Statistical Review and Evaluation

NDA#: 20-272/Class 1-P

Applicant: Janssen Research Foundation

Name of Drug: Risperidal (risperidone) tablets

Documents Reviewed: Vols 1.110, 1.117, 1.134, received 4/15/1992

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

Background

The sponsor has submitted 3 randomized, controlled, double-blind, multicenter trials (201: 6 weeks; 204: 8 weeks, 024: 8 weeks) in support of risperidone as a safe and effective treatment for schizophrenia. Trials 201 and 204 are placebo controlled, while 024 is a foreign dose-ranging study with 1 mg risperidone as the lowest dose.

This review summarizes the results of these trials with respect to four clinical endpoints which measured change from baseline: 1) Total BPRS (Brief Psychiatric Rating Scale), 2) the following 'Key' subset of the BPRS scales: hallucinatory behavior, conceptual disorganization, suspiciousness and unusual thought content, 3) negative symptoms (Total SANS in 201 and Total negative PANSS in 204, 024), and 4) clinical global impression of severity (CGI).

In addition, the results for BPRS and its Key subset are illustrated using time-to-event techniques. These estimate the duration of 'response', defined in terms of risperidone patients' performance relative to the natural course of the illness (estimated by the experience of placebo patients) over the length of the studies. 'Non-responders' are also examined.

Summary of Studies

Patient Numbers and Drop outs

Table 1 displays the number of patients randomized to each treatment for each study, together with the number of observed patients at each time point. In study 201, patients could be titrated up to 10 mg risperidone and 20 mg haloperidol during the first two weeks. In studies 204 and 024, patients were titrated up to their assigned dose group during the first week.

Table 2 and Figures 1 to 3 illustrate the probability of remaining

in each trial over time. The p-values less than .05 in the last column of table 2 indicate that in studies 201 and 204, placebo patients dropped out at rates statistically significantly greater than those who were taking risperidone. Approximately 50% of the risperidone patients completed studies 201 and 204.

Tables 2A,B, and C display the reasons and distributions of drop outs for each study. Insufficient response and adverse events account for the majority of drop outs.

Summary Analyses- Completer, Last Observation Carried Forward (LOCF) and the Role of Drop Outs

Table 3 summarizes the completers' mean changes from baseline and p-values (in parentheses) associated with comparisons to placebo in studies 201 and 204 and risperidone 1 mg in study 024. Note that in studies 204 and 024, increasing the dose does not lead to increasing effect.

In the LOCF analyses, all p-values were statistically significant for risperidone groups with respect to Total BPRS, Key BPRS and CGI. See medical officer's review.

Table 4 displays mean changes from baseline for Total Negative Symptoms.

Figures 4-9 display the sometimes dramatic effect of drop outs on the conversion of marginal or non-statistically significant completer group comparisons to highly statistically significant LOCF comparisons. Note that the first four groups of bars indicate the change from baseline among **drop outs,** whereas the last two groups of bars refer to the last week **completer** and LOCF comparisons, respectively. In studies 201 and 204, placebo drop outs fared worse than active drug drop outs nearly uniformly over time for all four clinical endpoints. There is a mixed response in study 024.

Exploratory Analyses of 'Responders'

Patient's Baseline as Response Criterion

The preceding results indicate that, on the whole, patients who took risperidone experienced greater remission of symptoms than those on placebo. However, due to the substantial number of patients who left the study prematurely, it is difficult to assign a 'treatment effect'. One alternative is simply to compute the number of patients who were at least 'minimally improved' on the CGI scale at the end of the study and divide that number by the number of patients in the intent-to-treat cohort (either identical to or close to the number of randomized patients). The difference between the percentages (drug-placebo) estimates the fraction of patients who receive a benefit attributable to the drug, given all

patients to whom it had been administered. This assumes, of ...se, that patients in the trial are reasonably representative of ... patients who will receive the drug and that the reasons and ...s for discontinuing use of the drug in the trial represent what ... happen in regular clinical practice. For instance, in study ... the percentages are 49% and 26% for risperidone and placebo, ...pectively. In study 204, they are 53%, 47%, 48%, and 21% for ... 6, 10, 16, and placebo, respectively. Pooling results from ...e trials provides an estimate of 27% with a 95% confidence ...erval of 18%-36% for the 'attributable fraction'.

...rnatively, we can ask the question: "Given the patients who ...-in in the study until the end, what is the fraction of patients ...e improvement is attributable to risperidone (conditional ...bability)"? In this case, the denominators are the numbers of ...ients who completed the study. Pooling patients from the two ...ls produces 65% for placebo and 81% for risperidone, resulting ...an attributable fraction of 16%. Since the number of patients is ...ntantially reduced by the end of the trials, the 95% confidence ...erval is wide: 1%-31%.

... profiles of improvement categories ('minimally improved', 'much ...roved', and 'very much improved') are also instructive. For ...cebo patients, the ratios are 2:5:4, whereas those for ...peridone are 2:8:5. Thus, risperidone patients have a greater ...rall response which is differentially weighted toward 'much ...roved'.

...tural Course of Illness as Response Criterion

...ther approach considers three features not included in the ...regoing analysis: 1) it allows statements about the probability ... benefiting over the time course of the trials in the presence of ... p outs, 2) it defines the treatment group comparison by ...paring the experience of those on drug directly to the ...tribution of placebo patients' experience over time, thus ...paring experience of being on drug to the natural course of the ...lness, and 3) it offers an approach to describing 'clinical ...fect' when the outcome is essentially continuous in nature.

...ther than defining a 'responder' as one who achieves an ...bitrarily determined change from his/her own baseline, we define ... 'responder' as a patient whose, for instance, Total BPRS change ...m baseline is greater than the placebo group's median at week 1 ... the trial. We then ask the question: "What is the probability ...t a typical patient will remain 'in response' for lengths of ...e defined by the visit schedule?" Such a 'life table' approach ... the preferred method in mortality studies. However, in the ...esent case, we measure the time to the first failure to be in ...sponse.

The Effect of Non-random Drop Outs

If drop outs in these trials had been random, then such an approach would yield relatively unbiased estimates of the probabilities we seek. However, the substantial loss of patients (censoring) is largely due to lack of effectiveness of the treatment (drug or placebo). Thus, as the trial progresses, the patients who 'survive' are not necessarily representative of the entire original cohort. Since patients on **all** treatments are dropping out, the bias washes out somewhat; however, the substantially greater drop out rates among placebo patients contributes to the conservativeness of the procedure. Two other features which make the procedure conservative are the following:

1) By far the more important is the likelihood that placebo patients who drop out are in worse condition than placebo patients who remain in the trial. This means that the placebo median change from baseline is <u>overestimated</u> (in terms of benefit) at each time point. Thus the standard for the drug patient is likely more difficult to meet than if the placebo patients had dropped out randomly.

2) The patient can 'respond' subsequent to 'failing'.

Consequently, the resulting probabilities of being in better condition than at least half the placebo patients (natural course) are lower bounds on the true probabilities.

Results

Table 5 displays the placebo groups' median changes from baseline for Total BPRS and Key BPRS.

Table 6 displays the percentage of responders in each risperidone group.

Table 7 displays (lower bound) probabilities for being in response for Total BPRS and Key BPRS. Only the 3 highest dose groups in study 204 are included. In an attempt to use all relevant information in the two studies, data have been pooled in the following way: 1) in Study 204, life table estimates have been pooled over the 3 risperidone groups and 2) that estimate and those from study 201 have been pooled. The fact that the trials' durations were slightly different is unlikely to affect the general conclusion. For Total BPRS, a 95% confidence interval for the probability of maintaining a condition better than the half of those not taking the drug <u>throughout the entire study</u> is centered at 54% with a range of [redacted]%, while that for Key BPRS is centered at 66% with a range of [redacted]%.

As stated earlier, these estimates suffer from the fact that we are

asking a question about the likely fate of a 'typical' patient on medication who started the trial (i.e., about an unconditional event) when likelihood of terminating prematurely is not random. An alternative quantity is the conditional probability of falling out of response given that a patient has 'survived' to a particular point in the trial. This perspective controls for risperidone patients dropping out, but is still subject to the underestimate of response due to the worse condition of placebo drop outs relative to continuing placebo patients.

Using information necessary for the calculation of the unconditional probabilities, we can estimate the conditional probabilities of falling out of response. They are relatively constant over time in the range of % . Thus, given that a patient is still in the trial at any particular visit, the probability of he/she remaining in response at least until the next visit is between %.

Responders Who Failed and Non-Responders Who Responded

It is of interest to note that over the 4 risperidone groups used in the pooled analysis, only % of the original responders 'responded' subsequent to failing.

In addition, 45% of those who **did not respond at week 1** never responded in the trial. Equal numbers of 'never-responders' left the trial at weeks 1, 2 and at the last visit. Very few patients left the trial between these times.

Finally, of those who **did not respond at week 1 who eventually responded**, very few attained a **sustained** response.

Conclusions

The results of these trials indicate that risperidone produces statistically significantly greater amelioration of selected symptoms of schizophrenia. Due to substantial non-random censoring, it is difficult to assign a particular 'treatment effect'. However, two approaches to estimating clinical prognosis suggest that:

1) On the basis of CGI severity, approximately % of patients started on risperidone will experience at least minimal improvement attributable to the drug within 8 weeks. This estimate assumes that clinical practice approximately reflects the treatment regimens in the trials.

2) On the basis of the natural course of the illness, as measured by Total and Key BPRS items over a period of 8 weeks in the placebo group, 60% is a conservative estimate of the fraction of patients who do better than half of those who do not take risperidone (beating the placebo median).

David Hoberman, Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 4-20-93

Dr. Dubey 4-20-93

This review consists of 5 pages of text, 11 tables and 9 figures

cc: NDA# 20-272
Orig. HFD-120
HFD-120/Dr. Laughren
HFD-120/Dr. Mosholder
HFD-120/Dr. Leber
HFD-120/Mr. Hardeman
HFD-344/Dr. Lisook
HFD-713/Dr. Hoberman
HFD-713/Dr. Nevius
HFD-713/Dr. Dubey [DRU 1.3.2 NDA]
chron.

Table 1

Study 201

	Rand	Base	Wk 1	Wk 2	Wk 3	Wk 4	Wk 6
RISP	53	50	49	36	40	33	28
HAL	53	52	52	40	35	26	23
PBO	54	51	51	40	26	21	16

Study 204

	Rand	Base	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8
RISP 2mg	87	87	87	75	55	42	35
RISP 6mg	86	84	84	79	67	55	54
RISP 10mg	87	82	80	72	59	53	47
RISP 16mg	88	84	83	74	68	56	55
HAL 20mg	87	85	85	72	52	41	37
PBO	88	83	82	67	48	34	26

Study 024

	Rand	Base	Wk 1	Wk 2	Wk 4	Wk 6	Wk 8
RISP 1mg	229	224	219	204	186	167	167
RISP 4mg	227	225	219	212	188	179	178
RISP 8mg	230	227	222	207	187	171	171
RISP 12mg	226	224	222	210	183	160	160
RISP 16mg	224	219	216	201	173	158	155
HAL 10mg	226	223	217	200	179	165	162

TABLE 2

Survival Analysis

Time in Days From Entry to Drop-out for All Reasons

Estimates

Risperidone Study 201

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Placebo	54	17	31.0	--
Risperidone	53	27	52.8	0.0358
Haloperidol	53	22	43.4	0.1896

*Pairwise comparisons to placebo using the logrank test

**At 42 days

Risperidone Study 204

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Placebo	88	27	30.7	--
Ris. 2mg	87	36	41.2	0.0729
Ris. 6mg	86	53	60.9	<0.0001
Ris. 10mg	87	48	55.2	0.0020
Ris. 16mg	88	54	61.4	<0.0001
Hal. 20mg	87	36	41.1	0.1050

*Pairwise comparisons to placebo using the logrank test

**At 56 days

191 378

Risperidone Study 024

Treatment Group	Intent-to-Treat Sample	Number Completed	Estimate**	P-value*
Ris. 1mg	229	171	76.3	--
Ris. 4mg	227	182	80.5	0.1504
Ris. 8mg	230	174	76.0	0.8622
Ris. 12mg	226	164	73.3	0.6614
Ris. 16mg	224	165	74.0	0.7495
Hal. 10mg	226	163	72.5	0.4949

*Pairwise comparisons to placebo using the logrank test

**At 56 days

Adenoma	
Fibroma	

(CONTINUED)

TABLE 2A

Number (%) of Patients Prematurely Discontinued From Study 201

Reason	Placebo	Risperidone	Haloperdol
Adverse Event	7 (13%)	6 (11.3%)	7 (13.2%)
Lack of Response	20 (37%)	8 (15.1%)	6 (11.3%)
Withdrew Consent	2 (3.7%)	2 (3.8%)	5 (9.4%)
Uncooperative	4 (7.4%)	9 (17%)	11 (20.8%)
Lost to Followup	2 (3.7%)	0	2 (3.8%)
Ineligible	1 (1.9%)	0	0
Other	1 (1.9%)	1 (1.9%)	0
Total	37 (68.5%)	26 (49.1%)	31 (58.5%)

TABLE 2B

PATIENTS PREMATURELY DISCONTINUED FROM STUDY 204

Reason	Placebo n=88	Ris 2 mg n=87	Ris 6 mg n=86	Ris 10 mg n=87	Ris 16 mg n=88	Hal [illegible] n
Adverse event	3 (3.4%)	2 (2.3%)	9 (10.5%)	4 (4.6%)	9 (10.2%)	6 (6.[illegible]
Insufficient Response	51 (58.0%)	41 (47.1%)	12 (14.0%)	25 (28.7%)	18 (20.5%)	36 (4[illegible]
Withdrew Consent	3 (3.4%)	5 (5.7%)	4 (4.7%)	3 (3.4%)	2 (2.3%)	2 (2.[illegible]
Uncooperative	4 (4.5%)	3 (3.4%)	6 (7.0%)	4 (4.6%)	2 (2.3%)	6 (6.[illegible]
Lost to follow up	0	0	1 (1.2%)	0	1 (1.1%)	1 (1.1[illegible]
Other	0	0	2 (2.3%)	3 (3.4%)	2 (2.3%)	[illegible]

TABLE 2C

Number of dropouts by treatment group in Study 024

Reason	Ris 1 mg n=229	Ris 4 mg n=227	Ris 8 mg n=230	Ris 12 mg n=226	Ris 16 mg n=224	Hal 10 mg n=226	Tot
Adverse experience	18	15	17	22	31	23	1
Death	0	0	0	0	1	0	
Suicidal	2	1	1	3	0	2	
Insufficient response	40	16	24	32	20	22	1
Intercurrent disease	2	0	0	1	1	0	
Intercurrent event	2	0	2	2	2	0	
Intercurrent treatment	0	0	0	0	1	2	
Lost to follow up	3	4	4	6	4	5	2
Selection criteria not met	1	0	1	0	0	0	
Sufficient response	0	1	0	1	0	1	
Patient's decision	3	7	9	6	7	15	4
Lack of motivation	3	5	5	5	5	5	2
Uncooperative	0	5	4	7	8	5	2
Other	1	2	1	1	3	3	11
Unspecified	0	0	0	0	0	0	1
Total (%)	58 (25%)	45 (20%)	56 (24%)	62 (27%)	59 (26%)	63 (28%)	342 (25%