State of Minnesota
County of Hennepin

District Court

Judicial District:	FOURTH
Court File Number:	27 CV 07-1679
Case Type:	Wrongful Death

Mary Weiss, on her own behalf and as Next of Kin
And Trustee of the Estate of Dan Markingson, deceased,

Plaintiff / Petitioner

and

Board of Regents For The
University of Minnesota; Dr. Stephen Olson;
Dr. Charles Schulz; Institutional Review Board
For the University of Minnesota; Astrazeneca
Pharmaceuticals, LP; Astrazeneca LP and
Zeneca, Inc.,

Defendant / Respondent

SUBPOENA IN A CIVIL CASE
(COMMAND TO APPEAR)
Minn. R. Civ. Pro. 45

EXHIBIT
Olson 1

TO: Defendant, Dr. Stephen Olson, and his attorneys, David D. Alsop, Esq., Gislason & Hunter LLP, 701 Zenia Avenue South, #500, Minneapolis, Minnesota 55415.

Name Address

☐ You are commanded to appear as a witness in the district court to give testimony at the place, date, and time specified below.

Place of Testimony	Courtroom
	Date and Time

X You are commanded to appear at the place, date and time specified below to testify at the taking of a deposition in the above case.

Place of Deposition	Date and Time
David D. Alsop, Esq. **Gislason & Hunter LLP** **701 Zenia Avenue South #500** **Minneapolis, MN 55415**	**April 30, 2007 9:00 A.M.**

X You are commanded to produce and permit inspection and copying of the listed documents or objects at the place, date and time specified below (attach list of documents or objects if necessary):

Place	Date and Time
***PLEASE BRING ANY AND ALL DOCUMENTS WHICH ARE OUTLINED IN EXHIBIT A, ALONG WITH THE SIGNED CERTIFICATION DOCUMENT.**	**April 30, 2007 9:00 A.M.**

☐ You are commanded to permit inspection of the following premises at the date and time specified below.

Premises	Date and Time

NOTE: FAILURE TO OBEY A SUBPOENA WITHOUT BEING EXCUSED IS A CONTEMPT OF COURT.

Gale D. Pearson Signature of Court Administrator / Plaintiff's Attorney / Defendant's Attorney (Circle)	4/5/07 Date
Pearson, Randall & Schumacher, P.A. **Suite 1025 Fifth Street Towers** **100 South Fifth Street** **Minneapolis, MN 55402** **Telephone: (612) 767-7500** **Facsimile: (612) 767-7501** Name, Address and Phone Number (if issued by Attorney as an Officer of the Court)	SEAL (if issued by Court Administration)

RETURN OF SERVICE

State of Minnesota

County of _____

I hereby certify and return that on _____ I served a copy of this subpoena upon the person named thereon. Service was made by:

☐ personally handing to and leaving with him or her a true and correct copy; or

☐ leaving a true and correct copy at his or her usual place of residence

_____
Address

with _____ a person of suitable age and discretion.
Name of Person

NOTARY STAMP, SIGNATURE AND DATE Subscribed and Sworn/Affirmed to before me on _____, 20_____ _____	Date _____ By _____ Title _____

NOTE: If served by someone other than a Law Enforcement Officer, signature must be notarized.

Rule 45, Minnesota Rules of Civil Procedure, provides that:

- A subpoena may be served by any person who is not a party and is not less than 18 years of age.
- Service of a subpoena shall be made by delivering a copy to the person named in the subpoena or by leaving a copy at the person's usual place of abode with some person of suitable age and discretion who resides there.
- A witness who is not a party to the action or an employee of a party (except a person appointed pursuant to Rule 30.02(f)) and who is required to give testimony or produce documents relating to a profession, business, or trade, or relating to knowledge, information, or facts obtained as a result of activities in such profession, business, or trade, is entitled to reasonable compensation for the time and expense involved in preparing for and giving such testimony or producing such documents and is entitled to have the amount of those expenses determined prior to complying with the subpoena.
- A person is not obligated to attend as a witness in a civil case unless one day's attendance and travel fees are paid or tendered in advance (see fees below), unless the subpoena is issued on behalf of the state of Minnesota, or the state's officer or agent.

Fees to be paid to witnesses shall be as follows (Minn. Stat. § 357.22):

- For attending in any action or proceeding in any court of record or before any officer, person or board authorized the take examination of witnesses, $20 for each day.
- For roundtrip travel estimated from the witness's residence at 28 cents per mile. If a witness lives outside the state, travel costs shall be estimated from the boundary line of the state where the witness crossed into Minnesota at 28 cents per mile. (Additional fees may be available for out of state witnesses).

In any proceeding where a parent or guardian attends the proceeding with a minor witness and the parent or guardian is not a witness, one parent or guardian shall be compensated in those cases where witness compensation is mandatory under Minn. State. § 357.22, and may be compensated when compensation is discretionary under those sections. No more than a combined total of $60 may be awarded to the parent or guardian and minor witness. Minn. Stat. § 357.242.

CERTIFICATION/DECLARATION
by Custodian of Records

A. RECORDS OF: Dan Markingson

Name Birth Date Dan Markingson DOB: 11/25/76

B. RECORDS I am duly authorized as Custodian of Records (or other CUSTODIAN qualified witness) with authority to certify records for:

Name of Business/Provider

Address

C. CERTIFICATION OF COMPLETE RECORDS: Including this Declaration, all documents, records, forms, tapes, correspondence, raw data, test forms, billing records, insurance records, correspondence of all kinds and all other things without limitation called for in this document or the Authorization or Subpoena Duces Tecum which are in my custody have been copied at my office, in my presence, and under my direction and control and the copies submitted with this Declaration These are true and complete copies. No documents, records or other things have been withheld in order to avoid their being copied (unless listed below).

To the best of my knowledge, all documents, records and other things referred to above were originally prepared or compiled by personnel of the above-named business or professional practice or office or person listed in the ordinary course of business. at or near the time of the acts, conditions or events recorded. No documents, records or other things have been withheld in order to avoid their being copied (unless listed below).
The documents, records and other things provided are dated from
to and include:

AND ALL MATERIALS OF ANY TYPE, NATURE OR QUANTITY PERTAINING TO THIS PATIENT IN ANY WAY: (including but not limited to)

ALL TREATMENT AND RELATED RECORDS including but not limited to: all Psychological, Psychiatric, Social Work, Psychotherapy, Testing and Assessment records of all kinds, as well as Ambulance Records, Neurology Records, ER Records, Pathology Reports & Records, History & Physical Exam, Medication Records, Narrative Reports, X-ray Records, Consultation Reports, All Therapy Records, Discharge Summary(s), Social History Records, Progress Records, Nurses Reports and Notes, Autopsy Reports and Records, Doctors' Notes, Orders and Reports, electronic data, e-mails, correspondence and everything else related in any way to this patient without exception of any kind.

ALL CORRESPONDENCE, INSURANCE, BILLING, AND ALL OFFICE FORMS AND RECORDS of ANY kind in any form INCLUDING but not limited to all insurance and billing forms, letters, notes and everything else including but not limited to ECG, EEG, EKG, blood tests, lab work, and alll related reports, All lab reports of any kind and everything else related in any way to this patient without exception of any kind. This includes but is not limited to all e-mails, tape recordings or video recordings of any kind related to this patient in any way.

ALL PSYCHOLOGICAL OR PSYCHIATRIC TESTING of all kinds including all raw test data, all answer sheets, all computer or other kinds of scoring protocols, copies of all tests, all notes taken during testing or interviews, and any and all reports, consent forms, billing records, financial records, tapes of any kind, and everything else related in any way to this patient without exception of any kind.

ANY AND ALL CORRESPONDENCE to and from any State or Federal agencies related to the Café Study or Dan Markingson, and/or Mr. Markingson's Suicide and related reporting obligations.

PLUS ANY AND ALL OTHER KINDS OF INFORMATION IN ANY FORM IN YOUR POSSESSION WITHOUT EXCEPTION RELATED IN ANY WAY TO THIS PATIENT

D. CERTIFICATION OF OMITTED RECORDS:
The following documents, records or other things were omitted because

E. CERTIFICATION OF NO RECORDS; A thorough search has been made for the documents, records or other things called for in the Authorization or Subpoena Duces Tecum and, based on the information provided, these items were not found.

F. DECLARATION: I DECLARE that the foregoing certification is true and correct.
Executed on at .
(date) (city) (state)

Print Name:
Signature/Date: /
Witnessed By:

RETURN TO:

Gale D. Pearson, Esq., #244673
Pearson, Randall & Schumacher, P.A.
Suite 1025 Fifth Street Towers
100 South Fifth Street
Minneapolis, MN 55402
Telephone: (612) 332-0351

STATE OF MINNESOTA

DISTRICT COURT

COUNTY OF HENNEPIN

FOURTH JUDICIAL DISTRICT
CASE TYPE: Wrongful Death

MARY WEISS, on her own behalf, and as The next of kin and Trustee of the estate of DAN MARKINGSON, deceased

Plaintiff,

v.

BOARD OF REGENTS FOR THE THE UNIVERSITY OF MINNESOTA; Dr STEPHEN OLSON; Dr. CHARLES SCHULZ ; INSTITUTIONAL REVIEW BOARD FOR THE UNIVERSITY OF MINNESOTA; ASTRAZENECA PHARMACEUTICALS LP, ASTRAZENECA LP, and ZENECA, INC.,

Defendants.

Civ. File No: 62-CO-06-11934

AMENDED VIDEOTAPE DEPOSITION NOTICE OF DR. STEPHEN OLSON

TO: Defendants Dr. Stephen Olson and Dr. Charles Schulz and their attorneys, David D. Alsop, Esq., Gislason & Hunter LLP, 701 Xenia Avenue South, Suite 500, Minneapolis, MN 55416; Defendant, Board of Regents of the University of Minnesota and their attorneys, David C. Hutchinson, Geraghty, O'Loughlin & Kenney, P.A., and Defendants, Astrazeneca Pharmaceuticals LP, Astrazeneca LP and Zeneca, Inc. and their attorneys Linda S. Svitak, Esq., Krisann Kleibacker Lee, Esq., Faegre & Benson LLP, 2200 Wells Fargo Center, 90 South Seventh Street, Minneapolis, MN 55402-3901.

PLEASE TAKE NOTICE, that pursuant to the Minnesota Rules of Civil Procedure, Plaintiff, through her undersigned attorneys, Gale D. Pearson, Esq. of Pearson, Randall & Schumacher, P.A. will take the Videotaped deposition of STEPHEN OLSON, M.D., in the above-entitled matter by Martha Rivard, Court Reporter, or any qualified Notary Public

on Monday, April 30, 2007, commencing at 9:00 A.M. at Gislason & Hunter, LLP, 701 Xenia Avenue South, Suite 500, Minneapolis, Minnesota 55416, and to bring with you for inspection and copying a complete copy of the medical record file of Dan Markingson, a/k/a Dan Weiss from the University of Minnesota and thereafter by adjournment until the same shall be completed.

DATED: April 5, 2007

Gale D. Pearson, Esq., #244673
Stephen J. Randall, Esq., #221910
Pearson, Randall & Schumacher, P.A.
Suite 1025 Fifth Street Towers
100 South Fifth Street
Minneapolis, MN 55402
Telephone: (612) 767-7500
Facsimile: (612) 767-7501

AFFIDAVIT OF SERVICE BY MAIL

STATE OF MINNESOTA)
)ss.
COUNTY OF HENNEPIN)

Sandra A. Torkelson, of the County of Hennepin, State of Minnesota, states that on the 6th day of April, 2007, she served the annexed Subpoena In a Civil Case and Amended Videotape Deposition Notice of Stephen Olson, M.D. on counsel listed below by U.S. Mail, therein named personally by depositing same in the U.S. Mail, postage prepaid, in Minneapolis, Minnesota, directed to said individual at his last known address:

David Alsop, Esq.
Gislason & Hunter, LLP
701 Xenia Avenue South, Suite 500
Minneapolis, MN 55416

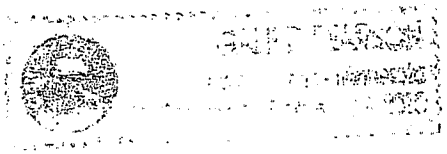
Linda Svitak, Esq.
Faegre & Benson, LLP
2200 Wells Fargo Center
90 South Seventh Street
Minneapolis, MN 55402

David C. Hutchinson, Esq.
Geraghty O'Loughlin & Kenney
386 North Wabasha Street
Suite 1400 Ecolab University Center
St. Paul, MN 55102-1308

Sandra A. Torkelson

Subscribed and sworn to before me
this 6th day of April, 2007.

Gerle D. Pearson
NOTARY PUBLIC



UNIVERSITY OF MINNESOTA PHYSICIANS PAGE: 1
SJH PRINTED: 03/05/2007 04:14PM

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MARKINGSON,DAN R M/R #0050043920 11/25/1976 M
SSN: 469-90-2422

1312 LIVINGSTON THEO I WEST ST PAUL,MN 55118-2409 651-457-6999

PR	FSC	CERT-ID/GROUP/ EFF/TERM DATE- INS CO NAME	REL	SUBSCRIBER HOME CLINIC
1	298 HPM	10156576//	SE	MARKINGSON,DANIEL A UNKNOWN

REGISTERED ON: 05/26/2000 BY: LKS
LAST UPDATED: 08/04/2004 BY: RTREG

CURRENT STATEMENT BALANCE: 0.00
LAST STATEMENT RUN# 0 BALANCE: 0.00 DATE: DUN LEVEL:

Open Cases: 0 Closed Cases 0

INVOICE	ADM/VIS	DISCH	PATIENT	MD	LOC	HO	BA	CHARGES	FSC	BALANCE
8435080	11/13/03		DAN R MARK	S OLSON	I	FAR	PAD	455.00	HPM	0.00
8435081	11/14/03		DAN R MARK	S OLSON	I	FAR	PAD	230.00	HPM	0.00
8435082	11/15/03		DAN R MARK	W MELLE	I	FAR	PAD	162.00	HPM	0.00
8463952	11/18/03		DAN R MARK	E HOLKE	I	FVR	NSP	950.00	HPM	0.00
8463953	11/17/03		DAN R MARK	S OLSON	I	FAR	PAD	162.00	HPM	0.00
8463954	11/18/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8463955	11/19/03		DAN R MARK	S OLSON	I	FAR	PAD	230.00	HPM	0.00
8463956	11/20/03		DAN R MARK	S OLSON	I	FAR	PAD	162.00	HPM	0.00
8463957	11/21/03		DAN R MARK	S OLSON	I	FAR	PAD	162.00	HPM	0.00
8463958	11/22/03		DAN R MARK	T MACKE	I	FAR	PAD	98.00	HPM	0.00
8471512	11/24/03		DAN R MARK	S OLSON	I	FAR	PAD	162.00	HPM	0.00
8471513	11/25/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8504181	11/29/03		DAN R MARK	S SCHUL	I	FAR	PAD	98.00	HPM	0.00
8504182	12/01/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8504183	12/02/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8504184	12/03/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8522219			DAN R MARK	E ECKER	I	FAR	PAD	162.00	HPM	0.00
8522220	11/28/03		DAN R MARK	E ECKER	I	FAR	PAD	98.00	HPM	0.00
8564741	12/05/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
8564742	12/06/03		DAN R MARK	S KIM	I	FAR	PAD	98.00	HPM	0.00
8564743	12/08/03		DAN R MARK	S OLSON	I	FAR	PAD	274.00	HPM	0.00
8599693	12/14/03		DAN R MARK	S OLSON	I	FAR	PAD	98.00	HPM	0.00
				TOTAL:				4189.00		0.00

EXHIBIT
Olson 2

STATE OF MINNESOTA
COUNTY OF DAKOTA

DISTRICT COURT - MENTAL HEALTH DIVISION
FIRST JUDICIAL DISTRICT

EXHIBIT
Olson 3

EXAMINER'S STATEMENT IN SUPPORT OF PETITION FOR COMMITMENT

In the matter of: Dan Markingson **Court File #:** _____

I am a licensed physician or licensed consulting psychologist, and I am knowledgeable, trained and practicing in the diagnosis and treatment of : ☒ Mental Illness ☐ Mental Retardation ☒ Chemical Dependency

I have examined the above named person with in the last 15 days, on Nov. 13, 2003 and the results of the examination are stated below.

Behavioral evidence to support commitment: Pt. reported to police, Regions + admitting resident that he was involved in a Satanic cult that would meet in Duluth soon - he had been chosen to be "the one" & would be asked to kill others "for the greater good" He has threatened to kill his mother, who he has a delusion is actually his grandmother. Probable development of a delusional system over 6-12 months, no prior psych Hx or treatment. Lacks insight, is now guarded & evasive

Diagnostic impressions and conclusions: Psychosis NOS: paranoid schizophrenia VS. psychotic mania vs. psychosis 2° medical condition. Pt is at high risk of acting on his delusions due to their persecutory/grandiose nature, delusions involving family, & his lack of insight & persistent rejection of any acknowledgment he has a mental illness

Recommended treatment: Inpatient hospitalization
Diagnostic evaluation, antipsychotic medication

I am of the opinion that the above-named person is in need of treatment and should be committed to a treatment facility.

(If mental illness is diagnosed) treatment with Neuroleptic medication is: ☒ recommended ☐ not recommended

The above-named person ☐ has ☒ lacks the capacity to make decisions regarding such treatment.
Reasons for this opinion:
Does not believe he has a mental illness - attributes all Sx to sleep deprivation for a few days

Date: 11/14/03
Signature _____

DAKOTA COUNTY
FILED
VAN A. BROSTROM, Court Administrator
NOV 17 2003
DEPUTY

Name: STEPHEN OLSON, MD
Address: FUMC
Phone: 612-273-8112

000132
FH

STATE OF MINNESOTA

DISTRICT COURT
FIRST JUDICIAL DISTRICT
DIVISION I

RE:
Daniel Markingson, RESPONDENT

REPORT OF PRE-PETITION
SCREENING TEAM

The undersigned, having been appointed to conduct an investigation pursuant to M.S. 253 B.07, Subd. 1, hereby makes the following written report:

1. A personal interview with the above Respondent on 11/14/03, and with staff of Fairview University Medical Center;
2. The Team also reviewed the medical records of Respondent at Fairview University Medical Center;
3. The following specific conduct of the Respondent is the basis for the Team's conclusions:

The Respondent is a male who will turn 27 years old on November 25, 2003. He does not have a history of psychiatric hospitalizations but per hospital records, his mother noted changes occurring with the Respondent approximately two years ago. He has been living in California, came to his mother's home in Minnesota in September and returned to California. In October he came to Minnesota a second time and had been here approximately three weeks before his current hospital admission. In recent months he has developed the delusional beliefs that his mother is really his grandmother, her boyfriend is really his biological father and the actress Angelina Jolie is really his sister. He explained it would be difficult to explain how he came to have these ideas because it was "hundreds of little connected things" starting four months ago when he began to receive messages from the media. He then began to believe that many people in the public were aware of him and that a dossier regarding him had been distributed through the public.

A week ago, the Respondent believed his mother was a lizard. The police were called, when on the date of admission (11/12/03), the Respondent made threats to his mother's boyfriend about slitting his mother's throat. The Respondent believed that he was to participate in a satanic ritual and that he was a "chosen one". He believed that potentially "certain people will have to be killed " and that he may be asked to kill people and was prepared to do so. The Respondent was first brought to Regions Hospital but was transferred to Fairview University Medical Center due to bed availability. Records indicate the Respondent showed no insight into why he was brought to the hospital. He was reported to be in a euphoric state when relating to the nurse about being "chosen" by this satanic cult and that it would be a privilege to do whatever they asked including kill people. He was initially unwilling to undergo an MRI or to accept offered medication.

The Respondent was diagnosed with:

Psychosis Not Otherwise Specified
Mood Disorder Not Otherwise Specified
Rule out Bipolar Affective Disorder with Psychosis
Rule out Schizophrenia

EXHIBIT
Olson 4

He was admitted to Station 12 at Fairview University Medical Center due to his delusions, impaired judgment and risk of harm to others. On 11/13/03 he appeared less anxious and more relaxed, pleasant and cooperative with staff. He agreed to undergo an MRI and was able to sleep. On interview with the psychiatrist, the Respondent began to acknowledge that some of his thinking

FH

may have been bizarre, but he attributed this to not sleeping and he did not believe he had any mental health issues that required treatment.

The Administration of Neuroleptic Medications

No advance directive or substitute treatment authority is known to exist for the Respondent. The Respondent is believed not to have the capacity to make decisions regarding Neuroleptic medications. Treatment with Neuroleptic medication is being recommended. The Respondent does not consent to accept prescribed Neuroleptic medication. The filing of a Jarvis Petition is being considered.

Interview with Proposed Patient

The Respondent was seen privately in a conference room at Station 12 at Fairview University Medical Center. He was appropriately groomed and dressed in casual street clothes. He was earlier given the written Notice of Pre-Petition Screening by staff at the request of the screener and he consented to be interviewed. The screener gave the Respondent an explanation of the commitment process but he indicated he was willing to be a voluntary patient and follow the doctor's recommendations at this time. He did not believe he had a mental illness but he admitted to having some odd thinking, which he attributed to sleep deprivation. He could not give a reason as to why he was unable to sleep, but he felt assured that he would now be doing better. The screener encouraged the Respondent to speak with the doctor about becoming a voluntary admission.

Following the interview, the screener spoke with the psychiatrist and social worker on the unit. They reported that the petition should proceed because of the nature of the bizarre beliefs held by the Respondent and his failure to acknowledge a mental illness as the cause of these beliefs. Although he was willing to become a voluntary patient, he believed his problems were caused by sleep deprivation.

4. The following reasonable alternatives were considered:

   a. Dismissal of petition was rejected because: The Respondent has been diagnosed with Psychosis NOS and Mood Disorder NOS, R/O Bipolar Affective Disorder with Psychosis, R/O Schizophrenia. He has had delusional thinking and beliefs. He allegedly made threats to slit his mother's throat and he stated he may be asked to kill people as part of a satanic ritual and he stated he was prepared to do so. He lacks insight to attribute these delusions to a mental illness and receive treatment, stating only he was deprived of sleep and he will be fine without treatment.

   b. Voluntary outpatient care was rejected because: The Respondent lacks the insight and willingness necessary to engage in outpatient care to a successful end. The Respondent's needs at present are greater than can be met by outpatient care.

   c. Informal admission to a treatment facility was rejected because: The Respondent lacks the insight and willingness necessary to admit to an inpatient treatment facility on a voluntary basis to a successful end as evidenced by the fact the Respondent required a 72-hour hold, he has not been accepting medication as prescribed, and he does not believe he has a mental illness.

   d. Appointment of a guardian or conservator was rejected because: A guardian or conservator could not admit the Respondent to a regional treatment center if that is deemed necessary. It is hoped that with treatment, the Respondent will be able to make appropriate decisions for himself.

5. The Screening Team recommends commitment of Respondent as: Mentally Ill

FH

Dated this 17th day of November, 2003

Signature: Ken Geister

Ken Geister
1 Mendota Rd W Ste 300
West St. Paul, MN 55118-4770
Phone: (651) 554-6423

FH

000710

EXHIBIT
5

STATE OF MINNESOTA

COUNTY OF DAKOTA

DISTRICT COURT
FIRST JUDICIAL DISTRICT
PROBATE COURT DIVISION

In The Matter of the Civil Commitment of

ORDER TO CONFINE, TO TRANSPORT FOR EXAMINATION, HEARING, APPOINTMENT OF ATTORNEY, EXAMINER AND NOTICE

DANIEL MARKINGSON

Respondent

Court File Number PX-03-10465

DOB: 11-25-76

1: A petition by KATHRYN KNIGHT, for the judicial commitment of the above named as a MENTALLY ILL person having been filed here, on NOVEMBER 17, 2003.

2: AND IT APPEARING that said respondent is probably dangerous to HIMSELF or society, and that the best interests of said respondent, the respondent's family and the public will be served by the immediate observation of said respondent as hereinafter provided.

3: IT IS ORDERED, that FAIRVIEW UNIVERSITY MEDICAL CENTER retain said DANIEL MARKINGSON in custody which institution is directed to retain said respondent for observation, evaluation, diagnosis, emergency treatment, care and confinement, and to prepare a Physician's Statement for Probable Cause Hearing regarding said respondent.

4: IT IS FURTHER ORDERED, that the persons taking the above-named respondent into custody or transporting the respondent (may – shall not) be in uniform, and (may-shall not) use a motor vehicle marked as a police vehicle.

5: IT IS ORDERED that Dr. James Jacobson is hereby appointed to examine the above named respondent at Fairview University Medical Center at such time as arranged by Dr. James Jacobson and make a written report to the court as to the condition of said respondent and the need for hospitalization; said report to be filed with the Court Administrator's Office and a copy filed with the county attorney and defense counsel 48 hours prior to the date set for hearing.

6: IT IS FURTHER ORDERED, that Joe Dalager whose address is 222 Grand Avenue, #100, South St. Paul, Minnesota 55075 and whose telephone number is (651) 451-6411 is hereby appointed attorney for said respondent subject to the right of said respondent to engage any other attorney the respondent may choose.

7: IT IS FURTHER ORDERED, that a preliminary probable cause hearing be held at the Dakota County Judicial Center, District Court, 1560 Highway 55, Hastings, Minnesota 55033 on November 20, 2003 at 9:00 a.m. and that the Dakota County Sheriff is directed to transport said respondent, together with Physician's Statement for Probable Cause Hearing, and the nurses' notes pertaining to said respondent's current confinement, to the above hearing.

8: IT IS FURTHER ORDERED, that a final hearing on said matter be held before the Court on November 26, 2003 at 9:00 a.m. or as soon thereafter as counsel can be heard at the Dakota County Judicial Center, 1560 Highway 55, Hastings, Minnesota 55033.

9: IT IS FURTHER ORDERED, that this Order and Notice together with a copy of the Petition for Judicial Commitment and Physician's Supporting Statement and pre-petition screening report be served personally upon said respondent and Fairview University Medical Center (by a uniformed-nonuniformed officer) and be served by mail upon Medical Records Fairview University Medical Center, Petitioner; Joe Dalager, Attorney for respondent; Dakota County Attorney's Office; Dr. James Jacobson; Dakota County Social Services; Mary Weiss, mother.

10: NOTICE IS HEREBY GIVEN, to the above named respondent that the grounds for the respondent's confinement are stated in the attached Petition for Judicial Commitment which alleges respondent to be mentally ill and that said respondent will be examined as to the respondent's mental and physical condition.

000073

11: FURTHER, NOTICE IS GIVEN to the above-named respondent that the respondent has the right to be examined by a doctor or doctors of the respondent's choice; that respondent may communicate by all reasonable means with a reasonable number of persons at reasonable hours of the day and night; and that respondent may consult privately with an attorney, at least one member of his family and with a personal physician.

12: YOU ARE FURTHER NOTIFIED, that a final hearing will be held on said Petition for Judicial Commitment within fourteen (14) days from the date of filing of said petition (unless said time is extended by the court for good cause) and that at least two (2) days' notice of the place, date and time of said hearing will be given to each of you.

Dated: 11/17/2003

Judge of District Court
Edward Lynch 2:00 p.m.

(*Court Seal*)

STATE OF MINNESOTA

COUNTY OF DAKOTA

RETURN OF SERVICE

I hereby certify and return that at said County and State, on the _____ day of _____, 200___, I served a copy of the above Order; Petition for Judicial Commitment, Physician's Supporting Statement and pre-petition screening report filed in this case upon the within named respondent Daniel Markingson, personally, by reading the same to him and handing to and leaving with him a true and correct copy thereof.

I hereby certifiy and return that at said County and State, on the _____ day of _____, 200__, I served a copy of the above Order; Petition for Judicial Commitment, Physician's Supporting Statement and pre-petition screening report upon the _____ and _____ personally, by handing to and leaving with (him/her –each of them) a true and correct copy thereof.

Dated: _____

Donald Gudmundson
Sheriff of Dakota County

By:_____
Deputy

DC

STATE OF MINNESOTA

COUNTY OF DAKOTA

DISTRICT COURT

FIRST JUDICIAL DISTRICT

In the Matter of the Civil Commitment of:

Dan Markingson,

Respondent.

FILE NO. PX-03-10465

FINDINGS OF FACT, CONCLUSIONS OF LAW AND ORDER FOR STAYED COMMITMENT

The above-entitled matter came on for preliminary and final hearing before the undersigned Judge of District Court on November 20, 2003, at the Dakota County Judicial Center, Hastings, Minnesota, upon a Petition for Judicial Commitment alleging Respondent to be mentally ill.

The Petition was filed with the Court on November 17, 2003 Kenneth Malvey, Assistant Dakota County Attorney, appeared as attorney for Petitioner. Respondent appeared personally and through his attorney, Joe Dalager, Esq.

Upon all of the files, records and proceedings, the Court hereby makes the following:

FINDINGS OF FACT

1. That all persons required by law have been provided with at least 24 hours written notice of this hearing.

2. That a commitment petition has been filed with the Court alleging the Respondent to be mentally ill.

3. That Respondent waives his right to have a preliminary hearing and final hearing in this matter and agrees to the STAYED commitment.

EXHIBIT

Dism 6

FILED DAKOTA COUNTY
VAN A. BROSTROM, Court Administrator
NOV 20 2003
BY _____ DEPUTY

OM 000063

4. That the rights of the Respondent have been protected throughout these proceedings and the Respondent admits that he is mentally ill and in need of treatment and agrees to a STAYED commitment to the Anoka Metro Regional Treatment Center.

5. That the Dakota County Social Services Department has developed a plan for services to treat the Respondent's mental illness which is agreeable to the Respondent. This treatment is available and accessible to the Respondent and public or private financial resources are available to pay for this treatment.

Based upon the foregoing Findings of Fact, the Court hereby makes the following:

CONCLUSIONS OF LAW AND ORDER FOR STAYED COMMITMENT

1. That the Respondent, Dan Markingson, is mentally ill and in need of treatment.

2. That the Respondent shall be committed to the Anoka Metro Regional Treatment Center. This commitment shall be STAYED for a period of six (6) months under the following terms and conditions:

a) That the Respondent remain hospitalized, cooperate with the treatment plan at Fairview University Medical Center until medically discharged, and follow all of the aftercare recommendations of the treatment team;

b) That the Respondent enter, participate in, and satisfactorily complete the inpatient/outpatient treatment program at and aftercare recommendations as determined by social worker;

c) That the Respondent cooperate with the treatment plan and follow the rules at any living facility as arranged by his social worker;

d) That the Respondent consent to admission or readmission to a hospital or

other appropriate care facility as determined by Respondent's social worker in the event of relapse;

e) That the Respondent take drugs or medications only as prescribed, and abstain from the use of any non-prescribed drugs or alcohol;

f) That the Respondent see a psychiatrist and/or therapist as frequently as recommended;

g) That the Respondent engage in no behavior which is threatening or injurious to self or others;

h) That the Respondent participate in any recommended day treatment program or community support services;

i) That the Respondent participate in family therapy if recommended;

j) That the Respondent sign releases of information authorizing his social worker and the various service providers to exchange information;

k) That the Respondent cooperate with his social worker as determined;

3. That the Pre-Petition Screening Report and all exhibits from the preliminary and final hearings shall be sealed until further Order of the Court.

4. That on June 17, 2004, the Court Administrator shall return all of the Petitioner's exhibits, except the court-appointed examiner's report, to the Dakota County Attorney.

5. That the Respondent's transportation back to Fairview University Medical Center shall be provided by the Dakota County Sheriff's Department.

6. That an Appendix A - Rights of Patients - has been attached to the Respondent's copy of this Order.

7. That the Respondent shall be granted passes as approved by the Respondent's treating physician.

Dated: November 20, 2003

BY THE COURT:

Robert F. Carolan
JUDGE OF DISTRICT COURT

OM 000066

20

November 20, 2003

Dear Dr. Olson:

Enclosed are all the emails written between "Deceived, Strung Along" (Dan Markingson) and michalethearchangel1. Keep in mind, this was the only way to get him home, and it was imperative that I do that. (There were many prior emails sent to two other hotmail accounts: "guardianangel daisy" and "guardianangel33314", both of which expired, as the hotmail accounts were not used for over a month.) After reading the ones to "michael" again for probably the tenth time, I find it absolutely necessary that Dan be confronted with these. They are the markers of his mental illness, and, therefore, I believe the key to his getting well. He needs to acknowledge that he did write these horrible emails, that he does have a mental illness and that he desperately needs treatment.

I hope also you have not stopped looking for a physical cause for his (physical and) mental problems, i.e. the weight loss, the greying hair, sensitivity to cold, etc. What then is causing all this? His TSH was 6.94 when tested at HealthPartners, and I believe you said it was in the area of 0.2 now. Is this fluctuation normal? (I am sorry, but I can leave no stone unturned in trying to get Dan well, and if this comes across as layman idiot who knows nothing about medicine, then that is what I am.)

I find it unacceptable that he could be released from Fairview-Riverside without a resolution. In fact, should he be released without his acknowledgement of an illness, he would be worse off than had be never been an in-patient. *He, of course, would take no medication, for, in his mind, there is no illness to medicate. His mind would deteriorate to the point where he will act on his evil thoughts. This will happen!*

The Daniel Weiss who was my son is a good, moral and well-liked person. The Dan Markingson I visit at the hospital is someone I don't know. I've even attached photocopies of envelopes of letters he wrote me after his name change. (Such change being prompted, he claimed, by my telling him it was the name of his grandfather. Not true!) The printing on the envelope is *very angry*, as you can see.

I am asking you not to release Dan at this point. I don't feel he has made any progress toward even acknowledging he has an illness. (I rather doubt he is taking his medication.) When he reaches that point of acceptance, and sincerely wants to get well, I would like him released to a halfway house for a month. I feel the company of others going through similar problems will be motivation for him to know he is not alone in mental illness and to work hard to pick up the pieces of his life.

Thank you.

EXHIBIT
Olson 7

om

MEMORANDUM

TO: ~~Ken Malvey (A-I)~~
~~Jennifer Jackson (J-M)~~ - Mitchell
~~Brittany Shively (N-Z)~~

FROM: Mental Health Unit Supervisors
Dakota County Social Services

DATE: 11/24/03

RE: Assignment of Mental Health Case Manager

The case of Daniel Markingson has been assigned to:

Mary Jones, Supervisor

- ☐ Patti Gmeiner
- ☐ Mary Hennen
- ☐ Duane Johnson
- ☐ Sherrie Johnson
- ☐ Fran McLaughlin
- ☐ Virginia Nygaard
- ☒ David Pettit
- ☐ Phia Xiong

Alex Lape, Supervisor

- ☐ Ken Brinkman
- ☐ Peggy Chun
- ☐ Ken Geister
- ☐ Trish Leonard
- ☐ Judy Scanlan
- ☐ Sandy Spillman
- ☐ Lisa Thomas
- ☐ Bev Westling

cc: Probate Court - Kay Mitchell
Judicial Center - Mitchell

EXHIBIT
Olson 8

O/dept/socserv/sup/mhassign.doc

000001
dc

Adult Consent Form

EXHIBIT
Olson 9

Protocol:	5077IL/0114 IND N0 32, 132
Title of Study:	Efficacy and Tolerability of Olanzapine, Quetiapine and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52 Week Comparison, The CAFÉ Study
Principal Investigator:	Dr. Stephen Olson
Co-Investigators:	Drs. Charles Schulz and John Vuchetich of the University of Minnesota
Sponsor:	AstraZeneca Pharmaceuticals

1. INTRODUCTION

You are being asked to take part in a research study. Before you decide to participate it is important for you to understand why the research is being done, what it will involve and the possible benefits, risks and discomforts to you of study participation. This process is known as "informed consent". This consent form describes the purpose, procedures, and possible benefits and risks of participating in this study. Please take time to read the following information carefully and discuss it with trusted family, friends, or health care providers if you wish.

The investigators listed above are in charge of the study; other professional persons may help them or act for them.

Your healthcare provider may be an investigator for this research project, and as an investigator, is interested both in your clinical welfare and in the conduct of this study. The investigator is being paid by AstraZeneca to conduct this study. AstraZeneca is the pharmaceutical company that manufactures and markets the medication quetiapine (Seroquel). Before entering this study or at any time during the study, you may ask for a second opinion about your care from another doctor who is in no way associated with this study. You are not under any obligation to participate in a research project offered by your doctor.

What are some general things you should know about research studies?
Research studies are designed to gain scientific knowledge that may help other people in the future. You may or may not receive any direct benefit from participating. There may also be risks associated with participating in research studies.

Your participation is voluntary. You may refuse to participate, or may withdraw your consent to participate in any study at any time, and for any reason, without jeopardizing your future care

at this institution or your relationship with your doctor. You do not have to participate in research in order to receive treatment.

Details about this particular study are discussed below. It is important that you understand this information so that you can decide in a free and informed manner whether you want to participate. You will be given a copy of this consent form. You are urged to ask the investigators named above, or staff members who may assist them, any questions you have about this study at any time.

2. PURPOSE OF THE RESEARCH STUDY

The purpose of this study is to compare the effectiveness and side effects of three antipsychotic medications: olanzapine, (Zyprexa®); quetiapine, (Seroquel®); and risperidone, (Risperdal®) for the treatment of schizophrenia, schizophreniform, or schizoaffective disorder. All of these medications are currently approved by the FDA for use in the United States.

We will study the main reasons why study participants stop taking each of the study medications because this problem sometimes is encountered in the treatment of your illness. We will also study the effects of the medications on your symptoms and functioning. We will study the side effects of the medications, your use of mental health services, and your quality of life.

A total of approximately 400 subjects at 24 institutions will participate in this study, including approximately 15 subjects from this institution. You must be 16 to 40 years of age to participate. Your active participation in this study will last for up to 12 months.

3. DESCRIPTION OF THE RESEARCH STUDY AND PROCEDURES

You will participate in up to 21 scheduled study visits (an initial visit to see if you qualify for the study, a baseline visit for additional tests and the assignment of a study medication, visits once a week for the first six weeks of treatment, once every other week for the next six weeks, and then monthly visits for the rest of the study).

If you are an outpatient you will come to the study doctor's office for these visits. If you are hospitalized, the study doctor will come to you for the study visits. If necessary due to a change in your condition we will schedule extra study visits at no cost to you.

There are two phases to this study. In the first phase, you will participate in an evaluation to determine if you are eligible for the study. In the second phase, you will be randomly assigned (like the flip of a coin) to one study medication, and will participate up to one year. You or your study doctor may decide to stop the study medication and end your participation in the study at any time. This could be because the study antipsychotic did not work well enough for you, because of side effects, or for other reasons.

Phase 1 Screening Visit: At your first study visit we will do the following:

- obtain written informed consent (this document) and answer any questions you may have about this study
- ask you about your medical history, including all medications you have taken, and about your drug and/or alcohol use
- conduct a physical examination which will include an opthalmologic exam for the detection of cataracts
- obtain vital signs
- conduct a complete psychiatric examination
- take a blood sample (1 tablespoon) for standard lab tests

The screening visit will take approximately 2 hours.

Phase 2:

If the results of the screening tests indicate that you are eligible to enter Phase 2 of the study, we will schedule your second (baseline) study visit within 2 weeks.

Baseline Visit: This visit will take approximately 3 hours of your time. During this visit we will do the following:

- ask you about your current symptoms, how it affects your day-to-day functioning and the history of how your illness began.
- give you computerized and pencil and paper tests of your coordination, memory, and problem solving abilities.
- ask you about your use of mental health services and your opinion about your illness and treatment.
- measure your height, weight, and hip and waist size.
- Vital signs (systolic and diastolic blood pressure) will be measured.
- take a sample of hair to test for use of illegal drugs.
- obtain a blood sample for evaluation of blood chemistries. It is important that you do not eat or drink (except for water) for 8 hours before giving us this blood sample, since we will be evaluating glucose and lipids in your blood, both of which may be affected by a meal.

At the end of the baseline visit you will be randomly (like the flip of a coin) assigned to receive capsules of olanzapine, or quetiapine, or risperidone. Your study doctor will work with you to discontinue any antipsychotic medicines you are taking and will start the new one gradually.

Neither you nor the study doctor will know which study medication you have been given. This is to make sure that neither you nor the study doctor's evaluation of how well the study drug works are affected by knowing what study drug you have been given. However, if in an emergency you need to know which study drug you have been taking, we can find out.

If the study antipsychotic medication is not effective for you, or you are having side effects that you cannot tolerate, you will discontinue from the study. Should you discontinue from the study, the study physician will provide immediate care for your psychotic illness, and will assist you in obtaining follow-up treatment, including starting you on a new antipsychotic medication if indicated.

During Phase 2 you will have weekly visits the first six weeks of treatment, then visits every two weeks for the next six weeks of treatment, and then monthly visits for the remainder of the study. At each study visit we will do a basic evaluation, taking from 30-60 minutes, depending on your clinical condition, as follows:

- Evaluate your current symptoms and any side effects that you might be experiencing. The dose of the study medication may be adjusted based on this information.
- Ask you about how regularly you are taking the study medication.
- Obtain your weight.
- Measure your vital signs up to and including visit 9, visit 12, visit 19 and end of study.

In addition, every four weeks (visits 4, 7, 9-19) we will ask you some more questions, taking about 15-30 minutes of your time, that include questions:

- About your use of health care services
- About your use of drugs and alcohol

We will also do other tests on certain study visits, as follows:

Visits 9, 12, and 19 or End of Study there will be additional evaluations, taking about 30 minutes of time, that include:

- obtain a blood sample for evaluation of blood chemistries. It is important that you do not eat or drink (except for water) for 8 hours before giving us this blood sample, since we will be evaluating glucose and lipids in your blood, both of which may be affected by a meal.
- ask you your opinion about the treatment that you have received for your illness.
- ask you a number of questions about your illness and how it affects your day to day functioning and your quality of life
- measure your waist, hips, and height

At visit 9 and 19 there will be other additional evaluations, taking about 3 hours of time:

- give you computerized and pencil and paper tests of your coordination, memory, and problem solving abilities.

At visit 12 and 19 we will also:

- obtain a hair sample for analysis for illegal drugs.

Also, during the course of the study (typically during the first 3 months of treatment) you will be offered 5 sessions of supportive and psychoeducational therapy that will provide you with information about your illness, and provide some emotional support during your recovery.

Final Visit: If you or your doctor decides to stop the study medication, this will end your participation in the study. During the final visit we will do the following:

- evaluate your current symptoms and any side effects that you might be experiencing.
- ask you about how regularly you are taking the study medication.
- ask you about your current symptoms, and how it affects your day to day functioning.

- give you computerized and pencil and paper tests of your coordination, memory, and problem solving abilities
- ask you about your use of mental health services and your opinion about your illness and treatment
- measure your height, weight, and hip and waist size, and vital signs
- take a sample of hair to test for use of illegal drugs
- obtain a blood sample for evaluation of blood chemistries. It is important that you do not eat or drink (except for water) for 8 hours before giving us this blood sample, since we will be evaluating glucose and lipids in your blood, both of which may be affected by a meal.

An opthalmologic exam for the detection of cataracts will be repeated at six month intervals and at the end of study.

General Information

Your study doctor may adjust your dose of study medication upward or downward. Additional medications may be recommended according to how you are doing.

You (and your family members, if they can attend study visits) will receive basic information about your illness, what you can expect to happen as the disease progresses, how you can deal with these changes, what you can expect from the study drug treatment and what mental health services and support groups are available to you locally.

For the first 3 months of the study we will telephone you a day or two before each scheduled study visit to remind you of your appointment. If you do not have a telephone, we will mail you a reminder. Later in the study, we may find it is not necessary to call or send you any reminders, but we will continue to do so if necessary.

At your monthly study visits you must return all unused study medication and empty medication bottles so we can count any remaining capsules.

At the end of the study, you must return any unused study drug to your study doctor.

Are there any reasons you should not participate?

You may not participate in this study if any of the following apply to you:

- you have an allergy to any of the study medications
- you have taken any antipsychotic for more than 16 weeks
- you are pregnant or breast feeding, or plan to become pregnant or to start breast feeding
- you have participated in a clinical trial of an investigational drug within 30 days of visit 1 of this study

4. RISKS AND INCONVENIENCES

There is a risk that your symptoms of your illness will not respond to the study medication. Your condition may worsen if the study drug is ineffective for you.

Antipsychotic medications are associated with a variety of side effects and risks that will be explained below. One of the goals of this study is to establish the relative frequency and importance of the side effects of these drugs.

Common side effects of antipsychotic drugs, when beginning treatment, include sleepiness that may affect mental and physical abilities required to operate an automobile or machinery. Increased appetite and weight gain may occur. You may experience a decrease in blood pressure when standing up that causes lightheadedness; this is most common early in treatment and will usually pass with time. High blood sugar and increases in blood levels of cholesterol and lipids (fats) may occur.

Additional side effects may include decreased interest in sex, decrease in sexual function and breast enlargement. If you are menstruating, you may experience irregularity in your cycle. These effects usually stop after the medication is stopped.

Other less common side effects that may occur include insomnia (difficulty sleeping),tremors, muscle stiffness and restlessness or an inability to sit still. You may experience an increase in chemicals in the blood made by the liver, and a decrease in your white blood cell count. Some patients get a rash (that is not a sunburn) that appears after spending a very short time in the sun. Dry mouth, blurred vision, and constipation may occur. Very rarely some people develop enlarged pupils, obstructed intestines, and retention of urine. This class of drugs, antipsychotics, has been rarely associated with interfering with body temperature regulation.

There are very rare, but potentially serious side effects associated with use of this class of drugs. This class of drugs rarely can cause neuroleptic malignant syndrome (NMS), a serious, potentially life-threatening disorder that includes symptoms such as fever, tight muscles, changes in blood pressure and heart rate, as well as confused thinking. We will watch for this carefully. If NMS occurs we will stop the study medication and make sure you get the treatment you need. Also, antipsychotics can cause a movement disorder called tardive dyskinesia (TD). In tardive dyskinesia, certain muscle groups (such as the lip and tongue muscles) will move even when the person does not want them to move. We will watch for this carefully during the study. If these movements occur, we will stop the medication. Most often the movements stop when the medicine is stopped but sometimes they are permanent.

As is true for all medications, the study drugs used in this study may involve other risks -- including possible life threatening reactions -- that are not known at present.

The study drug must be taken only by the person for whom it has been prescribed, and it should be kept out of the reach of children or others of limited capacity to read or understand.

If you experience a serious medical problem, the study sponsor will request access to your medical records for a minimum of 30 days after the event, or until your condition is resolved, in order to determine the medical outcome. This will be true even if you otherwise end participation in the study. Your permission for review of these records is granted by signing this form, but you can withdraw this consent at any time.

Your condition will be monitored closely by the study doctor and the study staff. If you or the study doctor decides to stop your participation in the study, you will receive appropriate follow-up treatment as determined by your study doctor.

At visits with a blood draw about 1 tablespoon of your blood will be drawn. Your body will quickly make up for this small blood loss. There may be temporary discomfort when blood samples are taken and there is a small risk of bruising, infection or inflammation at the needle stick site. Some people may feel faint or dizzy after giving only a small amount of blood. You will not leave the study doctor's office until you feel well.

What if we learn about new risks during the study?
You will be given any new information gained during the course of this study that might affect your willingness to continue your participation.

Pregnant women and nursing mothers are not allowed to enter this study. There may be unknown risks to your embryo, fetus, or unborn child. If you are a female of childbearing potential, you will be given a pregnancy test before entering the study. If you are not pregnant, we will ask you which method of birth control you use to prevent pregnancy. While participating in this study you must use a form of birth control that is approved by your study doctor. You agree to inform the study doctor immediately if you have a reason to suspect pregnancy, or circumstances have changed such that there is now a risk of becoming pregnant, or you have stopped using the approved form of birth control. By signing this consent form, you are confirming that to the best of your knowledge, you are not pregnant and are not planning to become pregnant during the study.

If you become pregnant, intend to start breast feeding, or have started to breast feed, you agree to notify the study doctor immediately because there may be unknown risks to an unborn child or nursing infant while you are taking the study medication.

If you become pregnant during your participation in the study, you will be withdrawn from active participation in the study.

If you become pregnant, all costs for pregnancy related care, child-birth, and post-partum/newborn care will be your responsibility. The study sponsor will request access to your medical records as well as your baby's hospital/clinic records from the time your pregnancy is discovered and for a minimum of 8 weeks after the birth of your child. Your permission for review of these records is granted by signing this form, but you can withdraw this consent at any time.

5. POSSIBLE BENEFITS TO PARTICIPANTS

There is no guarantee of benefit to you as a result of your participation in this study. You may or may not respond to treatment with the study drug. Taking part in this study may reduce the severity of your symptoms, however, you may experience either no improvement or a worsening of your condition. Your participation will contribute to a research study that may prove beneficial to you and to others in the future.

6. ALTERNATIVE TREATMENTS

You do not have to participate in this research study in order to receive treatment for your condition. All of the medications we will study are available to you through your study doctor. Your study doctor will discuss these alternatives with you before you agree to participate in this study.

7. COMPENSATION FOR ADVERSE EVENTS RESULTING FROM THIS STUDY

If you experience any side effect or injury, notify your doctor immediately so that you can receive appropriate medical treatment.

In the event that this research activity results in an injury, treatment will be available, including first aid, emergency treatment and follow-up care as needed. Care for such injuries will be billed in the ordinary manner, to you or your insurance company. If you think that you have suffered a research related injury and that you may be eligible for reimbursement of some medical care costs, let the study physicians know right away.

If you suffer any adverse reaction or other physical injury resulting directly from the research drug, AstraZeneca will provide reimbursement for the reasonable costs of medical treatment if:

- You took the study drug as instructed by your doctor
- Your injury was not deliberately caused
- The study doctor was immediately notified of your injury
- You followed the medical advice of your study doctor

You will not be reimbursed for lost wages or other damages or losses for medical expenses that have been covered by your medical or hospital insurance or by third party or governmental programs providing such coverage. No other form of compensation is available from AstraZeneca except remedies available under the law. Compensation for medical expenses is not an admission of fault or liability by AstraZenca or anyone else.

8. PAYMENT FOR PARTICIPATION IN STUDY

You will receive $20 each time you participate in one of the regular visits. This money is intended to help offset the cost of transportation and your effort.

9. EXPENSES (Cost of Participation in the Study)

You or your insurance provider will be responsible for paying for usual medical or psychiatric care during the study, including any medication other than the study medication that is needed to treat your condition. During Phase 1 the study will pay for a maximum of 3 days of hospitalization, during the time that you are completing the screening evaluation to determine if you are eligible for the study. All other costs related to hospitalization that you might need will be your responsibility.

10. PARTICIPATION IS VOLUNTARY

Your participation in this study is voluntary. You can refuse to participate or withdraw from this study at any time, without penalty or loss of benefits to which you are otherwise entitled.

11. CONFIDENTIALITY

All study data will be kept confidential; however, authorized personnel from AstraZeneca, its representatives, the FDA, other Department of Health and Human Services agencies, government agencies in other countries, and the Institutional Review Board may have access to the data. The data and results from this study may also be presented at scientific meetings or in publications, but in those presentations study participants will not be identified by name. **Information regarding your use of illegal drugs will remain confidential, however, certain kinds of information will be released if required by law (example: threats of violence).**

12. WHOM TO ASK IF YOU HAVE QUESTIONS

You have the right to ask, and have answered, any questions you may have about this research.

If you have any questions about this research study, ask the research study doctor, Dr. Olson at 612 273-9801, or the research staff, Jean Kenney or Elizabeth Lemke at 612 627-4840.

In case of emergency research related injury, you may call the Fairview University Medical Center Emergency Room at 612 273-6402. There is a psychiatry resident on call at all times. You may also contact or report to the emergency room most convenient to you.

This research has been reviewed and approved by the IRB at the University of Minnesota. If you have any questions or concerns regarding your rights as a research subject, you may contact the Patient Relations Department at Fairview University Hospital. They are located at B-310 Mayo Memorial Building, 420 Delaware Street S.E., Minneapolis, Minnesota 55455. The phone number is 612 273-5050.

13. RIGHT TO WITHDRAW AND TERMINATION PROCEDURES

You may withdraw from this study at any time without penalty or loss of benefits to which you are otherwise entitled. Your participation may be ended without your consent if you become ineligible to continue in the study, if the instructions of the study doctor are not followed, if you experience a study-related injury, or for any other reasons.

If you or the study doctor decides you will stop the study before it is complete, you will be required to notify the site and return all unused study drugs to the study doctor. You will be asked to participate in a final study visit that will last approximately 3 hours.

14. INFORMED CONSENT STATEMENT:

2

I, Dan *(name of subject), have read and I understand all the information in this in this consent form. I have been given the opportunity to discuss the information in this consent form and ask questions. I voluntarily consent to participate in this study. I understand I will receive a signed and dated copy of this consent form.* By signing this consent form I have not waived any of the legal rights which I otherwise would have as a subject in research study.

I authorize the release of my medical records to the sponsor (including its contractors and agents), the FDA and other government agencies.

Dan Markingson
Signature of Subject

11/21/03
Date of Signature (Month/Day/Year)

Dan Markingson
Printed name of Subject

Signature of Witness

11/21/03
Date of Signature (M/D/Y)

S.E. OLSON
Printed name of Witness

Jean M Kenney
Signature of Person Obtaining this Consent

11/21/03
Date of Signature (Month/Day/Year)

Jean M. Kenney
Printed Name of Person Obtaining this Consent

psy 000185

EVALUATION TO SIGN CONSENT FORM

DRM

Subject I.D. #: 00100013 Subject Initials: [redacted] Subject Source: Unit 12

Rater I.D. # _____ Rater Initials: JMK

Date of Rating: 11/21/2003 Date of Entry (Data Mgmt): __/__/__

Protocol (optional): CAFÉ Time Frame: _____

Notes (optional): _____

PROCEDURE:

Make a subjective judgement regarding Item 1 below. Ask the patient questions 2 – 5. The evaluator may select the language to use in asking the questions in order to help the patient understand them.

ITEMS:

1. Is the patient alert and able to communicate with the examiner?
   ✓ Yes ____ No.

2. Ask the patient to name at least two (2) potential risks incurred as a result of participating in the study.
   med won't work
   s/e (side effects)

3. Ask the patient to name at least two (2) things that will be expected of him/her in terms of patient cooperation during the study.
   come weekly
   take meds as directed

4. Ask the patient to explain what he/she would do if he/she decides that they no longer want to participate in the study.
   can w/drawal

5. Ask the patient to explain what he/she would do if he/she is experiencing distress or discomfort.
   Let us know

6. Ask the patient to explain how medications (or treatments) are assigned during the study.
   Randomly

EXHIBIT
olsen 10

SIGNATURES:

I hereby certify that the above patient is alert, able to communicate and able to give acceptable answers to items 2, 3, 4, 5 and 6 above.

PSY 000186

Jean M. Kinney 11/24/03 [signature] 11-21-03

Evaluator Date Witness Date

07/05/2000

U. Minnesota researchers to study schizophrenia

By Dylan Thomas

Minnesota Daily (U. Minnesota)

01/27/2003

(U-WIRE) MINNEAPOLIS — University of Minnesota researchers will participate in two of the largest-ever studies evaluating the effectiveness of a new generation of schizophrenia drugs used to treat an illness that often manifests itself around the transition from adolescence to adulthood.

The studies seek to provide researchers with valuable information about how newer medications are tolerated by patients compared with older-generation drugs whose benefits sometimes come at the cost of debilitating side effects.

Both the old and new drugs have been tested but not against each other on this scale.

The Clinical Antipsychotic Trials of Intervention Effectiveness trial will enroll patients that have been diagnosed with schizophrenia or a related disorder.

Those enrolled in the Comparisons for Atypicals for First Episode trial will be in the first stages of a psychosis, having been on schizophrenia drugs -- known as antipsychotics — for less than four months.

Elizabeth Lemke, coordinator of the CATIE trial and assistant coordinator of the CAFE trial, said the studies will try to imitate real-world clinical practice and situations. Researchers will not use placebos and there are few restrictions placed on the studies' participants.

For example, participants can be taking other medications, can have hyper tension or diabetes, go off their medication or skip appointments. Potential participants will not be excluded even if they are alcoholics or using street drugs, Lemke said.

Study participants will undergo physical and cognitive testing and will be monitored for side effects from the medications. The studies also provide patients with access to counseling and education in addition to medical and psychiatric care.

Stephen Olson, a University associate professor of psychiatry, said the importance of the studies lies in finding, "which medications people seem to prefer to stay on over a long term and under real world conditions."

EXHIBIT

Olson 11

Problems in the treatment of schizophrenia often arise when patients go off medication or switch medications frequently.

For example, some patients stop taking their medication once it has relieved their symptoms. However, most of those patients will relapse within two years, some suffering from more severe symptoms.

Also, many patients fare better when they stay on one medication for a long time rather than switching medications, Olson said.

Finding which drugs work best for different people might also help avoid the risks associated with taking them. While the older drugs might be more effective for some, their benefits come with the burden of serious side effects.

Olson said all classic antipsychotics — drugs developed in the 1950s through the early 1990s — can lead to a temporary condition similar to Parkinson's disease. Some taking the drugs become shaky, suffer from stiffness in their muscles, get restless or "look zombie-like in the most extreme forms," Olson said.

Among long-term users of these classic antipsychotics, about 30 percent to 40 percent could develop a potentially irreversible movement disorder, Olson said. The newer medications have a substantially lower incidence of those side effects.

THE ONSET AND TREATMENT OF SCHIZOPHRENIA

One of the CAFE participants is Jacob, a University first year majoring in English, who wished to be identified only by his first name. He is schizoaffective — displaying many of the symptoms of the disorder, but not yet diagnosed with full-blown schizophrenia.

Now 19, the symptoms of schizophrenia appeared unusually early for Jacob, when he was in his early teens.

"It was really horrible," he said. "I was paranoid, I thought everybody was out to get me, I had delusions of grandeur."

"Half the time, I would closet myself in the house, just to get away from all those evil, bad things out there that weren't really there."

Although his family noticed he "wasn't really social," other serious family issues prevented them from realizing the extent of the problem, Jacob said.

A year or two before coming to the University, he began to realize he had an illness.

"After a while, I started questioning it all, and I came to the realization that it just didn't make sense," Jacob said.

Problems in the treatment of schizophrenia often arise when patients go off medication or switch medications frequently.

For example, some patients stop taking their medication once it has relieved their symptoms. However, most of those patients will relapse within two years, some suffering from more severe symptoms.

Also, many patients fare better when they stay on one medication for a long time rather than switching medications, Olson said.

Finding which drugs work best for different people might also help avoid the risks associated with taking them. While the older drugs might be more effective for some, their benefits come with the burden of serious side effects.

Olson said all classic antipsychotics — drugs developed in the 1950s through the early 1990s — can lead to a temporary condition similar to Parkinson's disease. Some taking the drugs become shaky, suffer from stiffness in their muscles, get restless or "look zombie-like in the most extreme forms," Olson said.

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Although his family noticed he "wasn't really social," other serious family issues prevented them from realizing the extent of the problem, Jacob said.

A year or two before coming to the University, he began to realize he had an illness.

"After a while, I started questioning it all, and I came to the realization that it just didn't make sense," Jacob said.

He began to "half seriously" research mental illnesses and found his symptoms "just really match up well with schizophrenia."

At the University, Jacob talked with a doctor about possibly having schizophrenia and was sent to see Olson, who enrolled him in the CAFE study. Jacob began taking medication in December.

Although Jacob has been living with schizophrenia-like symptoms for years, others enrolled in the CAFE study, which focuses on those who have not been on medication long or at all, may have only recently had their first psychotic episode.

In these cases, recognition of the symptoms is very important, as recent research indicates early treatment might prevent or prolong the development of full-blown symptoms, Olson said.

Although the reasons for it are unclear, the symptoms of schizophrenia often develop — the end of adolescence and the beginning of adulthood — the age of a younger college student or high school student, he added.

Olson said some people may have a predisposition to the illness that interacts with the stresses of transitioning to adulthood, triggering a breakdown.

Another possibility is that the brain typically matures to a point at that age that allows people to make "critical and complex life decisions." For some reason, something prevents schizophrenics from developing that ability fully.

He said some people might struggle with the disease for a while before having a breakdown. The preliminary symptoms might appear as depression, withdrawal or difficulty with school or social situations. The person might become paranoid or exhibit odd behavior.

Many others, however, develop symptoms of psychosis within several days or weeks, Olson said.

Olson likens a person with untreated schizophrenia trying to function on a day-to-day basis to a car with a malfunctioning overdrive. He said they "... might be able to keep up in city streets at low speed, but as they get on the highway, they may be able to keep up even for a short time, but the engine's running way too fast — eventually it will burn up, blow up or it'll just stop."

But for Jacob, his involvement with the CAFE study has already had positive effects. Since going on medication, he has noticed he focuses more easily, does better in class and is dealing better with life in general.

Before going on medication, when faced with a problem in his life, he said he would "hide in my room and just basically try to ignore it."

Now, he said, "If there's a problem, I go out there and just ... face it and deal with it."

Report Options: Show Descriptions, Show Codes, Page Break Between Clients
Contacts from: 10/01/2003 to 06/21/2004 Case Manager: Pettit, David
Client: Markingson, Daniel Case Number: 141901-02-01 For: Pettit, David

Date: 11/26/2003 Time: 1.50 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 05 Hospital
Comment: mpls
Notes: Meeting with Dan, his mom, hospital social worker and his doctor. Dan conitinues to minimize his situation. His mother would prefer that he has a physical illness. I will put Dan on the waiting list for a rule 36 placement.

Secondary Time Entry: Time: 0.75
Activity: 206 Travel Outside County-MH only Service:

Date: 12/3/2003 Time: 2.00 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 05 Hospital
Comment: mpls*2
Notes: I brought Dan to an interview at Theo I. He was accepted and will be moving in on Monday. We discussed his going to the day treatment program at Fairview. He liked Theo. His mom and her man friend came to the interview also. I am a little concerned about his mother wanting him to see her man friends psychiatrist.

EXHIBIT 12

Secondary Time Entry: Time: 1.50
Activity: 206 Travel Outside County-MH only Service:

Date: 12/5/2003 Time: 0.25 By: Pettit, David
Activity: 216 Collat Cont Location: 03 Telephone-MH Only
Comment:
Notes: tel call from Dans mom asking me to read the emails in his chart. She did not say anything about keeping this from Dan

Date: 12/8/2003 Time: 0.25 By: Pettit, David
Activity: 216 Collat Cont Location: 03 Telephone-MH Only
Comment:
Notes: tel call to Theo asking them to help Dan do the GRH ap. and wanting to talk to Dan but he was out for a walk.

Date: 12/9/2003 Time: 0.25 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 03 Telephone-MH Only
Comment:
Notes: tel call with Dan who agreed to not going on passes longer than an hour. I set up an appointment to see him tomorrow.

Date: 12/9/2003 Time: 1.50 By: Pettit, David
Activity: 216 Collat Cont Location: 03 Telephone-MH Only
Comment:
Notes: tel calls with Dans mom, Kathleen the social worker at Fairview, Stacey from Theo I and discussions with Mary Jones. Dan was placed at Theo I yesterday and asked if he could go for a walk. He left at 1pm and went to his moms at around 7 pm. His mom came home at 8 pm to find him sitting on her steps. He wanted his billfold and his mom did not let him have it because she was afraid that he would take off for California. He told his mom that he fooled the doctors and asked her to expain what was going on. I said, "I need to know when it is happening" His mom brought him back to Theo and was upset that they had let him go out for such a long time. She said she wants him to be back in the hospital and to be put into an RTC.

I called to talk to Kathleen and she said that she would call and talk to Dans doctor. She called back and said that the doctor said that Dan could be hospitalized. I called and talked to Stacey and she will only let Dan go

out for an hour pass unless he is going to a program or with a responsable adult. I called Kathleen back and we talked about Dan staying at Theo and our keeping a close watch over thim. She called Dr Olson and he agreed to this plan. He refused to put it into writting. I asked her tto send me a note regarding this conversation.

I talked to Dans mom again and she was quite upset and continues to want to see Dan in an RTC. She hung up and said she was going to call her lawyer.

Tel referral to day treatment at Fairview.

Date: 12/10/2003 Time: 1.25 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 10 Not IMD Facility - MH only
Comment: WSP
Notes: MEETING WITH Dan at Theo I. We worked on an icsp, data base and fa. I also helped him call Linda Merkle to get some assistance in applying for SS. We worked on his grh ga application. He was very cooperative and friendly. He said he would prefer to go to day treatment at Fairview and continue with Dr Olson. His mom has been insisting that he go to ECC and see Dr Lopez there.

Secondary Time Entry: Time: 0.25
Activity: 207 Travel In County - MH only Service:

Date: 12/10/2003 Time: 0.25 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 03 Telephone-MH Only
Comment:
Notes: TEL CALL WITH Dans mom who wants to have Dan get on SS asap and is upset that she cannot get an up to date diagnosis from Dr Olson. She is quite determined to get Dan into AMRTC.

Date: 12/15/2003 Time: 0.25 By: Pettit, David
Activity: 216 Collat Cont Location: 03 Telephone-MH Only
Comment:
Notes: tel call wth [redacted] who asked for a statement about Dans car.

Date: 12/15/2003 Time: 1.00 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 10 Not IMD Facility - MH only
Comment: wsp
Notes: Meeting with Dan who called Social Security and they will be sending him an ap. We called Fairview Day treaement and set un an intake apointment. Staff report that he is doing well.

Secondary Time Entry: Time: 0.25
Activity: 207 Travel In County - MH only Service:

Date: 12/16/2003 Time: 0.25 By: Pettit, David
Activity: 300 Face:Face/DirectContact Location: 03 Telephone-MH Only
Comment:
Notes: tel calls with Dan and his mom. His mom is in a hurry to get him on SS so she plans on taking him to the ss office in St Paul tomorrow. She expected me to come with her and Dan but I told her I had other appointments. She asked me to tell Dan to go with her. I told her I would suggest it but I really couldn't tell him to go with her. She said she has had contact with Sen Colemans office and will be get assistance in getting Dan on SS asap. She also said she has a letter from DR Olson saying that Dan has had mental illness for over a year.

Secondary Time Entry: Time: 0.25
Activity: 216 Collat Cont Service:

copy for chart

0064419559 RRC
MARKINGSON, DAN R UNK ITC
[illegible]-04-39-20 HPI
11/12/03 OLSON, STEPHEN C
[illegible]-PRIMARY 11/25/76 M 26
[illegible] FUMC NO 1

Dan Markingson
12/8/03

Dan, Your discharge plan is based upon your agreement with the Dakota County Court and your FUMC treatment team that you will follow through with the following discharge plan. You have received papers from the court about your Stay of Commitment.

The following are appointments and recommendations for your after care:

1. **Keep appointments with FUMC clinic's Café Study. Your contact person in Jeaney Kenney 612-627-4363.**

2. **Keep all future appointments with your outpatient psychiatrist, Dr. Olson.**

3. **Call Eagan Counseling Clinic for an intake appointment for day treatment. They have received your application. Participate in day treatment with regular, predictable attendance.** 651-365-8222

4. **Do not drink alcohol or use drugs, which are not prescribed by your doctor.**

5. **Take all medications as prescribed by your doctor.**

EXHIBIT 13

6. **Follow your crisis plan and call your doctor or 911 if you feel unsafe and have thoughts of harming yourself or other people.**

Dan, Your treatment team wishes you a safe, smooth return to the community. Please know that it is important that you follow this aftercare plan, which you agreed to with your treatment team at FUMC and for which you are being held accountable to by the court. Consequences for not following this plan could result in court commitment to the hospital.

I, Dan Markingson, understand and agree to follow through with the above expectations.

X Dan Markingson
Dan Markingson

12/08/03
Date

OM 000165

2004 Safety Alert: SEROQUEL (quetiapine fumarate)

The following information is from AstraZeneca. Contact the company for a copy of any referenced enclosures.

January 30, 2004

Dear Health Care Provider,

AstraZeneca Pharmaceuticals LP would like to inform you of important labeling changes regarding SEROQUEL ® (quetiapine fumarate). The FDA has asked all manufacturers of atypical antipsychotic medications, including AstraZeneca, to add a Warnings statement describing the increased risk of hyperglycemia and diabetes in patients taking these medications, including SEROQUEL.

Accordingly, the SEROQUEL Prescribing Information has been updated with the addition of the following information:

EXHIBIT 14

WARNINGS

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical

CM_000169

antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control.

Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

AstraZeneca remains committed to providing you with the most current product information available for the management of your patients. You may immediately review the Warnings statement about hyperglycemia and diabetes mellitus in the SEROQUEL Prescribing Information by visiting the web site www.Seroquel.com. Updated package inserts containing the additional hyperglycemia and diabetes mellitus information will accompany the medication in the near future and you should, of course, refer to the insert for full Prescribing Information.

As always, we request that serious adverse events be reported to AstraZeneca at 1-800-236-9933 or to the FDA MedWatch program at 1-800-FDA-1088, by fax at 1-800-FDA-0178, or by email at www.fda.gov/medwatch. For additional medical information about SEROQUEL, please call 1-800-236-9933 from 9:00 am to 5:00 pm EST, Monday through Friday.

Sincerely,

/s/

Wayne Macfadden, MD

Senior Director/Clinical Research

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FDA/CDER/Office of Drug Safety
Web page last revised by pks April 8, 2004

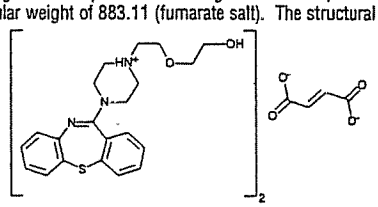
Seroquel®
(quetiapine fumarate)

Seroquel®
(quetiapine fumarate)

64251-00

DESCRIPTION

SEROQUEL (quetiapine fumarate) is a psychotropic agent belonging to a chemical class, the dibenzothiazepine derivatives. The chemical designation is 2-[2-(4-dibenzo *[b,f]* [1,4]thiazepin-11-yl-1-piperazinyl)ethoxy]-ethanol fumarate (2:1) (salt). It is present in tablets as the fumarate salt. All doses and tablet strengths are expressed as milligrams of base, not as fumarate salt. Its molecular formula is $C_{42}H_{50}N_6O_4S_2 \cdot C_4H_4O_4$ and it has a molecular weight of 883.11 (fumarate salt). The structural formula is:



Quetiapine fumarate is a white to off-white crystalline powder which is moderately soluble in water.

SEROQUEL is supplied for oral administration as 25 mg (round, peach), 100 mg (round, yellow), 200 mg (round, white), and 300 mg (capsule-shaped, white) tablets.

Inactive ingredients are povidone, dibasic dicalcium phosphate dihydrate, microcrystalline cellulose, sodium starch glycolate, lactose monohydrate, magnesium stearate, hypromellose, polyethylene glycol and titanium dioxide.

The 25 mg tablets contain red ferric oxide and yellow ferric oxide and the 100 mg tablets contain only yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacodynamics

SEROQUEL is an antagonist at multiple neurotransmitter receptors in the brain: serotonin $5HT_{1A}$ and $5HT_2$ (IC_{50s}=717 & 148nM respectively), dopamine D_1 and D_2 (IC_{50s}=1268 & 329nM respectively), histamine H_1 (IC_{50}=30nM), and adrenergic α_1 and α_2 receptors (IC_{50s}=94 & 271nM, respectively). SEROQUEL has no appreciable affinity at cholinergic muscarinic and benzodiazepine receptors (IC_{50s}>5000 nM).

The mechanism of action of SEROQUEL, as with other drugs having efficacy in the treatment of schizophrenia and acute manic episodes associated with bipolar disorder, is unknown. However, it has been proposed that this drug's efficacy in schizophrenia is mediated through a combination of dopamine type 2 (D_2) and serotonin type 2 ($5HT_2$) antagonism. Antagonism at receptors other than dopamine and $5HT_2$ with similar receptor affinities may explain some of the other effects of SEROQUEL.

SEROQUEL's antagonism of histamine H_1 receptors may explain the somnolence observed with this drug.

SEROQUEL's antagonism of adrenergic α_1 receptors may explain the orthostatic hypotension observed with this drug.

Pharmacokinetics

Quetiapine fumarate activity is primarily due to the parent drug. The multiple-dose pharmacokinetics of quetiapine are dose-proportional within the proposed clinical dose range, and quetiapine accumulation is predictable upon multiple dosing. Elimination of quetiapine is mainly via hepatic metabolism with a mean terminal half-life of about 6 hours within the proposed clinical dose range. Steady-state concentrations are expected to be achieved within two days of dosing. Quetiapine is unlikely to interfere with the metabolism of drugs metabolized by cytochrome P450 enzymes.

Absorption: Quetiapine fumarate is rapidly absorbed after oral administration, reaching peak plasma concentrations in 1.5 hours. The tablet formulation is 100% bioavailable relative to solution. The bioavailability of quetiapine is marginally affected by administration with food, with C_{max} and AUC values increased by 25% and 15%, respectively.

Distribution: Quetiapine is widely distributed throughout the body with an apparent volume of distribution of 10±4 L/kg. It is 83% bound to plasma proteins at therapeutic concentrations. *In vitro*, quetiapine did not affect the binding of warfarin or diazepam to human serum albumin. In turn, neither warfarin nor diazepam altered the binding of quetiapine.

Metabolism and Elimination: Following a single oral dose of ^{14}C-quetiapine, less than 1% of the administered dose was excreted as unchanged drug, indicating that quetiapine is highly metabolized. Approximately 73% and 20% of the dose was recovered in the urine and feces, respectively.

Quetiapine is extensively metabolized by the liver. The major metabolic pathways are sulfoxidation to the sulfoxide metabolite and oxidation to the parent acid metabolite; both metabolites are pharmacologically inactive. *In vitro* studies using human liver microsomes revealed that the cytochrome P450 3A4 isoenzyme is involved in the metabolism of quetiapine to its major, but inactive, sulfoxide metabolite.

Population Subgroups:

Age: Oral clearance of quetiapine was reduced by 40% in elderly patients (≥ 65 years, n=9) compared to young patients (n=12), and dosing adjustment may be necessary (See **DOSAGE AND ADMINISTRATION**).

Gender: There is no gender effect on the pharmacokinetics of quetiapine.

Race: There is no race effect on the pharmacokinetics of quetiapine.

Smoking: Smoking has no effect on the oral clearance of quetiapine.

Renal Insufficiency: Patients with severe renal impairment (Clcr=10-30 mL/min/1.73 m^2, n=8) had a 25% lower mean oral clearance than normal subjects (Clcr > 80 mL/min/1.73 m^2, n=8), but plasma quetiapine concentrations in the subjects with renal insufficiency were within the range of concentrations seen in normal subjects receiving the same dose. Dosage adjustment is therefore not needed in these patients.

Hepatic Insufficiency: Hepatically impaired patients (n=8) had a 30% lower mean oral clearance of quetiapine than normal subjects. In two of the 8 hepatically impaired patients, AUC and C_{max} were 3-times higher than those observed typically in healthy subjects. Since quetiapine is extensively metabolized by the liver, higher plasma levels are expected in the hepatically impaired population, and dosage adjustment may be needed (See **DOSAGE AND ADMINISTRATION**).

Drug-Drug Interactions: *In vitro* enzyme inhibition data suggest that quetiapine and 9 of its metabolites would have little inhibitory effect on *in vivo* metabolism mediated by cytochromes P450 1A2, 2C9, 2C19, 2D6 and 3A4.

Quetiapine oral clearance is increased by the prototype cytochrome P450 3A4 inducer, phenytoin, and decreased by the prototype cytochrome P450 3A4 inhibitor, ketoconazole. Dose adjustment of quetiapine will be necessary if it is coadministered with phenytoin or ketoconazole (See **Drug Interactions** under **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Quetiapine oral clearance is not inhibited by the non-specific enzyme inhibitor, cimetidine.

EXHIBIT 15

Quetiapine at doses of 750 mg/day did not affect the single dose pharmacokinetics of antipyrine, lithium or lorazepam (See **Drug Interactions** under **PRECAUTIONS**).

Clinical Efficacy Data

Bipolar Mania

The efficacy of SEROQUEL in the treatment of acute manic episodes was established in 3 placebo-controlled trials in patients who met DSM-IV criteria for Bipolar I disorder with manic episodes. These trials included patients with or without psychotic features and excluded patients with rapid cycling and mixed episodes. Of these trials, 2 were monotherapy (12 weeks) and 1 was adjunct therapy (3 weeks) to either lithium or divalproex. Key outcomes in these trials were change from baseline in the Young Mania Rating Scale (YMRS) score at 3 and 12 weeks for monotherapy and at 3 weeks for adjunct therapy. Adjunct therapy is defined as the simultaneous initiation or subsequent administration of SEROQUEL with lithium or divalproex.

The primary rating instrument used for assessing manic symptoms in these trials was the YMRS, an 11-item clinician-rated scale traditionally used to assess the degree of manic symptomatology (irritability, disruptive/aggressive behavior, sleep, elevated mood, speech, increased activity, sexual interest, language/thought disorder, thought content, appearance, and insight) in a range from 0 (no manic features) to 60 (maximum score).

The results of the trials follow:

Monotherapy

In two 12-week trials (n=300, n=299) comparing SEROQUEL to placebo, SEROQUEL was superior to placebo in the reduction of the YMRS total score at weeks 3 and 12. The majority of patients in these trials taking SEROQUEL were dosed in a range between 400 and 800 mg per day.

Adjunct Therapy

In this 3-week placebo-controlled trial, 170 patients with acute bipolar mania (YMRS ≥ 20) were randomized to receive SEROQUEL or placebo as adjunct treatment to lithium or divalproex. Patients may or may not have received an adequate treatment course of lithium or divalproex prior to randomization. SEROQUEL was superior to placebo when added to lithium or divalproex alone in the reduction of YMRS total score.

The majority of patients in this trial taking SEROQUEL were dosed in a range between 400 and 800 mg per day. In a similarly designed trial (n=200), SEROQUEL was associated with an improvement in YMRS scores but did not demonstrate superiority to placebo, possibly due to a higher placebo effect.

Schizophrenia

The efficacy of SEROQUEL in the treatment of schizophrenia was established in 3 short-term (6-week) controlled trials of inpatients with schizophrenia who met DSM III-R criteria for schizophrenia. Although a single fixed dose haloperidol arm was included as a comparative treatment in one of the three trials, this single haloperidol dose group was inadequate to provide a reliable and valid comparison of SEROQUEL and haloperidol.

Several instruments were used for assessing psychiatric signs and symptoms in these studies, among them the Brief Psychiatric Rating Scale (BPRS), a multi-item inventory of general psychopathology traditionally used to evaluate the effects of drug treatment in schizophrenia. The BPRS psychosis cluster (conceptual disorganization, hallucinatory behavior, suspiciousness, and unusual thought content) is considered a particularly useful subset for assessing actively psychotic schizophrenic patients. A second traditional assessment, the Clinical Global Impression (CGI), reflects the impression of a skilled observer, fully familiar with the manifestations of schizophrenia, about the overall clinical state of the patient. In addition, the Scale for Assessing Negative Symptoms (SANS), a more recently developed but less well evaluated scale, was employed for assessing negative symptoms.

The results of the trials follow:

(1) In a 6-week, placebo-controlled trial (n=361) involving 5 fixed doses of SEROQUEL (75, 150, 300, 600 and 750 mg/day on a tid schedule), the 4 highest doses of SEROQUEL were generally superior to placebo on the BPRS total score, the BPRS psychosis cluster and the CGI severity score, with the maximal effect seen at 300 mg/day, and the effects of doses of 150 to 750 mg/day were generally indistinguishable. SEROQUEL, at a dose of 300 mg/day, was superior to placebo on the SANS.

(2) In a 6-week, placebo-controlled trial (n=286) involving titration of SEROQUEL in high (up to 750 mg/day on a tid schedule) and low (up to 250 mg/day on a tid schedule) doses, only the high dose SEROQUEL group (mean dose, 500 mg/day) was generally superior to placebo on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and the SANS.

(3) In a 6-week dose and dose regimen comparison trial (n=618) involving two fixed doses of SEROQUEL (450 mg/day on both bid and tid schedules and 50 mg/day on a bid schedule), only the 450 mg/day (225 mg bid schedule) dose group was generally superior to the 50 mg/day (25 mg bid) SEROQUEL dose group on the BPRS total score, the BPRS psychosis cluster, the CGI severity score, and on the SANS.

Examination of population subsets (race, gender, and age) did not reveal any differential responsiveness on the basis of race or gender, with an apparently greater effect in patients under the age of 40 compared to those older than 40. The clinical significance of this finding is unknown.

INDICATIONS AND USAGE

Bipolar Mania

SEROQUEL is indicated for the treatment of acute manic episodes associated with bipolar I disorder, as either monotherapy or adjunct therapy to lithium or divalproex.

The efficacy of SEROQUEL in acute bipolar mania was established in two 12-week monotherapy trials and one 3-week adjunct therapy trial of bipolar I patients initially hospitalized for up to 7 days for acute mania (See **CLINICAL PHARMACOLOGY**). Effectiveness has not been systematically evaluated in clinical trials for more than 12 weeks in monotherapy and 3 weeks in adjunct therapy. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

Schizophrenia

SEROQUEL is indicated for the treatment of schizophrenia.

The efficacy of SEROQUEL in schizophrenia was established in short-term (6-week) controlled trials of schizophrenic inpatients (See **CLINICAL PHARMACOLOGY**).

The effectiveness of SEROQUEL in long-term use, that is, for more than 6 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use SEROQUEL for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (See **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

SEROQUEL is contraindicated in individuals with a known hypersensitivity to this medication or any of its ingredients.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including SEROQUEL. Rare cases of NMS have been reported with SEROQUEL. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis) and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever and primary central nervous system (CNS) pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for

which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown.

Given these considerations, SEROQUEL should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who appear to suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on SEROQUEL, drug discontinuation should be considered. However, some patients may require treatment with SEROQUEL despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics, including Seroquel. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (eg, obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General:

Orthostatic Hypotension: SEROQUEL may induce orthostatic hypotension associated with dizziness, tachycardia and, in some patients, syncope, especially during the initial dose-titration period, probably reflecting its α_1-adrenergic antagonist properties. Syncope was reported in 1% (23/2567) of the patients treated with SEROQUEL, compared with 0% (0/607) on placebo and about 0.4% (2/527) on active control drugs.

SEROQUEL should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease or conditions which would predispose patients to hypotension (dehydration, hypovolemia and treatment with antihypertensive medications). The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 25 mg bid (See **DOSAGE AND ADMINISTRATION**). If hypotension occurs during titration to the target dose, a return to the previous dose in the titration schedule is appropriate.

Cataracts: The development of cataracts was observed in association with quetiapine treatment in chronic dog studies (see Animal Toxicology). Lens changes have also been observed in patients during long-term SEROQUEL treatment, but a causal relationship to SEROQUEL use has not been established. Nevertheless, the possibility of lenticular changes cannot be excluded at this time. Therefore, examination of the lens by methods adequate to detect cataract formation, such as slit lamp exam or other appropriately sensitive methods, is recommended at initiation of treatment or shortly thereafter, and at 6 month intervals during chronic treatment.

Seizures: During clinical trials, seizures occurred in 0.6% (18/2792) of patients treated with SEROQUEL compared to 0.2% (1/607) on placebo and 0.7% (4/527) on active control drugs. As with other antipsychotics SEROQUEL should be used cautiously in patients with a history of seizures or with conditions that potentially lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Hypothyroidism: Clinical trials with SEROQUEL demonstrated a dose-related decrease in total and free thyroxine (T4) of approximately 20% at the higher end of the therapeutic dose range and was maximal in the first two to four weeks of treatment and maintained without adaptation or progression during more chronic therapy. Generally, these changes were of no clinical significance and TSH was unchanged in most patients, and levels of TBG were unchanged. In nearly all cases, cessation of SEROQUEL treatment was associated with a reversal of the effects on total and free T4, irrespective of the duration of treatment. About 0.4% (12/2791) of SEROQUEL patients did experience TSH increases in monotherapy studies. Six of the patients with TSH increases needed replacement thyroid treatment. In the mania adjunct studies, where SEROQUEL was added to lithium or divalproate, 12% (24/196) of SEROQUEL treated patients compared to 7% (15/203) of placebo treated patients had elevated TSH levels. Of the SEROQUEL treated patients with elevated TSH levels, 3 had simultaneous low free T4 levels.

Cholesterol and Triglyceride Elevations: In schizophrenia trials, SEROQUEL treated patients had increases from baseline in cholesterol and triglyceride of 11% and 17%, respectively, compared to slight decreases for placebo patients. These changes were only weakly related to the increases in weight observed in SEROQUEL treated patients.

Hyperprolactinemia: Although an elevation of prolactin levels was not demonstrated in clinical trials with SEROQUEL, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats (see **Carcinogenesis**). Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin dependent *in vitro*, a factor of potential importance if the prescription of these drugs is contemplated in a patient with previously detected breast cancer. Although disturbances such as galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds, the clinical significance of elevated serum prolactin levels is unknown for most patients. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Transaminase Elevations: Asymptomatic, transient and reversible elevations in serum transaminases (primarily ALT) have been reported. In schizophrenia trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 6-week placebo-controlled trials were approximately 6% for SEROQUEL compared to 1% for placebo. In acute bipolar mania trials, the proportions of patients with transaminase elevations of > 3 times the upper limits of the normal reference range in a pool of 3- to 12-week placebo-controlled trials were approximately 1% for both SEROQUEL and placebo. These hepatic enzyme elevations usually occurred within the first 3 weeks of drug treatment and promptly returned to pre-study levels with ongoing treatment with SEROQUEL.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event reported in patients treated with SEROQUEL especially during the 3-5 day period of initial dose-titration. In schizophrenia trials, somnolence was reported in 18% of patients on SEROQUEL compared to 11% of placebo patients. In acute bipolar mania trials using SEROQUEL as monotherapy, somnolence was reported in 16% of patients on SEROQUEL compared to 4% of placebo patients. In acute bipolar mania trials using SEROQUEL as adjunct therapy, somnolence was reported in 34% of patients on SEROQUEL compared to 9% of placebo patients. Since SEROQUEL has the potential to impair judgment, thinking, or motor skills, patients should be cautioned about performing activities requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Priapism: One case of priapism in a patient receiving SEROQUEL has been reported prior to market introduction. While a causal relationship to use of SEROQUEL has not been established, other drugs with alpha-adrenergic blocking effects have been reported to induce priapism, and it is possible that SEROQUEL may share this capacity. Severe priapism may require surgical intervention.

Body Temperature Regulation: Although not reported with SEROQUEL, disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing SEROQUEL for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. SEROQUEL and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Suicide: The possibility of a suicide attempt is inherent in bipolar disorder and schizophrenia: close supervision of high risk patients should accompany drug therapy. Prescriptions for SEROQUEL should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness: Clinical experience with SEROQUEL in patients with certain concomitant systemic illnesses (see Renal Impairment and Hepatic Impairment under **CLINICAL PHARMACOLOGY**, Special Populations) is limited.

SEROQUEL has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies. Because of the risk of orthostatic hypotension with SEROQUEL, caution should be observed in cardiac patients (see **Orthostatic Hypotension**).

Information for Patients

Physicians are advised to discuss the following issues with patients for whom they prescribe SEROQUEL.

Orthostatic Hypotension: Patients should be advised of the risk of orthostatic hypotension, especially during the 3-5 day period of initial dose titration, and also at times of re-initiating treatment or increases in dose.

Interference with Cognitive and Motor Performance: Since somnolence was a commonly reported adverse event associated with SEROQUEL treatment, patients should be advised of the risk of somnolence, especially during the 3-5 day period of initial dose titration. Patients should be cautioned about performing any activity requiring mental alertness, such as operating a motor vehicle (including automobiles) or operating hazardous machinery, until they are reasonably certain that SEROQUEL therapy does not affect them adversely.

Pregnancy: Patients should be advised to notify their physician if they become pregnant or intend to become pregnant during therapy.

Nursing: Patients should be advised not to breast feed if they are taking SEROQUEL.

Concomitant Medication: As with other medications, patients should be advised to notify their physicians if they are taking, or plan to take, any prescription or over-the-counter drugs.

Alcohol: Patients should be advised to avoid consuming alcoholic beverages while taking SEROQUEL.

Heat Exposure and Dehydration: Patients should be advised regarding appropriate care in avoiding overheating and dehydration.

Laboratory Tests

No specific laboratory tests are recommended.

Drug Interactions

The risks of using SEROQUEL in combination with other drugs have not been extensively evaluated in systematic studies. Given the primary CNS effects of SEROQUEL, caution should be used when it is taken in combination with other centrally acting drugs. SEROQUEL potentiated the cognitive and motor effects of alcohol in a clinical trial in subjects with selected psychotic disorders, and alcoholic beverages should be avoided while taking SEROQUEL.

Because of its potential for inducing hypotension, SEROQUEL may enhance the effects of certain antihypertensive agents.

SEROQUEL may antagonize the effects of levodopa and dopamine agonists.

The Effect of Other Drugs on Quetiapine

Phenytoin: Coadministration of quetiapine (250 mg tid) and phenytoin (100 mg tid) increased the mean oral clearance of quetiapine by 5-fold. Increased doses of SEROQUEL may be required to maintain control of symptoms of schizophrenia in patients receiving quetiapine and phenytoin, or other hepatic enzyme inducers (e.g., carbamazepine, barbiturates, rifampin, glucocorticoids). Caution should be taken if phenytoin is withdrawn and replaced with a non-inducer (e.g., valproate) (see **DOSAGE AND ADMINISTRATION**).

Divalproex: Coadministration of quetiapine (150 mg bid) and divalproex (500 mg bid) increased the mean maximum plasma concentration of quetiapine at steady state by 17% without affecting the extent of absorption or mean oral clearance.

Thioridazine: Thioridazine (200 mg bid) increased the oral clearance of quetiapine (300 mg bid) by 65%.

Cimetidine: Administration of multiple daily doses of cimetidine (400 mg tid for 4 days) resulted in a 20% decrease in the mean oral clearance of quetiapine (150 mg tid). Dosage adjustment for quetiapine is not required when it is given with cimetidine.

P450 3A Inhibitors: Coadministration of ketoconazole (200 mg once daily for 4 days), a potent inhibitor of cytochrome P450 3A, reduced oral clearance of quetiapine by 84%, resulting in a 335% increase in maximum plasma concentration of quetiapine. Caution is indicated when SEROQUEL is administered with ketoconazole and other inhibitors of cytochrome P450 3A (e.g., itraconazole, fluconazole, and erythromycin).

Fluoxetine, Imipramine, Haloperidol, and Risperidone: Coadministration of fluoxetine (60 mg once daily); imipramine (75 mg bid), haloperidol (7.5 mg bid), or risperidone (3 mg bid) with quetiapine (300 mg bid) did not alter the steady-state pharmacokinetics of quetiapine.

Effect of Quetiapine on Other Drugs

Lorazepam: The mean oral clearance of lorazepam (2 mg, single dose) was reduced by 20% in the presence of quetiapine administered as 250 mg tid dosing.

Divalproex: The mean maximum concentration and extent of absorption of total and free valproic acid at steady state were decreased by 10 to 12% when divalproex (500 mg bid) was administered with quetiapine (150 mg bid). The mean oral clearance of total valproic acid (administered as divalproex 500 mg bid) was increased by 11% in the presence of quetiapine (150 mg bid). The changes were not significant

Lithium: Concomitant administration of quetiapine (250 mg tid) with lithium had no effect on any of the steady-state pharmacokinetic parameters of lithium.

Antipyrine: Administration of multiple daily doses up to 750 mg/day (on a tid schedule) of quetiapine to subjects with selected psychotic disorders had no clinically relevant effect on the clearance of antipyrine or urinary recovery of antipyrine metabolites. These results indicate that quetiapine does not significantly induce hepatic enzymes responsible for cytochrome P450 mediated metabolism of antipyrine.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: Carcinogenicity studies were conducted in C57BL mice and Wistar rats. Quetiapine was administered in the diet to mice at doses of 20, 75, 250, and 750 mg/kg and to rats by gavage at doses of 25, 75, and 250 mg/kg for two years. These doses are equivalent

to 0.1, 0.5, 1.5, and 4.5 times the maximum human dose (800 mg/day) on a mg/m^2 basis (mice) or 0.3, 0.9, and 3.0 times the maximum human dose on a mg/m^2 basis (rats). There were statistically significant increases in thyroid gland follicular adenomas in male mice at doses of 250 and 750 mg/kg or 1.5 and 4.5 times the maximum human dose on a mg/m^2 basis and in male rats at a dose of 250 mg/kg or 3.0 times the maximum human dose on a mg/m^2 basis. Mammary gland adenocarcinomas were statistically significantly increased in female rats at all doses tested (25, 75, and 250 mg/kg or 0.3, 0.9, and 3.0 times the maximum recommended human dose on a mg/m^2 basis).

Thyroid follicular cell adenomas may have resulted from chronic stimulation of the thyroid gland by thyroid stimulating hormone (TSH) resulting from enhanced metabolism and clearance of thyroxine by rodent liver. Changes in TSH, thyroxine, and thyroxine clearance consistent with this mechanism were observed in subchronic toxicity studies in rat and mouse and in a 1-year toxicity study in rat; however, the results of these studies were not definitive. The relevance of the increases in thyroid follicular cell adenomas to human risk, through whatever mechanism, is unknown.

Antipsychotic drugs have been shown to chronically elevate prolactin levels in rodents. Serum measurements in a 1-yr toxicity study showed that quetiapine increased median serum prolactin levels a maximum of 32- and 13-fold in male and female rats, respectively. Increases in mammary neoplasms have been found in rodents after chronic administration of other antipsychotic drugs and are considered to be prolactin-mediated. The relevance of this increased incidence of prolactin-mediated mammary gland tumors in rats to human risk is unknown (see Hyperprolactinemia in **PRECAUTIONS, General**).

Mutagenesis: The mutagenic potential of quetiapine was tested in six *in vitro* bacterial gene mutation assays and in an *in vitro* mammalian gene mutation assay in Chinese Hamster Ovary cells. However, sufficiently high concentrations of quetiapine may not have been used for all tester strains. Quetiapine did produce a reproducible increase in mutations in one *Salmonella typhimurium* tester strain in the presence of metabolic activation. No evidence of clastogenic potential was obtained in an *in vitro* chromosomal aberration assay in cultured human lymphocytes or in the *in vivo* micronucleus assay in rats.

Impairment of Fertility: Quetiapine decreased mating and fertility in male Sprague-Dawley rats at oral doses of 50 and 150 mg/kg or 0.6 and 1.8 times the maximum human dose on a mg/m^2 basis. Drug-related effects included increases in interval to mate and in the number of matings required for successful impregnation. These effects continued to be observed at 150 mg/kg even after a two-week period without treatment. The no-effect dose for impaired mating and fertility in male rats was 25 mg/kg, or 0.3 times the maximum human dose on a mg/m^2 basis. Quetiapine adversely affected mating and fertility in female Sprague-Dawley rats at an oral dose of 50 mg/kg, or 0.6 times the maximum human dose on a mg/m^2 basis. Drug-related effects included decreases in matings and in matings resulting in pregnancy, and an increase in the interval to mate. An increase in irregular estrus cycles was observed at doses of 10 and 50 mg/kg, or 0.1 and 0.6 times the maximum human dose on a mg/m^2 basis. The no-effect dose in female rats was 1 mg/kg, or 0.01 times the maximum human dose on a mg/m^2 basis.

Pregnancy

Pregnancy Category C:

The teratogenic potential of quetiapine was studied in Wistar rats and Dutch Belted rabbits dosed during the period of organogenesis. No evidence of a teratogenic effect was detected in rats at doses of 25 to 200 mg/kg or 0.3 to 2.4 times the maximum human dose on a mg/m^2 basis or in rabbits at 25 to 100 mg/kg or 0.6 to 2.4 times the maximum human dose on a mg/m^2 basis. There was, however, evidence of embryo/fetal toxicity. Delays in skeletal ossification were detected in rat fetuses at doses of 50 and 200 mg/kg (0.6 and 2.4 times the maximum human dose on a mg/m^2 basis) and in rabbits at 50 and 100 mg/kg (1.2 and 2.4 times the maximum human dose on a mg/m^2 basis). Fetal body weight was reduced in rat fetuses at 200 mg/kg and rabbit fetuses at 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis for both species). There was an increased incidence of a minor soft tissue anomaly (carpal/tarsal flexure) in rabbit fetuses at a dose of 100 mg/kg (2.4 times the maximum human dose on a mg/m^2 basis). Evidence of maternal toxicity (i.e., decreases in body weight gain and/or death) was observed at the high dose in the rat study and at all doses in the rabbit study. In a peri/postnatal reproductive study in rats, no drug-related effects were observed at doses of 1, 10, and 20 mg/kg or 0.01, 0.12, and 0.24 times the maximum human dose on a mg/m^2 basis. However, in a preliminary peri/postnatal study, there were increases in fetal and pup death, and decreases in mean litter weight at 150 mg/kg, or 3.0 times the maximum human dose on a mg/m^2 basis.

There are no adequate and well-controlled studies in pregnant women and quetiapine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery: The effect of SEROQUEL on labor and delivery in humans is unknown.

Nursing Mothers: SEROQUEL was excreted in milk of treated animals during lactation. It is not known if SEROQUEL is excreted in human milk. It is recommended that women receiving SEROQUEL should not breast feed.

Pediatric Use: The safety and effectiveness of SEROQUEL in pediatric patients have not been established.

Geriatric Use: Of the approximately 3400 patients in clinical studies with SEROQUEL, 7% (232) were 65 years of age or over. In general, there was no indication of any different tolerability of SEROQUEL in the elderly compared to younger adults. Nevertheless, the presence of factors that might decrease pharmacokinetic clearance, increase the pharmacodynamic response to SEROQUEL, or cause poorer tolerance or orthostasis, should lead to consideration of a lower starting dose, slower titration, and careful monitoring during the initial dosing period in the elderly. The mean plasma clearance of SEROQUEL was reduced by 30% to 50% in elderly patients when compared to younger patients (see Pharmacokinetics under **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

The information below is derived from a clinical trial database for SEROQUEL consisting of over 3000 patients. This database includes 405 patients exposed to SEROQUEL for the treatment of acute bipolar mania (monotherapy and adjunct therapy) and approximately 2600 patients and/or normal subjects exposed to 1 or more doses of SEROQUEL for the treatment of schizophrenia.

Of these approximately 3000 subjects, approximately 2700 (2300 in schizophrenia and 405 in acute bipolar mania) were patients who participated in multiple dose effectiveness trials, and their experience corresponded to approximately 914.3 patient-years. The conditions and duration of treatment with SEROQUEL varied greatly and included (in overlapping categories) open-label and double-blind phases of studies, inpatients and outpatients, fixed-dose and dose-titration studies, and short-term or longer-term exposure. Adverse reactions were assessed by collecting adverse events, results of physical examinations, vital signs, weights, laboratory analyses, ECGs, and results of ophthalmologic examinations.

Adverse events during exposure were obtained by general inquiry and recorded by clinical investigators using terminology of their own choosing. Consequently, it is not possible to provide a meaningful estimate of the proportion of individuals experiencing adverse events without first grouping similar types of events into a smaller number of standardized event categories. In the tables and tabulations that follow, standard COSTART terminology has been used to classify reported adverse events.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Adverse Findings Observed in Short-Term, Controlled Trials

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Bipolar Mania: Overall, discontinuations due to adverse events were 5.7 % for SEROQUEL vs. 5.1% for placebo in monotherapy and 3.6% for SEROQUEL vs. 5.9% for placebo in adjunct therapy.

Schizophrenia: Overall, there was little difference in the incidence of discontinuation due to adverse events (4% for SEROQUEL vs. 3% for placebo) in a pool of controlled trials. However, discontinuations due to somnolence and hypotension were considered to be drug related (see **PRECAUTIONS**):

Adverse Event	SEROQUEL	Placebo
Somnolence	0.8%	0%
Hypotension	0.4%	0%

CONTINUED ON REVERSE SIDE

Adverse Events Occurring at an Incidence of 1% or More Among SEROQUEL Treated Patients in Short-Term, Placebo-Controlled Trials: The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the side effect incidence in the population studied.

Table 1 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during acute therapy of schizophrenia (up to 6 weeks) and bipolar mania (up to 12 weeks) in 1% or more of patients treated with SEROQUEL (doses ranging from 75 to 800 mg/day) where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 1. Treatment-Emergent Adverse Experience
Incidence in 3- to 12-Week Placebo-Controlled Clinical Trials[1]
for the Treatment of Schizophrenia and Bipolar Mania (monotherapy)

Body System/ Preferred Term	SEROQUEL (n=719)	Placebo (n=404)
Body as a Whole		
Headache	21%	14%
Pain	7%	5%
Asthenia	5%	3%
Abdominal Pain	4%	1%
Back Pain	3%	1%
Fever	2%	1%
Cardiovascular		
Tachycardia	6%	4%
Postural Hypotension	4%	1%
Digestive		
Dry Mouth	9%	3%
Constipation	8%	3%
Vomiting	6%	5%
Dyspepsia	5%	1%
Gastroenteritis	2%	0%
Gamma Glutamyl Transpeptidase Increased	1%	0%
Metabolic and Nutritional		
Weight Gain	5%	1%
SGPT Increased	5%	1%
SGOT Increased	3%	1%
Nervous		
Agitation	20%	17%
Somnolence	18%	8%
Dizziness	11%	5%
Anxiety	4%	3%
Respiratory		
Pharyngitis	4%	3%
Rhinitis	3%	1%
Skin and Appendages		
Rash	4%	2%
Special Senses		
Amblyopia	2%	1%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: accidental injury, akathisia, chest pain, cough increased, depression, diarrhea, extrapyramidal syndrome, hostility, hypertension, hypertonia, hypotension, increased appetite, infection, insomnia, leukopenia, malaise, nausea, nervousness, paresthesia, peripheral edema, sweating, tremor, and weight loss.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (18%), dizziness (11%), dry mouth (9%), constipation (8%), SGPT increased (5%), weight gain (5%), and dyspepsia (5%).

Table 2 enumerates the incidence, rounded to the nearest percent, of treatment-emergent adverse events that occurred during therapy (up to 3-weeks) of acute mania in 5% or more of patients treated with SEROQUEL (doses ranging from 100 to 800 mg/day) used as adjunct therapy to lithium and divalproex where the incidence in patients treated with SEROQUEL was greater than the incidence in placebo-treated patients.

Table 2. Treatment-Emergent Adverse Experience
Incidence in 3-Week Placebo-Controlled Clinical Trials[1]
for the Treatment of Bipolar Mania (Adjunct Therapy)

Body System/ Preferred Term	SEROQUEL (n=196)	Placebo (n=203)
Body as a Whole		
Headache	17%	13%
Asthenia	10%	4%
Abdominal Pain	7%	3%
Back Pain	5%	3%
Cardiovascular		
Postural Hypotension	7%	2%

Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

		SEROQUEL			
Dose Groups	Placebo	75mg	150mg	300mg	600mg	750mg
Parkinsonism	0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic Medications	14%	11%	10%	8%	12%	11%,

In six additional placebo-controlled clinical trials trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

An assessment of hematological parameters in short-term, placebo-controlled trials revealed no clinically important differences between SEROQUEL and placebo.

ECG Changes: Between group comparisons for pooled placebo-controlled trials revealed no statistically significant SEROQUEL/placebo differences in the proportions of patients experiencing potentially important changes in ECG parameters, including QT, QTc, and PR intervals. However, the proportions of patients meeting the criteria for tachycardia were compared in four 3- to 6-week placebo-controlled clinical trials for the treatment of schizophrenia revealing a 1% (4/399) incidence for SEROQUEL compared to 0.6% (1/156) incidence for placebo. In acute (monotherapy) bipolar mania trials the proportions of patients meeting the criteria for tachycardia was 0.5% (1/192) for SEROQUEL compared to 0% (0/178) incidence for placebo. In acute bipolar mania (adjunct) trials the proportions of patients meeting the same criteria was 0.6% (1/166) for SEROQUEL compared to 0% (0/171) incidence for placebo. SEROQUEL use was associated with a mean increase in heart rate, assessed by ECG, of 7 beats per minute compared to a mean increase of 1 beat per minute among placebo patients. This slight tendency to tachycardia may be related to SEROQUEL's potential for inducing orthostatic changes (see **PRECAUTIONS**).

Other Adverse Events Observed During the Pre-Marketing Evaluation of SEROQUEL

Following is a list of COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the ADVERSE REACTIONS section reported by patients treated with SEROQUEL at multiple doses ≥ 75 mg/day during any phase of a trial within the premarketing database of approximately 2200 patients treated for shizophrenia. All reported events are included except those already listed in Table 1 or elsewhere in labeling, those events for which a drug cause was remote, and those event terms which were so general as to be uninformative. It is important to emphasize that, although the events reported occurred during treatment with SEROQUEL, they were not necessarily caused by it.

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Nervous System: ***Frequent:*** hypertonia, dysarthria; ***Infrequent:*** abnormal dreams, dyskinesia, thinking abnormal, tardive dyskinesia, vertigo, involuntary movements, confusion, amnesia, psychosis, hallucinations, hyperkinesia, libido increased*, urinary retention, incoordination, paranoid reaction, abnormal gait, myoclonus, delusions, manic reaction, apathy, ataxia, depersonalization, stupor, bruxism, catatonic reaction, hemiplegia; ***Rare:*** aphasia, buccoglossal syndrome, choreoathetosis, delirium, emotional lability, euphoria, libido decreased*, neuralgia, stuttering, subdural hematoma.

Body as a Whole: ***Frequent:*** flu syndrome; ***Infrequent:*** neck pain, pelvic pain*, suicide attempt, malaise, photosensitivity reaction, chills, face edema, moniliasis; ***Rare:*** abdomen enlarged.

Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased,

Digestive		
Dry Mouth	19%	3%
Constipation	10%	5%
Metabolic and Nutritional		
Weight Gain	6%	3%
Nervous		
Somnolence	34%	9%
Dizziness	9%	6%
Tremor	8%	7%
Agitation	6%	4%
Respiratory		
Pharyngitis	6%	3%

[1] Events for which the SEROQUEL incidence was equal to or less than placebo are not listed in the table, but included the following: akathisia, diarrhea, insomnia, and nausea.

In these studies, the most commonly observed adverse events associated with the use of SEROQUEL (incidence of 5% or greater) and observed at a rate on SEROQUEL at least twice that of placebo were somnolence (34%), dry mouth (19%), asthenia (10%), constipation (10%), abdominal pain (7%), postural hypotension (7%), pharyngitis (6%), and weight gain (6%).

Explorations for interactions on the basis of gender, age, and race did not reveal any clinically meaningful differences in the adverse event occurrence on the basis of these demographic factors.

Dose Dependency of Adverse Events in Short-Term, Placebo-Controlled Trials

Dose-related Adverse Events: Spontaneously elicited adverse event data from a study of schizophrenia comparing five fixed doses of SEROQUEL (75 mg, 150 mg, 300 mg, 600 mg, and 750 mg/day) to placebo were explored for dose-relatedness of adverse events. Logistic regression analyses revealed a positive dose response ($p<0.05$) for the following adverse events: dyspepsia, abdominal pain, and weight gain.

Extrapyramidal Symptoms: Data from one 6-week clinical trial of schizophrenia comparing five fixed doses of SEROQUEL (75, 150, 300, 600, 750 mg/day) provided evidence for the lack of treatment-emergent extrapyramidal symptoms (EPS) and dose-relatedness for EPS associated with SEROQUEL treatment. Three methods were used to measure EPS: (1) Simpson-Angus total score (mean change from baseline) which evaluates parkinsonism and akathisia, (2) incidence of spontaneous complaints of EPS (akathisia, akinesia, cogwheel rigidity, extrapyramidal syndrome, hypertonia, hypokinesia, neck rigidity, and tremor), and (3) use of anticholinergic medications to treat emergent EPS.

		SEROQUEL				
Dose Groups	Placebo	75mg	150mg	300mg	600mg	750mg
Parkinsonism	0.6	-1.0	-1.2	-1.6	-1.8	-1.8
EPS incidence	16%	6%	6%	4%	8%	6%
Anticholinergic Medications	14%	11%	10%	8%	12%	11%

In six additional placebo-controlled clinical trials trials (3 in acute mania and 3 in schizophrenia) using variable doses of SEROQUEL, there were no differences between the SEROQUEL and placebo treatment groups in the incidence of EPS, as assessed by Simpson-Angus total scores, spontaneous complaints of EPS and the use of concomitant anticholinergic medications to treat EPS.

Vital Signs and Laboratory Studies

Vital Sign Changes: SEROQUEL is associated with orthostatic hypotension (see **PRECAUTIONS**).

Weight Gain: In schizophrenia trials the proportions of patients meeting a weight gain criterion of ≥7% of body weight were compared in a pool of four 3- to 6-week placebo-controlled clinical trials, revealing a statistically significantly greater incidence of weight gain for SEROQUEL (23%) compared to placebo (6%). In mania monotherapy trials the proportions of patients meeting the same weight gain criterion were 21% compared to 7% for placebo and in mania adjunct therapy trials the proportion of patients meeting the same weight criterion were 13% compared to 4% for placebo.

Laboratory Changes: An assessment of the premarketing experience for SEROQUEL suggested that it is associated with asymptomatic increases in SGPT and increases in both total cholesterol and triglycerides (see **PRECAUTIONS**).

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Digestive System: ***Frequent:*** anorexia; ***Infrequent:*** increased salivation, increased appetite, gamma glutamyl transpeptidase increased,

gingivitis, dysphagia, flatulence, gastroenteritis, gastritis, hemorrhoids, stomatitis, thirst, tooth caries, fecal incontinence, gastroesophageal reflux, gum hemorrhage, mouth ulceration, rectal hemorrhage, tongue edema; ***Rare:*** glossitis, hematemesis, intestinal obstruction, melena, pancreatitis.

Cardiovascular System: ***Frequent:*** palpitation; ***Infrequent:*** vasodilatation, QT interval prolonged, migraine, bradycardia, cerebral ischemia, irregular pulse, T wave abnormality, bundle branch block, cerebrovascular accident, deep thrombophlebitis, T wave inversion; ***Rare:*** angina pectoris, atrial fibrillation, AV block first degree, congestive heart failure, ST elevated, thrombophlebitis, T wave flattening, ST abnormality, increased QRS duration.

Respiratory System: ***Frequent:*** pharyngitis, rhinitis, cough increased, dyspnea; ***Infrequent:*** pneumonia, epistaxis, asthma; ***Rare:*** hiccup, hyperventilation.

Metabolic and Nutritional System: ***Frequent:*** peripheral edema; ***Infrequent:*** weight loss, alkaline phosphatase increased, hyperlipemia, alcohol intolerance, dehydration, hyperglycemia, creatinine increased, hypoglycemia; ***Rare:*** glycosuria, gout, hand edema, hypokalemia, water intoxication.

Skin and Appendages System: ***Frequent:*** sweating; ***Infrequent:*** pruritis, acne, eczema, contact dermatitis, maculopapular rash, seborrhea, skin ulcer; ***Rare:*** exfoliative dermatitis, psoriasis, skin discoloration.

Urogenital System: ***Infrequent:*** dysmenorrhea*, vaginitis*, urinary incontinence, metrorrhagia*, impotence*, dysuria, vaginal moniliasis*, abnormal ejaculation*, cystitis, urinary frequency, amenorrhea*, female lactation*, leukorrhea*, vaginal hemorrhage*, vulvovaginitis* orchitis*; ***Rare:*** gynecomastia*, nocturia, polyuria, acute kidney failure.

Special Senses: ***Infrequent:*** conjunctivitis, abnormal vision, dry eyes, tinnitus, taste perversion, blepharitis, eye pain; ***Rare:*** abnormality of accommodation, deafness, glaucoma.

Musculoskeletal System: ***Infrequent:*** pathological fracture, myasthenia, twitching, arthralgia, arthritis, leg cramps, bone pain.

Hemic and Lymphatic System: ***Frequent:*** leukopenia; ***Infrequent:*** leukocytosis, anemia, ecchymosis, eosinophilia, hypochromic anemia; lymphadenopathy, cyanosis; ***Rare:*** hemolysis, thrombocytopenia.

Endocrine System: ***Infrequent:*** hypothyroidism, diabetes mellitus; ***Rare:*** hyperthyroidism.

*adjusted for gender

Post Marketing Experience: Adverse events reported since market introduction which were temporally related to SEROQUEL therapy include: leukopenia/neutropenia. If a patient develops a low white cell count consider discontinuation of therapy. Possible risk factors for leukopenia/neutropenia include pre-existing low white cell count and history of drug induced leukopenia/neutropenia.

Other adverse events reported since market introduction, which were temporally related to SEROQUEL therapy, but not necessarily causally related, include the following: agranulocytosis, anaphylaxis, hyponatremia, rhabdomyolysis, syndrome of inappropriate antidiuretic hormone secretion (SIADH), and Steven Johnson syndrome (SJS).

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: SEROQUEL is not a controlled substance.

Physical and Psychologic dependence: SEROQUEL has not been systematically studied, in animals or humans, for its potential for abuse, tolerance or physical dependence. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of misuse or abuse of SEROQUEL, e.g., development of tolerance, increases in dose, drug-seeking behavior.

OVERDOSAGE

Human experience: Experience with SEROQUEL (quetiapine fumarate) in acute overdosage was limited in the clinical trial database (6 reports) with estimated doses ranging from 1200 mg to 9600 mg and no fatalities. In general, reported signs and symptoms were those resulting from an exaggeration of the drug's known pharmacological effects, i.e., drowsiness and sedation, tachycardia and hypotension. One case, involving an estimated overdose of 9600 mg, was associated with hypokalemia and first degree heart block. In post-marketing experience, there have been very rare reports of overdose of SEROQUEL alone resulting in death, coma or QTc prolongation.

Management of Overdosage: In case of acute overdosage, establish and maintain an airway and ensure adequate oxygenation and ventilation. Gastric lavage (after intubation, if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizure or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis. Cardiovascular monitoring should commence immediately and should include continuous electrocardiographic monitoring to detect possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with acute overdosage of SEROQUEL. Similarly it is reasonable to expect that the alpha-adrenergic-blocking properties of bretylium might be additive to those of quetiapine, resulting in problematic hypotension.

There is no specific antidote to SEROQUEL. Therefore appropriate supportive measures should be instituted. The possibility of multiple drug involvement should be considered. Hypotension and circulatory collapse should be treated with appropriate measures such as intravenous fluids and/or sympathomimetic agents (epinephrine and dopamine should not be used, since beta stimulation may worsen hypotension in the setting of quetiapine-induced alpha blockade). In cases of severe extrapyramidal symptoms, anticholinergic medication should be administered. Close medical supervision and monitoring should continue until the patient recovers.

DOSAGE AND ADMINISTRATION

Bipolar Mania

Usual Dose: When used as monotherapy or adjunct therapy (with lithium or divalproex), SEROQUEL should be initiated in BID doses totaling 100 mg/day on Day 1, increased to 400 mg/day on Day 4 in increments of up to 100 mg/day in BID divided doses. Further dosage adjustments up to 800 mg/day by Day 6 should be in increments of no greater than 200 mg/day. Data indicates that the majority of patients responded between 400 to 800 mg/day. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Schizophrenia

Usual Dose: SEROQUEL should generally be administered with an initial dose of 25 mg bid, with increases in increments of 25-50 mg bid or tid on the second and third day, as tolerated, to a target dose range of 300 to 400 mg daily by the fourth day, given bid or tid. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 2 days, as steady state for SEROQUEL would not be achieved for approximately 1-2 days in the typical patient. When dosage adjustments are necessary, dose increments/decrements of 25-50 mg bid are recommended. Most efficacy data with SEROQUEL were obtained using tid regimens, but in one controlled trial 225 mg bid was also effective.

Efficacy in schizophrenia was demonstrated in a dose range of 150 to 750 mg/day in the clinical trials supporting the effectiveness of SEROQUEL. In a dose response study, doses above 300 mg/day were not demonstrated to be more efficacious than the 300 mg/day dose. In other studies, however, doses in the range of 400-500 mg/day appeared to be needed. The safety of doses above 800 mg/day has not been evaluated in clinical trials.

Dosing in Special Populations

Consideration should be given to a slower rate of dose titration and a lower target dose in the elderly and in patients who are debilitated or who have a predisposition to hypotensive reactions (see **CLINICAL PHARMACOLOGY**). When indicated, dose escalation should be performed with caution in these patients.

Patients with hepatic impairment should be started on 25 mg/day. The dose should be increased daily in increments of 25-50 mg/day to an effective dose, depending on the clinical response and tolerability of the patient.

The elimination of quetiapine was enhanced in the presence of phenytoin. Higher maintenance doses of quetiapine may be required when it is coadministered with phenytoin and other enzyme inducers such as carbamazepine and phenobarbital (See Drug Interactions under **PRECAUTIONS**).

Maintenance Treatment: While there is no body of evidence available to answer the question of how long the patient treated with SEROQUEL should remain on it, the effectiveness of maintenance treatment is well established for many other drugs used to treat schizophrenia. It is recommended that responding patients be continued on SEROQUEL, but at the lowest dose needed to maintain remission. Patients should be periodically reassessed to determine the need for maintenance treatment.

Reinitiation of Treatment in Patients Previously Discontinued: Although there are no data to specifically address reinitiation of treatment, it is recommended that when restarting patients who have had an interval of less than one week off SEROQUEL, titration of SEROQUEL is not required and the maintenance dose may be reinitiated. When restarting therapy of patients who have been off SEROQUEL for more than one week, the initial titration schedule should be followed.

Switching from Antipsychotics: There are no systematically collected data to specifically address switching patients with schizophrenia from antipsychotics to SEROQUEL, or concerning concomitant administration with antipsychotics. While immediate discontinuation of the previous antipsychotic treatment may be acceptable for some patients with schizophrenia, more gradual discontinuation may be most appropriate for others. In all cases, the period of overlapping antipsychotic administration should be minimized. When switching patients with schizophrenia from depot antipsychotics, if medically appropriate, initiate SEROQUEL therapy in place of the next scheduled injection. The need for continuing existing EPS medication should be reevaluated periodically.

HOW SUPPLIED

25 mg Tablets (NDC 0310-0275) peach, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '25' on one side and plain on the other side, are supplied in bottles of 100 tablets and 1000 tablets, and hospital unit dose packages of 100 tablets.

100 mg Tablets (NDC 0310-0271) yellow, round, biconvex film coated tablets, identified with 'SEROQUEL' and '100' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

200 mg Tablets (NDC 0310-0272) white, round, biconvex, film coated tablets, identified with 'SEROQUEL' and '200' on one side and plain on the other side, are supplied in bottles of 100 tablets and hospital unit dose packages of 100 tablets.

300 mg Tablets (NDC 0310-0274) white, capsule-shaped, biconvex, film coated tablets, intagliated with 'SEROQUEL' on one side and '300' on the other side, are supplied in bottles of 60 tablets and hospital unit dose packages of 100 tablets.

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP].

ANIMAL TOXICOLOGY

Quetiapine caused a dose-related increase in pigment deposition in thyroid gland in rat toxicity studies which were 4 weeks in duration or longer and in a mouse 2 year carcinogenicity study. Doses were 10-250 mg/kg in rats, 75-750 mg/kg in mice; these doses are 0.1-3.0, and 0.1-4.5 times the maximum recommended human dose (on a mg/m^2 basis), respectively. Pigment deposition was shown to be irreversible in rats. The identity of the pigment could not be determined, but was found to be co-localized with quetiapine in thyroid gland follicular epithelial cells. The functional effects and the relevance of this finding to human risk are unknown.

In dogs receiving quetiapine for 6 or 12 months, but not for 1 month, focal triangular cataracts occurred at the junction of posterior sutures in the outer cortex of the lens at a dose of 100 mg/kg, or 4 times the maximum recommended human dose on a mg/m^2 basis. This finding may be due to inhibition of cholesterol biosynthesis by quetiapine. Quetiapine caused a dose related reduction in plasma cholesterol levels in repeat-dose dog and monkey studies; however, there was no correlation between plasma cholesterol and the presence of cataracts in individual dogs. The appearance of delta-8-cholestanol in plasma is consistent with inhibition of a late stage in cholesterol biosynthesis in these species. There also was a 25% reduction in cholesterol content of the outer cortex of the lens observed in a special study in quetiapine treated female dogs. Drug-related cataracts have not been seen in any other species; however, in a 1-year study in monkeys, a striated appearance of the anterior lens surface was detected in 2/7 females at a dose of 225 mg/kg or 5.5 times the maximum recommended human dose on a mg/m^2 basis.

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0202M17441

OLSON

UNIVERSITY OF MINNESOTA

105 AGENDA 05/22/04 EP/NDR

Ambulatory Research Center

Department of Psychiatry
Medical School

Riverside Professional Building
606–24th Avenue South
Suite 602
Minneapolis, MN 55454

May 10, 2004

Ms. Patrice Webster
Assistant Director
Institutional Review Board
University of Minnesota
MMC 820
D528 Mayo Memorial Building
420 Delaware St. SE
Minneapolis, MN 55455-0392

Re: "Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52-Week Comparison. **The CAFÉ Study.**

Human Subject's Code Number: **0202M17441**

Dear Ms. Webster,

This correspondence is a request for an expedited review as result of a sponsor initiated consent change. Recently the FDA issued a new warning about the risks of hyperglycemia and diabetes in patients taking atypical antipsychotic agents, including CAFÉ study medications Quetiapine, Risperidone, and Olanzapine. The current CAFÉ informed consent form includes information about hyperglycemia as a risk of CAFÉ study medications. However, diabetes was not included as a risk on the consent form. Enclosed you will find the sponsor approved wording that has added to reflect this in a new version of the adult consent form dated 3/24/04. Also attached is a paper regarding the ADA's guidelines for proper monitoring of patients on atypical antipsychotic medications for hyperglycemia and diabetes. Please be assured that the CAFÉ schedule of events provides adequate monitoring for hyperglycemia and diabetes according to the ADA's guidelines.

Please feel free to contact me for further information regarding this matter. I may be contacted at 612.273.9763. You may also feel free to contact Jean Kenney, primary Study Coordinator, at 612.627.4363

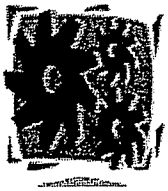
Note: Per Jean Kenney, the revised consent form is to be used to reconsent enrolled subjects only — study enrollment was completed at this site March 2004. PW

Sincerely,

Stephen Olson, M.D.
Principal Investigator
jmk/enclosures

EXHIBIT 16

IRB000229



Informed Consent Process MENU

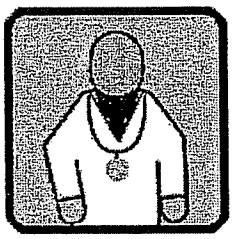
EXHIBIT 17

Selecting Participants

Recruitment of participants needs to be done in a nonbiased, non-power-based manner. It is important that none of the participants ever feel that if they do not participate in the study, they will be penalized. Convenience should not be the sole factor in the selection of participants. All avenues of recruiting participants should be investigated. The following relationships can be potentially troublesome for informed consent and have important points to be considered for ongoing care.

Doctor-Patient

Doctor-patient relationships between the investigator and participants should be avoided, when possible, to eliminate any power-based coercion. Patients can say no to someone they do not expect to see in the future, but it is very difficult for people to say no when they rely on someone for ongoing medical care.



Participants often depend on physicians to make treatment recommendations, and then they defer to the physician's professional knowledge and judgement. They may not read the consent document fully because the physician has already explained the procedure orally, and they consider the doctor the primary source for information.

There is a need to clearly distinguish the treatment from the research involvement and to exercise caution that the physician's influence does not dictate the subject's consent decision.

OM000020

Teacher-Student

Special consideration of recruitment is also needed for instances when an instructor wants to include his or her students in a research study. The teacher cannot assume everyone in the class wants to be involved in

the study. Students must be assured that their grade is not affected by their participation, and they should be able to decline participation without penalty.

Researchers may fail to identify the need for informed consent if the study is not perceived to have physical or psychological risks. Students may not see it this way. Participants, including students, have the right to refuse involvement in a research project even if there is no identified risk.

Employees as participants

Colleagues, subordinates, or peers should never be placed in a compromising situation with perceived retribution for not being a research participant. Recruiting through advertisements or a third party is a better strategy for avoiding coercion.

Proxy

When a participant is not of legal age or is deemed incompetent to consent to treatment, it is necessary for a proxy (family member, guardian, or friend) to decide consent.

Children

In justifying using children in your study, you must document the specific benefits the child will encounter. A parent or guardian must act as the proxy for the child and complete a parental permission form. Children also need to give their "assent." Assent is the affirmative agreement to participate in the study if the child is able to comprehend aspects of the research. You must develop a separate assent form. Try to tailor the assent document to the understanding of the child. Reasonable descriptions of discomfort should be included. Children can not give consent to research that entails risks that surpass the benefits.

Elderly

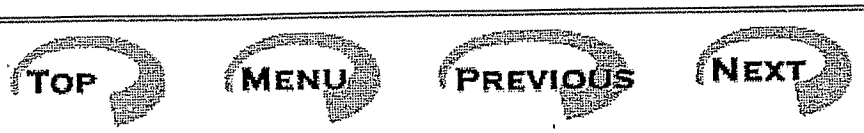
Participants that have diminished vision or hearing can oftentimes overcome the problems and consent themselves.

If the person is deemed to be incompetent, such as in the case of Alzheimer's disease or other brain diseases, the investigator must seek the consent of a proxy. The proxy may not know the wishes of the participant regarding research studies but should try to decide in the way the person would have decided. Investigators should ask proxies if they think that participants would have decided in the same manner if they were competent.

In either case, a proxy should discuss the decision with family members

OM 000021

and/or the medical staff caring for the person. Even if the participant has been judged incompetent, the person should be considered competent to refuse.



OM 000022

AUTHORIZATION AND CONSENT FOR RELEASE OF MEDICAL INFORMATION

PATIENT NAME: Dan Markingson BIRTHDATE: 11/25/76

SOCIAL SECURITY #: 469-90-2422 MEDICAL RECORD #: _____

OTHER NAMES USED: _____

Information Released From:

Dr. Stephen Olson / CAFÉ team
Doctor's name

Street Address

City *State* *ZIP*

Phone

Information Released To:

Mary Weiss (mother)
Doctor's name

536 2nd Ave
Street Address

South St Paul, MN 55076
City *State* *ZIP*

651-455-0035
Phone

The following information is to be released (check appropriate boxes):

- ☐ Discharge Summary
- ☐ Counselor's Discharge Summary
- ☐ History and Physical
- ☐ Operative Report
- ☐ Pathology Report
- ☐ Psychological Testing
- ☐ X-Ray Reports
- ☐ Lab Reports
- ☐ ECG/EEG Reports
- ☐ Outpatient/ER Report
- ☐ Consultation Report
- ☒ Other: verbal exchange

For the following time period or condition: _____

I am requesting this information for use by : Research

I understand I may revoke this consent at any time, and that the consent will automatically expire one year from the date of my signature.

I understand that there my be a retrieval and copy charge associated with the release.

I do not authorize further release by the receiving requestor to any third party. I understand that once information is released pursuant to this authorization, the faculty of physician named above cannot prevent the re-disclosure of that information.

All records pertaining to psychiatric/mental health, chemical dependency and/or AIDS/HIV related illness/testing will be released unless otherwise indicated by a check mark here: ☐

EXHIBIT 18

Dan Markingson
Signature of Patient

12/11/03
Date

Signature of Authorized Person

Date

Relationship to Patient

REASON PATIENT IS UNABLE TO SIGN: ☐ Minor ☐ Deceased ☐ Other_____

revised 11-30-01

2

WCST-64™: Computer Version for Windows®
Research Edition
by
Robert K. Heaton, PhD

Client Information

Last Name:	drm	**Test Date:**	03/02/2004
First Name:	<Not Specified>	**Report Name:**	
Client ID:	00100013	**Test ID:**	
Birthdate:	11/25/1976	**Rapport:**	<Not Specified>
Age:	27 yrs., 3 mo.	**Cooperation:**	<Not Specified>
Gender:	Male	**Effort:**	<Not Specified>
Ethnicity:	Caucasian (not of Hispanic Origin)	**On Medication:**	No
Education:	16 yrs.		
Handedness:	Right		
Occupation:	<Not Specified>		

Caveats

The Wisconsin Card Sorting Test-64 Card Version (WCST-64; Kongs, Thompson, Iverson, & Heaton, 2000) is an abbreviated form of the standard 128-card version of the Wisconsin Card Sorting Test (WCST; Heaton, 1981). The WCST-64 maintains the task requirements of the WCST, therefore, much of what is known about the WCST will generalize to the WCST-64. Although some of the WCST literature may not be directly applicable to the WCST-64, it will provide helpful information until additional WCST-64 studies become available.

Use of this report requires a thorough understanding of the WCST-64, its interpretation, and clinical applications as presented in the WCST-64 manual (Kongs, Thompson, Iverson, & Heaton, 2000). This report is intended for use by qualified professionals.

This report contains raw scores, as well as demographically corrected normative data developed by Kongs et al. (2000). These data were collected using the standard 64-card paper and pencil version of the WCST-64 (i.e., not the computerized version). Although research has demonstrated general equivalence between computerized administration and card administration of the WCST (Artiola i Fortuny & Heaton, 1996; Hellman, Green, Kern, & Christenson, 1992), to date no equivalence data have been gathered for the computerized administration of the Windows version of the WCST-64. For this reason, normative scores must be interpreted cautiously. To further estimate the potential effects of a different mode of administration on test performance, users of the WCST-64: CV for Windows should be familiar with the original card version.

Users should refer to the WCST-64 manual (Kongs et al., 2000) for the clinical interpretation of this score report. Clinical interpretation of the WCST-64 requires professional training and expertise in clinical psychology and/or neuropsychology. The utility and validity of the WCST-64 as a clinical measure of cognitive ability are directly related to the professional's background and knowledge, and, in particular, familiarity with the information contained in the WCST-64 manual.

WCST-64 results should be interpreted within the context of a larger clinical assessment battery and relevant clinical and historical information about this client. Additionally, use of WCST-64 scores for clinical or diagnostic decisions should not be attempted without a good understanding of brain-behavior relationships and the medical and psychological factors that affect them.

EXHIBIT 9

1

DRM / 00100013

Date/Time Discipline	Problem Category Title and Progress Note
3/25/04	Had conversation ⊂ (D)'s mother & her close friend Mike (who is also quite close to (D)). Gave examples of poor planning & judgment on (D)'s part. Says he's leaving for CA as soon as court order expires. Plan is to take a Greyhound until $ runs out & then hitchhike the rest of the way (this info from Dave Pettit, Dakota Co. case manager). Tells his mo & Mike his plan for a job is to give tours in his car but does not understand he needs added insurance. He has Ø place to live, no one to stay with & no $ saved. Has Ø been making car or ins. payments & does Ø question how this has been maintained (Mother has been funding this) Apparently he has cancelled medical appts for thyroid & hyperlipidemia which we have been advising for months now. He has cancelled ser. therapy appts & therapist reports he is Ø talking in sessions. Writer will get release for therapist to receive collateral info re: this. Mike states that when they are alone he will make statements such as "You & I are perfect" & will say this repeatedly & 'cold stare" Also similarly "How are you" Spent noc & didn't have meds & had no concern about taking them. Writer has left message ⊂ CCM ~ recommendations for extension of stay of commit. Will discuss further ⊂ input from DTP staff & grp home, mother & Dr. Olson, Kennedy

EXHIBIT 21

PSJ 000021

Patient initials: D R M

Site/Patient number: 0 0 1 0 0 0 1 3

Visit date (mm dd, yyyy): MAR 31 2004

Visit: V10

WORKBOOK SHEET #5

Recovery: Look at the following timeline of recovery and mark where you think you are in the recovery process.

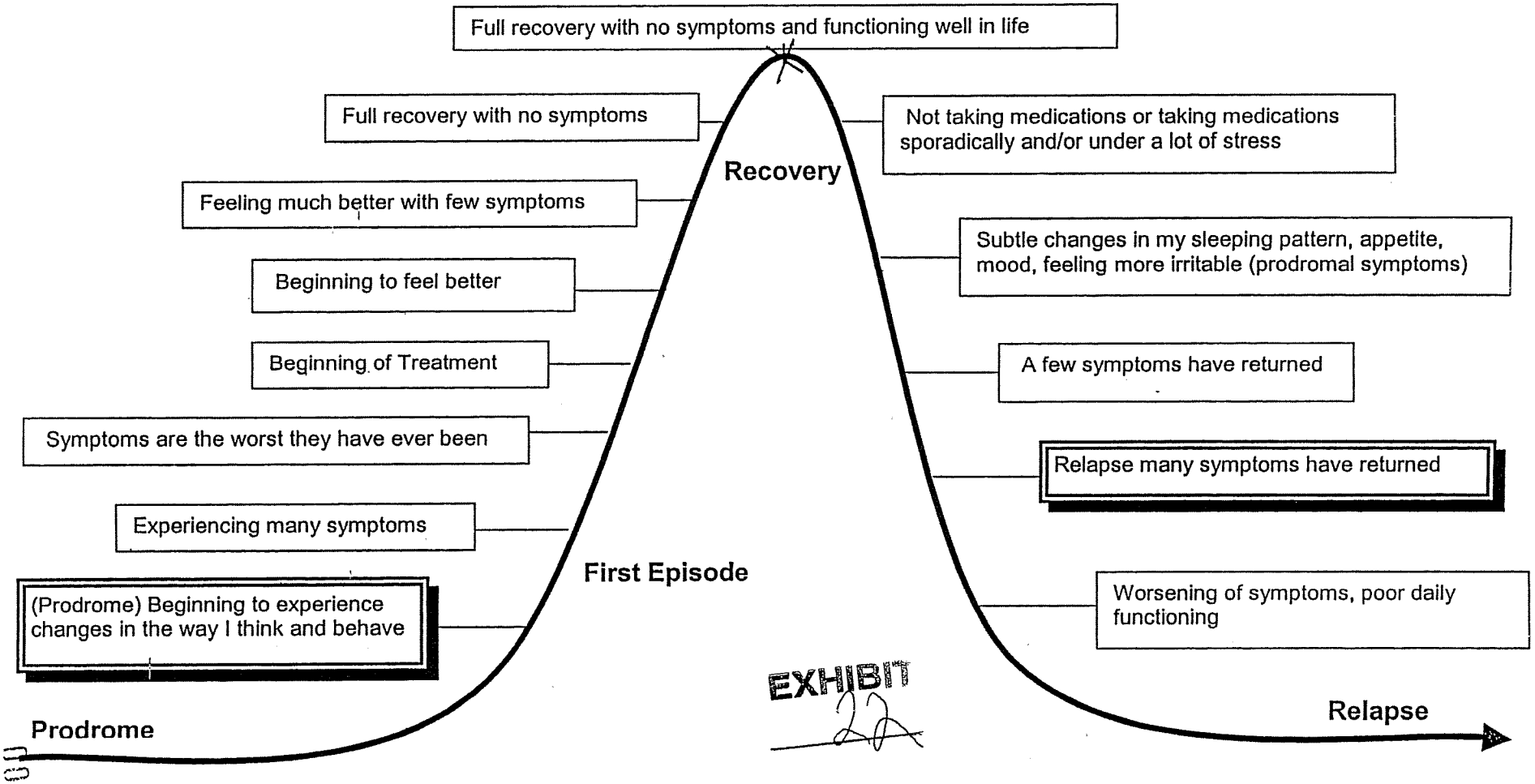


EXHIBIT 27

CS 000176

EXHIBIT
23

DRM/00100213

Date/Time Discipline	Problem Category Title and Progress Note
DMK 4/15/04	~~Weiss also said she would get a certified letter stating this.~~
4/15/04	Rec'd 2 phone calls, one from Mary W & one from her friend, Mike on Sunday, 4/18/04. Mary again reiterating (D)'s meds are Ø working, he is totally out of control. He says things such as "are you asking me or telling me." She also stated "Dr. we have to wait until he kills himself or someone else & anyone does anything." Mike Howard's message stated that he went over to see (D) & Mary confronted him & that he was angry & fists doubled, chest out & made comment, "I'm invincible." He is advising Mary to see attorney. "How can we expect a mentally ill person to make a decision about getting a second opinion." This writer called grp home to dok about this incident. apparently, there was a miscommunication & (D) & Ø receive the message that his mtr was picking him up for Easter & he had already eaten @ grp home. This staff person reports that (D) is doing well, he is spending more time & peers. They have seen no psychotic behaviors. (Kenney, LICSW)
4/15/04	Rec'd call on 4/9/04 as well from Mary Weiss - this is message transcribed from voice mail: "You heard (D) say loud & clear that he is Ø ready for another pt. he is Ø able to work, he cannot afford it, the drug is doing nothing. if anything happens to my son, I will have a certified letter stating that no one was willing to listen or A needs and he was pushed into an apartment. (Kenney, LICSW)

DAK 834
8/05/97

FINAL REPORT TO THE COURT
STAY OF COMMITMENT

TO: Dakota County Probate Court
Civil Commitment Division

Court File #: PX-03-10565
County Attorney File # _____

RE: Daniel R Markingson D.O.B. 11/25/1976

Date of Report: 5-4-04
Date Stay Ordered: 11-20-03

In Conformance with Minnesota Statute 253B.095, Subdivision 4, this report is submitted by David Pettit , Dakota County Case Manager, regarding the status of the above-named individual's stay of commitment.

FACTORS TO REPORT:
1. Detailed description of Respondent's compliance with Stay of Commitment over last 90-day period.
2. Any changes in the court ordered agreement or Respondent's diagnosis.
3. Whether an extension of the stay is necessary, specifically outlining the basis.
   If dismissal is recommended, Respondent's status in the community and why recommending dismissal.

1. Dan has been in compliance with his treatment except for an incident in which it was suspected that he was cheeking his medications. He has been going to day treatment, keeping his appointments with his psychiatrist and following the house rules at Theo I
2. Dans' current diagnosis is Schizophrenia, paranoid type. the court ordered agreement has not changed but will need to be updated if the extension is granted.
3. I am requested that the stay be extended based on a request from his psychiatrist which is enclosed and the concerns of Dans' mother. Dan continues to be guarded and minimizes his problems. His plans if he were to be released from his stay are vague and risky and do not include specific ways is which to care for his mental illness. His plan was to take a bus towards California and when his money ran out he would either stay were he ended up for awhile or hitch hike to Los Angeles. His mother fears that he would end up homeless and delusional and become a danger to himself or others.
4. Dismissal is not recommended

Signature of Dakota County Case Manager

5-4-04
Date

cc:

EXHIBIT
24

epha

000070
dc

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Department of Psychiatry
Medical School

F282/2A West Building
2450 Riverside Avenue
Minneapolis, MN 55454-1495

April 27, 2004

David Pettit, Case Manager
Dakota County Social Services
1 Mendota Road West, Suite 300
West St. Paul, MN 55118

Re: Daniel R. Markingson
D.O.B. – 11/25/1976

Dear Mr. Pettit:

I am recommending an extension of the stay of commitment for Dan Markingson, who has been a patient of mine for six months since his hospitalization when the commitment petition was filed. During this interval, Dan has remained in treatment and generally complied with the conditions set for the stay of commitment. He has however, indicated an intention to move back to California permanently when the commitment expires. He has little insight into his mental disorder and would be unlikely to voluntarily seek appropriate treatment if his condition worsens. I share his mother's concern that he would potentially place himself at risk of harm if he were to terminate his treatment or leave the state in his current condition. His delusional thinking would increase and dominate his behavior as it did prior to his hospitalization. Extension of the stay would permit more definitive intervention should his condition worsen, reducing the risk of inpatient readmission.

I hope this information is sufficient for the resolution of this situation. If you have any questions, call me at 612-273-9763.

Sincerely,

Stephen C. Olson, MD
Associate Professor of Psychiatry
Director, Schizophrenia Program

EXHIBIT
25

DAKOTA COUNTY
APR 29 2004
SOCIAL SERVICES

UNIVERSITY OF MINNESOTA

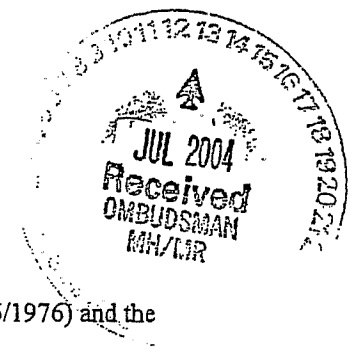
Twin Cities Campus

Department of Psychiatry
Medical School

F282/2A West Building
2450 Riverside Avenue
Minneapolis, MN 55454-1495

July 9, 2004

Jo Zillhardt, RN, C
Medical Review Coordinator
Office of the Ombudsman for Mental Health and Mental Retardation
State of Minnesota
121 7th Place E., Suite 420
Metro Square Building
St. Paul, MN 55101-2117



Dear Ms. Zillhardt:

Enclosed you will find the information you requested concerning Dan Markingson (DOB: 11/25/1976) and the CAFÉ study:

1. Information about the CAFÉ study – the informed consent provides all details concerning the study.
   a. Client informed consent – attached to this letter
   b. Progress notes - attached to this letter
   c. Laboratory results - attached to this letter
   d. There is no placebo arm to this study, therefore, the subject was receiving one of the following three FDA approved antipsychotics for the treatment of schizophrenia, schizophreniform, or schizoaffective disorder: olanzapine (Zyprexa®), quetiapine (Seroquel®) or risperidone (Risperdal®).

2. Unless a subject is fully committed and under a Jarvis order for forced medication, which specifically prohibits forced treatment under an experimental protocol, a commitment has no bearing on whether or not a subject would be deemed able to provide informed consent. In this case, Mr. Markingson was on a stay of commitment contingent on his cooperation with recommended appropriate treatment. Since the treatment in the CAFÉ study is consistent with standard treatment (an FDA approved antipsychotic, no restrictions on concurrent medications, etc.) and he was competent to provide informed consent, he entered the study thus satisfying the relevant terms of the stay. Had Mr. Markingson chosen not to participate, a similar regimen of medication and follow-up would have been recommended. His Dakota County case manager, who has final authority to determine if a stayed patient is complying with recommended treatment, was in favor of him participating, and this was cleared prior to Mr. Markingson enrolling in the study.

3. When any Serious Adverse Event (SAE) occurs, there is a specific protocol to follow. The CAFÉ study sponsor Astra-Zeneca, the study's Medical Director, the CAFÉ clinical research organization Quintiles were notified on May 11 as soon as we learned of the death, as was the Institutional Review Board (IRB) at the University of Minnesota. The IRB informs the Institutional Official for Human Subject Protections who reports the event to appropriate regulatory agencies including the FDA.

If I can be of further assistance, please do not hesitate to contact me or CAFÉ study coordinator, Jean Kenney, MSW, LICSW at (612) 627-4363.

Sincerely,

Stephen C. Olson, MD
Associate Professor of Psychiatry
Director, Schizophrenia Program
CAFÉ Principal Investigator
(612) 273-9763

JMK/Enclosures

EXHIBIT 29

OM 000181

AstraZeneca

Serious Adverse Event Report – Clinical Study

☒ Initial Report ☐ Follow up Report

ɔcol No.: 5077IL / 0114	Site No.: 010	Country: USA	Clintrace No.:
'lment No.: 0013	Randomization No.: 0013	Patient Initials: DRM	Weight: 179 lbs
Age: 27	Date of birth 25/Nov/1976 DD-MMM-YYYY	☒ Male ☐ Female	Height: 76 in

Serious Adverse Event (SAE):
(Main diagnosis): Suicide

Date AE Started: 08/May/2004
(DD-MMM-YYYY, 24-hour clock)
Date of first occurrence of symptoms, add time if relevant

Brief Description of SAE:
(Symptoms, course, treatment of SAE).
Subject has been compliant in CAFÉ study, currently on 4 study tablets twice per day (8 total). Reports from group home, county case manager and outpatient day treatment program have all indicated that DRM was invested in his treatment plan, cooperative with all treatments, including the provisions of his court ordered stay of commitment. Last study visit performed on 28 April, 2004. At this time, DRM denied all positive symptoms including depression, paranoia, delusional thinking or hallucinations. None of these symptoms were apparent in PANSS interview or throughout the visit. This presentation has been consistent throughout the majority of his involvement in the CAFÉ study. Also, consistent throughout the study has been DRM's presentation of guardedness and minimal insight. He acknowledged past symptoms but would continually deny any present concerns. Over the last few months, DRM's ADLs have deteriorated, often with a disheveled appearance and wearing the same clothes as previous visits. These observations were discussed with the subject. Prior to the SAE, client was said to have gone about his normal routine. He retired to bed, got up in the night and took a shower as was his typical behavior. Staff at the group [illegible]e noticed he was in the bathroom an unusual amount of time. [illegible] he did not respond to their inquiries, the bathroom door was to[illegible]d open. DRM was found dead apparently from suicide. This is said to have occurred at approximately 1 am on May 8, 2004. An autopsy may be pending, but we have insufficient data to know the details of this.

This study is no longer enrolling subjects as of March, 2004.

Date AE met Serious Criteria: 08/May/2004
DD-MMM-YYYY

Detection Date: 11/May/2004
DD-MMM-YYYY
Date when investigator became aware that event was a SAE

The Event is Serious due to:
- ☒ Death
- ☐ Life-threatening
- ☐ In-patient hospitalization or prolongation of existing hospitalization
- ☐ Persistent or significant disability/incapacity
- ☐ A congenital abnormality/birth defect
- ☐ Important medical event

If Hospitalized:
Date of hospitalization: N/A
DD-MMM-YYYY
Date of discharge:
DD-MMM-YYYY

AE Stopped:(if resolved): 08/May/2004
DD-MMM-YYYY
Last day when AE was present; add time if relevant

Outcome:
- ☐ Recovered/Resolved
- ☐ Recovering/Resolving
- ☐ Not recovered/Not resolved
- ☐ Recovered/Resolved with sequelae
- ☒ Fatal [a]

[a]Date of Death: 08/MAY/2004
Autopsy performed: ☐ No ☐ Yes (Attach report)
Probable cause of death:
Suicide

EXHIBIT 26

DS4 000143

Was the subject withdrawn from the study due to this serious adverse event?

YES ☐ NO ☐

Investigational Product(s) Olanzapine /Quetiapine / Risperidone	Route (e.g. oral, i.v., topical, inhaled)	Daily Frequency (e.g. q.d., b.i.d.)	Total Daily Dose Number of capsules	Duration of Therapy (DD-MMM-YYYY, e.g. 20-NOV-1997, 14:00) (Add 24-hour clock if relevant) Started	Duration of Therapy Stopped	Causality Assessment[b] (Yes or No)	Action Take[c] (0, 1, 2, 3 or N/A)
CAFÉ medication	oral	4 B.I.D	8	05-DEC-2003		☐ Yes ☒ No	0
						☐ Yes ☐ No	
						☐ Yes ☐ No	

[b] Causality Assessment:
Do you consider that there is a reasonable possibility that the event may have been caused by the drug?'

[c] Action Taken regarding investigational product:
0 = None
1 = Dose of investigational product changed, or not increased as per study protocol
2 = Investigational product temporarily stopped
3 = Investigational product stopped
N/A = Not Applicable (i. e. when patient is not on investigational product)

Treatment code broken by investigator: ☒ No ☐ Yes ☐ Not applicable

PSY 000188

AstraZeneca

Serious Adverse Event Report – Clinical Study

☐ Initial Report ☐ Follow up Report

Protocol No.: 5077IL / 0114	Site No.: 0010	Country: USA	Clintrace No.:
nsent No.: 0013	Randomization No.: 0013	Patient Initials: DRM	

Relevant Clinical Laboratory Assessments: ☒ Not performed ☐ Attached ☐ See below

(only SAE related assessments)

Assessment date: DD-MMM-YYYY	Sample Test & Result (Include unit)	Ref. Range (Include unit):	Assessment date: DD-MMM-YYYY	Sample Test & Result (Include unit)	Ref. Range (Include unit):

Relevant Other Testing: (Include date of exam and result)

Relevant Medical History: (e.g. concurrent diseases, previous history of present condition, allergies, previous drug reactions)

☐ None hypothyroidism treated with Synthroid. Hyperlipidemia - subject referred to medical doctor. No treatments given at this time.

Concomitant Drug Therapy (taken during last month) ☐ None

Exclude medicines given to treat Serious Adverse Event. If more space is required use second SAE form.

Drug(s) Trade name or generic name and formulation, strength	Route (e.g. oral, i.v., topical, inhaled)	Daily Frequency (e.g. q.d., b.i.d.)	Total Daily Dose (specify unit)	Duration of Therapy (DD-MMM-YYYY) Started	Duration of Therapy (DD-MMM-YYYY) Stopped	Causality Assessment[b] (Yes or No)	Indication for Use of Drug
Synthroid	oral	q.d.	50 ~~mg~~ mcg JKK 5/11/04	24-11-2003		☐ Yes ☒ No	hypothyroidism
						☐ Yes ☐ No	
						☐ Yes ☐ No	
						☐ Yes ☐ No	
						☐ Yes ☐ No	
						☐ Yes ☐ No	

Investigator name:	**Stephen C. Olson, MD**	Signature:	Stephen C. Olson
Address:	**University of Minnesota** Department of Psychiatry **606 24th Avenue South, Suite 602** **Minneapolis, MN 55454**	Date:	11 May 2004
Name of Person Reporting Event:	**Jean M. Kenney, MSW, LICSW**	Title of Person Reporting Event:	**Study Coordinator**
Phone number of Person Reporting Event:	**612-627-4363**	Date of this Report: **11/May/2004** Date Quintiles Notified: **11/May/2004**	

psy 000187

MINNESOTA REGIONAL CORONER'S OFFICE
Regina Medical Center
1175 Nininger Road, Hastings MN 55033
Phone: 651-480-4253 Fax: 651-480-4257

Case #: DC04-262 **Investigator:** Romann

Deceased: Markingson, Dan **DOB:** 11-25-76 **Sex:** M

Address: 1312 Livingston Ave, West St. Paul MN 55075

Place of Death: Same, bathroom

Time and Date of Death: 5/8/04 **Found:** 0225

Law Enforcement: WSP **Officers:**

CAUSE OF DEATH: Sharp force injuries to the neck and chest

DUE TO:

DUE TO:

OTHER SIGNIFICANT CONDITIONS: History of mental illness

Manner of Death: Suicide **Postmortem Examination:** Limited

Toxicology Findings: Blood drug screen: Caffeine present only; Vitreous ethanol: Negative

Mr. Markingson was a 46-year-old male with a past medical history of schizophrenia, hypothyroidism, and suicide ideations. In the fall of 2003 Mr. Markingson moved from California to Minnesota. He was hospitalized at Fairview University and then discharged to a group home in December 2003. He was part of a medication study trial and was presumably on one of three anti-psychotics. On May 8, 2004, the group home attendee went to check on him and found Mr. Markingson in a lifeless state in the bathroom. On a night stand in the bedroom was a note on which was written "I left this experience smiling!".

When first viewed by Coroner personnel, the body was lying in a bathtub. In his right hand was an opened utility knife and his left hand was within his left chest cavity through a gaping incision on his lower left chest. There were numerous other incisions on his neck. An external examination at the Coroner's Office showed incised wounds of the neck and left chest. The left hemidiaphragm was incised and the left lung was collapsed, and there were incisions on the pericardial sac but the heart was not incised.

EXHIBIT
27

Lindsey C. Thomas, M.D. June 4, 2004

Lindsey C. Thomas MD
6/17/04

OM 000189

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR

(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)

(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014.
Expiration Date: January 31, 2006.
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

JUL 12 2004 PM 3:07

1. NAME AND ADDRESS OF INVESTIGATOR

Stephen C. Olson, M.D.
University of Minnesota
Department of Psychiatry
F282/2A West
2450 Riverside Avenue
Minneapolis, MN 55454

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFIES THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS ATTACHED.

☒ CURRICULUM VITAE ☐ OTHER STATEMENT OF QUALIFICATIONS

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED.

University of Minnesota
Ambulatory Research Center
Riverside Professional Building
606 24th Avenue South, Suite 602
Minneapolis, MN 55454

NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY.

ntiles Laboratories Limited
Highlands Parkway, Suite 600
Smyrna, GA 30082

Psychemedics Corporation
5832 Uplander Way
Culver City, CA 90230-6608

NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)

University of Minnesota Research Subjects' Protection Programs
Institutional Review Board: Human Subjects Committee
Box 820
D528 Mayo Memorial Building
420 Delaware Street SE
Minneapolis, MN 55455-0392

NAMES OF THE SUBINVESTIGATORS *(e.g., research fellows, residents, associates)* WHO WILL BE ASSISTING THE INVESTIGATOR IN THE CONDUCT OF THE INVESTIGATION(S).

S. Charles Schulz, M.D.
John Vuchetich, M.D., Ph.D.
Jeannie Kenney, LICSW
Elizabeth Lemke, B.A.
Angela Guimaraes, B.A.
Christa Serureus-Johnson, B.A.
Tanya Adelman, B.A.

EXHIBIT
28

NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR.

Efficacy and Tolerability of Olanzapine, Quetiapine, and Risperidone in the Treatment of First Episode Psychosis: A Randomized Double Blind 52-Week Comparison

l Number: 5077IL/0114

IRB 000005

8. ATTACH THE FOLLOWING CLINICAL PROTOCOL INFORMATION:

☐ FOR PHASE 1 INVESTIGATIONS, A GENERAL OUTLINE OF THE PLANNED INVESTIGATION INCLUDING THE ESTIMATED DURATION OF THE STUDY AND THE MAXIMUM NUMBER OF SUBJECTS THAT WILL BE INVOLVED.

☑ FOR PHASE 2 OR 3 INVESTIGATIONS, AN OUTLINE OF THE STUDY PROTOCOL INCLUDING AN APPROXIMATION OF THE NUMBER OF SUBJECTS TO BE TREATED WITH THE DRUG AND THE NUMBER TO BE EMPLOYED AS CONTROLS, IF ANY; THE CLINICAL USES TO BE INVESTIGATED; CHARACTERISTICS OF SUBJECTS BY AGE, SEX, AND CONDITION; THE KIND OF CLINICAL OBSERVATIONS AND LABORATORY TESTS TO BE CONDUCTED; THE ESTIMATED DURATION OF THE STUDY; AND COPIES OR A DESCRIPTION OF CASE REPORT FORMS TO BE USED.

9. COMMITMENTS:

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64.

I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR art 312.

INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR:

1. Complete all sections. Attach a separate page if additional space is needed.
2. Attach curriculum vitae or other statement of qualifications as described in Section 2.
3. Attach protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND ATTACHMENTS TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND).

10. SIGNATURE OF INVESTIGATOR	11. DATE
[signature]	7/9/04

WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

Public reporting burden for this collection of information is estimated to average 100 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Food and Drug Administration
CBER (HFM-99)
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number."

Please DO NOT RETURN this application to this address. IRB 000006

UNIVERSITY OF MINNESOTA

Twin Cities Campus

Department of Psychiatry
Medical School

F282/2A West Building
2450 Riverside Avenue
Minneapolis, MN 55454-1495

October 25, 2004

To Whom It May Concern:

Re: Confirmation on Adverse Events

This is to confirm, that the University of Minnesota, **Department of Psychiatry,** has had no Adverse Events to report, while conducting Clinical Trials.

We hope this information is helpful to you in making a determination to participate in one of our offered studies.

Sincerely,

Stephen C. Olson, M.D.
Associate Professor of Psychiatry
Director, Schizophrenia Program

EXHIBIT
30

00 000129

Patient initials: D R M **Visit date (mm dd, yyyy):** 12 31 2005

Site/Patient number: 0 0 1 0 0 0 0 1 3 **Visit:** 4

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Rater Initials: JMK

Movement Ratings: Rate highest severity observed.

Facial and Oral Movements

1.	Muscles of Facial Expression (e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
2.	Lips and Perioral Area (e.g., puckering, pouting, smacking)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
3.	Jaw (e.g., biting, clenching, chewing, mouth opening, lateral movement)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
4.	Tongue (rate only increase in movement both in and out of mouth, NOT inability to sustain movement)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	

EXHIBIT 31

000417
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Patient initials: D R M **Visit date (mm dd, yyyy):** 03 02 2004

Site/Patient number: 0 0 1 0 0 0 1 3 **Visit:** 9

SIMPSON-ANGUS-ABBREVIATED

Rater Initials: SW

1. GAIT: The subject is examined as he walks into the examining room, his gait, the swing of his arms, his general posture, all form the basis for the overall score for this item. This is rated as follows:			
Gait	Normal	= 0	✓
	Diminution in swing while the patient is walking	= 1	
	Marked diminution in swing with obvious rigidity in the arm	= 2	
	Stiff gait with arms held rigidly before the abdomen	= 3	
	Stooped shuffling gait with propulsion and retropulsion	= 4	
2. ARM DROPPING: The subject and the examiner both raise their arms to shoulder height and let them fall to their sides. In a normal subject a stout slap is heard as the arms hit the sides. In the subject with extreme Parkinson's syndrome the arms fall very slowly.			
Arm Dropping	Normal, free fall with loud slap and rebound	= 0	✓
	Fall slowed slightly with less audible contact and little rebound	= 1	
	Fall slowed, no rebound	= 2	
	Marked slowing, no slap at all	= 3	
	Arms fall as though against resistance; as though through glue	= 4	
3. SHOULDER SHAKING: The subject's arms are bent at a right angle at the elbow and are taken one at a time by the examiner who grasps one hand and also clasps the other around the subject's elbow. The subject's upper arm is pushed to and from and the humerus is externally rotated. The degree of resistance from normal to extreme rigidity is scored as follows:			
Shoulder Shaking	Normal	= 0	✓
	Slight stiffness and resistance	= 1	
	Moderate stiffness and resistance	= 2	
	Marked rigidity with difficulty in passive movement	= 3	
	Extreme stiffness and rigidity with almost a frozen shoulder	= 4	
4. ELBOW RIGIDITY: The elbow joints are separately bent at right angles and passively extended and flexed with the subject's biceps observed and simultaneously palpated. The resistance to this procedure is rated.			
Elbow Rigidity	Normal	= 0	✓
	Slight stiffness and resistance	= 1	
	Moderate stiffness and resistance	= 2	
	Marked rigidity with difficulty in passive movement	= 3	
	Extreme stiffness and rigidity with almost a frozen elbow	= 4	

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Patient initials: D R M **Visit date (mm dd, yyyy):** 04 26 2004

Site/Patient number: 0 0 1 0 0 0 1 3 **Visit:** 11

ABNORMAL INVOLUNTARY MOVEMENT SCALE (AIMS)

Rater Initials: SCO

Movement Ratings: Rate highest severity observed.

Facial and Oral Movements

1.	Muscles of Facial Expression (e.g., movements of forehead, eyebrows, periorbital area, cheeks; include frowning, blinking, smiling, grimacing)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
2.	Lips and Perioral Area (e.g., puckering, pouting, smacking)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
3.	Jaw (e.g., biting, clenching, chewing, mouth opening, lateral movement)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	
4.	Tongue (rate only increase in movement both in and out of mouth, NOT inability to sustain movement)	None, Normal = 0	✓
		Minimal (may be extreme normal) = 1	
		Mild = 2	
		Moderate = 3	
		Severe = 4	

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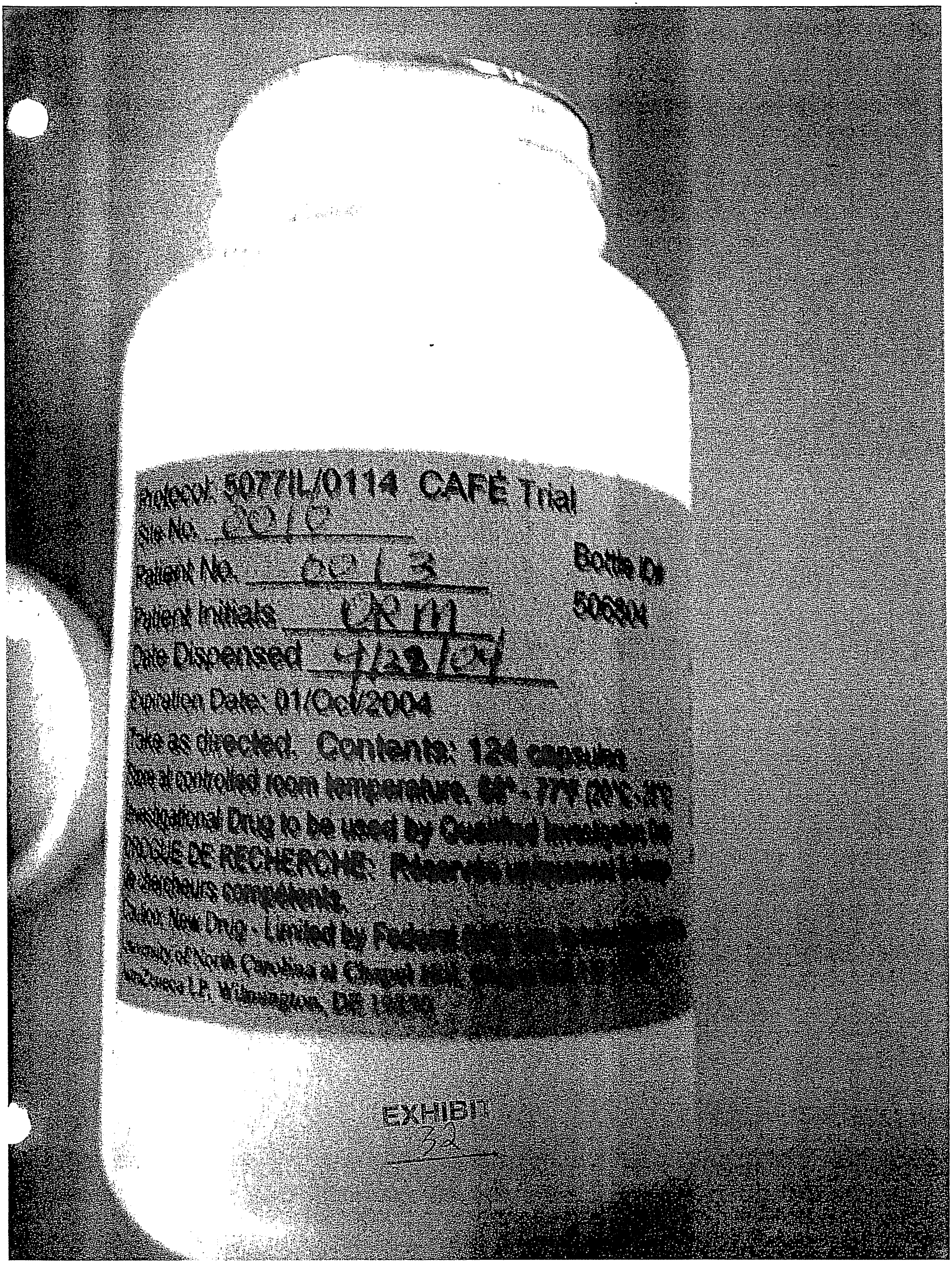
Protocol: 5077IL/0114 CAFÉ Trial
Site No.
Patient No.
Patient Initials
Date Dispensed
Expiration Date: 01/Oct/2004
Take as directed. Contents: 124
Store at controlled room temperature
DROGUE DE RECHERCHE:
chercheurs compétents.
EXHIBIT

EXHIBIT

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