NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey

Clozaril® (clozapine)

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1 Potential Bias in the Referral of Information to the SMB

1.1 FDA Issue No. 4:

The FDA reviewed data from the Clinical Global Impression of Change in Severity of Suicidality (CGI-SS) and found that "for both versions of the CGI-SS, the p-values for the between-treatment contrast using the ratings of the unblinded investigators were lower (in favor of clozapine) than those for the between-treatment contrast using the ratings of the blinded psychiatrist. While clearly not proof of bias in the unblinded investigators, these findings raise a concern about the possibility of bias. Furthermore, it is our (FDA) impression that the vast majority of events reviewed by the SMB were referred to the SMB by the unblinded investigators. The numbers of referrals and proportions of those referred who were judged to represent Type 1 events can be summarized as follows:"

	Clozaril	**Zyprexa**	**Difference**
Number of patients referred to SMB	122	157	35
Number patients with a SMB-determined Type 1 event	84% (102/122)	90% (141/157)	39

"It might be argued that, since the unblinded investigators had primary responsibility for deciding which events would be forwarded to the SMB, they may have, due to their bias for clozapine, forwarded more olanzapine events than clozapine events. Since there is clearly a high correlation between the number of referrals and the ultimate number of events judged to be Type 1, any bias in favor of clozapine in deciding which events to refer might have biased the overall results of this study in favor of clozapine."

Please fully clarify the source of referrals to the SMB. It is also critical to describe whether or not the medical monitor was blinded, and, if not, how this affected the referral rate. Finally, please provide a listing of the events referred by Ingenix staff to the unblinded investigators and for which the unblinded investigators decided not to send them on to the SMB.

1.2 Novartis Response to Issue No. 4:

The protocol required the principal investigator (PI) to assess and provide documentation concerning clinical events that might be considered a Type 1 event. To ensure that all potential Type 1 events were identified and subsequently reviewed by the SMB, the following procedures contributed to identification of potential Type 1 events (See Section 3.5.3 of the Clinical Study Report):

1. During scheduled site visits, the Clinical Research Associates (CRAs) reviewed source documents for any unreported potential Type 1 events. If any such cases were identified, the CRA informed the Medical Monitor. The Medical Monitor reviewed these cases and requested the site to send additional documentation and/or a Potential Endpoint Package (PEP).

2. Independently of the CRA site visits, the Medical Monitor reviewed the Serious Adverse Event Forms. If there was evidence of an unreported potential Type 1 event, the Medical Monitor asked the site whether the unreported event might be a potential Type 1 event. Based on the site response, the Medical Monitor requested via a telephone call or documented query that a PEP be prepared and submitted to the SMB, unless the PI provided documentation explicitly noting that this event did not involve suicidal behavior.

If, following the query, the PI's opinion was that an event was not related to suicidal behavior then a PEP was not completed. Because the unblinded PI ultimately decided what constituted suicidal behavior the potential for bias did exist. To investigate whether such referral bias was actually present during the study, Novartis performed the following retrospective review.

1.2.1 Methods

In the following, "patient" refers to all data in the InterSePT database for a particular patient.

Step 1: Identification of Non-PEP Patients

The database was divided into PEP and non-PEP patients, as it was assumed that the referral bias would have occurred in the non-PEP patients (i.e., patients without a potential Type 1 events during the study).

Step 2: Review of Non-PEP Patients

The following databases were used to identify all events potentially related to suicidal behavior:

1) Adverse Event (AE) database: Verbatim AE terms from the case report form (CRF) AE page.
2) Query database: Database of documented queries generated during the study.
3) Comments database: Comments of site staff recorded on the CRF Comments page.

On the basis of these three databases a search term dictionary was developed, which included all terms related to suicidal behavior (Appendix 1). The search term dictionary was embedded in a program that searched for matches between a dictionary term and the same term in a particular patient's data. The search term dictionary was validated by applying the dictionary terms to a random selection of PEP patients (Appendix 2). All of these PEP patients were successfully identified by the search program.

The search term dictionary was then applied to all non-PEP patients. Each search term match yielded the following patient profile (Appendix 3):

- Patient ID
- Patient's randomization date
- Patient's end of study date

- Retrieved dropout (RDO) index if the patient was a RDO patient
- Last date of follow-up, if RDO patient
- AE matches that included PI's AE term, AE start date, AE end date
- Query matches that included query CRF page, query panel, query text
- Comment matches that included comment record number, CRF identifier of comment, verbatim comment

Appendix 3 contains two types of lists. The first list contains patients who had at least one match with the AE database, and the second list contains a patients who did not have an AE match but at least one match with the Query and/or the Comments database(s).

The CRFs of patients from both lists were reviewed to identify unreported potential Type 1 events. This review encompassed not only AEs/SAEs, comments and queries but also all of the relevant clinical material within the CRF. The review focussed specifically on the following:

- Whether or not the PI was queried with respect to the occurrence of suicidal behavior
- If the PI was queried, the PI verbatim response to the query
- Whether or not the AE was potentially related to suicidal behavior
- If the AE was potentially related to suicidal behavior, whether or not it met the criteria for a PEP

The findings of the review are documented in the "Non-PEP Data Review Summary" (Appendix 4). Each summary concludes with the Novartis reviewer's assessment of whether or not the reviewed event met the criteria for a PEP. If the Novartis reviewer concluded that the event met the criteria for a PEP, then a Novartis physician reviewed the data to confirm that the event was a PEP.

1.2.2 Summary of Findings

There were 701 patients in the study that did not have a PEP. Matches to at least one term in the search term dictionary occurred in 279 (40%) of these patients. The review of the data for these 279 non-PEP patients indicates that 5 (0.01%) of these patients experienced an event that may have warranted the submission of a PEP to the SMB (Table 1). Clinical summaries including a Novartis conculsion for these five cases are provided in Appendix 5.

Table 1 Summary of Non-PEP Patients

Category	N
Total Non-PEP Patients	701
Total Non-PEP Patients with at least one match to search term dictionary (Appendicies 3 and 4)	279
Total Non-PEP Patients who experienced an event that may have warranted a PEP	5 (3 Clozaril, 2 Zyprexa)

(Appendix 5)	

1.2.3 Conclusion

The review of the non-PEP patients shows that, for 3 Clozaril and 2 Zyprexa patients, there were potential Type 1 events that were not referred to the SMB. On the basis of these findings it appears unlikely that a bias toward either treatment group existed during the conduct of InterSePT. The results of this review also suggest that, although the InterSePT study design did not completely exclude the potential for bias by the PIs, the PIs themselves acted without bias.

Appendix 1: Search Term Dictionary

Search Terms for Adverse Event Database	
Meddra System Organ Class	**PI's AE Term**
GI disorders	ABDOMINAL EVENTRATION(SUBSEQUENT TO SUICIDE ATTEMPT PRIOR STUDY START)
Injury and poisoning	ABRASION LEAFT HAND
	ABRASION ON LEFT-HAND
	ABRASION ON RIGHT SHIN/ACCIDENT
	ABRASION ON RIGHT SHIN/ACCIDENTAL
	ABRASION TO RGT. KNEE
	ACCIDENTAL FALL
	ACCIDENTAL OVERDOSE OF STUDY MEDICATION
	ACCIDENTAL PARIETAL INJURY
	ACCIDENTAL SUPERFICIAL BURN TO LEFT HAND
	ACCIDENTLY CUTTING OF HER FEET
	ACCIDENTLY CUTTING OF HER FEET CRACKED RIBS
	ALCOHOL BINGE
	ALCOHOL BINGES
	ANKLE INJURY-RIGHT (ACCIDENTAL INJURY)
	BLISTERS LEFT HAND
	BLISTERS ON FOOT (LEFT)
	BLISTERS ON HER BACK
	BROKEN ARM (LEFT) - ACCIDENTAL
	BROKEN LEG (RIGHT) (ACCIDENTAL)
	BRUISED RIGHT KNEE (ACCIDENTAL INJURY,DUE TO FALL)
	BRUISING TO BOTH KNEES (ACCIDENTAL)
	BURN LEFT MIDDLE FINGER (ACCIDENTAL)
	BURN ON CALF, ACCIDENTAL
	BURN TO RIGHT SHOULDER (ACCIDENTAL)
	COMA DUE TO OVERDOSE (OVERDOSE INTENTIONAL BUT NOT SUICIDE ATTEMPT)
	CONTUSION ON SCALP - ACCIDENTAL INJURY
	CRACK COCAINE OVERDOSE (ACCIDENTAL)
	CUT ON ARM (ACCIDENTAL)
	CUT ON HEAD (ACCIDENTAL)
	CUT RIGHT HAND SECONDARY TO ASSAULT
	DRUG INTOXICATION
	DRUG TOXICITY
	DRUNKENNESS
	ETOA (ALCOHOL) INTOXICATION
	FRACTURE IN ANKLE (NO ASSOCIATED SUICIDALITY)

	FRACTURE LEFT FOOT-ACCIDENTAL
	FRACTURE LEFT WRIST (ACCIDENTALFRACTURE OF LEFT ARM (ACCIDENTAL INJURY)
	FRACTURE OF LEFT LOWER EXTREMITY-ACCIDENTAL
	FRACTURE RIGHT ANKLE-ACCIDENTAL
	FRACTURE RIGHT WRIST-ACCIDENTAL FRACTURED RIGHT ARM
	FRACTURED SHOULDER
	FRONTAL INJURY(NOT RELATED TO SUICIDE ATTEMPT)
	GRAZES TO FOREHEAD (ACCIDENT FOLLOWING OVERDOSE)
	HAEMATOMA RIGHT HAND (DUE TO VENEPUNCTURE)
	HAND FRACTURE (ACCIDENTAL)
	HAND FRACTURE (NOT ASSOCIATED WITH SUICIDE ATTEMPT)
	HEAD ABRASION-ACCIDENTAL
	HEAD BRUISE IN PARIETAL REGION (ACCIDENTAL)
	HEAD INJURY
	INADVERTENT OVERDOSE
	INCISION (INJURY OF THE RIGHT HAND BY AN ACCIDENT)
	INJURED LEFT SHOULDER IN FALL (ACCIDENTAL)
	INJURED RIGHT ANKLE (ACCIDENTAL)
	INJURY OF LEFT ARM (ACCIDENTAL)
	INJURY OF LEFT KNEE (ACCIDENTAL INJURY)
	INJURY OF LEFT WRIST (ACCIDENTAL INJURY)
	INTENTIONAL OVERDOSE (NOT SUICIDE ATTEMPT)
	MINITHIN (OTC DIET AID) OVERDOSE - ACCIDENTAL
	MORPHINE OVERDOSE, INTENTIONAL (NOT RELATED TO A SUICIDE ATTEMPT)
	OVERDOSE
	OVERDOSE (CLEARLY NOT SUICIDE ATTEMPT)
	OVERDOSE (INTENTIONAL BUT NOT SUICIDE ATTEMPT) (NAI)
	OVERDOSE (NO ASSOCIATED SUICIDALITY)
	OVERDOSE (NOT SUICIDE ATTEMPT)
	OVERDOSE (NOT SUICIDE ATTEMPT,IMPULSIVE AFTER ROW WITH NEIGHBOURS)
	OVERDOSE (NOT SUICIDE ATTEMPT,NO SPECIFIC AIM)
	OVERDOSE (NOT SUICIDE ATTEMPT,PSYCHOSOCIAL STRESS)
	OVERDOSE (RELATED TO ECONOMIC & SOCIAL ISSUES-NO SUICIDE ATTEMPT MADE)

	SELF HARM (MADE SUPERFICIAL CUTS TO L FOREARM)
	SELF MUTILATION
	SELF MUTILATION (PT TRIED TO REMOVE TATTOOS)
	SLIGHT BURN VESICLES (ACCIDENTAL INJURY)
	SOFT TISSUE INJURY
	SUPERFICIAL ABRASION RIGHT HAND (ACCIDENTAL INJURY)
	SUPERFICIAL ABRASION RIGHT KNEE (ACCIDENTAL INJURY)
	SUPERFICIAL BURN (ACCIDENTAL)
	SUPERFICIAL CUT LFT WRIST INTENTIONAL (SELF-MUTILATION) NOT ATTEMPT
	SUPERFICIAL CUT ON FOREHEAD-ACCIDENT
	SUPERFICIAL FACIAL SKIN INJURY (ACCIDENTAL)
	SUPERFICIAL LACERATIONS BILATERAL SHINS-ACCIDENT
	SUPERFICIAL SCRATCH ON RIGHT HAND-RELATED TO ACCIDENTAL INJURY
	SUSPECTED OVERDOSE (ACCIDENTAL)
	UNINTENTIONAL OVERDOSE
	UNINTENTIONAL OVERDOSE OF 30MG ZYPREXA
	VERTEBRAL COMPRESSION FRACTURE (ACCIDENTAL)
	WALKED IN FRONT OF CAR (ACCIDENTAL
	WOUND IN FOREARM(RIGHT) (NOT SUICIDE ATTEMPT)
Psychiatric disorders	(PRUSIONISM) SELF MUTILATION
	BRUISE RIGHT HAND (ACCIDENTAL INJURY)
	BRUISE TO FOREHEAD (ACCIDENTAL INJURY)
	BRUISE TO L HAND (ACCIDENTAL
	BRUISED ANKLE
	BRUISED BOTH ARMS
	BRUISED EYE (DUE TO ACCIDENTAL FALL)
	BRUISED LEFT EYE
	BRUISED RIBS
	BRUISES (BOTH ARMS ACCIDENTAL)
	BRUISING TO RIGHT ELBOW
	DEATH BY SUICIDE(HANGING
	DESIRE TO SELF-HARM
	DESTRUCTIVE BEHAVIOR
	EXPRESSING SUICIDE IDEAS
	FEELING SUICIDAL
	FELT SUICIDAL
	FRACTURE OF RIGHT TIBIA AND FIBULA (SUICIDE

	ATTEMPT)
	HOSPITAL ADMISSION DUE TO STRESS
	HOSPITALISATION DUE TO INCREASING OF SCHIZOPHRENIA
	HOSPITALISATION DUE TO MEDICATION CHANGE DUE TO DEPRESSION
	HOSPITALISATION FOR ANXIETY
	HOSPITALISATION FOR THERAPY TITRATION DUE TO SUICIDAL IDEATION
	HOSPITALIZATION DUE TO INCREASING PSYCHOSIS
	HOSPITALIZATION DUE TO PREVENTION OF HETROAGRESIVE BEHAVIOR.
	HOSPITALIZATION TO PREVENT SUICIDE ATTEMPT
	HOSPITALIZED - SUICIDAL IDEATION
	IMMINENT RISK OF SUICIDE
	INCREASE IN SUICIDAL IDEATION
	INCREASE IN SUICIDAL IDEATIONS
	INCREASE IN SUICIDALITY
	INCREASE OF SUICIDAL IDEATION
	INCREASE OF SUICIDAL IDEATIONS
	INCREASE OF SUICIDALITY
	INCREASE OF SUICIDALITY,SUICIDAL THOUGHTS
	INCREASE OF SURVEILLANCE (BECAUSE PATIENT OVERDOSED ON ZOPICLONE)
	INCREASE SUICIDAL IDEATION
	INCREASE SUICIDALITY
	INCREASE SUICIDALITY HOSPITALIZATION
	INCREASED RISK OF SUICIDE
	INCREASED RISK OF SUICIDE ATTEMPT
	INCREASED SELF-HARM BEHAVIOR
	INCREASED SUCIDALITY
	INCREASED SUICIDAL IDEATION
	INCREASED SUICIDAL IDEATIONS
	INCREASED SUICIDAL THOUGHTS
	INCREASED SUICIDALITY
	INCREASED THOUGHTS OF SELF HARM
	INJURY OF LEFT WRIST (RELATED TO SUICIDE ATTEMPT)
	INJURY PAIN (DUE TO CUT ON LEFT LOWER ARM FROM SUICIDE ATTEMPT
	INTENTIONAL LACERATED RIGHT FOREARM-NOT RELATED TO SUICIDE ATTEMPT
	INTENTIONAL SUPERFICIAL CUT ON FOREARM RELATED TO SUICIDE ATTEMPT
	INTERMITTENT SUICIDAL IDEATION
	INTERMITTENT SUICIDAL IDEATIONS

	MILD SUICIDAL IDEATION
	MILDLY SUICIDAL
	OVERDOSE (SUICIDE ATTEMPT)
	OVERDOSE OF CON-MEDS (SUICIDE ATTEMPT)
	OVERDOSE/SUICIDE ATTEMPT
	OVERDOSE-INTENTIONAL-GESTURE
	OVERDOSE-SUICIDE ATTEMPT
	RIGHT FOOT METATARSUS FRACTURE (RELATED TO SUICIDE ATTEMPT)
	RISK OF SELF HARM
	SCRATCHES-LEFT FOREARM AND LEFT LEG (SELF-INFLICTED)
	SELF HARM (CUT LEFT FOREARM)(GESTURE NOT SUICIDE ATTEMPT)
	SELF INFLICTED BURNS LEFT HAND-NOT RELATED TO SUICIDE ATTEMPT
	SELF INFLICTED CUT TO LEFT ARM-NOT RELATED TO SUICIDE ATTEMPT
	SELF INFLICTED SCRATCHES TO LEFT ARM -NOT RELATED TO SUICIDE ATTEMPT
	SELF MUTILATION DELUSION
	SELF-HARM (IDEAS OF)
	SELF-HARM IDEATION
	SELF-HARM SUPERFICIAL LACERATIONS TO RIGHT FOOT (NOT SUICIDE ATTEMPT)
	SELF-INDUCED VOMITING
	SELF-MUTILATION
	SEVERELY SUICIDAL
	SUCIDAL IDEATION
	SUICICDAL IDEATION
	SUICIDAL
	SUICIDAL ATTEMPT - HANGING
	SUICIDAL ATTEMPT (OVERDOSE AND SWALLOWING A PIECE OF SOAP)
	SUICIDAL ATTEMPT BY JUMPING
	SUICIDAL ATTEMPT BY OVERDOSE
	SUICIDAL ATTEMPT/DRUG
	SUICIDAL ATTEMPT/OVERDOSE
	SUICIDAL GESTURE(MILD OVERDOSE)
	SUICIDAL IDEALISM
	SUICIDAL IDEAS
	SUICIDAL IDEATION
	SUICIDAL IDEATION AND PLAN
	SUICIDAL IDEATION INCREASE
	SUICIDAL IDEATION INCREASED
	SUICIDAL IDEATION SECONDARY TO CHRONIC BACK

	PAIN
	SUICIDAL IDEATION SECONDARY TO LEG PAIN AND HERNIATED DISC
	SUICIDAL IDEATION W/PLAN
	SUICIDAL IDEATION(VAGUE)
	SUICIDAL IDEATION/SUICIDE ATTEMPT
	SUICIDAL IDEATION-INTERMITTENT
	SUICIDAL IDEATION-PASSIVE
	SUICIDAL IDEATIONS
	SUICIDAL INTENTION
	SUICIDAL THINKING
	SUICIDAL THINKING WITH IMMINENT RISK OF SUICIDE
	SUICIDAL THOUGHT
	SUICIDAL THOUGHTS
	SUICIDAL THOUGHTS (INTERMITTENT)
	SUICIDAL THOUGHTS (SUICIDAL RISK)
	SUICIDAL THREATS
	SUICIDALITY
	SUICIDALITY (SUBSEQUENT HOSPITAL ADMISSION)
	SUICIDALITY(WORSENING)
	SUICIDE
	SUICIDE (JUMPING IN FRONT OF A TRAIN)-DEATH
	SUICIDE ATTEMPT
	SUICIDE ATTEMPT - OVERDOSE
	SUICIDE ATTEMPT (BLEACHED RIGHT AND LEFT EYES)
	SUICIDE ATTEMPT (CARBON MONOXIDE POISONING)
	SUICIDE ATTEMPT (CUTTING OF LEFT FOREARM)
	SUICIDE ATTEMPT (DUE TO ZYPREXA OVERDOSE)
	SUICIDE ATTEMPT (ELECTRICITY)
	SUICIDE ATTEMPT (HANGING)
	SUICIDE ATTEMPT (HANGING+PHLEBOTOMY)
	SUICIDE ATTEMPT (JUMPED IN A RIVER)
	SUICIDE ATTEMPT (JUMPED IN FRONT OF MOVING VEHICLE)
	SUICIDE ATTEMPT (OVERDOSE OF HEROIN)
	SUICIDE ATTEMPT (OVERDOSE OF RIVOTRIL)
	SUICIDE ATTEMPT (OVERDOSE)
	SUICIDE ATTEMPT (PATIENT STOOD ON BRIDGE)
	SUICIDE ATTEMPT (RAN ALONG CROWDED AVENUE-INTENTION OF BEING KILLED)
	SUICIDE ATTEMPT (RUSSIAN ROULETTE WITH GUN)
	SUICIDE ATTEMPT (SELF INFLICTED LACERATIONS TO RIGHT WRIST WITH BLADE)
	SUICIDE ATTEMPT (SLASHING OF LEFT ARM)

	SUICIDE ATTEMPT (TRAFFIC ACCIDENT)
	SUICIDE ATTEMPT (WALKED INTO TRAFFIC WITH EYES CLOSED)
	SUICIDE ATTEMPT (WENT INTO A LAKE)
	SUICIDE ATTEMPT (WRIST SLASHING)
	SUICIDE ATTEMPT (WRIST SLASHING,SELF MUTILATION)
	SUICIDE ATTEMPT BY ACUTE POLYPHARMACY INTOXICATION RESULTING IN DEATH
	SUICIDE ATTEMPT BY ASPHYXIATION
	SUICIDE ATTEMPT BY BURNING LEADING TO DEATH
	SUICIDE ATTEMPT BY HANGING
	SUICIDE ATTEMPT BY HANGING RESULTING IN DEATH
	SUICIDE ATTEMPT BY INGESTION OF LAMP OIL
	SUICIDE ATTEMPT BY INGESTION OF POISON
	SUICIDE ATTEMPT BY LACERATION
	SUICIDE ATTEMPT BY O.D.
	SUICIDE ATTEMPT BY OVERDOSE
	SUICIDE ATTEMPT BY OVERDOSE (DUE TO INCR. PSYCHOSIS,LIFE STRESS EVENT)
	SUICIDE ATTEMPT BY OVERDOSE (WITH PARACETAMOL (INTENTIONAL))
	SUICIDE ATTEMPT BY OVERDOSE ATTEMPT
	SUICIDE ATTEMPT BY OVERDOSE LEADING TO DEATH
	SUICIDE ATTEMPT BY OVERDOSE(GESTURE SEEKING)
	SUICIDE ATTEMPT BY POISONING BY KITCHENS GAS
	SUICIDE ATTEMPT BY SELF-MUTILATION
	SUICIDE ATTEMPT DUE TO PSYCHOSIS(SELFMUTILATION-PT CUT LEFT LOWER ARM)
	SUICIDE ATTEMPT VIA WRIST SLASHING
	SUICIDE ATTEMPT WITH OVERDOSE
	SUICIDE ATTEMPT, SELF-MUTILATION
	SUICIDE ATTEMPT/HANGING/DEATH
	SUICIDE ATTEMPT/INCREASE PSYCHOSIS
	SUICIDE ATTEMPT/OVERDOSE
	SUICIDE ATTEMPT/SELF HARM
	SUICIDE ATTEMPT-CUT WRIST WITH PAPER CLIP
	SUICIDE ATTEMPT-GESTURES
	SUICIDE ATTEMPT-HEAD BANGING
	SUICIDE ATTEMPT-LACERATIONS TO WRISTS
	SUICIDE ATTEMPT-OVERDOSE
	SUICIDE ATTEMPT-OVERDOSE OF RESTORIL
	SUICIDE ATTEMPT-OVERDOSE OF TRIAL AND

	CONCOMITANT MEDICATION
	SUICIDE GESTURE
	SUICIDE IDEATION
	SUICIDE INTENTIONS
	SUICIDE RISK
	SUICIDE THREAT
	SUICIDE/DEATH BY HANGING
	SUPERFICIAL ABRASIONS LEFT FOREARM(INTENTIONAL)
	SUPERFICIAL ABRASIONS LEFT WRIST (INTENTIONAL)
	SUPERFICIAL ABRASIONS RIGHT FOREARM (INTENTIONAL)
	SUPERFICIAL CUT TO LEFT FOREARM (GESTURE)
	SUPERFICIAL CUTS-LEFT FOREARM (SELF-INFLICTED)
	SUPERFICIAL LACERATIONS TO WRISTS (TO FEEL PAIN, NOT TO KILL HERSELF)
	SUPERFICIAL LACERATIONS TO WRISTS(TO EXPERIENCE PAIN,NOT ATTEMPT)
	SUPERFICIAL SCRATCHES-BOTH FOREARMS SELF-INFLICTED NOT SUICIDE ATTEMPT
	THOUGHTS OF OVERDOSING
	THOUGHTS OF SELF HARM
	THOUGHTS OF SELF-HARM (PATIENT DID NOT MAKE SUICIDE ATTEMPT)
	THOUGHTS OF SELF-HARM WITH SUICIDAL IDEATION
	THREAT OF FIRE SETTING
	THREATENING TO OVERDOSE
	WORSENING OF SUICIDALITY
	ZYPREXA OVERDOSE – INTENTIONAL
Social Circumstances	ADMISSION FOR OBSERVATION (FOR POSSIBLE REBOUND PSYCHOSIS)
	ADMISSION FOR RESPITE CARE
	ADMISSION FOR RESPITE CARE IN RESIDENTIAL HOME
	ADMISSION FOR SOCIAL REASON
	HOSP DUE TO FAMILY CONFLICT
	HOSPITAL ADMISSION(RESPITE CARE)
	HOSPITALISATION DUE TO FAMILY CONFLICT
	HOSPITALISATION DUE TO SOCIAL REASON
	HOSPITALISATION DUE TO SOCIAL REASONS
	HOSPITALISATION FOR LONELINESS
	HOSPITALISATION FOR SOCIAL REASON
	HOSPITALISATION FOR SOCIAL REASONS
	HOSPITALISATION FOR SOCIAL REASONS

	(PSYCHOSIS)
	HOSPITALIZATION DUE TO ASSESSMENT TO WORKING ABILITY
	HOSPITALIZATION DUE TO SOCIAL REASONS
	HOSPITALIZATION FOR SOCIAL REASON
	HOSPITALIZATION FOR SOCIAL REASONS
Surgical and Medical Procedures	BRUISING OVER R ANTECUBITAL FOSSA (ACCIDENTAL AND DUE TO VENEPUNCTURE)
	BRUISING OVER RIGHT ANTECUBITAL FOSSA-ACCIDENTAL DUE TO VENIPUNCTURE
	HOSPITALIZATION FOR BETTER SURVEILLANCE OF THE COMPLIANCE OF STUDY MED
	HOSPITALIZATION FOR PRACTICAL REASONS
Search Terms for Query and CRF Comments Databases	
Search Term	HIGHER LEVEL OF SURVEILLANCE FOR SUICIDALITY
	PE
	PEP
	POTENTIAL ENDPOINT
	SUICIDE ATTEMPT
	TYPE 1

Appendix 2: Validation of Search Term Dictionary

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-106-0010 (Randomization: 15OCT1998, EOS: 09FEB2001)

AE term	AE Dates
----------SUICIDAL IDEATION	09/06/2000 to 09/08/2000----------
----------SUICIDALITY	01/03/1999 to 01/05/1999----------

This patient has no Query matches.

This patient has no Comment matches.

[/proj/genesis/data/devl/CLEX123/CLEX123ABA451/final/pgm_eff/srchchku.sas] Table Generation: 10OCT02

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-114-0002 (Randomization: 16JUL1998, EOS: 08SEP1998)

AE term	AE Dates
----------SUICIDAL IDEATION	08/07/1998 to 08/12/1998----------

This patient has no Query matches.

This patient has no Comment matches.

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-123-0002 (Randomization: 12AUG1998, EOS: 08DEC1999, RDO Patient, RDO Last Date: 23AUG2000)

AE term	AE Dates
----------SUICIDALITY	12/10/1999 to 12/20/1999----------
----------SUICIDALITY	08/30/1998 to 09/17/1998----------
----------SUICIDE ATTEMPT (OVERDOSE)	11/24/1999 to 11/24/1999----------
----------SUICIDE ATTEMPT (OVERDOSE)	03/25/1999 to 03/26/1999----------

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This patient has no Query matches.

Matched Comment

Rec #	CRF Identifier	Comment
4	DC	(SUICIDE ATTEMPT). PLEASE NOTE THAT PT HAD EXTRA MEDICATION FROM

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-123-0007 (Randomization: 21AUG1998, EOS: 10NOV1998, RDO Patient, RDO Last Date: 04AUG1999)

AE term	AE Dates
----------SUICIDALITY	10/01/1998 to 10/22/1998----------

This patient has no Query matches.

This patient has no Comment matches.

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-125-0018 (Randomization: 27OCT1998, EOS: 23OCT2000)

AE term	AE Dates
----------SUICIDAL IDEATION	03/11/1999 to 03/19/1999----------
----------SUICIDALITY	12/28/1998 to 01/22/1999----------
----------SUICIDALITY	12/08/1998 to 12/10/1998----------

This patient has no Query matches.

This patient has no Comment matches.

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-304-0011 (Randomization: 12JAN1999, EOS: 09JAN2001)

AE term	AE Dates
----------BRUISED BOTH ARMS	04/26/2000 to 05/09/2000----------
----------BRUISED LEFT EYE	04/26/2000 to 05/09/2000----------
----------FEELING SUICIDAL	02/10/1999 to 02/22/1999----------
----------FEELING SUICIDAL	01/31/1999 to 02/09/1999----------
----------SUICIDAL IDEATION	10/09/1999 to 11/16/1999----------
----------SUICIDAL IDEATION	04/25/2000 to 05/04/2000----------
----------SUICIDALITY (SUBSEQUENT HOSPITAL ADMISSION)	06/06/2000 to 07/24/2000----------

This patient has no Query matches.

This patient has no Comment matches.

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-401-0003 (Randomization: 20AUG1998, EOS: 17AUG2000)

AE term	AE Dates
INCREASE OF SUICIDAL IDEATION	05/07/1999 to 06/07/1999
INCREASE OF SUICIDALITY	10/13/1999 to EOS
SUICIDAL IDEATION	04/16/1999 to 05/07/1999

This patient has no Query matches.

This patient has no Comment matches.

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-605-0006 (Randomization: 25AUG1998, EOS: 21AUG2000)

AE term	AE Dates
INCREASED RISK OF SUICIDE ATTEMPT	09/23/1998 to 11/02/1998
SUICIDAL IDEATION	05/05/1999 to 06/14/1999

This patient has no Query matches.

Matched Comment

Rec #	CRF Identifier	Comment
2	BK 6050006	THE PATIENT TOLD US,SHE HAD SUICIDE ATTEMPT WHEN SHE WAS 14 YEARS

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-903-0005 (Randomization: 10DEC1998, EOS: 03MAY1999, RDO Patient, RDO Last Date: 04DEC2000)

AE term	AE Dates
----------SUICIDE ATTEMPT (OVERDOSE)	01/06/1999 to 01/07/1999----------

This patient has no Query matches.

Matched Comment

Rec #	CRF Identifier	Comment
3	BK1	NUMBER OF LIFETIME SUICIDE ATTEMPTS(2 DOCUMENTED)7 IS THE BEST GUESS

Novartis PEP Patients For Search Term Review Protocol ABA451

Search Matches for ABA-451-956-0003 (Randomization: 23DEC1998, EOS: 19DEC2000)

AE term	AE Dates
----------SUICIDAL IDEATION	09/14/1999 to 11/04/1999----------
----------SUICIDE ATTEMPT BY INGESTION OF POISON	12/26/1998 to 12/26/1998----------
----------SUICIDE RISK	01/05/1999 to 01/15/1999----------

This patient has no Query matches.

Matched Comment

Rec #	CRF Identifier	Comment
1	DC	PATIENT DIDNT TAKE ZYPREXA FOR SEVERAL DAYS DUE TO HIS SUICIDE ATTEMPT

List of PEPs for Selected Patients

Patient ID	Event Date	Did SMB consider endpt?	Which type of endpt?
ABA-451-106-0010	01/03/1999	No	.
	09/06/2000	No	.
ABA-451-114-0002	08/07/1998	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-123-0002	03/25/1999	Yes	Suicide attempt
	04/10/2000	Yes	Hosp.risk suicide/incr.lvl.surv
	08/30/1998	Yes	Hosp.risk suicide/incr.lvl.surv
	11/24/1999	No	.
	12/10/1999	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-123-0007	01/13/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	04/26/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	10/01/1998	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-125-0018	03/11/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	12/31/1998	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-304-0011	01/31/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	06/06/2000	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-401-0003	05/07/1999	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-605-0006	05/19/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	09/23/1998	Yes	Hosp.risk suicide/incr.lvl.surv
ABA-451-903-0005	01/06/1999	Yes	Suicide attempt
ABA-451-956-0003	01/05/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	10/20/1999	Yes	Hosp.risk suicide/incr.lvl.surv
	12/26/1998	Yes	Suicide attempt

Appendix 3: Match Profiles for Non-PEP Patients

Appendix 4: Non-PEP Data Review Summary

Appendix 5: Summary of Non-PEP Patients

1. Patient 604-0022: Suicidal Ideation, December 6, 1998 (Clozaril)

This patient was randomized to Clozaril on Dec. 3, 1998 and 3 days later (Dec. 6, 1998) was hospitalized with the diagnosis of " Hospitalization due to psychosis".
The SAE report states that the patient's psychotic symptoms were not increased compared to baseline. The psychotic symptoms were also combined with depression and suicidal statement.
She was known for vagabond lifestyle. The dose of Clozaril was increased in order to avoid further "sauntering" and losing the patient.
PI was queried and respond on 20/01/00 confirmed that psychotic symptoms had not increased but that patient was hospitalized due to accompanying depression and suicidal ideation/statement. The rating scales from 2 days earlier (baseline) were:

CGI SS PI/BP-3(moderately suicidal)
CGI SP- 5 (markedly psychotic)
ISST PI/BP- wish to die-2 (moderately strong)
Living/vs dying-2(dying outweigh for living)
Desire to make suicidal attemt-2 (moderately strong)
Passive suicidal desire-2 (would avoid steps necessary to save or maintain life)
Frequency of suicidal ideation-2(persistent or continuous)
CDS hopelessness - 3 (severe), the rest of the ratings are 2(moderate)

Medical monitor queried the PI and reported: "Investigator confirmed that hospitalization was due to psychosis. The patient was hospitalized to ensure the proper level of psychiatric care and to prevent early discontinuation. No life treating condition occurred".

Conclusion: Taking into consideration the time of the event (3 days after randomization), the rating scales at baseline (2 days prior the event) and the confirmation from the investigator (see above) this event did not meet PEP criteria.

2. Patient 404-0008 Suicidal Ideation, November 13, 1999 (Clozaril)

Patient was hospitalized prior to the start of study18 Jan. 98 and discharged after the study end (3 January 2000).
The suicidal ideation was marked "severe" (same at baseline on CDS), but did not meet the definition of "serious". No action taken-was reported. There is no rescue intervention form filled out for this event.
On November 18, 1999 (3 days after the AE start date):
CGI-SS PI and BP 4-severely suicidal (baseline rating reported 3-moderately suicidal),
suicidality changed compared to baseline - 6 (much worse).
PI was not queried.
Conclusion: A PEP should have been completed and submitted.

3. Patient 303-0010: Suicide attempt by burning leading to death, October 10 , 2000 (Clozaril)

Occurred 4 days after the study completion (2 years and 4 days).

Conclusion: This event did not meet PEP criteria.

4. Patient 955-0014: Increase in suicidality, March 3, 1999 (Zyprexa)

Patient was hospitalized for increase in psychosis but SAE report specified that patient was not able to control his psychotic symptoms; subtle increase in suicidality and sentiments of hopelessness.

PI was queried and agreed on AE of Increase in suicidality.
The event was marked as follows:
seriousness- serious,
severity-severe,
action taken-hospitalization, concomitant medication.

Conclusion: A PEP should have been completed and submitted.

5. Patient 604-0029: Overdose, June 19,1999 (Zyprexa)

The PI clarified in the SAE report that the overdose was not a suicidal attempt. The patient wanted to treat her psychotic symptoms with a higher dose of a prescribed anxiolytic.

Conclusion: This event did not meet PEP criteria.