based on intent-to-treat dataset

Table 15 Summary of Significance Levels for Pairwise Comparisons (Sertindole vs. Placebo) In Study M91-645

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole vs Placebo) in Study M91-645							
Key Outcome Variables	Sertindole vs Placebo						
	Week ²						
	1	2	3	4	5	6	7
BPRS Total	*	*	-	*	*	*	*
LOCF	*	*	-	*	*	*	*
OC	*	*	-	*	*	-	-
BPRS Pos	-	t	t	*	*	*	*
LOCF	-	t	-	t	*	t	-
OC	-	t	-	t	*	t	-

1 Based on ANOVA
 * = $p \leq 0.05$
 t = $p \leq 0.10$
 - = $p > 0.10$

2 End of weeks 1-7

Table 16 Size of Treatment Effect In Study M91-645

Size of Treatment Effect in Study M91-645			
BPRS Total Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	38.1	+ 2.5	
Sertindole	31.5	- 7.2	9.7
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	13.8	+ 0.6	
Sertindole	11.9	- 3.9	4.5

1 Mean score at baseline
 2 Mean change from baseline to week 7 (LOCF)
 3 Difference in mean change from baseline to week 7 (LOCF) between sertindole and placebo

Discussion

The impression was that sertindole was superior to placebo in the LOCF analyses, though not in the OC analyses. It was felt that this was this result of the low completion rates; however, cohort analyses were not done for this study. Due to this and the fact

that patients with both schizophrenia and schizoaffective disorder were included, it was considered a supportive but not a key efficacy study.

Study M93-132

This was a randomized, 27-center (US), double-blind, parallel group, 12-month, fixed dose study comparing sertindole at one fixed dose (24 mg/day, given once daily) and haloperidol (10 mg/day, given once daily) for the treatment of psychosis in adult outpatients meeting DSM-III-R or DSM-IV criteria for schizophrenia. Patients had to be stable (without hospitalization due to a psychotic decompensation) on an antipsychotic medication (not including clozapine) for at least three months prior to entering the study. They could not be more than “moderately ill,” as defined by a CGI-severity score of less than or equal to four, at randomization.

During the 5-week transition period, the initial dose of sertindole was 4 mg once daily, with increases of 4 mg every fourth day until the maintenance dose of 24 mg/day was reached. The haloperidol was started at 5 mg once daily and then increased to the final dose of 10 mg/day after 15 days. Meanwhile, patients were tapered off their previous antipsychotics according to a protocol specified schedule over a 22-day period. The maintenance period was from week 6 to Month 12. Benztropine mesylate was permitted for extrapyramidal symptoms (EPS) but only on an as needed basis and for limited periods (seven days); it could be continued with repeat evaluation and documentation.

The efficacy measures included the PANSS, the BPRS, and the CGI, administered weekly during Weeks 1 to 8, every other week until Week 12, and monthly thereafter. However, the primary outcome variable was time to treatment failure, which was defined as one or more of the following:

- Patient required hospitalization due to an exacerbation of schizophrenia.
- Patient experienced $\geq 20\%$ deterioration in the total BPRS score from the primary baseline evaluation, or an increase of 8 or more points on the BPRS positive symptom score, or an increase of 5 or more points on the sum any two of the four positive symptom subscale items on the BPRS.
- Patient discontinued treatment due to lack of efficacy or noncompliance.
- Patient used antipsychotics other than the double-blind study drug.

The date for treatment failure was the earliest date on which at least one of the criteria was met during the maintenance period. Patients who discontinued treatment for reasons other than those defined as treatment failures were considered as censored observations on the day of termination. Supportive variables included the PANSS total score, the PANSS positive and negative subscales, the BPRS total score (weighted and unweighted), the BPRS positive symptom score, and the CGI Severity of Illness and Global Improvement subscales.

Two intent-to-treat (ITT) datasets were defined, one for the survival analysis of time to treatment failure (the primary outcome variable) and one for the analysis of the efficacy rating scales. The ITT dataset for the survival analysis included all patients who had a primary baseline evaluation (at the end of the transition period) for the PANSS and had at least one dose of blinded study drug during the maintenance period. The ITT dataset for the analysis of efficacy rating scales included all patients who had a primary baseline evaluation for the PANSS and at least one PANSS evaluation during the maintenance period.

The primary analysis examined treatment group differences in the number of days to treatment failure from the start of the maintenance period. The Kaplan-Meier survival curves for the two treatment groups, stratified by haloperidol use immediately prior to randomization, were compared by calculating the Wald statistic, and the failure hazard ratio was also determined. As part of this analysis, the proportion of patients who were not treatment failures at selected time points was calculated with associated 95% confidence intervals for each treatment group. Of note, survival analyses were also performed for days to each possible reason for treatment failure; however, time to treatment failure for each of the individual criteria was not pre-specified as a co-primary or supportive outcome variable.

The statistical model for the supportive analyses was ANOVA, or ANCOVA when appropriate, focusing on change from baseline (at the end of the transition period) to Month 12 for the supportive efficacy variables, with factors for treatment group, haloperidol use immediately prior to randomization, and the interaction. The exception was the CGI, which was analyzed using the Cochran-Mantel-Haenzel statistic, with prior haloperidol use as the strata.

Study Results

Patients in the survival intent-to-treat dataset were between the ages of 18 and 66 years, inclusive, with a mean age of 39 years. Sixty percent (60%) were Caucasian, 34% were African-American, 4% were classified as other, and 2% were Asian. Seventy-five (75%) of the patients were male. Treatment groups were comparable at baseline for the demographic variables. However, there were some differences on certain efficacy variables, and ANCOVAs (for the supportive analyses) were done in those instances.

Table 17 Intent-to-Treat Datasets In Study M93-132

Treatment Group	Number of Patients	
	Survival Dataset	Efficacy Dataset
Sertindole 24 mg/day	94	91
Haloperidol 10 mg/day	109	108

**Table 18 Completion Rates to 12 Months
In Study M93-132¹**

Treatment Group	Number of Patients (%)
Sertindole 24 mg/day	47/91 (52%)
Haloperidol 10 mg/day	58/108 (54%)

¹ based on efficacy intent-to-treat dataset

Time to treatment failure after the start of the maintenance period (the primary outcome variable) was not statistically significantly different between the sertindole and haloperidol groups. The Wald p-value was 0.278, and the failure hazard ratio for haloperidol vs. sertindole was 1.272. Of note, the median time to treatment failure for each group was not provided. So, although sertindole was similar to haloperidol in time to treatment failure, due to lack of a placebo control, one cannot assume that haloperidol was effective in this study, under these particular treatment conditions.

**Table 19 Survival Rates at Month 12 for Individual Failure Variables
In Study M93-132**

Reason	Sertindole 24 mg		Haloperidol 10 mg	
	Haloperidol-Stable (N=32)	Non- Haloperidol-Stable (N=62)	Haloperidol-Stable (N=42)	Non- Haloperidol-Stable (N=67)
Hospitalized for Psychotic Decompensation*	0.95	0.96	0.91	0.82
BPRS Deterioration	0.62	0.73	0.64	0.62
Discontinued Due to Lack of Efficacy	0.88	0.77	0.85	0.85
Discontinued Due to Noncompliance*	0.95	0.98	0.80	0.89
Neuroleptic Use	1.00	0.89	0.93	0.96

* Statistically significant for sertindole vs haloperidol at $p \leq 0.05$, two-tailed test
Cross Reference: Appendices C.8, D.2, D.12, D.16, and D.25

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For the PANSS total score, the PANSS positive and negative subscales, the BPRS total score, the BPRS positive symptom score, and the CGI Severity of Illness and Global Improvement subscales, there were no statistically significant differences between the sertindole and haloperidol groups from the primary baseline evaluation to Month 12 for either the OC or LOCF analyses.

Discussion

Assuming the hypothesis of this study was to show statistical superiority of sertindole over haloperidol over a 12-month period, the results were negative, as there was no

statistically significant difference between the sertindole and haloperidol treatment groups in the primary outcome measure, time to treatment failure. Although, at Month 12, as specified in the sponsor's proposed labeling, there were significant differences in the survival rates for two of the individual treatment failure variables (hospitalization for psychotic decompensation and discontinuation due to noncompliance), time to treatment failure for each of the individual criteria was not pre-specified as a co-primary or supportive outcome variable.

Comments on Other Important Clinical Issues Regarding the Efficacy of Sertindole for Psychosis

Question of Dose/Response for Efficacy

The impression was that two studies could be considered positive in support of the antipsychotic efficacy of sertindole: M93-113 (comparing sertindole doses of 12, 20, and 24 mg/day, haloperidol doses of 4, 8 or 16 mg/day, and placebo) and M93-098 (comparing sertindole doses of 20 and 24 mg/day, haloperidol 16 mg/day, and placebo). There was some evidence for the 12 mg dose in M93-113, but the 20 mg dose was superior to both the 12 mg and 24 mg doses. For M93-098, both the 20 and 24 mg doses were effective, with a small advantage for the 24 mg dose. Based on this data and the fact that sertindole is known to cause a dose-dependent QTc prolongation, the target dose range for the usual adult patient should encompass the lower and middle parts of the efficacy range, in this case 12 to 20 mg/day.

Clinical Predictors of Response

Our statistics team conducted an exploratory subgroup analysis (based on race and gender) for the studies M93-113 and M93-098. The results trended in the same direction (in favor of sertindole) across all subgroups except the "Other" race category for the 20 mg vs. placebo group in M93-098. However, the sample size for that group was very small.

Size of Treatment Effect

Table 20 Size of Treatment Effect for PANNS Total Score at Endpoint¹ (LOCF) for the Two Positive Schizophrenia Trials

Study M93-113		
Group	Mean Change ²	Effect Size ³
Sertindole 12 mg	-9.9	10.6
Sertindole 20 mg	-17.6	18.3
Sertindole 24 mg	-10.7	11.4
Study M93-098		
Group	Mean Change ²	Effect Size ³
Sertindole 12 mg	--	--
Sertindole 20 mg	-7.5	6.3
Sertindole 24 mg	-10.3	9.1

¹The endpoint is 8 weeks

²Mean change from baseline to endpoint (LOCF)

³Difference in mean change from baseline to endpoint (LOCF) between active drug groups and placebo

The effect size for the two positive studies (M93-113 and M93-098) ranged from 6.3 to 18.3, and this was felt to be comparable to effect sizes observed in positive trials for other antipsychotic drugs. These effect sizes were considered clinically meaningful and supportive of the antipsychotic claim for sertindole.

Duration of Treatment

The impression was that there were no adequate and well controlled relapse prevention trials in the sertindole development program to address the question of long-term efficacy. The newly submitted 12-month study (M93-132), comparing sertindole 24 mg/day and haloperidol 10 mg/day, does not meet these requirements, due to lack of superiority over haloperidol, given that there is no placebo control.

Conclusions Regarding Efficacy Data

Overall, studies M93-113 and M93-098 were considered positive studies in support of the claim of short-term antipsychotic efficacy for sertindole. It was felt that these data support a target dose range of 12 to 20 mg/day for the usual adult patient, with the acknowledgement that 12 mg/day may be less effective than 20 mg/day for some patients. There are no adequate and well controlled data to address the question of long-term efficacy.

6.2 Reduction of Risk of Fatal and Non-Fatal Suicide Attempts in Patients with Schizophrenia

The Sertindole Cohort Prospective (SCoP) Study

The sponsor's claim that sertindole reduces the risk of fatal and non-fatal suicide attempts in patients with schizophrenia is based on the results of the Sertindole Cohort Prospective (SCoP) study. The overall objective of this study was to compare the safety of sertindole and risperidone under normal conditions of use; the protocol was later amended in order to also compare the rates of fatal and non-fatal suicide attempts in the sertindole- and risperidone-treated patients. The SCoP Study will be described in its entirety, including the safety results, below.

Overview and Study Sites

This study was a randomized, open-label, parallel group, active-controlled, flexible dose, up to 63.5 month, multicenter trial in adult outpatients with schizophrenia. The protocol did not require the use of any classifications, such as DSM or ICD, or diagnostic instruments for diagnosis of schizophrenia. It was conducted at 593 centers (in 38 countries), all outside the U.S. Although there were many sites in Western Europe, a majority of the patients were enrolled at sites in Eastern Europe, the Philippines, Malaysia, South Korea, and India. The overall objective of this study was to compare the safety of sertindole and risperidone under normal conditions of use. Approximately 16 months after the first patient visit, the protocol was amended in order to also compare the rates of fatal and non-fatal suicide attempts in the sertindole and risperidone treated patients. The necessary data on patients who were already in the study—a total of 1917—was collected retrospectively, if necessary, through unclear methods. However, retrospective reporting only uncovered one suicide attempt that had not previously been reported using the standard definition of an adverse event.

Objectives

The first primary objective of the SCoP study was to compare the all-cause mortality in schizophrenic patients treated with sertindole versus risperidone under normal conditions of use. The second primary objective, included at the request of the Committee for Medicinal Products for Human Use (CHMP) of the European Union (EU), was to compare the rate of cardiac events (including arrhythmias) requiring hospitalization between the two groups. Of note, these objectives were not endorsed by the FDA.

Secondary objectives included between group comparisons of:

- Cause-specific fatal events (cardiac and suicide)
- Suicide attempts (fatal and non-fatal). (Of note, this analysis was added as part of a protocol amendment).

Subjects

A total of 9858 patients participated in the study. The number of patients randomized depended on the accumulated treatment exposure; at least 3800 patient years of exposure were required in each treatment group. This was part of an agreement between the sponsor and the Committee for Medicinal Products for Human Use (CHMP) of the European Union, and recruitment continued until the CHMP gave permission to stop the study. The inclusion criteria were deliberately broad in order to acquire a sample representative of the target population for sertindole. However, patients did have to meet the criteria set out in the local Summary of Product Characteristics (SPC) for both sertindole and risperidone. (If sertindole was not marketed in a particular country, the European Union SPC was used instead). Of note, the EU Summary of Sertindole Characteristics, which was appended to the protocol, does have many precautions, warnings, and contraindications. In particular, it does require ECG monitoring prior to and during treatment, with QT_c cutoffs for the initiation and continuation of treatment.

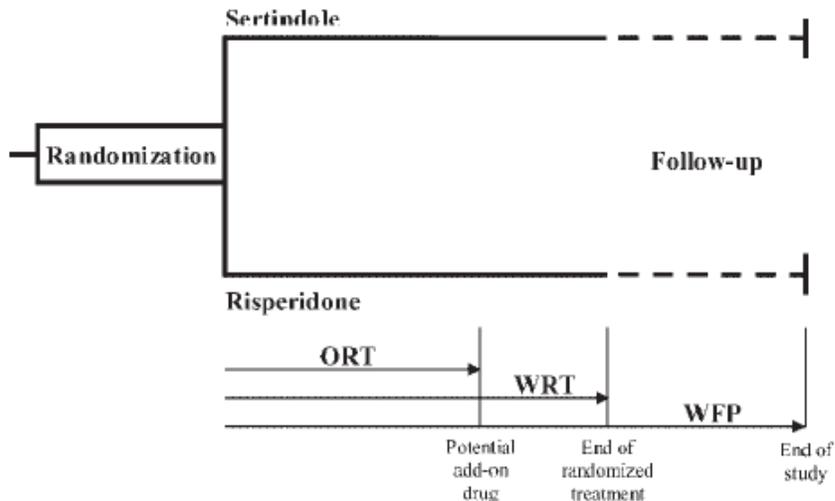
Study Design

Patients were randomized (1:1) to receive open-label treatment with either sertindole (n=4930) or risperidone (n=4928). The start and maintenance dosages as well as the dose titration were set by the investigator, in accordance with the local or European Union SPC. All concomitant medications were permitted, except, initially, other antipsychotics. However, during the course of the study, investigators were permitted to add on another antipsychotic to the randomized treatment if clinically indicated. Of note, except for information on other antipsychotics, complete data on concomitant medications was not collected in this study.

The following basic study periods were defined (see figure X):

- *Only Randomized Treatment (ORT) Period*: the period from the date of prescription of randomized treatment until randomized treatment was stopped (provided the patient did not continue treatment within the following 15 days) or the date of add-on antipsychotic(s), whichever occurred first.
- *Whole Randomized Treat (WRT) Period*: the period from the date of prescription of randomized treatment until randomized treatment was stopped (provided the patient did not continue treatment within 15 days), including the time the patient was treated in combination with another antipsychotic (add-on therapy, if indicated).
- *Whole Follow-up (WFP) Period*: the period from the date of prescription of randomized treatment until date of withdrawal from/completion of study. (Patients were followed, if willing, until the end of the entire study).

Figure 2 Design of SCoP Study



Assessments and Classification

Patients had contact with the investigator monthly during the first three months of treatment and on a quarterly basis thereafter, including after starting add-on therapy and even after discontinuing the study drug (unless they withdrew from the study or the study was terminated). The scheduled contact could either be a clinic visit or telephone contact with the patient or the patient's family/relative. However, between each telephone contact (scheduled study contact or unscheduled), the patient had to be seen in the clinic at least once.

The study assessments focused solely on the outcomes of interest, with the patients being otherwise assessed and managed by the investigators according to routine clinical practice. At each visit, the following information was collected:

- Vital Status (alive, deceased, unknown)
- Serious Adverse Events (SAEs), since last visit.
- Cardiac Adverse Events, since last visit.
- Hospitalizations (since last visit), excluding hospitalization related to the primary psychiatric disease but including hospitalizations due to imminent suicide risk or following a suicide attempt (suicide risk and attempt added as part of amendment)
- Suicide attempts/ideation/tendency with/without hospitalization (added as part of an amendment), since last visit.
- Duration of randomized treatment and any additional antipsychotic use

Of course, a serious adverse event form could be filled out at any time; there was no need to wait until a scheduled study contact. Of note, a SAE was defined as any

untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent disability/incapacity, is a congenital anomaly/birth defect, is a suicide attempt, or is medically important (refers to an event that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed).

In this study, the patients, the investigators, and the sponsor were unblinded to the patients' treatment. To allow an ongoing assessment of patient safety and review of the endpoints, two independent committees were established in agreement with the CHMP, the Independent Safety Committee (ISC) and the Independent Management Committee (IMC). The ISC and IMC were blinded to treatment, and their working procedures were reviewed and approved by the CHMP. Of particular interest is the ISC, which was comprised of seven members with backgrounds in cardiology, epidemiology, pharmacovigilance, psychiatry, and statistics. Three of the seven members were replaced over time, reportedly due to scheduling conflicts. During the study, investigators reported all SAEs (including suicide attempts/ideation/tendency) and cardiac AEs to Lundbeck, which in turn prepared blinded case report forms in CIOMS-1 format for evaluation and categorization by the ISC.

On a regular basis and at least every two months, depending on the number of cases reported, the ISC met. After each meeting, it issued a report summarizing the event classifications, conclusions, and any recommendations regarding the further conduct of the study. Based on the blinded case reports, the ISC classified the endpoint events into one of the following categories:

- Death (cardiac)
- Death (suicide)
- Death (other)
- Other endpoint event (cardiac)
- Other endpoint event (suicide attempt/ideation/tendency, with or without hospitalization)
- Other endpoint events (other)

Of note, if there was doubt as to the exact cause of death, especially if information was lacking, the case was conservatively classified as cardiac (putative) by default. Vascular deaths (for example non-cardiac thrombosis, embolus) were not considered cardiac deaths. At the completion of the study, all the deaths that had been classified as cardiac (definitive and putative) were reviewed to confirm the classification based on available information. The cardiac deaths were then subclassified:

- Documented cardiac arrhythmia causing death: a death with documented evidence for arrhythmia causing death, either directly or indirectly.
- Documented sudden unexpected death: a death that occurred within 24 hours of onset of reported symptoms and with no other obvious non-cardiac cause

- Other possible cardiac death: a death related to a complication of a serious non-arrhythmic cardiac event.

Also at the end of the study, all non-fatal cardiac events were subclassified either as “cardiac arrhythmia leading to hospitalization (an event with documented evidence of arrhythmia leading to hospitalization)” or as “other cardiac event”.

Analysis

The analysis of the first primary endpoint of all-cause mortality included all deaths occurring in the WRT+30 days period and was based on the times to death for those patients who died in the period and the censored survival times for those patients who were still alive. For patients who dropped out of the study, the censoring date was the drop out date or the date of the investigator’s last contact with the patient. The comparison of mortality rates between sertindole-treated patients and risperidone-treated patients was performed using Cox’s proportional hazards model, with variables for treatment group, age, and gender. With this model, the age and gender adjusted mortality ratio (MR) of the hazard for the sertindole-treated patients compared to that for the risperidone-treated patients was estimated. If the upper limit of the one-sided 95% confidence interval for the estimated MR turned out to be below the pre-specified equivalence limit of 1.5 (chosen in agreement with the CHMP), the null hypothesis of excess mortality in sertindole-treated patients was to be rejected.

The analysis of the second primary endpoint of cardiac events (including arrhythmias) requiring hospitalization during the WRT+30 days period was to use the same approach as the primary analysis of all-cause mortality. However, it turns out that the numbers were too small to allow for a meaningful analysis (see Results).

For the secondary endpoint of cause-specific fatal events (cardiac and suicide) during the WRT+30 days period, a Cox proportional hazards analysis resembling that which was carried out for all-cause mortality was performed (and 95% confidence limits calculated).

Finally, the analysis of the secondary endpoint of suicide attempts (fatal and non-fatal) also covered the WRT+30 days period. It was based on the time from start of randomized treatment to occurrence of the first attempt for those patients who attempted suicide in the period and the censored time values from start of randomized treatment to the end of the period for those patients who did not attempt suicide. The suicide attempt rates between the two treatment groups were compared using a Cox’s proportional hazards model with variables for treatment group, age, gender, total duration of schizophrenia, and time since last suicide attempt. With this model, the adjusted suicide attempt ratio (AR) of the hazard for sertindole-treated patients compared to that for risperidone-treated patients was estimated. The null hypothesis of no difference (AR=1) was tested against the one-sided (alpha=0.05) alternative of less suicide attempts in sertindole-treated patients (AR≤1).

Study Results

Patients in the all-patients-treated-set (defined as those who received at least one dose of randomized treatment) were between the ages of 18 and 85 years, with a mean age of 38 years. A little more than half (55%) of the patients in each treatment group were men. Other demographic information was more limited. At baseline, approximately two-thirds of patients in each treatment group had been diagnosed with schizophrenia five or more years prior to study entry. Few patients (12% in each treatment group) had a history of suicide attempts, and there were no relevant differences between the two treatment groups in the number of previous suicide attempts or in the time since the last suicide attempt. The proportions of patients who had previously received a typical antipsychotic, atypical antipsychotic, or both were similar in the two groups.

Total exposure to study drug in the WRT period was 6575 years for the sertindole group and 7572 years for the risperidone group, nearly twice the amount planned. The median number of days patients were exposed to study drug during the WRT period was smaller in the sertindole group (360 days) than in the risperidone group (476 days). Approximately 80% of the patients in the sertindole group and 90% of the patients in the risperidone group received doses of study drug within the recommended dose range (sertindole 12-20 mg/day and risperidone 2-8 mg/day), with the majority in each group in the middle to low end of that range. A relative minority of patients (361 in the sertindole group and 424 in the risperidone group) received add-on antipsychotic therapy during the WRT period.

All-cause Mortality

Table 21 Estimated Mortality Ratios for Sertindole versus Risperidone during the WRT+30 Days Period

Cox Analysis	Number of Deaths		Mortality Ratio	90% CI
	Sertindole	Risperidone		
As of CHMP Cut-off Date ¹ , original analysis ²	61	60	1.113	0.824-1.501
As of CHMP Cut-off Date ¹ , revised analysis ³	61	60	1.081	0.801-1.458
Including Study Close Period ⁴ , original analysis ²	64	61	1.148	0.855-1.542
Including Study Closure Period ⁴ , revised analysis ³	64	61	1.117	0.831-1.500

¹ The date the CHMP authorized the study to be terminated (September 20, 2007)

² Adjusting for age and gender only, as in the original analysis plan.

³ Adjusting for age, gender, history of suicide attempt within 5 years prior to study entry, last antipsychotic treatment (monotherapy or polytherapy), and time since start of study accrual (July 11, 2002)

⁴ Last patient visit was February 22, 2008

As the upper limit of the confidence interval was greater or equal to the pre-specified equivalence limit of 1.5, the null hypothesis of excess mortality in sertindole-treated patients should have been accepted. However, the sponsor believed that other variables not specified in the Statistical Analysis Plan (SAP) should have been added to the analysis. As seen in table 21, when the analysis was repeated using these additional variables, the upper bound of the mortality ratio for both the CHMP cut-off date and the period including study closure dropped to 1.5 or slightly below.

Of note, for these all-cause mortality analyses, the sponsor reported 90% confidence intervals (CI). However, as a standard practice, the FDA has been utilizing 95% CI in non-inferiority trials. None of the 95% CI for the above analyses were entirely below 1.5. Refer to the FDA Statistical Review and Evaluation for more details.

Cardiac Events, Including Arrhythmias, Requiring Hospitalization

In terms of the second primary endpoint, cardiac events, including arrhythmias, requiring hospitalization, there were too few cases to perform an analysis. During the WRT+30 days period, there were 5 SAEs with hospitalization in the sertindole group and 4 SAEs with hospitalization in the risperidone group coded to the MedDRA SOC *Cardiac Disorders*. Of these 9 cases, 3 were cardiac disorders with arrhythmia that occurred in the sertindole group, two of which are of particular interest (the third is a case of atrial flutter in a 64-year-old man with a history of alcoholism and COPD).

- Patient 485433, a 79-year-old woman with a history of hypertension (no other cardiac history specified) had been on sertindole for a total of 252 days when she had syncope during a routine ECG recording. The ECG showed Torsades de Pointes, but the patient recovered spontaneously. As a result, she was admitted, and later that same day she went into cardiac arrest. The patient was resuscitated and treated with xylocaine and amiodarone. A Holter monitor was placed during admission, which showed an increased QT_c interval (actual number not provided), with ventricular extrasystoles (but no ventricular arrhythmia). She was then taken off monitoring, and the sertindole was discontinued. Four days after discontinuation of sertindole, the patient was found dead in her bed at night. No autopsy was performed.
- Patient 793851, a 43-year-old woman with a history of hypertension as well as borderline QT_c prolongation at study entry had been on sertindole for more than 18 months when she developed symptomatic ventricular tachycardia. The patient reported giddiness, palpitations, and shortness of breath, and her heart rate ranged from 110 to 130 bpm. One week prior to the event, she was treated with an unknown antibiotic and Chinese cough medicine, but she did not receive other concomitant medications. She was admitted to a cardiac care unit and recovered. An “external cardiologist” concluded the ECG of her ventricular tachycardia was consistent with possible Torsades de Pointes. However, the sponsor says that the “the ECG from this event does not meet the exact criteria for this diagnosis.

Of note, no cases of documented or possible Torsades de Pointes in the risperidone group were reported.

Cardiac Deaths

For the secondary endpoint of cause-specific fatal events (cardiac), the SAP did not specify which event definition was to be used for the analysis. There were the SAEs with fatal outcome that were coded to the MedDRA SOC *Cardiac disorders* (essentially investigator-defined cardiac deaths), and there were the cardiac deaths as classified by the ISC. The sponsor therefore analyzed both.

Table 22 Estimated Hazard Ratios for Cardiac Death for Sertindole versus Risperidone during the WRT+30 Days Period

Cox Analysis	Number of Deaths		Hazard Ratio	p-value	95% CI
	Risperidone	Sertindole			
MedDRA coding					
Model a1 (report)	8	17	2.131	0.0809	0.911 – 4.985
Model b	8	17	2.173	0.0730	0.930 – 5.075
ISC classification					
Model a2 (report)	12	31	2.841	0.0022	1.454 – 5.550
Model b	12	31	2.848	0.0021	1.460 – 5.552

Model a1: Adjusted for age, gender, and last antipsychotic treatment (monotherapy, polytherapy)

Model a2: Adjusted for age, gender, last antipsychotic treatment (monotherapy, polytherapy), last suicide attempt within 5 years prior to study (yes, no), region (Europe, Asia), and time of study accrual

Model b: Adjusted for age and gender, only.

So, using either classification, sertindole-treated patients had a greater than two-fold higher risk of cardiac death during the WRT+30 days period. However, only the results for ISC classification were statistically significant.

Suicide Deaths/Completed Suicide

The sponsor analyzed the deaths coded using MedDRA as completed suicide (essentially investigator-defined suicide deaths) as well as the suicide deaths as classified by the ISC. Thirteen patients in the sertindole group and 21 patients in the risperidone group committed suicide as coded using MedDRA, while 14 patients in the sertindole group and 21 patients in the risperidone group committed suicide according to the ISC classification. The Cox analysis yielded similar results for the two classifications. Although there was a tendency for sertindole-treated patients to have a lower risk of completed suicide than risperidone-treated patients, these differences were not significant (estimated hazard ratios of 0.66, p=0.24 [MedDRA] and 0.72, p=0.32 [ISC]).

Suicide Attempts (fatal and non-fatal)

The sponsor analyzed suicide attempts (fatal and non-fatal) as reported by the investigator and coded using MedDRA as completed suicides or suicide attempts. It also analyzed suicide attempts (fatal and non-fatal) as classified by the ISC. (In the ISC working procedures, suicide attempt was defined as serious self-harm or intentional overdose or poisoning—even if the patient expressed no overt suicidal intention—as well as suicidal ideation or tendency, with and without hospitalization). However, these two analyses yielded conflicting results.

Table 23 Estimated Hazard Ratios for Suicide Attempt (Fatal and Non-Fatal) for Sertindole versus Risperidone During the WRT+30 Days Period

Cox Analysis	Number of Attempts		Suicide Attempt Ratio	95% CI
	Sertindole	Risperidone		
MedDRA coding	43	65	0.669	0.452-0.990
ISC classification	68	76	0.926	0.665-1.291

The sponsor believes the reason no difference was found using the ISC classification of suicide attempts was that the ISC used too broad a definition of suicide attempt. No information as to why this broader definition was chosen could be found in the ISC working procedures or memos.

The Review Team (clinical and statistical) was of the opinion that neither the investigators' nor the ISC's approach to the classification of suicide attempts was adequate. The investigators' classification was made in an unblinded and unsystematic manner. The ISC's classification, though blinded and more systematic, used a definition of suicide attempt that was too broad. We therefore proposed the sponsor reclassify and then reanalyze suicide attempts according to a new system (see below).

Additional Endpoints Requested by FDA

Sudden Cardiac Death

The Review Team consulted the QT Team in the Division of Cardiovascular and Renal Products to ask whether, in light of the QT prolongation seen with sertindole use, we should focus on any other safety endpoints. The QT team suggested that the most clinically relevant endpoint (more so than all-cause mortality or all cardiac deaths) would be sudden cardiac deaths (with any sudden unexplained deaths being conservatively classified as cardiac). The reason for this is that significant QT prolongation is associated with Torsades de Pointes, which is itself often never detected but usually leads to sudden death.

The ISC already subclassified definite and putative cardiac deaths into several categories, including documented sudden unexpected death, defined as a death that occurred within 24 hours of onset of symptoms and with no other obvious non-cardiac cause. This closely matches the ICD-10 definition for sudden cardiac death. During the WRT+30 days period, 13 patients in the sertindole group and 3 patients in the risperidone group met this definition for sudden cardiac death. We requested that the sponsor calculate the estimated hazard ratio, removing the following patients from the analysis (of note, this did not change the number of cases of sudden death):

- Those in the sertindole group who had risperidone added to their randomized treatment.
- Those in the risperidone group who had sertindole added to their randomized treatment.
- Those in either group who had certain QT prolonging antipsychotics (thioridazine, mesoridazine, ziprasidone, or pimozide) added to their randomized treatment.

Removing these patients and adjusting for age and sex, the estimated hazard ratio for sertindole vs. risperidone can be seen in the table below:

Table 24 Estimated Hazard Ratio for Sudden Cardiac Death for Sertindole versus Risperidone During the WRT+30 Days Period

Number of Sudden Cardiac Deaths		Hazard Ratio	95% CI
Sertindole	Risperidone		
13	3	5.102	1.453 – 17.913

Syncope, Palpitations, and Dizziness

The QT Team also suggested that an exploratory analysis be performed to compare the rates of syncope, palpitations, and dizziness between the sertindole- and risperidone-treated patients, as these are all potentially symptoms of an arrhythmia. For each of these events, the sponsor performed a Cox proportional hazards analysis based on the time from the start of randomized treatment to the first occurrence of the event, adjusting only for age and gender. At our request, the same patients were removed from this analysis as from the sudden death analysis (see above).

Table 25 Estimated Hazard Ratios for Selected Adverse Events for Sertindole versus Risperidone during the WRT+30 Days Period

Adverse Event	Number of Events		Hazard Ratio	p-value	95% CI
	Risperidone	Sertindole			
Syncope	3	7	2.598	0.1669	0.671 – 10.056
Palpitations	13	21	1.772	0.1052	0.887 – 3.540
Dizziness	4	14	3.847	0.0175	1.265 – 11.692

CI Confidence interval

Although the results are only statistically significant for dizziness, the point estimate for each of the hazard ratios is above one. The sponsor points out these symptoms may occur for many reasons, including the alpha-1-andrenoceptor antagonism effect of sertindole. However, the active comparator, risperidone, also has such effects, at least to a certain extent.

Suicide Attempts (fatal and non-fatal)

As mentioned above, the Review Team was of the opinion that neither the investigators' nor the ISC's approach to the classification of suicide attempts was adequate. Although the ISC was blinded to treatment, reducing the risk of bias in the ISC classification of suicide attempts, the definition the ISC used for suicide attempt was very broad, including suicidal ideation and tendency. We therefore requested the sponsor to reclassify the ISC identified suicide attempts (fatal and non-fatal) in a more systematic manner and to reanalyze the results.

We requested that the ISC identified suicide attempts be reclassified in the following manner:

- The blinded individual case reports (in CIOMS 1 format) for all the ISC identified suicide attempts (fatal and non-fatal) should be gathered.
- All of these blinded case reports should be forwarded to an outside independent consultant(s) with the proper expertise and training in reclassification. Ordinarily, these would be psychiatrists with special expertise in assessing suicidality.
- The consultants should code each of the case reports, using the following categories from the Columbia Classification Algorithm for Suicide Assessment (C-CASA):
 - No event (code 0)
 - Completed suicide (code 1)
 - Suicide attempt (code 2)
 - Preparatory acts toward imminent suicidal behavior (code 3)
 - Suicidal ideation (code 4)
 - Self-injurious behavior, intent unknown (code 5)

- Not enough information, fatal (code 6)
- Not enough information, non-fatal (code 7).

We then requested that the sponsor perform a Cox proportional hazards model analysis of time to the first suicide attempt (fatal and non-fatal) for sertindole vs. risperidone (using the same adjustments as in their original analysis) for all events coded 1, 2, or 3. We also asked for Kaplan-Meier estimates of cumulative event rates over time. Of note, the following patients were to be removed from the Cox proportional hazards model analysis:

- Those in the sertindole group who had risperidone added to their randomized treatment (before the first attempt, if any)
- Those in the risperidone group who had sertindole added to their randomized treatment (before the first attempt, if any)
- Those in either group who had clozapine added to their randomized treatment (before the first attempt, if any)

The reclassification and reanalysis have recently been completed. A review of their results will be included in an addendum to this review.

Demographic Analyses

Our statistics team performed exploratory subgroup analyses by gender and geographic region for all the above endpoints. A subgroup analysis by age was not included, as only 183 patients (less than 2%) were older than 65 years. For the results, please refer to the FDA Statistical Review and Evaluation.

Discussion

Although the first primary endpoint of the SCoP study was all-cause mortality, the Review Team is of the opinion that other endpoints are of greater clinical importance. Since the all-cause mortality rate is known to be significantly higher in schizophrenic patients than in the general population, any cardiac mortality signal could get lost if looking solely at all-cause mortality. Given the QT prolongation seen with sertindole use, our QT team suggested that the most clinically relevant endpoint would be sudden cardiac death (with any sudden unexplained deaths being conservatively classified as cardiac). The estimated hazard ratio (sertindole versus risperidone) turned out to be 5.102 [95% CI 1.453 to 17.913]. This is a significant and concerning result, indicating that sertindole-treated patients had an approximately five times higher risk of sudden cardiac death.

The sponsor maintains that the SCoP study shows a statistically significantly lower risk of suicide attempts (fatal and non-fatal) for sertindole-treated patients than for risperidone-treated patients. However, this result was based on reports by the investigators, who were not blinded to treatment, therefore introducing a potential

source of bias. The ISC, which was blinded to treatment, also classified suicide attempts, but their definition was too broad.

We asked the sponsor to reclassify and reanalyze the ISC identified suicide attempts. The sponsor submitted their results on 2/13/09. A review of their results will be included in an addendum to this review.

7 Review of Safety

Brief Safety Summary

Both the size of the safety database and the duration of exposure were adequate. The total exposure for the 2711 patients in the completed, non-Japanese, phase 2/3 schizophrenia trials was 1840 person-years. There were 801 patients who received sertindole for >6 months and 514 subjects who received sertindole for >12 months (section 7.2.1).

The main safety concerns are a significant, dose-dependent QTc prolongation (section 7.4.4), associated with a five-fold higher risk of sudden cardiac death in the SCoP Study (section 6.2). This is in addition to cases of torsades de pointes, both in SCoP and the rest of the clinical database.

There were no reported cases of significant liver toxicity, although there is some evidence that sertindole may cause mild, asymptomatic elevations in ALT and AST (section 7.4.2). Like other atypical antipsychotics, sertindole appears to cause increases in weight, fasting glucose, triglycerides, and probably total cholesterol (sections 7.4.2 and 7.4.3), but longer term studies are needed to fully characterize the metabolic risks. However, the risk of extrapyramidal symptoms (EPS) and seizures appears to be low (section 7.4.5). Based on the limited prolactin data available, the signal for prolactin elevation compared to the active control antipsychotic agent used in the clinical trials is equivocal, but there does seem to be a modest elevation in prolactin levels as compared to placebo (section 7.4.2).

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The evaluation of the safety of sertindole consisted of three general approaches:

- An assessment of the more serious adverse events (SAEs), specifically deaths, non-fatal serious adverse events, and adverse events that led to premature termination (AE dropouts), from the entire Japanese and non-

- Japanese study pools (N=21731 for sertindole) as well as the post-marketing spontaneous reports.
- A comparison of the common adverse events, laboratory findings, vital sign data, and ECG findings between sertindole (N=604) and placebo (N=237) within the pool of the three completed, non-Japanese, short-term, fixed-dose, placebo-controlled, phase 2/3 schizophrenia studies. The Japanese studies were not used, as Shionogi (Lunbeck's partner in Japan—the relationship between the two companies was terminated in 1998) limited reporting of adverse events to those considered by the investigators as having a casual relationship to study drug.
 - A review of the Sertindole Cohort Prospective (SCoP) Study, a large (N=9858), randomized, open-label study designed to compare the safety (in particular cardiac) of and the suicidality risk with sertindole and risperidone under normal conditions of use.

7.1.2 Adequacy of Data

An audit of adverse event categorization and the use of MedDRA preferred terms was performed by Dr. Greg Dubitsky, DPP Medical Officer. He looked at 15 case report forms and compared them to the corresponding narrative summary and MedDRA line listing. No major deficiencies were found.

Overall, the quality and completeness of the data appears adequate. Some critical analyses were initially missing, but the sponsor promptly provided them when requested to do so.

7.1.3 Pooling of Data across Studies/Clinical Trials to Estimate and Compare Incidence

The primary database used to estimate and compare incidence was the pool of the three completed, non-Japanese, short-term, fixed-dose, placebo-controlled, phase 2/3 schizophrenia studies (M93-113, M93-098, and M92-762). There was an additional non-Japanese, placebo-controlled, fixed-dose study that was not included (M92-817), as it was prematurely discontinued by the sponsor.

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The total exposure for the 2711 patients in the completed, non-Japanese, phase 2/3 schizophrenia trials was 1840 person-years.

Table 26 Number of Patients by Mean Dose and Duration of Treatment for All Completed, Non-Japanese, Phase 2/3 Schizophrenia Trials

Mean Dose (mg/day)	Number (%) Patients by Duration (Months) ^a					Total n (%)
	≤1 n (%)	>1 to 3 n (%)	>3 to 6 n (%)	>6 to 12 n (%)	>12 n (%)	
>0 to 8	319 (44.4)	75 (9.6)	8 (2.3)	8 (2.6)	13 (2.4)	423 (15.6)
>8 to 12	190 (26.4)	107 (13.6)	18 (5.2)	18 (5.8)	23 (4.2)	356 (13.1)
>12 to 16	149 (20.7)	163 (20.8)	66 (19.2)	34 (10.9)	60 (10.9)	472 (17.4)
>16 to 20	61 (8.5)	318 (40.5)	131 (38.1)	85 (27.2)	129 (23.5)	724 (26.7)
>20 to 24	0	122 (15.5)	117 (34.0)	165 (52.7)	314 (57.1)	718 (26.5)
>24	0	0	4 (1.2)	3 (1.0)	11 (2.0)	18 (0.7)
Total	719 (100.0)	785 (100.0)	344 (100.0)	313 (100.0)	550 (100.0)	2711 (100.0)

^a A month was defined as 30 days.

The following table compares the ICH guidelines for the number of patients exposed to the actual number exposed to doses >12 to >24 mg:

Table 27 Comparison of Actual Exposure in Completed, non-Japanese, Phase 2/3 Schizophrenia Trials to ICH Guidelines

Length of Exposure to Doses >12 to >24 mg	Number of Patients	
	ICH Guidelines	Actual
>6 months	300-600	801
>12 months	100	514
All Together	1500	1932

The mean age of these 2711 patients was 37.9 years, with a range of 14-73. Seventy-eight (78%) were Caucasian, 19% were Black or African-American, 1.7% were Asian, and 1.4% were other. Seventy-three (73%) of the patients were male.

7.2.2 Explorations for Dose Response

The primary database used to explore dose response was the pool of the three completed, non-Japanese, short-term, fixed-dose, placebo-controlled, phase 2/3 schizophrenia studies. The only other non-Japanese, placebo-controlled study was flexible dose, which precluded its use in explorations for dose response.

7.2.3 Special Animal and/or In Vitro Testing

Sertindole is a potent blocker of the delayed rectifier potassium current (I_{Kr}) and prolongs the QTc interval in animals and humans, an effect attributed to potent blockade of the hERG channel current. The sponsor recently submitted new

pharmacology and safety pharmacology studies, which were meant to support the hypothesis that sertindole, through inhibition of the late sodium current, might have a lower arrhythmogenic potential than other I_{Kr} blockers. At the request of our pharmacology/toxicology team, this evidence was evaluated by John Koerner, Ph.D., Senior Pharmacologist, Division of Cardiovascular and Renal Products. It was his opinion that “although inhibition of the late sodium current could theoretically attenuate risk of torsades de pointes with sertindole, the results are not definitive.”

7.2.4 Routine Clinical Testing

For the primary safety database, the type and frequency of vital sign, clinical laboratory, and ECG parameters measured and reported seems adequate. The schedule of safety assessments for these three studies can be found in Appendix G.

7.2.5 Metabolic, Clearance, and Interaction Workup

As of February 13, 2009, the Office of Clinical Pharmacology review team did not endorse any problems with the adequacy of the metabolic, clearance, and interaction workup.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Potential adverse effects based on those for similar drugs in the drug class include metabolic syndrome, extrapyramidal symptoms (EPS), neuroleptic malignant syndrome (NMS), and tardive dyskinesia (TD). For the primary safety database, most of the individual components of metabolic syndrome, including weight as well as fasting glucose, cholesterol, and triglycerides, are measured with sufficient frequency; however, waist circumference is not included. The sponsor did monitor for EPS and NMS through adverse event reporting. The studies were not of sufficient length to evaluate for TD, which can take many years to develop.

7.3 Major Safety Results

7.3.1 Deaths

At our request, the sponsor prepared a Death Line Listing (see Appendix B), including those deaths that occurred on placebo and active control, for the entire Japanese and non-Japanese study pools (N=21731 for sertindole). The safety cut off date for the ongoing studies and spontaneous reports is January 11, 2008. Although the line listing includes deaths that occurred greater than 30 days after the last dose of study drug, for the purposes of this review, all deaths that occurred between the time of randomization or start of dosing and 30 days after the last dose of study drug will be discussed below.

As sertindole has been under development for many years, in addition to the phase 2/3 studies, there have been various other studies, including epidemiological and large scale prospective safety studies. The deaths in each category of study (as well as the spontaneous reports) will be discussed separately, but in order to provide an overview of all study deaths, we had the sponsor prepare an enumeration of deaths, based on the primary cause, organized by MedDRA Preferred Term and study type (see Appendix C).

A. Completed Non-Japanese Studies

1. Phase 1 Studies

There was one death in the non-Japanese phase 1 studies (N=676). A 67-year-old man (M95-387-1024) had a “sudden cardiac death” 10 days after starting sertindole. An autopsy revealed “severe coronary atherosclerosis.”

2. Phase 2/3 Studies

a) Short-term Placebo-Controlled Schizophrenia Studies

In the pool of the five short-term, randomized, placebo-controlled, phase 2/3 studies (704 sertindole-treated patients and 290 placebo-treated patients), there was one death. A 40-year-old woman (M93-098-6185-1117) committed suicide 4 days after starting sertindole 8 mg/day.

b) All Phase 2/3 Studies

There were 28 deaths in all the non-Japanese phase 2/3 studies, 27 in sertindole-treated patients (N=2711) and one in a risperidone-treated patient. This reviewer examined the death line listing, looking for any unusual or otherwise remarkable events. Case narratives on the following subjects were requested:

- M93-113-3209-6415 (sepsis; convulsion; renal failure; thrombocytopenia; rhabdomyolysis)
- M93-132-8894-12004 (cardiac arrest; neoplasm malignant)

On review of the case narratives, it appears that the first subject died of septicemia (blood culture positive for streptococcus), confirmed by autopsy. His other symptoms were likely secondary to the septicemia. The second subject, who smoked 3-4 packs of cigarettes per day, was diagnosed with cancer of esophagus 18 months after starting sertindole (as part of two separate studies). He died of cardiac arrest in the context of anemia and septicemia while undergoing chemotherapy.

For a summary of the causes of death among sertindole-treated patients in all the phase 2/3 studies, see Table 28 below:

Table 28 Incidence of Adverse Events as Primary Reason for Death by High Level Group Term and High Level Term in Sertindole-Treated Patients: Completed Non-Japanese Studies (Phase II/III Studies in Schizophrenia Including Open-label)

MedDRA High Level Group Term/ MedDRA High Level Term	Total (N=2711)
Aneurysms and artery dissections	1
Aneurysms and dissections non-site specific	1
Breast neoplasm malignant and unspecified (incl. nipple)	1
Breast and nipple neoplasms malignant	1
Cardiac arrhythmias	2
Rate and rhythm disorders NEC	1
Ventricular arrhythmias and cardiac arrest	1
Chemical injury and poisoning	2
Poisoning and toxicity	2
Coronary artery disorders	2
Coronary artery disorders NEC	1
Ischaemic coronary artery disorders	1
Fatal outcomes	7
Death and sudden death	7
Gastrointestinal ulceration and perforation	1
Intestinal ulcers and perforation NEC	1
Infections - pathogen unspecified	2
Lower respiratory tract and lung infections	1
Sepsis, bacteraemia, viraemia and fungaemia NEC	1
Medication errors	1
Overdoses	1
Pulmonary vascular disorders	1
Pulmonary thrombotic and embolic conditions	1
Renal and urinary tract neoplasms malignant and unspecified	1
Bladder neoplasms malignant	1
Seizures (incl subtypes)	1
Generalised tonic-clonic seizures	1
Suicidal and self-injurious behaviors NEC	5
Suicidal and self-injurious behavior	5
Total	27

Note: Includes deaths that occurred within 30 days of last dose of study drug. If the days since last dose is not available for a patient, the death is presumed to be within 30 days of last dose.

To calculate mortality rates, only the non-Japanese phase 2/3 studies were used, again because Shionogi limited reporting of adverse events to those considered by the investigators as having a casual relationship to study drug.

Table 29 All-Cause Mortality Rates for Completed, Non-Japanese, Phase 2/3, Schizophrenia Studies

	Sertindole		Placebo
	All Phase 2/3	Placebo-Controlled	
Number of Deaths	27	1	0
Number of Patients	2711	704	290
Exposure (PY)	1840	65.5	26.6
Crude MR (%)	1.0	0.14	0
Adjusted MR (#deaths/1000 PY of exposure)	14.7	15.3	0

By comparison, the rates observed in the primary Abilify (aripiprazole) NDA (NDA 21-436) were, for the whole non-Japanese phase 2/3 study pool, 1.3% (crude rate) and 23.0/1000 PY's (exposure-adjusted rate) among aripiprazole-treated patients.

3. Sertindole Cohort Prospective (SCoP) Study

The SCoP study is reviewed in much greater detail elsewhere (see section 6.2.). There were 125 deaths in the SCoP study, 64 in sertindole-treated patients (N=4905) and 61 in risperidone-treated patients (N=4904). This reviewer examined the death line listing, looking for any unusual or otherwise remarkable events. One sertindole-treated patient (99824-PL025-16353, identified in the SCoP study report as patient 485433, a 79-year-old woman on sertindole 12 mg/day for 253 days) died of confirmed torsades de pointes; this case is discussed in the SCoP review. Case narratives on the following subjects were requested:

- 99824-GR001-15297 (neoplasm malignant)
- 99824-TR006-13031 (gastrointestinal disorder; death)

On review of the narratives, it appears that the first subject had a pre-existing lip carcinoma, which was found to have metastasized during the course of the study. The second subject died 11 months after the first dose of sertindole from a suspected gastrointestinal cancer (change in bowel habits, other digestive problems, weight loss); however, no autopsy was performed.

There were no other events that seemed unusual or unexpected. For a summary of the causes of death among sertindole-treated patients in SCoP, see Table 30 below:

Table 30 Incidence of Adverse Events as Primary Reason for Death by High Level Group Term and High Level Term in Sertindole-Treated Patients: SCoP

MedDRA High Level Group Term/ MedDRA High Level Term	Total (N=4905)
Aneurysms and artery dissections	1
Aortic aneurysms and dissections	1
Bacterial infectious disorders	1
Bacterial infections NEC	1
Bone and joint injuries	1
Lower limb fractures and dislocations ¹	1
Bronchial disorders (excl neoplasms)	1
Bronchospasm and obstruction	1
Cardiac arrhythmias	4
Rate and rhythm disorders NEC	3
Ventricular arrhythmias and cardiac arrest	1
Central nervous system vascular disorders	1
Central nervous system haemorrhages and cerebrovascular accidents	1
Coronary artery disorders	8
Ischaemic coronary artery disorders	8
Electrolyte and fluid balance conditions	1
Electrolyte imbalance NEC ²	1
Fatal outcomes	10
Death and sudden death	10
Gastrointestinal conditions NEC	1
Gastrointestinal disorders NEC	1
Gastrointestinal ulceration and perforation	1
Gastric ulcers and perforation	1
Heart failures	3
Heart failures NEC	3
Infections - pathogen unspecified	4
Lower respiratory tract and lung infections	3
Sepsis, bacteraemia, viraemia and fungaemia NEC	1
Injuries NEC	2
Cerebral injuries NEC	1
Non-site specific injuries NEC	1
Legal issues	1
Criminal activity ³	1
Lower respiratory tract disorders (excl obstruction and infection)	1
Lower respiratory tract inflammatory and immunologic conditions	1
Medication errors	1
Overdoses	1
Myocardial disorders	1
Cardiomyopathies	1

MedDRA High Level Group Term/ MedDRA High Level Term	Total (N=4905)
Pulmonary vascular disorders	2
Pulmonary thrombotic and embolic conditions	2
Respiratory and mediastinal neoplasms malignant and unspecified	1
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	1
Respiratory disorders NEC	5
Conditions associated with abnormal gas exchange	1
Respiratory failures (excl neonatal)	1
Respiratory tract disorders NEC	3
Suicidal and self-injurious behaviors NEC	13
Suicidal and self-injurious behavior	13
Total	64

Note: Includes deaths that occurred within 30 days of last dose of study drug. If the days since last dose is not available for a patient, the death is presumed to be within 30 days of last dose.

¹ Investigator term: "hip fracture"

² Investigator term: "sudden unexplained death; electrolyte imbalance; emphysema"

³ Investigator term: "violent death"

4. Other Studies in Schizophrenia (including the European Post-Marketing Observational Sertindole Project as well as various epidemiological and PET studies)

There were 56 deaths in the other completed non-Japanese studies in schizophrenia, 54 in sertindole-treated patients (N=11772), one in an olanzapine-treated patient, and one in a patient receiving sertindole in combination with another antipsychotic. This reviewer examined the death line listing, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

For a summary of the causes of death among sertindole-treated patients in these studies, see Table 31 below:

Table 31 Incidence of Adverse Events as Primary Reason for Death by High Level Group Term and High Level Term in Sertindole-Treated Patients: Completed Non-Japanese Studies (Other Studies in Schizophrenia Including PET, EPOS, and Epidemiological Studies)

MedDRA High Level Group Term/ MedDRA High Level Term	Total (N=11772)
Cardiac arrhythmias	2
Ventricular arrhythmias and cardiac arrest	2
Central nervous system vascular disorders	2
Central nervous system haemorrhages and cerebrovascular accidents	2
Coronary artery disorders	7
Ischaemic coronary artery disorders	7
Fatal outcomes	19
Death and sudden death	19
Gastrointestinal ulceration and perforation	1
Intestinal ulcers and perforation NEC	1
Infections - pathogen unspecified	3
Lower respiratory tract and lung infections	3
Injuries NEC	1
Non-site specific injuries NEC	1
Lower respiratory tract disorders (excl obstruction and infection)	1
Parenchymal lung disorders NEC	1
Medication errors	1
Overdoses	1
Miscellaneous and site unspecified neoplasms malignant and unspecified	1
Neoplasms malignant site unspecified NEC	1
Pulmonary vascular disorders	2
Pulmonary thrombotic and embolic conditions	2
Renal and urinary tract neoplasms malignant and unspecified	1
Bladder neoplasms malignant	1
Suicidal and self-injurious behaviors NEC	13
Total	54

Note: Includes deaths that occurred within 30 days of last dose of study drug. If the days since last dose is not available for a patient, the death is presumed to be within 30 days of last dose.

B. Completed Japanese Studies

There were 3 deaths in the completed Japanese studies, 2 in sertindole-treated patients (N=526) and one in a haloperidol-treated patient. One sertindole death was the result of suicide, while cause of the other death is listed as unknown.

C. Ongoing Studies

There were 5 deaths in the ongoing studies, all in sertindole-treated patients (N=1129). Three patients committed suicide, while the cause death for one is listed as unknown. The final patient died of dysphasia, cachexia, and dehydration in the context of Alzheimer's disease, COPD, and epilepsy.

D. Spontaneous Reports

The sponsor has received 39 spontaneous reports of death in patients taking sertindole. This reviewer examined the death line listing, looking for any unusual or otherwise remarkable events. The following safety report was requested:

- DKLU0200614 (ECG QT prolonged; overdose; sudden death; suicide attempt; ventricular fibrillation)

On review of the safety reports, it appears that the patient, a 43-year-old woman, was hospitalized after an overdose on various medications, including sertindole. Ten days after admission, her sertindole was restarted. Four days later, a few minutes before going into cardiac arrest, she was noted to have a "severely prolonged QT/QTc"; "this was with high certainty due to the effect of sertindole." A cardiologist reviewed the case, who felt that the most likely cause of death was torsades de pointes. Of note, it seems that the patient had a significantly prolonged QTc before restarting sertindole (it is unclear whether this was a residual effect of the overdose, as the only ECGs available were from this hospitalization and following a previous overdose).

There were no other events that seemed unusual or unexpected. For a summary of the causes of death in these reports, see Table 32 below:

Table 32 Incidence of Adverse Events as Primary Reason for Death by High Level Group Term and High Level Term in Sertindole-Treated Patients: Spontaneous Reports

MedDRA High Level Group Term/ MedDRA High Level Term	
Cardiac arrhythmias	3
Ventricular arrhythmias and cardiac arrest	3
Central nervous system vascular disorders	1
Central nervous system haemorrhages and cerebrovascular accidents	1
Fatal outcomes	21
Death and sudden death	21
Gastrointestinal stenosis and obstruction	1
Gastrointestinal stenosis and obstruction NEC	1
Infections - pathogen unspecified	2
Lower respiratory tract and lung infections	2
Medication errors	1
Overdoses	1
Pulmonary vascular disorders	3
Pulmonary thrombotic and embolic conditions	3
Respiratory disorders NEC	3
Conditions associated with abnormal gas exchange	1
Respiratory tract disorders NEC	2
Suicidal and self-injurious behaviors NEC	4
Suicidal and self-injurious behavior	4
Total	39

Note: Includes deaths that occurred within 30 days of last dose of study drug. If the days since last dose is not available for a patient, the death is presumed to be within 30 days of last dose.

7.3.2 Nonfatal Serious Adverse Events

The sponsor used the following definition for a serious adverse event (SAE):

A serious adverse event (experience) or reaction is any untoward medical occurrence that at any dose:

- *Results in death*
- *Is life-threatening*
- *Requires inpatient hospitalization or prolongation of existing hospitalization*
- *Results in persistent or significant disability/incapacity*
- *Is a congenital anomaly or birth defect*

The sponsor states that “important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may

require intervention to prevent one of the outcomes listed in the definition above...should also usually be considered serious.”

The sponsor reported all SAEs that occurred between the time of randomization or start of dosing and 30 days after the last dose of study drug. Of note, although cancer is not included in this definition, many of the individual studies did include cancer in their definition of a SAE, and reports of cancer can be found under deaths and non-fatal SAEs.

As a line listing of non-fatal serious adverse events would have been prohibitively long, the sponsor, at our request, prepared an enumeration of the non-fatal serious adverse events (see Appendix D), organized by MedDRA Preferred Term and study type, for the entire Japanese and non-Japanese study pools (N=21731 for sertindole).

A. Completed Non-Japanese Studies

1. Phase 1 Studies

There were 5 SAEs in the non-Japanese phase 1 studies (N=676). These included “hepatic function abnormal,” “diabetes mellitus,” “hepatic neoplasm,” “depression,” and “renal failure chronic.”

2. Phase 2/3 Studies

a) Short-term Placebo-Controlled Schizophrenia Studies

In the pool of the five short-term, randomized, placebo-controlled, phase 2/3 studies (704 sertindole-treated patients and 290 placebo-treated patients), there were a total 18 SAEs, 11 in the sertindole group and 7 in the placebo group. For a comparison of SAEs in the two groups (this time looking only at those SAEs that occurred in a greater percentage of sertindole-treated than placebo-treated patients), please see Table 33 below.

Table 33 Non-Fatal Serious Adverse Events in the Placebo-Controlled, Completed, Non-Japanese, Phase 2/3 Schizophrenia Studies Occurring in a Greater Percentage of Sertindole-Treated Than Placebo-Treated Patients

System Organ Class/Preferred Term ^a	Placebo (N = 290) n (%)	Sertindole (N = 704) n (%)
Infections and infestations		
Pneumonia	0	2 (0.3)
Injury, poisoning and procedural complications		
Intentional overdose	0	1 (0.1)
Investigations		
Blood glucose increased	0	1 (0.1)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)		
Basal cell carcinoma	0	1 (0.1)
Gastric cancer	0	1 (0.1)
Psychiatric disorders		
Agitation	0	1 (0.1)
Psychotic disorder	1 (0.3)	3 (0.4)
Suicidal ideation	0	1 (0.1)
Suicide attempt	0	2 (0.3)
^a Includes non-fatal SAEs which were reported on study drug and within 30 days of stopping the study drug		

There does not appear to be a significantly greater percentage of any particular non-fatal serious adverse event in the sertindole group than in the placebo group.

b) All Phase 2/3 Studies

For all the non-Japanese phase 2/3 studies (N=2711), this reviewer examined the table of non-fatal SAEs, looking for any unusual or otherwise remarkable events. Of note, there was one case of torsades de pointes and no reported cases of hepatotoxicity.

There were also various other events of concern, either due to the type of event or the number of such events. The JMP table containing a line listing of all the SAEs was then referenced to identify the individual subjects who had these events. For some of the subjects, an adequate explanation of the SAE could be determined from the JMP table (especially by looking at all the SAEs coded to the subject on that day). For the remaining subjects, case narratives were requested:

- **Confusional state**
 - M93-061-7783-4300

- **Pyrexia**
 - M93-132-8893-34005
 - M93-098-7131-2258
 - M93-098-9104-4405
 - M96-424-1988-1058
 - M93-113-4524-5315

- **Gastrointestinal hemorrhage**
 - M95-342-11226-1377
 - M93-061-7504-1104
 - M93-098-8453-1409
 - M93-061-7504-1101
 - M93-098-6541-2931

- **Loss of Consciousness**
 - M93-113-9133-7207

- **Syncope**
 - M92-817-7793-6003

- **Pneumonia**
 - M92-762-7133-2414
 - M93-113-7333-3609
 - M95-342-11152-1731
 - M93-132-8893-34005
 - M92-762-6644-2213
 - M92-817-7804-6607
 - M93-098-8519-1707
 - M93-113-9340-8107
 - M94-192-8879-77163
 - M93-061-7510-2411
 - M93-061-8706-4512

On review of the narratives:

- The confusional state was likely not related to sertindole, as it was associated with a lithium level of 3.4.
- None of the cases of pyrexia appear to be due to NMS or malignant hyperthermia. Subject M96-424-1988-1058, a 34-year-old man, did develop CPK elevation and acute renal failure in the context of a nonketotic hyperosmolar coma (NKHC) two weeks after starting sertindole. Although all his symptoms can be explained by NKHC, there are case reports of NMS

precipitating NKHC in patients with previously well-controlled blood glucose. Of note, the patient was found to be diabetic (with a blood sugar of 712 mg/dL) two weeks after another study, in which he took sertindole for 4 weeks (he was then lost to follow-up). So, it is unclear to what degree sertindole may have exacerbated underlying diabetes.

- None of the cases of gastrointestinal hemorrhage seem to be related to study drug. Subject M93-098-8453-1409, a 44-year-old man, did develop hematemesis in the context of diabetic ketoacidosis four months after starting sertindole. Endoscopy revealed esophagitis and duodenitis. It is possible that vomiting induced by the ketoacidosis led to the esophagitis and duodenitis, which eventually caused the hematemesis. Of note, the patient did not have a history of diabetes, so it is likely that sertindole either caused the diabetes or at least exacerbated the patient's previously undiagnosed diabetes.
- The loss of consciousness was clearly not related to sertindole, as it was the result of a suicide attempt by hanging.
- The case of syncope (M92-817-7793-6003) is actually a 50-year-old man with multiple syncopal episodes beginning 14 months after starting sertindole. The last two episodes, which occurred on the same day, led to hospitalization. The patient was found to be bradycardic, with a pulse of 35. The sertindole was discontinued, but, at least initially, he continued to have bradycardia. A thorough workup was completely negative. The patient had no further episodes of syncope or dizziness during his hospitalization, and his heart rate normalized. The investigator felt that this SAE was probably related to sertindole.
- All the cases of pneumonia appear to be infectious in etiology and unlikely related to study medication.

3. Sertindole Cohort Prospective (SCoP) Study

The SCoP study is reviewed in much greater detail elsewhere (see section 6.2). For the SCoP study (N=4905), this reviewer examined the table of non-fatal SAEs, looking for any unusual or otherwise remarkable events. Of note, there was one non-fatal case of torsades de pointes (in addition to the fatal one); the case is discussed in the SCoP review. There were also two cases of neuroleptic malignant syndrome (NMS).

4. Other Studies in Schizophrenia (including the European Post-Marketing Observational Sertindole Project as well as various epidemiological and PET studies)

For the other completed non-Japanese studies in schizophrenia (N=11772), this reviewer examined the table of non-fatal SAEs, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

B. Completed Japanese Studies

For the completed Japanese Studies (N=526), this reviewer examined the table of non-fatal SAEs, looking for any unusual or otherwise remarkable events. Of note, there were two cases of NMS.

C. Ongoing Studies

For the ongoing studies (N=1129), this reviewer examined the table of non-fatal SAEs, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

D. Spontaneous Reports

This reviewer examined the JMP table listing all the spontaneous reports of SAEs, looking for unusual or otherwise remarkable events. There were six cases of NMS and two cases of tardive dyskinesia. Case narratives on the following subjects were requested:

- Agranulocytosis
 - DKLU1030530
- Torsades de pointes
 - DKLU0980776
- Ventricular Fibrillation
 - DKLU0981114
 - DKLU0981344
- Jaundice
 - DKLU0961152

On review of the narratives:

- The information available for the case of agranulocytosis is very limited (for instance, no labs are available), so no determination can be made whether this SAE is related to study drug. Associated signs and symptoms were “hyponatremia, hypomagnesemia, hypokalemia, and QTc prolongation.”
- The torsades de pointes occurred in a 40-year-old woman taking sertindole 16 mg/day, with no known concomitant medications. She was admitted to the hospital after experiencing syncope, and, after a negative workup, she was transferred to psychiatry. The day of her transfer she had, for unclear reasons, an EEG with concurrent ECG monitoring. The ECG revealed a QTc of 600 msec and torsades de pointes. This episode was self-limited, but later

in the day, the torsades returned, and cardioversion was required. The sertindole was discontinued, and the patient eventually made a complete recovery.

- The first case of ventricular fibrillation occurred in a 41-year-old woman taking sertindole 12 mg/day. Concomitant medications were clonazepam and midazolam (dosing unclear). She was hospitalized after experiencing transitory loss of consciousness. Her ECG on admission revealed a QTc of 605 msec and inverse T-waves in the inferior/apical leads. Her blood pressure was 75/60, with a heart rate of 59 bpm. Her blood pressure normalized with treatment, but, 10 hours after admission, she again experienced transitory loss of consciousness and was admitted to the ICU, where she was placed on cardiac monitoring. In the ICU, she developed ventricular tachycardia (not otherwise specified) which “may have turned into ventricular fibrillation;” cardioversion was required. The patient eventually made a complete recovery. Of note, the sertindole was discontinued on the second day of her admission, and several months later, an ECG revealed a QTc of 470 msec.

The second case of ventricular fibrillation occurred in a 38-year-old woman who overdosed on 20-25 tablets of sertindole. At the time of the overdose, she was noted to have a QTc of 480 msec. Information on concomitant medications is not available.

- The case of jaundice occurred in a 73-year-old woman with no history of liver disease and only minimal use of alcohol. She developed nose bleeds and jaundice 1-1/2 months after starting sertindole (final dose 12 mg/day). She was also taking thioridazine and trimethoprim, but she had been on both for only a few days, and they had both been discontinued five days before the development of symptoms. The patient was hospitalized, and several days later her sertindole was discontinued. Of note, the liver function tests (LFTs) are included in the case narrative but are not readable. After 2-3 weeks, her LFTs returned to normal. The patient was started on olanzapine, and subsequently her LFTs increased again, but only until she was switched to another antipsychotic.

7.3.3 Dropouts and/or Discontinuations

As a line listing of dropouts and discontinuations would have been prohibitively long, the sponsor, at our request, prepared a table of the primary reasons for sertindole discontinuation (see Appendix E), organized by MedDRA Preferred Term and study type, for the entire Japanese and non-Japanese study pools (N=21731 for sertindole).

A. Completed Non-Japanese Studies

1. Phase 1 Studies

For the non-Japanese phase 1 studies, this reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

2. Phase 2/3 Studies

a) Short-term Placebo-Controlled Schizophrenia Studies

In the pool of the five short-term, randomized, placebo-controlled, phase 2/3 studies, there were no adverse events that lead to discontinuation in $\geq 1\%$ of the sertindole group.

b) All Phase 2/3 Studies

For all the non-Japanese phase 2/3 studies, prolonged QTc, ejaculation failure, and psychotic disorders were the only adverse events leading to withdrawal (excluding adverse events that led to death) reported in $>1\%$ of patients who received sertindole. This reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. Of note, there was one case of Stevens-Johnson Syndrome (SJS). Looking at the concomitant medication line listing, it does not appear that this patient was taking any medications commonly known to cause SJS. Otherwise, there were no unusual or unexpected events that were not already discussed under SAEs.

3. Sertindole Cohort Prospective (SCoP) Study

The SCoP study is reviewed in much greater detail elsewhere (see section 6.2). For the SCoP study, this reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. There were no unusual or unexpected events that were not already discussed under SAEs.

4. Other Studies in Schizophrenia (including the European Post-Marketing Observational Sertindole Project as well as various epidemiological and PET studies)

For the other completed non-Japanese studies in schizophrenia, this reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

B. Completed Japanese Studies

For the completed Japanese studies, this reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. There were no unusual or unexpected events that were not already discussed under SAEs.

C. Ongoing Studies

For the ongoing studies, this reviewer examined the table of reasons for sertindole discontinuation, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

7.3.4 Significant Adverse Events

A review of the adverse event line listing for the non-Japanese, phase 2/3 schizophrenia studies did not reveal any significant events not included under deaths, SAEs, or AE dropouts.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

A. Categorization of Adverse Events

Treatment-emergent adverse events were defined as “adverse events that have their onset in the during-dosing period with the condition that, if an adverse event occurred prior to the first dose of a double-blind study drug, the during-dosing report of the adverse event would be excluded from the safety analysis if the severity is greater prior to double-blind study drug administration than during dosing.” Of note, for all the non-Japanese studies, AEs were reported whether or not the problem was considered drug-related by the investigator.

The sponsored coded all the verbatim terms for treatment-emergent adverse events to MedDRA preferred terms. However, in MedDRA, the preferred terms are so detailed that adverse events end up being split into many categories, making it more difficult to detect any patterns.

B. Study Pooling

We focused on adverse event information pooled from the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. This study pool consisted of:

- two 8-week studies with placebo and haloperidol control groups (M93-113 and M93-098)
- one 40-day study with a placebo control group (M92-762)

These 3 fixed dose studies were administered as follows:

- 12, 20, and 24 mg/day for M93-113
- 20 and 24 mg/day for M93-098
- 8, 12, and 20 mg/day for M92-762

C. Common Drug-Related Adverse Events

The incidence of treatment-emergent adverse events reported at a rate of $\geq 2\%$ in any sertindole dose group and at a rate of >2 times placebo is summarized in Appendix F. The treatment-emergent adverse events occurring at a rate of $\geq 5\%$ in the total sertindole group and at a rate of >2 times placebo are:

- Nasal Congestion (22.0% in the sertindole group vs. 8.9% in the placebo group)
- Ejaculation failure (8.3% in the sertindole group vs. 0.8% in the placebo group)

Of note, dry mouth just misses the threshold of >2 times the placebo rate (9.9% vs. 5.1%).

7.4.2 Laboratory Findings

A. Extent of Laboratory Testing

Routine hematology, serum chemistry, and urinalysis data was obtained during the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. The tests used and their timing during each of the three studies is presented in Appendix G.

B. Potentially Clinically Significant Laboratory Changes

1. Mean Change from Baseline

a) Routine Serum Chemistries

The sponsor measured albumin, alkaline phosphatase, bicarbonate, BUN, calcium, chloride, creatinine, potassium, LDH, sodium, phosphorous, AST, ALT, total bilirubin, total protein, and uric acid.

The sponsor prepared a table comparing the mean change in routine serum chemistry values during treatment with sertindole (broken down by dose) and placebo (see Appendix H, Table 1). There were no notable changes in these values.

b) Metabolic Chemistries

The sponsor measured glucose, triglycerides, total cholesterol (all fasting). The mean change in metabolic chemistry values during treatment with sertindole (broken down by dose) and placebo can also be found in Appendix H, Table 1. These results are summarized below.

Table 34 Mean Change in Selected Clinical Chemistry Values From Baseline to Last Observation by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
Fasting Glucose (mg/dL)	0.1	7.9	5.8	8.1	0.2
Triglyceride (mg/dL)	1.1	28.4	27.5	19.7	-6.2
Total Cholesterol (mg/dL) [†]	-2.8	4.8	4.2	3.7	-3.0

[†] HDL and LDL not available

c) Prolactin

Although prolactin levels were not always routinely measured, we requested that the sponsor submit a table of the baseline and mean change from baseline to last observed value for prolactin in the non-Japanese, placebo-controlled studies. They submitted a similar table for the non-Japanese, active-controlled studies. Although both tables were broken down by dose group, for several of the groups, the number of patients with available baseline and endpoint prolactin data was small. The decision was therefore made, for each table, to pool all the sertindole dose groups, keeping in mind that more data is missing from the higher than the lower dose groups.

Table 35 Baseline and Mean Change from Baseline to Last Observed Value for Prolactin: Non-Japanese Studies

Placebo-Controlled Studies						Active-Controlled Studies					
All Sertindole			Placebo			All Sertindole			Haloperidol (16 mg)		
n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ
225	13.7	4.46	87	15.93	-0.62	70	10.9	1.53	35	10.89	14.71

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.
Normal prolactin range—Male 1.1-20.5 ng/mL; Female 1.8-26.5 ng/mL

In Study M95-342, the prolactin data was reported in different units (mU/L rather than ng/mL). As a result, the data was not pooled with the other active-controlled studies but instead presented in a separate table. Of note, in this study, much less prolactin data is missing for the various dose groups.

Table 36 Baseline and Mean Change from Baseline to Last Observed Value for Prolactin: Study M95-342

Sertindole								Haloperidol	
8 mg (N=120) n=112		16 mg (N=127) n=118		20 mg (N=128) n=120		24 mg (N=117) n=113		10 mg (N=125) n=119	
BL	Δ	BL	Δ	BL	Δ	BL	Δ	BL	Δ
1128	-559	1233	-423	900	90	829	157	984	87

N=Number in group; n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.
Normal prolactin range—Male 38-550 mU/L; Female 8-656 mU/L

In summary, for the placebo-controlled studies, the mean change for prolactin is somewhat higher for sertindole (all dose groups combined) than for placebo. For the pooled active-controlled studies, it appears that the mean change from baseline to last observed value for prolactin is much smaller for sertindole (all dose groups combined) than for haloperidol (16 mg). However, for study M95-342, which has more complete data, it appears that the mean change for the sertindole 20 mg and 24 mg dose groups is equal to or greater than for haloperidol (10 mg).

d) Hematology

The sponsor prepared a table comparing the mean change in hematology values during treatment with sertindole (broken down by dose) and placebo (see Appendix H, Table 2). No potentially clinically significant results were found.

e) Urinalysis

The sponsor prepared a table comparing the mean change in urinalysis values during treatment with sertindole (broken down by dose) and placebo (see Appendix H, Table 3). No potentially clinically significant results were found.

2. Outliers

a) Routine Serum Chemistries

The sponsor prepared a table comparing the percentage of patients meeting outlier criteria for routine serum chemistry values in the sertindole (broken down by dose) and placebo treatment groups (see Appendix H, Table 4; summary of outlier criteria can be found in Table 5). The potentially clinically significant results are summarized below.

Table 37 Percentage of Patients Meeting Outlier Criteria for Selected Routine Serum Chemistry Values by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter (Outlier Cut-off Criteria)	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
ALT (≥ 165 IU/L)	2.0%	3.2%	4.4%	4.6%	0%
AST (≥ 150 IU/L)	0%	1.6%	1.3%	0.6%	0%

Of note, there was only one bilirubin outlier (≥ 2.0 mg/dL), which was found in the 24 mg/day group. (There was no associated jaundice, and the patient was not one of the ALT or AST outliers). Among the ALT/AST outliers, the highest ALT peak was 435 U/L, while the highest AST peak was 345 U/L. Some of the patients had medical conditions (such as hepatitis C, alcoholism, and other substance abuse) or concomitant medications (such as isoniazid) that could contribute to elevated liver enzymes. Also, in a majority of patients, the enzymes normalized, either off or even while still on sertindole. Finally, the sponsor listed all the AEs and SAEs associated with these enzyme elevations, and there was no indication of any significant hepatotoxicity.

b) Metabolic Chemistries

The percentage of patients meeting outlier criteria for metabolic chemistry values in the sertindole (broken down by dose) and placebo treatment groups can also be found in Appendix H, Table 4. The results are summarized below.

Table 38 Percentage of Patients Meeting Outlier Criteria for Selected Metabolic Chemistry Values by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter (Outlier Cut-off Criteria)	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
Fasting Glucose (≥ 126 mg/dL)	24.5%	25.8%	31.9%	28.0%	19.6%
Triglyceride (≥ 200 mg/dL)	46.9%	41.1%	46.0%	53.1%	36.2%
Triglyceride (≥ 500 mg/dL)	6.1%	4.0%	7.1%	3.4%	4.0%
Total Cholesterol (> 240 mg/dL)	26.5%	25.0%	28.8%	31.4%	24.6%

For the metabolic chemistries, we also requested that the sponsor prepare a table comparing the percentage of patients meeting outlier criteria at endpoint but not at baseline in the sertindole (broken down by dose) and placebo treatment groups (see Appendix H, Table 6). The results are summarized below.

Table 39 Percentage of Patients Meeting Outlier Criteria for Selected Metabolic Chemistry Values at Endpoint but Not at Baseline: Studies M93-113, M93-098, and M92-762

Parameter (Outlier cut-off criteria)	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
Total Cholesterol (≥ 240 mg/dL)	8.2%	7.3%	6.2%	8%	5.4%
Glucose (> 126 mg/dL)	2.0%	8.1%	10.2%	7.4%	4.0%
Triglyceride (> 200 mg/dL)	10.2%	13.7%	13.3%	14.3%	8.5%
Triglyceride (> 500 mg/dL)	0%	0%	0.4%	0.6%	0%

Of note, the sponsor conducted a metabolic sub-study as part of the Sertindole Cohort Prospective (SCoP) Study. A total of 261 patients in 26 centers (3 centers in Poland, 12 in Russia, and 11 in the Ukraine) were enrolled. In addition to the standard SCoP assessments, these patients had various metabolic parameters, including fasting lipids and glucose, weight, waist circumference, and blood pressure, measured at baseline, week 8, week 12, and quarterly thereafter.

It is the opinion of the Review Team that this study does not adequately address the metabolic side effects of sertindole. The testing was limited to only a small fraction of the 9809 patients randomized in the SCoP study, with all the patients coming from Eastern Europe. This is despite the fact that the SCoP study was conducted at 593 centers in 38 countries. It is interesting to note, however, that a logistic regression analysis of the incidence of metabolic syndrome (as defined by the International Diabetes Foundation in 2005) at each visit and at last assessment (adjusted for baseline values of the metabolic variables and for sex) showed that there were no

statistically significant differences between the sertindole and risperidone treatment groups at Weeks 8, 12, 24, 36, or at the last assessment. At Week 48, there were too few patients to allow for a comparison between the treatment groups.

c) Prolactin

For the non-Japanese, placebo-controlled studies, the number of patients in each dose group for whom prolactin outlier data was available was higher (than the number for whom baseline and endpoint data was available), so there was no need to pool the groups.

Table 40 Number and Percent of Patients with Results above the Upper Limit of Normal for Prolactin: Non-Japanese, Placebo-Controlled Studies

Parameter	Sertindole														Placebo	
	4 mg		8 mg		12 mg		20 mg		24 mg		Flexible		Total		N	n (%)
	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)	N	n (%)		
Prolactin (ng/mL)	39	6 (15.4)	48	15(31.3)	124	42 (33.9)	117	49(41.9)	74	31(41.9)	26	23(88.5)	428	166 (38.8)	166	22 (13.3)

Note: Includes data from studies M91-645, M92-762, M92-817, and M93-113 (baseline data were not available for Study M93-098).
Normal range – Male: 1.1 – 20.5 ng/mL; Female: 1.8 – 26.5 ng/mL.

Of note, for the non-Japanese, placebo-controlled studies, the percentage of prolactin outliers is much greater for sertindole (for all except the 4 mg group) than for placebo.

d) Hematology

The sponsor prepared a table comparing the percentage of patients meeting outlier criteria for hematology values in the sertindole (broken down by dose) and placebo treatment groups (see Appendix H, Table 7; summary of outlier criteria can be found in Table 8). No potentially clinically significant results were found.

e) Urinalysis

The sponsor prepared a table comparing the percentage of patients meeting outlier criteria for urinalysis values in the sertindole (broken down by dose) and placebo treatment groups (see Appendix H, Table 9; summary of outlier criteria can be found in Table 10). No potentially clinically significant results were found.

C. Dropouts Due to Abnormal Laboratory Values

There were very few dropouts due to abnormal laboratory values:

Table 41 Number and Percentage of Patients Who Prematurely Terminated Due to Specific Abnormalities in Laboratory Values by Randomized Dose: Studies M93-113, M93-098, and M92-762

Adverse Event Category/Preferred Term	Placebo (n=237) N (%)	Sertindole Daily Dose				
		8 mg (n=52) N (%)	12 mg (n=127) N (%)	20 mg (n =239) N (%)	24 mg (n=186) N (%)	Total (n=604) N (%)
Blood glucose increased	1 (0.4)	0	0	0	1 (0.5)	1 (0.2)
Blood prolactin increased	0	0	1 (0.8)	0	0	1 (0.2)
Hepatic enzyme increased	0	0	0	2 (0.8)	0	2 (0.3)
Liver function test abnormal	0	0	1 (0.8)	2 (0.8)	0	3 (0.5)
Platelet count decreased	0	0	0	1 (0.4)	0	1 (0.2)

n = Number treated; N = Number prematurely terminating.

7.4.3 Vital Signs and Weight

A. Vital Sign/Weight Assessments

In the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies, vital sign measurements included oral temperature, supine and standing blood pressures, and heart rate, which were taken at screening, baseline, and each follow-up visit (see Appendix G). Weights were also obtained, including at baseline and endpoint. Of note, the protocol for one of these studies specifies that blood pressure measurements should be obtained after patients have been supine for 5 minutes and repeated 1 minute after sitting and standing.

B. Potentially Clinically Significant Vital Sign/Weight Changes

1. Mean Change from Baseline

The sponsor prepared a table comparing the mean change in vital sign/weight values during treatment with sertindole (broken down by dose) and placebo (see Appendix I, Table 1). The potentially clinically significant results are summarized below:

Table 42 Mean Change in Selected Vital Sign Values from Baseline to Last Observation by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
Pulse Rate (bpm)	-0.2	2.4	2.6	3.5	0.3
Weight (kg)	1.48	2.58	3.31	3.19	0.18

2. Outliers

The sponsor prepared a table comparing the percentage of patients meeting outlier criteria for vital sign/weight values in the sertindole (broken down by dose) and placebo treatment groups (see Appendix I, Table 2). The potentially clinically significant results are summarized below:

Table 43 Percentage of Patients Meeting Outlier Criteria for Selected Vital Sign Values by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
DBP (mmHg)					
High: ≥ 105 mmHg	7.8%	4.0%	2.7%	0%	1.3%
Pulse Rate (bpm)					
High: ≥ 120 bpm	11.8%	9.6%	8.4%	5.7%	4.5%
Weight (kg)					
Gained $\geq 7\%$ baseline weight	11.1%	21.3%	27.7%	27.4%	11%
Orthostatic Change: SBP (mmHg)					
Decreased ≥ 30 from supine	39.2%	21.8%	19.5%	14.9%	8.1%
Orthostatic Change: Pulse rate (bpm)					
Increased ≥ 20 from supine	80.4%	63.4%	56.0%	50.6%	57.5%

Of note, for all the completed, non-Japanese, phase 2/3 schizophrenia trials, 28.4% (769/2711) of patients had weight gain of $\geq 7\%$. Also, 1.1% (30/2711) had syncope. This compares to an incidence of syncope in the non-Japanese placebo-controlled studies of 0.57% (4/704) in the sertindole-treated patients and 0.69% (2/290) in the placebo-treated patients.

Looking at the above table, there appears to be, except for weight gain, an inverse dose response. However, pooling three studies with different dose groups and potentially

fairly different study populations could be confounding the detection of real dose response. Random variation could also be a confounder, especially for the 8 mg group, in which there are only 52 subjects. Finally, it is important to keep in mind that for orthostatic pulse change, there is a very high percentage of outliers in the placebo group, again potentially obscuring a dose response.

C. Dropouts Due to Vital Sign Abnormalities

No patients dropped out due to specific abnormalities in vital sign values for sertindole or placebo in the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies

7.4.4 Electrocardiograms (ECGs)

A. ECG Assessments

The timing of 12-lead ECGs in the pool of the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies is presented by study in Appendix G.

Of note, the ECGs from the sertindole trials were initially read and reported by the investigators while the studies were being conducted. In 1995, for the original NDA submission, the ECGs were read at Indiana University under the direction of Dr. Douglas P. Zipes. However, it was the sponsor's opinion that Dr. Zipes had "overread" the ECGs, supposedly resulting in an excess of ECGs with a QTc > 500 msec.

In 2002, the sponsor had a subset of ECGs meeting certain criteria (2248 total) re-read by eResearch Technology. The results of the re-read showed a significant reduction in the number of QTc outliers. The Division of Neuropharmacological Drug Products therefore requested a random sample of 150 ECGs in order to analyze, in a blinded manner, the QT and RR intervals.

The ECGs were read by Dr. Mehul Desai, a Medical Officer in the FDA's Division of Cardio-Renal Drug Products, and his results, in terms of the frequency of QT/QT_{C_B}/QT_{C_F} ≥ 500 msec, were closer to those obtained by the Indiana University group than by the eResearch group. In fact, questions were later raised about possible systematic flaws in eResearch's methodology.

In 2007, a second re-read of 2101 ECGs was performed by Covance Cardiac Services, the results of which are included in the resubmission of this NDA. We consulted the QT Team in the FDA's Division of Cardiovascular and Renal Products regarding the quality of this read. They had all 2101 ECGs uploaded into our ECG warehouse. After a preliminary review, they had some concerns regarding the Covance read. The QT Team therefore indicated that, for the purposes of this review, the most prudent

approach would be to use the original ECG read. However, they later stated in their consultative report that “the 2007 re-read of ECGs by Covance (which is now eRT) appears acceptable. Complexity arises in how to measure the QT interval in the setting of changes in T wave morphology (flattening/notching) and T-U merging that is observed with sertindole that makes it difficult to determine the end of the T wave offset and variability in the number of outliers with each read. It is important to note that drug induced T wave morphology changes with QT prolongation is associated with increased risk of torsades de pointes and sudden death.” For further information, please refer to their consultative report dated 02/12/09.

Another reason that the ECG analyses cited in this review are based on the original read is that the re-reads are only made up of a subset of the phase 2/3 ECGs.

B. Potentially Clinically Significant ECG Changes

1. Mean Change from Baseline

The sponsor prepared a table comparing the mean change in ECG values during treatment with sertindole (broken down by dose) and placebo (see Appendix J, Table 1). The potentially clinically significant results are summarized below:

Table 44 Mean Change in Selected ECG Parameters From Baseline to Last Observation by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
QT _{CB} interval (msec)	15.3	15.9	25.6	26.4	-4.6
QT _{CF} interval (msec)	14.5	13.5	22.1	23.9	-4.7
QT _{CB} = QT/√RR; QT _{CF} = QT/RR ^{1/3}					

The sponsor also prepared a similar table for each individual study in the pool of the 3 completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. The results were consistent with those above.

At the recommendation of our QT Team, we asked the sponsor to prepare a table of the $\Delta\Delta\text{QT}_B$ and $\Delta\Delta\text{QT}_F$ (defined as the mean difference of study drug and placebo after baseline correction) for each dose group with a 90%, two-sided confidence interval.

Table 45 Mean Difference in QT_{cB} and QT_{cF} (with 90% Confidence Interval), by Dose Group, in Study Drug and Placebo after Baseline Correction: Studies M93-113, M93-098, and M92-762

Parameter	Comparison	Mean Difference	90% Confidence Interval	
			Lower	Upper
QT _{cB} (msec)	Sertindole 8 mg vs. placebo	19.923	14.628	25.219
	Sertindole 12 mg vs. placebo	20.517	16.641	24.393
	Sertindole 20 mg vs. placebo	30.236	26.129	34.343
	Sertindole 24 mg vs. placebo	31.077	26.801	35.353
QT _{cF} (msec)	Sertindole 8 mg vs. placebo	19.199	14.763	23.635
	Sertindole 12 mg vs. placebo	18.256	14.998	21.514
	Sertindole 20 mg vs. placebo	26.859	23.487	30.231
	Sertindole 24 mg vs. placebo	28.716	24.838	32.594
QT _{cB} = QT/ \sqrt{RR} ; QT _{cF} = QT/RR ^{1/3}				

The sponsor also prepared a similar table for each individual study in the pool of the 3 completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. The results were consistent with those above, with the exception of smaller confidence intervals, which are to be expected with a larger sample size.

2. Outliers

The sponsor prepared a table comparing the percentage of patients meeting outlier criteria for ECG parameters in the sertindole (broken down by dose) and placebo treatment groups (see Appendix J, Table 2). The potentially clinically significant results are summarized below:

Table 46 Percentage of Patients Meeting Outlier Criteria for Selected ECG Parameters by Randomized Dose: Studies M93-113, M93-098, and M92-762

Parameter	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
QT_{C_B} Interval					
High: ≥500 msec	0%	0.8%	4.7%	6.1%	0.5%
≥30 msec prolonged from baseline	39.1%	46.6%	57.6%	62.9%	11.2%
≥60 msec prolonged from baseline	2.2%	5.9%	18.1%	23.3%	1.5%
QT_{C_F} Interval					
High: ≥500 msec	0%	0.8%	1.9%	2.5%	0%
≥30 msec prolonged from baseline	28.3%	32.2%	47.6%	52.2%	5.4%
≥60 msec prolonged from baseline	4.3%	0.8%	10.5%	17.0%	0%
QT _{C_B} = QT/√RR; QT _{C_F} = QT/RR ^{1/3}					

There appears to be a clear dose response for the percentage of patients meeting various QTc outlier criteria. Of note, the sponsor also prepared a similar table for each individual study in the pool of the 3 completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. The results were consistent with those above.

It is important to note that even if one were to use the sponsor's analysis of the Covance read, 1.3% of patients had an increase in QTc (Bazett's Correction) from normal at baseline to >500msec, which is still of concern.

C. Dropouts Due to Abnormalities in ECG Parameters

Very few patients dropped out due abnormalities in ECG parameters (see Table 47 below):

Table 47 Number and Percentage of Patients Who Prematurely Terminated From the Study Due to Specific Abnormalities in ECG Values by Randomized Dose: Studies M93-113, M93-098, and M92-762

Adverse Event Category/ Preferred Term	Placebo (n=237) N (%)	Sertindole Daily Dose				Total (n=604) N (%)
		8 mg (n=52) N (%)	12 mg (n=127) N (%)	20 mg (n=239) N (%)	24 mg (n=186) N (%)	
Electrocardiogram abnormal	0	0	0	1 (0.4)	1 (0.5)	2 (0.3)
Electrocardiogram QTc prolonged	0	0	0	3 (1.3)	0	3 (0.5)
Electrocardiogram QT prolonged	0	0	0	1 (0.4)	0	1 (0.2)
Electrocardiogram T wave amplitude decreased	0	0	0	0	0	0

n = Number treated; N = Number prematurely terminating

Of the two patients who discontinued due to “electrocardiogram abnormal,” one had T-wave flattening and prominent U-waves, while the other had a non-specific ST and T-wave abnormality, T-wave inversions, and a prolonged QTc.

7.4.5 Special Safety Analyses

1. Seizures

In the completed, non-Japanese, placebo-controlled studies, there were no seizures in sertindole-treated patients (see Table 48 below).

Table 48 Incidence and Rates of Patients with Seizures (MedDRA SMQ¹ Convulsions) for Completed, Non-Japanese, Phase 2/3, Schizophrenia Studies

	Sertindole		Placebo
	All Phase 2/3	Placebo-Controlled	
Patients with Seizure	34	0	3
Number of Patients	2711	704	290
Exposure (PY)	1840	65.5	26.6
Crude Seizure Rate (%)	1.3	0	1.0
Adjusted Seizure Rate (per 1000 PY of exposure)	18.5	0	112.8

¹SMQ=Standardized MedDRA Query

Of note, in all the completed, non-Japanese, phase 2/3, schizophrenia studies, there were two patients, both on sertindole, who had “status epilepticus.” Case narratives for these patients (M95-342-11209-2350 and M95-342-11218-2158) were requested.

On review of the narratives, it appears that first patient, a 30-year-old man, developed “status epilepticus” on day 181 of treatment with 24 mg of sertindole. The event reportedly did not lead to hospitalization, but further details about treatment were not provided. He completed the study, remaining on sertindole for a total of 875 days. His medical history was significant for febrile convulsions between the ages of 1 and 5, requiring antiepileptic therapy. The second patient, a 36-year-old woman, had a history of epilepsy and was reportedly noncompliant with her antiepileptic medications. On day 46 of treatment with 16 mg of sertindole, she had an “epileptic fit” in bed (the description does not sound like status epilepticus). Her husband, who was accustomed to this, went back to sleep without doing anything. Three hours later, he awoke to find her dead.

2. Completed Suicides and Suicide Attempts

An analysis of completed suicide and suicide attempts is also included in the review of the SCoP study (section 6.2), with a reclassification and reanalysis of the SCoP suicide data to be included in an addendum to this report.

At our request, the sponsor provided the number of AEs coded to the MedDRA terms completed suicide and suicide attempt for all the completed, non-Japanese, phase 2/3, schizophrenia studies (in particular the placebo-controlled studies). This allowed for calculation of the rate of completed suicides and suicide attempts in these studies. Of note, completed suicide and suicide attempt are mutually exclusive categories, with the exception of patients who had unsuccessful suicide attempts prior to a completed suicide.

Table 49 Incidence and Rates of Patients with MedDRA Preferred Term Completed Suicide and Suicide Attempt for Completed, Non-Japanese, Phase 2/3, Schizophrenia Studies

	Sertindole		Placebo
	All Phase 2/3	Placebo-Controlled	
Patients with Completed Suicide	5	1	0
Patients with Suicide Attempt	30	2	0
Number of Patients	2711	704	290
Exposure (PY)	1840	65.5	26.6
Crude Completed Suicide Rate	0.18%	0.14%	0%
Crude Suicide Attempt Rate	1.1%	0.28%	0%
Adjusted Completed Suicide Rate (per 1000 PY of exposure)	2.7	15.3	0
Adjusted Suicide Attempt Rate (per 1000 PY of exposure)	16.3	30.5	0

For the combined completed and attempted suicide in the placebo-controlled studies, the crude rate was not significantly higher for sertindole than for placebo (p=0.6).

3. Extrapyramidal Symptoms (EPS)

The analysis of EPS-related AEs was based on data from the pool of the three completed, non-Japanese, short-term, fixed dose, placebo-controlled studies. At our request, EPS-related AEs were grouped into six categories according to the MedDRA preferred term:

- *Dystonic Events*: dystonia, dysphonia, blepharospasm, muscle rigidity, musculoskeletal stiffness.
- *Parkinsonian Events*: Cogwheel rigidity, drooling, extrapyramidal disorder, hypertonia, masked facies, tremor, Parkinsonian rest tremor, Parkinsonian gait.
- *Akathisia Events*: akathisia, restlessness, psychomotor hyperactivity.
- *Dyskinetic Events*: Chorea, athetosis, dyskinesia, grimacing, tardive dyskinesia.
- *Residual Events*: movement disorder or muscle twitching.
- *Any Extrapyramidal Event*: any of the five terms identified above.

If a patient was coded to more than one term under a particular category, that patient was counted only once. For the results, see Table 50 below.

Table 50: Incidence of EPS-related Adverse Events by Category: Placebo Controlled, Fixed Dose Studies

EPS Category/ Preferred Term	Placebo (N = 237) n (%)	Sertindole				Total (N = 604) n (%)
		8 mg (N = 52) n (%)	12 mg (N = 127) n (%)	20 mg (N = 239) n (%)	24 mg (N = 186) n (%)	
Akathisia Events	21 (8.9)	1 (1.9)	12 (9.4)	13 (5.4)	19 (10.2)	45 (7.5)
Akathisia	13 (5.5)	1 (1.9)	8 (6.3)	3 (1.3)	12 (6.5)	24 (4.0)
Psychomotor hyperactivity	1 (0.4)	0	1 (0.8)	0	1 (0.5)	2 (0.3)
Restlessness	8 (3.4)	0	4 (3.1)	11 (4.6)	8 (4.3)	23 (3.8)
Dyskinetic Events	6 (2.5)	1 (1.9)	4 (3.1)	1 (0.4)	3 (1.6)	9 (1.5)
Athetosis	0	0	1 (0.8)	0	0	1 (0.2)
Chorea	0	0	0	0	1 (0.5)	1 (0.2)
Dyskinesia	4 (1.7)	0	1 (0.8)	1 (0.4)	2 (1.1)	4 (0.7)
Grimacing	1 (0.4)	0	0	0	0	0
Tardive dyskinesia	2 (0.8)	1 (1.9)	2 (1.6)	0	1 (0.5)	4 (0.7)
Dystonic Events	17 (7.2)	2 (3.8)	11 (8.7)	14 (5.9)	16 (8.6)	43 (7.1)
Blepharospasm	1 (0.4)	0	1 (0.8)	1 (0.4)	0	2 (0.3)
Dysphonia	0	0	0	1 (0.4)	0	1 (0.2)
Dystonia	5 (2.1)	0	3 (2.4)	0	2 (1.1)	5 (0.8)
Muscle rigidity	5 (2.1)	0	0	4 (1.7)	0	4 (0.7)
Musculoskeletal stiffness	8 (3.4)	2 (3.8)	8 (6.3)	9 (3.8)	15 (8.1)	34 (5.6)
Parkinsonian Events	26 (11.0)	2 (3.8)	11 (8.7)	23 (9.6)	32 (17.2)	68 (11.3)
Cogwheel rigidity	4 (1.7)	0	0	4 (1.7)	6 (3.2)	10 (1.7)
Drooling	0	1 (1.9)	2 (1.6)	1 (0.4)	3 (1.6)	7 (1.2)
Extrapyramidal disorder	13 (5.5)	0	4 (3.1)	16 (6.7)	21 (11.3)	41 (6.8)
Hypertonia	0	0	0	0	1 (0.5)	1 (0.2)
Masked facies	0	0	0	1 (0.4)	0	1 (0.2)
Parkinsonian rest tremor	1 (0.4)	0	2 (1.6)	0	0	2 (0.3)
Tremor	10 (4.2)	2 (3.8)	4 (3.1)	8 (3.3)	9 (4.8)	23 (3.8)
Residual Events	5 (2.1)	1 (1.9)	4 (3.1)	4 (1.7)	8 (4.3)	17 (2.8)
Movement disorder	5 (2.1)	1 (1.9)	3 (2.4)	4 (1.7)	8 (4.3)	16 (2.6)
Muscle twitching	0	0	1 (0.8)	0	0	1 (0.2)

Except for the parkinsonian and residual events in the 24 mg/day group, there is little difference between sertindole and placebo. However, looking at the individual EPS-related AEs, there does appear to be a dose response for extrapyramidal disorder. In

addition, in the 24 mg/day group, musculoskeletal stiffness, movement disorder, and extrapyramidal disorder occur at least twice the rate of placebo.

For the same pool of studies, we also requested a table of the change from baseline to endpoint (with standard deviation) in the Abnormal Involuntary Movement Scale (AIMS), the Barnes Akathisia Scale (BAS), and the Simpson-Angus Scale (SAS).

Table 51: Movement Scales Mean Change from Baseline to Endpoint Pooled Studies: M92-762, M93-098, and M93-113

Summary Statistics	Placebo (N=237)	Sertindole				
		8 mg (N=52)	12 mg (N=127)	20 mg (N=239)	24 mg (N=186)	Total (N=604)
BAS						
n	219	50	120	222	166	558
Mean	0.0	-0.3	-0.2	-0.7	-0.2	-0.4
Standard deviation	2.35	1.89	1.86	2.46	2.12	2.20
AIMS						
n	219	50	120	222	166	558
Mean	0.4	-0.7	-0.7	-0.9	-0.3	-0.7
Standard deviation	3.03	2.39	2.65	2.85	3.20	2.89
SAS						
n	219	50	120	221	166	557
Mean	-0.4	-0.6	-0.8	-0.3	-0.1	-0.4
Standard deviation	2.67	2.66	1.98	2.67	2.56	2.51

For all three scales, there is little difference between sertindole (at all doses) and placebo. In fact, for sertindole, the mean endpoint scores are consistently less than the baseline scores.

7.4.6 Immunogenicity

For the pool of the five short-term, randomized, placebo-controlled, phase 2/3 studies, the sponsor looked at the incidence of immune- or allergy-related adverse events. Only for “hypersensitivity” was there a greater incidence in the sertindole group than in the placebo group. Two patients (1.1%) in the 24 mg/day group and 1 patient (3.7%) in the flexible dose group had an AE coded to “hypersensitivity,” while none in the placebo group did.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

For the pool of the 3 completed, non-Japanese, short-term, fixed dose, placebo-controlled studies, the mean difference in QTc between study drug and placebo after baseline correction increases in an approximately dose dependent fashion. The same is true for the percentage of QTc outliers (see Tables 45 and 46). The following table summarizes the other clinically significant safety findings that approximate or suggest dose dependency, including those findings that start low and then rise to a plateau:

Table 52 Clinically Significant Safety Findings That Approximate or Suggest Dose Dependency

Safety Findings	Sertindole Daily Dose				Placebo
	8 mg	12 mg	20 mg	24 mg	
Labs					
Glucose Mean Change (mg/dL)	0.1	7.9	5.8	8.1	0.2
Glucose Outliers ¹	2.0%	8.1%	10.2%	7.4%	4.0%
Triglyceride Outliers ²	10.2%	13.7%	13.3%	14.3%	8.5%
Vital Signs					
Weight Outliers ³	11.1%	21.3%	27.7%	27.4%	11%
Adverse Events					
Dry Mouth	3.8%	7.1%	10.9%	12.4%	5.1%
Extrapyramidal Disorder	0%	3.1%	6.7%	11.3%	5.5%
Nasal Congestion	13.5%	18.9%	24.3%	23.7%	8.9%

¹Patients meeting outlier criteria (≥ 126 mg/dL) at endpoint but not at baseline

²Patients meeting outlier criteria (≥ 200 mg/dL) at endpoint but not at baseline

³Gained $\geq 7\%$ baseline weight

7.5.2 Time Dependency for Adverse Events

No analysis looking at the time dependency of adverse events, in particular tolerance to events and late onset events, is available.

7.5.3 Drug-Demographic Interactions

An analysis of the effect of demographic variables (age, gender, and race) on the incidence of common and likely adverse events ($\geq 5\%$ in sertindole-treated patients and ≥ 2 times the placebo rate) was performed by comparing drug:placebo odds ratios across demographic subgroups. Age subgroups were defined as 18-49 and ≥ 50 years old. Race subgroups were defined as Caucasian and non-Caucasian.

For each demographic subgroup, the drug:placebo ratio for a particular adverse event was computed from the pool of 5 non-Japanese, short-term, randomized, placebo-controlled studies. Then the Breslow-Day Chi Square test for homogeneity of the odds ratios across the subgroups for each demographic variable was performed and the p values were reviewed. Alpha was arbitrarily set at 0.05.

Of note, there were no statistically significant findings.

7.5.4 Drug-Disease Interactions

No new data are available on drug-disease interactions. There is class labeling on use in patients with concomitant illnesses, which will be discussed in the labeling review.

7.5.5 Drug-Drug Interactions

Specific labeling recommendations will be made by the Office of Clinical Pharmacology in their review. Sertindole is metabolized by the CYP2D6 and CYP3A isozymes. Population pharmacokinetic analyses detected that the plasma concentration of sertindole is increased by a factor of 2-3 in patients concurrently taking CYP2D6 inhibitors such as fluoxetine and paroxetine. There were minor increases (<25%) in sertindole concentrations for macrolide antibiotics (e.g. erythromycin, a CYP3A inhibitor) and calcium channel antagonists (diltiazem, verapamil, and nifedipine). It was also found that agents known to induce CYP isozymes, such as rifampin, carbamazepine, phenytoin, and phenobarbital, can decrease the plasma concentrations of sertindole by a factor of 2 to 3.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

None of the studies were adequate to definitively answer the question of carcinogenicity with sertindole. However, review of the SAEs from the entire Japanese and non-Japanese study pools (N=21731 for sertindole), which also included long-term data from studies such as SCoP, did not reveal an unexpectedly large number of cases of cancer or any particular patterns in those cases.

7.6.2 Human Reproduction and Pregnancy Data

There are no adequate and well-controlled studies with sertindole in pregnant women. It is not known whether sertindole or its metabolites are excreted in breast milk.

7.6.3 Pediatrics and Assessment of Effects on Growth

The safety (and effectiveness) of sertindole has not been established in individuals below the age of 18.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

1. Overdose

The following table summarizes the number of accidental and intentional overdoses, in particular deaths, by study type (non-Japanese). At our request, the search was limited to those cases in which sertindole was the only drug on which the patient overdosed (concomitant medications at therapeutic doses were allowed).

Table 53 Number of Total Overdoses and Overdose Deaths, by Study Type

Study Type	Total Overdoses	Overdose Deaths
Phase II/III	35	0
SCoP	18	1 (5.6%)
Others Studies in Schizophrenia	12	1 (8.3%)
Ongoing Studies	2	0
Spontaneous Reports	19	0
All Study Types	86	2 (2.3%)

Adverse events associated with overdose include vomiting, somnolence (including obtundation), slurred speech, extrapyramidal symptoms, mydriasis, tachycardia, hypotension (including circulatory collapse), convulsions, prolongation of the QTc interval, ventricular fibrillation, and cardiac arrest. Cases of torsades de pointes have been observed, though these have sometimes been confounded by overdoses of other drugs known to cause torsades de pointes.

The sponsor recommends that overdoses be treated with gastric lavage, with the possible administration of activated charcoal together with a laxative. Immediate cardiovascular monitoring is also recommended, including continuous electrocardiographic monitoring to detect possible arrhythmias. This monitoring should continue until the QTc interval has normalized. Of note, there is no antidote to sertindole, and it is not dialyzable.

2. Drug Abuse Potential

Sertindole has not been systematically studied in animals or humans for its potential for abuse, tolerance, or physical dependence. However, based on the pharmacology of sertindole, there is no reason to suspect any risk of abuse or dependence.

3. Withdrawal and Rebound

There was no study specifically designed to look at this.

7.7 Additional Submissions / Safety Issues

The sponsor submitted a 120-day Safety Update to the Integrated Summary of Safety. It includes safety information on sertindole that has become available since the cut-off date (January 11, 2008) for the NDA resubmission. The cut-off date for this update is July 11, 2008.

There are no new placebo-controlled studies. For the studies included in this update, please see the Table 54 below:

Table 54: Overview of Ongoing Studies, Studies in the Reporting Phase, or Completed Studies Since the NDA Resubmission

Status/Study	Design	Indication/Treatment Duration/ Sertindole Dosing Regimen
Completed		
11509A	<i>Efficacy and Safety Post-registration</i> Open-label, uncontrolled, post-marketing study in Russia	Schizophrenia 8 weeks Flexible, according to the SPC
In the Reporting Phase – Randomised, Double-blind Clinical Study		
11286	<i>Efficacy and Safety</i> Randomised, double-blind, parallel-group, active-comparator (olanzapine) study in Asia (China, South Korea, Taiwan)	Schizophrenia 12 weeks Flexible, 12 to 20mg/day
Ongoing – Studies Related to the SCoP Study		
99823	<i>Sertindole Post-marketing Surveillance</i> Open-label, uncontrolled, observational, multinational, post-marketing study	Schizophrenia Long-term Flexible, according to the SPC
12009A	<i>Study 99824 (SCoP) Extension</i> Open-label, uncontrolled, multinational, post-marketing study	Schizophrenia Long-term Flexible, according to the SPC
Ongoing – Post-marketing Study		
11720A	<i>European Sertindole Post-marketing Observational Study (ESPO)</i> Open-label, uncontrolled, observational, post-marketing study in Europe (Austria, the Czech Republic, Hungary, Slovakia)	Schizophrenia 15 weeks Flexible, according to the SPC
Ongoing – Randomised, Double-blind Clinical Study		
11723A	<i>Neurocognitive Effects</i> Randomised, double-blind, parallel-group, active-comparator (quetiapine) study in the United States	Schizophrenia 12 weeks Flexible, 12 to 20mg/day
SPC: Summary of Product Characteristics NDA resubmission cut-off date: 11 January 2008 120-day Safety Update cut-off date: 11 July 2008		

1. Study 11509A

A total of 30 patients were treated as part of this study. No serious adverse events were reported. A 27-year-old man withdrew due to adverse events. On Day 10 of treatment, he developed hypokinesia and dizziness, which worsened on Day 15 following alcohol intake. He stopped sertindole treatment, and three days later he had recovered.

2. Study 11286

A total of 389 patients were treated as part of this study, with 196 patients receiving sertindole. Nineteen patients in the sertindole group had serious adverse events, including one death (a suicide). This reviewer examined the table of SAEs, looking for

any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected.

Thirty-four patients in the sertindole group withdrew due to adverse events. The majority of adverse events leading to withdrawal in the sertindole group were in the SOCs "Psychiatric Disorders" (16 patients) and "Investigations" (12 patients, 11 of whom withdrew due to QT prolongation). This reviewer examined the table of adverse events leading to withdrawal, looking for any unusual or otherwise remarkable events. There were no events that seemed unusual or unexpected. Of interest, however, is that one patient withdrew due to hyperprolactinemia.

3. Study 99823

Three patients have been included in this study. No serious adverse events have been reported.

4. Study 12009A

A total of 18 patients in France have been included, 14 of whom were still ongoing as of the cut-off date (July 11, 2008). No serious adverse events have been reported. There is no information on adverse events leading to withdrawal.

5. Study 11720A (ESPO)

A total of 863 patients have been enrolled in this study. No serious adverse events have been reported. Since this is a post-marketing study (in Austria, the Czech Republic, Hungary, and Slovakia), the case report forms are not collected until the study is complete in a country. Therefore, no further information is available at this time.

6. Study 11723A

A total of 32 patients have been randomized. Although the sponsor does not give the number of patients randomized to sertindole, the protocol specifies that the patients should be equally distributed between the two treatment groups (sertindole vs. quetiapine). No serious adverse events have been reported. There is no information on adverse events leading to withdrawal.

7. Spontaneous Reports

There was one death among the new spontaneous reports. A 43-year-old man who participated in an investigator initiated trial had been treated with sertindole for approximately 23 weeks when he was found dead at home. Details of his death were not reported. Medical officers stated that the cause of death was esophageal varices

and ascites as a consequence of many years of alcohol abuse. However, no autopsy was performed.

Including the death above, the sponsor received 15 spontaneous serious reports for a total of 33 events. This reviewer examined the table of SAEs, looking for any unusual or otherwise remarkable events. Of note, there was a case of pericarditis. Otherwise, there were no events that seemed unusual or unexpected. Of interest, however, are two cases of neuroleptic malignant syndrome and one case of galactorrhea.

8 Postmarketing Experience

Sertindole has been launched in 38 countries in Europe, Latin America, and Asia. For the period 2006-2008, the best estimate of usage is 13,000 patient years, the majority of which came from non-European countries. Since 2002, when the EU lifted the marketing suspension for sertindole (see section 2.5, Summary of Presubmission Regulatory Activity Related to this Submission), the drug has not been withdrawn from any market. With the re-introduction of sertindole, the EU restricted its use by adding to the therapeutic indication: “due to cardiovascular safety concerns, sertindole should only be used for patients intolerant to at least one other antipsychotic agent”—today this remains unchanged. Other restrictions (see section 2.5) have now been lifted.

A Risk Management Plan (RMP) for sertindole (current version dated 5/6/2008) is in effect for Europe. There are no RMPs in effect for any other countries. The RMP in essence describes two pharmacovigilance programs:

- **Passive Pharmacovigilance Program:** Lundbeck has an established system for collection of adverse event/drug reaction information from the market and clinical trials as well as by surveillance of the literature. Additional information on cardiac and fatal events is sought systematically by asking reporters to fill out an “Information Retrieval Form.”
- **Active Pharmacovigilance Program:** Lundbeck has planned cohort studies with information from drug utilization databases and a disease specific database. However, up to now, the market share for sertindole in Europe has been small, so the number of prescriptions recorded in these databases has been insufficient. During 2009, it is expected that the number of patients in at least one of the databases will exceed the required number of 500, allowing the studies to begin.

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Phillip Kronstein, M.D.
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Of note, postmarketing data for deaths and non-fatal SAEs has been provided by the sponsor. This information has been included in the Integrated Review of Safety.

9 Appendices

9.1 Literature Review/References

A worldwide literature search was requested from the sponsor subsequent to the filing meeting for this application. Lundbeck responded on October 16, 2008 with a formal submission.

Published literature, with a cutoff date of January 11, 2008, was reviewed utilizing Datastar Medline and EMBASE. The search was designed to capture all relevant safety information pertaining to the use of sertindole and its metabolites, norsertindole and dehydrosertindole.

A total of 1459 unique references were indentified. Following the initial review of the publication, they were place into two major categories, “clinical” and “nonclinical.” The clinical articles were further classified as “relevant” and “not relevant” (all of the “nonclinical” articles were considered “not relevant”). The reasons to classify a publication as “not relevant” are listed in the table below, with the number of publications identified for each reason category:

Table 55 Reasons for Not Including a Clinical Publication as Relevant

Reasons	Number of Publications
Clinical	1049
General review of disease	68
Treatment guidelines	32
Practice guidelines	20
Not target compound	130
Sertindole pooled with other antipsychotics	11
Combination treatment	9
Government report	8
Editorial	60
Review article with no original data	678
Methodology	20
Clinical endpoint validation	6
Analytical methods	4
Compliance assessment	3

For as summary of the relevant clinical publications, please see the following table:

Table 56 Summary of Relevant Clinical Publications

Clinical Category	Total	Safety	Efficacy	Pharmacokinetics/ Pharmacodynamics
Clinical Trials	66	42	35	32
Meta-analysis	7	3	6	0
Retrospective Analysis	9	8	1	0
Case Report	18	13	13	1
Review Article With Original Data	5	3	4	1
Overall	105	69	59	34

The following persons reviewed these articles:

Table 57 Reviewers and Their Qualifications

Discipline	Name	Title
Safety	Jens Peter Balling, M.D.	Divisional Director International Safety & Pharmacovigilance (ISPV)
	Lasse Steen Ravn, Ph.D., M.D.	Section Leader, Psychosis International Safety and Pharmacovigilance
Efficacy	Raimund Buller, M.D.	Director International Clinical Research Psychosis
Pharmacokinetics/ Pharmacodynamics	Frank Larsen, Ph.D.	Senior Specialist (Clinical Pharmacology)

Lundbeck provided a certification, signed by Drs. Buller and Larsen, stating that “no new information essential for the efficacy and pharmacokinetics of sertindole including no new adequate and well-controlled clinical trials not carried out by Lundbeck was found.” An additional certification was later submitted, signed by Dr. Balling, stating that “no new information essential for the safety of sertindole was found.”

In addition, this reviewer performed a Pubmed search, looking for any articles on sertindole published since January 11, 2008. Sixteen articles were identified. Review of the article abstracts did not reveal any new safety issues.

Finally, there was a recent article by Wayne Ray, titled: “Atypical antipsychotic drugs and the risk of sudden cardiac death.” (N Engl J Med. 2009 Jan 15;360(3):225-35). Of note, sertindole is not included in Ray’s analysis.

9.2 Labeling Recommendations

Comments regarding the sponsor's proposed labeling will be provided in a separate document following the Advisory Committee meeting. Some important features of the sponsor's labeling regarding the safety of sertindole are provided below:

1. Black Box Warning

WARNING: SERTINDOLE HAS BEEN SHOWN TO PROLONG THE QT INTERVAL IN A DOSE DEPENDENT MANNER

Sertindole causes an increase in the QT in a dose dependent manner, with a mean change from baseline in QT_{CF} of approximately 23 msec in sertindole 20 mg/day. At that dose, approximately 1.3% of patients experienced an increase in QTc from normal at baseline to a level > 500 msec.

Some drugs that prolong the QT interval have been associated with the occurrence of Torsades de Pointes and with sudden unexplained death. Torsades de pointes has not been observed in association with the use of sertindole at recommended doses in premarketing studies. There have been very rare post-marketing reports of serious arrhythmia including Torsades de Pointes.

SERDOLECT should not be initiated in patients with a prolonged QT interval (QTc greater than 450 [male] or 470 [female] msec).

SERDOLECT should be discontinued in patients who are found to have persistent QTc measurements >500 msec.

After initiation of treatment with sertindole an ECG should be obtained after 3 to 4 weeks. An ECG is recommended after a further increase in dose, addition of drugs that prolong the QT interval or concomitant medication that may increase the sertindole concentration (potent CYP2D6 inhibitors, moderate CYP3A inhibitors).

SERDOLECT is contraindicated in patients with a history of QT prolongation and in patients with clinically significant cardiovascular disease, such as congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute).

2. Indications and Usage

SERDOLECT is indicated for the treatment of schizophrenia.

SERDOLECT is also indicated for reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia.

3. Dosage and Administration/ Usual Dose (2.1)

SERDOLECT should be administered on a once a day schedule, with or without meals, generally beginning with 4 mg/day initially and increasing by 4 mg/day every 2-3 days until the recommended target dose of 16 mg is reached. Dependent on individual patient response, the dose may be increased to 20 mg/day or decreased to 12 mg/day.

4. Contraindications

QT-prolongation

Because sertindole prolongs the QT interval in a dose dependent manner, it is contraindicated in patients with a history of QT prolongation and in patients with clinically significant cardiovascular disease such as congestive heart failure, cardiac hypertrophy, arrhythmia, or bradycardia (<50 beats per minute).

Furthermore, SERDOLECT should not be initiated in patients with corrected QT interval longer than 450 msec in males or 470 msec in females.

SERDOLECT is contraindicated in patients receiving drugs known to significantly prolong the QT interval. Relevant classes include:

- class Ia and III antiarrhythmics (e.g., quinidine, amiodarone, sotalol, dofetilide)
- some antipsychotics (e.g., thioridazine, ziprasidone)
- some macrolides (e.g., erythromycin)
- some quinolone antibiotics (e.g., gatifloxacin, moxifloxacin)
- some other drugs (e.g. lithium)

The above list is not exhaustive.

Metabolism

Given the dose dependent QT-prolongation observed with sertindole, drugs that inhibit sertindole metabolism should be co administered with caution.

CYP2D6 is the principal isozyme involved in the metabolism of sertindole, with CYP3A ordinarily having a secondary role. In CYP2D6 poor metabolizers (about 7% of Caucasians), the CYP3A system becomes the principal route for sertindole's clearance from the body. Therefore, sertindole is contraindicated in patients treated with potent inhibitors of CYP3A. Relevant classes include:

- systemic treatment with 'azole' antifungal agents (e.g., ketoconazole, itraconazole)
- some macrolide antibiotics (e.g., erythromycin, clarithromycin)
- HIV protease inhibitors (e.g., indinavir)
- some calcium channel blockers (e.g., diltiazem, verapamil, nifedepine)
- Other potent inhibitors of CYP3A (e.g., cimetidine)

The above list is not exhaustive.

Hypersensitivity

SERDOLECT is contraindicated in patients with a known hypersensitivity to sertindole or to any of the excipients.

Electrolyte disturbances

SERDOLECT is contraindicated in patients with known uncorrected hypokalaemia, and those with known uncorrected hypomagnesaemia. This may occur in patients with diarrhea or taking diuretics.

Hepatic Impairment

SERDOLECT is contraindicated in patients with severe hepatic impairment.

5. Warnings and Precautions

Fairly standard language is proposed for:

- Increased Mortality in Elderly Patients with Dementia-Related Psychosis
- Neuroleptic Malignant Syndrome (NMS)
- Tardive Dyskinesia
- Hyperglycemia and Diabetes Mellitus
- Orthostatic Hypotension
- Seizures
- Hyperprolactinemia
- Potential for Cognitive and Motor Impairment
- Body Temperature Regulation
- Dysphagia
- Priapism
- Use in Patients with Concomitant Illness

Of note, the section on Suicide (5.11) claims:

SERDOLECT has shown a significantly reduced risk of fatal and nonfatal suicide attempts in patients with schizophrenia. However, the possibility of a suicide attempt is inherent in schizophrenia and close supervision of high-risk patients should accompany drug therapy. Prescriptions for SERDOLECT should be written for the smallest quantity of tablets consistent with good patient management, in order to reduce the risk of overdose.

In addition, the section on Laboratory Tests (5.15) states:

No specific routine laboratory tests are recommended. Baseline serum potassium and magnesium should be measured and low serum potassium and magnesium should be corrected before starting with treatment with SERDOLECT. Patients who are treated

with diuretics during SERDOLECT therapy need periodic monitoring of serum potassium and magnesium. Patients with diabetes should closely monitor their blood glucose levels.

6. Clinical Studies

In addition to describing various placebo- and active-controlled trials, the sponsor makes claims in regard to the SCoP study:

In a randomized, active-controlled, open-label, prospective use study (n=9858) comparing the safety of SERDOLECT and risperidone, patients treated with SERDOLECT had comparable all-cause mortality and a significantly lower risk of fatal or non-fatal suicide attempts compared to patients treated with risperidone.

9.3 Advisory Committee Meeting

The Division plans to take this NDA to the Psychopharmacologic Drug Advisory Committee (PDAC) on April 7, 2009. The results of the committee meeting will be submitted in an addendum to this document. The committee will be asked to address issues of safety, especially in regard to QT prolongation and cardiovascular risk, and issues of efficacy, especially the claim that sertindole has been shown to significantly reduce the risk of fatal and nonfatal suicide attempts in patients with schizophrenia

9.4 Appendix Tables

Appendix A

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TABLE OF ALL STUDIES	
COMPLETED NON-JAPANESE STUDIES	
Phase I (Clinical Pharmacology Studies)	
Single Dose in Healthy Subjects	
M91-694 R&D/914/418, Report 492F/816 GXP 90104	Sertindole: A Phase 1 Single Dose Bioavailability Study in Healthy Male Volunteers.
M92-814 R&D/94/162 R&D/93/277, June 1993 Report 175F-303 and Abbott-81968 Drug Metabolism Report 16 GXP 92908	A comparison of the bioavailability of three 4 mg tablet formulations of sertindole (Protocol M92-814).
M93-037 R&D/94/222, April 1994 Report 176F-303 and Abbott-81968 Drug Metabolism Report 19 GXP 93104	A comparison of the bioavailability of 4 mg tablet and capsule formulations of sertindole (Abbott-81968) (Protocol M93-037).
M93-122 R&D/94/389, August 1994 Report 180F-303 Abbot-81968 Drug Metabolism Report 22 GXP 94113	A pilot comparison of the bioavailability of 4 mg tablet and capsule formulations of sertindole (Protocol M93-122).
M93-123 R&D/94/393, July 1994 Report 181F-303 Abbott-81968 Drug Metabolism Report 23 GXP 94114	A pilot comparison of the bioavailability of sertindole 4 mg tablets and 4 mg capsules using a new high-dose granulation (Protocol M93-123).
M94-152 R&D/95/058, April 1995 Report 182F-303 and	Comparative bioavailability of commercial 4 mg sertindole capsules (U.S. and Puerto Rico) to a reference formulation

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<p>Abbott-81968 Drug Metabolism Report 40 GXP 94117</p>	<p>A comparison of the relative bioavailability of sertindole commercial 4-mg capsule formulations (manufactured at Abbott Park and Puerto Rico facilities) to a reference 4-mg tablet formulation (Protocol M94-152).</p>
<p>M94-164 R&D/95/191, May 1995 Abbott-81968 Drug Metabolism Report 48</p>	<p>Effect of food and antacid on the relative bioavailability of sertindole tablet compared to sertindole solution (Protocol M94-164).</p>
<p>M94-186 R&D/95/104 Report 183F-303 Abbott-81968 Drug Metabolism Report 53 R&D/95/325, June 1995 GXP 95102</p>	<p>Comparative Bioavailability of Commercial 8 mg Sertindole Capsules (Puerto Rico) to a Reference Formulation. A comparison of the relative bioavailability of a sertindole commercial 8-mg capsule formulation (manufactured at Puerto Rico) to a reference tablet formulation (Protocol M94-186).</p>
<p>M95-333 R&D/95/824 Report 162F-303 GXP 95108</p>	<p>Comparative Bioavailability of 4 mg Sertindole Tablets (Lundbeck) to a Reference Formulation.</p>
<p>M95-334 R&D/95/825 Report 163F-303 GXP 95109</p>	<p>Comparative Bioavailability of 8 mg Sertindole Tablets (Lundbeck) to a Reference Formulation.</p>
<p>M95-335 R&D/95/826 Report 164F-303 GXP 95110</p>	<p>Comparative Bioavailability of 12 mg Sertindole Tablets (Lundbeck) to a Reference Formulation.</p>
<p>M95-336 R&D/95/827</p>	<p>Comparative Bioavailability of 16 mg Sertindole Tablets (Lundbeck) to a Reference Formulation.</p>

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Report 165F-303 GXP 95111	
M95-395 R&D/96/407 Report 167F-303 GXP 95122	Comparative Bioavailability of 16 mg sertindole capsules (Puerto Rico) to a Reference Formulation.
M95-417 R&D/96/408 Report 169F-303 GXP 95121	Comparative Bioavailability of 12 mg sertindole Capsules (Puerto Rico) to a Reference Formulation.
Multiple Dose in Healthy Subjects	
M91-613 R&D/95/088 Report 99F-831 R&D/94/609, August 1994 Abbott-81968 Metabolism Report 27 GXP 91915	A phase I, double-blind, placebo-controlled, escalating multiple oral dose, safety, tolerance, and pharmacokinetic study in healthy male subjects. Pharmacokinetics of sertindole in 4-8 mg escalating multiple oral dose study in normal subjects (Protocol M91-613).
M91-622 R&D/95/089 Report 174F-303 89101	A Double-Blind, Phase I, Placebo-Controlled, Rising, Single Oral Dose, Safety, Tolerance and Pharmacokinetic Study in Healthy Volunteers.
M91-623 R&D/95/090 GSP 90101	A double-blind, phase I, placebo-controlled, escalating, multiple oral dose, safety, tolerance, and pharmacokinetic study in healthy volunteers.
M91-689 R&D/95/091 R&D /93/141, May 1995 Abbott-81968 Drug Metabolism Report 13	A phase I, double-blind, placebo-controlled, escalating multiple dose study of sertindole in normal subjects.

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GXP 91917	Pharmacokinetics and pharmacodynamics of sertindole (Abbott-81968) in healthy male subjects: an escalating multiple oral dose study (Protocol M91-689).
M92-729 R&D/95/092 Report 112F-831 R&D/94/251, August 1994 Abbott-81968 Drug Metabolism Report 21 GXP 92904	An escalating, multiple dose trial of sertindole in normal subjects: a double-blind, placebo-controlled study. Pharmacodynamics and pharmacokinetics of sertindole in a 4-32 mg escalating multiple dose study in normal subjects (Protocol M92-729).
M92-749 R&D/94/824 Report 113F-831 R&D/94/446, July 1994 Abbott-81968 Drug Metabolism Report 24 GXP 92903	The Safety, Tolerability, and Pharmacokinetics of Sertindole When Administered in Three Titration Regimens to Normal Subjects: A Phase I, Double-Blind, Placebo-Controlled Study. Pharmacokinetics of sertindole in 4-20 mg titration regimen study in normal subjects (Protocol M92-749).
M94-150 Report 179F-303 and R&D/95/227, July 1995 Abbott-81968 Drug Metabolism Report 51 GXP 94112	Comparative Bioavailability of commercial 20 mg sertindole capsules (U.S.) to a reference formulation A comparison of the relative bioavailability of a sertindole commercial 20-mg capsule formulation (manufactured at Abbott Park) to a reference formulation (Protocol M94-150).

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<p>M94-151 Report 178F-303 and R&D/95/259, July 1995 Abbott-81968 Drug Metabolism Report 47 GXP 94111</p>	<p>Comparative bioavailability of commercial 20 mg sertindole capsules (Puerto Rico) to a reference formulation</p> <p>A comparison of the relative bioavailability of a commercial 20-mg sertindole capsule formulation (Puerto Rico manufactured) to a reference formulation (Protocol M94-151).</p>
<p>ADME in Healthy Subjects</p>	
<p>M93-121 R&D/95/371 R&D/95/109, April 1995 Abbott-81968 Metabolism Report 44 GXP 94108</p>	<p>A phase I study of the absorption, metabolism and excretion of [¹⁴C] sertindole in normal male subjects.</p> <p>Metabolism and disposition of sertindole in humans given a single 4 mg oral dose of [¹⁴C] sertindole (Protocol M93-121).</p>
<p>M94-242 R&D/95/686, July 1995 Lundbeck Report 001/830, 1995 Lundbeck Study 94102 GXP 94102</p>	<p>Pharmacokinetics of sertindole in relation to the dextromethorphan and mephenytoin oxidation polymorphism and to the activity of CYP3A4 in healthy volunteers.</p>
<p>Special Populations</p>	
<p>M94-142 R&D/95/667, September 1995 Abbott-81968 Drug Metabolism Report 64 GXP 94104</p>	<p>Pharmacokinetics of sertindole in male subjects with normal or impaired hepatic function.</p> <p>The pharmacokinetics of sertindole following administration of a single dose to normal subjects and to subjects with various degrees of hepatic function (Protocol M94-142).</p>
<p>M94-143 R&D/94/880</p>	<p>Pharmacokinetics of sertindole in male subjects with normal or impaired renal function.</p>

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R&D/95/114, April 1995 Abbott-81968 Drug Metabolism Report 46 GXP 94105	Evaluation of the pharmacokinetics of sertindole (Abbott-81968) in male subjects with various degrees of renal function (Protocol M94-143).
M94-144 R&D/94/908 R&D/95/218, August 1995 Abbott-81968 Drug Metabolism Report 49 GXP 94103	The effect of subject age on the multiple-dose pharmacokinetics of sertindole. The effect of age and gender on the multiple-dose pharmacokinetics of sertindole (Protocol M94-144).
M95-383 R&D/96/335 Report 166F-303 GXP 95245	The Safety and Tolerability of Sertindole in Elderly Patients with Dementia.
Drug-Interaction in Healthy Subjects	
M94-145 R&D/94/909 and R&D/94/800, February 1995 Abbott-81968 Drug Metabolism Report 33 GXP 94107	The effect of erythromycin on the pharmacokinetics of sertindole (Protocol M94-145).
M94-146 R&D/95/099 and Abbott-81968 Drug Metabolism Report 50 R&D/95/226, July 1995 GXP 94109	The effect of sertindole on the pharmacokinetics of terfenadine (Protocol M94-146).
M95-387 R&D/96/564 GXP 95119	The effect of Sertindole on the Pharmacokinetics of Digoxin.
M95-397 R&D/96/334 Report 160F-303	The effect of sertindole on the pharmacokinetics of Alprazolam.

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GXP 95120	
Positron Emission Tomography (PET) in Healthy Subjects	
M91-659 R&D/92/186 R&D/92/197, April 1992 Abbott-81968 Drug Metabolism Report 3 GXP 91916	Central D2-dopamine Receptor Occupancy After a Single Oral Dose of Sertindole in Normal Subjects: A Pilot Study. Pharmacokinetics of oral 4 mg sertindole (Abbott 81968) in two normal male volunteers (Protocol M91-659).
M95-344 Report 154-303 95223 GXP 95223	Neocortical 5-HT ₂ PET Receptor Occupancy After Multiple Oral Doses of Sertindole 12 mg Tablets in Healthy Subjects.
M96-438 GXP 95116 Report 202-303	Striatal D2 PET Receptor Occupancy After Multiple Oral Doses of Sertindole 12 mg Tablets in Healthy Subjects.
Special Study in Healthy Subjects	
M94-241 Lundbeck Study 94101 Report 130/838	Orthostatic Effects of Sertindole in Healthy Subjects.
Phase II/III Studies in Schizophrenia (Including Open-Label)	
Double Blind - Placebo-Controlled Clinical Studies	
M91-645 R&D/95/529, July 1995 Abbott-81968 Drug Metabolism Report 55 GXP 91914	The efficacy and tolerability of sertindole in schizophrenic and schizoaffective patients: a pilot, double-blind, placebo-controlled dose-ranging study. Pharmacokinetics of sertindole (Abbott-81968) in schizophrenic patients (Protocol M91-645).
M92-762 R&D/95/015, July 1995	A double-blind, placebo-controlled study of the safety and efficacy of sertindole in

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Abbott-81968 Drug Metabolism Report 39 GXP 92902	schizophrenic patients. Population pharmacokinetics and pharmacodynamics of sertindole and its primary metabolites in patients with schizophrenia (Protocol M92-762).
M92-817 R&D/94/163 Report 170F-303 GXP 92912	A Double-Blind, Placebo-Controlled, Haldol-Referenced Study of the Safety and Efficacy of Sertindole in Schizophrenic Patients.
M93-098 R&D/95/582, August 1995 Abbott-81968 Drug Metabolism Report 59 GXP 93304	A double-blind, placebo-controlled, haldol-referenced study of the safety and efficacy of sertindole in schizophrenic patients Population pharmacokinetics of sertindole in patients with schizophrenia participating in Study M93-098.
M93-113 GXP 94306	A Double-Blind, Placebo-Controlled, Dose-Response Comparison of the Safety and Efficacy of Three Doses of Sertindole and Three Doses of Haldol in Schizophrenic Patients.
Dose-Comparison Controlled Studies	
M91-675 R&D/95/334 Report 94/831 GXP 90201	A Double-Blind, Controlled, Phase II, Fixed Dose, Efficacy, Safety and Dose Range Study in Male Schizophrenic Patients.
Active-Controlled Studies	
M93-132 R&D/96/838 Report 171F-303-1997 GXP 94307	A Double-Blind Comparison of Sertindole and Haldol: An Assessment of the Chronic Safety, Efficacy, Quality of Life and Relapse in Stable Schizophrenic Patients.

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M95-342 Clinical Trial GCP 93302 Report 148-303-1997	A Dose Ranging Study Comparing the Efficacy, Tolerability and Safety of 4 Doses of Sertindole and 1 Dose of Haloperidol in Schizophrenic Patients. A Multinational, Prospective, Randomized, Double-Blind, Controlled, Parallel Group Study.
M95-372 95-244 Report 197-303-1999 GXP 95244	A double-blind, randomized, comparison of the safety and efficacy of Sertindole and Risperidone in the treatment of resistant schizophrenic patients.
96205 Report 271-303	Randomized, double-blind, four-armed, comparative trial of sertindole versus haloperidol investigating extrapyramidal effects in first-episode and previously-treated patients with schizophreniform disorder or schizophrenia.
97203 Report 198-303	A Comparative, Multi-Centre, Double-Blind Randomized Flexible Dose Study of the Efficacy and Safety of Sertindole in the Range of 12-14 mg Daily and Risperidone in the Range of 4-10 mg Daily in the Treatment of Schizophrenic Patients.
Uncontrolled Studies - Open-Label	
M91-671 GXP 91913	Sertindole Treatment of Schizophrenic Patients: An Open Label Safety Study.

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<p>M92-795 Abbott-81968 Drug Metabolism Report 63 R&D/95/617, August 1995 GXP 92911</p>	<p>An open-label assessment of the long-term safety of sertindole in the treatment of schizophrenic patients</p> <p>Population pharmacokinetics of sertindole in patients with schizophrenia participating in Study M92-795.</p>
<p>M93-061 R&D/95/584, August 1995 Abbott-81968 Drug Metabolism Report 61 GXP 93305</p>	<p>An open-label assessment of the long-term safety of sertindole in the treatment of patients with schizophrenia and other psychotic disorders</p> <p>Population pharmacokinetics of sertindole in patients with schizophrenia participating in Study M93-061.</p>
<p>M94-192 GXP 94308 C</p>	<p>An Open-Label Assessment of the Long-Term Safety of Sertindole in the Treatment of Patients with Schizophrenia.</p>
<p>M94-222 GXP 94312</p>	<p>An Open-Label Assessment of the Long-Term Safety of Sertindole.</p>
<p>M94-239 95207</p>	<p>A Rapid Dose Escalating Safety, Tolerability and Pharmacokinetic Study of Sertindole 4 to 24 mg in Schizophrenic Patients.</p>
<p>M95-339 93303 Report 185-303 93303</p>	<p>An Open-Label Assessment of the Long-Term Tolerability, Safety, and Efficacy of Sertindole in Schizophrenic Patients.</p>

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98205	Open-label follow up of the Comparative, Multi-Centre, Double-Blind, Randomized Flexible Dose Study of Efficacy and Safety of Sertindole in the Range of 12-14 mg Daily and Risperidone in the Range of 4-10 mg Daily in the Treatment of Schizophrenic Patients.
Other Studies in Schizophrenia	
Positron Emission Tomography (PET)	
M96-424 R&D/98/026 GXP 96204	A positron Emission Comparing Sertindole and Haloperidol in Schizophrenic Patients.
96202 95-116 Report 203-303-2001	Positron Emission Tomography studies on D2 Receptor Binding in Patients With Schizophrenia After Multiple Oral Dose of Sertindole (23-174) 20 mg.
Prospective Studies	
97201 Report 200/303	A post-marketing, referenced, observational, cohort, safety study of sertindole in the treatment of schizophrenic patients.
99824 SCoP	Sertindole versus risperidone safety outcome study: A randomized, partially-blinded, parallel-group, active-controlled, post-marketing study.
Epidemiological Studies	
98604 Report 217/313 ESES	A retrospective study to evaluate the modality of prescription of sertindole and the risk of occurrence of serious adverse events under sertindole treatment in routine practice.
98604-A3 Report 216/313 ESES	A nested case control study to search for risk factors associated with cardiac death occurrence.

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98604A	
98604-A5 The ERASMUS Study	Mortality during use of sertindole and other antipsychotics in the Netherlands and Belgium - a comparative cohort study.
98604-A6 Report 218/313 ESES 98604D	Multicentre international retrospective survey to identify patients treated with sertindole after its market suspension and assess rate of occurrence of serious adverse events.
98604-A7 ESES 98604E	The Niche Study.
99207 (Hospital PEM) 99207	Hospital-based, retrospective study of mortality experience in three comparative cohorts of patients who receive sertindole, risperidone, and olazapine (atypical antipsychotics). United Kingdom Psychiatric Pharmacy Group.
PEM	Comparative study of deaths and cardiac arrhythmias in the PEM studies of three atypical antipsychotic drugs.
Post-Marketing	
11509A	Efficacy and safety of Sertindole in patients with schizophrenia; open-label, one arm post-registration study in Russia
Other Populations	
M96-457 94311 Report 184-303 94311	The Efficacy and Tolerability of Sertindole in Elderly Patients with Prolonged Confusional State and Secondary Psychotic Symptoms. Pilot Evaluation.
M96-472 GXP 99903	A Double-Blind, Placebo-Controlled Study of the Safety and Efficacy of Sertindole in the Treatment of Patients With Generalized Anxiety

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Phase I (Clinical Pharmacology Studies) in Healthy Subjects	
Single Dose	
M95-328 9123A1910 GXP 92906	Phase I: Single dose study.
M95-347 9433A1914 GXP 95105	Clinical Report for Bioequivalence Study of Sertindole.
Multiple Dose	
M95-340 9225A1912 GXP 95114	Phase I: 7-day multiple dose study.
M95-341 9312A1913 GXP 95113	Phase I: 14-day multiple dose study.
Special Populations	
M97-690 10221 9624A1915	Pharmacokinetic Study of S-1991 in an Elderly Population (Shionogi).
Food Interaction	
M95-343 92907 9218A1911	Phase I Single Dose Study (Fed-fasted study).
Phase II/III Studies in Schizophrenia (including open-label)	
Double Blind - Active Controlled Studies	
M96-542 95246 9607A1931	Double-blind Randomised Controlled Study Comparing Sertindole with Haloperidol as Treatments for Patients with Schizophrenia

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M96-543 95247 9608A1932	Double-blind Randomised Controlled Study Comparing Sertindole with Mosapramine hydrochloride as Treatments for Patients with Schizophrenia
Open Label Studies (Uncontrolled)	
M95-278 93201 Shionogi Study 9406A1922 94202	Late Phase II Clinical Study of Sertindole.
M95-329 93201 Shionogi Study 9303A1921 93201	Early Phase II Clinical Study of Sertindole.
M95-346 95238 Report 151F-303 Shionogi Study 9407A1923 95238	Long-Term Clinical Study of Sertindole.
M97-689 10220 9625A1934	Results of Phase III Clinical Study of Sertindole: Clinical Investigation in an Elderly Population
96213 9615A1933	Results of Phase III Clinical Study of Sertindole - Long-duration Trial.
ONGOING NON- JAPANESE STUDIES	
Active-Controlled in Schizophrenia	
11286	A randomised, double-blind, parallel-group, flexible dose trial evaluating the efficacy and safety of 12-week treatment with sertindole or olanzapine in patients with schizophrenia in Asia.

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11723A	Neurocognitive Effects Randomised, double-blind, parallel-group, active comparator (quetiapine) study in the United States.
Other Studies in Schizophrenia - Open-Labeled	
99823	Sertindole post-marketing surveillance study.
11720A	Observational, non-interventional, open-label, one arm, uncontrolled, flexible-dose study evaluating population of patients treated with Serdolect®.
12009A	A prospective, open-label, single arm, multinational, multi-centre, flexible dose, extension study of the SCoP 99824 with sertindole for patients suffering from schizophrenia.

Appendix B

Death Line Listing: Completed Non-Japanese Phase I Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day) Treatment = Sertindole	MedDRA Preferred Term ^a	Investigator Term
M95-387--1024/ DKLU 0960568	M95-387	67	M	10	0	12	Sudden cardiac death	SUDDEN CARDIAC DEATH

^a The lower level term "Unknown cause of death" maps to the preferred term "death." Note: Autopsy revealed severe coronary atherosclerosis.

Death Line Listing: Completed Non-Japanese Phase II/III Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death Investigator Term
					Days Since Last Dose	Last Dose (total mg/day)		
M91-645-6293-9119/ DKLU0950476	M91-645	44	F	38	352	20	Neoplasm malignant	--
M92-762-7136-3103/ DKLU0950477	M92-795	39	M	16	108	12	Dehydration	AGITATION, PSYCHOTIC STATE
M92-762-7136-3108/ DKLU0960374	M92-795	38	M	512	145	8	Unknown cause of death	UNKNOWN
M93-098-8547-1920/ DKLU0950033	M92-795	60	M	25	5	24	Aneurysm; Hypotension; Pulmonary oedema	--
M93-113-9133-7209/ DKLU0950478	M92-795	32	M	120	10	24	Drug toxicity	OVERDOSE EFFECT
M93-113-9340-8107/ DKLU0950479	M92-795	50	M	51	6	24	Intestinal obstruction; Renal failure acute; Intestinal perforation; Arterial thrombosis	--
M93-061-6185-4901/ DKLU0940146	M93-061	71	F	34	1	24	Cardiac failure; Arrhythmia	--
M93-061-7510-2400/ DKLU0950481	M93-061	23	M	28	61	16	Completed suicide	SUICIDE
M93-061-7522-3801/ DKLU0950031	M93-061	43	F	356	3	24	Unknown cause of death	--
M93-061-8400-1817/ DKLU0950480	M93-061	53	M	277	69	24	Lung neoplasm malignant	--
M93-061-8402-2003/ DKLU0940114	M93-061	62	M	78	1	24	Arteriosclerosis coronary artery	--
M93-098-6185-1117/ DKLU0950030	M93-098	40	F	4	0	8	Completed suicide	--
M93-132-8848-25006/ DKLU0950014	M93-132	45	M	118	0	24	Pulmonary embolism	PULMONARY EMBOLISM
M94-192-8405-77031/ DKLU0960600	M94-192	23	M	4	1	8	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese Phase II/III Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	Investigator Term
					Days Since Last Dose	Last Dose (total mg/day)		
M93-061-8401-1911/ DKLU0971018	M94-222	67	F	1329	7	16	Breast cancer	BREAST CANCER
M93-098-7787-2313/ DKLU0950194	M94-222	51	M	154	1	24	Unknown cause of death	
M93-098-8453-1410/ DKLU0960255	M94-222	49	M	504	0	12	Unknown cause of death	UNKNOWN
M93-098-9047-4618/ DKLU0960602	M94-222	25	F	354	0	24	Suicide attempt	SUICIDE
M93-113-3209-6415/ DKLU0960604	M94-222	36	M	235	20	20	Sepsis; Convulsion; Renal failure; Thrombocytopenia; Rhabdomyolysis	SEPTICAEMIA, CONVULSIONS, KIDNEY FAILURE, THROMBOCYTOPENIA, RHABDOMYOLYSIS
M93-113-4524-5311/ DKLU0980290	M94-222	55	F	1205	23	20	Unknown cause of death	UNKNOWN
M93-113-8401-3701/ DKLU0950551	M94-222	57	F	331	1	20	Unknown cause of death	UNKNOWN
M93-113-8401-3704/ DKLU0960051	M94-222	40	F	304	13	24	Unknown cause of death	
M93-113-8853-1511/ DKLU0970266	M94-222	41	M	154	451	24	Asphyxia	ACCIDENTAL DROWNING
M93-113-8895-3301/ DKLU0950519	M94-222	40	M	371	0	24	Completed suicide; Intentional overdose	SUICIDE, INTENTIONAL OVERDOSE
M93-113-9133-7203/ DKLU0970234	M94-222	37	M	928	1	24	Pneumonia; Pyrexia	PNEUMONIA
M93-113-9133-7216/ DKLU0960601	M94-222	27	F	99	26	24	Suicide attempt	SUICIDE ATTEMPT
M93-132-4315-36004/ DKLU0971201	M94-222	31	F	1006	147	24	Unknown cause of death	UNKNOWN
M93-132-8887-27011/ DKLU0971103	M94-222	64	M	813	1	4	Bladder cancer	UNKNOWN

Death Line Listing: Completed Non-Japanese Phase II/III Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)		
						MedDRA Preferred Term ^a	Investigator Term	
M93-132-8887-27012/ DKLU0970308	M94-222	47	M	917	1	24	Myocardial infarction	SUDDEN DEATH , MYOCARDIAL INFARCTION
M93-132-8894-12004/ DKLU0960603	M94-222	55	M	532	24	24	Cardiac arrest; Neoplasm malignant	HEART ARREST, CARCINOMA
M95-342-11150-1803/ DKLU0960013	M95-339	22	M	93	1	20	Overdose	SUSPECTED SERTINDOLE OVERDOSE
M95-342-11159-1827/ DKLU0960833	M95-339	37	M	179	237	20	Unknown cause of death	UNKNOWN
M95-342-11159-1878/ DKLU0960476	M95-339	41	M	203	14	16	Unknown cause of death	UNKNOWN
M95-342-11210-1970/ DKLU0950296	M95-339	49	F	172	1	16	Alcohol poisoning	SEVERE ALCOHOL INTOXICATION
M95-342-11220-2193/ DKLU0971107	M95-339	36	F	713	70	24	Unknown cause of death	UNKNOWN
M95-342-11218-2158/ DKLU0950100	M95-342	35	F	21	8	16	Grand mal convulsion	EPILEPSY GRAND MAL
					Treatment = Placebo			
M93-061- -3809/ DKLU0950482	M93-061	73	F	--	--	--	Respiratory failure	--
M95-342- -1071/ DKLU0950322	M95-342	53	M	5	2	--	Unknown cause of death	--

Death Line Listing: Completed Non-Japanese Phase II/III Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death Investigator Term
					Since Last Dose	Last Dose (total mg/day)		
97203-45-1073/ DKLU0980751	97203	51	M	13	1	6	Delusion; Injury	WORSENING OF DELUSION
M95-372- -7404/ DKLU0970301	M95-372	30	M	--	--		Myocardial infarction	SUDDEN DEATH

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
Treatment = Sertindole								
99824-AT006-11171/ DKLU1010216	99824	23	M	272	15	20	Completed suicide	SUICIDE BY DROWNING
99824-AT007-11178/ DKLU1014900	99824	27	M	582	1	16	Aspiration	ASPIRATION
99824-AT026-11835/ DKLU1023317	99824	24	M	1136	1	20	Intentional overdose	OVERDOSE
99824-BE007-11080/ DKLU1008129	99824	26	M	159	3	20	Completed suicide; Brain damage	SUICIDE, SEVERE BRAIN INJURY
99824-BE032-11087/ DKLU1015776	99824	19	M	112	545	20	Completed suicide; Asphyxia	SUICIDE, DEATH ASPHYXADICON
99824-BE062-12067/ DKLU1011916	99824	57	M	207	4	24	Hip fracture	HIP FRACTURE
99824-BE064-13443/ DKLU1014539	99824	49	M	189	0	24	Myocardial infarction; Cardio- respiratory arrest	MYOCARDIAL INFARCTION, CARDIO- RESPIRATORY ARREST
99824-BE064-13484/ DKLU1020342	99824	48	M	38	715	16	Head injury	TRAUMA CAPITIS
99824-BG001- 18202/ DKLU1020120	99824	39	M	110	185	8	Myocardial infarction	MYOCARDIAL INFARCTION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-BG005- 30125/ DKLU1019693	99824	43	M	212	0	16	Completed suicide	SUICIDE
99824-CZ023-15647/ DKLU1015466	99824	59	F	296	0	20	Unknown cause of death	UNKNOWN
99824-DE003-10520/ DKLU1007840	99824	68	M	43	81	8	Fall; Head injury	SUDDEN FALL, HEAD INJURY
99824-DE010-14495/ DKLU1015330	99824	59	F	18	371	8	Completed suicide	SUICIDE
99824-EE001-15483/ DKLU1011415	99824	53	F	117	1	16	Asphyxia; Aspiration; Death	MECHANICAL ASPHYXIATION, ASPIRATION OF VOMIT- MASSES , FOUND DEAD
99824-EE003-15251/ DKLU1011494	99824	32	M	148	55	12	Completed suicide	SUICIDE
99824-EE005-15233/ DKLU1010351	99824	80	M	75	9	16	Cardiac failure acute; Myocardial ischaemia	ACUTE CARDIAC FAILURE, CHRONIC ISCHEMIC HEART DISEASE
99824-ES021-11309/ DKLU1017846	99824	41	M	524	209	20	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-FR013-10293/ DKLU1020021	99824	51	M	880	0	20	Unknown cause of death	UNKNOWN
99824-FR026-10259/ DKLU1020818	99824	34	F	61	1021	16	Drug toxicity; Alcohol poisoning; Accidental overdose	INTOXICATION WITH [MEDICATION AND] ALCOHOL, ACCIDENTAL OVERDOSE
99824-FR043-15076/ DKLU1011847	99824	24	M	17	80	4	Unknown cause of death	SUDDEN DEATH
99824-FR068-10442/ DKLU1009479	99824	29	F	45	0	20	Road traffic accident	DEATH IN A ROAD ACCIDENT
99824-FR095-10401/ DKLU1030547	99824	23	M	218	551	8	Completed suicide	HANGING [SUICIDE]
99824-GR001- 13971/ DKLU1023662	99824	55	M	1060	4	16	Lung neoplasm malignant	LUNG CANCER
99824-GR001- 15283/ DKLU1010997	99824	51	M	93	0	16	Cerebrovascular accident	ACUTE CEREBROVASCULAR ACCIDENT
99824-GR001- 15284/ DKLU1028927	99824	68	M	1413	7	16	Myocardial ischaemia	CORONARY HEART DISEASE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-GR001- 15297/ DKLU1014716	99824	63	M	205	81	8	Neoplasm malignant	THE PATIENT DIED DUE TO MALIGNANT TUMOUR, THE PATIENT DIED DUE TO MALIGNANT TUMOUR
99824-GR002- 14710/ DKLU1016356	99824	79	F	611	31	16	Unknown cause of death	UNKNOWN
99824-GR006- 16438/ DKLU1018001	99824	38	F	233	1	16	Cardiac arrest; Cardiac failure chronic; Obesity; Mental disorder	CARDIAC ARREST, CHRONIC CARDIAC FAILURE, CHRONIC CARDIAC FAILURE, OBESITY, PSYCHIATRIC DISORDER
99824-GR010- 16445/ DKLU1013136	99824	38	M	79	1	20	Myocardial infarction	INFARCT OF MYOCARDIUM
99824-HR009- 18310/ DKLU1024994	99824	57	M	165	342	12	Sudden death; Pyrexia	SUDDEN DEATH
99824-HU003- 14230/ DKLU1017137	99824	53	F	214	1	20	Completed suicide	COMPLETED SUICIDE DEFENESTRATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-HU003- 15712/ DKLU1012959	99824	26	M	108	0	16	Completed suicide; Poisoning; Overdose	SUICIDE, INTOXICATION, OVERDOSE
99824-HU010- 14071/ DKLU1014158	99824	26	M	73	390	20	Completed suicide	COMPLETED SUICIDE
99824-HU011- 14092/ DKLU1012416	99824	48	M	11	20	8	Pulmonary embolism	LUNG EMBOLISATION
99824-HU011- 14093/ DKLU1018608	99824	48	F	506	1	20	Pulmonary embolism	PULMONARY EMBOLISM
99824-HU018- 14302/ DKLU1015343	99824	41	F	247	0	6	Completed suicide; Overdose	SUICIDE, OVERDOSE
99824-HU018- 14309/ DKLU1011825	99824	53	F	135	107	12	Completed suicide; Poisoning	SUICIDE DEATH, INTOXICATION
99824-HU020- 14291/ DKLU1028015	99824	59	F	1429	1	8	Asphyxia	SUFFOCATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-HU022- 14123/ DKLU1008561	99824	30	M	28	1	16	Completed suicide	SUICIDE
99824-HU024- 14083/ DKLU1020279	99824	65	F	992	32	4	Pneumonia chlamydial; Pneumonia chlamydial; Acute respiratory distress syndrome; Septic shock; Cardiac arrest	PNEUMONIA CAUSED BY CHLAMYDIA, PNEUMONIA CAUSED BY CHLAMYDIA, ADULT RESPIRATORY DISTRESS SYNDROME, SEPTICAL SHOCK, CARDIAC ARREST
99824-HU024- 14088/ DKLU1021210	99824	29	F	36	1007	16	Cardiomyopathy	MYOCARDIAL DEGENERATION, MYOCARDIAL DEGENERATION
99824-HU027- 15761/ DKLU1014688	99824	55	F	73	263	16	Respiratory failure; Vascular insufficiency	RESPIRATORY AND BLOOD CIRCULATORY INSUFFICIENCY, RESPIRATORY AND BLOOD CIRCULATORY INSUFFICIENCY
99824-IN006-30725/ DKLU1021163	99824	25	M	116	1	12	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-KR007- 16492/ DKLU1013726	99824	36	M	60	1	20	Completed suicide	SUICIDE
99824-KR009- 16474/ DKLU1017245	99824	39	F	333	1	24	Unknown cause of death	UNKNOWN
99824-LT005-18781/ DKLU1024898	99824	22	M	566	28	12	Completed suicide; Head injury	JUMP FROM 9TH FLOOR, HEAD TRAUMA
99824-LV005-11230/ DKLU1019375	99824	61	F	153	14	4	Cardiac failure acute; Pulmonary oedema; Pneumonia aspiration	ACUTE HEART FAILURE, PULMONARY OEDEMA, BILATERAL ASPIRATION PNEUMONIA
99824-MY001- 12263/ DKLU1020154	99824	34	M	421	1	16	Cardiomyopathy	CARDIOMYOPATHY
99824-MY002- 16017/ DKLU1018738	99824	40	F	538	1	16	Acute myocardial infarction	ACUTE MYOCARDIAL INFARCTION
99824-MY003- 16743/ DKLU1013887	99824	32	F	36	86	20	Urinary tract infection; Septic shock; Fluid intake reduced; Dehydration	URINARY TRACT INFECTION, SEPTICAEMIC SHOCK, POOR ORAL INTAKE, DEHYDRATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-MY007- 16693/ DKLU1018101	99824	35	F	333	1	16	Unknown cause of death	UNKNOWN
99824-MY007- 16717/ DKLU1014325	99824	21	F	71	1	12	Unknown cause of death	UNKNOWN
99824-MY009- 18670/ DKLU1023945	99824	63	M	85	89	16	Road traffic accident; Pneumonia aspiration	MOTOR VEHICLE ACCIDENT, ASPIRATION PNEUMONIA
99824-MY012- 13335/ DKLU1019625	99824	34	M	65	1	16	Asthma; Respiratory failure; Asphyxia	ASTHMA, RESPIRATORY INSUFFICIENCY, SUFFOCATION
99824-PH001-12318/ DKLU1017903	99824	30	F	331	1	12	Acute myocardial infarction; Head injury; Cardio- respiratory arrest	ACUTE MYOCARDIAL INFARCTION, HEAD INJURY, CARDIO- RESPIRATORY ARREST
99824-PH001-16607/ DKLU1023891	99824	41	M	1028	6	12	Pneumonia; Sepsis; Cardiac arrest	PNEUMONIA, SEPSIS, CARDIAC ARREST
99824-PH001-16905/ DKLU1013218	99824	24	M	163	3	12	Aspiration; Asphyxia	ASPIRATION, ASPHYXIATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-PH001-17568/ DKLU1014085	99824	27	M	150	0	16	Fall; Cerebral haemorrhage traumatic	FALL, CEREBRAL HEMORRHAGE SECONDARY TO HEAD TRAUMA
99824-PH001-18949/ DKLU1026950	99824	32	F	60	142	12	Cerebrovascular accident; Hypertension	CEREBROVASCULAR ACCIDENT, HYPERTENSION STAGE II
99824-PH006-16289/ DKLU1018849	99824	38	M	678	1	20	Unknown cause of death	UNDETERMINED CAUSE OF DEATH
99824-PH007-16556/ DKLU1028549	99824	35	M	1323	1	16	Myocardial infarction	MYOCARDIAL INFARCTION
99824-PH009-17748/ DKLU1021087	99824	38	M	355	1	12	Unknown cause of death	UNKNOWN
99824-PH010-18896/ DKLU1024974	99824	58	F	395	0	12	Myocardial infarction	MYOCARDIAL INFARCTION
99824-PH010-18921/ DKLU1030553	99824	39	F	414	0	12	Unknown cause of death	UNKNOWN
99824-PH013-18882/ DKLU1026897	99824	33	M	549	147	12	Completed suicide; Cardiac arrest; Intentional overdose	SUICIDE , CARDIAC ARREST DUE TO DRUG OVERDOSE , OVERDOSE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-PL005-14017/ DKLU1026513	99824	35	M	1032	1	12	Aortic aneurysm rupture	DISSECTING ANEURISM OF AORTA ASCENDENS RUPTURE
99824-PL007-15096/ DKLU1025808	99824	52	F	707	1	16	Unknown cause of death	DEATH DURING SLEEP
99824-PL013-16373/ DKLU1016499	99824	36	F	135	155	16	Unknown cause of death	UNKNOWN
99824-PL015-17908/ DKLU1016877	99824	23	M	60	0	8	Completed suicide	DEATH - SUICIDE
99824-PL025-16353/ DKLU1013530	99824	79	F	253	4	12	Arrhythmia; Torsade de pointes	CARDIAC ARRHYTHMIAS, TORSADE DE POINTES
99824-PL030-15515/ DKLU1016295	99824	32	F	175	1	8	Arrhythmia	ARRHYTHMIA
99824-PL039-17436/ DKLU1018217	99824	67	M	428	46	16	Unknown cause of death	DEATH NOS
99824-PL039-17456/ DKLU1014285	99824	69	F	138	0	8	Pneumonia	PNEUMONIA
99824-PT005-11870/ DKLU1027012	99824	37	F	1378	1	20	Urinary tract infection; Sepsis	URINARY INFECTION, SEPSIS

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-RU006- 31180/ DKLU1021294	99824	30	M	106	10	16	Pulmonary embolism; Endocarditis bacterial	PULMONARY ARTERY THROMBOEMBOLY, ACUTE BACTERIAL ENDOCARDITIS OF MITRAL VALVE, ACUTE BACTERIAL ENDOCARDITIS OF MITRAL VALVE
99824-RU011- 30169/ DKLU1019840	99824	34	M	159	1	16	Myocardial ischaemia; Varicose vein	CHRONIC CORONARY HEART DISEASE, CHRONIC CORONARY HEART DISEASE, VARICOSE VEINS LOWER LIMBS, VARICOSE VEINS LOWER LIMBS
99824-RU020- 31239/ DKLU1024719	99824	54	M	133	12	12	Cardiac failure	CARDIAC FAILURE
99824-SG004-15838/ DKLU1020866	99824	33	M	153	161	16	Completed suicide	SUICIDE
99824-SK004-15022/ DKLU1011800	99824	50	F	57	15	16	Gastric ulcer perforation	ACUTE GASTRIC ULCER WITH PERFORATION, ACUTE GASTRIC ULCER WITH PERFORATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-SK006-11799/ DKLU1010121	99824	60	F	94	0	16	Obstructive chronic bronchitis with acute exacerbation	ACUTE EXACERBATION OF BRONCHITIS CHRONICA
99824-SK006-16871/ DKLU1015321	99824	48	F	125	196	8	Deep vein thrombosis; Pulmonary embolism	THROMBOSIS OF VEINS OF LOWER EXTREMITIES, THROMBOSIS OF VEINS OF LOWER EXTREMITIES, PULMONARY EMBOLISM
99824-TH001-16125/ DKLU1016746	99824	47	M	385	1	24	Respiratory failure; Shock	RESPIRATORY FAILURE, BLOOD CIRCULATORY FAILURE
99824-TH002-16149/ DKLU1016470	99824	36	F	479	1	12	Arrhythmia	CARDIAC ARRHYTHMIA NOS
99824-TH003-16165/ DKLU1026509	99824	39	F	672	547	16	Colon cancer	COLON CANCER
99824-TH006-16050/ DKLU1028916	99824	31	F	1189	1	16	Completed suicide	SUICIDE
99824-TH007-11586/ DKLU1015255	99824	28	M	85	1	16	Sudden death; Electrolyte imbalance; Emphysema	SUDDEN UNEXPLAINED DEATH, ELECTROLYTE IMBALANCE, EMPHYSEMA

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-TH010-18137/ DKLU1024000	99824	36	F	65	272	20	Cardiac arrest	CARDIAC ARREST
99824-TR006-13031/ DKLU1012068	99824	52	F	333	1	16	Gastrointestinal disorder; Death	MALIGNANCY, DEATH
99824-TR009-12653/ DKLU1024454	99824	57	M	1267	10	12	Cardio-respiratory arrest	CARDIOPULMONARY ARREST
99824-UA004- 12420/ DKLU1018149	99824	30	F	17	3	12	Completed suicide	COMPLETED SUICIDE
99824-UA014- 32728/ DKLU1025778	99824	24	M	198	1	16	Physical assault	VIOLENT DEATH
99824-UA015- 40219/ DKLU1025775	99824	25	M	90	3	12	Unknown cause of death	UNEXPECTED DEATH

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
Treatment = Risperidone								
99824-BE001-13514/ DKLU1020362	99824	29	M	51	634	3	Completed suicide	SUICIDE
99824-BE030-11011/ DKLU1013048	99824	63	F	66	443	2	Recurrent cancer	RECURRENT CANCER
99824-BE039-11959/ DKLU1008566	99824	34	F	35	707	4	Cervix carcinoma; Metastatic neoplasm	SPINOCELLULAR EPITHELIOMA, METASTATIC
99824-BE039-11966/ DKLU1023052	99824	23	M	8	1260	12	Completed suicide	COMPLETED SUICIDE
99824-BE041-11018/ DKLU1013925	99824	64	F	513	0	1	Breast cancer	CANCER OF THE BREAST 13 YEARS BEFORE THE STUDY
99824-BE065-12744/ DKLU1027727	99824	39	M	450	996	6	Lung neoplasm	PULMONARY NEOPLASIA
99824-BE072-12892/ DKLU1013162	99824	53	M	299	0	3	Aortic aneurysm rupture	AORTIC ANEURYSM RUPTURE
99824-BE074-12280/ DKLU1026318	99824	38	F	85	1460	9	Completed suicide	SUICIDE
99824-BE082-12794/ DKLU1024560	99824	33	M	268	1095	6	Hypercapnia	CARBONARCOSE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-BG001- 30374/ DKLU1023742	99824	55	M	358	1	2	Hepatic neoplasm malignant; Cardiac failure acute	HEPATIC CARCINOMA, ACUTE HEART FAILURE
99824-CZ003-13874/ DKLU1022086	99824	57	M	883	9	6	Drowning	DROWNING
99824-CZ018-14582/ DKLU1014408	99824	49	F	225	1	6	Pneumonia	PNEUMONIA
99824-CZ023-15637/ DKLU1015818	99824	52	F	538	0	4	Cerebral haemorrhage	CEREBRAL HAEMORRHAGE
99824-DE010-12995/ DKLU1008523	99824	69	M	57	7	4	Lymphoedema	LYMPHOEDEMA IN PULMONARY CARCINOMA
99824-DE024-10522/ DKLU1010195	99824	23	M	94	6	2	Intentional overdose	DRUG INTOXICATION
99824-DE030-15578/ DKLU1014025	99824	25	M	57	231	4	Intentional overdose	SUSPICION OF DRUG INTOXICATION
99824-DE044-12960/ DKLU1011144	99824	59	F	183	59	6	Brain neoplasm	INTRACEREBRAL TUMOR
99824-DE080-11699/ DKLU1011583	99824	37	M	55	1	6	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-EE005-15459/ DKLU1012259	99824	35	M	275	1	2	Completed suicide; Asphyxia	STRANGULATION SUICIDE, STRANGULATION
99824-FR009-10107/ DKLU1008506	99824	40	M	67	1	6	Completed suicide	SUICIDE BY HANGING
99824-FR026-10077/ DKLU1008105	99824	24	M	131	4	4	Completed suicide	SUICIDE
99824-FR026-10197/ DKLU1011519	99824	27	M	30	380	8	Unknown cause of death	UNATTENDED DEATH, FOUND DEAD
99824-FR069-10205/ DKLU1020705	99824	41	F	1147	4	16	Metastases to central nervous system	CEREBRAL METASTASIS
99824-FR080-10105/ DKLU1009262	99824	39	F	8	0	2	Completed suicide	SUICIDE
99824-GB003- 10807/ DKLU1010524	99824	61	F	174	41	6	Chronic obstructive pulmonary disease; Bronchopneumonia	CHRONIC OBSTRUCTIVE AIRWAYS DISEASE, BRONCHOPNEUMONIA
99824-GB004- 14421/ DKLU1019435	99824	77	F	866	9	10	Cardiac failure	HEART FAILURE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-GR001- 15282/ DKLU1011564	99824	64	M	147	0	6	Non-small cell lung cancer; Metastases to central nervous system; Epilepsy	NON SMALL CELL LUNG CANCER, BRAIN METASTASES, EPILEPTIC SEIZURES
99824-GR004- 13986/ DKLU1023664	99824	64	F	840	9	4	Cardio-respiratory arrest; Hypoxic encephalopathy	CARDIO-RESPIRATORY ARREST, HYPOXEMIC ENCEPHALOPATHY
99824-HR007- 18322/ DKLU1020712	99824	56	M	273	2	6	Epilepsy; Cardiopulmonary failure	EPI SEIZURES , CARDIO- RESPIRATORY INSUFFICIENCY
99824-HR009- 30015/ DKLU1025007	99824	74	F	293	87	2	Death; Cardiac failure; Pneumonia primary atypical; Sialoadenitis	DEATH, HEART FAILURE, ATYPICAL PNEUMONIA, SIALOADENITIS
99824-HR010- 18312/ DKLU1024605	99824	39	M	484	0	8	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-HU003- 14245/ DKLU1017968	99824	45	M	748	1	2	Hepatic cirrhosis; Hepatorenal syndrome; Granulomatous liver disease; Cardiopulmonary failure; Ascites	CIRRHOSIS LIVER, HEPATORENAL SYNDROME, HEPATITIS GRANULOMATOUS, HEPATITIS GRANULOMATOUS, INSUFFICIENT CARDIORESPIRATORY, ASCITES
99824-HU003- 15724/ DKLU1023719	99824	18	F	108	227	8	Completed suicide	SUICIDE ATTEMPT FATAL OUTCOME
99824-HU024- 14333/ DKLU1009507	99824	72	F	6	0	4	Pulmonary embolism	PULMONARY EMBOLISM
99824-HU028- 15810/ DKLU1011708	99824	35	M	113	1	4	Asphyxia	DEATH SUFFOCATION
99824-IN024-31010/ DKLU1028013	99824	66	F	261	5	4	Unknown cause of death	UNKNOWN
99824-KR006- 16884/ DKLU1028240	99824	55	F	168	1	3	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-KR010- 13457/ DKLU1017502	99824	31	F	220	0	8	Completed suicide	SUICIDE
99824-KR010- 17742/ DKLU1017631	99824	27	M	287	1	12	Completed suicide	SUICIDE
99824-LT002-12819/ DKLU1018526	99824	40	F	13	0	4	Completed suicide; Asphyxia	SUICIDE , ASPHYXIA DUE TO HANGING
99824-LT005-11065/ DKLU1019419	99824	45	M	253	0	6	Cardiac failure; Alcohol poisoning	HEART FAILURE, ALCOHOL INTOXICATION
99824-MY002- 15883/ DKLU1026683	99824	27	M	420	836	4	Cerebral toxoplasmosis	CEREBRAL TOXOPLASMOSIS
99824-MY004- 16066/ DKLU1019482	99824	45	F	14	7	2	Sepsis; Pneumonia; Infection in an immunocompromised host	SEPTICAEMIA, PNEUMONIA, INFECTION IN PATIENT WITH AIDS
99824-MY006- 15360/ DKLU1024465	99824	46	M	546	1	3	Sudden death	SUDDEN DEATH
99824-NO020- 10638/ DKLU1012284	99824	53	M	51	3	3	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-PH001-12322/ DKLU1014552	99824	48	M	38	0	1	Meningitis tuberculous; Sepsis	CNS INFECTION PROBABLY TUBERCULOSIS VS. BACTERIAL, SEPSIS
99824-PH001-16588/ DKLU1023630	99824	44	M	1022	1	2	Cardio-respiratory arrest	CARDIO-RESPIRATORY ARREST
99824-PH001-16601/ DKLU1026659	99824	38	M	1151	0	2	Convulsion; Blood electrolytes abnormal	SEIZURE DISORDER, ELECTROLYTE DISTURBANCES, ELECTROLYTE DISTURBANCES
99824-PH001-16950/ DKLU1014848	99824	53	F	86	229	2	Pneumonia	PNEUMONIA
99824-PH001-17089/ DKLU1014673	99824	41	M	67	219	2	Acute myocardial infarction	ACUTE MYOCARDIAL INFARCTION
99824-PH001-17106/ DKLU1015606	99824	35	M	306	1	2	Pancreatitis acute	ACUTE PANCREATITIS
99824-PH002-16978/ DKLU1019918	99824	35	M	538	1	6	Acute myocardial infarction	ACUTE MYOCARDIAL INFARCTION
99824-PH003-16315/ DKLU1023957	99824	36	M	640	1	1	Sudden death	UNKNOWN

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-PH007-16582/ DKLU1015201	99824	25	M	299	0	6	Completed suicide	SUICIDE
99824-PH007-17769/ DKLU1016519	99824	36	M	231	1	4	Status asthmaticus	STATUS ASTHMATICUS
99824-PH009-17766/ DKLU1020446	99824	48	M	99	188	0.5	Multiple injuries	MULTIPLE PHYSICAL INJURIES
99824-PL013-16371/ DKLU1016685	99824	45	M	272	0	5	Completed suicide	SUICIDE BY HANGING
99824-PT007-13562/ DKLU1013647	99824	53	F	259	161	1.5	Brain neoplasm	CEREBRAL TUMOUR
99824-PT021-13615/ DKLU1016132	99824	57	M	220	1	1	Completed suicide	SUICIDE
99824-PT021-13627/ DKLU1016133	99824	71	M	140	1	1	Myocardial infarction	HEART ATTACK
99824-RU011- 30167/ DKLU1026917	99824	66	M	657	0	2	Cardiac failure acute; Myocardial ischaemia	ACUTE HEART FAILURE, CARDIAC ISCHEMIA
99824-RU019- 31275/ DKLU1021111	99824	34	M	44	1	3	Drowning	DROWNING ACCIDENT

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-RU020- 40117/ DKLU1030316	99824	39	F	245	0	8	Completed suicide	SUICIDE
99824-SG003-15848/ DKLU1023318	99824	60	F	1009	1	2	Completed suicide	SUICIDE RESULTING IN DEATH
99824-SK001-15686/ DKLU1015328	99824	55	F	472	0	4	Hydrothorax	FLUIDOTHORAX
99824-SK006-14477/ DKLU1016817	99824	75	M	710	2	4	Myocardial ischaemia	ISCHEMIC HEART DISEASE
99824-SK006-14485/ DKLU1010418	99824	68	M	162	0	1.5	Colon cancer; Colon cancer	CARCINOMA COLI FLEXURA LIENALIS, CARCINOMA COLI FLEXURA LIENALIS
99824-SK006-16873/ DKLU1017309	99824	47	M	413	112	14	Peptic ulcer perforation; Peritonitis	PERFORATION PEPTIC ULCER, DIFFUSE PERITONITIS
99824-SK008-15010/ DKLU1020750	99824	63	F	409	64	4	Cardiac failure; Gallbladder cancer	HEART FAILURE, CANCER OF THE GALLBLADDER
99824-SK009-11805/ DKLU1012327	99824	40	M	56	1	5	Completed suicide	SUICIDE

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-TH005-17037/ DKLU1019321	99824	24	M	368	4	8	Unknown cause of death	UNKNOWN
99824-TH006-16033/ DKLU1016529	99824	33	M	488	0	6	Cerebrovascular disorder	R/O CEREBROVASCULAR DISEASE
99824-TH006-16048/ DKLU1022845	99824	43	M	927	5	3	Cerebral infarction	CEREBRAL INFARCT
99824-TH007-16773/ DKLU1013173	99824	27	M	150	3	6	Pneumonia aspiration; Convulsion; Electrolyte imbalance	ASPIRATED PNEUMONIA , SEIZURE, ELECTROLYTE IMBALANCE
99824-TH007-16800/ DKLU1027312	99824	41	F	1132	0	3	Completed suicide; Overdose	SUICIDE, OVERDOSE
99824-TH008-17023/ DKLU1030302	99824	43	M	877	53	3	Completed suicide	SUICIDE
99824-TR006-13023/ DKLU1010101	99824	39	M	168	0	6	Completed suicide	SUICIDE
99824-TR007-12606/ DKLU1028044	99824	35	F	1370	155	6	Asphyxia	FOOD ASPHYXIA
99824-TR010-13069/ DKLU1020122	99824	43	F	960	6	6	Diabetic coma	DIABETIC COMA
99824-TR019-13696/ DKLU1010938	99824	26	M	172	0	4	Carbon monoxide poisoning	CARBON MONOXIDE INTOXICATION

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia, Study 99824 (SCoP)

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
99824-TR025-17270/ DKLU1014104	99824	57	F	206	0	3	Non-Hodgkin's lymphoma	NON HODGKIN DIFFUSE LENFOMA
99824-UA004- 11278/ DKLU1020079	99824	44	F	209	1	2	Completed suicide	COMPLETED SUICIDE
99824-UA012- 33557/ DKLU1025756	99824	26	M	15	0	6	Completed suicide	COMPLETED SUICIDE

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

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NDA 20-644
SERDOLECT (Sertindole)

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
Treatment = Sertindole								
98604-FI019-965/ DKLU0200479	98604	37	F	690	--	16	Pulmonary Embolism	PULMONARY EMBOLISM
98604-FI083-946/ DKLU0200494	98604	30	F	--	--	12	Unknown cause of death	UNKNOWN
98604-EE005-825/ DKLU0200530	98604	26	F	685	--	4	Overdose	OVERDOSE
98604-NO018-1516/ DKLU0200535	98604	44	M	101	21	12	Myocardial infarction	ACUTE MYOCARDIAL INFARCTION
98604-NO062-1624/ DKLU0200589	98604	27	F	--	--	32	Completed Suicide	SUICIDE
98604-CH581-1662/ DKLU0200612	98604	54	F	151	0	48	Large intestine perforation	ISCHEMIC COLON PERFORATION
98604-BE206/ DKLU0200625	98604	47	M	--	--	--	Unknown cause of death	DEATH, SUICIDE, INFARCTION
98604-BE363/ DKLU0980874	98604	80	M	60	0	16	Myocardial infarction	ACUTE PULMONARY EDEMA
98604-AL3193/ DKLU0990011	98604	59	M	406	0	20	Completed suicide	SUICIDE
98604-NL31/ DKLU0981441	98604	56	M	110	1	16	Cerebral hemorrhage	CEREBRAL VASCULAR ACCIDENT
98604-NL179/ DKLU0981444	98064	50	M	294	--	4	Unknown cause of death	UNKNOWN

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term^a	Investigator Term
98604-NL821/ DKLU0981460	98604	27	M	745	1	8	Lung infiltration, ECG QT prolonged	CARDIAC DYSFUNCTION WITH SEVERE BILATERAL BRONCHOPNEUMONIA
98604-HU865/ DKLU0981475	98604	58	M	45	0	16	Completed suicide	SUICIDE
98604-NL837/ DKLU0981481	98604	63	F	616	0	24	Unknown cause of death	UNKNOWN
98604-HU636/ DKLU0981574	98604	34	F	48	0	16	Suicide attempt	SUICIDE
98604-HU726/ DKLU0981575	98604	31	F	10	1	12 (120 tablets of sertindole)	Overdose, cardiac arrest, completed suicide	HEART ARREST, SUICIDE ATTEMPT, OVERDOSE
98604-AU797/ DKLU0981600	98604	78	F	14	0	12	Cardiac arrest	SUDDEN CARDIAC ARREST
98604-NL419/ DKLU0981645	98604	24	F	--	--	--	Sudden death	HEART FAILURE
98604-AL2729/ DKLU0981661	98604	32	M	195	0	20	Completed suicide	SUICIDE
98604-AL1520/ DKLU0981778	98604	79	M	371	0	12	Unknown cause of death	DEATH, LOBAR PNEUMONIA
98604-AL1533/ DKLU0981779	98604	25	M	116	0	20	Completed suicide	SUICIDE
98604-AL2914/ DKLU0990027	98604	69	F	168	1	4	Myocardial infarction	HEART ATTACK

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
98604-UK222/ DKLU0990061	98604	46	M	215	0	16	Neoplasm malignant	CANCER OF THE PENIS
98604-AU663/ DKLU0990252	98604	74	M	25	10	4	Unknown cause of death	FALL INJURY
98604-NL124/ DKLU0990602	98604	68	M	208	22	8	Dyspnea, somnolence, pyrexia, pneumonia, dysphagia	PNEUMONIA
98604-HU121/ DKLU0990702	98604	71	F	5	27	8	Bladder cancer, renal impairment, azotemia	UNKNOWN
DKLU0961236§	98604	28	F	69	1	12	Completed suicide	SUICIDE
DKLU0970369§	98604	39	F	115	0	16	Unknown cause of death	UNKNOWN
DKLU0980205§	98604	59	F	12	0	4	Myocardial Infarction	MYOCARDIAL INFARCTION
DKLU0980295§	98604	59	F	15	1	16	Unknown cause of death	UNKNOWN
DKLU0980617§	98604	69	F	25	0	20	Unknown cause of death	EXITUS LETHALIS
DKLU0980666§	98604	32	F	38	0	20	Unknown cause of death	UNKNOWN
DKLU0980685§	98604	33	F	28	0	24	Sudden death	SUDDEN DEATH
DKLU0980690§	98604	58	M	23	0	8	Cardiac arrest	CARDIOPULMONARY ARREST
DKLU0981015§	98604	--	F	~42	--	24	Completed suicide	SUICIDE
DKLU0981108§	98604	25	M	243	0	24	Unknown cause of death	SUDDEN UNEXPECTED DEATH
DKLU0981128§	98604	32	F	283	0	16	Unknown cause of death	SUDDEN UNEXPLAINED DEATH
DKLU0981226§	98604	52	M	31	0	20	Pulmonary embolism	PULMONARY EMBOLISM
DKLU0981350§	98604	30	M	242	0	20	Unknown cause of death	UNKNOWN

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term^a	Investigator Term
DKLU0981625§	98604	68	M	629	1	16	Cardiac asthma, cardiac failure, myocardial infarction, sudden death	SUDDEN DEATH
DKLU0990017§	98604	58	F	315	0	16	Unknown cause of death	UNKNOWN
DKLU0990457§	98604	51	F	359	0	20	Epilepsy, myocardial infarction, pneumonia	MYOCARDIAL INFARCTION
DKLU0990769§	98604	32	F	--	--	20	Completed suicide	SUICIDE
DKLU0991322§	98604	62	M	--	--	4	Akinesia, pneumonia	DEATH DUE TO PNEUMONIA
97201- -S00112/ DKLU 0980556	97201	20	M	~120	--	20	Suicide attempt	SUICIDE ATTEMPT
97201- -S00118/ DKLU 0980927	97201	51	M	166	12	32	Myocardial infarction	CARDIAC INFARCTION
97201- -S00147/ DKLU 0981423	97201	62	F	133	79	18	Aspiration, Cerebral ischaemia	UNKNOWN
97201- -S00172/ DKLU 0981775	97201	39	M	323	11	4	Unkown cause of death	UNKNOWN
97201- -S00264/ DKLU 0980906	97201	28	M	81	32	20	Asphyxia, Cardiac arrest, Subarachnoid haemorrhage	ASYSTOLY IN COURSE OF DROWNING
97201- -S00373/ DKLU 0981149	97201	34	M	156	0	16	Injury	UNKNOWN
97201- -S00386/ DKLU 0981217	97201	42	M	121	0	16	Completed suicide	SUICIDE
97201- -S00579/ DKLU 0980941	97201	72	F	60	0	4	Unknown cause of death	UNKNOWN

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term^a	Investigator Term
97201- -S00585/ DKLU 0980884	97201	41	F	--	--	16	Respiratory arrest, Suicide attempt	SUICIDE ATTEMPT
97201- -S00974/ DKLU 0981406	97201	42	M	21	1	16	Unkown cause of death	UNKNOWN
97201- -S01090/ DKLU 0990392	97201	50	F	14	8	12	Cerebrovascular accident	STROKE
97201- -R00011/ DKLU 0981018	97201	74	F	--	--	--	Pneumonia	SUDDEN DEATH
Treatment = Olanzapine								
DKLU0980954§	98604	38	F	11	0	15	Cardiac failure, hepatic steatosis, renal cortical necrosis	SUDDEN DEATH
Treatment = Combination								
98604-HU205-1117/ DKLU0200586	98604	45	F	204	30	24	Unknown cause of death	STUPOR STATE
Treatment = Reference Group (None Identified)								
97201- -R00013/ DKLU 0981482	97201	53	M	--	--	--	Lung neoplasm malignant	LUNG CANCER
97201- -R00050/ DKLU 0980091	97201	81	M	--	--	--	Injury, Pneumonia	FALL
97201- -R00319/ DKLU 0981243	97201	26	M	--	--	--	Suicide attempt	SUICIDE ATTEMPT
97201- -R00398/ DKLU 0981519	97201	42	M	--	--	--	Injury	UNKNOWN
97201- -R00462/ DKLU 0981244	97201	90	F	--	--	--	Convulsion, Pyrexia, Sepsis	SEPTICAEMIA

Clinical Review
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 NDA 20-644
 SERDOLECT (Sertindole)

Death Line Listing: Completed Non-Japanese - Other Studies in Schizophrenia								
Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term^a	Investigator Term
97201- -R00463/ DKLU 0981100	97201	69	M	--	--	--	Sepsis	SEPTICAEMIA
97201- -R00608/ DKLU 0981782	97201	59	M	--	--	--	Myocardial infarction, Pneumonia	HEART ATTACK, PNEUMONIA
97201- -R00629/ DKLU 0981304	97201	61	M	--	--	--	Aspiration, Cardiac arrest, Coma	ASPIRATION
Did Not Receive Study Drug								
97201- -R11000/ DKLU 0981593	97201	34	M	--	--	--	Injury	TRAFFIC ACCIDENT

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

Death Line Listing: Completed Japanese Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day) Treatment = Sertindole	MedDRA Preferred Term ^a	Investigator Term
M95-346- -2307101/ DKLU 0950212	M95-346	35	M	179	1	16	Completed suicide	--
M95-346- -3442/ DKLU 0950311	M95-346	53	M	212	10	8	Unknown cause of death	Unknown
M96-542- -/ DKLU 0970198	M96-542	49	M	19	--	--	Completed suicide	SUICIDE

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

Death Line Listing: Ongoing Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day) Treatment = Sertindole		Investigator Term	
11286-CN007-1247/ DKLU 1028087	11286	34	F	70	13		Completed suicide	SUICIDE	
99823-NO004-558- NPU/ DKLU 1018953	99823	62	F	507	0	24	Drowning, Completed suicide	SUICIDE, POSSIBLE SUICIDE BY DROWNING	
99823-BE001-NPU/ DKLU 1017852	99823	46	M	937	0	16	Unknown cause of death	UNKNOWN	
99823-BE020-NPU- 133/ DKLU 1013074	99823	36	F	--	2	12	Completed suicide, Overdose	COMPLETED SUICIDE, OVERDOSE	
Sertindole-NPU- -/ DKLU 1013714	Sertindole -NPU	59	F	383	15	4	Dysphagia, Cachexia, Dehydration	DEHYDRATION, SWALLOW PROBLEMS, CACHEXIA	

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

Death Line Listing: Ongoing Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day) Treatment = Sertindole		Investigator Term	
11286-CN007-1247/ DKLU 1028087	11286	34	F	70	13		Completed suicide	SUICIDE	
99823-NO004-558- NPU/ DKLU 1018953	99823	62	F	507	0	24	Drowning, Completed suicide	SUICIDE, POSSIBLE SUICIDE BY DROWNING	
99823-BE001-NPU/ DKLU 1017852	99823	46	M	937	0	16	Unknown cause of death	UNKNOWN	
99823-BE020-NPU-	99823	36	F	--	2	12	Completed suicide, Overdose	COMPLETED SUICIDE,	

Death Line Listing: Ongoing Studies

Unique Patient ID/ DLKU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death
					Days Since Last Dose	Last Dose (total mg/day)		Investigator Term
133/ DKLK 1013074								OVERDOSE
Sertindole-NPU- -/ DKLU 1013714	Sertindole -NPU	59	F	383	15	4	Dysphagia, Cachexia, Dehydration	DEHYDRATION, SWALLOW PROBLEMS, CACHEXIA

^a The lower level term "Unknown cause of death" maps to the preferred term "death."

Death Line Listing: Spontaneous Reports

Unique Patient ID/ DKLU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		MedDRA Preferred Term ^a	Cause of Death Investigator Term
					Days Since Last Dose	Last Dose (total mg/day) Treatment = Sertindole		
DKLU0200521	--	91	F	497	40 -No death date on the CIOM	8 4	Unknown cause of death	UNKNOWN
DKLU0200614	--	43	F	926	0 - 5	16	Electrocardiogram QT prolonged, Overdose, Sudden death, Suicide attempt, Ventricular fibrillation	SUDDEN DEATH, OVERDOSE, SUICIDE ATTEMPT, VENTRICULAR FIBRILLATION, QT PROLONGED
DKLU0960858	--	37	F	92	0	24	Unknown cause of death	UNKNOWN
DKLU0961022	--	45	M	--	--	24	Unknown cause of death	UNKNOWN
DKLU0961069	--	76	F	2	-28	4	Pneumonia	BRONCHOPNEUMONIA
DKLU0961070	--	77	F	--	--	16	Vomiting, Abdominal pain, Intestinal obstruction	INTESTINAL OBSTRUCTION
DKLU0961084	--	70	M	39	0	4	Asphyxia	UNKNOWN
DKLU0970165	--	36	F	44	0	16	Pulmonary embolism, Malaise	PULMONARY EMBOLISM
DKLU0970285	--	79	M	--	--	8	Sudden death	SUDDEN DEATH
DKLU0970286	--	40	F	--	--	24	Death	ARRHYTHMIA
DKLU0970416	--	50	M	62	1	16	Unknown cause of death	UNKNOWN
DKLU0970765	--	49	F	226	0	12	Completed suicide	SUICIDE
DKLU0970825	--	35	M	15	1	24	Unknown cause of death	UNKNOWN
DKLU0980210	--	41	F	--	--	16	Unknown cause of death	UNKNOWN
DKLU0980254	--	32	F	22	1	20	Sudden death	UNKNOWN
DKLU0980549	--	27	F	587	1	16	Unknown cause of death	UNKNOWN

Death Line Listing: Spontaneous Reports

Unique Patient ID/ DKLU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)		
							MedDRA Preferred Term ^a	Investigator Term
DKLU0980639	--	37	M	173	0	20	Lung neoplasm malignant, Sudden death, Pneumonia	SUDDEN DEATH
DKLU0980687	--	49	F	5	4	16	Cardiac arrest, Pulmonary embolism	UNKNOWN
DKLU0980710	--	36	M	270	--	4	Cardiac arrest	CARDIO-RESPIRATORY STOP
DKLU0980812	--	61	F	86	1	16	Unknown cause of death	UNKNOWN
DKLU0980983	--	65	F	16	0	20	Pulmonary embolism	PULMONARY THROMBOEMBOLISM
DKLU0981168	--	34	M	14	1	8	Unknown cause of death	UNKNOWN
DKLU0981274	--		F	21	0	16	Suicide attempt	SUICIDE ATTEMPT
DKLU0981281	--	37	M	280	0	16	Unknown cause of death	UNKNOWN
DKLU0981452	--	58	M	168	0	16	Nasal congestion, Aspiration	UNKNOWN
DKLU0981503	--	40	F	4	1	16	Aspiration	ASPIRATION
DKLU0981594	--	38	F	--	--	12	Sudden death	SUDDEN DEATH
DKLU0990250	--	--	F	369	2	16	Cardiac failure, Cerebrovascular accident	STROKE
DKLU0990781	--	45	F	--	--	26	Unknown cause of death	UNKNOWN
DKLU0991091	--	--	F	147	0	16	Completed suicide	SUICIDE UNDER PSYCHOSIS
DKLU0991313	--	30	F	607	0	28	Unknown cause of death	UNKNOWN
DKLU0991684	--	48	M	736	8	24	Suicide attempt	SUICIDE ATTEMPT
DKLU1002707	--	36	F	--	--	16	Sudden death	SUDDEN UNEXPECTED DEATH
DKLU1026159	--	25	F	--	0	~16	Unknown cause of death	UNKNOWN
DKLU1027923	--	55	F	10	1	12	Unknown cause of death	UNKNOWN
DKLU1028445	--	--	F	--	--	--	Unknown cause of death	UNKNOWN
DKLU1030971	--	51	M	--	--	--	Cardiac arrest	ACUTE HEART ARREST

Death Line Listing: Spontaneous Reports

Unique Patient ID/ DKLU Number	Last Study Number	Age (years)	Sex	Duration of Exposure (days)	Last Study Drug		Cause of Death	
					Days Since Last Dose	Last Dose (total mg/day)	MedDRA Preferred Term ^a	Investigator Term
DKLU1032702	--	43	M	--	--	--	Unknown cause of death	UNKNOWN
DKLU0991172	--	44	M	41	2	3	Cardiac arrest	CARDIAC ARREST

Appendix C

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
Cardiac disorders	Acute myocardial infarction	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Arrhythmia	0	1 (0.04)	0	3 (0.06)	0	0	0	4 (0.02)
	Arteriosclerosis coronary artery	0	1 (0.04)	0	0	0	0	0	1(<0.01)
	Cardiac arrest	0	1 (0.04)	2 (0.02)	1 (0.02)	0	0	0	4 (0.02)
	Cardiac failure	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Cardiac failure acute	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Cardiac failure chronic	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Cardiomyopathy	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Cardio-respiratory arrest	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Myocardial infarction	0	1 (0.04)	7 (0.06)	5 (0.10)	0	0	0	13 (0.06)
Myocardial ischaemia	0	0	0	2 (0.04)	0	0	0	2 (0.01)	

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
Gastrointestinal disorders	Gastric ulcer perforation	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Gastrointestinal disorder	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Intestinal perforation	0	1 (0.04)	0	0	0	0	0	1(<0.01)
	Large intestine perforation	0	0	1 (0.01)	0	0	0	0	1(<0.01)
General disorders and administration site conditions	Death	0	7 (0.26)	15 (0.13)	13 (0.27)	1 (0.19)	0	1 (0.09)	37 (0.17)
	Pyrexia	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Sudden cardiac death	1 (0.15)	0	0	0	0	0	0	1(<0.01)
	Sudden death	0	4 (0.15)	4 (0.03)	1 (0.02)	0	0	0	9 (0.04)
Infections and infestations	Endocarditis bacterial	0	0	0	1 (0.02)	0	0	0	1(<0.01)

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Obstructive chronic bronchitis with acute exacerbation	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Pneumonia	0	1 (0.04)	3 (0.03)	2 (0.04)	0	0	0	6 (0.03)
	Pneumonia chlamydial	0	0	0	1 (0.02)	0	0	0	1(<0.01)
	Sepsis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Septic shock	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Injury, poisoning and procedural complications	Accidental overdose	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Alcohol poisoning	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Cerebral haemorrhage traumatic	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Drug toxicity	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Fall	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Head injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hip fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Injury	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Intentional overdose	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Overdose	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Road traffic accident	0	0	0	2 (0.04)	0	0	0	2 (0.01)
Metabolism and nutrition disorders	Dehydration	0	1 (0.04)	0	0	0	0	1 (0.09)	2 (0.01)
	Electrolyte imbalance	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Neoplasms benign, malignant and unspecified	Bladder cancer	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
(incl cysts and polyps)									
	Breast cancer	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Colon cancer	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Lung neoplasm malignant	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Neoplasm malignant	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
Nervous system disorders	Cerebral hemorrhage	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Cerebrovascular accident	0	0	1 (0.01)	2 (0.04)	0	0	0	3 (0.01)
	Grand mal convulsion	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Psychiatric disorders	Completed suicide	0	4 (0.15)	10 (0.08)	22 (0.45)	1 (0.19)	0	3 (0.27)	40 (0.18)
	Suicide attempt	0	2 (0.07)	3 (0.03)	0	0	0	0	5 (0.02)
Respiratory,	Asphyxia	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
thoracic and mediastinal disorders									
	Aspiration	0	0	1 (0.01)	3 (0.06)	0	0	0	4 (0.02)
	Asthma	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Lung infiltration	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Pneumonia aspiration	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pulmonary embolism	0	1 (0.04)	2 (0.02)	3 (0.06)	0	0	0	6 (0.03)
	Respiratory failure	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Social circumstances	Physical assault	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Vascular disorders	Aneurysm	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Aortic aneurysm rupture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Vascular	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Clinical Review
Phillip Kronstein, M.D.
NDA 20-644
SERDOLECT (Sertindole)

Summary of Primary Reason for Death by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary Reason for Death		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	insufficiency								
Total Deaths		1 (0.15)	36 (1.33)	56 (0.48)	92 (1.88)	2 (0.38)	0	5 (0.44)	192 (0.88)

Appendix D

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Blood and lymphatic system disorders	Anaemia	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Blood disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Haemorrhagic diathesis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hypochromic anaemia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Leukocytosis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Leukopenia	0	0	2 (0.02)	2 (0.04)	0	0	0	4 (0.02)
	Thrombocytopenia	0	0	2 (0.02)	0	0	0	0	2 (0.01)
Cardiac disorders	Angina pectoris	0	1 (0.04)	2 (0.02)	2 (0.04)	0	0	0	5 (0.02)
	Arrhythmia	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Arrhythmia supraventricular	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Atrial fibrillation	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Atrial flutter	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Atrioventricular block	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Atrioventricular block first degree	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Bradycardia	0	2 (0.07)	3 (0.03)	1 (0.02)	0	0	0	6 (0.03)
Bundle branch block	0	0	4 (0.03)	0	0	0	0	4 (0.02)	

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Cardiac arrest	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Cardiac disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Cardiac failure	0	0	2 (0.02)	1 (0.02)	0	0	0	3 (0.01)
	Cardiac failure acute	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Cardiac failure congestive	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Cardiomyopathy	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Cardiopulmonary failure	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Conduction disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Coronary artery disease	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Extrasystoles	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Long QT syndrome	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Myocardial infarction	0	3 (0.11)	3 (0.03)	2 (0.04)	0	0	1 (0.09)	9 (0.04)
	Myocardial ischaemia	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Palpitations	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)
	Pericarditis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sinus bradycardia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Sinus tachycardia	0	0	2 (0.02)	1 (0.02)	0	0	0	3 (0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Supraventricular tachycardia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Tachycardia	0	1 (0.04)	4 (0.03)	0	0	0	0	5 (0.02)
	Tachycardia paroxysmal	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Torsade de pointes	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Ventricular extrasystoles	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Ventricular tachycardia	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)
Ear and labyrinth disorders	Ear pain	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Vertigo	0	0	3 (0.03)	0	0	0	0	3 (0.01)
Endocrine disorders	Diabetes insipidus	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hyperprolactinaemia	0	1 (0.04)	0	3 (0.06)	0	0	0	4 (0.02)
	Hyperthyroidism	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pituitary-dependent Cushing's syndrome	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Eye disorders	Eye disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Eye haemorrhage	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Eyelid disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Meibomianitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Mydriasis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Oculogyric crisis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Retinal detachment	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
Gastrointestinal disorders	Abdominal discomfort	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Abdominal distension	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Abdominal pain	0	7 (0.26)	3 (0.03)	4 (0.08)	0	0	0	14 (0.06)
	Abdominal pain upper	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)
	Abdominal strangulated hernia	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Acute abdomen	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Anal fistula	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Aphthous stomatitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Appendicitis perforated	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Ascites	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Constipation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Diarrhoea	0	2 (0.07)	1 (0.01)	0	0	0	1 (0.09)	4 (0.02)
	Dry mouth	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Duodenal stenosis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Duodenal ulcer	0	0	0	2 (0.04)	0	0	0	2 (0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Duodenal ulcer haemorrhage	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Dysphagia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Erosive oesophagitis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Gastric haemorrhage	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastric polyps	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastric ulcer	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastritis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Gastrointestinal disorder	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
	Gastrointestinal haemorrhage	0	5 (0.18)	0	0	0	0	0	5 (0.02)
	Haematemesis	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
	Haematochezia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Ileus	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Inguinal hernia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Intestinal obstruction	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Large intestine perforation	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Melaena	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Nausea	0	7 (0.26)	1 (0.01)	1 (0.02)	0	0	0	9 (0.04)
	Oesophageal stenosis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Oesophageal ulcer	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Oesophageal ulcer haemorrhage	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Oesophagitis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Pancreatitis acute	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Peritonitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Rectal haemorrhage	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Rectal prolapse	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Tooth impacted	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Umbilical hernia	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Vomiting	0	10 (0.37)	1 (0.01)	2 (0.04)	0	0	0	13 (0.06)
General disorders and administration site conditions	Asthenia	0	5 (0.18)	0	1 (0.02)	0	0	0	6 (0.03)
	Chest pain	0	13 (0.48)	1 (0.01)	3 (0.06)	0	0	0	17 (0.08)
	Chills	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Condition aggravated	0	1 (0.04)	0	1 (0.02)	0	1 (8.33)	0	3 (0.01)
	Cyst	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Disease recurrence	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Drug ineffective	0	0	2 (0.02)	0	0	0	2 (0.18)	4 (0.02)
	Fatigue	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Feeling abnormal	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Gait disturbance	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Generalised oedema	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hyperthermia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Malaise	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Oedema	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Oedema peripheral	0	2 (0.07)	1 (0.01)	1 (0.02)	0	0	0	4 (0.02)
	Pain	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
	Pitting oedema	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pyrexia	0	7 (0.26)	3 (0.03)	1 (0.02)	1 (0.19)	0	0	12 (0.06)
Hepatobiliary disorders	Bile duct obstruction	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cholecystitis	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Cholecystitis acute	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Cholelithiasis	0	1 (0.04)	1 (0.01)	4 (0.08)	0	0	0	6 (0.03)
	Gallbladder disorder	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hepatic function abnormal	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Hepatocellular injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Immune system disorders	Hypersensitivity	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Infections and infestations	Abscess	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Appendicitis	0	2 (0.07)	0	4 (0.08)	0	0	1 (0.09)	7 (0.03)
	Bacterial infection	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Bacteriuria	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Breast abscess	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Bronchitis	0	2 (0.07)	0	4 (0.08)	0	0	0	6 (0.03)
	Bronchopneumonia	0	0	0	1 (0.02)	0	0	1 (0.09)	2 (0.01)
	Candidiasis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Cellulitis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dengue fever	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Diverticulitis	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Gangrene	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastroenteritis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastroenteritis bacterial	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Infection	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Laryngitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Parasitic gastroenteritis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pneumonia	0	10 (0.37)	6 (0.05)	7 (0.14)	0	1 (8.33)	0	24 (0.11)
	Pneumonia primary atypical	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Postoperative wound infection	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Pulmonary tuberculosis	0	0	0	4 (0.08)	0	0	0	4 (0.02)
	Pyelonephritis acute	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Sepsis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Sinusitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Subdural empyema	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Urinary tract infection	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
	Vaginal candidiasis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Wound infection staphylococcal	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Injury, poisoning and procedural complications	Accidental exposure	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Accidental overdose	0	8 (0.30)	0	3 (0.06)	0	0	0	11 (0.05)
	Acetabulum fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Alcohol poisoning	0	2 (0.07)	0	1 (0.02)	0	0	1 (0.09)	4 (0.02)
	Ankle fracture	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Burns third degree	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Compression fracture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Concussion	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Contusion	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Drug exposure during pregnancy	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Drug toxicity	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Face injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Fall	0	3 (0.11)	0	2 (0.04)	0	0	0	5 (0.02)
	Femoral neck fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Femur fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Fibula fracture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Foot fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gas poisoning	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gun shot wound	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Head injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Heat stroke	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Humerus fracture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Injury	0	1 (0.04)	4 (0.03)	0	1 (0.19)	1 (8.33)	0	7 (0.03)
	Intentional overdose	0	9 (0.33)	4 (0.03)	31 (0.63)	0	0	2 (0.18)	46 (0.21)
	Jaw fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Joint dislocation	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Joint injury	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Joint sprain	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Laceration	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Lower limb fracture	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Lumbar vertebral fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Medication error	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Multiple drug overdose intentional	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Multiple fractures	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Multiple injuries	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Overdose	0	37 (1.36)	34 (0.29)	18 (0.37)	0	0	2 (0.18)	91 (0.42)
	Pelvic fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Poisoning	0	0	1 (0.01)	2 (0.04)	0	0	0	3 (0.01)
	Road traffic accident	0	1 (0.04)	0	5 (0.10)	0	0	0	6 (0.03)
	Skin laceration	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Skull fracture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Spinal cord injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Therapeutic agent toxicity	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Thermal burn	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Tibia fracture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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	Traumatic brain injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Wound dehiscence	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Investigations	Alanine aminotransferase increased	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Investigations	Aspartate aminotransferase increased	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Investigations	Blood creatine phosphokinase increased	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
Investigations	Blood glucose increased	0	2 (0.07)	0	0	0	0	0	2 (0.01)
Investigations	Blood prolactin increased	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
Investigations	Blood triglycerides increased	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Investigations	Cardiac murmur	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Investigations	Electrocardiogram abnormal	0	2 (0.07)	7 (0.06)	0	0	0	0	9 (0.04)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
Investigations	Electrocardiogram PR prolongation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Investigations	Electrocardiogram QT corrected interval prolonged	0	3 (0.11)	0	0	0	0	0	3 (0.01)
Investigations	Electrocardiogram QT prolonged	0	11 (0.41)	31 (0.26)	23 (0.47)	0	0	2 (0.18)	67 (0.31)
Investigations	Electrocardiogram repolarisation abnormality	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Electrocardiogram T wave inversion	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Haematocrit decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Haemoglobin decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Heart rate increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hepatic enzyme increased	0	0	1 (0.01)	2 (0.04)	0	0	0	3 (0.01)
	Investigation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Weight decreased	0	2 (0.07)	2 (0.02)	1 (0.02)	0	0	0	5 (0.02)
	Weight increased	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)

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		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	White blood cell count decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	White blood cell count increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Metabolism and nutrition disorders	Anorexia	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Decreased appetite	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Dehydration	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Diabetes mellitus	1 (0.15)	4 (0.15)	0	4 (0.08)	0	0	0	9 (0.04)
	Diabetes mellitus inadequate control	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Diabetes mellitus insulin-dependent	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Diabetic ketoacidosis	0	3 (0.11)	0	0	0	0	0	3 (0.01)
	Electrolyte imbalance	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hyperlipidaemia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hypernatraemia	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Hypoglycaemia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hypokalaemia	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Hyponatraemia	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Obesity	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Type 2 diabetes mellitus	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Water intoxication	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Musculoskeletal and connective tissue disorders	Ankylosing spondylitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Arthritis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Back pain	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Flank pain	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Foot deformity	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Intervertebral disc protrusion	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Muscle spasms	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Osteoarthritis	0	1 (0.04)	0	2 (0.04)	0	0	0	3 (0.01)
	Osteonecrosis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Osteoporosis postmenopausal	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pain in extremity	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Rhabdomyolysis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Systemic lupus erythematosus	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Adrenal carcinoma	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Basal cell carcinoma	0	4 (0.15)	0	0	0	0	0	4 (0.02)
	Benign neoplasm of testis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Bladder cancer	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Breast cancer	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Breast neoplasm	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Colon cancer	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Gastric cancer	0	1 (0.04)	0	2 (0.04)	0	0	0	3 (0.01)
	Hepatic neoplasm	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Lung adenocarcinoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Lung neoplasm malignant	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Lymphoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Malignant melanoma	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Melanocytic naevus	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Multiple myeloma	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Neoplasm malignant	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Squamous cell carcinoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Squamous cell carcinoma of the cervix	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Thyroid cancer	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Uterine cancer	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Uterine leiomyoma	0	0	0	4 (0.08)	0	0	0	4 (0.02)
Nervous system disorders	Akathisia	0	2 (0.07)	0	0	0	0	1 (0.09)	3 (0.01)
	Amnesia	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Aphasia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Cerebral haemorrhage	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Cerebrovascular accident	0	0	0	3 (0.06)	0	0	0	3 (0.01)
	Cervicobrachial syndrome	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cogwheel rigidity	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Coma	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Convulsion	0	6 (0.22)	6 (0.05)	4 (0.08)	0	0	0	16 (0.07)
	Diabetic coma	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Dizziness	0	3 (0.11)	2 (0.02)	4 (0.08)	0	0	0	9 (0.04)
	Dyskinesia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dystonia	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Encephalitis	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Epilepsy	0	3 (0.11)	2 (0.02)	8 (0.16)	0	0	0	13 (0.06)
	Extrapyramidal disorder	0	5 (0.18)	0	0	0	0	0	5 (0.02)
	Facial palsy	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Grand mal convulsion	0	4 (0.15)	1 (0.01)	5 (0.10)	0	0	0	10 (0.05)
	Headache	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hypertonia	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Hypoglycaemic coma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hyporeflexia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Lethargy	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
	Loss of consciousness	0	4 (0.15)	8 (0.07)	2 (0.04)	0	0	0	14 (0.06)
	Mental impairment	0	24 (0.89)	0	0	0	0	0	24 (0.11)
	Movement disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Myoclonic epilepsy	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Neuroleptic malignant syndrome	0	0	0	2 (0.04)	2 (0.38)	0	0	4 (0.02)
	Neuropathy peripheral	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Parkinsonian crisis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Parkinsonism	0	1 (0.04)	0	0	0	0	1 (0.09)	2 (0.01)
	Postictal state	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Psychomotor hyperactivity	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Psychomotor skills impaired	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Somnolence	0	4 (0.15)	9 (0.08)	0	0	0	0	13 (0.06)
	Speech disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Status epilepticus	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Stupor	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Syncope	0	2 (0.07)	5 (0.04)	3 (0.06)	0	0	0	10 (0.05)
	Tonic clonic movements	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Transient ischaemic attack	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Tremor	0	2 (0.07)	1 (0.01)	0	1 (0.19)	0	0	4 (0.02)
Pregnancy, puerperium and perinatal conditions	Abortion	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Abortion spontaneous	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Blighted ovum	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Intra-uterine death	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pregnancy	0	1 (0.04)	0	3 (0.06)	0	0	0	4 (0.02)
	Premature labour	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Premature separation of placenta	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Stillbirth	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Unintended pregnancy	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
Psychiatric disorders	Abnormal behaviour	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Aggression	0	5 (0.18)	1 (0.01)	0	0	0	0	6 (0.03)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Agitation	0	19 (0.70)	3 (0.03)	0	0	0	0	22 (0.10)
	Alcohol abuse	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Alcohol withdrawal syndrome	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Alcoholism	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Anger	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Anxiety	0	27 (1.00)	5 (0.04)	0	0	0	0	32 (0.15)
	Apathy	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Bipolar I disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Catatonia	0	4 (0.15)	0	0	0	0	0	4 (0.02)
	Confusional state	0	5 (0.18)	4 (0.03)	1 (0.02)	0	0	0	10 (0.05)
	Delirium	0	2 (0.07)	1 (0.01)	2 (0.04)	0	0	0	5 (0.02)
	Delusion	0	10 (0.37)	0	0	0	0	0	10 (0.05)
	Delusion of grandeur	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Delusional disorder, persecutory type	0	2 (0.07)	2 (0.02)	0	0	0	0	4 (0.02)
	Depersonalisation	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Depressed mood	0	3 (0.11)	0	0	0	0	0	3 (0.01)
	Depression	1 (0.15)	27 (1.00)	7 (0.06)	4 (0.08)	0	0	1 (0.09)	40 (0.18)
	Depressive symptom	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Disorientation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dissociative disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Drug dependence	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Fear	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Flight of ideas	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hallucination	0	9 (0.33)	1 (0.01)	0	0	0	1 (0.09)	11 (0.05)
	Hallucination, auditory	0	6 (0.22)	1 (0.01)	0	0	0	0	7 (0.03)
	Hallucination, visual	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hallucinations, mixed	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hostility	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hypochondriasis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Impulse-control disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Impulsive behaviour	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Insomnia	0	4 (0.15)	2 (0.02)	0	0	0	0	6 (0.03)
	Intentional self-injury	0	1 (0.04)	0	4 (0.08)	0	0	1 (0.09)	6 (0.03)
	Major depression	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Mania	0	3 (0.11)	2 (0.02)	1 (0.02)	0	0	0	6 (0.03)
	Mental disorder	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Nightmare	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Obsessive-compulsive disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Panic disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Paranoia	0	9 (0.33)	1 (0.01)	0	0	0	0	10 (0.05)
	Persecutory delusion	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Polysubstance dependence	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Psychotic disorder	0	155 (5.72)	13 (0.11)	2 (0.04)	0	0	4 (0.35)	174 (0.80)
	Restlessness	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Schizoaffective disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Schizophrenia	0	22 (0.81)	0	0	0	0	6 (0.53)	28 (0.13)
	Schizophrenia, paranoid type	0	4 (0.15)	0	0	0	0	0	4 (0.02)
	Sleep disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Somatic delusion	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Somatic hallucination	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sopor	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Stress	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Suicidal behaviour	0	4 (0.15)	0	1 (0.02)	0	0	0	5 (0.02)
	Suicidal ideation	0	42 (1.55)	1 (0.01)	10 (0.20)	0	0	1 (0.09)	54 (0.25)
	Suicide attempt	0	22 (0.81)	33 (0.28)	50 (1.02)	1 (0.19)	0	2 (0.18)	108 (0.50)
	Thinking abnormal	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Thought blocking	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Renal and urinary disorders	Calculus urinary	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Enuresis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Haematuria	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Nephrolithiasis	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Pollakiuria	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Renal colic	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Renal failure	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Renal failure chronic	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Renal impairment	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Urge incontinence	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Urinary retention	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Reproductive system and breast disorders	Amenorrhoea	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Ejaculation disorder	0	1 (0.04)	1 (0.01)	0	0	0	1 (0.09)	3 (0.01)
	Ejaculation failure	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Erectile dysfunction	0	0	1 (0.01)	0	0	0	1 (0.09)	2 (0.01)
	Galactorrhoea	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Gynaecomastia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Menorrhagia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Metrorrhagia	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Ovarian rupture	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Rectocele	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Uterine enlargement	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Vaginal haemorrhage	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Apnoea	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Asthma	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Choking	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Chronic obstructive pulmonary disease	0	2 (0.07)	0	2 (0.04)	0	0	0	4 (0.02)
	Cough	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
	Dyspnoea	0	4 (0.15)	2 (0.02)	5 (0.10)	0	0	0	11 (0.05)
	Epistaxis	0	0	2 (0.02)	1 (0.02)	0	0	0	3 (0.01)
	Haemoptysis	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Lung disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Nasal dryness	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Nasal turbinate hypertrophy	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pharyngolaryngeal pain	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pleural effusion	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Productive cough	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pulmonary embolism	0	0	2 (0.02)	1 (0.02)	0	0	0	3 (0.01)
	Respiratory distress	0	3 (0.11)	0	0	0	0	0	3 (0.01)
	Respiratory failure	0	1 (0.04)	0	2 (0.04)	0	0	0	3 (0.01)
	Respiratory tract congestion	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sleep apnoea syndrome	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Skin and subcutaneous tissue disorders	Angioedema	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hyperhidrosis	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Purpura	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Rash	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Rash erythematous	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Rash macular	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Rash papular	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Rash pruritic	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Social circumstances	Alcohol use	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Drug abuse	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Drug abuser	0	2 (0.07)	0	1 (0.02)	0	0	0	3 (0.01)
	Family stress	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Social problem	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Social stay hospitalisation	0	17 (0.63)	0	1 (0.02)	0	0	0	18 (0.08)
	Substance abuse	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Treatment noncompliance	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Surgical and medical procedures	Caesarean section	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cholecystectomy	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Coronary artery bypass	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hernia repair	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hip surgery	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hospitalisation	0	27 (1.00)	0	0	0	0	0	27 (0.12)
	Hysterectomy	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Inguinal hernia repair	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Knee arthroplasty	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Oophorectomy bilateral	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Plastic surgery	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Psychosocial support	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Psychotherapy	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Non-Fatal Serious Adverse Events by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Non-Fatal Serious Adverse Events		Completed Non-Japanese Studies				Completed Japanese Studies (N=526)	Other Populations (N=12)	Ongoing Studies (N=1129)	Total (N=21731)
System Organ Class	Preferred Term	Phase I Studies (N=676)	Phase II/III Studies (N=2711)	Other Studies in Schizophrenia (N=11772)	SCoP (N=4905)				
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
	Testicular operation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Vascular disorders	Circulatory collapse	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Deep vein thrombosis	0	2 (0.07)	1 (0.01)	2 (0.04)	0	0	0	5 (0.02)
	Haematoma	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Hot flush	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hypertension	0	1 (0.04)	0	2 (0.04)	0	0	0	3 (0.01)
	Hypertensive crisis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Hypotension	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
	Labile hypertension	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Orthostatic hypotension	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Phlebitis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Thrombophlebitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Thrombosis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Appendix E

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
Blood and lymphatic system disorders	Anaemia	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Anemia	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Hypochromic anaemia	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Leukocytosis	0		1 (0.01)	0	0	0	0	1 (<0.01)
	Leukopenia	2 (0.30)	2 (0.07)	9 (0.08)	2 (0.04)	0	0	0	15 (0.07)
	Thrombocytopenia	0		3 (0.03)	0	0	0	0	3 (0.01)
Cardiac disorders	Angina pectoris	0		2 (0.02)	0	0	0	1 (0.09)	3 (0.01)
	Arrhythmia	0		7 (0.06)	1 (0.02)	0	0	0	8 (0.04)
	Arrhythmia atrial	0		1 (0.01)	0	0	0	0	1 (<0.01)
	Arteriosclerosis coronary artery	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Atrial fibrillation	0		1 (0.01)	0	0	0	0	1 (<0.01)
	Atrial flutter	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Atrioventricular block	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Atrioventricular block first degree	0		1 (0.01)	0	0	0	0	1 (<0.01)
	Bradycardia	0		9 (0.08)	1 (0.02)	0	0	0	10 (0.05)
	Bundle branch block	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Bundle branch block left	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Cardiac arrest	0	1 (0.04)	1 (0.01)	2 (0.04)	0	0	0	4 (0.02)
	Cardiac asthma	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Cardiac failure	0	0	4 (0.03)	1 (0.02)	0	0	0	5 (0.02)
	Cardiac failure acute	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Cardiac failure congestive	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cardiomyopathy	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Cardio-respiratory arrest	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Conduction disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Coronary artery disease	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Extrasystoles	0	1 (0.04)	4 (0.03)	0	0	0	0	5 (0.02)
	Heart disorder	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Long QT syndrome	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Myocardial infarction	0	2 (0.07)	4 (0.03)	1 (0.02)	0	0	0	7 (0.03)
	Myocardial ischaemia	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Palpitation	0	0	5 (0.04)	0	0	0	0	5 (0.02)
	Palpitations	1 (0.15)	4 (0.15)	0	1 (0.02)	0	0	0	6 (0.03)
	Pericarditis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sinus bradycardia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Sinus tachycardia	1 (0.15)	0	1 (0.01)	0	0	0	0	2 (0.01)
	Supraventricular tachycardia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Tachycardia	1 (0.15)	3 (0.11)	7 (0.06)	0	0	0	0	11 (0.05)
	Torsade de pointes	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Ventricular Extrasystoles	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Ventricular tachycardia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Ear and labyrinth disorders	Ear pain	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hearing impaired	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Tinnitus	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Vertigo	0	1 (0.04)	2 (0.02)	0	0	0	0	3 (0.01)
Endocrine disorders	Diabetes insipidus	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hyperprolactinaemia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Eye disorders	Amblyopia	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Eye pain	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Eyelid disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Meibomianitis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Oculogyric crisis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Retinal detachment	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Vision blurred	0	2 (0.07)	0	0	0	0	0	2 (0.01)
Gastrointestinal disorders	Abdomen Enlarged	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Abdominal discomfort	0	1 (0.04)	0	1 (0.02)	0	0	1 (0.09)	3 (0.01)
	Abdominal distension	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Abdominal pain	2 (0.30)	0	0	1 (0.02)	0	0	0	3 (0.01)
	Abdominal pain upper	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Abdominal strangulated hernia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Constipation	1 (0.15)	1 (0.04)	2 (0.02)	0	0	0	0	4 (0.02)
	Dry mouth	0	1 (0.04)	1 (0.01)	0	0	1 (8.33)	1 (0.09)	4 (0.02)
	Duodenal ulcer	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Dyspepsia	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Dysphagia	0	1 (0.04)	2 (0.02)	0	0	0	0	3 (0.01)
	Enamel anomaly	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Gastric haemorrhage	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastritis	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Gastrointestinal disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Gastrointestinal haemorrhage	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Hypoaesthesia oral	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Intestinal obstruction	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Nausea	1 (0.15)	4 (0.15)	8 (0.07)	1 (0.02)	0	0	0	14 (0.06)
	Pancreatitis acute	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Small bowel obstruction	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Stomach discomfort	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Tooth disorder	2 (0.30)	0	0	0	0	0	0	2 (0.01)
	Vomiting	0	11 (0.41)	1 (0.01)	1 (0.02)	0	0	2 (0.18)	15 (0.07)
General disorders and administration site conditions									
	Asthenia	0	8 (0.30)	3 (0.03)	1 (0.02)	0	1 (8.33)	0	13 (0.06)
	Chest discomfort	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Chest pain	1 (0.15)	4 (0.15)	3 (0.03)	1 (0.02)	0	0	0	9 (0.04)
	Chest Tightness	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Condition aggravated	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Death	1 (0.15)	10 (0.37)	4 (0.03)	0	0	0	0	15 (0.07)
	Disease recurrence	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Drug ineffective	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Edema of lower extremities	0	0	0	0	0	0	1 (0.09)	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Fatigue	0	5 (0.18)	10 (0.08)	0	1 (0.19)	0	1 (0.09)	17 (0.08)
	Feeling abnormal	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Fever	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Gait abnormal	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Irritability	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Malaise	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Oedema	0	1 (0.04)	14 (0.12)	0	0	0	0	15 (0.07)
	Oedema dependent	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Oedema peripheral	0	0	0	1 (0.02)	0	0	2 (0.18)	3 (0.01)
	Pain	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Pyrexia	0	1 (0.04)	1 (0.01)	2 (0.04)	0	0	0	4 (0.02)
	Sudden death	0	2 (0.07)	2 (0.02)	1 (0.02)	0	0	0	5 (0.02)
	Thirst	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
Hepatobiliary disorders	Cholecystitis acute	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Cholelithiasis	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Hepatic steatosis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hepatocellular injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Liver disorder	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
Immune system disorders	Hypersensitivity	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Infections and infestations	Appendicitis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Bronchitis	2 (0.30)	1 (0.04)	0	0	0	0	0	3 (0.01)
	Endocarditis bacterial	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Flu Syndrome	2 (0.30)	0	0	0	0	0	0	2 (0.01)
	Gangrene	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Gastroenteritis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hepatitis C	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Pharyngitis	2 (0.30)	0	0	0	0	0	0	2 (0.01)
	Pneumonia	0	4 (0.15)	5 (0.04)	2 (0.04)	0	0	0	11 (0.05)
	Pneumonia chlamydial	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pulmonary tuberculosis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Rhinitis	3 (0.44)	0	32 (0.27)	0	0	0	0	35 (0.16)
	Sepsis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Septic shock	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Urinary tract infection	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
Injury, poisoning and procedural complications	Accidental overdose	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Contusion	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Drug exposure during pregnancy	0	0	1 (0.01)	5 (0.10)	0	0	0	6 (0.03)
	Fall	0	0	1 (0.01)	2 (0.04)	0	0	0	3 (0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Femoral neck fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Foreign body trauma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hip fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Injury	0	0	1 (0.01)	0	1 (0.19)	0	0	2 (0.01)
	Intentional overdose	0	0	0	13 (0.27)	0	0	0	13 (0.06)
	Jaw fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Lower limb fracture	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Medication error	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Multiple fractures	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Overdose	0	4 (0.15)	9 (0.08)	12 (0.24)	0	0	1 (0.09)	26 (0.12)
	Poisoning	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Road traffic accident	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Spinal cord injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Therapeutic agent toxicity	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Traumatic brain injury	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
Investigations	Alanine aminotransferase increased	0	4 (0.15)	0	1 (0.02)	0	0	0	5 (0.02)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Aspartate aminotransferase increased	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Blood alkaline phosphatase increased	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Blood cholesterol increased	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Blood creatine phosphokinase increased	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Blood glucose increased	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Blood pressure diastolic increased	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Blood prolactin increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Electrocardiogram abnormal	0	7 (0.26)	11 (0.09)	0	1 (0.19)	0	0	19 (0.09)
	Electrocardiogram QT corrected interval prolonged	0	23 (0.85)	1 (0.01)	0	3 (0.57)	0	1 (0.09)	28 (0.13)
	Electrocardiogram QT prolonged	0	21 (0.77)	25 (0.21)	19 (0.39)	0	0	12 (1.06)	77 (0.35)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Electrocardiogram repolarisation abnormality	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Granulocyte count decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Heart rate increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hepatic enzyme abnormal	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Hepatic enzyme increased	0	2 (0.07)	1 (0.01)	1 (0.02)	0	0	1 (0.09)	5 (0.02)
	Hepatitis C positive	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Liver function test abnormal	0	9 (0.33)	0	0	0	0	0	9 (0.04)
	Neutrophil count decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Platelet count decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Platelet count increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Prostatic specific antigen increased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pulse absent	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	QT increased	0	0	48 (0.41)	0	0	0	0	48 (0.22)
	QT Interval Prolonged	1 (0.15)	0	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Semen abnormal	0	0	5 (0.04)	0	0	0	0	5 (0.02)
	SGOT Increased	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	SGPT Increased	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Weight decreased	0	1 (0.04)	0	1 (0.02)	1 (0.19)	0	0	3 (0.01)
	Weight increase	0	0	16 (0.14)	0	0	0	0	16 (0.07)
	Weight increased	0	13 (0.48)	0	1 (0.02)	0	0	0	14 (0.06)
	White blood cell count decreased	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Metabolism and nutrition disorders	Anorexia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Decreased appetite	0	0	0	1 (0.02)	1 (0.19)	0	0	2 (0.01)
	Diabetes mellitus	0	2 (0.07)	0	2 (0.04)	0	0	0	4 (0.02)
	Diabetic ketoacidosis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hyperlipidaemia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hypokalaemia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Obesity	0	1 (0.04)	2 (0.02)	0	0	0	0	3 (0.01)
	Polydipsia	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
Musculoskeletal and connective tissue disorders	Arthralgia	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Back Pain	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Muscle spasms	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Muscular weakness	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Musculoskeletal stiffness	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Myalgia	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Osteoarthritis	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Rhabdomyolysis	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Systemic lupus erythematosus	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Twitching	3 (0.44)	0	0	0	0	0	0	3 (0.01)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Basal cell carcinoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Bladder cancer	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Breast cancer metastatic	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Gastric cancer	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Lung adenocarcinoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Lung neoplasm malignant	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Lymphoma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Multiple myeloma	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
Nervous system disorders	Akathisia	3 (0.44)	6 (0.22)	0	0	1 (0.19)	0	2 (0.18)	12 (0.06)
	Akinesia	0	1 (0.04)	0	0	1 (0.19)	0	0	2 (0.01)
	Amnesia	0	0	1 (0.01)	1 (0.02)	0	0	0	2 (0.01)
	Ataxia	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Cerebral haemorrhage	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cerebrovascular accident	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Cogwheel rigidity	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Concentration impaired	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Convulsions	0	4 (0.15)	3 (0.03)	2 (0.04)	0	0	0	9 (0.04)
	Convulsions grand mal	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Disturbance in attention	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dizziness	5 (0.74)	11 (0.41)	16 (0.14)	3 (0.06)	0	0	1 (0.09)	36 (0.17)
	Drooling	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dyskinesia	0	1 (0.04)	3 (0.03)	0	0	0	0	4 (0.02)
	Dyskinesia tardive	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Dystonia	2 (0.30)	1 (0.04)	1 (0.01)	0	0	0	0	4 (0.02)
	Encephalitis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Epilepsy	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
	Extrapyramidal disorder	0	5 (0.18)	39 (0.33)	0	1 (0.19)	0	0	45 (0.21)
	Grand mal convulsion	0	3 (0.11)	0	1 (0.02)	0	0	0	4 (0.02)
	Headache	2 (0.30)	5 (0.18)	11 (0.09)	0	0	0	0	18 (0.08)
	Hyperkinesia	0	0	20 (0.17)	0	0	0	0	20 (0.09)
	HYPERTONIA	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hypoglycaemic coma	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hypokinesia	0	1 (0.04)	3 (0.03)	0	0	0	1 (0.09)	5 (0.02)
	Hypotonia	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Lethargy	0	2 (0.07)	1 (0.01)	0	0	0	0	3 (0.01)
	Loss of consciousness	0	2 (0.07)	2 (0.02)	0	0	0	0	4 (0.02)
	Migraine	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Neuroleptic malignant syndrome	0	0	0	0	2 (0.38)	0	0	2 (0.01)
	Paraesthesia	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Paresthesia	2 (0.30)	0	0	0	0	0	0	2 (0.01)
	Parkinsonian crisis	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Parkinsonism	0	1 (0.04)	0	0	0	0	1 (0.09)	2 (0.01)
	Postictal state	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Restless legs syndrome	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sedation	0	12 (0.44)	0	0	0	0	0	12 (0.06)
	Somnolence	2 (0.30)	7 (0.26)	29 (0.25)	0	0	2 (16.67)	0	40 (0.18)
	Speech disorder	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Status epilepticus	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Stupor	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Syncope	1 (0.15)	2 (0.07)	6 (0.05)	1 (0.02)	0	0	0	10 (0.05)
	Tonic clonic movements	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Tremor	1 (0.15)	3 (0.11)	7 (0.06)	0	0	0	0	11 (0.05)
Pregnancy, puerperium and perinatal conditions	Abortion spontaneous	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Blighted ovum	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Pregnancy	0	1 (0.04)	0	8 (0.16)	0	0	0	9 (0.04)
	Premature labour	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Premature separation of placenta	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Unintended pregnancy	0	0	3 (0.03)	0	0	0	0	3 (0.01)
Psychiatric disorders	Affect lability	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Aggression	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Aggressive reaction	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Agitation	1 (0.15)	5 (0.18)	18 (0.15)	0	1 (0.19)	0	2 (0.18)	27 (0.12)
	Anhedonia	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Anorgasmia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Anxiety	12 (1.78)	2 (0.07)	7 (0.06)	0	2 (0.38)	0	0	23 (0.11)
	Catatonia	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Completed suicide	0	4 (0.15)	3 (0.03)	1 (0.02)	0	0	0	8 (0.04)
	Confusion	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Confusional state	0	2 (0.07)	3 (0.03)	1 (0.02)	0	0	0	6 (0.03)
	Delirium	0	1 (0.04)	1 (0.01)	1 (0.02)	0	0	0	3 (0.01)
	Delusion	0	5 (0.18)	0	0	3 (0.57)	0	0	8 (0.04)
	Delusional perception	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Depersonalisation	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Depressed mood	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Depression	3 (0.44)	12 (0.44)	11 (0.09)	0	0	0	0	26 (0.12)
	Depressive symptom	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Drug dependence	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Dyslogia	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Dysphoria	0	0	0	0	0	0	1 (0.09)	1 (<0.01)
	Fear of weight gain	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hallucination	0	1 (0.04)	0	0	3 (0.57)	0	1 (0.09)	5 (0.02)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Hallucination, auditory	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Homicidal ideation	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Hypochondriasis	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Hypomania	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Insomnia	2 (0.30)	4 (0.15)	8 (0.07)	0	1 (0.19)	0	2 (0.18)	17 (0.08)
	Intentional self-injury	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Libido decreased	0	0	13 (0.11)	0	0	0	0	13 (0.06)
	Logorrhoea	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Major depression	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Male orgasmic disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Mania	0	2 (0.07)	0	1 (0.02)	0	0	1 (0.09)	4 (0.02)
	Manic reaction	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Nervousness	6 (0.89)	1 (0.04)	2 (0.02)	0	0	0	0	9 (0.04)
	Neurosis	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Nightmare	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Panic attack	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Panic disorder	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Paranoia	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Personality disorder	0	0	3 (0.03)	0	0	0	0	3 (0.01)
	Psychosis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

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System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Psychotic disorder	0	9 (0.33)	5 (0.04)	0	3 (0.57)	0	3 (0.27)	20 (0.09)
	Restlessness	0	1 (0.04)	1 (0.01)	0	1 (0.19)	0	0	3 (0.01)
	Schizophrenia	0	3 (0.11)	0	0	1 (0.19)	0	4 (0.35)	8 (0.04)
	Self injurious behaviour	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Sleep disorder	0	0	5 (0.04)	0	0	0	0	5 (0.02)
	Sopor	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Suicidal behaviour	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Suicidal ideation	0	24 (0.89)	0	3 (0.06)	0	0	0	27 (0.12)
	Suicide attempt	0	16 (0.59)	13 (0.11)	22 (0.45)	1 (0.19)	0	1 (0.09)	53 (0.24)
	Tension	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
	Thinking abnormal	3 (0.44)	0	0	0	0	0	0	3 (0.01)
Renal and urinary disorders	Enuresis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Pollakiuria	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Renal cortical necrosis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
Reproductive system and breast disorders	Amenorrhoea	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Ejaculation delayed	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Ejaculation disorder	0	12 (0.44)	36 (0.31)	0	0	0	2 (0.18)	50 (0.23)
	Ejaculation failure	0	40 (1.48)	21 (0.18)	0	0	0	0	61 (0.28)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Erectile dysfunction	0	11 (0.41)	1 (0.01)	0	0	0	1 (0.09)	13 (0.06)
	Galactorrhoea	0	0	4 (0.03)	0	0	0	0	4 (0.02)
	Gynaecomastia	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Impotence	0	0	9 (0.08)	0	0	0	0	9 (0.04)
	Menstrual disorder	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Retrograde ejaculation	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Sexual dysfunction	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Testicular pain	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
Respiratory, thoracic and mediastinal disorders	Acute respiratory distress syndrome	0	1 (0.04)	0	1 (0.02)	0	0	0	2 (0.01)
	Apnoea	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Aspiration	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Asthma	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Dyspnea	2 (0.30)	0	0	0	0	0	0	2 (0.01)
	Dyspnoea	0	2 (0.07)	7 (0.06)	4 (0.08)	0	0	0	13 (0.06)
	Epistaxis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Haemoptysis	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Lung disorder	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Nasal congestion	0	2 (0.07)	1 (0.01)	0	0	0	1 (0.09)	4 (0.02)
	Nasal dryness	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Pleural effusion	0	1 (0.04)	0	0	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Pneumonia aspiration	0	0	0	2 (0.04)	0	0	0	2 (0.01)
	Pulmonary embolism	0	0	1 (0.01)	2 (0.04)	0	0	0	3 (0.01)
	Pulmonary hypertension	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Pulmonary oedema	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Respiratory failure	0	0	0	2 (0.04)	0	0	0	2 (0.01)
Skin and subcutaneous tissue disorders	Alopecia	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Angioedema	0	0	2 (0.02)	0	0	0	0	2 (0.01)
	Pruritus	0	1 (0.04)	1 (0.01)	0	0	0	0	2 (0.01)
	Purpura	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Rash	1 (0.15)	0	1 (0.01)	0	0	0	0	2 (0.01)
	Rash erythematous	0	0	2 (0.02)	0	0	0	1 (0.09)	3 (0.01)
	Rash generalised	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Rash pruritic	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Stevens-Johnson syndrome	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Sweating increased	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Swelling face	0	2 (0.07)	0	0	0	0	0	2 (0.01)
Social circumstances	Drug abuser	0	2 (0.07)	0	0	0	0	0	2 (0.01)
Surgical and medical procedures	Caesarean section	0	0	0	1 (0.02)	0	0	0	1 (<0.01)

Summary of Primary Reason for Study Drug Discontinuation by System Organ Class and Preferred Term: Sertindole-Treated Patients									
Primary for Study Drug Discontinuation		Completed Non-Japanese Studies				Completed Japanese Studies (N=526) n (%)	Other Populations (N=12) n (%)	Ongoing Studies (N=1129) n (%)	Total (N=21731) n (%)
System Organ Class	Preferred Term	Phase I Studies (N=676) n (%)	Phase II/III Studies (N=2711) n (%)	Other Studies in Schizophrenia (N=11772) n (%)	SCoP (N=4905) n (%)				
	Cholecystectomy	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Hospitalisation	0	2 (0.07)	0	0	0	0	0	2 (0.01)
	Therapy cessation	0	0	0	0	1 (0.19)	0	0	1 (<0.01)
Vascular disorders	Aortic dissection	0	1 (0.04)	0	0	0	0	0	1 (<0.01)
	Circulatory failure	0	0	1 (0.01)	0	0	0	0	1 (<0.01)
	Hypertension	1 (0.15)	0	0	1 (0.02)	0	0	0	2 (0.01)
	Hypotension	0	3 (0.11)	17 (0.14)	0	0	0	0	20 (0.09)
	Hypotension postural	0	0	4 (0.03)	0	0	0	0	4 (0.02)
	Labile hypertension	0	0	0	1 (0.02)	0	0	0	1 (<0.01)
	Orthostatic hypotension	0	3 (0.11)	0	0	0	0	0	3 (0.01)
	Phlebitis	1 (0.15)	1 (0.04)	0	0	0	0	0	2 (0.01)
	Postural Hypotension	1 (0.15)	0	0	0	0	0	0	1 (<0.01)
	Thrombophlebitis deep	0	0	1 (0.01)	0	0	0	0	1 (<0.01)

Appendix F

Incidence of Adverse Events Reported for ≥2% of Sertindole-Treated Patients in Any Sertindole Dose Group and at ≥2 Times the Placebo Rate: the Fixed Dose Group Studies M93-113, M93-098, and M92-762						
System Organ Class / Preferred Term	Placebo (N = 237) n (%)	Sertindole				
		8 mg (N=52) n (%)	12 mg (N=127) n (%)	20 mg (N=239) n (%)	24 mg (N=186) n (%)	Total (N=604) n (%)
Eye disorders						
Eye pain	2 (0.8)	2 (3.8)	2 (1.6)	2 (0.8)	2 (1.1)	8 (1.3)
Ocular hyperaemia	1 (0.4)	0	3 (2.4)	0	1 (0.5)	4 (0.7)
Vision blurred	4 (1.7)	0	4 (3.1)	8 (3.3)	10 (5.4)	22 (3.6)
Gastrointestinal disorders						
Dry mouth	12 (5.1)	2 (3.8)	9 (7.1)	26 (10.9)	23 (12.4)	60 (9.9)
Flatulence	8 (3.4)	4 (7.7)	6 (4.7)	8 (3.3)	2 (1.1)	20 (3.3)
Stomach discomfort	6 (2.5)	3 (5.8)	6 (4.7)	6 (2.5)	12 (6.5)	27 (4.5)
General disorders and administration site conditions						
Chest discomfort	1 (0.4)	2 (3.8)	2 (1.6)	1 (0.4)	1 (0.5)	6 (1.0)
Chest pain	3 (1.3)	2 (3.8)	4 (3.1)	9 (3.8)	9 (4.8)	24 (4.0)
Gait disturbance	2 (0.8)	1 (1.9)	3 (2.4)	3 (1.3)	4 (2.2)	11 (1.8)
Mass	3 (1.3)	2 (3.8)	0	1 (0.4)	0	3 (0.5)
Oedema	0	1 (1.9)	3 (2.4)	2 (0.8)	0	6 (1.0)
Oedema peripheral	2 (0.8)	1 (1.9)	2 (1.6)	4 (1.7)	7 (3.8)	14 (2.3)
Pyrexia	1 (0.4)	3 (5.8)	3 (2.4)	4 (1.7)	3 (1.6)	13 (2.2)
Infections and infestations						
Nasopharyngitis	10 (4.2)	8 (15.4)	8 (6.3)	12 (5.0)	6 (3.2)	34 (5.6)
Rhinitis	2 (0.8)	0	4 (3.1)	8 (3.3)	3 (1.6)	15 (2.5)
Injury, poisoning and procedural complications						
Contusion	1 (0.4)	0	1 (0.8)	2 (0.8)	4 (2.2)	7 (1.2)

Incidence of Adverse Events Reported for ≥2% of Sertindole-Treated Patients in Any Sertindole Dose Group and at ≥2 Times the Placebo Rate: the Fixed Dose Group Studies M93-113, M93-098, and M92-762						
System Organ Class / Preferred Term	Placebo (N = 237) n (%)	Sertindole				
		8 mg (N=52) n (%)	12 mg (N=127) n (%)	20 mg (N=239) n (%)	24 mg (N=186) n (%)	Total (N=604) n (%)
Investigations						
Body temperature increased	2 (0.8)	3 (5.8)	2 (1.6)	1 (0.4)	0	6 (1.0)
Electrocardiogram QT prolonged	0	0	0	6 (2.5)	2 (1.1)	8 (1.3)
Liver function test abnormal	0	0	3 (2.4)	2 (0.8)	1 (0.5)	6 (1.0)
Weight increased	3 (1.3)	0	4 (3.1)	11 (4.6)	9 (4.8)	24 (4.0)
Musculoskeletal and connective tissue disorders						
Arthralgia	3 (1.3)	2 (3.8)	3 (2.4)	8 (3.3)	6 (3.2)	19 (3.1)
Muscle spasms	2 (0.8)	0	3 (2.4)	5 (2.1)	6 (3.2)	14 (2.3)
Musculoskeletal stiffness	8 (3.4)	2 (3.8)	8 (6.3)	9 (3.8)	15 (8.1)	34 (5.6)
Pain in extremity	14 (5.9)	0	18 (14.2)	13 (5.4)	15 (8.1)	46 (7.6)
Nervous system disorders						
Dizziness postural	3 (1.3)	2 (3.8)	5 (3.9)	5 (2.1)	5 (2.7)	17 (2.8)
Extrapyramidal disorder	13 (5.5)	0	4 (3.1)	16 (6.7)	21 (11.3)	41 (6.8)
Hypoaesthesia	2 (0.8)	1 (1.9)	2 (1.6)	4 (1.7)	4 (2.2)	11 (1.8)
Hypotonia	0	1 (1.9)	0	0	0	1 (0.2)
Movement disorder	5 (2.1)	1 (1.9)	3 (2.4)	4 (1.7)	8 (4.3)	16 (2.6)
Syncope	0	2 (3.8)	0	2 (0.8)	0	4 (0.7)
Psychiatric disorders						
Agitation	3 (1.3)	0	3 (2.4)	1 (0.4)	5 (2.7)	9 (1.5)
Renal and urinary disorders						
Micturition urgency	1 (0.4)	2 (3.8)	0	1 (0.4)	1 (0.5)	4 (0.7)

Incidence of Adverse Events Reported for $\geq 2\%$ of Sertindole-Treated Patients in Any Sertindole Dose Group and at ≥ 2 Times the Placebo Rate: the Fixed Dose Group Studies M93-113, M93-098, and M92-762						
System Organ Class / Preferred Term	Placebo (N = 237) n (%)	Sertindole				
		8 mg (N=52) n (%)	12 mg (N=127) n (%)	20 mg (N=239) n (%)	24 mg (N=186) n (%)	Total (N=604) n (%)
Reproductive system and breast disorders						
Ejaculation disorder	2 (0.8)	0	2 (1.6)	14 (5.9)	6 (3.2)	22 (3.6)
Ejaculation failure	2 (0.8)	0	13 (10.2)	23 (9.6)	14 (7.5)	50 (8.3)
Erectile dysfunction	1 (0.4)	1 (1.9)	2 (1.6)	8 (3.3)	3 (1.6)	14 (2.3)
Respiratory, thoracic and mediastinal disorders						
Dyspnoea	1 (0.4)	1 (1.9)	3 (2.4)	8 (3.3)	6 (3.2)	18 (3.0)
Epistaxis	4 (1.7)	1 (1.9)	5 (3.9)	3 (1.3)	4 (2.2)	13 (2.2)
Nasal congestion	21 (8.9)	7 (13.5)	24 (18.9)	58 (24.3)	44 (23.7)	133 (22.0)
Respiratory tract congestion	1 (0.4)	1 (1.9)	1 (0.8)	5 (2.1)	6 (3.2)	13 (2.2)
Rhinorrhoea	3 (1.3)	3 (5.8)	3 (2.4)	5 (2.1)	5 (2.7)	16 (2.6)
Wheezing	3 (1.3)	0	6 (4.7)	8 (3.3)	1 (0.5)	15 (2.5)
Skin and subcutaneous tissue disorders						
Skin lesion	2 (0.8)	0	3 (2.4)	2 (0.8)	1 (0.5)	6 (1.0)
Vascular disorders						
Orthostatic hypotension	0	0	3 (2.4)	3 (1.3)	4 (2.2)	10 (1.7)
Note: Adverse Events Reported for $\geq 2\%$ of Sertindole-treated Patients in the Any Sertindole Study Drug Group and Reported at < 2 Times the Placebo Rate Fixed Dose Group Studies (Sertindole Dose Groups): Constipation, Dyspepsia, Nausea, Vomiting, Fatigue, Myalgia, Dizziness, Headache, Sedation, Tremor, Insomnia, and Cough.						

Appendix G

Safety Parameters: Fixed-Dose, Placebo-Controlled Studies

Safety Assessments	M93-113	M93-098	M92-762
Vital Signs	Oral temperature, supine and standing blood pressure, and heart rate	oral temperature, blood pressure, and heart rate including orthostatic change from supine to standing	Oral body temperature. Vital signs including blood pressure and heart rate measurements, were obtained in the supine position (after at least 5 minutes) and after orthostatic challenge (after 1 minute sitting and after 1 minute standing)
Prolactin	-	-	Yes
Physical Examinations	Physical and neurological examinations	Physical and neurological examinations	Physical and neurological examinations
ECG	Resting 12-lead ECG	Resting 12-lead ECG	Resting 12-lead ECG
Safety Laboratory Tests ^a			
Hematology	White blood cell (WBC) count, differential count, red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and quantitative platelet count.	White blood cell (WBC) count, differential count, red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and quantitative platelet count	White blood cell (WBC) count, differential count (including the number of vacuolated lymphocytes), red blood cell (RBC) count, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and quantitative platelet count
Serum chemistry	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, SGOT/AST, SGPT/ALT, total bilirubin, total protein, albumin, cholesterol, triglycerides, calcium, inorganic phosphorus, uric acid, and LDH	Serum chemistry, including sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, SGOT/AST, SGPT/ALT, total bilirubin, total protein, albumin, total cholesterol, triglycerides, calcium, inorganic phosphate, uric acid, and LDH	Sodium, potassium, chloride, bicarbonate, glucose, blood urea nitrogen (BUN), creatinine, alkaline phosphatase, SGOT/AST, SGPT/ALT, total bilirubin, total protein, albumin, cholesterol, triglycerides, calcium, inorganic phosphorus, uric acid, prostate-specific antigen (PSA) and prostatic acid phosphatase (PAP) for male patients only, and lactate dehydrogenase (LDH)
Urinalysis	Specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, and microscopic examination of the urine if any of the preceding urine evaluations were abnormal	Specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, and microscopic examination of the urine if any of the preceding urine evaluations were abnormal	Specific gravity, pH, protein, glucose, ketones, urobilinogen, bilirubin, blood, and microscopic examination of the urine if any of the preceding urine evaluations were abnormal
Other laboratory	Serum pregnancy test for human	Serum pregnancy test for female patients of	A urine sample was tested for drugs of

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Safety Assessments	M93-113	M93-098	M92-762
tests	chorionic gonadotropin (β -HCG) for female patients of childbearing potential Serum evaluations for HBsAg and anti-hepatitis C antibodies Urine drug screen for drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite (benzoylecgonine), ethyl alcohol, methadone, opiates, phencyclidine (PCP), phenothiazines, propoxyphene, and tricyclic antidepressants Plasma sertindole concentrations	childbearing potential Serum evaluations for HBsAg and anti-hepatitis C antibodies Urine drug screen for drugs of abuse, including amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine metabolite (benzoylecgonine), ethyl alcohol, methadone, opiates, phencyclidine (PCP), phenothiazines, propoxyphene, and tricyclic antidepressants Plasma sertindole concentrations	abuse, including alcohol Serum sertindole concentrations
Other Safety Parameters	Medical and psychiatric histories	Medical and psychiatric histories	Medical and psychiatric histories
^a All scheduled blood and urine samples for clinical laboratory tests were to be collected under fasting conditions and handled in accordance with accepted laboratory procedures			

Study M93-113

Table 4													
Schedule of Activities													
Procedure	Screening Period (1 to 7 days prior to 1st dose of Placebo Lead-In)	Placebo Lead-In Period		Titration Period		Maintenance Period						Discharge Day	Follow- Up Visit [#]
		Week -1		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8		
		Days -7 to -2	Day -1 ^a	Day 7 ^a	Day 14 ^a	Day 21 ^a	Day 28 ^a	Day 35 ^a	Day 42 ^a	Day 49 ^a	Day 56	Day 57 ^a	
Informed Consent	X												
Medical History	X												
Physical Examination	X		X									X	X ^b
Neurological Examination	X		X									X	X ^b
Study Drug Administration ^c		X ^d	X	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e		
Vital Signs ^f	X		X	X	X	X	X	X	X	X		X	X ^b
Electrocardiogram	X		X		X	X		X		X		X	
Laboratory Analyses	X ^g		X	X	X	X	X	X	X	X		X	
Sertindole Concentration ^h			X	X	X	X	X	X	X	X		X	
Psychiatric Rating Scales	X		X ⁱ	X	X ⁱ	X	X	X ⁱ	X	X	X ⁱ	X ^{i,j}	
Movement Rating Scales	X		X	X	X	X	X	X	X	X	X	X	
Schedule for the Deficit Syndrome			X										
Adjunctive Drug Administration ^k	X	X	X	X	X	X	X	X	X	X	X	X	X ^b
Adverse Events		X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X ^e	X	X ^b
Serum Pregnancy Test ^l	X						X					X	

^a Patient awakened at 7 am
^b Completed only for patients not entering continuation study
^c At approximately 0900 and 2100 hours
^d Study drug was to be administered on Days -7 through -1 if patient was randomized early, study drug was to be administered from at least Day -4 through Day -1
^e Daily
^f Follow-up Visit performed only if patient did not continue into the continuation study
^g Includes hepatitis and urine drug screens
^h Within 1 hour prior to morning dose
ⁱ Scale for the Assessment of Negative Symptoms (SANS) also required
^j If not performed within the last 2 days
^k As needed
^l For females of childbearing potential only

Study M93-098

Table 3 Schedule of Activities													
Procedure	Screening Period (1 to 7 days prior to 1st dose of Placebo Lead-In)	Placebo Lead-In Period		Titration Period		Maintenance Period						Discharge Day Day 57 ^a	Follow- Up Visit
		Week -1		Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8		
		Days -7 to -2	Day -1 ^a	Day 7 ^a	Day 14 ^a	Day 21 ^a	Day 28 ^a	Day 35 ^a	Day 42 ^a	Day 49 ^a	Day 56		
Informed Consent	X												
Medical History	X												
Physical Examination	X		X ^b									X ^b	X ^c
Neurological Examination	X		X									X	X ^c
Study Drug Administration ^d		X ^e	X	X	X	X	X	X	X	X	X		
Vital Signs	X		X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X	X ^c
Electrocardiogram	X			X		X		X				X	
Laboratory Analyses (fasting)	X ^g		X	X	X	X	X	X	X	X		X	
Sertindole Concentration			X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X ^h	X ^h		X	
Psychiatric Rating Scales	X		X	X	X	X	X	X	X	X	X	X ⁱ	
Movement Rating Scales	X		X	X	X	X	X	X	X	X	X	X ⁱ	
Adjunctive Drug Administration ^j	X	X	X	X	X	X	X	X	X	X	X	X	X ^c
Adverse Events ^d		X	X	X	X	X	X	X	X	X	X	X	X ^c
Serum Pregnancy Test ^k	X						X					X	

^a Patient awakened at 0700 hours
^b Including digital rectal exam for male patients
^c Two weeks following discharge; only for patients not entering continuation study
^d Daily
^e Study drug was to be administered on Days -7 through -1; if patient was randomized early, study drug was to be administered from at least Day -4 through Day -1
^f Within 45 minutes prior to morning dose
^g Including urine drug screen and hepatitis screen
^h Within 1 hour prior to morning dose
ⁱ If one was not performed within previous 2 days
^j As needed
^k For females of childbearing potential only

Study M92-762

Table 3 Schedule of Study Activities														
Procedure	Screening Period	Placebo Lead-In Period		Titration Period				Maintenance Period				Discharge Day ^a	Follow-Up Visit	
		Week -1		Week 1		Week 2		Week 3	Week 4	Week 5	Week 6	Day 41		
		Days -7 to -2	Day -1	Day 6	Day 7	Day 12	Day 13	Day 19	Day 26	Day 33	Day 40			
Informed Consent	X													
Medical History	X													
Physical Examination	X ^b		X ^b									X ^c	X ^d	
Neurological Examination	X		X									X	X ^d	
Study Drug Administration		X ^e	X	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f			
Vital Signs	X	X ^f	X	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X ^f	X	X ^d	
Electrocardiogram	X		X			X			X			X		
Clinical Laboratory Profile	X ^{g,h}		X ^g		X		X	X	X ^g	X		X ^g		
Serum Sertindole Concentration			X		X		X	X	X	X		X		
Serum Sertindole Concentration (peak)								X ⁱ	X ⁱ	X ⁱ				
Serum Prolactin Concentration			X		X		X	X	X	X		X ^h		
Psychiatric Rating Scale Battery	X		X	X		X		X	X	X	X			
Movement Rating Scale Battery	X		X	X		X		X	X	X	X			
Adjunctive Drug Administration ^j	X	X	X	X	X	X	X	X	X	X	X			
Adverse Events		X	X	X	X	X	X	X	X	X	X	X	X ^d	

^a To be performed on the final study day or prior to discharge any time a patient discontinued
^b Included digital rectal examination for male patients unless a documented examination had been performed within previous 30 days; could be deferred until end of Titration Period.
^c Included digital rectal examination for male patients
^d To be completed only for patients not entering the continuation study
^e Study drug administered on Days -7 through -1; if patient was randomized early, study drug administered from at least Day -4 through Day -1
^f Daily
^g Included PSA and PAP for male patients only; not to be collected within 24 hrs after rectal examination
^h To be obtained at the same clock time as during the study
ⁱ Blood sample to be drawn eight hours after dosing on only one of the following study days: Day 19, 26, or 33
^j As needed

Appendix H

Table 1 Mean Change in Clinical Chemistry Values from Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	n	Sertindole Daily Dose												Placebo		
		8 mg			12 mg			20 mg			24 mg			n	BL	Δ
		BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ	n			
Albumin (g/dL)	48	4.47	-0.2	124	4.48	-0.16	226	4.48	-0.14	175	4.47	-0.09	224	4.49	0.02	
Alkaline Phosphate (IU/L)	48	86.6	-2.9	124	90.1	-5.1	226	87.6	-3.7	175	87.8	-3.7	224	86.0	-2.9	
Bicarbonate (mEq/L)	48	24.29	-1.5	123	24.12	-1.19	226	24.38	-0.88	175	24.46	-1.14	224	24.6	-0.36	
BUN (mg/dL)	48	11.7	0	124	11.8	0.1	226	12.2	-0.2	175	12.1	0.1	224	11.9	-0.3	
Calcium (mg/dL)	48	9.48	-0.17	124	9.37	-0.11	226	9.31	-0.08	175	9.28	-0.04	224	9.35	-0.01	
Cholesterol (mg/dL)	48	198.3	-2.8	124	192.5	4.8	226	197.8	4.2	175	194.2	3.7	224	198.1	-3.0	
Chloride (mEq/L)	48	102.3	2.8	124	103.1	1.7	226	103.0	1.2	175	103.2	1.3	224	103.0	0.6	
Creatinine (mg/dL)	48	1.194	-0.048	124	1.195	-0.049	226	1.153	-0.044	175	1.142	-0.03	224	1.147	-0.001	
Glucose (mg/dL)	48	96.2	0.1	124	91.6	7.9	226	97.9	5.8	175	95.8	8.1	224	95.1	0.2	
Potassium (mEq/L)	48	4.32	-0.14	124	4.32	-0.09	226	4.34	-0.12	175	4.38	-0.16	224	4.36	-0.08	
LDH (IU/L)	48	151.1	-0.3	123	163.5	-1.1	226	165.7	2.7	175	162.1	-0.3	224	164.2	0.5	
Sodium (mEq/L)	48	138.6	1.1	124	139.2	0.4	226	139.1	0.7	175	139.5	0.1	224	139.4	0.3	
Phosphorous (mg/dL)	48	3.62	0.10	124	3.69	0.02	226	3.72	0.09	175	3.68	0.10	224	3.71	-0.07	
PSA (IU/L)	40	0.570	0.058	43	0.633	0.007	42	0.510	-0.048		–	–	41	0.607	-0.098	
AST(SGOT) (IU/L)	48	21.5	0.7	124	23.1	1.1	226	22.1	2.6	175	22.3	0.5	224	21.7	0.6	
ALT(SGPT) (IU/L)	48	26.3	0.1	124	28.9	4.7	226	28.6	5.6	175	27.9	2.0	224	27.5	-1.8	
Total Bilirubin (mg/dL)	48	0.552	-0.019	124	0.519	-0.025	226	0.508	-0.032	175	0.510	-0.022	224	0.550	0.022	
Total Protein (g/dL)	48	7.39	-0.24	124	7.23	-0.23	226	7.24	-0.16	175	7.25	-0.13	224	7.24	-0.02	
Triglyceride (mg/dL)	48	169.0	1.1	124	141.8	28.4	226	148.2	27.5	175	145.7	19.7	224	153.9	-6.2	
Uric Acid (mg/dL)	48	5.48	0.51	124	5.51	0.64	226	5.39	0.54	175	5.52	0.40	224	5.45	0.58	

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.

Table 2 Mean Change in Hematology Values from Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ
Bands (%)	46	1.39	-0.41	122	0.39	0.24	223	0.27	0.10	174	0	0.01	221	0.24	0.01
Basophils (%)	46	0.02	0.05	123	0.57	0.02	223	0.79	-0.10	174	0.97	-0.06	221	0.76	0.05
Eosinophils (%)	46	2.07	-0.05	123	1.95	0.30	223	2.08	0.36	174	1.86	0.05	222	1.99	0.24
Hemoglobin (g/dL)	48	14.9	-0.68	124	14.6	-0.42	226	14.7	-0.49	174	14.5	-0.43	224	14.8	-0.05
Hematocrit (%)	48	46.4	-1.92	124	45.4	-1.25	226	45.7	-1.45	174	45.2	-1.20	224	45.9	0.00
Lymphocytes (%)	46	35.9	-0.12	123	31.2	0.11	223	30.4	-0.69	174	29.7	-1.35	222	30.1	6.82
Atypical Lymphocytes (%)	46	0.46	-0.22	122	1.36	-0.10	223	1.72	0.08	174	2.16	-0.13	221	1.68	0.17
Vacuolated Lymphocytes (%)	48	0.00	0.00	49	0.00	0.08	52	0.02	0.00		–	–	46	0.00	0.02
MCHC (g/dL)	48	32.1	-0.16	124	32.1	-0.03	226	32.2	-0.06	174	32.2	-0.13	224	32.4	-0.11
Mean Corpuscular Volume (fL)	48	91.7	-0.04	124	92.2	0.47	226	91.7	-0.26	174	91.8	-0.40	224	92.4	-0.03
Monocytes (%)	46	7.48	-0.58	123	6.85	-0.16	223	6.84	-0.04	174	6.75	0.04	222	6.72	0.28
Neutrophils (%)	46	52.3	1.56	123	57.5	-0.36	223	57.9	0.28	174	58.6	1.43	222	58.4	-1.68
Platelet Count (x10 ⁹ /L)	48	262	-18.0	124	272	-13.0	224	271	-12.4	173	267	-9.9	224	253	-0.1
Red Blood Cells (x10 ¹² /L)	48	5.08	-0.21	124	4.95	-0.16	226	5.00	-0.15	174	4.94	-0.11	224	4.98	0.003
White Cell Count (x10 ⁹ /L)	48	7.28	-0.32	124	7.66	-0.46	226	7.65	-0.55	174	7.47	-0.43	224	7.52	-0.28

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.

Table 3 Mean Change in Urinalysis Values from Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose												Placebo		
	n	8 mg		n	12 mg		n	20 mg		n	24 mg		n	BL	Δ
		BL	Δ		BL	Δ		BL	Δ		BL	Δ		BL	Δ
pH	46	5.92	0.03	122	5.95	-0.13	225	5.93	-0.15	170	5.94	-0.12	220	5.85	-0.12
Specific gravity	46	1.015	0	122	1.016	-0.001	225	1.018	-0.001	170	1.018	-0.001	220	1.018	0.000

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.

Table 4 Number and Percentage of Patients Meeting Outlier Criteria for Clinical Chemistry Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Albumin (g/dL)	49	0	0	124	0	0	226	0	0	175	0	0	224	0	0
Alkaline Phosphate (IU/L)	49	0	0	124	0	0	226	0	0	175	0	0	224	0	0
Bicarbonate (mEq/L)	49	1	2.0	124	0	0	226	0	0	175	0	0	224	0	0
BUN (mg/dL)	49	0	0	124	1	0.8	226	0	0	175	1	0.6	224	0	0
Calcium(mg/dL)	49	3	6.1	124	2	1.6	226	4	1.8	175	5	2.9	224	1	0.4
Cholesterol (mg/dL)	49	13	26.5	124	31	25.0	226	65	28.8	175	55	31.4	224	55	24.6
Chloride (mEq/L)	49	0	0	124	0	0	226	0	0	175	1	0.6	224	2	0.9
Creatinine (mg/dL)	49	0	0	124	1	0.8	226	1	0.4	175	0	0	224	0	0
Glucose (mg/dL)	49	12	24.5	124	32	25.8	226	72	31.9	175	49	28.0	224	44	19.6
Potassium (mEq/L)	49	1	2	124	0	0	226	3	1.3	175	5	2.9	224	4	1.8
LDH (IU/L)	49	0	0	124	0	0	226	0	0	175	0	0	224	0	0
Sodium (mEq/L)	49	1	2.0	124	1	0.8	226	3	1.3	175	2	1.1	224	4	1.8
Phosphorous (mg/dL)	49	1	2	124	3	2.4	226	3	1.3	175	2	1.1	224	4	1.8
PSA (IU/L)	41	0	0	44	1	2.3	66	0	0	32	1	3.1	69	1	1.4
AST(SGOT) (IU/L)	49	0	0	124	2	1.6	226	3	1.3	175	1	0.6	224	0	0
ALT(SGPT) (IU/L)	49	1	2.0	124	4	3.2	226	10	4.4	175	8	4.6	224	0	0
Total Bilirubin (mg/dL)	49	0	0	124	0	0	226	0	0	175	1	0.6	224	1	0.4
Total Protein (g/dL)	49	0	0	124	0	0	226	0	0	175	0	0	224	0	0
Triglyceride (mg/dL) ¹	49	23	46.9	124	51	41.1	226	104	46	175	93	53.1	224	81	36.2
Triglyceride (mg/dL) ²	49	3	6.1	124	5	4.0	226	16	7.1	175	6	3.4	224	9	4.0
Uric Acid (mg/dL)	49	2	4.1	124	6	4.8	226	3	1.3	175	6	3.4	224	8	3.6

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100; 1 = outlier ≥ 200mg/dL; 2 = outlier ≥ 500mg/dL

Table 5 Criteria for Very Low and Very High Clinical Chemistry Values in Placebo-Controlled Studies

Parameter	FDA Request Criteria	
	Very Low	Very High
Albumin	≤ 2.5 g/dL	–
Alkaline phosphatase	–	≥ 390 IU/L
Bicarbonate	≤ 12 mEq/L	≥ 38 mEq/L
BUN	–	≥ 30 mg/dL
Calcium	≤ 8.2 mg/dL	≥ 12 mg/dL
Chloride	≤ 90 mEq/L	≥ 118 mEq/L
Cholesterol	–	≥ 240 mg/dL
Creatinine	–	≥ 2.0 mg/dL
Glucose	≤ 45 mg/dL	≥ 126 mg/dL
LDH	–	≥ 750 IU/L
Inorganic Phosphorus	≤ 1.7 mg/dL	≥ 5.5 mg/dL
Potassium	≤ 3.0 mEq/L	≥ 6.0 mEq/L
PSA	–	≥ 1 x ULN
PAP	–	≥ 1 x ULN
SGOT/AST	–	≥ 150 IU/L
SGPT/ALT	–	≥ 165 IU/L
Sodium	≤ 130 mEq/L	≥ 150 mEq/L
Total bilirubin	–	≥ 2.0 mg/dL
Total protein	≤ 4.5 g/dL	≥ 10.0 g/dL
Triglycerides	–	≥ 200 and ≥ 500 mg/dL
Uric acid	–	–
Female	–	≥8.5 mg/dL
Male	–	≥10.5 mg/dL

ULN = Upper limit of normal.

Table 6 Number and Percent of Patients with Outlier Values for Glucose, Total Cholesterol, and Triglycerides at Endpoint but Not at Baseline: Placebo-Controlled, Fixed Dose Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Cholesterol (mg/dL)	49	4	8.2	124	9	7.3	226	14	6.2	175	14	8	224	12	5.4
Glucose (mg/dL)	49	1	2	124	10	8.1	226	23	10.2	175	13	7.4	224	9	4
Triglyceride (mg/dL) ¹	49	5	10.2	124	17	13.7	226	30	13.3	175	25	14.3	224	19	8.5
Triglyceride (mg/dL) ²	49	0	-	124	0	-	226	1	0.4	175	1	0.6	224	0	-

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100; 1 = outlier ≥ 200mg/dL; 2 = outlier ≥ 500mg/dL

Table 7 Number and Percentage of Patients Meeting Outlier Criteria for Hematology Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Bands (%)	48	1	2.1	124	3	2.4	224	4	1.8	174	1	0.6	222	3	1.4
Basophils (%)	48	0	0	124	0	0	224	1	0.4	174	0	0	222	0	0
Eosinophils (%)	48	2	4.2	124	3	2.4	224	5	2.2	174	5	2.9	223	6	2.7
Hemoglobin (g/dL)	49	0	0	124	3	2.4	226	6	2.7	174	5	2.9	224	5	2.2
Hematocrit (%)	49	1	2.0	124	5	4.0	226	13	5.8	174	8	4.6	224	12	5.4
Lymphocytes (%)	48	1	2.1	124	0	0	224	1	0.4	174	1	0.6	223	3	1.3
Atypical Lymphocytes (%)	48	1	2.1	124	7	5.6	224	16	7.1	174	7	4.0	222	20	9.0
Vacuolated Lymphocytes (%)	49	0	0	50	0	0	54	0	0	1	0	0	49	0	0
MCHC (g/dL)	49	0	0	124	0	0	226	0	0	174	0	0	224	0	0
Mean Corpuscular Volume (fL)	49	0	0	124	0	0	226	0	0	174	0	0	224	0	0
Monocytes (%)	48	4	8.3	124	3	2.4	224	8	3.6	174	1	0.6	223	6	2.7
Neutrophils (%)	48	1	2.1	124	1	0.8	224	0	0	174	0	0	223	2	0.9
Platelet Count (x10 ⁹ /L)	49	0	0	124	1	0.8	225	1	0.4	174	1	0.6	224	2	0.9
Red Blood Cells (x10 ¹² /L)	49	1	2.0	124	2	1.6	226	4	1.8	174	1	0.6	224	3	1.3
White Cell Count (x10 ⁹ /L)	49	0	0	124	3	2.4	226	3	1.3	174	6	3.4	224	9	4.0

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100.

Table 8 Criteria for Very Low and Very High Hematology Values in Placebo-Controlled Studies

Parameter	FDA Request Criteria	
	Very Low	Very High
Hemoglobin		
Female	≤ 9.5 g/dL	≥ 16.5 g/dL
Male	≤ 11.5 g/dL	≥ 18.5 g/dL
Hematocrit		
Female	≤ 32%	≥ 50%
Male	≤ 37%	≥ 55%
Red Blood Cells		
Female	≤ 3.5 x10 ¹² /L	≥ 6.0 x10 ¹² /L
Male	≤ 3.8 x10 ¹² /L	≥ 7.0 x10 ¹² /L
White Blood Cells		
Platelet Counts	≤ 75 x10 ⁹ /L	≥ 700 x10 ⁹ /L
Eosinophils	–	≥ 10%
Basophils	–	≥ 10%
Lymphocytes	–	≥ 75%
Monocytes	–	≥ 15%
Neutrophils	≤ 15%	–
Bands	–	≥ 10%
Mean Corpuscular Volume (fL)	≤ 0.8 x LLN	≥ 1.2 x ULN
Mean Corpuscular Hemoglobin Concentration (g/dL)	≤ 0.8 x LLN	≥ 1.2 x ULN
Atypical lymphocytes	–	≥ 5%
Vacuolated Lymphocytes	–	≥ 5%

LLN=lower limit of normal; ULN=upper limit of normal

Table 9 **Number and Percentage of Patients Meeting Outlier Criteria for Urinalysis Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)**

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Casts	0	0		0	0		1	0	0	0	0		2	0	0
Ketones	49	0	0	123	0	0	225	0	0	170	0	0	220	0	0
pH	49	0	0	123	1	0.8	225	1	0.4	170	0	0	220	2	0.9
Specific Gravity	49	0	0	123	0	0	225	0	0	170	0	0	220	0	0
Urinalysis Glucose	49	0	0	123	1	0.8	225	3	1.3	170	2	1.2	220	4	1.8
Urinalysis Protein	49	0	0	123	0	0	225	3	1.3	170	0	0	220	4	1.8
Urinalysis RBC	9	0	0	37	5	13.5	79	20	25.3	82	19	23.2	100	22	22.0
Urinalysis WBC	9	1	11.1	37	8	21.6	79	14	17.7	82	7	8.5	101	16	15.8

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100.

Table 10 Criteria for Very Low and Very High Urinalysis Values in Placebo-Controlled Studies

Parameter	FDA Request Criteria	
	Very Low	Very High
Specific gravity	≤ 1.001	
pH	≤ 4	≥ 9
Protein		≥ 3+ (≥10)
Ketones		≥ 4+
Red blood cells		
Female		≥ 10/hpf
Male		≥ 8/hpf
White blood cells		≥ 10/hpf (≥2+)
Casts		≥ 9
Glucose		≥ 4+

Appendix I

Table 1 Mean Change in Weight and Vital Sign Values From Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ
SBP (mmHg)	51	121.7	1.5	125	117.3	1.4	224	117.6	1.8	173	117.1	0.5	221	115.5	0.7
DBP (mmHg)	51	75.7	2.3	125	76.3	-2.4	224	75.4	-0.3	173	75.8	-1.7	221	74.6	-0.4
Pulse Rate (BPM)	51	85.3	-0.2	125	79.4	2.4	224	80.9	2.6	172	79.8	3.5	221	80.4	0.3
Temperature (°F)	52	97.9	-0.3	124	97.62	-0.2	224	97.68	-0.2	173	97.82	-0.2	218	97.71	0.05
Weight (kg)	36	79.28	1.48	89	81.04	2.58	155	78.59	3.31	135	80.18	3.19	164	79.22	0.18
Orthostatic Change: SBP (mmHg)	48	-3.6	-0.5	123	-2.5	-3.3	219	-2.6	-2.1	168	-2.2	-2	210	-1.6	-0.1
Orthostatic Change: Pulse Rate (bpm)	48	7.6	4.7	119	9.2	0.4	216	7.3	1.7	166	8.5	0.8	204	7.5	0.3

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline.

Table 2 Number and Percentage of Patients Meeting Outlier Criteria for Weight and Vital Sign Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
SBP (mmHg)															
Low: ≤90 mmHg	51	5	9.8	125	18	14.4	226	26	11.5	175	26	14.9	224	43	19.2
High: ≥180 mmHg	51	1	2	125	0	–	226	2	0.9	175	0	–	224	6	2.7
DBP (mmHg)															
Low: ≤50 mmHg	51	5	9.8	125	8	6.4	226	12	5.3	175	9	5.1	224	14	6.3
High: ≥105 mmHg	51	4	7.8	125	5	4	226	6	2.7	175	0	–	224	3	1.3
Pulse Rate (Beats/min)															
Low: ≤50 bpm	51	1	2	125	2	1.6	226	0	–	175	0	–	224	3	1.3
High: ≥120 bpm	51	6	11.8	125	12	9.6	226	19	8.4	175	10	5.7	224	10	4.5
Temperature															
Low: decreased ≥2°F from baseline	52	22	42.3	124	33	26.6	224	48	21.4	173	24	13.9	218	36	16.5
High: ≥ 101° F and increased ≥ 2°F from baseline	52	2	3.8	124	0	–	224	3	1.3	173	2	1.2	218	1	0.5
Weight (kg)															
Lost ≥7% baseline weight	36	0	–	89	3	3.4	155	1	0.6	135	3	2.2	164	9	5.5
Gained ≥7% baseline weight	36	4	11.1	89	19	21.3	155	43	27.7	135	37	27.4	164	18	11
Orthostatic Change: SBP (mmHg)															
Decreased ≥30 from supine	51	20	39.2	124	27	21.8	226	44	19.5	174	26	14.9	222	18	8.1
Orthostatic Change: Pulse Rate (bpm)															
Increased ≥20 from supine	51	41	80.4	123	78	63.4	225	126	56	172	87	50.6	219	126	57.5

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100.

Appendix J

Table 1 Mean Change in ECG Parameters Values from Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	n	Sertindole Daily Dose													
		8 mg		12 mg		20 mg		24 mg		Placebo					
		BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ
Heart Rate (bpm)	46	83.3	0.1	118	79.4	2.3	210	78.6	2.6	159	78.9	1.7	205	79.6	0.5
PR interval (msec)	46	151.6	-0.8	116	150.7	-0.5	210	152.8	-3.1	159	152.1	-1.9	205	154.1	-1.3
QRS duration (msec)	46	88.2	1.7	116	89.5	-0.8	210	87.9	-0.3	159	85.7	-0.7	205	87.8	1.0
QT interval (msec)	46	357.4	13.1	118	360.2	9.4	210	365.6	15.9	159	364.8	19.6	205	365.8	-4.8
QT _{CB} interval (msec)	46	417.4	15.3	118	411.1	15.9	210	414.5	25.6	159	414.9	26.4	205	417.1	-4.6
QT _{CF} interval (msec)	46	396.1	14.48	118	393.1	13.5	210	397.2	22.1	159	397.2	23.9	205	398.9	-4.7

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline; QT_{CB} = QT/√RR; QT_{CF} = QT/RR^{1/3}

Table 2 Number and Percentage of Patients Meeting Outlier Criteria for ECG Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose														
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Heart Rate (bpm)															
Low: ≤ 50 bpm and decreased ≥ 30 from baseline	46	0	–	118	1	0.8	210	0	–	159	0	–	205	1	0.5
High: from ≥ 120 bpm and increased ≥ 30 from baseline	46	0	–	118	1	0.8	210	2	1	159	0	–	205	1	0.5
PR Interval															
High: ≥ 210 msec	46	0	–	119	1	0.8	212	1	0.5	163	2	1.2	212	3	1.4
QT Interval															
High: ≥ 500 msec	46	0	–	119	1	0.8	212	1	0.5	163	0	–	212	0	–
QT_{C_B} Interval															
High: ≥ 500 msec	46	0	–	119	1	0.8	212	10	4.7	163	10	6.1	212	1	0.5
≥ 30 msec prolonged from baseline	46	18	39.1	118	55	46.6	210	121	57.6	159	100	62.9	205	23	11.2
≥ 60 msec prolonged from baseline	46	1	2.2	118	7	5.9	210	38	18.1	159	37	23.3	205	3	1.5
QT_{C_F} Interval															
High: ≥ 500 msec	46	0	–	119	1	0.8	212	4	1.9	163	4	2.5	212	0	–
≥ 30 msec prolonged from baseline	46	13	28.3	118	38	32.2	210	100	47.6	159	83	52.2	205	11	5.4
≥ 60 msec prolonged from baseline	46	2	4.3	118	1	0.8	210	22	10.5	159	27	17.0	205	0	–
QRS Duration															
High: ≥ 150 msec	46	0	–	119	0	–	212	0	–	163	1	0.6	212	1	0.5

n = Number tested; N = Number meeting outlier criteria; % = $N/n \times 100$; QT_{C_B} = QT/\sqrt{RR} ; QT_{C_F} = $QT/RR^{1/2}$

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-644/N_000
Drug Name: Sertindole
Indication(s): Treatment of schizophrenia and of reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia
Applicant: H. Lundbeck A/S
Date of Receipt: 02 July 2008
Review Priority: Standard

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Keywords: non-inferiority analysis

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1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor conducted the SCoP study to address the worldwide concerns about the potential QT prolongation and pre-specified the first primary endpoint to be the all-cause mortality, with the goal to demonstrate non-inferiority of sertindole to risperidone. However, it is not clear whether the sponsor has demonstrated the non-inferiority. Furthermore, analysis of this endpoint may not best address the underlying safety concerns. Other more relevant endpoints such as cardiac death, documented sudden cardiac death, dictionary-derived dizziness, seem to suggest a higher risk in the sertindole group. With regard to suicide attempts and completed suicide, although the numerical results trended in favor of sertindole, the evidence appears to be inconclusive based on the C-CASA re-classification.

From the statistical perspective, there was no convincing evidence to support the safety claim of suicidality reduction. Whether the sponsor has adequately established a benefit that could overcome the risk will be discussed at the Psychopharmacologic Drug Advisory Committee meeting.

1.2 Brief Overview of Clinical Studies

This is a resubmission by H. Lundbeck A/S (the manufacturer of sertindole). The application was originally filed by Abbott Laboratories in 1995. In the original submission by Abbott, efficacy in treating patients with schizophrenia was demonstrated, but FDA issued an Approvable Letter primarily due to the potential QT prolongation. Despite this, sertindole obtained a European Union authorization in 1996. Abbott subsequently amended its application in the United States in December 1996. However, FDA repeated the Approvable action. Given worldwide concerns about sertindole's potential QT prolongation and increased cardiac mortality, Abbott withdrew this NDA in January 1998. The European Union marketing authorizations of sertindole were suspended in the same year.

To address the worldwide concerns about the safety of sertindole, H. Lundbeck A/S, conducted the Sertindole Cohort Prospective (SCoP) Study (Study 99824) to evaluate its safety under normal conditions of use. This was an open-label, randomized, large trial comparing sertindole with risperidone on safety endpoints. It enrolled nearly 10,000 patients with roughly 14,000 patient-years exposure. The primary objective was to assess whether the perceived risk of increased mortality was in fact true. In addition, CHMP requested assessment of the frequency of cardiac events, including arrhythmias, requiring hospitalization. Since FDA expressed that an excess risk of cardiac deaths would not necessarily be reflected in a higher overall mortality, FDA also reviewed cardiac death data, documented sudden cardiac death (including cardiac origin probable) data, and certain dictionary-derived adverse events (syncope, palpitations, dizziness). In addition

to risk assessment, FDA also reviewed the suicidality data to determine whether the sponsor has established a benefit that could overcome the risk.

1.3 Statistical Issues and Findings

In the SCoP study, the sponsor chose all-cause mortality as the first primary endpoint because they believed that it was the only unbiased endpoint in a large study as such. FDA expressed a concern about the all-cause mortality endpoint because an excess risk of cardiac deaths for sertindole compared to risperidone would not necessarily be reflected in a higher overall mortality for sertindole, given the relatively higher mortality in this population from multiple causes, and suggested that the sponsor estimate the risk of the sudden unexpected death. Furthermore, FDA recommended that the sponsor do additional work to establish a benefit that could overcome the risk. Summarized below are results of these relevant endpoints as well as statistical issues.

- [1] **Potential Inflation of Overall Type I error Rate.** For a given endpoint, multiple data sets were generated based on different study periods and different classification approaches. Furthermore, multiple analyses (Cox models) were performed for a given data set. For example, the pre-specified primary Cox model for all-cause mortality included two covariates (age and sex) only. However, after data unblinding, the sponsor added 3 additional baseline covariates to the model via a model selection approach. Typically the reproducibility of the study result could be an issue if the same data set is used to develop the statistical model and test the treatment effect with the model developed by it, as in this study. A major concern is the potential inflation of the overall type I error rate due to multiple analyses (model fittings) for the same endpoint. If the results were generally consistent across different analyses (Cox models) and different study periods, the multiplicity issue may be alleviated. Otherwise, the results should be interpreted with great caution. With regard to the study period (refer to definitions in Section 3.2.4), although the sponsor pointed out that the ORT+1 study period could reduce certain confounding effects, one cannot ignore the add-on therapy period while patients still received the randomized treatment, if it's not clear which drug (the add-on or the randomized drug) contributed to the event; in addition, WRT+30 was the pre-specified study period for all analyses and report. If ORT+1 were considered the most appropriate study period, it should have been pre-specified as the primary study period. From the statistical perspective, shopping and picking after data unblinding is very problematic unless the purpose is to check the consistency. Beyond this, if there is a clinical uncertainty about which study period to rely on, to protect the public health, (a) on the risk side, it would be sensible for FDA to place more weight on the results that revealed large adverse event signals associated with sertindole, and (b) on the benefit side, to place more weight on the more conservative results.
- [2] **Duration of Exposure to Treatment.** Overall, shorter exposure durations were observed in the sertindole group whether based on the WRT or the ORT study period.

This might suggest a potential underestimation of a harmful trend for sertindole, such as suicide attempts.

- [3] **All-Cause Mortality.** The sponsor intended to demonstrate non-inferiority of sertindole to risperidone by showing that the two-sided 90% CI (confidence interval) of the hazard ratio (sertindole/ risperidone) was entirely below the pre-specified threshold 1.5. The FDA statistical reviewers have the following concerns:
- The sponsor indicated that the non-inferiority threshold was chosen as the largest ratio that was clinically acceptable to CHMP and that, at the same time, took into account the feasibility of conducting such a study. On face, a 50% non-inferiority margin seems to be quite liberal because it would suggest a non-inferiority if sertindole were shown to be at most 50% worse than risperidone. It is uncertain whether FDA can rely on this margin for drugs intended for the U.S. marketing, in particular when this is not the endpoint FDA would primarily focus on.
 - The sponsor utilized a two-sided 90% CI to compare with a pre-specified non-inferiority threshold. As a standard practice, FDA has been utilizing a two-sided 95% CI in non-inferiority analysis. Based on this standard practice, the upper limits of the 95% CIs generally exceeded 1.5, but were generally below 1.6. This suggests that one might be able to rule out that sertindole was more than roughly 60% worse than risperidone, but one cannot rule out that sertindole was 50% worse than risperidone, in the risk of all-cause mortality.
- [4] **Cardiac Events, Requiring Hospitalization.** The sponsor intended to demonstrate non-inferiority of sertindole to risperidone by showing that the two-sided 90% CI of the hazard ratio (sertindole / risperidone) was entirely below the pre-specified threshold 2. However, the analysis was not performed because of very few events.
- [5] **Cardiac Death.** Regardless of the coding approach, the results appear to be similar across different analysis models. The observed hazard ratios (sertindole/ risperidone) were all greater than 2. Moreover, the ISC classification seems to suggest a higher risk of cardiac death for the sertindole group at the nominal significance level of 0.05.
- [6] **Documented Sudden Cardiac Death (including Cardiac Origin Probable).** There were more events observed in the sertindole group as compared to the risperidone group (13 vs. 3). The observed hazard ratio (sertindole / risperidone) was around 5. The 95% CI was very wide, but was still entirely above 1, suggesting a higher risk of sudden cardiac death in the sertindole group than in the risperidone group at the nominal significance level of 0.05. The result was very similar after removing all patients in the sertindole group who had risperidone added to their treatment and all patients in the risperidone group who had sertindole added to their treatment. The result remained similar after further removing those patients who had thioridazine, mesoridazine, ziprasidone, or pimozide added to their randomized treatment from both treatment groups.

- [7] **Dictionary-Derived Adverse Events: Syncope, Palpitations, and Dizziness.** In these analyses, all patients in the risperidone group who had sertindole added to their randomized treatment and all patients in the sertindole group who had risperidone added to their randomized treatment were removed. Also, removed from both treatment groups were those patients who had thioridazine, mesoridazine, ziprasidone, or pimozide added to their randomized treatment. The results seem to suggest higher incidences of Dizziness for the sertindole group than the risperidone group at the nominal significance level of 0.05.
- [8] **Suicide Attempts.** Although the MedDRA coding suggested a lower risk of suicide attempts for the sertindole group than for the risperidone group at the nominal significance level of 0.05, this classification was performed by investigators who were not blind to the treatment. Hence, a bias may be introduced in determining suicide attempts. Although the ISC was blind to treatment, the ISC definition of suicide attempts was very broad because it included suicidal ideation and tendency. Therefore, FDA requested that the sponsor reclassify the ISC identified suicide attempts in a more systematic manner and reanalyze the data. Based on the C-CASA reclassification, the results did not suggest a statistically significant difference at the nominal significance level of 0.05, although there was a trend in favor of sertindole. Two patients with suicide attempts in the sertindole group were automatically excluded from the sponsor's analyses because these patients had missing covariate values. When the missing covariate values were imputed to bring these two patients back to analysis, the trend diminished regardless of study period. Similar finding was observed if the Cox model included only two covariates (age and sex) that had no missing values. In addition, shorter exposure durations were observed in the sertindole group. This may lead to underestimated hazards in the sertindole group.
- [9] **Completed Suicide.** The results appear to be similar in analyses regardless of the coding approach (MedDRA, ISC classification, or C-CASA reclassification). The observed hazard ratios (sertindole/ risperidone) for completed suicide trended in favor of sertindole, but the 95% CI did not suggest a statistically significant difference at the nominal significance level of 0.05. In addition, shorter exposure durations were observed in the sertindole group. This may lead to underestimated hazards in the sertindole group.
- [10] **Labeling Claim on Suicidality Reduction.** The sponsor proposed a safety claim that sertindole is indicated for reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia. From the statistical perspective, a multiple testing procedure to control the overall (studywise) type I error rate needs to be pre-specified for all efficacy and safety endpoints intended for claims. This is to avoid excess chance of false positive conclusions. In this study, completed suicide and suicide attempts were analyzed using multiple study periods. There was no pre-specified multiple testing procedure to address the multiple endpoints (completed suicide and suicide attempts) and multiple analyses issues, and all statistical analyses

were performed at the nominal significance level of 0.05. From the statistical perspective, there was no conclusive evidence to support the safety claim.

2 INTRODUCTION

2.1 Overview

This is a resubmission by H. Lundbeck A/S (the manufacturer of sertindole). The application was originally filed by Abbott Laboratories in 1995.

In the original submission by Abbott, efficacy in treating patients with schizophrenia was demonstrated, but FDA issued an Approvable Letter primarily due to the potential QT prolongation. Despite this, sertindole obtained a European Union authorization in 1996. Abbott subsequently amended its application in the United States in December 1996. However, FDA repeated the Approvable action and stated that sertindole could only be approved if Abbott agreed (1) to adopt labeling identifying sertindole as a treatment intended only for seriously ill schizophrenic patients failing to respond to, or intolerant of, alternative treatments, and (2) to market sertindole under a system of registration, distribution, and follow up that would permit the efficient and rapid identification of deaths and an estimate of the risk of overall mortality and SUD (sudden and unexpected deaths) associated with its use.

Given worldwide concerns about sertindole's potential QT prolongation and increased cardiac mortality, Abbott withdrew this NDA in January 1998. The European Union marketing authorizations of sertindole were suspended in the same year. Since then, non-clinical data had challenged the view that QT prolongation alone was sufficient to cause ventricular arrhythmias. Based on some evidence, CHMP (Committee for Medicinal Products for Human Use) opted to support the conditional re-introduction of sertindole in 2001, and the current sponsor, H. Lundbeck A/S, committed to conducting a large study to evaluate the safety of sertindole under normal conditions of use: the Sertindole Cohort Prospective (SCoP) Study (Study 99824). This was an open-label, randomized, large trial comparing sertindole with risperidone on safety endpoints. It enrolled nearly 10,000 patients with roughly 14,000 patient-years exposure. Based on the result of the first interim analysis (report dated 9 September 2005), CHMP reached a conclusion that sertindole could be marketed in European Union, however, with labeling that clearly indicated a significant cardiovascular risk and rendered sertindole second line.

In January 2006, a pre-NDA meeting was held between the current sponsor and FDA. At that meeting, the sponsor expressed that they had accumulated additional clinical data, in particular the data from the SCoP study. They felt that they had established the reasonable safety of sertindole in clinical use and wished to resubmit the NDA. FDA clearly conveyed its strong continuing concerns about the cardiovascular safety of sertindole. In particular, FDA remarked the following:

- Despite the preliminary results from the SCoP study, we remained concerned about substantial QTc prolongation with sertindole and what we believed was a substantial risk of excess cardiac deaths with this drug. Although the preliminary results from the SCoP study suggested no difference between sertindole and risperidone in overall mortality, there appeared to be an excess risk of cardiac deaths for sertindole. We noted that it would not necessarily be expected that an excess risk of cardiac deaths for sertindole compared to risperidone would be reflected in a higher overall mortality for sertindole, given the relatively higher mortality in this population from multiple causes.
- Given what we believe to be unacceptable risk associated with this drug, we strongly recommended that the sponsor do additional work to establish a benefit that could overcome this risk, e.g., effectiveness in patients shown to be refractory to standard antipsychotics or reduction in suicidality. We noted that the SCoP study was trending in favor of sertindole with regard to completed suicide.
- We recommended that the SCoP study be completed, i.e., to the pre-specified number of deaths.

In July 2008, primarily based on the SCoP study results, the sponsor filed this re-submission in response to FDA Approvable Letters and to support the claims of treatment of schizophrenia and of reducing the risk of fatal and non-fatal suicide attempts in patients with schizophrenia.

The overall objective of the SCoP study was to compare the safety of sertindole with that of risperidone under normal conditions of use. The primary objective was to assess whether the perceived risk of increased mortality was in fact true. In addition, CHMP requested assessment of the frequency of cardiac events, including arrhythmias, requiring hospitalization. Since FDA expressed that an excess risk of cardiac deaths would not necessarily be reflected in a higher overall mortality, during the NDA review FDA asked the sponsor to analyze the data of documented sudden cardiac death (including cardiac origin probable), as well as certain dictionary-derived adverse events (syncope, palpitations, dizziness). In addition to risk assessment, the sponsor added suicide attempts as a secondary endpoint to Protocol Amendment 7 (27 November 2003). This was based on an FDA suggestion in hope to establish a benefit that could overcome the risk.

The focus of this statistical review is on the safety evaluation of the SCoP study. Efficacy was demonstrated based on studies M93-098 and M93-113 in the original submission filed in 1995. To serve as reference, relevant information about efficacy studies is briefly summarized in Appendices.

2.2 Data Sources

This NDA is mainly a paper submission. The study report of the major safety study SCoP was submitted in a paper format. Associated data submitted by the sponsor are stored in the following directory of the CDER's electronic document room: \\Fdswa150\nonectd\N20644\N_000, where the first folder labeled "2008-0702" consists of data sets for the SCoP study. Folders (labeled with subsequent dates) in this directory include electronic study reports for all efficacy studies, as well as some of the sponsor's responses to FDA requests during the NDA review. Other responses are included in the CDER Document Room as well as the reviewing medical division's eRoom.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

Efficacy is not the focus of this statistical review because it was demonstrated based on data from the original submission in 1995. Please refer to Appendices for a brief summary of efficacy studies.

3.2 Evaluation of Safety

This section summarizes the major safety study: Sertindole Cohort Prospective (SCoP) study.

3.2.1 STUDY OBJECTIVE

H. Lundbeck A/S conducted this study in response to a request from CHMP (Committee for Medicinal Products for Human Use) to establish the safety of sertindole compared to that of a marketed product in the treatment of schizophrenia.

The overall objective of the study was to compare the safety of sertindole with that of risperidone under normal conditions of use. The primary objective of this study was to assess whether the perceived risk of increased mortality was in fact true. In addition to measuring mortality, CHMP requested assessment of the frequency of cardiac events, including arrhythmias, requiring hospitalization.

To further explore safety, the sponsor included the following assessments as secondary objectives:

- cause-specific fatal events (cardiac, suicide, others);
- hospitalizations, excluding hospitalizations related to the primary psychiatric disease;
- treatment duration.

In addition to risk assessment, the sponsor added suicide attempts as a secondary endpoint to Protocol Amendment 7 (27 November 2003). This was based on an FDA suggestion in hope to establish a benefit that could overcome the risk.

3.2.2 STUDY DESIGN

This was a multinational, multi-centre, randomized, open-label, parallel-group, active-controlled study in patients with schizophrenia. Patients were randomized (1:1) to treatment with sertindole or risperidone, and were assessed and managed by the investigators according to routine clinical practice. The study assessments were performed monthly during the first 3 months of treatment and on a quarterly basis thereafter. A safety follow-up visit was scheduled for 30 days after stopping the randomized treatment except if the patient withdrew consent. The total number of patients to be randomized depended on the accumulated treatment exposure; approximately 3800 patient-years of exposure in each treatment group were planned.

The SCoP study was designed in collaboration with CHMP as an open-label randomized study with minimum study management that focused on mortality and general patient safety. No efficacy measures were included.

3.2.3 SAFETY MEASURES

There were two primary safety endpoints in this study:

- Time to all-cause mortality. This was chosen by the sponsor as the first primary endpoint because the sponsor believed that it was the only unbiased endpoint in this study.
- Time to cardiac events, including arrhythmias, requiring hospitalization. The purpose of this endpoint was to capture the potential risk of arrhythmias with sertindole treatment that would lead to hospitalization but not necessarily to death.

The secondary safety variables for analysis were:

- cause-specific mortality (the specific causes were cardiac, suicide, and other);
- suicide attempts (fatal and non-fatal);
- hospitalization, excluding hospitalization related to the primary psychiatric disease;
- duration of randomized antipsychotic treatment.

3.2.4 STATISTICAL ANALYSIS PLAN

The description in this session is based on the final version of the sponsor's Statistical Analysis Plan (SAP) dated 20 December 2007. Any discrepancy between the statistical

analysis plan and the clinical study report will be discussed in the next section (Section 3.2.5 Study Results).

Primary Analysis Set: consisting of all randomized patients who took at least one dose of the randomized treatment. The sponsor considered this as the primary analysis set for analysis and reporting.

Study Periods: defined by the sponsor as below:

- **Only Randomized Treatment (ORT) Period** – the period from the date of prescription of randomized treatment until randomized treatment was stopped or the date of start of add-on antipsychotic(s), whichever occurred first; it follows that “ORT+1” denotes the ORT period plus one day;
- **Whole Randomized Treatment (WRT) Period** – the period from the date of prescription of randomized treatment until randomized treatment was stopped, including time the patient was treated in combination with another antipsychotic (if indicated) (add-on therapy);
- **Whole Follow-Up (WFP) Period** – the period from the date of prescription of randomized treatment until the date of withdrawal from/completion of the study;
- **WRT+30** – WRT period plus 30 days. The sponsor considered this as the primary study period for analysis and reporting.

Classification of Events. All serious and medically important adverse events were to be classified using the following two coding approaches respectively:

- **MedDRA** (Medical Dictionary for Regulatory Activities) coding – This was used by investigators, who were not blind to treatment.
- **ISC** (Independent Safety Committee) Classification – The ISC was blind to treatment and classified all SAEs (serious adverse events) based on a review of blinded “case reports” that were forwarded to the ISC on a weekly basis. This approach was based on a conservative evaluation in the case of unclear cases. By its nature, classification by the ISC was not directly comparable to the MedDRA coding.

Analysis of All-Cause Mortality. The primary analysis was based on the time to death for those patients who died. The all-cause mortality ratio (hazard ratio of sertindole to risperidone) was to be estimated using a Cox proportional hazards model with a variable of treatment group and to adjust the treatment comparison for baseline variables of age and sex. If the two-sided 90% CI (confidence interval) for the all-cause mortality ratio was entirely below the pre-specified threshold 1.5, the null hypothesis of an excess mortality in sertindole treated patients would be rejected. In other words, one would conclude non-inferiority of sertindole to risperidone if sertindole was shown to be at most 50% worse than risperidone in the risk of all-cause mortality. The sponsor indicated that this threshold (non-inferiority margin) was chosen as the largest ratio that was clinically acceptable to CHMP and that, at the same time, took into account the feasibility of conducting such a study. The sponsor further indicated that this threshold was approved by CHMP and that was prepared according to the CHMP requirements described in Annex IV *Conditions of the Marketing Authorizations: CHMP requirement in relation to*

post-marketing data. Several sensitivity or supportive analyses were proposed in the SAP.

Analysis of Cardiac Events (including Arrhythmia) Requiring Hospitalizations. If the number of events allow, analysis analogous to that of all-cause mortality would be applied, except that the pre-specified threshold for the non-inferiority test would be 2.0; i.e., if the two-sided 90% CI for the cardiac hospitalization ratio (hazard ratio of sertindole to risperidone) was entirely below 2.0, the null hypothesis of an excess of hospitalization with cardiac arrhythmia in sertindole treated patients would be rejected. In other words, one would conclude non-inferiority of sertindole to risperidone if sertindole was shown to be at most twice worse than risperidone in the risk of cardiac events requiring hospitalizations. Again, the sponsor indicated that this threshold (non-inferiority margin) was chosen in agreement with CHMP.

Analysis of Suicide Attempts (Fatal and Non-Fatal). Since FDA suggested that the sponsor establish a benefit that could overcome the risk, such as effectiveness in patients shown to be refractory to standard antipsychotics or reduction in suicidality, the sponsor added suicide attempts as a secondary endpoint in Protocol Amendment 7 (27 November 2003). By then the study already started, so data were collected retrospectively for some patients who were already enrolled. This endpoint was to be based on time to occurrence of the first attempt for those patients who attempted suicide. The primary goal was to demonstrate that sertindole-treated patients had lower risk in suicide attempts. The hazard ratio (sertindole/ risperidone) was to be estimated using a Cox proportional hazards model with variables of treatment, age, gender, total duration of schizophrenia prior to study entry, and time since last suicide attempt prior to study entry.

Analyses of Other Secondary Endpoints. In general, they were to be based on Cox proportional hazards models adjusting for the same covariates as described in the all-cause mortality analysis.

Multiplicity Adjustment. It appears that no multiplicity adjustments were addressed or specified among multiple safety endpoints and multiple analyses within each endpoint.

Interim Analyses. Two interim analyses of all-cause mortality were to be conducted accumulatively after every 50 events. The final analysis was to be conducted at approximately 150 deaths, which would provide 80% power to reject the null hypothesis at one-sided 5% significance level (or equivalently two-sided 10% significance level). The objective of the interim analyses was for possible early termination, only if sufficient evidence for a difference in mortality between the two treatments had been concluded (i.e., stopping for acceptance of null hypothesis only). The hazard ratio was to be compared with the stopping boundaries based on O'Brian-Fleming type boundaries.

3.2.5 STUDY RESULTS

3.2.5.1 Study Cut-Off Dates

Per the sponsor's study report, two interim analyses were conducted and neither one suggested an increase in the all-cause mortality for sertindole when compared with risperidone. The first interim analysis was based on 56 deaths collected by 11 July 2005. Based on the result of this interim analysis (report dated 9 September 2005), CHMP concluded that restrictions on the marketing and lunch activities could be lifted and the Summary of Products Characteristics was updated with added safeguards. The second interim analysis was based on 100 deaths collected by 11 January 2007. Based on the result of this interim analysis (report dated 7 March 2007), CHMP agreed that the SCoP study could be terminated as it was deemed highly unlikely that continuation of this study would have been of any added value or would have had a material impact on the overall conclusion of this study. The sponsor received the agreement on the termination decision on 20 September 2007, so they defined this date as the CHMP cut-off date.

The sponsor defined the study closure date as the date (22 February 2008) by which all patients had had last visit, including the 30-day safety follow-up contact for patients who had the randomized treatment ongoing at last visit.

3.2.5.2 Patient Disposition, Demographic and Baseline Characteristics

Patient disposition for all randomized patients is summarized in Table 1. A total of 9858 patients were randomized over 5 years, with 50% of the patients randomized to each treatment group. Of those, 9809 patients were included in the primary analysis set (all randomized patients who took at least one dose of randomized treatment). Of those in the primary analysis set, 50% of the patients were included in each treatment group. By the CHMP cut-off date, 5791 patients were still in the study, with proportions of 56% (= 2746/4905) in the sertindole group and 62% (= 3045/4904) in the risperidone group, respectively.

Table 1 Patient Disposition

	Number of Patients		
	Sertindole	Risperidone	All
Patients randomized	4930	4928	9858
Patients treated (primary analysis set)	4905	4904	9809
Patients in study by CHMP cut-off date	2746	3045	5791

[Source: Panel 15 of Sponsor's Study Report]

Reasons for stopping the randomized treatment are summarized in Table 2 for the primary analysis set. Of the 5791 patients in the study by the CHMP cut-off date, 4075 patients (1768 in the sertindole group and 2307 in the risperidone group) were still contributing to the WRT period and stopped taking the randomized treatment due to study closure.

FDA Reviewer Comments: The discontinuation rate due to patient/relative decision appears to be slightly higher in the sertindole group (22.3% compared to 18.7% in the risperidone group). It is not clear whether this rate was of clinical relevancy and could introduce a bias in favor of sertindole because of the potentially underestimated “harmful” trend.

Table 2 Reasons for Treatment Discontinuation during the WRT Period

	Number of Patients, n (%)		
	Sertindole n = 4905	Risperidone n = 4904	All n = 9809
Lack of efficacy	389 (7.9%)	377 (7.7%)	766 (7.8%)
Serious adverse event	99 (2.0%)	65 (1.3%)	164 (1.7%)
Non-serious adverse event	393 (8.0%)	179 (3.7%)	572 (5.8%)
Non-compliance	305 (6.2%)	262 (5.3%)	567 (5.8%)
Patient/relative decision	1092 (22.3%)	919 (18.7%)	2011 (20.5%)
Investigator decision	59 (1.2%)	82 (1.7%)	141 (1.4%)
Pregnancy	14 (<1%)	5 (<1%)	19 (<1%)
Sponsor study closure	1768 (36.0%)	2307 (47.0%)	4075 (41.5%)
Other	92 (1.9%)	104 (2.1%)	196 (2.0%)
Missing	694 (14.1%)	604 (12.3%)	1298 (13.2%)

[Source: Panel 16 of Sponsor’s Study Report]

Patient demographics at baseline for the primary analysis set are summarized in Table 3. Approximately 45% of the patients in each treatment group were women. The sponsor commented that this proportion was larger than usually seen in conventional, clinical studies in schizophrenia, but more representative of that for the population of patients treated with antipsychotic medication in daily, clinical practice.

The disease duration and history of suicide attempts at baseline are summarized in Table 4. Approximately 42% of the patients in each treatment group had been diagnosed with schizophrenia for more than 10 years. In 212 patients, the total duration of schizophrenia prior to study entry was unknown. Approximately 13% of the patients in each treatment group had a history of suicide attempts. There were 28 patients who did not have information about previous suicide attempts.

Table 3 Patient Demographics

	Sertindole n = 4905	Risperidone n = 4904	All n = 9809
Sex			
Male, n (%)	2710 (55.2%)	2716 (55.3%)	5426 (55.3%)
Female, n (%)	2195 (44.7%)	2188 (44.6%)	4383 (44.6%)
Age in years			
Mean (std. dev.)	38.4 (11.8)	38.3 (11.7)	38.3 (11.8)
Median	37.1	37.1	37.1

[Source: Panel 18 of Sponsor's Study Report]

Table 4 Disease Duration and History of Suicide Attempts

	Number of Patients, n (%)		
	Sertindole n = 4905	Risperidone n = 4904	All n = 9809
Total duration of schizophrenia			
Undefined	125 (2.5%)	87 (1.7%)	212 (2.1%)
< 5 years	1450 (29.5%)	1468 (29.9%)	2918 (29.7%)
5 – 10 years	1254 (25.5%)	1278 (26.0%)	2532 (25.8%)
> 10 years	2076 (42.3%)	2071 (42.2%)	4147 (42.2%)
Number of previous suicide attempts, n (%)			
Undefined	17 (<1%)	11 (<1%)	28 (<1%)
0	4281 (87.2%)	4288 (87.4%)	8569 (87.3%)
1	378 (7.7%)	377 (7.6%)	755 (7.6%)
2	125 (2.5%)	126 (2.5%)	251 (2.5%)
3	52 (1.0%)	53 (1.0%)	105 (1.0%)
4	18 (<1%)	13 (<1%)	31 (<1%)
5 or more	34 (<1%)	36 (<1%)	70 (<1%)
Time since last suicide attempt, n (%)			
Undefined	17 (2.7%)	11 (1.7%)	28 (2.2%)
< 1 year	122 (19.5%)	117 (19.0%)	239 (19.3%)
1 – 5 years	226 (36.2%)	218 (35.5%)	444 (35.8%)
> 5 years	259 (41.5%)	268 (43.6%)	527 (42.5%)

[Source: Panel 20 of Sponsor's Study Report]

3.2.5.3 Extent of Exposure to Randomized Treatment

Patient exposure to the randomized treatment during the WRT period is summarized in Table 5. Because the study design allowed patients to continue the treatment until study closure, many patients had treatment durations of several years. The median exposure time was 360 days for patients in the sertindole group and 476 days for patients in the risperidone group. The total exposure was 6575 patient-years in the sertindole group and 7572 patient-years in the risperidone group. This was nearly twice the planned amount in each treatment group.

FDA Reviewer Comments:

- To visually compare the WRT durations between treatment groups, an empirical CDF (cumulative distribution function) plot was made as displayed in Figure 1. In this figure, the vertical axis denotes the proportion of patients whose WRT durations were less than or equal to a given number of days (horizontal axis). For example, 50% of patients in the sertindole group had WRT durations up to approximately 360 days and 50% of patients in the risperidone group had WRT durations up to approximately 475 days. The observed exposure durations in the sertindole group seem to be generally shorter than those in the risperidone group. This might suggest a potential underestimation of a harmful trend for sertindole, such as suicide attempts.
- During the WRT period, patients could also receive add-on therapy in addition to the randomized treatment. Approximately 7% of the patients in the sertindole group and 9% of the patients in the risperidone group received add-on therapy. The ORT durations (i.e., durations excluding the add-on therapy period) were also compared as displayed in Figure 2. Again, this figure revealed a consistent trend as observed in that based on the WRT period.
- In summary, overall shorter exposure durations were observed in the sertindole group. This might suggest a potential underestimation of a harmful trend for sertindole, such as suicide attempts.

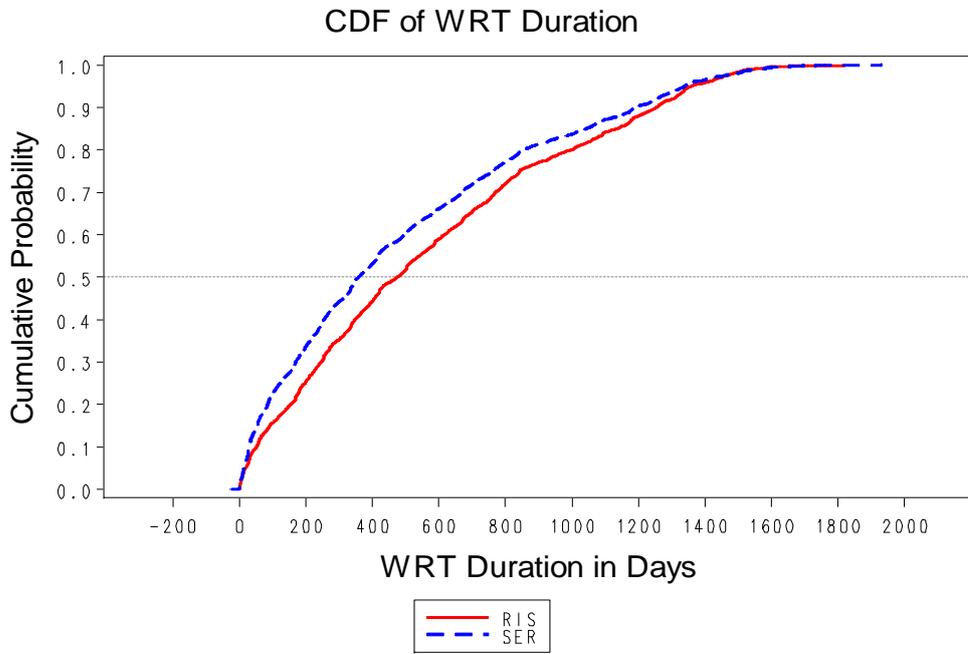
Table 5 Summary of Exposure to Randomized Treatment in 3-Month Intervals (WRT Period)

	RIS	SER	All
Patients treated, n	4904	4905	9809
Days exposed			
N	4904	4905	9809
Mean	564.0	489.6	526.8
Median	475.5	360.0	415.0
Std	433.4	430.5	433.5
Min	1	1	1
Max	1820	1930	1930
Period/Patients, n			
1 - 90 days	4904	4905	9809
91 - 180 days	4186	3882	8068
181 - 270 days	3764	3378	7142
271 - 360 days	3293	2864	6157
361 - 450 days	2899	2452	5351
451 - 540 days	2513	2087	4600
541 - 630 days	2208	1813	4021
631 - 720 days	1918	1586	3504
721 - 810 days	1638	1324	2962
811 - 900 days	1342	1103	2445
901 - 990 days	1124	916	2040
991 - 1080 days	988	814	1802
1081 - 1170 days	827	672	1499
1171 - 1260 days	674	549	1223
1261 - 1350 days	475	382	857
1351 - 1440 days	256	217	473
1441 - 1530 days	148	136	284
1531 - 1620 days	46	61	107
1621 - 1710 days	10	25	35
1711 - 1800 days	2	10	12
1801 - 1890 days	1	1	2
1891 ->	0	1	1
Period/Exposure (years)			
1 - 90 days	1102.4	1063.1	2165.5
91 - 180 days	985.4	894.4	1879.8
181 - 270 days	870.6	770.6	1641.2
271 - 360 days	764.5	658.9	1423.4
361 - 450 days	665.2	559.4	1224.6
451 - 540 days	584.7	483.9	1068.6
541 - 630 days	509.5	420.4	929.9
631 - 720 days	438.6	359.6	798.2
721 - 810 days	368.9	299.8	668.7
811 - 900 days	299.1	245.0	544.1
901 - 990 days	260.5	212.6	473.1
991 - 1080 days	224.8	184.1	408.7
1081 - 1170 days	184.2	150.0	334.2
1171 - 1260 days	138.7	113.4	252.1
1261 - 1350 days	91.8	75.4	167.2
1351 - 1440 days	50.2	43.2	93.4
1441 - 1530 days	24.0	25.4	49.3
1531 - 1620 days	7.4	10.5	17.9
1621 - 1710 days	1.6	3.9	5.5
1711 - 1800 days	0.3	1.0	1.3
1801 - 1890 days	0.1	0.2	0.3
1891 ->		0.1	0.1
Exposure (years)	7572.2	6574.9	14147.1

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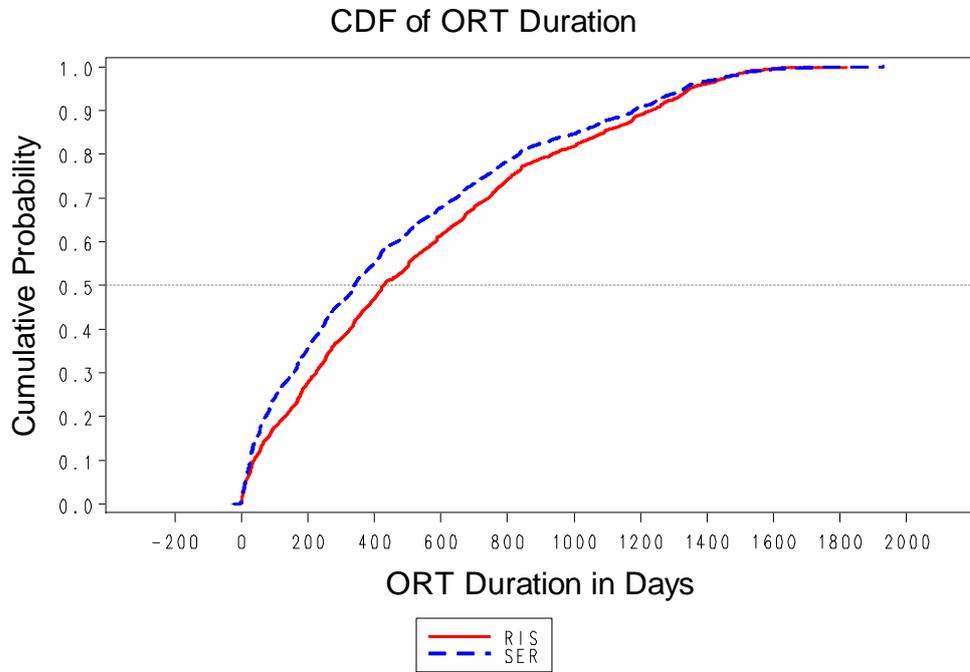
[Source: Panel 21 of Sponsor's Study Report]

Figure 1: Cumulative Distribution Function Plot of WRT Duration



[Source: FDA statistical reviewer Dr. Bai's results]

Figure 2: Cumulative Distribution Function Plot of ORT Duration



[Source: FDA statistical reviewer Dr. Bai's results]

3.2.5.4 Analysis of All-Cause Mortality (Sponsor's First Primary Endpoint)

The sponsor was concerned that the study closure might have introduced a bias, so they used the CHMP cut-off date (20 September 2007) as an alternative cut-off date in the analysis of all-cause mortality, in addition to using the study closure date (22 February 2008) as the data cut-off date. Table 6 summarizes the results, including the number of deaths and the estimates of the corresponding all-cause mortality ratios (i.e., hazard ratio of sertindole to risperidone), for the primary study period (WRT+30). It also includes the results from exploratory or sensitivity analyses by various study periods or various Cox models. By the CHMP cut-off date, a total of 121 patients (61 and 60 from the sertindole and the risperidone groups, respectively) died during the primary study period WRT+30. Additional 4 patients died (3 and 1 from the sertindole and the risperidone groups, respectively) by the study closure date.

The sponsor indicated that based on the actual number of deaths during the WRT+30 study period as of the CHMP cut-off date, the estimated mortality ratio (hazard ratio of sertindole to risperidone) was 1.081 with a 90% CI of 0.801 – 1.458. Similar results were obtained using the study closure date as the cut-off date: the estimated mortality ratio was 1.117 with a 90% CI of 0.831 – 1.500.

On 28 October 2008, FDA asked the sponsor to reanalyze all-cause mortality, after removing all patients in the sertindole group who had risperidone added to their randomized treatment and all patients in the risperidone group who had sertindole added to their randomized treatment. Per the sponsor's response, a total of 182 (3.7%) patients in the sertindole group and 114 (2.3%) patients in the risperidone group had the add-ons of their counterpart therapy, respectively. The Cox proportional hazards model resulted in an estimated hazard ratio (sertindole/risperidone) of 1.116 with a 90% CI of 0.829 – 1.502.

Figure 3 displays the cumulative probability of all-cause mortality with censoring information incorporated. The vertical axis indicates the proportion of patients who had died by a given time (horizontal axis). For example, less than 1% of patients (vertical axis) in each treatment group died by Day 300 (horizontal axis), and 2% of patients died by around Days 1000 – 1050.

FDA Reviewer Comments:

- Although all-cause mortality is a hard endpoint, different study periods and different cut-off dates yielded different data sets. Moreover, multiple statistical models (Cox models with various sets of covariates) were fitted to a given data set, even though only two covariates (age and sex) were pre-specified in the SAP for the primary Cox model. After data unblinding, the sponsor added 3 additional covariates to the model via a model selection approach. Typically the reproducibility of the study result could be an issue if the same data set is used to develop the statistical model and test the treatment effect with the model

- developed by it, as in this study. A major concern is the potential inflation of the overall type I error rate due to multiple analyses (model fittings) for the same endpoint. If the results were generally consistent across different analyses (Cox models) and different study periods, the multiplicity issue may be alleviated. Otherwise, the results should be interpreted with great caution and, to protect the public health, it would be sensible for FDA to place more weight on the result that revealed large adverse event signals associated with sertindole.
- The sponsor indicated that the non-inferiority threshold (1.5) was chosen as the largest ratio that was clinically acceptable to CHMP and that, at the same time, took into account the feasibility of conducting such a study. On face, 50% non-inferiority margin seems to be quite liberal because the non-inferiority could be concluded if sertindole was shown to be at most 50% worse than risperidone. It is uncertain whether FDA can rely on this margin for drugs intended for the U.S. marketing, in particular when this was not the endpoint FDA would primarily focus on.
 - The sponsor utilized a two-sided 90% CI to compare with a pre-specified threshold (non-inferiority margin). As a standard practice, FDA has been utilizing a two-sided 95% CI in non-inferiority analysis. Based on the standard practice, the upper limits of the 95% CIs generally exceeded 1.5, but were generally below 1.6. This suggests that one might be able to rule out that sertindole was approximately 60% worse than risperidone, but one cannot rule out that sertindole was 50% worse than risperidone, in the risk of all-cause mortality.

Table 6 Analysis Results of All-Cause Mortality (Primary Study Period WRT+30)

Study Period	Number of deaths / Number of patients		Hazard ratio (ser./ris.)	90% CI	95% CI ^a
	Ser.	Ris.			
As of CHMP cut-off date					
Cox model with two covariates (age, sex) -- SAP pre-specified					
WRT+30	61 /4905	60 /4904	1.113	0.824 – 1.501	0.778 – 1.590
Cox model with 3 additional covariates^b					
WRT+30	61	60	1.081	0.801 – 1.458	0.756 – 1.545
WRT+5	51	53	1.043	0.775 – 1.441	0.710 – 1.533
Study closure period					
Cox model with two covariates (age, sex) -- SAP pre-specified					
WRT+30	64	61	1.148	0.855 – 1.542	0.808 – 1.632
Cox model with 3 additional covariates^b					
WRT+30	64	61	1.117	0.831 – 1.500	0.786 – 1.587
WRT+5	53	54	1.066	0.775 – 1.466	0.729 – 1.558
WRT + 30, no add-on ^c	62/4723	61/4790	1.116	0.829 – 1.502	0.783 – 1.590

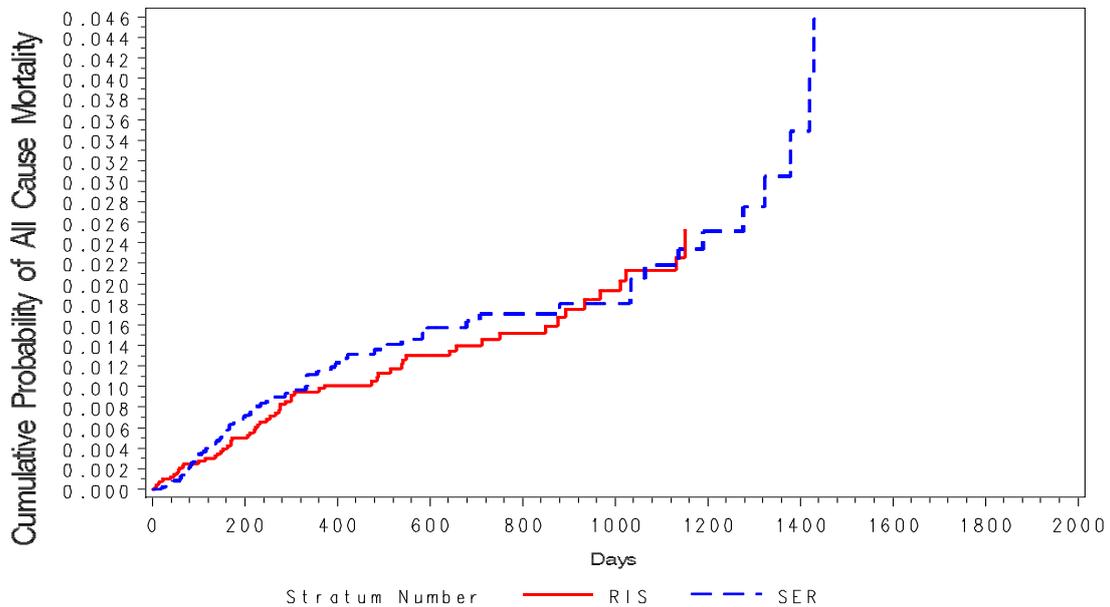
[Source: Panel 29 of Sponsor's Study Report and Sponsor's response document "Response to 28 October 2008 FDA Request – Question 1" (document dated 05 November 2008).]

^a The corresponding 95% CIs were derived by the FDA statistical reviewer, Dr. Bai.

^b The three additional covariates were: study accrual time, last suicide attempt within 5 years prior to study entry (yes or no), and last antipsychotic treatment (mono- or poly-therapy).

^c Patients in the sertindole group who had risperidone added to their randomized treatment and patients in the risperidone group who had sertindole added to their randomized treatment were removed.]

Figure 3 Cumulative Probability of All-Cause Mortality Over Time (Primary Study Period WRT+30)



[Source: FDA statistical reviewer Dr. Bai’s results. Data was cut off by the study closure date]

3.2.5.5 Analysis of Cardiac Events, Requiring Hospitalization (Sponsor’s Second Primary Endpoint)

Statistical analysis of this second primary endpoint was not performed due to the limited number of adverse events. There were only 5 and 4 SAEs requiring hospitalization (coded as MedDRA SOC Cardiac Disorders) in the sertindole and the risperidone groups, respectively. In comparison, ISC classified 4 cases of arrhythmia; only one of those four was coded differently from the MedDRA classification.

3.2.5.6 Analysis of Cardiac Death

Table 7 summarizes the sponsor’s analysis results for patients dying from an SAE coded as MedDRA SOC Cardiac disorders and those who were classified as cardiac by the ISC, respectively. This table includes the estimates obtained from Cox proportional hazards models adjusting for age, sex and other covariates as presented in the sponsor’s study report. Per the FDA request on 19 December 2008, the sponsor repeated the same analysis, but using two covariates only (age and sex), to adjust the treatment effect and the results are provided in the same table below.

FDA Reviewer Comments: Regardless of the coding method, the results appear to be similar across different Cox models. The observed hazard ratios (sertindole/risperidone) were all greater than 2. Moreover, the ISC classification suggested a higher risk of cardiac death at the nominal significance level of 0.05. Since the number of events was small, the FDA statistical reviewer Dr. Chen conducted an exploratory analysis based on an exact test to estimate the odds ratio¹ without considering when events occurred over time. Based on the MedDRA coding, the estimated odds ratio was 2.128 with a corresponding 95% CI of 0.870 – 5.704. Based on the ISC classification, the estimated odds ratio was 2.588 with a 95% CI of 1.290 – 5.539. The results appear consistent with those based on Cox models.

Table 7 Analysis Results of Cardiac Death (Primary Study Period WRT+30)

Analysis	Number of events		Hazard ratio (ser./ris.)	95% CI	p-value ^c
	Ser.	Ris.			
MedDRA coding					
Cox model with two covariates (age, sex) -- SAP pre-specified					
	17	8	2.173	0.930 – 5.075	0.0730
Cox model with one additional covariate^a					
	17	8	2.131	0.911 – 4.985	0.0809
ISC Classification					
Cox model with two covariates (age, sex) -- SAP pre-specified					
	31	12	2.848	1.460 – 5.552	0.0021
Cox model with 4 additional covariates^b					
	31	12	2.841	1.454 – 5.550	0.0022

[Source: Tables 50 and 51 of Sponsor's study report; Sponsor's email response document "Item 53 – Question 1" (email dated 22 December 2008).]

^a The additional covariate was last antipsychotic treatment (monotherapy, polytherapy).

^b The 4 additional covariates were last antipsychotic treatment (monotherapy, polytherapy), last suicide attempt within 5 years prior to study (yes, no), region (Europe, Asia), and time since start of study accrual.]

^c Nominal p-value, not adjusting for multiplicity.

¹ Odd ratio is the ratio of odds of developing a cardiac death in the sertindole group to that in the risperidone group. The exact confidence interval was derived using StatXact 8 by Cytel 2007. Refer to Section 14.3.2 of the User Manual for theory.

3.2.5.7 Analysis of Documented Sudden Cardiac Death

During the review, FDA asked the sponsor to analyze the data of documented sudden cardiac death (including cases with cardiac origin probable). Per the sponsor's response on 16 October 2008, 13 patients in the sertindole group and 3 patients in the risperidone group had a fatal SAE that was classified as sudden cardiac death. Table 8 summarizes the corresponding analysis results, where the hazard ratios (sertindole/risperidone) of sudden death were obtained using a Cox proportional hazards model adjusting for baseline covariates age and sex only.

On 28 October 2008, FDA asked the sponsor to reanalyze the documented sudden cardiac death, after removing all patients in the sertindole group who had risperidone added to their treatment and all patients in the risperidone group who had sertindole added to their treatment. A total of 182 and 114 patients in the sertindole and the risperidone groups had add-ons of their counterpart therapy, respectively. On 17 November 2008, FDA asked the sponsor to repeat this analysis once again, after removing those patients who had thioridazine, mesoridazine, ziprasidone, or pimozide added to their randomized treatment from both treatment groups. Per the sponsor's response, a total of 39 patients in each treatment group had those add-ons to their treatment.

FDA Reviewer Comments:

- Whether patients with add-on therapies were removed or not, the results appear consistent: an estimated hazard ratio of around 5 and a 95% CI of around 1.4 – 18, suggesting a higher risk in the sertindole group at the nominal significance level of 0.05.
- Since the number of events was small, the FDA statistical reviewer Dr. Chen conducted an exploratory analysis based on an exact test to estimate the odds ratio without considering when events occurred over time. Whether patients with add-on therapies were removed or not, the estimated odds ratios were above 4.0 and the corresponding 95% CIs were entirely above 1. These results appear consistent with those findings in the table.

Table 8 Analysis Results of Documented Sudden Cardiac Death (Primary Study Period WRT+30)

Populations	Number of events / Number of patients (%)		Hazard ratio (ser./ris.)	95% CI	p-value ^d
	Ser.	Ris.			
Cox model with two covariates (age, sex)					
All patients ^a	13 / 4905 (0.27%)	3 / 4904 (0.06%)	4.988	1.421 – 17.512	0.0121
No counterpart add-on ^b	13 / 4723 (0.28%)	3 / 4790 (0.06%)	5.102	1.453 – 17.915	0.011
No add-on ^c	13 / 4684 (0.28%)	3 / 4751 (0.06%)	5.102	1.453 – 17.913	0.011

[Source: Sponsor's response document "Response to 28 October 2008 FDA Request – Question 1" (document dated 5 November 2008), and "Response_33.1_4Dec2008.final.pdf" submitted to EDR on 12 December 2008.]

^a Primary analysis set.

^b Removing patients with add-on risperidone or sertindole.

^c Removing patients with counterpart add-on (risperidone or sertindole), or add-on thioridazine, mesoridazine, ziprasidone, or pimozide.

^d Nominal p-value, not adjusting for multiplicity.

3.2.5.8 Analysis of Syncope, Palpitations, and Dizziness Adverse Events

On 17 November 2008, FDA asked the sponsor to estimate the hazard ratio (sertindole / risperidone) for the following dictionary-derived adverse events: Syncope, Palpitations, and Dizziness, based on the Cox model adjusting for two covariates (age and sex) only. In this analysis, all the patients in the risperidone group who had sertindole added to their randomized treatment and all patients in the sertindole group who had risperidone added to their randomized treatment were removed. Also, removed from both treatment groups were those patients who had thioridazine, mesoridazine, ziprasidone, or pimozide added to their randomized treatment.

FDA Reviewer Comments: The results suggested higher incidences of dizziness for the sertindole group than the risperidone group (Table 9). Since the number of events was very small, the FDA statistical reviewer Dr. Chen performed an exploratory analysis to estimate the odds ratio based on an exact test without considering when events occurred over time. The results from the exact test appear consistent with those findings in Table 9.

Table 9 Analysis Results of Selected Adverse Events on Patients without Add-ons^a (Primary Study Period WRT+30)

Adverse Event	Number of events (%)		Hazard ratio ^b (ser./ris.)	95% CI	p-value ^c
	Ser. N = 4684	Ris. N = 4751			
Syncope	7 (0.15%)	3 (0.06%)	2.598	0.671 - 10.056	0.1669
Palpitations	21 (0.45%)	13 (0.27%)	1.772	0.887 – 3.540	0.1052
Dizziness	14 (0.30%)	4 (0.08%)	3.847	1.265 – 11.692	0.0175

[Source: Table 1 of Sponsor's "Response_33.2_Final_5Dec2008.pdf" submitted to EDR on 12 December 2008.

^a Patients who had the counterpart add-on (sertindole, risperidone), or who had thioridazine, mesoridazine, ziprasidone, or pimozone added to their randomized treatment were removed.

^b The hazard ratio was obtained after adjusting for two covariates (age and sex) only.]

^c Nominal p-value, not adjusting for multiplicity.

3.2.5.9 Analysis of Original Suicidality Data

3.2.5.9.1 Suicide Attempts

The MedDRA coding and the ISC classification identified 108 and 144 patients who had suicide attempts, respectively. Per the sponsor's result, the MedDRA classification suggested a lower risk of suicide attempts for the sertindole group than for the risperidone group at the nominal significance level of 0.05 (Table 10).

On 28 October 2008, FDA asked the sponsor to reanalyze suicide attempts, as defined by the ISC, after removing all patients in the sertindole treatment group who had risperidone or clozapine added to their randomized treatment and all patients in the risperidone group who had sertindole or clozapine added to their randomized treatment. Per the sponsor's response, a total of 326 (6.6%) patients in the sertindole group had risperidone or clozapine added to their randomized treatment and a total of 275 (5.6%) patients in the risperidone group had sertindole or clozapine added to their randomized treatment and. The estimated hazard ratio was close to 1 with a 95% CI covering 1.

FDA Reviewer Comments:

- Two different coding approaches were pre-planned in SAP, but their roles were unclear. If the intention was to demonstrate consistency, it was not achieved. On the other hand, if it was to demonstrate superiority based on either coding approach, then from the statistical perspective a pre-specified multiplicity

adjustment procedure would be needed, or the results could be difficult to interpret.

- Since the MedDRA coding was done by investigators who were not blind to the treatment, a bias could easily be introduced when classifying these events. Although the ISC was blind to the treatment, the ISC definition of suicide attempts was very broad, which includes suicidal ideation and tendency. Thus, FDA requested that the sponsor reclassify the ISC identified suicide attempts in a more systematic manner and reanalyze the data. On February 13, the sponsor submitted the analysis results of the re-classification to FDA. The results are summarized in the next section.
- The Cox model included covariates “total duration of schizophrenia” and “time since last suicide attempt”. There were 212 patients who had missing values of the former covariate and 28 patients who had missing values of the latter covariate. When data were analyzed using SAS, patients with missing covariate values were automatically excluded from analysis and this analysis may result in underestimated hazards in one of the treatment groups. Refer to the next section for details.

Table 10 Analysis Results of Suicide Attempts (Primary Study Period WRT+30)

Classification	Number of patients with suicide attempts / Total number of patients (%)		Hazard ratio (ser./ris.)	95% CI	p-value ^d
	Ser.	Ris.			
	Cox model with 4 covariates – SAP pre-specified^a				
MedDRA	43 / 4905 (0.88%)	65 / 4904 (1.33%)	0.669	0.452 – 0.989	0.0444
ISC	68 / 4905 (1.39%)	76 / 4904 (1.55%)	0.926	0.664 – 1.288	0.6432
ISC, no add-on ^c	67 / 4579 (1.46%)	72 / 4629 (1.56%)	0.967	0.690 – 1.355	0.8439
Cox model with one additional covariate^b					
MedDRA	43	65	0.669	0.452 – 0.990	0.0440
ISC	68	76	0.926	0.665 – 1.291	0.6508
ISC, no add-on ^c	67	72	0.973	0.694 – 1.363	0.8735

[Source: Panel 43 and Section 9.4 of Sponsor’s Study Report, and Sponsor’s response document “Response to 28 October 2008 FDA Request – Question 2” (email dated 6 November 2008).]

^a The protocol specified covariates were age, sex, duration of schizophrenia prior to study entry, last suicide attempt within 5 years.

^b The additional covariate was study accrual time.

^c Patients who had sertindole, risperidone or clozapine added to their randomized treatment were removed.

^d Nominal p-values, not adjusting for multiplicity.]

3.2.5.9.2 Completed Suicide

Based on the MedDRA coding, 34 patients had fatal SAEs coded as completed suicide: 13 in the sertindole group and 21 in the risperidone group. Based on the ISC classification, one additional sertindole patient was classified as had fatal SAEs coded as suicide. The Cox proportional hazards models for time to committing suicide are presented for both the MedDRA coding and the ISC classification in Table 11.

FDA Reviewer Comments:

- The results appear to be similar for these two classification approaches. The observed hazard ratios (sertindole/ risperidone) for completed suicide trended in favor of sertindole, but the 95% CI did not suggest a statistically significant difference at the nominal significance level of 0.05. It is noted that the Cox model utilized by the sponsor deviated from the pre-specified in SAP. It appears that the sponsor selected the best fitted model for analysis after data unblinding.
- Because the number of events was small, the FDA statistical reviewer Dr. Chen conducted an exploratory analysis to estimate the odds ratio based on an exact test without considering when events occurred over time. The exact test yielded an estimated odds ratio of 0.618 with a 95% CI of 0.284 – 1.295 based on the MedDRA coding and an estimated odds ratio of 0.666 with a 95% CI of 0.313 – 1.374 based on the ISC classification. These results appear consistent with those findings in Table 11.

Table 11 Analysis Results of Completed Suicide (Primary Study Period WRT+30)

Classification	Number of events		Hazard ratio ^a (ser./ris.)	95% CI	p-value ^b
	Ser.	Ris.			
MedDRA	13	21	0.662	0.331 – 1.323	0.2432
ISC	14	21	0.719	0.365 – 1.414	0.3390

[Source: Tables 65 and 66 of Sponsor's Study Report.

^a The hazard ratio was obtained after adjusting for the following 5 covariates: age, sex, suicide attempt within 5 years, last antipsychotic treatment, and study accrual time.

^b Nominal p-values, not adjusting for multiplicity.]

3.2.5.10 Analysis of Reclassified Suicidality Data

On 13 February 2009, the sponsor submitted the analysis results based on reclassification of ISC-identified suicide attempts according to the C-CASA (Columbia Classification Algorithm for Suicide Assessment).

Suicide Attempts. The sponsor repeated the analysis using the primary study period (WRT+30), as well as the ORT+1 period (Table 12). Their results in general trended in favor of sertindole although not statistically significant. The sponsor also compared the risks during the first year follow-up and concluded a stronger and more beneficial treatment effect of sertindole than risperidone during the first year follow-up. The sponsor further conducted analysis to assess the benefit for the high-risk subgroup of patients with a history of attempting suicide within 5 years before entering the study, and concluded a clear tendency for these patients to benefit more from sertindole than from risperidone, although not statistically significant, based on the ORT+1 study period.

Figure 4 displays the proportion of patients (vertical axis) who had suicide attempts by a given time (horizontal axis) after incorporating censoring information.

Completed Suicide. During the primary study period WRT+30, the C-CASA identified 34 completed suicides (13 in the sertindole group and 21 in the risperidone group), resulting in one less patient in the sertindole group as compared to the ISC classification. The sponsor reported that, during the ORT+1 study period, there were 9 and 19 completed suicides in the sertindole and risperidone groups, respectively, and concluded that the analysis result approached statistical significance with an observed hazard ratio of 0.502 (95% CI: 0.227 – 1.111), and a nominal p-value of 0.0898.

FDA Reviewer Comments:

- **Potential Confounding with Exposure Duration.** Although there was a trend in favor of sertindole in suicide attempts, it may be confounded by differential exposure durations observed between treatment groups. The exposure durations in the sertindole group were generally shorter than in the risperidone group, whether based on the WRT or the ORT study period (refer to Section 3.2.5.3). This may lead to underestimation of a harmful trend in the sertindole group.
- **WRT- vs. ORT-based Study Period.** The WRT+30 study period was the protocol-specified study period. The results based on this primary study period were quite consistent whether or not removing patients who received the counterpart add-on therapy or clozapine. The sponsor presented several supplementary analyses based on the ORT+1 study period because they believe that the ORT+1 study period could lead to reduction in possible confounding effects of add-on treatment, of discontinuation, and of the introduction of other treatments occurring immediately after drug switches. Although this could be true, one cannot ignore the add-on therapy period while patients still received the randomized treatment if it's not clear which drug (the add-on or the randomized drug) really contributed to the event; in addition, WRT+30 was the pre-specified

study period for all analyses and report. If ORT+1 were considered the most appropriate study period, it should have been pre-specified as the primary study period. From the statistical perspective, unless the purpose is to check the consistency, shopping and picking after data unblinding is very problematic because the study-wise type I error rate is very likely to be inflated. Beyond this, if there is a clinical uncertainty about which study period to rely on, it'd be sensible for FDA to place more weight on the study period that yielded more conservative results for the mission of protecting the public health.

- **Missing Covariate Values.** The Cox models used by the sponsor included covariates: “total duration of schizophrenia” and “time to last suicide attempt” prior to study entry. There were 212 patients who had missing values of the former covariate and 28 patients who had missing values of the latter covariate. When data were analyzed using SAS, patients with missing covariate values were automatically excluded from analysis. Among those, there were 2 patients who had suicide attempts and these two were in the sertindole group. Because these two patients were excluded from the sponsor’s analysis, the sponsor’s result underestimated the hazards in the sertindole group. To explore the impact of these two patients, the FDA statistical reviewers imputed missing covariate values² and found that the trend was not as favorable to sertindole as those derived by the sponsor regardless of the study period. The FDA statistical reviewers further explored the impact by using age and sex as the only two covariates in the Cox model as these were the only two covariates pre-specified for analyses of other endpoints and every patient had information about these two covariates. The results of these two analyses supported each other (Table 13). For complete suicide, FDA repeated the Cox model used by the sponsor, but imputed missing covariate values. The results are summarized in Table 14.
- **Summary.** Both suicide attempts and completed suicide were analyzed on several study periods. Results from different Cox models yielded different strengths of evidence. Shorter exposure durations observed in the sertindole group may lead to underestimated hazards in suicide attempts and completed suicide in the sertindole group. In summary, the analysis result of suicidality data was inconclusive although there was a trend in favor of sertindole.

² Missing values of covariates were imputed in the following way: (a) total duration of schizophrenia prior to study entry was considered to be less than 5 years if it was missing; (b) patient was considered to have no suicide attempts prior to study entry if time to last suicide attempt prior to study entry was missing

Table 12 Analysis Results of Suicide Attempts Based on C-CASA Reclassification

Study period	Number of patients with suicide attempts		Hazard ratio (ser./ris.)	95% CI	p-value ^b
	Ser.	Ris.			
WRT+30	47	66	0.730	0.500 – 1.068	0.1047
WRT+30, no add-on ^a	46	62	0.761	0.517 – 1.121	0.1676
ORT+1	36	54	0.661	0.430 – 1.017	0.0594

[Source: Panel 1 of Sponsor's response (EDR submission date: 13 February 2009). Covariates in the Cox model include the 4 protocol specified covariates (age, sex, duration of schizophrenia, last suicide attempt) and an additional covariate (study accrual time).

^a Patients who had sertindole, risperidone or clozapine added to their randomized treatment before suicide attempt were removed.

^b Nominal p-values, not adjusting for multiplicity.]

Table 13 FDA Analysis Results of Suicide Attempts Based on C-CASA Reclassification

Study period	Number of patients with suicide attempts / Total number of patients		Hazard ratio (ser./ris.)	95% CI	p-value ^c
	Ser.	Ris.			
	Cox model with 5 covariates^a				
WRT+30	47/ 4905	66/ 4904	0.762	0.524 – 1.109	0.1554
WRT+30, no add-on ^b	46/ 4579	62/ 4629	0.800	0.546 – 1.172	0.2511
ORT+1	36/ 4905	54/ 4904	0.703	0.460 – 1.072	0.1014
Cox model with 2 covariates only (age and sex)					
WRT+30	47	66	0.782	0.538 – 1.137	0.1980
WRT+30, no add-on ^b	46	62	0.831	0.568 – 1.218	0.3426
ORT+1	36	54	0.734	0.481 – 1.119	0.1510

[Source: FDA statistical reviewers Drs. Chen and Bai's results based on raw data.

^a Covariates included in the Cox model are the same as those used by the sponsor. However, in order to not miss out any patient who had suicide attempts from analysis, missing covariate values were imputed by the following: the duration of schizophrenia prior to study entry was considered to be less than 5 years if it's missing; patient was considered to have no suicide attempt prior to study entry if time since last suicide attempt was missing. The Cox model pre-specified in SAP consisted of 4 covariates. The results were consistent whether based on 4 or 5 covariates.

^b Patients who had sertindole, risperidone or clozapine added to their randomized treatment before suicide attempt were removed.

^c Nominal p-values, not adjusting for multiplicity.]

Table 14 **FDA** Analysis Results of Completed Suicide based on C-CASA Reclassification

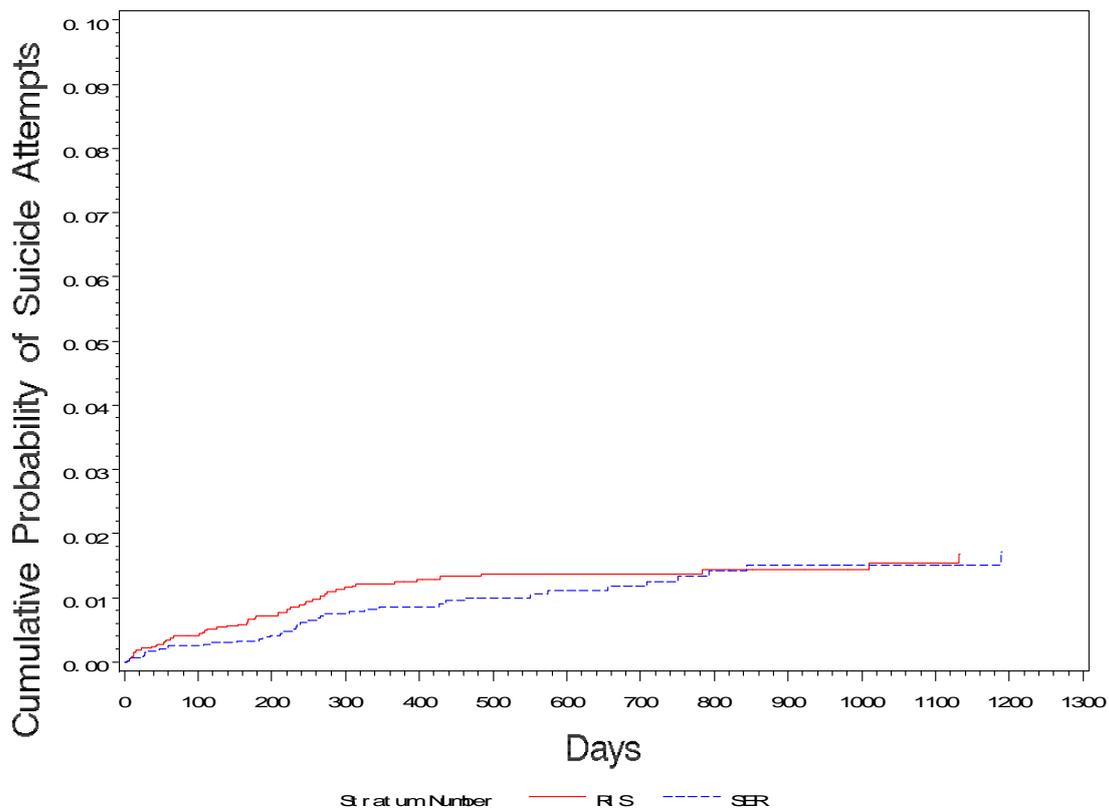
Study Period	Number of events		Hazard ratio ^a (ser./ris.)	95% CI	p-value ^b
	Ser.	Ris.			
WRT+30	13	21	0.829	0.308 – 2.235	0.7112
ORT+1	9	19	0.501	0.226 – 1.107	0.0876

[Source: FDA statistical reviewer Dr. Chen’s result.

^a The hazard ratio was obtained after adjusting for the following 5 covariates: age, sex, suicide attempt within 5 years, last antipsychotic treatment, and study accrual time. However, in order to not miss out any patient who had completed suicide from analysis, missing covariate values were imputed by the following: the duration of schizophrenia prior to study entry was considered to be less than 5 years if it’s missing; patient was considered to have no suicide attempt prior to study entry if time since last suicide attempt was missing; last antipsychotic treatment prior to study entry was considered “monotherapy” if it’s missing.

^b Nominal p-values, not adjusting for multiplicity.]

Figure 4 Cumulative Probability of Suicide Attempts Over Time Based on C-CASA Reclassification (Primary Study Period WRT+30)



[Source: FDA statistical reviewer Dr. Bai’s results]

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

Subgroup analyses by sex and region are explored based on the primary study period WRT+30. Per the sponsor's classification, Eastern Europe includes AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, LU, IT, NL, NO, PT, and SE. Western Europe includes BG, CZ, EE, HR, HU, LT, LV, PL, RO, RS, RU, SK, TR, and UA. Asia countries include HK, IN, KR, MY, PH, SG, TH, and TW. Subgroup analysis by age is skipped because only 183 patients (less than 2%) were older than 65 years.

Table 15 Exploratory Subgroup Analysis by Gender (WRT+30 Study Period)

Endpoint	Number of Events / Number of Patients		
	Sertindole	Risperidone	Total
All-cause mortality			
Male	37 / 2710	41 / 2716	78 / 5426
Female	27 / 2195	20 / 2188	47 / 4283
Cardiac death by MedDRA coding			
Male	9 / 2710	6 / 2716	15 / 5426
Female	8 / 2195	2 / 2188	10 / 4283
Cardiac death by ISC classification			
Male	15 / 2710	9 / 2716	24 / 5426
Female	16 / 2195	3 / 2188	19 / 4283
Documented sudden cardiac death			
Male	5 / 2710	3 / 2716	8 / 5426
Female	8 / 2195	0 / 2188	8 / 4283
Completed suicide by MedDRA coding			
Male	9 / 2710	13 / 2716	22 / 5426
Female	4 / 2195	8 / 2188	12 / 4283
Completed suicide by ISC classification			
Male	10 / 2710	14 / 2716	24 / 5426
Female	4 / 2195	7 / 2188	11 / 4283

(Table continues on next page.)

(cont. from the proceeding page)

Endpoint	Number of Events / Number of Patients		
	Sertindole	Risperidone	Total
Suicide attempts by MedDRA coding			
Male	24 / 2710	34 / 2716	58 / 5426
Female	19 / 2195	31 / 2188	50 / 4283
Suicide attempts by ISC classification			
Male	39 / 2710	39 / 2716	78 / 5426
Female	29 / 2195	37 / 2188	66 / 4283
Suicide attempts by <u>C-CASA re-classification</u>			
Male	24 / 2710	34 / 2716	58 / 5426
Female	23 / 2195	32 / 2188	55 / 4283

[Source: Sponsor's Response (dated 16 October 2008) to Filing Letter and Response (dated 13 February 2009) on reclassified suicidality data. Summary of suicide attempts based on C-CASA reclassification was prepared by FDA statistical reviewer Dr. Bai.]

Table 16 Exploratory Subgroup Analysis by Region (WRT+30 Study Period)

Endpoint	Number of Events / Number of Patients		
	Sertindole	Risperidone	Total
All-cause mortality			
Western Europe	14 / 840	15 / 835	29 / 1675
Eastern Europe	29 / 2705	26 / 2708	55 / 5413
Asia	21 / 1360	20 / 1361	41 / 2721
Cardiac death by MedDRA coding			
Western Europe	4 / 840	3 / 835	7 / 1675
Eastern Europe	7 / 2705	3 / 2708	10 / 5413
Asia	6 / 1360	2 / 1361	8 / 2721
Cardiac death by ISC classification			
Western Europe	7 / 840	3 / 835	10 / 1675
Eastern Europe	10 / 2705	2 / 2708	12 / 5413
Asia	14 / 1360	7 / 1361	21 / 2721
Documented sudden cardiac death			
Europe	4 / 3545	1 / 3543	5 / 7088
Asia	9 / 1360	2 / 1361	11 / 2721

(Table continues on next page.)

(cont. from the preceding page)

Endpoint	Number of Events / Number of Patients		
	Sertindole	Risperidone	Total
Completed suicide by MedDRA coding			
Western Europe	2 / 840	6 / 835	8 / 1675
Eastern Europe	8 / 2705	9 / 2708	17 / 5413
Asia	3 / 1360	6 / 1361	9 / 2721
Completed suicide by ISC classification			
Western Europe	3 / 840	7 / 835	10 / 1675
Eastern Europe	8 / 2705	9 / 2708	17 / 5413
Asia	3 / 1360	5 / 1361	8 / 2721
Suicide attempts by MedDRA coding			
Western Europe	10 / 840	18 / 835	28 / 1675
Eastern Europe	22 / 2705	29 / 2708	51 / 5413
Asia	11 / 1360	18 / 1361	29 / 2721
Suicide attempts by ISC classification			
Western Europe	20 / 840	24 / 835	44 / 1675
Eastern Europe	25 / 2705	33 / 2708	58 / 5413
Asia	23 / 1360	19 / 1361	42 / 2721
Suicide attempts by <u>C-CASA re-classification</u>			
Western Europe	11 / 840	19 / 835	30 / 1675
Eastern Europe	23 / 2705	30 / 2708	53 / 5413
Asia	13 / 1360	17 / 1361	30 / 2721

[Source: Sponsor's Response (dated 16 October 2008) to Filing Letter and Response (dated 13 February 2009) on reclassified suicidality data. Summary of suicide attempts based on C-CASA reclassification was prepared by FDA statistical reviewer Dr. Bai.]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor conducted this study in response to a request from CHMP to establish the safety of sertindole compared to that of a marketed product in the treatment of schizophrenia. The sponsor chose all-cause mortality as the primary endpoint because they believed that it was the only unbiased endpoint in a large study as such. Per the CHMP request, the sponsor added "cardiac events, including arrhythmias, requiring hospitalization" as the second primary endpoint.

FDA had a concern about the all-cause mortality endpoint because an excess risk of cardiac deaths for sertindole compared to risperidone would not necessarily be reflected

in a higher overall mortality for sertindole, given the relatively higher mortality in this population from multiple causes, and suggested that the sponsor estimate the risk of the sudden unexpected death. Furthermore, FDA recommended that the sponsor do additional work to establish a benefit that could overcome the risk, for example, effectiveness in patients shown to be refractory to standard antipsychotics or reduction in suicidality.

The following summarizes the safety results and statistical issues.

- [1] **Potential Inflation of Overall Type I error Rate.** For a given endpoint, multiple data sets were generated based on different study periods and different classification approaches. Furthermore, multiple analyses (Cox models) were performed for a given data set. For example, the pre-specified primary Cox model for all-cause mortality included two covariates (age and sex) only. However, after data unblinding, the sponsor added 3 additional covariates to the model via a model selection approach. Typically the reproducibility of the study result could be an issue if the same data set is used to develop the statistical model and test the treatment effect with the model developed by it, as in this study. A major concern is the potential inflation of the overall type I error rate due to multiple analyses (model fittings) for the same endpoint. If the results were generally consistent across different analyses (Cox models) and different study periods, the multiplicity issue may be alleviated. Otherwise, the results should be interpreted with great caution. With regard to the study period, although the sponsor pointed out that the ORT+1 study period could lead to reduction in certain confounding effects, one cannot ignore the combination therapy period while patients still received the randomized treatment, if it's not clear which drug (the add-on or the randomized drug) contributed to the event; in addition, WRT+30 was the pre-specified study period for all analyses and report. If ORT+1 were considered the most appropriate study period, it should have been pre-specified as the primary study period. From the statistical perspective, shopping and picking after data unblinding is very problematic unless the purpose is to check the consistency. Beyond this, if there is a clinical uncertainty about which study period to rely on, to protect the public health, (a) on the risk side, it would be sensible for FDA to place more weight on the results that revealed large adverse event signals associated with sertindole, and (b) on the benefit side, to place more weight on the more conservative results.
- [2] **Duration of Exposure to Treatment.** Overall, shorter exposure durations were observed in the sertindole group whether based on the WRT or the ORT study period. This might suggest a potential underestimation of a harmful trend for sertindole, such as suicide attempts.
- [3] **All-Cause Mortality.** The sponsor intended to demonstrate non-inferiority of sertindole to risperidone by showing that the two-sided 90% CI of the hazard ratio (sertindole/ risperidone) was entirely below the pre-specified threshold 1.5. The FDA statistical reviewers have the following concerns:

- The sponsor indicated that the non-inferiority threshold was chosen as the largest ratio that was clinically acceptable to CHMP and that, at the same time, took into account the feasibility of conducting such a study. On face, a 50% non-inferiority margin seems to be quite liberal because it would suggest a non-inferiority if sertindole were shown to be at most 50% worse than risperidone. It is uncertain whether FDA can rely on this margin for drugs intended for the U.S. marketing, in particular when this is not the endpoint FDA would primarily focus on.
 - The sponsor utilized a two-sided 90% CI to compare with a pre-specified non-inferiority threshold. As a standard practice, FDA has been utilizing a two-sided 95% CI in non-inferiority analysis. Based on this standard practice, the upper limits of the 95% CIs generally exceeded 1.5, but were generally below 1.6. This suggests that one might be able to rule out that sertindole was more than roughly 60% worse than risperidone, but one cannot rule out that sertindole was 50% worse than risperidone, in the risk of all-cause mortality.
- [4] **Cardiac Events, Requiring Hospitalization.** The sponsor intended to demonstrate non-inferiority of sertindole to risperidone by showing that the two-sided 90% CI of the hazard ratio (sertindole / risperidone) was entirely below the pre-specified threshold 2. However, the analysis was not performed because of very few events.
- [5] **Cardiac Death.** Regardless of the coding approach, the results appear to be similar across different analysis models. The observed hazard ratios (sertindole/ risperidone) were all greater than 2. Moreover, the ISC classification seems to suggest a higher risk of cardiac death for the sertindole group at the nominal significance level of 0.05.
- [6] **Documented Sudden Cardiac Death (including Cardiac Origin Probable).** There were more events observed in the sertindole group as compared to the risperidone group (13 vs. 3). The observed hazard ratio (sertindole / risperidone) was around 5. The 95% CI was very wide, but was still entirely above 1, suggesting a higher risk of sudden death in the sertindole group than in the risperidone group at the nominal significance level of 0.05. The result was very similar after removing all patients in the sertindole group who had risperidone added to their treatment and all patients in the risperidone group who had sertindole added to their treatment. The result remained similar after further removing those patients who had thioridazine, mesoridazine, ziprasidone, or pimozone added to their randomized treatment from both treatment groups.
- [7] **Dictionary-Derived Adverse Events: Syncope, Palpitations, and Dizziness.** In these analyses, all patients in the risperidone group who had sertindole added to their randomized treatment and all patients in the sertindole group who had risperidone added to their randomized treatment were removed. Also, removed from both treatment groups were those patients who had thioridazine, mesoridazine, ziprasidone, or pimozone added to their randomized treatment. The results seem to

suggest higher incidences of dizziness for the sertindole group than the risperidone group at the nominal significance level of 0.05.

- [8] **Suicide Attempts.** Although the MedDRA coding suggested a lower risk of suicide attempts for the sertindole group than for the risperidone group at the nominal significance level of 0.05, this classification was performed by investigators who were not blind to the treatment. Hence, a bias may be introduced in determining suicidality attempts. Although the ISC was blind to treatment, the ISC definition of suicide attempts was very broad because it included suicidal ideation and tendency. Therefore, FDA requested that the sponsor reclassify the ISC identified suicide attempts in a more systematic manner and reanalyze the data. Based on the C-CASA reclassification, the results did not suggest a statistically significant difference at the nominal significance level of 0.05 although there was a trend in favor of sertindole. Two patients with suicide attempts in the sertindole group were automatically excluded from the sponsor's analyses because these patients had missing covariate values. When the missing covariate values were imputed to bring these two patients back to analysis, the trend diminished regardless of study period. Similar finding was observed if the Cox model included two covariates only (age and sex) that had no missing values. In addition, shorter exposure durations were observed in the sertindole group. This may lead to underestimated hazards in the sertindole group.
- [9] **Completed Suicide.** The results appear to be similar in analyses regardless of the coding approach (MedDRA, ISC classification or C-CASA reclassification). The observed hazard ratios (sertindole/ risperidone) for completed suicide trended in favor of sertindole, but the 95% CI did not suggest a statistically significant difference at the nominal significance level of 0.05. In addition, shorter exposure durations were observed in the sertindole group. This may lead to underestimated hazards in the sertindole group.
- [10] **Labeling Claim on Suicidality Reduction.** The sponsor proposed a safety claim that sertindole is indicated for reducing the risk of fatal and nonfatal suicide attempts in patients with schizophrenia. From the statistical perspective, a multiple testing procedure to control the overall (studywise) type I error rate needs to be pre-specified for all efficacy and safety endpoints intended for claims. This is to avoid excess chance of false positive conclusions. In this study, completed suicide and suicide attempts were analyzed using multiple study periods. There was no pre-specified multiple testing procedure to address the multiple endpoints (completed suicide and suicide attempts) and multiple analyses issue, and all statistical analyses were performed at the nominal significance level of 0.05. From the statistical perspective, there was no conclusive evidence to support the safety claim.

5.2 Conclusions and Recommendations

There have been worldwide concerns about the potential QT prolongation and increased cardiac mortality associated with sertindole. The sponsor conducted this study to address

these concerns and pre-specified the first primary endpoint to be the all-cause mortality, with the goal to demonstrate non-inferiority of sertindole to risperidone. However, it is not clear whether the sponsor has demonstrated the non-inferiority. Furthermore, analysis of this endpoint may not best address the underlying safety issues. Other more relevant endpoints such as documented sudden cardiac death, cardiac death, dictionary-derived dizziness, seem to suggest a higher risk in the sertindole group. With regard to suicide attempts and completed suicide, although the numerical results trended in favor of sertindole, the evidence was inconclusive based on the C-CASA re-classification.

From the statistical perspective, there was no convincing evidence to support the safety claim of suicidality reduction. Whether the sponsor has adequately established a benefit that could overcome the risk will be discussed at the Psychopharmacologic Drug Advisory Committee meeting.

Appendices

The original NDA submission filed in 1995 included results of several efficacy studies in support of the claim for treatment in schizophrenia. Of those, FDA considered Studies M93-098 and M93-113 positive. Results of these two studies, as well as other efficacy studies, are summarized here.

A.1 Efficacy Study M93-098

This was an 8-week, double-blind, placebo-controlled, Haldol-referenced study to evaluate the safety and efficacy of sertindole doses in schizophrenic patients. A total of 462 patients were randomized: 116 patients to placebo, 117 to sertindole 20 mg, 114 to sertindole 24 mg, and 115 to Haldol 16 mg among 30 centers in the United States. During the titration period (Days 1- 15), the active doses were escalated at the rate of 4 mg every fourth day until the patient reached the assigned dosage. The objective of this study was to assess the efficacy and safety of two sertindole groups compared with Haldol and placebo when administered to hospitalized schizophrenic patients who were neuroleptic-responsive or had never been treated with neuroleptic agent.

The primary efficacy endpoint was change from baseline to the final evaluation in the PANSS total score. The protocol-specified primary efficacy analysis was the “weighted” comparison from the two-way ANOVA (analysis of variance) with factors for treatment group, center, and their interaction. Thus, the overall treatment would be a weighted linear combination of the center-specific treatment differences with weights dependent on the sample size for each treatment group in the center. The FDA statistical reviewer Dr. Hoberman commented that the weighted average of the center-specific treatment difference with treatment by center interaction in the model was interesting, but possibly mis-conceived because these weights were useful when there was an assumption that the treatment differences were the same over all centers as in the case of the ANOVA model without interaction. When the interaction was left in the model, there was no assumption about a common expected value for treatment differences. Regardless of weighted or unweighted (typically used) analysis, both sertindole 20 mg and sertindole 24 mg demonstrated efficacy with respect to the primary efficacy endpoint.

Table 17 summarizes the reasons for patient discontinuation from this study. Table 18 displays the sponsor’s analysis results of the primary efficacy endpoint, as well as secondary endpoints. No key secondary endpoint was pre-specified and no multiplicity adjustment procedure was pre-specified to control the overall (study-wise) type I error rate due to multiple doses in combination with multiple endpoints. However, since the actual nominal p-values for both doses were very small on the PANSS total score, Dr. Hoberman concluded that any symmetric correction for multiple comparisons would also yield statistically significant results. Table 19 summarizes the mean change in PANSS total score from baseline to each visit, as well as the number of patients remaining in the study at each visit. Table 20 summarizes the subgroup analysis results of the primary

endpoint by sex and race. The summary was based on raw means and no statistical model was fitted to the data. The results suggested a consistent trend in favor of both sertindole doses for each gender and for the two major race categories, which accounted for approximately 90% of patients in this study. Subgroup analysis by age is skipped because in general no one was older than 65 years old.

Conclusion: This study demonstrated the efficacy of both sertindole 20 mg and sertindole 24 mg in treating hospitalized schizophrenia patients.

Table 17 Summary of Reasons for Patient Discontinuation (Study M93-098)

Reason for Discontinuation	Placebo (N=116)	Sertindole 20 mg (N=117)	Sertindole 24 mg (N=114)	Haldol 16 mg (N=115)
Ineffectiveness	45 (39%)	31 (26%)	33 (29%)	28 (24%)*
Adverse Event	7 (6%)	12 (10%)	8 (7%)	10 (9%)
Noncompliance	6 (5%)	5 (4%)	3 (3%)	1 (1%)
Personal	1 (1%)	4 (3%)	3 (3%)	2 (2%)
Lost to Follow-up	2 (2%)	5 (4%)	2 (2%)	3 (3%)
Other	11 (9%)	14 (12%)	13 (11%)	16 (14%)
Total	72 (62%)	71 (61%)	62 (54%)	60 (52%)

* p<0.05 versus placebo

[Source: Table 6 of Sponsor’s Study Report]

Table 18 Analysis Results of Mean Change from Baseline to Final Evaluation in PANSS, BPRS, and CGI Scores Using LOCF Method (Study M93-098)

Variable	Placebo (N=106)		Sertindole 20 mg (N=111)		Sertindole 24 mg (N=108)		Haldol 16 mg (N=113)	
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change
PANSS								
Total	64.4	-1.2	60.6	-7.5*†	62.8	-10.3*†	65.1	-13.3*†
Positive	16.7	-1.0	15.8	-3.2*†	15.9	-3.3*†	17.7	-5.8*†
Negative	17.4	-0.5	16.0	-1.3	17.5	-2.5*†	16.4	-1.3
BPRS								
Total	35.3	-1.7	33.5	-4.8*†	34.4	-6.5*†	36.1	-9.1*†
	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score
CGI ^a	4.7	4.1	4.7	3.6 [#]	4.8	3.6 [#]	4.9	3.2 [#]

* p<0.05 versus placebo from weighted comparison of ANOVA
† p<0.05 versus placebo from unweighted comparison of ANOVA
p<0.05 versus placebo from Cochran-Mantel-Haenszel analysis
^a Baseline is severity (1-7) where 1 = normal and 7 = among most extremely ill; Final Score is improvement (1-7) where 1 = very much improved, 4 = no change, and 7 = very much worse

[Source: Table 10 of Sponsor’s Study Report]

Table 19 Analysis Results of Mean Change from Baseline to Each Evaluation in PANSS Total Score (Study M93-098)

Study Days	Placebo		Sertindole 20 mg		Sertindole 24 mg		Haldol 16 mg	
	LOCF (N=106)	OC (N=a)	LOCF (N=111)	OC (N=a)	LOCF (N=108)	OC (N=a)	LOCF (N=113)	OC (N=a)
Baseline	64.4	64.4	60.6	60.6	62.8	62.8	65.1	65.1
Day 7	-1.8	-1.8	-2.9	-2.9	-2.4	-2.4	-5.7*†	-5.7*†
Day 14	-3.1	-3.4	-5.3	-6.8	-4.8	-6.7	-9.0*†	-9.7*†
Day 21	-3.2	-5.0	-5.2	-6.5	-6.8	-10.6	-10.3*†	-11.1†
Day 28	-2.8	-8.0	-6.0†	-9.2	-6.5	-11.0	-10.7*†	-13.1
Day 35	-2.9	-11.2	-6.1†	-11.5	-8.8*†	-15.6	-11.9*†	-16.7
Day 42	-2.4	-11.3	-6.4†	-13.8	-8.9*†	-17.0	-13.0*†	-20.0
Day 49	-2.3	-11.1	-7.0†	-15.8	-9.4*†	-18.5	-12.9*†	-20.5†
Day 56	-1.2	-10.3	-7.5*†	-17.1	-10.3*†	-20.2	-13.3*†	-21.9*†
a N's for the observed cases analysis:								
Day:	<u>7</u>	<u>14</u>	<u>21</u>	<u>28</u>	<u>35</u>	<u>42</u>	<u>49</u>	<u>56</u>
Placebo	106	95	83	69	59	55	47	44
Sertindole 20 mg	111	97	92	74	61	53	48	44
Sertindole 24 mg	107	94	88	75	68	59	56	49
Haldol 16 mg	113	104	89	72	67	61	58	55
* p≤0.05 versus placebo from weighted comparison of ANOVA								
† p≤0.05 versus placebo from unweighted comparison of ANOVA								

[Source: Table 12 of Sponsor's Study Report]

Table 20 Subgroup Analysis of Mean Change from Baseline to Final Evaluation in PANSS Total Score (Study M93-098)

Subgroup		20 mg vs. placebo	24 mg vs. placebo
Sex			
Male	Number of subjects	84 vs. 82	84 vs. 82
	Mean Change in PANSS (SE)	-3.0 (3.38)	-5.7 (3.38)
Female	Number of subjects	27 vs. 24	24 vs. 24
	Mean Change in PANSS (SE)	-16.8 (6.94)	-20.6 (7.58)
Race			
Caucasians	Number of subjects	76 vs. 66	68 vs. 66
	Mean Change in PANSS (SE)	-5.2 (3.87)	-5.6 (3.79)
Blacks	Number of subjects	23 vs. 25	30 vs. 25
	Mean Change in PANSS (SE)	-12.8 (6.05)	-16.0 (7.06)
Others	Number of subjects	12 vs. 15	10 vs. 15
	Mean Change in PANSS (SE)	2.1 (9.05)	-14.3 (8.75)

[Source: FDA statistical reviewer Dr. Bai's raw-mean results without model fitting.]

A.2 Efficacy Study M93-113

This was an 8 week, double-blind, placebo-controlled, dose-response comparison of safety and efficacy of three sertindole doses and three Haldol doses in schizophrenic patients. A total of 497 patients were randomized in equal ratios to each of the 7 treatment groups: placebo, 3 fixed sertindole doses (12, 20 and 24 mg/day) and 3 fixed Haldol doses (4, 8 and 16 mg/day). During the titration period (Days 1 – 15), sertindole was escalated at the rate of 4 mg every fourth day, while Haldol was escalated at the same rate every third day, until the assigned dosage was reached. This study was conducted in 41 centers in the United States and 2 in Canada. The original objective of this study was to compare sertindole to Haldol with respect to medication-induced acute movement disorders (MIAMDs), not efficacy in the treatment of schizophrenia. Due to the lack of dose response in the data, the objective was changed and the primary analysis was changed accordingly (from a simple linear regression to a typical ANOVA).

The primary efficacy endpoint was change from baseline to the final evaluation in the PANSS total score. The protocol-specified primary efficacy analysis was the “weighted” comparison from the two-way ANOVA (analysis of variance) with factors for treatment group, center, and their interaction. Thus, the overall treatment would be a weighted linear combination of the center-specific treatment differences with weights dependent on the sample size for each treatment group in the center. The FDA statistical reviewer Dr. Hoberman had a concern about the weighted approach (refer to comments in Section A.1). Regardless of weighted or unweighted (typically used) analysis, both sertindole 20 mg and sertindole 24 mg demonstrated efficacy with respect to the primary efficacy endpoint.

Table 21 summarizes the reasons for patient discontinuation from this study. Table 22 displays the sponsor’s analysis results of the primary efficacy endpoint, as well as secondary endpoints. No key secondary endpoint was pre-specified and no multiplicity adjustment procedure was pre-specified to control the overall (study-wise) type I error rate due to multiple doses in combination with multiple endpoints. Although the nominal statistical significances were achieved for all three sertindole doses, the FDA statistical reviewer Dr. Hoberman concluded that efficacy was demonstrated in the 20 mg and 24 mg doses, after applying the Dunnett’s procedure to adjustment for multiplicity.

Table 23 summarizes the mean change in PANSS total score from baseline to each visit, as well as the number of patients remaining in the study at each visit. Table 24 summarizes the subgroup analysis results of the primary endpoint by sex and race. The summary was based on raw means without any model fitting. In general, there was a consistent trend in favor of sertindole doses for each gender and each race category. Subgroup analysis by age is skipped because in general no one was older than 65 years old.

Conclusion: This study demonstrated the efficacy of both sertindole 20 mg and sertindole 24 mg in schizophrenic patients.

Table 21 Summary of Reasons for Patient Discontinuation (Study M93-098)

Reason for Discontinuation	Placebo (N=73)	Sertindole 12 mg (N=76)	Sertindole 20 mg (N=68)	Sertindole 24 mg (N=72)	Haldol 4 mg (N=71)	Haldol 8 mg (N=67)	Haldol 16 mg (N=70)
Ineffectiveness	28 (38%)	21 (28%)	16 (24%)	19 (26%)	18 (25%)	9 (13%)*	11 (16%)*
Adverse Event	1 (1%)	3 (4%)	6 (9%)	3 (4%)	5 (7%)	10 (15%)*	4 (6%)
Noncompliance	2 (3%)	4 (5%)	3 (4%)	3 (4%)	4 (6%)	3 (4%)	3 (4%)
Personal	0 (0%)	1 (1%)	1 (1%)	2 (3%)	4 (6%)	2 (3%)	2 (3%)
Lost to Follow-up	3 (4%)	3 (4%)	3 (4%)	1 (1%)	2 (3%)	5 (7%)	5 (7%)
Other [#]	3 (4%)	10 (13%)	4 (6%)	10 (14%)*	6 (8%)	4 (6%)	8 (11%)
Total	37 (51%)	42 (55%)	33 (49%)	38 (53%)	39 (55%)	33 (49%)	33 (47%)

* p<0.05 versus placebo from Fisher's exact test
[#] Includes administrative reasons

[Source: Sponsor's Table 7 in Sponsor's Study Report]

Table 22 Analysis Results of Mean Change from Baseline to Final Evaluation in PANSS, BPRS, and CGI Scores Using LOCF Method (Study M93-113)

Variable	Placebo (N=71)		Sertindole 12 mg (N=72)		Sertindole 20 mg (N=65)		Sertindole 24 mg (N=70)		Haldol 4 mg (N=68)		Haldol 8 mg (N=63)		Haldol 16 mg (N=68)	
	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC
PANSS														
Total	62.0	0.7	63.2	-9.9*†	70.5*†	-17.6*†	65.2	-10.7*†	69.0*†	-11.8*†	64.8	-16.5*†	67.1	-11.9*†
Positive	16.0	0.0	16.3	-2.4*	17.9	-4.8*†	16.5	-3.2*†	17.7	-2.7*	16.7	-5.6*†	17.3	-4.3*†
Negative	17.0	-0.7	17.2	-2.8	18.8†	-4.4*†	17.8	-2.3	17.7	-2.7	17.0	-3.3	17.3	-2.4
BPRS														
Total	34.4	-0.9	35.1	-6.7*†	39.2*†	-10.3*†	37.1	-8.2*†	38.9*†	-8.0*†	36.7	-10.4*†	38.3	-8.8*†
	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS
CGI^a	4.7	4.2	4.7	3.5 [#]	4.9	3.3 [#]	4.6	3.6 [#]	4.9	3.7	4.7	3.1 [#]	4.9	3.5 [#]

MB = Mean baseline
 MC = Mean change
 FS = Final improvement score
 * p<0.05 versus placebo from weighted comparison of the ANOVA
 † p<0.05 versus placebo from unweighted comparison of the ANOVA
[#] p<0.05 versus placebo from Cochran-Mantel-Haenszel analysis
^a Baseline mean is severity (1-7) where 1 = normal and 7 = among most extremely ill; Final Score is improvement (1-7) where 1 = very much improved, 4 = no change, and 7 = very much worse

[Source: Sponsor's Table 11 in Sponsor's Study Report]

Table 23 Analysis Results of Mean Change from Baseline to Each Evaluation in PANSS Total Score (Study M93-113)

Study Days	Placebo		Sertindole 12 mg		Sertindole 20 mg		Sertindole 24 mg		Haldol 4 mg		Haldol 8 mg		Haldol 16 mg	
	LOCF (N=71)	OC (N=#)	LOCF (N=72)	OC (N=#)	LOCF (N=65)	OC (N=#)	LOCF (N=70)	OC (N=#)	LOCF (N=68)	OC (N=#)	LOCF (N=63)	OC (N=#)	LOCF (N=68)	OC (N=#)
Baseline	62.0	62.0	63.2	63.2	70.5*†	70.5*†	65.2	65.2	69.0*†	69.0*†	64.8	64.8	67.1	67.1
Day 7	-1.1	-1.1	-2.2	-2.2	-2.6	-2.6	-3.7	-3.7	-10.2*†	-10.2*†	-8.1*†	-8.1*†	-6.4	-6.4
Day 14	0.0	-1.7	-4.2	-4.5	-7.4*†	-7.7*†	-4.2*	-4.3	-12.6*†	-12.9*†	-10.6*†	-10.1*†	-7.6*	-7.8*
Day 21	-1.1	-3.9	-6.2	-7.0	-9.9*	-10.8*	-5.9*	-7.0	-13.2*†	-14.2*†	-15.3*†	-16.1*†	-8.0*	-10.1*
Day 28	0.6	-4.4	-7.3*	-10.3	-12.5*†	-17.9*†	-8.1*†	-14.7*†	-13.1*†	-18.3*	-16.0*†	-19.3*†	-8.9*	-13.1
Day 35	0.7	-6.4	-8.4*†	-13.5	-15.2*†	-21.4*†	-9.0*†	-17.9*	-12.8*†	-19.1*	-17.1*†	-21.5*†	-11.8*†	-17.0†
Day 42	-1.0	-11.3	-8.3*†	-14.4	-15.5*†	-22.4*†	-8.1*	-17.6	-12.7*†	-21.8*	-15.8*†	-20.8	-11.2*†	-16.7
Day 49	1.0	-9.4	-9.4*†	-17.6	-14.8*†	-21.8*†	-9.7*†	-21.8*	-11.7*†	-21.3	-17.4*†	-23.6*	-10.9*†	-16.8
Day 56	0.7	-10.9	-9.9*†	-21.5	-17.6*†	-27.0*	-10.7*†	-25.5	-11.8*†	-22.1	-16.5*†	-22.2	-11.9*†	-17.5

N's for the observed cases analysis:

Day:	7	14	21	28	35	42	49	56
Placebo	71	68	64	55	47	43	40	37
Sertindole 12 mg	71	66	62	55	47	41	38	34
Sertindole 20 mg	65	62	57	46	44	39	39	36
Sertindole 24 mg	68	63	58	47	40	38	36	33
Haldol 4 mg	68	66	59	44	38	35	33	32
Haldol 8 mg	62	59	54	48	45	39	35	32
Haldol 16 mg	68	65	58	50	45	42	38	36

* p≤0.05 versus placebo from weighted comparison of the ANOVA
† p≤0.05 versus placebo from unweighted comparison of the ANOVA

[Source: Sponsor's Table 13 in Sponsor's Study Report]

Table 24 Subgroup Analysis of Mean Change from Baseline to Final Evaluation in PANSS Total Score (Study M93-113)

Subgroup		12 mg vs. placebo	20 mg vs. placebo	24 mg vs. placebo
Sex				
Male	Number of subjects	58 vs. 55	49 vs. 55	48 vs. 55
	Mean Change in PANSS (SE)	-9.69 (4.45)	-18.99 (4.97)	-13.8 (4.39)
Female	Number of subjects	14 vs. 16	16 vs. 16	22 vs. 16
	Mean Change in PANSS (SE)	-15.96(9.91)	-15.25(8.86)	-3.25 (9.73)
Race				
Caucasians	Number of subjects	46 vs.40	42 vs. 40	43 vs. 40
	Mean Change in PANSS (SE)	-16.6 (5.38)	-20.3 (5.93)	-10.2 (5.43)
Blacks	Number of subjects	19 vs. 21	19 vs. 21	22 vs. 21
	Mean Change in PANSS (SE)	-3.5 (6.78)	-9.8 (6.73)	-8.1 (7.31)
Others	Number of subjects	7 vs. 10	4 vs. 10	5 vs. 10
	Mean Change in PANSS (SE)	-8.7 (14.14)	-17.5 (15.05)	-25.8 (12.22)

[Source: FDA statistical reviewer Dr. Bai's raw-mean results without model fitting.]

A.3 Other Efficacy Studies

Other efficacy studies are briefly summarized below.

Study M92-762: This was a randomized, 16-center, double-blind, 40-day, fixed dose study comparing sertindole at three fixed doses (8, 12 and 20 mg/day) with placebo. Sertindole dose was titrated at the rate of 4 mg every fourth day to the assigned dosage. The primary efficacy endpoint was change from baseline in the BPRS total score. None of these doses demonstrated a statistically significant difference from placebo with respect to the primary endpoint based on the intent-to-treat analysis set (198 patients). The sponsor indicated a statistically significant difference between the 20 mg dose and placebo (Table 25). However, it was based on the “evaluable” data set (153 patients), not the intent-to-treat analysis set. In addition, no multiplicity adjustment was considered in making those multiple comparisons.

Table 25 Analysis Results of Mean Change from Baseline to Final Evaluation in PANSS, BPRS, and CGI Scores Using LOCF Method (Study M92-762)

Intent-to-Treat Dataset								
Variable	Placebo (N=47)		Sertindole 8 mg (N=50)		Sertindole 12 mg (N=50)		Sertindole 20 mg (N=51)	
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change
PANSS	56.6	-5.0	60.1	-3.5	60.3	-8.6	60.0	-12.6
BPRS Total								
Unwt.	50.3	-4.2	50.9	-2.8	52.3	-5.7	50.5	-8.0
Wt.	117.4	-10.0	118.6	-6.7	121.7	-13.2	119.1	-19.4
	Baseline	Final Improvement Score	Baseline	Final Improvement Score	Baseline	Final Improvement Score	Baseline	Final Improvement Score
CGI#	4.9	3.9	4.8	4.2	4.9	3.7	4.7	3.2*†
Evaluable Dataset								
Variable	Placebo (N=38)		Sertindole 8 mg (N=35)		Sertindole 12 mg (N=40)		Sertindole 20 mg (N=40)	
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change
PANSS	57.6	-5.8	59.6	-5.0	59.1	-12.1	59.2	-16.9*
BPRS Total								
Unwt.	50.7	-4.8	51.1	-4.4	51.7	-8.0	50.1	-10.4*
Wt.	119.1	-11.8	119.6	-10.2	120.5	-18.4	117.6	-25.4*
	Baseline	Final Improvement Score	Baseline	Final Improvement Score	Baseline	Final Improvement Score	Baseline	Final Improvement Score
CGI#	4.8	3.8	4.9	4.0	4.9	3.5	4.6	2.9*†

Unwt = Unweighted Wt = Weighted
 * p<0.05 versus placebo for weighted comparison of ANOVA
 † p<0.05 versus placebo for unweighted comparison of ANOVA
 # Baseline score indicates severity, where 1 = normal, 7 = among most extremely ill; final score indicates improvement from baseline where 1 = very much improved, 4 = no change, and 7 = very much worse; values are means

[Source: Table 10 of Sponsor’s Study Report]

Study M91-645: This was a phase II, randomized, 6-center (US), double-blind, 7-week, dose-ranging, pilot study comparing sertindole with placebo in hospitalized schizophrenic or schizoaffective patients. During the titration period (Days 1 – 35), each patient received a daily dose of 4 mg on Days 1 through 3, then the dose could be increased no more frequently than every four days until the maximum dose of 20 mg was achieved. Only 38 patients were randomized in this study. Of those, 34 patients (23 in the sertindole group and 11 in the placebo group) were in the intent-to-treat analysis set and 17 patients completed the study. A total of 92% of the randomized patients were male. Four patients in the intent-to-treat population had schizoaffective disorder (Table 26). The primary efficacy endpoint was change from baseline to the final evaluation in the

BPRS total score. Although the sponsor demonstrated a statistically significant difference between sertindole and placebo (Table 27), it was uncertain whether the result was robust and interpretable because this study was very small and the completion rate was also low.

Table 26 Summary of Psychiatric History Variables (Study M91-645)

Psychiatric History Variable	Placebo		Sertindole	
	Randomized (N=11)	Intent-to-Treat (N=11)	Randomized (N=27)	Intent-to-Treat (N=23)
DSM-III-R				
Paranoid Schizophrenia	6 (55%)	6 (55%)	18 (67%)	15 (65%)
Residual Schizophrenic	3 (27%)	3 (27%)	2 (7%)	2 (9%)
Schizoaffective	1 (9%)	1 (9%)	3 (11%)	3 (13%)
Unspecified Schizophrenia	1 (9%)	1 (9%)	4 (15%)	3 (13%)
History of Drug Abuse				
No	4 (36%)	4 (36%)	9 (33%)	7 (30%)
Yes	7 (64%)	7 (64%)	18 (67%)	16 (70%)
ECT				
No	10 (91%)	10 (91%)	26 (96%)	23 (100%)
Yes	1 (9%)	1 (9%)	1 (4%)	0 (0%)
Age at Onset (years)				
Mean	21.9	21.9	22.9	23.6
Range	16.0 - 33.0	16.0 - 33.0	15.0 - 39.0	16.0 - 39.0
Number of Hospitalizations				
1 - 5	6 (55%)	6 (55%)	10 (37%)	9 (39%)
6 - 10	4 (36%)	4 (36%)	10 (37%)	7 (30%)
11 - 15	0 (0%)	0 (0%)	2 (7%)	2 (9%)
16 or more	1 (9%)	1 (9%)	5 (19%)	5 (22%)
Number of Hospitalizations Longer than One Year				
0	10 (91%)	10 (91%)	26 (96%)	22 (96%)
1	1 (9%)	1 (9%)	0 (0%)	0 (0%)
2	0 (0%)	0 (0%)	1 (4%)	1 (4%)
Time Since Last Hospitalization (years)				
Median	0.5	0.5	0.5	0.4
Range	0.04 - 3.8	0.04 - 3.8	0.03 - 3.4	0.03 - 3.4

[Source: Table 9 of Sponsor's Study Report]

Table 27 Analysis Results of Mean Change from Baseline to Final Evaluation in BPRS Scores (Study M91-645)

BPRS Results for Intent-to-Treat Analysis						
Scores	Placebo (N=11)		Sertindole (N=23)		p-value	
	Mean Baseline	Mean Change	Mean Baseline	Mean Change	Wt	Unwt
Unweighted Total	56.1	2.5	49.5	-7.2	0.033	0.027
Positive Symptoms Subscale	17.8	0.6	15.9	-3.9	0.004	0.002
Weighted Total	127.8	9.5	116.3	-17.7	0.012	0.010
Wt = weighted comparison for change from baseline						
Unwt = unweighted comparison for change from baseline						

[Source: Table 10 of Sponsor's Study Report]

Study M95-342: This was an 8-week study, comparing four doses of sertindole (8, 16, 20 and 24 mg/day) and a fixed dose (10 mg/day) of haloperidol in patients with schizophrenia. It was conducted by 89 investigators in 11 European countries. A total of 617 patients were randomized. This study was designed to identify the optimal dose/dosage regimen for sertindole, so it did not include a placebo group and the dose effect was estimated relative to the effect observed in the sertindole 8 mg group. The primary efficacy endpoint was change from baseline to the final evaluation in the PANSS total score. To assess whether there was a monotonic dose response relationship, the sponsor used the Jonckhere-Terpstra test (with country as a blocking factor). Pairwise comparisons between treatment groups were made based on the "weighted comparison" from the two-way ANOVA using treatment group, country, and their interaction as factors. (Refer to Section A.1 for "weighted" comparison.) There was no prospectively defined multiplicity adjustment procedure to control the study-wise type I error rate due to multiple comparisons. There was no statistically significant evidence to support the monotonic dose response relationship.

Study 97203: This was a 12-week double-blind, randomized study using flexible doses of sertindole in the range of 12 to 24 mg compared with 4 to 10 mg of risperidone. A total of 187 schizophrenic patients were randomized and 176 of them were included in the intent-to-treat analysis set. The primary efficacy endpoint was change from baseline to the final evaluation in the PANSS total score. The primary analysis was ANCOVA with treatment group, study center, and their interaction as factors, and the baseline PANSS total score as the covariate. The LOCF data set did not lead to a statistically significant difference between these two treatment groups although the OC data set (120 patients) did.

Study 96205: This was a 12-week randomized, double-blind, 4-armed, flexible dose study investigating extrapyramidal effects in first-episode and previously-treated patients with schizophreniform disorder or schizophrenia. The primary objective was to evaluate the safety and tolerability profile and the secondary objective included comparison of effects on cognitive parameters between sertindole (10 to 24 mg once daily) and haloperidol (5 to 15 mg once daily). Approximately 200 patients (100 first-episode and 100 chronically ill) were planned for enrollment. However, the study was prematurely discontinued because sertindole was withdrawn from the European Union market and, as a result, only 40 patients were randomized. The sponsor acknowledged that the results from the statistical analyses could not be used as confirmatory evidence because the study was prematurely discontinued.

M93-132: This was a 12-month, randomized, double-blind, parallel-group study comparing sertindole (24 mg/day) with haloperidone (10 mg/day) when administered to schizophrenic outpatients who had been stable on a neuroleptic agent (excluding clozapine) for at least three months. This study included a double-blind transition period (through Week 5) and a double-blind maintenance period (through Month 12). Patients were stratified into two groups: (a) those currently stabilized on haloperidol and (b) those stabilized on all other neuroleptic medications. A total of 282 patients were randomized. The primary efficacy endpoint was time to treatment failure during the maintenance period and the result was not statistically significant different between treatment groups.

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/s/

Peiling Yang
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Yeh-Fong Chen
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James Hung
3/9/2009 10:00:54 PM
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Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: February 12, 2009

From: CDER DCRP QT Interdisciplinary Review Team

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Keith Kiedrow
Regulatory Project Manager
Division of Psychiatry Products

Subject: QT-IRT Consult to NDA 20644

This memo responds to your consult to us dated 15 Aug 2008 regarding QT related issues with Sertindole under NDA 20644, Sponsored by Lundbeck, Inc. The QT-IRT received and reviewed the following materials:

- Your consult
- Waveforms submitted to the ECG warehouse from phase 2 and 3 clinical trials
- CSR for the SCoP study
- Sponsor's Response to FDA request dated December 5 2008 and Feb 5 2009
- Previous QT-IRT and DCRP reviews for sertindole
- Original Review of NDA 20644 by Earl Hearst, MD
- 2007 Electrocardiogram Reread Report (June 27 2008)

Questions from the Review Division

1. The 2nd re-read of ECG's (looking at QT outliers), as discussed in the consult from 5/7/07, has now been performed by Covance Central Diagnostics, an independent contractor hired by the sponsor. We request the QT team's input in assessing this 2nd re read.

QT-IRT Response

The 2007 re-read of ECGs by Covance (which is now eRT) appears acceptable. Complexity arises in how to measure the QT interval in the setting of changes in T wave morphology (flattening/notching) and T-U merging that is observed with sertindole that makes it difficult to

determine the end of the T wave offset and variability in the number of outliers with each read. It is important to note that drug induced T wave morphology changes with QT prolongation is associated with increased risk of TdP and sudden death.

2. Please comment on the sponsor's proposed labeling in regard to QT prolongation effect.

QT-IRT Response

We defer our recommendations with respect to labeling and REMS to after the scheduled advisory committee meeting.

3. In light of all the information now available on sertindole, is there anything else the sponsor should do (studies, analysis, etc.) to further clarify/quantify the QT risk?

QT-IRT Response

The estimated hazard ratio (sertindole versus risperidone), adjusting for age and sex, was 5.0 (95% CI: 1.4 to 17.5), showing a statistically significant ($p=0.0121$) higher risk of documented sudden death (including cases with cardiac origin probable) in the sertindole group than in the risperidone group. A trend is also observed with syncope although confounded by the $\alpha 1$ antagonistic effect of sertindole.

We do not think any further studies or analysis is required to quantify the QT risk.

4. Please comment on the sponsor's choice of all-cause mortality as the primary endpoint for the SCoP Study and suggest alternatives if appropriate.

QT-IRT Response

Sudden death/Sudden cardiac death per the ICD 10 is a more appropriate mortality endpoint with respect to QT-prolongation related adverse events compared to the active comparator, risperidone. The broad endpoint of all-cause mortality could mask any potential increase in cardiovascular mortality that may be apparent.

We are unable to further comment about the appropriateness of all cause mortality as the primary endpoint for the SCoP. We defer this to the review division since cardiac mortality due to sudden cardiac death has to be weighed against other causes of mortality in the patient population.

Background

Sertindole is an atypical antipsychotic agent, the original NDA (20-644) for which was submitted in September 1995. An "Approvable" Action Letter was issued on June 16, 1997, with the greatest issues of concern being (1) a dose dependent QTc prolongation in phase II/III studies, and (2) a seemingly disproportionate incidence of sudden and unexpected deaths (SUDDS) among schizophrenics treated with sertindole as compared to those treated with other recently developed anti-psychotic drugs. The sponsor withdrew the NDA in January 1998.

The sponsor has recently re-submitted the NDA. DCRP has performed various consults in the intervening years regarding QT signals. The most recent consults (under IND 38,373) were performed by Mehul Desai, M.D. in May 2007 and January 2004. The most notable addition to this NDA is a randomized, active-controlled, open-label, prospective use study (SCoP Study; $n=9858$) comparing the safety of sertindole and risperidone. The sponsor reports that that

sertindole had comparable all-cause mortality. Based on this study, the sponsor proposes that although sertindole has the potential to prolong the QT interval, this does not appear to translate into an increased safety risk.

Previous Clinical Experience:

Previous ECG assessments in Phase 2 and 3 Clinical studies

The sponsor recently submitted tables for ECG parameters including $\Delta\Delta\text{QTcB}$ and $\Delta\Delta\text{QTcF}$ for pooled data and individual studies (M93-113, M93-098, and M92762)

Table 1 Mean Change in ECG Parameters Values from Baseline to Last Observation by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose												Placebo		
	8 mg			12 mg			20 mg			24 mg			n	BL	Δ
	n	BL	Δ	n	BL	Δ	n	BL	Δ	n	BL	Δ			
Heart Rate (bpm)	46	83.3	0.1	118	79.4	2.3	210	78.6	2.6	159	78.9	1.7	205	79.6	0.5
PR interval (msec)	46	151.6	-0.8	116	150.7	-0.5	210	152.8	-3.1	159	152.1	-1.9	205	154.1	-1.3
QRS duration (msec)	46	88.2	1.7	116	89.5	-0.8	210	87.9	-0.3	159	85.7	-0.7	205	87.8	1.0
QT interval (msec)	46	357.4	13.1	118	360.2	9.4	210	365.6	15.9	159	364.8	19.6	205	365.8	-4.8
QT _{cB} interval (msec)	46	417.4	15.3	118	411.1	15.9	210	414.5	25.6	159	414.9	26.4	205	417.1	-4.6
QT _{cF} interval (msec)	46	396.1	14.48	118	393.1	13.5	210	397.2	22.1	159	397.2	23.9	205	398.9	-4.7

n = Number tested; BL = Mean baseline value; Δ = Mean change from baseline; $\Delta\Delta$ = mean difference of study drug and placebo after baseline correction with a 90% 2-sided confidence interval.

Source; Sponsors table 11 from Response to FDA request dated December 5 2008

Table 2 Mean Difference and 90% Confidence Interval of Study Drug and Placebo after Baseline Correction by Dose Group: Placebo Controlled, Fixed Dose Studies (M93-113, M93-098, M92-762)

Parameter	Comparison	Mean Difference	90% Confidence Interval	
			Lower	Upper
QT _{C_B} (msec)	Sertindole 8 mg vs. placebo	19.923	14.628	25.219
	Sertindole 12 mg vs. placebo	20.517	16.641	24.393
	Sertindole 20 mg vs. placebo	30.236	26.129	34.343
	Sertindole 24 mg vs. placebo	31.077	26.801	35.353
QT _{C_F} (msec)	Sertindole 8 mg vs. placebo	19.199	14.763	23.635
	Sertindole 12 mg vs. placebo	18.256	14.998	21.514
	Sertindole 20 mg vs. placebo	26.859	23.487	30.231
	Sertindole 24 mg vs. placebo	28.716	24.838	32.594

Source: Sponsors table 12 from Response to FDA request dated December 5 2008)

Table 3 Number and Percentage of Patients Meeting Outlier Criteria for ECG Values by Randomized Dose: Fixed Dose, Placebo-Controlled Studies (M93-113, M93-098, and M92-762)

Parameter	Sertindole Daily Dose												Placebo		
	8 mg			12 mg			20 mg			24 mg			Placebo		
	n	N	%	n	N	%	n	N	%	n	N	%	n	N	%
Heart Rate (bpm)															
Low: ≤50 bpm and decreased ≥30 from baseline	46	0	–	118	1	0.8	210	0	–	159	0	–	205	1	0.5
High: from ≥120 bpm and increased ≥30 from baseline	46	0	–	118	1	0.8	210	2	1	159	0	–	205	1	0.5
PR Interval															
High: ≥210 msec	46	0	–	119	1	0.8	212	1	0.5	163	2	1.2	212	3	1.4
QT Interval															
High: ≥500 msec	46	0	–	119	1	0.8	212	1	0.5	163	0	–	212	0	–
QT _{C_B} Interval															
High: ≥500 msec	46	0	–	119	1	0.8	212	10	4.7	163	10	6.1	212	1	0.5
≥30 msec prolonged from baseline	46	18	39.1	118	55	46.6	210	121	57.6	159	100	62.9	205	23	11.2
≥30 msec to <60 msec prolonged from baseline	46	17	37.0	118	55	46.6	210	113	53.8	159	91	57.2	205	22	10.7
≥60 msec prolonged from baseline	46	1	2.2	118	7	5.9	210	38	18.1	159	37	23.3	205	3	1.5
QT _{C_F} Interval															
High: ≥500 msec	46	0	–	119	1	0.8	212	4	1.9	163	4	2.5	212	0	–
≥30 msec prolonged from baseline	46	13	28.3	118	38	32.2	210	100	47.6	159	83	52.2	205	11	5.4
≥30 msec to <60msec prolonged from baseline	46	12	26.1	118	38	32.2	210	97	46.2	159	80	50.3	205	11	5.4
≥60 msec prolonged from baseline	46	2	4.3	118	1	0.8	210	22	10.5	159	27	17.0	205	0	–
QRS Duration															
High: ≥150 msec	46	0	–	119	0	–	212	0	–	163	1	0.6	212	1	0.5

n = Number tested; N = Number meeting outlier criteria; % = N/n x 100.

(Source: Sponsors table 13 from Response to FDA request dated December 5 2008)

Reviewer's Comments: As indicated above and in the earlier DPP review by Dr. Earl Hearst, dose dependent QT prolongation was noted in the clinical program. Although there were no cases of TdP in the clinical trials there was an increase in the number of sudden unexplained /or unobserved deaths.

ECG Reads for Phase 2 and 3 Clinical trials

Source: 2007 Electrocardiogram Reread Report (27 June 2008)

The ECGs from the sertindole clinical trials were initially read and reported by the investigators while the studies were being conducted. For the original NDA submission, the ECGs were "overread" in 1995 at Indiana University under the direction of Dr. Douglas P. Zipes. Sertindole was later acquired by Lundbeck and the new Sponsor had the ECGs re-read by eRT in 2002. All healthy subjects and patients who had received sertindole in Phase I, II and III studies and who had a QT, QT_{CB} or QT_{CF} ≥500 ms were included. While the mean changes in QTc from baseline were similar between the original and e-Research readings, no QTcF measured over 500 ms per the eRT re-read. Dr. Mehul Desai from DCRP also looked at a subset of 150 ECGs in a blinded fashion. The sponsor then proceeded to obtain another ECG re-read by Covance in 2007. The methodologies in the 3 reads were as follows:

The 2002 Re-read was performed on paper ECGs using digitizing board and magnifying lamp to aid the placement of calipers. The ECGs were read by multiple readers. It was noted during the 2002 Re-read that some ECGs had abnormal U-waves. However, there was no specific methodology enforced to evaluate this further.

Table 4 Methodologies: Overread, 2002 Re-read, and 2007 Re-read

Organization	Overread	Reread	
		2002	2007
Third Party Reader	University of Indiana	eResearch Technologies (eRT)	Covance Cardiac Services
Methodology			
Access to treatment code	Yes	No	No
Number of readers	>1	>1	1
All leads measured	Yes	No	No
Lead reported	Longest QT	II or V5 or Another Lead	II, V2, or V5
Interval determination:			
3 consecutive beats	Not Specified	Yes	Yes
QT measurement	Standard	Standard	Standard and U-Wave

Source Table1, Electrocardiogram Reread Report (27 June 2008)

The 2007 Re-read was designed to reduce the inherent variability since the ECGs were old and had not been acquired digitally. During this 2007 Re-read, ECGs were digitized and analysis was performed using ECG analysis software allowing placement of calipers with a resolution of 1 ms. In addition, the ECGs were to be read twice (without the U-wave [standard read] and with the U-wave [U-wave read]).

The following steps were taken with the 2007 Re-read to reduce the variability in the reads and to avoid the introduction of bias:

- One cardiologist would read the ECGs.
- The same lead was used for the standard read and the U-wave read.

- Lead II would be evaluated for 3 consecutive beats, and if not readable, V2 followed by V5 would be permitted in order to be able to compare the results of the standard read and the U-wave read for the same ECG (paired analysis).
- If both reads were not available, the cardiologist would review the ECGs and confirm that the read could not be done due to the poor quality of the ECG tracing.
- Duplicate copies of ECGs would be provided to be read as an internal quality control check. (Covance Cardiac Services did not know which tracings were copies of other tracings.)
- It would be confirmed that the U-wave QT was longer than the standard read QT for an individual ECG record. (In view of the age and quality of the ECGs, it was agreed with Covance Cardiac Services that “empirically” a standard read could not be more than 20 to 25 ms longer than a U-wave read.)

ECGs Excluded From the 2007 Analyses:

With the criterion of using the same lead for the standard read and the U-wave read, and using the criterion of the standard read being not more than a 25 ms longer than the U-wave read, only one ECG had a standard read QTc that was longer than the U-wave QT. For Patient 63604 in Study M92-795, the standard read QT was 148 ms longer than the U-wave read even though the same lead was used to measure the QT. For this reason, this ECG was excluded from the analyses.

Around 20 ECGs were excluded from the 2007 analyses because only one lead was technically available. Of note, 5 ECGs with U-wave reads above 500 ms were excluded from paired analysis because readings in accordance with standard methodology could not be performed.

Results:

Table 5 2007 Reread Compared to 1997 Overread: ECG QTc (Bazett's Correction and Fridericia's Correction), Standard Read and U-Wave Read (All ECGs Excluding Duplicates from the 1997 Overread and the 2007 Reread)

Parameter	N	Prolonged	
		>500 msec	≤500 msec
1997 Overread, Longest Lead		2007 Reread, Standard (Lead II, V2, or V5)	
Fridericia's Correction			
Prolonged >500 msec	97	34	63
Prolonged ≤500 msec	1489	14	1475
Missing	5	0	5
Bazett's Correction			
Prolonged >500 msec	227	83	144
Prolonged ≤500 msec	1359	13	1346
Missing	5	1	4
1997 Overread, Longest Lead		2007 Reread, U-Wave (Lead II, V2, or V5)	
Fridericia's Correction			
Prolonged >500 msec	97	48	49
Prolonged ≤500 msec	1489	26	1463
Missing	5	0	5
Bazett's Correction			
Prolonged >500 msec	227	115	112
Prolonged ≤500 msec	1359	22	1337
Missing	5	1	4

Source: Appendix B

Source: Table 6, Electrocardiogram Reread Report (27 June 2008)

Reviewers Comments: More subjects had an absolute QTcF over 500 ms with the U wave read compared to the standard read on review of the results for all ECGs (Table 5) and the paired data from the placebo controlled studies (Table 6).

Table 6 Number of Patients With an On-Drug ECG QTc (Bazett’s Correction and Fridericia’s Correction) >500 ms (Paired Data): 2007 ECG Standard Read and U-Wave Read, Placebo-Controlled Studies M93-098 and M93-113

Type of Read	Number of Patients: QTc >500 msec							
	Bazett’s Correction				Fridericia’s Correction			
	Placebo		Sertindole 20 mg		Placebo		Sertindole 20 mg	
	N ^a	n ^b (%)	N ^a	n ^b (%)	N ^a	n ^b (%)	N ^a	n ^b (%)
Standard Read	137	3 (2.2)	140	6 (4.3)	137	0	140	2 (1.4)
U-Wave Read	137	3 (2.2)	140	13 (9.3)	137	2 (1.5)	140	5 (3.6)

^a N = Number of patients with an ECG in the ECG analysable set post baseline.

^b n = Number of patients with an ECG in the ECG analysable set with a QTc >500 msec.

Source: *Appendix B*

Source: Table 10, Electrocardiogram Reread Report (27 June 2008)

Sponsor’s Conclusions:

Sertindole causes an increase in the QT in a dose-dependent manner. In placebo-controlled studies, the mean QTc (Fridericia’s correction) change from baseline was approximately 23 ms for patients who received chronic treatment with sertindole. An increase in QTc from normal at baseline to >500 ms was noted in 1.3% of patients.

Sertindole Cohort Prospective Study (SCoP)

- Multinational, multi-centre, randomized, partially-blinded, parallel-group, active-comparator study (n=9858).
- The patients were randomized (1: 1) to treatment with sertindole or risperidone. The start and maintenance dosages as well as dose titration were set by the investigator, in accordance with the national Summary of Product Characteristics (SPC) or the European Union SPC.
- Study assessments were performed monthly during the first 3 months of treatment and on a quarterly basis thereafter. The patients were assessed and managed by the investigators according to routine clinical practice.
- A safety follow-up visit was scheduled for 30 days after stopping investigational medicinal product (IMP), except if the patient withdrew consent.
- The patients were followed up for the entire duration of the study, that is, also after they started add-on therapy or discontinued IMP and until they withdrew from the study or the study was terminated.
- To allow an ongoing assessment of patient safety and review of the endpoints, two independent committees, the Independent Safety Committee (ISC) and the Independent Management Committee (IMC), were established in agreement with the Committee for Medicinal Products for Human Use (CHMP).

Diagnosis and Main Inclusion Criteria:

- Patients with schizophrenia who were at least 18 years of age
- who met the criteria set out in the national SPCs (or the EU SPC for sertindole if sertindole was not marketed in that country) for both sertindole and risperidone

- for whom new or a change in antipsychotic treatment was indicated

The sertindole SPC is more restrictive than the risperidone SPC by excluding patients with cardiovascular contraindications, by requiring an ECG at baseline, by selecting patients intolerant to at least one other antipsychotic, and by excluding acute patients in need of rapid symptom relief. Regular post-baseline ECGs (week 4, week 12 and every 12 weeks there-after) were required for the sertindole-treated patients but not for those treated with risperidone.

Statistical Methods:

- The following basic study periods were defined:
 - Only Randomized Treatment (ORT) Period - the period from the date of prescription of randomized treatment until randomized treatment was stopped (provided the patient did not continue treatment within the following 15 days) or the date of start of add-on antipsychotic(s), whichever occurred first
 - Whole Randomized Treatment (WRT) Period - the period from the date of prescription of randomized treatment until randomized treatment was stopped (provided the patient did not continue treatment within the following 15 days), including the time the patient was treated in combination with another antipsychotic (if indicated) (add-on therapy)
 - Whole Follow-up (WFP) Period - the period from the date of prescription of randomized treatment until the date of withdrawal from/ completion of the study
- The WRT+30 days period constitutes the key period for the analysis and reporting of events. The definition of the WRT and ORT periods did not include an event if the patient took the last dose of IMP the day before the event occurred or if the patient had not yet taken the IMP on the day of the event (unless the treatment was continued or restarted within 15 days); therefore, the WRT+1 day period was also considered. This period was pre-defined in the Statistical Analysis Plan (SAP) as a sensitivity analysis.

End Points:

- First primary endpoint was all-cause mortality. The upper limit of the one-sided 95% CI for the estimated all-cause mortality ratio had to be <1.5 for the null hypothesis of excess mortality in sertindole treated patients to be rejected.
- Second primary endpoint was cardiac events, including arrhythmias, requiring hospitalization.
- Secondary endpoints included cause-specific fatal events (classified as cardiac, suicide, or other), suicide attempts (fatal and non-fatal), hospitalizations, and treatment duration.

SAE Classification:

The ISC used the case definitions listed below to classify events. For clarification and to conform with actual practice, the definitions described in the ISC working procedures were reviewed and revised by the ISC (Appendix 1.4):

- Death:
 - Suicide was attributed based on the death certificate, and other information from investigators.
 - Cardiac death:

- a death where pre- or post-mortem documentation of a cardiac condition could be reasonably linked to the death
- sudden cardiac death - a death that was sudden (within 24 hours of onset of symptoms) and unexpected (no other obvious non-cardiac cause)
- a death related to a complication of a serious cardiac event (for example, sepsis during prolonged coma after heart arrest)
- Other - a death that was not a suicide or a cardiac death
- Other event:
 - A non-fatal event that did not lead to hospitalization (except for suicidal behavior) was not considered an endpoint event.
 - An episode of serious self-harm or intentional overdose or poisoning was considered as a suicidal behavior event even if the patient expressed no overt suicidal intention

During the study, cardiac events were classified as definite or putative. If there was doubt as to the exact cause of death, especially if information was lacking, the case was conservatively classified as putative cardiac by default. Vascular deaths (for example, non-cardiac thrombosis, embolus) were not considered cardiac deaths.

At completion of the study, all events that had been classified as cardiac (definitive or putative) were reviewed to confirm the classification based on available information. Furthermore, the fatal and non-fatal SAEs classified as cardiac or putative cardiac were subclassified:

- fatal SAEs:
 - documented cardiac arrhythmia causing death - a death with documented evidence for arrhythmia causing death, directly or indirectly
 - documented sudden unexpected death - a death that occurred within 24 hours of onset of symptoms and with no other obvious non-cardiac cause
 - other possibly cardiac death - a death related to a complication of a serious nonarrhythmic cardiac event
- non-fatal SAEs:
 - cardiac arrhythmia leading to hospitalization - an event with documented evidence of arrhythmia leading to hospitalization
 - other cardiac event.

Results:

First primary endpoint:

The all-cause mortality ratio (adjusted for age, sex, time since last suicide attempt, previous polytherapeutic treatment, and study accrual time) during WRT+30 (including closure period) for sertindole vs. risperidone was 1.081 (90% CI 0.801-1.458).

As of the CHMP cut-off date, 121 patients had died in the WRT+30 days period. The number of patients who died was similar in the two treatment groups: 61 in the sertindole group and 60 in the risperidone group. During the study closure period, an additional 4 patients died, resulting in a total of 125 patients who died in the WRT+30 days period: 64 in the sertindole group and 61 in the risperidone group.

Second primary endpoint:

Cardiac Events, Including Arrhythmias, Requiring Hospitalization-An analysis was not performed due to the limited number of events.

There were 5 SAEs with hospitalization in the sertindole group (3 with arrhythmia) and 4 SAEs with hospitalization in the risperidone group coded the MedDRA SOC Cardiac Disorders. The ISC classified 4 cases of arrhythmia, the same three in the sertindole group but one additional one in the risperidone group.

Patient 485433, a 79-year-old woman, died from cardiac arrhythmia [Torsades de Pointes] (DKLUI013530) and arteriosclerotic degeneration of the myocardium (according to death certificate) on (b) (4), after 252 days of treatment with sertindole. No autopsy was performed. Medical history comprised hypertension since 2002. On (b) (4), 4 days prior to her death, she had syncope during routine ECG recording. The ECG showed Torsades de Pointes, but the patient recovered spontaneously. The patient was admitted, but later on the same day had cardiac arrest, was resuscitated, and treated with xylocaine and amiodarone. A Holter monitoring performed during admission showed increased QTc interval without ventricular arrhythmia, only ventricular extrasystoles. Following this, the patient was taken off cardiac monitoring. Four days after discontinuation of sertindole, she was found dead in her bed at night. The event was considered not related to IMP by the investigator.

Patient 793851, a 43-year-old woman with hypertension, had symptomatic ventricular tachycardia (DKLUI016275) on (b) (4) (after more than 18 months of sertindole treatment). The patient reported giddiness, palpitations, and shortness of breath. Heart rate ranged from 110 to 130 bpm. She was treated at the cardiac care unit and recovered on (b) (4)-(A). One week prior to the event, she was treated with an unknown antibiotic and Chinese cough medicine. She did not receive other concomitant medication. ECG showed borderline QTc prolongation before study entry. An external cardiologist concluded that the ECG showed ventricular tachycardia compatible with possible Torsades de Pointes. However, the ECG from the event does not meet the exact criteria for this diagnosis. The event was considered probably related to IMP by the investigator.

Patient 117812, a 64-year-old man, was hospitalized due to fever (39°C) and tachycardia (150bpm) after 6 days of treatment with IMP. The ECG revealed atrial flutter (DKLUI009010).

In addition, Patient 155747, a 37-year-old man, had a transient asymptomatic repolarization abnormality showing T-wave platoid (QTc not evaluable) (conduction disorder; DKLUI011179) during hospitalization due to schizophrenia. The patient had received sertindole for 35 days.

The other cases of hospitalization with cardiac disorder were, in the sertindole group, 1 case of cardiac failure acute and, in the risperidone group, 2 cases of angina unstable and a myocardial infarction (same patient), and 1 case of cardio-respiratory arrest, none of which were considered to be related to potential proarrhythmic effects.

Two patients with hospitalization had cardiac SAEs coded to the SOC Investigations, neither of which showed arrhythmia. Both patients were in the sertindole group and both had electrocardiogram QT prolonged

In addition, Patient 764415, a 26-year-old man, had electrocardiogram QT corrected interval prolonged (DKLUI016159, sertindole group) during hospitalization due to intentional overdose (with sertindole, diazepam, and trihexyphenidyl); the event was considered probably related to IMP by the investigator.

Fatal Serious Adverse Events Classified as Cardiac (Secondary Endpoint):

Table 7 Sub-classification of Fatal SAEs Classified as Cardiac (ISC Classification)(APTS)

	RIS	SER	All
Serious Adverse Events, n	15	40	55
WRT+30d period, n			
D_Cardiac Documented Arrhythmia	1	1	2
D_Cardiac Documented sudden death	3	9	12
D_Cardiac Documented sudden death with cardiac origin probable	0	4	4
D_Cardiac Not sufficiently documented case for any assessment	4	12	16
D_Cardiac With identified cause of death (Non cardiac)	4	5	9
WRT period, n			
D_Cardiac Documented Arrhythmia	0	1	1
D_Cardiac Documented sudden death	0	1	1
D_Cardiac Documented sudden death with cardiac origin probable	0	0	0
D_Cardiac Not sufficiently documented case for any assessment	2	6	8
D_Cardiac With identified cause of death (Non cardiac)	1	1	2
ORT period, n			
D_Cardiac Documented Arrhythmia	0	1	1
D_Cardiac Documented sudden death	0	1	1
D_Cardiac Documented sudden death with cardiac origin probable	0	0	0
D_Cardiac Not sufficiently documented case for any assessment	2	5	7
D_Cardiac With identified cause of death (Non cardiac)	1	1	2
WFP period, n			
D_Cardiac Documented Arrhythmia	1	1	2
D_Cardiac Documented sudden death	4	9	13
D_Cardiac Documented sudden death with cardiac origin probable	0	5	5
D_Cardiac Not sufficiently documented case for any assessment	5	18	23
D_Cardiac With identified cause of death (Non cardiac)	5	7	12

99824 (FINAL) EV_6 13JUN2008:15:00:02 1790/

Source: Panel 34, CSR for Study 99824

In April 2008, the Independent Safety Committee (ISC) sub-classified all *sudden unexplained deaths*, all of which, by default, were classified as *cardiac*, into three mutually exclusive categories [refer to the ISC meeting minutes dated 23 April 2008]:

- *documented sudden death (including cases with cardiac origin probable)*
- *with identified cause of death (non-cardiac)*
- *not sufficiently documented case for any assessment*

The first sub-classification is identical to "cardiac documented sudden death" + "cardiac documented sudden death with cardiac origin probable". According to this sub-classification, 13 patients in the sertindole group and 3 patients in the risperidone group had a fatal SAE that was sub-classified as documented sudden death (including cases with cardiac origin probable) in the WRT+30 days period; 4 of these 13 cases were assessed with cardiac origin probable.

The sponsor compared the hazard rate of documented sudden death (including cases with cardiac origin probable) between the sertindole and risperidone groups, as requested by the division, using a Cox model including variables for treatment group, age, and sex.

The estimated hazard ratio (sertindole versus risperidone), adjusting for age and sex, was 5.0 (95% CI: 1.4 to 17.5), showing a statistically significant (p=0.0121) higher risk of documented sudden death (including cases with cardiac origin probable) in the sertindole group than in the risperidone group.

A Cox Proportional Hazard analysis has been performed to determine the hazard ratio of sertindole *versus* risperidone for each of the MedDRA coded events *Syncope*, *Palpitations*, and *Dizziness*. The analysis has been limited to the WRT+30 days period, removing all patients in the sertindole group who had risperidone added to their randomized treatment and all patients in the risperidone group who had sertindole added to their randomized treatment **and** removing all patients who had thioridazine, mesoridazine, ziprasidone, or pimozide added to their randomized treatment.

Table 8 Estimated Hazard Ratios for Selected Adverse Events for Sertindole *Versus* Risperidone

Adverse Event	Number of Events		Hazard Ratio	p-value	95% CI
	Risperidone	Sertindole			
Syncope	3	7	2.598	0.1669	0.671 – 10.056
Palpitations	13	21	1.772	0.1052	0.887 – 3.540
Dizziness	4	14	3.847	0.0175	1.265 – 11.692

CI Confidence interval

Source: Table 1 from Item 33, question 2, Sponsors response to FDA dated Dec 5, 2008.

Reviewer’s Comments: There is a statistically significant increased risk of sudden cardiac death with sertindole. TdP has been observed on treatment. A trend is also observed with syncope although confounded by the $\alpha 1$ antagonistic effect of sertindole.

Reviewer’s ECG Assessments for the Phase 2 and 3 studies:

Waveforms submitted to the ECG warehouse were reviewed (both standards and U wave reads). Over 95% of ECGs were read in the primary lead II. Over 36% of ECGs had significant QT bias (i.e. QT interval for the ECGs were shorter than the ECG warehouse automated algorithm computed interval measurement but the values were similar for both reads).

Several values were missing in the ECG metric file limiting our computation of QT bias by treatment. However mean QT bias for sertindole was less than QT bias for placebo. As expected QT bias was less for the U wave read compared to the standard read. While the T wave offset was debatable even in some of the U wave reads (see Figure 1 and

Figure 4), overall this read appears to be acceptable.

As mentioned in earlier consults, complexity arises in how to measure the QT interval in the setting of changes in T wave morphology (flattening/notching) and T-U merging that is observed

Figure 2 ECG from patient post-treatment with 24 mg sertindole (haldol stable stratum), U wave read

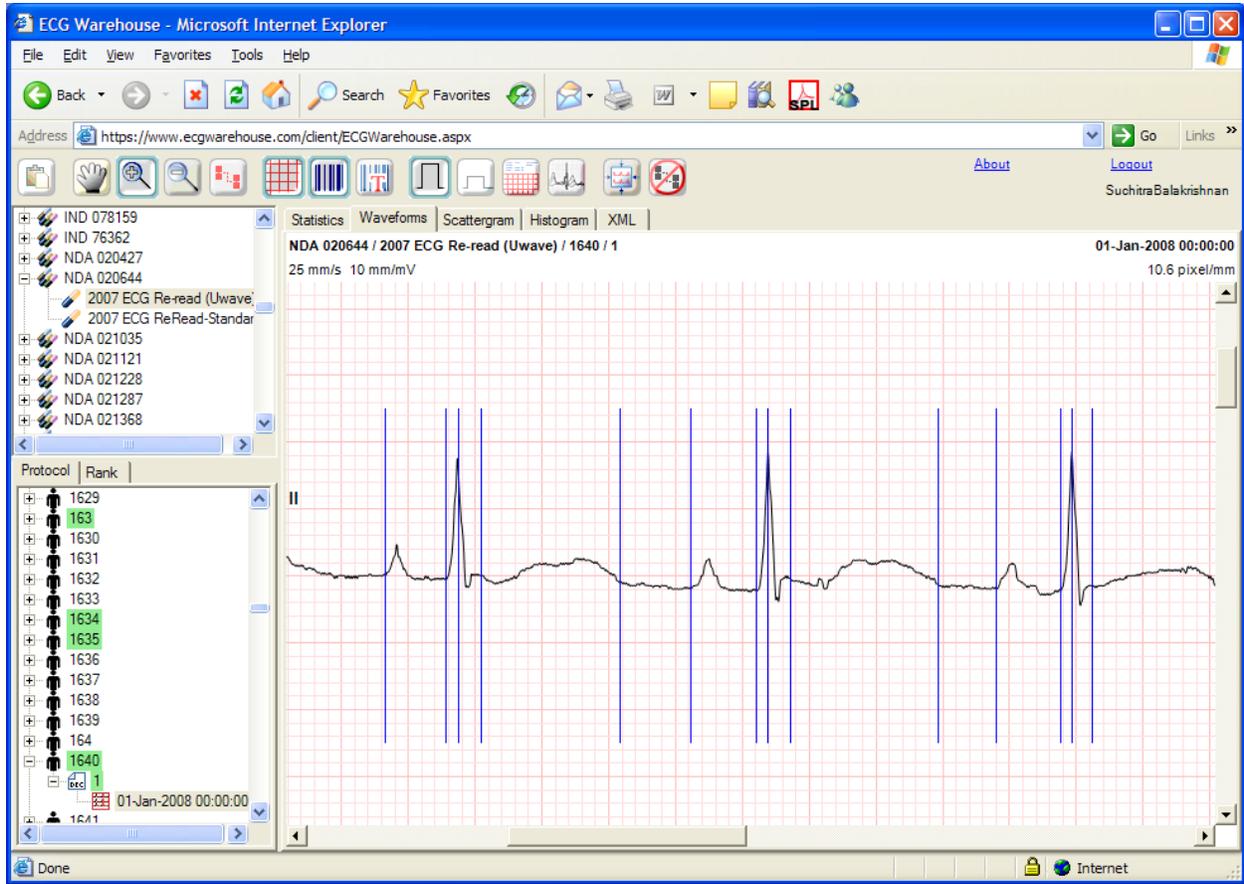


Figure 3 ECG from patient post-treatment with placebo, U wave read

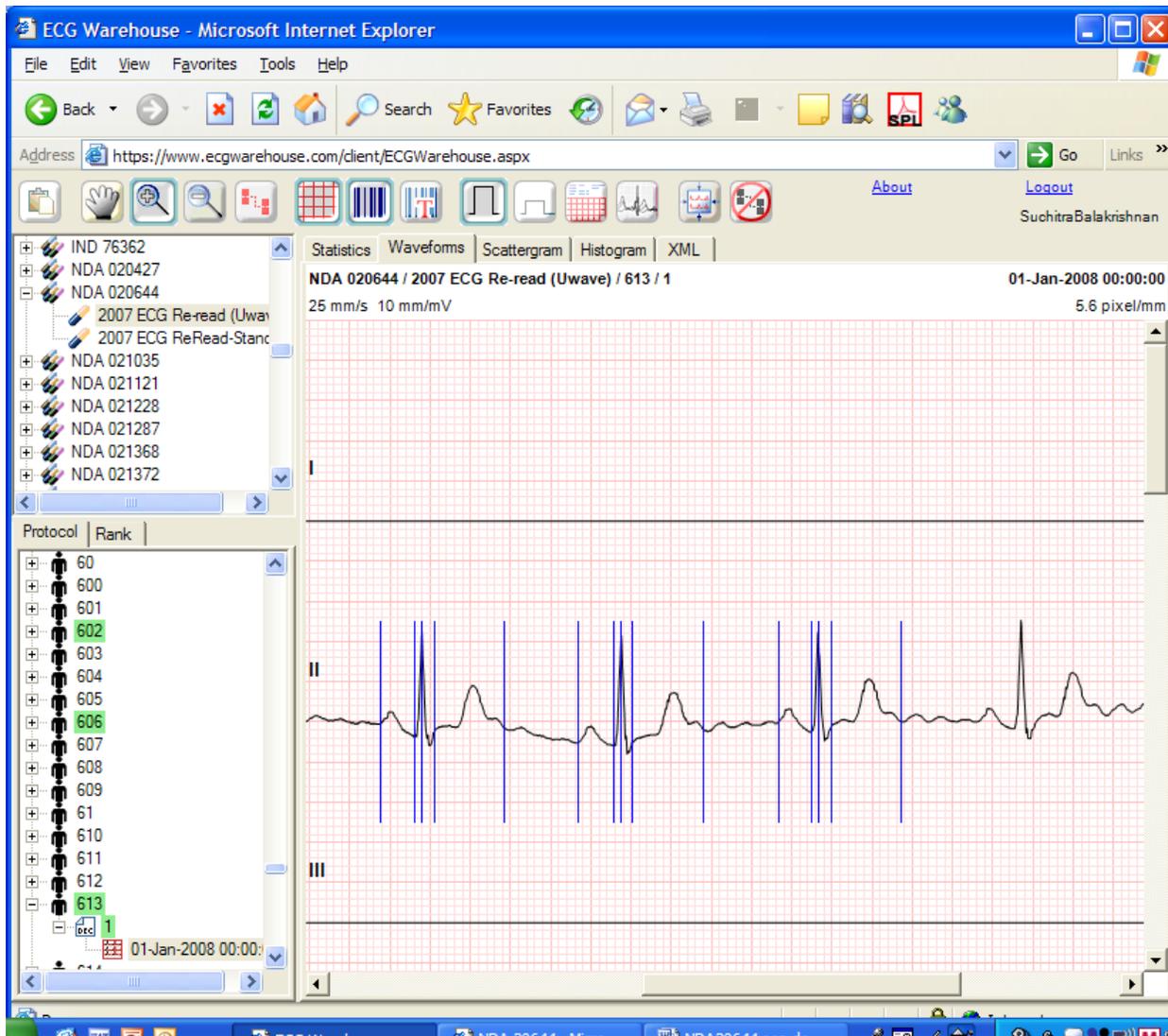


Figure 4 ECG from patient post-treatment with 24 mg sertindole (haldol stable stratum), U wave read

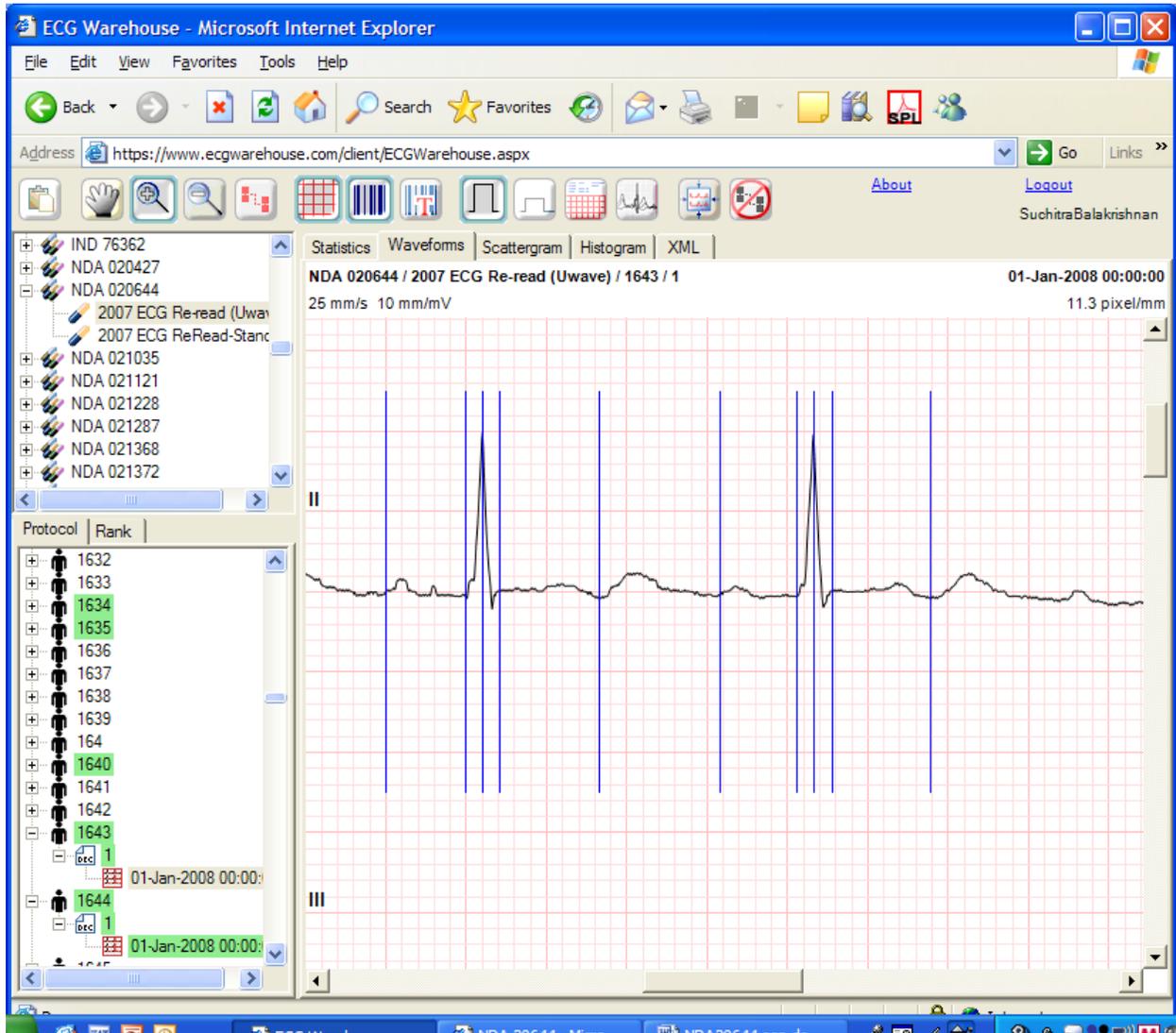


Figure 5 ECG from patient post-treatment with 24 mg sertindole, standard read

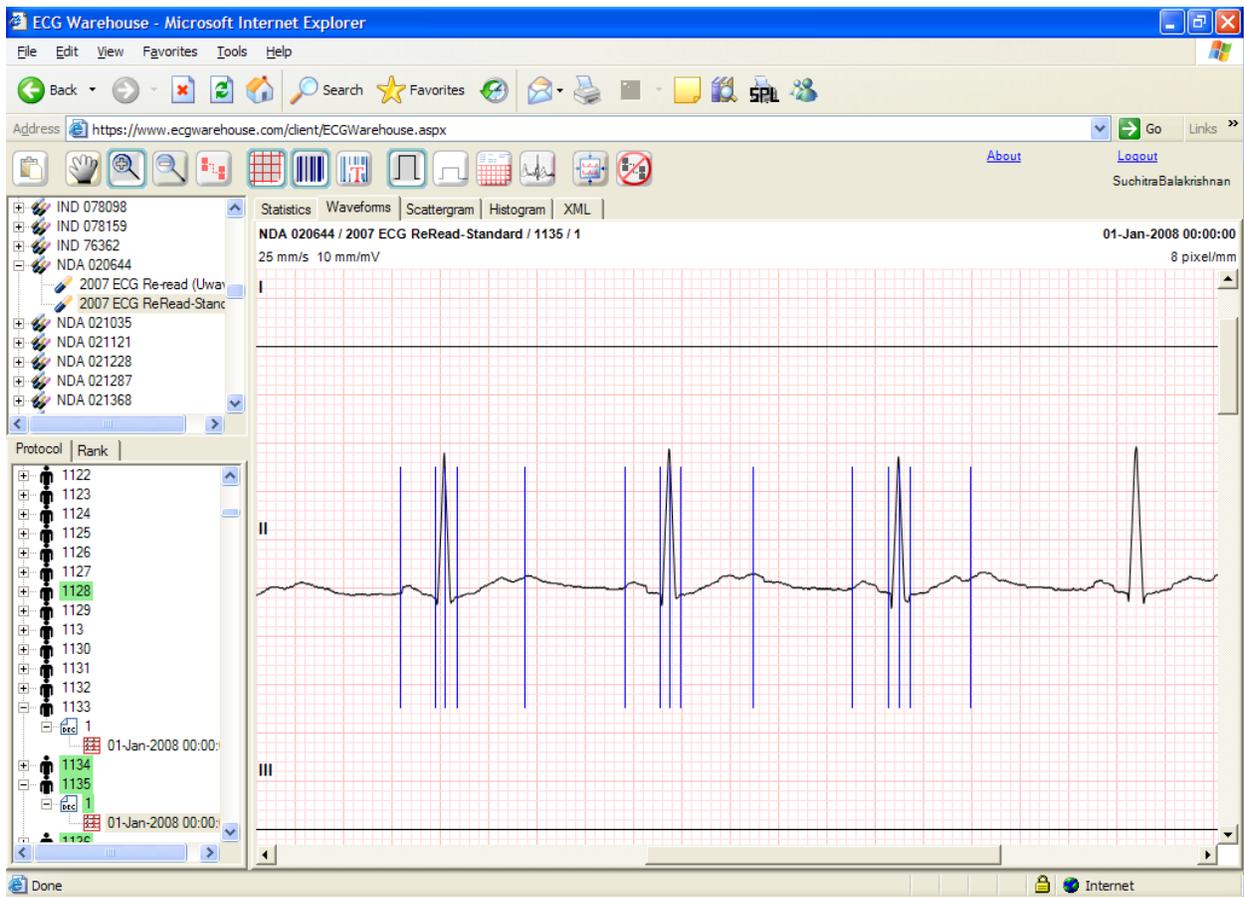


Figure 6 ECG from patient post-treatment with 24 mg sertindole, standard read



**This is a representation of an electronic record that was signed electronically and
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/s/

Suchitra Balakrishnan
2/12/2009 10:20:32 AM
MEDICAL OFFICER

Norman Stockbridge
2/12/2009 10:28:08 AM
MEDICAL OFFICER

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: August 22, 1996

FROM: Thomas P. Laughren, M.D. *TPL*
Group Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approvable Action for
Serlect (sertindole) for the treatment of psychotic
disorders

TO: File NDA 20-644
[Note: This overview should be filed with the 9-29-95
original submission.]

1.0 BACKGROUND

Sertindole is being proposed for use in the management of the manifestations of psychotic disorders in a dose range of 4-24 mg/day.

IND 38,373 for sertindole was originally submitted 11-27-91. Several key meetings were held during the development of sertindole:

10-21-93: End-of-phase 2 meeting

-We discussed the progress of development thus far and the plans for phase 3. In particular, the sponsor noted an interest in comparisons with haloperidol, and we advised them of the need for a fair comparison, i.e., a design in which haloperidol would be given in an optimal manner. We suggested the desirability of a dose comparison trial, i.e., one that compared the dose response curves for the two drugs. We also encouraged the sponsor to conduct an adequate relapse prevention trial, i.e., one that randomized responders on open sertindole to continuation on sertindole or switch to placebo. Finally, we questioned whether or not they had adequately explored the dose response curve for sertindole.

-The sponsor responded in part to our advice regarding an adequate comparative trial with a protocol for study 113, comparing 3 different doses for each of haloperidol and sertindole with placebo. Despite this improvement in the design, we cautioned them regarding the lack of consensus about how to fairly compare two drugs, in particular the population studied (e.g., it would not be acceptable to compare sertindole with haloperidol in patients who already failed on haloperidol) and the adequate use of anticholinergic drugs to control EPS with haloperidol.

7-27-95: Pre-NDA meeting.

-This was a general discussion of the progress of the development program and the plans for NDA submission, including possible claims. We again cautioned the sponsor about the difficulties in making claims for comparative advantages of their drug over haloperidol. Regarding the issue of long-term effectiveness data, it was clear the sponsor had not accepted our advice to conduct an adequate and well controlled study to address this issue. Most of this meeting was focused on technical details regarding the format and content of the NDA, and in fact, this was followed by a number of more informal contacts over the next few months to work out the details of formatting the NDA submission.

The original NDA 20-592 for sertindole was submitted 9-29-95.

Sertindole was the subject of a 7-15-96 meeting of the PDAC, and the Committee voted unanimously in favor of its efficacy (6 vs 0). The response was more mixed for safety (4 in favor, 2 opposed).

2.0 CHEMISTRY

Sertindole is a phenylindole derivative. The proposed capsule strengths are 4, 8, 20, and 24 mg.

The drug substance is produced in Denmark and the drug product in Puerto Rico. Both sites have been inspected and are acceptable.

The environmental assessment review is completed, and the deficiencies will be conveyed in the approvable letter.

The proposed name Serlect has been judged acceptable by the Nomenclature Committee.

There are no outstanding chemistry issues at this time.

3.0 PHARMACOLOGY

Sertindole displays high receptor binding affinity in vitro (Ki's in the low nanomolar range) at the following receptor sites: 5HT_{2A/C}, D₂, and α_1 -adrenergic. Sertindole has moderate affinity (Ki's in the midnanomolar range) for D₁ receptors and sigma type 2, and low affinity (Ki's in the low micromolar range) for α_2 -adrenergic, H₁, and sigma type 1 receptors. Sertindole has almost no affinity for 5HT_{1A}, 5HT₃, muscarinic cholinergic, β -adrenergic, and PCP receptors.

Sertindole appears to selectively inhibit mesolimbic dopaminergic neurons, e.g., it was shown to inhibit spontaneously active dopamine neurons in the mesolimbic ventral tegmental area (VTA) without affecting dopamine neurons in the substantia nigra compacta (SNC).

Toxicity findings of interest included lens opacity in rats and mice, possible melanin binding in rats, bone fragility in mice, testicular and prostate changes in several species, and QT prolongation in dogs.

Findings revealed in mouse (0.3, 1, 3, and 10 mg/kg/day X 24 months) and rat (0.1, 0.5, 1, and 3 mg/kg/day X 24 months) carcinogenicity studies included: (1) increases in pituitary gland adenomas in female mice at 1, 3, and 10 mg/kg; (2) increases in mammary gland adenomas and carcinomas in females but not males of both species at dosages of 1, 3, and 10 mg/kg in the mouse and at 0.5, 1, and 3 mg/kg in the rat; (3) increases in pancreatic islet cell tumors at 1 and 3 mg/kg in female rats. These findings are likely related to chronically elevated prolactin levels associated with sertindole, are seen with many other antipsychotic drugs, and are of unknown clinical significance. There was also a positive trend for increased hematopoietic lymphomas in male and female mice.

A variety of mutagenicity tests were mostly negative, but polyploidy was observed in 2 in vitro assays (human lymphoma and rat bone marrow).

Fertility effects of sertindole were limited to a decrease in mating performance in male rats, probably due to an inhibition of semen emission, and changes in the estrus cycle in female rats and mice.

Segment II studies in rats and rabbits given 6 to 10 times the human dose revealed no effect in rats, however, there were slight increases in skeletal and cardiovascular variations in rabbits at 6 times the human dose, a dose associated with maternal toxicity. A segment III study in rats revealed an increase in pup deaths, a delay in the descent of the testes, and a delay in vaginal opening at doses 1.3 to 4 times the human dose.

Serlect has been to the CAC and the conclusion was that the findings are those predicted for drugs in this class and can be handled in labeling.

In addition, the approvable letter will ask for a commitment by the sponsor to conduct an animal toxicology study to follow up on the finding of bone fragility observed in the mouse carcinogenicity study.

4.0 BIOPHARMACEUTICS

Sertindole is slowly absorbed after oral administration and concentration peaks at about 10 hours. Food does not significantly affect the rate or extent of sertindole absorption. Sertindole is extensively distributed and highly protein bound, i.e., approximately 99% over a concentration range of 1 to 1000 ng/mL. Sertindole has time dependent kinetics, with clearance decreasing upon multiple dosing. However, at steady state, clearance is dose independent and concentrations are proportional to dose in a range of 4-24 mg/day. Sertindole has an elimination half-life of approximately 3 days, and reaches steady state in about 3-4 weeks.

Cytochromes P450 3A4 and 2D6 contribute to the formation of the major metabolites, dehydrosertindole and norsertindole, both of which appear to be pharmacologically inactive in vivo. 2D6 appears to be the principle pathway, however, in 2D6 poor metabolizers, or those converted to poor metabolizer status by concomitant drug use (e.g., fluoxetine), the 3A pathway may take on a greater role.

Single dose studies revealed little effect of renal impairment or age on sertindole pharmacokinetics. A study in patients with liver disease revealed about a 70% decrease in clearance in patients with compromised liver function. Sertindole's clearance is on average 20% lower in females compared to males. Blacks have 20% lower mean sertindole clearances than Caucasians. Slower titration and lower maintenance doses may be appropriate in the elderly and in patients with compromised hepatic function.

Population pharmacokinetic studies revealed that the clearance of sertindole is reduced by about 50% in patients co-administered fluoxetine or paroxetine, but no effect on clearance was seen with concomitant use of 3 other 2D6 substrates (sertraline, TCAs, or propranolol). Smaller reductions in clearance (<25%) were observed with concomitant use of erythromycin, a 3A inhibitor. There is an approximate doubling in the clearance of sertindole with co-administration of carbamazepine or phenytoin, both P450 inducers, and a lesser effect of tobacco use (15% increase).

An in vivo study of sertindole (multiple dose) and terfenadine (single dose) revealed a 28% increase in terfenadine's AUC as well as a slight increase in QTc.

Comment: Given the importance of the 2D6 pathway, I think all potent 2D6 inhibitors should be contraindicated, and caution should be observed with any drugs known to inhibit 2D6. Given the importance of the 3A pathway in the presence of limited or absent 2D6 activity, I think that potent 3A inhibitors should also be contraindicated. Thus, I have proposed an expanded list (compared to the sponsor's list) of drugs to contraindicate.

The approvable letter will provide dissolution specs and will also request additional in vitro work to further evaluate the inhibitory effects of sertindole on various p450 isozymes, since little is known at present.

5.0 CLINICAL DATA

5.1 Efficacy Data

5.1.1 Summary of Studies Pertinent to Efficacy Claims

Our review of the effectiveness of sertindole in the treatment of psychosis focused on 4 short-term, placebo-controlled trials (M93-113, M93-098, M92-762, and M91-645) in schizophrenic patients. A fifth placebo-controlled trial (M92-817) looking at 4 and 12 mg/day doses was discontinued following an interim analysis because of disappointing results and a belief that the selected doses were too low. Other studies not included in our efficacy review were 4 long-term, open label studies (M93-061, M94-222, M92-795, and M91-671), a long-term active control study comparing sertindole and haloperidol (M93-132), and a study designed to look exclusively at the feasibility of more rapid titration (M94-239).

5.1.1.1 Study M93-113

This was a randomized, 43-center (US), double-blind, parallel group, 8-week, fixed-dose study comparing sertraline at 3 fixed doses [12, 20, or 24 mg/day, on a qd schedule; initial dose was 4 mg/day with titration to assigned dose at the rate of 4 mg q 4 days], haloperidol at 3 fixed doses [4, 8, or 16 mg/day; initial dose was 4 mg/day, with increases to 8 mg after 3 days and then to 16 mg after another 3 days], and placebo, for the treatment of psychosis in adult inpatients meeting DSMIII-R or DSMIV criteria for schizophrenia. Patients had to have scores on any 2 of the positive BPRS items summing to 8 and could not have had a decrease of more than 20% on the BPRS Total during the placebo lead-in period.

Benzotropine mesylate was permitted for EPS, but only on as needed basis and for limited periods (7 days); it could be continued with repeat evaluation.

The primary efficacy assessments included the PANSS, the BPRS, the SANS, and the CGI, all administered weekly during the 8 week trial. The PANSS is a 30-item scale in which is embedded the 18-items of the BPRS, however, in this program, the BPRS was administered separately. In the following, I will focus on 4 efficacy measures: the PANSS total score, the BPRS positive symptom score (sum of 4 items: conceptual disorganization, unusual thought content, hallucinations, and suspiciousness), the PANSS Negative subscale, and the CGI-Severity score.

-The PANSS total score (using 0-6 scaling for individual items) ranges from 0 to 180.

-The BPRS positive symptom score ranges from 0 to 24.

-The PANSS Negative subscale ranges from 0 to 42.

-The CGI-Severity score ranges from 1 to 7, where 1 is normal and 7 is among the most extremely ill patients.

Our review focused on the intent-to-treat sample, i.e., all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one followup time. The statistical model used was ANOVA, or ANCOVA when appropriate, focusing on change from baseline for the measures noted, and including treatment, investigator, and treatment-by-investigator terms, except for the CGI which was analyzed using the Cochran-Mantel-Haenzel statistic with centers as strata.

Patients were approximately 75% male, approximately 60% Caucasian, and the mean age was late 30's. The treatment groups were comparable at baseline on the demographic variables, however, there were some differences on certain efficacy variables, and ANCOVAs were done in those instances.

Study Results

The intent-to-treat dataset was as follows:

Placebo	(71)
Sertindole 12 mg/day	(72)
Sertindole 20 mg/day	(65)
Sertindole 24 mg/day	(70)
Haloperidol 4 mg/day	(68)
Haloperidol 8 mg/day	(63)
Haloperidol 16 mg/day	(68)

Completion rates to 8 weeks were as follows:

Placebo	36/71 (51%)
Sertindole 12 mg/day	33/72 (46%)
Sertindole 20 mg/day	31/65 (48%)
Sertindole 24 mg/day	33/70 (47%)

Haloperidol 4 mg/day	32/68 (47%)
Haloperidol 8 mg/day	34/63 (54%)
Haloperidol 16 mg/day	33/68 (49%)

[See appendices for tables providing significance levels for pairwise comparisons and treatment effect sizes.]

Despite several requests for information on the extent or benzotropine use in this study, no information was provided by the sponsor. Thus, it was not possible to evaluate whether or not haloperidol was used in an optimal manner, i.e., with adequate concomitant use of an anticholinergic drug.

Impression:

While there was some evidence for superiority of sertindole over placebo at all 3 doses, the evidence was most persuasive at the middle dose, i.e., 20 mg/day. Using Dunnett's criterion, both the 20 and the 24 mg groups were superior to placebo in the LOCF analyses at the 8-week endpoint for PANSS Total and CGI Severity. The evidence was less compelling in the OC analyses, without any of the key variables reaching statistical significance at the 8-week endpoint for the Dunnett's criterion. However, for 20 mg, most variables met criteria for either $p < 0.05$ or a positive trend at the 8-week endpoint. The poorer outcome in the OC analyses may have resulted from the substantial attrition almost always observed in placebo-controlled schizophrenia trials. Dr. Hoberman provided plots of scores for the various dropout cohorts, and for all the dropout cohorts the 20 mg patients were doing better than placebo at the point of dropout, and thus, I am less concerned about this discrepancy. Although statistically this was not a strikingly positive study, the effect size as measured by difference between drug and placebo in change from baseline was impressive, especially for the 20 mg group (18 PANSS units). I agree with Drs. Hearst and Hoberman that this was a positive study for both the 20 and the 24 mg/day doses.

5.1.1.2 Study M93-098

This was a randomized, 30-center (US), double-blind, parallel group, 8-week, fixed-dose study comparing sertindole at 2 fixed doses [20 and 24 mg/day, on a qd schedule; initial dose was 4 mg/day with titration to assigned dose at the rate of 4 mg q 4 days], haloperidol at a fixed dose of 16 mg/day [initial dose was 4 mg/day, with increases of 4 mg q 4 days until reaching 16 mg], and placebo for the treatment of psychosis in adult inpatients meeting DSMIII-R or DSMIV criteria for schizophrenia. Patients had to have scores on any 2 of the positive BPRS items summing to 8 and could not have had a decrease of more than 20% on the BPRS Total during the placebo lead-in period.

Benzotropine mesylate was permitted for EPS, but only on as needed basis and for limited periods (7 days); it could be continued with repeat evaluation.

The primary efficacy assessments included the PANSS, the BPRS, and the CGI, all administered weekly during the 8 week trial. In the following, I will focus on 4 efficacy measures: the PANSS total score, the BPRS positive symptom score, the PANSS Negative subscale, and the CGI-Severity score.

Our review focused on the intent-to-treat sample, i.e., all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one followup time. The statistical model used was ANOVA, focusing on change from baseline for the measures noted, and including treatment, investigator, and treatment-by-investigator terms, except for the CGI which was analyzed using the Cochran-Mantel-Haenzel statistic with centers as strata.

Patients were approximately 75% male, approximately 2/3 Caucasian, and the mean age was late 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Study Results

The intent-to-treat dataset was as follows:

Placebo	(106)
Sertindole 20 mg/day	(111)
Sertindole 24 mg/day	(108)
Haloperidol 16 mg/day	(113)

Completion rates to 8 weeks were as follows:

Placebo	43/106 (41%)
Sertindole 20 mg/day	44/111 (40%)
Sertindole 24 mg/day	49/108 (45%)
Haloperidol 16 mg/day	54/113 (48%)

[See appendices for tables providing significance levels for pairwise comparisons and treatment effect sizes.]

As was the case for study 113, insufficient information was provided by the sponsor regarding the concomitant use of benzotropine.

Impression:

Both the 20 and 24 mg sertindole dose groups were generally superior to placebo in the LOCF analyses at the 8-week endpoint, with or without a correction for multiple comparisons (see Hoberman review). The evidence for these dose groups was less compelling in

the OC analyses, likely because of the substantial attrition almost always observed in placebo-controlled schizophrenia trials. Dr. Hoberman provided plots of scores for the various dropout cohorts, and for most of the dropout cohorts the sertindole patients were doing better than placebo at the point of dropout, and thus, I am less concerned about this discrepancy. The effect size as measured by difference between drug and placebo in change from baseline was less impressive for this study than for 113, nevertheless, I consider this a clinically meaningful effect. I agree with Drs. Hearst and Hoberman that this is a positive study for both the 20 and 24 mg/day doses. There was no apparent advantage for the higher 24 mg dose group.

5.1.1.3 Study M92-762

This was a randomized, 16-center (US), double-blind, parallel group, approximately 7-week, fixed-dose study comparing sertindole at 3 fixed doses [8, 12, and 20 mg/day, on a qd schedule; initial dose was 4 mg/day, with titration to assigned dose at the rate of 4 mg q 4 days] and placebo for the treatment of psychosis in adult inpatients meeting DSMIIIR criteria for schizophrenia.

Benzotropine mesylate was permitted for EPS, but only on as needed basis and for limited periods (7 days); it could be continued with repeat evaluation.

The primary efficacy assessments included the PANSS, the BPRS, and the CGI, all administered weekly during the 7 week trial. In the following, I will focus on 3 efficacy measures: the PANSS total score, the BPRS positive symptom score, and the PANSS Negative subscale.

Our review focused on the intent-to-treat sample, i.e., all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one followup time. The statistical model used was ANOVA, focusing on change from baseline for the measures noted, and including treatment, investigator, and treatment-by-investigator terms, except for the CGI which was analyzed using the Cochran-Mantel-Haenzel statistic with centers as strata.

Patients were approximately 95% male, approximately 50% Caucasian, and the mean age was late 30's. The treatment groups were comparable at baseline on the demographic and the key efficacy variables.

Study Results

The intent-to-treat dataset was as follows:

Placebo	(47)
Sertindole 8 mg/day	(50)

Sertindole 12 mg/day	(50)
Sertindole 20 mg/day	(51)

Completion rates to day 40 were as follows:

Placebo	24/47 (51%)
Sertindole 8 mg/day	20/50 (40%)
Sertindole 12 mg/day	29/50 (58%)
Sertindole 20 mg/day	27/51 (53%)

[See appendices for tables providing significance levels for pairwise comparisons and treatment effect sizes.]

Impression:

This was a negative study with virtually no statistically significant differences favoring sertindole over placebo. While the change from baseline in PANSS Total Score for the 20 mg sertindole group was roughly the same for this study as for 098, the change in the placebo group was so prominent as to preclude any between group differences. There was no active control group to assess the sensitivity of this study to detect a drug effect.

5.1.1.4 Study M91-645

This was a randomized, 6-center (US), double-blind, parallel group, 7-week, titration study comparing sertindole (4-20 mg/day, on a qd schedule) and placebo for the treatment of psychosis in adult inpatients meeting DSMIII-R criteria for schizophrenia or schizoaffective disorder.

Benzotropine mesylate was permitted for EPS, but only on as needed basis and for limited periods (7 days); it could be continued with repeat evaluation.

The primary efficacy assessments included the BPRS and the CGI, both administered weekly during the 7 week trial. In the following, I will focus on 2 efficacy measures: the BPRS total score and the BPRS positive symptom score.

Our review focused on the intent-to-treat sample, i.e., all patients randomized who received at least one dose of assigned treatment and for whom efficacy assessments were available at baseline and at least one followup time. The statistical model used was ANOVA, and ANCOVA when appropriate, focusing on change from baseline for the BPRS measures noted, and including treatment, investigator, and treatment-by-investigator terms. The CGI was analyzed using the Cochran-Mantel-Haenzel statistic with centers as strata.

Patients were approximately 90% male, approximately 60% Caucasian, and the mean age was mid 30's. The treatment groups were

comparable at baseline on the demographic variables, however, there were some differences on certain efficacy variables, and ANCOVAs were done in these instances. The mean dose for sertindole completers at 40 days was 17 mg/day.

Study Results

The intent-to-treat dataset was as follows:

Placebo	(11)
Sertindole	(23)

Completion rates to 7 weeks were as follows:

Placebo	3/11 (27%)
Sertindole	11/23 (48%)

[See appendices for tables providing significance levels for pairwise comparisons and treatment effect sizes.]

Impression:

Sertindole was superior to placebo in the LOCF analyses. Although this was not the case for the OC analyses, the likely explanation is the low completion rates. Cohort analyses were not done for this study, however, I consider it a supportive study favoring sertindole in the treatment of psychosis.

5.1.2 Comment on Other Important Clinical Issues Regarding the Efficacy of Sertindole for Psychosis

Evidence Bearing on the Question of Dose/Response for Efficacy

The two studies that can be considered positive in support of the antipsychotic efficacy of sertindole were 113, comparing sertindole doses of 12, 20, and 24 mg/day with placebo, and 098, comparing sertindole doses of 20 and 24 mg/day, haloperidol 16 mg/day and placebo. There was some support for the 12 mg dose in 113, albeit less optimal than that observed for the 20 mg dose. In general for study 113, the 20 mg dose was the best performing dose, with 24 mg as second best. For study 098, both the 20 and 24 mg/day doses were effective, but essentially indistinguishable. On the basis of these data, it seems to me that 12 to 20 mg/day should be the target dose range for the usual adult patient. I have proposed labeling language that recommends 12 to 20 mg as the target dose range, but that also acknowledges (1) no advantage for 24 mg over 20 mg/day, and (2) a less optimal effect for the 12 mg dose.

Clinical Predictors of Response

PANSS total score data for the sertindole 20 mg/day dose groups from studies M92-762, M93-098, and M93-113 were pooled for efficacy analyses of demographic subgroups, based on age, gender, and race.

There was no indication from these analyses of differential treatment effect on the basis of these subgroupings.

Size of Treatment Effect

Size of Treatment Effect for PANSS Total Score at Endpoint ¹ (LOCF) in 3 Schizophrenia Studies			
Study	Sertindole 20 mg	Placebo	Difference
M93-113	-17.6	+0.7	18.3
M93-098	-7.5	-1.2	6.3
M92-762	-12.6	-5.0	7.6

1 The endpoint is 8 weeks for 113 and 098, and 7 weeks for 762.

The effect size for the 2 positive studies (M93-113 and M93-098) ranged from 6.3 to 18.3 and were comparable to effect sizes observed in positive trials for other antipsychotic drugs. I consider these effect sizes clinically meaningful and these data supportive of the antipsychotic claim for sertindole.

Duration of Treatment

There were no adequate and well controlled relapse prevention trials in the sertindole development program to address the question of long-term efficacy. We will request that the sponsor agree to an adequately designed relapse prevention trial as a phase 4 commitment, i.e. a trial involving randomization to continuation on sertindole or switch to placebo in patients responding during open treatment with sertindole.

5.1.3 Conclusions Regarding Efficacy Data

In summary, I consider studies M93-113 and M93-098 positive studies in support of the claim of short-term antipsychotic efficacy for sertindole. Overall, these data support a target dose range of 12 to 20 mg/day for the usual patient, with acknowledgement that 12 mg/day may be less effective than 20 mg for some patients. The one deficiency of this program is the lack of adequate and well controlled data to address the question of long-term efficacy.

5.2 Safety Data

Clinical Data Sources for Safety Review

The safety data for sertindole, including the original submission and the amendments in response to our requests for additional

information, were reviewed by Dr. Hearst (review dated 7-17-96). This original review was based on an integrated database with a cutoff date of 6-15-95 and on additional serious event reporting with cutoff dates of 8-1-95 for serious events and 9-15-95 for deaths.

2355 human subjects were exposed to sertindole in the development program, including 435 in phase 1 studies, 1446 in phase 2-3 Abbott-sponsored trials, and 474 in phases 1-3 NonAbbott-sponsored studies.

Patients in Abbott's phase 2-3 integrated database (for n=1446) were roughly 1/4 female, roughly 2/3 Caucasian, and predominantly middle-aged. In fact, there were only 20 patients \geq 65.

Regarding drug exposure, the most relevant dose range is 20-24 mg/day, since there was a suggestion that 12 mg/day is somewhat less effective than 20 mg/day. Approximately 57% of sertindole-treated patients in these phase 2-3 studies received modal sertindole doses in this 20-24 mg/day range. Approximately 75% of exposures were for 24 weeks or less. Nevertheless, there were approximately 350 patients who received sertindole for \geq 24 weeks, including 195 patients who were dosed for greater than 48 weeks.

No post-marketing data were available for this drug.

Deaths

There were 18 deaths reported among sertindole-treated patients overall in the original NDA, including 8 in the integrated database for which the denominator and full exposure data were available. There were no deaths among placebo or active control patients. When adjusted for duration of exposure, the mortality rate for sertindole was comparable to the NDA database rate for risperidone. However, as I note later under the section on QT prolongation, this comparison is flawed since there was a much higher proportion of deaths due to suicide in the risperidone sample than in the sertindole sample, where about half the patients had sudden unexplained deaths. These cases will be discussed under the heading of QT prolongation to follow.

Adverse Dropouts

Based on a pool of 5 short-term, placebo-controlled trials, the common and drug-related adverse events leading to dropout for sertindole (incidence at least 0.4% and at least twice the placebo rate) included the following: ECG abnormal, postural hypotension, QT prolongation, abnormal LFTs, somnolence, and abnormal ejaculation.

Serious Events Search

A search for serious events, using FDA's definition, identified 100 patients among the 1446 sertindole-treated patients in the phase 2-3 studies. In addition, there were 3 phase 1 sertindole-treated patients and 7 sertindole-treated patients from the non-Abbott sponsored studies who experienced serious adverse events. Most common were overdose, suicide attempt, and depression.

Other Searches

Analyses focused on suicides and suicidality revealed comparable time-adjusted overall suicidality rates for sertindole in this phase 2-3 database and for risperidone in its phase 2-3 studies. There does not appear to be any drug-related risk for such events, i.e., these findings are likely secondary to the primary schizophrenic illness being treated.

Other Safety Findings

Common/Drug-Related AEs: The common and drug-related adverse event profile for sertindole (incidence at least 5% and at least twice the placebo rate) included the following: rhinitis, abnormal ejaculation, dry mouth, and vaginitis.

LAB: Laboratory changes of interest included increases in LFTs, prolactin, cholesterol, triglycerides, and glucose (see discussion under summary of important adverse events).

VS: Vital sign changes of interest included blood pressure and heart rate responses to orthostatic challenge (see discussion under summary of important adverse events).

ECG: The ECG change of interest was QT prolongation (see discussion under summary of important adverse events).

Ophthalmological Findings: Sertindole was associated with anterior suture lens opacities in rats, and posterior capsular opacities, cataracts, and patchy hyperreflectivity of the ocular fundus (retina) in mice. On the basis of these findings, ophthalmological exams were done pre- and post-treatment for 139 patients. The findings observed were minimal and of the type expected in this population. Thus, no special ophthalmological monitoring would seem to be indicated for sertindole, however, these findings will be noted in labeling.

Withdrawal Phenomena/Abuse Potential: Since the sponsor did not systematically collect adverse event data following withdrawal of sertindole, there was no opportunity to look systematically for withdrawal phenomena/abuse potential. Animal studies did not suggest any abuse potential.

Human Reproductive Data: There were 2 pregnant women exposed to sertindole during the development program, with both pregnancies terminated by abortion (1 spontaneous and 1 elective). Thus there is essentially no human experience pertinent to the question of teratogenic risk.

Overdose Experience: The overdose experience with sertindole consisted of clinical reports from 26 patients in clinical trials, with estimated doses ranging from 40 to 240 mg. The usual clinical findings included somnolence, slurred speech, tachycardia, hypotension, and transient prolongation of the QT interval. Apparently none of these patients had QTc's that met the > 500 msec criterion. There were 2 fatal overdoses, both involving other drugs in addition to sertindole.

Comparison of Sertindole and Haloperidol Regarding EPS:

For study 113, the percentages of patients reporting any EPS-related adverse events by study group were as follows:

<u>Treatment Group</u>	<u>% Reporting any EPS-Related AEs</u>
Placebo	27%
Sertindole 12 mg	21%
Sertindole 20 mg	13%
Sertindole 24 mg	24%
Haloperidol 4 mg	44%
Haloperidol 8 mg	55%
Haloperidol 12 mg	56%

The findings from the EPS rating scales and the data regarding use of anti-EPS medications were consistent with the above findings.

I believe that these data from study 113 demonstrate that sertindole, at the doses effective in treating psychotic symptoms, has little potential for inducing acute extrapyramidal symptoms. These data are also suggestive of an advantage of sertindole over haloperidol in this regard, since I believe the doses compared are in fact equi-effective.

However, there are difficulties in interpreting these data. One problem is that these patients were not naive to treatment with haloperidol, and therefore, there is the possibility that they did not adequately tolerate prior treatment with haloperidol, e.g., EPS. To the extent that was the case, the trial would have been biased against haloperidol. Of course, we do not have knowledge of such intolerance, nevertheless, the possibility of such intolerance complicates the interpretation of this trial. A second problem is the issue of whether or not haloperidol was administered in an optimal manner for that drug. Since haloperidol is clearly known to have a substantial risk of EPS, it is not uncommon to

administer anticholinergic medications on a prophylactic and continuous basis with haloperidol. That was not done here, and as noted earlier, the sponsor has not even been willing or able to provide us detailed information on the extent of benzotropine use in this trial. Finally, there is the issue of which EPS data were used in the comparative analyses. The sponsor has acknowledged that the worst on drug EPS scores were used in the comparison, which for haloperidol would have meant that those scores used would always have represented assessments in patients during a time they were not receiving benzotropine, rather than on optimal treatment, which, in my view, would have been the only fair comparison. Thus, I feel that these data cannot serve as a basis for claims of superiority of sertindole over haloperidol regarding acute EPS, and they cannot be included in labeling since they could easily be misinterpreted.

Summary of Drug Interactions

Drug-Demographic: A search for drug-demographic interactions was conducted with the pool of placebo-controlled haloperidol-referenced trials. Odds ratios (sertindole vs placebo) were calculated for all reported adverse events. Our attempt to explore for drug-demographic interactions was limited to age and sex, and these analyses did not reveal any important differences. However, there was limited power to detect any but very substantial differences.

Drug-Disease: Except for pk studies in subjects with renal or hepatic impairment, there were no systematic attempts to explore for drug/disease interactions. A decreased clearance of sertindole was found for hepatically impaired but not renally impaired patients.

Drug-Drug: (see Biopharm and Pharm sections)

Summary of Important Adverse Events Considered Drug-Related

QT Prolongation:

Sertindole is associated with QT prolongation in a dose dependent manner. An illustration of this fact are the data on mean change from baseline in QTc for study 762:

<u>Treatment Group</u>	<u>Mean Change from BL in QTc (msec)</u>
Placebo	+ 1.1
Sertindole 8 mg	+15.2
Sertindole 12 mg	+20.0
Sertindole 20 mg	+31.9

The data from studies 113 and 098 are consistent with the dose dependency illustrated for 762.

Another way of looking at this effect is to observe the proportions of patients in different treatment groups who meet a criterion for having an increase from baseline in QT of potential clinical significance. The criterion chosen was having an on-treatment QTc of > 500 msec, and the data from study 113 illustrate the dose dependency for this outcome:

<u>Treatment Group</u>	<u>% with QTc > 500 msec</u>
Placebo	0%
Sertindole 12 mg	0%
Sertindole 20 mg	7%
Sertindole 24 mg	8%

The data from studies 762 and 098 are consistent with the dose dependency illustrated for 113.

Another source of information on QT prolongation is the group of overdoses with sertindole, and although none of the overdose cases apparently met the criterion of having QTc's > 500 msec, several of these patients were characterized qualitatively by their physicians as having QT prolongation.

The QT changes seen with sertindole, both in terms of mean change from baseline and for proportions of patients meeting the > 500 msec criterion, are of the same magnitude as those seen with other drugs recognized as having this problem (e.g., sotalol, bepridil, and lidoflazine). Thus sertindole clearly belongs to the class of drugs that are recognized as having a potential to prolong the QT. At the same time, sertindole clearly differs from other antipsychotic drugs, and this is illustrated directly with the drug haloperidol, which was an active control in most of the sertindole trials and was indistinguishable from placebo in those trials. This difference is illustrated indirectly for the recently approved antipsychotic risperidone which, along with the active control haloperidol, was also indistinguishable from placebo on these measures of QT prolongation. Thus, although risperidone carries a Warning about the potential for QT prolongation on the basis of several patients exceeding a QTc criterion of 450 msec and a few overdose cases associated with QT prolongation, sertindole clearly stands apart from that drug regarding this effect. [Note: Dr Mosholder reported to me that only 1 risperidone patient out of 1429 exposed met the > 500 msec criterion (on QT or QTc), compared to 89 sertindole patients out of 1446 exposed.]

The concern about drugs that prolong the QT interval is their association with a potentially serious arrhythmia, torsade de pointes, and sudden unexplained death (SUD). Torsade de pointes can predispose patients to fatal ventricular arrhythmias, however, the relationship between QT prolongation, torsade de pointes, and SUD is not well defined. Nevertheless, it is clear that other drugs with a similar effect on QT as that observed with sertindole have been associated with an increased incidence of both torsade de pointes and SUD. These drugs have also been associated with symptomatic torsade de pointes, i.e., patients have been observed to have symptoms such as dizziness, palpitations, and/or syncope, which upon further evaluation, e.g., ECG or Holter monitor, are also observed to have torsade.

The relevant question then is to what extent has sertindole been associated with torsade de pointes, symptomatic or not, and sudden unexplained death (SUD). Abbott and its consultants argued that despite extensive ECG monitoring (over 10,000 individual ECGs), no torsade was observed. The counter argument, advanced by Drs. Lipicky and Ganley, is that all those ECGs add up to a small total amount of monitoring time (perhaps 30-40 hours), relative to the total person time for sertindole (> 1000 person years). A better way of detecting torsade would be Holter monitoring, however, even extensive Holter monitoring may not detect torsade for a drug that has the potential for inducing torsade and SUDs, as illustrated by Dr. Lipicky's example of bepridil. For sertindole, the extent of Holter monitoring was limited to 6 asymptomatic patients in study M93-132 and 1 patient with syncope who had a grossly abnormal ECG at baseline. In study 132, the 6 sertindole patients were compared with 6 haloperidol patients, however, Dr. Ganley points out that insufficient details are provided to know exactly what was measured and, more important, this comparison was underpowered to conclude anything. Thus, the finding of no difference between sertindole and haloperidol in study 132 offers no reassurance. What is more perplexing is why patients with syncope were not more aggressively evaluated for the possibility of torsade. In a 7-12-96 submission, the sponsor reported 23 instances of syncope during phase 1 studies and 23 during phase 2-3 studies. Only 1 of the phase 2-3 patients had a Holter monitor done (noted above) and 1 other phase 2-3 patient had an ECG. One might argue that, given sertindole's α_1 antagonism, syncope is not an unexpected event and wouldn't need more aggressive workup. However, most of the reported cases of syncope occurred after initial titration and, therefore, it would seem less likely to me that the syncope could be attributed to this effect. It is

noteworthy that about 1/3 of these phase 2-3 patients had dose reductions following their syncopal episodes. Nevertheless, it is true to say that symptomatic torsade de pointes was not observed in this fairly large exposure to sertindole. One might expect that if patients were having repeated episodes of dizziness, palpitation, and/or syncope, they would eventually have been adequately worked up and that torsade, if present, would have been detected.

The second finding associated with drugs that prolong the QT is sudden unexplained death (SUD). There did appear to be an excess of SUDs associated with sertindole. Drs. Lipicky and Ganley conclude that there were 12 such deaths, and the details of those deaths are provided in reviews by Dr. Ganley and Dr. Hearst. These were patients who were found dead in bed, who died while walking down the street, or who otherwise died under circumstances that were not predictive of their deaths. This is not to say that most, if not all, of these patients had other findings that would have increased their risk of dying, but at least in these 12 cases our experts did not consider those other factors sufficient to explain the timing of their deaths. Abbott's own experts agreed in many of these cases that a role for sertindole could not be ruled out, but in fairness, their experts were not as convinced as ours that the deaths might have been caused by sertindole.

Abbott and its consultants argued against the importance of this observation by comparing all cause mortality for sertindole with that seen for risperidone, the most recently approved antipsychotic drug. While it's true that all cause mortality is similar for the 2 drugs, we don't believe it is a reasonable comparison, given the very different distribution of deaths for the two drugs. The most obvious difference is in the proportions of deaths due to suicide, i.e., about 1/4 for sertindole compared to over 2/3 for risperidone. The interest here is not in comparing all cause mortality, but rather, in comparing deaths that may be related to the signal of concern, i.e., QT prolongation. Sudden unexplained deaths are the deaths of interest, and clearly sertindole is different from risperidone from that standpoint. I think the reasonable conclusion has to be that one cannot compare these 2 populations since the distribution of deaths appears to be so different.

Comment: We are left with the uncomfortable finding of a fairly prominent increase in the QT interval associated with the use of sertindole, in fact at the doses that have been shown to be optimal for treating psychosis. While one can

argue that the observation for torsade was inadequate, the fact is that no symptomatic torsade was observed with sertindole use despite the fairly extensive experience with this drug. There were a number of sudden unexplained deaths associated with sertindole, but experts disagree on the likelihood that sertindole had a role in any of these deaths. It would appear that there is a consensus that sertindole, because of its prolongation of the QT interval, has the potential for causing torsade de pointes and/or sudden death, whatever the relationship between torsade and sudden death turns out to be. However, it isn't possible to estimate the risk for either event given the existing data, and experts disagree in their impressions about what the risk might actually be.

Schizophrenia is a serious illness, and one for which we don't have particularly effective treatments. While there are many available treatments, probably 1/3 of patients don't respond very well to any of the drugs administered. We are generally agreed that sertindole has met the test for being considered effective in the short-term treatment of psychosis. However, it has not been shown to have any advantages over any other antipsychotic drugs in terms of efficacy. Of course, it is always possible, even though not demonstrated, that some patients among the heterogeneous mix of patients who meet diagnostic criteria for schizophrenia may respond better to sertindole than to other available drugs. This is usually the argument for making new drugs available, even with their own panoply of risks and despite their not having any demonstrated advantages over other drugs.

This set of findings was presented to the Psychopharmacological Drugs Advisory Committee on July 15, 1996. They voted unanimously in favor of the effectiveness of sertindole (6 vs 0), and a majority considered sertindole to have an acceptable enough safety profile to justify approval (4 vs 2). There was no vote on the issue of whether or not sertindole should be labeled as a second line drug given its cardiovascular risks, however, there was a mixed view among those offering opinions on this matter.

This is a difficult decision for me. While I am greatly concerned about the QT prolongation along with the SUDs associated with sertindole use, I'm not convinced that there is enough evidence to conclude that the potential risks for this drug, especially since they cannot be estimated, overcome its potential benefits. Nevertheless, I feel that the adverse findings are sufficiently alarming to justify labeling

sertindole as a second line drug for treating psychosis, and I have included this qualification in the draft labeling. I have also proposed a black box warning regarding the finding of QT prolongation and the risk of torsade and sudden death. I have followed Dr. Ganley's advice about incorporating in labeling other risk factors, e.g., hypokalemia and bradycardia, and I have also added congenital long QT syndrome and a history of arrhythmias as contraindications. In the sections on potential drug interactions, I have taken a more conservative position than Abbott regarding the risks of using sertindole with drugs that inhibit 2D6 and 3A. Thus, I have proposed an expanded list of contraindicated drugs and I have expanded the discussion under Drug Interactions on the risks that I believe would be inherent in such combinations. I have also followed Dr. Ganley's advice in recommending more aggressive evaluation of patients having symptoms that might be related to torsade, and I have added a section under information for patients recommending that physicians alert patients to symptoms that may necessitate further workup. Finally, although Drs. Lipicky and Ganley did not offer any advice on routine baseline and followup monitoring for sertindole treated patients, I have proposed some monitoring that can be subject to negotiation. I recognize that the value of such monitoring is difficult to prove, nevertheless, I think that common sense would dictate that some type of routine monitoring is justified.

In addition, I believe that the approval of this drug must be accompanied by a commitment from Abbott to collect data subsequent to marketing that further enhance our understanding of the cardiovascular risks of sertindole. In the first place, I think a registry is needed so that all patients receiving sertindole can be identified. This will permit a cohort mortality study of the type done with clozapine to be done for sertindole. Mortality can be determined using social security information and sertindole can serve as its own control to determine the relative risk of death with or without this drug. In addition, Abbott should commit to doing a study focused on observing sertindole exposed patients for torsade de pointes. This could be accomplished with extensive Holter monitoring on a cohort of patients exposed to sertindole. The details of both studies should be worked out prior to approval.

Orthostatic Hypotension: As an α_1 -antagonist, it was not unexpected that sertindole would be associated with postural hypotension. This effect was observed initially in phase 1 studies where 10% (10/145) of subjects who had orthostatic

challenges experienced decreases in systolic BP and increases in heart rate, including 1 patient with syncope. In a pool of placebo-controlled phase 2-3 studies, 7% of sertindole-treated patients compared to 2% of placebo patients ($p < 0.05$) met criteria for an important systolic blood pressure decrease in response to an orthostatic challenge. Also in that pool, 9% of sertindole-treated patients compared to 3% of placebo patients ($p < 0.05$) met criteria for an important heart rate increase in response to an orthostatic challenge. In addition, 1% (15/1446) of phase 2-3 patients exposed to sertindole experienced 1 or more syncopal episodes. Although none of these patients having syncopal episodes discontinued for these episodes, 7 other patients did discontinue for either postural hypotension (5) or tachycardia (2). All patients having syncopal episodes fully recovered and apparently none of these patients was observed to have QT prolongation in association with their syncopal episodes (see QT prolongation section above for discussion of inadequacy of workup of patients with syncope).

Increased Hepatic Transaminases:

-A tendency to increased transaminase values was noted in phase 1 studies, where the proportions of sertindole-treated patients normal at baseline who met criteria during treatment for very high SGPT (≥ 165) or SGOT (≥ 150) were 1% (5/412) and <1% (2/417), respectively.

-In the pool of all placebo-controlled short-term phase 2-3 trials, there was a significant mean increase from baseline on SGPT for sertindole (+4) compared to a mean decrease for placebo (-2) ($p \leq 0.05$). In that same pool, the proportions of sertindole- and placebo-treated patients normal at baseline who met criteria during treatment for very high SGPT (≥ 165) were 2% (13/554) for sertindole and 0% (0/215) for placebo ($p \leq 0.05$). The comparable data for very high SGOT (≥ 150) were 1% (4/617) for sertindole and 0% (0/252) for placebo (NS). None of the patients with increased SGPTs had levels > 400 , and only 3 were discontinued for the increases. Of these 3, 2 were normal at final visit, and no data were available on the third patient. Of the 10 patients continued, 8 patients normalized during continued treatment and 2 were resolving at study completion. None of these patients had any signs or symptoms or any other lab findings suggestive of liver toxicity.

-In the pool of long-term open studies, the proportions of sertindole-treated patients normal at baseline who met criteria during treatment for very high SGPT (≥ 165) or SGOT (≥ 150) were 2% (17/874) and 1% (11/972), respectively. Except for 1 of these patients who died from multiple drug toxicities (morphine, codeine, and diazepam), the others either resolved on treatment or shortly thereafter, and none had other findings suggestive of liver toxicity.

-Over the entire 1446 sertindole exposed patients in Abbott's phase 2-3 program, 11 were discontinued for abnormal liver function tests, however, none of these patients had other findings suggestive of liver toxicity.

-Thus, it would appear that sertindole, as for many other psychotropics, induces asymptomatic increases in transaminases in a small percentage of exposed patients that are of unknown clinical significance. Nevertheless, I have proposed that this finding be noted as a Precaution in labeling.

Hyperglycemia: A slight tendency to hyperglycemia was observed in the short-term placebo controlled trials with sertindole, i.e., there was a mean increase in serum glucose of 6 mg/dL among sertindole patients compared to an increase of 1 mg/dL in placebo patients ($p < 0.05$). Of 21 patients with diabetes mellitus treated with sertindole in the development program, 5 were observed to have at least 1 serum glucose value exceeding 175 mg/dL at some point on treatment. These findings merit a mention in Precautions.

Weight Gain and Associated Changes:

-A possible tendency to weight gain was noted in phase 1 studies, where the proportions of sertindole-treated patients in phase 2-3 studies who met criteria during treatment for very high weight increase ($\geq 15\%$ from baseline) was 1% (3/338). Changes in cholesterol and triglycerides are often associated with weight increases. The proportions of sertindole-treated patients normal at baseline who met criteria during treatment for very high cholesterol (≥ 600 mg/dL) or triglycerides (≥ 600 mg/dL) were 0% (0/335) and 1% (5/378), respectively.

-In the pool of all placebo-controlled short-term phase 2-3 trials, there was a significant increase in mean weight change from baseline for sertindole (+2.8 kg) compared to placebo (+0.2 kg) ($p \leq 0.05$). In that same pool, the proportions of sertindole- and placebo-treated patients normal at baseline who met criteria during treatment for very high weight increase ($\geq 15\%$ from baseline) were 5% (25/488) for sertindole and 2% (3/196) for placebo ($p \leq 0.05$).

-In the pool of all placebo-controlled short-term trials, there was a significant increase in mean change from baseline on cholesterol for sertindole (+3 mg/dL) compared to placebo (-3 mg/dL) ($p \leq 0.05$). Similarly, there was a significant increase in mean change from baseline on triglycerides for sertindole (+25 mg/dL) compared to placebo (-5 mg/dL) ($p \leq 0.05$).

-In that same pool, the proportions of sertindole- and placebo-treated patients normal at baseline who met criteria during treatment for very high cholesterol (≥ 600 mg/dL) were 0% (0/381) for sertindole and 0% (0/146) for placebo (NS). The comparable data for very high triglycerides (≥ 600 mg/dL)

were 1% (3/547) for sertindole and <1% (1/220) for placebo (NS).

-In the pool of long-term open studies, there was a mean increase in weight from baseline for sertindole-treated patients of 4 kg. Approximately 14% (133/938) of sertindole-treated patients in these long-term trials had weight gain of \geq 15% of baseline weight. 4 of these patients discontinued due to weight gain.

-In that same pool of long-term open studies, the proportions of sertindole-treated patients normal at baseline who met criteria during treatment for very high cholesterol (\geq 600 mg/dL) or triglycerides (\geq 600 mg/dL) were 0% (0/578) and 1% (7/758), respectively.

-Over the entire 1446 sertindole exposed patients in Abbott's phase 2-3 program, 4 were discontinued for weight gain (i.e., the 4 patients from the long-term studies noted above).

-Thus, it would appear that sertindole, as for many other psychotropics, is associated with weight gain in some patients, associated with increases in cholesterol and triglyceride increases. I have proposed that this finding be noted as a Precaution in labeling

Seizures: Seizures are known to occur more frequently among schizophrenic patients taking antipsychotic drugs than in the general population. Thus, it is not surprising that seizures were reported in association with sertindole use. Overall, 15 seizures were reported in patients taking sertindole in this development program. 8 of these occurred among the 1446 patients in Abbott's integrated database (0.6%). 7 additional sertindole patients experienced seizures, including 2 in ongoing Abbott studies and 5 in non-Abbott sponsored studies. Although a number of these patients had alternative plausible reasons for having seizures, it is also quite possible that sertindole had a facilitative role.

Abnormal Ejaculation: In the placebo and halperidol controlled study pool, this was one of 4 events that met our criteria for being common and drug related. This event was reported at an incidence of 14% in sertindole patients vs 3% in placebo patients ($p < 0.05$). Patients having this complaint apparently have experienced primarily either absent or reduced volume of ejaculate. This finding apparently has not been associated with decreased libido, erectile capacity, or orgasm. The likely basis for this effect is the α_1 -antagonistic action of sertindole.

Hyperprolactinemia: While the mean prolactin levels of sertindole treated patients in short-term trials remained within the normal range for this parameter, these levels were, nevertheless, clearly distinguishable from the levels observed in placebo patients, and thus, revealed a prolactin elevating effect of sertindole. This effect persisted during longer

term exposure. Furthermore, the animal studies with sertindole revealed the typical pattern of prolactin related changes seen with this class of drugs. I would consider sertindole to be representative of the class of antipsychotic drugs regarding prolactin elevating effects. Thus, I have proposed the standard prolactin statement for labeling rather than the modified version proposed by Abbott.

Neuroleptic Malignant Syndrome (NMS): Sertindole shares with other antipsychotic drugs a dopamine antagonizing action and therefore also a potential for NMS. Thus, I have proposed the standard labeling language for this serious event rather than the slightly modified language proposed by the sponsor. It is noteworthy that there were two sertindole-treated patients from the nonAbbott sponsored studies who had findings suggestive of NMS, although there were alternative possible explanations for the findings and a definitive NMS diagnosis was not made in either case.

Tardive Dyskinesia (TD): Sertindole shares with other antipsychotic drugs a dopamine antagonizing action and therefore also a potential for TD. Thus, I have proposed the standard labeling language for this serious event rather than the modified language proposed by the sponsor. It is noteworthy that 17 patients in the development program were apparently diagnosed with TD for the first time, however, most of these diagnoses (13/17) were made within a 2 month interval of stopping a prior neuroleptic and starting sertindole. The other 4 patients all had long histories of neuroleptic treatment.

5.3 Clinical Sections of Labeling

We have substantially rewritten the clinical sections of the draft labeling that is included with the approvable letter. The explanations for the changes are provided in bracketed comments in the draft labeling.

6.0 WORLD LITERATURE

Dr. Hearst reviewed the published literature for sertindole included in the NDA and did not discover any previously unrecognized important safety concerns for this drug. We will ask for a literature update in the approvable letter.

7.0 FOREIGN REGULATORY ACTIONS

Sertindole is approved in the UK, but, to my knowledge, not yet marketed at this time. We will ask for an update on the regulatory status of sertindole in the approvable letter.

8.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

Sertindole was the subject of a 7-15-96 meeting of the PDAC, and the Committee voted unanimously in favor of its efficacy (6 vs 0). The response was more mixed for safety (4 in favor, 2 opposed).

9.0 DSI INSPECTIONS

As of this date, we have not received any responses from DSI on the routine inspections for this NDA. However, many of the investigators are familiar to us and have passed recent inspections. Thus, despite the absence of final responses from DSI, I recommend that we forward an approvable package in anticipation of obtaining responses prior to an approvable action.

10.0 LABELING AND APPROVABLE LETTER

10.1 Final Draft of Labeling Attached to Approvable Package

Our proposed draft of labeling is attached to the approvable letter. As noted, we have made substantial changes to the sponsor's draft dated 9-29-95. Other sections have also been substantially modified.

10.2 Foreign Labeling

Sertindole is approved in the UK, and we have reviewed the approved labeling for that country. Our proposed labeling is much stronger, particularly regarding the QT prolongation seen with sertindole. Indeed, the UK labeling barely notes the existence of this important finding.

10.3 Approvable Letter

The approvable letter includes draft labeling and requests for a safety update, a literature update, a regulatory status update, a relapse prevention trial, a registry and cohort mortality study, a Holter monitor study, an animal toxicity study to explore the finding of bone fragility in mice, additional in vitro work to explore the possibility of P450 inhibitory effects of sertindole,

adoption of our dissolution specs, repair of EA deficiencies, and repair of other minor chemistry deficiencies.

11.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that Abbott has submitted sufficient data to support the conclusion that sertindole is effective for the short-term treatment of psychosis. However, I believe that sertindole also has a risk of serious cardiovascular events, including the possibility of sudden death. While it is not possible based on the data available to quantitate these risks, in my view the potential for the occurrence of such events is great enough that sertindole, while it may be approved, should not be a first line treatment. Furthermore, I believe it should have very strong labeling, including a black box warning regarding the problem of QT prolongation and the associated risks. I believe Abbott must also agree to the postmarketing collection of data that will further our understanding of this potentially serious problem. With these qualifications, I recommend that we issue the attached approvable letter with our labeling proposal and the above noted requests for updates, etc., in anticipation of final approval.

cc:

Orig NDA 20-644

HFD-120

HFD-120/TLaughren/PLeber/EHearst/AMosholder/SHardeman

HFD-100/RTemple

DOC: MEMSRTPS.AE1

Summary of Significance Levels¹ (2-sided) for Pairwise Comparisons
 (Sertindole 12, 20, and 24 mg/day vs Placebo) in Study M93-113

Key Outcome Variables	Sertindole 12 vs Pbo								Sertindole 20 vs Pbo								Sertindole 24 vs Pbo							
	Week ²								Week ²								Week ²							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
PANSS Total	-	-	-	-	-	-	-	-	-	*	t	*	*	*	*	*	-	t	-	*	*	t	*	*
LOCF	-	-	-	-	-	-	-	-	-	*	*	*	*	*	*	*	-	-	-	*	*	t	*	*
OC	-	-	-	-	-	-	-	-	-	*	-	*	*	*	*	t	-	-	-	*	*	-	-	-
BPRS Pos	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS Neg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	t	-	-	-	-	-	-	-	-	*	-	t	*	t	*	-	-	-	-	-	-	-	-	
OC	t	-	-	-	-	-	-	-	-	t	-	-	*	-	-	-	-	-	-	-	-	-	-	
CGI Severity	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1 Based on ANOVA

* = p ≤ 0.05

t = p ≤ 0.10

- = p > 0.10

* = p ≤ 0.021 (critical p-value for Dunnett's Test)

2 End of weeks 1-8

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Haloperidol 4, 8, and 16 mg/day vs Placebo) in Study M93-113																
Key Outcome Variables	Haloperidol 4 vs Pbo				Haloperidol 8 vs Pbo				Haloperidol 16 vs Pbo							
	Week ²				Week ²				Week ²							
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
PANSS Total																
LOCF	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*	*
OC	*	*	*	*	t	t	t	-	*	*	*	*	t	t	t	-
BPRS Pos																
LOCF	*	*	t	-	-	-	-	-	*	*	*	*	*	*	*	*
OC	*	*	*	t	-	-	-	-	*	*	*	*	*	*	*	*
PANSS Neg																
LOCF	t	t	-	-	-	-	-	-	t	-	-	t	*	-	t	t
OC	t	-	-	-	-	-	-	-	t	-	-	-	-	-	-	-
CGI Severity																
LOCF	*	*	*	t	*	-	*	t	*	*	*	*	*	*	*	*
OC	*	*	*	t	-	t	-	-	*	*	*	*	*	*	*	*

1 Based on ANOVA
 * = p ≤ 0.05
 t = p ≤ 0.10
 - = p > 0.10
 * = p ≤ 0.021 (critical p-value for Dunnett's Test)

2 End of weeks 1-8

Size of Treatment Effect in Study M93-113

PANSS Total Score

Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	62.0	+ 0.7	
Sertindole 12	63.2	- 9.9	10.6
Sertindole 20	70.5	- 17.6	18.3
Sertindole 24	65.2	- 10.7	11.4
Haloperidol 4	69.0	- 11.8	12.5
Haloperidol 8	64.8	- 16.5	17.2
Haloperidol 16	67.1	- 11.9	12.6

BPRS Positive Score

Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	12.1	- 1.0	
Sertindole 12	12.3	- 3.0	2.0
Sertindole 20	12.4	- 3.4	2.4
Sertindole 24	12.0	- 3.0	2.0
Haloperidol 4	12.7	- 2.6	1.6
Haloperidol 8	12.4	- 4.3	3.3
Haloperidol 16	12.7	- 3.7	2.7

PANSS Negative Score

Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	17.0	- 0.7	
Sertindole 12	17.2	- 2.8	2.1
Sertindole 20	18.8	- 4.4	3.7
Sertindole 24	17.8	- 2.3	1.6
Haloperidol 4	17.7	- 2.7	2.0
Haloperidol 8	17.0	- 3.3	2.6
Haloperidol 16	17.3	- 2.4	1.7

CGI Severity Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	4.7	0.0	
Sertindole 12	4.7	- 0.4	0.4
Sertindole 20	4.9	- 0.7	0.7
Sertindole 24	4.6	- 0.5	0.5
Haloperidol 4	4.9	- 0.4	0.4
Haloperidol 8	4.7	- 0.7	0.7
Haloperidol 16	4.9	- 0.6	0.6

- 1 Mean score at baseline
- 2 Mean change from baseline to week 8 (LOCF)
- 3 Difference in mean change from baseline to week 8 (LOCF) between active drug groups and placebo

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole 20 & 24, and Haloperidol 16 mg/day, vs Placebo) in Study M93-098																								
Key Outcome Variables	Sertindole 20 vs Pbo				Sertindole 24 vs Pbo				Haloperidol 16 vs Pbo															
	Week ²				Week ²				Week ²															
	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8	1	2	3	4	5	6	7	8
PANSS Total																								
LOCF	-	-	t	*	*	*	*	*	-	-	t	*	*	*	*	*	*	*	*	*	*	*	*	*
OC	-	-	-	-	-	-	-	t	-	-	t	-	-	-	-	t	*	*	*	t	-	t	*	*
BPRS Pos																								
LOCF	*	*	*	*	*	*	*	*	-	-	*	t	*	*	*	*	*	*	*	*	*	*	*	*
OC	*	*	*	*	-	t	*	*	-	t	-	-	-	-	-	-	*	*	*	*	*	*	*	*
PANSS Neg																								
LOCF	-	-	-	*	t	t	-	t	-	-	-	*	*	*	*	*	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
CGI Severity																								
LOCF	-	*	-	*	*	*	*	*	-	t	*	*	*	*	*	*	-	*	*	*	*	*	*	*
OC	-	*	-	*	t	t	t	*	-	t	t	-	*	-	*	*	-	*	*	*	*	*	*	*

1 Based on ANOVA

* = p ≤ 0.05

t = p ≤ 0.10

- = p > 0.10

2 End of weeks 1-8

Size of Treatment Effect in Study M93-098			
PANSS Total Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	64.4	- 1.2	
Sert. 20	60.6	- 7.5	6.3
Sert. 24	62.8	- 10.3	9.1
Hlprdl. 16	65.1	- 13.3	12.1
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	12.2	- 1.2	
Sert. 20	12.0	- 3.0	1.8
Sert. 24	12.1	- 2.8	1.6
Hlprdl. 16	13.1	- 4.3	3.1
PANSS Negative Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	17.4	- 0.5	
Sert. 20	16.0	- 1.3	0.8
Sert. 24	17.5	- 2.5	2.0
Hlprdl. 16	16.4	- 1.3	0.8
CGI Severity Score			
Group	Baseline ¹	BL - Wk 8 ²	Difference ³
Placebo	4.7	- 0.1	
Sert. 20	4.7	- 0.4	0.3
Sert. 24	4.8	- 0.4	0.3
Hlprdl. 16	4.9	- 0.7	0.6

- 1 Mean score at baseline
- 2 Mean change from baseline to week 8 (LOCF)
- 3 Difference in mean change from baseline to week 8 (LOCF) between active drug groups and placebo

Summary of Significance Levels¹ (2-sided) for Pairwise Comparisons
(Sertindole 8, 12, and 20 vs Placebo) in Study M92-762

Key Outcome Variables	Sertindole 8 vs Pbo				Sertindole 12 vs Pbo				Sertindole 20 vs Pbo									
	6	12	19	26	33	40	6	12	19	26	33	40	6	12	19	26	33	40
PANSS Total	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
BPRS Pos	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
PANSS Neg	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
LOCF	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
OC	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-

1 Based on ANOVA

* = $p \leq 0.05$

t = $p \leq 0.10$

- = $p > 0.10$

2 End of days 6-40

Size of Treatment Effect in Study M92-762			
PANSS Total Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	56.6	- 5.0	
Sert. 8	60.1	- 3.5	1.5
Sert. 12	60.3	- 8.6	3.6
Sert. 20	60.0	- 12.6	7.6
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	12.0	- 1.8	
Sert. 8	12.5	- 1.8	0
Sert. 12	12.7	- 2.3	0.5
Sert. 20	11.9	- 3.1	1.3
PANSS Negative Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	15.0	- 1.3	
Sert. 8	15.1	- 0.2	- 1.1
Sert. 12	15.3	- 2.1	+ 0.8
Sert. 20	17.6	- 23.0	+ 22.0

- 1 Mean score at baseline
- 2 Mean change from baseline to week 7 (LOCF)
- 3 Difference in mean change from baseline to week 7 (LOCF) between active drug groups and placebo

Summary of Significance Levels ¹ (2-sided) for Pairwise Comparisons (Sertindole vs Placebo) in Study M91-645							
Key Outcome Variables	Sertindole vs Placebo						
	Week ²						
	1	2	3	4	5	6	7
BPRS Total							
LOCF	*	*	-	*	*	*	*
OC	*	*	-	*	*	-	-
BPRS Pos							
LOCF	-	t	t	*	*	*	*
OC	-	t	-	t	*	t	-

- 1 Based on ANOVA
 * = $p \leq 0.05$
 t = $p \leq 0.10$
 - = $p > 0.10$

- 2 End of weeks 1-7

Size of Treatment Effect in Study M91-645			
BPRS Total Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	38.1	+ 2.5	
Sertindole	31.5	- 7.2	9.7
BPRS Positive Score			
Group	Baseline ¹	BL - Wk 7 ²	Difference ³
Placebo	13.8	+ 0.6	
Sertindole	11.9	- 3.9	4.5

- 1 Mean score at baseline
 2 Mean change from baseline to week 7 (LOCF)
 3 Difference in mean change from baseline to week 7 (LOCF) between sertindole and placebo

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 23, 1997

FROM: Thomas P. Laughren, M.D. *TPL*
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Non-Approval Action for
Serlect (sertindole) for the treatment of psychotic
disorders

TO: File NDA 20-644
[**Note:** This overview should be filed with the 12-13-96
submission.]

1.0 BACKGROUND

In our 10-2-96 approvable letter, we requested a safety update, a foreign regulatory update, a world literature update, a commitment to conduct a relapse prevention study, a commitment to conduct a holter monitor study for detection of Torsade de Pointes, and a commitment to conduct an animal toxicology study of sertindole's effects on bone composition. Importantly, because of the concern about QT prolongation and the risk of sudden death, we asked Abbott to propose a system for registration, distribution, and follow up that would permit the identification of deaths and an estimate of the risk of sudden death with this drug. In the biopharmaceutics area, we identified our preferred dissolution methodology and specifications. In the CMC area, we made several minor requests and noted several deficiencies in the EA. We also attached our proposal for labeling, including a requirement for a black box warning regarding QT prolongation and a second-line status. Abbott responded formally to the approvable letter with the 12-13-96 submission.

Dr. Earl Hearst reviewed the clinical sections of the 12-13-96 response to the approvable letter, including the safety update, the literature update, and the regulatory status update.

We faxed a response to the sponsor's labeling proposal (included in the 12-13-96 response to the approvable letter), and the sponsor responded with a fax delivered on 5-19-97. Their revised labeling continued, in my view, to be unacceptable, and I have attached to this memo what I consider to be an acceptable version of labeling for this product, assuming the sponsor were, at some future time, willing to accept the need for a registry for this product. This draft labeling includes bracketed comments explaining the continued basis for disagreement, and these issues are summarized more briefly under section 9.0 of this memo.

2.0 SAFETY UPDATE

The safety update submitted with the 12-13-96 resubmission was reviewed by Dr. Hearst (review dated 5-6-97). This update was based on an updated integrated database with a cutoff date of 5-1-96. The cutoff date for inclusion of serious events was also 5-1-96, but was 8-15-96 for deaths. The total for human subjects exposed to sertindole in the development program had increased to 2851 (up from 2355), including 657 in phase 1 studies (up from 435) and 2194 in phase 2-3 studies (up from 1446). The revised person-time estimate for sertindole exposure in phase 2-3 trials was 1024 patient-years, compared to 477 in the original submission. Given the size of the increment in exposed patients, Abbott decided to redo some of the incidence tables, resulting in revised estimates for some of the values in labeling.

Dr. Hearst has reviewed the safety update in some detail, and I refer to his review. My focus here will be on a few issues I consider particularly important and also any data resulting in a proposed change to labeling:

2.1 Deaths, Other Serious Adverse Events, and Adverse Dropouts

Deaths

In the original NDA there were 18 deaths reported in association with sertindole use, including 8 in the integrated database that could be used in mortality rate calculations. The sponsor celebrated the fact that the overall mortality for sertindole was comparable to that seen for risperidone using similar methods. I considered that a flawed comparison because of the much higher proportion of unexplained deaths for sertindole than for risperidone.

With the safety update, there are now a total of 30 deaths reported in association with sertindole use, including 23 in the integrated database. Six of these occurred more than 30 days following discontinuation of sertindole and cannot be reasonably considered drug related. Of the 24 deaths, only 18 had full exposure data and could be used in mortality rate calculations. The sponsor has again celebrated the fact that the overall mortality for sertindole was comparable to that seen for risperidone using similar methods. Nevertheless, I still consider this a flawed comparison for the reasons noted above.

As of our 4-28-97 meeting with the sponsor, there were 10 additional deaths, either as spontaneous reports from other countries where sertindole has now been marketed or from clinical trials. These included 3 sudden and unexplained deaths. The sponsor estimated 928 PEY of use for these 3 SUDs, yielding a SUDs rate of 3.2/1000 PEY for the most recent experience (mostly spontaneous reporting), compared to a rate of 2.9 for the premarketing database. They celebrated this finding as evidence of a relatively low and expected rate. However, I view this as a signal, given the likelihood of underreporting of deaths from postmarketing experience.

Other Serious Adverse Events

While there were additional serious adverse events reported since the original submission, i.e., a total of 128 new patients/subjects with a serious adverse event, there was no change in the pattern of reported events or the emergence of new events to suggest that any previously unrecognized serious adverse events were causally linked to sertindole use.

Adverse Events Leading to Dropout

There were also 130 new sertindole patients/subjects who dropped out due to adverse events. However, the pattern of common and drug-related adverse events leading to dropout for sertindole-exposed patients was very similar for the expanded phase 2-3 database compared to the original database, and included: abnormal ejaculation, QT prolongation, suicide attempt, abnormal LFTs, and somnolence.

2.1 Other Adverse Events of Special Interest and/or for Which Labeling Changes Have Been Proposed

QT Prolongation

Very little new information was provided in the safety update pertinent to QT prolongation. Data from study M95-342 [4 doses of sertindole (8, 16, 20, and 24 mg) vs haloperidol 20 mg] were presented, essentially supporting the dose dependent increase in QT already well characterized from earlier studies. Also summarized were data from study M95-383 in 16 elderly dementia patients, revealing the expected increase in QT. 2 of those 16 patients (13%) had at least one QTc > 500 msec. In addition, Holter monitor data were described for 4 patients who had Holter monitoring for specific medical events. We had known about only 1 of these patients previously. None of these Holter monitors apparently revealed torsade episodes.

Syncope/Postural Hypotension

Although there were more cases of syncope with the expanded database, the overall rate of syncope was still 1% (21/2194). As was the case for the originally submitted data, no patients discontinued for syncope and none were observed to have QT prolongation in association with the syncope. However, as noted earlier, few of these patients were properly evaluated with Holter monitoring to observe for possible torsade.

Seizures

There were additional seizures in the expanded database, resulting in a revised estimate of seizure incidence for labeling: 1% (22/2194).

Weight Gain

The expanded database resulted in revised estimates of mean increase from baseline in weight (5 kg), proportion of patients having a weight gain of $\geq 15\%$ of baseline weight [21% (240/1159)], and numbers of patients discontinuing for weight gain (7).

Overdose

There were additional overdose cases in the expanded premarketing database, yielding a total of 33 cases for the revised integrated database. There were also 4 cases of sertindole overdose from an ongoing study, one of which resulted in a death and was judged to be probably sertindole-related. We also now have two overdose cases (one from Finland and one from France), both recovered, that were associated with documented torsade de pointe.

3.0 WORLD LITERATURE UPDATE

The sponsor's literature update covered the period from the cutoff date for the original NDA submission (8-18-95) to 11-1-96, and included 77 clinical and 20 preclinical references. Only a bibliography was provided. Christopher Silber, M.D. from Abbott provided a warrant that he had "reviewed the literature and nothing was found which would adversely affect conclusions about the safety of Serlect." Dr. Hearst reviewed the titles for all the clinical and preclinical references, and also the search methodology used. To the extent one can based on a review of titles, he agreed with the conclusion of Dr. Silber.

4.0 FOREIGN REGULATORY UPDATE

The following update is based on information provided by the sponsor at our 4-28-97 meeting with them:

Sertindole is approved in the following countries: United Kingdom, Portugal, Belgium, Denmark, Finland, Luxembourg, Netherlands, Germany, Greece, Ireland, Spain, Austria, Italy, and Czech Republic.

Abbott withdrew applications from Sweden and France when those countries agreed to approval of sertindole only as a second line antipsychotic agent.

Applications are pending in Norway, Hungary, Slovakia, South Africa, Turkey, New Zealand, Australia, and Poland.

Sertindole has been rejected in 2 countries: Switzerland and Canada.

-Apparently it was rejected in Switzerland due to a concern that it was less efficacious than haloperidol.

-It was rejected in Canada on the basis of a judgement that its benefits did not outway its risks.

5.0 REQUEST FOR RELAPSE PREVENTION TRIAL

Abbott has apparently completed a relapse prevention trial and will submit the results of this trial early in 1997.

6.0 REQUEST FOR HOLTER MONITOR STUDY

Abbott argued that there would be little value in conducting Holter monitoring in a cohort of sertindole-exposed patients.

Comment: After further discussion, we mutually agreed that it would not be feasible to conduct a study of the size needed to provide us sufficient reassurance to justify weakening of the labeling language pertinent to QT prolongation, risk of torsade, etc.

7.0 REQUEST FOR SPECIAL MEASURES TO ENSURE DETECTION OF SERIOUS CARDIAC EVENTS AND ESTIMATION OF RISK OF SUDDEN CARDIAC DEATH

As noted in our 10-2-96 approvable letter, two findings, i.e., (1) a dose dependent QT prolongation with sertindole and (2) what we considered to be a disproportionate number of sudden and unexpected deaths (SUDs) occurring in the sertindole premarketing experience, led us to be concerned about the possibility of excessive mortality, in particular SUDs, in association with sertindole use compared to other antipsychotic drug products. Because of this concern, we asked Abbott to propose a system for registration, distribution, and follow up that would permit the efficient identification of deaths and an estimate of the risk of overall mortality and SUDs with this drug.

In their 12-13-96 response and in our joint meeting on 4-28-97, they have argued against a registry, suggesting that it would not be able to test the hypothesis of interest, i.e., how sertindole compares to other antipsychotics.

Alternatively, they proposed the following in their 12-13-96 response:

-Monthly reporting of all spontaneously reported sertindole deaths, with followup of all cardiovascular and sudden deaths.

-Large, randomized, prospective study comparing the rate of sudden death for sertindole and another antipsychotic agent. They argued that, for this trial to be successful, sertindole would need to have "unencumbered" labeling and no "registration-related restrictions."

Subsequent Proposals:

4-28-97 Meeting with Abbott:

At our 4-28-97 meeting with the sponsor, they indicated that they no longer intended to conduct a large, prospective, randomized trial, due to the expense of such a study. Rather, they indicated

they are conducting two postmarketing studies, one involving the UK Mediplus database and a second Lundbeck study in the European Union. The Mediplus database would identify cohorts of patients prescribed sertindole and comparator antipsychotics and would permit the comparison of rates of overall mortality and sudden unexpected death (SUD). One problem is that Mediplus is a relatively small database. The proposed Lundbeck study would involve about 13 countries and would compare cohorts of patients prescribed sertindole with those given usual care for outcomes of overall mortality and SUD (roughly 4000 per group). They again argued against doing a registry in the US. We asked if they would consider doing a cohort mortality component to the Lundbeck study, i.e., comparing sertindole patients while on drug and after discontinuation, for those who for whatever reason were discontinued. This same design was used for exploring our concern about an apparent increased mortality with Clozaril use, and in fact, it turned out that the discontinued group had a comparable overall mortality and thus provided reassurance regarding our concern. They indicated that they would ask but suggested it was unlikely since Lundbeck was an independent organization.

5-16-97 Package:

Abbott came in with a more detailed plan for postmarketing studies in a 5-16-97 package, including 3 components:

(1) Automated Database Studies:

The first component of their proposed program consists of nonrandomized studies involving two UK databases (Mediplus and GPRD) and COMPASS (Medicaid from the US). They have estimated that these databases would be able to accrue approximately 2000 person years (PY) for sertindole, i.e., 378 PY from the combined UK databases and 1648 from COMPASS, within 2 years.

(2) Lundbeck Study

The second component is the nonrandomized Lundbeck study, for which they estimate approximately 4000 PY for sertindole, however, the time frame for this accrual is not identified. They have chosen not to adopt our suggestion, made at our 4-28-97 meeting, for adding a cohort mortality component to this study.

(3) Postmarketing Surveillance

The third component of their program is routine reporting of spontaneous reports from the countries in which sertindole is marketed or will be marketed in the near future. They estimate

exposure in the UK and Europe for the periods July, 97' through July, 98' and July 98' through July, 99' at approximately 11000 PY and 22000 PY, respectively. For the US, they estimate exposure for the first and second years of marketing at roughly 25000 PY and 38000 PY, respectively.

Comment:

In my view, there are significant concerns about the "automated database studies" and the Lundbeck study with regard to whether or not they are capable of addressing the need for a rapid detection of the possibility of excess risk of overall mortality and SUDs in particular in association with sertindole use:

-In the first place there is a problem with inadequate sample size and the estimates of patient accrual. Greg Burkhart has commented on this problem in more detail (see memo dated 5-22-97). The sample would need to be large enough to rule out a relative risk for all cause mortality of 1.5 for sertindole compared to another treatment. To have this assurance, the confidence limits would need to be narrow, with the upper bound not exceeding 1.5. By our calculations, this would necessitate samples of roughly 4000 PY per group for all cause mortality, and about 27,000 per group for SUDs. Assuming it would be sufficient to examine all cause mortality, their proposed combined "automated database program" would fall far short. They have estimated 2000 PY of sertindole exposure in the first 2 years of the "automated database studies" (UK + COMPASS), with most of the data coming from COMPASS. Their estimates for what exposure would accrue from Medicaid seem extraordinarily generous and unrealistic to me. The Lundbeck study has still not been presented in sufficient detail to assess whether or not the sample accrual estimate is realistic, nor has the time frame for accrual been identified.

-There is also a question of whether or not the outcomes of interest can be readily captured from these databases. For the Medicaid component, this may be very difficult and very time-consuming. The Lundbeck study has not been presented in sufficient detail to assess whether or not the outcomes even can be captured.

-A third problem is a basic design flaw. It is quite likely that, given the knowledge of sertindole's risk for QT prolongation, prescribing will be differential, with patients deemed to be at greater risk of catastrophic cardiovascular events being less likely to be prescribed sertindole. This could bias these proposed studies in favor of sertindole and would complicate their interpretation.

The routine reporting on spontaneous reports is of little value for the purpose of detecting an excess risk of mortality or SUDs for sertindole, since mortality is common in the treated population and SUDs are not unexpected.

Our approvable action for this NDA was conditioned upon Abbott's agreeing to establishing what would essentially be a registry for sertindole to track all use in the US, and my view on this matter has not changed. For the reasons noted above, I am not confident that the postmarketing program Abbott has proposed will be capable of efficiently detecting an excess of overall mortality or SUDs for sertindole. If a registry were in place in the US, we would at least be able to track the incidence of SUDs in US patients taking this drug. Over time it would also be possible to conduct a cohort mortality study to assess whether or not there is in fact excess mortality associated with sertindole, compared to a cohort of former users. If, as Abbott estimates, there would be 25,000 PY of US exposure after the first year of marketing and an additional 38,000 PY after the second year, there would, if these estimates are accurate, be ample US data to conduct the cohort mortality study.

In the absence of a US registry, I cannot recommend the approval of this product.

8.0 REQUEST FOR ANIMAL TOXICOLOGY STUDY OF SERTINDOLE'S EFFECTS ON BONE COMPOSITION

Abbott argued against the need to conduct the requested study on the basis of (1) the fact that the finding (hindlimb fractures) occurred only in mice, (2) a wide margin of safety based on exposure, and (3) the sponsor's view that mice are especially sensitive to sertindole.

Comment:

The pharmacology/toxicology group has not found these arguments persuasive, and I agree (see review by Dr. Freed dated 5-7-97). Our continuing requirement for such a study needs to be noted in our action letter.

9.0 LABELING

On 5-2-97, we faxed a counter-proposal [LABSRTPS.AP1] to Abbott's 12-13-96 version of labeling, and they responded by fax with another counter-proposal on 5-19-97. Although I am now

recommending a non-approval action, I have, nevertheless, reviewed this most recent proposal, and I have prepared an alternative version of labeling [LABSRTPS.AP2] which is an attachment to this memo. I will comment here on the clinical issues for which there was continuing disagreement:

-Under Clinical Pharmacology, Pharmacodynamics, I continue to believe it is not useful to speculate about the possible basis for apparent differences in the EPS profile for sertindole, and thus, I have not included the proposed changes to the second paragraph. I also believe it would not be useful to speculate about the possibility of a mitigating effect of the mild tachycardia associated with sertindole on its arrhythmogenic potential, and thus, I have not added the proposed explanatory language for the third paragraph.

-Under Indications and Usage, the sponsor has proposed an alternative first paragraph that tends to soften the restrictive message conveyed in our proposed labeling. I disagree with the alternative version, and I prefer the language I proposed in the 5-2-97 draft. Thus I have made no changes to the first paragraph.

-Under Contraindications, the sponsor has proposed some minor modifications to this section, in particular, rewording of the language for 3A inhibitors to suggest caution but not absolute contraindication with the weaker inhibitors. I agree with this proposed change and have included this statement with slight modification to at least suggest caution with the weaker 3A inhibitors.

-Under Warnings, QT Prolongation,..., the sponsor has again proposed an alternative Warnings statement.

-The sponsor has divided our first paragraph into 2 paragraphs. In their first paragraph, they again minimize the ECG changes by presenting the data in terms of % change from baseline for the group overall rather than mean change from baseline for the most clinically relevant dose, i.e., 20 mg. They also fail to note the proportion of patients at the 20 mg dose meeting a criterion of QTc > 500msec while on treatment, as our labeling does. They have also again proposed other language that tends to soften the impact of the Warning statement.

-I have maintained our originally proposed language for the first paragraph, except that I have added information pertaining to the 2 cases of torsade with overdose that the sponsor has now acknowledged in its proposed language for this section.

-They have again added language (in what is their 3rd paragraph) to suggest that the mild tachycardia and alpha-1 antagonism associated with sertindole may mitigate the arrhythmogenic potential of this

drug. We had rejected such speculation previously and so I have not added this language. However, we may need to revisit this again with our consultants from HFD-110.

-The sponsor has adopted our paragraph addressing baseline and followup evaluations, except for the advice to avoid treatment in patients with baseline QTc's > 450 msec. I have maintained our originally proposed language.

-The sponsor has adopted our last paragraph addressing further evaluation of patients who experience dizziness, etc, except for a mention of Holter monitoring. I have maintained our originally proposed language.

-Under Precautions, General, Orthostatic Hypotension, the sponsor has proposed some changes to this statement to emphasize that torsade is not the only event that may be the basis for the symptoms noted. I generally agree, however, I still feel that torsade should be specifically mentioned, and I added a modified version of what the sponsor has proposed.

-Under Precautions, Information for Patients, the sponsor has proposed a modified version of the statement regarding QT prolongation, to minimize any linkage of sertindole use with sudden death. I agree that the actual risk has not yet been definitively established, and so it is reasonable to make the linkage more indirect. I have proposed a modified version of what they had suggested.

-Under Precautions, Drug Interactions, the sponsor has proposed a modification of the recommendation for weaker 3A inhibitors, and I agree. My only change has been to recommend caution with these weaker inhibitors; the sponsor's language makes no recommendation.

-Under Adverse Reactions, the sponsor has again proposed presenting a table of EPS results from study 113 to make the point that sertindole is indistinguishable from placebo with regard to emergent EPS and anti-EPS medication use at all three doses utilized, unlike haloperidol that was worse than placebo in this regard for all three of its dose groups. I don't dispute the validity of the findings, but I have consistently objected on grounds that it is not a fair comparison, since haloperidol is ordinarily used with prophylactic anti-EPS medication, and that option was not available in study 113. We have tried to consider an approach to analyzing these study results to tease out the EPS response in haloperidol patients during periods when they were receiving at least some anti-EPS treatment, but that appears to be essentially impossible given the design of this study. The sponsor is willing to concede on the fairness issue only to the extent of acknowledging in the study summary that haloperidol patients were

not optimally treated with anti-EPS medications. That statement, however, is lost in the detail of the sponsor's lengthy description of that study proposed for labeling.

The issue is particularly troubling since we knew very early on that Abbott was choosing to focus on this advantage as a major feature of its development program for this drug, and we advised them repeatedly that the comparison would need to be fair, i.e., that haloperidol patients would need to be optimally treated. They ignored the advice and they now want to celebrate a finding in labeling that is arguably misleading.

On the other hand, there is undoubtedly some advantage in having a drug for treating psychosis for which one does not need to use prophylactic anti-EPS medication. It is also worth noting that it is not the only antipsychotic drug in this category. In any case, I think the finding can be included in labeling, but in order to minimize the potential for the finding to be misleading, I have proposed a briefer statement that both summarizes the findings but also provides more balance in revealing the limitations. I don't see any need for including a lengthy table with multiple data points simply to make the point that sertindole is no different than placebo regarding emergent EPS.

-Under Dosage and Administration, the sponsor has proposed several changes:

-They want to minimize the restrictions on the indication by softening the language. I continue to feel that Serlect must be restricted to refractory or intolerant patients. Thus, I have not made their proposed changes.

-Under "Usual Dose," they have questioned the advice given for titrating nonresponding patients at 12 mg to higher doses. My rationale for proposing that clinicians wait 3-4 weeks was to give the drug a chance to reach steady state and to give it a chance to work, since drugs in this class often take several weeks or more to have an antipsychotic effect, perhaps even after reaching steady state. Given the safety concern for this drug, in particular at the 20 mg dose level, I think the advice is reasonable. Thus, I have not made their proposed changes.

-Under "Switching . . .," they have again proposed detailed advice regarding the switching of patients from other antipsychotics to sertindole, in the absence of any systematically collected data. This assumes we know what is best, when we have no information at all, and I prefer to use our originally proposed language.

-For the Patient Package Insert, the sponsor proposed some additional language in one subsection, i.e., "What important information should I know about Serlect." This language provides

additional context for this statement, i.e., that SUDs have been reported in schizophrenic patients whether or not they are receiving treatment. I do not object to this addition, however, I have edited the new language slightly.

10.0 BIOPHARMACEUTICS

The sponsor accepted our proposed dissolution method and specifications.

11.0 CHEMISTRY, MANUFACTURING, AND CONTROLS

Abbott responded to all CMC issues raised in the 10-2-96 approvable letter, and the Chemistry group found this response acceptable.

12.0 ENVIRONMENTAL ASSESSMENT

Abbott responded to all EA issues raised in the 10-2-96 approvable letter, and the EA group found this response acceptable.

13.0 DSI INSPECTIONS

DSI has inspected several sites selected from among the key studies for this NDA, and has issued an overall recommendation of "acceptable" regarding their inspections of these sites.

14.0 CONCLUSIONS AND RECOMMENDATIONS

Dr. Hearst has recommended that this NDA not be approved until the sponsor has demonstrated in an adequate and well controlled investigation that sertindole is superior to a standard treatment in schizophrenic patients who have failed first line therapy. Since such data have not been provided, I interpret his view as a recommendation for non-approval at this time.

While I understand this position, I do not agree with his requirement for actual evidence of superiority in advance of approval, for the reasons noted in my 8-22-96 memo. In the case of Clozaril, we did require such evidence prior to approval, however, the risk was real rather than theoretical for Clozaril. For sertindole, while there is a very strong suspicion of risk, it is not possible to quantitate the actual risk at present.

On the other hand, I believe that the suspicion of risk is strong enough to justify asking for a registry as a condition for marketing this drug in the US. As noted earlier, I am not confident that the proposed epidemiologic studies will result in a sufficiently rapid and interpretable estimate of any excess mortality that may be associated with sertindole use. Indeed, if sertindole were marketed under these circumstances, a many fold excess risk of SUDs for sertindole could go undetected for years, and might never be detected if Abbott failed to follow through on even the marginal program they have proposed. Since the sponsor has not agreed to a registry, I cannot recommend that we issue an approval letter at this time, and I have prepared a non-approval letter to accompany this package. However, I recognize that there may not be agreement with this recommendation, and consequently, I have also attached a labeling document with this memo that proposes labeling I would find acceptable were the sponsor to agree to a registry. As noted earlier, we were unable to reach agreement with the sponsor on labeling, and the attached labeling document identifies and provides explanations for these areas where there is disagreement.

cc:

Orig NDA 20-644

HFD-120/DivFile

HFD-120/TLaughren/PLeber/EHearst/AMosholder/SHardeman

HFD-101/RTemple

DOC: MEMSRTPS.NA1

Statistical Review and Evaluation

APR 10 1996

NDA#: 20-644

Applicant: Abbott Laboratories

Name of Drug: Sertindole

Documents Reviewed: Vols 1.528-1.535

Medical Officer: Earl Hearst, M.D., HFD-120

RETURN
Earl Hearst
APR 12 1996

Background

The sponsor has submitted five (5) randomized, placebo-controlled, double-blind trials in support of sertindole (S) for the treatment of schizophrenia. One Phase II trial (M92-817) using 2 doses of S (4 and 12 mg) was stopped for efficacy failure as a result of an interim analysis. Another Phase II trial (M92-762) using 3 doses of S (8, 12, and 20 mg) did not produce statistically significant results but strongly suggested efficacy of 20 mg. Trial M91-645 was a very small (total 38 patients) dose titration study. **This review concentrates only on the two placebo controlled Phase III trials (M93-098 and M93-113) among which, 5 of the 6 S arms had doses of at least 20 mg/day.**

Trial M93-098

This trial randomized a total of 462 patients: 116 patients to placebo, 117 to Sertindole 20mg (S20), 114 to Sertindole 24mg (S24), and 115 to Haldol 16mg (H16) among 30 investigators in the US. The study was originally designed with 25 centers randomizing 400 patients (4/cell). For inclusion, patients had to 1) have scores on any 2 of the 4 'positive BPRS items' to be at least 8, and 2) total BPRS from Screening to the end of the 2 week placebo lead-in period could not have decreased by more than 20%. Patients were then titrated (double-blind) to their nominal doses for 2 weeks and subsequently treated for a maintenance period of 6 weeks.

A subsequent amendment increased enrollment to 500 and calculated the power to detect an effect size of .37 and .42 to be 83% for the S20 arm and 91% for the S24 arm, respectively (10/28/94). In addition, **a previous version of the protocol apparently contained Hochberg's modified Bonferroni procedure because an amendment deletes that item in the list of references 12/22/93.** The 12/22/93 amendment also specifies that the primary group comparisons, except the CGI, will be made with the "weighted" comparison from the two-way ANOVA with factors for treatment group, center, and their interaction. Thus, the overall treatment difference will be a weighted linear combination of the center-specific treatment differences with weights $W_i = (N_{i1} * N_{i2}) / (N_{i1} + N_{i2})$ for treatments 1 and 2 in center i. The Van Elteren analysis using a stratified Wilcoxon approach became a secondary analysis.

The CGI was to be analyzed using Cochran-Mantel-Haenszel statistic with centers as strata.

Regardless of the primary endpoint stated in the protocol, the Division has focused on four: the PANSS, the BPRS 'positive' items, the PANSS 'negative' items, and the CGI (1=very much improved to 7=very much worse).

In the protocol, "evaluable" patients are defined as having at least one evaluable rating for efficacy on or after day 16. Other criteria were to be determined before breaking the blind. The report states only that "the 'evaluable' dataset excluded patients who were deemed non evaluable at a classification meeting held prior to breaking the study blind. Based on the section in the report entitled Protocol Deviations, nonevaluable patients appear to be protocol violators.

Results

Table 1 indicates that cell sizes ranged from 0 to 12. The report states that "sites with no patients in one or both of the two treatment groups being compared were omitted from the analysis".

Table 2 displays the demographic and baseline characteristics of the patients. There were no clinically relevant imbalances among treatment groups.

Table 3 displays the frequencies and types of premature terminations. The dropout rates in the S arms for lack of efficacy were less but not statistically significantly lower than that for placebo.

Figure 1 displays the Kaplan Meier plot for time to dropout for any reason, while Figure 2 displays that for dropout due to lack of efficacy.

Figure 3 displays the point estimates and confidence intervals of treatment differences on the Total PANSS for each center. The sponsor states that there was significant treatment by center interaction in the comparisons of both S20 and S24 to placebo. However, this reviewer has determined that they make no impact on the ultimate interpretation of the study.

Figure 4 displays the empirical distribution function for the total PANSS for the 4 treatment arms

Table 4 displays the results of the Intent to Treat (all randomized patients who had at least one PANSS evaluation performed after the start of the double-blind treatment but no later than one day after the last dose of study drug) analysis using LOCF. **S24 was statistically better than placebo for Total PANSS and PANSS negative items. S20 was significantly better for the Total PANSS, and both S groups were significantly better than placebo on the CGI. Note that a total of 24 randomized patients are not included in the ITT analyses due to not having had any follow up evaluation after baseline.**

Table 5 displays means and p-values over time for the four primary endpoints.

Table 6 displays the results for the **BPRS positive subscale**. Both Sertindole groups were significantly better than placebo.

Table 7 displays the results for the **CGI** indicating both Sertindole arms were statistically different from placebo. Table 7 displays the CGI data in terms of discrete amounts of improvement from baseline.

Table 8 displays the percentage of patients with various levels of improvement from baseline.

Examination of actual p-values for the total PANSS indicates that statistical significances in both groups reached p-values at least as low as .025, indicating that any symmetric correction for multiple comparisons would also yield statistically significant results. In addition, results from the Van Elteren tests supported those using ANOVA.

The Issue of Dropouts

Since only approximately 50 patients in each group completed the entire 8 weeks, it is unreasonable to expect statistical significance among completers. Instead it is instructive to examine the effect of dropouts on the LOCF analyses of the 4 endpoints. **Figures 5-8** display bar graphs indicating the contribution of each dropout cohort to the final LOCF analysis. It is apparent that early dropouts had influence on the final results.

Discussion

The primary endpoint, viz the weighted average of the center-specific treatment differences with **treatment by center interaction in the model**, is interesting but possibly mis-conceived: these weights are useful when there is an assumption that the treatment differences are the **same** over all centers as in the case of the ANOVA model **without interaction**. Generally, using the normal distribution for maximum likelihood estimation, they yield the most efficient (lowest variance) estimate of a common mean over strata when **the standard errors for stratum-specific estimates are not the same for each stratum**. Note that the expected value of the treatment difference is not a function of the weights, since the stratum-specific treatment differences are assumed to have **the same expected value** for each center. But when the interaction term is **left in the model**, there is no assumption about a common expected value for treatment differences. In this case, the weights used by the sponsor have no useful purpose in terms of efficiency and the estimate of the treatment difference over centers becomes a function of the cell sizes that happened to occur in the trial. In fact, the most efficient estimate for the treatment difference in this case (actual interaction) is the sponsor's **unweighted** analysis which uses the arithmetic average of the center-specific treatment differences. Even if one proposes the following rationale (unstated in the NDA) for the sponsor's analysis: "We assume a common treatment difference but we want to spend an extra degree of freedom in the hopes of decreasing the mean square

error", this would still not be an efficient analysis since it is not based on a least squares solution. It so happens that, in this trial, treatment by center interaction **was** significant and both analyses yield similar results with the **unweighted** approach producing slightly lower p-values.

Trial M93-113

This trial randomized a total of 497 patients: 73 patients to placebo, 76 to Sertindole 12mg (S12), 68 to Sertindole 20mg (S20), 72 to Sertindole 24 mg (S24), 71 to Haldol 4mg (H4), 67 to Haldol 8mg (H8), and 70 to Haldol 16mg (H16) among 41 investigators in the US and 2 in Canada. Enrollment lasted 13 months, 6 months more than the protocol estimated and recruited almost 80 more patients than planned. For inclusion, patients had to 1) have scores on any 2 of the 4 'positive BPRS items' to be at least 8, and 2) total BPRS from Screening to the end of the 2 week placebo lead-in period could not have decreased by more than 20%. Patients were then titrated (double-blind) to their nominal doses for 2 weeks and subsequently treated for a maintenance period of 6 weeks.

The objective of the study was to compare Sertindole to Haldol with respect to **medication-induced acute movement disorders (MIAMDs)**, not efficacy of Sertindole in the treatment of schizophrenia. The power calculation was based upon 75 patients/group producing between 62% to 83% power to detect a difference in the percentage of patients who experience MIAMDs.

However, the **primary analysis for efficacy** in the protocol is simple linear regression of dose of sertindole (with placebo as the 'zero' dose group) on change from baseline to the final evaluation. Only patients with a baseline and at least one total PANSS evaluation after randomization were to be included. "Supportive" analyses included weighted and unweighted ANOVA's as in **trial M93-098**. The six pairwise comparisons with placebo are mentioned; however, there is no stated multiple comparison procedure.

Subsequently, due to the lack of dose response in the data, the simple linear regression was changed in the study report to regular ANOVA's.

Results

Table 1 indicates that cell sizes ranged from 0 to 7 with numerous missing cells. **With a planned 420 patients among 40 centers with 7 treatment groups in each center (less than 2 patients/cell), this trial was clearly not adequately designed to produce an easily interpreted analysis which accounts for center.** The report states that "sites with no patients in one or both of the two treatment groups being compared were omitted from the analysis".

Table 2 displays the demographic and baseline characteristics of the patients. There were no clinically relevant imbalances among treatment groups.

Table 3 displays the frequencies and types of premature terminations. The dropout rates in the S arms for lack of efficacy were less but not statistically significantly lower than that for placebo.

Figures 1 and 2 display the Kaplan-Meier plots for time to dropout for any reason and lack of efficacy, respectively.

Figure 3 displays the empirical distribution functions for the for the S groups and placebo for the total PANSS.

Table 4 displays the results of the Intent to Treat (all randomized patients who had at least one PANSS evaluation performed after the start of the double-blind treatment but no later than one day after the last dose of study drug) analysis using LOCF. Also each pairwise comparison was made using only those investigators who had at least one patient in placebo and at least one in the active group being compared to placebo. **S24 was statistically better than placebo for Total PANSS and PANSS negative items. S20 was significantly better for the Total PANSS. BPRS total and CGI were also significantly better for sertindole doses of at least 20 mg. The sponsor also reports a significant difference on the SANS for the S20 group. Note that a total of 20 randomized patients are not included in the ITT analyses due to not having had any follow up evaluation after baseline.**

Figures 4a-4d display the dropout cohort bar charts for S20, while **Figures 5a-5d** display those for S24. The same pattern is seen as in **Trial M93-098**.

Discussion

In view of the possible severe multiple comparison problem affecting Type I error, this reviewer thinks that it is reasonable to regard the primary comparisons to be each sertindole drug against placebo. Using the Dunnett's critical value of approximately .021 (two-sided), the p-values suggest that 20 mg or 24 mg sertindole to be different from placebo on the **Total PANSS**. Results on the **positive symptoms of the BPRS** produce nominal significance but only borderline results not reaching statistical significance when Dunnett's correction is taken into account. The results for **negative symptoms** are also equivocal with only S20 achieving nominal statistical significance at 8 weeks on both the **SANS** ($p=.023$) and **negative PANSS** ($p=.026$). Results on the CGI suggest efficacy of both S20 and S24.

Reviewer's Comment

Even though the sample size in **Trial M93-113** was not based upon efficacy considerations and had only approximately 60% of the patients as **Trial M93-098**, it was sufficient to demonstrate statistical significances with or without correction for multiple comparisons to placebo for at least the total PANSS and CGI. However, the performance of the 20 mg dose in the former trial stands out because the baseline averages for the **total PANSS** were the same in both trials, but

the LOCF change from baseline in 113 was 10 points greater than in 098 (-17 vs -7, respectively).

After pooling the 3 large studies and examining whether treatment benefit differed among age categories, race or gender, the sponsor concluded that "these analyses did not reveal any clinically relevant differences in treatment response". This reviewer concurs.


David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Sahlroot *JTS 4-2-96*

Dr. Chi *Chi*
4/10/96

cc:

NDA# 20-644

HFD-701/Dr. Anello

HFD-120/Dr. Leber

HFD-120/Dr. Laughren

HFD-120/Dr. Hearst

HFD-120/Mr. Purvis

HFD-120/Mr. Hardeman

HFD-344/Dr. Lisook

HFD-710/Dr. Chi

HFD-710/Dr. Sahlroot

HFD-710/Dr. Hoberman

HFD-710/chron

TRIAL M93-098

Table 1
List of Investigators and Number of Patients Randomized
by Treatment Group

Investigator	City/State	Placebo	Sertindole 20 mg	Sertindole 24 mg	Haldol 16 mg
Abuzzahab	Minneapolis, MN	4	3	4	4
Alam	Chicago, IL	5	4	4	4
Ananth	Torrance, CA	0	1	0	0
Borison	Augusta, GA	8	8	8	9
Braus	Madison, WI	2	2	3	3
Carroll	Columbus, OH	2	2	2	2
Crayton	Hines, IL	2	2	2	2
Ferguson	Salt Lake City, UT	3	4	3	3
Friedhoff	New York, NY	2	2	3	2
Garbutt	Raleigh, NC	4	3	4	4
Geracioti	Cincinnati, OH	4	3	4	4
Gewirtz/ Sharif	Queens, NY Queens, NY	3	4	3	2
Glick	Stanford, CA	4	3	5	2
Greenberg	Northport, NY	3	3	2	3
Hamner	Charleston, SC	3	4	2	4
Knesevich	Dallas, TX	2	2	2	2
Lindenmayer/ Bark	New York, NY/ New York, NY	6	6	7	6
Lohr	San Diego, CA	3	4	3	2
McEvoy	Butner, NC	3	3	3	3
Merideth	San Diego, CA	8	8	8	9
Oxenkrug	Boston, MA	3	3	3	3
Plotkin	Los Angeles, CA	2	1	2	2
Potkin	Orange, CA	12	11	11	12
Ramirez	Brecksville, OH	3	4	2	2
Schulz [#]	Cleveland, OH	1	1	0	1
Tamminga	Baltimore, MD	2	2	2	2
Targum	Upland, PA	8	9	8	9
Tran-Johnson	San Diego, CA	7	8	8	8
Tucker	Oklahoma City, OK	5	5	5	4
Westermeyer	Minneapolis, MN	2	2	1	2
Total		116	117	114	115

[#] Appears as "Schultz" in Appendices C and D
Cross Reference: Appendix C.2.3

Table 2
Summary of Demographic Characteristics: Intent-to-Treat Dataset

Demographic Characteristic	Placebo (N=106)	Sertindole 20 mg (N=111)	Sertindole 24 mg (N=108)	Haldol 16 mg (N=113)
Gender				
Female	24 (23%)	27 (24%)	24 (22%)	29 (26%)
Male	82 (77%)	84 (76%)	84 (78%)	84 (74%)
Race				
African-American	25 (24%)	23 (21%)	30 (28%)	30 (27%)
Caucasian	66 (62%)	76 (68%)	68 (63%)	67 (59%)
Other	15 (14%)	12 (11%)	10 (9%)	16 (14%)
Age (years)				
Mean	38.2	38.7	37.0	38.7
Range	19 - 62	22 - 63	18 - 63	21 - 67
Height (inches)				
Mean	(N=105) ^b 68.2	(N=110) ^b 68.2	(N=107) ^b 68.1	67.7
Weight^a (pounds)				
Mean	(N=105) ^b 171.4	(N=110) ^b 170.5	(N=106) ^b 183.2	171.1

^a Statistically significantly different among groups

^b Baseline values not obtained for some patients;

TABLE 2 (Cont)
**Summary of Psychiatric History Variables:
 Intent-to-Treat Dataset@**

Psychiatric History Variable	Placebo (N=106)	Sertindole 20 mg (N=111)	Sertindole 24 mg (N=108)	Haldol 16 mg (N=113)
DSM-III-R				
Disorganized	5 (5%)	5 (5%)	2 (2%)	3 (3%)
Catatonic	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Paranoid	70 (66%)	71 (64%)	74 (69%)	78 (69%)
Residual	2 (2%)	3 (3%)	3 (3%)	4 (4%)
Unspecified	29 (27%)	31 (28%)	29 (27%)	28 (25%)
Number of Hospitalizations				
0	6 (6%)	3 (3%)	5 (5%)	3 (3%)
1-5	30 (28%)	37 (34%)	44 (41%)	42 (37%)
6-10	37 (35%)	33 (30%)	33 (31%)	42 (37%)
11-15	15 (14%)	17 (15%)	13 (12%)	11 (10%)
16 or more	18 (17%)	20 (18%)	13 (12%)	15 (13%)
Age at Diagnosis (years)	(N=103)	(N=109)	(N=106)	(N=108)
Mean	22.6	23.4	23.3	23.3
Range	10 - 45	8 - 46	4 - 63	5 - 44
Days of Hospitalization Before Randomization	(N=69)	(N=74)	(N=71)	(N=78)
Mean	33.9	38.0	23.4	19.8
Range	5 - 477	4 - 1004	4 - 356	4 - 520
No. of Suicide Attempts				
0	65 (61%)	59 (54%)	67 (62%)	68 (61%)
1-5	37 (35%)	49 (45%)	37 (34%)	43 (38%)
≥ 6	4 (4%)	2 (2%)	4 (4%)	1 (1%)
Last Suicide Attempt				
Past Year	7 (17%)	9 (18%)	6 (15%)	8 (19%)
1-5 years	16 (39%)	16 (32%)	15 (38%)	13 (30%)
≥ 6 years	18 (44%)	25 (50%)	19 (48%)	22 (51%)
History of ECT				
No	91 (90%)	95 (89%)	94 (91%)	102 (94%)
Yes	10 (10%)	12 (11%)	9 (9%)	7 (6%)
Age of 1st Anti-Psychotic (years)	(N=90)	(N=99)	(N=93)	(N=92)
Mean	23.6	24.8	24.6	24.4
Range	13 - 45	14 - 46	9 - 63	14 - 45

@ Complete psychiatric history not collected for all patients
 Cross Reference: Appendices C.5.2, C.5.5, C.5.8, and D.6

Reason for Discontinuation	Placebo (N=116)	Sertindole 20 mg (N=117)	Sertindole 24 mg (N=114)	Haldol 16 mg (N=115)
Ineffectiveness	45 (39%)	31 (26%)	33 (29%)	28 (24%)*
Adverse Event	7 (6%)	12 (10%)	8 (7%)	10 (9%)
Noncompliance	6 (5%)	5 (4%)	3 (3%)	1 (1%)
Personal	1 (1%)	4 (3%)	3 (3%)	2 (2%)
Lost to Follow-up	2 (2%)	5 (4%)	2 (2%)	3 (3%)
Other	11 (9%)	14 (12%)	13 (11%)	16 (14%)
Total	72 (62%)	71 (61%)	62 (54%)	60 (52%)

* p<0.05 versus placebo

Variable	Placebo (N=106)		Sertindole 20 mg (N=111)		Sertindole 24 mg (N=108)		Haldol 16 mg (N=113)	
	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change	Baseline Mean	Mean Change
PANSS								
Total	64.4	-1.2	60.6	-7.5*†	62.8	-10.3*†	65.1	-13.3*†
Positive	16.7	-1.0	15.8	-3.2*†	15.9	-3.3*†	17.7	-5.8*†
Negative	17.4	-0.5	16.0	-1.3	17.5	-2.5*†	16.4	-1.3
BPRS								
Total	35.3	-1.7	33.5	-4.8*†	34.4	-6.5*†	36.1	-9.1*†
	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score
CGI ^a	4.7	4.1	4.7	3.6 [#]	4.8	3.6 [#]	4.9	3.2 [#]

* p<0.05 versus placebo from weighted comparison of ANOVA
† p<0.05 versus placebo from unweighted comparison of ANOVA
p<0.05 versus placebo from Cochran-Mantel-Haenszel analysis
^a Baseline is severity (1-7) where 1 = normal and 7 = among most extremely ill; Final Score is improvement (1-7) where 1 = very much improved, 4 = no change, and 7 = very much worse
Add 30 to total PANSS and 18 to total BPRS baseline scores to obtain the values corresponding to the published scale (see Section 4.11.2)

TABLE 5

Study M93-098
Mean Change from Baseline in PANSS Total Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 20 mg	111	60.6	111	-2.9	111	-5.3	111	-5.2	111	-6.0	111	-6.1	111	-6.4	111	-7.0	111	-7.0
Sertindole 24 mg	108	62.8	108	-2.4	108	-4.8	108	-6.8	108	-6.5	108	-8.8	108	-8.9	108	-9.4	108	-10.0
Haloperidol 16 mg	113	65.1	113	-5.7	113	-9.0	113	-10.3	113	-10.7	113	-11.9	113	-13.0	113	-12.9	113	-13.0
Placebo	106	64.4	106	-1.8	106	-3.1	106	-3.2	106	-2.8	106	-2.9	106	-2.4	106	-2.3	106	-1.8

2-Sided P-Values for Pairwise Comparisons

Sertindole 20 mg vs. Pbo	0.218	0.281	0.182	0.081	0.028	0.039	0.010	0.010	0.001
Sertindole 24 mg vs. Pbo	0.942	0.491	0.299	0.076	0.059	0.027	0.010	0.011	<0.001
Haloperidol 16 mg vs. Pbo	0.549	0.040	0.008	0.014	0.004	0.003	<0.001	<0.001	<0.001

Table 1120

Study M93-098

Mean Change from Baseline in PANSS Negative Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 20 mg	111	16.0	111	-0.5	111	-0.7	111	-0.7	111	-1.4	111	-1.4	111	-1.3	111	-1.3	111	-1.3
Sertindole 24 mg	108	17.5	108	-0.9	108	-1.3	108	-1.8	108	-1.7	108	-2.2	108	-2.4	108	-2.2	108	-2.5
Haloperidol 16 mg	113	16.4	113	-0.3	113	-1.1	113	-1.3	113	-1.1	113	-1.5	113	-1.6	113	-1.5	113	-1.3
Placebo	106	17.4	106	-0.4	106	-0.9	106	-0.9	106	-0.7	106	-0.8	106	-0.6	106	-0.7	106	-0.5

2-Sided P-Values for Pairwise Comparisons

Sertindole 20 mg vs. Pbo	0.240	0.663	0.927	0.572	0.049	0.071	0.060	0.105	0.071
Sertindole 24 mg vs. Pbo	0.230	0.512	0.353	0.130	0.033	0.028	0.018	0.046	0.006
Haloperidol 16 mg vs. Pbo	0.153	0.971	0.527	0.559	0.275	0.202	0.101	0.127	0.161

TABLE 5 (Cont)

Study M93-098
Mean Change from Baseline in BPRS Positive Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 20 mg	111	12.0	111	-1.2	111	-2.2	111	-2.5	111	-2.6	111	-2.7	111	-2.8	111	-2.9	111	-3.0
Sertindole 24 mg	108	12.1	108	-0.9	108	-1.5	108	-2.1	108	-1.9	108	-2.5	108	-2.5	108	-2.8	108	-2.8
Haloperidol 16 mg	113	13.1	113	-2.3	113	-3.1	113	-3.7	113	-4.0	113	-4.0	113	-4.2	113	-4.3	113	-4.3
Placebo	106	12.2	106	-0.7	106	-1.1	106	-1.3	106	-1.4	106	-1.4	106	-1.3	106	-1.3	106	-1.2
2-Sided P-Values for Pairwise Comparisons																		
Sertindole 20 mg vs. Pbo	0.957		0.011		<0.001		<0.001		<0.001		0.002		<0.001		<0.001		<0.001	
Sertindole 24 mg vs. Pbo	0.761		0.170		0.104		0.041		0.064		0.030		0.006		0.013		0.004	
Haloperidol 16 mg vs. Pbo	0.131		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001		<0.001	

Study M93-098

Mean Change from Baseline in CGI Severity Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 20 mg	111	4.7	111	-0.1	111	-0.3	111	-0.3	111	-0.3	111	-0.3	111	-0.4	111	-0.4	111	-0.4
Sertindole 24 mg	108	4.8	108	-0.1	108	-0.2	108	-0.3	108	-0.3	108	-0.4	108	-0.4	108	-0.4	108	-0.4
Haloperidol 16 mg	112	4.9	112	-0.3	112	-0.4	112	-0.5	112	-0.5	112	-0.6	112	-0.6	112	-0.6	112	-0.7
Placebo	106	4.7	106	-0.1	106	0.0	106	-0.1	106	-0.1	106	-0.1	106	-0.1	106	-0.1	106	-0.1
2-Sided P-Values for Pairwise Comparisons																		
Sertindole 20 mg vs. Pbo	0.218		0.461		0.053		0.120		0.012		0.016		0.007		0.005		<0.001	
Sertindole 24 mg vs. Pbo	0.658		0.571		0.064		0.025		0.027		0.004		0.010		0.012		0.001	
Haloperidol 16 mg vs. Pbo	0.821		0.135		0.009		0.009		0.003		0.002		0.002		0.002		<0.001	

Table 6
Mean Change From Baseline to Final Evaluation in BPRS Subscale Scores Using LOCF Method: Intent-to-Treat Dataset

Variables	Placebo (N=106)		Sertindole 20 mg (N=111)		Sertindole 24 mg (N=108)		Haldol 16 mg (N=113)	
	Baseline	Mean Change	Baseline	Mean Change	Baseline	Mean Change	Baseline	Mean Change
Positive Symptoms	12.2	-1.2	12.0	-3.0*†	12.1	-2.8*†	13.1	-4.3*†
Hostility	3.0	0.6	2.7	-0.1	2.8	-0.1	2.5	-0.5*
Withdrawal/Retardation	5.9	-0.5	5.5	0.0	6.2	-0.8	5.5	-0.2
Anxious Depression	5.0	-0.7	5.1	-0.7	5.1	-1.2	5.3	-1.6*

* p≤0.05 versus placebo from weighted comparison of ANOVA
† p≤0.05 versus placebo from unweighted comparison of ANOVA
Add 4 for Positive Symptoms, 5 for Hostility, 3 for Withdrawal/Retardation, and 3 for Anxious Depression to baseline score to obtain the value corresponding to the published scale (see Section 4.11.2)

6

Table 7
CGI Mean Scores at Baseline and at Final Evaluation Using LOCF Method: Intent-to-Treat Dataset^a

Method	Placebo (N=106)		Sertindole 20 mg (N=111)		Sertindole 24 mg (N=108)		Haldol 16 mg (N=113)	
	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score	Baseline Mean	Final Improvement Score
LOCF	4.7	4.1	4.7	3.6*	4.8	3.6*	4.9	3.2*

^a Baseline is severity (1-7) where 1 = normal and 7 = among most extremely ill; Final Score is improvement (1-7) where 1 = very much improved, 4 = no change, and 7 = very much worse
* p≤0.05 versus placebo from Cochran-Mantel-Haenszel analysis

7

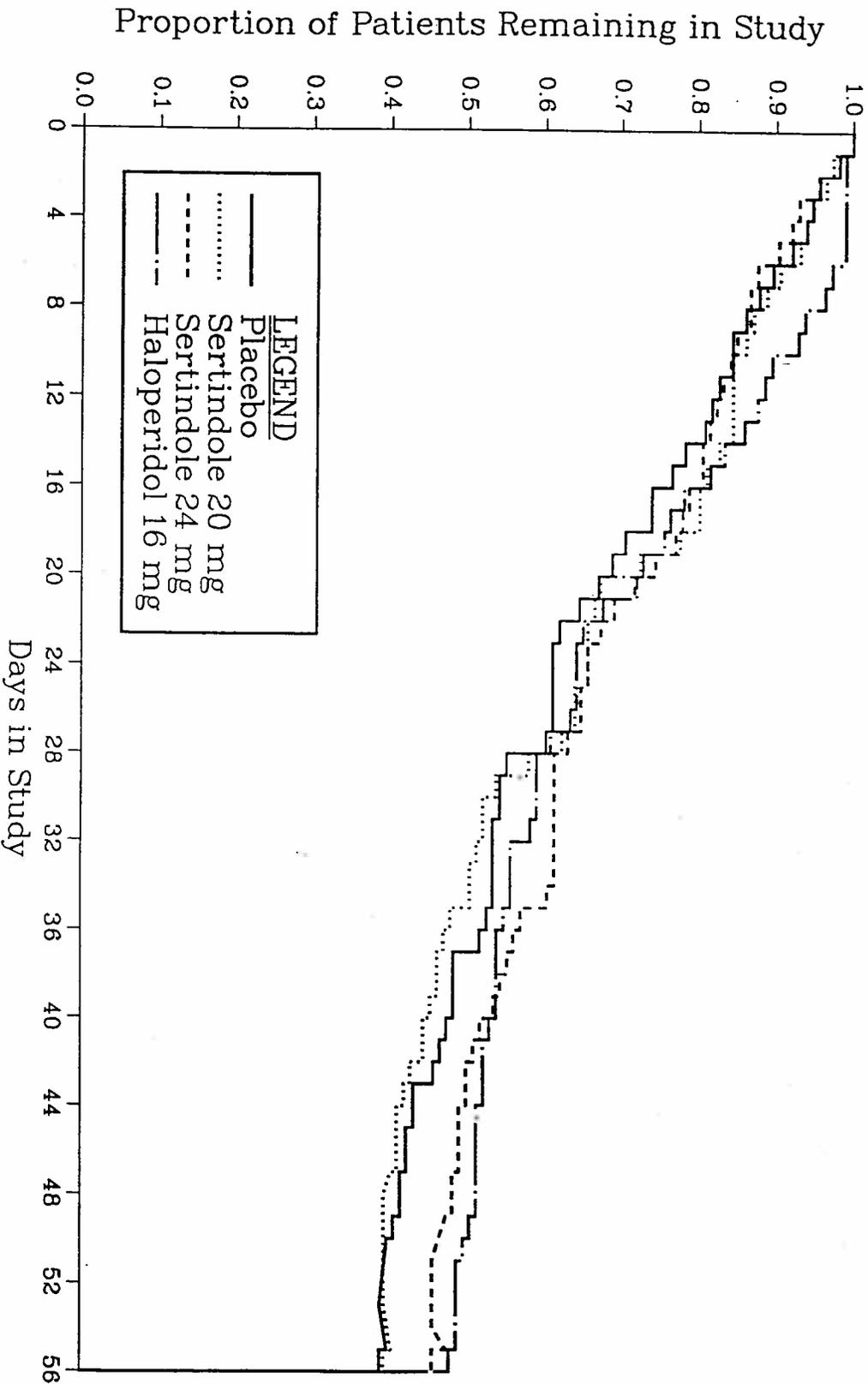
Table 8
Number (%) of Patients Experiencing Improvement as Indicated by CGI Scores: Intent-to-Treat Dataset

Improvement	Placebo (N=106)	Sertindole 20 mg (N=111)	Sertindole 24 mg (N=108)	Haldol 16 mg (N=113)
At least very much improvement	3 (3%)	7 (6%)	7 (7%)	8 (7%)
At least much improvement	18 (17%)	32 (29%)*	28 (26%)	34 (30%)*
At least minimal improvement	42 (40%)	57 (51%)	54 (50%)	69 (61%)*

* p≤0.05 versus placebo from Cochran-Mantel-Haenszel analysis

8

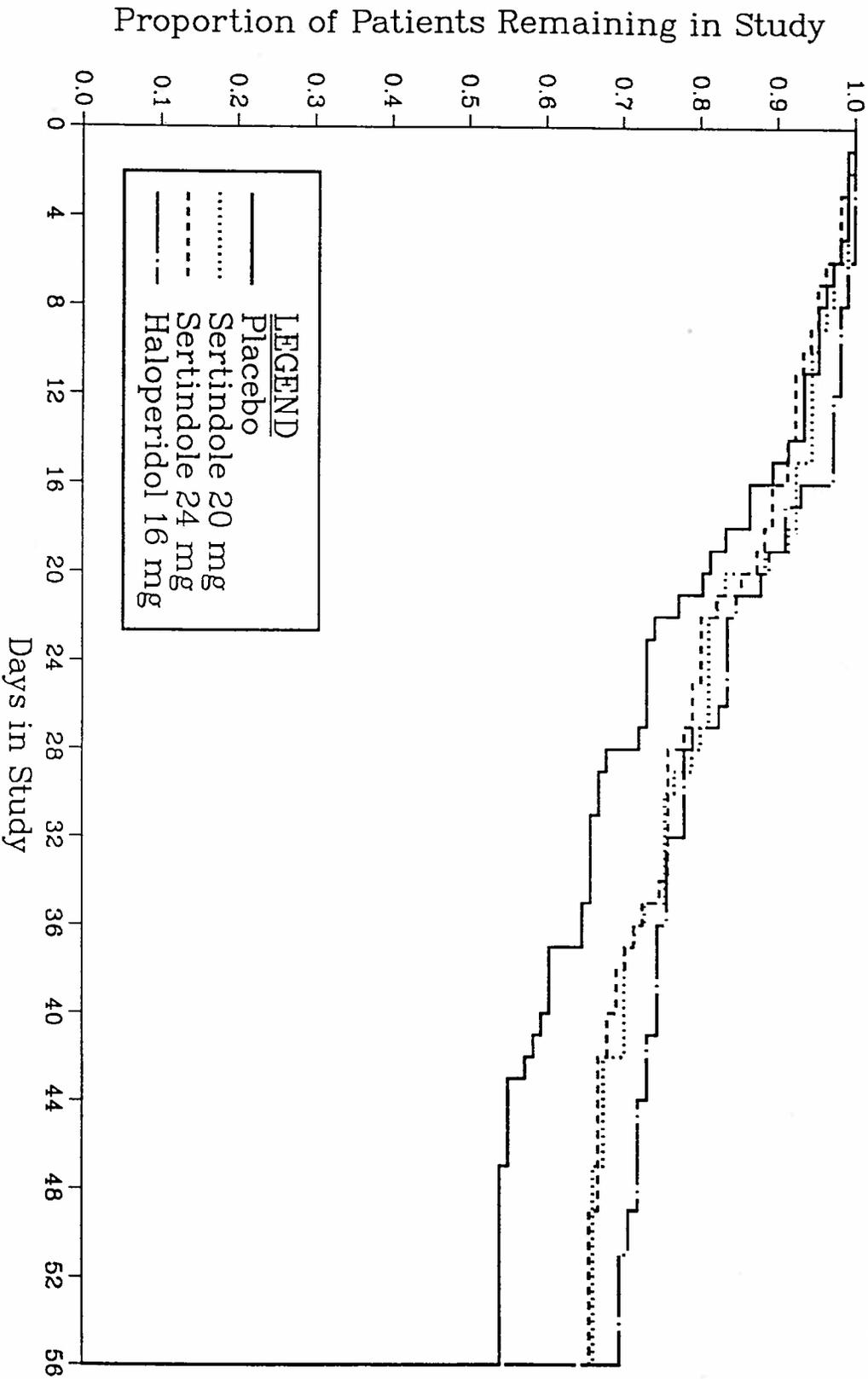
FIGURE 1



Kaplan-Meier Plots for Time to Exit Study for Any Reason in Study M93-098

Note: Nine patients who completed the study on 53-55 were censored.

FIGURE 2



Kaplan-Meier Plots for Time to Exit Study Due to Lack of Efficacy in Study M93-098

Note: Nine patients who completed the study on days 53-55 were censored.

FIGURE 3

Profiles of Unweighted Mean Differences for Sertindole 20 mg, Sertindole 24 mg, and Haldol 16 mg Compared With Placebo for Total PANSS Score

Sertindole 20 mg

Sertindole 24 mg

Haldol 16 mg

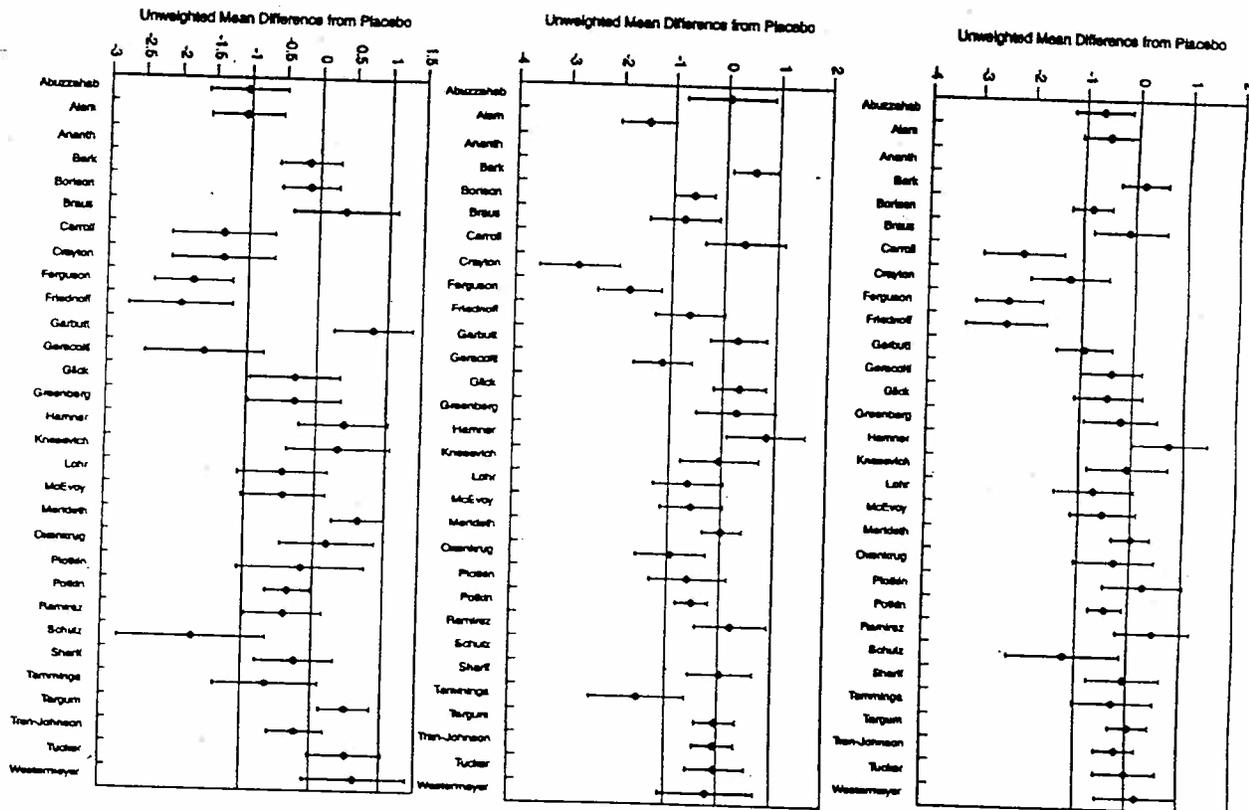


FIGURE 4

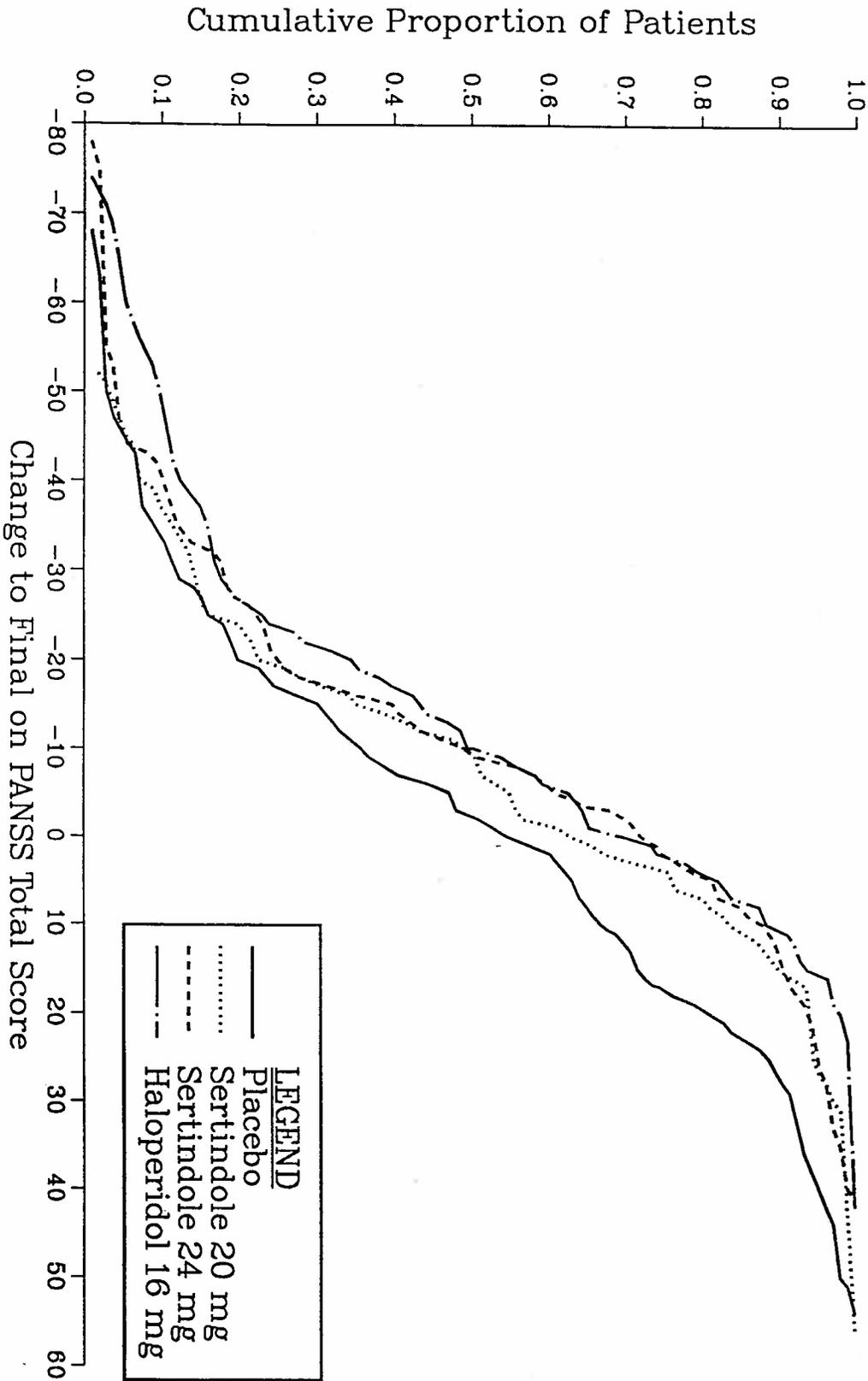
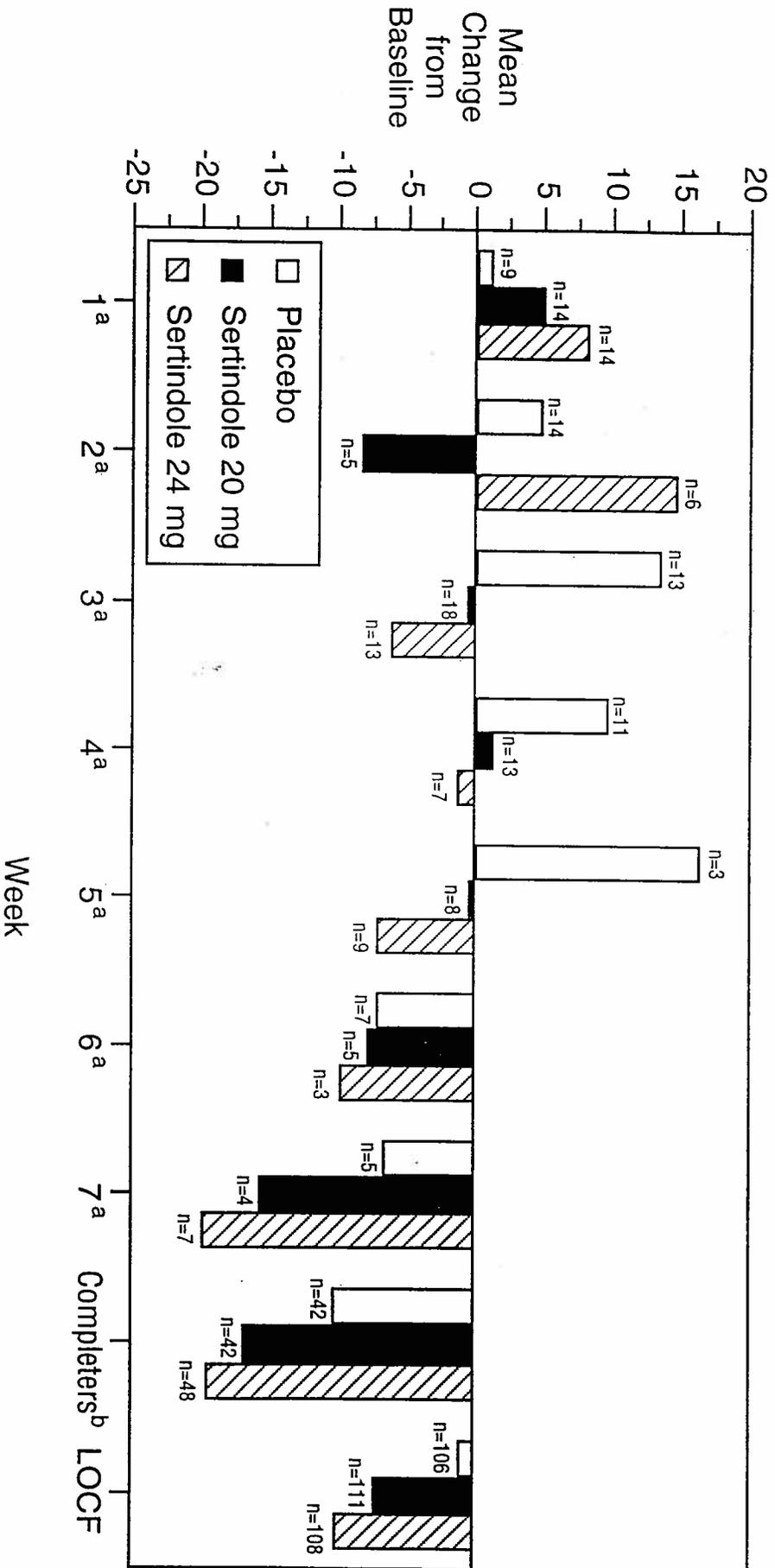


Figure 11
Empirical Distribution Function for Change to Final on
PANSS Total Score for Study M93-098

Figure 5 M93-098: PANSS Total Score – Patients Dropped By Week

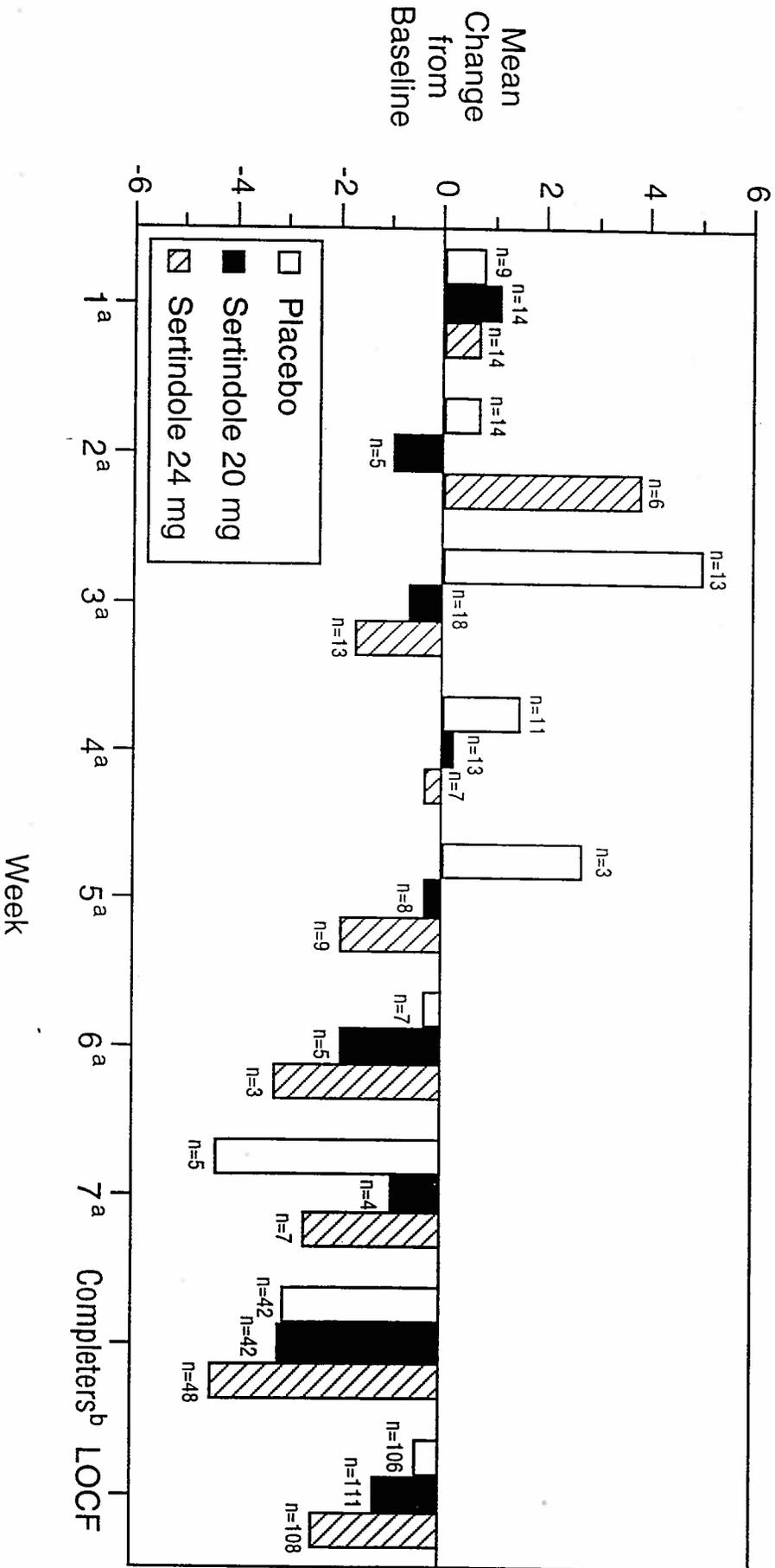


^a Includes patients who completed referenced week visit but dropped before next week visit.

^b Two placebo patients, two sertindole 20 mg patients, and one sertindole 24 mg patient who had a Day 56 evaluation but dropped before Day 56 are excluded.

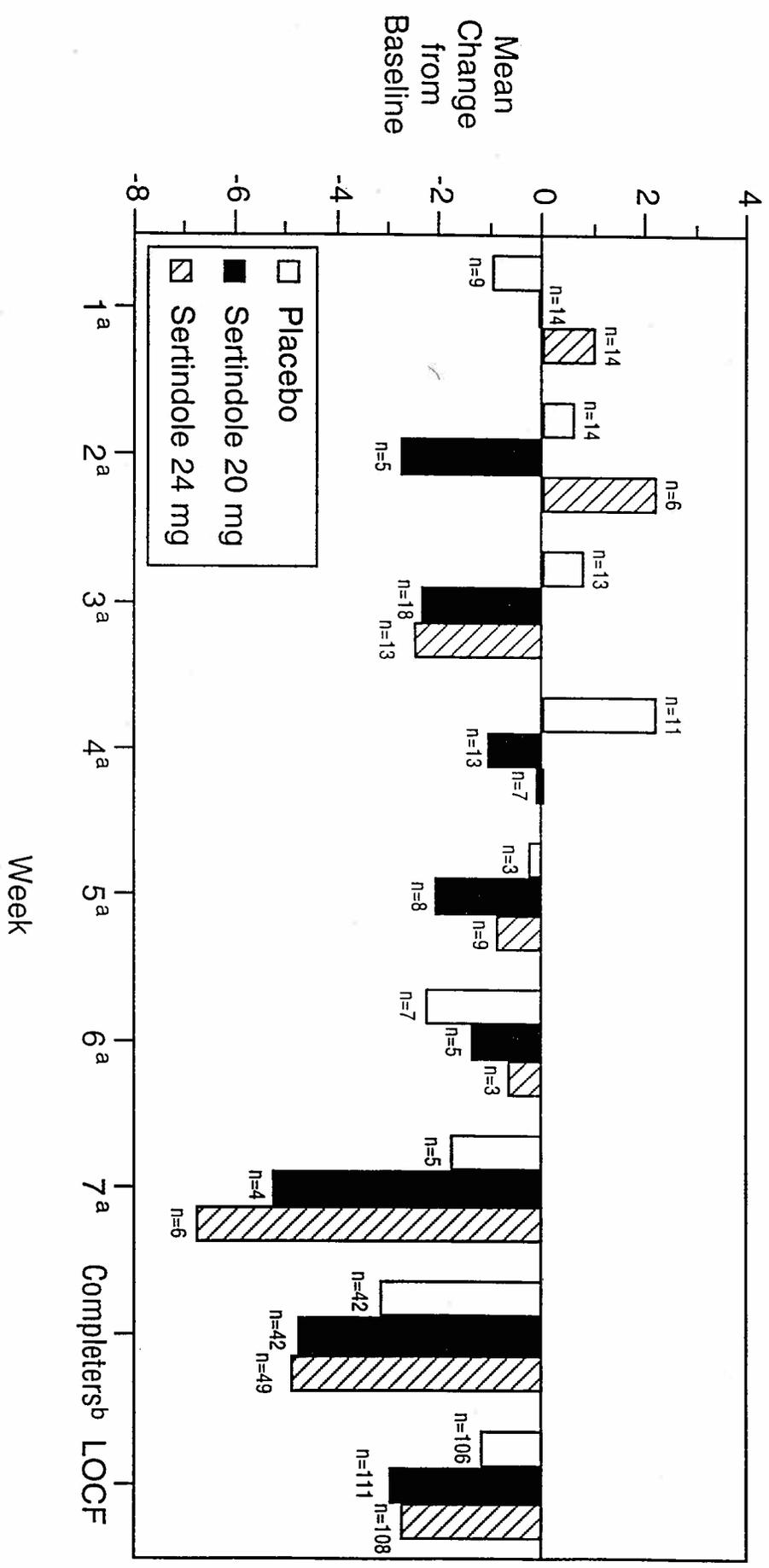
Figure 6

M93-098: PANSS Negative Scale Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.
^b Two placebo patients, two sertindole 20 mg patients, and one sertindole 24 mg patient who had a Day 56 evaluation but dropped before Day 56 are excluded.

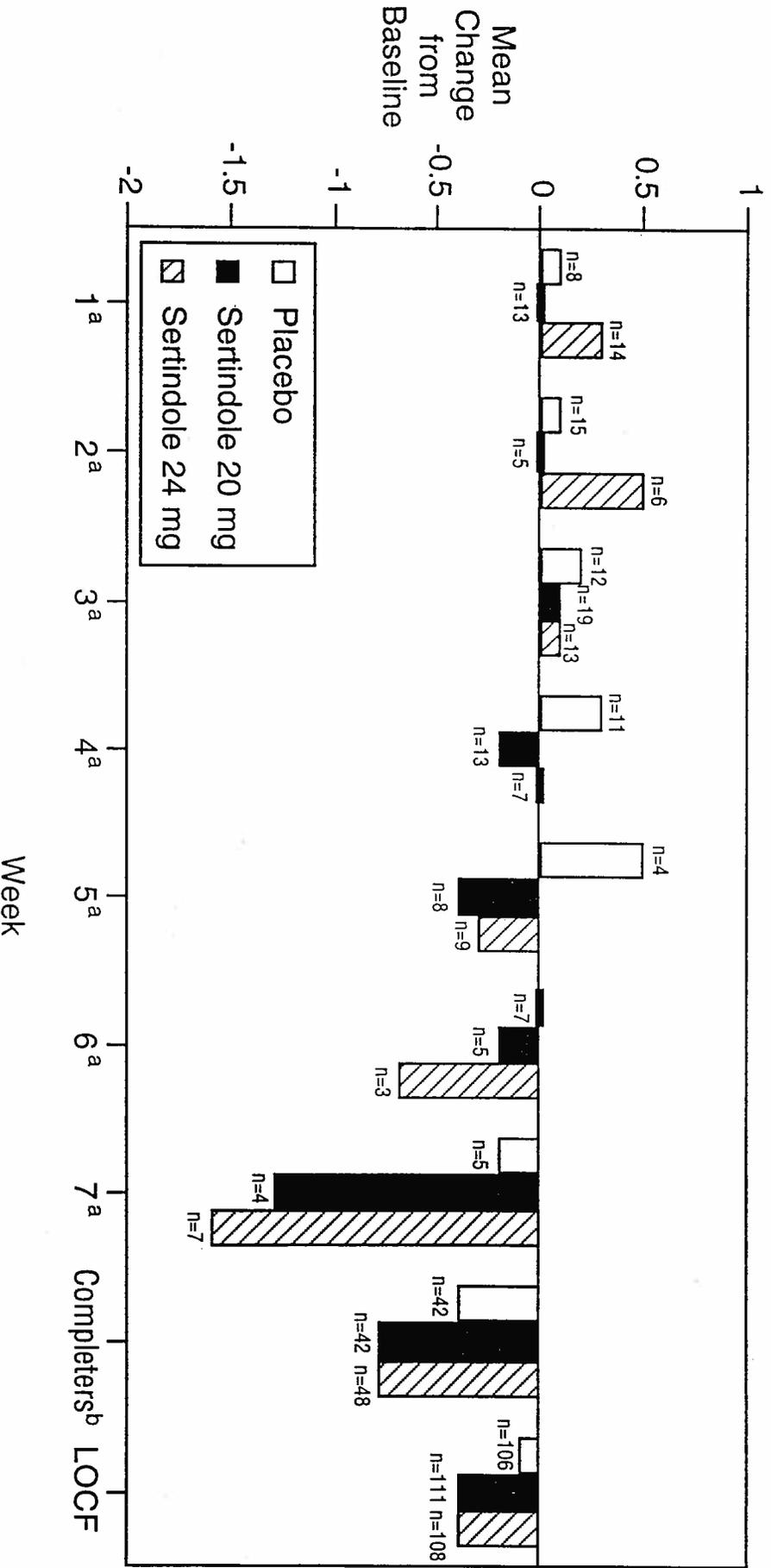
Figure 7 M93-098: BPRS Positive Symptoms Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

^b Two placebo patients, two sertindole 20 mg patients, and one sertindole 24 mg patient who had a Day 56 evaluation but dropped before Day 56 are excluded.

Figure 8 M93-098: CGI Severity – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

^b Two placebo patients, two sertindole 20 mg patients, and one sertindole 24 mg patient who had a Day 56 evaluation but dropped before Day 56 are excluded.

TRIAL M93-113

Table 1

List of Investigators and Number of Patients Randomized by Treatment Group

Investigator	City/State	PBO	Sert 12 mg	Sert 20 mg	Sert 24 mg	Hal 4 mg	Hal 8 mg	Hal 16 mg
Adan	Miami, FL	2	2	2	2	2	2	1
Ainslie	Coatesville, PA	3	3	3	3	3	3	3
Allan	Montrose, NY	2	3	2	2	2	2	2
Atri	Richmond, VA	0	0	0	1	1	1	0
Baker	Pittsburgh/Bridgeville, PA	1	1	2	1	1	1	2
Beitman	Columbia/Fulton, MO	1	2	1	2	1	1	1
Brown	Mountain Home, TN	1	1	1	1	1	1	1
Canive	Albuquerque, NM	2	3	2	1	2	2	2
Carman	Atlanta, GA	2	2	2	2	2	2	2
Daniel	Falls Church, VA	2	2	3	2	2	2	3
Dott	Galveston, TX	2	3	3	3	2	3	3
Edwards	Fort Meade, SD	1	2	2	2	1	1	1
Fenton	Rockville, MD	1	0	0	0	0	0	0
Freidli	Lexington, KY	0	1	0	0	0	0	0
Funderburg/Ereshfsky#	San Antonio, TX	3	2	2	2	2	2	3
Gladson	Decatur, GA	1	1	0	0	0	1	0
Hamilton	Houston, TX	1	2	1	1	2	2	1
Haque	Allen Park, MI	1	2	1	2	2	1	2
Hartford	Cincinnati, OH	2	1	1	1	1	1	1
Horne	North Las Vegas, NV	3	3	2	2	2	2	3
Houck	Birmingham, AL	0	1	0	0	1	0	0
Jampala	Dayton, OH	0	1	0	0	0	0	0
Karson	North Little Rock, AR	1	1	1	1	2	1	1
Labelle	Ottawa, Canada	1	2	2	1	2	1	2
Larson	Milwaukee, WI	3	3	2	3	2	3	2
Lesem/Claghorn#	Bellaire, TX	4	3	3	4	3	3	3
Liskow	Kansas City, MO	1	1	0	1	1	0	1
Logue	Birmingham/Bessemer, AL	4	4	4	5	5	5	4
Makela/Clausell#	Morgantown, WV	1	1	0	1	1	1	0
Moore/Shillcutt#	Milledgeville/Macon, GA	0	0	1	1	0	1	1
Morphy	Buffalo, NY	1	0	1	0	1	1	1
Posever	Jamaica Plain, MA	1	1	1	1	1	1	1
Risch	Charleston, SC	2	2	2	3	2	2	2
Rosenthal	San Diego, CA	2	2	2	2	2	2	2
Rotrosen	New York, NY	2	2	2	2	2	2	2
Sheehan	Tampa, FL	1	0	0	1	0	0	0
Silverstone	Edmonton, Canada	2	1	2	2	2	1	1
Swann	Houston, TX	2	1	1	1	1	1	1
Tapp	Tacoma, WA	1	1	1	1	1	1	2
Thomas	Denver, CO	1	1	1	1	1	1	1
Volavka	Orangeburg/New York, NY	4	3	3	3	4	2	4
Vora	Newark, NJ	2	3	2	2	2	2	2
Zimbhoff	Upland, CA	6	6	7	6	6	6	6
Total		73	76	68	72	71	67	70

Co-investigators

PBO = Placebo, Sert = Sertindole, Hal = Haldol

Table 2							
Summary of Demographic Characteristics: Intent-to-Treat Dataset							
Demographic Characteristic	Placebo (N=71)	Sertindole 12 mg (N=72)	Sertindole 20 mg (N=65)	Sertindole 24 mg (N=70)	Haldol 4 mg (N=68)	Haldol 8 mg (N=63)	Haldol 16 mg (N=68)
Gender							
Female	16 (23%)	14 (19%)	16 (25%)	22 (31%)	11 (16%)	13 (21%)	16 (24%)
Male	55 (77%)	58 (81%)	49 (75%)	48 (69%)	57 (84%)	50 (79%)	52 (76%)
Race[#]							
African-American	21 (30%)	19 (26%)	18 (28%)	22 (31%)	21 (31%)	23 (37%)	22 (32%)
Caucasian	40 (56%)	46 (64%)	42 (65%)	43 (61%)	38 (56%)	35 (56%)	37 (54%)
Oriental	0 (0%)	0 (0%)	1 (2%)	0 (0%)	1 (1%)	0 (0%)	0 (0%)
Other	10 (14%)	7 (10%)	4 (6%)	5 (7%)	8 (12%)	5 (8%)	9 (13%)
Age (years)							
Mean	38.7	37.8	40.5	39.4	38.2	39.5	39.1
Range	18 - 63	18 - 67	18 - 64	18 - 63	19 - 62	19 - 65	18 - 65
Height (cm)							
Mean	(N=70) 173.6	(N=71) 174.5	(N=64) 172.1	(N=70) 174.0	(N=67) 174.4	(N=61) 172.5	(N=66) 173.4
Weight (kg)							
Mean	(N=70) 79.1	(N=72) 79.4	(N=64) 79.7	(N=70) 78.5	(N=67) 77.3	(N=63) 77.9	(N=68) 80.6

[#] Due to rounding, total may not equal 100%

Table 2 (Cont)
Summary of Psychiatric History Variables:
Intent-to-Treat Dataset@

Psychiatric History Variable	Placebo	Sertindole 12 mg	Sertindole 20 mg	Sertindole 24 mg	Haldol 4 mg	Haldol 8 mg	Haldol 16 mg
DSM-III-R	(N=71)	(N=72)	(N=65)	(N=70)	(N=68)	(N=63)	(N=68)
Disorganized	2 (3%)	3 (4%)	5 (8%)	2 (3%)	2 (3%)	1 (2%)	1 (1%)
Catatonic	1 (1%)	0 (0%)	0 (0%)	0 (0%)	1 (1%)	1 (2%)	0 (0%)
Paranoid	46 (65%)	45 (63%)	39 (60%)	44 (63%)	50 (74%)	45 (71%)	45 (66%)
Residual	2 (3%)	2 (3%)	3 (5%)	3 (4%)	3 (4%)	0 (0%)	3 (4%)
Unspecified	20 (28%)	22 (31%)	18 (28%)	21 (30%)	12 (18%)	16 (25%)	19 (28%)
Number of Hospitalizations	(N=71)	(N=72)	(N=63)	(N=70)	(N=68)	(N=63)	(N=68)
0	3 (4%)	3 (4%)	3 (5%)	3 (4%)	4 (6%)	3 (5%)	4 (6%)
1-5	22 (31%)	19 (26%)	14 (22%)	23 (33%)	23 (34%)	21 (33%)	15 (22%)
6-10	16 (23%)	23 (32%)	24 (38%)	22 (31%)	16 (24%)	19 (30%)	20 (29%)
11-15	16 (23%)	5 (7%)	10 (16%)	10 (14%)	9 (13%)	6 (10%)	14 (21%)
16 or more	14 (20%)	22 (31%)	12 (19%)	12 (17%)	16 (24%)	14 (22%)	15 (22%)
Age at Diagnosis (years)	(N=70)	(N=70)	(N=63)	(N=68)	(N=66)	(N=61)	(N=66)
Mean	22.1	22.4	23.2	22.4	23.3	22.8	22.5
Range	11 - 37	13 - 42	9 - 43	8 - 41	8 - 62	8 - 41	10 - 43
Days of Hospitalization Before Randomization	(N=29)	(N=34)	(N=28)	(N=32)	(N=30)	(N=27)	(N=32)
Mean	123	132	97	326	98	64	64
Range	7 - 2907	4 - 2099	6 - 1514	5 - 5713	3 - 2052	6 - 413	5 - 1115
Last Suicide Attempt	(N=38)	(N=25)	(N=27)	(N=27)	(N=32)	(N=26)	(N=27)
Past Year	5 (13%)	2 (8%)	6 (22%)	7 (26%)	8 (25%)	11 (42%)	3 (11%)
1-5 years	17 (45%)	13 (52%)	8 (30%)	10 (37%)	10 (31%)	6 (23%)	8 (30%)
≥ 6 years	16 (42%)	10 (40%)	13 (48%)	10 (37%)	14 (44%)	9 (35%)	16 (59%)
No. of Suicide Attempts	(N=71)	(N=72)	(N=65)	(N=70)	(N=68)	(N=63)	(N=68)
0	33 (47%)	47 (65%)	38 (58%)	43 (61%)	36 (53%)	36 (57%)	41 (60%)
1-5	34 (48%)	21 (29%)	26 (40%)	23 (33%)	31 (46%)	24 (38%)	27 (40%)
≥ 6	4 (6%)	4 (6%)	1 (2%)	4 (6%)	1 (1%)	3 (5%)	0 (0%)
History of ECT	(N=71)	(N=72)	(N=65)	(N=70)	(N=68)	(N=63)	(N=68)
No	65 (92%)	64 (89%)	55 (85%)	62 (89%)	59 (87%)	56 (89%)	58 (85%)
Yes	6 (8%)	8 (11%)	10 (15%)	8 (11%)	9 (13%)	7 (11%)	10 (15%)
Age of 1st Anti-Psychotic (years)	(N=62)	(N=56)	(N=56)	(N=59)	(N=52)	(N=51)	(N=55)
Mean	22.9	23.0	23.4	24.1	23.9	23.7	23.2
Range	12 - 37	14 - 42	13 - 43	11 - 48	12 - 62	15 - 41	10 - 43
Schedule for Deficit Syndrome	(N=71)	(N=72)	(N=64)	(N=68)	(N=68)	(N=61)	(N=67)
Deficit	42 (59%)	42 (58%)	38 (59%)	35 (52%)	37 (54%)	42 (69%)	40 (60%)
Nondeficit	29 (41%)	30 (42%)	26 (41%)	33 (49%)	31 (46%)	19 (31%)	27 (40%)

@ Complete psychiatric history not collected for all patients

Table 3
Number and Percentage of Patients Who Prematurely Discontinued

Reason for Discontinuation	Placebo (N=73)		Sertindole 12 mg (N=76)		Sertindole 20 mg (N=68)		Sertindole 24 mg (N=72)		Haldol 4 mg (N=71)		Haldol 8 mg (N=67)		Haldol 16 mg (N=70)	
Ineffectiveness	28 (38%)		21 (28%)		16 (24%)		19 (26%)		18 (25%)		9 (13%)*		11 (16%)*	
Adverse Event	1 (1%)		3 (4%)		6 (9%)		3 (4%)		5 (7%)		10 (15%)*		4 (6%)	
Noncompliance	2 (3%)		4 (5%)		3 (4%)		3 (4%)		4 (6%)		3 (4%)		3 (4%)	
Personal	0 (0%)		1 (1%)		1 (1%)		2 (3%)		4 (6%)		2 (3%)		2 (3%)	
Lost to Follow-up	3 (4%)		3 (4%)		3 (4%)		1 (1%)		2 (3%)		5 (7%)		5 (7%)	
Other [#]	3 (4%)		10 (13%)		4 (6%)		10 (14%)*		6 (8%)		4 (6%)		8 (11%)	
Total	37 (51%)		42 (55%)		33 (49%)		38 (53%)		39 (55%)		33 (49%)		33 (47%)	

* p<0.05 versus placebo from Fisher's exact test

Includes administrative reasons

Table 4
Mean Change From Baseline to Final Evaluation in PANSS, BPRS, and CGI Scores Using LOCF Method: Intent-to-Treat Dataset

Variable	Placebo (N=71)		Sertindole 12 mg (N=72)		Sertindole 20 mg (N=65)		Sertindole 24 mg (N=70)		Haldol 4 mg (N=68)		Haldol 8 mg (N=63)		Haldol 16 mg (N=68)	
	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC	MB	MC
	PANSS													
Total	62.0	0.7	63.2	-9.9*†	70.5*†	-17.6*†	65.2	-10.7*†	69.0*†	-11.8*†	64.8	-16.5*†	67.1	-11.9*†
Positive	16.0	0.0	16.3	-2.4*	17.9	-4.8*†	16.5	-3.2*†	17.7	-2.7*	16.7	-5.6*†	17.3	-4.3*†
Negative	17.0	-0.7	17.2	-2.8	18.8†	-4.4*†	17.8	-2.3	17.7	-2.7	17.0	-3.3	17.3	-2.4
BPRS														
Total	34.4	-0.9	35.1	-6.7*†	39.2*†	-10.3*†	37.1	-8.2*†	38.9*†	-8.0*†	36.7	-10.4*†	38.3	-8.8*†
	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS	MB	FS
CGI ^a	4.7	4.2	4.7	3.5 [#]	4.9	3.3 [#]	4.6	3.6 [#]	4.9	3.7	4.7	3.1 [#]	4.9	3.5 [#]

MB = Mean baseline

MC = Mean change

FS = Final improvement score

* p<0.05 versus placebo from weighted comparison of the ANOVA

† p<0.05 versus placebo from unweighted comparison of the ANOVA

p<0.05 versus placebo from Cochran-Mantel-Haenszel analysis

^a Baseline mean is severity (1-7) where 1 = normal and 7 = among most extremely ill; Final Score is improvement (1-7) where 1 = very much improved, 4 = no change, and 7 = very much worse

Add 30 to total baseline score for PANSS to obtain the value corresponding to the published scale (see Section 4.11.2) add 18 to total baseline score for BPRS to obtain the value corresponding to the published scale (see Section 4.11.2)

TABLE 5

Study M93-113
Mean Change from Baseline in PANSS Total Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 12 mg	72	63.2	72	-2.2	72	-4.2	72	-6.2	72	-7.3	72	-8.4	72	-8.3	72	-9.4	72	-9.9
Sertindole 20 mg	65	70.5	65	-2.6	65	-7.4	65	-9.9	65	-12.5	65	-15.2	65	-15.5	65	-14.8	65	-17.6
Sertindole 24 mg	70	65.2	70	-3.7	70	-4.2	70	-5.9	70	-8.1	70	-9.0	70	-8.1	70	-9.7	70	-10.7
Haloperidol 4 mg	68	69.0	68	-10.2	68	-12.6	68	-13.2	68	-13.1	68	-12.8	68	-12.7	68	-11.7	68	-11.8
Haloperidol 8 mg	63	64.8	63	-8.1	63	-10.6	63	-15.3	63	-16.0	63	-17.1	63	-15.8	63	-17.4	63	-16.5
Haloperidol 16 mg	68	67.1	68	-6.4	68	-7.6	68	-8.0	68	-8.9	68	-11.8	68	-11.2	68	-10.9	68	-11.9
Placebo	71	62.0	71	-1.1	71	0.0	71	-1.1	71	0.6	71	0.7	71	-1.0	71	1.0	71	0.7

2-Sided P-Values for Pairwise Comparisons

Sertindole 12 mg vs. Pbo	0.648	0.323	0.174	0.134	0.053	0.023	0.049	0.021	0.013
Sertindole 20 mg vs. Pbo	0.012	0.303	0.022	0.069	0.016	0.005	0.008	0.004	0.002
Sertindole 24 mg vs. Pbo	0.630	0.284	0.051	0.130	0.041	0.030	0.053	0.023	0.016
Haloperidol 4 mg vs. Pbo	0.013	0.004	0.003	0.020	0.013	0.027	0.049	0.023	0.030
Haloperidol 8 mg vs. Pbo	0.468	0.002	0.004	0.002	<0.001	<0.001	0.002	<0.001	0.001
Haloperidol 16 mg vs. Pbo	0.166	0.078	0.069	0.183	0.084	0.025	0.045	0.027	0.019

Study M93-113

Mean Change from Baseline in Total SANS Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week							
	Baseline		Week 2		Week 5		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 12 mg	65	51.4	65	-2.7	65	-7.7	65	-12.5
Sertindole 20 mg	60	53.8	60	-6.2	60	-12.7	60	-13.2
Sertindole 24 mg	63	51.6	63	-1.0	63	-6.1	63	-7.1
Haloperidol 4 mg	65	53.3	65	-8.7	65	-11.6	65	-10.9
Haloperidol 8 mg	57	49.1	57	-3.8	57	-11.3	57	-10.8
Haloperidol 16 mg	65	50.9	65	-5.9	65	-5.9	65	-7.1
Placebo	68	50.7	68	-0.8	68	-1.6	68	-2.1

2-Sided P-Values for Pairwise Comparisons

Sertindole 12 mg vs. Pbo	0.838	0.341	0.205	0.134
Sertindole 20 mg vs. Pbo	0.262	0.234	0.029	0.023
Sertindole 24 mg vs. Pbo	0.830	0.748	0.299	0.266
Haloperidol 4 mg vs. Pbo	0.197	0.018	0.027	0.094
Haloperidol 8 mg vs. Pbo	0.156	0.980	0.184	0.321
Haloperidol 16 mg vs. Pbo	0.851	0.158	0.247	0.190

TABLE 5 (CONT)

Study M93-113

Mean Change from Baseline in BPRS Positive Scores

Last Observation Carried Forward Method

Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 12 mg	72	12.3	72	-1.1	72	-2.2	72	-2.0	72	-2.2	72	-2.6	72	-2.4	72	-2.7	72	-3.0
Sertindole 20 mg	65	12.4	65	-0.5	65	-1.5	65	-2.0	65	-2.4	65	-2.9	65	-3.3	65	-3.1	65	-3.4
Sertindole 24 mg	70	12.0	70	-1.0	70	-1.6	70	-1.9	70	-2.3	70	-2.5	70	-2.5	70	-2.6	70	-3.0
Haloperidol 4 mg	68	12.7	68	-2.1	68	-2.8	68	-2.8	68	-2.7	68	-2.7	68	-2.8	68	-2.5	68	-2.6
Haloperidol 8 mg	63	12.4	63	-2.2	63	-3.3	63	-3.8	63	-4.0	63	-4.3	63	-4.3	63	-4.4	63	-4.3
Haloperidol 16 mg	68	12.7	68	-1.9	68	-2.4	68	-3.0	68	-3.3	68	-3.6	68	-3.6	68	-3.6	68	-3.7
Placebo	71	12.1	71	-0.8	71	-0.8	71	-0.9	71	-1.1	71	-1.2	71	-1.3	71	-0.7	71	-1.0

2-Sided P-Values for Pairwise Comparisons

Sertindole 12 mg vs. Pbo	0.982	0.696	0.138	0.322	0.310	0.138	0.148	0.071	0.037
Sertindole 20 mg vs. Pbo	0.554	0.890	0.226	0.215	0.164	0.137	0.053	0.026	0.041
Sertindole 24 mg vs. Pbo	0.369	0.492	0.123	0.131	0.090	0.169	0.137	0.068	0.023
Haloperidol 4 mg vs. Pbo	0.460	0.017	0.005	0.053	0.109	0.253	0.209	0.101	0.105
Haloperidol 8 mg vs. Pbo	0.631	0.002	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Haloperidol 16 mg vs. Pbo	0.346	0.036	0.030	0.012	0.025	0.021	0.017	0.006	0.008

Study M93-113

Mean Change from Baseline in CGI Severity Scores

Last Observation Carried Forward Method

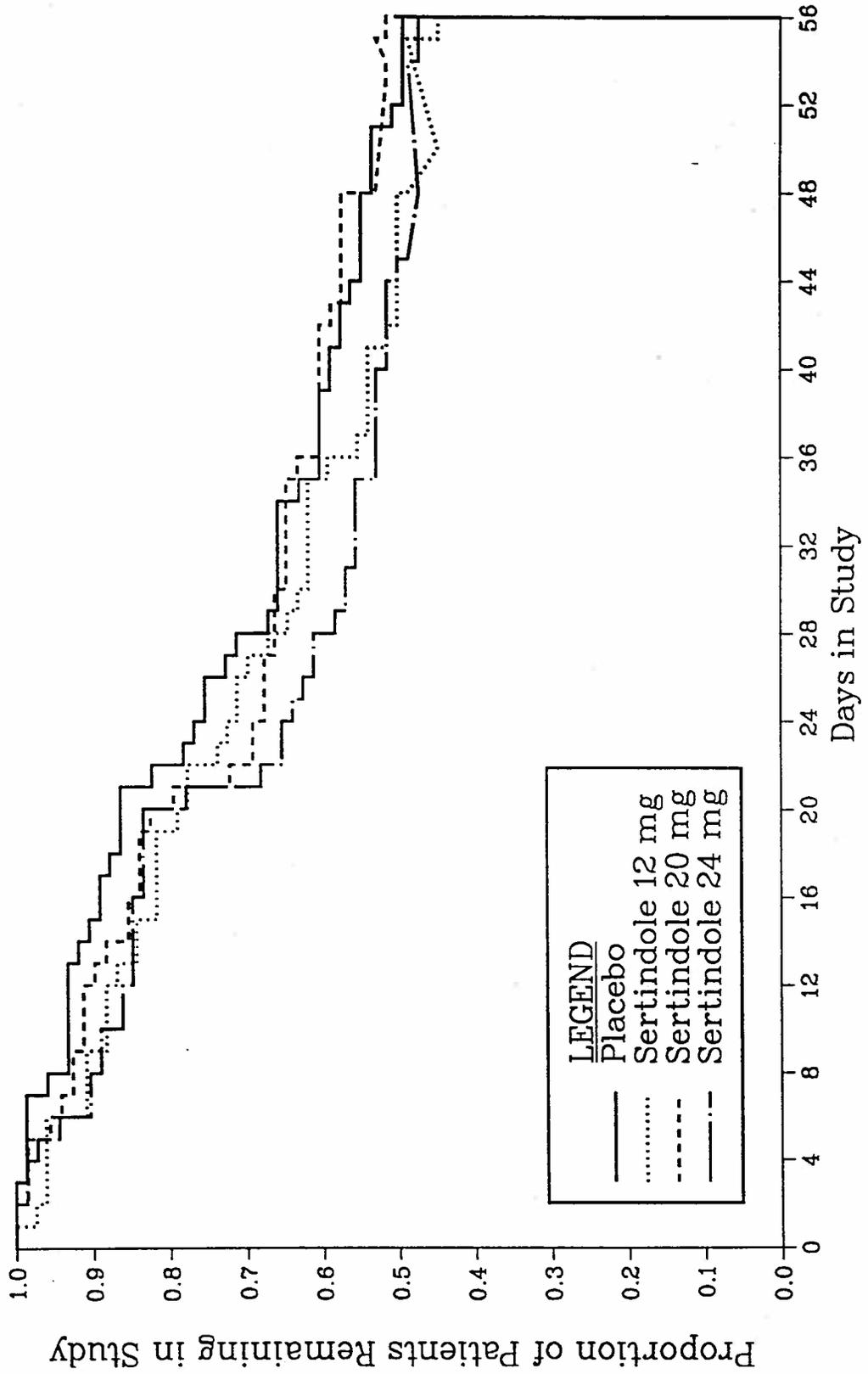
Treatment Groups	Treatment Week																	
	Baseline		Week 1		Week 2		Week 3		Week 4		Week 5		Week 6		Week 7		Week 8	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Sertindole 12 mg	72	4.7	72	-0.1	72	-0.1	72	-0.2	72	-0.3	72	-0.4	72	-0.3	72	-0.4	72	-0.4
Sertindole 20 mg	65	4.9	65	-0.1	65	-0.1	65	-0.3	65	-0.4	65	-0.6	65	-0.6	65	-0.6	65	-0.7
Sertindole 24 mg	70	4.6	70	-0.2	70	-0.2	70	-0.3	70	-0.4	70	-0.5	70	-0.4	70	-0.5	70	-0.5
Haloperidol 4 mg	68	4.9	68	-0.3	68	-0.4	68	-0.4	68	-0.4	68	-0.4	68	-0.3	68	-0.3	68	-0.4
Haloperidol 8 mg	63	4.7	63	-0.2	63	-0.4	63	-0.7	63	-0.7	63	-0.8	63	-0.7	63	-0.7	63	-0.7
Haloperidol 16 mg	68	4.9	68	-0.3	68	-0.4	68	-0.5	68	-0.5	68	-0.5	68	-0.5	68	-0.6	68	-0.6
Placebo	71	4.7	71	0.0	71	0.0	71	0.0	71	0.0	71	0.1	71	0.0	71	0.1	71	0.0

2-Sided P-Values for Pairwise Comparisons

Sertindole 12 mg vs. Pbo	0.571	0.352	0.758	0.190	0.191	0.067	0.200	0.034	0.092
Sertindole 20 mg vs. Pbo	0.057	0.371	0.435	0.076	0.034	0.001	0.004	0.001	0.006
Sertindole 24 mg vs. Pbo	0.681	0.042	0.097	0.015	0.011	0.002	0.006	<0.001	0.005
Haloperidol 4 mg vs. Pbo	0.061	0.001	0.005	0.016	0.065	0.040	0.145	0.020	0.083
Haloperidol 8 mg vs. Pbo	0.393	<0.001	0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002
Haloperidol 16 mg vs. Pbo	0.126	0.036	0.016	0.001	0.020	0.001	0.017	0.002	0.021

Figure 1

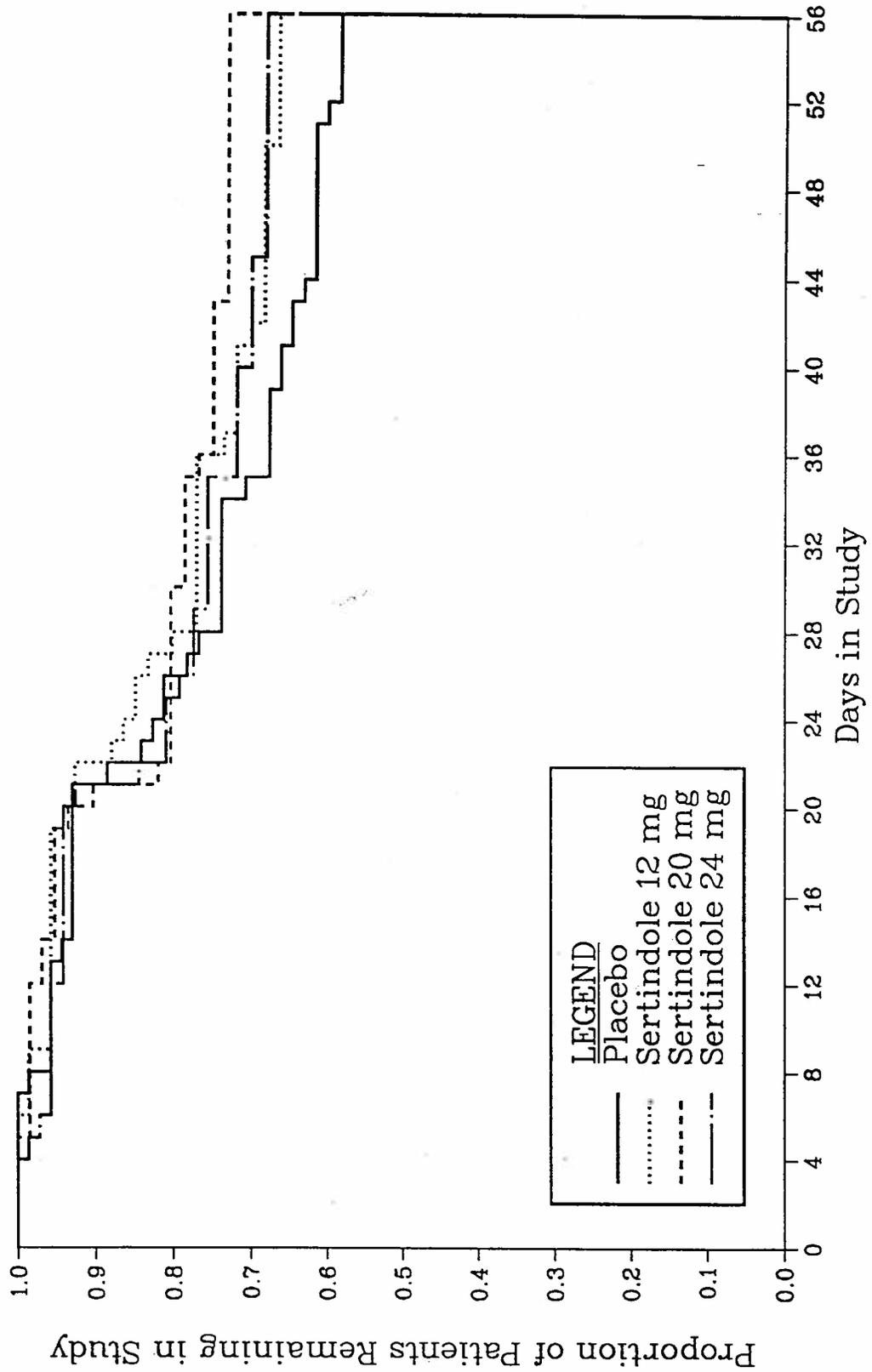
Kaplan-Meier Plots for Time to Exit Study for Any Reason
in Study M93-113: Sertindole and Placebo



Note: Six patients who completed the study on days 54 and 55 were censored.

FIGURE 2

Kaplan-Meier Plots for Time to Exit Study Due to Lack of Efficacy
in Study M93-113: Sertindole and Placebo



Note: Six patients who completed the study on days 54 and 55 were censored.

FIGURE 3

Empirical Distribution Function for Change to Final on PANSS Total Score for Study M93-113: Sertindole and Placebo

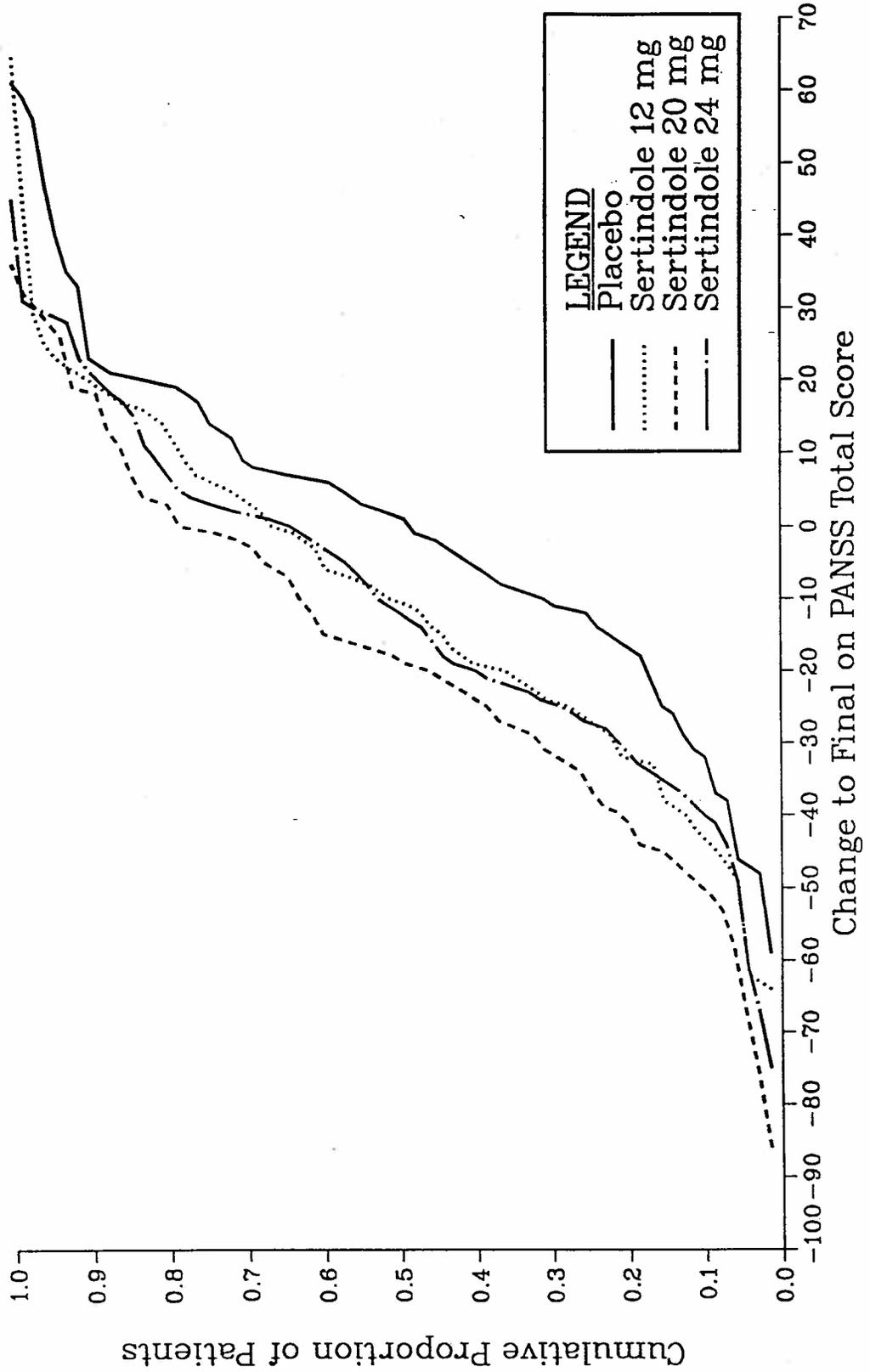
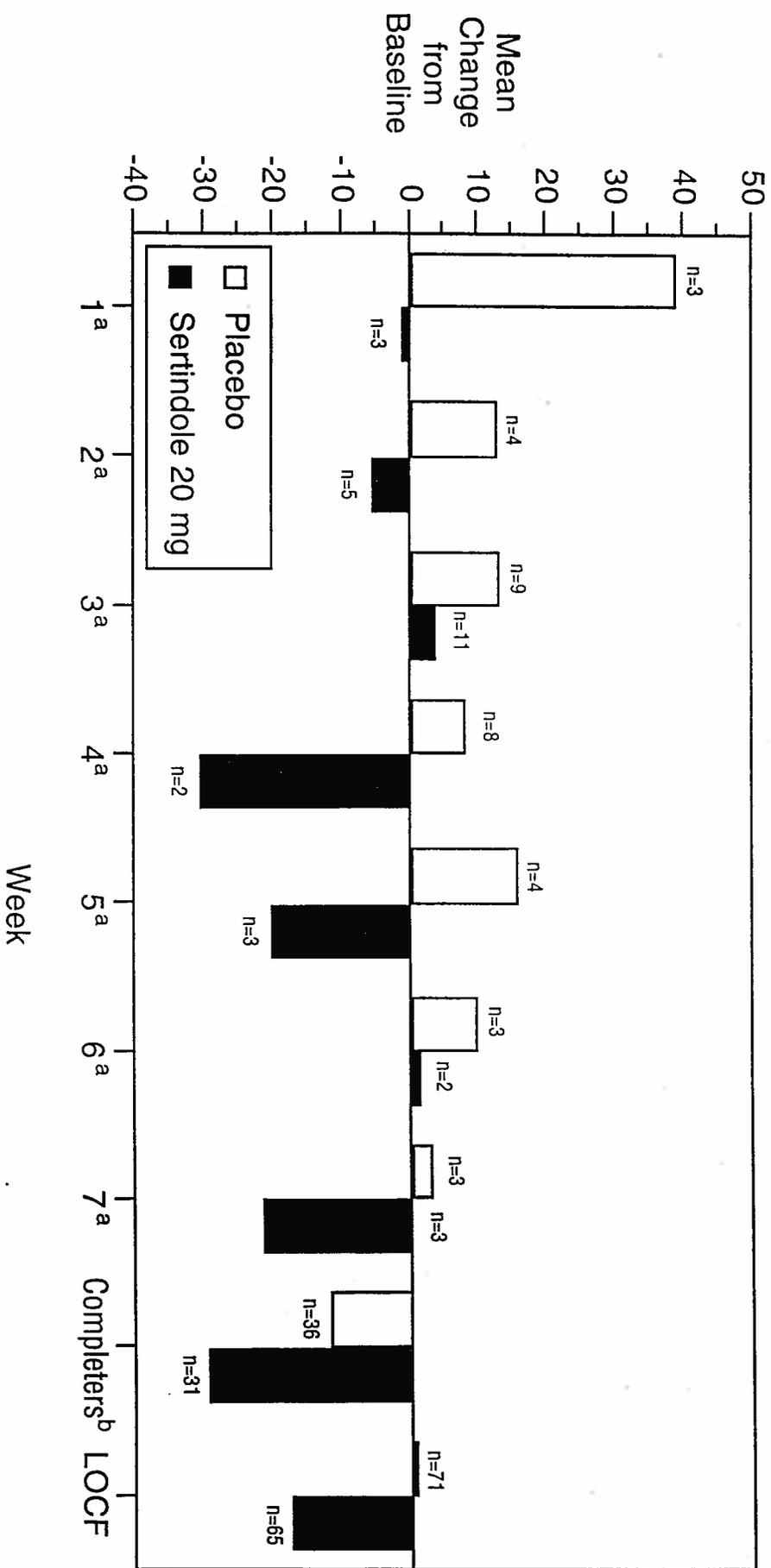


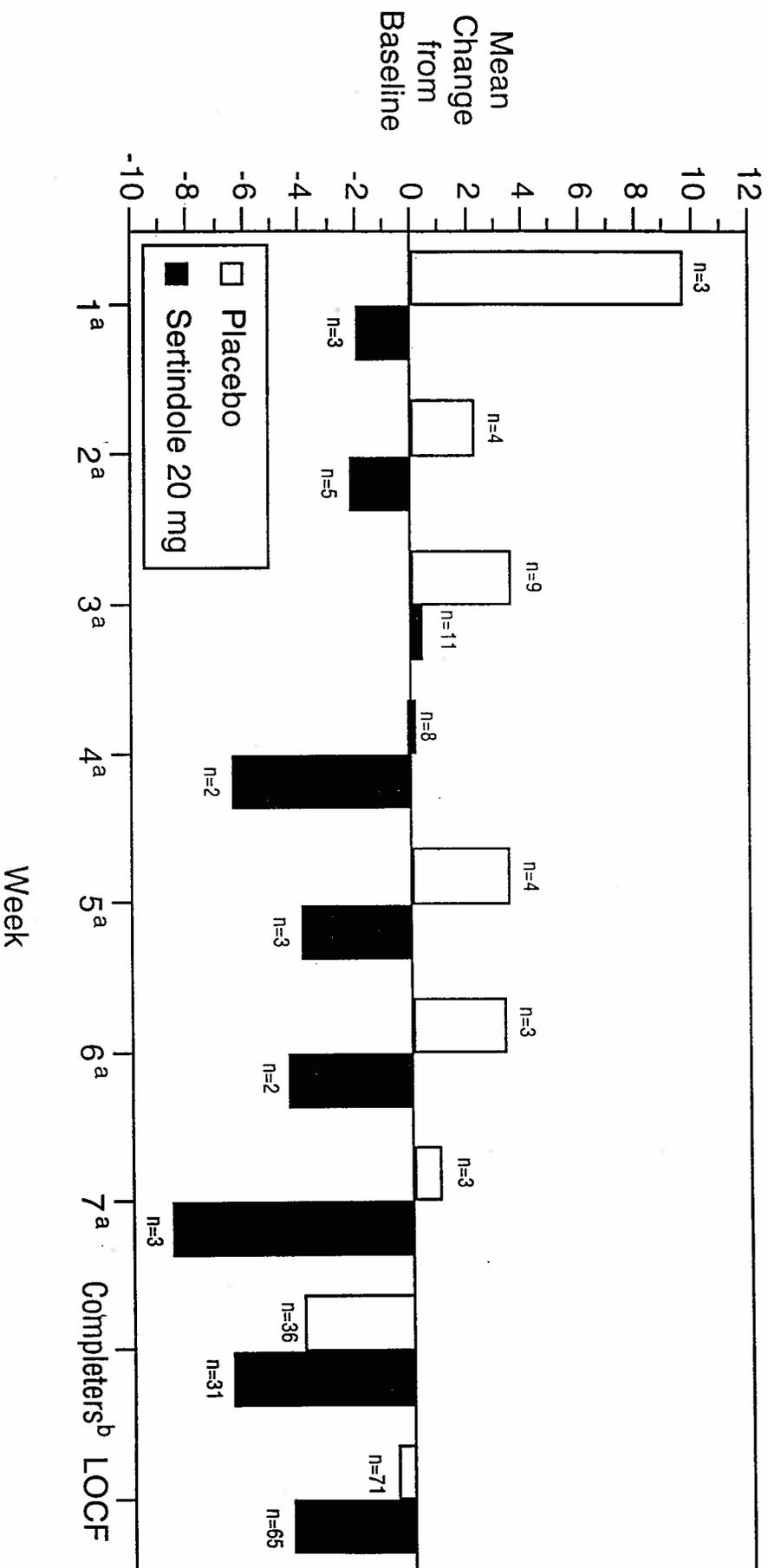
Figure 4a

M93-113: PANSS Total Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.
^b One placebo patient and five sertindole 20 mg patients who had a Day 56 evaluation but dropped before Day 56 are excluded.

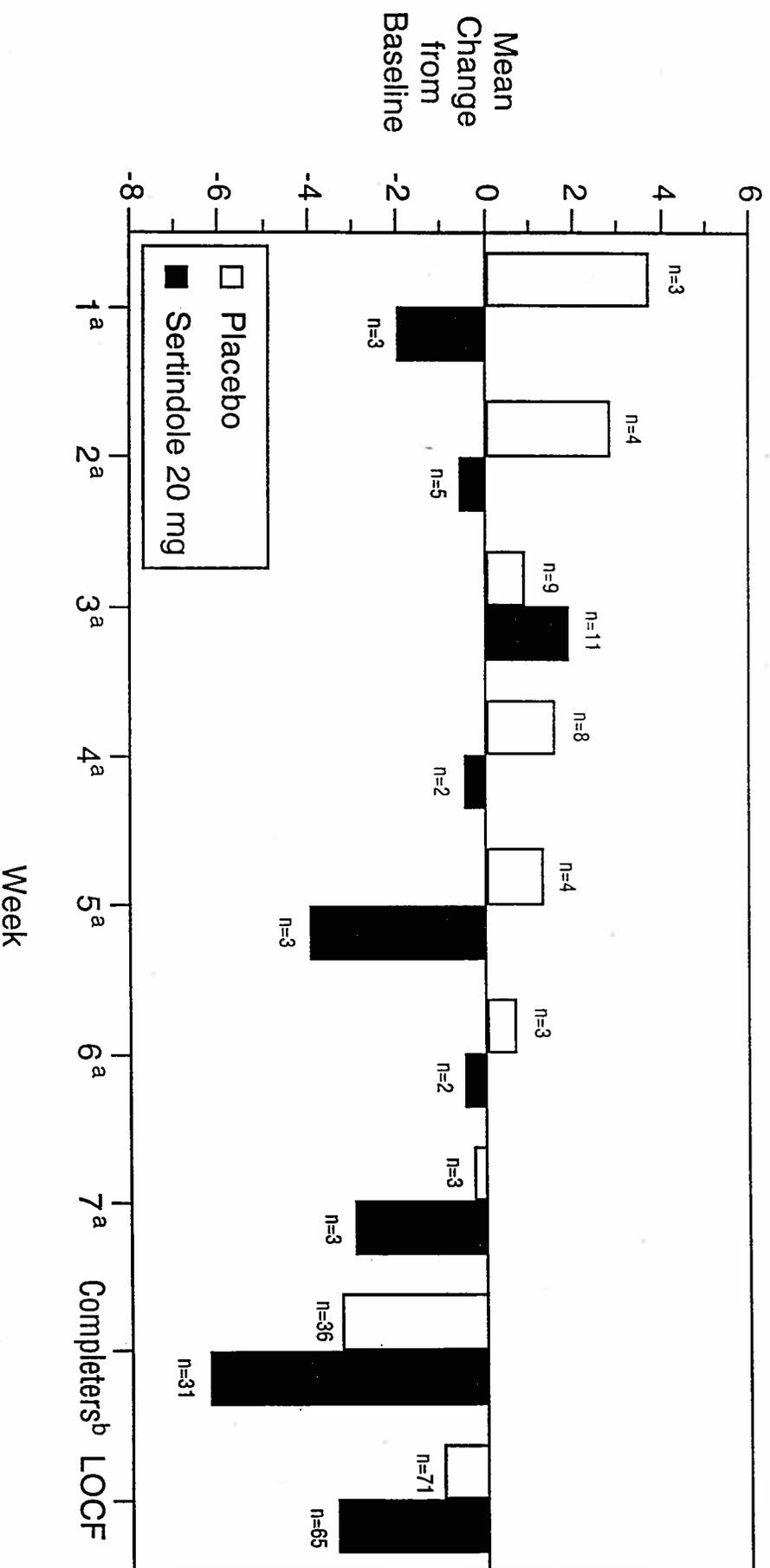
Figure 4b M93-113: PANSS Negative Scale Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

^b One placebo patient and five sertindole 20 mg patients who had a Day 56 evaluation but dropped before Day 56 are excluded.

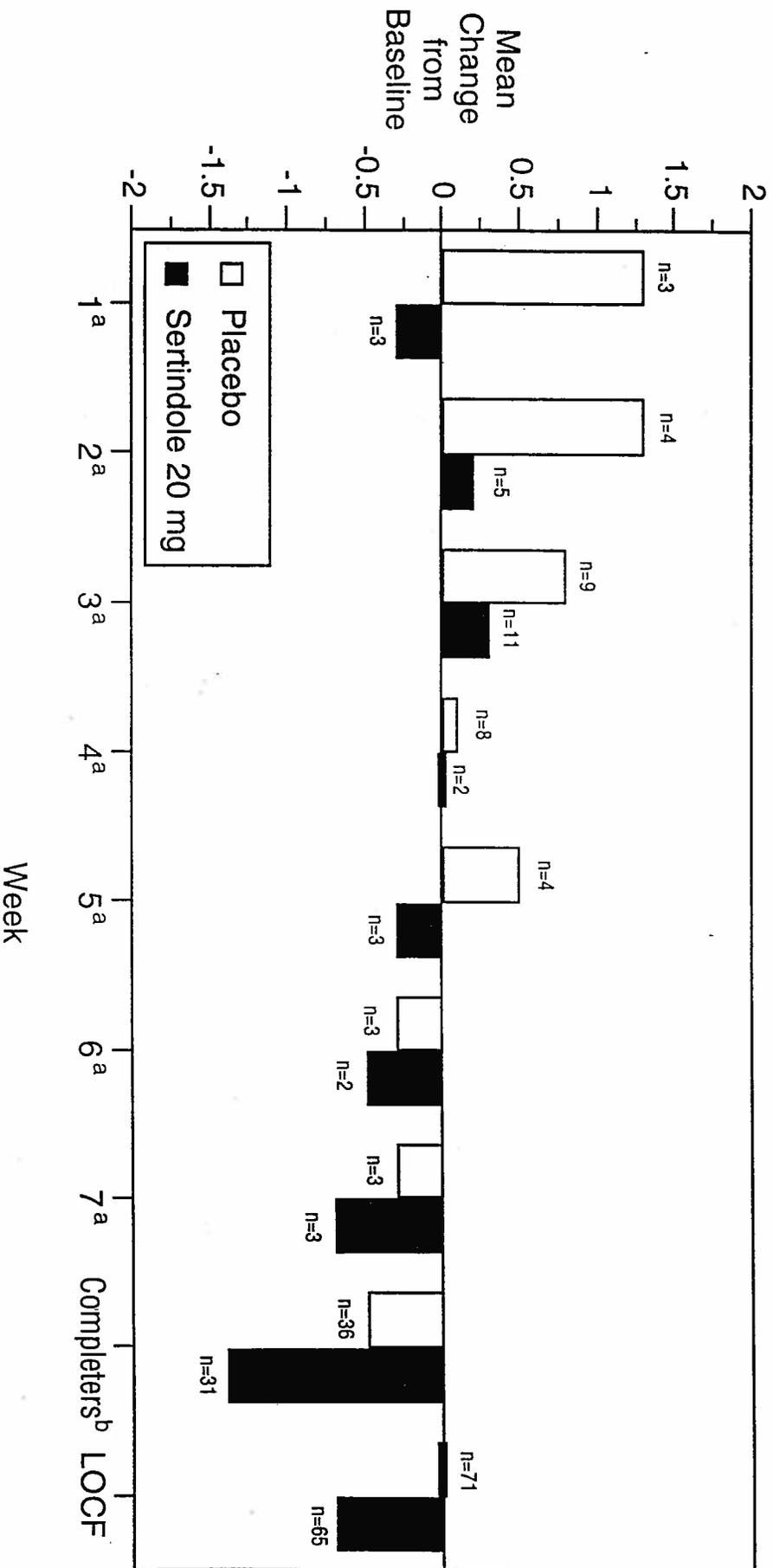
Figure 4c M93-113: BPRS Positive Symptoms Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

^b One placebo patient and five sertindole 20 mg patients who had a Day 56 evaluation but dropped before Day 56 are excluded.

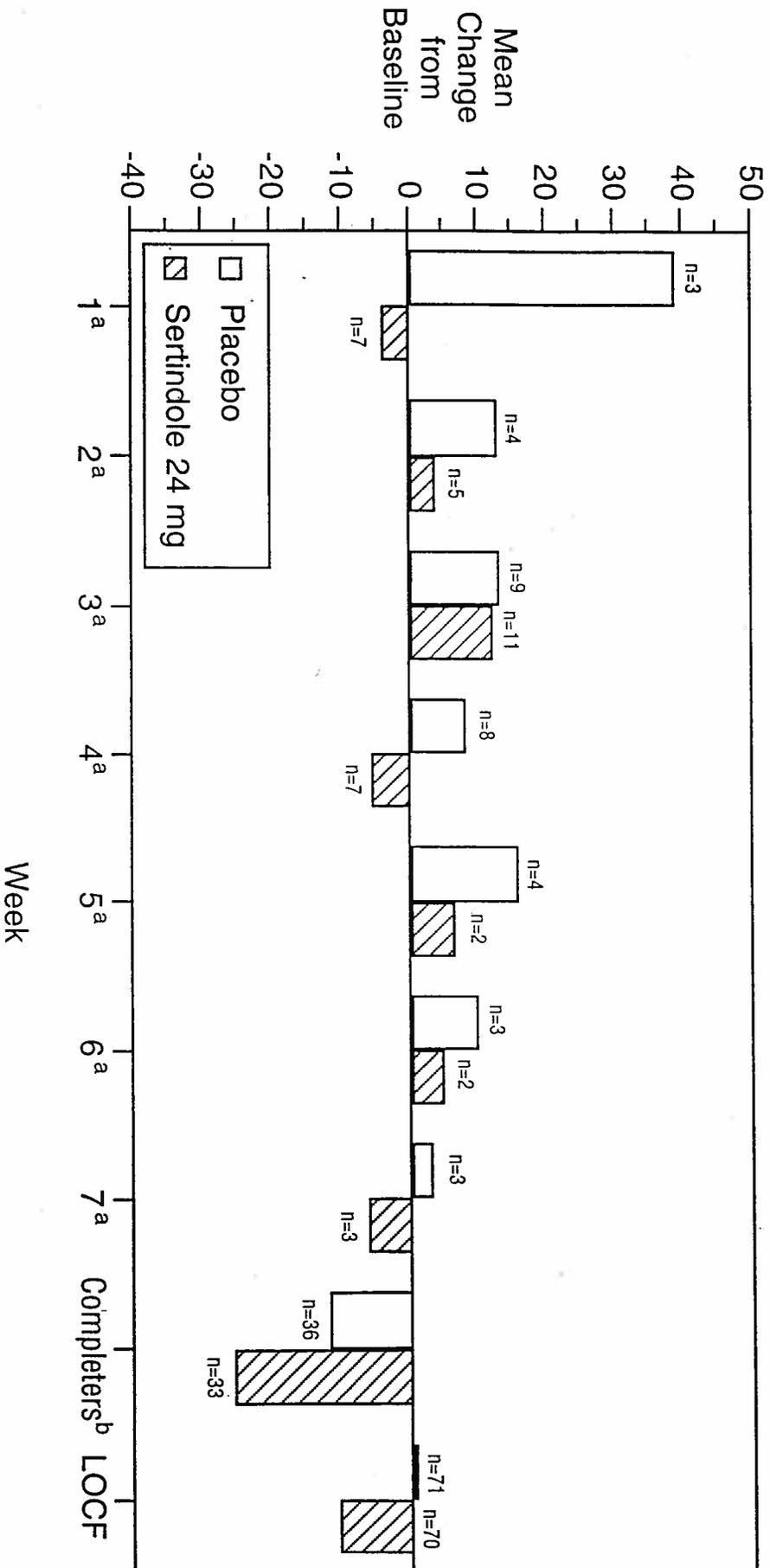
Figure 4d M93-113: CGI Severity – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

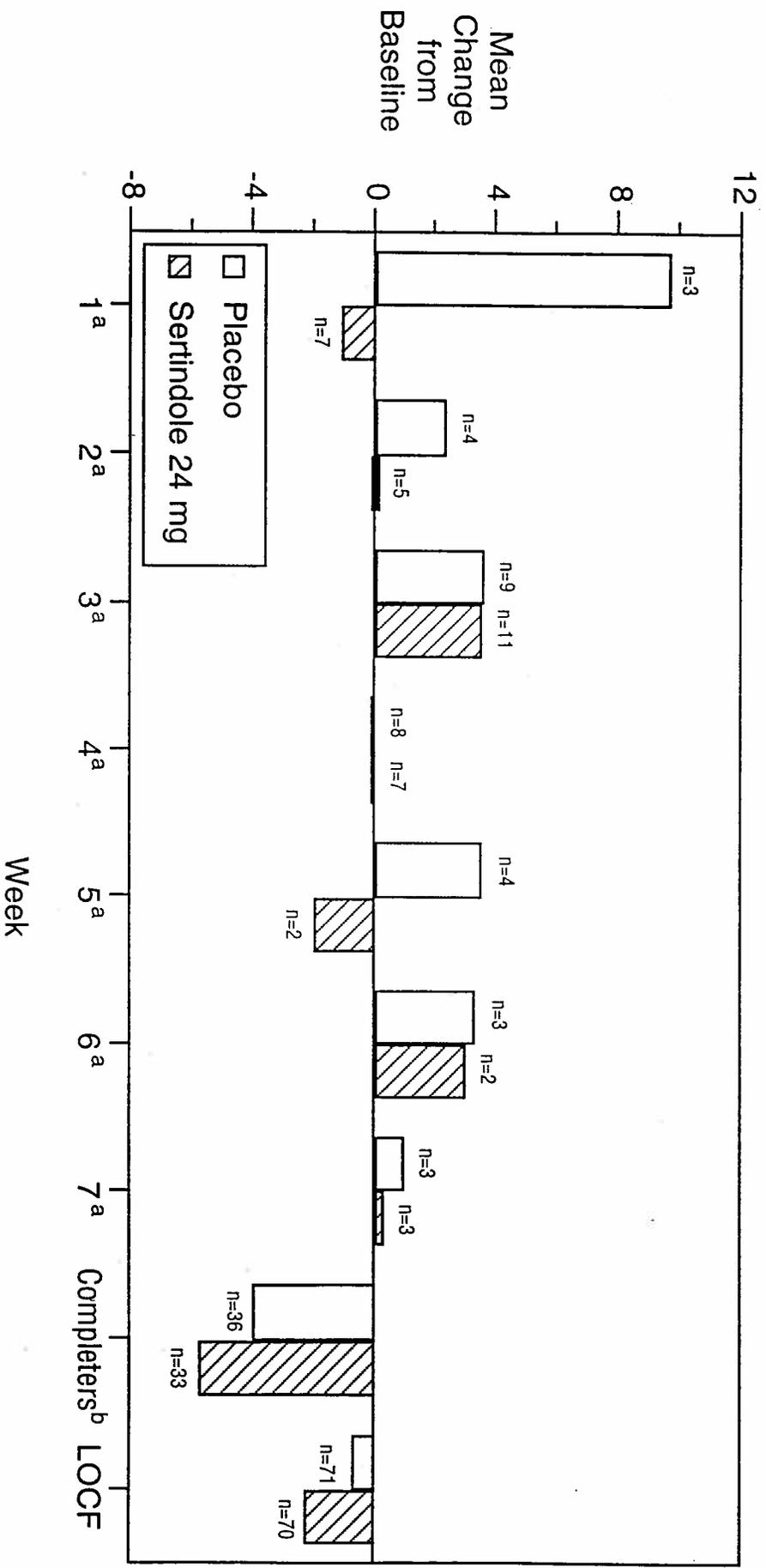
^b One placebo patient and five sertindole 20 mg patients who had a Day 56 evaluation but dropped before Day 56 are excluded.

Figure 5a M93-113: PANSS Total Score – Patients Dropped By Week



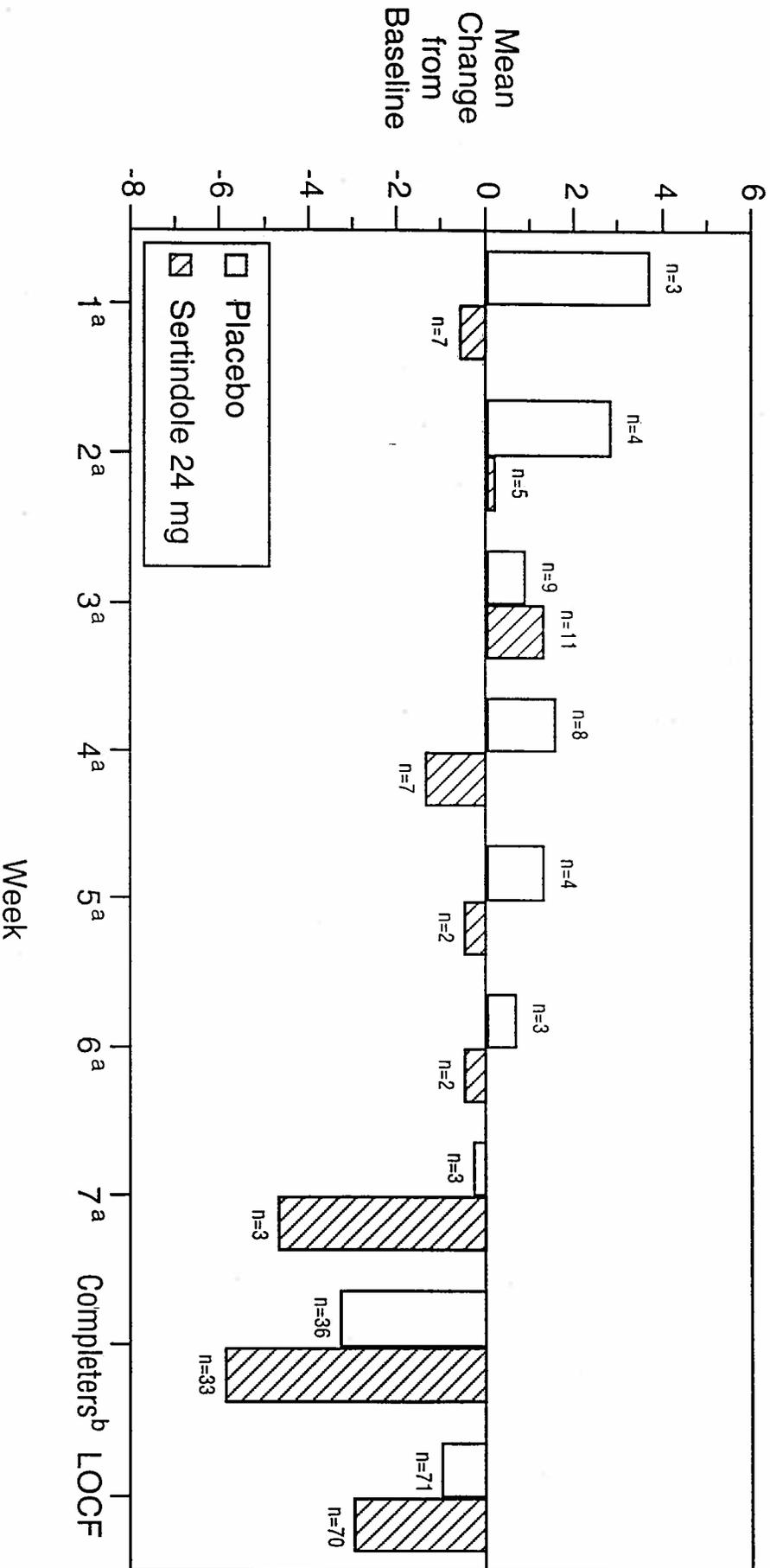
^a Includes patients who completed referenced week visit but dropped before next week visit.
^b One placebo patient who had a Day 56 evaluation but dropped before Day 56 is excluded.

Figure 5b M93-113: PANSS Negative Scale Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.
^b One placebo patient who had a Day 56 evaluation but dropped before Day 56 is excluded.

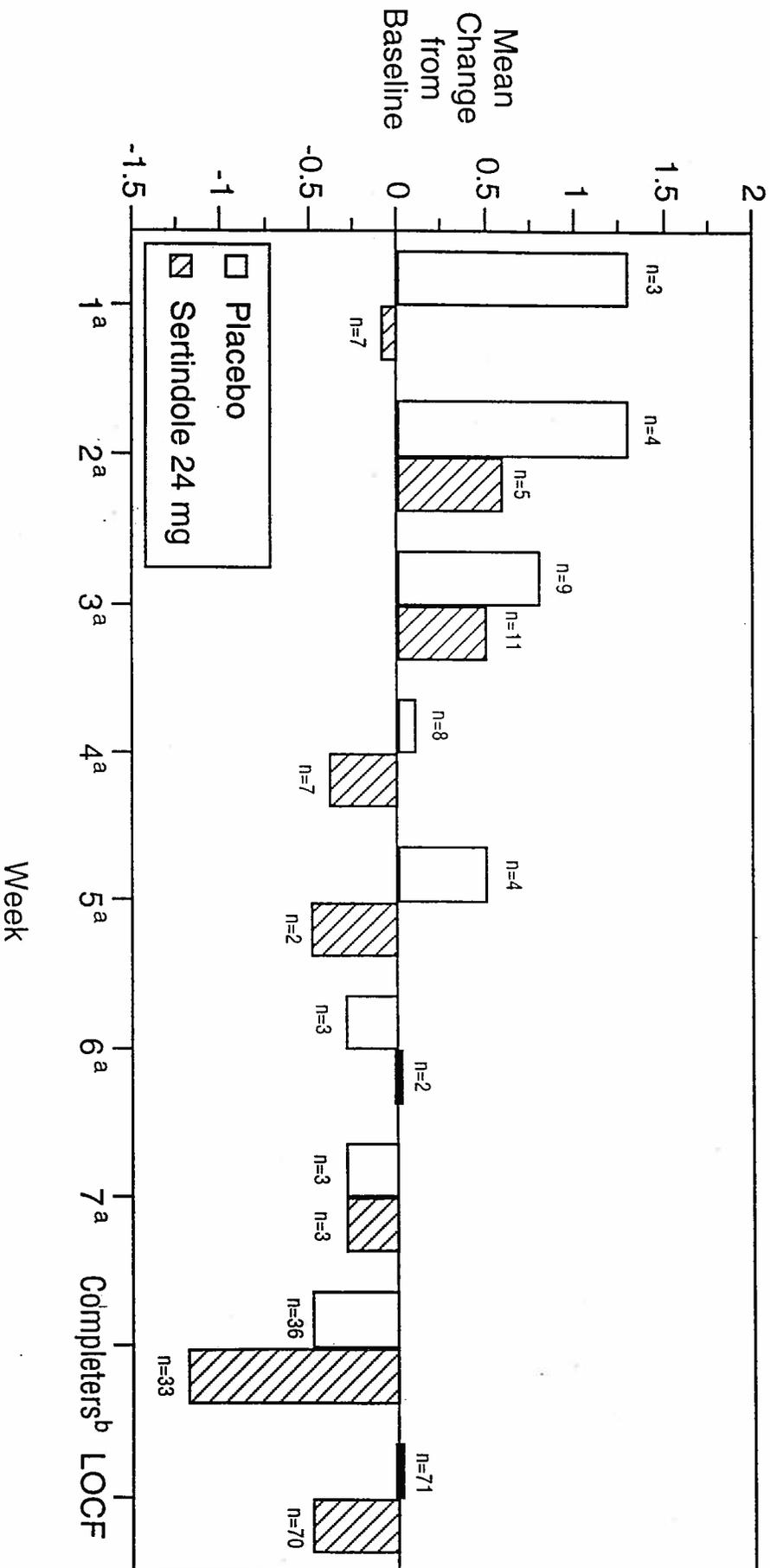
Figure 5c M93-113: BPRS Positive Symptoms Score – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.

^b One placebo patient who had a Day 56 evaluation but dropped before Day 56 is excluded.

Figure 5B M93-113: CGI Severity – Patients Dropped By Week



^a Includes patients who completed referenced week visit but dropped before next week visit.
^b One placebo patient who had a Day 56 evaluation but dropped before Day 56 is excluded.