CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number:	**20588/S002 AND 20272/S007**
Trade Name:	**Risperdal**
Generic Name:	**Risperidione**
Sponsor:	**Janssen Research**
Approval Date:	**October 17, 1997**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION: 20588/S002 AND 20272/S007

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	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				X
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Final Printed Labeling		X		
Medical Review(s)	X			
Chemistry Review(s)				X
EA/FONSI				X
Pharmacology Review(s)				X
Statistical Review(s)	X			
Microbiology Review(s)				X
Clinical Pharmacology Biopharmaceutics Review(s)	X			
Bioequivalence Review(s)				X
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Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: 20588/S002 AND 20272/S007

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-272 / S-007
NDA 20-588 / S-002

OCT 17 1997

Janssen Research Foundation
Attention: Todd D. McIntyre, Ph.D.
1125 Trenton-Harbourton Road
Post Office Box 200
Titusville, NJ 08560-0200

Dear Dr. McIntyre:

Please refer to the following supplemental new drug applications submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act:

1. Risperdal (risperidone) 1mg, 2mg, 3mg, 4mg Tablets
   NDA 20-272: Supplement 007
   Submitted: November 26, 1996
   Received: November 29, 1996
   User Fee Goal Date: November 29, 1997

2. Risperdal (risperidone) 1mg/mL Oral Solution
   NDA 20-588: Supplement 002
   Submitted: November 27, 1996
   Received: December 2, 1996
   User Fee Goal Date: December 2, 1997

These supplemental applications provide for the administration of risperidone tablets and oral solution in either a once daily (QD), or twice daily (BID) dosing regimen.

We have completed the review of these supplemental applications, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the enclosed marked-up draft labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the enclosed marked-up draft labeling.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved supplemental NDAs 20-272 / S-007, 20-588 / S-002. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drugs become available, revision of that labeling may be required.

Should a letter communicating important information about these drug products (i.e., a "Dear Doctor" letter) be issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to these NDAs and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20852-9787

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Steven D. Hardeman, R.Ph., Project Manager, at (301) 594-5533.

Sincerely yours,

10/17/97

Paul Leber, M.D.
Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20588/S002 AND 20272/S007

MEDICAL REVIEW(S)

REVIEW AND EVALUATION OF CLINICAL DATA

NDA: 20-272

SPONSOR: Janssen

DRUG: Risperidone (Risperdal) tablets

INDICATION: Antipsychotic

MATERIAL SUBMITTED: Supplement 7 for Once Daily Dosing Regimen

DATE SUBMITTED: 11/26/96

DATE RECEIVED: 11/29/96

USER FEE DUE DATE: 11/29/97

REVIEWER: Andrew Mosholder, M.D.

1. Background

Risperdal labeling currently recommends dosing with a BID regimen, consistent with how patients were dosed in the pivotal clinical trials. This supplement provides labeling to allow dosing on a QD schedule. In support of this, the sponsor has submitted data from 3 randomized controlled trials; two of these were two-arm studies in which all patients received risperidone treatment, either QD or BID. The third trial was a 3 arm study comparing risperidone given BID, risperidone given QD, and placebo. This trial (RIS-USA-72) is thus the primary source of data on the effectiveness of QD dosing and will be the focus of the efficacy review. In addition, safety data accrued from QD dosing was compiled by Janssen, and these data will be reviewed to ensure that QD dosing does not entail unusual adverse reactions.

The proposed labeling for this supplement is as follows:

Under Precautions/General/Orthostatic Hypotension, the initial dose for normal adults is recommended as 2 mg total (either QD or 1 mg BID).

Under Dosage and Administration, Usual Initial Dose: "Risperdal (risperidone) can be administered on either a BID or QD schedule. In early clinical trials, Risperdal was generally administered at 1 mg BID initially, with increases in increments of 1 mg BID on the second and third day, as tolerated, to a target dose of 3 mg BID by the third day. Subsequent controlled trials have indicated that most patients tolerate equally well receiving these total daily doses in either a BID or QD regimen. However, regardless of which regimen is employed, in some patients a slower titration may be medically appropriate. Further dosage adjustments, if indicated, should generally occur at intervals of not less than 1 week, since steady state for the active metabolite would not be achieved for approximately 1 week in the typical patient. When dosage adjustments are necessary, small dose increments/decrements of 1-2 mg are recommended."

Under Dosage and Administration, Dosage in Special Populations: "If you are considereing employing a once-a-day dosing regimen in the elderly or debilitated patient, it is recommended that the patient be titrated on a twice a day regimen for 2-3 days at the target dose. Subsequent switches to a once a day dosing regimen can be done thereafter."

2. Clinical Data Sources

Janssen included three studies in their integrated safety database for once-a-day dosing. The table below summarizes these three studies.

RIS-USA-72	DB, 28 site, randomized, parallel group, placebo controlled; inpatient schizophrenic subjects (n= approx. 80 per treatment); risperidone 4 mg QD and 8 mg QD versus placebo; 4 weeks.
RIS-USA-60	DB, 42 site, randomized, parallel group trial; inpatient schizophrenic subjects (n=approx. 210 per group); risperidone 3 mg BID versus 6 mg QD; 4 weeks.
RIS-INT-10 (Canada and Europe)	DB, randomized, 48 site, parallel group trial; acute exacerbation of schizophrenia (n=approx. 90 per group); risperidone 4 mg BID versus 8 mg QD; 6 weeks.

Of these, only study 72 was capable by design of being informative regarding efficacy of once a day dosing, and thus will be the focus of the efficacy review.

For the assessment of safety of once a day dosing, all three studies were pooled into an integrated safety data base. The following summarizes the exposure in this database.

Treatment Group	N	Patient-years
Risperidone QD	487	35.1
Risperidone BID	328	24.9
Placebo	83	Not provided

Janssen pooled data from the three studies within dose groups, for comparisons between QD and BID regimens. The following summary table, showing the treatment groups in each study, may be useful in reference to some of the safety analyses that follow below.

Treatment groups by protocol

Protocol	8 mg QD	6 mg QD	4 mg QD	4 mg BID	3 mg BID	Pbo
RIS-USA-72	X		X			X
RIS-USA-60		X			X	
RIS-INT-10	X			X		

The sponsor's table E (see attachments) summarizes the patient demographics for this safety database. Apparently, the term "white" was used in U.S. studies and the term "caucasian" was used in the foreign trial, and these categories are shown separately. The sample was predominantly male, and predominantly white or caucasian, with a mean age of roughly 38 years.

The sponsor's table F (see attachments) summarizes the dose and duration of treatment for the integrated safety database. Note that the duration of exposure is consistent with the design of the respective clinical trials.

Other safety data

The sponsor did provide a literature search and a survey of miscellaneous Janssen studies in which once a day dosing was employed. These data are noted in the safety section that follows the efficacy review.

3. Efficacy

Study RIS-USA-72

Investigators

Attached to this review is the sponsor's list of investigators. This study was conducted in the U.S. and comprised a total of 28 principal investigators. Note that Dr. Richard Borison, formerly with the Medical College of Georgia, and now under investigation for research misconduct, was among the investigators. His site contributed 10 subjects (risperidone 4 mg/d n=4, risperidone 8 mg/d n=3, placebo n=3).

Study Plan

Objective

The stated purpose of this study was to compare the safety and efficacy of risperidone 4 mg QD and 8 mg QD to placebo in schizophrenic subjects.

Population

Eligible subjects were males or females in good health, aged 18-65 years, with a DSM-IV diagnosis of schizophrenic disorder (any subtype). Subjects were required at baseline to be inpatients, and to have a PANSS score of 80-120 and a score of at least 8 on any two of the BPRS psychosis cluster items combined (i.e., conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, and unusual thought content). Exlusion criteria included history of NMS, QT prolongation, other psychiatric illness, seizures, substance dependence, pregnancy, lactation, inadequate contraception (for females), hypersensitivity to risperidone, poor response to risperidone or other antipsychotic drugs previously, recent use of other psychotropic drugs, and dangerousness to self or others. In addition, patients whose first psychotic episode had occurred less than a year previously were excluded. The targeted enrollment was 80/group (240 total).

Design

This was a randomized, double blind, parallel group study. Screening of patients included history and physical examination, orthostatic vital signs, clinical laboratories, ECGs, and the PANSS. Eligible patients were randomized to one of three treatments (placebo, risperidone 4 mg QD, or risperidone 8 mg QD) for a duration of four weeks; initial dosage was titrated at a rate of 2 mg/d for both risperidone

groups. Patients were required to remain in the hospital for at least 2 weeks. Weekly PANSS assessments were the sole efficacy measure. Acceptable concomitant medications included lorazepam, chloral hydrate, anti-EPS medication, and beta blockers for akathisia. Safety assessments included orthostatic vital signs, clinical laboratories, ECGs, and the ESRS.

Analysis Plan

The defined primary outcome measure was the proportion of patients in each group achieving a 20% decrease in total PANSS score from baseline. The primary analysis planned was the Cochran Mantel Haenszel test stratified by investigator, carrying forward the last observation. Analysis of mean change from baseline for the PANSS and its subscales was planned as a secondary analysis, using ANOVA with treatment, investigator, and treatment x investigator. A traditionally defined intent-to-treat population was stipulated. The protocol allowed an interim analysis, for administrative purposes.

Study Conduct/Outcome

Patient Disposition

The table below summarizes the disposition of patients in each treatment group. Note that dropout for inadequate response was most frequent in the placebo group, and that dropout for adverse experience was more frequent in the 2 drug groups.

Number of Patients Prematurely Discontinued From Study

Reason	Placebo (n=83)	Risperidone 4 mg QD (n=85)	Risperidone 8 mg QD (n=78)
Adverse Experience	0	6	5
Inadequate Response	11	4	4
Chose to discontinue	10	14	10
Poor Compliance	3	2	4
Lost to Followup	1	1	2
Ineligible	1	0	0
Other	1	0	0
Total	27	27	25

The table below summarizes the patient completion rate by week of the trial. In this study, all patients who were screened were randomized, even though screening and randomization were performed separately.

Patient Completion Rates, STUDY RIS-USA-72						
Treatment Groups	Number Randomized	Intent-to-Treat Sample*	Number (%) of Patients Completing			
			Week 1	Week 2	Week 3	Week 4
Risperidone 4 mg QD	85	82	82 (100)	72 (88)	66 (80)	58 (71)
Risperidone 8 mg QD	78	75	75 (100)	68 (91)	59 (79)	53 (71)
Placebo	83	79	79 (100)	67 (85)	62 (78)	56 (71)

*Patients who received assigned medication and had one or more efficacy assessments

Demographics/Group Comparability

The table below summarizes the demographic characteristics of the sample. Note that the sample was predominantly male, and roughly 50% white. There were no gross imbalances between groups with respect to demographic characteristics. Mean total PANSS score was approximately 94 for all three groups. (Note: this table depicts data for the set of all randomized patients; demographic data for the intent to treat sample, which had 10 fewer patients, was not submitted.)

Study RIS-USA-72 Demographic Characteristics							
Treatment Groups	n	Age (years)		Sex (n)		Race (n)	
		Mean	S.D.	Male	Female	White	Non-White
Risperidone 4 mg QD	85	38	9	67	18	50	35
Risperidone 8 mg QD	78	38	9	64	14	38	40
Placebo	83	38	11	65	18	48	35

Concomitant Medications

Roughly a third of patients in each treatment group received lorazepam; likewise for chloral hydrate. Anti-EPS medications were used somewhat more frequently in the risperidone groups than in the placebo group. Exact data on concomitant medication use are difficult to determine in the submission, as it appears that some medications were recorded by generic name and others with the proprietary name, resulting in duplication.

Efficacy Results

Primary Outcome Measure

The following table summarizes the results for the sponsor's primary outcome measure, the percentage of patients achieving a 20% or more reduction in PANSS total score from baseline at day 28.

Parameter	Placebo	Risperidone 4 mg QD	Risperidone 8 mg QD
%, LOCF	46.8	64.6	76.0
p-value versus pbo., LOCF*	-	0.036	<0.001
%, OC	60.7	76.3	88.9
p-value versus pbo., OC*	-	0.076	<0.001

*C-M-H test

Thus there was statistical evidence for the efficacy of 8 mg QD under both LOCF and OC analyses, while the 4 mg QD treatment group showed statistical superiority only with the LOCF method.

Secondary Outcome Measures

On the PANSS total score, both doses showed statistical superiority over placebo at the end of the study with the observed cases analysis; with LOCF, the 8 mg dose result was statistically significant and the 4 mg dose result was very close to statitsically significant ($p=0.051$). Results on the key BPRS psychosis items (see above) showed superiority for both doses, with both LOCF and OC methods. The derived BPRS total score did not demonstrate statistical significance except for the 8 mg dose with the LOCF analysis. Finally, on the PANSS negative symptom subscale both doses were superior to placebo with the OC analysis but only the 4 mg dose with the LOCF analysis. Complete data displays for these variables are shown in the sponsor's tables which are attached to this review.

Subgroup analyses

The sponsor provided only descriptive statistics of the efficacy results with the sample divided by age group, race and gender. No compelling differences on the outcome measures were disclosed by this analysis.

Conclusions

This study provides evidence that risperidone administered once a day is effective in the treatment of exacerbation of schizophrenic symptoms, relative to placebo. Generally, the results were somewhat more robust for the higher (8 mg) dose. Results from this study do not address, of course, the question of comparing once a day to BID administration.

Other Studies

RIS-USA-60 was a randomized, double blind, parallel group, multicenter study comparing 4 weeks of treatment with risperidone 6 mg QD and 3 mg BID, in psychotic schizophrenic patients. A total of 429 patients participated. The BID group had numerically superior efficacy results, and on the primary outcome measure of percentage of patients meeting the criterion for response (20% reduction in total

PANSS) the results did not meet Janssen's criterion for therapeutic equivalence. That is, the 90% confidence limit for the difference between the two treatments did not include zero. Standard hypothesis testing with an alpha of 0.05 for the difference between the two treatments was not performed.

RIS-INT-10 was a double blind 6 week controlled trial involving 187 patients with acute exacerbation of schizophrenia, randomized to risperidone 8 mg QD or 4 mg BID. Efficacy results on the PANSS were similar between the groups, and the results met the sponsor's criterion for therapeutic equivalence.

Efficacy Conclusions

The data from study RIS-72-USA, the main focus of this efficacy review, indicate that once a day dosing of risperidone is effective in the treatment of psychosis relative to placebo. This is not to say that QD and BID dosing are equally effective, of course, and in fact the BID group in study RIS-USA-60 had a somewhat superior outcome. The results of study RIS-INT-10 were uninformative, as no difference was found between treatments.

4. Bioequivalence Trial

Study RIS-BEL-33 was an open, two treatment crossover study comparing the pharmacokinetics of an investigational 8 mg risperidone tablet given once a day to 4 mg BID, at steady state. Subjects were 24 schizophrenic patients stabilized on risperidone. The duration of treatment was one week for each arm. The mean concentration at steady state was 31 ng/ml for the 8 mg tablet and 33 ng/ml for 4 mg BID. The mean concentration at steady state for what the sponsor terms the "active moiety" (risperidone plus 9-OH-risperidone) was 90 ng/ml for the 8 mg tablet and 98 ng/ml for 4 mg BID. Please refer to the OCPB review for details.

Safety

The primary data base for the safety assessment of once a day dosing comprises the three studies described above, RIS-USA-72, RIS-USA-60 and RIS-INT-10. Where feasible, comparisons between QD and BID regimens are emphasized in this review. Additional data was provided by the sponsor's literature review and a few previous studies involving once a day dosing.

Deaths

No deaths are reported in the submission.

Other Serious Adverse Events

There were a total of 40 serious adverse events in the primary integrated database studies. The majority of these involved exacerbation of the subject's psychiatric symptomatology and will not be reviewed herein. Other serious adverse events are listed by body system in the Review of Systems that follows.

Dropouts

A total of 86 out of 815 risperidone treated patients in the integrated database withdrew with adverse events. No placebo patients withdrew because of adverse events. As shown in the table below, the total number of droupouts for adverse events did not appear to be clearly related to dosage or regimen.

Dropout rate for adverse events by treatment group, integrated database trials

	All risp.	8 mg QD	6 mg QD	4 mg QD	4 mg BID	3 mg BID	Pbo
N	815	181	221	85	108	220	83
% Dropout for Adverse Event	10.6	6.6	13.1	7.1	11.1	12.3	0

From the pool of all risperidone patients, the following adverse events resulted in 1% or more of the 815 patients discontinuing (from sponsor's table AE.6C): agitation, insomnia, somnolence, anxiety, psychosis, aggressive reaction, extrapyramidal disorder, hyperkinesia, headache, dyspepsia, vomiting, tachycardia.

By inspection, the rate of dropout for these adverse events did not show a consistent pattern related to dose or regimen. These adverse events are consistent with the safety profile of risperidone known from previous clinical trial data.

Adverse Event Incidence

The sponsor's table K is attached to this review, showing adverse events for which the incidence was at least 5%, by treatment group. These adverse events are not inconsistent with the previously reported adverse event profile for risperidone. A comparison between BID and QD dosing was made using the individual trial data from study RIS-USA-60 (3 mg BID versus 6 mg QD) and RIS-INT-10 (4 mg BID versus 8 mg QD). This permitted comparison of the same total daily dose within the same study, for QD and BID regimens. For no adverse event was the incidence in the once a day group twice that of the BID group, and in most cases the incidences were similar.

Laboratory Findings

Clinical laboratory batteries were obtained during treatment in all 3 trials in the integrated database. The sponsor provided an analysis of patients in the integrated database meeting criteria for possibly clinically significant laboratory abnormalities. The criterion values used for these determinations were taken from this Division's Draft Guidelines on Preparing the ISS. Inspection of the rates of possibly clinically significant laboratory abnormalities for risperidone 3 mg BID compared to risperidone 6 mg QD and for risperidone 4 mg BID compared to 8 mg QD did not reveal any pattern suggesting an increased risk for laboratory abnormalities with once a day dosing, for any of the laboratory parameters tested. For all risperidone groups, low hematocrit was more common than in the placebo group, although the significance of this was not clear.

Vital Signs

Vital signs were obtained in all 3 trials contributing to the integrated database, and orthostatic vital signs were obtained in two of the three trials. In a manner similar to the analysis of laboratory

abnormalities, the sponsor employed predetermined criteria for possibly clinically significant changes in vital signs during treatment. Weight gain (of 7% or more) and increased standing heart rate (>120 bpm and increase of ≥15 bpm) were the only vital sign abnormalities clearly associated with risperidone in comparison to placebo. Examination of the incidences for these by treatment group did not suggest a relationship to dosage regimen. These findings are consistent with previous risperidone clinical trial data.

In study RIS-USA-60, there were no statistically significant differences between the 6 mg QD and the 3 mg BID groups with respect to mean change from baseline on any vital sign parameters. This study did not include orthostatic vital signs.

In study RIS-INT-10 there were no significant differences between the 4 mg BID and 8 mg QD groups on mean change from baseline for any vital sign parameter (supine or standing).

ECGs

In study RIS-USA-60, ECGs were obtained at baseline and at the end of the study. There were no statistically significant differences between the 6 mg QD and the 3 mg BID groups on mean change from baseline in heart rate, QRS duration, QT interval, or QTc interval. For PR interval, the mean change from baseline with 6 mg QD at week 4 was 2.16 msec, while the corresponding value with 3 mg BID was -0.78, a statistically significant difference. Mean QTc interval decreased by roughly 1 msec from baseline for both groups. Mean heart rate increased slightly (roughly 3 bpm) in both groups.

In study RIS-USA-72, ECGs were obtained at baseline and endpoint also. The only statistically significant finding compared to the placebo group was a mean increase in heart rate of about 6 bpm for the 8 mg QD group. The mean QTc interval increased by no more than 4 msec in either drug group, which was not statistically significant.

In RIS-INT-10, one patient developed treatment emergent QTc prolongation, but this was less than 500 msec.

On balance, there were no compelling ECG findings related to dosage regimen in this data set.

Review of Systems

I will list here the serious adverse events by body system from the integrated database. Serious adverse events that were deemed related to the patient's underlying psychiatric illness are not included.

<u>Cardiovascular</u>

Possibly drug related
Patient 0162: 34 y.o. female developed first degree AV block, dizziness, orthostasis
Patient 209: 30 y.o. females developed face edema, tachycardia

Unlikely to be drug related
Patient 0605: 51 y.o. male diagnosed with idiopathic hypertrophic subaortic stenosis.

Patient 1604: 44 y.o. male developed ECG findings consistent with ischemia
Patient 0173: 48 y.o. male suffered myocardial infarction

Gastrointestinal

Patient 3703: 31 y.o. male developed gastritis and GI bleeding (unlikely to be drug related)

Hemic and Lymphatic

None

Metabolic and Endocrine

Patient 4201: 30 y.o. male developed hyponatremia, convulsions, pneumonia (unlikely to be drug related)

Musculoskeletal

Patient 3811: 45 y.o. male fractured ankle (unlikely to be drug related)

Nervous

EPS (likely drug related):
Patient 1204 : 36 y.o. female hospitalized for EPS (dystonia and hyperkinesia)
Patient 4008: 38 y.o. male hospitalized for dystonia

Seizures (possibly drug related):
Patient 0245: 46 y.o. male suffered grand mal seizure 2 days after stopping drug
Patient 267: 44 y.o. female suffered convulsions

Respiratory
None.

Dermatologic

None.

Special Senses

None.

Genitourinary

Patient 3418: 43 y.o. female underwent bladder suspension surgery (unlikely to be drug related)
Patient 4002: 61 y.o. male hospitalized for evaluation of urinary incontinence (unlikely to be drug related)

Miscellaneous

Patient 0501: 47 y.o. female had surgery for melanoma (unlikely to be drug related)
Patient 2602: 54 y.o. male hospitalized for cellulitis (unlikely to be drug related)
Patient 2003: 27 y.o. male developed hallucinations, tachycardia, sweating, anorexia, attributed to alcohol abuse (unlikely to be drug related)

On balance, there were relatively few serious adverse events that were reasonably attributable to the effects of risperidone, and those that were likely to be drug related were consistent with the previously known safety profile.

Miscellaneous safety data

In the bioequivalence study RIS-BEL-33 described previously, no subjects withdrew for adverse events.

The sponsor compiled reports of other miscellaneous studies they had sponsored, and reports from the literature, in which risperidone had been administered once a day (vol. 27 of the submission, and section 9 of the ISS). None of these reports had relevance to the question of efficacy.

One study for which the sponsor presented safety findings in more detail, RIS-DEN-1, was a clinical pharmacology study of risperidone 1 mg/d X 2 wks administered to 14 elderly psychiatric patients. Findings included significant lowering of diastolic and systolic blood pressures 1.5 hours after dosing, by roughly 20 mm Hg for supine systolic BP. ECG changes with drug included prolongation of the mean PR interval, by 16 ms; the mean QTc interval was decreased with drug. One subject experienced a seizure. In my view the blood pressure changes illustrate the fact that caution is indicated when prescribing risperidone for the elderly, but this would not be unique to the once a day regimen.

In study RIS-FRG-9005, one patient receiving risperidone 8 mg/d discontinued for "circulatory failure," which I am assuming meant something akin to postural hypotension; details were not provided. Similarly, the sponsor cited two case reports in the literature describing orthostatic collapse with risperidone 1-2 mg/d. Orthostasis is not unusual with risperidone treatment.

The remainder of the studies and literature reports cited did not present any evidence of unusual risks associated with once a day dosing.

Overall Safety Conclusions

The data do not indicate unique adverse drug reactions or patterns of side effects caused by administration of risperidone on a once a day schedule, relative to the known safety profile of the drug when administered BID.

5. Overall Conclusions and Recommendations

Janssen has presented evidence that risperidone is effective in the treatment of psychosis when administered once a day. Further, examination of safety data in patients administered the drug once daily does not reveal any unique hazards for this dosing regimen. These data do not establish, of course, that once a day dosing is "therapuetically equivalent" to BID dosing, merely that QD dosing,

like BID dosing, is an active treatment against the symptoms of psychosis.

With respect to the sponsor's proposed labeling, I note that they have not proposed any addition to the "Clinical Trials" subsection. In the Dosage and Administration changes, I would question the statement that QD and BID dosing are "equally well tolerated" as being too promotional.

This supplement should be considered approvable, in my opinion.

9/23/97

Andrew Mosholder, M.D.
Medical Officer, HFD-120

NDA 20-272 (tablet)
NDA 20-588 (concentrate)
Div File
HFD-120 Laughren/Hardeman/Mosholder
HFD-710 Hoberman

10-15-97
we have reached agreement
with sponsor on final labeling
+ we can now proceed directly
to approval. See memo &
file for more detailed response.
Thomas P. Laughren, MD
TL, DDP

Table E. Summary of patient demographics in double-blind studies - All patients

Parameter	Pbo (N=83)	All Ris (N=815)	Ris 4 mg QD (N=85)	Ris 3 mg BID (N=220)	Ris 6 mg QD (N=221)	Ris 4 mg BID (N=108)	Ris 8 mg QD (N=181)	All Pts (N=898)
Age, mean (years)	38.2	37.6	38.2	38.9	38.8	34.6	35.9	37.6
range	18-66	17-68	19-62	19-62	17-68	18-58	19-65	17-68
Sex, % male	78.3	74.0	78.8	72.3	77.4	67.6	73.5	74.4
Race, N (%)								
Black	27 (32.5%)	232 (28.5%)	26 (30.6%)	88 (40.0%)	82 (37.1%)	4 (3.7%)	32 (17.7%)	259 (28.8%)
Caucasian	0 (0.0%)	197 (24.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	100 (92.6%)	97 (53.6%)	197 (21.9%)
Hispanic	6 (7.2%)	51 (6.3%)	8 (9.4%)	15 (6.8%)	20 (9.0%)	0 (0.0%)	8 (4.4%)	57 (6.3%)
Indic	0 (0.0%)	5 (0.6%)	1 (1.2%)	2 (0.9%)	2 (0.9%)	0 (0.0%)	0 (0.0%)	5 (0.6%)
Mixed	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	2 (0.2%)
Oriental	2 (2.4%)	17 (2.1%)	0 (0.0%)	6 (2.7%)	3 (1.4%)	4 (3.7%)	4 (2.2%)	19 (2.1%)
Polynesian/East	0 (0.0%)	2 (0.2%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	1 (0.6%)	2 (0.2%)
White	48 (57.8%)	309 (37.9%)	50 (58.8%)	109 (49.5%)	112 (50.7%)	0 (0.0%)	38 (21.0%)	357 (39.8%)
Mean height (cm)*	-	172.5	-	172.4	173.7	171.9	170.6	172.5
range		127-206		140-206	135-201	152-191	127-192	127-206
Mean weight (kg)	79.0	79.2	81.8	80.2	80.8	75.0	77.4	79.2
range	46-134	41-200	45-162	46-140	41-152	48-129	41-200	41-200

*Data for height for the placebo group, risperidone 4 mg QD group and risperidone 8 mg QD group were not gathered.

Table F. Summary of daily dose and duration for risperidone therapy

Daily dose	N	Treatment duration						Total Patient Years
		1 day	2-10 days	11-21 days	22-35 days	36-49 days	50-64 days	
U.S. Patients								
All Ris	604	4 (0.7%)	69 (11.4%)	93 (15.4%)	438 (72.5%)	-	-	38.7
Ris 4 mg QD	85	0 (0.0%)	13 (15.3%)	11 (12.9%)	61 (71.8%)	-	-	5.4
Ris 3 mg BID	220	2 (0.9%)	20 (9.1%)	34 (15.5%)	164 (74.5%)	-	-	14.4
Ris 6 mg QD	221	0 (0.0%)	26 (11.8%)	39 (17.6%)	156 (70.6%)	-	-	14.1
Ris 8 mg QD	78	2 (2.6%)	10 (12.8%)	9 (11.5%)	57 (73.1%)	-	-	4.9
Non-U.S.								
All Ris	211	-	17 (8.1%)	19 (9.0%)	20 (9.5%)	148 (70.1%)	7 (3.3%)	21.2
Ris 4 mg BID	108	-	9 (8.3%)	12 (11.1%)	10 (9.3%)	75 (69.4%)	2 (1.9%)	10.5
Ris 8 mg QD	103	-	8 (7.8%)	7 (6.8%)	10 (9.7%)	73 (70.9%)	5 (4.9%)	10.6
All patients								
All Ris	815	4 (0.5%)	86 (10.6%)	112 (13.7%)	458 (56.2%)	148 (18.2%)	7 (0.9%)	59.9
Ris 4 mg QD	85	0 (0.0%)	13 (15.3%)	11 (12.9%)	61 (71.8%)	0 (0.0%)	0 (0.0%)	5.4
Ris 3 mg BID	220	2 (0.9%)	20 (9.1%)	34 (15.5%)	164 (74.5)	0 (0.0%)	0 (0.0%)	14.4
Ris 6 mg QD	221	0 (0.0%)	26 (11.8%)	39 (17.6%)	156 (70.6%)	0 (0.0%)	0 (0.0%)	14.1
Ris 4 mg BID	108	0 (0.0%)	9 (8.3%)	12 (11.1%)	10 (9.3%)	75 (69.4%)	2 (1.9%)	10.5
Ris 8 mg QD	181	2 (1.1%)	18 (9.9%)	16 (8.8%0	67 (37.0%)	73 (40.3%)	5 (2.8%)	15.6

TRIAL CONTRIBUTION

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SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

	PLACEBO				RIS 4MG QD				RIS 8MG QD					
			DIFF FROM BASE				DIFF FROM BASE				DIFF FROM BASE			TREATMENT BY INVESTIG. INTERACTION
PARAMETER	N	MEAN	MEAN	S.E.	N	MEAN	MEAN	S.E.	N	MEAN	MEAN	S.E.	OVERALL P-VALUE!	P-VALUE
TOTAL PANSS SCORE (RANGE: 30-210)														
BASELINE	79	94.23			82	94.70			75	94.09			0.925	0.642
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
DAY 8	79	84.48	-9.75*	1.72	82	85.17	-9.52*	1.20	75	86.01	-8.08*	1.46	0.586	0.607
DAY 15	79	82.85	-11.38*	2.19	82	80.39	-14.30*	1.64	75	79.36	-14.73*	1.78	0.542	0.418
DAY 22	78	81.41	-12.74*	2.63	82	76.91	-17.78*	2.01	75	75.28	-18.81*	2.03	0.183	0.463
DAY 28	79	81.62	-12.61*	2.70	82	75.26	-19.44*	2.11	75	72.79	-21.31*	2.20	0.043	0.545
OBSERVED CASE ANALYSIS														
DAY 8	79	84.48	-9.75*	1.72	82	85.17	-9.52*	1.20	75	86.01	-8.08*	1.46	0.586	0.607
DAY 15	67	80.04	-14.00*	2.36	72	79.14	-15.68*	1.70	68	78.06	-16.24*	1.70	0.628	0.200
DAY 22	61	76.23	-17.70*	2.78	66	74.26	-20.59*	2.14	59	71.88	-22.29*	1.91	0.207	0.645
DAY 28	56	74.25	-19.36*	2.94	59	70.27	-25.02*	2.19	54	67.54	-27.02*	2.06	0.044	0.780

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARE MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

ANALYSIS AT BASELINE IS BASED ON VALUES AT THAT VISIT, WHEREAS AT OTHER VISITS ANALYSIS IS BASED UPON DIFFERENCES FROM BASELINE.
P-VALUES FOR OVERALL AND PAIRWISE COMPARISONS ARE FROM TWO-WAY ANOVA WITHOUT INTERACTIONS.
P-VALUES FOR INTERACTION ARE FROM TWO-WAY ANOVA WITH INTERACTIONS.

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PAIRWISE² COMPARISON PLACEBO VS. RIS 4MG QD	PAIRWISE² COMPARISON PLACEBO VS. RIS 8MG QD
TOTAL PANSS SCORE (RANGE: 30-210)		
BASELINE	0.717	0.962
LAST OBSERVATION CARRIED FORWARD ANALYSIS		
DAY 8	0.866	0.334
DAY 15	0.338	0.338
DAY 22	0.130	0.095 #
DAY 28	0.051 $	0.019 ##
OBSERVED CASE ANALYSIS		
DAY 8	0.866	0.334
DAY 15	0.452	0.365
DAY 22	0.180	0.092 #
DAY 28	0.041 $$	0.022 ##

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
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P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

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SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PLACEBO N	PLACEBO MEAN	PLACEBO DIFF FROM BASE MEAN	PLACEBO DIFF FROM BASE S.E.	RIS 4MG QD N	RIS 4MG QD MEAN	RIS 4MG QD DIFF FROM BASE MEAN	RIS 4MG QD DIFF FROM BASE S.E.	RIS 8MG QD N	RIS 8MG QD MEAN	RIS 8MG QD DIFF FROM BASE MEAN	RIS 8MG QD DIFF FROM BASE S.E.	OVERALL P-VALUE!	TREATMENT BY INVESTIG. INTERACTION P-VALUE
NEGATIVE PANSS SUBSCALE (RANGE: 7-49)														
BASELINE	79	23.20			82	24.40			75	24.39			0.222	0.662
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
DAY 8	79	21.46	-1.75*	0.54	82	22.23	-2.17*	0.44	75	23.27	-1.12*	0.50	0.255	0.446
DAY 15	79	20.99	-2.22*	0.63	82	21.12	-3.28*	0.51	75	21.59	-2.80*	0.60	0.591	0.246
DAY 22	78	20.55	-2.68*	0.70	82	20.22	-4.18*	0.54	75	20.61	-3.77*	0.64	0.331	0.153
DAY 28	79	20.59	-2.61*	0.72	82	19.82	-4.59*	0.55	75	19.99	-4.40*	0.64	0.110	0.157
OBSERVED CASE ANALYSIS														
DAY 8	79	21.46	-1.75*	0.54	82	22.23	-2.17*	0.44	75	23.27	-1.12*	0.50	0.255	0.446
DAY 15	67	20.27	-2.85*	0.67	72	21.13	-3.60*	0.52	68	21.31	-3.26*	0.58	0.749	0.065
DAY 22	61	19.34	-3.85*	0.76	66	19.83	-4.77*	0.56	59	19.78	-4.66*	0.62	0.419	0.122
DAY 28	56	19.09	-4.04*	0.81	59	18.98	-5.64*	0.60	54	19.06	-5.69*	0.58	0.073	0.388

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
? P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARES MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
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P-VALUES FOR INTERACTION ARE FROM TWO-WAY ANOVA WITH INTERACTIONS.

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

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TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PAIRWISE² COMPARISON PLACEBO VS. RIS 4MG QD	PAIRWISE² COMPARISON PLACEBO VS. RIS 8MG QD
NEGATIVE PANSS SUBSCALE (RANGE: 7-49)		
BASELINE	0.155	0.116
LAST OBSERVATION CARRIED FORWARD ANALYSIS		
DAY 8	0.742	0.216
DAY 15	0.326	0.808
DAY 22	0.139	0.394
DAY 28	0.050 $$	0.101
OBSERVED CASE ANALYSIS		
DAY 8	0.742	0.216
DAY 15	0.449	0.730
DAY 22	0.218	0.302
DAY 28	0.045 $$	0.047 ##

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
² P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARE MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

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P-VALUES FOR INTERACTION ARE FROM TWO-WAY ANOVA WITH INTERACTIONS.

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SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

	PLACEBO				RIS 4MG QD				RIS 8MG QD				
PARAMETER	N	MEAN	DIFF FROM BASE MEAN	S.E.	N	MEAN	DIFF FROM BASE MEAN	S.E.	N	MEAN	DIFF FROM BASE MEAN	S.E.	OVERALL P-VALUE[1]	TREATMENT BY INVESTIG. INTERACTION P-VALUE
DERIVED BPRS (RANGE: 18-126)														
BASELINE	79	54.29			82	53.73			75	53.44			0.735	0.805
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
DAY 8	79	48.08	-6.22*	1.02	82	47.94	-5.79*	0.75	75	48.47	-4.97*	0.85	0.534	0.764
DAY 15	79	46.86	-7.43*	1.24	82	45.15	-8.59*	1.02	75	44.44	-9.00*	1.04	0.701	0.377
DAY 22	78	45.99	-8.17*	1.50	82	43.12	-10.61*	1.23	75	41.80	-11.64*	1.20	0.216	0.422
DAY 28	79	45.94	-8.35*	1.54	82	42.07	-11.66*	1.27	75	40.65	-12.79*	1.30	0.095	0.578
OBSERVED CASE ANALYSIS														
DAY 8	79	48.08	-6.22*	1.02	82	47.94	-5.79*	0.75	75	48.47	-4.97*	0.85	0.534	0.764
DAY 15	67	45.19	-8.91*	1.36	72	44.13	-9.38*	1.06	68	43.71	-9.81*	1.03	0.779	0.252
DAY 22	61	42.82	-11.00*	1.55	66	41.35	-12.17*	1.34	59	39.73	-13.92*	1.18	0.207	0.600
DAY 28	56	41.52	-12.23*	1.69	59	38.88	-15.14*	1.29	54	37.31	-16.39*	1.31	0.095	0.695

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
[1] ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
[2] P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARE MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

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SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PAIRWISE² COMPARISON PLACEBO VS. RIS 4MG QD	PAIRWISE² COMPARISON PLACEBO VS. RIS 8MG QD
DERIVED BPRS (RANGE: 18-126)		
BASELINE	0.627	0.438
LAST OBSERVATION CARRIED FORWARD ANALYSIS		
DAY 8	0.777	0.281
DAY 15	0.492	0.444
DAY 22	0.188	0.097 #
DAY 28	0.097 $	0.041 ##
OBSERVED CASE ANALYSIS		
DAY 8	0.777	0.281
DAY 15	0.585	0.506
DAY 22	0.254	0.080 #
DAY 28	0.066 $	0.053 #

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
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P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
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#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

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SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PLACEBO N	PLACEBO MEAN	PLACEBO DIFF FROM BASE MEAN	PLACEBO DIFF FROM BASE S.E.	RIS 4MG QD N	RIS 4MG QD MEAN	RIS 4MG QD DIFF FROM BASE MEAN	RIS 4MG QD DIFF FROM BASE S.E.	RIS 8MG QD N	RIS 8MG QD MEAN	RIS 8MG QD DIFF FROM BASE MEAN	RIS 8MG QD DIFF FROM BASE S.E.	OVERALL P-VALUE[1]	TREATMENT BY INVESTIG. INTERACTION P-VALUE
TOTAL KEY BPRS ITEMS (RANGE 4-28)														
BASELINE	79	15.97			82	16.16			75	16.27			0.486	0.403
LAST OBSERVATION CARRIED FORWARD ANALYSIS														
DAY 8	79	13.94	-2.04*	0.38	82	13.82	-2.34*	0.29	75	14.08	-2.19*	0.32	0.718	0.932
DAY 15	79	13.61	-2.37*	0.47	82	12.39	-3.77*	0.38	75	12.47	-3.80*	0.42	0.029	0.158
DAY 22	78	13.18	-2.78*	0.53	82	11.79	-4.37*	0.47	75	11.45	-4.81*	0.47	0.014	0.515
DAY 28	79	13.00	-2.97*	0.55	82	11.30	-4.85*	0.49	75	11.04	-5.23*	0.49	0.006	0.376
OBSERVED CASE ANALYSIS														
DAY 8	79	13.94	-2.04*	0.38	82	13.82	-2.34*	0.29	75	14.08	-2.19*	0.32	0.718	0.932
DAY 15	67	13.21	-2.82*	0.52	72	12.06	-4.07*	0.40	68	12.10	-4.06*	0.44	0.042	0.325
DAY 22	61	12.36	-3.64*	0.60	66	11.26	-4.85*	0.52	59	10.59	-5.41*	0.46	0.028	0.734
DAY 28	56	11.70	-4.11*	0.67	59	10.14	-6.02*	0.54	54	9.85	-6.09*	0.50	0.011	0.290

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
[1] ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
[2] P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARE MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

ANALYSIS AT BASELINE IS BASED ON VALUES AT THAT VISIT, WHEREAS AT OTHER VISITS ANALYSIS IS BASED UPON DIFFERENCES FROM BASELINE.
P-VALUES FOR OVERALL AND PAIRWISE COMPARISONS ARE FROM TWO-WAY ANOVA WITHOUT INTERACTIONS.
P-VALUES FOR INTERACTION ARE FROM TWO-WAY ANOVA WITH INTERACTIONS.

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA
PROTOCOL : RIS-USA-72

TABLE EFF.2: SUMMARY RESULTS OF PANSS SCORES (DIFFERENCE FROM BASELINE)(CONTINUED)

POPULATION: INTENT-TO-TREAT
SOURCE: INVESTIGATOR'S EVALUATION

PARAMETER	PAIRWISE² COMPARISON PLACEBO VS. RIS 4MG QD		PAIRWISE² COMPARISON PLACEBO VS. RIS 8MG QD	
TOTAL KEY BPRS ITEMS (RANGE 4-28)				
BASELINE	0.319		0.281	
LAST OBSERVATION CARRIED FORWARD ANALYSIS				
DAY 8	0.418		0.727	
DAY 15	0.017	$$	0.025	##
DAY 22	0.023	$$	0.006	##
DAY 28	0.010	$$	0.004	##
OBSERVED CASE ANALYSIS				
DAY 8	0.418		0.727	
DAY 15	0.023	$$	0.035	##
DAY 22	0.034	$$	0.013	##
DAY 28	0.006	$$	0.016	##

* TWO-SIDED P-VALUE <= 0.05 FOR PAIRED T-TEST OF NO DIFFERENCE FROM BASELINE ON RAW MEANS.
! ANOVA TEST OF NO DIFFERENCE BETWEEN TREATMENT GROUPS.
² P-VALUES ASSOCIATED WITH FISHER'S LSD PROCEDURES ON LEAST SQUARE MEANS.
P: TWO-SIDED P-VALUE <= 0.10 WITH PLACEBO HAVING LOWER SCORES; PP: P-VALUE <= 0.05.
$: TWO-SIDED P-VALUE <= 0.10 WITH RIS 4MG QD HAVING LOWER SCORES; $$: P-VALUE <= 0.05.
#: TWO-SIDED P-VALUE <= 0.10 WITH RIS 8MG QD HAVING LOWER SCORES; ##: P-VALUE <= 0.05.

ANALYSIS AT BASELINE IS BASED ON VALUES AT THAT VISIT, WHEREAS AT OTHER VISITS ANALYSIS IS BASED UPON DIFFERENCES FROM BASELINE.
P-VALUES FOR OVERALL AND PAIRWISE COMPARISONS ARE FROM TWO-WAY ANOVA WITHOUT INTERACTIONS.
P-VALUES FOR INTERACTION ARE FROM TWO-WAY ANOVA WITH INTERACTIONS.

Table K. Most commonly observed (≥5%) adverse events U.S. and worldwide

Body System Adverse event	Pbo	All Ris	Ris 4 mg QD	Ris 3 mg BID	Ris 6 mg QD	Ris 4 mg BID	Ris 8 mg QD
Heart rate and rhythm disorders tachycardia	0 (0.0%) 0 (0.0%)	28 (4.6%) 22 (3.6%)	3 (3.5%) 3 (3.5%)	13 (5.9%) 11 (5.0%)	9 (4.1%) 8 (3.6%)	-	3 (3.8%) 0 (0.0%)
Worldwide (all patients, including U.S.)							
Total number of patients	83	815	85	220	221	108	181
Psychiatric disorders Insomnia Agitation Somnolence Anxiety	51 (61.4%) 35 (42.2%) 25 (30.1%) 9 (10.8%) 12 (14.5%)	419 (51.4%) 193 (23.7%) 134 (16.4%) 117 (14.4%) 106 (13.0%)	61 (71.8%) 36 (42.4%) 19 (22.4%) 22 (15.9%) 12 (14.1%)	82 (37.3%) 23 (10.5%) 28 (12.7%) 28 (12.7%) 17 (7.7%)	99 (44.8%) 29 (13.1%) 37 (16.7%) 31 (14.0%) 13 (5.9%)	62 (57.4%) 35 (32.4%) 15 (13.9%) 4 (3.7%) 34 (31.5%)	115 (63.5%) 70 (38.7%) 35 (19.3%) 32 (17.7%) 30 (16.6%)
Central & Peripheral Nervous System Headache Extrapyramidal disorder Hyperkinesia Dizziness Hypokinesia	40 (48.2%) 33 (39.8%) 1 (1.2%) 2 (2.4%) 3 (3.6%) 0 (0.0%)	359 (44.0%) 176 (21.6%) 81 (9.9%) 59 (7.2%) 58 (7.1%) 11 (1.3%)	49 (57.6%) 27 (31.8%) 9 (10.6%) 7 (8.2%) 9 (10.6%) 1 (1.2%)	88 (40.0%) 49 (22.3%) 16 (7.3%) 12 (5.5%) 17 (7.7%) 1 (0.5%)	89 (40.3%) 47 (21.3%) 9 (4.1%) 13 (5.9%) 11 (5.0%) 1 (0.5%)	48 (44.4%) 12 (11.1%) 20 (18.5%) 9 (8.3%) 3 (2.8%) 6 (5.6%)	85 (47.0%) 41 (22.7%) 27 (14.9%) 18 (9.9%) 18 (9.9%) 2 (1.1%)
Gastrointestinal System Constipation Dyspepsia Nausea Vomiting Dry mouth Tooth ache	38 (45.8%) 11 (13.3%) 9 (10.8%) 6 (7.2%) 10 (12.0%) 2 (2.4%) 7 (8.4%)	259 (31.8%) 69 (8.5%) 68 (8.3%) 66 (8.1%) 53 (6.5%) 38 (4.7%) 13 (1.6%)	37 (43.5%) 9 (10.6%) 8 (9.4%) 10 (11.8%) 8 (9.4%) 7 (8.2%) 1 (1.2%)	70 (31.8%) 21 (9.5%) 19 (8.6%) 17 (7.7%) 15 (6.8%) 13 (5.9%) 7 (3.2%)	77 (34.8%) 19 (8.6%) 22 (10.0%) 15 (6.8%) 13 (5.9%) 8 (3.6%) 4 (1.8%)	29 (26.9%) 10 (9.3%) 3 (2.8%) 9 (8.3%) 6 (5.6%) 4 (3.7%) 0 (0.0%)	46 (25.4%) 10 (5.5%) 16 (8.8%) 15 98.3%) 11 (6.1%) 6 (3.3%) 1 (0.6%)
Body as a whole - general disorders Fatigue	17 (20.5%) 0 (0.0%)	125 (15.3%) 35 (4.3%)	16 (18.8%) 3 (3.5%)	39 (17.7%) 11 (5.0%)	26 (11.8%) 7 (3.2%0	12 (11.1%) 4 (3.7%)	32 (17.7%) 10 (5.5%)
Respiratory system Rhinitis Pharyngitis Sinusitis	14 (16.9%) 9 (10.8%) 5 (6.0%) 6 (7.2%)	93 (11.4%) 49 (6.0%) 14 (1.7%) 4 (0.5%)	14 (16.5%) 7 (8.2%) 3 (3.5%) 2 (2.4%)	29 (13.2%) 16 (7.3%) 3 (1.4%) 0 (0.0%)	26 (11.8%) 19 (8.6%) 4 (1.8%) 0 (0.0%)	9 (8.3%) 3 (2.8%) 0 (0.0%) 0 (0.0%)	15 (8.3%) 4 (2.2%) 4 (2.2%) 2 (1.1%)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20588/S002 AND 20272/S007

STATISTICAL REVIEW(S)

COMPLETED SEP 19 1997

SEP 19 1997

Statistical Review and Evaluation

NDA#: 20-272/SE2-007

Applicant: Janssen

SEP 19 1997

Name of Drug: Risperidal

Documents reviewed: Vols 35, 38

Medical Officer: Andrew Mosholder, M.D., HFD-120

Background

The sponsor has submitted 3 randomized clinical trials in support of once-a-day dosing of Ridperidal for the treatment of psychotic disorders. Trial RIS-USA-72 is placebo controlled with two arms of Risperidal [Ris]: 4 mg QD and 8 mg QD. Trials RIS-USA-60 and RIS-INT-10 compare 3 mg BID to 6 mg QD and 4 mg BID to 8 mg QD, respectively. At a meeting on September 25, 1996, the sponsor was told that the latter two non-placebo controlled trials would not be useful information for the purpose of assessing efficacy. They were told that if the placebo controlled trial showed efficacy, then they would get approval for once-a-day dosing. Consequently, this review examines only trial RIS-USA-72.

Trial RIS-USA-72

A total of 246 patients were randomized among 28 centers in the US to placebo (N=83), Risperidal 4 mg QD (N=85) or Risperidal 8 mg QD (n=78). The duration of the trial was 28 days with visits at baseline and weeks 1, 2, 3, and 4. **The protocol-specified endpoint was the proportion of patients who achieved an at least 20% decrease (improvement) on the total PANSS score using LOCF (response rate). The denominator for the calculation of % change from baseline is (baseline - 30), not the baseline itself.** Response rates were compared using CMH controlling for investigator. Secondary endpoints were the mean total PANSS and those for subscales (negative symptoms, positive symptoms, and general pathology), derived BPRS total and the key BPRS cluster. The sample size was based on the assumption of a 57% response rate for both Ris doses and 34% for placebo. **Although the sample size was computed on the basis of a Bonferroni correction, there is no explicit analysis plan for multiple comparisons of the two doses against control.** The data set to be analyzed consisted of all those who took drug, had a baseline evaluation and at least one post-baseline evaluation.

Of the 246 patients randomized, 10 had no post-baseline observation and were therefore excluded from all efficacy analyses. In addition, due to some empty cells, 5 investigators with 5 or fewer patients were pooled for the purpose of analysis.

There was no evidence of differential premature overall discontinuation rates with 1/3 in each arm dropping out before 28 days. However there was some indication that placebo patients dropped out more frequently due to inadequate response: 13% placebo and 5% in each of the Ris groups (p=.06).

Table 1 displays the baseline information for the groups. There were no important demographic or prognostic imbalances among the treatment arms at baseline. **Table 2** displays the results for clinical response rates, while **Table 3** and **Table 4** display the results of comparisons of means for the various scales using LOCF and observed cases, respectively. For the LOCF analysis, both doses are significant for the total PANSS, only 4 mg QD is significant on the negative PANSS, and both doses are significant on the key BPRS. The observed cases analyses yield similar results.

Bar charts in **Figures 1, 2 and 3** display the average scores for cohorts of dropouts, completers and LOCF data sets during the trial for Total PANSS, Negative PANSS and Key BPRS, respectively. **White bars** are placebo, **grey bars** are 4 mg QD and **black bars** are 8 mg QD. For all three endpoints, placebo patients dropped out in worse condition than drug patients. However, the observed case analysis at 28 days showed statistical differences from placebo on its own.

The sponsor also did a stepwise logistic analysis which selected diagnosis and age as significant explanatory variables while race and gender were not.

Discussion

On the basis of the response rate, total PANSS, and the key BPRS, 8 mg QD was shown to be effective. The status of 4 mg QD could be made an issue because there was no *a priori* plan for controlling Type I error for both doses against the control. For **response rates**, application of the Bonferroni correction (α=.025) renders 4 mg QD not significantly different from placebo for both the LOCF and observed cases analyses at 28 days. For the **ANOVA's**, the sponsor has reported Fisher's LSD (thus testing each comparison at a nominal α of .05) which is valid when there are only two active groups. The overall ANOVA p-value for 'treatment' using the total PANSS, including 'center' but not 'treatment-by-center interaction' was .0425. The protocol specified the interaction term, but the sponsor does not report the overall p-value for treatment with the interaction in the model. At any rate, Fisher's LSD method was not pre-specified, and a Bonferroni correction would render the 4 mg QD's p-value of .036 for response rate non-significant. So would Dunnett's method with a nominal α of .028. Lastly, the exploratory logistic analysis of the response rates indicates statistical significance for both doses.

With regard to Dr. Borison's data, placebo patients in his center tended to improve from baseline more than patients on 8 mg QD. The differences between placebo and 4 mg QD were less marked. Consequently there does not appear to be a compelling reason to ask that the supplement to be re-analyzed without Dr. Borison's data.

Conclusion

By focusing on the ANOVA's of the group means, one can conclude that both 4 mg QD and 8 mg QD are statistically significantly different from placebo for major clinical endpoints.

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr Sahlroot JTS 9/12/97

Dr Chi 9/19/97

cc:
NDA# 20-272/SE2-007
HFD-120/Dr. Leber
HFD-120/Dr. Laughren
HFD-120/Dr. Mosholder
HFD-120/Mr. Purvis
HFD-120/Mr. Hardeman
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710Dr. Sahlroot
HFD-710/Dr. Hoberman
HFD-710/chron

TABLE 1

	Treatment			
	Placebo (N = 83)	Risperidone 4 mg QD (N = 85)	Risperidone 8 mg QD (N = 78)	Total (N =246)
Sex				
Male	65 (78.3%)	67 (78.8%)	64 (82.1%)	196 (79.7%)
Female	18 (21.7%)	18 (21.2%)	14 (17.9%)	50 (20.3%)
Race				
White	48 (57.8%)	50 (58.8%)	38 (48.7%)	136 (55.3%)
Black	27 (32.5%)	26 (30.6%)	31 (39.7%)	84 (34.1%)
Oriental	2 (2.4%)	-	-	2 (0.8%)
Hispanic	6 (7.2%)	8 (9.4%)	8 (10.3%)	22 (8.9%)
Indic	-	1 (1.2%)	-	1 (0.4%)
Polynesian	-	-	1 (1.3%)	1 (0.4%)
Age (years)				
Mean ± s.d.	38.2 ± 11.06	38.2 ± 9.35	38.1 ± 8.74	38.2 ± 9.74
Median	37	38	38.5	38
Range	18 - 66	19 - 62	19 - 65	18 - 66
Weight (kg)	[N = 78]	[N = 82]	[N = 73]	[N = 233]
Mean ± s.d.	79.0 ± 17.44	81.7 ± 20.04	83.4 ± 24.14	81.3 ± 20.62
Median	77.2	76	79.9	77.2
Range	46.3 - 133.9	44.9 - 161.6	49.5 - 199.8	44.9 - 199.8
Diagnosis				
Disorganized	2 (2.4%)	3 (3.5%)	1 (1.3%)	6 (2.4%)
Paranoid	60 (72.3%)	53 (62.4%)	58 (74.4%)	171 (69.5%)
Residual	1 (1.2%)	-	-	1 (0.4%)
Undifferentiated	20 (24.1%)	29 (34.1%)	19 (24.4%)	68 (27.6%)

Parameter (range)#	Placebo (N=83)	Ris 4mg QD (N=85)	Ris 8mg QD (N=78)	Overall p-value
	mean	mean	mean	
Total PANSS (30-210)	94.3	94.3	93.9	.958
Positive PANSS (7-49)	23.8	24.2	23.8	.532
Negative PANSS (7-49)	23.3	24.2	24.2	.258
G. Psychopath.(16-112)	47.2	45.8	45.9	.336
Derived BPRS (18-126)	54.4	53.6	53.3	.682
Key BPRS (4-28)	16.0	16.2	16.2	.528
Anergia (4-28)	10.8	11.2	11.2	.698
Thought Disturb.(4-28)	14.2	14.5	14.3	.464
Activation (3-21)	8.3	8.3	8.0	.804
Paranoid/Bellig.(3-21)	8.8	8.5	8.4	.611
Depression (4-28)	12.3	11.1	11.3	.031*

*: $p<=0.05$

#: Higher value denotes greater severity

TABLE 2

Clinical Response (CR) Rate at Endpoint--Day 28 via LOCF (Primary Endpoint) and Day 28 via OC.

Percent of patients with clinical response					
Visit #	Placebo	Risp 4 mg QD	Risp 8 mg QD	P-values*	
				Placebo vs 4 mg	Placebo vs 8 mg
Day 28 (LOCF)	46.8% (37/79)	64.6% (53/82)	76.0% (57/75)	0.036	<0.001
Day 28 (OC)	60.7% (34/56)	76.3% (45/59)	88.9% (48/54)	0.076	<0.001

* Cochran-Mantel-Haenszel test controlling for investigator.

TABLE 3

Mean Differences in PANSS Scores at Day 28 - LOCF

Parameter (range)#	Placebo (N=79)		Ris 4mg QD (N=82)		Ris 8mg QD (N=75)		Fisher's LSD p-values	
	mean	change	mean	change	mean	change	Placebo vs Ris 4mg	Placebo vs Ris 8mg
Total PANSS (30-210)	81.62	-12.61	75.26	-19.44	72.79	-21.31	0.051	0.019*
Positive PANSS (7-49)	20.39	-3.41	17.71	-6.51	16.84	-6.97	0.006**	0.002**
Negative PANSS (7-49)	20.59	-2.61	19.82	-4.59	19.99	-4.40	0.050*	0.101
G. Psychopath.(16-112)	40.63	-6.59	37.73	-8.34	35.96	-9.93	0.305	0.073
Derived BPRS (18-126)	45.94	-8.35	42.07	-11.66	40.65	-12.79	0.097	0.041*
Key BPRS (4-28)	13.00	-2.97	11.30	-4.85	11.04	-5.23	0.010**	0.004**
Anergia (4-28)	9.41	-1.39	9.43	-1.84	9.29	-1.99	0.344	0.294
Thought Disturb.(4-28)	11.87	-2.35	10.29	-4.15	10.11	-4.23	0.008**	0.009**
Activation (3-21)	7.14	-1.11	6.79	-1.59	6.24	-1.81	0.285	0.120
Paranoid/Bellig.(3-21)	7.90	-0.82	6.57	-1.93	6.17	-2.23	0.046*	0.016*
Depression (4-28)	9.62	-2.67	8.99	-2.16	8.84	-2.53	0.283	0.618

*: p<=0.05; **: p<=0.01
#: Higher values denote greater severity

TABLE 4

Mean Differences in PANSS Scores at Day 28 - Observed Case

Parameter (range)#	Placebo (N=56)		Ris 4mg QD (N=59)		Ris 8mg QD (N=54)		Fisher's LSD p-values	
	mean	change	mean	change	mean	change	Placebo vs Ris 4mg	Placebo vs Ris 8mg
Total PANSS (30-210)	74.25	-19.36	70.27	-25.02	67.54	-27.02	0.041*	0.022*
Positive PANSS (7-49)	17.96	-5.50	15.78	-8.39	15.13	-8.63	0.006**	0.012*
Negative PANSS (7-49)	19.09	-4.04	18.98	-5.64	19.06	-5.69	0.045*	0.047*
G. Psychopath.(16-112)	37.20	-9.82	35.51	-10.98	33.35	-12.70	0.306	0.091
Derived BPRS (18-126)	41.52	-12.23	38.88	-15.14	37.31	-16.39	0.066	0.053
Key BPRS (4-28)	11.70	-4.11	10.14	-6.02	9.85	-6.09	0.006**	0.016*
Anergia (4-28)	8.71	-1.88	9.03	-2.44	9.04	-2.61	0.227	0.185
Thought Disturb.(4-28)	10.70	-3.48	9.37	-4.95	9.00	-4.98	0.013*	0.037*
Activation (3-21)	6.43	-1.71	6.29	-2.19	5.78	-2.39	0.156	0.130
Paranoid/Bellig.(3-21)	6.61	-1.80	5.63	-2.95	5.33	-3.22	0.043*	0.029*
epression (4-28)	9.07	-3.36	8.56	-2.61	8.17	-3.19	0.302	0.581

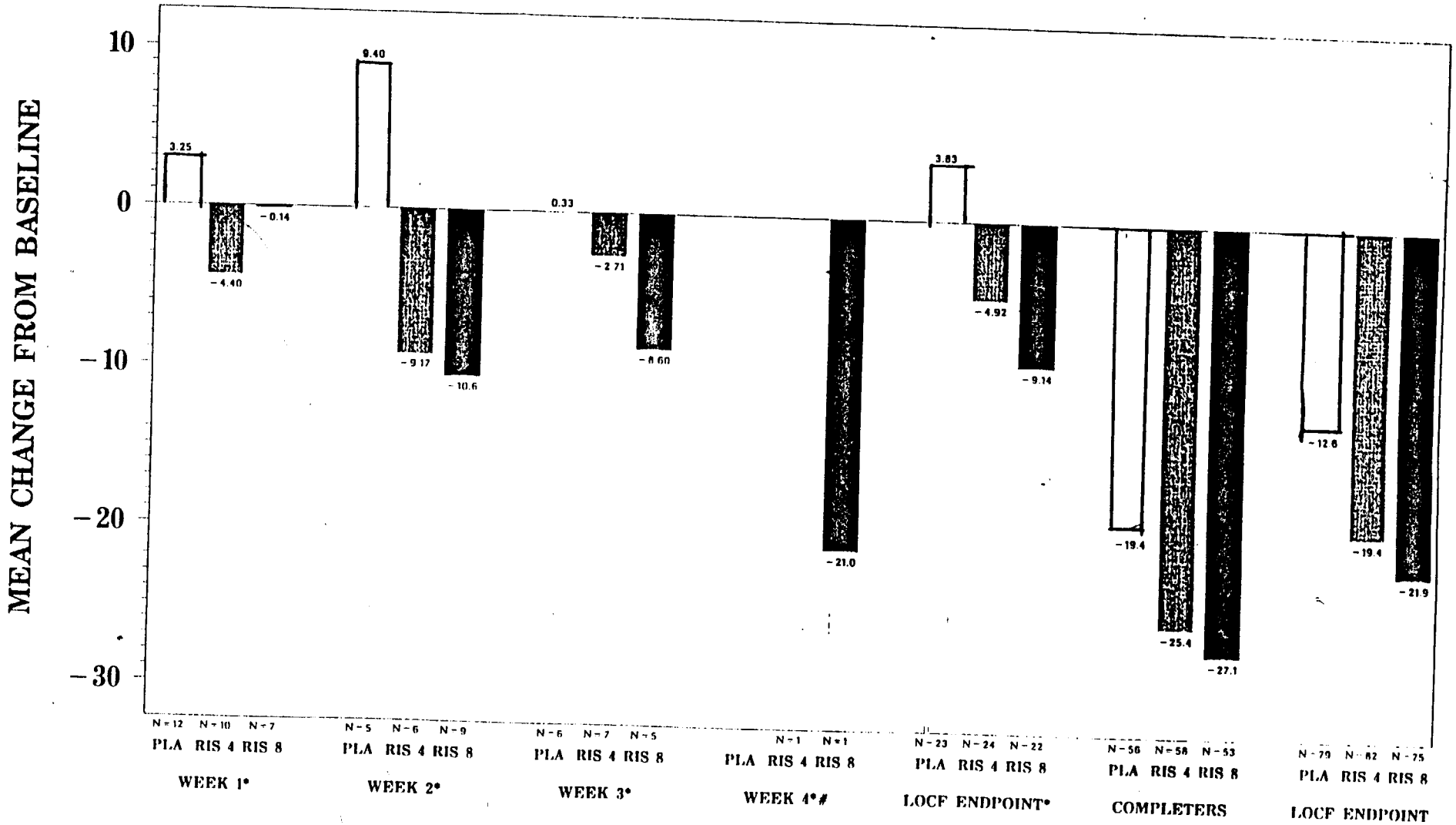
*: p<=0.05; **: p<=0.01
#: Higher values denote greater severity

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA

PROTOCOL: RIS – USA – 72

MEAN CHANGE FROM BASELINE PANSS SCORES FOR DISCONTINUED SUBJECTS AND COMPLETERS

PANSS SCORE = TOTAL PANSS SCORE



* INCLUDES ONLY LAST SCORES BEFORE D/C FOR DISCONTINUED SUBJECTS; # THESE TWO PATIENTS DISCONTINUED JUST BEFORE COMPLETING THE STUDY; NOTE THAT 10 SUBJECTS WHO DISCONTINUED DID NOT HAVE POST-BASELINE PANSS SCORES

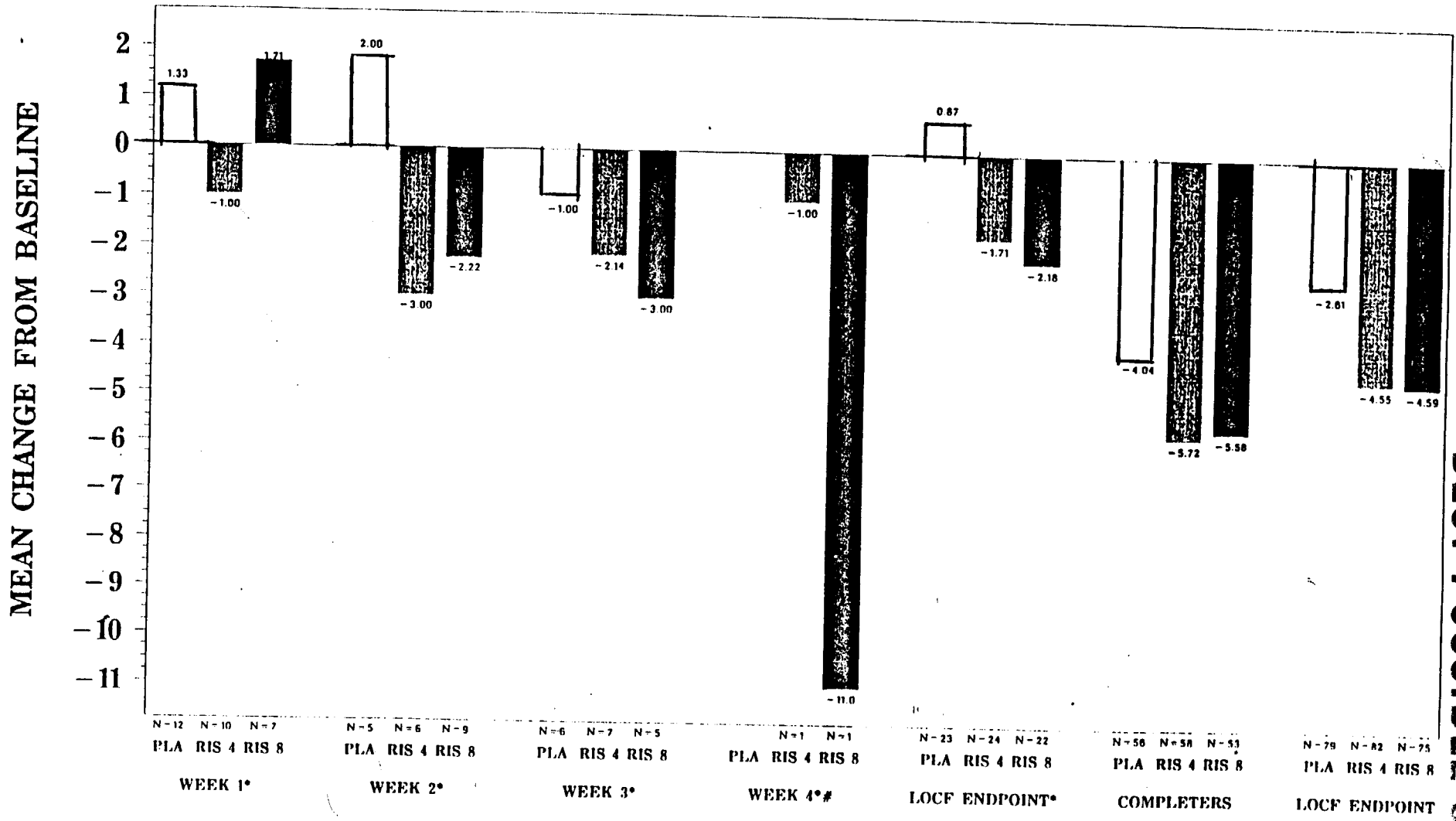
FIGURE 1

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA

PROTOCOL: RIS – USA – 72

MEAN CHANGE FROM BASELINE PANSS SCORES FOR DISCONTINUED SUBJECTS AND COMPLETERS

PANSS SCORE = NEGATIVE PANSS SUBSCALE



WEEKS ON TREATMENT

FIGURE 2

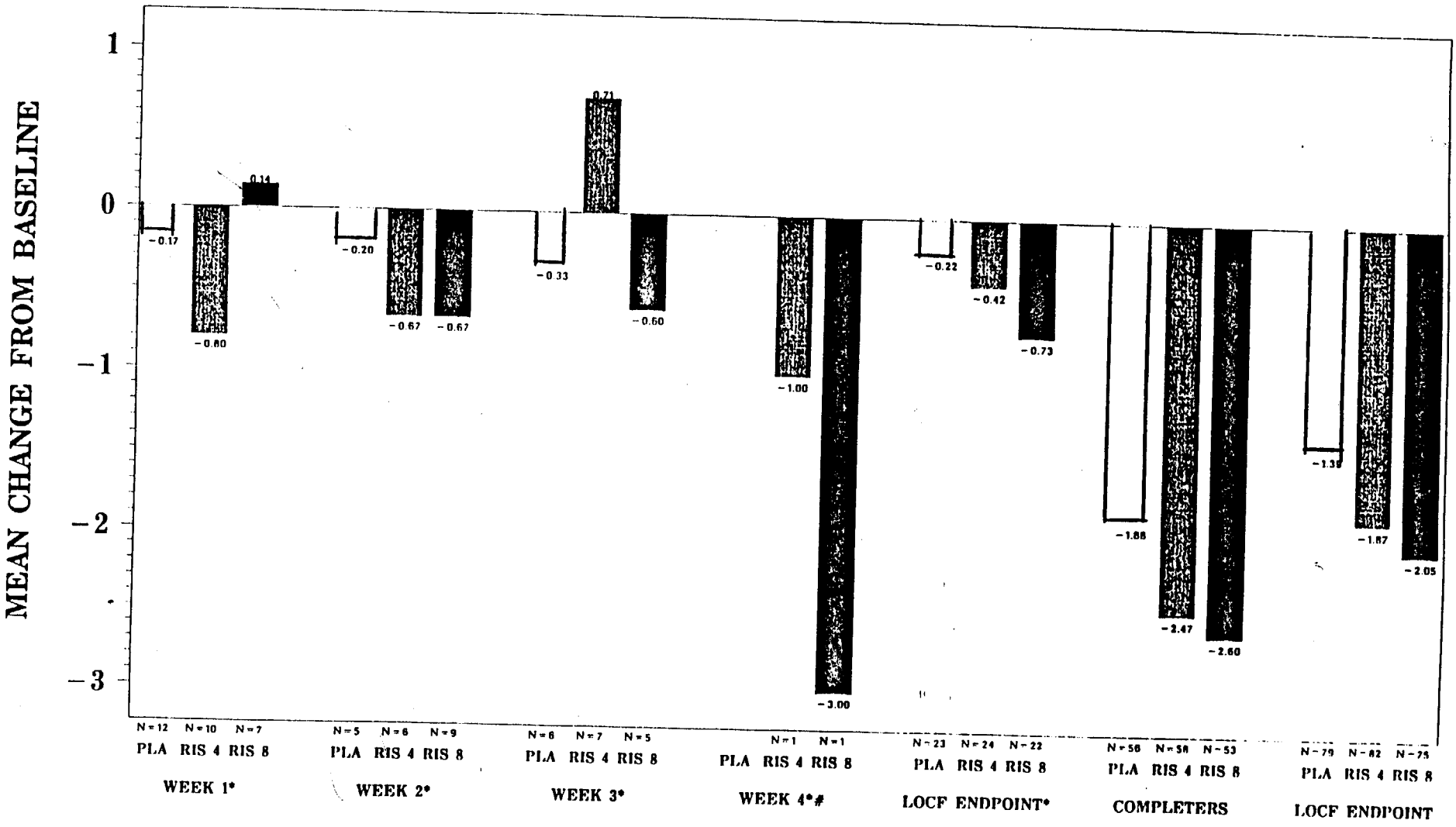
* INCLUDES ONLY LAST SCORES BEFORE D/C FOR DISCONTINUED SUBJECTS; # THESE TWO PATIENTS DISCONTINUED JUST BEFORE COMPLETING THE STUDY; NOTE THAT 10 SUBJECTS WHO DISCONTINUED DID NOT HAVE POST-BASELINE PANSS SCORES

SAFETY AND EFFICACY OF RISPERIDONE 8MG QD AND 4MG QD COMPARED TO PLACEBO IN THE TREATMENT OF SCHIZOPHRENIA

PROTOCOL: RIS – USA – 72

MEAN CHANGE FROM BASELINE PANSS SCORES FOR DISCONTINUED SUBJECTS AND COMPLETERS

PANSS SCORE = TOTAL KEY BPRS ITEMS



WEEKS ON TREATMENT

* INCLUDES ONLY LAST SCORES BEFORE D/C FOR DISCONTINUED SUBJECTS; # THESE TWO PATIENTS DISCONTINUED JUST BEFORE COMPLETING THE STUDY; NOTE THAT 10 SUBJECTS WHO DISCONTINUED DID NOT HAVE POST-BASELINE PANSS SCORES

FIGURE 3

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20588/S002 AND 20272/S007

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

SEP 8 1997

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA NUMBER: 20,272 **SPONSOR:** Janssen Research Foundation
Titusville, NJ 08560-0200

SUBMISSION DATE: November 26, 1996

OCPB RECEIPT DATE: December 6, 1996

DRUG NAME: Risperdal® (Risperidone)

DOSAGE FORM: Tablets (4 mg and 8 mg)

INDICATION: Psychosis **REVIEWER NAME:** Vijay K. Tammara, Ph.D.

SUBJECT: Label Change: Addition of QD Dosing Regimen

BACKGROUND:

Risperdal® (risperidone) is an anti-psychotic drug marketed by Janssen. It is currently available as 1 mg, 2 mg, 3 mg, and 4 mg tablets; although a 5 mg tablet has also been approved, it is not currently marketed (original OCPB review dated: Nov 12, 1993).

The current submission is a Supplemental Application to the original New Drug Application for Risperdal® (risperidone) Tablets. This application contains a bioequivalence study (RIS-BEL-33) involving an immediate release dosage formulation in two different strengths (new 8 mg tablet and 4 mg existing marketed tablet) to demonstrate bioequivalence between a once a day (Treatment A; QD new 8 mg) and twice a day (Treatment B; BID of existing 4 mg) dosing regimen of Risperdal for both rate and extent of absorption under steady-state conditions. It was an open two-way crossover study in 24 chronic schizophrenic patients stabilized on 4 mg risperidone bid for at least two weeks prior to the trial. Patients received treatments A and B each for one week according to a randomized crossover scheme. Blood samples prior to dosing on days 6 and 7 and at 0.5, 1, 2, 4, 8, 12, and 24 hours for treatment A; and at 0.5, 1, 2, 4, 8, and 12 hours for treatment B after dosing on day 7 were taken to measure the plasma concentrations of risperidone and the active moiety (risperidone plus 9-hydroxy risperidone) using radioimmunoassays.

The sponsor had also submitted three well-controlled clinical trials (RIS-USA-72, RIS-USA-60, and RIS-INT-10) to support the new QD dosing regimen.

RESULTS:

Only 23 subjects completed the study. Two patients had unusually low plasma levels for both risperidone and the active moiety. Hence, data from these patients was excluded in calculating relative bioavailability and average steady-state plasma concentrations. Further, the sponsor reported that 6 patients were classified as poor metabolizers and the other 15 as extensive metabolizers. The data of poor metabolizers was excluded to calculate mean steady-state pharmacokinetic parameters. However, the pooled data of 21 subjects (inclusive of poor and extensive metabolizers) was used to calculate relative bioavailability and average steady-state plasma concentration for both treatments. The relative bioavailabilities for risperidone and active moiety were 93% with 90% confidence intervals of 81-106% (risperidone) and 86-99% (active moiety) indicating comparable bioavailability of 8 mg once daily and 4 mg twice daily dosing regimen (Attachment 1). However, the two treatments can not be concluded as bioequivalent as steady state pharmacokinetic parameters such as Cmax, Cmin, and $AUC_{0-\tau}$ were not tested for bioequivalence.

Comment:

1) The sponsor should perform 90% confidence interval analysis using the two one-sided t-test procedure for all key pharmacokinetic parameters (Cmax, Cmin and $AUC_{0-\tau}$) of risperidone, its active metabolite, 9-hydroxy-risperidone, and the active moiety (risperidone+9-hydroxy-risperidone) to show bioequivalence between two treatments using log transformed values.

RECOMMENDATION:

From a pharmacokinetic standpoint, bioequivalency between 8 mg risperidone tablet given as once a day (QD) and 4 mg tablet given as twice a day (BID) has not been demonstrated.

Please, forward this **Recommendation** and **Comment 1** to the sponsor.

Tammara 09/08/97

Vijay K. Tammara, Ph.D.
Division of Pharmaceutical Evaluation I

RD/FT initialed by Raman Baweja, Ph.D. R. Baweja 9/8/97.

cc: NDA 20-272, HFD-120, HFD-860 (Tammara, Baweja, Malinowski), and CDR (Barbara Murphy for Drug files).

ATTACHMENT I

SYNOPSIS

Trial identification and protocol summary

Company: JANSSEN RESEARCH FOUNDATION **Finished product:** Risperdal **Active compound:** (R064766)	
Title: A bioequivalence study comparing an 8-mg risperidone tablet with a 4-mg risperidone tablet in chronic schizophreaic patients. Part I: Pharmacokinetics	**Trial No.:** RIS-BEL-33 **Clinical phase:** III
Investigator: J. Peuskens, M.D.	**Country:** Belgium
Reference: JRF, Clinical Research Report RIS-BEL-33, February 1995	
Trial period: Start: 5 April 1994 End: 27 October 1994	**No. of investigators:** 3 **No. of subjects:** 24
Objectives: To compare the steady-state oral bioavailability of an 8-mg risperidone tablet with a 4-mg risperidone tablet in chronic schizophrenic patients.	
Trial design: open, randomized, two-way cross-over.	

Subject selection

- Inclusion criteria:
  - male or female between 18 and 65 years of age.
  - fulfilling the diagnostic criteria of chronic or subchronic schizophrenia as defined by DSM-III-R (295.21-295.22-295.11-295.12-295.31-295.32-295.91-295.92-295.61-295.62).
  - patients are stabilized on oral risperidone 4 mg twice daily for at least 2 weeks.
  - patients (or their legal guardians) give their informed consent prior to entry into the trial.
- Exclusion criteria:
  - female patients of reproductive age without adequate contraception.
  - female patients who are pregnant or lactating.
  - patients with mental disorders on Axis I (DSM-III-R) other than schizophrenia.
  - patients who have received a depot neuroleptic injection within one treatment cycle at the time of selection.
  - patients with clinically relevant organic or neurologic diseases.
  - patients with clinically relevant abnormal laboratory tests.
  - patients with clinically relevant abnormal ECG findings.
  - patients with a febrile illness 3 days prior to the first drug administration.
  - patients who have donated blood within 60 days prior to the trial.
  - patients who have been included in trials with investigational drugs during the 4 weeks preceding the trial.

Treatment	A	B
Dosage form	an 8-mg risperidone tablet	a 4-mg risperidone tablet
Dosing regimen	8 mg per os, once daily for one week	4 mg per os, twice daily for one week
Batch number	93K15/F64	93E13/F12
Disallowed medication	none	

Assessments	Plasma concentrations of risperidone and the active moiety (sum of risperidone and its active metabolite, 9-hydroxy-risperidone) prior to the morning drug intake on day 6 and day 7 of each treatment and at the following time points on day 7 after the morning drug intake: treatment A: 0.5, 1, 2, 4, 8, 12 and 24 hours post-dose treatment B: 0.5, 1, 2, 4, 8 and 12 hours post-dose
Bioanalysis	Radioimmunoassay procedures (RIA I and II) were used to determine the plasma concentrations of risperidone (RIA I) and the active moiety (RIA II). The detection limits were 0.1 ng/ml (RIA I) and 0.2 ng/ml (RIA II).
Pharmacokinetic analysis	• C_{min}, C_{max}, T_{max}, AUC_{0-12h}, $AUC_{0-\infty}$, C_{ss} and F_{rel} based on actual plasma concentration-time curve and the non-compartmental analysis.
Statistical methods	• Descriptive statistics for the pharmacokinetic parameters and for the risperidone and active moiety plasma concentration at each blood sampling time-point. • Analysis of Variance for both C_{ss} (= $AUC_{0-\tau}/\tau$, τ is the dosing interval) and log of C_{ss}. . • Classical 90%-confidence interval of the C_{ss} ratio (treatment A vs B).

Main features of the trial sample and summary of the results

Baseline characteristics - patient disposition	
Number of subjects entered (M/F) Age: mean±SD (min-max), years Weight: mean±SD (min-max), kg Height: mean±SD min-max), cm	13/11 36 ± 7 (23-54) (excluding the drop-out) 69 ± 15 (40-94) (excluding the drop-out) 169 ± 11 (148-193) (excluding the drop-out)
Drop-outs: number / reason	1 / patient became uncooperative

Results: Pharmacokinetics

Table 1. Relative bioavailability

Parameters	Least-squares means (ANOVA)[a] -test (treatment A)- (8 mg once daily)	-reference (treatment B)- (4 mg twice daily)	F_{rel} (%)	90% C.I.
-Risperidone				
C_{ss}, ng/ml[b]	30.6	32.8	93	81-106
log C_{ss} [c]	19.5	21.9	89	79-100
-Active moiety				
C_{ss}, ng/ml	90.3	97.6	93	86-99
log C_{ss} [c]	81.3	90.3	90	85-96

[a] n=21,excluding two patients who had very low plasma levels due to either possible non-compliance (patient no. 2) or the concomitant intakes of carbamazepine (patient no. 12).

[b] C_{ss} =AUC0-τ/τ (for treatment A, τ=24 hours; for treatment B, τ=12 hours).

[c] data analysed on log-scale but statistics transformed back to linear scale.

Table 2 Median steady-state fluctuation

Parameters (n=23)	-test (treatment A)- (8 mg once daily)	-reference (treatment B)- (4 mg twice daily)
-Risperidone		
C_{av}, ng/ml [a]	13.6	17.3
C_{min}, ng/ml	2.4	7.2
C_{max}, ng/ml	76.3	48.2
Fluctuation, % [b]	382	183
-Active moiety		
C_{av}, ng/ml	71.5	80.4
C_{min}, ng/ml	40	58.4
C_{max}, ng/ml	142	113
Fluctuation,%	145	66.4

[a] C_{av} = AUC0-τ/τ (for treatment A, τ = 24 hours; for treatment B, τ = 12 hours).

[b] Fluctuation, % = (C_{max}-C_{min})/C_{av} x 100%, n = 22, patient no. 2 was not included who showed little or no fluctuations.

Conclusions

There was no difference in the steady-state average plasma concentrations of risperidone and the active moiety (risperidone plus 9-hydroxy-risperidone) in schizophrenic patients following the 8-mg risperidone once-daily regimen and the 4-mg risperidone twice-daily regimen. The ratios of the steady-state average plasma concentrations of both risperidone and the active moiety following the two treatments fell within the acceptance range of bioequivalence. The median trough and peak levels of the active moiety under the 8-mg risperidone once-daily regimen were 68% and 126% of those seen under the 4-mg risperidone twice-daily regimen, respectively.

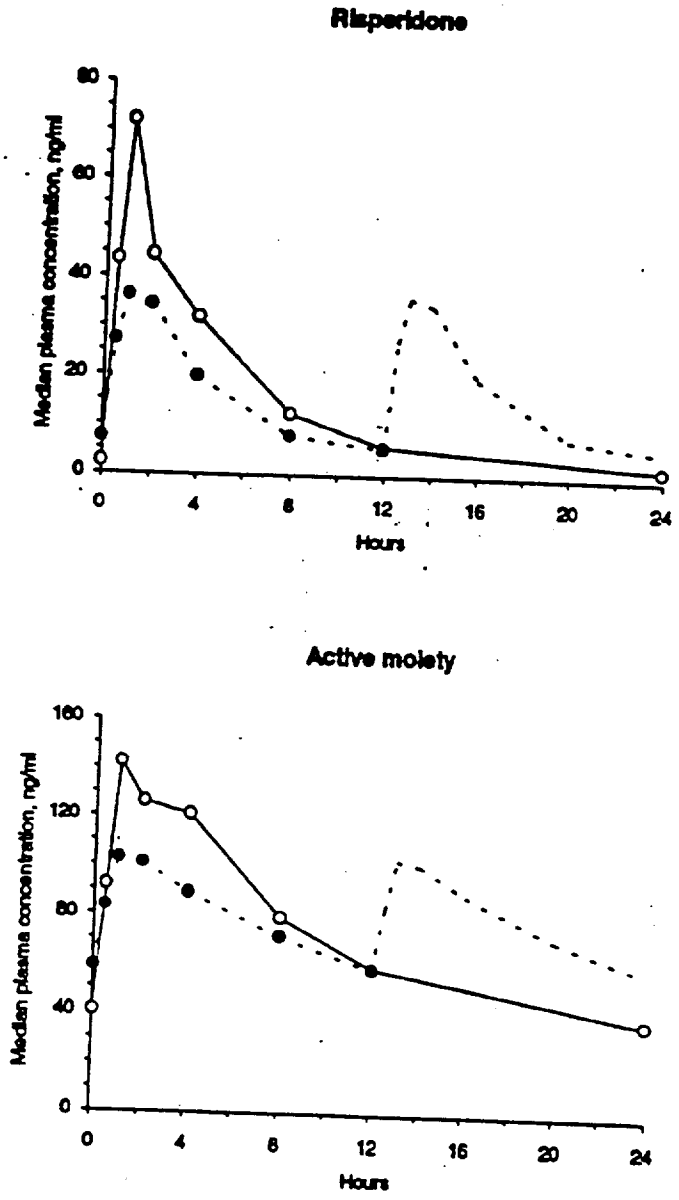


Figure 1: Plasma concentrations of risperidone (upper graph) and active moiety (lower graph) following the day 7 oral administration of 8 mg risperidone (open symbols: risperidone 8 mg once daily treatment) or 4 mg risperidone (closed symbols: risperidone 4 mg twice daily treatment). The dotted line without symbols corresponds to the predicted steady-state plasma drug concentrations after a second dose of the 4 mg bid treatment, which is identical to the profile observed after the first 4 mg dose of day 7.

Table 7: Steady-state pharmacokinetic parameters of risperidone in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment A: an 8-mg risperidone tablet once daily for one week

Patient	Day 6	Day 7				
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-24h} ng.h/ml	F_{rel}[1] %
1						
2						
3						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
median	1.98	1.0	2.35	76.3	326	94.3
mean[3]	1.91	1.1	2.04	63.8	318	94.6
S.D.[3]	0.84	0.5	0.87	23.0	120	28.3
maximum						
minimum						

[1] Relative bioavailability (treatment A vs. treatment B). See section 3.5.3. for definition.
[2] No sample.
[3] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 7: Continued
Steady-state pharmacokinetic parameters of risperidone in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment B: a 4-mg risperidone tablet twice daily for one week

Patient	Day 6	Day 7			
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-12h} ng h/ml
1					
2					
3					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
23					
24					
median	5.62	1.0	7.23	48.2	208
mean[1]	5.00	1.5	5.89	37.9	181
S.D.[1]	2.87	1.1	3.62	17.6	78
maximum					
minimum					

[1] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 9: Steady-state pharmacokinetic parameters of active moiety in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment A: an 8-mg risperidone tablet once daily for one week

Patient	Day 6	Day 7					
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-24h} ng.h/ml	F_{rel}[1] %	Metabolic[2] index
1							
2							
3							
5							
6							
7							
8							
9							
10							
11							
12							
13							
14							
15							
16							
17							
18							
19							
20							
21							
22							
23							
24							
median	36.6	1.0	40.0	142	1715	95.6	0.23
mean[5]	39.4	1.3	41.8	155	1754	92.7	0.18
S.D.[5]	11.9	0.9	11.6	50	394	16.2	0.06
maximum							
minimum							

[1] Relative bioavailability (treatment A vs. treatment B).
[2] Metabolic index = AUC risperidone/AUC active moiety after the treatment A.
[3] No sample.
[4] Not calculated (see text for explanation).
[5] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

Table 9: Continued

Steady-state pharmacokinetic parameters of active moiety in patients taking an 8-mg risperidone tablet once daily for one week (treatment A) and a 4-mg risperidone tablet twice daily for another week (treatment B) according to a randomized cross-over scheme.

Treatment B: a 4-mg risperidone tablet twice daily for one week

Patient	Day 6	Day 7				
	C_{min} ng/ml	T_{max} h	C_{min} ng/ml	C_{max} ng/ml	AUC_{0-12h} ng.h/ml	Metabolic index[1]
1						
2						
3						
5						
6						
7						
8						
9						
10						
11						
12						
13						
14						
15						
16						
17						
18						
19						
20						
21						
22						
23						
24						
median	55.7	2.0	58.4	113	965	0.24
mean[3]	54.6	2.4	59.3	112	967	0.19
S.D.[3]	11.3	1.9	10.7	34	254	0.07
maximum						
minimum						

[1] Metabolic index = AUC risperidone/AUC active moiety after the treatment B.

[2] Not calculated (see text for explanations).

[3] For extensive metabolisers only. Excluding poor metabolisers 1, 3, 5, 6, 8 and 13 and patients 2 and 12 (See text for detailed explanations).

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 20588/S002 AND 20272/S007

ADMINISTRATIVE DOCUMENTS

EXCLUSIVITY SUMMARY for NDA # 20-272 / 20-588 **SUPPL #** 5-007 / 5-002

Trade Name Risperdal / Tabs + Oral Soln **Generic Name** Risperidone

Applicant Name Janssen Research Foundation **HFD-** 120

Approval Date, if known 10/17/97

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

   a) Is it an original NDA?

   YES /___/ NO /X/

   b) Is it an effectiveness supplement?

   YES /X/ NO /___/

   If yes, what type? (SE1, SE2, etc.) _____

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

   YES /X/ NO /___/

   If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

   _____

   _____

   If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

   _____

   _____

d) Did the applicant request exclusivity?

YES /___/ NO /X/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx-to-OTC switches should be answered NO-please indicate as such.)

YES /___/ NO /X/ OTC Switch /___/

If yes, NDA #_____ Drug Name _____

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /X/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /X/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20272 Risperdal® (risperidone) tablets

NDA# 20-588 Risperdal Oral Solution

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /X/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

YES /___/ NO /___/

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /X/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

R15-U5A-72

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /X/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

R15-USA-72 _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # YES /X/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /___/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /X/

If yes, explain: _____

_____

Steven D Hardman R.Ph. 12/15/97
Signature Date
Title: Project Manager

Signature of Division Director 12/16/97
Date

cc: Original NDA Division File HFD-93 Mary Ann Holovac

Memorandum

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: October 17, 1997

FROM: Paul Leber, M.D.
Director,
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Risperdal qd and bid dosing supplements approval actions

TO: Files
NDA 20-272 / S-007
NDA 20-588 / S-002

This memorandum documents for the file the basis for my decision to approve two supplements to the approved NDAs for two oral formulations of Risperdal that allow for the once a day (qd) administration of these drug products.

The decision to approve turns entirely on biopharmacokinetic and clinical considerations. The same review team worked on both applications. Dr. Mosholder did the primary clinical review. Biostatistic and biopharmacokinetic consultative reviews were provided, respectively, by Dr. Hoberman (9/19/97) and Dr. Tammara (9/08/97).

The elements/issues that factored critically in the decision to approve the supplements are enumerated in Dr. Laughren's 10/15/97 memorandum to the file of NDA 20-272.

I will review only the highlights of the process that support the conclusion that Risperdal Tablets will be effective in use on qd dosing schedule.

Efficacy

To begin, knowledge that both solid and liquid Risperdal oral formulations are effective when administered bid reduces the burden of evidence

reasonably required to support a conclusion that these formulations will be effective in use when equimolar amounts are administered on a once a day schedule. In fact, had Risperdal been shown to be bioequivalent in regard to both the rate and extent of systemic absorption, no clinical trials would have been required to support approval of these supplements.

In the absence of 'bioequivalence,' however, a direct demonstration of Risperdal's effectiveness in use and safety for use is required.

Of the 3 clinical trial results potentially relevant to the approval of these supplements, only one, RIS-USA-72, which compares the effect, over 28 days, of 4 and 8 mg single daily doses of risperidone with placebo, speaks to the question of effectiveness in use. The two remaining studies compare the same total daily dose given bid and qd (i.e., 3 bid vs 6 qd in RIS-USA 60 and 4 bid vs 8 qd in RIS-INT-10); as equivalence trials, these may speak to safety for use of the qd regimen, but not to the issue of efficacy.

As the table below (reproduced from Table 2 in the attachments to Dr. Hoberman's 9/19/97 review) documents, RIS-USA-72 provides strong statistically significant findings supporting the efficacy of a single 8 mg daily dose of Risperdal. A patient has a "Clinical Response" if they experience a 20% or greater decrement from baseline on his/her Total PANSS LOCF score.

Clinical Response (CR) Rate at Endpoint–Day 28 via LOCF (Primary Endpoint) and Day 28 via OC.

Percent of patients with clinical response					
Visit #	Placebo	Risp 4 mg QD	Risp 8 mg QD	P-values*	
				Placebo vs 4 mg	Placebo vs 8 mg
Day 28 (LOCF)	46.8% (37/79)	64.6% (53/82)	76.0% (57/75)	0.036	<0.001
Day 28 (OC)	60.7% (34/56)	76.3% (45/59)	88.9% (48/54)	0.076	<0.001

* Cochran-Mantel-Haenszel test controlling for investigator.

The 'p' values reported for the placebo vs 4 mg daily dose contrast appear

to be nominally at or near statistical significance. As Dr. Hoberman observes, however, the analysis plan for the study did not include a method to adjust the interpretation of the statistical analysis results for the two possible pairwise comparisons to placebo. If a Bonferroni correction is applied, the 4 mg vs placebo contrast does not attain significance.

While once a day dosing is effective, it is not at all clear from the evidence submitted that a given dose of Risperdal administered once a day is equivalent clinically to 1/2 that dose administered twice a day[1]. To the contrary, as Dr. Mosholder points out (his review of 9/23/97), there is some evidence that the bid regimen is clinically superior to the once a day regimen, at least when the total daily dose is 6 mg. Specifically, in study RIS-USA-60, the group randomized to 3 mg bid has a numerically superior outcome to those randomized to 6 mg once a day and the 90% CL for the difference between outcome for the BID and QD groups does not include zero. Study RIS-INT-10 does not replicate this finding for an 8 mg qd vs 4 mg bid dose, however.

Safety for Use

Based on information submitted to the original NDA where doses in considerable excess of those recommended in approved product labeling were evaluated, there is little reason to expect that the highest recommended dose of Risperdal poses an unacceptable risk when administered in a single daily dose. This expectation is confirmed by the reports submitted to these supplements concerning clinical experience gained with some 487 subjects and patients who were administered single daily doses of risperidone (see Dr. Mosholder's systematic and detailed review) .

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[1] From the perspective of systemic bioavailability, the identical daily dose of risperidone given on a once a day regimen leads to a slightly lower steady state AUC than a bid regimen in respect both to risperidone and/or the sum of the concentrations of resperidone and its active metabolite, 9-OH risperidone. (see RIS-BEL-33)

Labeling

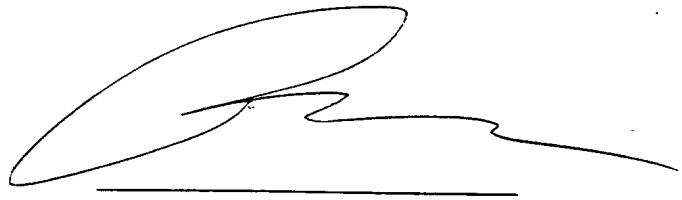
The review team, under the direction of Dr. Laughren has worked with the sponsor to develop a revised version of labeling that will allow Risperdal to be deemed safe and effective for use under conditions of use that include once a day dosing. The changes made affect the Clinical Trials, The Precautions (Orthostatic Hypotension) and Dosage and Administration Sections. I find them fully acceptable.

Conclusion

Based upon the information and findings just summarized, I can conclude responsibly that Risperdal has been shown, within the meaning of the Act, to be both safe for use and effective in use under the conditions of use recommended in the labeling attached to the approval action letter. The proposed labeling, in my judgment, is neither false nor misleading in any particular.

Action

An approval action for NDA 20-272 / S-007 and NDA 20-588 / S-002 should be approved.



Paul Leber, M.D
10/17/97

cc:
NDA 20-272
NDA 20-588
HFD-101
Temple
HFD-120
Katz
Laughren
Mosholder
Hardeman
HFD-710
Hoberman