

**AMENDMENT TO:**

**Review and Evaluation of Clinical Data  
NDA #19-758/S-047**

**Sponsor:** Novartis  
**Drug:** Clozaril  
**Proposed Indication:** Suicidality  
**Material Submitted:** Twenty-five Potential Endpoint Packages (PEP's)  
**Correspondence Date:** August 26, 2002  
**Date Received:** August 27, 2002

**I. Background**

Supplement S-047 seeks approval for the use of Clozaril to reduce the risk of suicidality in patients with schizophrenia or schizoaffective disorder. Evidence of this effect rests primarily on the results of study ABA 451. In this trial, patients were randomized to treatment with either Clozaril or Zyprexa over a period of 2 years and monitored for the emergence of suicide-related events (completed suicides, significant suicide attempts, and hospitalizations or increased surveillance due to imminent suicide risk, all called Type 1 events), or changes in a global rating of suicidality (CGI-SS) by a blinded psychiatrist at the site (Type 2 events). The protocol specified that all clinical data regarding events considered potential Type 1 events by the unblinded principal investigator at each site were to be referred to a CRO (Ingenix), which was to censor any information that might reveal the patient's treatment group. After censoring, these data constituted Potential Endpoint Packages (PEP's) which were forwarded to an independent panel of 3 clinicians with expertise in suicidality (the Suicide Monitoring Board or SMB) for determination of whether the patient had experienced a Type 1 event. Additionally, these censored data were forwarded to the blinded psychiatrist (BP) for assessment. However, the primary efficacy analysis utilized only the determination of the SMB.

In all, PEP's for 254 potential Type 1 events among Clozaril patients and 309 among Zyprexa patients were

referred to the SMB. These events are cross-tabulated by the determination of the SMB and by the BP in the table below.

<b>ENUMERATION OF PEP'S REFERRED TO THE SMB BY SMB &amp; BP DETERMINATIONS</b>				
	<b>Clozaril (N=254)</b>		<b>Zyprexa (N=309)</b>	
	<b>BP Event</b>	<b>BP No Event</b>	<b>BP Event</b>	<b>BP No Event</b>
<b>SMB Event</b>	208	9	227	37
<b>SMB No Event</b>	28	9	29	16

Most of the events were classified the same way by both the SMB and the BP's (85% and 79% in the Clozaril and Zyprexa groups, respectively). But, it was noted that the percentage of referred events which were confirmed by the SMB but not deemed to be events by the BP differed significantly between the two groups (9/254 or 4% of the Clozaril events and 37/309 or 12% of the Zyprexa events;  $p=0.0003$ , Mantel-Haenszel Chi-Square).<sup>1</sup> This raised the possibility that the SMB differentially over-read the events in the Zyprexa group, leading to an inflated number of Type 1 events in the Zyprexa group and, thus, biasing the study results in favor in Clozaril. Also, this observation suggests the possibility that perhaps the SMB had become unblinded to the treatment assignment of some patients.

To investigate this possibility, it was decided to audit a 25% sample of the 103 events for which the SMB and BP determinations were discrepant. A random sample of 25 of these 103 events was selected (in proportion to the number of events in the corresponding four cells in the above table). The PEP's for these 25 events were then requested from Novartis.

Upon submission, each PEP was examined by the undersigned to determine whether the SMB determination appeared reasonable and to detect any information in the PEP that could have unblinded the SMB members. The results of this audit are presented below.

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<sup>1</sup> The percentages of events confirmed by the BP's but not confirmed by the SMB were about equal between the two groups: 11% and 9% for Clozaril and Zyprexa, respectively.

## II. Review of PEP's

A listing of the 25 audited PEP events is provided in the appendix to this review. For each event, this listing indicates whether a Type 1 event was deemed to have occurred by 1) the SMB, 2), the BP, and 3) by me.

Despite discrepant judgements between the SMB and BP for all of these events, I identified only 3 events in which I felt that the SMB may have erred. These events are summarized below.

#1 Clozaril patient 131-0001, 8-6-98 event: The PI indicated on the IRSRH form that the event had low risk of injury and there was only occasional suicidal ideation. The SAF indicates that this was an attention-seeking gesture. Clinical progress notes indicate that the patient did not want to live but does not mention any plan to attempt suicide. The patient was admitted to a crisis unit to remove her from a stressful situation. The SMB classified this event as a hospitalization due to imminent suicide risk. I feel that the evidence does not support an imminent suicide risk.

#2 Clozaril patient 120-0003, 9-2-98 event: A consultation report indicates that the patient wished to kill himself and was contemplating taking an overdose. This led to hospital admission. The SMB did not feel that this was due to imminent suicide risk. I feel that there is sufficient evidence to indicate the presence of an imminent suicide risk.

#3 Zyprexa patient 106-0010, 1-3-99 event: The PI stated on the IRSRH form that the patient "wasn't suicidal." However, a hospital assessment note indicates that the patient had command hallucinations to kill himself and planned to buy drugs and take an overdose. The patient was admitted with q15 minute checks. The SMB did not feel that this was a Type 1 event. I believe that this admission was due to an imminent risk of suicide.

Thus, it appears that the SMB overreported one event and underreported one event in the Clozaril group and underreported one event in the Zyprexa group. If these findings are projected to the entire study sample and adjustments made, there would be no change in the number of Clozaril Type 1 events and an increase in the number of

Zyprexa Type 1 events, which would favor the Clozaril group to an even greater extent than the face determinations.

In the course of reviewing these records, I noted 23 instances among events in 6 Clozaril and 9 Zyprexa patients where the assigned treatment group was clearly indicated in the PEP. This could have unblinded SMB members to treatment assignment and possibly led to bias in their determinations. However, in only one of these 15 patients did I feel that the SMB had possibly erred in their determination (event #2 above). In that case, the SMB did not confirm a Type 1 event in a Clozaril patient which I felt had occurred. Such a finding has the potential to produce a bias in favor of Clozaril. However, the SMB determinations appeared to be appropriate for the other 14 events where unblinding and bias could have occurred; this includes four events where knowledge of treatment assignment could have been used to make determinations that favored Clozaril but were not. Thus, it is difficult to conclude that unblinding and consequent biased determinations had occurred at the SMB level in this study.

### **III. Conclusions**

This audit revealed no evidence of systematic, inappropriate SMB determinations of suicidality that, on the whole, would have biased the study results in favor of Clozaril. Although there was evidence of possible unblinding at the SMB level, it cannot be concluded that this produced biased determinations by the SMB.

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August 30, 2002

cc: NDA #19-758  
HFD-120 (Div. File)  
HFD-120/GDubitsky  
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APPENDIX LIST OF AUDITED POTENTIAL ENDPOINT PACKAGES AND DETERMINATIONS OF TYPE 1 EVENTS <sup>2</sup>					
Patient Number	Event Date	TX	+/- Type 1 Event		
			SMB	BP	FDA Reviewer
131-0001	06AUG1998	CLOZ	<b>+</b>	-	<b>-</b>
402-0008	16MAR2000	CLOZ	+	-	+
105-0014	26APR1999	ZYP	+	-	+
105-0020	17NOV1998	ZYP	+	-	+
105-0030	04FEB2000	ZYP	+	-	+
106-0005	11OCT1998	ZYP	+	-	+
115-0001	03FEB1999	ZYP	+	-	+
115-0001	18AUG1999	ZYP	+	-	+
302-0030	31MAR1999	ZYP	+	-	+
304-0001	23JUL1998	ZYP	+	-	+
956-0003	26DEC1998	ZYP	+	-	+
110-0003	06JAN1999	CLOZ	-	+	-
116-0009	14AUG1999	CLOZ	-	+	-
117-0016	11MAY1999	CLOZ	-	+	-
120-0003	15AUG1998	CLOZ	-	+	-
120-0003	02SEP1998	CLOZ	<b>-</b>	+	<b>+</b>
122-0006	26SEP1998	CLOZ	-	+	-
125-0004	09NOV1998	CLOZ	-	+	-
103-0001	13OCT1998	ZYP	-	+	-
106-0010	03JAN1999	ZYP	<b>-</b>	+	<b>+</b>
120-0006	09MAY1999	ZYP	-	+	-
401-0023	24MAR2000	ZYP	-	+	-
401-0023	27OCT2000	ZYP	-	+	-
604-0011	25FEB2000	ZYP	-	+	-
701-0019	09NOV1999	ZYP	-	+	-

<sup>2</sup> +/- means Type 1 event deemed to have occurred/not occurred. TX= treatment group, SMB= Suicide Monitoring Board assessment, BP= Blinded Psychiatrist assessment, FDA Reviewer= my assessment. Instances of disagreement between the SMB and my assessment are bolded.

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/s/

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I agree that this audit provides reassurance about the  
correctness of SMB classifications of potential Type 1  
events.--TPL