CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20639

STATISTICAL REVIEW(S)

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 2, 1997

FROM: Lilia Talarico, M.D., Acting Director, Division of Gastrointestinal and Coagulation Drug Products, HFD-180

SUBJECT: Hematology Consultation re: Leukopenia and Neutropenia associated with the administration of Seroquel

TO: NDA 20-639

THROUGH: P. Leber, M.D., Director, Division of Neuropharmacologic Drug Products
Dr. Laughren

Background Information

Seroquel (quetiapine fumarate) is a dibenzothiazepine derivative developed by Zeneca Pharmaceuticals for the management of the manifestations of psychotic disorders. The proposed mechanism of action of quetiapine is through a combination of dopamine-D2 and serotonin-5HTP-receptor antagonism.

Seroquel has been evaluated in a total study population of 2462 subjects; 300 of these subjects participated in Phase I studies and 2162 patients participated in Phase II/III clinical trials. The 2162 patients in Phase II/III trials included 1710 subjects exposed to quetiapine in controlled trials and 452 subjects treated in uncontrolled trials. A total of 804 patients entered in controlled trials were also enrolled in uncontrolled trials, therefore, the total population of uncontrolled trials was 1256.

In Phase I studies, the extent of exposure ranged from 1 to 35 days and the dose ranged from 25 to 750 mg/day. In Phase II/II studies, most subjects (86%) received Seroquel for 6 weeks or less. The majority of subjects (72%) received mean daily dose greater than 150 mg/day and 21% had mean daily dose greater than 450 mg/day.

The mean age of the patients enrolled in the Phase II/III trials was 38 years. The majority of patients were Caucasian, males, and younger than 40 years of age.

In the clinical trials, Seroquel was compared to placebo (n=206) or to active controls including Haloperidol (n=320) and Chlorpromazine (n=100).
The total exposure to quetiapine, placebo, and active controls in Phase II/III studies was 565.1 patient/yeras for quetiapine-treated patients (199 patient-

years in controlled clinical trials and 386 patient/years in uncontrolled trials), 51.5 patient/yeras for the active control patients (42.3 for haloperidol and 9.2 for chlorpromazine), and 14.6 patient/years for placebo.

NDA 20-639 has been submitted for the approval of Seroquel for the treatment of psychotic disorders. The safety review has shown an increased incidence of leukopenia/neutropenia in patients treated with quetiopine compared to placebo or active control regimens. A consult to our division has been requested for the evaluation of this hematological adverse event.

Review of the Hematologic data

The material reviewed for this consult include the NDA ISS and summary tables, the 4-month Safety Update, the sections of the Phase II/III clinical trial reports dealing with hematological adverse events, and Dr. Gerson's report. The following review concerns exclusively the hematological abnormalities reported in the study population of the Phase II/III clinical trials of Seroquel for the treatment of psychosis.

The following standard definition was used for the assessment of leukopenia/neutropenia:

Leukopenia: Total WBC <3000/uL
Neutropenia: Absolute neutrophil count < 1500/uL
Mild: ANC ≥1000 <1500/uL
Moderate: ANC ≥500 <1000/uL
Severe: ANC <500/uL
Agranulocytosis: ANC <500 with clinical manifestations

The sponsor's definitions of clinically significant leukopenia/neutropenia are the following:

Leukopenia: Total WBC ≤2800/uL
Neutropenia: ANC ≤1500/uL

Summary of the hematological data reported in the ISS and in the 4-month SU

Integrated Summary of Safety (ISS): In the Phase I studies, two quetiapine-treated patients (0.7%) had clinically significant low WBC and 12 patients had clinically significant low ANC. In none of the patients was a pattern of progressive decline detected as most patients had either baseline low values or intermittent/isolated low values throughout the study. None of the patients experienced clinical adverse events related to the reduction in WBC/ANC or were withdrawn from the studies because of hematological adverse events.

In Phase II/III controlled studies, quetiapine was compared to placebo, haloperidol or chlorpromazine in short term trials (≤ 6 weeks) and to haloperidol in long-term studies. Clinically significant low WBC occurred in 10/1274 (0.8%) of patients with baseline WBC counts in the Quetiapine-treated

group compared to 0/206 in the placebo control group or 0/420 in the active control-treated groups. Significantly low ANC occurred in 2.8% of patients in Quetiapine-treated group compared to 1.1% in the haloperidol short-term group, 2.1% in the chlorpromazine group and 1% in the placebo group in the short-term studies. In the long-term, haloperidol-controlled trial, clinically significant low WBC occurred in 1.3% and clinically significant low ANC occurred in 3% of quetiapine-treated patients, compared to 0 and 0.85% respectively in the haloperidol group.
Four patients treated with quetiapine in the controlled Phase II/III trials (0.2%) were withdrawn from the study because of leukopenia, compared to no patients from the comparison drugs or placebo groups.

In the uncontrolled trials, which included a total population of 1256 patients (452 patients plus 804 patients from the controlled trials), clinically significant low WBC occurred in 12 (1%) quetiapine-treated patients. A total of 43 patients had low ANC. Nine patients (0:7%) were withdrawn from the study because of leukopenia and/or neutropenia, one patient was withdrawn because of anemia, and one patient for eosinophilia. The proportion of patients who shifted from normal baseline to low WBC or ANC values were 0/479 for WBC and 4/479 (0.5%) for ANC compared to 0/195 in the placebo group.

Overall, in Phase II/III studies, the proportion of quetiapine-treated patients with clinically significant low WBC, defined as < 2800 uL, was 0.9% (22/2162) and the proportion patients with clinically significant low ANC, defined as < 1500 uL, was 3.8% (84/2162). For comparison, no patients in the placebo group or in the haloperidol-treated group had clinically significant low WBC. Clinically significant neutropenia was reported in 1.4% of placebo patients, in 1.6% of haloperidol, and in 2.1% of chlorpromazine-treated patients.

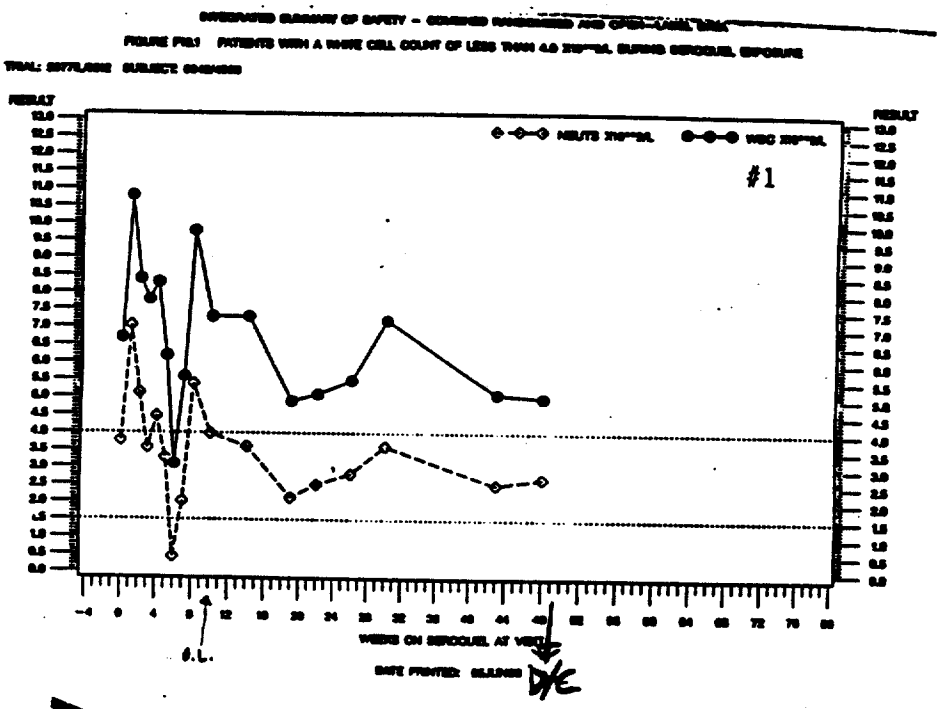
Four-month Safety Update (SU): Review of the hematological adverse events for the combined randomized and open-label patient populations treated with quetiapine shows a total of 42 patients with WBC <3.000/uL. Thirty-two (32) of these 42 patients had clinically significant low WBC (<2.800/uL).
A total of 91 patients had clinically significant low ANC (<1.500/uL) including 4 patients with severe neutropenia (ANC <500/uL), 20 patients with ANC ≥500 <1.000/uL, and 67 patients with ANC ≥1.000 <1500/uL.

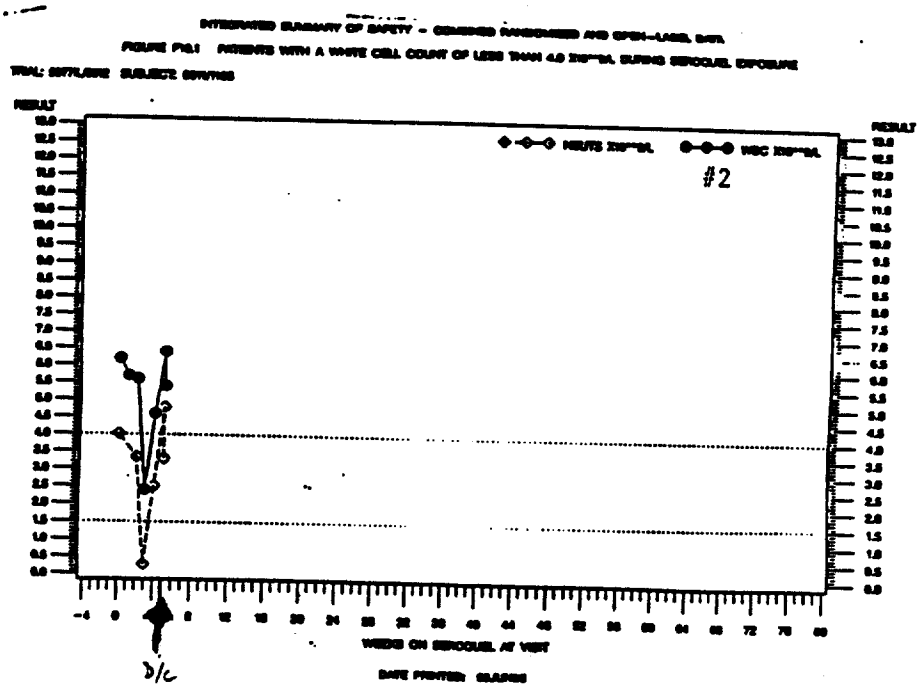
Two of the 279 patients treated with haloperidol had WBC <3.000/uL. Four placebo patients, two chlorpromazine-treated patients and four haloperidol-treated patients had ANC ≥1.000 and <1.500/uL. One patient in the haloperidol group and one patient in the placebo group had ANC >0.5 <1.000/uL

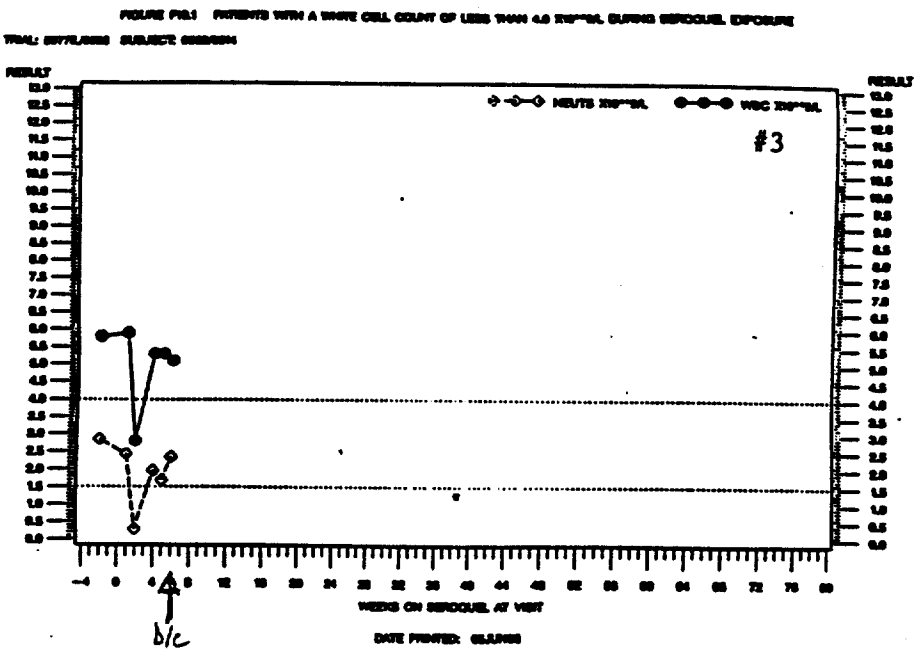
In conclusion, the overall incidence of clinically significant neutropenia reported in the 4-month SU was 4.0% in the quetiapine-treated group, 2.4% in the placebo group, 2.0% in the chlorpromazine-treated group and 1.6% in the haloperidol-treated group.

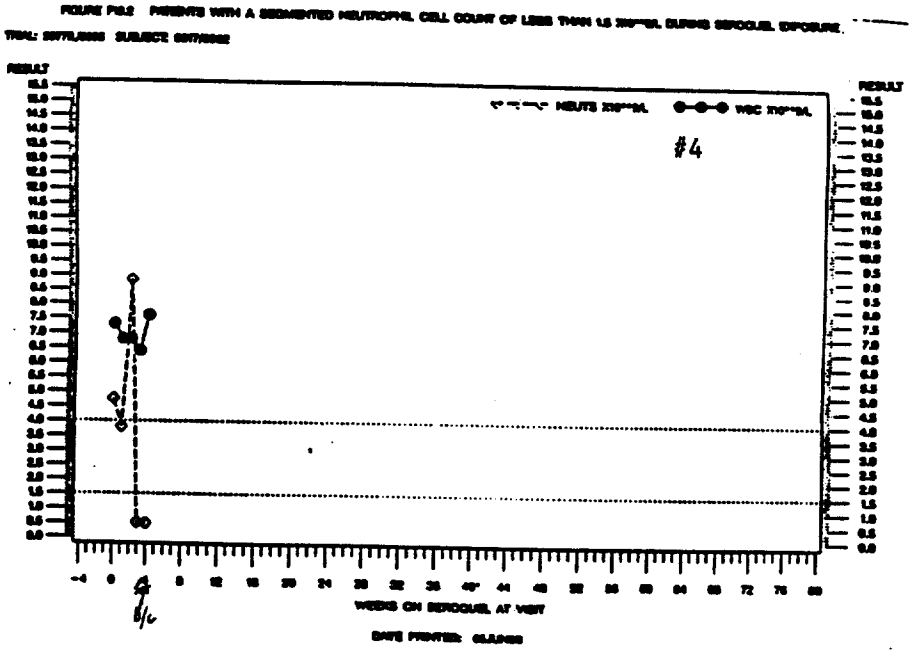
Patterns of Neutropenia observed in the Quetiapine-treated groups

None of the four patients with severe neutropenia (ANC <500.uL) in the quetiapine group had clinical manifestations (agranulocytosis). The patterns of WBC and ANC for these four patients are shown in the appended graphs. Both WBC and ANC improved in three patients despite continuation of therapy with quetiapine (graphs 1, 2, 3). In the fourth patient, the neutropenia improved after discontinuation of quetiapine, however, the discrepancy between WBC and nadir ANC raises the possibility of an erroneous ANC value (graph 4).





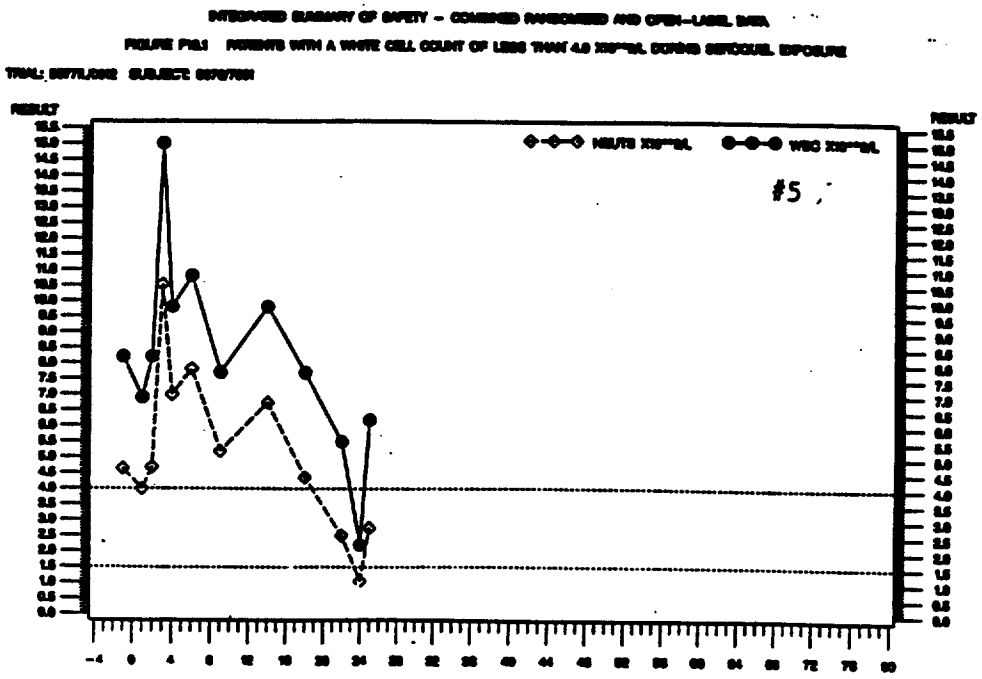


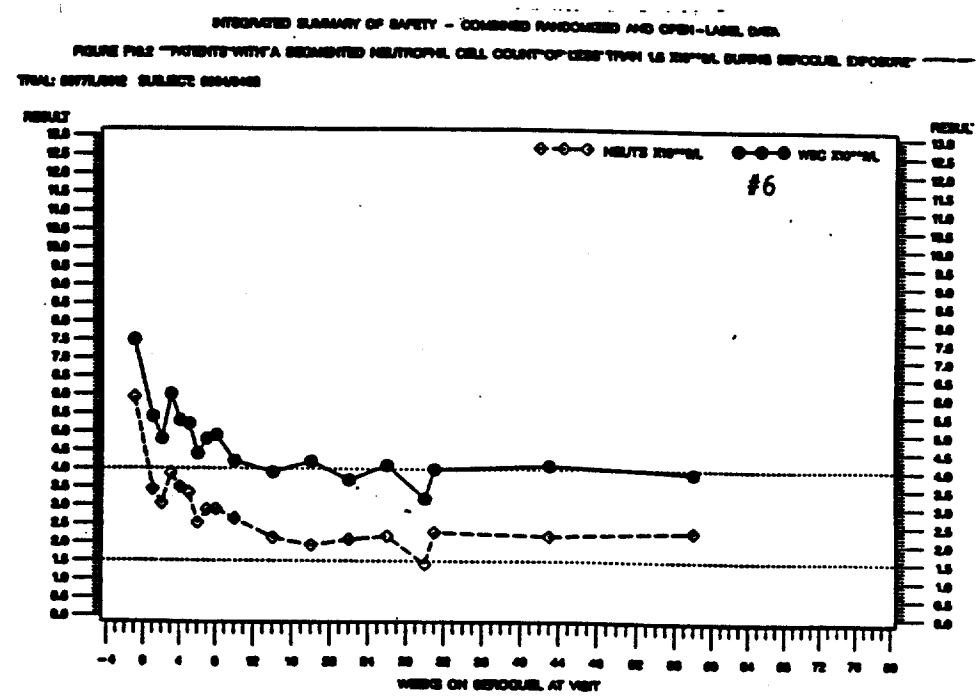


Nine patients who experienced moderate or mild neutropenia while of therapy with quetiapine had baseline WBC below normal (<4000/uL), and 11 patients had baseline ANC below normal. In these patients, the counts either improved on therapy or remained subnormal throughout the treatment period without further reduction .

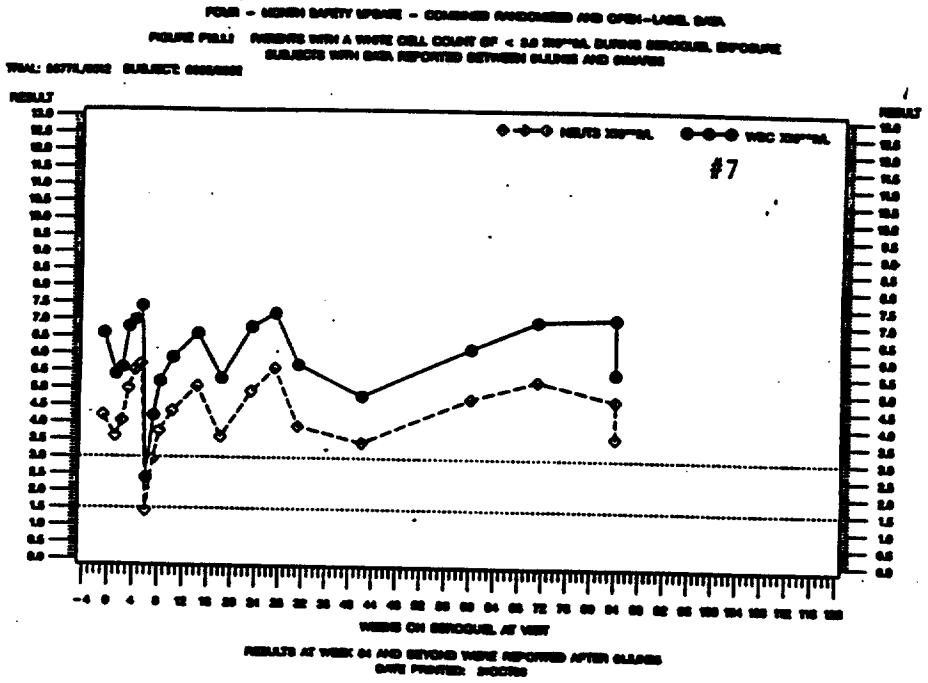
In six patients, discontinuation of Quetiapine at the nadir of WBC or ANC resulted in improvement of counts.

One patient experienced progressive reduction in WBC/ANC which was promptly reversed by discontinuation of study drug (graph 5). Two additional patients exhibited a pattern of progressive reduction of WBC/ANC which, however, stabilized over a long period of time. One of these patients is represented in fig 6.





In most of the remaining patients, the abnormal WBC/ANC values observed during treatment with Quetiapine represented intermittent or isolated events (graphs 7).



Other hematological abnormalities

A total of 105 patients had low hematocrit (Hct) which was defined as significantly low of <37% for males and <=32% for females. A total of 41 patients (34 males and 7 females) had decreased hemoglobin levels which were <10 g/dl in 13 patients, 7 males and 6 females. Hemoglobin was defined as significantly low of ≤11.5 g/dl in males and ≤9.5 g/dl in females.

Twelve (12) patients had thrombocytopenia with platelet counts ranging from 12.000 to 75.000 uL. Platelet count was defined as significantly low of ≤75.000/uL.
One patient had concomitant thrombocytopenia and leukopenia and one patient had pancytopenia.

The material reviewed did not contain additional information that would allow further evaluation of the anemia and thrombocytopenia. The tables of the hematology values included in the clinical laboratory section of the ISS combine the abnormally high and low values of Hgb or Htc with little additional information.

Comments and Recommendations:

Review of the safety data for the Phase II/III patient population indicate that Quetiapine is associated with an incidence of leukopenia of 1.9% (42/2162) and/or neutropenia of 4.2% (91/2162). In comparison, the overall incidence of leukopenia/neutropenia was 1.9% in the placebo group and in the active comparator groups. Specifically, the incidence rates for leukopenia/neutropenia were 2% and 1.8%, respectively, for both chlorpromazine and haloperidol.

In the quetiapine-treated group, which consisted of 2162 patients and had a drug exposure of >600 patient/years, four cases of severe neutropenia were reported. None of these cases presented with clinical manifestations of agranulocytosis.
The majority of cases of leukopenia/neutropenia observed in the study population were mild or moderate, and, furthermore, the majority were isolated or intermittent events occurring throughout the administration of the drug. The increased incidence of such events in the quetiapine-treated groups compared to placebo or active comparators and, in some cases, the progressive decline of WBC/ANC or the prompt recovery of WBC/ANC following drug discontinuation support a causal relationship to quetiapine administration.

The pathogenetic mechanism of this apparently benign leukopenia/neutropenia associated with quetiapine is unclear but appears to be similar to that associated with the use of drugs such as beta-lactim antibiotics. In the study population, no severe adverse events were associated with the occurrence of leukopenia/neutropenia, however the pcssibility that more severe cases may occur once the treated population is expanded cannot be excluded.

It is of note that 41 patients in the 4-month SU (31 patients in the ISS) had developed clinically significant anemia, including 13 with hemoglobin levels <10 g/dl), and twelve patients developed thrombocytopenia (platelet counts <75.000/uL). One patient in the placebo grroup and one patient in the chlorpromazine group had Hgb levels <10 g/dl. The material reviewed for the consult does not permit additional evaluation of these abnormal findings, however, one can assume that these patients would have been excluded from study participation if the anemia or the thrombocytopenia had been present at baseline.
Few patients had concomitant depression of more than one cell line. Patient #0010/1014 in study 5077IL/0048 had leukopenia and thrombocytopenia; patient # 0005/0502 in study 5077IL/0015 had pancytopenia. These cases raise the possibility of drug-related marrow suppression of a much greater clinical significance which should be evaluated in depth with review of CRFs and follow-up data. The sponsor should be requested to provide detailed information for these patients.

Lilia Talarico MD

Lilia Talarico, M.D.

NDA: 20,639
Drug: Seroquel (Quetiapine fumarate)
Sponsor: Zeneca
Date: 7/18/97

1. The FDA's Division of Neuropharmacology has requested a consult from HFD-510 regarding the affect of a new, not yet marketed, anti-psychotic medication, Seroquel, on thyroid function in the controlled phase II-III clinical trials. Please also see my review on this dated, 5/29/97.

On 3/27/97, Zeneca submitted a print-out of all patients developing thyroid abnormalities during treatment for each of the controlled phase II-III trials (Note: trial 12 data was included, but it is not a controlled trial because only Seroquel was administered). Using this database, I determined the number and % of patients in each study who had normal baseline TFTs, but developed thyroid abnormalities on treatment and presented this information in the table on pages 7-8 of my 5/29/97 consult review. In calculating the frequency of these abnormalities, I used for the denominator, the total number of patients in whom thyroid function was measured in each study rather than the number of patients with normal baseline thyroid function. On June 23, 1997, Zeneca provided me with the latter information. Since the majority of patients enrolled had normal thyroid function at baseline, the frequencies reported in the table on the following page, are similar to those reported in the table on pages 7-8 of my initial review. (Note: the thyroid abnormalities developing on treatment were divided into clinically significant based on Zeneca's definition, designated CS, and when abnormal but not clinically significant, they were designated as "not". H= high, l= low, S= Seroquel, P= placebo, H= Haloperidol and C= Chlorpromazine).

Trial	Rx	low TT4 N %	low FT4 N %	low TT3 N %	high TSH N %	h TSH+ l FT4 h TSH+ l TT4 N %	l TSH+ l FT4 l TSH+ l TT4 N %
0004, 0006, 0008, 0013	S	35 not, 8.3%	29 not, 14.6%	17 not, 4.2%	4 not, 1.0%	3, 1.8%[a] 1, 0.3%[b]	0, 0% 4, 1.1%[f]
		13 CS, 3.1%	11 CS, 5.6%	2 CS, 0.5%	3 CS, 0.7%		
	P	1 not, 0.6%	1 not, 2.6%	2 not, 1.2%	1 not, 0.6%	0, 0% 0, 0%[c]	0, 0% 0, 0%
		1 CS, 0.6%	0 CS, 0%	0 CS, 0%	2 CS, 1.2%		
0012	S	not done	44 not, 10.7%	not done	3 not, 0.7%	0, 0%	1, 0.3%[g]
			7 CS, 1.7%		0 CS, 0%		
0013+ 0014	S	7 not, 3.4%	42 not, 11.6%	3 not, 1.5%	3 not, 0.8%	3, 0.9%[a] 1, 0.6%[b]	0, 0% 0, 0%
		6 CS, 3.0%	18 CS, 5.0%	1 CS, 0.5%	4 CS, 1.1%		
	H	1 not, 2.5%	2 not, 1.0%	0 not, 0%	0 not, 0%	0, 0% 0, 0%	0, 0% 0, 0%
		0 CS, 0%	0 CS, 0%	0 CS, 0%	0 CS, 0%		
0007	S	21 not, 23.1%	not done	13 not, 15.7%	1 not, 1.1%	- 1, 1.3%[d]	- 2, 2.5%[h]
		2 CS, 2.2%		6 CS, 7.2%	0 CS, 0%		
	C	1 not, 1.2%		6 not, 7.1%	2 not, 2.4%	- 0, 0%	- 0, 0%
		1 CS, 1.2%		2 CS, 2.4%	1 CS, 1.2%		
0015	S	11 not, 5.4%	27 not, 13.5%	3 not, 1.5%	4 not, 2.1%	2, 1.2%[e] 0, 0%	0, 0% 0, 0%
		3 CS, 1.5%	12 CS, 6.0%	1 CS, 0.5%	2 CS, 1.0%		
	H	0 not, 0%	2 not, 5.4%	1 not, 2.9%	0 not, 0%	0, 0% 0, 0%	0, 0% 0, 0%
		0 CS, 0%	0 CS, 0%	0 CS, 0%	0 CS, 0%		

Footnotes:
a: pts. 0013/0003/0315, 0013/0012/1204, 0013/0020/2003
b: pt. 0013/0003/0315
c: placebo pt. 0004/0001/0010 had a very low TT4 (27.0 nmol/L, normal: 64.4-167.3 nmol/L) at week 2, but was normal 4 days later (70.8 nmol/L) without supplemental T4 rx. I included this patient in my original table, but have correctly deleted it here.
d: pt. 0007/0017/0007
e: pts. 0015/0019/1905 and 0015/0030/3001
f: pts. 0006/0003/0302, 0008/0008/0002, 0008/0020/0001, 0008/0042/1508
g: pt. 0012/0029/2908
h: pt. 0007/0003/0002 who was begun on T4 replacement rx. and pt. 0007/0004/0007

Summary of above table:
(S= Seroquel, P= placebo, H= Haldol, C= Chlorpromazine, hi= high, lo= low):

Rx	lo TT4 N, %	lo FT4 N, %	lo TT3 N, %	hi TSH N, %	Hypothyroidism hi TSH+lo FT4 N, % hi TSH+lo TT4 N, %	lo TSH+lo FT4 N, % lo TSH+lo TT4 N, %
S	85/717 11.9%	150/974 15.4%[a]	42/681 6.2%	21/1273 1.6%[b]	5/883, 0.6%[c] 2/612, 0.3%[e]	1/883, 0.1%[d] 6/612, 1.0%[f]
P	2/176 1.1%	1/39 2.6%	2/163 1.2%	3/167 1.8%	0/33, 0% 0/144, 0%	0/33, 0% 0/144, 0%
H	1/74 1.4%	4/234 1.7%	1/75 1.3%	0/237 0%	0/217, 0% 0/67, 0%	0/217, 0% 0/67, 0%
C	2/86 2.3%	not done	8/85 9.4%	3/85 3.5%	- 0/75, 0%	- 0/75, 0%

Footnotes:
a: excluding trial 12 which is not a controlled trial, 99/562 or 17.6% Seroquel rx'd pts. developed lo FT4.
b: excluding trial 12, 18/861 Seroquel rx'd pts. developed hi TSH.
c: hypothyroidism manifested as hi TSH+ lo FT4 occurred within 6 wks. of Seroquel rx. in 4/5 pts. and at wk. 36 in the remaining pt. One pt. was on Seroquel 150 mg/day, 2 pts. were on 600 mg/day and 2 pts. were on 750 mg/day.

d: hypothyroidism manifested as lo TSH+ lo FT4 occurred within 6 wks. of Seroquel rx. and on Seroquel 900 mg/day in 1 pt. in trial 12 (0012/0029/2908).

e: hypothyroidism manifested as a hi TSH+ lo TT4 occurred within 6 wks. of Seroquel rx. The dose was reported in only 1 of these 2 pts. and was Seroquel 750 mg/day.

f: hypothyroidism manifested as lo TSH+ lo TT4 occurred within 4 wks. of initiating Seroquel rx. The Seroquel doses at which this occurred were reported in only 3 of these pts. and were 250 mg/day in one pt. and 750 mg/day in the other 2 pts.

Conclusions (based on this review and my previous review, dated 5/29/97):

A. In the controlled phase II-III trials (excluding trial 12 which is not a controlled trial), the following conclusions can be drawn regarding the affect of Seroquel on thyroid function:

1. Seroquel primarily was associated with a dose-related decrease in TT4 and FT4 without an associated change in TSH. Mean TT4 decreased from baseline by ~ 15 nmol/L and mean FT4 by ~ 3 pmol/L at Seroquel doses up to 300 mg/day. At doses of 600-750 mg/day, the corresponding decreases were up to 39 nmol/L and 6 pmol/L.

2. In patients with normal baseline thyroid function, hypothyroidism, manifested as an abnormal TSH and low FT4 occurred in 5/883 (0.6%) Seroquel treated pts. compared to 0% in the placebo and active control (Haldol and Chlorpromazine) groups. Hypothyroidism manifested as an abnormal TSH and low TT4 occurred in 8/612 (1.3%) Seroquel treated pts. compared to 0% in the placebo and active control groups. Only 1 of these patients was placed on T4 replacement therapy, but, note, that study duration was short (≤ 6 wks.) in all but one of these trials.

3. 1.2% Seroquel treated pts. with subclinical hypothyroidism at baseline developed hypothyroidism manifested as high TSH and low FT4 during the study. (Note: in 2 of these pts., Lithium was recently discontinued). In this same subset, 0.3% (2/751) developed hypothyroidism manifested as high TSH and low TT4. The corresponding incidence in the placebo and active control groups was 0%. Exogenous T4 replacement therapy was begun in only 1 of these pts., but, again, note, the short study duration in all but one of these trials.

4. There were no withdrawals from these controlled studies due to abnormalities in thyroid function.

5. "Thyroid disorder" was reported as an adverse event in 0.5% (10/2162) Seroquel treated subjects compared to 0% in the placebo and active control groups.

B. In the uncontrolled trials, 7% (5/73) subjects had a

clinically significant low FT4 associated with a clinically significant high TSH. In 2 of these subjects, these abnormalities were present at baseline, and, in another, baseline TSH was high. In 2 of these 5 subjects, baseline TFTs were normal, but hypothyroidism developed on Seroquel, with one of these pts. being placed on exogenous T4 rx.

C. In the thyroid data document prepared by Zeneca for submission to the UK Committee on Safety of Medicines, 0.4% (10/2386) had a clinically significant TSH. The majority of these pts. were from the open label extension of the controlled phase II-III trials or from the uncontrolled trials. The high TSH was associated with a decrease in FT4 in all of these pts., with decreases in FT4 from baseline ranging from 14-67% (specific thyroid function data in these pts. was requested in my 5/29/97 review, but I do not know if HFD-120 has requested this data because, to date, I have not yet received it). These elevations in TSH were reported as adverse events in 5 pts. 6 of these 10 pts. were begun on T4 replacement therapy. However, this figure may be an underestimate of the incidence of hypothyroidism and number of pts. who were subsequently begun on exogenous T4 therapy, if all the pts. who developed hypothyroidism in the controlled trials were not subsequently followed. This appears to be the case for 2 pts.: 0013/0022/2205 and 0014/0016/1605.

Recommendations:

Seroquel appears to have an antithyroid effect, most likely the mechanism is peripheral (similar to Dilantin and Tegretol) rather than central (i.e. mediated through the hypothalamic-pituitary-thyroid axis), because in only a small number of patients, is a TSH elevation associated with the decrease observed in TT4 and/or FT4. It is suggested that the label provide these incidences. Please note: in the copy of the proposed label faxed to me on 7/18/97 by Dr. Laughren, it states that Seroquel produces a 20% decrease in TT4 and FT4 at the higher end of the therapeutic dose range. In the data I received for review, the sponsor provided this information in terms of mean change from baseline, expressed as nmol/L for TT4 and pmol/L for FT4, not as a percent decrease (for specifics, refer to page 12 of my 5/29/97 review and to page 4 of this review).

To address the issue raised by Dr. Temple and HFD-120 regarding monitoring of thyroid function in patients receiving Seroquel, it would appear to be more fruitful to target such monitoring to patients at risk for hypothyroidism rather than requiring routine monitoring in all patients taking Seroquel. Patients at risk include women, elderly, patients who have been treated for Graves disease, patients with a family history of Hashimoto's or autoimmune thyroiditis (because HLA related), patients who have received external beam radiotherapy for head

and neck cancer or lymphoma, patients with hyperlipidemia and patients on concomitant therapy with drugs that may potentially affect thyroid hormone levels, particularly Lithium in this patient population. In addition, patients with documented hypothyroidism may require an increase in their thyroxine dose when Seroquel therapy is initiated, and, therefore, they should also be monitored. A serum TSH, measured by a sensitive immunoradiometric assay, is the single most useful test for screening thyroid function in a patient at risk except for patients with secondary or tertiary hypothyroidism, in which case, a FT4 will need to be measured. The Sponsor has stated that there may be age- and gender-related differences among Seroquel treated pts. for changes in TFTs and this analysis should be requested because it may be helpful in targeting the subset of patients in whom routine monitoring would be fruitful.

In the Adverse Reactions section of the package insert, Laboratory Changes subsection, add: "...free T4 and total T3..." after "total T4".

Suggested Requests of the Sponsor:

1. Provide an analysis of the thyroid function data by age and gender.
2. Provide all thyroid function data for the 10 patients listed in table 10, thyroid data document prepared for submission to the UK Committee on Safety of Medicines.
3. Inquire if the Sponsor is planning to conduct any studies to delineate the mechanism of Seroquel's affect on thyroid function.

Jean Temeck, M.D. 7/21/97

cc. HFD-510: Dr. Orloff and Mr. McCort
HFD-120: Dr. Laughren, Dr. Mosholder and Mr. Hardeman

concur
D. Orloff
7-21-97

concur
Mosholder 7-21-97

RETURN
JUN 04 1997

MAY 30 1997

Consult request from HFD-120 (Division of Neuropharmacological Drug Products), dated 4/17/97, regarding the effect of Seroquel (Quetiapine) on thyroid function

Documents provided for review:

Integrated Summary of Safety (ISS),
Clinical Trial Report for trial 0015 (book 1 of 46),
Report prepared by Zeneca for the UK Committeee on Safety of Medicines regarding the thyroid data,
Displays of thyroid clinical data and concomitant medications in patients enrolled in the controlled phase II-III trials who developed high TSH, low TT4, FT4 and low TT3,
Expert reports by Dr. Woolf and Dr. Toft,
Final draft Seroquel labeling submitted by Zeneca

Date of review: 5/29/97

Seroquel is indicated for the treatment of psychotic disorders.

The following phase II and III clinical trials were conducted:

a. Short-term placebo-controlled (≤ 6 wks.):
-5077 IL/0004: n=12 (8 on Seroquel, 4 on placebo), 3 wk. study, doses studied: 25-250 mg/day
-5077 IL/0006: n=109 (54 on Seroquel and 55 on placebo), 6 wk. study, doses up to 750 mg/day were studied (but doses > 500 mg/day, were administered for a max. of 14 days).
-204636/0008: n=286 (190 on Seroquel with 94 patients on doses up to 250 mg/day and 96 pts. on doses up to 750 mg/day- with doses > 500 mg/day, administered for a max. of 14 days; 96 pts. on placebo), 6 wk. study.
-5077 IL/0013: n=361 (153 pts. on Seroquel ≤ 300 mg/day, 51 pts. on 600 mg/day and 54 pts. on 750 mg/day; 52 pts. on Haldol and 51 pts. on placebo), 6 wk. study.

b. Short-term active-controlled trials:
-5077 IL/0013: see above
-5077 IL/0014: n=448 (Seroquel n=221 on 50-800 mg/day and Haldol n=227), 6 wk. study
-204636/0007: n=201 (Seroquel n=101 on 75-750 mg/day and Chlorpromazine n=100), 6 wk. study

c. Long-term active-controlled trial:
-5077 IL/0015: n=301 (Seroquel: 85 pts. on 75 mg/day, 88 on 300 mg/day and 87 on 600 mg/day; Haldol n=41), 1 yr. study.

d. Trial 0012: a multicenter, double-blind, randomized 6 week comparison of Seroquel 450 mg/day administered bid vs. 450 mg/day administered tid, using a subtherapeutic dose of Seroquel (50 mg/day) as the control. 618 pts. total were enrolled.

1. Phase 1 clinical trials:

A. Mean Changes from Baseline-

Variable	N	Seroquel Pre-rx. Mean ± S.D.	Seroquel Post-rx. Mean ± S.D.	Change Mean ± S.D.
TT4(nmol/L)	57	92.1 (45.1)	73.4 (33.6)	-18.7 (25.3)
FT4(pmol/L)	122	18.9 (4.3)	14.2 (3.7)	-4.7 (4.4)
TT3(nmol/L)	11	28.6 (59.5)[a]	1.9 (0.3)	-26.7 (59.5)
TSH (mIU/L)	141	1.77 (1.4)	2.28 (1.8)	0.52 (1.7)

a: The pre-rx. total T3 (TT3) value of 28.6 nmol/L is probably an error as normal ranges are generally 1.2-3.0 nmol/L.

Comment: although normal serum ranges for these thyroid hormones was not provided, it appears that the means would be within the normal ranges for most laboratories. There were decreases from baseline in mean TT4 and FT4 (the marked change in TT3 is probably an error), and a small increase in mean TSH.

B. Clinically significant values (CS values)-

These were defined as < 0.8 xLLN (lower limit of normal) or > 1.2 xULN (upper limit of normal).

Excluding subjects with abnormal baseline values, 24 patients (pts.) had significantly low free T4 (FT4) values on Seroquel, but in only one of these pts. (pt. 0016/0001/0047), was this accompanied by a high TSH (this subject developed hypothyroidism: on day 20, free T4 decreased from 11.1 pmol/L at baseline to 7.7 pmol/L on day 20; the corresponding changes in TSH were 1.9 mIU/L and 9.1 mIU/L. No further information was available.). 3 pts. had CS high TSH values. There were no clinically significant changes in either total T3 (TT3) or total T4 (TT4).

2. Phase II-III clinical trials:

Data from the following trials are presented here:

a. short-term (≤ 6wks.), placebo-controlled trials (trials 004, 006, 008 and 0013)

b. short-term active-controlled trials (trials 0013- haloperidol: note this trial had 3 rx. arms: Seroquel, placebo and haloperidol; 0014- haloperidol and 0007- chlorpromazine).

c. long-term (1 year) active-controlled (haloperidol) trial

A. Mean changes in serum thyroid hormone levels from baseline to end of study for the phase II-III trials (Note: the baseline and end of treatment means were all within normal limits. Abbreviations: S= Seroquel, P= placebo, H= Haloperidol, C= Chlorpromazine, chg.= change. Units of measurement: for TT4, TT3, TBG, rT3 (reverse T3)- nmol/L, FT4- pmol/L, TSH- mIU/L).

Trial	Rx	TT4 N	TT4 Mean chg.	FT4 N	FT4 Mean chg.	TT3 N	TT3 Mean chg.	TSH N	TSH Mean chg.	TBG N	TBG Mean chg.	rT3 N	rT3 Mean chg.
004, 006, 008, 0013	S	443,	-21	212,	-4.4	432,	-0.1	441,	0.1	212,	492	199,	0
	P	184,	-1.8	44,	-0.9	178,	0.0	181,	-0.1	45,	-286	45,	0
013 + 014	S	213,	-23	384,	-3.4	210,	0.0	384,	-0.1	212,	492	199,	0
	H	42,	-2.5	209,	-0.3	42,	0.0	210,	-0.3	42,	61	44,	0
0007	S	91,	-17			90,	-0.1	92,	0.2				
	C	90,	-4.5			91,	0.1	92,	0.2				
0015	S	211,	-12	211,	-1.9	209,	-0.1	211,	-0.1	174,	-1243	168,	0
	H	36,	0.9	38,	0.7	36,	0.0	38,	-0.1	32,	1086	32,	0

Comment: The above data indicate that Seroquel was associated with a mean decrease in TT4, which did not worsen with longer duration of Seroquel therapy. This mean decrease in TT4 was associated with some decrease in mean FT4 and small to no change in the other thyroid hormone parameters. These data suggest that the decrease observed in TT4 is not mediated through the hypothalamic-pituitary-thyroid axis or through TBG.

B. Shift Table results- normal baseline to low or high end-of-treatment in the short-term, placebo-controlled phase II-III trials (S= Seroquel, P= placebo):

Rx.	nl. to low TT4 N (%)	nl. to low FT4 N (%)	nl. to low TT3 N (%)	nl. to high TSH N (%)	nl. to low TSH N (%)
S	14 (3.2%)	12 (5.7%)	2 (0.5%)	3 (0.7%)	14 (3.2%)
p	0	0	1 (0.6%)	1 (0.6%)	7 (3.9%)

Comment: The only significant frequency differences between Seroquel and placebo were for TT4 and FT4 (the frequency of shifts in TT3, TSH, and, not shown above, TBG and rT3 were comparable between the Seroquel and placebo rx'd gps.). For TT4, the # (%) of pts. who shifted from normal baseline to low end of study values were 14/443 (3.2%) in the Seroquel gp. and 0% in the placebo gp.; the corresponding values for FT4 were 12/212 (5.7%) in the Seroquel gp. and 0% in the placebo gp.

C. Clinically significant (CS) changes (<0.8xLLN or >1.2xULN) in TFTs in the controlled phase II-III trials in pts. with either normal baseline or baseline not CS as defined above (hi= high, lo= low, S= Seroquel, P= placebo, H= Haloperidol and C= Chlorpromazine):

Trial	Rx.	low TT4 N , %	low FT4 N , %	low TT3 N , %	high TSH N , %	hi TSH+lo FT4 or TT4 N , %
004, 006, 008, 0013	S	20, 4.6%				3(a) , 0.7%
	P	1, 0.5%				0
0013+ 0014	S	8, 3.8%	24, 6%	3, 1.4%	9, 2.3%	2(b) , 5.2%
	H	0	0	0	1, 0.5%	0
0007	S	2, 2.1%		10, 10.5%	0	0
	C	2, 2.1%		4, 4.2%	4, 4.2%	1 , 1%
0015	S		17, 8%		6, 2.8%	2© , 0.9%
	H		0		0	0

cells left blank if data was not provided in ISS.
a= pt. 0013/0003/0315: nl. base. FT4 and TSH became hypothyroid on S 750 mg/day at wk. 6
pt. 0013/0016/1605: increased base. TSH became hypothyroid on S 600 mg/day at wk. 6
pt. 0008/0028/0111: hx. pre-existing Li-induced hypothyroidism

b= pt. 0013/0003/0315 and 0013/0016/1605: see above

c= pt. 0015/014/01409: elevated base. TSH
became hypothyroid on S 300 mg/day at wk. 4
pt. 0015/006/00604: hypothyroid at baseline
placed on L-T4 (levothyroxine) rx. during S 600 mg/day

Note: on page 104 of the ISS, the sponsor states: "A greater number of exposures to levothyroxine in patients treated with higher Seroquel doses is necessary to fully evaluate the effects of Seroquel treatment on peripheral thyroid hormone metabolism in euthyroid patients on thyroid replacement therapy."

D. On March 27, 1997, Zeneca submitted a raw database of pts. who had either normal or low baseline TSH and developed high TSH during study and pts. who had normal or high baseline TT4, FT4 or TT3 and developed low levels of one or more of these parameters during study. Using Zeneca's definition of CS changes, **the incidence of CS changes in TFTs in the controlled phase II-III trials** were: (Note: **The baseline value was not CS for the specific thyroid parameter under study.** TFTs were done biweekly x 3 weeks in trial 4; weekly x 6 wks in trials 6, 7 and 8; at baseline and week 6 in trials 12, 13 and 14 and periodically throughout the one year trial 15): **Table D1:**

Trial	Rx.	low TT4 N, %	low FT4 N, %	low TT3 N, %	high TSH N, %	high TSH+lo FT4 or TT4 N, %
004, 006, 008, 0013	S	18,4.1% (a)	13,6.3% ©	3, 0.7% (d)	3, 0.7% (e)	1, 0.5% (g)
	P	1,0.5% (b)	0, 0%	0, 0%	2, 1.2% (f)	0, 0%
0012*	S	not done	7, ? (h)	not done	0, 0%	0, 0%
0013+ 0014	S	8,3.8% (I)	20,5.2%	1, 0.5% (j)	4, 1.0%	1, 0.3% (k)
	H	0, 0%	0, 0%	0, 0%	0, 0%	0, 0%
0007	S	2,2.1% (l)	not	6, 6.3% (n)	0, 0%	0, 0%
	C	1,1.1% (m)	done	2, 2.1% (o)	1, 1.0% (p)	0, 0%

0015	S H	4,1.9% (q) 0, 0%	13,6.1% (r) 0, 0%	1, 0.5% (s) 0, 0%	2, 0.9% (t) 0, 0%	1, 0.5% (u) 0, 0%

Comment re above table D1: the incidences of CS changes approximate those reported by Zeneca in the ISS.
*= trial 12 was conducted with Seroquel only (see pp.1 for details). **Note: no pt. in the hi TSH + lo TT4/FT4 column was on drugs affecting TFTs or was placed on exogenous T4 rx.**
a= of the 10 Seroquel pts. with subsequent TT4 values, only 1 (10%) had all normal subsequent TT4 values. 1 of these 18 pts. was recently off Lithium.
b= this 1 placebo pt. (100%) had all nl. subsequent TT4s.
c= FT4 was not measured in trials 0004, 0006 and 0008. 1 of these 13 Seroquel pts. was recently off Lithium.
d= of the 2 Seroquel pts. with subsequent TT3 values, 0% had all nl. subsequent TT3 values.
e= of the 2 Seroquel pts. with subsequent TSH values, 2 (100%) had all nl. subsequent TSH values.
f= of the 2 placebo pts. with subsequent TSH values, only 1 (50%) had all nl. subsequent TSHs.
g= pt. 0013/0003/0315 with nl. baseline TFTs, developed hypothyroidism on Seroquel 750 mg at wk. 6.
h= # pts. in whom FT4 was measured, was not reported.
I= TT4 was not measured in trial 14. 1 of these 8 Seroquel pts. was recently off Lithium
j= TT3 was not measured in trial 14.
k= Seroquel treated pt. 0013/0003/0315
l= of the 2 Seroquel pts. with subsequent TT4 values, only 1 (50%) had all nl. subsequent TT4 values.
m= in this 1 Chlorpromazine pt., all subsequent TT4 values were normal.
n= in 1 of these Seroquel pts, the low TT3 was associated with a low TT4. Of the 6 pts. with subsequent TT3 values, only 3 (50%) had all nl. subsequent TT3 values.
o= in the 1 Chlorpromazine treated pt. with subsequent TT3 values, the levels were normal.
p= in this 1 pt., all subsequent TSH values were nl.
q= of the 3 Seroquel pts. with subsequent TT4 values, 2 pts. (67%) had all nl. subsequent TT4 values.
r= of the 8 Seroquel pts. with subsequent FT4 values, 3 pts. (38%) had all nl. subsequent values.
s= this 1 pt. had subsequent nl. TT3
t= of the 1 pt. with subsequent TSH values, all were nl.
u= pt. 0015/0030/3001 who had nl. baseline TFTs but developed a low FT4 (12.9 pmol/L with LLN= 15.4 pmol/L) at week 4 and a high TSH (7.9 mIU/L with nl. to 5.5) at wk. 5 on Seroquel 600 mg/day.

Using the above raw database, the **frequency of thyroid abnormalities** developing during treatment **in the phase II-III controlled clinical trials in pts. with normal baseline TFTs were**: (Note: the abnormalities were divided into CS based on Zeneca's definition and not CS, designated as "not" when the values were abnormal but not CS): **Table D2:**

Trial	Rx.	low TT4 N, %	low FT4 N, %	low TT3 N, %	high TSH N, %	hi TSH+lo FT4 or TT4 N, %
0004, 0006, 0008, 0013	S	35 not, 8.0%(a) 13 CS, 3.0%(b)	29 not, 14.1%(e) 11 CS, 5.3%(e)	17 not, 4.0% (f) 2 CS, 0.5% (g)	4 not, 1.0% (I) 3 CS, 0.7% (j)	3, 1.5% (m)
	P	1 not, 0.5%(c) 1 CS, 0.5%(d)	1 not, 2.3%(e) 0 CS, 0%	2 not, 1.1% (h) 0 CS, 0%	1 not, 0.6% (k) 2 CS, 1.2% (l)	1, 0.5% (n)
0012	S	not done	44 not, ? % (o) 7 CS, ? % (o)	not done	3 not, ? % (o) 0 CS, 0%	0, 0%
0013+ 0014	S	7 not, 3.3%(p) 6 CS, 2.8%(q)	42 not, 10.9%(r) 18 CS, 4.7%(s)	3 not, 1.4% (t) 1 CS, 0.5%	3 not, 0.8% (u) 4 CS, 1.0% (v)	3, 0.8% (m)
	H	1 not, 2.4% 0 CS, 0%	2 not, 0.9% 0 CS, 0%	0 not, 0% 0 CS 0%	0 not, 0% 0 CS, 0%	0, 0%
0007	S	21 not, 22.1% (w) 2 CS, 2.1%(x)	not done	13 not, 13.7%(aa) 6 CS, 6.3%(bb)	1 not, 1.0%(ee) 0 CS, 0%	0, 0% (hh)
	C	1 not, 1.1%(y) 1 CS, 1.1%(z)		6 not, 6.3%(cc) 2 CS, 2.1%(dd)	2 not, 2.1% (ff) 1 CS, 1.0% (gg)	0, 0%

0015	S	11 not, 5.2%(ii) 3 CS, 1.4%(jj)	27 not, 12.7%(kk) 12 CS, 5.7%(ll)	3 not, 1.4% (nn) 1 CS, 0.5% (oo)	4 not, 1.9% (qq) 2 CS, 0.9% (rr)	1, 0.5% (ss)
	H	0 not, 0% 0 CS, 0%	2 not, 5.3%(mm) 0 CS, 0%	1 not, 2.8% (pp) 0 CS, 0%	0 not, 0% 0 CS, 0%	0, 0%

Note: none of the pts. listed in the last column: high TSH with low TT4 and/or FT4 were on drugs known to affect thyroid function and none were placed on levothyroxine replacement therapy.

Comments regarding Table D2 which depicts the frequency of thyroid abnormalities, occurring in the controlled phase II-III trials in pts. with normal baseline TFTs:

1. The major difference between Seroquel and control (either placebo or active control) in TFTs was the high incidence of low TT4 and FT4 which occurred on Seroquel therapy.

2. The majority of these decreases in TT4 and FT4 were ≤ 20% decrease from baseline, i.e. not clinically significant by Zeneca's definition.

3. The majority of these pts. were not on drugs known to affect thyroid function; therefore, these changes can be most probably attributable to Seroquel.

4. The majority of Seroquel treated pts. in whom the decrease from baseline in TT4, FT4 and TT3 were not clinically significant, had follow-up values which were all normal.

5. In pts. with normal baseline TFTs, hypothyroidism (high TSH and low TT4/FT4) occurred in 1.5% Seroquel treated pts. in the placebo-controlled trials and 0.7% in the active-controlled trials. The hypothyroidism occurred at week 6 of Seroquel in 3 pts. and week 36 in the fourth pt. The Seroquel doses at which this occurred were: 150 mg/day in 1 pt., 600 mg/day in another and 750 mg/day in the remaining 2 pts. The incidence of hypothyroidism in the placebo gp. was 0.5%, and was 0% in the Haldol and Chlorpromazine gps.

Footnotes for table D2:

a= 22/35 Seroquel pts. with not CS low TT4 had follow-up values. These f/u TT4 values were all were nl. in 13 pts. (59%). 1/35 pts. was recently off Lithium.

b= 7/13 Seroquel pts. with CS low TT4 had f/u values. These f/u TT4 values were all nl. in only 1 pt. (14%). 1/13 pts. was recently off Lithium.

c and d= f/u TT4 values were nl. in both of these placebo pts.

e= FT4 values were not done in trials 4, 6 and 8. No f/u FT4 values were obtained in trial 13. 3/29 Seroquel pts. with

not CS low FT4 were recently taken off Lithium. 1/11 Seroquel pts. with CS low FT4 was recently taken off Lithium.

f= in 3 of these 17 Seroquel pts., the low TT3 was associated with a low TT4 and/or FT4 and in another pt., with an elevated TSH. In addition, there was one pt. (0013/0003/0315) where the low TT3 was part of full-blown hypothyroidism. 10/17 Seroquel pts. with not CS low TT3 had f/u values. These f/u TT3 values were all nl. in 7 pts. (70%).

g= only 1 Seroquel pt. with a CS low TT3 had f/u and TT3 values remained low.

h= f/u TT3 values were all nl. in ½ placebo pts. (50%).

I= 2 of these Seroquel pts. also has low TT4. F/u TSH values were obtained in 2/4 Seroquel pts. with a not CS elevated TSH and were nl. in both of these.

j= 1 of these Seroquel pts. (0013/0003/0315) became hypothyroid on the drug. F/u TSH values were obtained in 2/3 Seroquel pts. with a CS elevated TSH and were nl. in 1 of these (50%).

k= f/u TSH values were nl. in this placebo pt.

l= f/u TSH values were nl. in ½ of these placebo pts. with CS high TSH.

m= pts. 0013/0003/0315 (see above) and pts. 0013/0012/1204 and 0013/0020/2003, all of whom had nl. baseline TFTs and developed hypothyroidism on wk. 6 of Seroquel, 150 and 750 mg/day.

n= placebo pt. 0004/0001/0010.

o= # pts. in who FT4 was measured, was not reported.

p= 1 of these 7 pts. was recently off Lithium. TT4 was not measured in trial 14.

q= 1 of these 6 pts. was recently taken off Lithium.

r= 3/29 pts. were recently taken off Lithium.

s= 1/11 pts. was recently taken off Lithium.

t= 1 of these 3 pts. was recently taken off Tegretol. The low TT3 was associated with hypothyroidism in one pt., 0013/0003/0315 and; in another pt., 0013/0020/2001, with low TT4 and FT4. TT3 was not measured in trial 14.

u= 2 Seroquel pts. also with low TT4

v= 1 of these Seroquel pts. became hypothyroid on the drug (0013/0003/0315)

w= 19/21 Seroquel pts. had f/u TT4s and these were all nl. in 12 pts. (63%)

x= f/u TT4 values were nl. in 1 (50%) of these 2 Seroquel pts.

y= f/u TT4 was nl. in this Chlorpromazine pt.

z= f/u TT4 was nl. in this Chlorpromazine pt.

aa= f/u TT3 was nl. in 7/13 (54%) Seroquel pts.

bb= f/u TT3 was nl. in 3/6 (50%) Seroquel pts.

cc= f/u TT3 was nl. in 3/5 (60%) Chlorpromazine pts.

dd= f/u TT3 remained low in the 1 Chlorpromazine pt. who had f/u

TT3.

ee= f/u TSH was nl. in this Seroquel pt.

ff= f/u TSH remained high in the 1 pt. with f/u TSH

gg= f/u TSH was nl. in this 1 Chlorpromazine pt.

hh= 1 Seroquel pt., 0007/0017/0007, developed an elevated TSH and low TT4 on Seroquel but these occurred at different visits.

ii= Lithium was listed as a concomitant medication in one of these Seroquel pts. F/u TT4s were obtained in 9 of these pts. and were nl. in 6 (67%)

jj= Lithium was d/c'd on the baseline day in one of these Seroquel pts. F/u TT4 was nl. in only 1 of these 3 pts. (33%).

kk= f/u FT4 was nl. in 14/19 Seroquel pts. (74%)

ll= f/u FT4 was nl. in 4/9 Seroquel pts. (44%)

mm= f/u FT4 was nl. in both of these Haldol pts.

nn= all 3 Seroquel pts. had an associated low TT4 and/or FT4. F/u TT3 was nl. in the 1 pt. who had f/u values.

oo= this Seroquel pt. had an associated low FT4. F/U TT3 was nl. in this pt.

pp= f/u TT3 was nl. in this Haldol pt.

qq= one of the Seroquel pts. had a concomitant low FT4 and, another, a high TT3. F/U TSH was nl. in 3/4 (75%) of these pts.

rr= f/u TSH was nl. in the 1 Seroquel pt. in which this was done.

ss= pt. 0015/0019/1905 with nl. baseline TFTs who became hypothyroid on Seroquel 600 mg/day at week 36. Note, pt. 0015/0030/3001 also developed a high TSH and low FT4 on Seroquel but these occurred at different visits.

D3:

Using the raw database, 8 pts. with subclinical hypothyroidism at baseline (high TSH), developed hypothyroidism (high TSH in conjunction with a low FT4) in the controlled phase II-III trials. All were on Seroquel. These pts. were:

Trial 13: 0016/1605 (recently off Lithium), 0017/1710, 0021/2105

Trial 12: 0001/0128

Trial 14: 0051/5112

Trial 15: 0014/1409, 0017/1701 (Li d/c'd base. day), 0029/2902

Hypothyroidism occurred within 6 wks. of initiating Seroquel therapy. The doses ranged from 600-1800 mg/day. One of these pts. (0013/0021/2105) was begun on T4 replacement therapy.

Since I do not know how many pts. in trial 12 had FT4 measurements, I cannot calculate the incidence. Excluding this trial, 7 pts. (7/598= 1.2%) with subclinical hypothyroidism developed hypothyroidism on Seroquel in the controlled phase II-III trials. This 1.2% incidence on Seroquel corresponds to a 0% incidence on placebo, Haldol and Chlorpromazine.

D4:

Using the raw database, 6 pts. with normal baseline TFTs developed a low TSH in conjunction with a low TT4/FT4 on Seroquel in the controlled phase II-III trials. All were on Seroquel. These pts. were:
Trial 6: 0003/0302
Trial 7: 0004/0007
Trial 8: 0008/0002, 0020/0001, 0042/1508
Trial 12: 0029/2908

Hypothyroidism occurred within 4 wks. of initiating Seroquel therapy. Seroquel doses were reported in 4 of these pts. and ranged from 250 mg/day in 1 pt. to 750-900 mg/day in the remaining pts. The incidence of hypothyroidism as manifested by a low TSH and low TT4/FT4 in the phase II-II controlled trials (excludes trial 12) in pts. with nl. baseline TFTs was 0.7% (5/727) on Seroquel and 0% in the placebo, Haldol and Chlorpromazine gps.

In summary, based on the raw database, the incidence of hypothyroidism in the phase II-III clinical trials was:

<u>Pts. with nl. base. TFTs who developed high TSH and low TT4/FT4:</u>
in the placebo-controlled trials:
1.5% on Seroquel vs. 0.5% on placebo
in the active-controlled trials:
0.7% on Seroquel vs. 0% Haldol and 0% Chlorpromazine

<u>Pts. with nl. base. TFTs who developed low TSH and low TT4/FT4:</u>
0.7% on Seroquel vs. 0% placebo, 0% Haldol and 0% Chlorpr.

<u>Pts. with subclinical hypothyroidism at base. who became hypoth.:</u>
1.2% on Seroquel vs. 0% placebo, 0% Haldol and 0% Chlorpr.

Exogenous T4 therapy was begun in only 1 of the above pts. (0013/0021/2105) who had subclinical hypothyroidism at baseline.

Per the raw database, a total of 3 pts. were begun on T4 replacement therapy in the controlled phase II-III trials. All were on Seroquel. These pts. were:
0013/0021/2105 who had subclinical hypothyroidism at base.
0007/0003/0002 who had nl. base. TFTs but developed a low TSH and TT3 at wk. 2 Seroquel and a low TT4 at wks. 3 and 4.
0015/0006/0604 who was hypothyroid at baseline.

E. Relationship of Seroquel dose to changes in TFTs:

Data to look at this relationship to dose was derived from trials 0013 and 0015.

Mean change from baseline to end-of-rx. by Seroquel (abbreviated as S) **dose** (note: for trial 0013, the # of subjects with paired measurements for each thyroid function test ranged from 34-44, and for trial 0015, ranged from 50-73, and the units of measurement are the same as above):

Trial/S Dose	TT4	FT4	TT3	TSH	TBG	rT3
0013/75 mg 0015/75 mg	-11.4 0.5	-2.5 -0.9	0.0 -0.1	-0.2 -0.2	1167 -1114	0.0 0.0
0013/150 mg	-15.1	-2.8	0.1	-0.2	1609	0.0
Trial/S Dose	TT4	FT4	TT3	TSH	TBG	rT3
0013/300 mg 0015/300 mg	-20.6 -12.2	-4.5 -1.5	0.1 -0.1	0.1 0.0	184 -1471	0.0 0.0
0013/600 mg 0015/600 mg	-30.9 -24.0	-6.2 -3.3	-0.2 -0.2	-0.3 -0.1	-61 -1113	0.0 0.0
0013/750 mg	-38.9	-5.9	-0.3	-0.8	-534	-0.1

Comment: there is a clear dose-related mean decrease in TT4 and FT4. The mean decreases in these variables at each dose, were similar in both the short and long-term trials. The mean decrease in TT3 was smaller than for TT4 and occurred only at the higher doses (600 and 750 mg).

F. Withdrawals from controlled studies due to thyroid function abnormalities: none

G. "Thyroid disorder" reported as an Adverse Event in the combined phase II-III trials:

Sponsor states on page 167, ISS, that "Thyroid disorder" was reported as an adverse event in 0.5% subjects (10/2162 from the combined phase II-III trials), yielding an event rate of 1.7 per 100 subject-years of follow-up. The corresponding incidence of thyroid disorder as an AE was 0% in each of the placebo, Haldol and Chlorpromazine groups.

3. Uncontrolled trials:

5/73 subjects (7%) had CS low FT4 values associated with CS high TSH. In 2 of these 5 subjects, these abnormalities were present at baseline and, in another, baseline TSH was high. In the remaining 2 subjects (0015/0020/2007 and 0012/0022/2205),

hypothyroidism developed on Seroquel therapy, with one of these subjects (0015/0020/2007) being placed on levothyroxine replacement therapy.

There were no withdrawals due to thyroid function abnormalities.

4. overall summary of CS changes in TSH as provided by Zeneca to the UK Committee on Safety of Medicines:

Overall, 2.3% pts. (55/2387) on Seroquel, 1.5% (3/206) on placebo and 3% (3/101) on chlorpromazine in the phase II/III trials had normal baseline TSH and at least one elevated level during treatment.

10 Seroquel pts. (0.4%) had a CS increase in TSH (nl. base. TSH). The majority of them are from the open-label extension of the controlled phase II-III trials and were submitted with the safety update (clarified by Dr. Mosholder in a phone conversation with Zeneca) or were from the uncontrolled trials. However, in 2 of these pts., the high TSH was first noted at week 4 (0013/0022/2205 and 0014/0016/1605) and should have been included in my database. This requires clarification. In any event, the high TSHs occurred in conjunction with variable decreases in FT4 ranging from a 14-67% decrease from baseline (levels were not provided). The elevations in TSH were reported as adverse events in 5 pts. 6 pts. received T4 replacement therapy.

5. Overall Summary:

The controlled phase II-III trials indicate that Seroquel is primarily associated with decreases in TT4 and FT4 and that these decreases are dose-related and do not worsen during long-term treatment. The fact that in the majority of pts. these changes are not accompanied by changes in TSH indicates that the mechanism of Seroquel's affect on thyroid function is most probably peripheral rather than central (i.e. not mediated through the hypothalamic-pituitary-thyroid axis). This pattern of change appears to be similar to that observed with Dilantin and Tegretol.

The Sponsor states there may be age- and gender-related differences among Seroquel-treated pts. for changes in TT4, FT4 and TT3 and this analysis should be requested.

The Sponsor should also clarify why pts. 0013/0022/2205 and 0014/0016/1605 were not listed in the raw database they provided of pts. who developed abnormal TFTs in the phase II-III controlled clinical trials. Also, they should provide FT$ values for the 10 pts. listed in table 10 of this report.

Sponsor states on page 333, ISS, that: "Monitoring for the occurrence of hypothyroidism in subjects concurrently

administered Quetiapine will require the assessment of a full battery of thyroid tests, including TSH values." "Further in vitro studies are required to fully delineate the mechanism of Quetiapine's effects on thyroid hormone function." On page 340, ISS, Sponsor states "Dose-related decreases in total T4 and free T4 values without associated increases in serum TSH values were observed, but without clinical sequelae. This is brought to the attention of the prescriber in the Precautions section of the labeling." The Sponsor should be asked to provide this wording which they appear to have inadvertently omitted from the label. Also, in the package insert, Adverse Reactions section, Laboratory Changes subsection, add: "...free T4 and total T3..." after "total T4". It is worth noting that Dr. Toft, consultant to Zeneca, recommends that thyroid function should be measured in pts. with established hypothyroidism or who are at risk for hypothyroidism (e.g. due to a family hx. of Hashimoto's thyroiditis) because these pts. may either require an increase in thyroxine dose to compensate for the increased metabolic clearance of thyroid hormones induced by Seroquel or, due to limited thyroid reserve, may experience an increase in TSH when taking Seroquel. These suggestions appear reasonable. The Sponsor might be asked if they have any plans to delineate the effect of Seroquel on thyroid function.

Jean Temeck, M.D.

cc. HFD-510: Dr. Orloff and Mr. McCort
HFD-120: Dr. Laughren, Dr. Mosholder and Mr. Hardeman

D. Orloff
5-30-97

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Statistical Review and Evaluation

IND #: 32,132 (NDA #: 20-639)
Applicant: Zeneca Pharmaceuticals
Drug Name: Seroquel (ICI 204,636)
Document Reviewed: Vols. 1.1, 52.1,52.7,57.1,57.6 and Data diskettes

MAR 18 1997

1 INTRODUCTION

In this submission, the sponsor reported the results of two 2-year carcinogenicity studies in mice and rats. The titles of the studies are "Two year oncogenicity study in mice: dietary administration" (TCM/600) and "Two-year oncogenicity study in rats: oral administration" (TCR/1624). This review pertains to thess studies.

2 STUDY OVERVIEW

2.1 TCM/600 - the Mouse Study

The study reported the results of two experiments, one in male and one in female mice. The study was designed to determine the oncogenic potential of the test article (ICI 204,636, used within its predicted shelf-life) dietarily administered (test article mixed into the diet) to C57BL/10J$_f$CD-1/Alpk mice for a period covering the largest part of its life-span. Dose levels of 0, 20, 75 and 250 mg/kg/day were selected together with an additional rising dose level started at 250 mg/kg/day which was increased until the maximum tolerated dose was considered to have been reached at 750 mg/kg/day. Total duration of dosing is at least 104 weeks. Control group received 100 mice and each dose group received 50 mice in either sex.

Inspections for mortality or gross abnormality were made twice daily and a detailed physical examination (including gentle palpation for the presence of masses) was done weekly.

The sponsor's Results

a) Mortality

Survival was compared between groups using the log rank statistic separately for each sex (Kalbfleish and Prentice, 1980) and two-sided significance levels. An overall chi-square statistic was used to examine the homogeneity of animal survival in the different groups.

Tests did not show any statistically significant positive linear trend in mortality with increasing dose in either sex (males,

χ_4^2=6.11, p>.05; females, χ_4^2=1.05, p>.05).

b) Tumor Incidence

The primary statistical method used was Peto et al. (1980) which allows for the differences in animal mortality and the fatal or prevalence context of information of the tumor. The prevalence intervals used for the adjustment of mortality were (expressed in days) 1-455, 456-546, 547-637 and terminal sacrifice. Intervals prior to the first occurrence of a tumor were discarded. A subsequent interval containing no occurrences for each group was combined with the interval immediately prior to it. For the tumor incidence trend with dose analysis, the continuity corrected Peto chi-squared statistic was used where there were 6 or more tumors and a permutation analogue was used otherwise. The multiplicity correction used a method due to Tukey.

The sponsor made the following observations:

1. A statistically significant increase in the tumor incidence of follicular adenomas of the thyroid gland was detected in males given 250 and 750 mg/kg/day. They were predominantly found in males at terminal necropsy and were not fatal.

2. A statistically significant decrease in the tumor incidence of hepatocellular carcinomas, pulmonary adenomas and testicular Leydig cell tumors were found in males given 750 mg/kg/day.

3. A statistically significant decrease in the incidence of histiocytic sarcomas of the liver, ovarian tubular adenomas and pituitary adenomas were seen in females given 750 mg/kg/day.

4. Certain categories of tumor were also combined across all organs. They were composite lymphoma, histiocytic sarcoma, malignant lymphoma lymphoblastic, angiosarcoma, and angiosarcoma or angioma.

Reviewer's Analysis and Comments

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs provided by the statisticians of the SARB of the old Division of Biometrics, CDER/FDA.

Mortality

The purposes of the survival data analysis are (1) to examine the significance of the differences in survival among the treatment groups (the homogeneity test), and (2) to determine the

significance of positive or negative linear trend (dose-mortality trend test). Two statistical tests were used: Cox test statistic and generalized Kruskal-Wallis test statistic. The background for these tests can be found in Lin et al., 1994 and Thomas et al. , 1976.

The standard time intervals (0-365d, 366-548d, 549-654d, 655-728d, 728d+) for two-year animal studies were used. The cumulative mortality rates and the survival at terminal sacrifice for each dose group can be found in Table 1.

The results of this reviewer's analysis were consistent with the sponsor's results. Neither Cox test nor generalized K-W test showed a statistically significant ($p>0.05$) positive linear trend or an increase in mortality in any treated group compared with the control in either sex. There was no statistical evidence indicating a difference in mortality among the five dose groups ($p>0.15$). The survival curves are displayed in Figure 1 for male mice and Figure 2 for female mice.

Tumor Incidence

Using the method of Peto et al. (1980), this reviewer applied the death-rate method to fatal tumors and prevalence method to incidental tumors using standard time intervals of two-year animal studies. Tables 2 and 3 summarize the results of this reviewer's analysis for male and female mice that follows the FDA draft document "Guidance for industry on statistical aspects of design, analysis and interpretation of animal carcinogenicity studies". In general, the exact p-value is used to assess statistical significance, but for those tumors that are fatal to some animals but nonfatal to others the asymptotic p-value may be used. The p-values presented in the tables have not been adjusted for multiple testings. A rule proposed in the FDA draft Guidance document was used to adjust for multiple testings, based on which a positive linear trend is considered not to occur by chance alone if the p-value is less than 0.005 for a common tumor (tumor with incidence rate in the control group greater than 1%) and 0.025 for a rare tumor (tumor with incidence rate less than or equal to 1%). By use of this rule, Thyroid gland adenoma - follicular [B] showed a significant positive linear trend (tumor incidence: 0 (control), 0 (low dose), 0 (median dose), 4 (high dose), 29 (highest dose)) in male mice (see Table 2), but it was not significant in female mice (see Table 3).

The results of this reviewer's analysis using standard two-year time intervals were consistent with the sponsor's results using different time intervals (1-455d, 456-546d, 547-637d, 637d+) in terms of statistical significance after multiple testing adjustments.

2.2 TCR/1624 - the Rat Study

The study reported the results of two experiments, one in male and one in female rats. The study was designed to determine the oncogenic potential of the test article (ICI 204,636, used within its predicted shelf-life) orally administered to Charles River Wistar rats for a period covering the largest part of its life-span. Dose levels of 0, 20, 75 and 250 mg/kg/day were selected. The animals were allocated to the groups using a replicate system (a method of random allocation of animals and cages to groups). Total duration of dosing is at least 104 weeks. Control group received 100 rats and each dose group received 50 rats in either sex.

Inspections for mortality or gross abnormality were made twice daily and a detailed physical examination (including gentle palpation for the presence of masses) was done weekly.

The sponsor's Results

a) Mortality

Survival was compared between groups using the log rank statistic separately for each sex (Kalbfleish and Prentice, 1980) and two-sided significance levels. An overall chi-square statistic was used to examine the homogeneity of animal survival in the different groups.

Tests did not show any statistically significant positive linear trend in mortality with increasing dose in either sex (males, $\chi^2(df=3)=0.49$, $p>.05$; females, $\chi^2(df=3)=2.89$, $p>.05$).

b) Tumor Incidence

The primary statistical method used was Peto et al (1980). The prevalence intervals used for the adjustment of mortality were (expressed in days) 1-364, 365-455, 456-546, 547-637 and terminal sacrifice. Intervals prior to the first occurrence of a tumor were discarded. A subsequent interval containing no occurrences for each group was combined with the interval immediately prior to it. For the tumor incidence trend with dose analysis, the continuity corrected Peto chi-squared statistic was used where there were 6 or more tumors and a permutation analogue was used otherwise. The multiplicity correction used a method due to Tukey.

The sponsor made the following observations:

1. A statistically significant increase in the incidence of adenocarcinoma of the mammary gland was found in all dosed female

groups (10%, 26%, 22% and 32% - Group I to IV respectively). The total incidence of mammary gland benign and malignant tumors (females: 68%, 90%, 84% and 68% - Group I to IV respectively) did not show an increasing trend through the dose groups).

2. A statistically significant increase in the incidence of follicular adenoma of the thyroid gland was detected in the Group IV males (6%, 6%, 0%, 32% - Group I to IV respectively). A single follicular adenoma was seen in a Group IV female.

3. A statistically significant reduction in the number of subcutaneous fibromas in Group III and IV males, testicular Leydig cell tumors in all dosed groups, thyroid perifollicular cell adenomas particularly in the high dose females, uterine stromal polyps at all dose levels and squamous carcinomas of the oral cavity in Group III and IV females occurred.

Reviewer's Analysis and Comments

This reviewer performed independent analyses on the survival and tumor data submitted by the sponsor, using the programs provided by the statisticians of the SARB of the old Division of Biometrics, CDER/FDA.

Mortality

Two statistical tests were used (Cox test statistic and generalized Kruskal-Wallis test statistic) to examine the significance of the differences in survival among the treatment groups (the homogeneity test), and (2) to determine the significance of positive or negative linear trend (dose-mortality trend test).

The standard time intervals (0-365d, 366-548d, 549-654d, 655-728d, 728d+) for two-year animal study were used. The cumulative mortality rates and the survival at terminal sacrifice for each dose group can be found in Table 4.

The results of this reviewer's analysis were consistent with the sponsor's results. Neither Cox test nor generalized K-W test showed a statistically significant ($p>0.05$) positive linear trend or an increase in mortality in any treated group compared with the control in either sex. There was no statistical evidence indicating a difference in mortality among the four dose groups ($p>0.15$). The survival curves are displayed in Figure 3 for male rats and Figure 4 for female rats.

Tumor Incidence

Using the method of Peto et al. (1980), this reviewer

applied the death-rate method to fatal tumors and prevalence method to incidental tumors using standard time intervals of two-year animal studies. Tables 5 and 6 summarize the results of this reviewer's analysis for male and female rats that follows the FDA draft document "Guidance for industry on statistical aspects of design, analysis and interpretation of animal carcinogenicity studies". In general, the exact p-value is used to assess statistical significance, but for those tumors that are fatal to some animals but nonfatal to others the asymptotic p-value may be used. The p-values presented in the tables have not been adjusted for multiple testings. A rule proposed in the FDA draft Guidance document was used to adjust for multiple testings, based on which a positive linear trend is considered not to occur by chance alone if the p-value is less than 0.005 for a common tumor (tumor with incidence rate in the control group greater than 1%) and 0.025 for a rare tumor (tumor with incidence rate less than or equal to 1%). By use of this rule, (1) Thyroid gland adenoma - follicular [B] showed a significant positive linear trend (tumor incidence: 6 (control), 3 (low dose), 0 (median dose), 16 (high dose)) in male rats (see Table 5), but it was not significant in female rats, (2) Mammary Gland adenocarcinoma [M] showed a significant positive linear trend (tumor incidence: 10 (control), 13 (low dose), 11 (median dose), 16 (high dose)) in female rats (see Table 6), but it was not significant in male rats.

The results of this reviewer's analysis using standard two-year time intervals were consistent with the sponsor's results using different time intervals (1-455d, 456-546d, 547-637d, 637d+) in terms of statistical significance after multiple testing adjustments.

3 VALIDITY OF THE DESIGN

To evaluate the validity of the experimental design of carcinogenicity studies, the following two issues are considered (1) Were enough animals exposed for a sufficient length of time to allow for late developing tumors? (2) Were the dose levels high enough to pose a reasonable tumor challenge in the animals? There has been no consensus among experts regarding the number of animals and length of time at risk, although most carcinogenicity studies are designed to run for two years with 50 animals per treatment group.

The following are some rules of thumb regarding these two issues as suggested by experts in the field. Haseman (1985) investigated the first issue. Based on the data from 21 studies using Fisher 344 rats and B6C3F1 mice conducted at the National Toxicology Program (NTP), he found that on the average, approximately 50% of the animals in the high dose group survived the 2-year study

period. According to my personal communication with Dr. Karl Lin, Division of Biometrics II, CDER, FDA, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals in the high dose group, after 80-90 weeks, would be considered as a sufficient number and adequate exposure. However, the percent could be lower or higher if the number of animals used in each treatment/sex group is larger or smaller than 50 so that there would be 20-30 animals still alive after the 80-90 weeks. Chu, Cueto and Ward (1981) proposed that "To be considered adequate, an experiment that has not shown a chemical to be carcinogenic would have groups of animals with greater than 50% survival at 1-year". From these sources, it appears that the proportions of survival at 1-year, week 80-90 and at 2-year are of interest in determining the adequacy of exposure and the number of animals at risk.

For the adequacy of the chosen dose levels, it is generally accepted that the high dose should be close to the MTD (maximum tolerated dose). Chu, Cueto and Ward (1981) suggested:
(I) "A dose is considered adequate if there is a detectable weight loss of up to 10% in a dosed group relative to the controls."
(II) "The administered dose is also considered an MTD if dosed animals exhibit clinical signs or severe histopathologic toxic effects attributed to the chemical".
(III) "In addition, doses are considered adequate if the dosed animals show a slight increased mortality compared to the controls."

Bart, Chu, and Tarone (1979) stated that the mean body weight curves over the entire study period should be taken into consideration with the survival curves, when adequacy of dose levels is to be examined. In particular, "usually, the comparison should be limited to the early weeks of a study when no or little mortality has yet occurred in any of the groups. Here a depression of the mean weight in the treated groups is an indication that the treatment has been tested on levels at or approaching the MTD."

Based on the above suggestions and recommendations, this reviewer examines the validity of the experimental design of the mouse and the rat studies.

3.1 TCM/600 - Mouse

The proportions of survival at the end of 1 year were 96% for male mice and 88% for female mice in the highest dose group. These proportions were 68% for male mice and 54% for female mice at the end of 2-year study . Using the above survival criteria, it is reasonable to conclude that there were enough number of

mice exposed for sufficient amount of time to Seroquel in both sexes.

The body weight gain information is summarized below (data are from Table 4 of the sponsor's report in Vol.57.1). Relative to the control, decrement of body weight gain in the highest dose group is 36% (45%) for male mice and 22% (18%) for female mice at the end of the study (% in parentheses are those at the end of week-72, not shown in summary Table below). The mortality rates did not show increased trend with dose in either male or female mice. Thus, assessing whether the highest dose was close to the MTD proved more difficult. There was weight reduction in the dosed animals. But, these reductions are far beyond 10% for both male and female mice. To draw conclusion in this regard, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

Summary Table from Table 4 of the sponsor's report in Vol.57.1

Sex	Group	Median Body weight in grams(n) Beginning of study	End of study	Difference	% change from Cntl
Male mice	Cntl	19.9(100)	32.8(48)	12.9	
	Low	20.2(50)	32.6(22)	12.4	96%
	Med	20.2(50)	31.8(24)	11.6	90%
	High	20.2(50)	30.8(30)	10.6	82%
	Top	20.6(50)	28.9(34)	8.3	64%
Female mice	Cntl	16.2(100)	27.4(52)	11.2	
	Low	15.8(50)	26.8(30)	11	98%
	Med	16.5(50)	26.5(26)	10	89%
	High	16.1(50)	26.5(27)	10.4	93%
	Top	16.2(50)	24.9(27)	8.7	78%

3.2 TCR/1624 - Rat

The proportions of survival at the end of 1 year were 78% for male rats and 88% for female rats in the high dose group. Although these proportions were lower than 50% at the end of 2-year (36% for male rats and 42% for female rats), they were higher than 50% at the end of 80-90 weeks (58% for male rats and 56% for female rats). Using the above survival criteria, it is reasonable to conclude that there were enough number of rats exposed for sufficient amount of time to Seroquel in both sexes.

The body weight gain information is summarized below (data are

from Table 4 of the sponsor's report in Vol.52.1). Relative to the control, decrement of body weight gain in the highest dose group is 39% (31%) for male rats and 31% (26%) for female rats at the end of study (% in parentheses are those at the end of week-72, not shown in Summary Table below). The mortality rates did not show any ordering with dose in either male or female rats. Thus, assessing whether the high dose was close to the MTD proved more difficult. There was weight reduction in the dosed animals. But, these reductions are far beyond 10% for both male and female rats. Mortality did not show any association with dose. To draw conclusion in this regard, all clinical signs and histopathological effects in the treated rats should be taken into consideration.

Summary Table from Table 4 of the sponsor's report in Vol.52.1

Sex	Group	Median Body weight in grams(n)		Difference	% change from Cntl
		Beginning of study	End of study		
Male rats	Cntl	215(99)	750(33)	535	
	Low	209(50)	706(14)	497	93%
	Med	214(50)	587(17)	373	70%
	High	224(49)	570(18)	346	61%
Female rats	Cntl	173(100)	494(42)	321	
	Low	170(50)	498(27)	328	102%
	Med	176(50)	453(18)	277	86%
	High	175(50)	396(21)	221	69%

4 CONCLUSION

In the 2-year mouse study, no statistically significant positive linear trend or heterogeneity in mortality between control and four dose groups was detected in either sex. In male mice, tumor incidence of thyroid gland adenoma - follicular [B] was shown to have a positive linear trend with p-value of 0.0000. None of the other tested tumor types showed a statistically significant positive linear trend in either sex. The evaluation of the design validity suggested that the highest dose used in mouse study appeared to be greater than the MTD. To draw any final conclusion for this issue, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

In the 2-year rat study, no statistically significant positive linear trend or heterogeneity in mortality between control and three dose groups was detected in either sex. Tumor incidence of (1) Thyroid gland adenoma - follicular [B] in male rats and

Mammary Gland adenocarcinoma [M] in female rats were shown to have a positive linear trend with p-values of 0.0000 and 0.0021 (<0.005), respectively. None of the other tested tumor types showed a statistically significant positive linear trend in either sex. The evaluation of the design validity suggested that the high dose used in rat study also appeared to be greater than the MTD. To draw any final conclusion for this issue, all clinical signs and histopathological effects in the treated mice should be taken into consideration.

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References:

1. Bart, Chi, and Tarone (1979). "Statistical Issues in Interpretation of Chronic Bioassay Tests for Carcinogenicity." Journal of the National Cancer Institute Vol.62, pp.957-974.

2. Chu, Cueto and Ward (1981). "Factors in the evaluation of 200 national cancer institute carcinogen bioassay." Journal of Toxicology and Environmental Health. Vol.8, pp.251-280.

3. Gart, J.J, Krewski, D., Lee, D.N., Tarone, R.E., and Wahrendorf, J. (1986). "Statistical methods in Cancer Research. Volume III - The design and analysis of long-term animal experiments", pp.1-219, International Agency for Research on Cancer, Lyon.

4. Haseman, J.K. (1983). "A re-examination of false-positive rates for carcinogenesis studies." Fundamental and Applied Toxicology 3, pp. 334-9.

5. Haseman, J.K. (1985). "Issues in carcinogenicity testing: Dose selection." Fundamental and Applied Toxicology, Vol. 5., pp. 66-78.

6. Lin et al. (1994). "Statistical Review and Evaluation of Animal Tumorigenicity Studies." Statistics in the Pharmaceutical Industry. Marcel Dekker, Inc. pp. 19-57.

7. Peto et al (1980).. "Guidelines for Simple, Sensitive Significance Tests for Carcinogenic Effects in Long-Term Animal Experiments. In Long-Term and Short-Term Screening Assays for Carcinogens: A critical Appraisal, International Agency for Research on Cancer, Lyon, France. IARC Monographs Supplement 2. pp. 311-426.

8. Thomas et al. (1976). "Trend and Homogeneity Analyses of Proportions and Life Table Data." Computers and Biomedical Research. pp. 373-81.

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Sue-Jane Wang

Sue-Jane Wang, Ph.D.
Mathematical Statistician

Concur:

3/14/97

Todd Sahlroot, Ph.D.
Team Leader

3/18/97

George Chi, Ph.D.
Director, DB-I

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cc: IND
HFD-120/Dr. Leber
HFD-120/Dr. Fitzgerald
HFD-120/Dr. Freed
HFD-120/Mr Hardeman, CSO
HFD-344/Dr. Lisook
HFD-710/Dr. Chi
HFD-710/Dr. Sahlroot
HFD-710/Dr. Wang
HFD-710/chron

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This review consists of 12 pages of text followed by 6 tables and 4 figures with a total of 22 pages.

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Table 1 - Intercurrent mortality rates (Study TCM/600)

Male Mice

Time (days)	0 mg/kg/d	20 mg/kg/d	75 mg/kg/d	250 mg/kg/d	250-750mg/kg/d	Total
0-365	2* 2.00&	1 2.00	2 4.00	1 2.00	2 4.00	8
366-548	7 9.00	6 14.00	3 10.00	2 6.00	4 12.00	22
549-654	13 22.00	7 28.00	11 32.00	10 26.00	6 24.00	47
655-728	30 52.00	13 54.00	10 52.00	7 40.00	4 32.00	64
TERM. SAC.#	48 48.00	23 46.00	24 48.00	30 60.00	34 68.00	159
Total	100	50	50	50	50	300

Female Mice

Time (days)	0 mg/kg/d	20 mg/kg/d	75 mg/kg/d	250 mg/kg/d	250-750mg/kg/d	Total
0-365	2* 2.00&	0 0.00	3 6.00	0 0.00	6 12.00	11
366-548	8 10.00	6 12.00	5 16.00	5 10.00	7 26.00	31
549-654	18 28.00	5 22.00	3 22.00	9 28.00	5 36.00	40
655-728	20 48.00	9 40.00	12 46.00	9 46.00	5 46.00	55
TERM. SAC.#	52 52.00	30 60.00	27 54.00	27 54.00	27 54.00	163
Total	100	50	50	50	50	300

* No. of animals dying or being sacrificed during the time interval
& Cumulative mortality rate
# The entry for Terminal sacrifice represents the number of animals surviving till the end of the study and the Cumulative survival rate

Table 2. Tests for positive trend in tumor incidence ( ) male mice)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H	T
ADRENAL GLANDS	Cortical adenoma (B)	S	0.6982	0.75710	0	1	0	0	0
BONE AND MARROW - FEMUR	Angiosarcoma (M)	S	0.4025	0.46115	0	0	0	1	0
EPIDIDYMIDES	Histiocytic sarcoma (M)	M	0.8802	0.88470	3	2	2	1	0
HARDERIAN GLANDS	Adenoma (B)	M	0.9630	0.94835	3	3	1	1	0
HEART	Angioma (B)	S	0.6982	0.75710	0	1	0	0	0
INTESTINE - DUODENUM	Adenoma (B)	S	0.3281	0.53200	0	0	1	0	0
INTESTINE - ILEUM	Composite lymphoma (M)	M	0.7768	0.79985	1	0	1	0	0
INTESTINE - JEJUNUM	Composite lymphoma (M)	S	0.8022	0.81675	1	0	1	0	0
KIDNEYS	Adenoma tubular epithelium (B)	S	0.4749	0.61425	0	0	1	1	0
LIVER	Angioma (B)	S	0.8022	0.81675	1	0	1	0	0
LIVER	Angiosarcoma (M)	M	0.9354	0.92580	5	1	1	2	0
LIVER	Hepatocellular adenoma (B)	S	0.0864	0.06430	2	2	0	0	3
LIVER	Hepatocellular carcinoma (M)	M	1.0000	0.90145	3	0	0	0	0
LIVER	Histiocytic sarcoma (M)	M	0.8069	0.82235	2	2	2	2	0
LUNGS	Adenocarcinoma (M)	M	0.4010	0.46215	1	0	0	2	0
LUNGS	Adenoma (B)	S	0.9996	0.99375	8	4	3	0	0
LYMPH NODE - MANDIBULAR	Composite lymphoma (M)	S	0.1259	0.08635	0	0	0	1	1
LYMPH NODE - MESENTERIC	Adjacent tissue angioma (B)	S	0.2138	0.03400	0	0	0	0	1
LYMPH NODE - MESENTERIC	Composite lymphoma (M)	M	0.6169	0.61590	50	28	26	28	33
LYMPH NODE - MESENTERIC	Histiocytic sarcoma (M)	M	1.0000	0.81175	2	0	0	0	0
LYMPH NODE - MESENTERIC	Malignant lymphoma - lymphoblastic (M)	M	0.6865	0.72870	2	0	0	2	0
LYMPH NODES - NON-PROTOCOLLE	Composite lymphoma (M)	M	0.9251	0.92005	3	2	1	2	0
ORAL CAVITY	Ossifying fibroma (B)	S	0.3281	0.53200	0	0	1	0	0
PITUITARY GLAND	Pars distalis adenoma (B)	S	0.3912	0.41255	2	0	0	2	1
SKIN - NON-PROTOCOLLED	Angioma (B)	S	0.4583	0.41675	1	1	0	0	1
SKIN - NON-PROTOCOLLED	Fibrosarcoma (M)	S	0.4916	0.65465	0	0	1	0	0
SPLEEN	Angioma (B)	S	0.5312	0.64615	0	1	0	0	0
SPLEEN	Angiosarcoma (M)	M	0.7639	0.80415	1	1	1	0	0
SPLEEN	Composite lymphoma (M)	M	0.6874	0.69800	11	4	4	2	4
SPLEEN	Malignant lymphoma - lymphocytic (M)	S	1.0000	0.75315	1	0	0	0	0
STOMACH	Adenoma (B)	S	0.6982	0.75710	0	1	0	0	0
STOMACH	Squamous papilloma (B)	S	0.5857	0.62995	1	0	0	2	0
TESTES	Benign Leydig cell tumour (B)	S	0.9924	0.93475	3	1	0	0	0
THYMUS	Adjacent tissue angioma (B)	S	1.0000	0.77815	1	0	0	0	0
THYMUS	Malignant lymphoma - lymphoblastic (M)	S	0.1590	0.01495	0	0	0	0	1
THYROID GLAND	Adenoma - follicular (B)	S	0.0000	0.00000	0	0	0	4	29

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le 3. Tests for positive trend in tumor incidence (TCM/60(le mice)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H	T
ADRENAL GLANDS	Benign phaeochromocytoma (B)	S	0.6363	0.69375	0	1	0	0	0
ADRENAL GLANDS	Cortical adenoma (B)	S	0.6809	0.72740	0	1	0	0	0
BONE AND MARROW - FEMUR	Angiosarcoma (M)	M	0.0779	0.04065	0	0	0	1	1
BONE AND MARROW - FEMUR	Histiocytic sarcoma (M)	M	0.6087	0.70780	1	0	1	1	0
BONE AND MARROW - STERNUM	Malignant lymphoma - lymphoblastic (M)	S	0.1638	0.01640	0	0	0	0	1
CERVIX	Histiocytic sarcoma (M)	S	0.5626	0.61290	1	0	1	2	0
EARS	Squamous carcinoma (M)	S	0.3202	0.38840	0	0	0	1	0
HARDERIAN GLANDS	Adenocarcinoma (M)	M	0.7432	0.77330	1	0	1	0	0
HARDERIAN GLANDS	Adenoma (B)	S	0.9429	0.93185	7	0	2	2	0
INTESTINE - DUODENUM	Adenoma (B)	S	0.3313	0.39925	0	0	0	1	0
INTESTINE - DUODENUM	Malignant lymphoma - lymphoblastic (M)	S	0.6586	0.72040	0	1	0	0	0
INTESTINE - ILEUM	Composite lymphoma (M)	S	0.3313	0.39925	0	0	0	1	0
INTESTINE - ILEUM	Histiocytic sarcoma (M)	S	0.6802	0.72365	0	1	0	0	0
INTESTINE - JEJUNUM	Histiocytic sarcoma (M)	S	1.0000	0.75165	1	0	0	0	0
KIDNEYS	Malignant lymphoma - lymphoblastic (M)	S	0.3313	0.39925	0	0	0	1	0
LIMBS AND TAIL	Chondromyxoid fibroma (B)	S	0.6809	0.72740	0	1	0	0	0
LIMBS AND TAIL	Myxoma (B)	S	1.0000	0.75165	1	0	0	0	0
LIMBS AND TAIL	Osteoma (B)	S	0.5455	0.18125	0	0	0	0	1
LIVER	Angiosarcoma (M)	S	1.0000	0.74700	1	0	0	0	0
LIVER	Hepatocellular adenoma (B)	S	0.5500	0.71385	0	0	0	0	0
LIVER	Hepatocellular carcinoma (M)	M	0.5666	0.67425	1	0	1	1	0
LIVER	Histiocytic sarcoma (M)	M	0.8999	0.89445	9	6	0	0	2
LUNGS	Adenoma (B)	S	0.8990	0.88485	2	1	2	0	0
LUNGS	Osteosarcoma (M)	S	0.1496	0.01250	0	0	0	0	1
LYMPH NODE - MANDIBULAR	Composite lymphoma (M)	S	0.8996	0.81890	1	1	0	0	0
LYMPH NODE - MESENTERIC	Composite lymphoma (M)	M	0.8088	0.79870	59	28	29	31	26
LYMPH NODE - MESENTERIC	Histiocytic sarcoma (M)	S	0.4969	0.65515	0	0	1	0	0
LYMPH NODE - MESENTERIC	Malignant lymphoma - lymphoblastic (M)	M	0.1725	0.13585	2	1	0	0	2
LYMPH NODES - NON-PROTOCOLLE	Composite lymphoma (M)	M	0.2501	0.24895	3	1	4	0	3
OVARIES	Granulosa cell carcinoma (M)	S	1.0000	0.74100	1	0	0	0	0
OVARIES	Luteoma (B)	S	0.6809	0.72740	0	1	0	0	0
OVARIES	Tubular adenoma (B)	S	1.0000	0.88190	3	0	0	0	0
PITUITARY GLAND	Pars distalis adenoma (B)	S	0.9522	0.94870	21	11	8	9	5
PITUITARY GLAND	Pars distalis carcinoma (M)	S	0.8996	0.81890	1	1	0	0	0
PITUITARY GLAND	Pars intermedia adenoma (B)	S	0.2817	0.23715	1	1	0	0	1
PREPUTIAL GLAND	Adenocarcinoma (M)	S	1.0000	0.74360	1	0	0	0	0
SALIVARY GLANDS - PAROTID	Adjacent tissue angioma (B)	S	0.4969	0.65515	0	0	1	0	0
SKIN - NON-PROTOCOLLED	Fibrosarcoma (M)	S	0.3313	0.39925	0	0	0	1	0
SKIN - NON-PROTOCOLLED	Squamous carcinoma (M)	S	0.4969	0.65515	0	0	1	0	0
SKIN - PROTOCOLLED	Angioma (B)	S	0.2545	0.28605	0	0	0	1	0
SPLEEN	Angiosarcoma (M)	S	1.0000	0.75165	1	0	0	0	0
SPLEEN	Composite lymphoma (M)	M	0.2461	0.25000	8	4	3	5	5
SPLEEN	Lymphatic leukaemia (lymphoblastic) (M)	S	0.3260	0.38745	0	0	0	1	0
SPLEEN	Malignant lymphoma - lymphoblastic (M)	S	1.0000	0.74550	1	0	0	0	0
STOMACH	Adenoma (B)	S	1.0000	0.72565	1	0	0	0	0
THYMUS	Composite lymphoma (M)	S	0.4969	0.65515	0	0	1	0	0
THYMUS	Malignant lymphoma - lymphoblastic (M)	M	0.9070	0.85830	1	2	0	0	0
THYROID GLAND	Adenoma - follicular (B)	S	0.1127	0.09305	1	2	0	1	2
UTERUS	Adenocarcinoma (M)	S	0.1656	0.01680	0	0	0	0	1
UTERUS	Adenoma (B)	S	0.7484	0.77795	1	0	1	0	0
UTERUS	Angioma (B)	S	0.9775	0.92470	2	3	0	0	0
UTERUS	Histiocytic sarcoma (M)	M	0.6747	0.68850	6	6	7	4	3
UTERUS	Polyp (adenomatous) (B)	S	0.9176	0.83460	1	1	0	0	0
UTERUS	Polyp (stromal) (B)	S	0.6809	0.72740	0	1	0	0	0
VAGINA	Histiocytic sarcoma (M)	S	0.3313	0.39925	0	0	0	1	0
VERTEBRAL COLUMN	Angiosarcoma (M)	S	0.1656	0.01680	0	0	0	0	1
VERTEBRAL COLUMN	Histiocytic sarcoma (M)	S	0.5666	0.70050	0	0	2	0	0
VERTEBRAL COLUMN	Osteosarcoma (M)	M	0.6275	0.75345	0	1	1	0	0

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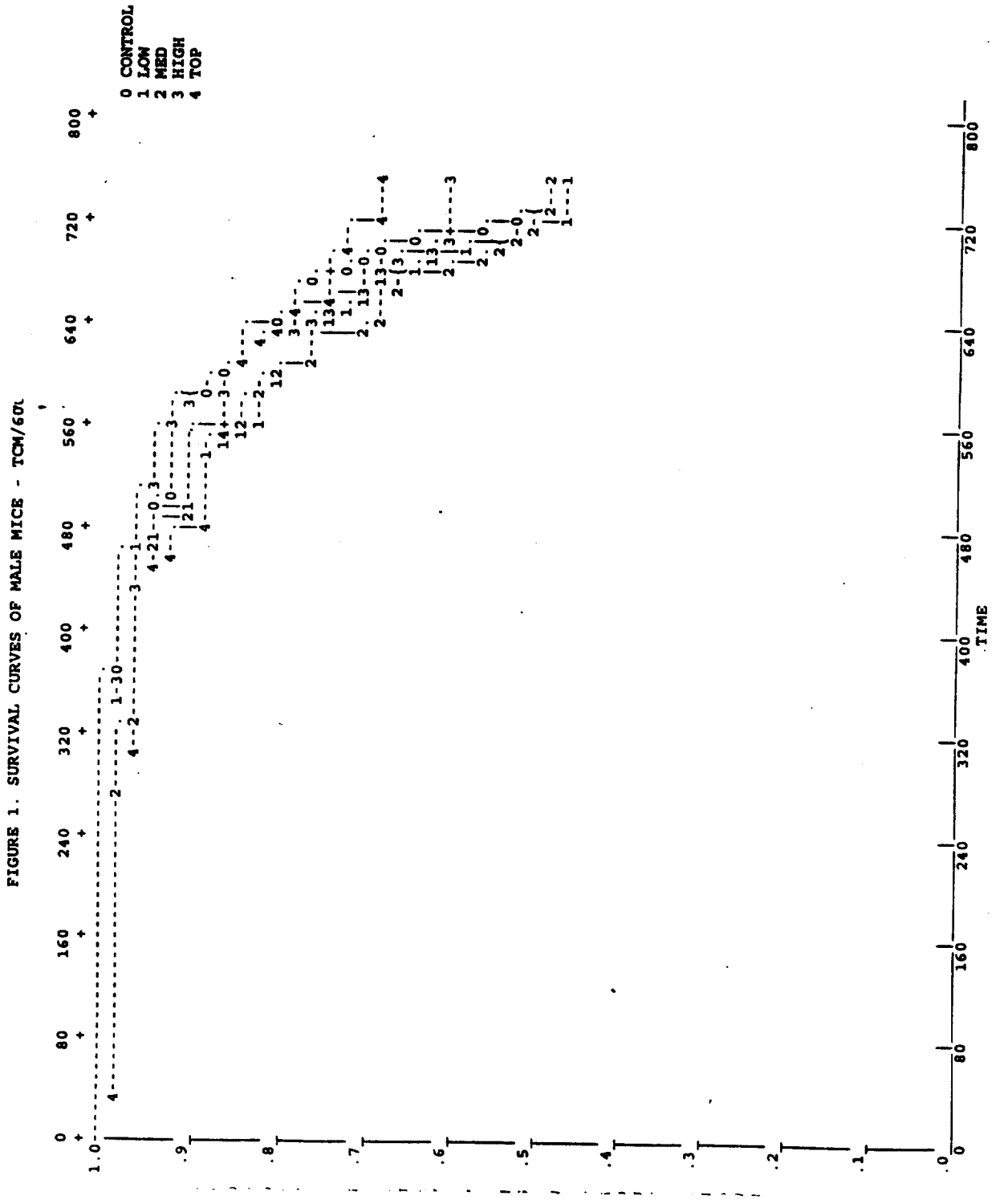

FIGURE 1. SURVIVAL CURVES OF MALE MICE - TCM/60

FIGURE 2. SURVIVAL CURVES OF FEMALE MICE - TCM/600

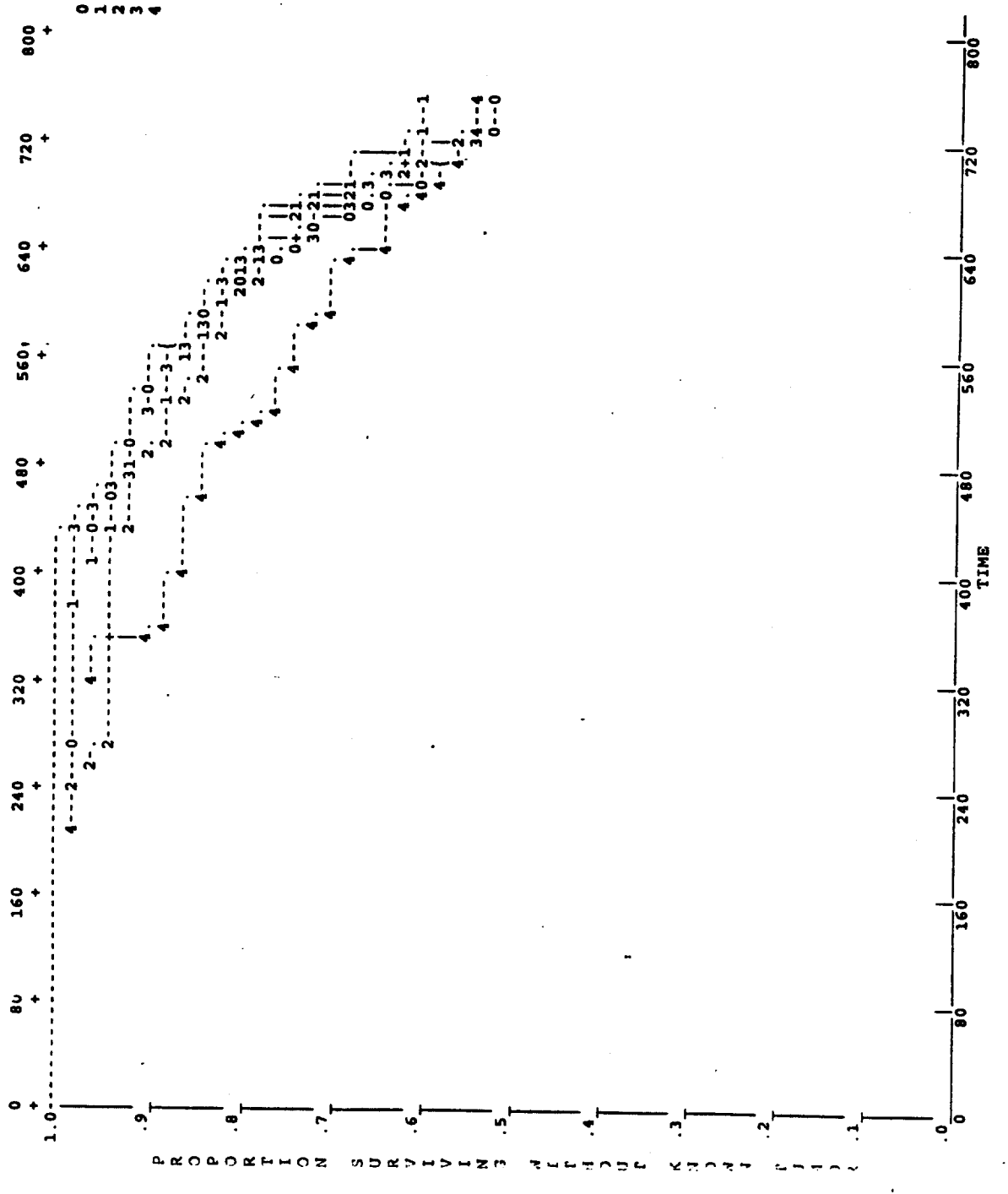

Table 4. Intercurrent mortality rates (study TCR/1624)

Male rats

Time (days)	0 mg/kg/d	20 mg/kg/d	75 mg/kg/d	250 mg/kg/d	Total
0-365	11* 11.00&	3 6.00	11 22.00	11 22.00	36
366-548	20 31.00	7 20.00	7 36.00	2 26.00	36
549-654	20 51.00	10 40.00	8 52.00	8 42.00	46
655-728	15 66.00	14 68.00	7 66.00	11 64.00	47
TERM. SAC.#	34 34.00	16 32.00	17 34.00	18 36.00	85
Total	100	50	50	50	250

Female Rats

Time (days)	0 mg/kg/d	20 mg/kg/d	75 mg/kg/d	250 mg/kg/d	Total
0-365	4* 4.00&	2 4.00	8 16.00	6 12.00	20
366-548	16 20.00	10 24.00	4 24.00	6 24.00	36
549-654	19 39.00	5 34.00	10 44.00	10 44.00	44
655-728	19 58.00	6 46.00	10 64.00	7 58.00	42
TERM. SAC.#	42 42.00	27 54.00	18 36.00	21 42.00	108
Total	100	50	50	50	250

* No. of animals dying or being sacrificed during the time interval
& Cumulative mortality rate
# The entry for Terminal sacrifice represents the number of animals surviving till the end of the study and the Cumulative survival rate

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Table 5. Tests for positive trend in tumor incidence (T '24 male rats)

Organ Name	Tumor Name	MSFLG	t P-Value	Asymptotic P-value	C	L	M	H
ABDOMINAL CAVITY	Malignant fibrohistiocytic sarcoma (M)	S	0.6276	0.70845	0	1	0	0
ADRENAL GLANDS	Benign pheochromocytoma (B)	S	0.3415	0.35075	7	3	8	4
ADRENAL GLANDS	Cortical adenoma (B)	S	0.5169	0.52840	5	4	3	3
ADRENAL GLANDS	Cortical carcinoma (M)	S	0.0429	0.00425	0	0	0	2
ADRENAL GLANDS	Malignant pheochromocytoma (M)	S	0.5024	0.54000	3	0	2	1
BONE AND MARROW - FEMUR	Lymphatic leukaemia (lymphoblastic) (M)	S	0.4255	0.41400	2	0	1	1
BONE AND MARROW - FEMUR	Osteosarcoma (M)	S	1.0000	0.75700	1	0	0	0
BONE AND MARROW - STERNUM	Lymphatic leukaemia (lymphoblastic) (M)	S	1.0000	0.83975	2	0	0	0
BRAIN	Benign astrocytoma (B)	S	0.8794	0.81925	2	1	0	0
BRAIN	Malignant astrocytoma (M)	S	0.4118	0.48635	0	0	1	0
BRAIN	Malignant oligodendroglioma (M)	S	0.2207	0.03525	0	0	0	1
CRANIAL CAVITY	Osteoma (B)	S	0.6140	0.69430	0	1	0	0
EPIDIDYMIDES	Mesothelioma (B)	S	0.6112	0.59935	0	0	1	0
HARDERIAN GLANDS	Adenocarcinoma (M)	S	0.2114	0.03165	0	0	0	1
INTESTINE - ILEUM	Adenocarcinoma (M)	S	1.0000	0.77150	1	0	0	0
INTESTINE - JEJUNUM	Malignant lymphoma (lymphoblastic) (M)	S	0.2340	0.03955	0	0	0	1
KIDNEYS	Clear cell carcinoma (M)	S	0.4118	0.48635	0	0	1	0
KIDNEYS	Lipoma (B)	S	1.0000	0.84490	2	0	0	0
LIMBS AND TAIL	Benign fibrous histiocytoma (B)	S	1.0000	0.77685	1	0	0	0
LIMBS AND TAIL	Keratoacanthoma (B)	S	0.4118	0.48635	0	0	1	0
LIMBS AND TAIL	Liposarcoma (M)	S	0.6809	0.71235	0	1	0	0
LIMBS AND TAIL	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.77405	1	0	0	0
LIVER	Cholangioma (B)	S	1.0000	0.77150	1	0	0	0
LIVER	Hepatocellular adenoma (B)	S	0.3663	0.36995	6	0	1	3
LUNGS	Adenoma (B)	S	1.0000	0.85500	2	0	0	0
LYMPH NODE - MANDIBULAR	Angioma (B)	S	0.6944	0.78360	0	1	0	0
LYMPH NODE - MESENTERIC	Angioma (B)	S	0.3047	0.31130	4	1	3	2
LYMPH NODES - NON-PROTOCOLLE	Angioma (B)	S	1.0000	0.74890	1	0	0	0
LYMPH NODES - NON-PROTOCOLLE	Malignant lymphoma (lymphoblastic) (M)	S	0.6083	0.70655	0	1	0	0
MAMMARY GLANDS	Fibroadenoma (B)	M	0.0512	0.04070	0	3	1	3
MAMMARY GLANDS	Fibroma (B)	M	0.7729	0.79785	2	0	1	0
MUSCLE - SKELETAL	Angioma (B)	S	0.7778	0.77050	1	1	0	0
NASAL CAVITY	Squamous carcinoma (M)	S	1.0000	0.76350	1	0	0	0
ORAL CAVITY	Ameloblastoma (M)	S	0.5901	0.69115	0	1	0	0
ORAL CAVITY	Osteosarcoma (M)	S	1.0000	0.77410	1	0	0	0
ORAL CAVITY	Squamous carcinoma (M)	M	0.4366	0.48510	1	2	1	1
PANCREAS	Exocrine adenocarcinoma (M)	S	0.5896	0.68430	0	1	0	0
PANCREAS	Exocrine adenoma (B)	S	0.8255	0.82260	5	3	4	1
PANCREAS	Islet cell adenoma (B)	S	0.5512	0.56150	3	4	5	2
PANCREAS	Islet cell carcinoma (M)	M	0.1951	0.19875	1	4	2	3
PARATHYROID GLANDS	Parathyroid adenoma (B)	S	0.4172	0.23865	1	0	0	1
PITUITARY GLAND	Adenoma (B)	M	0.0735	0.07120	32	23	13	24
PROSTATE GLAND	Adenocarcinoma (M)	S	0.4118	0.48635	0	0	1	0
PROSTATE GLAND	Adenoma (B)	S	0.7762	0.78605	2	0	1	0
SALIVARY GLANDS - PAROTID	Adenocarcinoma (M)	S	0.4180	0.50380	0	0	1	0
SALIVARY GLANDS - PAROTID	Malignant fibrohistiocytic sarcoma (M)	S	0.2118	0.03220	0	0	0	1
SALIVARY GLANDS - SUBMAXILLA	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.77690	1	0	0	0
SEMINAL VESICLES	Adenoma (B)	S	0.3865	0.34350	1	1	0	1
SKIN - NON-PROTOCOLLED	Angioma (B)	S	0.2118	0.03220	0	0	0	1
SKIN - NON-PROTOCOLLED	Angiosarcoma (M)	S	0.4194	0.49070	0	0	1	0
SKIN - NON-PROTOCOLLED	Fibroma (B)	M	0.9889	0.98270	15	6	3	2
SKIN - NON-PROTOCOLLED	Lipoma (B)	M	0.5878	0.61420	2	2	1	1
SKIN - NON-PROTOCOLLED	Malignant fibrohistiocytic sarcoma (M)	S	0.6177	0.70485	0	1	0	0
SKIN - NON-PROTOCOLLED	Squamous carcinoma (M)	M	0.4993	0.64100	0	1	1	0
SKIN - NON-PROTOCOLLED	Squamous papilloma (B)	S	0.8938	0.88120	2	4	3	0
SPLEEN	Angioma (B)	S	0.5652	0.67385	0	1	0	0
SPLEEN	Angiosarcoma (M)	S	1.0000	0.77370	1	0	0	0
SPLEEN	Monocytic leukaemia (M)	S	0.2295	0.03880	0	0	0	1
TESTES	Benign Leydig cell tumour (B)	S	1.0000	0.99100	10	1	0	0
TESTES	Mesothelioma (B)	S	0.6809	0.71235	0	1	0	0
THORACIC CAVITY	Malignant fibrohistiocytic sarcoma (M)	S	0.6299	0.70920	0	1	0	0
THYMUS	Benign mixed thymoma (B)	M	0.1327	0.12000	3	0	2	3
THYMUS	Malignant fibrohistiocytic sarcoma (M)	S	0.6000	0.70415	0	1	0	0
THYMUS	Malignant thymic lymphoma (lymphoblasti	S	0.1959	0.02620	0	0	0	1
THYROID GLAND	Adenoma (follicular) (B)	M	0.0000	0.00000	6	3	0	16
THYROID GLAND	Parafollicular adenoma (B)	S	0.9091	0.89760	6	3	0	1
VERTEBRAL COLUMN	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.75400	1	0	0	0

Table 6. Tests for positive trend in tumor incidence (TC female rats)

Organ Name	Tumor Name	MSFLG	Exact P-Value	Asymptotic P-value	C	L	M	H
ABDOMINAL CAVITY	Leiomyoma (B)	S	0.5477	0.68300	0	1	0	0
ADRENAL GLANDS	Benign pheochromocytoma (B)	S	0.9267	0.91645	5	4	5	0
ADRENAL GLANDS	Cortical adenoma (B)	S	0.8474	0.84815	5	4	2	1
ADRENAL GLANDS	Cortical carcinoma (M)	S	1.0000	0.76490	1	0	0	0
AORTA	Angioma (B)	S	1.0000	0.75925	1	0	0	0
BONE AND MARROW - FEMUR	Lymphatic leukaemia (lymphoblastic) (M)	S	0.5837	0.68745	0	1	0	0
BONE AND MARROW - FEMUR	Myeloid leukaemia (myelocytic) (M)	S	0.1938	0.02535	0	0	0	1
BRAIN	Malignant oligodendroglioma (M)	S	1.0000	0.75715	1	0	0	0
CERVIX	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.84560	2	0	0	0
INTESTINE - DUODENUM	Adenocarcinoma (M)	S	0.3758	0.46140	0	0	1	0
INTESTINE - JEJUNUM	Adenocarcinoma (M)	S	0.3773	0.46075	0	0	1	0
INTESTINE - JEJUNUM	Leiomyoma (B)	S	1.0000	0.75925	1	0	0	0
KIDNEYS	Lipoma (B)	S	0.3611	0.46230	0	0	1	0
LIVER	Cholangioma (B)	S	0.1944	0.02510	0	0	0	1
LIVER	Hepatocellular adenoma (B)	S	0.1623	0.15245	5	2	2	4
LUNGS	Adenocarcinoma (M)	S	1.0000	0.75925	1	0	0	0
LUNGS	Adenoma (B)	S	1.0000	0.75925	1	0	0	0
LUNGS	Lymphosarcoma (lymphoblastic) (M)	S	1.0000	0.76350	1	0	0	0
LYMPH NODE - MESENTERIC	Angioma (B)	S	0.1263	0.08985	0	0	1	1
LYMPH NODE - MESENTERIC	Angiosarcoma (M)	S	1.0000	0.75980	1	0	0	0
LYMPH NODE - MESENTERIC	Malignant lymphoma (lymphoblastic) (M)	S	0.3611	0.46230	0	0	1	0
MAMMARY GLANDS	Adenocarcinoma (M)	M	0.0021	0.00120	10	13	11	16
MAMMARY GLANDS	Adenoma (B)	S	0.1944	0.02510	0	0	0	1
MAMMARY GLANDS	Fibroadenoma (B)	M	0.9887	0.98730	53	30	25	16
MAMMARY GLANDS	Fibroma (B)	M	0.7262	0.73530	5	2	5	1
MAMMARY GLANDS	Fibrosarcoma (M)	S	0.3840	0.47170	0	0	1	0
MUSCLE - SKELETAL	Liposarcoma (M)	S	0.6111	0.68830	0	1	0	0
ORAL CAVITY	Squamous carcinoma (M)	M	0.9916	0.95710	5	2	0	0
OVARIES	Granulosa cell adenoma (B)	S	0.8724	0.84270	3	0	1	0
OVARIES	Sertoli cell tumour (B)	S	0.5681	0.71535	0	1	0	0
OVARIES	Sertoli cell tumour (M)	S	1.0000	0.75925	1	0	0	0
OVARIES	Stromal tumour (B)	S	0.6111	0.68830	0	1	0	0
PANCREAS	Exocrine adenoma (B)	S	1.0000	0.88900	3	0	0	0
PANCREAS	Islet cell adenoma (B)	S	0.9230	0.89885	4	1	1	0
PANCREAS	Islet cell carcinoma (M)	M	0.1669	0.17175	1	2	2	2
PITUITARY GLAND	Adenoma (B)	M	0.4670	0.46995	47	30	14	24
PITUITARY GLAND	Carcinoma (M)	M	0.6133	0.67460	1	1	2	0
SKIN - NON-PROTOCOLLED	Fibroma (B)	M	0.7742	0.77860	4	3	1	1
SKIN - NON-PROTOCOLLED	Lipoma (B)	M	0.7455	0.77570	2	0	1	0
SKIN - NON-PROTOCOLLED	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.84140	2	0	0	0
SKIN - NON-PROTOCOLLED	Squamous carcinoma (M)	M	0.6653	0.76055	0	2	0	0
SPLEEN	Angioma (B)	S	1.0000	0.75925	1	0	0	0
SPLEEN	Monocytic leukaemia (M)	M	1.0000	0.84090	2	0	0	0
THORACIC CAVITY	Malignant Schwannoma (M)	S	1.0000	0.75930	1	0	0	0
THYMUS	Benign mixed thymoma (B)	M	0.4141	0.42505	5	4	2	3
THYMUS	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.76355	1	0	0	0
THYMUS	Malignant thymic lymphoma (lymphocytic)	S	0.5939	0.66745	1	0	1	0
THYROID GLAND	Adenoma (follicular) (B)	S	0.1944	0.02510	0	0	0	1
THYROID GLAND	Parafollicular adenoma (B)	S	0.9796	0.96535	7	2	2	0
URINARY BLADDER	Transitional cell papilloma (B)	S	1.0000	0.75925	1	0	0	0
UTERUS	Adenocarcinoma (M)	S	1.0000	0.88015	3	0	0	0
UTERUS	Deciduoma (B)	S	0.3611	0.46230	0	0	1	0
UTERUS	Polyp (adenomatous) (B)	S	1.0000	0.75830	1	0	0	0
UTERUS	Polyp (stromal) (B)	M	0.9838	0.97675	21	2	1	3
VAGINA	Angioma (B)	S	1.0000	0.75830	1	0	0	0
VAGINA	Fibroma (B)	S	0.6675	0.73935	1	1	1	0
VAGINA	Malignant fibrohistiocytic sarcoma (M)	S	1.0000	0.76025	1	0	0	0

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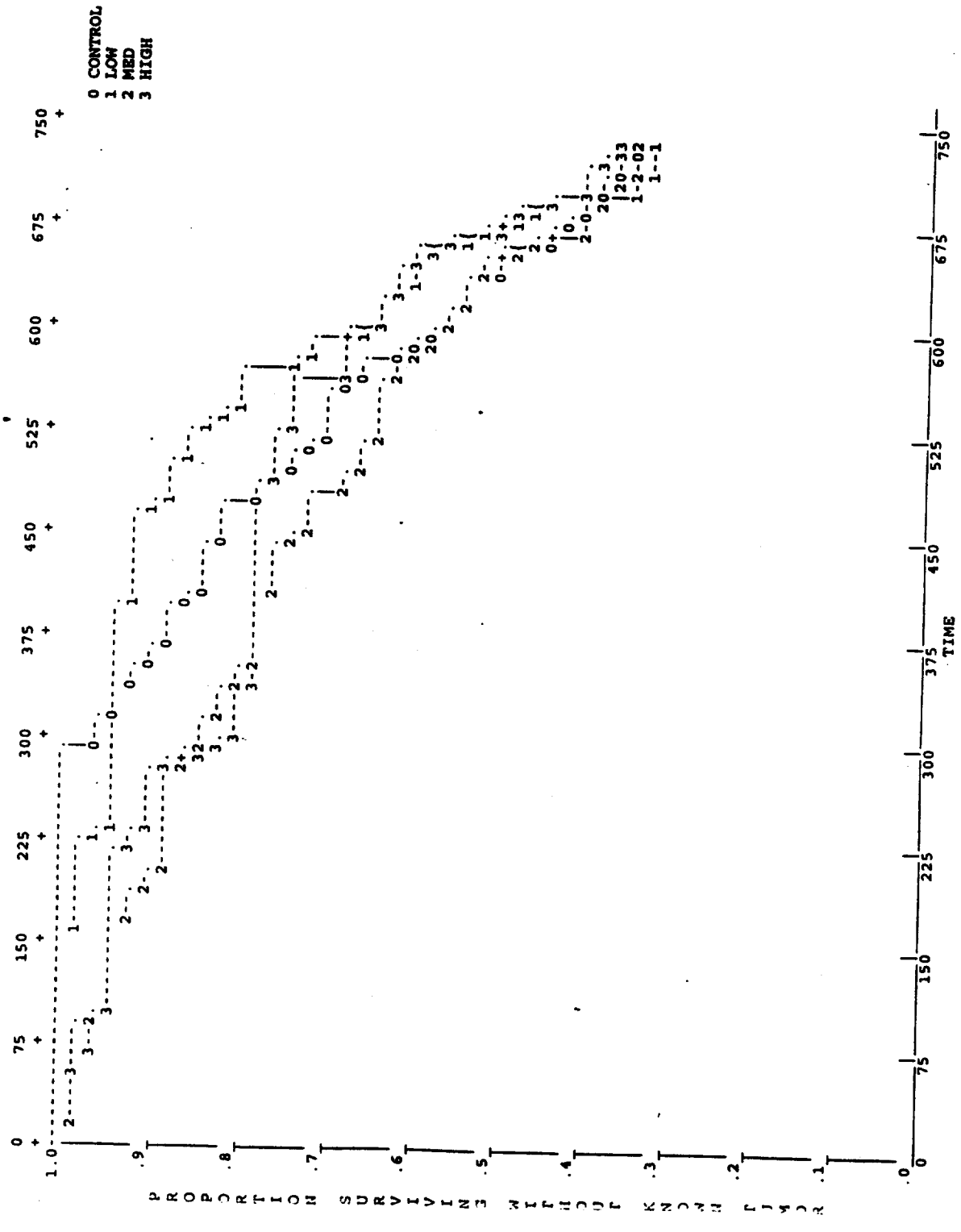
FIGURE 3. SURVIVAL CURVES OF MALE RATS (TCR



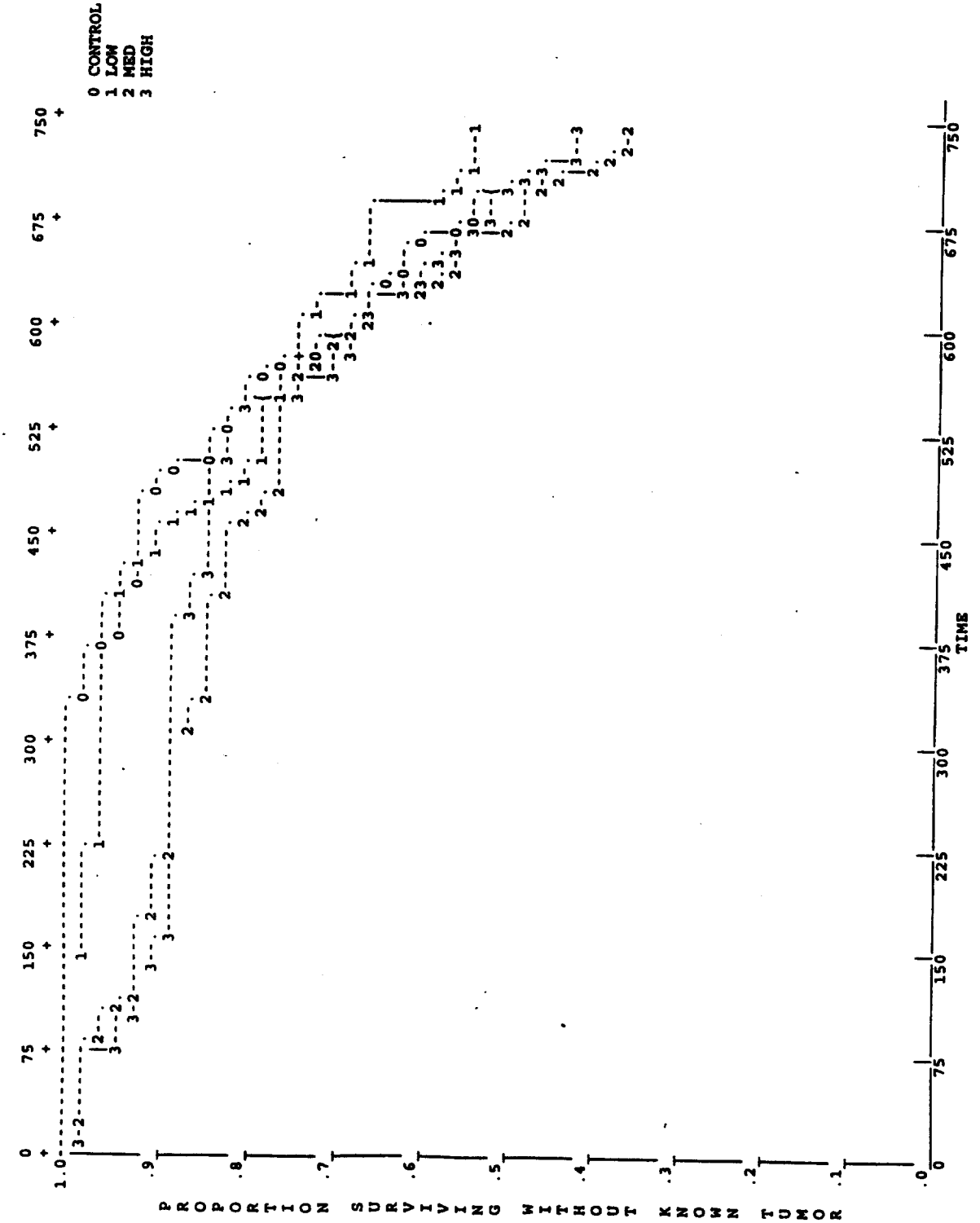


FIGURE 4. SURVIVAL CURVES OF FEMALE RATS (TCR