CENTER FOR DRUG EVALUATION AND RESEARCH

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STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-173 / N000
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Applicant:	Eli Lilly and Company
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Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	George Kordzakhia, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D; Kooros Mahjoob, Ph.D.
Medical Division:	Division of Psychiatry Products
Clinical Team:	Jing Zhang, M.D., Reviewer Gwen Zornberg, M.D., Team Leader
Project Manager:	Mr. Keith Kiedrow

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1 EXECUTIVE SUMMARY

1.1 CONCLUSIONS AND RECOMMENDATIONS

Study HGJZ

In the primary analysis of the PANSS Total score, patients on olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were observed to show statistically significant improvement over patients in the placebo treatment group.

Study HGKA

The 3 higher dose olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance effect compared with the low dose (45mg/ 4 weeks) for stabilized patients with schizophrenia.

1.2 BRIEF OVERVIEW OF CLINICAL STUDIES

The sponsor submitted results of two pivotal studies F1D-MC-HGJZ and F1D-MC-HGKA in support of efficacy of olanzapine pamoate depot.

In Study F1D-MC-HGJZ, a multicenter, randomized, double-blind, placebo-controlled study, olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) was compared with placebo in the treatment of patients with schizophrenia over an 8-week study period. A total of 466 patients entered Study Period I, 404 patients were enrolled, and 267 patients completed the study. The most common reasons for discontinuing the study were lack of efficacy and patient decision.

Study F1D-MC-HGKA was a large, randomized, double-blind study examining the maintenance of effect of olanzapine pamoate depot (OP Depot) compared to oral olanzapine and a low OP Depot dose group in the treatment of schizophrenia for up to 24 weeks. The study had two primary objectives: (1) to demonstrate that the OP Depot doses of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks were all superior to a low 45 mg/4 weeks dose in terms of time to exacerbation of symptoms of schizophrenia, and (2) to demonstrate that the 2-week dosing interval of OP Depot was non-inferior to daily oral olanzapine in terms of exacerbation rates at 24 weeks. Since Division of Psychiatry does not accept non-inferiority efficacy claims for labeling purposes in this indication, this reviewer will evaluate only the superiority objective.

Outpatients, age 18–70 and diagnosed with schizophrenia, were tapered off their previous antipsychotic medications and converted to open-label oral olanzapine within 4 weeks. Patients had to demonstrate clinical stability for 4 weeks on 10, 15, or 20 mg/day or oral olanzapine to be eligible for randomization to the double-blind maintenance period. A total of 1065 patients were randomized to one of 5 treatment groups in a 2:1:1:1:2 ratio: 405 mg/4 weeks OP Depot 300 mg/2 weeks OP Depot, 150 mg/2 weeks OP Depot, 45 mg/4 weeks OP Depot, or oral olanzapine. Patients randomized to oral olanzapine remained on the dose at which they had been stabilized previously.

1.3 STATISTICAL ISSUES AND FINDINGS

Study HGJZ

All three olanzapine pamoate depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001.

Study HGKA

Each of the higher olanzapine pamoate depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (nominal p-values from the log-rank test : <.001, <.001, and =.006, respectively).

In general, no statistical issues are identified in both studies.

2 INTRODUCTION

2.1 OVERVIEW

The sponsor submitted results of two pivotal studies in support of efficacy of olanzapine pamoate depot. Study F1D-MC-HGJZ had an 8 week double–blind active treatment period. Study F1D-MC-HGJZ was a maintenance study with double-blind maintenance phase up to 24 weeks.

2.2 DATA SOURCES

Data used for review are from the electronic submission received on April 30, 2007. The network path is \\Cdsesub1\NONECTD\N22173 in the EDR.

3 STATISTICAL EVALUATION

3.1 EVALUATION OF EFFICACY

3.1.1 STUDY F1D-MC-HGJZ (ACUTE PHASE)

3.1.1.1 Objective

The primary objective of Study HGJZ was to demonstrate superiority of olanzapine pamoate depot (OP depot) 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks dosages compared with placebo/2 weeks in change from baseline to endpoint in the Positive and Negative Syndrome Scale (PANSS) Total score in the treatment of patients with schizophrenia.

3.1.1.2 Study Design

Study HGJZ was a randomized, double-blind, parallel study that evaluated OP depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) versus placebo in the treatment of patients with schizophrenia. The study consisted of two study periods.

Study Period I was the washout period (see Table 1), with a duration of 2 to 7 days. Patients were inpatients and were expected to meet all the inclusion/ exclusion criteria and complete all examinations prior to entering Visit 2 (Period II). After the washout period, patients were randomized to one of four treatment injections every 2 weeks and entered an 8-week double-blind treatment period. Patients who were randomized to 405 mg/4weeks OP depot received a placebo injection at every other injection visit. During the first 2 weeks following randomization, patients were expected to be inpatients and were assessed daily. During the remainder of Study Period II (after Visit 16), visits occurred weekly.

Table 1. HGJZ Study Design

Study Period I	Study Period II	
Washout	Double-Blind Treatment	Continued Double-Blind Treatment
2-7 days	2 weeks Inpatient	6 weeks Inpatient/Outpatient
Visit 1	Visits 2-16	Visits 17-22

Source: Corresponds to Figure HGJZ.9.1, HGJZ Study Report

3.1.1.3 Patient Disposition, Demographic and Baseline Characteristics

The study was conducted at 42 study centers in three countries (United States, Croatia, and Russia). A total of 466 patients entered Study Period I, where 62 patients failed screening. The two primary reasons for screening failure were patient decision (n=29) and entry criteria not met (n=29). Table 2 presents a summary of patient disposition in HGJZ Study Period II. A total of 404 eligible patients were randomized in a 1:1:1:1 ratio to receive double-blind OP depot 300 mg/2 weeks, (n=100), OP depot 405 mg/4 weeks (n=100), OP depot 210 mg/2 weeks (n=106), or placebo (n=98) during Study Period II. A total of 267 (66%) patients completed the study.

Table 2. HGJZ Study Period II Patient Disposition

	Double-Blind Treatment			
Patients	**OPD 300mg/ 2 weeks**	**OPD 405 mg/ 4 weeks**	**OPD 210 mg/ 2 weeks**	**Placebo**
Randomized	100	100	106	98
Discontinued	33	28	34	42
Adverse Event	6	4	3	5
Lack of Efficacy	13	10	12	24
Patient Decision	9	12	15	9
Physician Decision	5	1	1	2
Sponsor Decision	0	1	0	0
Protocol Violation	0	0	1	1
Lost to Follow-up	0	0	2	1
Completed	67	72	72	56

Source: HGJZ Study Report, Figure HGJZ.10.1 (pg 67)

Table 3 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) and PANSS Total score at baseline for all randomized patients. Patients randomized were predominantly male (n=285, 70.5%) and Caucasian (n=226, 55.9%). The average age of enrolled patients was 40 years, with a range of 18 to 74 years. There were no statistically significant differences across all treatment groups with respect to these physical characteristics and baseline score.

Table 3. HGJZ Baseline Characteristics All Randomized Patients

Variable	**OPD300/2weeks** N=100	**OPD405/4weeks** N=100	**OPD210/2weeks** N=106	**Placebo** N=98	**Total** N=404
Gender					
Female	28 (28%)	27 (27%)	27 (25.5%)	37 (37.8%)	119 (29.5%)
Male	72 (72%)	73 (73%)	79 (74.5%)	61 (62.2%)	285 (70.5%)
Origin					
Caucasian	58 (58%)	54	61	53	226
African	38 (38%)	36	35	37	146
Hispanic	4 (4%)	6	9	3	22
Native American	0	1	0	1	2
East Asian	0	2	1	3	6
West Asian	0	1	0	1	2
Age (years)					
Mean(sd)	41.5 (11.1)	39.5 (11.4)	39.8 (10.8)	42.6 (11.2)	40.8 (11.16)
Median	42.35	39.8	41.92	44.23	41.88
Maximum	74.12	65.5	69.04	74.04	74.12
Minimum	18.82	19.7	18.71	18.20	18.20
Weight (kg)					
Mean (SD)	85.5 (20.8)	87.3 (22.1)	87.0 (21.5)	82.2 (19.1)	85.5 (20.9)
Median	82.70	83.70	86.95	79.20	82.70
Maximum	149.00	161.00	152.70	151.40	161.00
Minimum	50.00	42.20	51.60	51.10	42.20
PANSS Total Score at Baseline (ITT population)					
Number of patients	98	100	106	98	402
Mean (SD)	102.58 (15.58)	101.33 (14.41)	99.55 (15.77)	100.60 (16.67)	100.99 (15.61)
Min, Max	73.00, 144.00	74.00, 147.00	71.00, 163.00	73.00, 155.00	71.00, 163.00

Source: HGJZ Study Report, Table HGJZ.11.1 (pg 89)

3.1.1.4 Statistical Methodologies

The primary and secondary analyses were performed on an intent-to-treat (ITT) basis. For each efficacy variable, the analysis included all randomized patients with baseline and postbaseline observations. The primary efficacy variable was the PANSS Total score, and LOCF change from baseline to the endpoint visit in PANSS Total score was the primary efficacy measure. The primary comparisons of interest were the pairwise contrast of each OP depot treatment group versus placebo (300 mg/2 weeks versus placebo, 405 mg/4 weeks versus placebo, and 210 mg/2 weeks versus placebo). An ANOVA LOCF model was used to evaluate the efficacy of the doses and included the terms of treatment and investigator study site.

The sequential pairwise contrasts of each treatment group versus placebo were used in the following sequence: 1) 300 mg/2 weeks versus placebo; 2) 405 mg/4 weeks versus placebo; and 3) 210 mg/2 weeks versus placebo. The 405 mg/4 weeks versus placebo contrast was declared statistically significant only if both this comparison and the first comparison (300 mg/2 weeks versus placebo) were statistically significant. Similarly, the 210 mg/2 weeks versus placebo contrast was declared statistically significant only if all three comparisons were statistically significant. Because of a priori specification of the sequence, no further adjustments to the significance levels were necessary, and each contrast was compared at the significance level of 0.05.

3.1.1.5 Results of Efficacy Analysis

Primary Analysis

Efficacy analysis based on ANOVA model was performed for the 8-week double blind phase of the study. All randomized patients with baseline and at least one postbaseline observations (n=98, OP depot 300 mg/2 weeks; n=100, OP depot 405 mg/4 weeks; n=106, OP depot 210 mg/2 weeks; and n=98, placebo) were included in the primary efficacy analysis. Patients in OP depot treatment groups, 300 mg/2 weeks, 405 mg/4 weeks and 210mg/2 weeks showed statistically significant improvement over patients in the placebo treatment group after one-week of double-blind treatment. All three OP depot treatment groups were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score.

Table 4. PANSS Total Score LS Mean Change from Baseline to Endpoint, HGJZ Study Period II (ITT Population)

		Placebo	**OPD 300mg/ 2w**	**OPD 405 mg/4w**	**OPD 210 mg/2w**
No patients	N=402	98	98	100	106
Change from Baseline	Mean (SD)	-8.51 (23.03)	-26.32 (24.93)	-22.57 (22.15)	-22.49 (21.84)
Placebo-adjusted difference	LS mean (SE)	NA	-18.23 (2.82)	-14.43 (2.80)	-14.87 (2.76)
	95% CI	NA	(-23.78, -12.68)	(-19.93, -8.93)	(-20.29,-9.44)
	P-Value	NA	<0.0001	<0.0001	<0.0001

Source: Reviewer's results
Note: The reported p-values and 95% CI's are nominal and are not adjusted for multiplicity.

Table 5. PANSS Total Score LS Mean Change from Baseline by Visit, HGJZ Study Period II (ITT Population)

Visit (week)	**Placebo**	**OPD 300 mg/2w**	**OPD 405mg/4w**	**OPD 210mg/2w**
	Mean (SE)	Mean (SE); p-value vs. placebo	Mean (SE); p-value vs. placebo	Mean (SE); p-value vs. placebo
5 (week 0.43)	-4.61 (1.18)	-8.44 (1.16); 0.011	-7.94 (1.15); 0.025	-7.42 (1.10); 0.056
9 (week 1)	-8.03 (1.45)	-14.05 (1.44); 0.001	-12.48 (1.43); 0.016	-13.11 (1.37); 0.005
16 (week 2)	-8.70 (1.73)	-17.71 (1.72); <0.001	-15.10 (1.70); 0.003	-15.17 (1.63); 0.002
17 (week 3)	-7.62 (1.90)	-20.00 (1.89); <0.001	-16.39 (1.87); <0.001	-17.39 (1.79); <0.001
18 (week 4)	-5.97 (2.04)	-20.20 (2.01); <0.001	-17.57 (2.00); <0.001	-18.77 (1.92); <0.001
19 (week 5)	-6.48 (2.09)	-21.31 (2.06); <0.001	-19.64 (2.05); <0.001	-20.33 (1.96); <0.001
20 (week 6)	-6.37 (2.13)	-22.91 (2.11); <0.001	-20.45 (2.09); <0.001	-21.46 (2.01); <0.001
21 (week 7)	-6.35 (2.16)	-23.96 (2.14); <0.001	-21.02 (2.17); <0.001	-21.99 (2.03); <0.001
22 (week 8)	-5.87 (2.22)	-24.11 (2.19); <0.001	-20.30 (2.17); <0.001	-20.74 (2.09); <0.001

Source: Reviewer's results
Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

Sensitivity Analysis

This reviewer conducted sensitivity analysis on the primary endpoint. Change from baseline in PANSS Total score was analyzed by mixed effect repeated measures model. The model included treatment, investigator, visit, and interaction of treatment by visit as fixed effects, and baseline as a covariate. The unstructured variance-covariance matrix was used. In the analysis data set PANSS.xpt submitted by the sponsor, the patient with subject ID 5032 (investigator ID 47) has two identical PANSS Total score records for visit 17. The duplicate observation was excluded from the analysis. The findings support the primary analysis results.

Table 6. PANSS Total Score Change from Baseline Visitwise LS means, Mixed Effects Repeated Measures model (ITT Population).

Visit (week)	Study Treatment	Number of patients	LS Mean (SE)	p-value when compared with Placebo
5 (0.43)	Placebo	97	-4.59 (1.15)	
5 (0.43)	OPD 300 mg/ 2w	94	-8.55 (1.15)	0.008
5 (0.43)	OPD 405 mg/4w	98	-8.03 (1.13)	0.020
5 (0.43)	OPD 210 mg/2w	105	-7.63 (1.09)	0.036
9 (1)	Placebo	95	-8.78 (1.36)	
9 (1)	OPD 300 mg/2w	92	-15.26 (1.37)	<0.001
9 (1)	OPD 405 mg/4w	93	-13.99 (1.36)	0.004
9 (1)	OPD 210 mg/2w	100	-13.74 (1.30)	0.005
16 (2)	Placebo	86	-11.29 (1.73)	
16 (2)	OPD 300 mg/2w	90	-20.63 (1.72)	<0.001
16 (2)	OPD 405 mg/4w	88	-17.88 (1.72)	0.005
16 (2)	OPD 210 mg/2w	94	-17.10 (1.65)	0.012
17 (3)	Placebo	82	-11.05 (1.95)	
17 (3)	OPD 300 mg/2w	85	-23.72 (1.93)	<0.001
17 (3)	OPD 405 mg/4w	88	-20.22 (1.92)	<0.001
17 (3)	OPD 210 mg/2w	90	-20.28 (1.85)	<0.001
18 (4)	Placebo	74	-8.75 (2.17)	
18 (4)	OPD 300 mg/2w	81	-24.29 (2.12)	<0.001
18 (4)	OPD 405 mg/4w	81	-21.86 (2.12)	<0.001
18 (4)	OPD 210 mg/2w	83	-21.93 (2.06)	<0.001
19 (5)	Placebo	68	-9.19 (2.25)	
19 (5)	OPD 300 mg/2w	76	-25.69 (2.18)	<0.001
19 (5)	OPD 405 mg/4w	77	-24.27 (2.18)	<0.001
19 (5)	OPD 210 mg/2w	79	-23.83 (2.11)	<0.001
20 (6)	Placebo	62	-9.44 (2.31)	
20 (6)	OPD 300 mg/2w	69	-28.09 (2.25)	<0.001
20 (6)	OPD 405 mg/4w	77	-25.30 (2.22)	<0.001
20 (6)	OPD 210 mg/2w	75	-25.33 (2.17)	<0.001
21 (7)	Placebo	60	-9.60 (2.38)	
21 (7)	OPD 300 mg/2w	68	-29.58 (2.30)	<0.001
21 (7)	OPD 405 mg/4w	73	-26.28 (2.27)	<0.001
21 (7)	OPD 210 mg/2w	72	-26.46 (2.22)	<0.001
22 (8)	Placebo	56	-9.32 (2.52)	
22 (8)	OPD 300 mg/2w	67	-30.75 (2.41)	<0.001
22 (8)	OPD 405 mg/4w	71	-25.71 (2.38)	<0.001
22 (8)	OPD 210 mg/2w	72	-25.06 (2.33)	<0.001

Source: Reviewer's results

Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

3.1.1.6 Reviewer's Comments.

All three OP depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001.

3.1.2 STUDY HGKA (LONG-TERM)

3.1.2.1 Objective

The primary objectives were to determine comparative efficacy in patients with schizophrenia as follows:

1. 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks OP Depot versus 45 mg/4 weeks OP Depot.
2. Pooled 2-Week Olanzapine Pamoate (OP) Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) versus oral olanzapine (10, 15, and 20 mg)

For the OP Depot dose comparison, the primary objective was to demonstrate superior efficacy of 300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks as compared to 45 mg/4 weeks in terms of time to exacerbation of symptoms of schizophrenia. For the OP Depot versus oral olanzapine comparison, the primary objective was to demonstrate noninferior efficacy of Pooled 2-Week OP Depot (300 mg/2 weeks pooled with 150 mg/2 weeks) as compared with 10, 15, and 20 mg oral olanzapine in terms of exacerbation rates after 24 weeks of maintenance treatment. Since Dvision of Psychiatry Products does not accept non-inferiority efficacy claims for labeling purposes in this indication, this reviewer will evaluate only the superiority objective.

3.1.2.2 Study Design

This was a multicenter, randomized, double-blind, parallel study that compared the safety and efficacy of Olanzapine Pamoate (OP) Depot with oral olanzapine, as well as with 45 mg/4 weeks OP Depot, in patients meeting Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revised) (DSM-IV [DSM-IV-TR]) criteria for schizophrenia. Patients eligible to enroll in the study were clinically stable on antipsychotic medication. The study was conducted by 113 investigators at 112 study centers in 26 countries. A total of 1065 patients 18-71 years of age were randomized in a 2:1:1:1:2 ratio, into 1 of 5 treatment groups: 405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively.

Study Period I was a 2- to 9-day lead-in screening period. Patients receiving oral antipsychotic medication (other than clozapine) continued treatment, whereas patients receiving treatment with an injectable antipsychotic received the last injection at least 2 weeks (or 1-injection interval, whichever was longer) prior to Visit 2. Patients taking risperidone long-acting injections received their last injection at least 4 weeks prior to Visit 2.

Study Period II was a conversion and stabilization period during which patients were discontinued from their current antipsychotic medication (unless it was olanzapine) and converted to oral olanzapine monotherapy (at 10, 15, or 20 mg/day). All patients began the conversion to oral olanzapine monotherapy after enrollment (Visit 2). To enter Study Period III, patients had to demonstrate stability for 4 weeks (5 consecutive visits) during Study Period II by meeting the following stabilization criteria:

- No dose change of oral olanzapine monotherapy (fixed at 10, 15, or 20 mg/day)

- CGI-I score equal to 1, 2, 3, or 4 (when compared with Visit 1 CGI-S score)
- BPRS Positive score <=4 on each of the following items: conceptual disorganization, suspiciousness, hallucinatory behavior, and unusual thought content.

The length of time a patient remained in Study Period II was dependent on the patient's time of conversion from their existing antipsychotic therapy and how quickly stabilization criteria were met. The maximum length of Study Period II was 8 weeks and included Visit 2 up to Visit 10. In cases where stabilization criteria were met before the 8-week maximum length of Study Period II, the patient skipped to Visit 10 (in Study Period III).

Study Period III was a 24-week maintenance period consisting of double-blind treatment with either oral olanzapine or OP Depot. Patients were assessed weekly from Visit 10 to Visit 22, and then every other week from Visit 22 to Visit 28. Inspections of the injection area (left and right buttocks) were performed at Visit 10, and abnormalities were noted as preexisting conditions. Patients were randomized to 1 of 5 treatment groups in a 2:1:1:1:2 ratio (405 mg/4 weeks, 300 mg/2 weeks, 150 mg/2 weeks, 45 mg/4 weeks OP Depot, or oral olanzapine, respectively). To maintain the blind, patients who were randomized to the 4-week OP Depot treatment groups also received injections of placebo every 4 weeks (alternating every 2 weeks with the OP Depot injection) and placebo oral study drug daily. Patients randomized to the 2-week OP Depot treatment groups received OP Depot injections every 2 weeks and placebo oral study drug daily. Patients randomized to the oral olanzapine arm received injections of placebo every 2 weeks. Patients randomized to oral olanzapine received the same olanzapine dose that they were stabilized on during Study Period II. Patients remained on a fixed dose of injectable and oral study drug throughout Study Period III. During Study Period III (Visit 11 to Visit 28), CGI-I scores were obtained by comparing them with the Visit 10 CGI-S score.

Study Period IV was an up-to 24-week open-label restabilization period for patients who were discontinued from double-blind therapy (Study Period III) due to exacerbation of symptoms associated with schizophrenia. The purpose of the restabilization period was to ensure that patients who suffered an exacerbation were restabilized before ending study participation.

3.1.2.3 Patient Disposition, Demographic and Baseline Characteristic

The study was conducted by 113 investigators at 112 study centers in 26 countries. Of the 1315 patients screened, 1205 patients entered the Conversion/ Stabilization Phase. The two most common reasons for screening failure prior to the Conversion/ Stabilization Phase (Study Period II) were entry criteria not met (n=50) and patient decision (n=34). The most common reason for patient discontinuation during the Conversion/Stabilization Phase (Study Period II) was patient decision (n=53). Table 7 presents a summary of patient disposition following randomization into the Double-Blind Maintenance Phase (Study Period III) of Study HGKA. Of the 1205 patients entering the Conversion/Stabilization Phase, 1065 eligible patients were randomized in a 2:1:1:1:2 ratio to receive double-blind OP Depot (405 mg/4 weeks [n=318], 300 mg/2 weeks [n=141], 150 mg/2 weeks [n=140], 45 mg/4 weeks [n=144]) or oral olanzapine (n=322), respectively, during the Double-Blind Maintenance Phase (Study Period III). A total 753 of the 1065 eligible patients (70.7%) completed Study HGKA.

Table 7. HGKA Patient Disposition from Randomization (Study Period III)

	Double-Blind Maintenance Phase				
	Total Number of Randomized patients N=1065				
Patients	**OP Depot 405 mg/ 4 weeks**	**OP Depot 300 mg/ 2 weeks**	**OP Depot 150 mg/ 2 weeks**	**OP Depot 45 mg/ 4 weeks**	**Oral Olanzapine 10, 15, or 20 mg/ day**
Randomized, N=	318	141	140	144	322
Discontinued, N=	96	34	50	68	64
Lost to Follow up	5	2	3	2	2
Adverse Event	10	4	7	6	8
Lack of Efficacy	2	2	4	2	4
Protocol Violation	5	4	3	1	3
Physical Decision	8	3	2	3	4
Patient Decision	27	12	9	10	20
Sponsor Decision	0	0	0	2	0
Patients Entering Open-Label Re-stabilization phase	39	7	22	42	23
Completers, N=	222	107	90	76	258

Source: Figure HGKA.10.2, HGKA Study Report (pg. 98)

Table 8 summarizes baseline physical characteristics (gender, ethnic origin, age, BMI, and weight) for all randomized patients. The patient population was predominantly male (65.4%) and Caucasian (71.8%), and included patients aged 18 to 71 years with a mean age of 39 years at baseline. There were no statistically significant differences across treatment groups with respect to baseline physical characteristics. The observed Extracted Brief Psychiatric Rating Scale (BPRS) Total and Positive Subscale mean scores at baseline for the 45mg/4 weeks OP Depot group appeared to be higher compared with other treatment groups. This difference was considered not clinically meaningful by the sponsor.

Table 8. HGKA Baseline Physical Characteristics for all Randomized Patients (Study Period III)

Variable	OPD150/2w (N=140)	OPD300/2w (N=141)	OPD405/4w (N=318)	OPD45/2w (N=144)	OLZ (N=322)	Total (N=1065)
Gender						
Female	56 (40%)	46 (32.6%)	106 (33.3%)	48 (33.3%)	113 (35.1%)	369 (34.6%)
Male	84 (60%)	95 (67.4%)	212 (66.7%)	96 (66.7%)	209 (64.9%)	696 (65.4%)
Origin						
Caucasian	96	99	230	106	234	765
African	8	7	12	5	13	45
Hispanic	26	25	51	21	53	176
Native American	0	0	0	1	0	1
East Asian	8	9	20	8	15	60
West Asian	2	1	5	3	7	18
Age (years)						
Mean (SD)	37.7 (10.5)	39.5 (11.2)	39.0 (11.3)	39.5 (11.6)	39.0 (11.6)	39.0 (11.3)
Median	36.75	39.24	37.99	39.07	38.94	38.39
Maximum	64.63	68.85	70.77	66.19	69.61	70.77
Minimum	18.29	20.61	18.12	18.10	18.92	18.10
Weight (kg)						
Mean (SD)	78.4 (16.5)	75.3 (15.6)	77.9 (15.7)	78.4 (17.3)	77.0 (16.0)	77.4 (16.1)
Median	76.00	73.50	76.75	79.45	75.60	76.00
Maximum	126.80	144.20	124.80	143.00	123.00	144.20
Minimum	47.60	36.90	39.00	43.00	43.50	36.90
Extracted BPRS Total Score						
Mean (SD)	11.54 (7.85)	12.99 (9.10)	12.14 (7.80)	13.42 (8.13)	12.46 (8.19)	12.44 (8.15)
Median	10.00	11.00	11.00	13.00	11.50	12.00
Min, Max	0.00, 33.00	0.00, 33.00	0.00, 39.00	0.00, 33.00	0.00, 40.00	0.00, 40.00
Extracted BPRS Positive Score						
Mean (SD)	3.18 (2.39)	3.17 (2.76)	3.22 (2.57)	3.65 (2.69)	3.33 (2.60)	3.30 (2.60)
Median	3.00	2.50	3.00	3.50	3.00	3.00
Min, Max	0.00, 11.00	0.00, 10.00	0.00, 12.00	0.00, 11.00	0.00, 12.00	0.00, 12.00

Source: Table HGKA.11.5, HGKA Study Report (pg. 143); Summary of the Extracted BPRS Total and Extracted BPRS Positive scores at Baseline are the Reviewer's Results.

3.1.2.4 Statistical Methodologies and Endpoints

Primary and secondary analyses were performed on an intent-to-treat (ITT) basis. An ITT analysis is an analysis of data by the treatment groups to which patients were assigned by random allocation, even if the patient did not take the assigned treatment, did not receive the correct treatment, or otherwise did not follow the protocol. To be included in an efficacy analysis, patients had to have both a baseline and a post-baseline observation.

Time to exacerbation of symptoms of schizophrenia was the primary efficacy endpoint. In general, exacerbation is a worsening in particular items of the BPRS or hospitalization for positive psychotic symptom psychopathology. For this study, exacerbation of symptoms of schizophrenia was defined as follows:

- An increase on any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of >=2 on that specific item since randomization at Visit 10, or
- An increase of any of the BPRS Positive items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score >4 and an absolute increase of >=4 on the BPRS Positive subscale (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization at Visit 10, or
- Hospitalization due to worsening of positive psychotic symptoms.

The primary superiority comparison of interest involved comparing time to exacerbation of the higher dose OP Depot arms (405 mg/4 weeks, 300 mg/2 weeks, and 150 mg/2 weeks) individually versus the time to exacerbation of the low-dose OP Depot arm (45 mg/4 weeks). The log-rank test was used to assess the pairwise comparisons of time to exacerbation of symptoms.

To control the overall Type I error, pairwise tests were conducted sequentially in the following OP Depot dose order: 1) 300 mg/2 weeks versus 45 mg/4 weeks; 2) 405 mg/4 weeks versus 45 mg/4 weeks; and 3) 150 mg/2 weeks versus 45 mg/4 weeks. Thus, the 405 mg/4 weeks versus 45 mg/4 weeks OP Depot comparison were declared statistically significant only if both this comparison and the first comparison (300 mg/2 weeks versus 45 mg/4 weeks) were statistically significant. The 150 mg/2 weeks versus 45 mg/4 weeks OP Depot were declared statistically significant only if all 3 comparisons were statistically significant.

3.1.2.5 Results of Efficacy Analysis

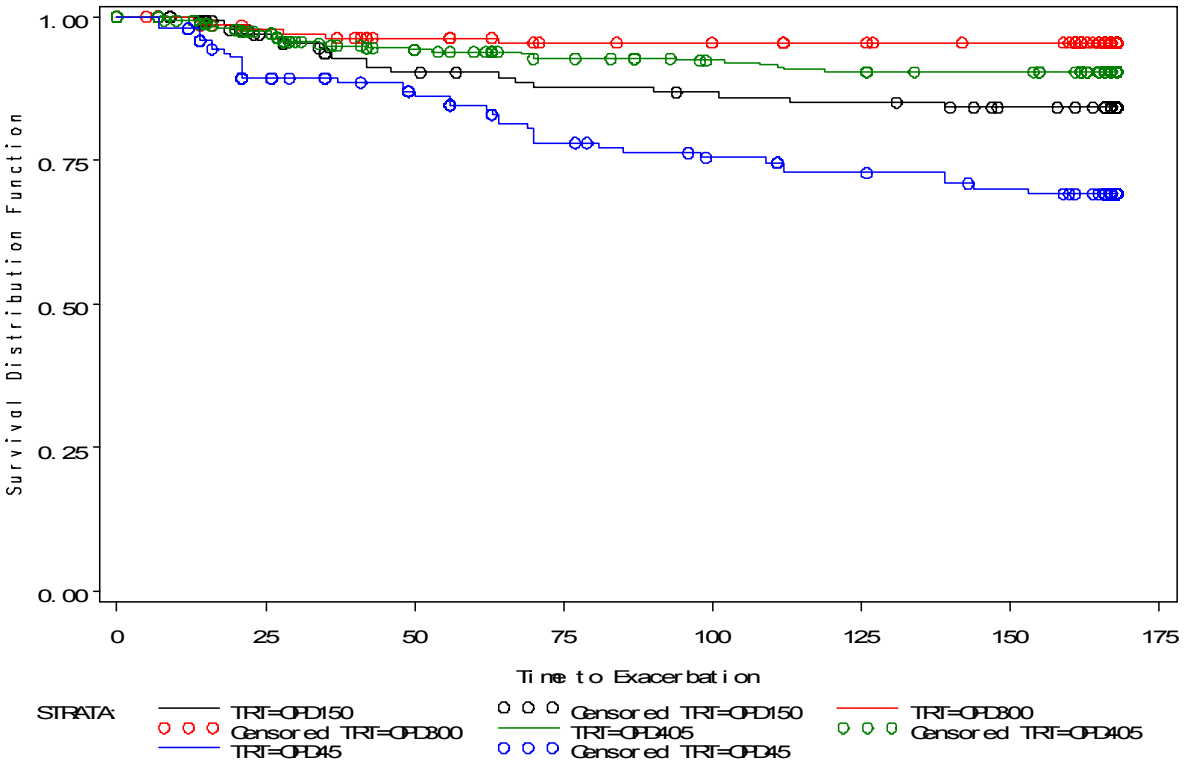
All 1065 randomized patients were included in the primary efficacy analyses. As a primary analysis, the log-rank test was used to assess the pairwise comparisons of time to exacerbation of symptoms. Each of the higher OP Depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (nominal p-values: <.001, <.001, and =.006, respectively).

Table 9. Log-rank Test of Time to Exacerbation. OPD150, OPD300, OPD405 vs OPD45.

P-values from Log-Rank Test		
OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
<0.001	<0.001	0.006

Source: Figure HGKA.11.2. , HGKA Study Report (pg .200)
Note: The reported p-values are nominal p-values and are not adjusted for multiplicity.

Figure 1. Kaplan-Meier curves of Time to Exacerbation for the double-blind maintenance phase (curves from top to bottom: OPD300mg/2weeks, OPD405mg/4weeks. OPD150mg/2weeks, OPD45mg/4weeks).



[Source: Reviewer's results]

Table 10. HGKA Summary of the Patients who had Exacerbation and Censored Patients

	OPD300mg/2w	OPD405mg/4w	OPD150mg/2w	OPD45mg/4w
Total number of patients	141 (100%)	318 (100%)	140 (100%)	144 (100%)
Patients who had exacerbation	6 (4.3%)	27 (8.5%)	19 (13.6%)	39 (27.1%)
Patients who were censored	135 (95.7%)	291 (91.5%)	121 (86.4%)	105 (72.9%)

Source: Reviewer's Results

To explore the treatment effect, this reviewer used a Cox proportional hazard model with treatment effect to estimate the hazard ratio (OPD 300 vs OPD45, OPD405 vs OPD45 and OPD150 vs OPD45) and corresponding 95% confidence intervals. The Cox-proportional hazard analysis supported the results of the primary analysis.

Table 11. Exploratory Analysis: Cox-proportional Hazard Analysis of Time to Exacerbation

	OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
Hazard Ratio (HR)	0.137	0.286	0.474
95% CI for HR	(0.058, 0.323)	(0.175, 0.468)	(0.274, 0.821)

Source: Reviewer's results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Recall that exacerbation of symptoms of schizophrenia was defined mainly in terms of Extracted Brief Psychiatric Rating Scale (BPRS) Positive Subscale score. Since the 45mg /4 weeks OP Depot group had the highest observed mean score on Extracted BPRS Positive subscale at baseline, this reviewer explored the impact of the baseline BPRS Positive subscale score on the primary analysis results by considering Cox proportional hazard model with treatment effect and BPRS Positive baseline score as a covariate. The baseline score appeared to be a significant predictor of time to exacerbation (parameter estimate 0.105, p-value 0.007). The results generally still support the superiority of higher doses to the low dose of 45mg/4weeks.

Table 12. Exploratory analysis: Cox-proportional Hazard Analysis of Time to Exacerbation with BPRS Positive Subscale Baseline Score as a Covariate

	OPD300 vs OPD45	OPD405 vs OPD45	OPD150 vs OPD45
Hazard Ratio (HR)	0.143	0.296	0.496
95% CI for HR	(0.060, 0.337)	(0.181, 0.484)	(0.286, 0.859)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

3.1.2.6 Reviewer's Comments

Superiority of the three higher OP Depot dose groups (300mg/2 weeks, 405mg/4 weeks, and 150 mg/2 weeks) was demonstrated in comparison to a low OP Depot dose group (45 mg/4 weeks) with respect to time to exacerbation. Each of the higher OP Depot doses was statistically superior to the 45 mg/4-weeks dose (nominal p-values from the log-rank test: <.001, <.001, and =.006, respectively).

3.2 EVALUATION OF SAFETY

Not evaluated by this reviewer. Please refer to clinical review of this application for a detailed safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 GENDER, RACE AND AGE

4.1.1 STUDY HGJZ

This reviewer conducted exploratory subgroup analysis on the primary efficacy variable, PANSS Total score, using ANOVA models, including the terms for treatment and investigator study site. The subgroups of interest included age (dichotomized by age greater than or equal to 40 versus others), gender and origin (dichotomized by Caucasian versus others). For all OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 210 mg/2 weeks), the treatment effect appeared to be numerically in favor of olanzapine (when compared with placebo) among all subgroups.

Table 13. Subgroup Analysis by Age: PANSS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
Younger than 40 years					
No patients	179	37	43	51	48
Change from Baseline	Mean (SD)	-7.65 (19.29)	-23.63 (22.00)	-21.78 (21.27)	-23.56 (20.89)
Placebo-adjusted difference	LS mean	NA	-14.96 (4.43)	-12.92 (4.19)	-15.68 (4.45)
	95% CI	NA	(-23.73, -6.19)	(-21.19, -4.64)	(-24.47, -6.89)
40 years or older					
No patients	223	61	55	49	58
Change from Baseline	Mean (SD)	-9.03 (25.17)	-28.42 (27.01)	-23.39 (23.22)	-21.60 (22.73)
Placebo adjusted difference	LS mean	NA	-21.30 (4.13)	-14.96 (4.25)	-14.30 (4.11)
	95% CI	NA	(-29.45, -13.15)	(-22.40, -6.20)	(-23.34, -6.58)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 14. Subgroup Analysis by Gender: PANSS Total Score Mean Change from Baseline to Endpoint (ITT Population)

		Placebo	OPD 300mg/2w	OPD 405 mg /4w	OPD 210 mg/2w
Males					
No patients	283	61	70	73	79
Change from Baseline	Mean (SD)	-7.44 (22.18)	-28.47 (25.24)	-21.62 (21.04)	-21.54 (19.07)
Placebo-adjusted difference	LS mean	NA	-20.27 (3.27)	-13.06 (3.21)	-14.96 (3.19)
	95% CI	NA	(-26.72, -13.83)	(-19.39,-6.74)	(-21.24, -8.68)
Females					
No patients	119	37	28	27	27
Change from Baseline	Mean (SD)	-10.27(24.57)	-20.93 (23.72)	-25.15 (25.14)	-25.26 (28.71)
Placebo adjusted difference	LS mean	NA	-12.02 (6.88)	-15.38 (6.81)	-12.11 (7.12)
	95% CI	NA	(-25.69, 1.65)	(-28.91, -1.85)	(-26.26, 2.05)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 15. Subgroup Analysis by Origin: PANSS Total Score Mean Change from Baseline to Endpoint (ITT Population)

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
Caucasian					
No patients	225	53	57	54	61
Change fr. Baseline	Mean (SD)	-4.30 (23.25)	-25.37 (24.43)	-24.07 (22.47)	-22.80 (23.59)
Placebo-adjusted difference	LS mean	NA	-22.56 (4.02)	-20.78 (4.07)	-20.05 (3.98)
	95% CI	NA	(-30.49, -14.63)	(-28.80, 12.75)	(-27.90, -12.20)
Other					
No patients	177	45	41	46	45
Change fr. Baseline	Mean (SD)	-13.47(21.99)	-27.63 (25.86)	-20.80 (21.87)	-22.07 (19.46)
Placebo adjusted difference	LS mean	NA	-11.81 (4.23)	-6.57 (4.04)	-9.26 (4.14)
	95% CI	NA	(-20.17, -3.44)	(-14.56, 1.43)	(-17.44, -1.09)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.1.2 STUDY HGKA

The reviewer conducted the exploratory Cox-proportional hazard analysis of time to exacerbation for age, gender and origin subgroups. Among all the subgroups, the treatment effect appeared to be numerically in favor of high dose OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks) when compared with OPD 45 mg/ 2 weeks.

Table 16. Subgroup Analysis by Age: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Younger than 40year			
Hazard Ratio (HR)	0.159	0.321	0.556
95% CI for HR	(0.047, 0.539)	(0.159, 0.645)	(0.268, 1.154)
Older than 40 years			
Hazard Ratio (HR)	0.119	0.261	0.412
95% CI for HR	(0.035, 0.398)	(0.131, 0.521)	(0.175, 0.970)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 17. Subgroup Analysis by Gender: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Male			
Hazard Ratio (HR)	0.158	0.219	0.514
95% CI for HR	(0.061,0.412)	(0.116, 0.411)	(0.265, 0.995)
Female			
Hazard Ratio (HR)	0.081	0.461	0.426
95% CI for HR	(0.010, 0.621)	(0.207, 1.027)	(0.160, 1.137)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

Table 18. Subgroup Analysis by Origin: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD 300 vs OPD 45	OPD 405 vs OPD 45	OPD 150 vs OPD 45
Caucasian			
Hazard Ratio (HR)	0.144	0.243	0.426
95% CI for HR	(0.056, 0.368)	(0.138, 0.428)	(0.224, 0.810)
Other			
Hazard Ratio (HR)	0.129	0.529	0.777
95% CI for HR	(0.015, 1.070)	(0.184, 1.527)	(0.250, 2.412)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2 OTHER SPECIAL/SUBGROUP POPULATIONS

This reviewer conducted exploratory subgroup analysis of efficacy by region for both studies.

4.2.1 STUDY HGJZ

For all OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 210 mg/2 weeks), the treatment effect appeared to be numerically in favor of olanzapine (when compared with placebo) within both subgroups.

Table 19. Subgroup Analysis by Region: PANSS Total Score Mean Change from Baseline to Endpoint (ITT population).

		Placebo	OPD 300 mg/2w	OPD 405 mg/4w	OPD 210 mg/2w
US					
No patients	313	76	77	78	82
Change from Baseline	Mean (SD)	-9.62 (23.69)	-27.00 (26.65)	-21.85 (22.61)	-21.93 (20.74)
Placebo-adjusted difference	LS mean	NA	-17.95 (3.10)	-12.67 (3.07)	-13.43 (3.04)
	95% CI	NA	(-24.06, -11.85)	(-18.72, -6.62)	(-19.42, -7.44)
Eastern Europe (Russia and Croatia)					
No patients	89	22	21	22	24
Change from Baseline	Mean (SD)	-4.68 (20.61)	-23.81 (17.53)	-25.14 (20.70)	-24.42 (25.62)
Placebo adjusted difference	LS mean	NA	-19.10 (6.63)	-20.56 (6.56)	-19.76 (6.42)
	95% CI	NA	(-32.30, -5.90)	(-33.61, -7.51)	(-32.53, -6.99)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity.

4.2.2 STUDY HGKA

Based on the exploratory Cox-proportional hazard analysis of time to exacerbation by region, the treatment effect appeared to be numerically in favor of high dose OP depot treatment arms (300 mg/2 weeks, 405 mg/4 weeks and 150 mg/2 weeks) when compared with OPD 45 mg/ 2 weeks.

Table 20. Summary of the Patients who had Exacerbation by Region.

	OPD 300mg / 2 weeks	**OPD 405mg/ 4 weeks**	**OPD 150mg/ 2 weeks**	**OPD 45mg/ 4 weeks**
Eastern Europe				
Total number of Patients	24	62	28	27
Patients who had exacerbation	2	2	5	10
Western Europe				
Total number of Patients	47	101	41	44
Patients who had exacerbation	2	11	5	13
South and North America				
Total number of Patients	39	80	36	40
Patients who had exacerbation	1	4	2	6
Other				
Total number of Patients	31	75	35	33
Patients who had exacerbation	1	10	7	10

Source: Reviewer's Results

Table 21. Subgroup Analysis by Region: Cox-proportional Hazard Analysis of Time to Exacerbation.

	OPD300 vs OPD45	**OPD405 vs OPD45**	**OPD150 vs OPD45**
Eastern Europe			
Hazard Ratio (HR)	0.192	0.079	0.446
95% CI for HR	(0.042, 0.877)	(0.017, 0.359)	(0.152, 1.305)
Western Europe			
Hazard Ratio (HR)	0.127	0.332	0.398
95% CI for HR	(0.029, 0.563)	(0.149, 0.742)	(0.142, 1.118)
South and North America			
Hazard Ratio (HR)	0.155	0.308	0.345
95% CI for HR	(0.019, 1.286)	(0.087, 1.093)	(0.070, 1.709)
Other			
Hazard Ratio (HR)	0.083	0.388	0.609
95% CI for HR	(0.011, 0.650)	(0.162, 0.934)	(0.232, 1.601)

Source: Reviewer's Results
Note: The reported 95% CI's are nominal CI's and are not adjusted for multiplicity

5 SUMMARY AND CONCLUSIONS

5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE

Study HGJZ

All three olanzapine pamoate depot treatment groups (OP depot 300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were statistically superior to placebo in mean change from baseline to the endpoint visit in PANSS Total score. The nominal p-values of pairwise comparisons with placebo obtained from ANOVA model with treatment and investigator effects were all < 0.001.

Study HGKA

Each of the higher olanzapine pamoate depot doses (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) was statistically superior to the 45 mg/4-weeks dose with respect to time to exacerbation of symptoms (p-values from the log-rank test : <.001, <.001, and =.006, respectively).

In general, no statistical issues are identified in both studies.

5.2 CONCLUSIONS AND RECOMMENDATIONS

Study HGJZ

In the primary analysis of the PANSS Total score, patients on olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 210 mg/2 weeks) were observed to show statistically significant improvement over patients in the placebo treatment group.

Study HGKA

The 3 higher dose olanzapine pamoate depot (300 mg/2 weeks, 405 mg/4 weeks, and 150 mg/2 weeks) treatment groups showed positive maintenance effect compared with the low dose (45mg/ 4 weeks) for stabilized patients with schizophrenia.

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/s/

George Kordzakhia
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Peiling Yang
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Kooros Mahjoob
12/18/2007 05:30:48 PM
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoepidemiology and Statistical Science
Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDIES

IND/NDA Number:	NDA 22-173
Drug Name:	Zyprexa, (Olanzapine)
Indication(s):	104 Week Carcinogenicity in Rats
Applicant:	Eli Lilly and Company
	2001 West Main Street, Greenfield, IN 46140
Documents Reviewed:	Electronic submission, Dated May 24, 2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Mohammad Atiar Rahman, Ph.D.
Concurring Reviewer:	Karl Lin, Ph.D.
Medical Division:	Division of Psychiatry products
Reviewing Pharmacologist:	Sonia Tabacova, Ph.D.
Project Manager:	Keith J. Kiedrow
Keywords:	Carcinogenicity, Dose-Response

Table of Contents

1. Background

In this submission the sponsor included report of an animal carcinogenicity study in rats. This study was intended to assess the carcinogenic potential of Zyprexa in rats when administered once a month through intramuscular injection for about 104 weeks. It should be noted that the common regulatory requirement for carcinogenicity experiment is to include studies in two species, one in rats and one in mice. In the present form of this drug, Zyprexa is an extended release formulation of the previous regular Zyprexa. During the submission of regular Zyprexa a two species study was conducted and was reviewed by the agency. Hence, in a pre-submission meeting it was agreed that a carcinogenicity study only in the rat will suffice the requirement for this extended release formulation (Dr. Lois Fried's review of 3/26/03, page 14). Results of this review have been discussed with the reviewing pharmacologist Dr. Tabacova.

2. Design

Two separate experiments, one in males and one in females were conducted. In each of these two experiments there were three treated groups (Groups 3. 4, and 5), and one untreated control group (Group1). In this review these groups will referred to as low, medium, high and control groups. Two hundred and forty Fischer 344 rats of each sex were randomly allocated to the treated and control groups in equal size of 60 animals. The dose levels for treated males were 5, 10, and 20 mg/kg of the study drug for low, medium, and high dose groups, respectively. The control stayed without treatment. The dose levels for treated females were 10, 25, and50 mg/kg of the study drug for low, medium, and high dose groups, respectively. The control stayed without treatment. In addition to these treatment groups, an extra group of 60 animals were added to each sex (Group 2). The males in these additional group received 37 mg/kg of pamoic acid while the females received 92.5 mg/kg of pamoic acid through once a month intramuscular injection. Pamoic acid was evaluated since it represents the part of the molecule that would be released on ionization of Zyprexa and since no published carcinogenicity data could be cited supporting its (pamoic acid) long term safety by this or any other rout of administration. In this review this group will be referred to as positive control.

Animals were checked daily for mortality and morbidity. Body weights were measured pretreatment and at weekly intervals for the first 14 weeks, then every other week. The animals were checked regularly for the presence of any body mass. All observations were recorded pre-dose and at weekly intervals for the first 14 weeks, then every other week. A complete histopathological examination was performed on all animals found dead, killed moribund, or sacrificed during or at the end of the experiment.

2.1. Sponsor's analyses

2.1.1. Survival analysis

Mortality data were evaluated for a dose-related increasing trend using the methods described in Tarone's paper (Tarone 1975). A one-sided score trend test was conducted at the .05 significance level.

Sponsor's findings: Sponsor's findings showed survival rates in untreated control, positive control, low, medium, and high dose groups of 45%, 48%, 50%, 45%, and 35%, respectively in males, and 65%, 55%, 72%, 70%, and 72%, respectively in females. Sponsor's analysis showed no significant difference among untreated control, low, medium, and high dose groups or between untreated control and positive control.

2.1.2. Tumor data analysis

Tumor data were evaluated using Peto's survival-adjusted trend test (Peto et al. 1980) for dose response relationship among untreated control, low, medium, and high dose groups. The analysis intervals for incidental neoplasms were: Weeks 0 through 52, 53 through 78, 79 through 92, and 93 till termination of the live phase. An incidence rate was analyzed only if the total number of occurrences of the neoplasm in a treated group was 2 or more either under or over that of the control group. Peto's trend test for a positive linear trend in incidence rate was conducted at the significance levels of .025 and .005 for rare and common neoplasms following the recommendation of Lin and Rahman (Lin and Rahman 1998), respectively, using PROC MULTTEST in the SAS system. Common neoplasms were defined as those with a historical incidence in controls of more than 1% and rare neoplasms as 1% or less (Lin 2001). Since the standard normal approximation used in the analysis of tumor data may lead to artificially small p-values in the presence of low neoplasm incidence (Ali 1990), exact permutation trend test (Gart *et al.* 1986) was performed for those site/neoplasm combinations with total neoplasm incidence less than or equal to 10 (Ali 1990). The exact permutation trend test was implemented using PROC MULTTEST in the SAS system and by specifying the PERMUTATION =1000 option. Further evaluations of dose-related neoplasm incidence were carried out using Peto's trend test in the sequential fashion described in Tukey *et al.* (1985). Findings which resulted in one-sided p-values less than or equal to the specified significance level were documented and discussed. For cases when a negative trend was indicated, a two-sided test at the specified significance level was used to determine the significance of a dose-related decrease.

The statistical methods for comparing untreated control and positive control groups followed those described for the comparison of untreated control, low, medium, and high dose groups. One-sided tests for the incidence rates of neoplasms and mortality were performed for increases in positive control animals compared with untreated control animals.

Sponsor's findings: Sponsor's analyses did not show statistically significant dose-response relationship among untreated control, low, medium, and high dose groups in any of the tested tumor types. Sponsor's analysis also did not show statistically significant difference between untreated control and positive control in any of the tested tumor types.

2.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses. Data used in this reviewer's analyses were provided by the sponsor electronically.

2.2.1. Survival analysis

The survival distributions of animals in all five treated groups were estimated by the Kaplan-Meier product limit method. The homogeneity of survival distributions was tested using the Cox test (Cox, 1972) and the Generalized Wilcoxon test (Gehan, 1965). The intercurrent mortality data are given in Tables 1A and 1B in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1A and 1B in the appendix for males and females, respectively. Results of the tests for homogeneity of survivals are given in Tables 2A and 2B in the appendix for males and females, respectively.

Reviewer's findings: The tests showed no statistically significant differences in survivals across treatment groups in either sex. Pairwise comparisons showed no statistically significant difference between the untreated control and positive control or between the untreated control and any of the treated groups in either sex.

2.2.2. Tumor data analysis

In this study, since assessing the carcinogenic effect of the study drug was the main interest, for the primary tumor data analysis the pamoic acid group was excluded. Tumor data were analyzed for dose-response relationship using the methods described in the paper of Peto et al. (1980). Pairwise comparisons between treated groups and control, and control and pamoic acid group were performed using the age adjusted Fisher exact test. Since the sponsor classified the tumor types as 'cause of death' and 'not a cause of death', following Peto et al., this reviewer applied the 'death rate method' and the 'prevalence method' for these two categories of tumors respectively, to test the dose-response relationship[1]. For tumor types occurring in the two categories, a combined test of 'death rate method' and the 'prevalence method' was performed. For the calculation of p-values, the Exact Permutation method was used. The actual dose levels of treatment groups were used as the weights for the dose-response relationship analysis. The time intervals used were 0 - 52, 53 - 78, 79 - 91, 92 - 104 weeks, and terminal sacrifice for both sexes.

The tumor rates and the p-values of the tumor types tested for dose-response relationship are listed in Table 3A and 3B in the appendix for males and females, respectively. The p-values for pairwise comparisons between the control and individual treated group are given in Table 4A and 4B in the appendix for males and females, respectively.

Multiple testing adjustment: Adjustment for the multiple dose-response relationship testing was done using the results of Lin and Rahman (1998), which recommends, in order to keep the false-positive rate at the nominal level of approximately 10%, the use of a significance level α=0.025 rare tumors and α=0.005 for common tumors for a submission with two studies, and the use of a significance level α=0.05 rare tumors and α=0.01 for common tumors for a submission with one study. A rare tumor is defined as one in which the published spontaneous tumor rate is less than 1%. Adjustment for multiple pairwise comparisons was done using the results of Haseman (1983), which recommends, in order to keep the false-positive rate at the nominal level of approximately 10%, the use a significance level α=0.05 for rare tumors and α=0.01 for common tumors,.

Based on the results of Lin and Rahman the incidence of none of the tested tumor types in either sex was considered to have statistically significant dose-response relationship. Also based on the results of Haseman, none of the pairwise comparisons of treated groups with the untreated control was considered to be statistically significant in either sex.

3. Evaluation of validity of the design of the rat study

As has been noted, the tumor data analyses showed no statistically significant dose-response relationship in any tested single tumor type. However, before drawing any conclusion regarding the non-carcinogenic potential of the drug in rats, it is important to look into the following two issues, as have been pointed out in the paper by Haseman (1984).

(i) Were enough animals exposed, for a sustained amount of time, to the risk of late developing tumors?
(ii) Were dose levels high enough to pose a reasonable tumor challenge to the animals?

There is no consensus among experts regarding the number of animals and length of time at risk, although most

[1] In this reviewer's analysis the phrase "Dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rates as dose increases.

carcinogenicity studies are designed to run for two years with fifty animals per treatment group. The following are some rules of thumb regarding these two issues as suggested by experts in this field:

Haseman (1985) has done an investigation on the first issue. He gathered data from 21 studies using Fischer 344 rats and B6C3Fl mice conducted at the National Toxicology Program (NTP). It was found that, on the average, approximately 50% of the animals in the high dose group survived the two-year study period. Also, in a personal communication with Dr. Karl Lin of Division of Biometrics-6, Haseman suggested that, as a rule of thumb, a 50% survival of 50 initial animals or 20 to 30 animals still alive in the high dose group, between weeks 80-90, would be consider as a sufficient number and adequate exposure. In addition Chu, Cueto and Ward (1981), suggested that" to be considered adequate, an experiment that has not shown a chemical to be carcinogenic should have groups of animals with greater than 50% survival at one-year."

It appears, from these three sources that the proportions of survival at 52 weeks, 80-90 weeks, and two years are of interest in determining the adequacy of exposure and number of animals at risk.

Regarding the question of adequate dose levels, it is generally accepted that the high dose should be close to the maximum tolerated dose (MTD). In the paper of Chu, Cueto and Ward (1981), the following criteria are mentioned for dose adequacy. A high dose is considered as close to MTD if any of the criteria is met.

(i) "A dose is considered adequate if there is a detectable loss in weight gain 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."

We will now investigate the validity of the Zyprexa rat carcinogenicity study, in the light of the above guidelines.

The following is the summary of survival data in the high dose groups:

Percentage of survival in the high dose group at the end of Weeks 52, 78, and 91

	Percentage of survival		
	End of 52 weeks	End of 78 weeks	End of 91 weeks
Male	100%	90%	77%
Female	100%	92%	88%

Based on the survival criterion Haseman proposed, it could be concluded that enough animals in both sexes were exposed to the high dose for a sufficient amount of time.

The following table shows the percent difference in mean body weight gain from the concurrent control, defined as,

$$\text{Percent difference} = \frac{(\text{Final BW} - \text{Baseline BW})_{\text{Treated}} - (\text{Final BW} - \text{Baseline BW})_{\text{Control}}}{(\text{Final BW} - \text{Baseline BW})_{\text{Control}}} \times 100$$

Percent Difference in Mean body Weight Gain from Combined Controls

Male			Female		
Low	Medium	High	Low	Medium	High
1.24	1.10	-1.88	3.76	- 2.50	-4.03

Source: Table 5 of sponsor's submission

Therefore, relative to the control, there had been about 2% decrement in body weight gain in male high dose group and about 4% decrement in body weight gain in female high dose group.

The mortality rates at the end of the experiment were as follows:

Percentage of Mortality at the End of the Experiment

Male	**Cont.**	**Low**	**Medium**	**High**
	53%	52%	55%	65%
Female	**Cont.**	**Low**	**Medium**	**High**
	33%	28%	30%	27%

This shows that the morality rate of in the high dose group in males is 12% higher than the control, while in female it is about 6% lower in high dose group than to the control.

Thus, from the body weight gain and mortality data it can be concluded that for males the used high dose level might have reached the MTD. The females in the high dose group showed about 6% lower mortality than the control, but had about 4% decrement in body weight gain. Therefore, the used high dose might have also reached the MTD for females. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

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4. Summary

In this submission the sponsor included reports of an animal carcinogenicity study in rats. This study was intended to assess the carcinogenic potential of Zyprexa in rats when administered once a month through intramuscular injection for about 104 weeks. It should be noted that the common regulatory requirement of carcinogenicity experiments is to include studies in two species, one in rats and one in mice. In the present form of this drug, Zyprexa is an extended release formulation the previously regular Zyprexa. During the submission of regular Zyprexa a two species study was conducted and reviewed. Hence, in a pre-submission meeting it was agreed that a carcinogenicity study only in the rat will suffice the requirement for this extended release formulation.

In this review, the phrase "dose-response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor rate as dose increases.

This study had three study drug treated groups and one untreated control group. Besides these four

treatment groups there was one positive control group. The animals in the positive control group were treated with pamoic acid. The group size was 60. The dose levels for males treated groups were 5, 10, and 20 mg/kg/day and for females they were 10, 25, and 50 mg/kg/day. The males in pamoic acid group received 37 mg/kg/day, wile the female received 92.5 mg/kg/day. The controls remained without any test article.

Tests did not show statistically significant differences in survivals across treatment groups in either sex. Tests did not show statistically significant dose-response relationship or pairwise difference in tumor incidence between the untreated control and any of the treated groups in any observed tumor types. From the mortality and body weight data it can be concluded that the used high dose might have reached MTD in both sexes. For a final determination of the adequacy of the doses used, other clinical signs and histopathological toxic effects must be considered.

Mohammad Atiar Rahman, Ph.D.
Mathematical Statistician

Concur: Karl Lin, Ph.D.
Team Leader, Biometrics-6

cc:
Archival NDA 22-173
Dr. Launghren
Dr. Tabacova
Mr. Kiedrow
Dr. Machado
Dr. Lin
Dr. Rahman
Dr. O'Neill
Ms. Patricianl

5. Appendix

Table 1A: Intercurrent Mortality Rate
Male Rats

	Control		Pamoic Acid 37 mg/kg		5 mg/kg/day		10 mg/kg/day		20 mg/kg/day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	1	1.7	0	0	2	3.3	1	1.7	0	0
53 - 78	4	8.3	5	8.3	8	16.7	6	11.7	6	10.0
79 - 91	10	25.0	7	20.0	9	31.7	2	15.0	8	23.3
92 - 104	17	53.3	18	50.0	12	51.7	24	55.0	25	65.0
Term. Sac.	28	46.7	30	50.0	29	48.3	27	45.0	21	35.0

Table 1B: Intercurrent Mortality Rate
Female Rats

	Control		Pamoic Acid 92.5 mg/kg		10 mg/kg/day		25 mg/kg/day		50 mg/kg/day	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum %
0 - 52	0	0	0	0	1	1.7	0	0	0	0
53 - 78	6	10.0	2	3.3	3	6.7	4	6.7	5	8.3
79 - 91	2	13.3	11	21.7	6	16.7	4	13.3	2	11.7
92 - 103	12	33.3	14	45.0	7	28.3	10	30.0	9	26.7
Term. Sac.	40	66.7	33	55.0	43	71.7	42	70.0	44	73.3

Table 2A: Intercurrent Mortality Comparison
Male Rats

		Including the Pamoic Acid Group		Excluding the Pamoic Acid Group	
Method	Test	Statistic	P-value	Statistic	P-value
Cox	Homogeneity	3.0648	0.5470	2.1696	0.5380
Kruskal-Wallis	Homogeneity	3.0451	0.5503	2.0564	0.5608

Table 2B: Intercurrent Mortality Comparison
Female Rats

		Including the Pamoic Acid Group		Excluding the Pamoic Acid Group	
Method	Test	Statistic	P-value	Statistic	P-value
Cox	Homogeneity	5.4440	0.2447	0.4266	0.9347
Kruskal-Wallis	Homogeneity	4.6967	0.3199	0.3928	0.9417

Table 3A

Tumor Rates and Dose-Response Relationship p-values of Tested Tumors
Male Rats - Fed Over 104 Weeks

Organ	Tumor	Control	5mg	10mg	20mg	P-value
adrenal gland(s)	adenoma	0	0	0	1	0.3205
	pheochromocytoma	6	2	3	8	0.1705
	pheochromocytoma - malign	1	1	0	2	0.2267
bone, femur	sarcoma	1	0	0	0	1.0000
cerebellum	astrocytoma	1	0	0	0	1.0000
cerebrum	ependymoma	0	0	1	0	0.5116
	mixed glioma	0	0	1	0	0.4929
	osteoma	0	0	1	0	0.5301
colon	adenocarcinoma	0	1	0	0	0.7559
gland, preputial	adenoma	0	2	0	0	1.0000
	carcinoma	0	0	2	0	0.2500
	keratoacanthoma	1	0	0	0	1.0000
jejunum	adenocarcinoma	0	0	0	1	0.2384
kidney(s)	adenoma	0	0	1	0	0.4571
	nephroblastoma	0	1	0	0	0.7500
liver	adenoma	0	1	2	0	0.6598
lung	adenoma	0	0	0	1	0.2000
mammary gland, male	adenocarcinoma	1	0	0	1	0.5291
	adenoma	1	0	0	0	1.0000
	fibroadenoma	2	0	0	0	1.0000
	fibroma	1	0	2	0	0.6745
	sarcoma	1	0	0	1	0.6207
non-specified	meningioma	0	1	0	0	1.0000
pancreas	adenoma - islet cell	6	5	4	4	0.7011
	adenoma - mixed islet-aci	0	0	1	0	0.4571
	carcinoma - islet cell	3	0	2	1	0.7658
	sarcoma	1	0	0	0	1.0000
pituitary	adenoma - pars distalis	30	28	21	23	0.8991
	adenoma - pars intermedia	1	1	0	0	0.9418
	carcinoma - pars distalis	0	1	0	1	0.3168
prostate	adenoma	1	0	0	0	1.0000
skin	adenoma	1	0	0	0	1.0000
	basal cell tumor	0	1	0	0	0.7821
	carcinoma	0	2	0	0	0.7821
	hemangiosarcoma	0	0	0	1	0.3205
	keratoacanthoma	1	0	1	0	0.8407
	papilloma	0	0	2	0	0.4258
subcutis	adenocarcinoma	0	1	0	0	0.5000
	carcinoma	1	0	0	0	1.0000
	fibroma	0	2	0	1	0.3968
	keratoacanthoma	1	0	0	0	1.0000
testis(es)	adenoma	41	42	41	40	0.5456
thyroid	adenoma - c-cell	3	0	1	2	0.5788
	adenoma - follicular cell	1	0	0	0	1.0000
	carcinoma - c-cell	0	1	0	1	0.2720
	carcinoma - follicular ce	1	0	0	0	1.0000

Table 3B
Tumor Rates and Dose-Response Relationship p-values of Tested Tumors
Female Rats - Fed Over 104 Weeks

Organ	Tumor	Control	10mg	25mg	50mg	P-value
adrenal gland(s)	adenoma	1	0	1	1	0.4139
	pheochromocytoma	1	1	1	2	0.2687
	pheochromocytoma - malign	2	0	0	0	1.0000
bone, femur	histiocytic sarcoma	0	1	0	0	0.7633
cervix	leiomyoma	0	0	1	0	0.5089
eye(s)	fibrosarcoma	0	1	0	0	0.7633
gland, clitoral	keratoacanthoma	0	0	1	0	0.6000
liver	adenoma	0	0	1	1	0.1968
lung	adenoma	1	0	0	0	1.0000
mammary gland, femal	adenocarcinoma	3	1	3	1	0.7528
	adenoma	1	0	1	0	0.7066
	fibroadenoma	12	13	14	15	0.2795
	rhabdomyosarcoma	0	0	0	1	0.2162
	schwannoma	1	0	0	0	1.0000
non-specified	keratoacanthoma	1	0	0	0	1.0000
	sarcoma	0	0	0	1	0.5000
pancreas	adenoma	0	0	1	1	0.1968
	adenoma - islet cell	0	1	0	0	0.7633
	adenoma - mixed islet-aci	1	0	0	0	1.0000
	carcinoma - islet cell	1	0	0	0	1.0000
parathyroid	adenoma	0	1	0	0	0.7517
pituitary	adenoma - pars distalis	28	28	20	24	0.8491
	carcinoma - pars distalis	0	0	0	2	0.0674
skin	basal cell tumor	0	0	0	1	0.2604
	keratoacanthoma	0	0	0	1	0.2162
	papilloma	1	0	2	0	0.7029
thymus	thymoma	0	2	0	0	0.8236
thyroid	adenoma - c-cell	2	2	0	6	0.0505
	adenoma - follicular cell	0	1	0	0	0.7633
tongue	papilloma	1	0	0	0	1.0000
urinary bladder	adenoma	1	0	1	1	0.4125
uterus	endometrial stromal polyp	7	8	4	9	0.3826
	leiomyoma	2	1	0	1	0.7926
	schwannoma	0	1	0	0	0.6842
vagina	sarcoma	0	0	1	0	0.5089

Table 4A

Pairwise Comparisons of Treated Groups with Control
Male Rats - Fed Over 104 Weeks

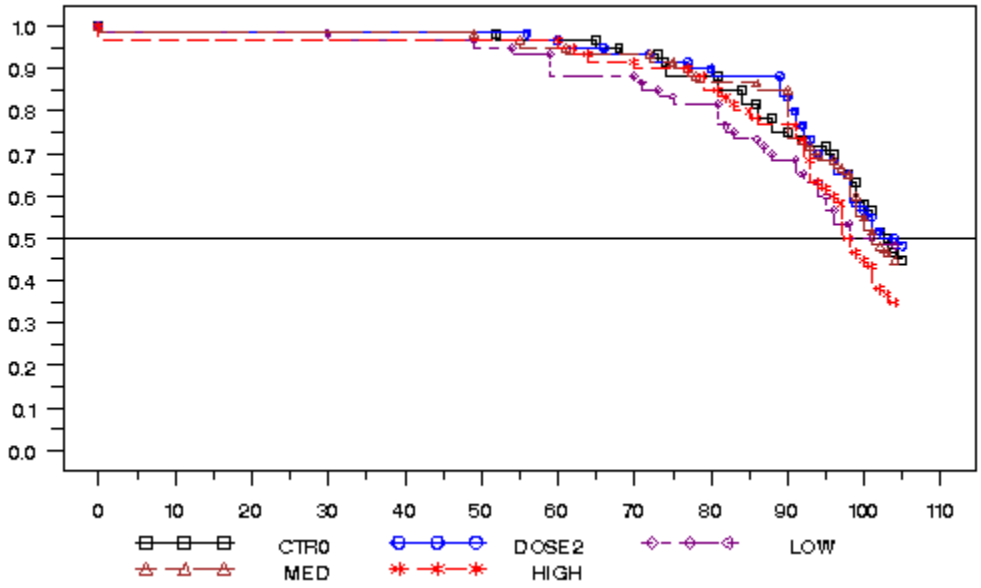
Organ	Tumor	Cont. Vs 5mg	Cont. vs 10mg	Cont. vs 20mg
adrenal gland(s)	adenoma	.	.	0.5952
	pheochromocytoma	0.9674	0.8902	0.3927
	pheochromocytoma - malign	0.7415	1.0000	0.4008
bone, femur	sarcoma	1.0000	1.0000	1.0000
cerebellum	astrocytoma	1.0000	1.0000	1.0000
cerebrum	ependymoma	.	0.5000	.
	mixed glioma	.	0.5000	.
	osteoma	.	0.5312	.
colon	adenocarcinoma	0.5140	.	.
gland, preputial	carcinoma	.	0.5000	.
	keratoacanthoma	.	1.0000	.
jejunum	adenocarcinoma	.	.	0.5000
kidney(s)	adenoma	.	0.4909	.
	nephroblastoma	0.6667	.	.
liver	adenoma	0.5088	0.3366	.
lung	adenoma	.	.	0.4286
mammary gland, male	adenocarcinoma	1.0000	1.0000	0.7727
	adenoma	1.0000	1.0000	1.0000
	fibroadenoma	1.0000	1.0000	1.0000
	fibroma	1.0000	0.4681	1.0000
	sarcoma	1.0000	1.0000	0.8483
pancreas	adenoma - islet cell	0.7266	0.7011	0.7884
	adenoma - mixed islet-aci	.	0.4909	.
	carcinoma - islet cell	1.0000	0.8344	0.9313
	sarcoma	1.0000	1.0000	1.0000
pituitary	adenoma - pars distalis	0.6579	0.9743	0.8747
	adenoma - pars intermedia	0.7077	1.0000	1.0000
	carcinoma - pars distalis	0.4953	.	0.5046
prostate	adenoma	1.0000	1.0000	1.0000
skin	adenoma	1.0000	1.0000	1.0000
	basal cell tumor	0.4138	.	.
	carcinoma	0.2544	.	.
	hemangiosarcoma	.	.	0.5952
	keratoacanthoma	1.0000	0.7889	1.0000
	papilloma	.	0.2364	.
subcutis	adenocarcinoma	0.5000	.	.
	carcinoma	1.0000	1.0000	1.0000
	fibroma	0.5000	.	0.5000
	keratoacanthoma	1.0000	.	.
testis(es)	adenoma	0.3875	0.6485	0.5035
thyroid	adenoma - c-cell	1.0000	0.9488	0.8006
	adenoma - follicular cell	1.0000	1.0000	1.0000
	carcinoma - c-cell	0.5088	.	0.4691
	carcinoma - follicular ce	1.0000	1.0000	1.0000

Table 4B

Pairwise Comparisons of Treated Groups with Control
Female Rats - Fed Over 104 Weeks

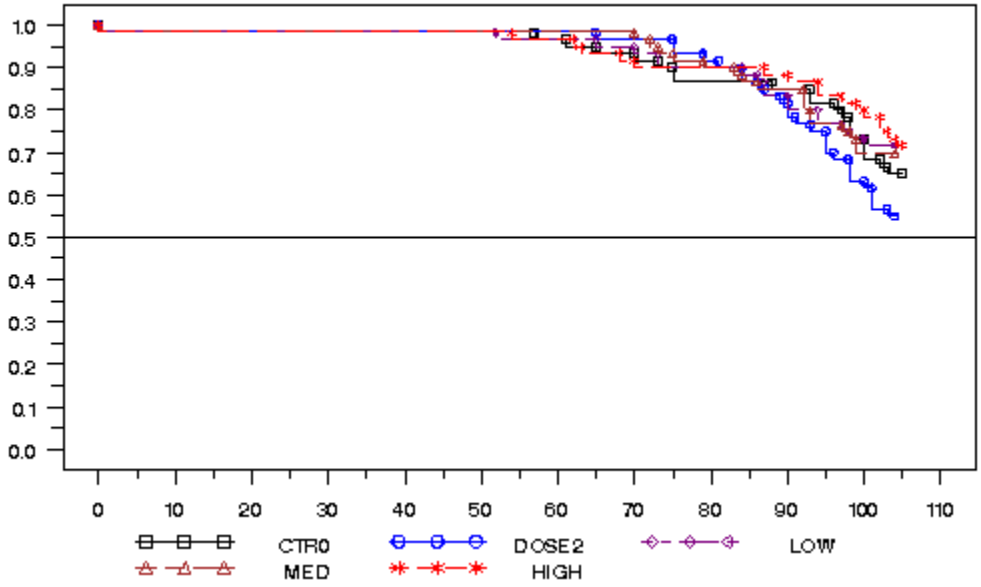
Organ	Tumor	Cont. vs 10mg	Cont. vs 25mg	Cont. vs 50mg
adrenal gland(s)	adenoma	1.0000	0.7651	0.7279
	pheochromocytoma	0.6140	0.7339	0.4408
	pheochromocytoma - malign	1.0000	1.0000	1.0000
bone, femur	histiocytic sarcoma	0.5181	.	.
cervix	leiomyoma	.	0.5122	.
eye(s)	fibrosarcoma	0.5181	.	.
liver	adenoma	.	0.5122	0.5238
lung	adenoma	1.0000	1.0000	1.0000
mammary gland, femal	adenocarcinoma	0.9295	0.6470	0.9378
	adenoma	1.0000	0.8182	1.0000
	fibroadenoma	0.4551	0.3975	0.3791
	rhabdomyosarcoma	.	.	0.4000
	schwannoma	1.0000	1.0000	1.0000
non-specified	keratoacanthoma	.	.	1.0000
	sarcoma	.	.	0.5000
pancreas	adenoma	.	0.5122	0.5238
	adenoma - islet cell	0.5181	.	.
	adenoma - mixed islet-aci	1.0000	1.0000	1.0000
	carcinoma - islet cell	1.0000	1.0000	1.0000
parathyroid	adenoma	0.5200	.	.
pituitary	adenoma - pars distalis	0.6080	0.9159	0.8688
	carcinoma - pars distalis	.	.	0.2714
skin	basal cell tumor	.	.	0.5238
	keratoacanthoma	.	.	0.4000
	papilloma	1.0000	0.5185	1.0000
thymus	thymoma	0.2764	.	.
thyroid	adenoma - c-cell	0.7191	1.0000	0.1655
	adenoma - follicular cell	0.5181	.	.
tongue	papilloma	1.0000	1.0000	1.0000
urinary bladder	adenoma	1.0000	0.7595	0.7622
uterus	endometrial stromal polyp	0.5796	0.9087	0.4338
	leiomyoma	0.8925	1.0000	0.8963
	schwannoma	0.3684	.	.
vagina	sarcoma	.	0.5122	.

Figure 1A: Kaplan-Meier Survival Functions for Male Rats Including the Pamoic Group
Species: Rat, Sex: Male, MDA 22077



X-Axis: Weeks, Y-Axis: Survival rates

Figure 1B: Kaplan-Meier Survival Functions for Female Rats
Species: Rat, Sex: Female, MDA 22077



X-Axis: Weeks, Y-Axis: Survival rates

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