

**ADDENDUM**  
**Review and Evaluation of Clinical Data**  
**NDA #20-644**

**Sponsor:** Lundbeck USA, Inc.  
**Drug:** SERDOLECT (Sertindole)  
**Proposed Indication:** Schizophrenia, Reduction in the Risk of Fatal and Non-Fatal Suicide Attempts in Schizophrenia  
**Material Submitted:** Re-analysis of Suicide Attempts Using C-CASA Ratings  
**Correspondence Date:** February 13, 2009  
**Date Received:** February 17, 2009

**I. Background**

This is an addendum to the Sertindole Clinical Review (NDA 20-644) dated March 10, 2009. Section 6.2 discusses the Sertindole Cohort Prospective (SCoP) Study, the overall objective of which was to compare the safety of sertindole (n=4930) and risperidone (n=4928) under normal conditions of use. However, 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 sponsor originally presented two analyses of suicide attempts during the WRT+30 day period, which was the pre-specified period for the analysis and reporting of events in the clinical study report. (The Whole Randomized Treatment or WRT period was defined as 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). The first analysis was based on suicide attempts (fatal and non-fatal) as reported by the investigators and then coded using MedDRA as completed suicides or suicide attempts. The second analysis was based on suicide attempts (fatal and non-fatal) as classified by the Independent Safety Committee (ISC), which was blinded to treatment. However, these two analyses yielded conflicting results:

**Table 1 Original Analysis of Results for Suicide Attempts (Fatal and Non-Fatal) During the WRT+30 Days Period**

Classification	Number of Attempts		Hazard Ratio (ser./ris.)	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 FDA 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 fashion. The ISC's classification, although blinded and more systematic, used a definition of suicide attempt that was too broad, for instance including suicidal ideation and tendency. We therefore proposed that the sponsor reclassify the ISC identified suicide attempts (fatal and non-fatal) in a more systematic manner, as described in section II (methodology) below, and reanalyze suicide attempts.

## **II. Requested Reclassification and Reanalysis of Fatal and Non-Fatal Suicide Attempts**

### Methodology

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 (which included fatal and non-fatal attempts as well as ideation and tendency) 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)

## Results

In response to our request, the sponsor forwarded a total of 159 cases (blinded CIOMS forms previously assessed by the ISC as completed suicide/attempt/suicidal ideation and tendency in the WRT+30 days period) to Dr. Kelly Posner at Columbia University, who reclassified them in a blinded fashion using the C-CASA.

The sponsor analyzed the time to first suicide attempt for all events coded 1, 2, or 3 according to C-CASA, utilizing the same Cox Proportional Hazards model and adjustments as in the original analysis. As requested, patients with add-on risperidone, sertindole, or clozapine at the time of the attempt were removed. Of note, the reason sertindole and risperidone add-ons were removed is that one cannot make attribution in cases where a patient is on both. Clozapine add-ons were removed because clozapine is indicated for reducing the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder who are judged to be at risk of re-experiencing suicidal behavior.

However, the results of the sponsor's and the FDA's analysis differ. Of the 5 covariates in the analysis, 212 patients were missing "total duration of schizophrenia" and 28 were missing "time to last suicide attempt." These patients were therefore automatically excluded from the analysis. It is important to note that, among them, there were 2 patients who had suicide attempts and were in the sertindole group. Because these two patients were dropped from the sponsor's analysis, the sponsor's result underestimated the hazards in the sertindole group. The FDA statistical reviewers imputed the missing covariate values (see the FDA Statistical Review for details) for all the patients who had been excluded by the sponsor and then repeated the analysis. Of note, different imputations of the missing covariates yielded similar results.

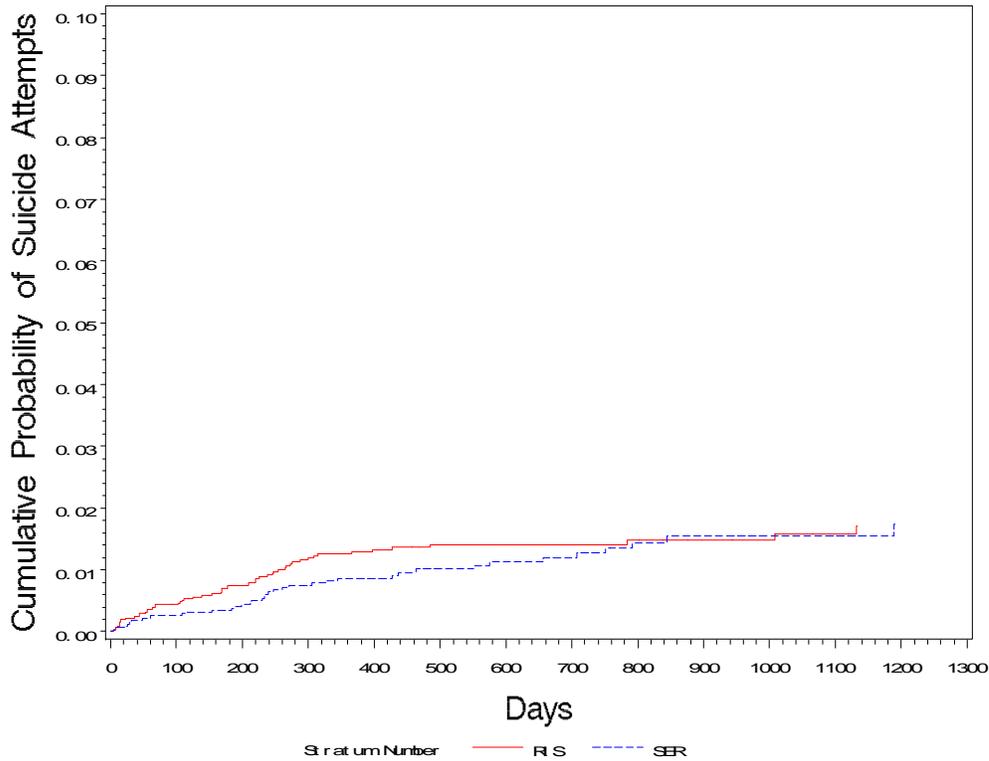
**Table 2 Analysis of Results for Suicide Attempts (Fatal and Non-Fatal) During the WRT+30 Days Period Based on C-CASA Reclassification**

Analysis	Number of Attempts		Hazard Ratio (ser./ris.)	95% CI	p-value
	Sertindole	Risperidone			
Sponsor	44 <sup>a</sup>	62	0.761	0.517-1.121	0.1676
FDA	46	62	0.800	0.546-1.172	0.2511

<sup>a</sup> The sponsor counted 46 suicide attempts but only included 44 in their analysis

Looking at the cumulative probability of suicide attempts (see Figure 1), there is little separation between the curves, which come together around Day 750.

**Figure 1 Cumulative Probably of Suicide Attempts (Fatal and Non-Fatal) During the WRT+30 Days Period Based on FDA Analysis<sup>1</sup>**



<sup>1</sup>By FDA Statistical Reviewer, Steven Bai, Ph.D.

Although WRT+30 days was the pre-specified period for the analysis and reporting of events in the clinical study report, the sponsor presented a supplementary analysis based the ORT+1 day period. (The Only Randomized Treatment or ORT Period was defined as 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, whichever occurred first). The sponsor argues that this period is more relevant and in line with the approach used by the FDA in recent meta-analyses of the potential risk of suicidality (suicidal behavior or ideation) with other drugs. Repeating the above analyses for the ORT+1 day period, the following results were obtained. Again, different imputations of the missing covariates yielded similar results.

**Table 3 Analysis of Results for Suicide Attempts (Fatal and Non-Fatal) During the ORT+1 Day Period Based on C-CASA Reclassification**

Analysis	Number of Attempts		Hazard Ratio (ser./ris.)	95% CI	p-value
	Sertindole	Risperidone			
Sponsor	34 <sup>a</sup>	54	0.661	0.430-1.017	0.0594
FDA	36	54	0.703	0.460-1.072	0.1014

<sup>a</sup>The sponsor counted 36 suicide attempts but only included 34 in their analysis

Of note, the sponsor presented two additional analyses, both of which the Review Team did not consider a reliable way to assess for a possible reduction in suicidality. The first additional analysis looked at time to first suicide attempt for only the first year of treatment. This is an arbitrary cut-off, especially considering that sufficient numbers of patients remained in the study to allow for an analysis encompassing at least the first 3 years of treatment (see Table 4 below). The second additional analysis looked just at completed suicides. However, there are a wide variety of factors that determine whether or not someone dies in a suicide attempt, many of which are completely unrelated to the degree of suicidal intent.

**Table 4 Patients Remaining in Study (ORT+1)<sup>1</sup> at Years 1, 2, and 3**

Treatment	Total Subjects	# (Proportion) of Patients Remaining in Trial at the End of:		
		Year 1	Year 2	Year 3
Sertindole	4905	2335 (.48)	1235 (.25)	602 (.12)
Risperidone	4904	2741 (.56)	1501 (.31)	715 (.15)

<sup>1</sup>ORT+1 was chosen over WRT+30 because it provides a more conservative estimate of the number of people remaining in the study

### III. Conclusions and Recommendations

For the period WRT+30 days (the pre-specified period for the analysis and reporting of events in the clinical study report), both the sponsor and the FDA analysis revealed no significant difference in the time to first suicide attempt (fatal and non-fatal, defined as C-CASA codes 1, 2, and 3) for sertindole vs. risperidone ( $p=0.1676$  and  $p=0.2511$ , respectively). Although it was not requested by the FDA, the sponsor elected to repeat the analysis for the period ORT+1 day, and their results appeared to be marginal ( $p=0.0594$ ). The FDA analysis for the ORT+1 day period also revealed no significant difference in the time to first suicide attempt for sertindole vs. risperidone, with the p-value barely demonstrating a trend ( $p=0.1014$ ). In conclusion, the analysis of the data based on the C-CASA reclassification does not support a significant reduction in fatal and non-fatal suicide attempts in patients with schizophrenia treated with sertindole vs. risperidone.

Phillip D. Kronstein, MD  
March 23, 2009

cc: Keith Kiedrow  
Ni Khin  
Thomas Laughren  
Mitch Mathis  
Gregory Dubitsky  
Peiling Yang  
Yeh-Fong Chen

-----  
**This is a representation of an electronic record that was signed electronically and  
this page is the manifestation of the electronic signature.**  
-----

/s/

-----  
Phillip D Kronstein  
3/23/2009 01:48:36 PM  
MEDICAL OFFICER

Ni Aye Khin  
3/23/2009 03:03:54 PM  
MEDICAL OFFICER