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
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-192 / N000
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Keywords: Clinical studies; NDA review; Pharmacogenomics; Subgroup analyses

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

The sponsor submitted four short-term studies and three long-term studies to seek claims for efficacy and safety of iloperidone in the treatment of adult schizophrenia. Efficacy for the schizophrenia subsample was demonstrated from two studies: ILP3005ST and VP-VYV-683-3101. The efficacy in study ILP3005ST was demonstrated by the change from baseline to Week 6 in the Brief Psychiatric Rating Scale (BPRS) total score. The efficacy in study VP-VYV-683-3101 was demonstrated by the change from baseline to Week 4 in the Positive and Negative Syndrome Scale (PANSS) total score.

In study ILP3005ST, the PANSS total score, PANSS positive subscale, PANSS negative subscale, CGI severity scale, and CGI improvement scale were not pre-specified. They only serve exploratory purposes and do not support labeling claims.

In study VP-VYV-683-3101, the BPRS total score, PANSS positive subscale, PANSS negative subscale, CGI severity scale, and CGI improvement scale were not pre-specified. They do not support labeling claims.

Study ILP3000ST was considered negative based on the primary hypothesis. All labeling efficacy claims with respect to this study were not justified.

The findings based on the genetic subgroup that the treatment benefit was enhanced among patients carrying the *CNTF FS63Ter* (-/-) genotype were suggestive, but not conclusive to support labeling claims.

The long-term non-inferiority claim based on studies ILP3001, ILP3002, and ILP3003 did not have a regulatory merit given the designs and analyses of these studies.

1.2 Brief Overview of Clinical Studies

Study ILP3000ST was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, United States study. The study investigated three doses: iloperidone 4 mg/day, 8 mg/day, and 12 mg/day. The study also included haloperidol (15 mg/day) for assay sensitivity. The duration of the double-blind phase was 42 days. Six hundreds and twenty one subjects between the age of 18 and 68 were randomized. The primary efficacy variable was the change from baseline to Day 42 in the PANSS total score. The primary hypothesis was the combined 8 mg/day and 12 mg/day against placebo.

Study ILP3004ST was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, international study. The duration of the double-blind phase was 42 days. Six hundreds and sixteen subjects from the age of 17 to 67 were randomized to either iloperidone 4-8 mg/day, iloperidone 10-16 mg/day, risperidone 4-8 mg/day, or placebo. The primary efficacy variable was the change from baseline to Day 42 in the BPRS total score.

Study ILP3005ST was a randomized, double-blind, placebo-controlled, parallel-group, multi-center, international study. Two dose groups of iloperidone were investigated: 12-16 mg/day and 20-24 mg/day. The study also included risperidone 6-8 mg/day for assay sensitivity. The initial randomization scheme was a 2:1:1 ratio (iloperidone 12-16 mg/day, risperidone 6-8 mg/day, and placebo, respectively). The decision to include the high dose group (iloperidone 20-24 mg/day) occurred after the initiation of the study and was depended on the outcome of study ILP3004ST. With the addition of the iloperidone 20-24 mg/d, patients were randomized in a ratio of 1:2:1:1 to iloperidone 12-16 mg/day, iloperidone 20-24 mg/day, risperidone, or placebo, respectively. Subjects in the study were between 18 and 65 years old. Seven hundreds and six (706) subjects were randomized. The primary efficacy variable was the change from baseline to Day 42 in the BPRS total score.

Study VP-VYV-683-3101 was a randomized, double-blind, placebo-controlled, parallel-group, multi-center study. Six hundreds and six subjects (606) between the age of 18 and 65 from India and the United States were randomized. The randomized ratio was 2:1:1 to iloperidone 24 mg/day, ziprasidone 160 mg/day, or placebo, respectively. The double-blind phase lasted for four weeks. The primary endpoint was the change from baseline to Week 4 in the PANSS total score.

Studies ILP3001, ILP3002, ILP3003 were randomized, multi-center, double-blind, active-controlled, flexible dose studies. Subjects were randomized in a 3:1 ratio to receive either iloperidone 4-16 mg/day or haloperidol 5-20 mg/day. The duration of the study was 52 weeks. The primary hypothesis was the non-inferiority of iloperidone versus haloperidol in the time to relapse based on a pooled analysis of these three studies.

Study ILP3000ST was deemed negative from a regulatory perspective. Studies ILP3001, ILP3002, ILP3003 had serious flaws in the design that made the interpretation difficult. Except study VP-VYV-683-3101, all above-mentioned studies included both schizophrenia and schizoaffective patients. Because the indication sought is schizophrenia, this review will focus on the schizophrenia efficacy evaluation of studies ILP3004ST, ILP3005ST, and VP-VYV-683-3101.

1.3 Statistical Issues and Findings

The sponsor submitted four short-term studies and three long-term studies. Except study VP-VYV-683-3101, all studies included both schizophrenia and schizoaffective patients. The sponsor claimed all four studies demonstrated at least one positive dose against placebo. However, based on the primary hypotheses, only one study was positive for the schizophrenia and schizoaffective population: Study ILP3004ST.

On the other hand, when considering the schizophrenia sample only, study ILP3004ST was no longer positive. Instead, studies ILP3005ST and VP-VYV-683-3101 were positive.

Study VP-VYV-683-3101 evaluated the dose 24 mg/day. Study ILP3005ST evaluated two dose groups: 12-16 mg/day and 20-24 mg/day. Although both dose groups showed

2. INTRODUCTION

2.1 Overview

This review provides a statistical evaluation of iloperidone in the treatment of schizophrenia.

According to the sponsor, iloperidone is a new chemical entity belonging to the chemical class of piperidinyl-benzisoxazole derivatives. The clinical development of iloperidone was initiated by Hoechst Marion Roussel (HMR) in 1990. Norvatis Pharmaceuticals licensed iloperidone in 1998 and continued its development program. In 2004, Vanda Pharmaceuticals Inc. licensed iloperidone and continued its clinical development program. This submission contains clinical studies from all three sponsors.

Schizophrenia is a common disorder affecting approximately 1% of the population. The characteristics of the illness include both the positive symptoms (for example, hallucinations and delusions) and negative symptoms (for example, apathy, blunted affect and social withdrawal) as well as cognitive impairment (for example, attention deficit, learning and memory). The illness is also lethal with an estimate of more than 10% of patients with schizophrenia completing suicide in their lifetime. The costs of schizophrenia in terms of care and lost of productivity place a high social and financial burden on the patient, family, and community.

According to the sponsor, none of the currently available treatment for schizophrenia is curative and there remains a significant unmet medical need. It is estimated that approximately 75% of the patients discontinue their medication within 18-month period for both lack of efficacy and side effects. The most common and worrisome side effects of the available antipsychotics are weight gain, diabetes, extrapyramidal symptoms, prolactin elevation, sedation, and QT prolongation.

In this application, the sponsor submitted four short-term studies and three long term studies in order to demonstrate the efficacy and safety of iloperidone in the treatment of schizophrenic adult patients. The four short-term phase III studies were ILP3000ST, ILP3004ST, ILP3005ST, and VP-VYY-683-3101. The three long-term studies were ILP3001, ILP3002, and ILP3003.

Except study VP-VYY-683-3101, all studies mentioned above included both schizophrenia and schizoaffective patients. Because the indication for this application is schizophrenia, this review will differentiate the schizophrenia samples and the (schizophrenia + schizoaffective) samples.

2.2 Data Sources

The sponsor's submitted data are stored in the following directory of the CDER's electronic document room:
\\Cdsesub1\evsprod\NDA022192\0000.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Study ILP3004ST

3.1.1.1 Objectives

Primary: The objective of the initial double-blind phase (6 weeks) was to evaluate the efficacy and safety of two non-overlapping dose ranges of iloperidone (4-8 mg/d, administered as 2-4 mg twice daily, and 10-16 mg/d, administered as 5-8 mg twice daily) and risperidone 4-8 mg/d (administered as 2-4 mg twice daily) compared with placebo, over 42 days in patients with an acute or subacute exacerbation of schizophrenia or schizoaffective disorder.

Secondary: Secondary objectives of the study include:

- To evaluate the effects of iloperidone on neurocognitive function
- To measure the impact of iloperidone on resource utilization
- To explore the relationship of certain genotypes and treatment effect

3.1.1.2 Study Design

This was a prospective, international, randomized, double-blind, parallel-group, multi-center study with three phases: pre-randomization, initial double-blind, and long-term double-blind. The pre-randomization phase consisted of a screening period and a placebo run-in period. The placebo run-in period lasted 3 days. For patients who showed clinical improvement compared to screening, the placebo run-in phase was extended (up to an additional 7 days) until the patient's psychiatric status returned back to a level comparable to that at screening. The initial 6-week double-blind phase consisted of titration (days 1-7) and maintenance periods (days 8-42). In the titration period, subjects were titrated to the target dose. In the maintenance period, flexible dosing regimens were administered within the target dose ranges. The treatment arms were iloperidone 4-8 mg/d, iloperidone 10-16 mg/d, risperidone 4-8 mg/d, and placebo. The dosing schedule is summarized in Table 1.

Table 1. Dosing schedule for the 6-week initial double-blind phase

Drug	Iloperidone 4-8 mg/d			Iloperidone 10-16 mg/d			Risperidone			Placebo		
Titration target dose	6 mg/d			12 mg/d			6 mg/d					
Daily dose (mg)	Total	a.m.	p.m.	Total	a.m.	p.m.	Total	a.m.	p.m.	Total	a.m.	p.m.
Titration period (Days 1-7)												
Day 1	2	1	1	2	1	1	2	1	1	P	P	P
Day 2	2	1	1	2	1	1	4	2	2	P	P	P
Day 3	4	2	2	4	2	2	6	3	3	P	P	P
Day 4	4	2	2	4	2	2	6	3	3	P	P	P
Day 5	6	3	3	8	4	4	6	3	3	P	P	P
Day 6	6	3	3	8	4	4	6	3	3	P	P	P
Day 7	6	3	3	12	6	6	6	3	3	P	P	P
Flexible maintenance dosing period (Days 8-42)												
Day 8 to 42	4/A or 6/B or 8/C	2 or 3 or 4	2 or 3 or 4	10/A or 12/B or 16/C	5 or 6 or 8	5 or 6 or 8	4/A or 6/B or 8/C	2 or 3 or 4	2 or 3 or 4	P/A or P/B or P/C	P or P or P	P or P or P

P=placebo

(Source: ILP3004st-legacy Report; Table 3-3, page 30)

Subjects between 18-65 years old were enrolled from June 1999 to May 2000. Eligible patients were those who met the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) of schizophrenia with suffixes 10 (disorganized), 30 (paranoid), 70 (schizoaffective), or 90 (undifferentiated); had a total PANSS score of at least 60 at screening and baseline; had a PANSS item score of at least 4 ("moderate") on at least 3 of the following 5 symptoms: delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution. Originally, the primary efficacy variable was the PANSS total score. Under protocol amendment 2 (November, 1999), the primary efficacy variable was revised to the 18-item PANSS-derived BPRS score. Primary efficacy was assessed at screening, baseline, and on Days 7, 14, 21, 28, 35, and 42 or the last visit before discontinuation.

It was determined that 150 patients per arm were needed for an 80% power and with a two-sided alpha = 0.05 to detect a 4-point difference in the BPRS total score, with a standard deviation of 12 (source: protocol amendment 2).

3.1.1.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 42 (or premature discontinuation) on the 18-item PANSS-derived BPRS score. The primary analysis model was an analysis of covariance (ANCOVA) with terms for treatment, center, baseline (as covariate), and the treatment-by-baseline interaction. Missing values were imputed by the Last-Observation-Carried-Forward (LOCF) method. To control for multiplicity in the analysis, a sequential testing procedure was employed. First, a comparison was carried out between the 10-16 mg/d group and the placebo group. If this test was significant at the 0.05 level, a subsequent pairwise comparison of the iloperidone 4-8 mg/d group with placebo would be tested at the 0.05 level (source: protocol amendment 2).

3.1.1.4 Efficacy Results

3.1.1.4.1 Study Population

Seven hundreds and ninety-four (794) subjects were screened for the study from Australia, Belgium, Canada, France, Hungary, South Africa, and United States. The randomized sample included 616 patients. The disposition of patients is presented in Table 2. Unsatisfactory therapeutic effect and withdrawal of consent were main reasons for discontinuing the study. There were about twice as many patients in the placebo arm experienced unsatisfactory therapeutic effect than in the treatment arms. About 50% of the subjects discontinued prematurely before the end of the initial 6-week double-blind phase.

Table 41 in the Appendix summarizes the disposition of the schizophrenia subsample. The distribution was similar to the overall sample.

Table 2. Study ILP3004ST: disposition of patients

	Ilo 4-8 mg/d N=153	Ilo 10-16 mg/d N=154	Risp 4-8 mg/d N=153	Placebo N=156	Total N=616
Discontinued (days 1-42) – n (%)	79 (51.6)	67 (43.5)	64 (41.8)	94 (60.3)	304 (49.4)
Adverse experiences	5 (3.3)	6 (3.9)	12 (7.8)	11 (7.1)	34 (5.5)
Unsatisfactory therapeutic effect	36 (23.5)	33 (21.4)	24 (15.7)	64 (41.0)	157 (25.5)
Protocol violation	3 (2.0)	3 (2.0)	1 (0.7)	0 (0.0)	7 (1.1)
Withdrawal of consent	28 (18.3)	21 (13.6)	12 (7.8)	14 (9.0)	75 (12.2)
Lost to follow-up	7 (4.6)	4 (2.6)	14 (9.2)	5 (3.2)	30 (4.9)
Death	0 (0.0)	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Completed (days 1-42)	74 (48.4)	87 (56.5)	89 (58.2)	62 (39.7)	312 (50.6)

(Source: ILP3004st-legacy Report; Table 7-1, page 49)

Table 3 summarizes key demographic and baseline disease characteristics of the randomized sample. The ratio of male to female was about 2 to 1. Subjects were between the ages of 17 and 67 with the average age of 39. The majority of subjects were Caucasian and black. Oriental and other races accounted for about 7% of the sample. About 22% of the patients were diagnosed with schizoaffective disorder. The mean BPRS total score at baseline was 55 and ranged from 33 to 89. The distribution of the demographic data for the schizophrenia subsample is presented in Table 42 in the Appendix.

Table 3. Study ILP3004ST: demographic and baseline disease characteristics (randomized sample)

	Ilo 4-8 mg/d N=153	Ilo 10-16 mg/d N=154	Risp 4-8 mg/d N=153	Placebo N=156	Total N=616
Age (yr) n					
Mean (SD)	38.4 (10.7)	39.3 (10.1)	37.5 (11.8)	38.8 (10.5)	38.5 (10.8)
Median	40.0	39.0	37.0	39.0	39.0
Min – Max	19 – 64	18 – 66	17 – 67	19 – 66	17 - 67
Sex – n (%)					
Male	105 (68.6)	109 (70.8)	115 (75.2)	104 (66.7)	433 (70.3)
Female	48 (31.4)	45 (29.2)	38 (24.8)	52 (33.3)	183 (29.7)
Race – n (%)					
Caucasian	92 (60.1)	91 (59.1)	92 (60.1)	89 (57.1)	364 (59.1)
Black	53 (34.6)	48 (31.2)	50 (32.7)	53 (34.0)	204 (33.1)
Other	8 (5.2)	15 (9.7)	11 (7.2)	14 (8.9)	48 (7.8)
DSM-IV diagnosis					
Disorganized	19 (12.4)	8 (5.2)	11 (7.2)	9 (5.8)	47 (7.6)
Paranoid	81 (52.9)	87 (56.5)	83 (54.3)	90 (57.7)	341 (55.4)
Schizoaffective	30 (19.6)	29 (18.8)	38 (24.8)	37 (23.7)	134 (21.8)
Undifferentiated	23 (15.0)	30 (19.5)	21 (13.7)	20 (12.8)	94 (15.3)
Baseline BPRS-total score					
N	151	154	152	155	612
Mean (SD)	55.0 (8.8)	54.1 (9.1)	54.9 (10.1)	54.3 (9.8)	54.6 (9.4)
Median	56.0	54.0	54.0	53.0	54.0
Min – Max	33 – 82	35 – 82	35 – 89	34 – 82	33 – 89

(Source: ILP3004st-legacy Report; Table 7-3, page 51, Table 7.4-2, page 338, and reviewer's results)

3.1.1.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from baseline to the end visit (Day 42 or early discontinuation) on the 18-item PANSS-derived BPRS total score. The difference was taken as end visit – baseline. Thus, a positive score represented an improvement. The primary efficacy variable was analyzed by an ANCOVA model with treatment, center, baseline (as covariate), and the treatment-by-baseline interaction. The primary efficacy analysis was based on the modified intent-to-treat analysis (MITT) set. All randomized subjects who had a baseline and at least one post-baseline assessment were included. The sponsor's primary efficacy result is presented in Table 4. Because iloperidone 10-16 mg dose group was significant, iloperidone 4-8 mg dose group was tested and was also positive. Both doses of iloperidone were statistically significantly superior to placebo.

It is noted that the efficacy results presented here are for all patients including the schizoaffective patients. The results excluding the schizoaffective patients will be presented section *3.1.1.4.3*.

Table 4. Study ILP3004ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
Sample size	143	149	146	152
LS Means*	6.24	7.15	10.28	2.47
Difference from placebo	3.77	4.68	7.80	
(95% confidence interval)	(0.84, 6.69)	(1.83, 7.52)	(4.93, 10.68)	
Unadjusted p-values	0.012	0.001	<0.001	

(Source: Reproduced from ILP3004st-legacy Report; Table 9.1-2, page 543 and reviewer's results)
* Reviewer's note: Positive changes indicate improvements

3.1.1.4.3 Reviewer's Results and Comments

The efficacy results presented in Table 4 included 22% of schizoaffective patients. Because the indication sought is schizophrenia, to explore whether iloperidone was still effective among schizophrenia patients, this reviewer performed an analysis excluding schizoaffective patients. The results in Table 5 and Table 6 revealed that iloperidone groups did not separate from placebo.

Table 5. Study ILP3004ST: reviewer's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
Sample size	115	121	110	116
LS Means *	5.77	6.51	10.31	4.86
Difference from placebo	0.91	1.66	5.46	
(95% confidence interval)	(-2.33, 4.16)	(-1.52, 4.83)	(2.23, 8.69)	
Unadjusted p-values	0.581	0.306	0.001	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

Table 6. Study ILP3004ST: Adjusted mean change from baseline up to end of week 6 in the BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8mg	Ilo 10-16mg	Risp	Pbo	Ilo 4-8mg – Pbo		Ilo 10-16mg – Pbo		Risp – Pbo	
					Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	3.73	3.28	5.94	3.15	0.59	0.634	0.13	0.914	2.79	0.023
Week 2	4.09	4.76	8.01	5.12	-1.03	0.456	-0.36	0.787	2.88	0.036
Week 3	4.20	5.84	8.51	4.78	-0.59	0.702	1.05	0.483	3.72	0.015
Week 4	5.53	6.10	9.93	4.63	0.90	0.572	1.47	0.347	5.30	0.001
Week 5	5.80	6.13	10.10	4.42	1.38	0.394	1.71	0.279	5.68	0.001
Week 6	5.77	6.51	10.31	4.86	0.91	0.581	1.66	0.306	5.46	0.001

(Source: reviewer's results)

* Reviewer's note: p-values are not adjusted for multiple comparisons; positive changes indicate improvements

Based on these analyses, it appears that this study is no longer positive to support an efficacy claim for the schizophrenia indication.

3.1.2 Study ILP3005ST

3.1.2.1 Objectives

Primary: The primary objective of the initial double-blind phase was to determine the efficacy and safety of iloperidone 12-16 mg/day (administered as 6 or 8 mg twice daily) and 20-24 mg/day (administered as 10 or 12 mg twice daily) and risperidone 6-8 mg/day (administered as 3 or 4 mg twice daily) compared with placebo over 42 days in patients with schizophrenia or schizoaffective disorder.

Secondary: To demonstrate the effect of iloperidone on negative symptoms of schizophrenia over 42 days.

3.1.2.2 Study Design

This was a prospective, randomized, double-blind, placebo- and active-controlled, multi-center study. The study included three phases: a pre-randomization phase (Day –30 to Day 0) that included a screening period and a three-day placebo run-in period; a short-term double-blind phase (Days 1 – 42) that consisted of the titration and maintenance periods; all patients who completed 42 days of the short-term double-blind phase had an option to continue into the long-term open-label phase. Two doses of the investigational drug were studied (12-16 mg/day and 20-24 mg/day). Risperidone (6-8 mg/day) was included as an active control. All dosing was twice daily.

For the iloperidone 12-16 mg/day group, the dosage was increased every other day until the target dosage of 12 mg/day was reached on Day 7. For the 20-24 mg/day group, daily dosage increase was made up to 12 mg/day (Days 4 and 5). Thereafter, the dosage was increased every day until the target dose of 20 mg/day was reached on Day 7. After achieving the target dose, investigators had an option to increase the dosage to a higher maintenance dose in order to explore additional benefit. Thus, for group 12-16 mg/day, the dosage could be increased

to 16 mg/day; for group 20-24 mg/day, the dosage could be increased to 24 mg/day.

Initially patients were randomized to one of three treatment groups in a 2:1:1 ratio (iloperidone 12-16 mg/day, risperidone, and placebo, respectively). The decision to include the high dose group (iloperidone 20-24 mg/day) occurred after the initiation of the study and depended on the outcome of study ILP3004ST. When it was determined that patients might benefit from iloperidone doses > 16 mg/day, randomization to iloperidone 20-24 mg/day was initiated. From that point on, patients were randomized in a ratio of 1:2:1:1 (iloperidone 12-16 mg/day, iloperidone 20-24 mg/day, risperidone, or placebo, respectively).

Between April 2000 and March 2001, subjects between 18-65 years old were recruited to participate in the study from Canada, Croatia, Germany, Hungary, Israel, Poland, South Africa, and USA. Patients recruited were those diagnosed with schizophrenia according to the DSM-IV criteria with suffixes 10 (disorganized), 30 (paranoid), 70 (schizoaffective), or 90 (undifferentiated); had a PANSS total score of at least 60 at screening and baseline; had a rating of at least "4" ("moderate") on at least 3 of the following 5 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behavior, grandiosity, and suspiciousness/persecution.

It was determined that 150 patients/arm were needed to detect a difference of 4 points (standard deviation 12) with 80% power and a two-sided alpha = 0.05. The sponsor planned to randomize the initial 300 patients in a ratio of 2:1:1 (iloperidone 12-15 mg/d, risperidone, placebo). With the addition of the 20-24 mg/day, the randomization ratio would be changed to 1:2:1:1 (iloperidone 12-16 mg/d, iloperidone 20-24 mg/d, risperidone, placebo) for the subsequent 375 patients. Thus it appeared that if the 20-24 mg/d was not included, then the planned sample size would be 300:150:150 (iloperidone 12-16 mg/d, risperidone, placebo, respectively). If the 20-24 mg/day was included, then the planned sample size would be 225:150:150:150 (iloperidone 12-16 mg/d, iloperdione 20-24 mg/d, risperidone, placebo, respectively).

3.1.2.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary endpoint was the change from baseline to Day 42 (LOCF) in the 18-item BPRS extracted from the PANSS total score. To handle multiplicity in the analyses, the sequential testing procedure was employed. The primary comparison was between the iloperidone 12-16 mg/day and placebo. If this test was significant at an alpha = 0.05, a subsequent pairwise comparison of iloperidone 20-24 mg/day to placebo would be considered at a 0.05 level. The primary analysis model was an ANCOVA model with treatment, center, baseline (covariate), and the treatment-by-baseline interaction. Baseline was adjusted by subtracting the average baseline score from each baseline score. The primary endpoint was assessed at baseline, on days 7, 14, 21, 28, 35, and 42 or early discontinuation.

3.1.2.4 Efficacy Results

3.1.2.4.1 Study Population

The study was conducted in 67 centers from Canada, Croatia, Germany, Hungary, Israel, Poland, South Africa, and USA. Nine hundreds and forty-five (945) subjects were screened and 706 subjects were randomized. The sponsor's disposition of patients is presented in Table 7. There were six subjects who were classified as neither discontinuation nor completion in the sponsor's data. According to this reviewer, three patients could be classified as protocol violations (2 patients left the hospital, 1 failed screening); two patients could be classified as consent withdrawals; one patient was randomized but was unknown of the status of completion or discontinuation. Unsatisfactory therapeutic effect and withdrawal of consent were main reasons for discontinuing the study. Iloperidone and placebo groups had approximately three times as many patients dropping out due to unsatisfactory therapeutic effect as compared to the risperidone group. Overall, 41% of the subjects discontinued before the end of the initial double-blind period (Days 42).

Table 7. Study ILP3005ST: disposition of patients

	Ilo 12-16 mg/d N= 244	Ilo 20-24 mg/d N= 145	Risp 6-8 mg/d N= 157	Placebo N= 160	Total N= 706
Discontinued (days 1-42) – n (%)	113 (46)	59 (41)	45 (29)	73 (46)	290 (41)
Adverse experiences	9 (3.7)	7 (4.8)	8 (5.1)	6 (3.8)	30 (4.3)
Abnormal test/lab procedure/values	1 (0.4)	0 (0.0)	1 (0.6)	2 (1.2)	4 (0.4)
Unsatisfactory therapeutic effect	57 (23.4)	33 (22.8)	12 (7.6)	46 (28.8)	148 (21.0)
Condition no longer requires drug	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Protocol violation	4 (1.6)	1 (0.7)	3 (1.9)	1 (0.6)	9 (1.3)
Withdrawal of consent	29 (11.9)	12 (8.3)	14 (8.9)	12 (7.5)	67 (9.5)
Lost to follow-up	9 (1.3)	6 (0.9)	7 (1.0)	6 (0.9)	28 (4.0)
Administrative problems	3 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.4)
Completed (days 1-42)	127 (52)	85 (59)	111 (71)	87 (54)	410 (59)

(Source: ILP3005st-legacy Report; Table 7-1, page 57)

The disposition of schizophrenia patients is summarized in Table 43 in the Appendix and is similar to the disposition of all randomized patients (schizophrenia and schizoaffective).

The demographic and baseline disease characteristics of the randomized sample are summarized in Table 8. The average age of the sample was 39 years old and ranged from 18 to 69 years. There were approximately twice as many males than females. Caucasian and black patients dominated the sample. Oriental and other races accounted for only 6% of the sample. The sample included about 22% of schizoaffective patients.

A summary of demographic and baseline disease characteristics for the randomized schizophrenia subsample is presented in Table 44 in the Appendix. The distribution looks similar to the overall sample.

Table 8. Study ILP3005ST: demographic and baseline disease characteristics (randomized sample)

	Ilo 12-16 mg/d N= 244	Ilo 20-24 mg/d N= 145	Risp 6-8 mg/d N= 157	Placebo N=160	Total N= 706
Age (yr) n					
Mean (SD)	38.9 (11.0)	37.3 (10.7)	39.8 (10.4)	39.0 (10.3)	38.8 (10.7)
Median	38.0	38.0	39.0	39.5	39.0
Min – Max	18 – 65	19 – 65	18 – 64	18 – 69	18 – 69
Sex – n (%)					
Male	146 (59.8)	99 (68.3)	96 (61.2)	94 (58.8)	435 (61.6)
Female	98 (40.2)	46 (31.7)	61 (38.9)	66 (41.3)	271 (38.4)
Race – n (%)					
Caucasian	163 (66.8)	102 (70.3)	120 (76.4)	110 (68.8)	495 (70.1)
Black	68 (27.9)	33 (22.8)	27 (17.2)	39 (24.4)	167 (23.7)
Other	13 (5.3)	10 (6.9)	10 (6.4)	11 (6.9)	44 (6.2)
DSM-IV diagnosis					
Disorganized	7 (2.9)	11 (7.6)	5 (3.2)	5 (3.1)	28 (4.0)
Paranoid	162 (66.4)	89 (61.4)	106 (67.5)	108 (67.5)	465 (65.9)
Schizoaffective	56 (23.0)	31 (21.4)	31 (19.8)	40 (25.0)	158 (22.4)
Undifferentiated	19 (7.8)	14 (9.7)	15 (9.6)	7 (4.4)	55 (7.8)
Baseline BPRS-total score					
N	241	144	155	160	700
Mean (SD)	54.4 (7.4)	55.0 (8.3)	55.1 (8.7)	55.3 (8.1)	54.9 (8.1)
Median	54.0	55.0	54.0	55.0	55.0
Min – Max	39 – 79	36 – 85	38 – 92	35 – 90	35 – 92

(Source: ILP3005st-legacy Report; Tables 7.4-1 and 7.4-2, pages 374 & 380 and reviewer's results)

3.1.2.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary efficacy variable was the change from baseline to endpoint (Day 42 or early discontinuation) on the 18-item PANSS-derived BPRS total score. The difference was taken as endpoint – baseline. Thus, a positive score represented an improvement. The primary endpoint was analyzed by an ANCOVA model with treatment, center, baseline (as covariate), and the treatment-by-baseline interaction. The primary efficacy analysis was based on the modified intent-to-treat (MITT) analysis set. All randomized subjects who have a baseline and at least one post-baseline assessment were included. The sponsor's primary analysis is presented in Table 9. Because dose group 12-16 mg/day did not separate from placebo, dose group 20-24 mg/day was not tested.

The efficacy results presented here are for all patients including the schizoaffective patients. The results excluding the schizoaffective patients will be presented section *3.1.2.4.4*.

Table 9. Study ILP3005ST: sponsor's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) in the MITT sample

	Ilo 12-16 mg	**Ilo 20-24 mg**	**Risp 6-8 mg**	**Placebo**
Sample size	230	141	148	152
LS Means*	7.1	8.6	11.5	5.0
Difference from placebo	2.1	3.5	6.5	
(95% confidence interval)	(-0.3, 4.5)	(0.8, 6.2)	(3.8, 9.1)	
Unadjusted p-values	0.090	0.010	<0.001	

(Source: Reproduced from ILP3005st-legacy Report; Table 9.1-2, page 586 and reviewer's results)
* Reviewer's note: Positive changes indicate improvements

3.1.2.4.3 Sponsor's Efficacy Results for the CNTF subgroup

In an effort to identify genetic factors that may associate with treatment response to iloperidone, the sponsor explored a polymorphism in the CNTF (ciliary neurotrophic factor) gene. Patients enrolled in study ILP3005ST were given an option to participate in the pharmacogenetics (PG) sub-study. Of patients enrolled, the sponsor reported 39% consented to participate in the PG sub-study. The results of the pharmacogenetic sub-study are presented in Table 10.

Table 10. Study ILP3005ST: Sponsor's Efficacy Results by genetic subgroups: Change from baseline at Week 6: ANCOVA (LOCF) analysis (PG Population)

	N	BPRS	P value*	PANSS	P value*
CNTF (+)					
Iloperidone 12-16 mg/d	20	-7.5	0.580	-10.0	0.586
Iloperidone 20-24 mg/d	5	-8.2	0.677	-11.0	0.677
Risperidone 6-8 mg/d	11	-7.3	0.631	-10.7	0.631
Placebo	10	-4.2		-6.3	
CNTF (-)					
Iloperidone 12-16 mg/d	56	-13.0	0.009	-20.3	0.004
Iloperidone 20-24 mg/d	34	-10.4	0.218	-17.0	0.089
Risperidone 6-8 mg/d	42	-11.1	0.046	-17.6	0.046
Placebo	34	-4.8		-9.8	
ALL PG patients					
Iloperidone 12-16 mg/d	76	-11.3	0.025	-17.4	0.026
Iloperidone 20-24 mg/d	39	-9.8	0.219	-15.9	0.138
Risperidone 6-8 mg/d	53	-11.9	0.008	-19.0	0.006
Placebo	44	-6.6		-10.1	

(Source: Summary-clin-efficacy-schizophrenia; Table 69, pages 72)

* Reviewer's note: negative changes indicate improvement. P-values are comparisons against placebo and are unadjusted for multiplicity.

With the dataset provided by the sponsor by e-mail on May 13, 2008, this reviewer performed the above analyses and found some differences in the results. This reviewer used the same model as the primary analysis model stratifying by the *CNTF* polymorphism. The reviewer's results are summarized in Table 11. It was not clear what model the sponsor used to generate Table 10 above in "All PG patients".

Table 11. Study ILP3005ST: Reviewer's Efficacy Results by genetic subgroups: Change from baseline at Week 6: ANCOVA (LOCF) analysis (PG Population)

	N	BPRS	P value*	PANSS	P value*
CNTF (+)					
Iloperidone 12-16 mg/d	20	-7.5	0.549	-10.0	0.676
Iloperidone 20-24 mg/d	5	-8.2	0.564	-11.0	0.676
Risperidone 6-8 mg/d	11	-7.3	0.592	-10.7	0.643
Placebo	10	-4.2		-6.3	
CNTF (-)					
Iloperidone 12-16 mg/d	56	-13.0	0.005	-20.3	0.004
Iloperidone 20-24 mg/d	34	-10.4	0.136	-17.0	0.071
Risperidone 6-8 mg/d	42	-11.1	0.061	-17.6	0.043
Placebo	34	-6.8		-9.8	
ALL PG patients					
Iloperidone 12-16 mg/d	76	-11.2	0.018	-17.4	0.024
Iloperidone 20-24 mg/d	39	-9.9	0.137	-16.3	0.093
Risperidone 6-8 mg/d	53	-11.2	0.030	-17.9	0.026
Placebo	44	-6.7		-10.2	

(Source: Reviewer's results)
* Reviewer's note: negative changes indicate improvement. P-values are comparisons against placebo and are unadjusted for multiplicity.

The above tables include both schizophrenia and schizoaffective patients. Of note, the dose-response trend observed in the MITT was not supported by the analysis results using all PG patients. The following table (Table 12) contains the schizophrenia sample only. There was no dose-response trend observed.

Table 12. Study ILP3005ST: Reviewer's Efficacy Results by genetic subgroups: Change from baseline at Week 6: ANCOVA (LOCF) analysis (PG Population-Schizophrenia sample)

	N	BPRS	P value*	PANSS	P value*
CNTF (+)					
Iloperidone 12-16 mg/d	13	-5.7	0.498	-6.1	0.852
Iloperidone 20-24 mg/d	3	-12.6	0.424	-11.9	0.714
Risperidone 6-8 mg/d	10	-1.2	0.868	-0.4	0.884
Placebo	5	0.1		-2.8	
CNTF (-)					
Iloperidone 12-16 mg/d	46	-15.3	<0.001	-24.9	<0.001
Iloperidone 20-24 mg/d	27	-12.6	0.016	-21.7	0.007
Risperidone 6-8 mg/d	31	-12.1	0.017	-18.8	0.024
Placebo	25	-6.0		-9.0	
ALL PG patients					
Iloperidone 12-16 mg/d	59	-12.4	0.029	-19.6	0.041
Iloperidone 20-24 mg/d	30	-10.8	0.192	-18.3	0.135
Risperidone 6-8 mg/d	41	-11.5	0.094	-18.4	0.106
Placebo	30	-7.4		-11.7	

(Source: Reviewer's results)
* Reviewer's note: negative changes indicate improvement. P-values are comparisons against placebo and are unadjusted for multiplicity.

3.1.2.4.4 Reviewer's Results and Comments

The efficacy results presented in Table 9 included 22% of schizoaffective patients. Because the indication sought is schizophrenia, to explore whether iloperidone was effective among schizophrenia patients, this reviewer performed an analysis

excluding schizoaffective patients. The results in Table 13 suggested that both dose groups of iloperidone were superior to placebo among schizophrenia patients.

Table 13. Study ILP3005ST: reviewer's primary efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	178	111	119	113
LS Means *	7.4	8.8	11.4	4.3
Difference from placebo	3.1	4.5	7.1	
(95% confidence interval)	(0.3, 5.9)	(1.3, 7.6)	(4.0, 10.2)	
Unadjusted p-values	0.033	0.005	<0.001	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

Table 14 presents the change from baseline in the BPRS total score (LOCF) over time. Numerical treatment differences were seen from Week 3 to Week 6 for both iloperidone groups.

Table 14. Study ILP3005ST: Adjusted mean change from baseline up to end of week 6 in the BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 12-16mg	Ilo 20-24mg	Risp 6-8mg	Pbo	Ilo 12-16mg - Pbo		Ilo 20-24mg - Pbo		Risp - Pbo	
					Diff	p-value*	Diff	p-value*	Diff	p-value*
Week 1	2.5	3.1	5.0	3.0	-0.5	0.614	0.2	0.862	2.1	0.033
Week 2	4.7	5.5	8.8	4.1	0.7	0.559	1.4	0.247	4.7	<0.001
Week 3	6.9	6.9	10.0	3.9	3.0	0.022	3.1	0.034	6.1	<0.001
Week 4	7.7	7.9	11.1	4.8	2.9	0.033	3.2	0.037	6.3	<0.001
Week 5	7.8	8.9	11.7	4.8	3.0	0.038	4.1	0.010	6.9	<0.001
Week 6	7.4	8.8	11.4	4.3	3.1	0.033	4.5	0.005	7.1	<0.001

(Source: reviewer's results)
* Reviewer's note: p-values are not adjusted for multiple comparisons; positive changes indicate improvements

An analysis based on observed cases (OC) is presented in Table 15. The results based on observed cases appeared consistent with the LOCF analysis.

Table 15. Study ILP3005ST: reviewer's efficacy results: change from endpoint to baseline in BPRS total score (OC) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	102	72	92	60
LS Means *	13.9	13.5	14.4	9.3
Difference from placebo	4.6	4.2	5.1	
(95% confidence interval)	(1.3, 7.9)	(0.7, 7.8)	(1.7, 8.4)	
Unadjusted p-values	0.006	0.019	0.003	

(Source: reviewer's results)
Reviewer's note: positive changes indicate improvements

As a further supportive analysis of the primary results, a mixed-model for repeated measures (MMRM) was performed excluding schizoaffective patients. The model included baseline BPRS total score as a covariate, treatment, center, and visit

week as fixed factors, and treatment-by-visit interaction. The method of estimation was restricted maximum likelihood. The model utilized an unstructured within subject covariance structure. The results are presented in Table 16.

Table 16. Study ILP3005ST: reviewer's MMRM results: change from endpoint to baseline in BPRS total score (OC) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8mg	Placebo
LS Means	9.9	10.3	13.0	5.5
Difference from placebo	4.4	4.8	7.5	
(95% confidence interval)	(1.2, 7.7)	(1.3, 8.3)	(4.1, 10.9)	
Unadjusted p-values	0.008	0.008	<0.001	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

ANCOVA (LOCF) analysis on the PANSS (instead of the BPRS):
The primary efficacy variable for this study was the BPRS total score. Because other studies in this application used the PANSS total score, to check the consistency of the results, Table 17 presents the efficacy results using the PANSS total score. The results on the PANSS total score support the BPRS analysis.

Table 17. Study ILP3005ST: reviewer's efficacy results: change from endpoint to baseline in PANSS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Sample size	178	111	119	113
LS Means *	11.7	14.7	19.1	6.7
Difference from placebo	5.1	8.1	12.5	
(95% confidence interval)	(0.4, 9.7)	(2.9, 13.2)	(7.4, 17.6)	
Unadjusted p-values	0.034	0.002	<0.001	

(Source: reviewer's results)
Reviewer's note: positive changes indicate improvements

Initially, patients were randomized into one of the three treatment arms in a 2:1:1 ratio (iloperidone 12-16 mg, risperidone 6-8 mg, and placebo, respectively). When it was determined that patients might benefit from iloperidone at higher doses, iloperidone dose group 20-24 mg was added. From that point on, patients were randomized in a 1:2:1:1 ratio to one of the four arms: iloperidone 12-16 mg, iloperidone 20-24 mg, risperidone, or placebo, respectively. To evaluate the consistency of the treatment effect for patients entering the trial before and after the high dose group was added, this reviewer performed an analysis stratified by the entering date of the iloperidone 20-24 mg. The first patient in the iloperidone 20-24 mg group entered the study and had the first examination date on July 28, 2000. Thus in this analysis, all patients who enrolled and had their first examination date before July 28, 2000 were considered pre-dose group modification (pre-dose). Remaining patients were classified as post-dose group modification (post-dose). Table 18 summarizes this analysis. The treatment effect for the iloperidone 12-16 mg dose group was numerically seven times larger post-dose modification than pre-dose modification. An examination of the demographic and baseline characteristics (Appendix, Table 46) revealed that for

pre-dose modification patients, dose group 12-16 mg enrolled slightly younger patients, slightly more male patients, fewer Caucasians, and patients with slightly lower baseline BPRS total score. There were a number of investigational sites that started enrolling patients after the dose modification. These sites did not enroll any patients before the dose group 20-24 mg was added. There were 5 centers from the U.S. and Canada (17 subjects), 4 centers from Croatia (63 subjects), 3 centers from Germany (9 subjects), 1 center from Hungary (12 subjects), and 3 centers from Israel (26 subjects). It is not clear if these differences attribute to the difference in the observed treatment effects pre- and post-dose modification.

Table 18. Study ILP3005ST: reviewer's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample; Pre- versus Post-dose modification

	Ilo 12-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Pre-dose modification				
Sample size	68	NA	38	39
LS Means *	5.14		10.60	4.60
Difference from placebo	0.54		6.00	
(95% confidence interval)	(-5.20, 6.28)		(-0.35, 12.35)	
Unadjusted p-values	0.851		0.064	
Post-dose modification				
Sample size	110	111	81	74
LS Means *	8.05	9.27	11.32	4.43
Difference from placebo	3.63	4.84	6.90	
(95% confidence interval)	(0.02, 7.23)	(1.28, 8.41)	(3.07, 10.73)	
Unadjusted p-values	0.049	0.008	<0.001	

(Source: reviewer's results)
Reviewer's note: positive changes indicate improvements

In summary, this study demonstrated that iloperidone 12-16 mg/d and 20-24 mg/d were efficacious for the acute treatment of schizophrenia through the change from baseline to endpoint in the BPRS total score, with the effect in 12-16 mg/d group primarily seen after adding the 20-24 mg/d group. The high dose group exhibited a greater numerical improvement as compared to the low dose group. However, both iloperidone dose groups showed smaller numerical improvements as compared to risperidone.

3.1.3 Study VP-VYV-683-3101

3.1.3.1 Objectives

Primary: The primary objectives of the study are: 1) to evaluate the efficacy of a 24 mg/d iloperidone compared with placebo, administered twice daily over 28 days to schizophrenic patients and 2) to assess the efficacy of a 24 mg/d iloperidone dose in schizophrenic patients lacking the CNTF FS63Ter polymorphism compared with schizophrenic patients treated with placebo lacking the CNTF FS63Ter polymorphism

Secondary: The secondary objectives are:

- To assess the efficacy of a 24 mg/d iloperidone dose in schizophrenic patients lacking CNTF FS63Ter polymorphism versus iloperidone patients who harbor the CNTF FS63Ter polymorphism.
- To characterize the efficacy, tolerability and safety of a 24 mg/d iloperidone dose and a 160 mg/d ziprasidone dose compared with placebo, administered twice daily over 28 days to schizophrenic patients.

3.1.3.2 Study Design

This was a prospective, randomized, double-blind, placebo- and ziprasidone-controlled, parallel group, multi-center study. Patients were randomized in a 2:1:1 ratio to receive iloperidone (24 mg/day), ziprasidone (160 mg/day), or placebo, respectively. The study consisted of three phases: a pre-randomization phase (Days –14 to –3), a short-term double-blind phase (Days 1 to 28), and a long-term open-label phase. Patients went through the titration period from Days 1 to 7. Once the patients reached their target dose, they maintained on the dosage from Days 8 to 28. During the 4 weeks of the short-term phase, patients remained in the hospitals. Day passes could be allowed at the investigator's discretion during weeks 3 and 4. Patients who completed the short-term, double-blind phase had an option to continue receiving medication for an additional 175 days. This review will focus on the short-term, double-blind phase.

Between November 2005 and September 2006, patients between the ages of 18 and 65 years were recruited to participate in the study. They must have a diagnosis of schizophrenia according to the DSM-IV criteria with suffixes 10 (disorganized), 30 (paranoid), or 90 (undifferentiated); a CGI-S of at least 4 at baseline; a PANSS total score of at least 70 at screening and baseline; a rating of at least "4" ("moderate") on at least 2 of the following 4 PANSS positive symptoms: delusions, conceptual disorganization, hallucinatory behavior, and suspiciousness/persecution at screening and baseline.

The sample size calculation was based on the PANSS-derived BPRS change from baseline at endpoint. It was determined that 300 patients for iloperidone and 150 patients for placebo were needed to detect a 4-point difference at a 90% power and a two-sided alpha = 0.05. The standard deviations were assumed to be 11.9 for iloperidone, 12.6 for placebo, and 12.0 for ziprasidone.

3.1.3.3 Efficacy Endpoints and Analyses

Primary endpoint and analysis: The primary efficacy measurement was the change from baseline to endpoint of the PANSS total score. The primary endpoint was analyzed by an MMRM model with fixed terms for treatment, pooled center, time (visit day), baseline (covariate), and baseline-by-time, and treatment-by-time interactions. If the primary hypothesis was rejected, the null hypothesis that there was no difference between iloperidone and placebo-treated patients who lacked the *CNTF FS63Ter* polymorphism was tested. The primary endpoint was assessed at screening and baseline, on Days 7, 10, 14, 21, and 28 or early discontinuation.

3.1.3.4 Efficacy Results

3.1.3.4.1 Study Population

This study was conducted in 32 U.S. centers and 9 Indian centers. Five hundreds and ninety three (593) subjects were randomized in a 2:1:1 ratio to iloperidone, ziprasidone, or placebo. About 35% of the subjects discontinued the study prematurely. The primary reasons for discontinuation were consent withdrawal and unsatisfactory therapeutic effect. Consent withdrawals were higher in the iloperidone group than in the ziprasidone and placebo arms. Dropouts due to adverse events were lower in iloperidone arm than in ziprasidone and placebo. Table 19 summarizes the disposition of the randomized sample.

Table 19. Study VP-VYV-683-3101: disposition of patients (randomized sample)

	Ilo 24 mg/d N= 303	Zipra 160 mg/day N= 151	Placebo N= 152	Total N= 606
Randomization assigned in error	8	2	3	13
Randomized patients	295 (97.4)	149 (98.7)	149 (98.0)	593 (97.9)
Discontinued (days 1-28) – n (%)				
Protocol deviation	2 (2.0)	1 (2.0)	1 (1.7)	4 (1.9)
Adverse event(s)	16 (15.7)	13 (25.5)	11 (18.6)	40 (18.9)
Lost to follow-up	0	0	2 (3.4)	2 (0.9)
Death	0	0	0	0
Consent withdrawal	59 (57.8)	23 (45.1)	21 (35.6)	103 (48.6)
Unsatisfactory therapeutic effect	21 (20.6)	12 (23.5)	19 (32.2)	52 (24.5)
Other	4 (3.9)	2 (3.9)	5 (8.5)	11 (5.2)
Completed (days 1-42)	193 (65.4)	98 (65.8)	90 (60.4)	381 (64.2)

(Source: vp-vyv-683-3101 Report; Table 8, page 54)

The demographic and baseline disease characteristics of the randomized sample are summarized in Table 20. Subjects in the study were between the age of 18 and 65 with an average age of 40 years old. About 80% of the subjects were male. Black/African Americans accounted for about 50% of the patients and Caucasians accounted for another 35%. The majority of patients were diagnosed with paranoid form of schizophrenia. The baseline PANSS total score was 92 on average.

Table 20. Study VP-VYV-683-3101: demographic and baseline disease characteristics (randomized sample)

	Ilo 24 mg/d N= 295	Zipra 160 mg/d N= 149	Placebo N= 149	Total N= 593
Age (yr) n				
Mean (SD)	39.5 (10.4)	40.0 (9.9)	40.7 (10.4)	39.9 (10.3)
Median	41.0	41.0	41.0	41.0
Min – Max	18 – 65	20 – 61	19 – 64	18 – 65
Sex – n (%)				
Male	245 (83.1)	113 (75.8)	114 (76.5)	472 (79.6)
Female	50 (17.0)	36 (24.2)	35 (23.5)	121 (20.4)
Race – n (%)				
Caucasian	111 (37.6)	51 (34.2)	46 (30.9)	208 (35.2)
Black	147 (49.8)	76 (51.0)	76 (51.0)	299 (50.4)
Asian	25 (8.5)	12 (8.1)	15 (10.1)	52 (8.8)
Other	12 (4.1)	10 (6.7)	12 (8.1)	34 (5.7)
DSM-IV diagnosis				
Disorganized	13 (4.4)	3 (2.0)	7 (4.7)	23 (3.9)
Paranoid	246 (83.4)	127 (85.2)	128 (85.9)	501 (84.5)
Undifferentiated	36 (12.2)	19 (12.8)	14 (9.4)	69 (11.6)
Baseline PANSS-total score				
N	294	148	145	587
Mean (SD)	92.7 (13.1)	90.9 (11.5)	90.3 (11.2)	91.7 (12.2)
Median	91	90	89	90
Min – Max	70 – 139	70 – 130	71 – 117	70 – 139

(Source: vp-vyv-683-3101 Report; Tables 10, 7.4-2, pages 57, 123)

3.1.3.4.2 Sponsor's Efficacy Results for Primary Endpoint

The primary endpoint was the change from baseline in PANSS total score. The primary analysis model was a mixed model for repeated measures with adjusted baseline score as a fixed covariate, treatment, pooled center, visit time as fixed factors, treatment-by-time and baseline-by-time interaction. The within subject covariance matrix was unstructured. The primary efficacy analysis was based on the modified intent-to-treat (MITT) analysis set. All randomized subjects who have a baseline and at least one post-baseline assessment were included. The sponsor's primary efficacy result is presented in Table 21.

Table 21. Study VP-VYV-683-3101: Sponsor's Primary Efficacy Results: Change from Baseline in PANSS total score in the MITT sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Sample size	283	144	140
LS Means*	-12.0	-12.3	-7.1
Difference from placebo	-4.9	-5.2	
(95% confidence interval)	(-8.5, -1.4)	(-9.2, -1.1)	
Unadjusted p-values	0.007	0.012	

(Source: vp-vyv-683-3101 Report; Table 9.2.1-2a, page 201)

* Reviewer's note: negative differences indicate improvement.

3.1.3.4.3 Sponsor's Efficacy Results for Key Secondary Endpoint

The sponsor's results on the key secondary endpoint are presented in Table 22. Patients in the iloperidone group lacking the *CNTF* polymorphism (*CNTF (-)*)

exhibited a significantly greater improvement from baseline in PANSS total score than did patients in the placebo group who also lacked the *CNTF* polymorphism.

Table 22. Study VP-VYV-683-3101: Reviewer's Primary Efficacy Results by genetic subgroups: Change from Baseline in PANSS total score in the MITT sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
CNTF (+)			
Sample size	61	23	31
LS Means*	-12.1	-11.0	-12.3
Difference from placebo	0.3	1.4	
(95% confidence interval)	(-7.2, 7.8)	(-7.9, 10.7)	
Unadjusted p-values	0.944	0.770	
CNTF (−)			
Sample size	218	118	107
LS Means*	-12.1	-12.4	-5.7
Difference from placebo	-6.3	-6.7	
(95% confidence interval)	(-10.4, -2.3)	(-11.2, -2.1)	
Unadjusted p-values	0.002	0.004	

(Source: Reviewer's results. These results are slightly different than the sponsor's results reported on vp-vyv-683-3101 Report; Table 9.2.1-2b, page 203)
* Reviewer's note: negative differences indicate improvement.

3.1.3.4.4 Sponsor's Other Efficacy Results

Primary analysis on the BPRS (instead of the PANSS):

The sponsor also performed an analysis using the BPRS total score instead of the PANSS total score. The results are reported in Table 23. The results are consistent with the primary analysis.

Table 23. Study VP-VYV-683-3101: Sponsor's Efficacy Results: Change from Baseline in BPRS total score in the MITT sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Sample size	283	144	140
LS Means*	-7.4	-7.2	-4.6
Difference from placebo	-2.8	-2.6	
(95% confidence interval)	(-5.0, -0.6)	(-5.1, -0.1)	
Unadjusted p-values	0.013	0.042	

(Source: vp-vyv-683-3101 Report; Table 9.2.2-2a, page 231)
* Reviewer's note: negative differences indicate improvement.

Primary analysis over time:

The primary analysis over time is presented in Table 24. Consistent numerical improvements for iloperidone were seen from week 2 to week 4.

Table 24. Study VP-VYV-683-3101: Adjusted mean change from baseline up to end of week 6 in the PANSS total score, MMRM analysis; MITT sample

	Ilo 24mg	Zip 160mg	Pbo	Ilo 24mg - Pbo Diff	Ilo 24mg - Pbo p-value*	Zip - Pbo Diff	Zip - Pbo p-value*
Week 1	-4.3	-6.6	-4.2	-0.1	0.942	-2.3	0.060
Week 2	-8.7	-10.0	-5.8	-2.8	0.063	-4.2	0.015
Week 3	-10.6	-11.5	-6.8	-3.7	0.023	-4.7	0.012
Week 4	-12.0	-12.3	-7.1	-4.9	0.007	-5.2	0.012

(Source: vp-vyv-683-3101 Report; Table 9.2.1-2a, pages 200-201)

* Reviewer's note: p-values are not adjusted for multiple comparisons; positive changes indicate improvements

Primary endpoint ANCOVA (LOCF)

An ANCOVA analysis on the change from baseline to week 4 with missing values imputed by the last observation carried forward (LOCF) method agrees with the primary analysis. The results are presented in Table 25 and Table 26.

Table 25. Study VP-VYV-683-3101: Sponsor's Primary Efficacy Sensitivity Analysis: Change from Baseline in PANSS total score in the MITT sample (LOCF)

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Sample size	283	144	140
LS Means*	-11.1	-12.0	-6.8
Difference from placebo	-4.2	-5.1	
(95% confidence interval)	(-7.5, -0.9)	(-8.9, -1.3)	
Unadjusted p-values	0.014	0.008	

(Source: vp-vyv-683-3101 Report; Table 9.2.1-3a, page 206)

* Reviewer's note: negative difference signifies improvement.

Table 26. Study VP-VYV-683-3101: Reviewer's Efficacy Results by genetic subgroups: Change from Baseline in PANSS total score in the MITT sample (LOCF)

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
CNTF (+)			
Sample size	61	23	31
LS Means*	-13.8	-13.3	-12.1
Difference from placebo	-1.7	-1.2	
(95% confidence interval)	(-10.7, 7.3)	(-11.5, 9.2)	
Unadjusted p-values	0.711	0.822	
CNTF (−)			
Sample size	218	118	107
LS Means*	-11.3	-11.6	-5.6
Difference from placebo	-5.7	-6.0	
(95% confidence interval)	(-9.4, -2.0)	(-10.2, -1.8)	
Unadjusted p-values	0.003	0.005	

(Source: reviewer's results)

* Reviewer's note: negative difference signifies improvement.

An analysis based on the change from baseline to week 4 using observed cases (OC) did not reveal a difference between iloperidone and placebo. The observed

treatment difference diminishes as compared to the MMRM and LOCF analyses. This was probably due to a higher effect seen in the placebo group.

Table 27. Study VP-VYV-683-3101: Sponsor's Primary Efficacy Sensitivity Analysis: Change from Baseline in PANSS total score in the OC sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Sample size	200	102	93
LS Means*	-14.6	-16.4	-12.8
Difference from placebo	-1.8	-3.6	
(95% confidence interval)	(-5.3, 1.8)	(-7.6, 0.4)	
Unadjusted p-values	0.334	0.078	

(Source: vp-vyv-683-3101 Report; Table 9.2.1-3a, page 209)
* Reviewer's note: negative difference signifies improvement.

3.1.3.4.5 Reviewer's Results and Comments
This reviewer confirms the findings on the primary analysis and key secondary analysis as presented in Table 21 and Table 22. Iloperidone at 24 mg/day is effective in lowering the PANSS total score from baseline to Week 4.

On March 14, 2008 teleconference with the Division of Scientific Investigations, complications in the inspection of Site # 032 were reported. Site #032 contributed 11 subjects to the study. The following table presents an analysis of the primary efficacy variable with Site # 032 excluded.

Table 28. Study VP-VYV-683-3101: Reviewer's Primary Efficacy Results: Change from Baseline in PANSS total score in the MITT sample (Site #032 excluded)

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Sample size	276	143	137
LS Means*	-11.8	-12.1	-8.1
Difference from placebo	-3.8	-4.0	
(95% confidence interval)	(-7.3, -0.3)	(-8.0, -0.0)	
Unadjusted p-values	0.036	0.047	

(Source: Reviewer's results)
* Reviewer's note: negative difference signifies improvement.

3.1.4 Study ILP3000ST

This was a prospective, randomized, double-blind, parallel-group, multi-center, United States study that included three phases: pre-randomization (Day –30 to Day 0), initial double-blind (Days 1 - 42), and long-term double-blind (Days 43 – 182). The pre-randomization period included screening and a 3-day single-blind placebo run-in. The initial double-blind phase included a titration period and a fixed-dose maintenance period. After completing the 6-week initial double-blind phase, patients had the option to continue treatment in the long-term double-blind phase. The first patient recruited for the study was in October, 1998. The last patient completed the study was in August, 1999.

The primary objectives of the initial double-blind phase (first 6 weeks) were to determine the efficacy and safety of iloperidone 4, 8, and 12 mg/d (administered as 2, 4, and 6 mg twice daily) and haloperidol 15 mg/day (7.5 mg twice daily) compared to that

of placebo over 42 days in schizoaffective or schizophrenic patients with acute or subacute exacerbation.

The primary efficacy variable was the change from baseline to the end visit (Day 42 or premature discontinuation) on the total score of the PANSS. The primary analysis model was an analysis of covariance (ANCOVA) with terms for treatment, center, baseline (as covariate), and the treatment-by-baseline interaction. The baseline was adjusted by subtracting each baseline score by the average of all baseline scores. Missing values were imputed by the Last-Observation-Carried-Forward (LOCF) method. The primary comparison of interest was between the combined 8 mg/day and 12 mg/day dose groups and placebo.

The sponsor's primary efficacy result is presented in Table 39 in the Appendix. The trial was inconclusive on separating the combined iloperidone 8 mg/day and 12 mg/day from placebo (p-value = 0.065).

The efficacy results presented in Table 39 included 31% of schizoaffective patients. Because the indication sought is schizophrenia, to explore the efficacy of iloperidone among schizophrenia patients, this reviewer performed an analysis excluding schizoaffective patients. The results in Table 40 in the Appendix revealed that iloperidone 8 mg and 12 mg combined group did not separate from placebo (p-value=0.148).

Based on the primary comparison of interest, the combined iloperidone 8 mg and 12 mg doses did not separate from placebo. Haloperidol arm provided assay sensitivity for this study. Therefore, this reviewer deemed this study negative. The labeling claim that the 12 mg dose group was superior to placebo was post-hoc and did not have a regulatory merit.

3.1.5 Studies ILP3001, ILP3002, ILP3003

These were randomized, multi-center, double-blind, active-controlled, flexible dose studies. Subjects were randomized in a 3:1 ratio to either iloperidone 4-16 mg/day or haloperidol 5-20 mg/day. The duration of each study was 52 weeks. These studies included both schizoaffective and schizophrenia patients. They were conducted between 1999 and 2001.

Originally, the primary variable was the change from baseline to Week 52 in the PANSS total score. During the interactions with the European Medicines Evaluation Agency (EMEA), the sponsor was advised that, in order to demonstrate the long-term maintenance effect, efficacy analyses should be based on a time to relapse of schizophrenia/schizoaffective symptoms. Relapse was defined as any of the following: a) an increase (worsening) of the PANSS total score of at least 25%, including at least a 10 point increase; b) discontinuation due to lack of efficacy; c) aggravated psychosis with hospitalization; or d) a 2-point increase (worsening) of the CGI-C score after Week 6. Based upon the advice from the EMEA, the protocols were amended to include the time to relapse analysis. The primary efficacy analysis was amended to use pooled data

from studies ILP3001, ILP3002, and ILP3003. Patients were included in the analysis population for the primary efficacy endpoint of the pooled analysis if they responded to treatment after 6 weeks. Responders were defined as those who completed the initial double-blind phase of 6 weeks, showed a reduction in the PANSS total score of at least 20% at Weeks 4 and 6 compared to baseline, had a CGI Improvement score of less that 4, took at least one dose of long-term double-blind study medication, and had at least one efficacy assessment during the long-term double-blind phase. Based on a pooled analysis of these three studies, the sponsor concluded that iloperidone was non-inferior to haloperidol on the time to relapse.

These studies had several limitations. The non-inferiority design is not thought of as an optimal design for the schizophrenia indication. The studies did not include a placebo arm that made the interpretation of the non-inferiority more difficult. The pooling of studies for efficacy analysis is not the current standard practice for the Division of Psychiatry. More seriously, by changing the analysis plan from a change-from-baseline analysis to a time-to-relapse analysis, the analysis population was amended. Only patients who responded at Day 42 were included in the time-to-relapse analysis. Thus, the randomization may be violated.

For these reasons, the results on the long-term efficacy of iloperidone were not evaluated in this review and any potential claims with respect to the long-term efficacy of iloperidone were diminished.

3.2 Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Study ILP3004ST

4.1.1.1 Gender

The primary analysis stratified by gender for the schizophrenia subsample is presented below. Risperidone group had the largest mean change from baseline for both males and females. Iloperidone 4-8 mg/d group showed a marginal numerical improvement over placebo for both males and females. Iloperidone 10-16mg/d dose group appeared worse than placebo among females. However, the sample size for female patients was only about a third of the sample sizes for male patients.

Table 29. Study ILP3004ST: reviewer's primary efficacy results by gender: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
Female				
Sample size	33	36	21	33
LS Means *	5.43	3.97	11.67	4.39
Difference from placebo	1.04	-0.42	7.29	
(95% confidence interval)	(-6.61, 8.69)	(-7.65, 6.82)	(-1.81, 16.38)	
Unadjusted p-values	0.787	0.909	0.115	
Male				
Sample size	82	85	89	83
LS Means *	5.97	5.72	9.30	4.85
Difference from placebo	1.13	0.87	4.46	
(95% confidence interval)	(-2.66, 4.91)	(-2.83, 4.57)	(0.81, 8.10)	
Unadjusted p-values	0.559	0.644	0.017	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

4.1.1.2 Race

Because 60% of the subjects were Caucasian and 33% of the subjects were black/African American, race was dichotomized into Caucasian versus others. The primary analysis stratified by race is summarized below. It doesn't appear that iloperidone worked consistently for Caucasian and other patients.

Table 30. Study ILP3004ST: reviewer's primary efficacy results by race: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
Caucasian				
Sample size	48	48	42	52
LS Means *	10.13	5.77	11.78	7.23
Difference from placebo	2.90	-1.46	4.55	
(95% confidence interval)	(-1.86, 7.66)	(-6.26, 3.34)	(-0.26, 9.37)	
Unadjusted p-values	0.230	0.549	0.063	
Others				
Sample size	67	73	68	64
LS Means *	4.77	6.80	10.52	5.08
Difference from placebo	-0.32	1.72	5.43	
(95% confidence interval)	(-4.87, 4.24)	(-2.65, 6.09)	(0.98, 9.89)	
Unadjusted p-values	0.892	0.438	0.017	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

4.1.1.3 Age

Because the majority of the subjects (99%) were under the age of 65, the primary efficacy analysis stratified by age was omitted from this review.

4.1.2 Study ILP3005ST

4.1.2.1 Gender

The primary analysis by gender is presented below. The treatment differences appeared larger for female patients than male patients.

Table 31. Study ILP3005ST: reviewer's primary efficacy results by gender: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 10-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Female				
Sample size	65	30	46	43
LS Means *	8.83	10.97	15.00	3.75
Difference from placebo	5.09	7.22	11.25	
(95% confidence interval)	(0.32, 9.85)	(1.43, 13.02)	(5.87, 16.62)	
Unadjusted p-values	0.037	0.015	<0.001	
Male				
Sample size	113	81	73	70
LS Means *	6.48	7.98	9.88	4.17
Difference from placebo	2.32	3.81	5.71	
(95% confidence interval)	(-1.46, 6.10)	(-0.20, 7.83)	(1.53, 9.90)	
Unadjusted p-values	0.229	0.062	0.008	

(Source: reviewer's results)

* Reviewer's note: positive changes indicate improvements

4.1.2.2 Race

Because 70% of the subjects were Caucasian and 24% of the subjects were Black, race was dichotomized to Caucasians versus others. The primary analysis stratified by race is presented below. The effect of iloperidone 10-16 mg/d was similar for Caucasians and other races. The effect of iloperidone 20-24 mg/d was seen only in the Caucasian patients.

Table 32. Study ILP3005ST: reviewer's primary efficacy results by gender: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 10-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
Caucasians				
Sample size	128	78	92	76
LS Means *	6.02	8.34	10.86	2.19
Difference from placebo	3.83	6.15	8.67	
(95% confidence interval)	(0.25, 7.42)	(2.21, 10.09)	(4.84, 12.49)	
Unadjusted p-values	0.036	0.002	<0.001	
Others				
Sample size	50	33	27	37
LS Means *	10.79	7.57	11.57	7.57
Difference from placebo	3.21	0.00	3.99	
(95% confidence interval)	(-1.81, 8.24)	(-5.76, 5.76)	(-1.77, 9.76)	
Unadjusted p-values	0.208	1.000	0.173	

(Source: reviewer's results)

* Reviewer's note: positive changes indicate improvements

4.1.2.3 Age

Because schizophrenia subjects in this study were between 18 and 65 years old, the analysis stratified by age was omitted from this review.

4.1.3 Study VP-VYV-683-3101

4.1.3.1 Gender

The primary analysis stratified by gender is presented below. It appeared that the treatment differences were larger for female patients than for male patients. However, iloperidone appeared to be efficacious in both males and females.

Table 33. Study VP-VYV-683-3101: Reviewer's Primary Efficacy Results by Gender: Change from Baseline in PANSS total score in the MITT sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Females			
Sample size	49	36	31
LS Means*	-16.01	-16.07	-7.25
Difference from placebo	-8.76	-8.83	
(95% confidence interval)	(-17.07, -0.45)	(-17.65, -0.00)	
Unadjusted p-values	0.039	0.050	
Males			
Sample size	234	108	109
LS Means*	-11.25	-11.27	-6.38
Difference from placebo	-4.86	-4.88	
(95% confidence interval)	(-8.79, -0.94)	(-9.45, -0.32)	
Unadjusted p-values	0.015	0.036	

(Source: reviewer's results)

* Reviewer's note: negative difference signifies improvement.

4.1.3.2 Race

Due to small sample sizes, race was dichotomized into Black/African Americans versus Caucasians/Others. The primary efficacy analysis by race is presented below. A larger treatment difference was seen for Caucasian/Other races as compared to Black/African American patients. This could be due to the large placebo effect in Black/African Americans.

Table 34. Study VP-VYV-683-3101: Reviewer's Primary Efficacy Results by Race: Change from Baseline in PANSS total score in the MITT sample

	Ilo 24 mg/d	Zipra 160 mg/d	Placebo
Caucasians/Others			
Sample size	142	72	67
LS Means*	-11.80	-11.47	-4.43
Difference from placebo	-7.37	-7.04	
(95% confidence interval)	(-12.97, -1.77)	(-13.43, -0.65)	
Unadjusted p-values	0.010	0.031	
Black/African Americans			
Sample size	141	72	73
LS Means*	-12.57	-14.00	-10.37
Difference from placebo	-2.20	-3.63	
(95% confidence interval)	(-6.74, 2.34)	(-8.82, 1.57)	
Unadjusted p-values	0.342	0.171	

(Source: reviewer's results)

* Reviewer's note: negative difference signifies improvement.

4.1.3.3 Age

Because subjects in this study were between 18 and 65 years old, an analysis stratified by age was omitted from this review.

4.2 Other Subgroups

4.2.1 Study ILP3004ST

4.2.1.1 U.S.A. versus non-U.S.A.

The primary analysis stratified by U.S. versus non-U.S. is summarized below. The responses seemed to be higher among U.S. patients.

Table 35. Study ILP3004ST: reviewer's primary efficacy results by region: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 4-8 mg	Ilo 10-16 mg	Risp	Placebo
U.S.A.				
Sample size	55	62	49	59
LS Means *	6.22	4.62	8.99	2.36
Difference from placebo	3.85	2.26	6.63	
(95% confidence interval)	(-0.78, 8.49)	(-2.14, 6.65)	(2.06, 11.20)	
Unadjusted p-values	0.102	0.312	0.005	
Non-U.S.A.				
Sample size	60	59	61	57
LS Means *	6.68	8.76	12.22	7.83
Difference from placebo	-1.14	0.94	4.39	
(95% confidence interval)	(-5.80, 3.52)	(-3.70, 5.57)	(-0.22, 9.01)	
Unadjusted p-values	0.629	0.691	0.062	

(Source: reviewer's results)

* Reviewer's note: positive changes indicate improvements

4.2.2 Study ILP3005ST

4.2.2.1 U.S.A. versus non-U.S.A.

Subjects from this study came from Canada, Croatia, Germany, Hungary, Israel, Poland, South Africa, and the United States. The primary analysis stratified by U.S. versus non-U.S. is presented below. Larger numerical treatment effects were seen in both iloperidone groups in non-U.S.A. patients as compared to U.S.A. patients.

Table 36. Study ILP3005ST: reviewer's primary efficacy results by region: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample

	Ilo 10-16 mg	Ilo 20-24 mg	Risp 6-8 mg	Placebo
U.S.A.				
Sample size	75	50	48	53
LS Means *	6.53	6.66	8.99	5.44
Difference from placebo	1.08	1.21	3.54	
(95% confidence interval)	(-3.06, 5.22)	(-3.32, 5.74)	(-0.98, 8.07)	
Unadjusted p-values	0.607	0.599	0.124	
Non-U.S.A.				
Sample size	103	61	71	60
LS Means *	8.33	10.56	13.28	3.45
Difference from placebo	4.89	7.11	9.84	
(95% confidence interval)	(1.02, 8.75)	(2.80, 11.42)	(5.65, 14.02)	
Unadjusted p-values	0.014	0.001	<0.001	

(Source: reviewer's results)
* Reviewer's note: positive changes indicate improvements

4.2.3 Study VP-VYV-683-3101

Because the majority of the subjects from this study were from the U.S.A., the primary analysis stratified by country was omitted.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The sponsor submitted four short-term studies and three long-term studies. Except study VP-VYV-683-3101, all studies included both schizophrenia and schizoaffective patients. The sponsor claimed all four studies demonstrated at least one positive dose against placebo. However, based on the primary hypotheses, only one study was positive for the schizophrenia and schizoaffective population: Study ILP3004ST.

On the other hand, when considering the schizophrenia sample only, study ILP3004ST was no longer positive. Instead, studies ILP3005ST and VP-VYV-683-3101 were positive.

Study VP-VYV-683-3101 evaluated the dose 24 mg/day. Study ILP3005ST evaluated two dose groups: 12-16 mg/day and 20-24 mg/day. Although both dose groups showed statistical significance against placebo based on the primary analysis, evidence for the high dose group (20-24 mg/day) appeared stronger than for the dose group 12-16 mg/day. The dose group 20-24 mg/day seemed to have a larger numerical treatment difference against placebo than the dose group 12-16 mg/day. Though study ILP3005ST was not designed to compare the active control (risperidone) to iloperidone, numerical evidence suggested that the active control resulted in a larger treatment effect than the low dose group (see Appendix, Table 45). In addition, in study ILP3004ST, the dose group 10-16 mg/day did not separate from placebo.

The three long-term studies were active control, non-inferior studies. These studies faced several limitations. Currently, the Division of Psychiatry does not consider a non-inferior, active-controlled study as an appropriate design for the schizophrenia indication.

Originally, the study was planned for an analysis of change from baseline to endpoint in the PANSS total score. However, during the interactions with the European Medicines Evaluation Agency, the analysis was changed to a time to recurrence of schizophrenia/schizoaffective symptoms. The analysis population was also amended to reflect the new efficacy endpoint. The efficacy evaluations were based on the pooled data from studies ILP3001, ILP3002, and ILP3003. More importantly, only patients who responded at Day 42 were included in the analysis population of the long-term maintenance. Thus the randomization may be compromised. Furthermore, the pooling of studies for efficacy evaluation is not the current standard practice of the Division of Psychiatry. In addition, these studies did not include a placebo arm that made the interpretation difficulty for this indication. For these reasons, the value of the long-term efficacy claim is diminished.

Several secondary endpoints (BPRS, PANSS positive subscale, PANSS negative subscale, CGI Improvement, CGI-Severity) were claimed. However, they were not pre-specified and thus can only serve as exploratory findings.

The findings on the *CNTF FS63Ter* subgroup were suggestive, but not conclusive to support labeling claims for the following reasons: 1) in study VP-VYV-683-3101, the findings suggested a greater treatment effect in the *CNTF* (-) subgroup; however, in the *CNTF* (+) subgroup, the treatment benefit appeared vanished; 2) in study ILP3005ST, an exploratory analysis was performed on the *CNTF* genotype subgroup, the findings in study ILP3005ST were not consistent with the findings in study VP-VYV-683-3101: numerical improvements were seen in both *CNTF* subgroups; 3) an analysis based on study ILP3005ST was post-hoc. Thus, the findings on study VP-VYV-683-3101 regarding the *CNTF* subgroup have not been replicated.

Study ILP3005ST was an international study. The numerical treatment effects observed for the two iloperidone dose groups were marginal for the United States (U.S.) patients and were about one-fifth of the treatment effects seen in the non-U.S. patients. However, study VP-VYV-683-3101 was a predominant U.S. study and it was positive.

5.2 Conclusions and Recommendations

The sponsor submitted four short-term studies and three long-term studies to seek claims for efficacy and safety of iloperidone in the treatment of adult schizophrenia. Efficacy for the schizophrenia subsample was demonstrated from two studies: ILP3005ST and VP-VYV-683-3101. The efficacy in study ILP3005ST was demonstrated by the change from baseline to Week 6 in the Brief Psychiatric Rating Scale (BPRS) total score. The efficacy in study VP-VYV-683-3101 was demonstrated by the change from baseline to Week 4 in the Positive and Negative Syndrome Scale (PANSS) total score.

In study ILP3005ST, the PANSS total score, PANSS positive subscale, PANSS negative subscale, CGI severity scale, and CGI improvement scale were not pre-specified. They only serve exploratory purposes and do not support labeling claims.

In study VP-VYV-683-3101, the BPRS total score, PANSS positive subscale, PANSS negative subscale, CGI severity scale, and CGI improvement scale were not pre-specified. They do not support labeling claims.

Study ILP3000ST was considered negative based on the primary hypothesis. All labeling efficacy claims with respect to this study were not justified.

The findings based on the genetic subgroup that the treatment benefit was enhanced among patients carrying the *CNTF FS63Ter* (-/-) genotype were suggestive, but not conclusive to support labeling claims.

The long-term non-inferiority claim based on studies ILP3001, ILP3002, and ILP3003 did not have a regulatory merit given the designs and analyses of these studies.

6. APPENDIX

This appendix contains supplemental tables and figures that were not presented in the main text.

6.1 Study ILP3000ST

Table 37. Study ILP3000ST: disposition of patients

	Ilo 4 mg/d N= 121	Ilo 8 mg/d N= 125	Ilo 12 mg/d N= 124	Hal 15 mg/d N= 124	Placebo N= 127	Total N=621
Discontinued (days 1-42) – n (%)	69 (57.0)	80 (64.0)	72 (58.1)	81 (65.3)	87 (68.5)	389 (62.6)
Adverse experiences	6 (5.0)	12 (9.6)	7 (5.7)	11 (8.9)	8 (6.3)	44 (7.1)
Unsatisfactory therapeutic effect	36 (29.8)	38 (30.4)	36 (29.0)	31 (25.0)	44 (34.7)	185 (29.8)
Protocol violation	1 (0.8)	2 (1.6)	3 (2.4)	4 (3.2)	1 (0.8)	11 (1.8)
Withdrawal of consent	18 (14.9)	21 (16.8)	22 (17.7)	29 (23.4)	26 (20.5)	116 (18.7)
Lost to follow-up	6 (5.0)	5 (4.0)	2 (1.6)	6 (4.8)	5 (3.9)	24 (3.9)
Administrative problems	2 (1.7)	2 (1.6)	2 (1.6)	0 (0.0)	3 (2.4)	9 (1.4)
Completed (days 1-42)	52 (43.0)	45 (36.0)	52 (41.9)	43 (34.7)	40 (31.5)	232 (37.4)

(Source: ILP3000st-legacy Report; Table 7-1, page 50)

Table 38. Study ILP3000ST: demographic and baseline disease characteristics (randomized sample)

	Ilo 4 mg/d N= 121	Ilo 8 mg/d N= 125	Ilo 12 mg/d N= 124	Hal 15mg/d N = 124	Placebo N= 127	Total N=.621
Age (yr)						
Mean (SD)	38.4 (8.9)	37.0 (9.6)	40.1 (10.1)	39.1 (9.4)	39.3 (10.2)	38.8 (9.7)
Median	39.0	38.0	41	40.0	39.0	39.0
Min – Max	21 – 65	18 – 68	18 – 68	19 – 59	19 – 66	18 - 68
Sex – n (%)						
Male	82 (67.8)	94 (75.2)	91 (73.4)	85 (68.6)	90 (70.9)	442 (71.2)
Female	39 (32.2)	31 (24.8)	33 (26.6)	39 (31.5)	37 (29.1)	179 (28.8)
Race – n (%)						
Caucasian	57 (47.1)	49 (39.2)	67 (54.0)	58 (46.8)	64 (50.4)	295 (47.5)
Black	52 (43.0)	58 (46.4)	44 (35.5)	54 (43.6)	55 (43.3)	263 (42.4)
Other	12 (9.9)	18 (14.4)	13 (10.5)	12 (9.7)	8 (6.3)	63 (10.2)
DSM-IV diagnosis – n (%)						
Disorganized	2 (1.7)	4 (3.2)	3 (2.4)	2 (1.6)	2 (1.6)	13 (2.1)
Paranoid	76 (62.8)	67 (53.6)	71 (57.3)	62 (50.0)	68 (53.5)	344 (55.4)
Residual	0 (0.0)	0 (0.0)	1 (0.8)	1 (0.8)	0 (0.0)	2 (0.3)
Schizoaffective	32 (26.5)	37 (29.6)	35 (28.2)	46 (37.1)	43 (33.9)	193 (31.2)
Undifferentiated	11 (9.1)	16 (12.8)	14 (11.3)	13 (10.5)	14 (11.0)	68 (11.0)
Missing		1 (0.8)				1 (0.2)
Baseline PANSS-total score						
N	121	123	123	119	127	613
Mean (SD)	95.2 (15.4)	96.0 (15.8)	95.8 (16.0)	95.7 (15.5)	94.6 (16.8)	95.4 (15.9)
Median	94	94	95	93	94	94
Min – Max	66 – 145	64 – 157	61 – 145	62 – 134	60 – 146	60 – 157

(Source: ILP3000st-legacy Report; Tables 7.4-1 & 7.4-2, pages 351 & 355 and reviewer's results)

Table 39. Study ILP3000ST: sponsor's primary efficacy results: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal	Placebo
Sample size	113	114	115	229	115	117
LS Means*	9.0	7.8	9.9		13.9	4.6
Difference from	4.4	3.2	5.2	4.2	9.3	
placebo (95% CI)	(-0.8, 9.5)	(-2.0, 8.3)	(0.1, 10.4)	(-0.3, 8.6)	(4.1, 14.4)	
Unadjusted p-values	0.097	0.228	0.047	0.065	<0.001	

(Source: Reproduced from ILP3004st-legacy Report; Table 9.1-2, page 492 and reviewer's results)
* Reviewer's note: Positive changes indicate improvements

Table 40. Study ILP3000ST: change from endpoint to baseline in PANSS total score (LOCF) in the MITT sample (excluding schizoaffective patients)

	Ilo 4 mg	Ilo 8 mg	Ilo 12 mg	Ilo 8+12mg	Hal	Placebo
Sample size	83	78	82	160	70	78
LS Means*	9.2	4.8	10.1		12.9	3.5
Difference from	5.7	1.4	6.7	4.0	9.4	
placebo (95% CI)	(-0.5, 12.0)	(-4.9, 7.7)	(0.4, 13.0)	(-1.4, 9.5)	(2.9, 16.0)	
Unadjusted p-values	0.072	0.666	0.037	0.148	0.005	

(Source: reviewer's results)
* Reviewer's note: Positive changes indicate improvements

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6.2 Study ILP3004ST

Table 41. Study ILP3004ST: disposition of patients (excluding schizoaffective patients)

	Ilo 4-8 mg/d N=123	Ilo 10-16 mg/d N=125	Risp 4-8 mg/d N=115	Placebo N=119	Total N=482
Discontinued (days 1-42) – n (%)	66 (53.7)	55 (44.0)	48 (41.7)	66 (55.5)	235 (48.8)
Adverse experiences	3 (2.4)	5 (4.0)	9 (7.8)	6 (5.0)	23 (4.8)
Unsatisfactory therapeutic effect	31 (25.2)	26 (20.8)	17 (14.8)	47 (39.5)	121 (25.1)
Protocol violation	1 (0.8)	1 (0.8)	1 (0.9)	0 (0.0)	3 (0.6)
Withdrawal of consent	25 (20.3)	20 (16.0)	11 (9.6)	8 (6.7)	64 (13.3)
Lost to follow-up	6 (4.9)	3 (2.4)	10 (8.7)	5 (4.2)	24 (5.0)
Completed (days 1-42)	57 (46.3)	70 (56.0)	67 (58.3)	53 (44.5)	247 (51.2)

(Source: Reviewer's results)

Table 42. Study ILP3004ST: demographic and baseline disease characteristics (randomized sample) (excluding schizoaffective patients)

	Ilo 4-8 mg/d N=123	Ilo 10-16 mg/d N=125	Risp 4-8 mg/d N=115	Placebo N=119	Total N=482
Age (yr) n					
Mean (SD)	38.5 (11.3)	38.9 (10.3)	37.2 (12.0)	37.9 (10.5)	38.1 (11.0)
Median	40.0	39.0	36.0	38.0	39.0
Min – Max	19 – 64	18 – 66	17 – 67	19 – 66	17 – 67
Sex – n (%)					
Male	88 (71.5)	89 (71.2)	92 (80.0)	85 (71.4)	354 (73.4)
Female	35 (28.5)	36 (28.8)	23 (20.0)	34 (28.6)	128 (26.6)
Race – n (%)					
Caucasian	71 (57.7)	75 (60.0)	70 (60.9)	66 (55.5)	282 (58.5)
Black	46 (37.4)	38 (30.4)	37 (32.2)	43 (36.1)	164 (34.0)
Other	6 (4.9)	12 (9.6)	8 (6.9)	10 (8.4)	36 (7.5)
DSM-IV diagnosis					
Disorganized	19 (15.5)	8 (6.4)	11 (9.6)	9 (7.6)	47 (9.8)
Paranoid	81 (65.9)	87 (69.6)	83 (72.2)	90 (75.6)	341 (70.8)
Undifferentiated	23 (18.7)	30 (24.0)	21 (18.3)	20 (16.8)	94 (19.5)
Baseline BPRS-total score					
N	122	125	114	118	479
Mean (SD)	55.0 (9.2)	53.3 (9.1)	54.7 (10.0)	53.7 (9.5)	54.2 (9.4)
Median	56.0	54.0	55.0	53.0	54.0
Min – Max	33 – 82	35 – 82	35 – 86	34 – 81	33 – 86

(Source: Reviewer's results)

6.3 Study ILP3005ST

Table 43. Study ILP3005ST: disposition of patients (randomized schizophrenia subsample)

	Ilo 12-16 mg/d N= 188	Ilo 20-24 mg/d N= 114	Risp 6-8 mg/d N= 126	Placebo N= 120	Total N= 548
Discontinued (days 1-42) – n (%)	88 (46.8)	42 (36.8)	35 (27.8)	57 (47.5)	222 (40.5)
Adverse experiences	5 (2.7)	6 (5.3)	4 (3.2)	5 (4.2)	20 (3.7)
Abnormal test/lab procedure/values	1 (0.5)	0 (0.0)	1 (0.8)	1 (0.8)	3 (0.6)
Unsatisfactory therapeutic effect	51 (27.1)	22 (19.3)	10 (7.9)	37 (30.8)	120 (21.9)
Condition no longer requires drug	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)
Protocol violation	1 (0.5)	2 (0.9)	3 (1.6)	4 (0.8)	5 (0.9)
Withdrawal of consent	22 (11.7)	10 (8.8)	13 (10.3)	9 (7.5)	54 (9.9)
Lost to follow-up	5 (2.7)	3 (2.6)	5 (4.0)	4 (3.3)	17 (3.1)
Administrative problems	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)
Completed (days 1-42)	100 (53.2)	72 (63.2)	91 (72.2)	63 (52.5)	326 (59.5)

(Source: reviewer's results)

Table 44. Study ILP3005ST: demographic and baseline disease characteristics (randomized schizophrenia subsample)

	Ilo 12-16 mg/d N= 188	Ilo 20-24 mg/d N= 114	Risp 6-8 mg/d N= 126	Placebo N=120	Total N= 548
Age (yr) n					
Mean (SD)	39.0 (11.4)	36.1 (10.9)	40.0 (10.7)	38.4 (10.4)	38.5 (11.0)
Median	38.0	36.0	39.5	38.0	38.0
Min – Max	18 – 65	19 – 65	18 – 64	18 – 64	18 – 65
Sex – n (%)					
Male	120 (63.8)	84 (73.7)	78 (61.9)	75 (62.5)	357 (65.2)
Female	68 (36.2)	30 (26.3)	48 (38.1)	45 (37.5)	191 (34.8)
Race – n (%)					
Caucasian	129 (68.6)	79 (69.3)	97 (77.0)	82 (68.3)	387 (70.6)
Black	53 (28.2)	27 (23.7)	21 (16.7)	30 (25.0)	131 (23.9)
Other	6 (3.2)	8 (7.0)	8 (6.3)	8 (6.7)	30 (5.5)
Baseline BPRS-total score					
N	186	113	123	120	542
Mean (SD)	54.6 (7.5)	55.3 (8.5)	55.7 (8.6)	55.3 (8.6)	55.2 (8.2)
Median	54.5	55.0	55.0	55.0	55
Min – Max	39 – 79	39 – 85	38 – 92	35 – 90	35 – 92

(Source: reviewer's results)

Table 45. Study ILP3005ST: reviewer's efficacy results: change from endpoint to baseline in BPRS total score (LOCF) (excluding schizoaffective patients); MITT sample, risperidone-referenced

	Ilo 12-16 mg	**Ilo 20-24 mg**	**Risp 6-8 mg**	**Placebo**
Sample size	178	111	119	113
LS Means *	7.4	8.8	11.4	4.3
Difference from risperidone**	-4.04	-2.66		-7.13
(95% confidence interval)	(-6.82, -1.25)	(-5.76, 0.45)		(-10.20, -4.05)
Unadjusted p-values	0.005	0.093		<0.001

(Source: reviewer's results)

* Reviewer's note: positive changes indicate improvements.

** Risperidone is used as a reference. All differences are against risperidone.

Table 46. Study ILP3005ST: demographic and baseline disease characteristics (MITT schizophrenia subsample stratified by the date of treatment arms modification)

	Ilo 12-16 mg/d	Ilo 20-24 mg/d	Risp 6-8 mg/d	Placebo	Total
Pre-dose modification					
Age (yr) n	68	NA	38	39	145
Mean (SD)	38.8 (11.3)		41.1 (10.8)	35.6 (8.7)	38.6 (10.6)
Median	39.5		41.0	36.0	38.0
Min – Max	18 – 61		22 – 62	18 – 55	18 – 62
Sex – n (%)					
Male	51 (75.0)	NA	24 (63.2)	28 (71.8)	103 (71.0)
Female	17 (25.0)		14 (36.8)	11 (28.2)	42 (29.0)
Race – n (%)					
Caucasian	41 (60.3)	NA	22 (57.9)	21 (53.9)	84 (57.9)
Black	25 (36.8)		14 (36.8)	16 (41.0)	55 (37.9)
Other	2 (2.9)		2 (5.2)	2 (5.1)	6 (4.1)
Baseline BPRS-total score					
N	68	NA	38	39	145
Mean (SD)	53.3 (7.7)		55.0 (8.7)	57.0 (7.8)	54.7 (8.1)
Median	53.0		54.5	56.0	55.0
Min – Max	40 – 79		38 – 77	41 – 77	38 – 79
Post-dose modification					
Age (yr) n	110	111	81	74	376
Mean (SD)	39.5 (11.8)	36.2 (10.9)	40.1 (10.6)	39.7 (10.8)	38.7 (11.2)
Median	38.5	36.0	39.0	41.0	38.0
Min – Max	21 – 65	19 – 65	18 – 64	18 – 64	18 – 65
Sex – n (%)					
Male	62 (56.4)	81 (73.0)	49 (60.5)	42 (56.8)	234 (62.2)
Female	48 (43.6)	30 (27.0)	32 (39.5)	32 (43.2)	142 (37.8)
Race – n (%)					
Caucasian	87 (79.1)	78 (70.3)	70 (86.4)	55 (74.3)	290 (77.1)
Black	19 (17.3)	25 (22.5)	5 (6.2)	13 (17.6)	62 (16.5)
Other	4 (3.6)	8 (7.2)	6 (7.3)	6 (8.1)	24 (6.3)
Baseline BPRS-total score					
N	110	111	81	74	376
Mean (SD)	55.4 (7.3)	55.1 (8.1)	55.9 (8.6)	54.7 (9.1)	55.3 (8.2)
Median	56.0	55.0	55.0	55.0	55.0
Min – Max	39 – 71	39 – 75	38 – 92	35 – 90	35 – 92

(Source: reviewer's results)

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STATISTICAL REVIEW AND EVALUATION

Carcinogenicity Studies

NDA/Serial Number:	22- 192
Drug Name:	iloperidone
Indication:	Schizophrenia
Applicant:	Vanda Pharmaceuticals
Date:	Sept. 27, 2007
Statistical Reviewer:	Roswitha Kelly, M.S./OTS/OB/DB6
Concurring Reviewers:	Karl Lin, Ph.D.,/OTS/OB/DB6
Medical Division:	Division of Psychiatry Products/OND/ODEI/DPP
Pharm/Tox Team:	Sonia Tabacova, Ph.D. /OND/ODEI/DPP
Project Manager:	Kim Updegraff, R.Ph., M.S. /OND/ODEI/DPP

Keywords: iloperidone, carcinogenicity, mortality, Kaplan-Meier estimates, exact permutation tests, validity

Distribution: NDA 22-192/iloperidonet
OND/ODEI/DPP/ K.Updegraff R.Ph./S. Tabacova, Ph.D.
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1. EXECUTIVE SUMMARY

1.1. Conclusions and Recommendations

The 24-month oncogenicity study in [redacted] CD®(SD)BR **RATS** from [redacted] had 60 animals per gender in each of the two vehicle control groups and in each of the three dose groups. Dose levels of 4, 8, and 16 mg/kg/day were administered via gavage and necropsies were performed on all animals and all tissues were microscopically examined. Both the reviewer and the sponsor concluded that survival was not affected by the treatment. Individual tumor/tissue combinations did not approach statistical significance. However, the combined incidences for islet cell adenomas and islet cell carcinomas in the pancreas of the female rats almost reached statistical significance at the α-level for common tumors. As this finding was not robust, the reviewer evaluated the validity of both the female and the male rat studies. She concluded that there were sufficient numbers of animals exposed sufficiently long to allow for late developing tumors. However, it seemed that the high dose exceeded the MTD. The sponsor had concluded that the MTD was either attained or exceeded. Whether either the male or the female rat study can be considered valid in the presence of no statistically significant increases in tumors is left to the expertise of the reviewing pharmacologist. b(4)

The 24-month oncogenicity study in [redacted] CD-1®(ICR)BR **MICE** from [redacted] had 60 animals per gender in each of two vehicle control groups and in three treated groups. The test article was administered at levels of 2.5, 5.0, and 10 mg/kg/day via gastric intubation and necropsies were performed on all animals and all tissues were microscopically examined. Due to high mortality among the high dose animals, both male and female high dose groups were terminated early and the remaining animals were allowed to live longer. The reviewer and the sponsor used somewhat different approaches for handling the multiple sacrifices. Both the sponsor and the reviewer concluded that survival was affected by treatment. Also, both the sponsor and the reviewer concluded that no tumor finding reached the proper statistical significance levels. The sponsor concluded that the MTD was exceeded based on the decreased survival in all treated groups compared to the control groups. The reviewer agreed with this statement with respect to the female mice. However, in the reviewer's evaluations of the validity of the male mouse study, a small but consistent average body weight reduction of the high dose group compared to the control could be indicative that the high dose was close to the MTD. Whether this conclusion is appropriate in the light of the great effect of the high dose on mortality, is left to the expertise of the reviewing pharmacologist. b(4)

1.2. Brief Overview of Carcinogenicity Studies

The study : [redacted] CD®(SD)BR **RATS** was a standard whole life oncogenicity study where all animals were necropsied and all tissues were microscopically examined. There b(4)

were two identical controls and dose levels 4, 8, and 16 mg/kg/day were administered via gavage.

The study in —:CD-1®(ICR)BR **MICE** was planned as a standard whole life oncogenicity study where all animals were necropsied and all tissues were microscopically examined. There were two identical controls and dose levels 2.5, 5, and 10 mg/kg/day were administered via gastric intubation. There were an unusual number of early deaths which were attributed to intubation errors. These decedents were replaced by stock animals. Further, due to high mortality in the high dose animals, these groups were terminated early. The remaining female mice were terminated a week later, whereas the remaining male mice lasted the full two years. b(4)

1.3. Statistical Issues and Findings

There were no major statistical issues in the rat data. For the mouse data there was the complication of having the high dose males and females terminated early but not one of the two control groups as well, which would have provided a comparison group. Therefore, the reviewer performed several analyses. One for each gender where all mice were censored at the week of the early termination and an additional analysis per gender, where the high dose was omitted and trend tests performed on the remaining groups using their terminal sacrifice time. The sponsor used a different approach which assigned the various terminal sacrifices to the proper groups and analyzed tumor data in one overall approach. The sponsor's and the reviewer's final conclusion were identical.

2. INTRODUCTION

2.1. Overview

The 24-month oncogenicity study in — CD®(SD)BR **RATS** from ——— ——— had 60 animals per gender in each of the two vehicle control groups and in each of the three dose groups. Dose levels of 4, 8, and 16 mg/kg/day were administered via gavage. Water and feed was available ad lib. throughout the study. Necropsies were performed on all animals and all tissues were microscopically examined. b(4)

The 24-month oncogenicity study in — CD-1®(ICR)BR **MICE** from ——— ——— had 60 animals per gender in each of two vehicle control groups and in three treated groups. The test article was administered at levels of 2.5, 5.0, and 10 mg/kg/day via gastric intubation. Water and feed was available ad lib. throughout the study. Necropsies were performed on all animals and all tissues were microscopically examined. Due to high mortality among the high dose animals, both male and female high dose groups were terminated in week 82. The remaining females were euthanized in week 90, whereas the remaining males were euthanized in week 105. Very early deaths (24 females and 11 males) were replaced with stock animals. Most of these deaths were ascribed to intubation trauma.

2.2. Data Sources

The sponsor provided the tumor and survival data for each species as SAS transport files. The reviewer did not encounter any difficulties in analyzing theses tumor data sets provided by the sponsor, except that the mouse data needed to be modified to permit analyses using the various terminal sacrifices.

2.3. Statistical Issues

The sponsor apparently treated all tumors incidental to death. They used Peto's analyses only on some of the tumor findings. They assigned special time intervals to the times of the various sacrifices and analyzed the tumor data in one analysis per gender. They planned to follow any statistically significant tumor increases with Fisher's Exact tests between treated groups and individual and combined control groups. The sponsor did combine the two identical control groups in their trend tests and used the α-levels suggested by FDA to compensate for the multiplicity problem.

The reviewer employed the 'web-carcin' software made available to OB reviewers by Dr. T. Guo and Ms. F. Zhou, both of DB2. This software automatically provides two-sided trend analyses of mortality and mortality-adjusted tests for one-sided linear increases in tumor incidences with dose. The primary method of tumor analysis was the exact permutation trend test with the combined control groups. A normal approximation to the test is used when the number of tumor-bearing animals is sufficiently large or when fatal and incidental tumors of the same kind are combined and their number of tumor-bearing animals is sufficiently large. The reviewer applied the same levels of significance for common and rare tumors as the sponsor did.

There were no major statistical issues in the rat data. For the mouse data there was the complication of having the high dose males and females terminated early but not one of the control groups. Therefore, the reviewer performed the following analyses: one per gender where all mice were censored at the week of the early termination, and one additional analysis per gender, where the high dose was omitted and trend tests performed with the remaining groups and their terminal sacrifice.

It is noted that the label for the mouse data read 'rats' and were filed in the rat folder. Similarly the rat data were labeled 'mouse' and had been filed in the mouse folder. The species were properly identified within each data set.

3. STATISTICAL EVALUATION

3.1. Rat Study

This was a 24-month oncogenicity study in — CD®(SD)BR rats from ——— ——— There were 60 animals per gender in each of the two vehicle control groups b(4)

and in each of the three dose groups. Dose levels of 4, 8, and 16 mg/kg/day were administered via gavage. Upon arrival, all animals were housed three per cage (by sex) for a minimum of three days. Thereafter, all animals were housed individually in wire-mesh cases. Animals were assigned to treatment based on randomized block design, where body weight strata provided the blocks. Water and feed was available ad lib. throughout the study. Necropsies were performed on all animals and all tissues were microscopically examined.

3.1.1. Sponsor's Results

After 103 weeks of treatment, the sponsor observed survival rates of 33 – 47% among the female rats and of 33 – 50% among the male rats. The survival rates of the two control groups and the high dose animals were similar and the sponsor concluded that 'survival was unaffected by test article administration.'

The sponsor reported that there were no trends indicating an increased incidence in tumors of any type, including mammary fibroadenomas or adenocarcinomas. The sponsor concluded that the 'MTD was attained or exceeded based on decreases of more than 20% for body weight changes' from the start of the study in all iloperidone-treated animals compared to the control groups.

3.1.2. Reviewer's Results

3.1.2.1. Female Rats

The reviewer used the sponsor's SAS transport file for rats to analyze the mortality and tumor data of the female gender. She observed almost identical numbers of animals surviving till the terminal sacrifice and agreed with the sponsor's conclusions, that survival was not affected by the test article (Tables 1, 2 and Figure 1).

The sponsor provided incidence tables for several mammary and pituitary tumors among the females. The reviewer obtained the identical incidences for each these tumors per treatment group. As the tumor/tissue combinations were recorded in the data set, none reached statistical significance. Combining benign islet cell adenomas and malignant islet cell carcinomas in the pancreas led to incidences of 2, 2, 0, 3, 7 for the two control, low, medium and high dose groups, respectively, which are identical to the sponsor's numbers. The p-value for the exact permutation trend test was of 0.0084, which is not significant at an α-level of 0.005. The asymptotic test produced a p-value of 0.0051, which is very close to the criterion for a significant trend in a common tumor. It may ultimately be decided that this finding is not of importance however the reviewer was surprised that the sponsor stated 'the significance level of 0.05 for islet cell tumors (adenomas and carcinomas) was not considered to be indicative of a test article related effect'. In the reviewer's opinion, the finding is significant at a higher α-level than 0.05.

Table 1: Mortality of Female Rats

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
	0-52	60	1	59	98.3	1.7
	53-78	59	11	48	80.0	20.0
CTR1	79-91	48	15	33	55.0	45.0
	92-103	33	11	22	36.7	63.3
	FINALKILL104-106	22	22	0		
	0-52	60	2	58	96.7	3.3
	53-78	58	12	46	76.7	23.3
CTR2	79-91	46	14	32	53.3	46.7
	92-103	32	11	21	35.0	65.0
	FINALKILL104-106	21	21	0	0.0	100.0
	0-52	60	2	58	96.7	3.3
	53-78	58	8	50	83.3	16.7
LOW	79-91	50	11	39	65.0	35.0
	92-103	39	9	30	50.0	50.0
	FINALKILL104-106	30	30	0		
	0-52	60	2	58	96.7	3.3
	53-78	58	5	53	88.3	11.7
MED	79-91	53	9	44	73.3	26.7
	92-103	44	16	28	46.7	53.3
	FINALKILL104-106	28	28	0		
	0-52	60	1	59	98.3	1.7
	53-78	59	7	52	86.7	13.3
HIGH	79-91	52	16	36	60.0	40.0
	92-103	36	15	21	35.0	65.0
	FINALKILL104-106	21	21	0		

Table 2: Mortality Trends among Female Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	4.5358	0.2091	4.3873	0.2226
Depart from Trend				
Dose-Mortality Trend	0.1551	0.6937	0.5994	0.4388
Homogeneity	4.6910	0.3205	4.9867	0.2887

Figure 1: Kaplan Meier Survival Curves for Female Rats

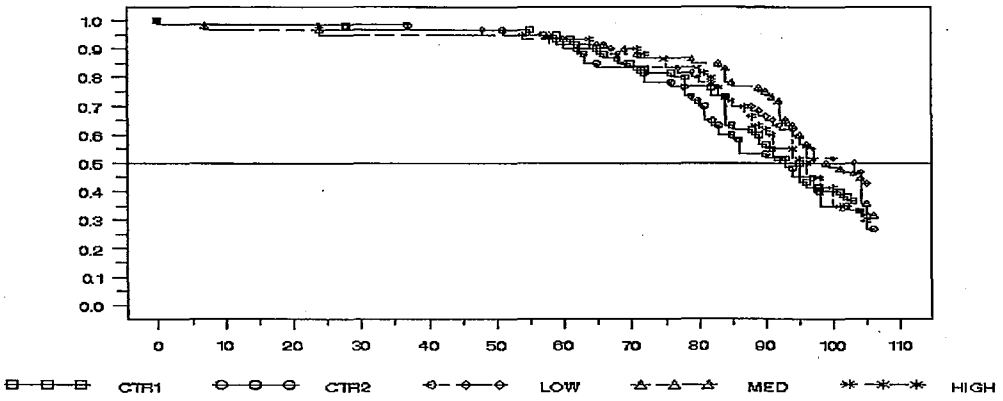

Table 3: Tumor Trends in Female Rats*

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001002	#B PHEOCHROMOCYTOMA	2	1	2	2	2	0.4453	0.4243
AD	ADRENAL GLANDS	HP001015	#M CARCINOMA, CORTICAL	1	0	1	0	0	0.8749	0.8478
AD	ADRENAL GLANDS	HP001019	#B ADENOMA, CORTICAL	0	4	2	1	0	0.9720	0.9536
AD	ADRENAL GLANDS	HP001024	#M PHEOCHROMOCYTOMA	0	1	0	1	0	0.7029	0.6774
BR	BRAIN	HP007008	#B ASTROCYTOMA	0	0	0	0	2	0.0391	0.0086
CX	CERVIX	HP063001	#M LEIOMYOSARCOMA	1	0	0	0	0	1.0000	0.8596
CX	CERVIX	HP063002	#B LEIOMYOMA	2	0	0	0	0	1.0000	0.9290
CX	CERVIX	HP063011	#M SCHWANNOMA MALIGNANT	2	0	0	0	0	1.0000	0.9276
DU	DUODENUM	HP010002	#B LEIOMYOMA	1	0	0	0	0	1.0000	0.8569
EY	EYES/OPTIC N.	HP014012	#M CARCINOMA, SQUAMOUS CELL	0	0	0	1	0	0.4050	0.3673
HE	HEART	HP017013	#M CHONDROSARCOMA	0	0	0	1	0	0.4000	0.3755
JE	JEJUNUM	HP019004	#M LEIOMYOSARCOMA	0	0	0	0	1	0.1765	0.0404
LI	LIVER	HP021011	#B ADENOMA, HEPATOCELLULAR	2	3	0	1	1	0.8835	0.8617
LI	LIVER	HP021021	#M CARCINOMA, HEPATOCELLULAR	1	0	0	0	1	0.3953	0.2898
LU	LUNGS	HP026008	#B ADENOMA, BRONCHIOLAR/ALVEOL	1	0	0	0	0	1.0000	0.8320
MG	MAMMARY GLAND	HP027002	#B FIBROADENOMA	34	39	26	21	21	1.0000	0.9999
MG	MAMMARY GLAND	HP027003	#M ADENOCARCINOMA	10	21	15	20	12	0.7716	0.7638
MG	MAMMARY GLAND	HP027007	#B ADENOMA	1	4	0	2	1	0.8320	0.8134

OV	OVARIES	HP033004	#B GRANULOSA CELL TUMOR	1	0	1	0	0	0.8777	0.8329
OV	OVARIES	HP033005	#M GRANULOSA CELL TUMOR	0	1	0	0	0	1.0000	0.8600
PA	PANCREAS	HP034007	#B ADENOMA, ISLET CELL	2	2	0	2	5	0.0561	0.0427
PA	PANCREAS	HP034014	#M CARCINOMA, ISLET CELL	0	0	0	1	2	0.0335	0.0149
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	52	51	32	20	29	1.0000	1.0000
PI	PITUITARY	HP040002	#B ADENOMA, PARS INTERMEDIA	0	0	0	1	0	0.4016	0.3660
PI	PITUITARY	HP040006	#M CARCINOMA, PARS DISTALIS	1	0	1	1	0	0.7065	0.6993
PT	PARATHYROID	HP035002	#B ADENOMA	1	0	0	0	1	0.4190	0.3337
SK	SKIN	HP046001	#B KERATOACANTHOMA	0	0	1	1	1	0.1630	0.1322
SK	SKIN	HP046014	#B ADENOMA, BASAL CELL	0	0	1	0	0	0.5714	0.5783
SY	SYSTEMIC TUMORS	HP025001	#M SARCOMA, HISTIOCYTIC	3	2	3	0	0	0.9935	0.9823
SY	SYSTEMIC TUMORS	HP025002	#M LYMPHOMA, MALIGNANT	1	0	1	0	0	0.8433	0.8214
SY	SYSTEMIC TUMORS	HP025003	#M HEMANGIOSARCOMA	3	1	0	0	0	1.0000	0.9734
SY	SYSTEMIC TUMORS	HP025004	#B HEMANGIOMA	1	0	0	0	0	1.0000	0.8320
TG	THYROID GLANDS	HP053002	#B ADENOMA, FOLLICULAR	2	1	0	0	1	0.7980	0.7699
TG	THYROID GLANDS	HP053003	#B ADENOMA, C-CELL	8	3	5	7	6	0.5190	0.5060
TG	THYROID GLANDS	HP053008	#M CARCINOMA, C-CELL	0	2	0	0	0	1.0000	0.8864
TG	THYROID GLANDS	HP053009	#M CARCINOMA, FOLLICULAR CELL	0	1	1	0	0	0.8777	0.8329
TH	THYMUS GLAND	HP052003	#M THYMOMA, MALIGNANT	0	0	0	2	0	0.3074	0.2375
TH	THYMUS GLAND	HP052004	#B THYMOMA	1	1	0	1	0	0.8189	0.7927
UT	UTERUS	HP060006	#B POLYP	3	3	5	2	4	0.4468	0.4322
VA	VAGINA	HP061010	#B SCHWANNOMA	0	0	0	1	0	0.5000	0.4388
XX	EXTERNAL SURFACE	HP075003	#B PAPILLOMA	0	1	0	0	0	1.0000	0.8600
XX	MASS(ES)	HP084002	#B FIBROMA	0	0	1	3	0	0.3568	0.3318
XX	MASS(ES)	HP084009	#B NEOPLASM, NEURAL CREST	1	0	0	0	0	1.0000	0.8600
XX	MASS(ES)	HP084011	#M SCHWANNOMA, MALIGNANT	0	1	0	0	0	1.0000	0.8502
XX	MASS(ES)	HP084012	#M RHABDOMYOSARCOMA	1	0	0	0	0	1.0000	0.8577
XX	MASS(ES)	HP084013	#M FIBROSARCOMA	0	1	0	1	1	0.3019	0.2556
XX	MASS(ES)	HP084025	#M SARCOMA, UNDIFFERENTIATED	0	1	0	0	0	1.0000	0.8490
XX	MASS(ES)	HP084029	#M CARCINOMA, ZYMBAL'S GLAND	1	0	0	3	0	0.5377	0.5056
XX	ABSCESS(ES)	HP094002	#M CARCINOMA, ZYMBAL'S GLAND	0	0	0	1	0	0.4286	0.3867
XX	ADIPOSE TISSUE	HP095003	#B HIBERNOMA	0	0	0	0	1	0.1721	0.0388

* Tumor incidences are shown for each control group but were combined for the trend tests.

3.1.2.2. Male Rats

The reviewer also used the sponsor's SAS transport file for rats to analyze the mortality and tumor data of the male gender. She again observed almost identical numbers of animals surviving until the terminal sacrifice and agreed with the sponsor's conclusions, that survival was not affected by the test article (Tables 4, 5 and Figure 2). None of the tumor findings increased significantly with dose (Table 6)

Table 4: Mortality of Male Rats

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
	0-52	60	3	57	95.0	5.0
	53-78	57	7	50	83.3	16.7
CTR1	79-91	50	10	40	66.7	33.3
	92-103	40	10	30	50.0	50.0
	FINALKILL104-106	30	30	0		
	0-52	60	4	56	93.3	6.7
	53-78	56	7	49	81.7	18.3
CTR2	79-91	49	8	41	68.3	31.7
	92-103	41	15	26	43.3	56.7
	FINALKILL104-106	26	26	0		
	0-52	60	3	57	95.0	5.0
	53-78	57	12	45	75.0	25.0
LOW	79-91	45	6	39	65.0	35.0
	92-103	39	13	26	43.3	56.7
	FINALKILL104-106	26	26	0		
	0-52	60	6	54	90.0	10.0
	53-78	54	8	46	76.7	23.3
MED	79-91	46	12	34	56.7	43.3
	92-103	34	14	20	33.3	66.7
	FINALKILL104-106	20	20	0	0.0	100.0
	0-52	60	3	57	95.0	5.0
	53-78	57	8	49	81.7	18.3
HIGH	79-91	49	7	42	70.0	30.0
	92-103	42	10	32	53.3	46.7
	FINALKILL104-106	32	32	0		

Table 5: Mortality Trends among Male Rats

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	5.3811	0.1459	4.8803	0.1808
Depart from Trend				
Dose-Mortality Trend	0.0506	0.8221	0.0036	0.9519
Homogeneity	5.4316	0.2458	4.8839	0.2994

Figure 2: Kaplan Meier Survival Curves for Male Rats

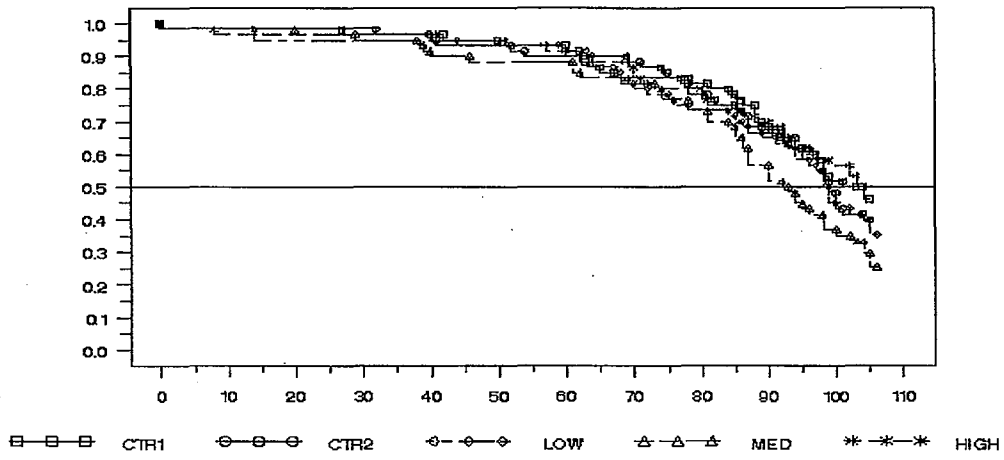

Table 6:Tumor Trends in Male Rats*

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001002	#B PHEOCHROMOCYTOMA	3	11	9	7	9	0.3405	0.3288
AD	ADRENAL GLANDS	HP001019	#B ADENOMA, CORTICAL	0	3	0	1	1	0.6329	0.6079
AO	AORTA	HP003005	#B CHONDROMA	0	0	1	0	0	0.5821	0.6410
BR	BRAIN	HP007008	#B ASTROCYTOMA	0	3	1	2	1	0.6003	0.5846
BR	BRAIN	HP007014	#B OLIGODENDROGLIOMA	0	0	0	0	1	0.1976	0.0478
CE	CECUM	HP008006	#B LEIOMYOMA	1	0	0	0	1	0.4397	0.3253
EY	EYES/OPTIC N.	HP014004	#M MELANOMA, MALIGNANT-AMELANO	1	0	0	0	0	1.0000	0.8408

EY	EYES/OPTIC N.	HP014008	#B ADENOMA, MEIBOMIAN GLAND	0	1	0	0	0	1.0000	0.8408
HE	HEART	HP017009	#B MESOTHELIOMA, ATRIOCAVAL	0	0	2	2	0	0.4979	0.4692
JE	JEJUNUM	HP019003	#M ADENOCARCINOMA	0	0	0	0	1	0.2326	0.0592
KI	KIDNEYS	HP020004	#B LIPOMA	1	0	0	1	0	0.6855	0.6670
KI	KIDNEYS	HP020016	#B ADENOMA, RENAL CELL	0	1	0	0	0	1.0000	0.8451
KI	KIDNEYS	HP020025	#M LIPOSARCOMA	0	0	0	0	1	0.1613	0.0342
LI	LIVER	HP021011	#B ADENOMA, HEPATOCELLULAR	1	1	0	0	1	0.6036	0.5554
LI	LIVER	HP021015	#B CHOLANGIOMA	1	0	0	0	1	0.4122	0.3202
LI	LIVER	HP021021	#M CARCINOMA, HEPATOCELLULAR	2	3	5	0	2	0.7797	0.7645
LM	LYMPH NODE,MES	HP024012	#B LYMPHANGIOMA	0	1	0	0	0	1.0000	0.8504
LU	LUNGS	HP026008	#B ADENOMA, BRONCHIOLAR/ALVEOL	0	1	0	0	0	1.0000	0.8393
LU	LUNGS	HP026010	#M CARCINOMA, BRONCHIOLAR/ALVE	1	0	0	0	0	1.0000	0.8378
PA	PANCREAS	HP034007	#B ADENOMA, ISLET CELL	3	2	3	8	6	0.0511	0.0423
PA	PANCREAS	HP034014	#M CARCINOMA, ISLET CELL	0	2	0	1	0	0.8272	0.8173
PI	PITUITARY	HP040001	#B ADENOMA, PARS DISTALIS	37	33	38	29	30	0.9732	0.9708
PI	PITUITARY	HP040002	#B ADENOMA, PARS INTERMEDIA	1	0	0	1	0	0.6692	0.6800
PI	PITUITARY	HP040006	#M CARCINOMA, PARS DISTALIS	0	0	1	0	0	0.5971	0.6543
PT	PARATHYROID	HP035002	#B ADENOMA	0	3	0	3	1	0.4618	0.4386
PW	PATELLA	HP022001	#M FIBROSARCOMA	0	1	0	0	0	1.0000	0.8393
SK	SKIN	HP046001	#B KERATOACANTHOMA	3	5	1	1	2	0.8844	0.8682
SK	SKIN	HP046013	#B ADENOMA, SEBACEOUS GLAND	0	0	0	1	0	0.4286	0.3536
SK	SKIN	HP046015	#M BASAL CELL CARCINOMA	0	0	0	0	1	0.2388	0.0630
SV	SEMINAL VESICLES	HP044009	#B ADENOMA	0	0	0	1	1	0.1134	0.0687
SY	SYSTEMIC TUMORS	HP025001	#M SARCOMA, HISTIOCYTIC	2	6	2	4	1	0.9061	0.8920
SY	SYSTEMIC TUMORS	HP025002	#M LYMPHOMA, MALIGNANT	1	0	1	4	0	0.4633	0.4442
SY	SYSTEMIC TUMORS	HP025003	#M HEMANGIOSARCOMA	0	3	2	4	0	0.7483	0.7324
SY	SYSTEMIC TUMORS	HP025004	#B HEMANGIOMA	2	0	3	0	1	0.6894	0.6750
TE	TESTES	HP051005	#B ADENOMA, INTERSTITIAL CELL	2	2	2	2	0	0.9092	0.8882
TG	THYROID GLANDS	HP053002	#B ADENOMA, FOLLICULAR	1	3	2	0	2	0.6550	0.6378
TG	THYROID GLANDS	HP053003	#B ADENOMA, C-CELL	7	7	11	3	6	0.8390	0.8286
TG	THYROID GLANDS	HP053008	#M CARCINOMA, C-CELL	1	0	0	0	0	1.0000	0.8393
TH	THYMUS GLAND	HP052003	#M THYMOMA, MALIGNANT	1	0	1	0	0	0.8092	0.8014
TH	THYMUS GLAND	HP052004	#B THYMOMA	1	0	0	1	0	0.6787	0.6885

XX	EXTERNAL SURFACE	HP075003	#B PAPILLOMA	2	0	2	0	0	0.9153	0.8941
XX	CRANIAL CAVITY	HP077001	#M SCHWANNOMA	0	1	0	0	0	1.0000	0.8445
XX	MASS(ES)	HP084002	#B FIBROMA	3	6	2	3	4	0.6216	0.6089
XX	MASS(ES)	HP084003	#B LIPOMA	2	3	0	1	2	0.6471	0.6300
XX	MASS(ES)	HP084007	#M MELANOMA, MALIGNANT-AMELANO	1	0	0	0	0	1.0000	0.8393
XX	MASS(ES)	HP084009	#B NEOPLASM, NEURAL CREST	0	0	0	1	0	0.4419	0.3563
XX	MASS(ES)	HP084011	#M SCHWANNOMA, MALIGNANT	0	0	0	1	0	0.3913	0.3706
XX	MASS(ES)	HP084013	#M FIBROSARCOMA	0	1	0	0	0	1.0000	0.8378
XX	MASS(ES)	HP084014	#B MYXOMA	1	0	0	0	0	1.0000	0.8393
XX	MASS(ES)	HP084016	#B PAPILLOMA	0	1	0	0	0	1.0000	0.8393
XX	MASS(ES)	HP084023	#M MALIGNANT FIBROUS HISTIOCYT	0	0	0	0	1	0.2085	0.0510
XX	MASS(ES)	HP084025	#M SARCOMA, UNDIFFERENTIATED	0	0	1	0	1	0.2038	0.1685
XX	MASS(ES)	HP084029	#M CARCINOMA, ZYMBAL'S GLAND	0	0	1	2	1	0.1709	0.1396
XX	MAMMARY GLAND	HP090005	#B ADENOMA	0	0	0	1	0	0.3871	0.3433
XX	MAMMARY GLAND	HP090006	#B FIBROADENOMA	2	0	5	0	1	0.7394	0.7230
XX	MAMMARY GLAND	HP090007	#M ADENOCARCINOMA	0	0	0	0	2	0.0557	0.0129
XX	ADIPOSE TISSUE	HP095002	#B LIPOMA	0	0	0	0	1	0.1613	0.0342
XX	DIAPHRAGM	HP096002	#M LIPOSARCOMA	0	0	0	1	0	0.3871	0.3433

- Tumor incidences are shown per control group but were combined for the trend tests.

3.1.2.3. Validity of Male and Female Rat Study

In case the borderline significant increase in pancreatic islet cell adenomas and carcinomas (combined) among the female rats is not considered a clear finding, the reviewer evaluated the validity of this study as well as that of the male rats, where no increase in tumor incidences approached statistical significance. Two criteria are considered for this purpose:

i) Were sufficient numbers of animals exposed long enough to allow for late-developing tumors?
ii) Did the high dose provide a sufficient tumor challenge?

The number of animals and the length of exposure can be assessed at weeks 52, 80-90, and at termination, but are generally considered adequate if 20-30 animals survive through weeks 80-90. With at least 20 animals in any group of the male and female animals lasting till study end at week 103, the reviewer concluded that there were sufficient numbers of animals exposed long enough. In determining whether the high dose provided an adequate tumor challenge, one expects the high dose to be close to the MTD. The following criteria are employed in this assessment:

iii) A dose is considered adequate if there is a detectable reduction in average body weight of up to 10% in a dosed group relative to the controls, or
iv) A dose is considered adequate if the dosed animals show a slightly increased mortality compared to the controls, or
v) A dose is considered an MTD if the dosed animals exhibit severe toxic effects attributed to the chemical. This latter evaluation is performed by the pharmacologist/toxicologist.

The high dose females had lower average body weights than the combined controls early on. By week 26, their average body weight was 11% lower than the one of the combined controls. This difference continued to increase till 23% at study end (week 103). There was no statistically significant difference in the mortality experience of the female rats. Numerically, the high dose and the two control groups had basically identical mortality experiences and this criterion cannot be used to establish the high dose as being close to the MTD. Based on the body weight data it seems that the high dose exceeded the MTD for the female rats.

The high dose male rats experienced more pronounced lower average body weights than the combined controls. The difference was already 24% by week 26 and increased to a maximum of 31% by week 78. By week 103 the difference had fallen back to 28%. The mortality experience of the high dose male rats was basically identical to the one of the combined controls and this criterion cannot be used to establish the high dose as being close to the MTD either. Again, based on body weight data it seems that the high dose exceeded the MTD for the male rats.

The sponsor had concluded that the MTD 'was attained or exceeded based on decreases of more than 20% for body weight changes from interval 0 (the initiation of dosing) in all IL0522-treated groups when compared to the control groups.'

The final decision whether the study in either gender can be considered valid in the presence of no statistically significant increases in tumors (or of only an almost statistically significant finding among the females), is left to the expertise of the reviewing pharmacologist.

3.2. Mouse Study

This study was planned as a 24-month oncogenicity study in [redacted]D-1®(ICR)BR mice from [redacted] but the high doses had to be terminated early. There were 60 animals per gender in each of two vehicle control groups and in three treated groups. The test article was administered at levels of 2.5, 5.0, and 10 mg/kg/day via gastric intubation. Upon arrival, all animals were housed three per cage (by sex) for a minimum of three days. Thereafter, all animals were housed individually in wire-mesh cases. Animals were assigned to treatment based on randomized block design, where body weight strata provided the blocks. Water and feed was available ad lib. throughout

b(4)

the study. Necropsies were performed on all animals and all tissues were microscopically examined.

Due to high mortality among the high dose animals, both male and female high dose groups were terminated in week 82. The remaining females were euthanized in week 90, whereas the remaining males were euthanized in week 105. Very early deaths (24 females and 11 males) were replaced with stock animals. Most of these deaths were ascribed to intubation trauma.

3.2.1. Sponsor's Results

The sponsor noted decreased survival in all treated groups but especially among the treated females. When the survival of the high dose males and females had fallen to about 33%, both groups were terminated in week 82. The remaining female groups were terminated in week 90 and the remaining male mice were euthanized in week 104. The sponsor concluded that the 'MTD was exceeded based on the decreased survival of all ILO522-treated groups when compared to the control group.'

The sponsor reported some increases in non-neoplastic and neoplastic microscopic findings. In particular alveolar-bronchiolar adenomas were 'slightly' increased in the low dose males and showed a p-value of <0.05 with the Peto method. This p-level was not statistically significant at the α-level for common tumors (0.005).

3.2.2. Reviewer's Results

3.2.2.1. Female Mice

The reviewer used the sponsor's SAS transport file for mice to analyze the mortality and tumor data of the female gender. Compared to the sponsor's Table 1 in their Final Report, she observed identical numbers of animals surviving to various study weeks and until the early terminal sacrifice and very similar numbers for the animals living to the late sacrifice. The tests for increased mortality with dose were highly statistically significant when all animals were censored at the time when the high dose was terminated (Tables 7, 8 and Figure 3). Tables 13, 14, and Figure 5 in the Appendix give the survival results when the high dose is excluded. There still remained a highly statistically significant negative effect on survival of the low and mid-dose animals, which confirms the sponsor's statement that 'Test article-related reductions in survival were noted in all treated groups and were more pronounced in the female groups.'

The sponsor provided incidence tables for the mammary tumors among the females. The reviewer obtained the identical incidences for each these tumors per treatment group. The sponsor discussed the increase of the low-dosed animals compared to the controls (0, 1, and 12 for control 1, control 2, and low dose, respectively). However, as the incidences for the mid- and high dose animals were only 2 and 1 respectively, a trend test was not statistically significant. Any combination of tumors present in the mammary gland would

not result in a statistically significant trend test. Whether the substantial increase seen in the low-dose females presents a finding of clinical importance is left to expertise of the reviewing pharmacologist. In the reviewer's analyses and consistent with the sponsor's report, none of the trend tests for increases in tumor incidences with dose approached statistical significance when all dose groups were used or when the high dose group was excluded from the analyses (Tables 9 and 15).

Table 7: Mortality Table for Female Mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	60	8	52	86.7	13.3
	53-78	52	8	44	73.3	26.7
	79-82	44	1	43	71.7	28.3
	FINALKILL 83-91	43	43	0		
CTR2	0-52	60	5	55	91.7	8.3
	53-78	55	7	48	80.0	20.0
	79-82	48	2	46	76.7	23.3
	FINALKILL 83-91	46	46	0		
LOW	0-52	60	9	51	85.0	15.0
	53-78	51	13	38	63.3	36.7
	79-82	38	3	35	58.3	41.7
	FINALKILL 83-91	35	35	0		
MED	0-52	60	10	50	83.3	16.7
	53-78	50	17	33	55.0	45.0
	79-82	33	3	30	50.0	50.0
	FINALKILL 83-91	30	30	0		
HIGH	0-52	60	20	40	66.7	33.3
	53-78	40	18	22	36.7	63.3
	79-82	22	1	21	35.0	65.0
	FINALKILL 83-91	21	21	0		

Table 8: Mortality Trends for Female Mice

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.5279	0.9127	0.8590	0.8353
Depart from Trend				
Dose-Mortality Trend	32.0283	0.0000	32.4510	0.0000
Homogeneity	32.5563	0.0000	33.3100	0.0000

Figure 3: Kaplan-Meier Survival Curves for Female Mice

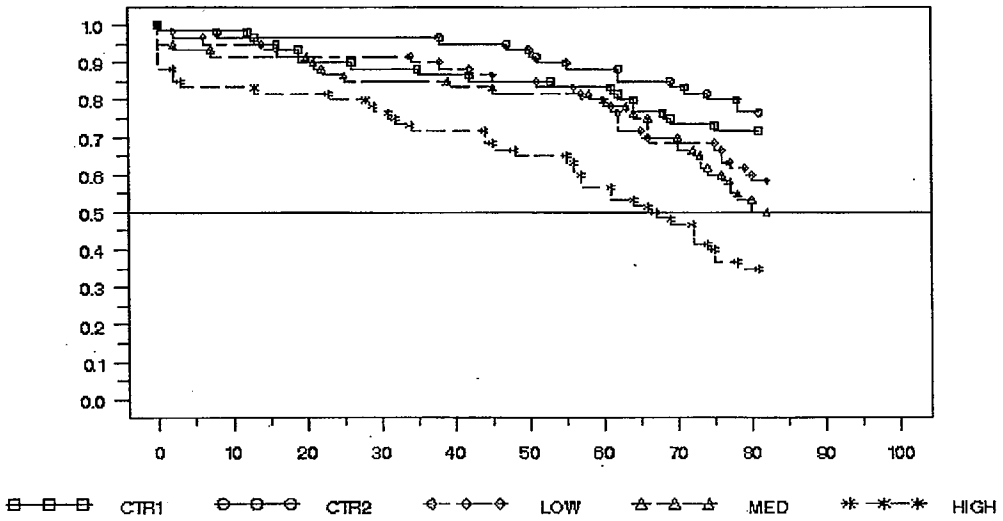

Table 9: Trend Trends for Female Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001006	#B PHEOCHROMOCYTOMA	0	0	1	0	0	0.4885	0.5650
KI	KIDNEYS	HP020022	#M CARCINOMA, RENAL CELL	0	0	1	0	0	0.4041	0.3892
LI	LIVER	HP021004	#B ADENOMA, HEPATOCELLULAR	1	2	1	1	0	0.8777	0.8626
LU	LUNGS	HP026003	#B ADENOMA, BRONCHIOLAR/ALVEOL	6	4	4	1	2	0.8594	0.8466
LU	LUNGS	HP026005	#M CARCINOMA, BRONCHIOLAR/ALVE	2	0	0	1	0	0.8370	0.8125
MG	MAMMARY GLAND	HP027004	#M ADENOCARCINOMA	0	1	12	2	1	0.3635	0.3541
MG	MAMMARY GLAND	HP027009	#B ADENOMA	0	0	1	0	0	0.5059	0.5752
MG	MAMMARY GLAND	HP027010	#M ADENOACANTHOMA	0	0	1	0	0	0.5059	0.5752
OV	OVARIES	HP033006	#B LUTEOMA	1	0	0	0	0	1.0000	0.8220
OV	OVARIES	HP033016	#B CYSTADENOMA	0	1	0	0	0	1.0000	0.8967
PA	PANCREAS	HP034017	#M CARCINOMA, ISLET CELL	0	1	0	0	0	1.0000	0.8217
PI	PITUITARY	HP040004	#B ADENOMA, PARS DISTALIS	1	0	0	1	0	0.5497	0.5621
PI	PITUITARY	HP040008	#B ADENOMA, PARS INTERMEDIA	0	0	0	0	1	0.4043	0.1623
SK	SKIN	HP046011	#B TRICHOEPITHELIOMA	0	0	0	1	0	0.2914	0.2790

SK	SKIN	HP046015	#B ADENOMA, SEBACEOUS	0	0	0	1	0	0.2914	0.2790
SY	SYSTEMIC TUMORS	HP015001	#M LYMPHOMA, MALIGNANT	10	11	11	3	3	0.9244	0.9145
SY	SYSTEMIC TUMORS	HP015002	#M SARCOMA, HISTIOCYTIC	2	0	3	1	0	0.5112	0.5055
SY	SYSTEMIC TUMORS	HP015003	#M HEMANGIOSARCOMA	2	2	1	2	1	0.4969	0.4923
SY	SYSTEMIC TUMORS	HP015004	#B HEMANGIOMA	0	0	1	2	0	0.4246	0.4006
TG	THYROID GLANDS	HP053007	#B ADENOMA, FOLLICULAR CELL	0	0	0	0	1	0.2903	0.1062
UB	URINARY BLADDER	HP059015	#M LEIOMYOSARCOMA	0	0	0	0	1	0.1221	0.0187
UT	UTERUS	HP060004	#B POLYP, ENDOMETRIAL STROMAL	8	2	1	1	1	0.9583	0.9415
UT	UTERUS	HP060005	#M SARCOMA, STROMAL CELL	4	1	0	0	0	1.0000	0.9612
UT	UTERUS	HP060016	#B LEIOMYOMA	1	0	0	1	0	0.7263	0.7097
XX	HARDERIAN GLANDS	HP081003	#B ADENOMA	1	0	2	0	0	0.7145	0.7107

3.2.2.2. Male Mice

The reviewer used the sponsor's SAS transport file for mice to analyze the mortality and tumor data of the male gender. Compared to the sponsor's Table 1 in their Final Report, she observed almost identical numbers of animals surviving to various study weeks and to the early and to the late terminal sacrifices. When the high-dose animals were included and all animals censored at time of their (the high-dose's) termination, the trend tests in mortality were highly statistically significant (p=0.0000), (Tables 10, 11 and Figure 4). When the high dose animals were excluded from the mortality analyses, the trend tests were statistically significant only at α=0.05 (Cox p-value=0.0490, Kruskal-Wallis p-value=0.0511) (Tables 16, 17 and Figure 6).

The sponsor discussed a 'slight increase in the incidence of alveolar-bronchiolar adenomas' in the low dose males when compared to the control groups. They explained their analysis approach specifically for the lung tumors (p. 35 in sponsor's Final Report) and reported a statistical significant finding at the 0.05 level for alveolar-bronchiolar adenomas by the method of Peto. An analysis of alveolar-bronchiolar carcinomas or of the combined tumor types did not attain such a level of significance. As these tumors are considered common, the finding was not considered statistically significant the proper α - level (α=0.005). The reviewer is not clear how the sponsor reached a p-value of <0.05 for the observed incidences of 7, 8, 12, 7, 2 (control 1, control 2, low, medium, and high dose groups respectively). The exact permutation trend test with all groups (and censored at the time of the terminal sacrifice of the high dose) produced a p-value of 0.8415 which was corroborated by the normal approximation test with a p-value of 0.8319 (Table 12). When the high dose was excluded and the terminal sacrifice was after week 103, the respective p-values were 0.3252 and 0.3028. Granted, the sponsor used a somewhat different approach in that he analyzed all treatment groups together by creating special

intervals for the various scheduled sacrifices. However, it seems unusual that a sequence of such numbers could result in a minimally statistically significant linear trend. However, more importantly, the sponsor's and the reviewer's conclusions are consistent in that these findings do not approach the level of statistical significance necessary for common tumors. The reviewer also agreed with the sponsor that neither alveolar-bronchiolar carcinomas in the lung or any other tumor finding approached statistical significance when all dose groups were used nor when the high dose was excluded (Tables 12 and 18).

Table 10: Mortality Table for Male Mice

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	60	10	50	83.3	16.7
	53-78	50	2	48	80.0	20.0
	79-82	48	1	47	78.3	21.7
	FINALKILL 83-105	47	47	0		
CTR2	0-52	60	8	52	86.7	13.3
	53-78	52	9	43	71.7	28.3
	79-82	43	1	42	70.0	30.0
	FINALKILL 83-105	42	42	0		
LOW	0-52	60	11	49	81.7	18.3
	53-78	49	2	47	78.3	21.7
	79-82	47	1	46	76.7	23.3
	FINALKILL 83-105	46	46	0		
MED	0-52	60	12	48	80.0	20.0
	53-78	48	9	39	65.0	35.0
	79-82	39	2	37	61.7	38.3
	FINALKILL 83-105	37	37	0		
HIGH	0-52	60	17	43	71.7	28.3
	53-78	43	17	26	43.3	56.7
	79-82	26	5	21	35.0	65.0
	FINALKILL 83-105	21	21	0		

Table 11: Mortality Trends in Male Mice

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	3.7745	0.2869	2.4885	0.4774
Depart from Trend				
Dose-Mortality Trend	25.6299	0.0000	20.7569	0.0000
Homogeneity	29.4044	0.0000	23.2453	0.0001

Figure 4: Kaplan Meier Survival Curves for Male Mice

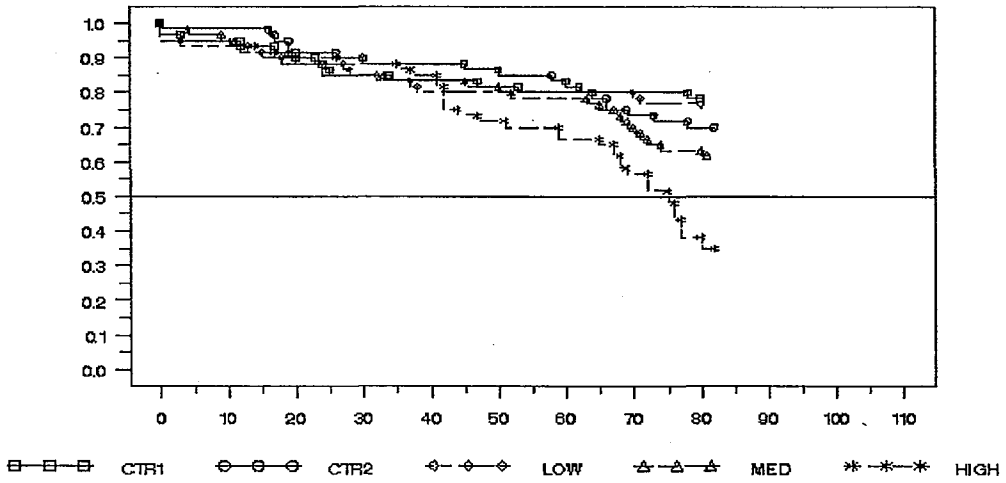

Table 12: Tumor Trends for Male Mice

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	HIGH	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001002	#B ADENOMA, CORTICAL	1	0	0	1	0	0.5632	0.5632
AD	ADRENAL GLANDS	HP001006	#B PHEOCHROMOCYTOMA	1	0	0	0	0	1.0000	0.8375
DU	DUODENUM	HP010004	#M SARCOMA, UNDIFFERENTIATED	0	0	1	0	0	0.6157	0.6655
GB	GALLBLADDER	HP016011	#M SARCOMA, UNDIFFERENTIATED	0	0	0	1	0	0.3099	0.3023
GB	GALLBLADDER	HP016012	#B ADENOMA, PAPILLARY	0	0	1	0	0	0.5673	0.5975
KI	KIDNEYS	HP020022	#M CARCINOMA, RENAL CELL	0	0	1	0	0	0.5389	0.5798
KI	KIDNEYS	HP020024	#B ADENOMA, RENAL CELL	0	0	0	1	0	0.3005	0.2802
LI	LIVER	HP021004	#B ADENOMA, HEPATOCELLULAR	5	5	3	0	1	0.9818	0.9698
LI	LIVER	HP021009	#M CARCINOMA, HEPATOCELLULAR	3	2	0	3	1	0.6040	0.5919
LU	LUNGS	HP026003	#B ADENOMA, BRONCHIOLAR/ALVEOL	7	8	12	7	2	0.8415	0.8319
LU	LUNGS	HP026005	#M CARCINOMA, BRONCHIOLAR/ALVE	5	3	4	2	0	0.9449	0.9270
PI	PITUITARY	HP040004	#B ADENOMA, PARS DISTALIS	0	0	0	1	0	0.3060	0.2796

PI	PITUITARY	HP040008	#B ADENOMA, PARS INTERMEDIA	0	0	0	1	0	0.3060	0.2796
SG	SALIVARY GLANDS	HP043013	#B SCHWANNOMA	0	0	0	1	0	0.3021	0.2808
SG	SALIVARY GLANDS	HP043014	#M ADENOCARCINOMA	0	0	1	0	0	0.4507	0.4277
ST	STOMACH	HP049014	#M ADENOCARCINOMA	0	0	1	0	0	0.4375	0.4222
ST	STOMACH	HP049016	#M SARCOMA, UNDIFFERENTIATED	0	0	1	0	0	0.6842	0.7268
SY	SYSTEMIC TUMORS	HP015001	#M LYMPHOMA, MALIGNANT	3	4	1	3	2	0.3597	0.3479
SY	SYSTEMIC TUMORS	HP015002	#M SARCOMA, HISTIOCYTIC	2	1	0	0	0	1.0000	0.9397
SY	SYSTEMIC TUMORS	HP015003	#M HEMANGIOSARCOMA	1	3	5	1	0	0.7714	0.7566
SY	SYSTEMIC TUMORS	HP015004	#B HEMANGIOMA	1	0	1	1	0	0.7813	0.7726
TE	TESTES	HP051009	#B ADENOMA, INTERSTITIAL CELL	1	0	2	1	0	0.5728	0.5671
TG	THYROID GLANDS	HP053010	#M CARCINOMA, FOLLICULAR CELL	0	0	1	0	0	0.5340	0.5720
TH	THYMUS GLAND	HP052021	#B THYMOMA	0	0	1	0	0	0.5615	0.6191
XX	EXTERNAL SURFACE	HP076004	#B PAPILLOMA, SKIN	0	0	0	1	0	0.3005	0.2802
XX	EXTERNAL SURFACE	HP076014	#B NERVE SHEATH TUMOR	0	0	1	0	0	0.5389	0.5798
XX	SUBCUTIS	HP098004	#B LIPOMA	0	0	1	0	0	0.6842	0.7229

3.2.2.3. Validity of Male and Female Mouse Study

There was not a single statistically significant tumor trend among either gender whether all treatment groups were used and censored at the time the high dose was terminated or whether the high dose was excluded from the analyses and the remaining groups were censored at their later terminal sacrifice. Hence the validity of the studies needs to be established. A whole life carcinogenicity study is considered valid despite no significant tumor findings if the following two criteria are met:

vi) Were sufficient numbers of animals exposed long enough to allow for late-developing tumors?
vii) Did the high dose provide a sufficient tumor challenge?

The number of animals and length of exposure can be assessed at weeks 52, 80-90, and at termination, but are generally considered adequate if 20-30 animals survive through weeks 80-90. Though the high dose was terminated early for both genders at week 83, there were still 21 male and female mice alive before their early sacrifice. The control and other treatment groups had at least 30 animals left at that time point. Hence there were sufficient numbers of animals exposed long enough to allow for late-developing tumors.

In determining whether the high dose provided an adequate tumor challenge, one expects the high dose to be close to the MTD. The following criteria are employed in this assessment:

viii) A dose is considered adequate if there is a detectable reduction in average body weight of up to 10% in a dosed group relative to the controls, or
ix) A dose is considered adequate if the dosed animals show a slightly increased mortality compared to the controls, or
x) A dose is considered an MTD if the dosed animals exhibit severe toxic effects attributed to the chemical. This latter evaluation is performed by the pharmacologist/toxicologist.

The high dose females actually had up to 9 % **greater** average body weights than the controls, and this criterion cannot be used to establish the high dose as an MTD. The high dose group had twice the cumulative mortality by week 83 than the one averaged over the two controls, a finding which was highly statistically significant. The sponsor noted that the MTD was exceeded based on mortality findings, which are fully corroborated by the reviewer's analyses.

There was a detectable reduction in average body weights of the high dose males versus the vehicle controls. As early as weeks 1 - 3 and again after week 22, the average body weights of the high dose males were generally 4 - 5 percent lower than the one of the combined controls. This would establish the high dose as an MTD and the male mouse study as valid despite no positive tumor findings.

The final decision whether the study can be considered valid for either gender is left to the expertise of the reviewing pharmacologist.

4. CONCLUSIONS

The 24-month oncogenicity study in — CD®(SD)BR **RATS** from ——— had 60 animals per gender in each of the two vehicle control groups and in each of the three dose groups. Dose levels of 4, 8, and 16 mg/kg/day were administered via gavage and necropsies were performed on all animals and all tissues were microscopically examined. Both the reviewer and the sponsor concluded that survival was not affected by the treatment. Individual tumor/tissue combinations did not approach statistical significance. However, the combined incidences for islet cell adenomas and islet cell carcinomas in the pancreas of the females approached statistical significance at the α-level for common tumors. The p-value from the Exact Permutation Trend Test fell short at 0.0084 but the normal approximation test had a p-value of 0.0051. As this finding was not robust, the reviewer evaluated the validity of both the female and the male rat study. She concluded that there were sufficient numbers of animals exposed sufficiently long to allow for late developing tumors. In determining whether the high dose presented a sufficient tumor challenge, i.e. was close to the MTD, the mortality could not be used. For both males and the females, the high dose groups experienced either slightly better

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(males) or identical cumulative mortality by the end of the study. The high dose males had pronounced lower average body weights than their combined controls. The high dose females had lower body weight that their controls which reached 11 % by week 26 but continued to increase to 23 % by study end. The sponsor concluded that the MTD was either attained or exceeded based on body weight changes, i.e. differences in body weight increases, of more than 20 %. The reviewer based her calculations on differences of average body weights of the high dose compared to the controls at the various time points, where the results for the females were not as pronounced. Whether either the male or the female rat study can be considered valid in the presence of no (or only almost) statistically significant increases in tumors is left to the expertise of the reviewing pharmacologist.

The 24-month oncogenicity study in — CD-1®(ICR)BR **MICE** from ———— ———— had 60 animals per gender in each of two vehicle control groups and in three treated groups. The test article was administered at levels of 2.5, 5.0, and 10 mg/kg/day via gastric intubation and necropsies were performed on all animals and all tissues were microscopically examined. Due to high mortality among the high dose animals, both male and female high dose groups were terminated in week 82. The remaining females were euthanized in week 90, whereas the remaining males were euthanized in week 105. Very early deaths (24 females and 11 males) were replaced with stock animals. Most of these deaths were ascribed to intubation trauma. Due to the early termination of the high dose animals but not of one of the control groups, the reviewer performed two sets of analyses: one (per gender) where all animals were used but all were censored at the time of the terminal sacrifice of the high dose animals, and one (again per gender) where the high dose was excluded and the remaining animals analyzed using their terminal sacrifice time. When all animals were used, the increase in mortality with dose was highly statistically significant for both the male and female mice. When the high dose animals were excluded from the analyses, the trends for increase in mortality among the male mice were now statistically significant at only α=0.05 whereas for the females the high level of significance did essentially not change. Among the male mice there were no statistically significant increases in tumor findings whether the high dose was included or excluded in the analyses. The sponsor reported the same conclusions when the appropriate α-levels are applied. There was one minor discrepancy between the sponsor's and the reviewer's analysis results for the increase in alveolar-bronchiolar adenomas in the lungs of the male mice. The reviewer's trend tests were clearly non-significant, whereas the sponsor's use of 'the method of Peto' led to a significant finding at α=0.05. The sponsor had described their analyses of the lung tumors in detail but did not provide the numeric results. Though the reviewer is not clear what caused this difference in findings, it is of no great consequence as the sponsor's finding did not approach the proper α-level for common tumors (α=0.005). Again, both the sponsor and the reviewer concluded that no tumor finding reached the proper statistical significance level in either gender. The sponsor concluded that the MTD was exceeded based on the decreased survival in all treated groups compared to the control groups. The reviewer agreed with this statement with respect to the female mice. However, in the reviewer's evaluations of the average body weights of the male mice, one could conclude that the study was valid, as the high dose had average body weights of 4 to 5 percent lower than their controls for

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most of the study. The treatment's effect on mortality or on the average body weights appear to lead to conflicting conclusions. The final decision as to the validity of either mouse study in the presence of no statistically significant increase in any tumor is left to the expertise of the reviewing pharmacologist.

5. APPENDIX: Analyses of the Mouse Data with the High Dose Excluded

5.1. Female Mice

The high dose was terminated at week 83 and the remaining groups were terminated a week later. In the main body of the review the results are presented where all treatment groups are used but censored at week 83. Here, the mortality and tumor findings are investigated with the high dose group excluded but study end is week 90. The survival analyses resulted in no change in the highly statistically significant effect of the treatment on mortality (Tables 13 and 14 and Figure 5). As in the analysis involving all treatment groups, no tumor finding approached statistical significance (Table 15).

Table 13: Mortality of Female Mice without High Dose

Analysis of Mortality		No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
CTR1	0-52	60	8	52	86.7	13.3
	53-78	52	8	44	73.3	26.7
	79-89	44	4	40	66.7	33.3
	FINALKILL 90-91	40	40	0		
CTR2	0-52	60	5	55	91.7	8.3
	53-78	55	7	48	80.0	20.0
	79-89	48	8	40	66.7	33.3
	FINALKILL 90-91	40	40	0		
LOW	0-52	60	9	51	85.0	15.0
	53-78	51	13	38	63.3	36.7
	79-89	38	15	23	38.3	61.7
	FINALKILL 90-91	23	23	0		
MED	0-52	60	10	50	83.3	16.7
	53-78	50	17	33	55.0	45.0
	79-89	33	13	20	33.3	66.7
	FINALKILL 90-91	20	20	0		

Table 14: Mortality Trends for Female Mice without High Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	1.3964	0.4975	1.2482	0.5357
Depart from Trend				
Dose-Mortality Trend	19.6599	0.0000	16.4231	0.0001
Homogeneity	21.0564	0.0001	17.6713	0.0005

Figure 5: Kaplan Meier Survival Curves for Female Mice without High Dose

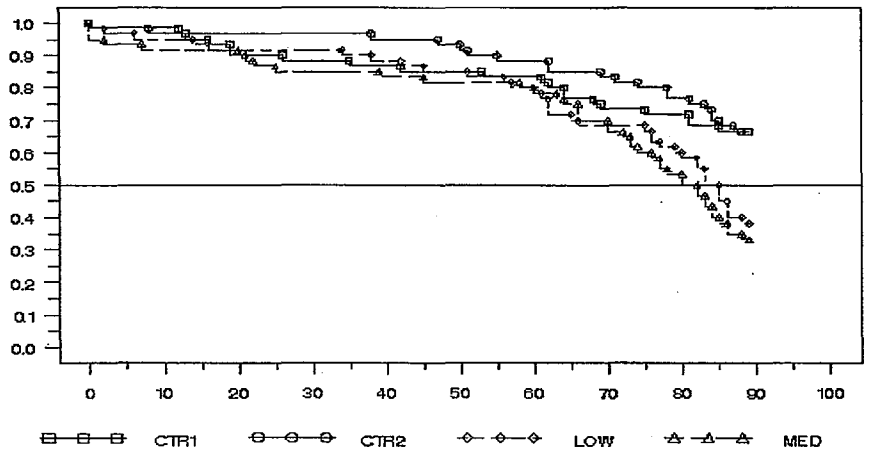

Table 15: Tumor Trends for Female Mice without High Dose

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001006	#B PHEOCHROMOCYTOMA	0	0	1	0	0.3443	0.3444
KI	KIDNEYS	HP020022	#M CARCINOMA, RENAL CELL	0	0	1	0	0.4041	0.3892
LI	LIVER	HP021004	#B ADENOMA, HEPATOCELLULAR	1	2	1	1	0.5734	0.5359
LU	LUNGS	HP026003	#B ADENOMA, BRONCHIOLAR/ALVEOL	6	4	4	1	0.8990	0.8755
LU	LUNGS	HP026005	#M CARCINOMA, BRONCHIOLAR/ALVE	2	0	0	1	0.6562	0.5783
MG	MAMMARY GLAND	HP027004	#M ADENOCARCINOMA	0	1	12	2	0.0757	0.0600
MG	MAMMARY GLAND	HP027009	#B ADENOMA	0	0	1	0	0.3644	0.3643

MG	MAMMARY GLAND	HP027010	#M ADENOACANTHOMA	0	0	1	0	0.3644	0.3643
OV	OVARIES	HP033006	#B LUTEOMA	1	0	0	0	1.0000	0.8271
OV	OVARIES	HP033016	#B CYSTADENOMA	0	1	0	0	1.0000	0.9395
PA	PANCREAS	HP034017	#M CARCINOMA, ISLET CELL	0	1	0	0	1.0000	0.8262
PI	PITUITARY	HP040004	#B ADENOMA, PARS DISTALIS	1	0	0	1	0.3422	0.2427
SK	SKIN	HP046011	#B TRICHOEPITHELIOMA	0	0	0	1	0.1626	0.0447
SK	SKIN	HP046015	#B ADENOMA, SEBACEOUS	0	0	0	1	0.1626	0.0447
SY	SYSTEMIC TUMORS	HP015001	#M LYMPHOMA, MALIGNANT	10	11	11	3	0.8570	0.8411
SY	SYSTEMIC TUMORS	HP015002	#M SARCOMA, HISTIOCYTIC	2	0	3	1	0.3521	0.3104
SY	SYSTEMIC TUMORS	HP015003	#M HEMANGIOSARCOMA	2	2	1	2	0.5515	0.5108
SY	SYSTEMIC TUMORS	HP015004	#B HEMANGIOMA	0	0	1	2	0.1611	0.1095
UT	UTERUS	HP060004	#B POLYP, ENDOMETRIAL STROMAL	8	2	1	1	0.9581	0.9357
UT	UTERUS	HP060005	#M SARCOMA, STROMAL CELL	4	1	0	0	1.0000	0.9504
UT	UTERUS	HP060016	#B LEIOMYOMA	1	0	0	1	0.5330	0.4150
XX	HARDERIAN GLANDS	HP081003	#B ADENOMA	1	0	2	0	0.4883	0.4199

5.2. Male Mice

The high dose was terminated at week 83 and the remaining groups were terminated at week 104. In the main body of the review the results are presented where all treatment groups are used but censored at week 83. Here, the mortality and tumor findings are investigated with the high dose group excluded but study end is week 104. The survival analyses resulted in a large reduction of the previously highly statistically significant effect of the treatment on mortality. Now the trend tests for increased mortality with dose are barely significant at α=0.05 (Tables 16 and 17 and Figure 6). As in the analysis involving all treatment groups, no tumor finding approached statistical significance (Table 18).

Table 16: Mortality for Male Mice without High Dose

	Analysis of Mortality	No. Risk	No. Died	No. Alive	Pct Survival	Pct Mortality
	0-52	60	10	50	83.3	16.7
	53-78	50	2	48	80.0	20.0
CTR1	79-91	48	4	44	73.3	26.7
	92-103	44	12	32	53.3	46.7
	FINALKILL104-105	32	32	0		
	0-52	60	8	52	86.7	13.3
	53-78	52	9	43	71.7	28.3
CTR2	79-91	43	3	40	66.7	33.3
	92-103	40	9	31	51.7	48.3
	FINALKILL104-105	31	31	0		
	0-52	60	11	49	81.7	18.3
	53-78	49	2	47	78.3	21.7
LOW	79-91	47	10	37	61.7	38.3
	92-103	37	11	26	43.3	56.7
	FINALKILL104-105	26	26	0		
	0-52	60	12	48	80.0	20.0
	53-78	48	9	39	65.0	35.0
MED	79-91	39	8	31	51.7	48.3
	92-103	31	8	23	38.3	61.7
	FINALKILL104-105	23	23	0		

Table 17: Mortality Trends for Male Mice without High Dose

	Method			
	Cox		Kruskal-Wallis	
	Statistics	P-Value	Statistics	P-Value
Time-Adjusted Trend Test	0.0396	0.9804	0.0686	0.9663
Depart from Trend				
Dose-Mortality Trend	3.8756	0.0490	3.8065	0.0511
Homogeneity	3.9152	0.2708	3.8751	0.2753

Figure 6: Kaplan Meier Survival Curves for Male Mice without High Dose

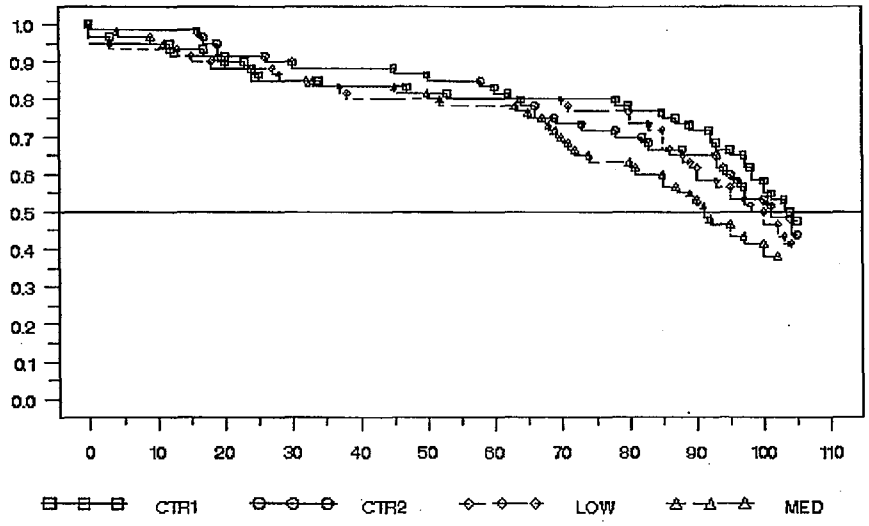

Table 18: Tumor Trends in Male Mice without High Dose

Organ Code	Organ Name	Tumor Code	Tumor Name	CTR1	CTR2	LOW	MED	P-Value (Exact Method)	P-Value (Asymptotic Method)
AD	ADRENAL GLANDS	HP001002	#B ADENOMA, CORTICAL	1	0	0	1	0.5525	0.4581
AD.	ADRENAL GLANDS	HP001006	#B PHEOCHROMOCYTOMA	1	0	0	0	1.0000	0.8539
DU	DUODENUM	HP010004	#M SARCOMA, UNDIFFERENTIATED	0	0	1	0	0.5156	0.4885
GB	GALLBLADDER	HP016011	#M SARCOMA, UNDIFFERENTIATED	0	0	0	1	0.2018	0.0729
GB	GALLBLADDER	HP016012	#B ADENOMA, PAPILLARY	0	0	1	0	0.5926	0.5077
KI	KIDNEYS	HP020022	#M CARCINOMA, RENAL CELL	0	0	1	0	0.4375	0.4222
KI	KIDNEYS	HP020024	#B ADENOMA, RENAL CELL	0	0	0	1	0.2000	0.0764
LI	LIVER	HP021004	#B ADENOMA, HEPATOCELLULAR	5	5	3	0	0.9897	0.9787
LI	LIVER	HP021009	#M CARCINOMA, HEPATOCELLULAR	3	2	0	3	0.4385	0.3995
LU	LUNGS	HP026003	#B ADENOMA, BRONCHIOLAR/ALVEOL	7	8	12	7	0.3252	0.3028
LU	LUNGS	HP026005	#M CARCINOMA, BRONCHIOLAR/ALVE	5	3	4	2	0.7223	0.6954
PI	PITUITARY	HP040004	#B ADENOMA, PARS DISTALIS	0	0	0	1	0.2130	0.0759
PI	PITUITARY	HP040008	#B ADENOMA, PARS INTERMEDIA	0	0	0	1	0.2000	0.0705
SG	SALIVARY	HP043013	#B SCHWANNOMA	0	0	0	1	0.2054	0.0741

	GLANDS								
SG	SALIVARY GLANDS	HP043014	#M ADENOCARCINOMA	0	0	1	0	0.4507	0.4277
ST	STOMACH	HP049014	#M ADENOCARCINOMA	0	0	1	0	0.4375	0.4222
ST	STOMACH	HP049016	#M SARCOMA, UNDIFFERENTIATED	0	0	1	0	0.5500	0.5120
SY	SYSTEMIC TUMORS	HP015001	#M LYMPHOMA, MALIGNANT	3	4	1	3	0.6196	0.5894
SY	SYSTEMIC TUMORS	HP015002	#M SARCOMA, HISTIOCYTIC	2	1	0	0	1.0000	0.9397
SY	SYSTEMIC TUMORS	HP015003	#M HEMANGIOSARCOMA	1	3	5	1	0.5189	0.4859
SY	SYSTEMIC TUMORS	HP015004	#B HEMANGIOMA	1	0	1	1	0.4267	0.3643
TE	TESTES	HP051009	#B ADENOMA, INTERSTITIAL CELL	1	0	2	1	0.3584	0.2989
TG	THYROID GLANDS	HP053010	#M CARCINOMA, FOLLICULAR CELL	0	0	1	0	0.4375	0.4222
TH	THYMUS GLAND	HP052021	#B THYMOMA	0	0	1	0	0.4691	0.4725
XX	EXTERNAL SURFACE	HP076004	#B PAPILLOMA, SKIN	0	0	0	1	0.3200	0.1629
XX	EXTERNAL SURFACE	HP076014	#B NERVE SHEATH TUMOR	0	0	1	0	0.4375	0.4222
XX	SUBCUTIS	HP098004	#B LIPOMA	0	0	1	0	0.5610	0.5254

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Concur with review

Secondary (Pharmacogenetics) Statistical Review

Subject: NDA 22-192 / N000

Drug Name: Iloperidone

Indication: Treatment of schizophrenia

Medical Division: Division of Psychiatric Products

Background

The purpose of this memo is to facilitate the statistical review and evaluation by Dr. Phillip Dinh in the context of interpreting evidence on "whether iloperidone is shown superior to placebo in the schezophrenia patients who carry the CNTF FS63Ter(-/-) genotype" that has potential labeling consideration, see Appendix that included review recommendation by Dr. Dinh, the process of the blood sample collection of CNTF gene for pharmacogenetic (PG) assessment, and relevant text in the Sponsor's proposed label dated March 17, 2008. Of note, the efficacy of iloperidone in schizophrenia patients was demonstrated in ILP3005ST and VP-VYV-683-3101, see Appendix (Table A.1 and Table A.2).

Assessment of clinical benefit described in the CNTF(-/-) patient subset

Two studies contained the genetic CNTF data: ILP3005ST (abbreviated as ILP3005) and VP-VYV-683-3101 (abbreviated as VP-3101). VP-3101 was prospectively planned to assess iloperidone effect in a stepdown manner, testing whether iloperiodone 24 mg/day is superior to placebo in the intent-to-treat schizophrenia patients, and then testing whether the superior iloperidone effect, if concluded, is shown in the CNTF (-/-) subgroup. The prospectively specified CNTF (-/-) subgroup objective in VP-3101 (study period 2005-2006) was based on the exploratory PG analyses in the 31% mITT patients in the completed ILP3005 (study period 2000-2001). The major design differences between the two studies are briefly summarized in Table 1.

Table 1. Major design/analysis differences between ILP3005 and VP-3101

Key Design Element	ILP3005	VP-3101
Patient population	78% schizophrenia; 22% schizoaffective In 31% PG patients: 76% schizophrenia	100% schizophrenia
Patient sources	Canada, Croatia, Germany, Hungary, Israel, Poland, South Africa, and USA	US (32 sites) and India (9 sites)
Iloperidone dosing	flexible dosing	fixed dose
dose regimen	12-16 mg/d (6 or 8 mg BID) 20-24 mg/d (10 or 12 mg BID) (added after completion of Study 3004*: ~30% accrual)	24 mg/d
Active comparator	risperidone 6-8 mg/d	ziprazidone 160 mg/d
Primary endpoint	BPRS total score (sub-items of PANSS-T)	PANSS total score
Assessment time	change from baseline at 6 weeks	at 4 weeks
Primary analysis	LOCF	MMRM with time variable

* Study 3004 – an international 6wk BPRS study consists of two flexible groups with sequential decision testing high dose, then testing low dose (10-16mg/d vs pbo, p=0.001; 4-8mg/d vs pbo, p=0.012; risperidone vs. pbo, p<0.001).

I investigated the prevalence of CNTF(-/-) genotype in schizophrenia patients. The observed prevalence was 81% in the convenience PG sample of ILP3005, and 78% in VP-3101 (excluding 1.7% patients with CNTF data missing). The prevalence was also estimated based on race (W:B), gender (M:F) within each study. The observed prevalence in white patients and in both gender groups did not deviate much from the overall prevalence. Blacks (17% in ILP3005 and 50% in VP-3101) had a higher prevalence (91% in ILP3005 and 86% in VP-3101) in both studies.

- Exploratory PG analyses in schizophrenia patients: ILP3005

In the mITT analysis of ILP3005, there appeared to be a dose-response trend with BPRS and PANSS endpoints measured at week 6, see Table A.1. The effect was much higher in risperidone (the active control for checking assay sensitivity) than in iloperidone. This apparent dose-response trend was not shown in the voluntary PG patients. It was not clear what baseline characteristics differences there might be in the schizophrenia patients between the mITT set and the exploratory PG subset. The exploratory analyses showed that both the low-dose iloperidone and risperidone might have a treatment effect in the limited schizophrenia CNTF(-/-) subgroup.

Table 2. Exploratory pharmacogenetic analysis of iloperidone in Schizophrenia patients : ILP3005

ILP3005ST	BPRS (Primary)			PANSS		
31% of mITT	Ilop 12-16	Ilop 20-24	Risp 6-8	Ilop 12-16	Ilop 20-24	Risp 6-8
CNTF PG pts*	-5.0	-3.4	-4.1	-7.9	-6.6	-6.7
unadj. p-value	0.029	0.192	0.094	0.0141	0.135	0.106
CNTF (-/-)	-9.3	-6.6	-6.1	-15.9	-12.7	-9.8
unadj. p-value	<0.001	0.016	0.017	<0.001	0.007	0.024
Non-CNTF(-/-)	5.8	12.7	1.3	3.3	9.1	-2.4
unadj. p-value	0.498	0.424	0.868	0.852	0.714	0.884

* estimated difference relative to placebo at wk 6: negative changes indicate improvements; extracted from Reviewer Table 12 (by CNTF status); of note, the gender/race subsets in non-CNTF(-/-) had too few patients.

- Consistency assessment of efficacy in schizophrenia PG CNTF subsets:VP-3101

The overall significant iloperidone effect measured by change from baseline at week 4 using the PANSS total score shown in Table A.2 appeared to be consistent by gender, by race, and similar to the observed ziprasidone effect, see Table 3. The treatment effects of iloperidone and ziprasidone appeared to be larger in females (21% of mITT) as compared to males, and in whites/others (50% of mITT) as compared to blacks.

Table 3. The analysis results of PANSS total score (the primary efficacy endpoint) in VP-3101*

PANSS	mITT by Gender**			mITT by Race**		
	Ilop 24 mg	Zipra 160 mg			Ilop 24 mg	Zipra 160 mg
M (79%)	-4.86 (0.015	-4.88 (0.036		White/other	-7.37 (0.010	-7.04 (0.031)
F (21%)	-8.76 (0.039	-8.83 (0.050)		Black(50%	-2.20 (0.342)	-3.63 (0.171)
	mITT within CNTF (-/-) (79%)			mITT within Non-CNTF (-/-) (21%)		
eff est***	-6.3 (-5.7)	-6.7 (-6.0)		eff est***	0.3 (-1.7)	1.4 (-1.2)
unadj. p***	0.002 (0.003	0.004 (0.005		unadj. p***	0.94 (0.711)	0.77 (0.882)
Gender				Gender		
M (81%)	-6.7 (0.003)	-7.2 (0.006)		M (72%)	0.7 (0.871)	5.2 (0.344)
F (19%)	-9.1 (0.087)	-7.3 (0.167)		F (28%)	-5.0 (0.506)	-11.4 (0.241)
Race				Race		
W (32%)	-9.58 (0.017)	-7.41 (0.102)		W (45%)	-7.29 (0.229)	-1.40 (0.857)
B (54%)	-5.2 (0.042)	-6.4 (0.028)		B (35%)	10.4 (0.066)	7.8 (0.288)
O (14%)	-4.5 (0.468)	-12.2 (0.085)		O (20%)	-1.8 (0.862)	-2.7 (0.818)

* estimated difference r.t. to placebo; negative value indicates improvement. 9 patients with CNTF missing not included.
** Reviewer Tables 33 (by gender); 34 (by race); 22 (by CNTF); subset of subset analyses for this memo: MMRM.
*** effect estimates based on MMRM (LOCF); unadjusted p-value based on MMRM (LOCF)

Although assessment of treatment effect in the CNTF(-/-) subgroup was prospectively specified, randomization was not stratified by the CNTF status. No baseline imbalances were indicated as per Dr. Dinh's analyses. The Iloperidone effect shown in the CNTF(-/-) patient subset appeared to be consistent in each gender subset and in each race (W:B) subset. The magnitudes of the observed effect appeared to be similar in iloperidone and in ziprasidone. In the non-CNTF(-/-) subgroup, both iloperidone and ziprasidone seemed to yield little effect. It may be important to assess the safety in the non-CNTF(-/-) subset to understand the benefit/risk for iloperidone and

ziprazidone. Please see medical review and evaluation by Drs. Chuen and Khin for this safety evaluation.

Conclusion from the pharmacogenetic analyses

The exploratory PG study in ILP3005 seemed to suggest that low flexible dose (12-16 mg/d) of iloperidone has a beneficial effect. The iloperidone 20-24 mg/d effect and risperidone 6-8 mg/d effect, which were shown significant in the mITT schizophrenia patients, were not evident in the exploratory schizophrenia PG subset.

The registration study VP-3101 (1.7% with CNTF status missing) showed a superior overall iloperidone fixed dose (24 mg/d) effect. The effect appeared to be consistent in gender, and, in race (W/O:B) subgroups; all reached nominal statistical significance except the black subgroup (50% of mITT). As per the analysis by the CNTF status, the iloperidone effect appeared to be primarily in the CNTF(-/-) subgroup and also seemed to be consistent in gender subsets and in race subsets. No consistent effect was seen in the non-CNTF(-/-) subgroup; numerically, iloperidone appeared to have some effect in the female non-CNTF(-/-) and white/other non-CNTF(-/-) subgroups. Similar results were seen in the ziprazidone group.

In summary, both iloperidone 24 mg/d and ziprazidone 160 mg/d seem to have a beneficial effect in the CNTF(-/-) genotype subgroup consisting approximately 78%-80% mITT patients, which was prospectively studied in one Trial (VP-3101). Of note, the study also showed a beneficial effect in iloperidone and ziprazidone in all comers regardless of the CNTF status.

Sue-Jane Wang, Ph.D.
Associate Director, Pharmacogenomics and Adaptive Design
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Appendix.

- Extracted from Dr. Phillip Dinh's review relating to CNTF labeling recommendation

The findings on the *CNTF FS63Ter* subgroup are suggestive, but not conclusive to support a labeling claim for the following reasons: 1) in study VP-VYV-683-3101, the findings suggested a greater treatment effect in the *CNTF* (-) subgroup; however, in the *CNTF* (+) subgroup, the treatment benefit appeared vanished; 2) in study ILP3005ST, an exploratory analysis was performed on the *CNTF* genotype subgroup, the findings in study ILP3005ST were not consistent with the findings in study VP-VYV-683-3101: numerical improvements were seen in both *CNTF* subgroups; 3) an analysis based on study ILP3005ST was post-hoc. Thus, the findings on study VP-VYV-683-3101 regarding the *CNTF* subgroup have not been replicated.

- The process of the blood samples drawn to assess the pharmacogenomics of the CNTF gene on the iloperidone effect in Study#VP-VYV-683-3101 can be found in Section 9.5.1.5 of the clinical study report and is copied below.

9.5.1.5. Pharmacogenomic assessments

Two 3-mL blood samples were drawn from all patients who participated in the short-term, double-blind study. The blood samples were collected in 3-mL [redacted], which were completely and gently inverted ~10 times to prevent clotting. Sites in the United States sent the samples at room temperature on the day of collection to [redacted] a central laboratory. Sites in India stored the blood samples frozen on site at <-20°C until shipment on dry ice on the day of collection to [redacted] DNA was extracted from these samples to prospectively confirm preliminary associations between polymorphisms in the *CNTF* and *CYP2D6* genes and iloperidone response.

b(4)

- Relevant text in the Sponsor's proposed label dated March 17, 2008.

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/s/

Sue Jane Wang
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