A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY TO ASSESS THE EFFECTS OF SERTRALINE, ALONE AND WITH DIAZEPAM, ON PSYCHOMOTOR PERFORMANCE

STUDY REPORT: PROTOCOL 206

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TITLE OF STUDY: Study Report:Protocol 206

A Double-blind Placebo-Controlled, Crossover Study To Assess The Effects of Sertraline, Alone and with Diazepam, on Psychomotor Performance.

I, Dr Ian Hindmarch, have read the attached report of the clinical study which I have undertaken with oral doses of Sertraline, 25, 50, 75 and 100 mg.I confirm that the report accurately presents the study as undertaken and that I am in full agreement with the conclusions drawn.

Signed [redacted]

Date 9/V/88

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SYNOPSIS

PROTOCOL 206 : A DOUBLE-BLIND, PLACEBO-CONTROLLED, CROSS-OVER STUDY TO ASSESS THE EFFECTS OF SERTRALINE, ALONE AND WITH DIAZEPAM, ON PSYCHOMOTOR PERFORMANCE

Investigator : Dr. I. Hindmarch

A. STUDY DESIGN:
This double-blind placebo-controlled cross-over study in healthy volunteers was designed to compare the effects of 150mg sertraline daily for 7 days with those of placebo on psychomotor performance and on subjective feeling states before and after concurrent administration of 5mg/day diazepam for the last 3 days.

B. SUBJECTS:

	Sertraline	Placebo
Entered Treatment	5	7
Assessed for psychomotor performance	0	0
Assessed for safety	5	7

Psychomotor performance was not assessed because of premature termination of the study.

C. DRUG ADMINISTRATION:
The study was terminated before administration of diazepam to any subject and before the cross-over.

Sertraline was given as 3 x 50mg capsules or 3 x matching placebo once daily for 2-4 days. Diazepam was not administered.

D. RESULTS:
1. Effects on psychomotor performance and subjective feelings: no conclusions could be reached as the study was prematurely terminated.
2. Safety:
No. of subjects with treatment-related:

side-effects	5/5(5)	1/7(1)
abnormal laboratory test results	0/5(0)	0/7(0)

() Resulting in discontinuation from treatment.

E. CONCLUSIONS:

This double-blind, placebo-controlled, cross-over study of sertraline in 12 healthy female volunteers was prematurely terminated on day 4 due to complaints of intolerable side-effects by 6 volunteers, 5 of whom were found to be receiving sertraline when the double-blind code was broken. No assessment of psychomotor performance nor of mood was done.

There were no laboratory test abnormalities or clinically significant changes in vital signs related to the study medication. Side-effects in the sertraline group were tremor, insomnia, nausea, asthenia and agitation experienced by all volunteers; dizziness, sweating, dry mouth, and anxiety were reported by four volunteers. Other, less frequent side-effects included headache, somnolence, clammy skin, hypertonia (stiff jaw), vision abnormalities, confusion, vertigo, flushing, mydriasis and rigors (coldness, shivering), none of which required treatment. Some of these side-effects caused concern which may have increased the reporting of symptoms.

One volunteer on placebo reported a variety of mild to moderate side-effects of the same type as the sertraline group.

However, the reason for the high frequency of side-effects in this study remains unknown and this pattern of intolerance to sertraline has not been repeated in other studies.

STUDY REPORT

I. PURPOSE OF STUDY

To assess the effects of repeated daily doses of sertraline on psychomotor performance and compare them with those of matched placebo before and after concurrent administration of diazepam.

II. TRIAL DESIGN

This was to be a double-blind placebo-controlled cross-over study of sertraline in 12 healthy volunteers.

Each volunteer was to receive either sertraline 150mg or placebo once daily for 7 days (6 subjects on each treatment) according to a predetermined randomisation together with diazepam 5mg daily for the last 3 days. The subjects were then to receive the alternative regimen for a further 7 days, with diazepam as before for the last 3 days. A battery of psychomotor tests, a sleep evaluation questionnaire and visual analogue scales of patients' feeling states (mood tests) were to be completed during each treatment period and at the end of the study.

Safety data were to include assessments of side-effects, vital signs and laboratory tests.

FLOW CHART OF INTENDED STUDY ASSESSMENTS AND DOSING

		PERIOD 1			PERIOD 2		FINAL ASSESSMENT
ASSESSMENT DAY-->	SCREENING	1	5(+)	7	8	12(+) 14	15
CLINICAL EXAMINATION	X						X
DEMOGRAPHY	X						
PSYCHOMOTOR PERFORMANCE	X(*)	X	X	X	X	X	X
MOOD TESTS		X	X	X	X	X	X
VITAL SIGNS	X	X	X	X	X	X	
SIDE-EFFECTS		X	X	X	X	X	X
LABORATORY TESTS	X	X		X		X	
DOSAGE							
DOUBLE-BLIND THERAPY		X-------->X			X--------->X		
DIAZEPAM			X--->X			X---->X	

KEY

X : Single assessment.
X-->X : Dosing on day marked and those intervening.
(*) : These tests were to be performed to familiarise the subjects with the tests and to minimise learning effect during the trial.
(+) : All assessments were scheduled pre-dose and 2 hours post-dose.

III. SUBJECT SELECTION CRITERIA

A. For Inclusion in Study:

1. Healthy volunteers, aged 18 to 50 years.

2. No evidence of concomitant disease based upon medical history and full physical examination, and with clinical laboratory test results within the normal range for that laboratory.

3. Body weight within the range 60-90kg, and within 10% of ideal for age, height and frame size.

4. Subjects not having received any drug therapy within two weeks prior to the study.

5. Written informed consent.

B. For Exclusion from the Study:

1. Females of child-bearing potential, defined as not using reliable contraceptive methods, pregnant or lactating females.

2. Any gastro-intestinal condition possibly affecting absorption of the drug.

3. Evidence of significant haematological, vascular, renal, hepatic, gastro-intestinal or neurological disease, including all forms of epilepsy, or of any other systemic disease.

4. A history of drug or alcohol abuse, drug allergies or history of psychiatric disease including depressive episodes.

5. Subjects having received a trial medication within 3 months of the start of the study, or regularly taking psychotropic drugs.

IV. CLINICAL OBSERVATIONS AND LABORATORY MEASUREMENTS

A. Psychometric Tests:

Following selection, volunteers were to be familiarised with the test procedures and apparatus, to minimise learning effects during the study period.

The volunteers were to be transported daily from their homes to the Unit for the period of study and were to be discharged finally only after both physical and psychological assessment.

No alcohol was permitted for the period from 24 hours prior to baseline to the end of the study, and intake of caffeine-containing beverages was to be maintained at the subjects' normal intake. Concomitant therapy was not permitted.

On days 1, 5 and 7 of each week immediately prior to dosing, and 2 hours post-dosing on day 5 of each week, a battery of psychometric tests was to be completed. These comprised Critical Flicker Fusion (CFF), Complex Reaction Time (CRT), Visual Analogue Scales (VAS) of mood (subjective feelings) and mental arithmetic.

Additionally a sleep evaluation questionnaire (SEQ) was to be completed each day. All methods were in accordance with those previously described by Hindmarch (1975) and by Hindmarch and Parrott (1979).

B. Safety:

1) Side-effects:

During the study, subjects were to be asked to complete side-effect questionnaires at the same time points as psychomotor tests were performed. All reported side-effects were to be recorded together with details of time of onset, duration and the investigator's opinion of relationship to treatment. Leading questions were not permitted.

2) Laboratory Safety Tests:

The following laboratory tests were to be measured at screening during the week prior to the study and on days 1,7 and 14:

Haematology: haemoglobin, haematocrit, red blood cell, white blood cell differential and platelet counts.

Biochemistry: serum sodium, potassium, chloride, urea, creatinine, alkaline phosphatase, gamma GT, AST (SGOT), ALT (SGPT), bilirubin, glucose.

Urine: Pregnancy test at baseline.

3) Other safety parameters

At screening assessment and prior to discharge from the study a physical examination was required. In addition blood pressure and pulse, both erect and supine, were also required at the same times as the psychometric tests.

V. DEVIATIONS FROM THE PROTOCOL

Only female subjects were selected for the study. However, all subjects satisfied the criteria of using reliable contraceptive methods and had a negative pregnancy test prior to the starting of the study.

The study was terminated on day 4 (see section VI); observations thereafter were not undertaken but additional laboratory safety tests, including determination of plasma sertraline concentrations, were undertaken on day 7, together with blood pressure and heart rate measurements. As a result of the premature termination of the study, the data have been treated as from a parallel group design.

One volunteer (No 007) received the study medication in reverse order to the one she was allocated thus resulting in five sertraline-treated and seven placebo-treated volunteers in the first week (Tables 1 and 2).

Plasma sertraline concentrations on Day 7 indicated that subjects 006 and 009 may have received incorrect dosage on one occasion. The samples however, were in poor condition and an error on labelling may have occurred.

Three subjects received therapy during the two weeks prior to and during the study.

Sertraline group:

001 - Oral contraceptive
005 - Antifungal therapy (not specified)

Placebo group:

002 - Oral iron

In addition, two subjects received other therapy whilst in the study:

Sertraline group:

010 - Aspirin/codeine (Codis) on one occasion.

Placebo group:

006 - Aspirin preparations on more than one occasion.

Eight subjects (001, 004, 007, 008, 009, 010, 011 and 012) weighed less than 60kg, the minimum specified in the inclusion criteria.

Only supine blood pressure was recorded.

VI. TRIAL INCLUSIONS/EXCLUSIONS

A. Discontinuing therapy

All volunteers in the sertraline regimen and one volunteer in the placebo regimen discontinued on or before day 4 of the study due to side-effects (Tables 3 and 4). The study was therefore terminated on day 4.

VII. STATISTICAL METHODOLOGY

No statistical analyses have been done.

VIII. BASELINE SUBJECT CHARACTERISTICS

The demographic data of the participating subjects are summarised in Table 5 and the concurrent diseases at baseline in Table 6. There was only one volunteer with "mononeuritis multiplex" (carpal tunnel syndrome).

IX. DRUG ADMINISTRATION

Each subject was to receive, according to a pre-determined randomisation, seven days treatment with sertraline and seven days treatment with placebo. The treatment order was not followed by one subject - see Section V. The medication was administered as three capsules daily (of 50mg sertraline or of placebo) given as a single dose in the morning. Due to the discontinuation of the study no subjects reached day 5 of the study period and therefore none received diazepam, which was to be given on the 5th-7th days of each treatment period. (Table 8). Concomitant therapy was taken by 5 subjects. (Table 7). See also Section V.

X. RESULTS

Safety:

1. Side-effects

Table 9 displays the incidence and Table 10 the severity of side-effects by organ system.

One placebo subject and all five sertraline treated subjects experienced side-effects.

Side-effects in the sertraline group were tremor, insomnia, nausea, asthenia and agitation (all volunteers), dizziness, sweating, dry mouth, and anxiety (four out of five

volunteers), headache, somnolence, cold clammy skin, hypertonia (stiff jaw) and visual abnormalities (three out of five volunteers). All but one of the sertraline subjects reported side-effects from the first day of dosing. Other side-effects included confusion, vertigo, flushing, mydriasis, and rigors (coldness, shivering).

Twenty six out of 72 (36%) of the side-effect incidences (dizziness(2), headache(3), tremor(2), agitation(3), anxiety(2), insomnia(4), somnolence(3), nausea(4), palpitations(1), rigors(1) and asthenia(1)) were reported as severe, the remainder being of mild to moderate or unspecified severity, none of which required treatment.

One volunteer allocated to placebo reported a variety of mild to moderate side-effects - of the same type as the sertraline group - none of which required treatment, but which led to discontinuation of trial treatment. However, this subject had measurable sertraline plasma levels.

All the side-effects started 3-4 hours after dosing, were maximal 8-12 hours post-dose and were reported by the investigator to have caused the subjects concern.

Plasma sertraline and desmethylsertraline levels, determined 3-5 days after the last study drug administration, did not suggest that the side-effect incidence was associated with abnormally high concentrations of drug. (See also section X.3. - Plasma drug levels).

2. Laboratory test results

There were no abnormal test results possibly related to therapy (category 9) (Table 11). The review of test results was conservative in that abnormalities were ascribed as possibly related to study therapy if there were no positive indications of other causality. The review procedure is detailed in Appendix I, which also lists abnormal values judged not to be related to study drug (categories 1-8).

3. Other safety parameters

- blood pressure, pulse.

There were no clinically relevant changes in pulse rate or supine blood pressure between day 1 and day 7. Mean values were as follows:-

	Sertraline		Placebo[a]	
	Day 1	Day 7	Day 1	Day 7
Systolic BP (mmHg)	107	107	114	113
Diastolic BP (mmHg)	73	71	76	76
Pulse rate (b/minute)	72	70	77	76

[a] excluding subject 008 - baseline data only recorded.

- Plasma drug levels

Blood samples were obtained on day 7 of the study and whole blood concentrations of sertraline and its desmethyl metabolite were determined by Huntingdon Research Centre using gas chromatography. Samples arrived in poor condition at the laboratory and were insufficient for repeat assay. The concentrations of plasma sertraline and desmethylsertraline levels determined 3 to 5 days after the last study drug administration ranged between <5ng/ml and 48ng/ml. (Table 12).

Although volunteers #006 and #009 were supposedly on placebo they had detectable plasma levels of sertraline (13 and 19ng/ml respectively) but no metabolite was detected. In addition volunteer #006 discontinued the study dose due to side effects which were similar to the side effects reported by the volunteers on sertraline. No explanation can be offered for these findings. Subjects #010 and 012 had no detectable levels of sertraline but had metabolite present indicating that they had received sertraline.

SUMMARY

This double-blind, placebo-controlled, cross-over study in healthy volunteers was designed to compare the effects of four once daily doses of 150mg sertraline with those of placebo, before and with concurrent administration of 5mg diazepam for a further three days, on psychomotor performance, mood and a sleep assessment questionnaire. Twelve female volunteers entered the study.

Due to intolerable side-effects in 6 subjects (five found to be on sertraline) the study was terminated on day 4 and thus no subjects were assessable for effects on psychomotor performance, mood or sleep.

The most frequently reported side-effects in the sertraline regimen were tremor, insomnia, nausea, asthenia and agitation (all volunteers), dizziness, sweating, dry mouth, and anxiety (4/5 volunteers), headache, somnolence, cold clammy skin, hypertonia (stiff jaw) and vision abnormalities (3/5 volunteers), all of which were reported from the first dosing day. Other side-effects included confusion, vertigo, flushing, mydriasis and rigors (coldness, shivering). Severe side-effects included dizziness, headache, tremor, agitation, anxiety, insomnia, somnolence, nausea, palpitations, rigors and asthenia, amounting to 36% of the total number of symptoms, none of which required treatment. Some side-effects caused concern and may have resulted in over-reporting of symptoms. However, plasma levels of sertraline determined 3 to 5 days after the last study drug administration did not support the possibility of high levels of drug due to relatively low body weight as causative. Therefore the reason for the high frequency of side-effects in this study remains unknown. Most importantly, it is not reflective of the overall side-effect experience with sertraline.

One volunteer in the placebo regimen complained of a variety of side-effects - of similar type to the sertraline group - all of mild to moderate degree, but which necessitated withdrawal from the study.

All side-effects disappeared on discontinuation of treatment.

There were no clinically significant laboratory test abnormalities.

REFERENCES

1. Hindmarch I, 1975
A 1-4 Benzodiazepine, Temazepam (K 3917), its effect on some psychological parameters of sleep and behaviour.
Arzneim Forsch, 25, 1836-1839.

2. Hindmarch I and Parrot AC, 1979
The effects of repeated nocturnal doses of clobazam, dipotassium chlorazepate and placebo on subjective ratings of sleep and early morning behaviour and objective measures of arousal psychomotor performance anxiety.
Brit. J. Clin. Pharmacol., 8, 325-329.

TABLES

TABLE 1

SUBJECT EVALUATION GROUPS

EVALUATION SUBGROUP	NUMBERS OF SUBJECTS	
	SERTRALINE	PLACEBO
ENTERED TREATMENT	5	7
COMPLETED TREATMENT	0	0
COMPLETED STUDY	0	0
PSYCHOMOTOR TESTS	0	0
SAFETY ANALYSES:		
Side Effects	5	7
Laboratory Tests	5	7
Vital Signs	5	7

TABLE 2

ADMINISTRATION SCHEDULE

Subject Number	First Dosing Period	Second Dosing Period
001	Sertraline	Placebo
002	Placebo	Sertraline
003	Sertraline	Placebo
004	Placebo	Sertraline
005	Sertraline	Placebo
006	Placebo	Sertraline
007*	Placebo	Sertraline
008	Placebo	Sertraline
009	Placebo	Sertraline
010	Sertraline	Placebo
011	Placebo	Sertraline
012	Sertraline	Placebo

* Subject 7 was mistakenly given placebo in the first period as displayed in the table.

N.B. The investigator stopped the study before the first period was complete. Therefore the data displayed in all other tables are as for a parellel group study.

TABLE 3

SUMMARY OF SUBJECTS DISCONTINUING STUDY

REASON FOR DISCONTINUATION	NUMBER OF SUBJECTS	
	Sertraline	Placebo
RELATED TO STUDY DRUG		
Safety:		
Side effects	5	1
NOT RELATED TO STUDY DRUG		
Other (*)	0	6

(*) Investigator stopped the trial due to the high incidence of side effects

TABLE 4

REASONS FOR DISCONTINUING TREATMENT - SUBJECT LISTING

SUBJECT NUMBER	SEX	AGE (YRS)	DOSE AT TIME OF WITHDRAWAL (mg/day)	DURATION OF TREATMENT (days)	REASONS FOR DISCONTINUATION
SERTRALINE					
001	F	35	150	3	Side effects: agitation, anxiety, insomnia, dizziness, headache, tremor, vision abnormal, anorexia, diarrhoea, nausea, asthenia, rigors
003	F	27	150	4	Side effects: agitation, insomnia, dystonia, headache, tremor, sweating increased, mouth dry, vision abnormal, dysphagia, nausea, asthenia
005	F	35	150	3	Side effects: agitation, anxiety, insomnia, somnolence, dizziness, tremor, sweating increased, flushing, mouth dry, skin cold clammy, anorexia, nausea, palpitations, asthenia, rigors
010	F	36	150	3	Side effects: agitation, anxiety, insomnia, somnolence, dystonia, confusion, dizziness, headache, tremor, sweating increased, flushing, mouth dry, mydriasis, skin cold clammy, vision abnormal, dysphagia, nausea, tooth disorder, palpitations, asthenia, malaise
012	F	37	150	2	Side effects: agitation, anxiety, insomnia, somnolence, dystonia, dizziness, tremor, sweating increased, mouth dry, skin cold clammy, eye pain, nausea, asthenia
PLACEBO					
002	F	33	0	4	Investigator terminated the study
004	F	34	0	4	Investigator terminated the study
006	F	40	0	3	Side effects: aggressive reaction, agitation, anxiety, insomnia, somnolence, coordination abnormal, dizziness, headache, tremor, nausea, asthenia, fatigue, malaise
007	F	36	0	4	Investigator terminated the study
008	F	35	0	4	Investigator terminated the study
009	F	43	0	4	Investigator terminated the study
011	F	37	0	4	Investigator terminated the study

NOTE : Some of the side effects listed may have disappeared before the study was terminated. However it was their presence in such large numbers at some stage during the study which caused the investigator to stop the study. Thus all side effects have been listed for all subjects.

TABLE 5

SUBJECT AGE AND WEIGHT

	Sertraline	Placebo
	Female	Female
No. of Subjects	5	7
Age Category		
<15	0	0
15-24	0	0
25-34	1	2
35-44	4	5
>44	0	0
Mean Age (yrs)	34.0	36.9
Age Range	27- 37	33- 43
Mean Weight (kg)	56.3	56.8
Weight Range	47- 65	45- 70

TABLE 6

CONCURRENT DISEASES AT BASELINE

Disease	Sertraline	Placebo
Mononeuritis of upper limb/mononeuritis multiplex	1	0
Number of subjects with at least one concurrent disease	1	0

TABLE 7

CONCOMITANT THERAPY DURING DOUBLE-BLIND TREATMENT

THERAPY	NUMBER OF SUBJECTS	
	Sertraline	Placebo
CONTRACEPTIVES	1	0
DRUGS USED IN ANEMIAS	0	1
DRUGS USED IN RHEUMATIC DISEASES AND GOUT	1	1
ANTI-INFECTIVE SKIN PREPARATIONS	1	0
NUMBER OF SUBJECTS WITH AT LEAST ONE CONCURRENT THERAPY	3	2

TABLE 8

TOTAL DURATION OF DOUBLE-BLIND TREATMENT (days)

	Treatment Group	
	Sertraline	Placebo
Number of Subjects	5	7
Duration (days)		
<4	4	1
4-10	1	6
>10	0	0
Mean Duration	3.0	3.9
Range (Days)	2 - 4	3 - 4

TABLE 9

INCIDENCE OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

NUMBER OF SUBJECTS:	Sertraline	Double Blind Placebo
Evaluable	5	7
With Side Effects	5	1
Withdrawn with Side Effects	5	1
SIDE EFFECTS BY ORGAN SYSTEM		
NUMBER OF SUBJECTS WITH:		
Psychiatric Disorders	5	1
Centr & Periph Nerv Syst Disorders	5	1
Autonomic Nervous System Disorders	4	0
Special Senses Disorders	4	0
Gastro-Intestinal Disorders	5	1
Cardiovascular Disorders	2	0
Body as a Whole - General Disorders	5	1

Information on relationship to study drug was not recorded.

TABLE 10

SEVERITY OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Psychiatric Disorders										
Aggressive Reaction	0	0	0	0	0	1	1	0	0	0
Agitation	5	2	0	3	0	1	1	0	0	0
Anxiety	4	1	1	2	0	1	1	0	0	0
Insomnia	5	0	1	4	0	1	0	1	0	0
Somnolence	3	0	0	3	0	1	0	1	0	0
Centr & Periph Nerv Syst Disorders										
Confusion	1	0	0	0	1	0	0	0	0	0
Coordination Abnormal	0	0	0	0	0	1	0	0	0	1
Dizziness	4	0	2	2	0	1	1	0	0	0
Headache	3	0	0	3	0	1	0	1	0	0
Hypertonia	3	0	0	0	3	0	0	0	0	0
Tremor	5	2	1	2	0	1	1	0	0	0
Autonomic Nervous System Disorders										
Sweating Increased	4	2	2	0	0	0	0	0	0	0
Flushing	2	0	2	0	0	0	0	0	0	0
Mouth Dry	4	2	2	0	0	0	0	0	0	0
Mydriasis	1	0	0	0	1	0	0	0	0	0
Skin Cold Clammy	3	1	0	0	2	0	0	0	0	0
Special Senses Disorders										
Eye Pain	1	0	0	0	1	0	0	0	0	0
Vision Abnormal	3	2	1	0	0	0	0	0	0	0

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

TABLE 10 (continued)

SEVERITY OF SIDE EFFECTS DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Gastro-Intestinal										
Anorexia	2	0	0	0	2	0	0	0	0	0
Diarrhoea	1	0	0	0	1	0	0	0	0	0
Dysphagia	2	0	0	0	2	0	0	0	0	0
Nausea	5	1	0	4	0	1	0	1	0	0
Tooth Disorder	1	0	0	0	1	0	0	0	0	0
Cardiovascular Disorders										
Palpitations	2	0	1	1	0	0	0	0	0	0
Body as a Whole - General Disorders										
Asthenia	5	3	1	1	0	1	1	0	0	0
Fatigue	0	0	0	0	0	1	0	0	0	1
Malaise	1	0	0	0	1	1	0	0	0	1
Rigors	2	0	1	1	0	0	0	0	0	0
Totals (*)	72	16	15	26	15	13	6	4	0	3

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

(*) The numbers in this row are the total numbers of side effects and not the numbers of subjects with side effects.

TABLE 11

LABORATORY TEST ABNORMALITIES - MAY BE RELATED TO TREATMENT

LABORATORY TEST	SUBJECT NUMBER	UNITS	NORMAL LIMITS	BASELINE VALUE	MOST DIVERGENT VALUE
Sertraline					
No drug-related abnormalities					
Double Blind Placebo					
No drug-related abnormalities					

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TABLE 12

Concentrations of Sertraline and Desmethylsertraline in whole blood samples from subjects receiving Sertraline, 150mg daily

Results are expressed as ng/ml

Patient No.	Concentration of Sertraline	Concentration of Desmethylsertraline
1	33	84
2	ND	ND
3	11	20
4	ND	ND
5	48	110
6	13	ND
7	ND	ND
9	18	ND
10	ND	31
11	ND	ND
12	ND	39

ND = Not detected < 5ng/ml

No data available for volunteer 008 (insufficient sample)

It can be seen that volunteers 006 and 009 although on placebo had detectable plasma levels of sertraline but of no metabolite. No explanation can be offered for these findings. Subjects 010 and 012 had no detectable sertraline, but had metabolite present.

APPENDIX I

APPENDIX I

SUPPLEMENTAL ADVERSE EVENT DATA

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 1 INCIDENCE OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

	Sertraline	Double Blind Placebo
NUMBER OF SUBJECTS:		
Evaluable	5	7
With Side Effects	5	1
Withdrawn with Side Effects	5	1
SIDE EFFECTS BY ORGAN SYSTEM		
NUMBER OF SUBJECTS WITH:		
Psychiatric Disorders	5	1
Centr & Periph Nerv Syst Disorders	5	1
Autonomic Nervous System Disorders	4	0
Special Senses Disorders	4	0
Gastro-Intestinal Disorders	5	1
Cardiovascular Disorders	2	0
Body as a Whole - General Disorders	5	1

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 2 SEVERITY OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Psychiatric Disorders										
Aggressive Reaction	0	0	0	0	0	1	1	0	0	0
Agitation	5	2	0	3	0	1	1	0	0	0
Anxiety	4	1	1	2	0	1	1	0	0	0
Insomnia	5	0	1	4	0	1	0	1	0	0
Somnolence	3	0	0	3	0	1	0	1	0	0
Centr & Periph Nerv Syst Disorders										
Confusion	1	0	0	0	1	0	0	0	0	0
Coordination Abnormal	0	0	0	0	0	1	0	0	0	1
Dizziness	4	0	2	2	0	1	1	0	0	0
Headache	3	0	0	3	0	1	0	1	0	0
Hypertonia	3	0	0	0	3	0	0	0	0	0
Tremor	5	2	1	2	0	1	1	0	0	0
Autonomic Nervous System Disorders										
Sweating Increased	4	2	2	0	0	0	0	0	0	0
Flushing	2	0	2	0	0	0	0	0	0	0
Mouth Dry	4	2	2	0	0	0	0	0	0	0
Mydriasis	1	0	0	0	1	0	0	0	0	0
Skin Cold Clammy	3	1	0	0	2	0	0	0	0	0
Special Senses Disorders										
Eye Pain	1	0	0	0	1	0	0	0	0	0
Vision Abnormal	3	2	1	0	0	0	0	0	0	0

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 2 SEVERITY OF SIDE EFFECTS (ALL CAUSALITIES) DURING DOUBLE-BLIND TREATMENT

ORGAN SYSTEM Side Effect	Sertraline					Double Blind Placebo				
	Number of Subjects	1	2	3	NS	Number of Subjects	1	2	3	NS
Gastro-Intestinal										
Anorexia	2	0	0	0	2	0	0	0	0	0
Diarrhoea	1	0	0	0	1	0	0	0	0	0
Dysphagia	2	0	0	0	2	0	0	0	0	0
Nausea	5	1	0	4	0	1	0	1	0	0
Tooth Disorder	1	0	0	0	1	0	0	0	0	0
Cardiovascular Disorders										
Palpitations	2	0	1	1	0	0	0	0	0	0
Body as a Whole - General Disorders										
Asthenia	5	3	1	1	0	1	1	0	0	0
Fatigue	0	0	0	0	0	1	0	0	0	1
Malaise	1	0	0	0	1	1	0	0	0	1
Rigors	2	0	1	1	0	0	0	0	0	0
Totals (*)	72	16	15	26	15	13	6	4	0	3

SEVERITY CODES : 1 = MILD 2 = MODERATE 3 = SEVERE NS = NOT SPECIFIED

(*) The numbers in this row are the total numbers of side effects and not the numbers of subjects with side effects.

LABORATORY TEST RESULTS OUTSIDE NORMAL RANGE CONSIDERED NOT RELATED TO DRUG

All laboratory test data for each subject were reviewed. For each parameter where results deviated from the normal range, the most abnormal value was recorded and the pattern of abnormal values categorized. Each pattern of abnormal values was considered potentially related to drug therapy unless it fell into one of the following categories.

List 1 defines abnormalities when the baseline value was normal or was missing. List 2 defines changes when the baseline was abnormal.

Category N The baseline value was normal, abnormal or missing and all values during therapy were within the normal range. This category ensures that all patients are accounted for.

Category 1 The baseline value was outside the normal range and the deviation of the most abnormal value from baseline during therapy was so small as to be clinically insignificant.*

Category 2 The baseline value was normal or missing and the deviation of the most abnormal value from normal during therapy was so small as to be clinically insignificant.**

Category 3 The baseline value was normal or missing and there was a single, significant abnormal value which returned to normal during therapy.

The baseline value was outside the normal range and there was a single divergent value that differed significantly from baseline, but returned to within these limits during therapy.

Category 4 The baseline value was normal or missing and there were two or three significant abnormal values within a six (6) week period that all lie on the same side of the normal range; no value reached the level of marked abnormality and the last two values during therapy were within normal limits. The abnormal values were consecutive or were interspersed with normal values.

The baseline value was outside the normal range and there were two or more significant abnormal values compared to baseline within a six (6) week period and all lie on the same side of the normal range as the baseline; the values did not differ significantly from baseline for the last two values during therapy. The abnormal values were consecutive, or there were abnormal values differing significantly from baseline, interspersed with values differing less than the insignificant percent from baseline.

Category 5 There was a documented laboratory error.

Category 6 The abnormality appeared likely to be due to the primary disease or to a coexisting disease process.

Category 7 The abnormality appeared likely to be due to concomitant drug therapy.

Category 8 The abnormality was considered to be clinically insignificant or not due to therapy upon review by a physician.

Abnormalities which were considered to be potentially related to drug therapy were assigned to Category 9 and may be found in the body of this study summary.

The abnormalities not related to drug are recorded in Table 3.

* See List 2
** See List 1

LIST 1

DEFINITION OF ABNORMAL TEST VALUES WHEN BASELINE VALUE WAS NORMAL OR MISSING

LABORATORY TEST	CLINICALLY RELEVANT DIRECTION[a]	ABNORMALITY	MARKED ABNORMALITY
HGB	Decrease	10%	25%
HCT	Decrease	10	25
RBC	Either	10	25
PLATELETS	Decrease	10	25
WBC	Either	10	25
NEUTROS (ABS)	Either	10	25
EOS (ABS)	Increase	25	50
BASOS (ABS)	Increase	25	50
LYMPHS (ABS)	Either	10	25
MONOS (ABS)	Increase	25	50
BANDS (ABS)	Increase	10	25
TOTAL BILIRUBIN	Increase	10	50
DIRECT BILIRUBIN	Increase	10	50
INDIRECT BILIRUBIN	Increase	10	50
TOTAL PROTEIN	Either	5	25
SERUM ALBUMIN	Either	5	25
SERUM GLOBULIN	Either	10	50
SGOT	Increase	10	50
CPK	Increase	10	50
SGPT	Increase	10	50
GGT	Increase	10	50
LDH	Increase	10	50
ALKALINE PHOSPHATASE	Increase	10	50
BLOOD UREA	Increase	10	50
BUN	Increase	10	50
CREATININE	Increase	10	50
URIC ACID	Increase	10	50
SODIUM	Either	5	25
POTASSIUM	Either	5	25
CHLORIDE	Either	5	25
CO2	Either	5	25
CALCIUM	Either	5	25
INORGANIC PHOSPHORUS	Either	5	25
GLUCOSE, FASTING	Either	10	50
GLUCOSE, RANDOM	Either	10	50

[a] Only clinically relevant direction of abnormality considered and percent limits applied to the limit on normal range closest to that abnormality.

LIST 2

DEFINITION OF ABNORMAL TEST VALUES WHEN BASELINE VALUE WAS ABNORMAL

LABORATORY TEST	CLINICALLY RELEVANT DIRECTION[a]	ABNORMALITY	MARKED ABNORMALITY
HGB	Decrease	5%	10%
HCT	Decrease	5	10
RBC	Either	5	10
PLATELETS	Decrease	10	25
WBC	Either	20	50
NEUTROS (ABS)	Either	10	25
EOS (ABS)	Increase	25	50
BASOS (ABS)	Increase	25	50
LYMPHS (ABS)	Either	10	25
MONOS (ABS)	Increase	25	50
BANDS (ABS)	Increase	10	25
TOTAL BILIRUBIN	Increase	10	50
DIRECT BILIRUBIN	Increase	10	50
INDIRECT BILIRUBIN	Increase	10	50
TOTAL PROTEIN	Either	5	25
SERUM ALBUMIN	Either	5	25
SERUM GLOBULIN	Either	10	50
SGOT	Increase	20	50
CPK	Increase	20	50
SGPT	Increase	20	50
GGT	Increase	20	50
LDH	Increase	20	50
ALKALINE PHOSPHATASE	Increase	20	50
BLOOD UREA	Increase	10	50
BUN	Increase	10	50
CREATININE	Increase	10	50
URIC ACID	Increase	10	50
SODIUM	Either	5	25
POTASSIUM	Either	5	25
CHLORIDE	Either	5	25
CO2	Either	5	25
CALCIUM	Either	5	25
INORGANIC PHOSPHORUS	Either	5	25
GLUCOSE, FASTING	Either	20	50
GLUCOSE, RANDOM	Either	20	50

[a] Only clinically relevant direction of abnormality considered and percent limits applied to the change from abnormal baseline.

APPENDIX I SUPPLEMENTAL ADVERSE EVENT DATA FOR PROTOCOL 206 (HINDMARCH)

TABLE 3 LABORATORY TEST RESULTS OUTSIDE NORMAL RANGE CONSIDERED NOT RELATED TO TREATMENT

SERTRALINE TREATMENT GROUP

LABORATORY TEST	SUBJECT ID	NORMAL RANGE	UNITS	BASELINE VALUE	MOST DIVERGENT VALUE	CATEGORY
No laboratory abnormalities						

DOUBLE BLIND PLACEBO TREATMENT GROUP

LABORATORY TEST	SUBJECT ID	NORMAL RANGE	UNITS	BASELINE VALUE	MOST DIVERGENT VALUE	CATEGORY
Haematocrit	002	37-47	%	36.1	36.3	1
	006	37-47	%	36.2	33.8	8
Red Blood Cells	006	3.9-5.6	10**12/L	4.11	3.82	2
WBC	006	4-11	10**9/L	5.9	3.3	8

PROTOCOL

PROTOCOL

A DOUBLE BLIND CROSSOVER STUDY TO ASSESS THE EFFECTS OF SERTRALINE ON PSYCHOMOTOR PERFORMANCE AND INTERACTION WITH DIAZEPAM

INVESTIGATOR	:	Dr. I. Hindmarch
LOCATION	:	Department of Psychology, University of Leeds, Leeds, U.K.
NO. OF SUBJECTS	:	12 - completing the full study period.
DURATION OF STUDY	:	4 weeks (for twelve volunteers to be studied)
START OF STUDY	:	February 1983.

Aims

(1) To assess the effects of sertraline if any, on psychomotor performance.

(2) To investigate the interaction with diazepam and CP-51,974, if any, on psychomotor performance.

Subject Selection Criteria

A. Inclusions:

1. Normal, healthy volunteers between the ages of 18 and 50 years.

2. No evidence of concomitant disease based upon history, full physical examination and clinical laboratory tests. Laboratory tests results at the screening examination must be within normal limits.

3. Volunteers will weigh no more than 90 or less than 60kgs and should be within 10% of the ideal weight for age and height as established by the Metropolitan Life Insurance Company Statistical Bulletin, November-December 1959, "Desirable Weights of Adults" (Appendix I).

4. Subjects must be off any drug therapy for at least two weeks prior to participation in the study and during the whole study period.

5. The investigator will obtain written informed consent from each subject.

B Exclusions:

1. Females of childbearing potential, pregnancy and lactation.

2. Volunteers with any gastrointestinal condition possibly affecting absorption of the drug will be excluded.

3. Volunteers with evidence of significant haematological/vascular, renal, hepatic, gastrointestinal or neurological disease (including all forms of epilepsy and a past history of depressive episodes) or any other systemic disease.

4. Volunteers with known drug or alcohol abuse, drug allergies or history of psychiatric disease.

5. Participation in a non registered drug study within 3 months prior to entering this study.

6. Volunteers who regularly take psychotropic drugs.

N.B. Volunteers who are blood donors should not give blood over the period of the study and for four weeks thereafter.

Drug and Dose

Capsules containing 50mg of sertraline and matching placebo will be supplied. The volunteers will receive in random, double blind fashion both sertraline or placebo, 3 capsules at 9.00 a.m. for 7 days each. Six subjects will receive sertraline and then placebo, and 6 subjects will receive drugs in the reverse order. In addition all subjects will receive diazepam 5mg (9.00 a.m.) on the 5th, 6th & 7th days of each treatment period.

SCHEDULE OF ASSESSMENTS

Screening Assessment

(1) Physical Examination.
(2) Laboratory tests - biochemistry and haematology.
(3) Medical history.
(4) Body weight and height.
(5) Written informed consent.
(6) Pregnancy test for females.

Providing this information complies with selection criteria the subjects may be entered into the study. They will be allocated a code number from the randomisation list.

During the pre treatment period the subjects will be familiarised with the test procedures and apparatus. Practicing will be conducted to minimise learning effects during the study period.

Assessments

Day 1 (Baseline), 5, 7, 12, 14 immediately prior to receipt of study drug. In addition also 2 hours post dosing on Days 5 and 12.

(1) Critical Flicker Fusion (CFF).
(2) Complex Reaction Time (CRT).
(3) Subjective Feeling States Visual Analogue Scale (VAS).
(4) Mental Arithmetic.
(5) Sleep Evaluation Questionnaire (SEQ)
(6) Blood pressure and pulse, both erect and supine.
(7) Side effects.
(8) Blood chemistry/haematology (baseline only).

Days 7 and 14

(1) Blood chemistry, haematology.

Day 15

(1) CFF.
(2) CRT
(3) VAS.
(4) SEQ.
(5) Physical Examination.
(6) Side Effects.
(7) Mental Arithmetic.

If, at the 15 day assessment, there is no evidence of psychological impairment or physical disturbance subjects may be allowed home.

Concurrent Therapy - none is allowed.

For the period from 24 hours prior to baseline to the end of the study subjects must refrain from drinking alcohol.

During assessment days subjects should ingest no more than their normal intake of stimulating drinks, coffee/coca cola etc.

Description of Assessments

(1) Laboratory tests:

- Haematology - Full blood count, white count plus differential, platelets.

- Biochemistry- Sodium, potassium, chloride, urea, creatinine, glucose, alkaline phosphatase, gamma glutamyl transferase, bilirubin, SGOT, SGPT.

(2) Critical Flicker Fusion.
(3) Complex Reaction Time.
(4) Visual Analogue Scale - subjective feeling states assessment.
(5) Mental Arithmetic.
(6) Sleep Evaluation Questionnaire.

(2-6 are according to the method of Hindmarch 1975 and Hindmarch and Parrot 1979.)

(8) Blood pressure and pulse -
These have to be measured after 15 minutes resting recumbent and two minutes after standing. The arm wearing the sphygmomanometer must be supported. The diastolic pressure is judged using the Korotkoff V sound. Automatic blood pressure recording equipment will be used for all subjects.

Side Effects

Should the subjects experience untoward effects these should be recorded on the case record forms supplied. Any serious side effects should be treated according to standard clinical practice. Decisions as to whether the subject should continue in the study will be made by a qualified medical practitioner associated with the study. Any changes in liver function test should be followed according to the schedule in Appendix II.

Results

All case record forms should be returned to Pfizer in Sandwich without delay for scrutiny and data banking.

Ethical Approval

This protocol was reviewed and approved by the European Ethical Review Committee on Saturday, 29th January 1983.

FLOW CHART

	Screening	Baseline	Days 5 Pre	5 Post	7	12 Pre	12 Post	14	15
Physical Examination	X								X
Biochemistry/Haematology	X	X			X			X	
Medical History	X								
Body Weight/Height	X								
Written Consent	X								
CFF		X	X	X	X	X	X	X	X
CRT		X	X	X	X	X	X	X	X
VAS		X	X	X	X	X	X	X	X
Mental Arithmetic		X	X	X	X	X	X	X	X
SEQ		X	X	X	X	X	X	X	X
Side Effects		X	X	X	X	X	X	X	X

Drug Intake - Placebo/Sertraline Day 1-7 8-14
- Diazepam Day 5-7 12-14

Pre - Post - Refers to Pre and 2 hours Post dosing respectively.

APPROVAL

The undersigned acknowledges possession of, and has read a written summary of the preclinical and clinical data available on sertraline and has discussed these data and their implications with Dr. D. Doogan of Pfizer Central Research. Having fully considered all the information available, the undersigned considers that it is ethically justifiable to give the compound to volunteers in his care, according to the agreed protocol. In addition, he agrees that the trial will be carried out in conformance with the revised Declaration of Helsinki (Tokyo 1975), and the laws and regulations relevant to the use of new therapeutic agents in the United Kingdom.

Signed: [redacted] Date: 15/ii/83

(Clinical Investigator)
Dr. I. Hindmarch,
Department of Psychology,
University of Leeds,
Leeds.

Counter signed: [redacted] Date: 15/2/83

(Responsible Pfizer Physician)
Dr. D.P. Doogan,
Clinical Research Department,
Pfizer Central Research,
Sandwich, Kent.

REFERENCES

Hindmarch I, 1975
A 1-4 Benzodiazepine, Temazepam (K 3917), its effect on some psychological parameters of sleep and behaviour.
ARZNEIM FORSCH, 25, 1836-1839.

Hindmarch I and Parrot AC, 1979
The effects of repeated nocturnal doses of clobazam, dipotassium chlorazepate and placebo on subjective ratings of sleep and early morning behaviour and objective measures of arousal psychomotor performance anziety.
Brit. J. Clin. Pharmac., 8, 325-329.

APPENDIX I

METROPOLITAN LIFE INSURANCE
DESIRABLE WEIGHTS FOR MEN AND WOMEN

Height (in shoes, 1-inch heels)		Weight (pounds) in Indoor Clothing[1]		
		Small Frame	Medium Frame	Large Frame
Feet	Inches	Men		
5	2	112-120	118-129	126-141
5	3	115-123	121-133	129-144
5	4	118-126	124-136	132-148
5	5	121-129	127-139	135-152
5	6	124-133	130-143	138-156
5	7	128-137	134-147	142-161
5	8	132-141	138-152	147-166
5	9	136-145	142-156	151-170
5	10	140-150	146-160	155-174
5	11	144-154	150-165	159-179
6	0	148-158	154-170	164-184
6	1	152-162	158-175	168-189
6	2	156-167	162-180	173-194
6	3	160-171	167-185	178-199
6	4	164-175	172-190	182-204
(in shoes, 2-inch heels)		Women		
4	10	92-98	96-107	104-119
4	11	94-101	98-110	106-122
5	0	96-104	101-113	109-125
5	1	99-107	104-116	112-128
5	2	102-110	107-119	115-131
5	3	105-113	110-122	118-134
5	4	108-116	113-126	121-138
5	5	111-119	116-130	125-142
5	6	114-123	120-135	129-146
5	7	118-127	124-139	133-150
5	8	122-131	128-143	137-154
5	9	126-135	132-147	141-158
5	10	130-140	136-151	145-163
5	11	134-144	140-155	149-168
6	0	138-148	144-159	153-173

[1]Courtesy of the Metropolitan Life Insurance Company. Derived primarily from data of the Build and Blood Pressure Study, 1959 Society of Actuaries.
[2]For nude weight, deduct 5-7 pounds (male) or 2-4 pounds (women)

APPENDIX II

LIVER FUNCTION TEST ABNORMALITIES

Procedure

1. Obtain repeat data within 24 hours. If confirmed:

2. Withdraw the subject from the study.

3. Complete laboratory screen plus prothrombin time, alkaline phosphatase isoenzymes, protein immunoelectrophoresis and blood alcohol to be performed within 3 days and repeated until results return to within normal limits.

4. If the results do not return to within normal limits within two weeks - obtain consultation with hepatologist/gastroenterologist.

APPENDIX III

1. RATIONALE FOR THE STUDY

Sertraline is a psychotropic drug. At present it has only been studied in institutionalised subjects. When the decision to study out patients is made we need to advise physicians on the possible consequences of prescribing sertraline and tranquillisers concurrently. Also we wish to know if sertraline alone will cause any impairment of psychomotor performance.

The psychological tests as described by Hindmarch 1975 and Hindmarch and Parrot 1979 have been shown to be discriminative of placebo - psychotropic drug differences.

2. ETHICAL CONSIDERATIONS

a. This study is to be performed in accordance with the provisions as set out in the Declaration of Helsinki (revised, Tokyo 1975). A copy is available on request.

b. The purpose of the study and the procedures involved must be explained fully to each subject in terminology which he can understand before inclusion in the study.

c. Each subject must provide written informed consent to participate in the study.

d. The protocol will have prior approval from the appropriate Ethical Review Committee.

3. PATIENT WITHDRAWAL

All subjects will be free to withdraw if they do not wish to continue. Such subjects will be replaced by further volunteers.

4. REPORTING OF SIDE EFFECTS/ADVERSE REACTION

The nature, severity, time of onset, duration and treatment of any symptoms or adverse reaction observed or volunteered by the patient will be recorded on the case record. Leading questions will not be asked.

Any serious reaction will be reported immediately by telephone to:

[redacted]

Pfizer Central Research,
Sandwich, Kent,
CT13 9NJ.

Telephone: (0304) 616161, Ext. 6124 - Office
[redacted] - Home

5. CASE RECORDS

All data will be recorded in the case records provided, preferably using a black ball point pen (to facilitate photocopying) and sent to Pfizer Central Research as soon as possible after completion.

6. DRUG STORAGE AND ACCOUNTABILITY

The investigating physician will be responsible for recording the receipt and usage of all drug supplies and for supervising the storage and allocation of these supplies.

All unused or expired drug supplies will be returned promptly to Pfizer Central Research.

7. PUBLICATION OF DATA

All data arising from the study will remain the property of Pfizer Central Research. Prior to submission of the data for publication, Pfizer Central Research reserve the right to comment upon, or correct the data where appropriate. Intention to publish or present the results of the study will be discussed before agreement to participate in the study.

8. LEGAL LIABILITY

Indemnity letter.

VOLUNTEER INFORMATION SHEET

Study 50/70-1 - Sertraline

The study in which you are being invited to participate is to assess the effects, if any, of a new antidepressant drug (sertraline) on psychological measurements and coordination. It will also assess whether the effects caused by a tranquilliser are changed by giving sertraline at the same time.

Diazepam (Valium ^{R}) has been chosen as a tranquilliser. It can have no effect at all or in some people cause sleepiness, dizziness and incoordination.

This drug has been given to more than 100 subjects and has been shown to be safe for further studies. There were no significant effects on blood measurements, heart or blood pressure. Side effects were generally mild and self limiting. The most frequent symptoms were insomnia, tremor, nausea and headache.

In this study, should your screening results comply with selection criteria you will be entered into the study. During this time you will be asked to perform daily psychological tests such as mental arithmetic, reaction timing and recognition of patterns. In addition blood will be withdrawn for laboratory analysis.

You will have to take the study drug in the morning for 14 days. On the last three days of each week you will be given diazepam. On the morning of the 15th day you will be discharged from the study providing the results of the psychological and laboratory tests are within normal limits.

Please remember that no alcohol should be consumed for 24 hours prior to entering the clinic and for the duration of the study. You should also try not to drink any more than your usual amount of coca cola, coffee, etc.

If, at any time, you experience any unwanted or unexpected effects, please inform the person in charge of the study. You are free to withdraw from the study at any time.