

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

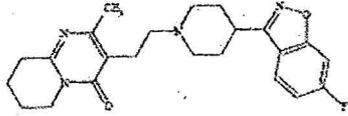
APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 20-272	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C On behalf of Janssen, L.P. 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL®		7. NONPROPRIETARY NAME Risperidone		SE5-046	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Schizophrenia in Adolescents (13 to 17 years of age)				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets		14. POTENCY 0.25, 0.5, 1, 2, 3 and 4 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES <input type="checkbox"/> NO <input type="checkbox"/> REVIEWED YES <input type="checkbox"/> NO <input type="checkbox"/>	
					
17. COMMENTS This efficacy supplement provides for the use of risperidone tablets for the treatment of schizophrenia in adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "Description" and "How Supplied" sections of labeling. In particular, the drug product is described as capsule-shaped, [redacted] tablets. This issue was consulted to DMETS and they have recommended that the description of tablets as capsule-shaped is acceptable but [redacted] ; redundant (Please refer to Mr. Richard Abate's review dated 3/29/2007). I agree with their recommendation since the tablets are not biconvex in appearance. Minor editorial changes to the "Description" section are found acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-05-2007
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

b(4)

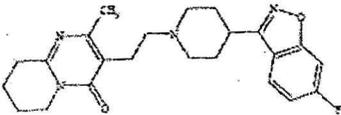
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram
6/5/2007 03:45:28 PM
CHEMIST

Jim Vidra
6/5/2007 04:49:17 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 20-272	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C On behalf of Janssen, L.P. 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL®		7. NONPROPRIETARY NAME Risperidone		SE5-047	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Bipolar 1 Disorder in Children (10 to 12 years of age) and Adolescents (13 to 17 years of age).				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Tablets		14. POTENCY 0.25, 0.5, 1, 2, 3 and 4 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES_ NO REVIEWED YES_ NO	
					
17. COMMENTS This efficacy supplement provides for the use of risperidone tablets for the treatment of Bipolar 1 Disorder in children (10 to 12 years of age) and adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in children and adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "Description" and "How Supplied" sections of labeling. In particular, the drug product is described as capsule-shaped, [redacted] tablets. This issue was consulted to DMETS and they have recommended that the description of tablets as capsule-shaped is acceptable but [redacted] is redundant (Please refer to Mr. Richard Abate's review dated 3/29/2007). I agree with their recommendation since the tablets are not biconvex in appearance. Minor editorial changes to the "Description" section are found acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-05-2007
<u>DISTRIBUTION</u>	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

b(4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram

6/5/2007 03:47:29 PM

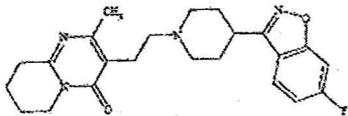
CHEMIST

Jim Vidra

6/5/2007 04:53:40 PM

CHEMIST

APPEARS THIS WAY ON ORIGINAL

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 20-588	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C On behalf of Janssen, L.P. •1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL® Oral Solution		7. NONPROPRIETARY NAME Risperidone		SE5-036	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Schizophrenia in Adolescents (13 to 17 years of age)				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Oral Solution		14. POTENCY 1 mg/mL			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	
					
17. COMMENTS This efficacy supplement provides for the use of Risperdal Oral Solution for the treatment of schizophrenia in adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "Description", "How Supplied" and "Storage and Handling" sections of labeling. The proposed minor editorial changes to the above sections are found to be acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-05-2007
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

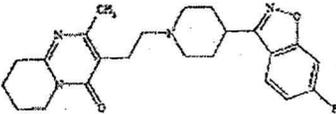
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram
6/5/2007 03:49:18 PM
CHEMIST

Jim Vidra
6/5/2007 04:58:06 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 20-588	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C On behalf of Janssen, L.P. 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL® Oral Solution		7. NONPROPRIETARY NAME Risperidone		SE5-037	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Bipolar 1 Disorder in Children (10 to 12 years of age) and Adolescents (13 to 17 years of age).				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Oral Solution		14. POTENCY 1 mg/mL			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	
					
17. COMMENTS This efficacy supplement provides for the use of Risperdal Oral Solution for the treatment of Bipolar 1 Disorder in children (10 to 12 years of age) and adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in children and adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "Description", "How Supplied" and "Storage and Handling" sections of labeling. The proposed minor editorial changes to the above sections are found to be acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-05-2007
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

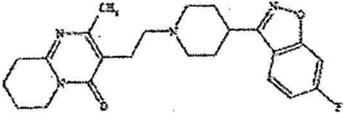
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram
6/5/2007 03:51:04 PM
CHEMIST

Jim Vidra
6/5/2007 05:01:41 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 21-444	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C. On behalf of Janssen, L.P. 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL® M-Tab® Orally Disintegrating Tablets		7. NONPROPRIETARY NAME Risperidone		SE5-020	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Schizophrenia in Adolescents (13 to 17 years of age)				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Orally Disintegrating Tablet		14. POTENCY 0.5, 1, 2, 3 and 4 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Fluoro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	
					
17. COMMENTS This efficacy supplement provides for the use of Risperdal® M-Tab® Orally Disintegrating Tablets for the treatment of schizophrenia in adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "How Supplied" section of labeling. The proposed minor editorial change to the above section is found to be acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-07-2007
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

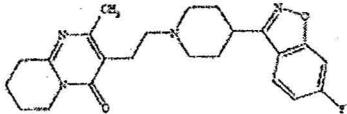
**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram
6/8/2007 12:29:53 PM
CHEMIST

Jim Vidra
6/8/2007 04:44:02 PM
CHEMIST

APPEARS THIS WAY ON ORIGINAL

CHEMIST'S REVIEW #1		1. ORGANIZATION ONDQA/DPE/Branch VII		2. NDA NUMBER 21-444	
3. NAME AND ADDRESS OF APPLICANT (<i>City and State</i>) Johnson & Johnson Pharmaceutical Research & Development, L.L.C On behalf of Janssen, L.P. 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200.				4. AF NUMBER	
				5. SUPPLEMENT (S) NUMBER(S) DATES(S)	
6. NAME OF DRUG RISPERDAL® M-Tab® Orally Disintegrating Tablets		7. NONPROPRIETARY NAME Risperidone		SE5-021	12-21-2006
8. SUPPLEMENT PROVIDES FOR: A Response to Pediatric Written Request, Treatment of Bipolar 1 Disorder in Children (10 to 12 years of age) and Adolescents (13 to 17 years of age).				9. AMENDMENTS DATES	
10. PHARMACOLOGICAL CATEGORY Antipsychotics		11. HOW DISPENSED RX <input checked="" type="checkbox"/> OTC		12. RELATED IND/NDA/DMF	
13. DOSAGE FORM(S) Orally Disintegrating Tablet		14. POTENCY 0.5, 1, 2, 3 and 4 mg			
15. CHEMICAL NAME, STRUCTURE, MOLECULAR FORMULA AND MOLECULAR WEIGHT: 3-[2-[4-(6-Flouro-1,2-benzisoxazol-3-yl)-1-piperidinyl]ethyl]-6,7,8,9-tetrahydro-2-methyl-4H-pyrido[1,3-a]pyrimidin-4-one				16. RECORDS AND REPORTS CURRENT YES__ NO REVIEWED YES__ NO	
					
17. COMMENTS This efficacy supplement provides for the use of Risperdal® M-Tab® Orally Disintegrating Tablets for the treatment of Bipolar 1 Disorder in children (10 to 12 years of age) and adolescents (13 to 17 years of age). This application has been submitted in response to a formal written request from the Agency to provide information from studies in pediatric patients. Based on the results obtained, the applicant has indicated that the effectiveness of the drug product in children and adolescent patients has been established. The applicant has cross-referenced entire CMC information that was submitted in previously approved supplements and that there are no new CMC information included in this submission. The applicant is proposing minor editorial changes to "How Supplied" section of labeling. The proposed minor editorial change to the above section is found to be acceptable. A claim for categorical exclusion from filing an environmental assessment under 21 CFR 25.31 (b) has been submitted. The applicant's claim is found to be acceptable.					
18. CONCLUSIONS AND RECOMMENDATIONS Provided information is found to be adequate. This supplement is recommended for approval from the standpoint of chemistry, manufacturing and controls.					
19. REVIEWER					
NAME Nallaperumal Chidambaram, Ph.D.		SIGNATURE			DATE COMPLETED 06-07-2007
DISTRIBUTION	ORIGINAL NDA	DIVISION FILE	Reviewer: N. Chidambaram Ph.D.	CSO: K. Updegraff HFD-130	Branch Chief: James Vidra Ph.D.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Nallaperumal Chidambaram

6/8/2007 12:31:58 PM

CHEMIST

Jim Vidra

6/8/2007 04:54:26 PM

CHEMIST

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

ENVIRONMENTAL ASSESSMENT

Johnson & Johnson Pharmaceutical Research & Development, L.L.C.

Environmental Assessment

sNDA Categorical Exclusion for Risperdal® Oral for Pediatric Indications

R064766

Department: Chemistry, Manufacturing & Controls
Document No.: EDMS-PSDB-6063879:2.0
Report No.: EAUS-CE-R064766-ORL-NDA-V01

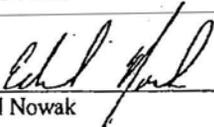
Confidentiality Statement

The information in this document contains trade secrets and commercial information that are privileged or confidential and may not be disclosed unless such disclosure is required by applicable law or regulations. In any event, persons to whom the information is disclosed must be informed that the information is *privileged* or *confidential* and may not be further disclosed by them. These restrictions on disclosure will apply equally to *all* future information supplied to you which is indicated as *privileged* or *confidential*.

CATEGORICAL EXCLUSION

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD), Raritan, NJ, certifies that the above referenced action meets the criteria for a categorical exclusion defined in the regulations (21 CFR 25.31[b]), and that to the knowledge of J&JPRD, no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

APPROVER:


Edward Nowak
Director
Global Environmental, Health, & Safety

10 November 2006
Date

APPEARS THIS WAY ON ORIGINAL

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

PHARMACOLOGY REVIEW(S)

Barry N. Rosloff, Ph. D.
6/11/07

NDA 20-272 (S-046/047), 20-588 (S-036/037), and 21-444 (S-020/021)

These supplements are for the use of risperdal in adolescents with schizophrenia and in children and adolescents with bipolar disorder. To support the previously approved supplements for the use of risperdal in children with autism, a juvenile rat study was performed. As indicated in the files for the above NDAs, it was felt that the doses in this rat study were not high enough, and therefore a rat study using higher doses, as well as a juvenile dog study, is being performed as a phase IV commitment to the autism supplements. The previously performed rat study plus the additional phase IV studies are adequate to support the use of risperdal in children with bipolar disorder in the present supplements. (Juvenile animal studies are not necessary to support use in adolescents).

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Barry Rosloff
6/12/2007 11:55:40 AM
PHARMACOLOGIST

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

STATISTICAL REVIEW(S)



X
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Pharmacoeconomics and Statistical Science
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number: 20-272 SE 046, 20-272 SE 047, 20-588 SE 036, 20-588 SE 037,
21-444 SE 020, 21-444 SE 021

Drug Name: Risperidone (Risperdal®)

Indication(s): Treatment of schizophrenia and bipolar disorder in adolescents

Applicant: Johnson & Johnson Pharmaceutical Research & Development,
L.L.C.

Date(s): December 21, 2006

Review Priority: Priority

Biometrics Division: Biometrics I (HFD-710)

Statistical Reviewer: John Lawrence

Concurring Reviewers: Peiling Yang, Team Leader
H. M. James Hung, Division Director

Medical Division: Division of Psychiatric Drug Products

Clinical Team: June Cai, Medical Reviewer

Project Manager: Kimberly Updegraff

Keywords:

Pediatric studies

Table of Contents

1. EXECUTIVE SUMMARY	3
1.1 CONCLUSIONS AND RECOMMENDATIONS	3
1.2 BRIEF OVERVIEW OF CLINICAL STUDIES	3
1.3 STATISTICAL ISSUES AND FINDINGS	3
2. INTRODUCTION	4
2.1 OVERVIEW	4
2.2 DATA SOURCES	4
3. STATISTICAL EVALUATION	5
3.1 EVALUATION OF EFFICACY	5
3.1.1 <i>Evaluation of Efficacy- RIS-SCH-302</i>	5
3.1.2 <i>Evaluation of Efficacy- RIS-USA-231</i>	8
3.1.3 <i>Evaluation of Efficacy- RIS-BIM-301</i>	10
3.2 EVALUATION OF SAFETY	14
4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS	15
4.1 GENDER, RACE AND AGE	15
4.1.1 <i>Efficacy findings Gender, Race and Age- RIS-SCH-302</i>	15
4.1.2 <i>Efficacy findings Gender, Race and Age- RIS-USA-231</i>	15
4.1.3 <i>Efficacy findings Gender, Race and Age- RIS-BIM-301</i>	16
4.2 OTHER SPECIAL/SUBGROUP POPULATIONS	16
5. SUMMARY AND CONCLUSIONS	16
5.1 STATISTICAL ISSUES AND COLLECTIVE EVIDENCE	16
5.2 CONCLUSIONS AND RECOMMENDATIONS	17

APPEARS THIS WAY ON ORIGINAL

1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrate that risperidone is effective in treating these subjects.

1.2 Brief Overview of Clinical Studies

There are three placebo-controlled randomized double blind studies in pediatric subjects. Studies RIS-SCH-302 and RIS-USA-231 evaluated the safety and efficacy of risperidone in adolescents with schizophrenia. RIS-BIM-301 evaluated the safety and efficacy of risperidone in adolescents with bipolar disorder.

1.3 Statistical Issues and Findings

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrated that risperidone is effective. There are no statistical issues for any of the three studies for the primary endpoint. However, no multiple comparison procedure was planned for secondary endpoints in any study. For each secondary endpoint, nominal p-values were reported. See Sections 3.1.1, 3.1.2, and 3.1.3 for the efficacy results of the individual studies.

APPEARS THIS WAY ON ORIGINAL

2. INTRODUCTION

2.1 Overview

The sponsor submitted these studies to fulfill a pediatric written request.

~~Study RIS-SCN-302 (submitted under NDA 20-272) was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B). The study comprised 2 phases: a screening phase (with a possible washout period) and a 6-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 7; the investigator then titrated the dosage to the maximum tolerated dosage within the target dosage range up to Day 14 to optimize efficacy while minimizing adverse effects. Subjects could be enrolled as inpatients or outpatients as clinically indicated. A subject was considered as having completed the study if they had completed all assessments at Week 6 (Visit 6) of the double-blind treatment phase.~~

Study RIS-USA-231 (submitted under NDA 20-272) was an 8-week, randomized, double-blind, parallel-group, multicenter clinical study conducted at 41 sites in 8 countries. Subjects were randomly assigned to 1 of 2 treatment groups:

- Risperidone low dose group: oral risperidone 0.15–0.6 mg/day for subjects weighing ≥ 50 kg or 0.003–0.012 mg/kg/day for subjects weighing < 50 kg
- Risperidone high dose: oral risperidone 1.5–6 mg/day for subjects weighing ≥ 50 kg or 0.03–0.12 mg/kg/day for subjects weighing < 50 kg

The study comprised 2 phases: a screening phase (with a possible washout period) and an 8-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 12. The investigator could then adjust the dosage to achieve the maximum tolerated dose within the target dosage range; however, the dose was to remain stable during the last 4 weeks of the double-blind phase.

Study RIS-BIM-301 (submitted under NDA 20-272) evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy (0.5–2.5 mg/day and 3–6 mg/day) versus placebo in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of Bipolar I disorder who were experiencing a manic or mixed episode (Young Mania Rating Scale [YMRS] ≥ 20). Efficacy was primarily based on the improvement in severity of mania during the 3-week treatment period, measured by the change in total score (consensus final score) of the YMRS from baseline to endpoint.

2.2 Data Sources

Electronic study reports and data sets (\\Cdsub1\n20272\S_046 and \\Cdsub1\n20272\S_0467)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 Evaluation of Efficacy- RIS-SCH-302

Study RIS-SCH-302 was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B). The study comprised 2 phases: a screening phase (with a possible washout period) and a 6-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 7; the investigator then titrated the dosage to the maximum tolerated dosage within the target dosage range up to Day 14 to optimize efficacy while minimizing adverse effects. Subjects could be enrolled as inpatients or outpatients as clinically indicated. A subject was considered as having completed the study if they had completed all assessments at Week 6 (Visit 6) of the double-blind treatment phase.

160 subjects are included in the intent-to-treat analysis set. The demographics for the ITT population appear in Table 1. The majority was white, roughly 2/3 were male, and all were older than 12 years old. There appeared to be roughly the same distribution in each treatment group.

Table 1 Patient Demographics (ITT analysis set)

	— PLACEBO — (N=54)	RIS 1-3 mg (N=55)	RIS 4-6 mg (N=51)	— Total — (N=160)
Age, years				
N	54	55	51	160
Mean (SD)	15.5 (1.38)	15.7 (1.33)	15.7 (1.29)	15.6 (1.33)
Median	16.0	16.0	16.0	16.0
Range	(13:17)	(13:17)	(13:17)	(13:17)
Sex, n (%)				
N	54	55	51	160
Female	19 (35)	25 (45)	14 (27)	58 (36)
Male	35 (65)	30 (55)	37 (73)	102 (64)
Race, n (%)				
N	54	55	51	160
American Indian/Alaskan Native	0	0	1 (2)	1 (1)
Asian	22 (41)	18 (33)	18 (35)	58 (36)
Black or African American	5 (9)	3 (5)	7 (14)	15 (9)
Mixed	0	1 (2)	1 (2)	2 (1)
White	27 (50)	33 (60)	24 (47)	84 (53)

Source: Study Report, p 73.

Roughly ¾ of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 2.

Table 2 Subject Disposition and Discontinuation Reasons (ITT analysis set)

	PLACEBO (N=54)	RIS 1-3 mg (N=55)	RIS 4-6 mg (N=51)	Total (N=160)
State of Termination				
Termin. Reason	n (%)	n (%)	n (%)	n (%)
Completed	36 (67)	45 (82)	44 (86)	125 (78)
Discontinued	18 (33)	10 (18)	7 (14)	35 (22)
Adverse event	3 (4)	3 (5)	4 (8)	9 (6)
Insufficient response	13 (24)	3 (5)	1 (2)	17 (11)
Subject ineligible to continue the trial	0	1 (2)	0	1 (1)
Subject withdrew consent	2 (4)	3 (5)	1 (2)	6 (4)
Other	1 (2)	0	1 (2)	2 (1)

Source: Study Report, p 72.

The primary efficacy measure was the change from baseline in the Positive and Negative Symptoms of Schizophrenia (PANSS) total score at the Day 43 (6-week) end point. The primary analysis used an ANCOVA model with factors for treatment, baseline value, and country. The last observed value was carried forward (from Day 8, 15, or 29) for subjects with missing values at Day 43. To account for multiple comparisons, a step-down sequential testing strategy was used. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 3. Both doses showed a significantly larger decrease in the PANSS total score compared to placebo.

Table 3 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores - Change From Baseline to Day 43 End Point- Efficacy Analysis Set.

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Baseline			
N	54	54	50
Mean (SD)	93.3 (10.37)	95.4 (11.01)	93.0 (11.87)
Median (Range)	94.0 (63:120)	96.0 (67:120)	90.0 (71:117)
Day 43 End Point			
N	54	54	50
Mean (SD)	84.4 (16.59)	74.1 (17.79)	71.8 (18.35)
Median (Range)	86.0 (42:126)	74.5 (34:124)	71.0 (34:117)
Change from Baseline			
N	54	54	50
Mean (SD)	-8.9 (16.11)	-21.3 (19.61)	-21.2 (18.29)
Median (Range)	-7.0 (-53:21)	-19.0 (-69:35)	-20.0 (-60:22)
P-value (minus PLACEBO)**		<0.001	<0.001
Diff. of LS Means (SE)		-11.0 (3.02)	-12.8 (3.07)
95% CI		(-17.95; -5.99)	(-18.83; -6.71)

Source: Study Report, p 86 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 4. There is a

numerical difference between each of the two risperidone groups and placebo at each visit in favor of the risperidone groups.

Table 4 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) – Efficacy Analysis Set.

	N	Mean	SD	Change from Baseline	
				Mean	SD
Placebo Group					
Baseline	54	93.2	10.27		
Day 8 OC	54	91.1	11.29	-2.1	7.23
Day 8 LOCF	54	91.1	11.29	-2.1	7.23
Day 15 OC	52	86.3	11.57	-6.8	9.48
Day 15 LOCF	54	86.9	11.94	-6.3	9.92
Day 29 OC	51	85.4	14.35	-7.9	13.66
Day 29 LOCF	54	86.0	14.47	-7.2	13.77
Day 43 OC	35	78.4	13.43	-14.8	13.70
Day 43 LOCF	54	84.4	16.59	-8.9	16.11
Risperidone 1-3 mg					
Baseline	54	95.4	11.01		
Day 8 OC	54	89.9	12.89	-5.5	10.19
Day 8 LOCF	54	89.9	12.89	-5.5	10.19
Day 15 OC	51	81.9	14.16	-13.8	12.30
Day 15 LOCF	54	82.9	14.93	-12.5	14.06
Day 29 OC	50	77.5	14.30	-18.2	14.33
Day 29 LOCF	54	79.0	15.32	-16.4	16.09
Day 43 OC	44	70.1	15.81	-26.6	16.22
Day 43 LOCF	54	74.1	17.79	-21.3	19.61
Risperidone 4-6 mg					
Baseline	50	93.0	11.87		
Day 8 OC	50	87.5	13.59	-5.5	9.29
Day 8 LOCF	50	87.5	13.59	-5.5	9.29
Day 15 OC	48	78.9	13.50	-14.0	12.35
Day 15 LOCF	50	79.9	14.36	-13.2	12.89
Day 29 OC	43	73.4	12.77	-19.1	11.25
Day 29 LOCF	50	76.8	15.52	-16.2	14.05
Day 43 OC	43	67.6	15.17	-24.9	15.73
Day 43 LOCF	50	71.8	18.35	-21.2	18.29

Source: Study Report, Attachment 2.1.1.2.

3.1.2 Evaluation of Efficacy- RIS-USA-231

Study RIS-USA-231 was an 8-week, randomized, double-blind, parallel-group, multicenter clinical study conducted at 41 sites in 8 countries. Subjects were randomly assigned to 1 of 2 treatment groups:

- Risperidone low dose group: oral risperidone 0.25–0.6 mg/day for subjects weighing ≥ 50 kg or 0.003–0.012 mg/kg/day for subjects weighing < 50 kg
- Risperidone high dose: oral risperidone 1.5–6 mg/day for subjects weighing ≥ 50 kg or 0.03–0.12 mg/kg/day for subjects weighing < 50 kg

The study comprised 2 phases: a screening phase (with a possible washout period) and an 8-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 12. The investigator could then adjust the dosage to achieve the maximum tolerated dose within the target dosage range; however, the dose was to remain stable during the last 4 weeks of the double-blind phase.

279 subjects are included in the intent-to-treat analysis set, 257 subjects in the mITT analysis set (diagnosis of schizophrenia and an age > 12 years and ≤ 17 years at baseline), 255 subjects in the efficacy analysis set (excludes 2 subjects due to Good Clinical Practice noncompliance). The demographics for the mITT population appear in Table 5. The majority was white, roughly half were male, and all were older than 12 years old. There appeared to be roughly the same distribution in each treatment group.

Table 5 Patient Demographics (mITT analysis set)

	RIS LOW DOSE (N=132)	RIS HIGH DOSE (N=125)	-- Total -- (N=257)
Age, years			
N	132	125	257
Mean (SD)	15.6 (1.32)	15.6 (1.25)	15.6 (1.28)
Median	16.0	16.0	16.0
Range	(13:17)	(13:17)	(13:17)
Age in classes, n (%)			
N	132	125	257
>12 years	132 (100)	125 (100)	257 (100)
Sex, n (%)			
N	132	125	257
Female	51 (39)	60 (48)	112 (44)
Male	80 (61)	65 (52)	145 (56)
Race, n (%)			
N	131	123	254
Black or African American	20 (15)	17 (14)	37 (15)
Mixed	0	2 (2)	2 (1)
White	111 (85)	104 (85)	215 (85)

Source: Study Report, p 86.

Roughly $\frac{2}{3}$ of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 6.

Table 6 Subject Disposition and Discontinuation Reasons (Intent-to-treat analysis set)

State of Termination Term Reason	RIS LOW DOSE	RIS HIGH DOSE	Total
	(N=141) n (%)	(N=138) n (%)	(N=279) n (%)
Completed	87 (62)	97 (70)	184 (66)
Discontinued	54 (38)	41 (30)	95 (34)
Adverse event	6 (4)	8 (6)	14 (5)
Insufficient response	27 (19)	20 (14)	47 (17)
Subject ineligible to continue the trial	3 (2)	2 (1)	5 (2)
Subject lost to follow-up	3 (2)	0	3 (1)
Subject withdrew consent	10 (7)	6 (4)	16 (6)
Subject non-compliant	0	1 (1)	1 (<1)
Other	5 (4)	4 (3)	9 (3)

Source: Study Report, p 83.

The primary efficacy measure was the change from baseline in the Positive and Negative Symptoms of Schizophrenia (PANSS) total score at the Day 56 (8-week) end point. The primary analysis used an ANCOVA model with factors for treatment, baseline value, and country. The last observed value was carried forward (from Day 7, 14, 28, or 42) for subjects with missing values at Day 56. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 7. The high dose group showed a significantly larger decrease in the PANSS total score compared to the low dose.

Table 7 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores - Change From Baseline to Day 56 End Point- Efficacy Analysis Set.

	RIS LOW DOSE	RIS HIGH DOSE
Baseline		
N	131	124
Mean (SD)	93.3 (14.14)	96.4 (15.39)
Median (Range)	94.0 (61;119)	97.0 (63;126)
Day 56 End Point		
N	131	124
Mean (SD)	80.8 (24.33)	72.8 (23.53)
Median (Range)	80.0 (33;132)	71.0 (31;146)
Change from Baseline		
N	131	124
Mean (SD)	-12.5 (20.32)	-23.6 (23.83)
Median (Range)	-11.0 (-68;29)	-23.0 (-94;51)
P-value		<0.001
(minus RIS LOW DOSE)*		
Diff. of LS Means (SE)		-10.3 (2.65)
95% CI		(-15.53;-5.09)

Source: Study Report, p 103 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 8. There is a numerical difference between the two groups at each visit in favor of the high dose group.

Table 8 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) - Modified ITT Analysis Set.

	Risperidone Low Dose					Risperidone High Dose				
	N	Mean	SD	Change from Baseline		N	Mean	SD	Change from Baseline	
				Mean	SD				Mean	SD
Baseline	131	93.3	14.14			124	96.4	15.39		
Day 7 OC	130	88.3	18.31	-5.0	10.86	123	87.7	16.34	-8.8	12.06
Day 7 LOCF	130	88.3	18.31	-5.0	10.86	123	87.7	16.34	-8.8	12.06
Day 14 OC	123	83.6	16.81	-9.9	11.34	121	80.6	16.05	-15.7	13.75
Day 14 LOCF	131	84.3	18.33	-9.0	12.56	124	81.5	17.07	-14.9	14.91
Day 28 OC	112	82.2	19.09	-11.5	14.10	113	75.4	17.05	-20.9	15.94
Day 28 LOCF	131	83.3	20.37	-9.9	15.14	124	76.6	18.39	-19.8	17.41
Day 42 OC	97	76.2	20.53	-16.1	17.68	97	71.3	18.56	-25.5	18.76
Day 42 LOCF	131	81.2	23.14	-12.0	18.92	124	74.9	21.04	-21.5	20.44
Day 56 OC	82	72.0	20.40	-19.5	18.98	87	66.5	18.16	-30.9	20.07
Day 56 LOCF	131	80.8	24.33	-12.5	20.32	124	72.8	22.52	-23.6	22.83

Source: Study Report, Attachment 2.1.1.3.

3.1.3 Evaluation of Efficacy- RIS-BIM-301

Study RIS-BIM-301 evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy (0.5-2.5 mg/day and 3-6 mg/day) versus placebo in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of Bipolar I disorder who were experiencing a manic or mixed episode (Young Mania Rating Scale [YMRS] ≥ 20). Efficacy was primarily based on the improvement in severity of mania during the 3-week treatment period, measured by the change in total score (consensus final score) of the YMRS from baseline to endpoint.

169 subjects are included in the intent-to-treat analysis set. The demographics appear in Table 9. The majority was white, roughly half were male, and 40% were under 12 years old. There appeared to be roughly the same distribution in each treatment group.

APPEARS THIS WAY ON ORIGINAL

Table 9 Patient Demographics (Intent-to-treat analysis set)

	--- PLACEBO --- (N=58)	RIS 0.5-2.5 mg (N=50)	-RIS 3-6 mg- (N=61)	--- Total --- (N=169)
Age, years				
N	58	50	61	169
Mean (SD)	13.1 (2.20)	13.4 (2.03)	13.1 (2.12)	13.2 (2.11)
Median	13.0	13.0	13.0	13.0
Range	(10;17)	(10;17)	(10;17)	(10;17)
Age in classes, n (%)				
N	58	50	61	169
<12 years	24 (41)	18 (36)	25 (41)	67 (40)
>12 years	34 (59)	32 (64)	36 (59)	102 (60)
Sex, n (%)				
N	58	50	61	169
Female	30 (52)	22 (44)	35 (57)	87 (51)
Male	28 (48)	28 (56)	26 (43)	82 (49)
Race, n (%)				
N	58	50	61	169
American Indian/Alaskan Native	1 (2)	2 (4)	0	3 (2)
Asian	0	1 (2)	0	1 (1)
Black or African American	10 (17)	10 (20)	9 (15)	29 (17)
Mixed	2 (3)	2 (4)	2 (3)	6 (4)
White	45 (78)	35 (70)	50 (82)	130 (77)

Source: Study Report, p 98.

Roughly 80% of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 10.

APPEARS THIS WAY ON ORIGINAL

Table 10 Subject Disposition and Discontinuation Reasons (Intent-to-treat analysis set)

State of Termination Term Reason	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	Total (N=169) n (%)
All subjects				
Completed	46 (79)	45 (90)	46 (75)	137 (81)
Discontinued	12 (21)	5 (10)	15 (25)	32 (19)
Adverse event	4 (7)	3 (6)	10 (16)	17 (10)
Insufficient response	2 (3)	0	2 (3)	4 (2)
Subject ineligible to continue the study	0	1 (2)	0	1 (1)
Subject lost to follow-up	1 (2)	0	2 (3)	3 (2)
Subject withdrew consent	2 (3)	1 (2)	1 (2)	4 (2)
Subject non-compliant	1 (2)	0	0	1 (1)
Other	2 (3)	0	0	2 (1)
	PLACEBO (N=24) n (%)	RIS 0.5-2.5 mg (N=18) n (%)	RIS 3-6 mg (N=25) n (%)	Total (N=67) n (%)
≤12 years				
Completed	22 (92)	17 (94)	17 (68)	56 (84)
Discontinued	2 (8)	1 (6)	8 (32)	11 (16)
Adverse event	0	0	4 (16)	4 (6)
Insufficient response	0	0	1 (4)	1 (1)
Subject lost to follow-up	0	0	2 (8)	2 (3)
Subject withdrew consent	1 (4)	1 (6)	1 (4)	3 (4)
Other	1 (4)	0	0	1 (1)
	PLACEBO (N=34) n (%)	RIS 0.5-2.5 mg (N=32) n (%)	RIS 3-6 mg (N=36) n (%)	Total (N=102) n (%)
>12 years				
Completed	24 (71)	28 (88)	29 (81)	81 (79)
Discontinued	10 (29)	4 (13)	7 (19)	21 (21)
Adverse event	4 (12)	3 (9)	6 (17)	13 (13)
Insufficient response	2 (6)	0	1 (3)	3 (3)
Subject ineligible to continue the study	0	1 (3)	0	1 (1)
Subject lost to follow-up	1 (3)	0	0	1 (1)
Subject withdrew consent	1 (3)	0	0	1 (1)
Subject non-compliant	1 (3)	0	0	1 (1)
Other	1 (3)	0	0	1 (1)

Source: Study Report, p 95.

The primary efficacy variable was the change in the total YMRS consensus final score from baseline to the Day 21 endpoint (i.e. the last post-baseline observation carried forward to the Day 21 endpoint). The primary analysis used an ANCOVA model with factors for treatment, baseline value, investigator, and diagnosis (mixed or manic). The last observed value was carried forward (from Day 7 or 14) for subjects with missing values at Day 21. To account for two comparisons, a sequential testing procedure was used starting with the high dose versus placebo. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 11. Both risperidone treated groups show significantly lower scores at Day 21 compared to placebo.

Table 11 Young Mania Rating Scale Adolescent Version (YMRS) Consensus Total Scores - Change From Baseline to Day 21 Endpoint- ITT with a Post-Baseline Observation Analysis Set.

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Baseline			
N	57	49	60
Mean (SD)	31.0 (7.45)	31.1 (5.97)	30.5 (5.92)
Median (Range)	31.0 (19;45)	31.0 (16;44)	31.0 (20;44)
Day 21 endpoint			
N	57	49	60
Mean (SD)	21.9 (9.51)	13.6 (7.22)	13.9 (9.70)
Median (Range)	23.0 (3;44)	13.0 (0;30)	11.5 (0;40)
Change from Baseline			
N	57	49	60
Mean (SD)	-9.1 (10.95)	-18.5 (9.70)	-16.5 (10.29)
Median (Range)	-8.0 (-36;23)	-17.0 (-39;-3)	-18.0 (-35;0)
P-value(minus PLACEBO)(a,b)		<0.001	<0.001
Diff. of LS Means (SE)		-9.2 (1.76)	-8.0 (1.70)
95% CI		(-12.69;-5.74)	(-11.33;-4.62)

Source: Study Report, p 120 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 12. There is a numerical difference between each of the two risperidone groups and placebo at each visit in favor of the risperidone groups.

APPEARS THIS WAY ON ORIGINAL

Table 12 Young Mania Rating Scale Adolescent Version (YMRS) Consensus Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) – ITT with a Post-Baseline Observation Analysis Set.

	N	Mean	SD	Change from Baseline	
				Mean	SD
Placebo Group					
Baseline	57	31.0	7.46		
Day 7 OC	57	25.4	7.67	-5.6	8.06
Day 7 LOCF	57	25.4	7.67	-5.6	8.06
Day 14 OC	49	20.3	8.63	-11.0	9.83
Day 14 LOCF	57	21.7	8.98	-9.2	10.60
Day 21 OC	47	20.5	9.41	-10.0	10.12
Day 21 LOCF	57	21.9	9.51	-9.1	10.95
Risperidone 0.5-2.5 mg					
Baseline	49	31.1	5.97		
Day 7 OC	48	20.4	8.48	-10.6	9.75
Day 7 LOCF	48	20.4	8.48	-10.6	9.75
Day 14 OC	47	13.6	7.26	-17.5	9.36
Day 14 LOCF	49	13.8	7.19	-17.3	9.34
Day 21 OC	45	12.1	6.82	-18.8	9.71
Day 21 LOCF	49	12.6	7.22	-18.5	9.70
Risperidone 3-6 mg					
Baseline	60	30.5	5.92		
Day 7 OC	59	21.7	8.63	-8.7	6.71
Day 7 LOCF	59	21.7	8.63	-8.7	6.71
Day 14 OC	53	12.2	7.15	-18.1	7.30
Day 14 LOCF	60	14.0	8.58	-16.5	8.48
Day 21 OC	46	12.3	8.49	-18.0	9.17
Day 21 LOCF	60	13.9	9.70	-16.5	10.29

Source: Study Report, Attachment 2.1.1.1.

3.2 Evaluation of Safety

See medical officer's review.

APPEARS THIS WAY ON ORIGINAL

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 Efficacy findings Gender, Race and Age- RIS-SCH-302

The results for the primary endpoint in subgroups defined by gender and race appear in Table 13. Numerically, the results appear to show both the low and high dose groups were better than placebo in each subgroup.

Table 13 Results for primary endpoint in demographic subgroups

Demographic Subgroup		PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Sex	N			
	Female	19	24	14
	Male	35	30	36
Race	N			
	Non-white	27	32	27
	White	27	32	33
	Mean (SD)			
	Diff. of LS means (95% CI)			
	Female	-11.6 (12.01)	-22.8 (23.62)	-26.3 (21.40)
	Male	-7.4 (17.94)	-20.2 (16.04)	-19.2 (16.85)
	Non-white	-15.9 (17.61)	-30.1 (18.77)	-27.8 (21.33)
	White	-1.9 (10.80)	-15.3 (18.08)	-13.5 (9.58)
	Diff. of LS means (95% CI)			
	Female		-11.2 (-21.53;-0.85)*	-14.2 (-25.78;-3.52)
	Male		-11.8 (-19.32;-4.29)*	-12.2 (-19.33;-5.09)
	Non-white		-11.1 (-21.39;-0.77)*	-13.4 (-23.18;-3.57)
	White		-12.5 (-19.42;-5.65)***	-12.3 (-19.77;-4.77)

Source: Study Report p. 101

4.1.2 Efficacy findings Gender, Race and Age- RIS-USA-231

The results for the primary endpoint in subgroups defined by gender and race appear in Table 14. Numerically, the results appear to favor the high dose groups over the low dose in each subgroup.

Table 14 Results for primary endpoint in demographic subgroups

Demographic Subgroup	Change from baseline at Day 56 end point in total PANSS score			
	RIS LOW DOSE		RIS HIGH DOSE	
	N	Mean (SD)	N	Mean (SD)
				Diff. of LS Means (95% CI)
Sex				
Female	51	-14.5 (19.72)	59	-22.8 (25.88)
Male	80	-11.2 (20.72)	65	-24.3 (19.85)
				-13.4 (-20.23;-6.55)***
Race				
Non-White	20	-12.7 (19.16)	19	-30.6 (21.95)
White	110	-12.7 (20.45)	103	-21.9 (21.50)
Black	20	-12.7 (19.16)	17	-39.9 (24.16)
				-16.4 (-31.53;-1.23)*

Source: Study Report p. 116

4.1.3 Efficacy findings Gender, Race and Age- RIS-BIM-301

The results for the primary endpoint in subgroups defined by gender, race and age appear in Table 15. Numerically, the results appear to favor the risperidone treated groups over placebo in each subgroup.

Table 15: Results for primary endpoint in demographic subgroups

	Change From Baseline at Day 21 Endpoint in Total YMRS Score					
	PLACEBO		RIS 0.5-2.5 mg		RIS 3-6 mg	
	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
			Diff. of LS Means (95% CI)		Diff. of LS Means (95% CI)	
Sex						
Female	29	-10.7 (10.47)	22	-15.1 (7.06)	35	-17.1 (9.98)
			-4.5 (-9.53;0.46)			-5.7 (-10.17;-1.22)*
Male	28	-7.5 (11.37)	27	-21.3 (10.77)	25	-15.7 (10.85)
			-14.7 (-20.43;-8.95)***			-10.9 (-16.98;-4.78)***
Race						
Non-White	13	-7.8 (6.44)	14	-17.6 (9.92)	10	-13.7 (12.52)
			-8.5 (-16.84;-0.11)*			-8.9 (-18.68;0.81)
White	44	-9.5 (11.99)	35	-18.9 (9.73)	50	-17.1 (9.83)
			-9.0 (-13.25;-4.83)***			-8.5 (-12.40;-4.58)***
Race (Non-Black versus Black)						
Black	10	-6.8 (5.47)	9	-20.9 (9.60)	9	-12.0 (11.99)
			-11.5 (-22.94;-0.12)*			-4.3 (-16.98;8.46)
Non-Black	47	-9.6 (11.77)	40	-18.0 (9.77)	51	-17.3 (9.88)
			-8.6 (-12.58;-4.63)***			-8.6 (-12.35;-4.84)***
Age						
≤12 years	24	-6.1 (11.07)	18	-18.6 (10.00)	24	-18.0 (9.51)
			-14.0 (-21.50;-6.54)***			-13.1 (-19.71;-6.40)***
>12 years	33	-11.3 (10.49)	31	-18.5 (9.69)	36	-15.6 (10.80)
			-6.5 (-10.88;-2.03)*			-5.1 (-9.22;-1.03)*

Source: Study Report p. 139

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrated that risperidone is effective. There are no statistical issues for any of the three studies for the primary endpoint. However, no multiple comparison procedure was planned for secondary endpoints in any study. For each secondary endpoint, nominal p-values were reported. See Sections 3.1.1, 3.1.2, and 3.1.3 for the efficacy results of the individual studies.

5.2 Conclusions and Recommendations

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrate that risperidone is effective in treating these subjects.

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

John Lawrence
5/16/2007 11:51:55 AM

BIOMETRICS

Peiling Yang
5/16/2007 12:04:05 PM
BIOMETRICS

James Hung
5/16/2007 12:07:36 PM
BIOMETRICS

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

Clinical Pharmacology/Biopharmaceutics Review BPCA Summary Review

PRODUCT (Generic Name):	Risperidone
PRODUCT (Brand Name):	Risperdal
DOSAGE FORM:	Tablets
DOSAGE STRENGTHS:	0.25mg, 0.5mg, 1 mg, 2mg, 3mg, and 4 mg
NDA:	20-272/20588
NDA TYPE:	Supplement for Schizophrenia and Bipolar disorder in children and adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	December 22, 2006
SPONSOR:	Johnson and Johnson
OND DIVISION:	HFD

EXECUTIVE SUMMARY

Risperdal is currently indicated in the treatment of schizophrenia or bipolar I in adults. It has been believed that the pharmacokinetics of Risperdal in children (less than 12 years), adolescents (12 to 17 years) and adults, are similar. Results from the current population pharmacokinetic analysis indicates that the pharmacokinetics are similar after correction for body weight. However there was no dose response for efficacy. Therefore no dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years) for schizophrenia or bipolar I disorder.

This sNDA includes a meta analysis of several population pharmacokinetic studies done in children and adolescents with several different titrated dosage regimens based upon either once-a-day or twice-a-day maximum tolerated dose or maximum tolerated dose/kg/day. Targeted titrated maximum tolerated doses ranged from 0.5mg/day to 6

mg/day while dose titrations based upon weight ranged between 0.007 to 0.12 mg/kg/day.

The population pharmacokinetic study was done in 472 children and adolescents patients, ages 6-18 (studies ris,-bim-301, ris-usa-231, ris-usa-160) . Study durations were from 12-21 days.

The overall conclusions from the pharmacokinetic studies in adolescents and children were:

- The exposure in children and adolescents was similar based upon mg/kg body weight.
- A dose response relationship was not observed for the schizophrenia study in adolescents or for the bipolar I study in children/adolescents.
- No dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years).

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested by the reviewer.

C:\Data\REVIEWS\NDA\RISPERDAL_NDA20272JANDJ\PEDWREQ\BPCASummaryRisperidol.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Raman Baweja
6/14/2007 10:25:32 AM

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

DRUG: Risperidone

PRIMARY REVIEWER: Andre Jackson

NDA: 20272/20588

TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 0.25mg, 0.5mg, 1 mg,
2mg, 3mg and 4mg

APPLICANT: Johnson and Johnson Submission Dates: December 22, 2006

INDICATIONS: Schizophrenia , Bipolar Disorder

TABLE OF CONTENTS

Executive Summary.....	2
Introduction.....	2
Summary.....	3
COMMENTS TO MEDICAL REVIEWER.....	3
Objective of the analysis.....	3
Methods.....	4
Overview of Study Designs.....	4
ASSAY VALIDATION.....	4
Analytical.....	4
Study RIS-BIM-301- (STUDY 1) CHILDREN AND ADOLESCENTS (10-17 YEARS).....	5
STUDY RIS-USA-231 (STUDY 2) ADOLESCENTS.....	7
STUDY RIS-USA-160 (STUDY 3)- CHILDREN AND ADOLESCENTS.....	9
STUDY RIS-USA-239-(STUDY 4)-ADULTS.....	10
STUDY RIS-IND-2 (STUDY 5) ADULTS.....	12
STUDY RIS-IND25-(STUDY 6)- ADULTS.....	13
STUDY RIS-P01-103-(STUDY 7)- ADULTS.....	15
STUDY RSA-5-(STUDY 8)- ADULTS.....	19
STUDY R076477-SCH-102 STUDY 9- ADULTS.....	21
PHARMACOKINETIC ANALYSIS.....	24
Planned Analysis for Risperidone and the Active Moiety.....	25
IDENTIFICATION OF OUTLIERS.....	25
DERIVED, TRANSFORMED AND MISSING DATA.....	26
POPULATION MODELING.....	27
MODEL QUALIFICATION.....	27
ESTIMATION METHOD.....	27
STRUCTURAL MODEL SELECTION.....	28
Statistical Model Selection.....	29
Covariate Analysis.....	30
Final PK Model on Index Dataset.....	31
FINAL PK MODEL AND EFFECT OF CO-MEDICATIONS.....	31
Model-Based Simulations.....	32
RESULTS.....	32
Demographic and Baseline Characteristics.....	32
FIRM'S ANALYSIS.....	34
ACTIVE MOIETY INDEX DATA SET.....	34
MODEL QUALIFICATION.....	36
EFFECT OF CO-MEDICATIONS.....	38
FINAL PK MODEL OF THE ACTIVE MOIETY - FULL DATASET.....	38
SIMULATIONS.....	41
RISPERIDONE INDEX DATA SET.....	44

Pharmacokinetic Parameters.....	44
COVARIATE SELECTION – INDEX DATASET	46
Model Qualification.....	48
Effect of Co-Medications	50
FINAL PK MODEL OF RISPERIDONE – FULL DATASET	51
FDA ANALYSIS	58
BASE MODEL -ACTIVE-MOIETY	58
FINAL MODEL ACTIVE MOIETY	59
BASE MODEL -RISPERIDONE.....	61
DISCUSSION	63
FIRM'S PROPOSED LABEL.....	64
FDA LABEL	66
SIGNATURES	69

EXECUTIVE SUMMARY

A study was done combining data from several centers in children and adolescents ages 5-18 yrs to determine if the pharmacokinetics were similar or different from that previously observed in adults. The study data from 3 study sites were analyzed by mixed effects modeling to identify any important covariates which impacted Risperidone pharmacokinetics in adolescents. These results were contrasted with those in adults. The study results indicated that weight normalized mean exposure, based upon trough levels prior to dosing, in children, adolescents and adults was comparable. Pharmacokinetics of the active moiety (risperidone + 9-hydroxy risperidone) and risperidone alone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight. The recommended dose for schizophrenia is ~~1 mg~~ QD while that for bipolar should be initiated at 0.5 mg QD with adjustments of 0.5-1 mg/day as tolerated to a recommended dose of 2.5 mg/day. Based on the final results and the lack of a dose response no dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years).

b(4)

INTRODUCTION

Risperidone is completely absorbed after oral administration, reaching peak plasma concentrations within 1 to 2 hours. The absorption is not affected by food and thus risperidone can be given with or without meals. Risperidone is metabolized by CYP2D6 to 9-hydroxy-risperidone, which has a similar pharmacological activity as risperidone. Risperidone plus 9-hydroxy-risperidone form the active antipsychotic fraction (active moiety). Another metabolic pathway of risperidone is N-dealkylation. Risperidone is subject to CYP2D6-mediated genetic polymorphism. Extensive metabolizers (EMs) convert risperidone rapidly into 9-hydroxy-risperidone, while poor metabolizers (PMs) convert it much more slowly. EMs, therefore, have

lower risperidone and higher 9-hydroxy-risperidone concentrations than PMs. The PK of the active moiety, after single and multiple doses are similar in EMs and PMs of CYP2D6.

After oral administration to psychotic patients, risperidone is eliminated with a half-life of about 3 hours. The elimination half-life of 9-hydroxy-risperidone and of the active moiety is 24 hours. Steady-state of risperidone is reached within 1 day in most patients. Steady state of 9-hydroxy-risperidone is reached within 4-5 days of dosing. Risperidone plasma concentrations are dose-proportional in the dose-range of 1 to 16 mg daily (0.5 to 8 mg b.i.d.).

Risperidone is rapidly distributed. The volume of distribution is 1 to 2 L/kg. In plasma, risperidone is bound to albumin and alpha1-acid glycoprotein. The plasma protein binding of risperidone is 88%, while that of 9-hydroxy-risperidone is 77%.

SUMMARY

Based on the current population PK analysis, pharmacokinetics of the active moiety and risperidone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight. Based on the final results of the covariate analysis for the active moiety, no dose adjustments based on body weight are warranted in children and adolescents (between 10-17 years).

COMMENTS TO MEDICAL REVIEWER

1. Pharmacokinetics of the active moiety (risperidone + 9-hydroxy risperidone) and risperidone alone are comparable in children (less than 12 years), adolescents (12 to 17 years) and adults, after correction for body weight.
2. Because of the lack of a dose response fixed dosing regimens are acceptable to OCP for schizophrenia or for bipolar I disorder.

OBJECTIVE OF THE ANALYSIS

The objectives of the population PK analysis of risperidone and the active moiety were:

- To get estimates of the typical PK parameters of risperidone and the active moiety in the target populations and of their inter- and intraindividual variability;
- To evaluate the effect of patients' demographic characteristics and other covariates on the PK of risperidone and the active moiety;
- To compare the PK of risperidone and the active moiety between children/adolescents and adults.

METHODS

Overview of Study Designs

The current analysis consisted of modeling the PK of risperidone and of the active moiety separately, in a pooled database including children, adolescents and adults with bipolar I disorder or schizophrenia following oral administration of risperidone. The following studies were used:

STUDY #	STUDY	DEMOGRAPHICS	FORMULATION
1	RIS -BIM-301	CHILDREN AND ADOLESCENTS (10-17 YRS)	0.25MG-4 MG TABLETS
2	RIS-USA-231	ADOLESCENTS (13-17 YRS)	0.1 MG/L AND 1.0 MG/ML SOLN
3	RIS-USA-160	CHILDREN AND ADOLESCENTS (5 to <12 YRS) (12 to < 18 YRS)	0.01 TO 0.08 mg/kg TABLETS
4	RIS-USA-239	ADULTS	TABLET
5	RIS-IND-2	ADULTS	TABLET
6	RIS-IND-25	ADULTS	TABLET
7	RIS-P01-103	ADULTS	TABLET
8	RIS-RSA-5	ADULTS	TABLET
9	R076477-SCH-102	ADULTS	TABLET

b(4)

b(4)

The 1-mg/mL oral solution is bioequivalent to the marketed 1-mg tablet. The marketed 1-mg tablet, when given as 2x1 mg or 4x1 mg tablets, is bioequivalent to marketed 2-mg and 4-mg risperidone tablets. Bioequivalence was also shown between the 0.5-mg research tablet (when given as 2x0.5 mg tablets) and the 1-mg marketed risperidone tablet.

ASSAY VALIDATION

ANALYTICAL

Two moieties were analyzed Risperidone and 9-hydroxy-risperidone.

Risperidone and active moiety (Risperidone + 9-hydroxy-risperidone) levels were reported.



b(4)

Study RIS-BIM-301- (STUDY 1) CHILDREN AND ADOLESCENTS (10-17 YEARS)

Objective: assess the efficacy, safety, tolerability and PK of two dosage ranges of risperidone monotherapy (0.5 to 2.5 mg/day and 3 to 6 mg/day) versus placebo, and explore the PK/PD relationship to efficacy and safety.

Population: 169 enrolled (58 placebo and 101 risperidone) children and adolescents (10-17 years) with a DSM-IV diagnosis of Bipolar I disorder experiencing a manic or mixed episode (Young Mania Rating Scale ≥ 20).

Design: randomized, placebo-controlled, double-blind, 3-arm, multicenter Phase 3 study. The study was composed of a screening phase (with a

possible washout period) and a 3-week double blind treatment phase. Subjects were randomized to receive 1 of 3 oral treatments: placebo tablets, risperidone tablets 0.5 to 2.5 mg (Dosage Group A), or risperidone tablets 3 to 6 mg (Dosage Group B). Study medication was dosed once daily and titrated to reach the minimum of their assigned target dosage of 0.5 mg/day (Dosage Group A) and 3 mg/day (Dosage Group B) by Day 7. Further increases in the maximally tolerated dosage were to be made by Day 10. After Day 10, adjustments to the dosage were not to be made and subjects were to be maintained within the target dosage (0.5-2.5 mg/day for Dosage Group A and 3-6 mg/day for Dosage Group B) range from Days 10 to 21.

Plasma concentrations of the active moiety were calculated as the sum of risperidone and 9-hydroxy-risperidone. The relationship between the predose steady-state plasma concentrations of the active moiety and risperidone were used to determine the attainment of steady-state.

Plasma samples were taken on Day 14, one sample before drug intake and one at least 1 hour after. On Day 7 and on Day 21, one sample was collected before study drug intake.

(Day 21) and its efficacy parameter YMRS and safety parameters (QTcLD and SAS) was explored graphically via scatter plots.

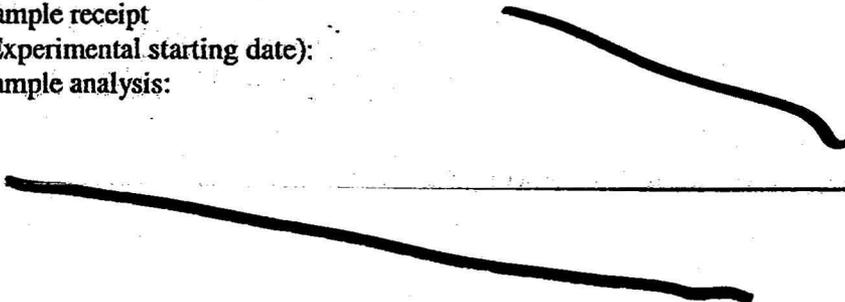
Subjects who gave permission for DNA sample collection were genotyped for CYP2D6. At Day 7, the daily dose of risperidone was 0.5 mg and 2.0 mg in the Dosage Group A and B, respectively. At Day 14 and 21, the median daily dose of risperidone was 2.5 mg/day (range: 0.5-2.5 mg/day) for Dosage Group A and 5.0-6.0 mg/day (range 3.0-6.0 mg/day) in Dosage Group B.

STUDY RIS USA 301-STUDY 1
First Sampling Date: January 6, 2004

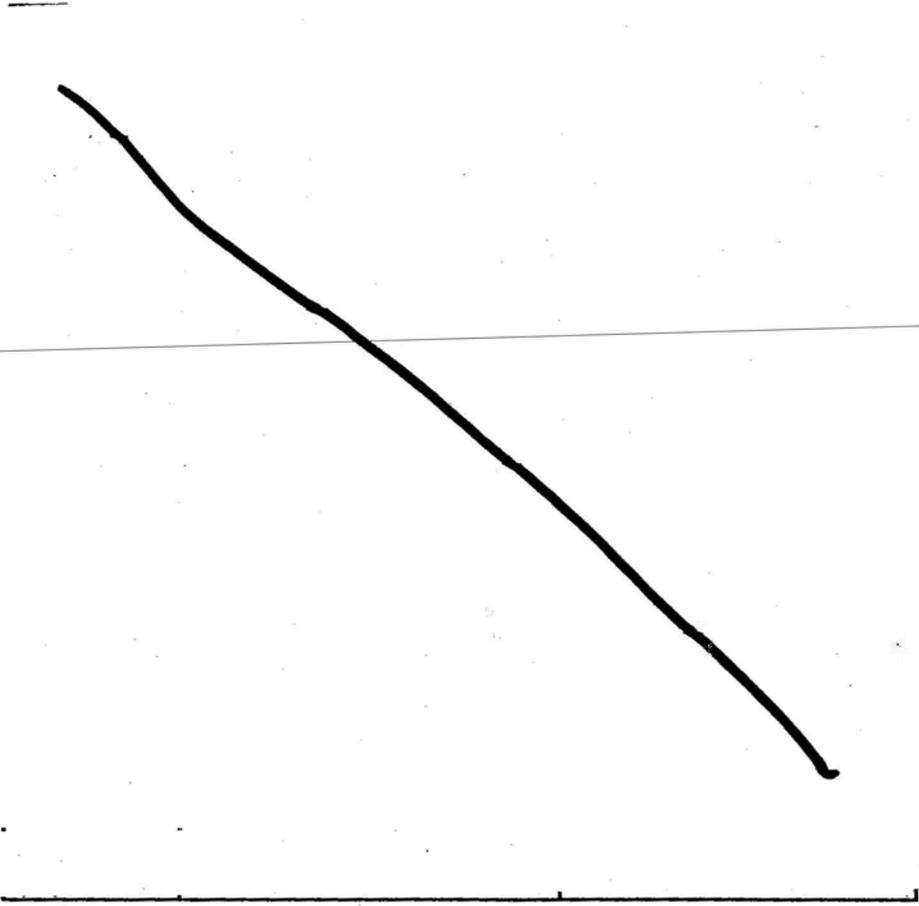
Study dates:

starting date completion date

Sample receipt
(Experimental starting date):
Sample analysis:



b(4)



b(4)

STUDY RIS-USA-231 (STUDY 2) ADOLESCENTS

Objective: assess the efficacy, safety, tolerability and PK of risperidone during 8 weeks randomized, double-blind, parallel-group, multicenter study in adolescents (aged 13-17 years) with schizophrenia and suffering from an acute episode of treatment and to explore the PK/PD relationship to efficacy and safety.

Population: 279 enrolled adolescents with schizophrenia.

Design: randomized, double-blind, parallel-group, multicenter Phase 3 study.

Subjects were randomized to receive 1 of 2 risperidone treatments: low dose (<50 kg: 0.007-0.012 mg/kg/day; >50 kg: 0.35-0.6 mg/day) and high dose (<50 kg: 0.07-0.12 mg/kg/day; >50 kg: 3.5-6 mg/day) (dose range: post protocol amendment 3). Study medication was provided as an oral solution containing risperidone at concentrations of either 0.1 mg/mL or 1 mg/mL. Study

medication was dosed once daily (o.d.) or twice daily (b.i.d.) and titrated to the target dosage by Day 12.

The relationship between the predose steady-state plasma concentrations of the active moiety (Day 56) and selected efficacy parameters (PANSS and CGI) and safety parameters (QTcLD and SAS) was explored graphically via scatter plots.

~~Subjects who gave permission for DNA sample collection were genotyped for CYP2D6.~~

Limited blood samples were collected at Days 28 (pre- and post dose) and 56 (predose) for the determination of plasma concentrations of risperidone and 9-hydroxy-risperidone in patients treated with risperidone. Plasma concentrations of the active moiety were calculated as the sum of risperidone and 9-hydroxy-risperidone. Post dose samples were collected between 1-2 hours after drug intake; only predose samples collected between 6-48 hours (b.i.d. regimen) or 8-36 hours (o.d. regimen) were included in the analysis.

There were two additional adult studies that were used to compare with the adolescent and child data. These were subjects with bipolar disorder (Studies RIS-USA-23928 and RIS-IND-229) with sparse sampling.

Analytical

Study BIM-231-STUDY 2

First Sampling Date: May 14, 2001

Study dates:

starting date

completion date

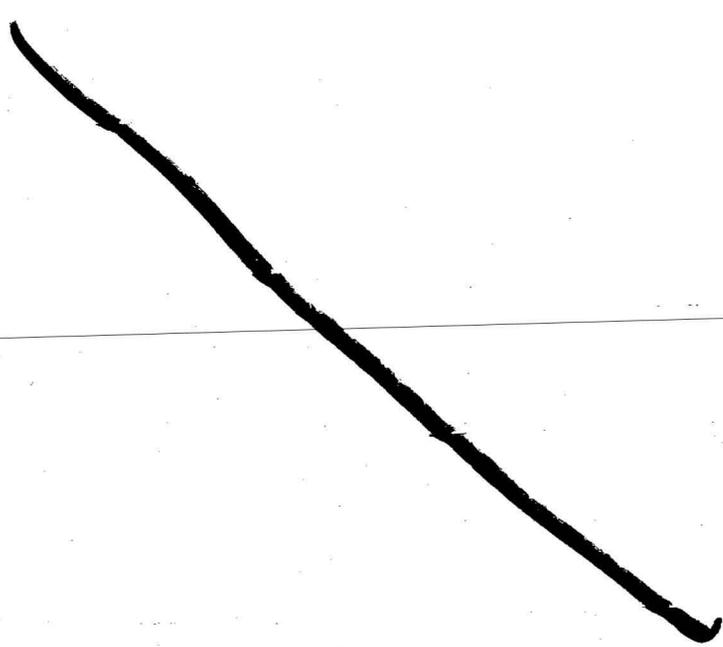
Sample receipt

(Experimental starting date):

Sample analysis:

[Large handwritten scribble covering the study dates section]

b(4)



b(4)

STUDY RIS-USA-160 (STUDY 3)- CHILDREN AND ADOLESCENTS

Objective: determine the PK and safety of risperidone (0.01 to 0.08 mg/kg/day, b.i.d. dosing), 9-hydroxy-risperidone and of the active moiety at steady state.

Population: 24 children and adolescents (aged 5 years to less than 18 years).

Design: open-label, multicenter, Phase 1 study with 2 periods: screening/run-in (7 to 30 Days) i.e., a maintenance dose of risperidone and a single day for PK monitoring and check-out.

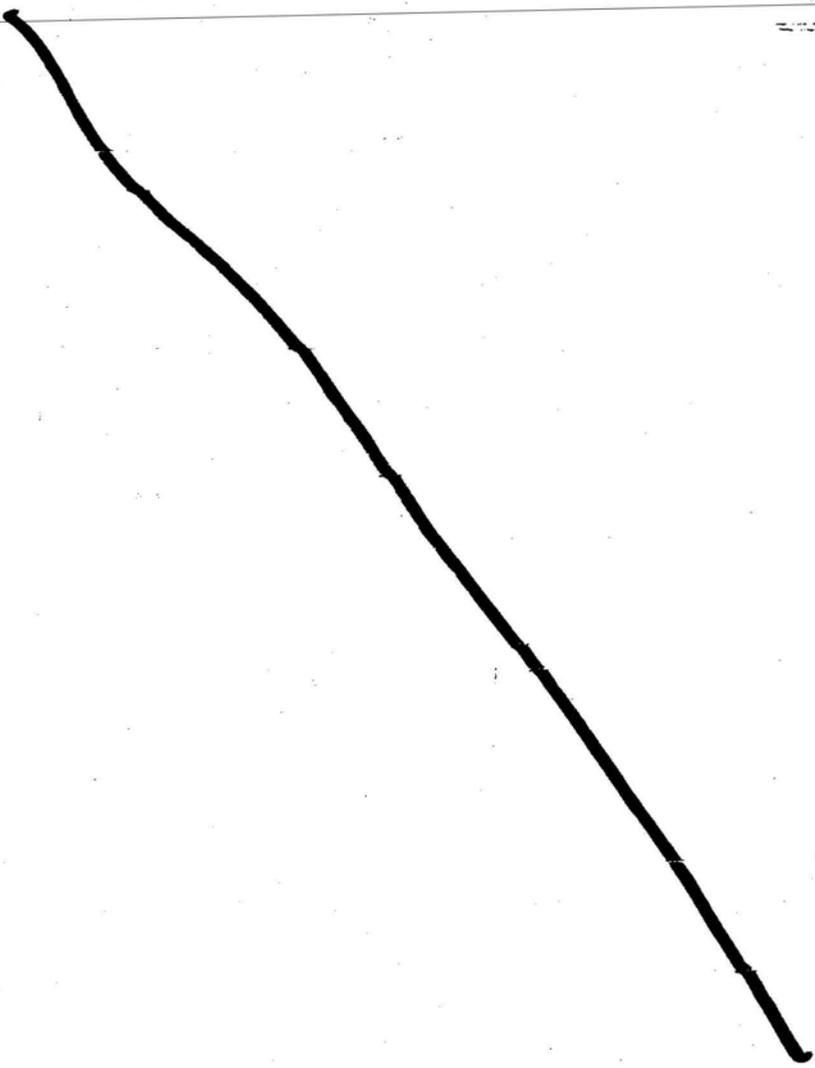
The subjects were divided into 2 groups: 12 children (aged 6-11 years and weighing between 20-61 kg) and 12 adolescents (aged 12-16 years and weighing between 33-92 kg). A complete urinary output was also collected: from 0 to 6 hours, and from 6 to 12 hours after dosing. Subjects were phenotyped for CYP2D6 using the risperidone metabolic ratio (i.e., $AUC_{TSS,risperidone}/AUC_{TSS,9-hydroxy-risperidone}$), and genotyped for CYP2D6. Subjects with a risperidone metabolic ratio higher than 1 were categorized as PMs for CYP2D6, and subjects with a ratio of less than 1 as EMs for CYP2D6. The daily dose of risperidone ranged between 0.25 - 1.5 mg b.i.d. for children, and between 0.75 - 1.75 mg b.i.d. for adolescents, or expressed per kg body weight equivalent to a range of 0.024 - 0.074 mg/kg/day (mean 0.049 mg/kg/day) for children, and 0.016 - 0.076 mg/kg/day (mean 0.041 mg/kg/day) for adolescents.

Blood samples were collected immediately before (0 hour), and 2, 4, 8, and 12 hours after the morning dose on the PK monitoring day.

ANALYTICAL
STUDY RIS-USA-160-STUDY 3

starting date

completion date



b(4)

STUDY RIS-USA-239-(STUDY 4)-ADULTS

Objective: assess the efficacy, safety, tolerability and PK of dosage range (1

to 6 mg/day) of risperidone compared to placebo during 3 weeks of treatment, and explore the PK/PD relationship.

Population: 259 treated (125 placebo, 134 risperidone) adult patients with Bipolar I Disorder who are suffering a manic episode.

Design: randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 3 study. Flexible doses of risperidone (1 to 6 mg/day) or placebo were administered. Patients were titrated and evening doses were adjusted through the end of treatment period. Only subjects randomized to the risperidone treatment group were taken into account in the current analysis.

ANALYTICAL

STUDY RIS-USA-239-STUDY 4

Trial dates: Start: 29 November 2000 | end: 23 May 2002

starting date

completion date

Sample receipt:

Sample analysis:

b(4)

STUDY RIS-IND-2 (STUDY 5) ADULTS

Objective: To assess the efficacy and safety of risperidone dosage range (1 to 6 mg/day) compared with placebo during 3 weeks of treatment in subjects with Bipolar I disorder suffering a manic or mixed episode. The primary efficacy measure was the change in mean YMRS total score from baseline to endpoint.

Population: 290 treated (144 placebo, 146 risperidone) adult patients with Bipolar I Disorder who are suffering a manic or mixed episode.

Design: randomized, placebo-controlled, double-blind, parallel-group, multicenter Phase 3 study. A flexible doses of risperidone (1 to 6 mg/day) or placebo were administered, after dose escalation. Randomized patients were stratified by the presence or absence of psychotic features at baseline and by center. Following randomization and the initiation of double-blind study drug therapy, a minimum of 7 full days of inpatient hospitalization was required. Subjects assigned to the risperidone treatment group received a single 3-mg dose on Day 1.

Table 3-3: Dosing Schedule for the Double-Blind Phase (RIS-IND-2)

Day	Placebo (mg/day)	Risperidone (mg/day)
1	0	3
2	0	2-4
3	0	1-5
4-21	0	1-6

Sampling

Sparse PK samples were taken on week 1 and week 3. All blood for PK samples were drawn immediately before the intake of trial medication (predose), except that on Day 7 a second sample was to be drawn post-dose at least 1 hour after the first withdrawal.

ANALYTICAL

RIS-IND-2: STUDY=5

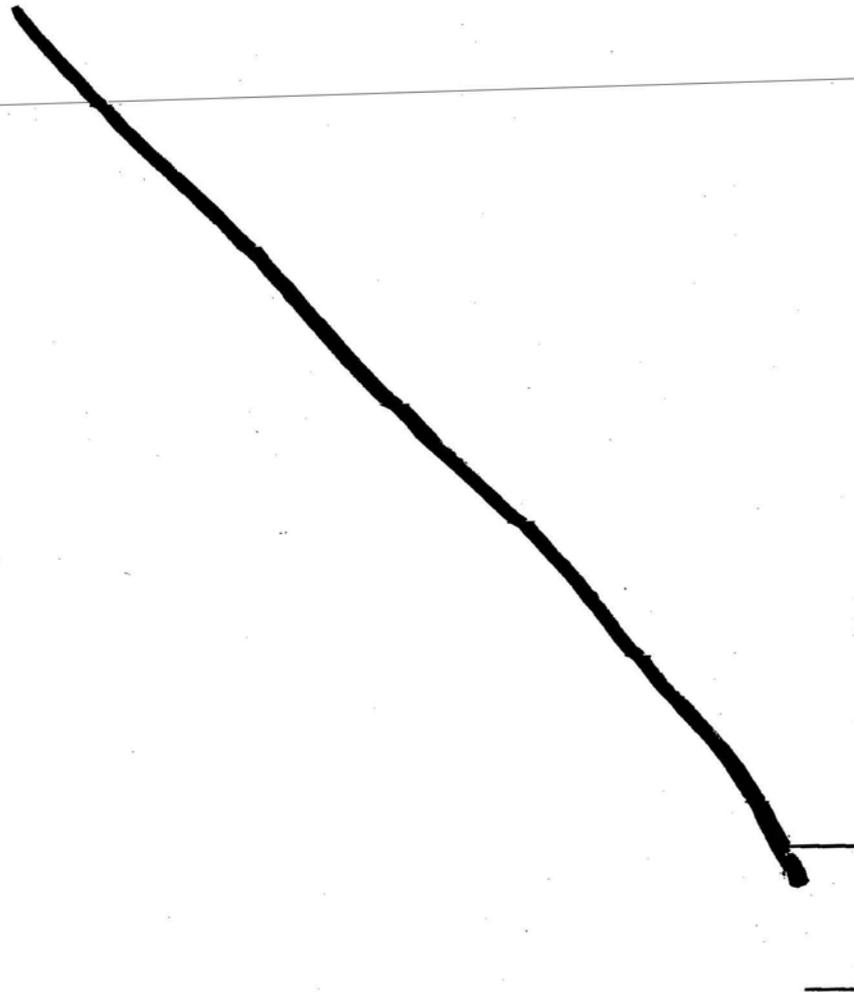
Trial dates: Start: 12 Mar 2001 | end: 24 Dec 2001

Study dates

Starting date Completion date

Sample receipt: [REDACTED]

Sample analysis: [REDACTED]



b(4)

STUDY RIS-IND25-(STUDY 6)- ADULTS

Objective: To determine the oral bioequivalence of a single dose of 2 mg risperidone given as a [REDACTED] tablet (F556) with that of the 2-mg conventional RISPERDAL tablet (F37) in healthy volunteers.

b(4)

The primary objective was to show bioequivalence with respect to

risperidone and active moiety. Additionally, the bioavailability of 9-hydroxyrisperidone was compared.

TRIAL DESIGN AND PLAN

This was an open-label, randomized, phase I trial with a 2-treatment, 2-period crossover design balanced for residual effect in healthy subjects.

In total, 40 subjects (22M/18F) were to receive a single dose of 2 mg risperidone as a [redacted] tablet (Treatment A) and as a RISPERDAL tablet (Treatment B). A washout period of at least 10 days was foreseen between both treatments (max. 3 weeks). Each intake was to be followed by a 96-hour evaluation period for pharmacokinetics and safety assessments.

b(4)

DOSING AND PK SAMPLING

Table 3-1: Flowchart

Trial day ^{a)}	Time	Drug intake ^{b)}	PK blood sample	Other
Pretrial day (Screening)				Physical examination, laboratory safety, ECG, BP, HR, pregnancy test
Day -1 (Baseline)				ECG, HR, BP, drug screen, urine pregnancy test
Day 1	predose		X	HR, BP, Laboratory safety ^{c)}
	0 h	X		
	0.25 h		X	
	0.5 h		X	
	1 h		X	
	1.5 h		X	
	2 h		X	
	3 h		X	
	4 h		X	HR, BP, Standard meal ^{d)}
	5 h		X	
	6 h		X	
	8 h		X	HR, BP
12 h		X		
	16 h		X	
Day 2	24 h		X	HR, BP
	32 h		X	
Day 3	48 h		X	
Day 4	72 h		X	
Day 5 (end of the session)	96 h		X	Physical examination, laboratory safety, ECG, BP, HR ^{e)}

a) In each session, Treatment A or B was administered according to the randomization scheme.

b) Treatment A: single oral administration of a 2-mg risperidone [redacted] tablet.
Treatment B: single oral administration of a 2-mg risperidone RISPERDAL tablet.

c) Laboratory safety sample only predose Session 1.

d) All meals served at the trial centre were scheduled and standardized on Day 1. However, only the first meal following drug intake is mentioned in the flowchart. →

e) All these assessments were performed at the end of the trial only.

b(4)

ANALYTICAL

RIS-IND-25: (STUDY 6)

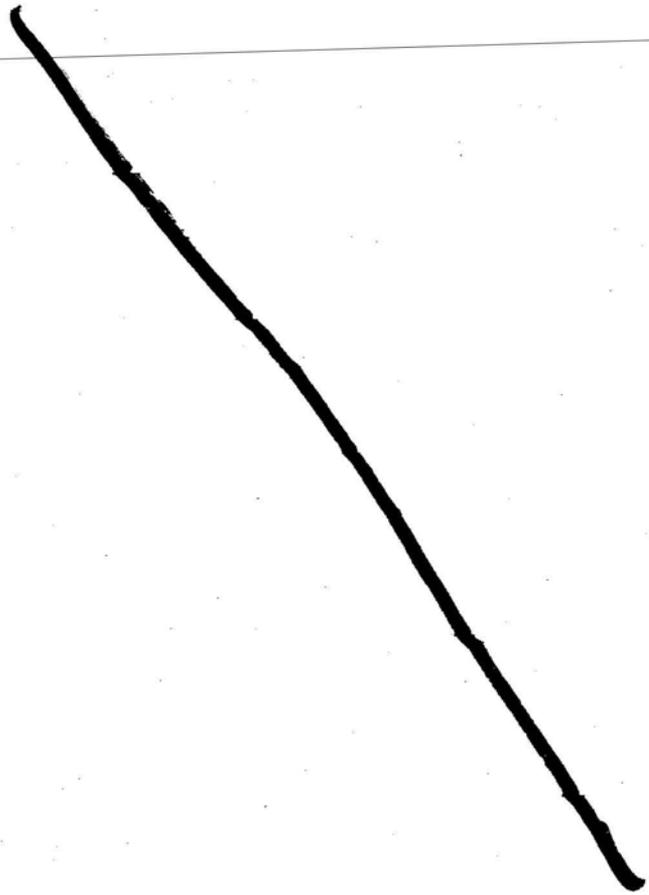
Trial dates: Start: 07 November 2000 | end: 19 January 2001

Sample receipt:

Analytical Study Plan:

Sample analysis:

2
1
1



b(4)

STUDY RIS-P01-103-(STUDY 7)- ADULTS

Objective: The primary objective of this study, was to demonstrate the bioequivalence, with respect to risperidone and its active moiety, of a single oral dose of risperidone given as a 4-mg orally-disintegrating tablet and as a 4-mg conventional RISPERDAL tablet.

Study Design

This was a single-center, Phase 1, open, randomized, 2-way crossover bioequivalence study in 40 subjects with schizophrenia or schizoaffective disorder. The study consisted of 2 treatment periods, 5 days per period, separated by a washout period of at least 10 days between administration of study drug on Day 1 of Period 1 and administration of study drug on Day 1 of Period 2. The study duration was approximately 6 weeks (including the screening period). Subjects remained in the study facility for approximately 18 days.

DOSING AND PK SAMPLING

APPEARS THIS WAY ON ORIGINAL

Table 1. Time and event schedule for study RIS-PO1-RO3

(Study RIS-P01-103)				
Study Day	Time	Drug Intake ^a	PK Blood Sampling	Other Procedures ^b
Prestudy (screening)	≤3 weeks before Day 1 of Period 1			Informed consent signed; inclusion/exclusion criteria; record body weight, height, demographic information; physical examination; psychiatric/medical history; smoking history; blood samples collected for hematology and serum chemistry; urine sample for urinalysis; breath alcohol test; serum pregnancy test for women; urine drug test; ECG; BP, HR recorded
Day -3				Admission to study center
Day -1 or Day 1 of Period 1, predose				Breath alcohol test; urine drug test; urine pregnancy test for women
The procedures below occur in both Period 1 and Period 2 ^a :				
Day 1	predose		X	Start of semi-recumbent position
	0 h	X ^c		
	0.25 h		X	
	0.5 h		X	
	0.75 h		X	
	1 h		X	
	1.5 h		X	
	2 h		X	End of semi-recumbent position.
	3 h		X	
	4 h		X	Standard meal served ^d
	5 h		X	
	6 h		X	
	8 h		X	
	12 h		X	
Day 2	16 h		X	
	24 h		X	
	36 h		X	
Day 3	48 h		X	
Day 4	72 h		X	
Day 5 of Period 1	96 h		X	
End of Study				
End of Study (Day 5 of Period 2 or Early Termination)	96 h		X	Physical Examination; blood samples collected for hematology and serum chemistry; urine sample collected for urinalysis; ECG; BP and HR recorded; discharge

^a A 10-day washout period separated the dose of study medication on Day 1 of Period 1 from the dose administered on Day 1 of Period 2.

^b Adverse events were recorded and monitored beginning with the first study-related procedure through the posttreatment procedures at the end of the study. Concomitant therapies were recorded throughout the study.

^c One treatment was given in each period, either Treatment A (1 oral conventional RISPERDAL 4-mg tablet) or Treatment B (1 risperidone 4-mg orally-disintegrating tablet). Subjects fasted for 10 hours before drug administration and continued fasting until 4 hours after dose administration. They refrained from water intake for 2 hours before until 2 hours after dose administration.

^d All meals served on Day 1 were scheduled and standardized. Only the first meal after drug administration is cited.

ANALYTICAL

RIS-P01-103: STU=7
DATE STUDY INITIATED:
21 June 2003
DATE STUDY COMPLETED:
21 July 2003

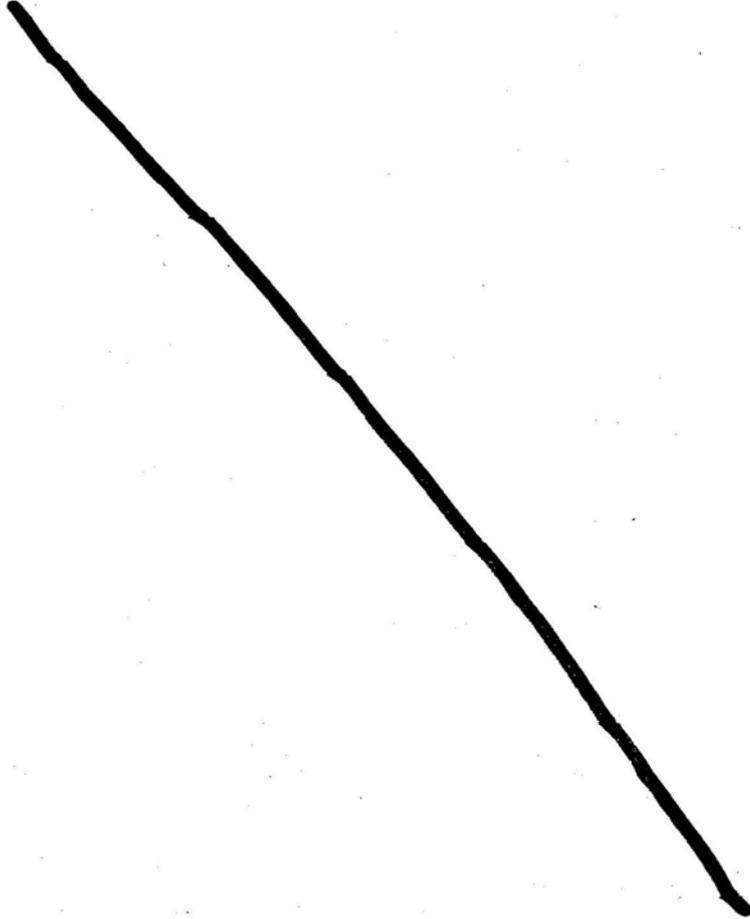
Starting date

Completion date

Sample receipt:

Analytical Protocol:

Experiment (sample analysis):



b(4)

STUDY RSA-5-(STUDY 8)- ADULTS

OBJECTIVE:

The primary objective of this study was to demonstrate the bioequivalence with respect to risperidone and active moiety between a single oral dose of 4 mg risperidone given as a 4 mg tablet manufactured [REDACTED] and as a 4 mg RISPERDAL_v currently marketed tablet.

b(4)

Study Design

This was a Phase I, open, randomized, 2-way cross-over bioequivalence study in 36 subjects with schizophrenia or schizoaffective disorder. The subjects received in a randomized manner a single oral dose of 4 mg risperidone on two occasions:

- Treatment A: RISPERDAL_v marketed tablet;
- Treatment B: tablet manufactured [REDACTED]

[REDACTED] The pharmacokinetics of risperidone were assessed up to 96 hours post dosing. The wash-out period between treatments was at least 10 days. The duration of the study was approximately 6 weeks

b(4)

DOSING AND PK SAMPLING

APPEARS THIS WAY ON ORIGINAL



b(4)

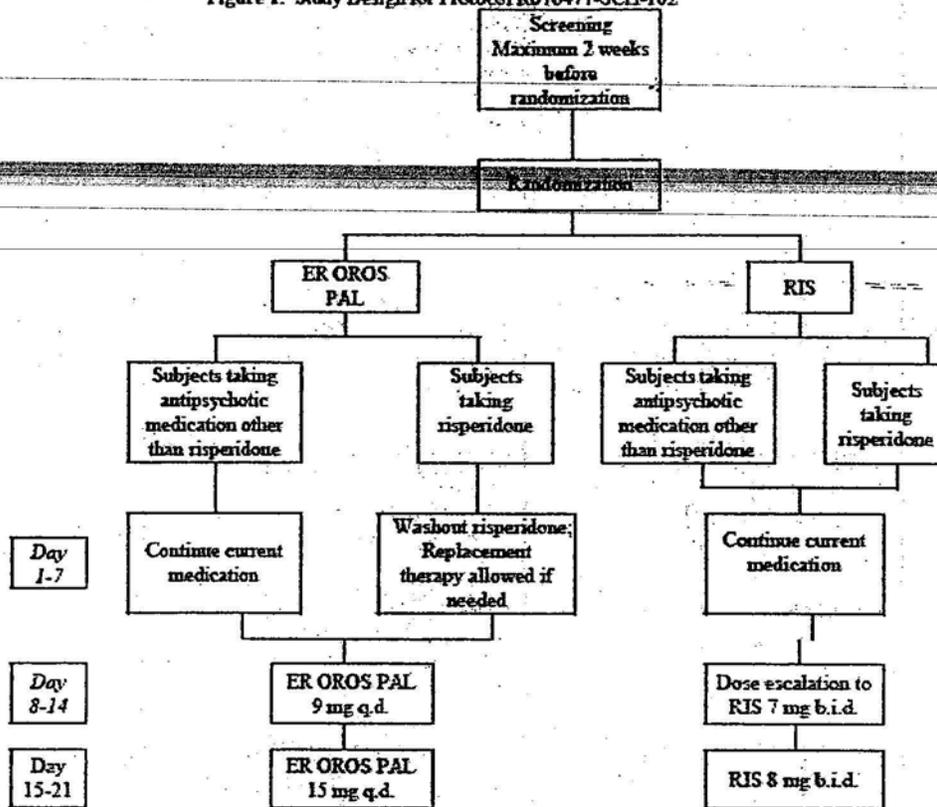
STUDY R076477-SCH-102 STUDY 9- ADULTS

OBJECTIVE:

The primary objectives of the study were to compare the steady-state pharmacokinetics of paliperidone after oral administration of 15 mg ER OROS paliperidone once daily with the steady-state pharmacokinetics of paliperidone after oral administration of 8 mg IR risperidone twice daily; and to explore the dose-proportionality of 9 mg and 15 mg ER OROS paliperidone.

Study Design

Figure 1: Study Design for Protocol R076477-SCH-102



A dose of 15 mg ER OROS paliperidone once daily was chosen because this is the highest dose of ER OROS paliperidone that is proposed for use in the Phase 3 studies. The dose of risperidone was chosen because 8 mg twice daily is the highest registered dose of risperidone. Study medication was administered after a (high-fat) breakfast as in a previous study the exposure to paliperidone increased by circa 10% after intake of food. Food does not affect the pharmacokinetics of risperidone. The study was done in 17 subjects (17 M/2F)

DOSING AND PK SAMPLING

APPEARS THIS WAY ON ORIGINAL

- Subjects randomly assigned to the risperidone treatment group who were taking prestudy antipsychotics other than risperidone received a 1-mg risperidone tablet every 12 hours on Day 8. On Days 9 through 14, doses of risperidone were increased by 1 mg every 12 hours daily, so that on Day 14, subjects received 7 mg every 12 hours as shown in Table 2.

Table 2: Dosage Escalation (Prestudy Other Antipsychotics)
(Study R076477-SCH-102)

Day	Dosing Regimen	Total Daily Dose
8	1 mg b.i.d.	2 mg
9	2 mg b.i.d.	4 mg
10	3 mg b.i.d.	6 mg
11	4 mg b.i.d.	8 mg
12	5 mg b.i.d.	10 mg
13	6 mg b.i.d.	12 mg
14	7 mg b.i.d.	14 mg

- For subjects randomly assigned to the risperidone treatment group taking prestudy risperidone, the dose was divided into twice daily doses (every 12 hours) starting on Day 8. Subjects received escalating doses of risperidone (according to Table 3) from at least 3 mg every 12 hours on Day 8 up to 7 mg every 12 hours on Day 14. Study drug was given in equal doses every 12 hours, as 1-mg tablets.

Table 3: Dosage Escalation (Prestudy Risperidone)
(Study R076477-SCH-102)

Day	Dosing Regimen	Total Daily Dose
8	3 mg b.i.d.	6 mg
9	3 mg b.i.d.	6 mg
10	3 mg b.i.d.	6 mg
11	4 mg b.i.d.	8 mg
12	5 mg b.i.d.	10 mg
13	6 mg b.i.d.	12 mg
14	7 mg b.i.d.	14 mg

(e.g., a subject is on a prestudy risperidone daily dose of 6 mg; subject will receive doses, as above, from Days 8 through 14.)

- All subjects randomly assigned to the risperidone treatment group received 8 mg risperidone (2 tablets of 4 mg) every 12 hours on Days 15 to 21.

Drug Sampling

Immediately before dosing on Day 8 (baseline), Days 11 to 14, and Days 18 to 21; at 2, 4, 6, 9, 12, 16, 19, 22, and 24 hours after dosing on Day 14; and at 2, 4, 6, 9, 12, 16, 19, 22, 24, 27, 30, 34, 40, 48, 72, 96, and 120 hours after dosing on Day 21 for subjects receiving ER OROS paliperidone; immediately before the morning dose on Day 8 (baseline) and Days 18 to 21; and at 1, 2, 3, 4, 6, 8, 12, 13, 14, 15, 16, 24, 36, 48, 72, 96, and 120 hours after the morning dose on Day 21 for subjects receiving risperidone.

R076477-SCH-102: STUDY=9

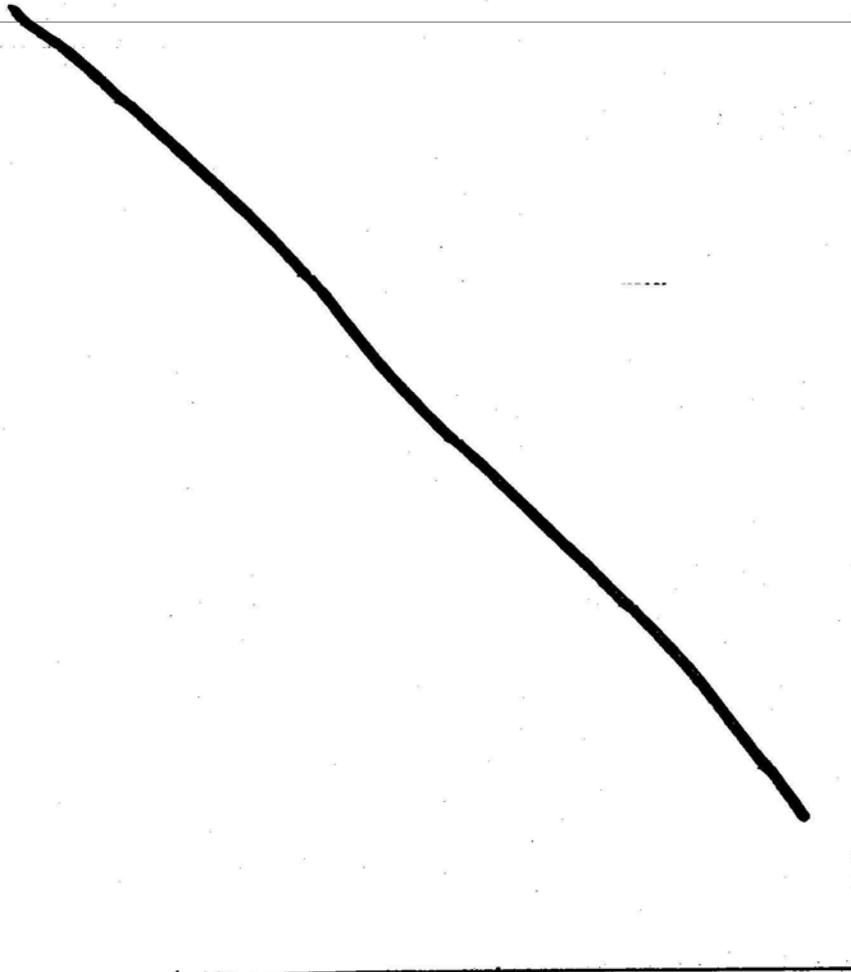
Study dates:

starting date

completion date

Sample receipt:

Sample analysis:



b(4)

PHARMACOKINETIC ANALYSIS

At this stage, the full dataset was split into an index dataset and a qualification dataset: 70% of the subjects of each study were randomly selected for the

index dataset, and the remaining 30% constituted the qualification dataset.

When concomitant medication was present one day before the PK sampling day, the flag for concomitant medication was set to 1 (present) on the PK day even though the concomitant medication was stopped the day before.

Planned Analysis for Risperidone and the Active Moiety

The analysis consisted of two separate population PK analyses, one for risperidone and one for the active moiety in the pool of children, adolescent and adult subjects after oral administration of risperidone. For both risperidone and the active moiety (i.e., sum of the risperidone + 9 hydroxy risperidone plasma levels), the population PK analysis consisted of the following steps:

- An exploratory analysis of concentration-time data and covariates; identification of potential outliers. At this stage, prior PK and other relevant information to support the structural model selection was used, particularly, the results of previous modeling activities.
- Using the index dataset, evaluation of a base and a covariate model (demographics, body size variables, and study).
- Model qualification and model adjustment if needed.
- Estimation of the model on the full dataset and exploration of the effect of concomitant medications.
- Estimation of the final model, with the effect of concomitant medications.

IDENTIFICATION OF OUTLIERS

Data points were considered as potential outliers if they substantially deviated from adjacent points in the concentration-time profiles.

Final outlier identification was performed after selecting a structural model and was based on the graphical exploration of individual and population residuals (weighted and non-weighted). After the model development was complete, the final model was fitted to the entire data set with all excluded outliers in, and the results were compared.

Outlier identification in the sparse data set was performed through a different approach. Initially, posterior predictions were generated for each individual by fitting the structural model to the sparse data. Individual and population residuals (weighted and non-weighted) were analyzed graphically and potential outliers were identified. For individuals with outliers, the observations were plotted against the time since the last dose (one subject per panel) and were superimposed with the corresponding individual and population predictions. The outliers that deviated both in terms of residuals

and observations were finally identified and excluded unless other factors (like co-administration of other drugs) caused the deviation of the concentration from predicted levels.

DERIVED, TRANSFORMED AND MISSING DATA

If a given covariate, either categorical or continuous, was missing in more than 15% of patients, it was omitted from the analysis. If necessary, an analysis of subpopulations was performed. In the current dataset, weight and height were missing for two subjects in Study RIS-USA-239: the missing values were replaced by the median, by sex, in the study population.

For the exploratory data analysis, the creatinine clearance (CRCL) in the populations derivation used the Cockcroft-Gault equation for all subjects, pediatric and adults. The influence of CRCL on the active moiety and risperidone PK was explored in NONMEM using several different values using the Schwartz equation for the pediatric population or the Cockcroft-Gault equation for the adult population. Creatinine clearance (CRCL in mL/min) was derived within the NMTRAN control file.

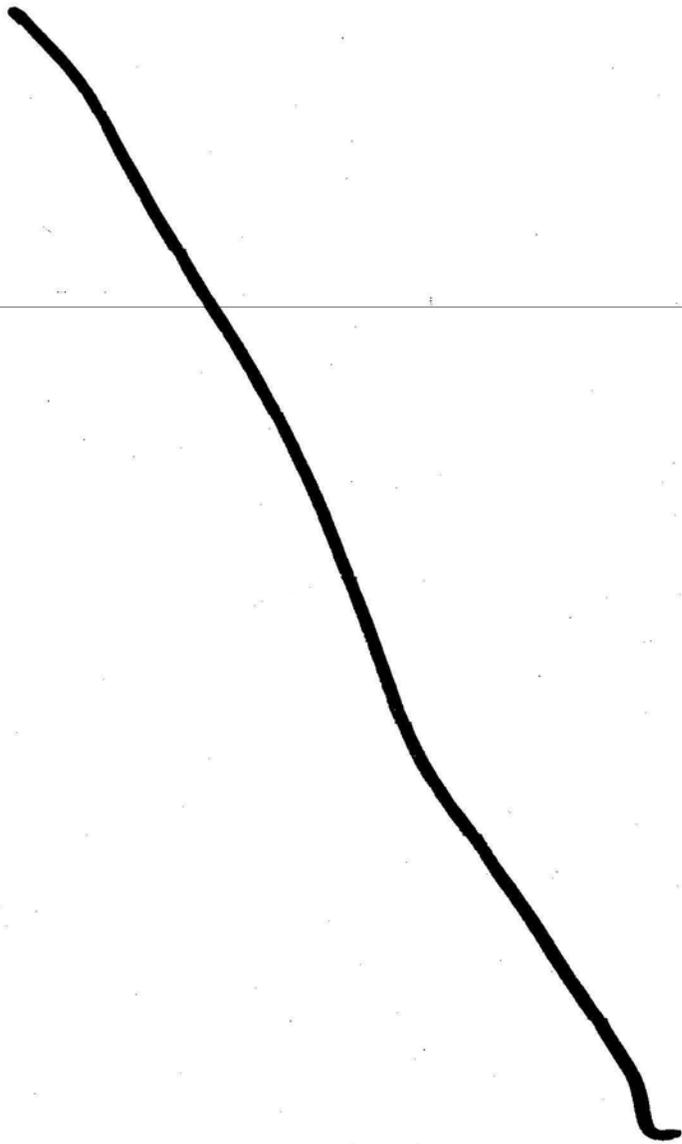
5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



b(4)

b(4)

RESULTS

Demographic and Baseline Characteristics

Table 4 Summary statistics of demographic and baseline characteristics

		Children	Adolesc- ents (12	Adults	All
		(<12)	17)	(>17)	
Age (y)	N	52	252	476	780
	Mean	10.41	15.11	33.73	26.19
	SD	1.48	1.30	13.04	14.00
	Median	10.70	15.20	32.85	18.10
	Min	6.20	12.10	17.10	6.20
Weight (kg)	N	52	252	476	780
	Mean	38.66	60.84	68.62	64.11
	SD	9.92	12.74	18.49	18.07
	Median	38.65	59.75	65.00	62.00
	Min	20.30	30.50	35.00	20.30
Height (cm)	N	52	252	476	780
	Mean	140.38	166.12	167.72	165.38
	SD	9.82	5.69	5.99	11.94
	Median	140.34	166.00	167.60	166.00
	Min	119.00	139.70	134.60	113.00
	Max	156.20	187.96	196.00	196.00

Age Class

		Children	Adolesc- ents (12	Adults	All
		(<12)	17)	(>17)	
Body Surface Area (m ²)	N	52	252	476	780
	Mean	1.22	1.67	1.78	1.71
	SD	0.19	0.21	0.28	0.29
	Median	1.22	1.67	1.74	1.70
	Min	0.80	1.09	1.17	0.80
Serum Creat (µmol/L)	N	52	252	476	780
	Mean	49.04	63.80	76.73	70.71
	SD	8.01	13.14	17.13	17.54
	Median	53.00	62.00	76.00	71.00
	Min	35.00	35.00	35.00	35.00
CRCL (mL/min) using Schwartz formula for actual BSA	N	52	252	476	780
	Mean	101.08	137.59	115.33	121.57
	SD	23.99	33.09	33.67	34.89
	Median	100.58	133.01	112.60	117.60
	Min	53.73	55.05	51.87	51.87
	Max	162.40	254.36	312.24	312.24

		Children	Adolesc- ents (12	Adults	All
		(<12)	17)	(>17)	
Sex	N	34	141	291	469
	%	65.38	55.95	61.76	60.13
Female	N	18	111	183	311
	%	34.62	44.05	38.24	39.87
Race	N	35	198	213	446
	%	67.31	78.57	44.75	57.18
Black	N	14	43	106	163
	%	26.92	17.06	22.27	20.90
Oriental	N	0	2	0	2
	%	0	0.79	0	0.26
Other	N	3	9	157	169
	%	5.77	3.57	32.98	21.67

Table 5 The number of subjects (%) taking the selected concomitant medications included in the population PK analysis.

Concomitant medications	Number of subject (%)
Anticholinergics	56 (7.18)
CYP2D6 inhibitor	22 (2.82)
CYP3A4 inhibitor	16 (2.05)
PGP inhibitor	16 (2.05)
RISPERDAL®	8 (1.03)
PGP inducer	7 (0.90)
CYP3A4 inducer	3 (0.38)
CYP2D6 inducer	1 (0.13)
Methylphenidate	1 (0.13)
Mood stabilizer	1 (0.13)

Due to the small numbers of subjects receiving concomitant CYP3A4 inducers, CYP2D6 inducers, methylphenidate or mood stabilizers was too small to allow analysis.

FIRM'S ANALYSIS

ACTIVE MOIETY INDEX DATA SET

The best model to describe the concentrations of the active moiety was a two-compartment model, with first order input and a lag time.

Allometric scaling factors for clearance and volume and the effect of creatinine clearance (derived with the Schwartz formula for the actual CRCL) were included *a priori* in the model.

To correct for the underprediction at the beginning of the distribution phase observed in the data rich studies, a study effect was tested on the volume of the central compartment. The volume of the central compartment was shown to be lower in Studies RIS-USA-160, RIS-NED-25, RIS-P01-103 and RIS-RSA-5.

Interindividual variability (IIV) was estimated for apparent clearance (CL/F), apparent central volume (V₂/F), K_a and relative bioavailability (F₁). Two separate additive models described the residual error: one for the single dose studies and the other one for the repeated dosing studies. The firm's base model control stream for the active moiety is presented in Appendix I

The population estimates for the base model (using the FO method) are reported in Table 6.

Table 6. Base Model Parameters for Active Moiety After Oral Administration of Risperidone. Results were obtained With the Index Dataset, Using the FO Method

Parameter	Estimates (SE)	95% CI	%CV
CL/F(L/h)= $\theta_1 \cdot (\text{Weight}/70)^{\theta_2} + \theta_3 \cdot \text{CRCL}$		[2.91; 4.81]	
θ_1		[0.007; 0.0214]	
θ_2			
V2/F(L)= $(\theta_4 + \text{STU3} \cdot \theta_5 + \text{FLAG} \cdot \theta_6) \cdot (\text{Weight}/70)$		[135; 171]	
θ_4		[-88.4; -45]	
θ_5		[-70.8; -36.6]	
θ_6			
V3/F(L)= $\theta_7 \cdot (\text{Weight}/70)$		[72.9; 97.9]	
θ_7			
Q/F(L/h)		[1.24; 1.70]	
θ_8			
Ka (h ⁻¹)		[4.20; 6.76]	
θ_9			
ALAG1 (h)		[0.236; 0.244]	
θ_{10}			
F1			
IIV on CL: ω_1^2		[0.0379; 0.0917]	25.5
IIV on V2: ω_2^2		[-0.0181; 0.0391]	10.2
IIV on Ka: ω_3^2		[3.64; 8.90]	250.4
IIV on F1: ω_4^2		[0.127; 0.267]	44.4
Residual variability on log(conc)			
Study 6, 7, 8 : σ^2		[0.0472; 0.0912]	Sd 0.263
Study 1, 2, 3, 4, 5, 9: σ^2		[0.18; 0.305]	Sd 0.490

b(4)

Study: 1=RIS-BM-301, 2=RIS-USA-231, 3=RIS-USA-160, 4=RIS-USA-239, 5=RIS-IND-2,
6=RIS-NED-23, 7=RIS-P01-103, 8=RIS-RSAS, 9=R076477-SCH-102.
CRCL: Creatinine clearance derived using Schwartz' formula for actual BSA
FLAG=1 if study 6, 7 or 8; FLAG=0 otherwise
STU3=1 if study 3; STU3=0 otherwise
IIV is Inter-Individual variability

The population absorption rate constant (i.e., the formation rate constant) is 5.48 h⁻¹; the lag-time is 0.24 h. The IIV estimated for Ka is large, 250% CV. This is likely the result of insufficient information to estimate Ka in sparse sampling studies and may not reflect the true value of between subjects' variability in rate of absorption and/or conversion

COVARIATE SELECTION-INDEX DATA SET

Most of the covariates did not significantly affect the PK:

The following covariates were selected to be evaluated further:

- on apparent clearance:

effect of Study 9 (Study R076477-SCH-102), age and race (Black) and

- on F1: effect of Study 7 (Study RIS-P01-103) and age.

After inclusion of those covariates in a full model, a backward deletion procedure was applied as summarized in Table 7.

Table 7 . Backward Deletion of Covariates - Active Moiety, Index Dataset

Run	Feature removed	MOF	Δ MOF	Conclusion
RUN181	Full model	-1441.013	NA ^a	
RUN182	Study 9 on CL	-1440.729	-0.284	NS ^b , run182: new reference
RUN183	Study 7 on F1	-1432.461	-8.268	p<0.005
RUN184	Age on F1	-1439.701	-1.028	NS, run184: new reference
RUN185	Age on CL	-1431.805	-7.896	p<0.005
RUN186	Race (black) on CL	-1432.706	-1.695	p<0.005
RUN187	Final model	-1439.701		Eta on V2 close to zero, remove from run188
RUN188	Final model 1	-1439.701		

NA^a: Not Applicable

NS^b: Not Significant

MODEL QUALIFICATION

Figure 2 presents the diagnostic plots of the model qualification, PRED vs. DV, IPRED vs. DV, WRES vs. PRED and IRES vs. IPRED.

Figure 3. External Qualification of the Active Moiety Final Model – Qualification Dataset

a. PRED Versus DV

APPEARS THIS WAY ON ORIGINAL

 1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

EFFECT OF CO-MEDICATIONS

The effect of co-medication was assessed using the full dataset. A summary of the univariate analyses of DDI is reported in Table

Table 8. Drug drug interactions –Active moiety

Run	Feature tested	MOF	ΔMOF	Conclusion
RUN221	Reference	-1955.993	NA ^a	Final model on full dataset
RUN222	D6IH on CL	-1957.102	-1.109	NS ^b
RUN223	A4IH on CL	-1957.301	-1.308	NS
RUN224	GPID on CL	-1962.792	-6.799	NS
RUN225	GPIH on CL	-1957.936	-1.943	NS
RUN226	CHOL on CL	-1960.597	-4.604	NS
RUN228	D6IH on F1	-1956.771	-0.778	NS
RUN229	A4IH on F1	-1956.003	-0.01	NS
RUN230	GPID on F1	-1964.679	-8.686	p<0.005
RUN231	GPIH on F1	-1956.103	-0.11	NS
RUN232	CHOL on F1	-1961.003	-5.01	NS
RUN233	RIS on F1	-1957.3	-1.307	NS

^aNot Applicable

^bNS: Not Significant

There were no significant drug drug interactions indicated except for GPID (PGP inducers) however, this PGP inducers effect should be interpreted with caution since only 7 out of 780 patients took this medication.

FINAL PK MODEL OF THE ACTIVE MOIETY – FULL DATASET

After including all significant effects, the final PK parameters of the active moiety were estimated using the FOCE method. To obtain a minimization with a successful covariance step, the model had to be further simplified: the covariance between CL/F and F1 was removed and the random effect on Ka was deleted.

Table 9. Final Model Parameters for Active Moiety After Oral Administration of Risperidone. Results are Obtained With the Full Dataset, Using the FOCE Method

Parameter	Estimates (SE)	95% CI	%CV
CL/F(L/h)=(θ_1 *(Weight/70) ^{0.75} + θ_6 *CRCL + θ_9 *BLAC)*(Age/18.1)** θ_{10}		[3.77; 5.57]	
θ_1		[0.00172; 0.01454]	
θ_6		[0.521; 1.231]	
θ_9		[-0.242; -0.122]	
θ_{10}			
V2/F (L)=(θ_2 + FLAG* θ_8) *(Weight/70)		[122; 150]	
θ_2		[-53.7; -27.1]	
θ_8			
V3/F (L)= θ_3 *(Weight/70)		[70.7; 102.1]	
θ_3			
Q/F (L/h)		[1.15; 1.53]	
θ_4			
Ka (h ⁻¹)		[1.91; 2.87]	
θ_5			
ALAG1 (h)		[0.230; 0.240]	
θ_7			
F1=1 + θ_{11} *GPID		[-0.751; -0.183]	
θ_{11}			
IIV on CL: ω_1^2		[0.0273; 0.0897]	24.2
IIV on F1: ω_2^2		[0.042; 0.168]	32.4
IOV on F		[0.069; 0.243]	39.5
Residual variability on log(conc)			
Study 6, 7 or 8 : σ_1^2		[0.22; 0.32]	Sd 0.520
Study 1, 2, 3, 4, 5 or 9: σ_2^2		[0.114; 0.258]	Sd 0.431

Study: 1=RIS-BIM-301, 2=RIS-USA-231, 3=RIS-USA-160, 4=RIS-USA-239, 5=RIS-IND-2,
6=RIS-NED-25, 7=RIS-P01-103, 8=RIS-RSA5, 9=R076477-SCH-102.

CRCL: Creatinine clearance derived using Schwartz' formula for actual BSA

BLAC=1 if race is black; BLAC=0 otherwise

FLAG=1 if study 3, 6, 7 or 8; FLAG=0 otherwise

GPID=1 if concomitant treatment with PGP Inducer; GPID=0 otherwise

IIV is Inter-Individual variability

IOV is Inter-occasion variability defined by weeks of treatment (at WEEK=0; WEEK=1; WEEK=2;
WEEK=3; WEEK=4; WEEK>5)

b(4)

Figure 4. Goodness-of-Fits Plots for the Active Moiety Final Model – Full Dataset, Adolescent Only

APPEARS THIS WAY ON ORIGINAL

1 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

The equation to predict the apparent clearance of the active moiety is:

~~_____~~

b(4)

For a non-Black (BLAC=0) typical patient, with weight 62 kg, aged 18.1 years, with a creatinine clearance 117.6 mL/min, the apparent clearance is equal to 5.22 L/h.

The apparent clearance was slightly higher in Black patients, by 0.9 L/h, or approximately 17% for a typical adult.

SIMULATIONS

The firm conducted simulations to establish exposure as a function of age. Two different dosing regimens administration (3 mg/day, either q.d. or b.i.d. with a split dose) were simulated at steady state. Depending on the number of different patients in each of the original datasets, simulations were replicated up to approximately 1000 patients.

APPEARS THIS WAY ON ORIGINAL

Figure 5. Simulated Concentrations of Active Moiety in NonBlack Subjects Treated With 3 mg/day (Split b.i.d Dose) of Risperidone (5th, 25th, 50th, 75th and 95th percentile

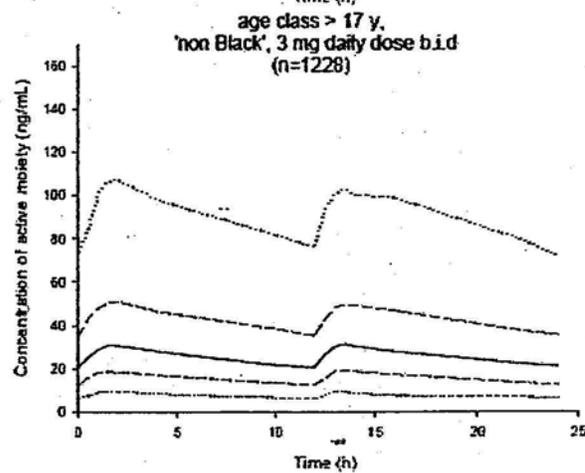
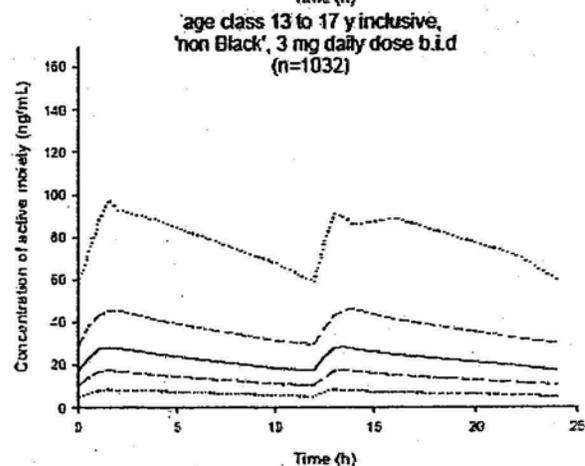
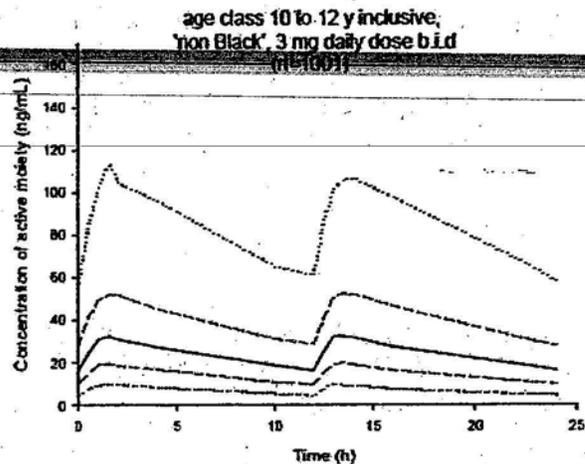
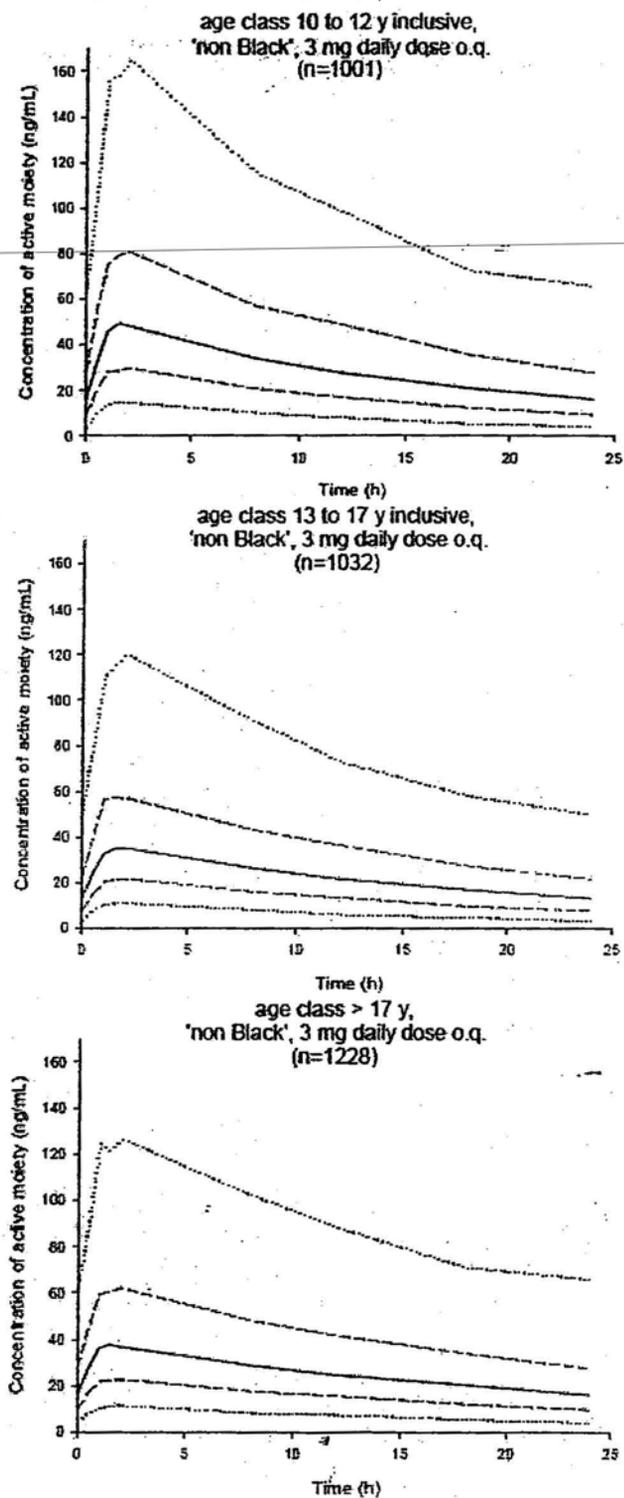
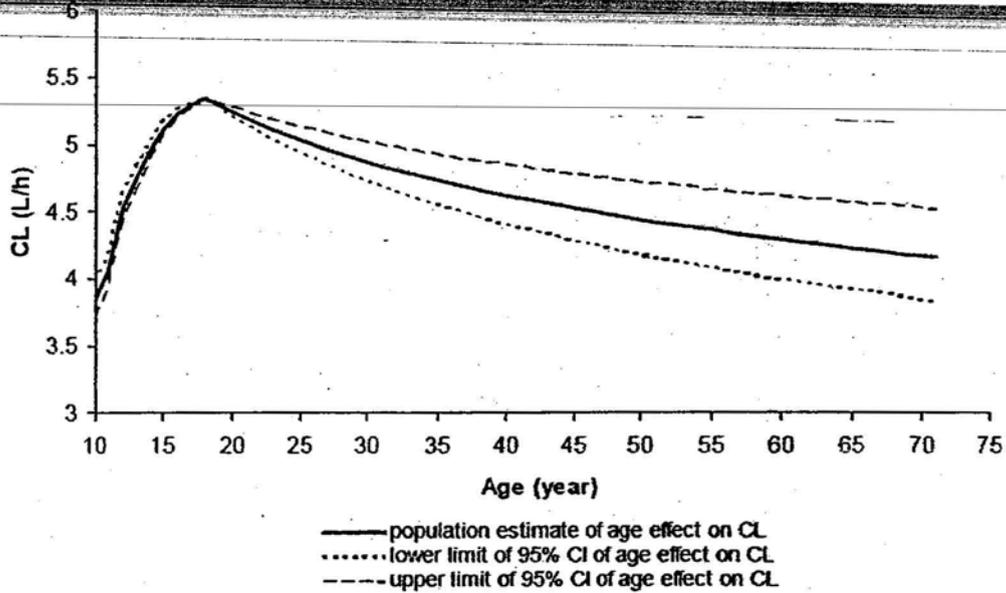


Figure 5. Simulated Concentrations of Active Moiety in NonBlack Subjects Treated With 3 mg/day (qd Dose) of Risperidone (5th, 25th, 50th, 75th and 95th percentile.

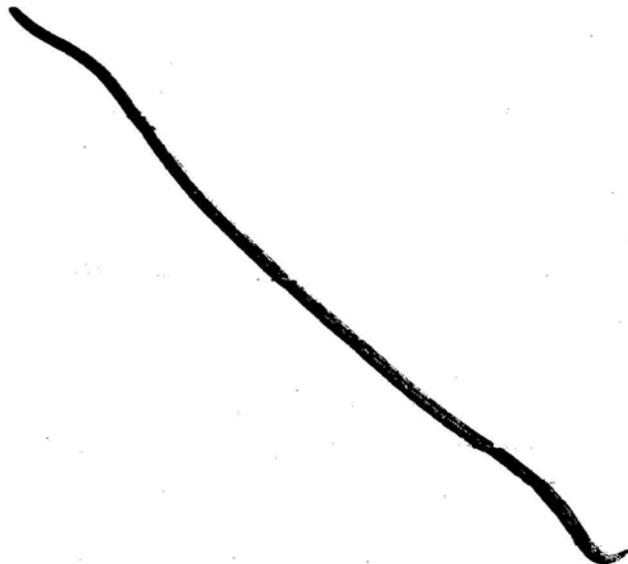


Similar simulated results were seen for the black subjects except the resulting levels were lower due to the increased clearance as previously discussed.

Figure 6. Effect of Age on Active Moiety Clearance in Different Age Groups.



This figure shows that the age effect on apparent clearance is moderate, the most rapid change in clearance is due to the change in median body weight during the child's growth.



b(4)

13 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

There appeared to be underprediction at the higher concentrations and overprediction at the lower concentrations

Two different subpopulations of subjects were identified, that could be assumed to represent intermediate/poor metabolizers and extensive metabolizers, although no confirmation of such categorization could be done in the absence of complete genotype and/or phenotype data.

After allometric scaling, the PK of risperidone was similar between children, adolescents and adults. The risperidone apparent clearance and the volume of distribution at steady state for the three age classes and subpopulations are:

Parameter	Child, body weight: 39 Kg; age: 11 yr		Adolescent, body weight: 60 Kg, age: 15 yr		Adult, body weight: 70 Kg; age: 33 yr	
	Subpopulation	Subpopulation	Subpopulation	Subpopulation	Subpopulation	Subpopulation
	1	2	1	2	1	2
CL/F (L/h)	5.47	20.8	7.56	28.7	8.48	32.2
Vd _{ss} (L)	143.6	176.6	220.9	271.7	257.7	317.0

(Subpopulation 1 is identified as the IM/PM population while subpopulation 2 represents the EM population)

FDA ANALYSIS

The data which the firm submitted did not have plasma stability data to cover the 5 yr storage period for some of the samples. Therefore an analysis was undertaken involving the deletion of Study 2 in adolescents for the active moiety and risperidone for the base model.

b(4)

BASE MODEL -ACTIVE-MOIETY

Base model for Active moiety

Parameter	Firm's analysis Estimate(SE)	FDA analysis	FDA analysis without study 2
CL			
θ_1		3.86(0.484)	4.15(0.561)
θ_6		0.0142(0.00365)	0.0121(0.00435)
V2/F			
θ_2		153(9.25)	161(11.2)
θ_8		-65.7(11.6)	-72.9(13)
θ_9		-53.7(8.7)	-60.4(10)
V3/F θ_3		85.4(6.39)	85.2(6.35)

b(4)

Q/F θ_4
Ka θ_5
ALAG1 θ_7
F1
IIV on CL ω^2_1
IIV on V2 ω^2_2
IIV on Ka ω^2_3
IIV on F1 ω^2_4
Residual variability
Study 1,2,3,4,5,9: σ^2_1
Study 6,7,8: σ^2_2

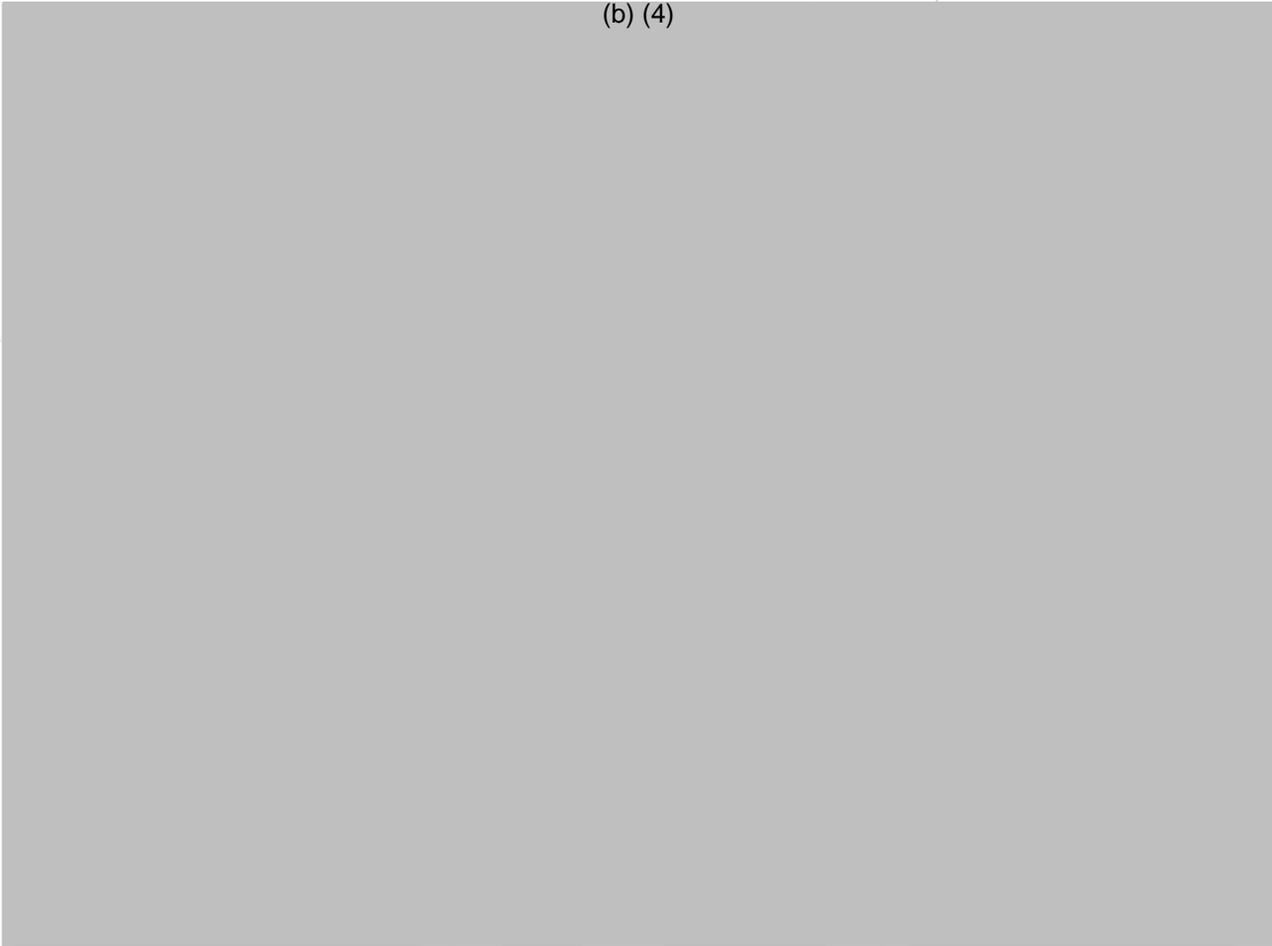
1.47(0.119)	1.48(0.122)
5.48(0.654)	5.48(0.657)
0.24(0.00189)	0.24(0.00189)
1 Fixed	1 Fixed
0.0648(0.0137)	0.068(0.0158)
0.0105(0.0146)	0.0076(0.0139)
6.27(1.34)	6.31(1.36)
0.197(0.0358)	0.225(0.048)
0.0692(0.0112)	0.0692(0.0112)
0.24 (0.033)	0.24 (0.044)

b(4)

FINAL MODEL ACTIVE MOIETY

FINAL MODEL WOULD NOT RUN ON MY COMPUTER BUT DID RUN ON YANING'S RESULTS WERE FOUND TO BE THE SAME AS FOR THE SPONSOR.

(b) (4)



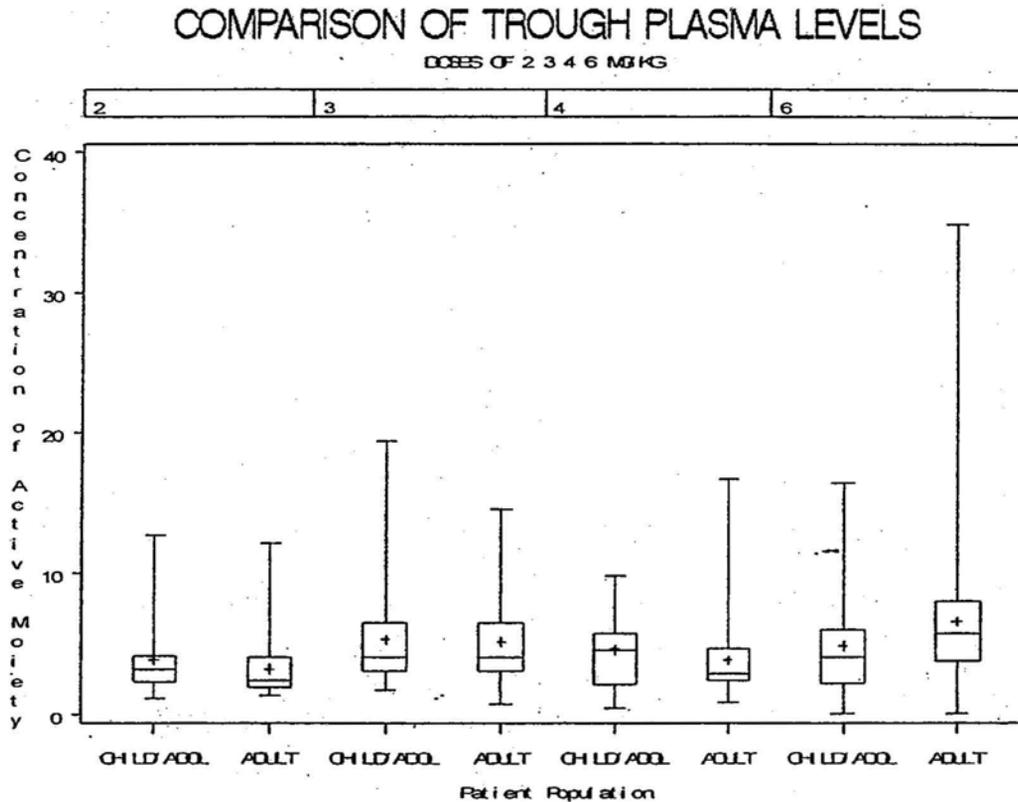
COMMENT

1. There was minimal change in the base model results with study 2 deleted.
2. FDA results for the base and final models were identical to the firm's results

The firm's analysis was further checked by selecting times after dose for the observed data based upon the sampling schedules for studies 1, 2 and 3. These were used to make comparisons to the other adult studies at the same times after dose for the intensive sampling studies.

Trough samples were selected based upon time of last dose that were comparable between the studies. These were further sorted based upon dose with the final concentrations normalized to dose.:

Figure 9. Comparison of adolescent and adult data observed data as a function of normalized dose for Active moiety at trough.



Comment:

1. Mean values for the active moiety were similar for adults and children and adolescents at trough based upon mg/kg.

BASE MODEL - RISPERIDONE

Table 12 Comparative results were:

Parameter	Firm's analysis Estimate (Rel SE)	FDA analysis (Rel SE)	FDA analysis without study 2 (Rel SE)
Ka		6.03(9.1)	6.03(9.0)
CL			
θ_2		49(12.9)	51(13.4)
θ_9		0.782(11.8)	0.782(11.8)
V2/F θ_3		323(13.6)	331(14.1)
V3/F θ_4		256(21.6)	255(23.3)
Q/F θ_5		6.96(16.2)	7.3(17.9)
ALAG1 θ_6		0.24(0.8)	0.24(0.8)
F1			
Population 1: θ_7		3.5(12.3)	3.6(14.1)
Population 2		1(fixed)	1(fixed)
Proportion population 1: p(1)= θ_8		0.346(24.2)	0.35(20.3)
Proportion population 2: 1-p(1)		0.654	0.654
IIV on Ka ω^2_1		8.3(22.8)	8.3(22.8)
IIV on CL ω^2_2		0.332(17.3)	0.38(20.2)
IIV on V2 ω^2_3		0.261(22.1)	0.30(24.2)
Residual variability Study 1,2,3,4,5,9: σ^2_1		0.073(19.1)	0.073(19.1)
Study 6,7,8: σ^2_2		0.828 (11.5)	0.837 (11.5)

b(4)

COMMENTS

1. There was minimal change in the base model results with study 2 deleted.
2. FDA results for the base and final models were identical to the firm's results

Table 13. Final Model Parameters for Risperidone After Oral Administration. Results are Obtained With the Full Dataset, Using the FOCE Method.

Parameter	Firm's Estimates (SE)	FDA Estimates (SE)
K_a (h ⁻¹) Study 1,2,3,4,5,9: θ_{10} Study 6,7,8 : θ_{10}		
CL/F (L/h)= $\theta_2*(Weight/70)^{0.75}$ θ_9 POP1 θ_2 θ_9		
V_2/F (L)= $\theta_3*(Weight/70)$ θ_3		
V_3/F (L)= $\theta_4*(Weight/70)$ θ_4		
Q/F (L/h) θ_5		
ALAG1 (h) θ_6		
F1 Population 1: θ_7 Population 2		
Proportion population 1: $P(1)=\theta_8$ Proportion population 2: $1-P(1)$		
IIV on CL: ω_2 1		
IIV on V2: ω_2 2		
IIV on F1: ω_2 3		
Residual variability on log(conc) Study 1, 2, 3, 4, 5, 9: σ_2 1 Study 6, 7, 8 : σ_2 2		

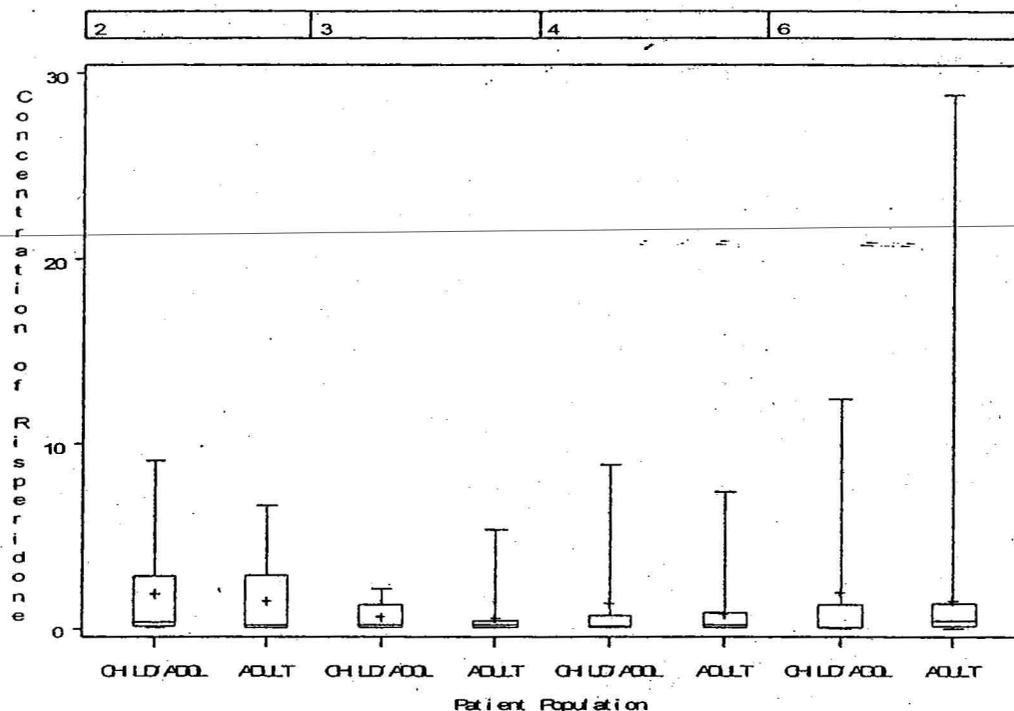
b(4)

An analysis of the trough times after dose concentrations were selected based upon the sampling schedules for studies 1, 2 and 3 and analyzed the same as those for the active moiety.

Figure 10. Comparison of adolescent and adult data observed data as a function of normalized dose for Risperidone at trough.

COMPARISON OF TROUGH PLASMA LEVELS

DOSES OF 2 3 4 6 MG/KG



DISCUSSION

The results from this analysis indicates that based upon the model developed to describe risperidone and the active moiety that there are differences in clearance between adolescents, children, and adults.

Values for the standard errors indicated that the parameters were estimated with precisions usually less than 25%. The residual variability remained high suggesting that assumptions about dosing history may be incorrect or sampling date/time may not be accurate for some subjects at steady state.

The analysis of the raw trough data based upon time after dosing supports the model results indicating that weight normalized doses are comparable in children, adolescents and adults in the dose range 2,3,4,5 and 6 mg/kg. However based upon the lack of a clear dose response relationship for both indications dosing based upon body weight is not recommended. Recommended doses for schizophrenia is 3 mg QD while that for bipolar should be initiated at 0.5 mg QD with adjustment of 0.5-1 mg/day as tolerated.

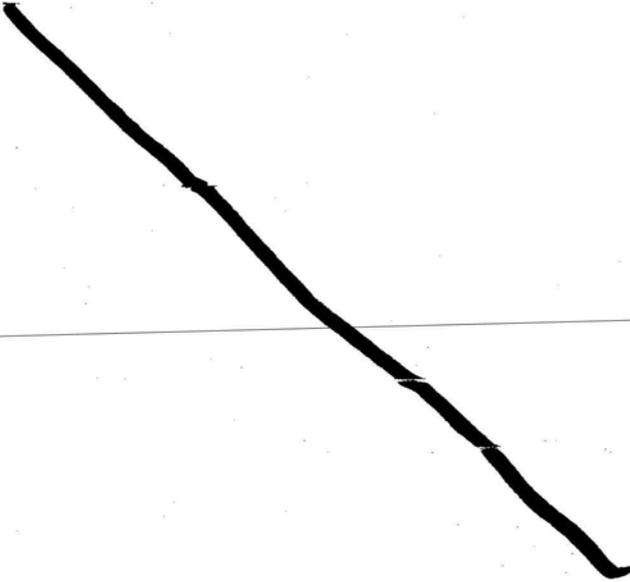
5 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)



b(4)

SIGNATURES

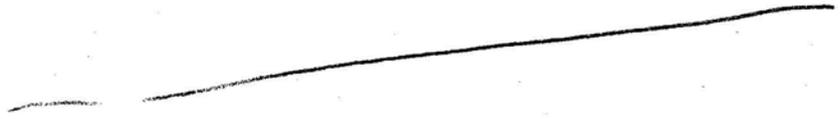
Andre Jackson _____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-866, HFD-860(Mehta, Baweja, Jackson)

C:\Data\REVIEWS\INDA\RISPERDAL_NDA20272JOJNSO&JOHNSON\PEDWR-
EQ.doc

APPENDIX I
FIRM'S BASE MODEL FOR ACTIVE MOIETY



b(4)

6 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
6/13/2007 07:59:56 AM
BIOPHARMACEUTICS

Yaning Wang
6/13/2007 01:28:58 PM
BIOPHARMACEUTICS

Raman Baweja
6/13/2007 03:08:22 PM
BIOPHARMACEUTICS

APPEARS THIS WAY ON ORIGINAL

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Risperidone
NDA: 20272/SE5-046,047
20588/SE5-036,037
2144/ SE5-020,021

PRIMARY REVIEWER: Andre Jackson
TYPE: NDA

FORMULATION: Oral Tablet

STRENGTH: 0.25mg, 0.5mg, 1 mg,
2mg, 3mg and 4mg

APPLICANT: Johnson and Johnson

Submission Dates: June 25, 2007

INDICATIONS: Schizophrenia , Bipolar Disorder

REVIEW OF A LABELLING SUPPLEMENT

➤ New Label Entry 1

DOSAGE AND ADMINISTRATION

	Initial Dose	Titration	Target Dose	Effective Dose Range
Schizophrenia - adults (2.1)	2 mg /day	1-2 mg daily	4-8 mg daily	4-16 mg /day
Schizophrenia - adolescents (2.1)	0.5mg /day	0.5- 1 mg daily	3mg /day	1-6 mg /day
Bipolar mania - adults (2.2)	2-3 mg /day	1mg daily	1-6mg /day	1-6 mg /day
Bipolar mania in children/ adolescents (2.2)	0.5 mg /day	0.5-1mg daily	2.5mg /day	0.5-6 mg /day
Irritability associated with autistic disorder (2.3)	0.25 mg /day (<20 kg) 0.5 mg /day (≥20 kg)	0.25-0.5 mg at ≥ 2 weeks	0.5 mg /day (<20 kg) 1 mg /day (≥20 kg)	0.5-3 mg /day

FDA Comment:

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 2

DOSAGE AND ADMINISTRATION

Schizophrenia

Adolescents

The dosage of RISPERDAL[®] should be initiated at 0.5 mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 3 mg/day. Although efficacy has been demonstrated in studies of adolescent patients with schizophrenia at doses between 1 and 6 mg/day, no additional benefit was seen above 3 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

There are no controlled data to support the longer term use of RISPERDAL[®] beyond 8 weeks in adolescents with schizophrenia. The physician who elects to use RISPERDAL[®] for extended periods in adolescents with schizophrenia should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

FDA Comment:

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 3

Bipolar Mania

Pediatrics

The dosage of RISPERDAL[®] should be initiated at 0.5mg once daily, administered as a single-daily dose in either the morning or evening. Dosage adjustments, if indicated, should occur at intervals not less than 24 hours, in increments of 0.5 or 1 mg/day, as tolerated, to a recommended dose of 2.5 mg/day. Although efficacy has been demonstrated in studies of pediatric patients with bipolar mania at doses between 0.5 and

6 mg/day, no additional benefit was seen above 2.5 mg/day, and higher doses were associated with more adverse events. Doses higher than 6 mg/day have not been studied.

Patients experiencing persistent somnolence may benefit from administering half the daily dose twice daily.

FDA Comment:

The entry is acceptable and is supported by information either in the current label under Dosage and Administration or in the NDA 20272.

➤ New Label Entry 3

Irritability Associated with Autistic Disorder – Pediatrics (Children and Adolescents)

The safety and effectiveness of RISPERDAL[®] in pediatric patients with autistic disorder less than 5 years of age have not been established.

The dosage of RISPERDAL[®] should be individualized according to the response and tolerability of the patient. The total daily dose of RISPERDAL[®] can be administered once daily, or half the total daily dose can be administered twice daily.

Dosing should be initiated at 0.25 mg per day for patients < 20 kg and 0.5 mg per day for patients ≥ 20 kg. After a minimum of four days from treatment initiation, the dose may be increased to the recommended dose of 0.5 mg per day for patients < 20 kg and 1 mg per day for patients ≥ 20 kg. This dose should be maintained for a minimum of 14 days. In patients not achieving sufficient clinical response, dose increases may be considered at ≥ 2-week intervals in increments of 0.25 mg per day for patients < 20 kg or 0.5 mg per day for patients ≥ 20 kg. Caution should be exercised with dosage for smaller children who weigh less than 15 kg.

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Drug Interactions

The firm has incorporated the requested changes

➤ Drugs That Inhibit CYP 2D6 and Other CYP Isozymes

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Carbamazepine and Other Enzyme Inducers

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

➤ Drugs Metabolized by CYP 2D6

FDA Comment:

The entry is acceptable and is identical to that in the approvable letter to the firm dated 6/07.

SIGNATURES

Andre Jackson _____
Reviewer, Psychiatric Drug Products, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 20-272, HFD-860(Mehta, Baweja, Jackson)
C:\Data\REVIEWS\NDA\IRISPERDAL_NDA20272JANDJIPEDWREQ\LABELLIN
SUPPL.doc

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
8/1/2007 10:37:45 AM
BIOPHARMACEUTICS

Raman Baweja
8/1/2007 05:34:53 PM
BIOPHARMACEUTICS
This DFS signoff for NDA 20272/046 & 047 also
serves as signoff for NDA 20588/036 & 037,
and NDA 21444/020 & 021.

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

OTHER REVIEW(S)

MEMORANDUM

Division of Medication Errors and Technical Support
Office of Surveillance and Epidemiology
HFD-420; White Oak 22, Room 4447
Center for Drug Evaluation and Research

To: Thomas Laughren, MD
Director, Division of Psychiatry Products, HFD-130

Through: Nora Rosellé, Pharm. D, Team Leader
Denise Toyer, Pharm. D, Deputy Director
Carol Holquist, R.Ph., Director
Division of Medication Errors and Technical Support, HFD-420

From: Richard Abate, R.Ph., MS, Safety Evaluator
Division of Medication Errors and Technical Support, HFD-420

CC: Nallaperum Chidambaram, Ph.D.
Chemist, Division of Post-Marketing Evaluation

Date: February 22, 2007

Subject: **DMETS Insert Labeling Review**
Risperdal (risperidone) tablets,
NDA: 20-272, 20-588, 21-444, ██████████ **b(4)**
Sponsor: Janssen

OSE Consult #: 2007-326

This memorandum is in response to a February 7, 2007 request from your Division for review and comment on the description sections of the Insert labeling for Risperdal Tablets. The proposed labeling adds the description of "capsule-shaped" ██████████ " along with colors to the tablets in Section 3 "DOSAGE FORMS AND STRENGTHS" and Section 16 "HOW SUPPLIED/STORAGE AND HANDLING" whereas the current insert labeling describes each tablet by color alone. The Chemistry reviewer raised a concern of possible patient confusion regarding the proposed "capsule-shaped" description of the tablets in the labeling. Following DMETS review of the insert labeling, we have the following comments:

- b(4)**
1. DMETS believes the description of "capsule-shaped" will not be confusing for patients. The description, "capsule-shaped," accurately describes the oblong shape of the Risperdal tablets. Tablets, described as capsule-shaped, are often referred to as caplets. The dosage form, caplet, is frequently used for non-prescription drug products (e.g. Tylenol[®], Sudafed[®], and Motrin[®] IB) and is therefore a familiar term for both healthcare professionals and patients. In addition, the US Pharmacopeia makes reference to the caplet designation in its definition of a tablet.

2.

_____ Generally, "capsule-shaped" suggests
the sides will be convex as a capsule has round sides.
confusing as healthcare professionals may not be familiar with the word or understand

b(4)

3.

Delete the trailing zeros that appear in Section 2.3, "Irritability Associated with Autistic Disorder," of the package insert labeling. FDA launched a campaign on June 14, 2006, warning health care providers and consumers not to use error-prone abbreviations, acronyms, or symbols. Trailing zeros are one of these dangerous abbreviations. Thus, we request that the review Divisions not approve the use of trailing zeros in their labels and labeling as the potential for a ten-fold dosing error exists if the decimal point is not readily apparent. Additionally, the use of terminal zeros in the expression of strength or volume is not in accordance with the General Notices (page 10) of 2004 USP, which states, "... to help minimize the possibility of error in the dispensing and administration of the drugs...the quantity of active ingredient when expressed in whole numbers shall be shown without a decimal point that is followed by a terminal zero." We further note that the use of trailing zeros are specifically listed as dangerous abbreviations, acronyms, or symbols in the 2006 National Patient Safety Goals of The Joint Commission for Accreditation of Hospitals (JCAHO).

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Angela Robinson, Project Manager, at 301-796-2284.

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Richard Abate
3/29/2007 10:51:25 AM
DRUG SAFETY OFFICE REVIEWER

Nora L. Roselle
3/29/2007 11:31:20 AM
DRUG SAFETY OFFICE REVIEWER

Denise Toyer
3/29/2007 12:49:39 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/29/2007 12:57:53 PM
DRUG SAFETY OFFICE REVIEWER

APPEARS THIS WAY ON ORIGINAL

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

20-272/S046/S047

20-588/S036/S037

21-444/S020/S021

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

SECTION 13: PATENT DECLARATION

The undersigned declares that the following patents cover formulations, compositions and/or methods of use listed in accordance with 21 U.S.C. 355 (b) or (c) for drug products containing the same active moiety as the studied drug, RISPERIDONE® TABLET (ORAL RISPERDAL). These drug products are currently approved under section 505 of the Federal Food, Drug and Cosmetic Act.

PATENT NO.	TYPE	EXPIRATION	PATENT OWNER
4,804,663	Composition of Matter	Dec. 29, 2007	Janssen Pharmaceutica NV
5,688,801	Method of Use	Nov. 18, 2014	Alkermes, Inc.
5,770,231	Formulation	Nov. 19, 2013	Alkermes, Inc.
5,792,477	Formulation	May 2, 2017	Alkermes, Inc. & Janssen Pharmaceutica
5,916,598	Formulation	May 2, 2017	Alkermes, Inc.
5,965,168	Formulation	Nov. 19, 2013	Alkermes, Inc.
6,110,503	Formulation	May 2, 2017	Alkermes, Inc.
6,110,921	Method of Use	Nov. 19, 2013	Alkermes, Inc.
6,194,006	Formulation	Dec. 30, 2018	Alkermes, Inc.
6,264,987	Formulation	May 19, 2020	Alkermes, Inc.
6,368,632	Method of Use	Nov. 19, 2013	Alkermes, Inc.
6,379,703	Formulation	Dec. 30, 2018	Alkermes, Inc.
6,379,704	Formulation	May 19, 2020	Alkermes, Inc.
6,403,114	Formulation	May 2, 2017	Alkermes, Inc.
6,534,092	Formulation	May 19, 2020	Alkermes, Inc.
6,596,316	Formulation	Dec. 30, 2008	Alkermes, Inc.
5,453,425	Formulation	Jul. 11, 2014	Janssen Pharmaceutica N.V.
RE 39181	Formulation	Jul. 11, 2014	Janssen Pharmaceutica N.V.
5,648,093	Formulation	Jul. 15, 2014	Janssen Pharmaceutica, Inc.
6,224,905	Formulation	Jun 10, 2017	Janssen Pharmaceutica N.V.

Hal Brent Woodrow
Hal B. Woodrow
for Janssen, L.P. as
Assistant Secretary for General Partner
Janssen Pharmaceutica, Inc.

30 November 2006
Date:

1.3.5.3 EXCLUSIVITY REQUEST

On behalf of Janssen L.P., Johnson & Johnson Pharmaceutical Research & Development, L.L.C. herewith submits this supplemental New Drug Application (sNDA) as a complete response to the Pediatric Written Request for RISPERDAL[®] (risperidone), issued originally on 25 November 2002, and amended on 19 December 2003. All studies have been completed and the study reports are herein submitted or incorporated by reference in the parallel sNDAs for pediatric Schizophrenia and Bipolar I Disorder, within the time frame stipulated in the Written Request amendment (31 December 2007).

In accordance with the exclusivity provisions of section 505A of the Federal Food, Drug and Cosmetic Act, on behalf of Janssen L.P., Johnson & Johnson Pharmaceutical Research & Development, L.L.C. requests six months of pediatric exclusivity.

APPEARS THIS WAY ON ORIGINAL

EXCLUSIVITY SUMMARY

NDA # 20-272

SUPPL # SE5/046&047

HFD # 130

20-588

SE5/036&037

21-444

SE5/020&021

Trade Name: Risperdal Tablets [20-272]; Risperdal Oral Solution [20-588]; Risperdal M-Tab Orally Disintegrating Tablets [21-444]

Generic Name: risperidone

Applicant Name: Johnson & Johnson PR&D

Approval Date, If Known: 8-22-07

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

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

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES

NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

SE5

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

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:

see above

d) Did the applicant request exclusivity?

YES NO

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

e) Has pediatric exclusivity been granted for this Active Moiety?

Yes, February 28, 2007 under these supplemental NDAs

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

Yes

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

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

YES NO

IF THE ANSWER TO QUESTION 2 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 NO

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

NDA# 20-272	Risperdal (risperidone) Tablets
NDA# 20-588	Risperdal (risperidone) Oral Solution
NDA# 21-444	Risperdal M-Tab (risperidone) Orally Disintegrating Tablets

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. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs 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 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 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:

(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

(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

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:

Explain:

! 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

If yes, explain:

APPEARS THIS WAY ON ORIGINAL

Name of person completing form: Kimberly Updegraff, M.S., R.Ph.
Title: Regulatory Health Project Manager
Date: 8/24/2007

Name of Office/Division Director signing form: Thomas P. Laughren, M.D.
Title: Director, Division of Psychiatry Products

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Thomas Laughren
9/19/2007 09:19:43 AM

APPEARS THIS WAY ON ORIGINAL

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA# : 20-272 Supplement Type (e.g. SE5): SE5 Supplement Number: 046 & 047
20-588 SE5 036 & 037
21-444 SE5 020 & 021

Stamp Date: December 21, 2006 PDUFA Goal Date: June 21, 2007

HFD 130 Trade and generic names/dosage form: Risperdal (risperidone) Tablets (NDA 20-272) Solution (NDA 20-588), & Orally Disintegrating Tablets (NDA 21-444)

Applicant: Johnson & Johnson Pharmaceutical R&D, LLC Therapeutic Class: Antipsychotic

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration?

- Yes. Please proceed to the next question.
 No. PREA does not apply. Skip to signature block.

* SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.

Indication(s) previously approved (please complete this section for supplements only): Schizophrenia (short- and long-term treatment); Bipolar Disorder (monotherapy and concomitant tx with lithium or valproate); Irritability associated with Autistic Disorder

Each indication covered by current application under review must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: Schizophrenia – Adolescent

Is this an orphan indication?

- Yes. PREA does not apply. Skip to signature block.
 No. Please proceed to the next question.

Is there a full waiver for this indication (check one)?

- Yes: Please proceed to Section A.
 No: Please check all that apply: Partial Waiver Deferred X Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
 Disease/condition does not exist in children
 Too few children with disease to study
 There are safety concerns
 Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. 13 - Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 17 Tanner Stage _____

Comments: Written Request Fulfilled

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

NDA [REDACTED]

Page 3

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH
STAFF at 301-796-0700

(Revised: 10/10/2006)

APPEARS THIS WAY ON ORIGINAL

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: Bipolar Disorder – Children and Adolescents

Is this an orphan indication?

Yes. PREA does not apply. Skip to signature block.

~~* No. Please proceed to the next question.~~

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

* No: Please check all that apply: Partial Waiver Deferred Completed

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. 0 Tanner Stage _____
Max _____ kg _____ mo. _____ yr. 9 Tanner Stage _____

Reason(s) for partial waiver:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- * Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is

complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below)::

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Reason(s) for deferral:

- Products in this class for this indication have been studied/labeled for pediatric population
- Disease/condition does not exist in children
- Too few children with disease to study
- There are safety concerns
- Adult studies ready for approval
- Formulation needed
- Other: _____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg _____ mo. _____ yr. _____ Tanner Stage _____
Max _____ kg _____ mo. _____ yr. _____ Tanner Stage _____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 10/10/2006)

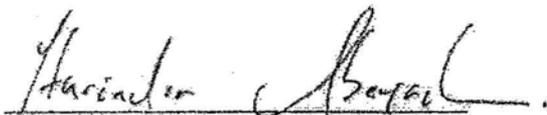
Pediatric Use Waiver Request

This supplement (NDA 20-272; NDA 20-588; NDA 21-444) provides efficacy and safety data in pediatric patients 10-17 years of age for RISPARDAL® (risperidone) Tablets, Oral Solution and Orally Disintegrating Tablets in the treatment of mania of bipolar disorder.

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. (J&JPRD) is requesting, however, a partial waiver from conducting pediatric studies under the Pediatric Research Equity Act (PREA) for NDA 20-272; NDA 20-588; NDA 21-444 for the treatment of bipolar disorder for children ≤ 9 years of age. As stated in the Written Request dated 25 November 2002, bipolar disorder below the age of 10 years is considered both uncommon and difficult to diagnose.

In compliance with 21 CFR 314.55, J&JPRD is submitting this statement to NDAs 20-272, 20-588, and 21-444 for RISPARDAL® (risperidone) Tablets, Oral Solution and Orally Disintegrating Tablets, respectively.

J&JPRD hereby requests a partial waiver for pediatric studies in the treatment of bipolar disorder for children ≤ 9 years of age.



Harindra R. Abeysinghe, Ph.D.
Associate Director
North America Regional Liaison
Regulatory Affairs

29 NOV 06

Date

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Kimberly Updegraff
6/18/2007 03:35:50 PM

APPEARS THIS WAY ON ORIGINAL

**DEBARMENT CERTIFICATION
RISPERIDONE TABLETS**

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. certifies that we did not and will not use in any capacity the services of any person debarred under Section 306 of the Federal Food Drug and Cosmetic Act in connection with this application.


Kathleen Basmadjian, Ph.D.
Senior Director
Global Regulatory Affairs

08 DEC 06
Date

APPEARS THIS WAY ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION		PRESCRIPTION DRUG USER FEE COVERSHEET	
Form Approved: OMB No. 0910 - 0297 Expiration Date: December 31, 2006 See instructions for OMB Statement.			
A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm			
1. APPLICANT'S NAME AND ADDRESS JOHNSON AND JOHNSON Harindra Abeyasinghe 1125 Trenton-Harbourton Road P.O.Box 200 Titusville NJ 08560 US		4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER 20-272	
2. TELEPHONE NUMBER 609-730-6212		5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL? <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM. IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW: <input checked="" type="checkbox"/> THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION <input type="checkbox"/> THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:	
3. PRODUCT NAME RISPERDAL Tablets (Risperidone)		6. USER FEE I.D. NUMBER PD3006790	
7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION. <input type="checkbox"/> A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 (Self Explanatory) <input type="checkbox"/> THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act <input type="checkbox"/> A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE <input type="checkbox"/> THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALY			
8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? <input type="checkbox"/> YES <input checked="" type="checkbox"/> NO			
Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to: Department of Health and Human Services Food and Drug Administration CDER, HFD-99 1401 Rockville Pike Rockville, MD 20852-1448 Food and Drug Administration CDER, HFD-94 12420 Parkdawn Drive, Room 3046 Rockville, MD 20852 An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.			
SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE <i>Harindra Abeyasinghe</i>		TITLE ASSOC. DIRECTOR REGULATORY AFFAIRS	DATE 1 DEC 06
9. USER FEE PAYMENT AMOUNT FOR THIS APPLICATION \$448,100.00			
Form FDA 3397 (12/03)			

(IBE_PRMT_CLOSE_G) (Print Cover sheet)

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

- (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators	see attached list	

- (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).
- (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME Harindra R. Abeyasinghe, Ph. D.	TITLE Associate Director, Global Regulatory Affairs
FIRM / ORGANIZATION Johnson & Johnson Pharmaceutical Research and Development, LLC	
SIGNATURE  For Harindra Abeyasinghe	DATE Dec. 8, 2006

b(6)

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

MEMORANDUM

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

CLINICAL INSPECTION SUMMARY

DATE: May 21, 2007

TO: Kimberly Updegraff, Regulatory Project Manager
June Cai, M.D., Medical Officer
Thomas Laughren, M.D., Director
Division of Psychiatry Products, HFD-130

THROUGH: Constance Lewin, M.D., M.P.H., Branch Chief
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

FROM: Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 20-272 SE5-046, 047

SPONSOR: Johnson & Johnson

DRUG: Risperidone (Risperdal®)

CHEMICAL CLASSIFICATION: 6

THERAPEUTIC CLASSIFICATION: Priority, Therapeutic Gain

INDICATION: Pediatric schizophrenia and bipolar disorder

CONSULTATION REQUEST DATE: February 15, 2007

DIVISION ACTION GOAL DATE: May 25, 2007

PDUFA GOAL DATE: June 21, 2007

I. BACKGROUND

Clinical investigator inspections were requested at four clinical sites that performed studies for which the sponsor submitted data in NDA 20-272 SE5-046, 047. The clinical investigator inspection was conducted according to the Compliance Program 7348.811, the Inspection Program for Clinical Investigators. The inspections covered work performed under protocols RIS-BIM-301 and RIS-SCH-302.

In this supplemental NDA, the sponsor has included results of protocols RIS-BIM-301 and RIS-SCH-302. The protocol RIS-BIM-301 was a randomized, placebo-controlled, double-blind, 3-arm, multicenter study in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) diagnosis of Bipolar I disorder experiencing a manic or mixed episode. The protocol RIS-SCH-302 was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B).

Basis for Sites Selection: Three clinical sites (Drs. Delbello, Nadukuru, and Gundugurti) were inspected so far. The results of Dr. Holloway's site inspection are not available at this time because the inspection is pending with an anticipated start date of May 25, 2007. These sites were selected for inspection due to enrollment of large numbers of study subjects and pediatric exclusivity submission. The goals of inspection included validation of submitted data and compliance of study activities with FDA regulations. Among the elements reviewed for compliance were subject record accuracy, informed consent, protocol inclusion/exclusion criteria, adherence to protocol, randomization procedures, and documentation of adverse events.

II. RESULTS (by site):

Clinical Investigator/Site	Protocol(s)	Inspection Date	EIR Received Date	Preliminary Classification
Dr. Melissa Delbello Psychiatric Professional Services, Inc. 231 Albert Sabin Way Cincinnati, OH 45267	RIS-BIM-301	4/19-5/2/2007	Pending	NAI
Dr. Willis Holloway Cutting Edge Research Group 3140 W. Britton Road Oklahoma City, OK 73120	RIS-BIM-301	5/25-6/1/2007	Pending	Not known until inspection is completed
Dr. Raju Nadukuru Nooka Government Hospital for Mental Care Visakhapatnam 530 017, India	RIS-SCH-302	4/30-5/4/2007	Pending	NAI

2. **Dr. Raju Nadukuru Nooka** **18 subjects**
Visakhapatnam, India

a. What was inspected?

The FDA investigator reviewed the records for all 18 subjects enrolled in the study. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the supplemental NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. The FDA investigator noted no deficiencies or discrepancies in the data. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. All subjects appeared to meet the inclusion-exclusion criteria before being enrolled into the study. No underreporting of adverse events was noted.

Recommendation: Data from this clinical site appear acceptable for use in support of this supplemental NDA.

3. **Dr. Rao Gundugurti Prasad** **13 subjects**
Hyderabad, India

a. What was inspected?

The FDA investigator reviewed the records for all 13 subjects enrolled in the study. The FDA investigator reviewed the source documents, CRFs and compared with data listing provided by the sponsor as part of the supplemental NDA submission. The inspection encompassed an audit of all subjects' consent forms.

b. Limitations of inspection: None.

c. General observations/commentary:

Data in sponsor-provided data listings, including efficacy and safety endpoints, were supported by data in source documents and case report forms. The FDA investigator noted no deficiencies or discrepancies in the data. There was adequate documentation in the source documents to assure all subjects were actually enrolled in the study and treated throughout the study. All subjects

appeared to meet the inclusion-exclusion criteria before being enrolled into the study. No underreporting of adverse events was noted.

Recommendation: Data from this clinical site appear acceptable for use in support of this supplemental NDA.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

In general, for the three clinical investigator sites inspected, there was sufficient documentation to assure that all audited subjects did exist, fulfilled the eligibility criteria, received the assigned study medication, and had their primary efficacy endpoint captured as specified in the protocol. No underreporting of adverse events was noted. Overall, data generated for protocols RIS-BIM-301 and RIS-SCH-302 at these clinical sites appear acceptable for use in support of supplemental NDA 20-272 SE5-046, 047.

As I stated above, the results of Dr. Holloway's site inspection are not available at this time because the inspection is pending with an anticipated start date of May 25, 2007. Inspection summary addendum will be generated if conclusions significantly change upon receipt and review of the EIR of Dr. Holloway.

{See appended electronic signature page}

Jose Javier Tavarez, M.S.
Good Clinical Practice Branch I, HFD-46
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Constance Lewin, M.D., M.P.H.
Branch Chief
Good Clinical Practice Branch I
Division of Scientific Investigations

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Jose Tavarezpagan
5/21/2007 04:23:59 PM
CSO

Constance Lewin
5/21/2007 04:29:00 PM
MEDICAL OFFICER

APPEARS THIS WAY ON ORIGINAL

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA #	20-272	Supplement #	046 & 047	Efficacy Supplement Type	SE-	SE5
	20-588		036 & 037			SE5
	21-444		020 & 021			SE5

Proprietary Name: Risperdal Tablets, Oral Solution, M-Tab Orally Disintegrating Tablets
Established Name: risperidone
Strengths: Tablets: 0.25, 0.5, 1, 2, 3, 4 mg
Oral Solution: 1mg/ml in 30ml bottle
M-Tab Orally Disintegrating Tablets: 0.5, 1, 2, 3, 4 mg

Applicant: Johnson & Johnson Pharmaceutical R&D, LLC
Agent for Applicant (if applicable):

Date of Application: December 21, 2006
Date of Receipt: December 21, 2006
Date clock started after UN: December 21, 2006
Date of Filing Meeting: February 6, 2007
Filing Date: February 19, 2007
Action Goal Date (optional): June 20, 2007 User Fee Goal Date: June 21, 2007

Indication(s) requested: Adolescent Schizophrenia ; Child and Adolescent Bipolar Disease

Type of Original NDA:	505	(b)(1)	<input checked="" type="checkbox"/>	(b)(2)	<input type="checkbox"/>
AND (if applicable)					
Type of Supplement:	505	(b)(1)	<input checked="" type="checkbox"/>	(b)(2)	<input type="checkbox"/>

NOTE:

(1) If you have questions about whether the application is a 505(b)(1) or 505(b)(2) application, see Appendix A. A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application or efficacy supplement is a (b)(2), complete Appendix B.

Review Classification: S P
Resubmission after withdrawal? Resubmission after refuse to file?
Chemical Classification: (1,2,3 etc.)
Other (orphan, OTC, etc.)

Form 3397 (User Fee Cover Sheet) submitted: YES NO

User Fee Status: Paid Exempt (orphan, government)
Waived (e.g., small business, public health)

NOTE: If the NDA is a 505(b)(2) application, and the applicant did not pay a fee in reliance on the 505(b)(2) exemption (see box 7 on the User Fee Cover Sheet), confirm that a user fee is not required by contacting the User Fee staff in the Office of Regulatory Policy. The applicant is required to pay a user fee if: (1) the product described in the 505(b)(2) application is a new molecular entity or (2) the applicant claims a new indication for a use that has not been approved under section 505(b). Examples of a new indication for a use include a new indication, a new dosing regime, a new patient population, and an Rx-to-OTC switch. The best way to determine if the applicant is claiming a new indication for a use is to compare the applicant's

proposed labeling to labeling that has already been approved for the product described in the application. Highlight the differences between the proposed and approved labeling. If you need assistance in determining if the applicant is claiming a new indication for a use, please contact the User Fee staff.

- Is there any 5-year or 3-year exclusivity on this active moiety in any approved (b)(1) or (b)(2) application? YES NO
If yes, explain: Pediatric Exclusivity was granted February 28, 2007

Note: If the drug under review is a 505(b)(2), this issue will be addressed in detail in appendix B.

- Does another drug have orphan drug exclusivity for the same indication? YES NO

- If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]? YES NO

If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

- Is the application affected by the Application Integrity Policy (AIP)? YES NO
If yes, explain:

- If yes, has OC/DMPQ been notified of the submission? YES NO

- Does the submission contain an accurate comprehensive index? YES NO
If no, explain:

- Was form 356h included with an authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. agent must sign.

- Submission complete as required under 21 CFR 314.50? YES NO
If no, explain:

- Answer 1, 2, or 3 below (do not include electronic content of labeling as an partial electronic submission).

1. This application is a paper NDA YES

2. This application is an eNDA or combined paper + eNDA YES

This application is: All electronic Combined paper + eNDA

This application is in: NDA format CTD format

Combined NDA and CTD formats

Does the eNDA, follow the guidance?
(<http://www.fda.gov/cder/guidance/2353fnl.pdf>) YES NO

If an eNDA, all forms and certifications must be in paper and require a signature.

If combined paper + eNDA, which parts of the application were submitted in electronic format?

Additional comments:

3. This application is an eCTD NDA. YES

If an eCTD NDA, all forms and certifications must either be in paper and signed or be electronically signed.

Additional comments:

- Patent information submitted on form FDA 3542a? YES NO
- Exclusivity requested? YES, X 6 months NO
NOTE: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES NO
If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge"

- Are the required pediatric assessment studies and/or deferral/partial waiver/full waiver of pediatric studies (or request for deferral/partial waiver/full waiver of pediatric studies) included? YES NO
- If the submission contains a request for deferral, partial waiver, or full waiver of studies, does the application contain the certification required under FD&C Act sections 505B(a)(3)(B) and (4)(A) and (B)? YES NO
- Is this submission a partial or complete response to a pediatric Written Request? YES NO

If yes, contact PMHT in the OND-IO

- Financial Disclosure forms included with authorized signature? YES NO
(Forms 3454 and/or 3455 must be included and must be signed by the APPLICANT, not an agent.)

NOTE: Financial disclosure is required for bioequivalence studies that are the basis for approval.

- Field Copy Certification (that it is a true copy of the CMC technical section) YES NO
- PDUFA and Action Goal dates correct in tracking system? YES NO
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name and applicant name correct in COMIS? If not, have the Document Room make the corrections. Ask the Doc Rm to add the established name to COMIS for the supporting IND if it is not already entered.
- List referenced IND numbers:
- Are the trade, established/proper, and applicant names correct in COMIS? YES NO
If no, have the Document Room make the corrections.
- End-of-Phase 2 Meeting(s)? Date(s) _____ NO
If yes, distribute minutes before filing meeting.

- Pre-sNDA Meeting(s)? Date(s) September 19, 2006 NO
If yes, distribute minutes before filing meeting.
- Any SPA agreements? Date(s) _____ NO
If yes, distribute letter and/or relevant minutes before filing meeting.

Project Management

- If Rx, was electronic Content of Labeling submitted in SPL format? YES NO
If no, request in 74-day letter.
- If Rx, for all new NDAs/efficacy supplements submitted on or after 6/30/06:
Was the PI submitted in PLR format? YES NO
If no, explain. Was a waiver or deferral requested before the application was received or in the submission? If before, what is the status of the request:
- If Rx, all labeling (PI, PPI, MedGuide, carton and immediate container labels) has been consulted to DDMAC? YES NO
- If Rx, trade name (and all labeling) consulted to OSE/DMETS? YES NO
- If Rx, MedGuide and/or PPI (plus PI) consulted to ODE/DSRCS? N/A YES NO
- Risk Management Plan consulted to OSE/IO? N/A YES NO
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling submitted? NA YES NO

If Rx-to-OTC Switch or OTC application: NA

- Proprietary name, all OTC labeling/packaging, and current approved PI consulted to OSE/DMETS? YES NO
- If the application was received by a clinical review division, has DNPCE been notified of the OTC switch application? Or, if received by DNPCE, has the clinical review division been notified? YES NO

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? NA YES NO

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES NO
If no, did applicant submit a complete environmental assessment? YES NO
If EA submitted, consulted to EA officer, OPS? YES NO

- Establishment Evaluation Request (EER) submitted to DMPQ? YES NO
- If a parenteral product, consulted to Microbiology Team? NA YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: February 6, 2007

NDA #: 20-272 SE5/046&047 ; 20-588 SE5/036&037 ; 21-444 SE5/020&021

DRUG NAMES: Risperdal Tablets, Oral Solution, M-Tab Orally Disintegrating Tablets

APPLICANT: Johnson & Johnson PR&D

BACKGROUND: Molecular entity approved since 1993. This is a submission to fulfill a Pediatric Written Request made by the Agency on November 25, 2002, amended on December 19, 2003. The submission hopes to fulfill the requirements for adolescent schizophrenia and child and adolescent bipolar disease.

ATTENDEES:

Thomas Laughren	Division Director
Mitchell Mathis	Deputy Director
Ni Khin	Medical Team Leader
June Cai	Medical Reviewer
Peiling Yang	Statistics Team Leader
John Lawrence	Statistics Reviewer
Raman Baweja	OCP Team Leader
Ron Kavanagh	OCP Reviewer
Jose Tavaréz-Pagan	DSI Reviewer
Chidambaram Nallaperum	Chemistry Reviewer

ASSIGNED REVIEWERS (including those not present at filing meeting) :

<u>Discipline/Organization</u>	<u>Reviewer</u>
Medical:	June Cai
Secondary Medical:	NA
Statistical:	John Lawrence
Pharmacology:	Barry Rossloff
Statistical Pharmacology:	NA
Chemistry:	Chidambaram Nallaperum
Environmental Assessment (if needed):	NA
Biopharmaceutical:	Ron Kavanagh (reassigned to Andre Jackson)
Microbiology, sterility:	NA
Microbiology, clinical (for antimicrobial products only):	NA
DSI:	Jose Tavaréz-Pagan
OPS:	NA
Regulatory Project Management:	Kimberly Updegraff
Other Consults:	NA

Per reviewers, are all parts in English or English translation? YES NO

If no, explain:

CLINICAL FILE REFUSE TO FILE

- Clinical site audit(s) needed? YES NO
If no, explain:
- Advisory Committee Meeting needed? YES, date if known _____ NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?
N/A YES NO

CLINICAL MICROBIOLOGY N/A FILE REFUSE TO FILE

STATISTICS N/A FILE REFUSE TO FILE

BIOPHARMACEUTICS FILE REFUSE TO FILE

- Biopharm. study site audits(s) needed? YES NO

PHARMACOLOGY/TOX N/A FILE REFUSE TO FILE

- GLP audit needed? YES NO

CHEMISTRY FILE REFUSE TO FILE

- Establishment(s) ready for inspection? YES NO
- Sterile product? YES NO
- If yes, was microbiology consulted for validation of sterilization? YES NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:
(Refer to 21 CFR 314.101(d) for filing requirements.)

- The application is unsuitable for filing. Explain why:
- The application, on its face, appears to be well-organized and indexed. The application appears to be suitable for filing.
 - No filing issues have been identified.
 - Filing issues to be communicated by Day 74. List (optional): In letter

ACTION ITEMS:

1. Ensure that the review and chemical classification codes, as well as any other pertinent

classification codes (e.g., orphan, OTC) are correctly entered into COMIS.

2. If RTF, notify everybody who already received a consult request of RTF action. Cancel the EER.
3. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
4. If filed, complete the Pediatric Page at this time. (If paper version, enter into DFS.)
5. Convey document filing issues/no filing issues to applicant by Day 74.

Kimberly Updegraff, M.S., R.Ph.
Regulatory Project Manager

APPEARS THIS WAY ON ORIGINAL



Food and Drug Administration
Rockville, MD 20857

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

NDA 20-272

Janssen Research Foundation
Attn: Claude McGowan, Ph.D.
Assistant Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Dr. McGowan:

Please refer to the Written Request, originally issued on November 25, 2002, that you received from the Center for Drug Evaluation and Research.

BPCA § 18: Minority Children and Pediatric Exclusivity Program

We are amending the "Format of reports to be submitted" section of your Written Request to require submitted reports to include more specific information on racial and ethnic minorities, in accordance with Section 18, *Minority Children and Pediatric-Exclusivity Program*, of the Best Pharmaceuticals for Children Act (BPCA) (Public Law 107-109). All other terms stated in our original Written Request remain the same.

Format of reports to be submitted:

In addition, the reports are to include information on the representation of pediatric patients of ethnic and racial minorities. All pediatric patients enrolled in the study(s) must be categorized using one of the following designations for race: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander or White. For ethnicity one of the following designations must be used: Hispanic/Latino or Not Hispanic/Latino.

BPCA § 9: Public Dissemination of Medical and Clinical Pharmacology Review Summaries for All Fileable Supplements Submitted in Response to Written Requests

We note that the July 2002 re-issued Written Request notified you that an application submitted in response to a Written Request would be subject to the disclosure provisions of the BPCA. This letter also reminds you that in accordance with Section 9 of the BPCA, *Dissemination of Pediatric Information*, if a pediatric supplement is submitted in response to a Written Request and filed by FDA, FDA will make public a summary of the medical and clinical pharmacology reviews of pediatric studies conducted. This disclosure, which will occur within 180 days of supplement submission, will apply to all supplements submitted in response to a Written Request issued or re-issued under BPCA and filed by FDA, regardless of the following circumstances:

- (1) the type of response to the Written Request (complete or partial);
- (2) the status of the supplement (withdrawn after the supplement has been filed or pending);
- (3) the action taken (i.e. approval, approvable, not approvable); or
- (4) the exclusivity determination (i.e. granted or denied).

FDA will post the medical and clinical pharmacology review summaries on the FDA website at [<http://www.fda.gov/cder/pediatric/Summaryreview.htm>] and publish in the Federal Register a notification of availability.

Page 2

If you have any questions regarding this letter or the BPCA, please contact the Division of Pediatric Drug Development at (301) 594-7337. If you believe that the Written Request should be amended, please contact the review division directly.

Sincerely,

{See appended electronic signature page}

M. Dianne Murphy, M.D.
Director
Office of Counter-terrorism and Pediatric Drug
Development
Center for Drug Evaluation and Research

APPEARS THIS WAY ON ORIGINAL

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Dianne Murphy
5/7/04 02:32:05 PM

APPEARS THIS WAY ON ORIGINAL