CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-121/S-017

Trade Name: CONCERTA

Generic Name: (methylphenidate HCL)

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

Approval Date: June 27, 2008

Indication: Provides for the use of Concerta (methylphenidate HCL) tablets for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (18 years and older)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

CONTENTS

Reviews / Information Included in this NDA Review.

Approval Letter	**X**
Other Action Letters	
Labeling	**X**
Summary Review	**X**
Officer/Employee List	**X**
Office Director Memo	
Cross Discipline Team Leader Review	**X**
Medical Review(s)	**X**
Chemistry Review(s)	**X**
Environmental Assessment	
Pharmacology Review(s)	**X**
Statistical Review(s)	**X**
Microbiology Review(s)	
Clinical Pharmacology/Biopharmaceutics Review(s)	**X**
Other Reviews	**X**
Risk Assessment and Risk Mitigation Review(s)	
Proprietary Name Review(s)	
Administrative/Correspondence Document(s)	**X**

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-121/S-015/S-017

Johnson and Johnson Pharmaceutical Research &
Development, L.L.C
Attention: Ann Jenkins-Frison
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms Jenkins-Frison:

Please refer to your supplemental new drug applications dated May 17, 2007 (S-015) and August 29, 2007 (S-017), submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Concerta (methylphenidate HCl) Extended-Release tablets.

We acknowledge receipt of your submissions submitted to S-017 dated December 6, and 21, 2007, February 8, 2008, February 29, 2008, March 13, 2008, June 5, 2008, June 19, 2008 and June 24, and 25, 2008.

These supplemental new drug applications provide for the following revisions to product labeling:

S-015

- Revisions to the Adverse Reactions-Post-Marketing Experience section.

S-017

- Provides for the use of Concerta (methylphenidate HCl) tablets for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (18 years and older).

We have completed our review of these applications, as amended. They are approved effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

The final printed labeling (FPL) must be identical to the enclosed labeling. Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug. You are also responsible for assuring that the wording in this printed labeling is identical to that of the approved content of labeling in the structured product labeling (SPL) format.

As soon as possible, but no later than 14 days from the date of this letter, please submit the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html that is identical to the enclosed labeling text. Upon receipt, we will transmit that version to the National Library of Medicine for public dissemination. For administrative purposes, please designate this submission, "SPL for

approved supplements 21-121/S-015/S-017.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. Clinical trials in the pediatric population have been performed in children 6 years of age and older, and Concerta is adequately labeled for use in the pediatric population. We are waiving pediatric studies in children under 6 years of age because it is difficult to diagnose ADHD in this age group. Therefore, no additional studies are needed in this pediatric group.

We are waiving the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of prescribing information. This waiver applies to all future supplements containing revised labeling unless we notify you otherwise.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this the Division of Psychiatry Products and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important safety related information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit an electronic copy of the letter to both this NDA and to the following address:

MedWatch
Food and Drug Administration
HFD-001, Suite 5100
5515 Security Lane
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call CDR Nicholette Hemingway, Regulatory Project Manager, at (301) 796-1365.

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

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
6/27/2008 09:08:44 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CONCERTA® safely and effectively. See full prescribing information for CONCERTA®.

CONCERTA® (methylphenidate HCl) Extended-Release Tablets CII
Initial U.S. Approval: 2000

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

----------RECENT MAJOR CHANGES ----------

- Indications and Usage, Usage in Adults (1) 06/2008
- Dosage and Administration, Adult Dosing (2.2, 2.3); Dose Titration (2.4); Maintenance/Extended Treatment (2.5) 06/2008
- Contraindications, Hypersensitivity to Methylphenidate (4.1) 06/2008

----------INDICATIONS AND USAGE----------

CONCERTA® is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. (1)

----------DOSAGE AND ADMINISTRATION----------

- CONCERTA® should be taken once daily in the morning and swallowed whole with the aid of liquids. CONCERTA® should not be chewed or crushed. CONCERTA® may be taken with or without food. (2.1)
- For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. (2.2)
- For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. (2.2)
- For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment. (2.3)

----------DOSAGE FORMS AND STRENGTHS----------

Tablets: 18, 27, 36, and 54 mg (3)

----------CONTRAINDICATIONS----------

- Known hypersensitivity to the product (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

----------WARNINGS AND PRECAUTIONS----------

- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with pre-existing psychiatric illness. Clinical evaluation for Bipolar Disorder is recommended prior to stimulant use. Monitor for aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures (5.3)
- Visual Disturbance: difficulties with accommodation and blurring of vision have been reported with stimulant treatment.(5.5)
- Long-Term Suppression of Growth: monitor height and weight at appropriate intervals in pediatric patients (5.4)
- Gastrointestinal obstruction with pre-existing GI narrowing (5.6)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy (5.7)

----------Adverse Reactions----------

The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. (6.1 and 6.2)

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. (6.3)

To report SUSPECTED ADVERSE REACTIONS, contact McNeil Pediatrics at 1-888-440-7903 or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------

- Do not use CONCERTA® in patients currently using or within 2 weeks of using an MAO inhibitor (7.1)
- CONCERTA® may increase blood pressure; use cautiously with vasopressors (7.2)
- Inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants (7.3)
- Serious adverse events when using methylphenidate in combination with clonidine (7.4)

----------USE IN SPECIFIC POPULATIONS----------

- Caution should be exercised if administered to nursing mothers (8.3)
- Safety and efficacy has not been established in children less than six years old or elderly patients greater than 65 years of age (8.4 and 8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA APPROVED MEDICATION GUIDE.

Revised: Draft 06/27/2008

FULL PRESCRIBING INFORMATION: CONTENTS

FULL PRESCRIBING INFORMATION

DRUG DEPENDENCE
CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE

CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65 *[see Clinical Studies (14)]*.

A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

1.2 Need for Comprehensive Treatment Program

CONCERTA® is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social). Drug treatment may not be indicated for all patients with ADHD. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders,

including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

CONCERTA® should be administered orally once daily in the morning with or without food.

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed *[see Patient Counseling Information (17)]*.

2.2 Patients New to Methylphenidate

The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate or stimulants other than methylphenidate is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults (see Table 1).

TABLE 1. CONCERTA® Recommended Starting Doses and Dose Ranges

Patient Age	Recommended Starting Dose	Dose Range
Children 6-12 years of age	18 mg/day	18 mg - 54 mg/day
Adolescents 13-17 years of age	18 mg/day	18 mg - 72 mg/day not to exceed 2 mg/kg/day
Adults 18-65 years of age	18 or 36 mg/day	18 mg - 72 mg/day

2.3 Patients Currently Using Methylphenidate

The recommended dose of CONCERTA® for patients who are currently taking methylphenidate twice daily or three times daily, at doses of 10 to 60 mg/day is provided in Table 2. Dosing recommendations are based on current dose regimen and clinical judgment. Conversion dosage should not exceed 72 mg daily.

TABLE 2. Recommended Dose Conversion from Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	Recommended CONCERTA® Starting Dose
5 mg Methylphenidate twice daily or three times daily	18 mg every morning
10 mg Methylphenidate twice daily or three times daily	36 mg every morning
15 mg Methylphenidate twice daily or three times daily	54 mg every morning
20 mg Methylphenidate twice daily or three times daily	72 mg every morning

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

2.4 Dose Titration

Doses may be increased in 18 mg increments at weekly intervals for patients who have not achieved an optimal response at a lower dose. Daily dosages above 54 mg in children and 72 mg in adolescents have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.

A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

2.5 Maintenance/Extended Treatment

There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.

The effectiveness of CONCERTA® for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.6 Dose Reduction and Discontinuation

If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.

If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

CONCERTA® (methylphenidate HCl) Extended-Release Tablets are available in the following dosage strengths: 18 mg tablets are yellow and imprinted with "alza 18," 27 mg tablets are gray and imprinted with "alza 27," 36 mg tablets are white and imprinted with "alza 36," and 54 mg tablets are brownish-red and imprinted with "alza 54."

4 CONTRAINDICATIONS

4.1 Hypersensitivity to Methylphenidate

Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with CONCERTA®. Therefore, CONCERTA® is contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.6)]*.

4.2 Agitation

CONCERTA® is contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma

CONCERTA® is contraindicated in patients with glaucoma.

4.4 Tics

CONCERTA® is contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.4)]*.

4.5 Monoamine Oxidase Inhibitors

CONCERTA® is contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO-inhibitor (hypertensive crises may result) *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults

Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mmHg) and average heart rate (about 3 to 6 bpm) *[see Adverse Reactions (6.5)]*, and individuals may have larger increases. While the mean changes alone would not be expected to have short-term

consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications, should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.2 Psychiatric Adverse Events

Pre-Existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in patients with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive

behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

5.4 Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth, however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.5 Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

5.6 Potential for Gastrointestinal Obstruction

Because the CONCERTA® tablet is nondeformable and does not appreciably change in shape in the GI tract, CONCERTA® should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, “short gut” syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudoobstruction, or Meckel’s diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, CONCERTA® should only be used in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.

5.7 Hematologic Monitoring

Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Drug Dependence *[see Box Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.4)]*
- Visual Disturbance *[see Warnings and Precautions (5.5)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.6)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.7)]*

The most common adverse reaction in double-blind clinical trials (>5%) in pediatric patients (children and adolescents) was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis *[see Adverse Reactions (6.1)]*.

The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased *[see Adverse Reactions (6.3)]*.

The development program for CONCERTA® included exposures in a total of 3733 participants in clinical trials. Children, adolescents, and adults with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies (see Table 3). Safety was assessed by collecting adverse events, vital signs, weights, ECGs, and by performing physical examinations and laboratory analyses.

Table 3. CONCERTA® Exposure in Double-Blind and Open-Label Clinical Studies

Patient Population	N	Dose Range
Children	2216	18 to 54 mg once daily
Adolescents	502	18 to 72 mg once daily
Adults	1015	18 to 108 mg once daily

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.

Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of CONCERTA® based on the comprehensive assessment of the available adverse event information. A causal association for CONCERTA® often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.

The majority of adverse reactions were mild to moderate in severity.

6.1 Commonly-Observed Adverse Reactions in Double-Blind, Placebo-Controlled Clinical Trials

Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Children and Adolescents

Table 4 lists the adverse reactions reported in 1% or more of CONCERTA®-treated children and adolescent patients in 4 placebo-controlled, double-blind clinical trials.

Table 4. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Children and Adolescent Patients in 4 Placebo-Controlled, Double-Blind Clinical Trials of CONCERTA®

System/Organ Class Adverse Reaction	CONCERTA® (n=321) %	Placebo (n=318) %
Gastrointestinal Disorders		
Abdominal pain upper	5.9	3.8
Vomiting	2.8	1.6
General Disorders		
Pyrexia	2.2	0.9
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Nervous System Disorders		
Dizziness	1.9	0
Psychiatric Disorders		
Insomnia	2.8	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.3
Pharyngolaryngeal pain	1.2	0.9

The majority of adverse reactions were mild to moderate in severity.

Adults

Table 5 lists the adverse reactions reported in 1% or more of CONCERTA®-treated adults in 2 placebo-controlled, double-blind clinical trials.

Table 5. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Adult Patients in 2 Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	CONCERTA® (n=415) %	Placebo (n=212) %
Cardiac Disorders		
Tachycardia	4.8	0
Palpitations	3.1	0.9
Ear and Labyrinth Disorders		
Vertigo	1.7	0
Eye Disorders		
Vision blurred	1.7	0.5
Gastrointestinal Disorders		
Dry mouth	14.0	3.8
Nausea	12.8	3.3
Dyspepsia	2.2	0.9
Vomiting	1.7	0.5
Constipation	1.4	0.9
General Disorders and Administration Site Conditions		
Irritability	5.8	1.4
Infections and Infestations		
Upper respiratory tract infection	2.2	0.9
Investigations		
Weight decreased	6.5	3.3

Table 5. Adverse Reactions Reported by ≥1% of CONCERTA®-Treated Adult Patients in 2 Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	CONCERTA® (n=415) %	Placebo (n=212) %
Metabolism and Nutrition Disorders		
Decreased appetite	25.3	6.6
Anorexia	1.7	0
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.9	0
Nervous System Disorder		
Headache	22.2	15.6
Dizziness	6.7	5.2
Tremor	2.7	0.5
Paresthesia	1.2	0
Sedation	1.2	0
Tension headache	1.2	0.5
Psychiatric Disorders		
Insomnia	12.3	6.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.9	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0
Agitation	2.2	0.5
Aggression	1.7	0.5
Bruxism	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect lability	1.4	0.9
Confusional state	1.2	0.5
Tension	1.2	0.5
Respiratory, Thoracic and Mediastinal Disorders		
Pharyngolaryngeal pain	1.7	1.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.1	0.9

* Included doses up to 108 mg.

The majority of ADRs were mild to moderate in severity.

6.2 Other Adverse Reactions Observed in CONCERTA® Clinical Trials

The following adverse reactions occurred in <1% of all patients in the above double-blind, placebo-controlled clinical trial data sets. In addition, the following also includes all adverse reactions reported in CONCERTA®-treated subjects who participated in open-label studies. Adverse reactions listed in Tables 4 and 5 above are not included below.

Blood and Lymphatic System Disorders: Leukopenia

Eye Disorders: Dry eyes

Gastrointestinal Disorders: Abdominal pain, Diarrhea, Stomach discomfort

General Disorders and Administrative Site Conditions: Fatigue, Feeling jittery

Investigations: Blood pressure increased, Cardiac murmur, Heart rate increased

Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence

Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Sleep disorder, Tearfulness, Tic

Reproductive System and Breast Disorders: Erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: Dyspnea

Skin and Subcutaneous Tissue Disorders: Rash, Rash-Macular

Vascular Disorders: Hypertension

6.3 Discontinuation Due to Adverse Reactions

In the 4 placebo-controlled studies of children and adolescents, 2 CONCERTA® patients (0.6%) discontinued due to adverse reactions of depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%) and 4 placebo subjects (1.3%) discontinued due to adverse reactions of headache and insomnia, irritability, psychomotor hyperactivity, and tic (1 each, 0.3%).

In the 2 placebo-controlled studies of adults, 24 CONCERTA® patients (5.8%) and 4 placebo patients (1.9%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the CONCERTA® patients included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the 11 open-label studies of children, adolescents and adults, 265 CONCERTA® patients (7.4%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.3%), irritability (0.8%), anxiety (0.8%), decreased appetite (0.7%), headache (0.6%), and tic (0.6%).

6.4 Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with CONCERTA®.

In a second uncontrolled study (n=682 children) the cumulative incidence of new onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

6.5 Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both CONCERTA® once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with CONCERTA® and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for CONCERTA® and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with CONCERTA® at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for CONCERTA® and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for CONCERTA® and placebo at the end of the double-blind treatment (3.6 and –1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for CONCERTA® and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.1])*.

6.6 Post-Marketing Experience

The following additional adverse reactions have been identified during post-approval use of CONCERTA®. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:

Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura

Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles

Eye Disorders: Diplopia, Mydriasis, Visual disturbance

General Disorders: Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Therapeutic response decreased

Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC

Investigations: Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal

Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching

Nervous System Disorders: Convulsions, Grand mal convulsions, Dyskinesia

Psychiatric Disorders: Disorientation, Hallucinations, Hallucinations auditory, Hallucinations visual, Mania

Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema

Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

CONCERTA® should not be used in patients being treated (currently or within the proceeding 2 weeks) with MAO inhibitors *[see Contraindications (4.5)]*.

7.2 Vasopressor Agents

Because of possible increases in blood pressure, CONCERTA® should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.1)]*.

7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (eg, phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

7.4 Clonidine

Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2 agonists has not been systematically evaluated.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively.

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. CONCERTA® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of CONCERTA® on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if CONCERTA® is administered to a nursing woman.

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

8.4 Pediatric Use

CONCERTA® should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

8.5 Geriatric Use

CONCERTA® has not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

CONCERTA®, like other methylphenidate products, is classified as a Schedule II controlled substance by federal regulation.

9.2 Abuse

See warning containing drug abuse information *[see Box Warning]*.

9.3 Dependence

See warning containing drug dependence information *[see Box Warning]*.

9.4 Human Data

In two placebo-controlled human abuse potential studies, oral doses of CONCERTA were compared to oral doses of immediate-release methylphenidate in individuals with a history of recreational stimulant use to assess relative abuse potential. Both studies were validated by statistical differentiation between immediate-release methylphenidate and placebo on the primary subjective measure of Drug Liking.

In one study, CONCERTA (108 mg) produced increases in subjective responses on two (Drug Liking, Abuse Potential) of five scales that were statistically indistinguishable from immediate-release methylphenidate (60 mg). In the other study, CONCERTA (54 mg and 108 mg) produced statistically significant increases in subjective responses compared to placebo on nine scales (Drug Liking, Overall Drug Liking, Good Effects, High, Take Drug Again, Euphoria, Amphetamine, Stimulation-Euphoria, and Stimulation-Motor).

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of CONCERTA® overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, mydriasis, and dry mouth.

10.2 Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must

be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for CONCERTA® overdosage has not been established.

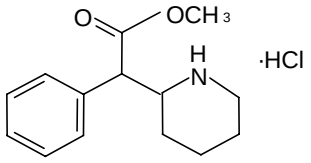
The prolonged release of methylphenidate from CONCERTA® should be considered when treating patients with overdose.

10.3 Poison Control Center

As with the management of all overdosage, the possibility of multiple drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

11 DESCRIPTION

CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \bullet HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

11.1 System Components and Performance

CONCERTA® uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system, which resembles a conventional tablet in appearance, comprises an osmotically active trilayer core surrounded by a semipermeable membrane with an immediate-release drug overcoat. The trilayer core is composed of two drug layers containing the drug and excipients, and a push layer containing osmotically active components. There is a precision-laser drilled

orifice on the drug-layer end of the tablet. In an aqueous environment, such as the gastrointestinal tract, the drug overcoat dissolves within one hour, providing an initial dose of methylphenidate. Water permeates through the membrane into the tablet core. As the osmotically active polymer excipients expand, methylphenidate is released through the orifice. The membrane controls the rate at which water enters the tablet core, which in turn controls drug delivery. Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA®. The biologically inert components of the tablet remain intact during gastrointestinal transit and are eliminated in the stool as a tablet shell along with insoluble core components. It is possible that CONCERTA® extended-release tablets may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

12.3 Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 to 10 hours.

CONCERTA® once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily (see Figure 1). The relative bioavailability of CONCERTA® once daily and methylphenidate three times daily in adults is comparable.

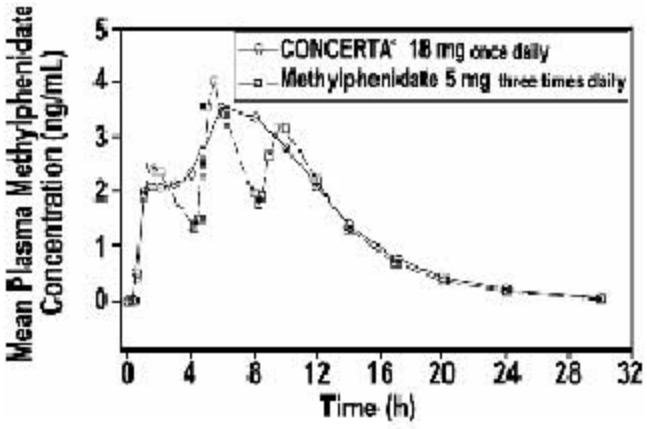


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.

The mean single dose pharmacokinetic parameters in 36 healthy adults following the administration of CONCERTA® 18 mg once daily and methylphenidate 5 mg three times daily are summarized in Table 6.

TABLE 6. Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

Parameters	CONCERTA® (18 mg once daily) (n=36)	Methylphenidate (5 mg three times daily) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

The pharmacokinetics of CONCERTA® were evaluated in healthy adults following single and multiple dose administration (steady-state) of doses up to 144 mg/day. The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of CONCERTA® in a dose range of 18 to 144 mg.

Dose Proportionality

Following administration of CONCERTA® in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\text{-}inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\text{-}inf)}$ increased disproportionately with respect to dose. Following administration of CONCERTA®, plasma concentrations of the l-isomer were approximately 1/40th the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once daily CONCERTA® doses from 54 to 144 mg/day resulted in linear and dose proportional increases in C_{max} and AUC_{inf} for total

methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of CONCERTA®, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 hours.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of CONCERTA® is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{0\text{-}inf}$ values for CONCERTA® were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving CONCERTA®, dose-adjusted $AUC_{0\text{-}inf}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents

compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of CONCERTA® has not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of CONCERTA® in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of CONCERTA®.

Hepatic Insufficiency

There is no experience with the use of CONCERTA® in patients with hepatic insufficiency.

[Section 12.4 deleted—reasoning presented in prior bracketed comment.]

13 NON-CLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively.

14 CLINICAL STUDIES

CONCERTA® was demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

14.1 Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12 years. The controlled studies compared CONCERTA® given once daily (18, 36, or 54 mg), methylphenidate given three times daily over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was CONCERTA® versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention / Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention / Overactivity subscale versus placebo was shown consistently across all three controlled studies for CONCERTA®. The scores for CONCERTA® and placebo for the three studies are presented in Figure 2.

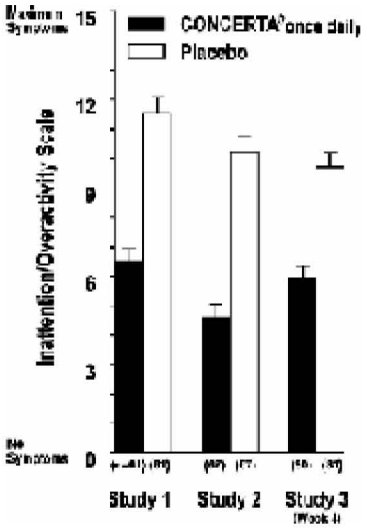


Figure 2: Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with CONCERTA® once-daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.

In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated statistically significant improvements in attention and behavior in patients treated with CONCERTA® versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for CONCERTA® and placebo.

*Swanson, Kotkin, Agler, M-Fynn and Pelham

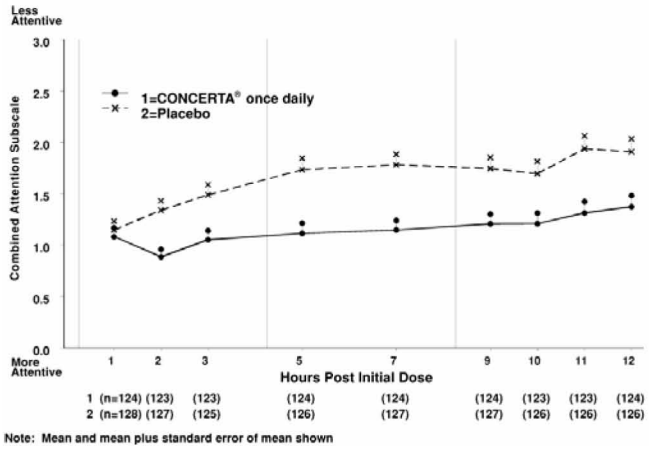


Figure 3: Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)

14.2 Adolescents

In a randomized, double-blind, multi-center, placebo-controlled trial (Study 4) involving 177 patients, CONCERTA® was demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 years at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of CONCERTA® (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that CONCERTA® was statistically significantly superior to placebo.

14.3 Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared CONCERTA® administered once daily and placebo in a multicenter, parallel group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel group, 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

Study 5 demonstrated the effectiveness of CONCERTA® in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to CONCERTA® and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that CONCERTA® was statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel group, dose-response study (5-week duration) with 3 fixed dose groups (18, 36, and 72 mg). Patients were randomized to receive CONCERTA® administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of CONCERTA® were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

15 REFERENCES

American Psychiatric Association. Diagnosis and Statistical Manual of Mental Disorders. 4th ed. Washington DC: American Psychiatric Association 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with “alza 18”. The 27 mg tablets are gray and imprinted with “alza 27”. The 36 mg tablets are white and imprinted with “alza 36”. The 54 mg tablets are brownish-red and imprinted with “alza 54”. All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg	100 count bottle	NDC 17314-5850-2
27 mg	100 count bottle	NDC 17314-5853-2
36 mg	100 count bottle	NDC 17314-5851-2
54 mg	100 count bottle	NDC 17314-5852-2

Storage and Handling

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Information for Patients

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for CONCERTA®. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Patients should be informed that CONCERTA® should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that CONCERTA® does not adversely affect their ability to engage in such activities.

For more information call 1-888-440-7903.

Manufactured by:

ALZA Corporation
Mountain View, CA 94043

Manufactured for:
McNeil Pediatrics, Division of Ortho-McNeil-Pharmaceuticals, Inc.
Titusville, NJ 08560

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XXXXXXX PI

Revised: June 2008

Medication Guide

MEDICATION GUIDE
CONCERTA® (kon SER-ta)
(methylphenidate HCl) Extended-release Tablets CII

Read the Medication Guide that comes with CONCERTA® before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about you or your child's treatment with CONCERTA®.

What is the most important information I should know about CONCERTA®?

The following have been reported with use of methylphenidate HCl and other stimulant medicines:

1. Heart-related problems:
- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting CONCERTA®.

Your doctor should check you or your child's blood pressure and heart rate regularly during treatment with CONCERTA®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking CONCERTA®.

2. Mental (Psychiatric) problems:
All Patients
- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child have any new or worsening mental symptoms or problems while taking CONCERTA®, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What Is CONCERTA®?

CONCERTA® is a central nervous system stimulant prescription medicine. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD).** CONCERTA® may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

CONCERTA® should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

CONCERTA® is a federally controlled substance (CII) because it can be abused or lead to dependence. Keep CONCERTA® in a safe place to prevent misuse and abuse. Selling or giving away CONCERTA® may harm others, and is against the law.
Tell your doctor if you or your child have (or have a family history of) ever abused or been dependent on alcohol, prescription medicines or street drugs.

Who should not take CONCERTA®?
CONCERTA® should not be taken if you or your child:
- are very anxious, tense, or agitated
- have an eye problem called glaucoma
- have tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard to control repeated movements or sounds.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.
- are allergic to anything in CONCERTA®. See the end of this Medication Guide for a complete list of ingredients.

CONCERTA® should not be used in children less than 6 years old because it has not been studied in this age group.
CONCERTA® may not be right for you or your child. Before starting CONCERTA® tell your or your child's doctor about all health conditions (or a family history of) including:
- heart problems, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome

- seizures or have had an abnormal brain wave test (EEG)
- esophagus, stomach, or small or large intestine problems

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

Can CONCERTA® be taken with other medicines?

Tell your doctor about all of the medicines that you or your child take including prescription and nonprescription medicines, vitamins, and herbal supplements. CONCERTA® and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking CONCERTA®.

Your doctor will decide whether CONCERTA® can be taken with other medicines.

Especially tell your doctor if you or your child takes:
- anti-depression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking CONCERTA® without talking to your doctor first.

How should CONCERTA® be taken?
- **Take CONCERTA® exactly as prescribed.** Your doctor may adjust the dose until it is right for you or your child.
- **Do not chew, crush, or divide the tablets.** Swallow CONCERTA® tablets whole with water or other liquids. Tell your doctor if you or your child cannot swallow CONCERTA® whole. A different medicine may need to be prescribed.
- CONCERTA® can be taken with or without food.
- Take CONCERTA® once each day in the morning. CONCERTA® is an extended release tablet. It releases medication into your/your child's body throughout the day.
- The CONCERTA® tablet does not dissolve completely in the body after all the medicine has been released. You or your child may sometimes notice the empty tablet in a bowel movement. This is normal.
- From time to time, your doctor may stop CONCERTA® treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking CONCERTA®. Children should have their height and weight checked often while taking CONCERTA®. CONCERTA® treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much CONCERTA® or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of CONCERTA®?
See "What is the most important information I should know about CONCERTA®?" for information on reported heart and mental problems.

Other serious side effects include:
- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision
- blockage of the esophagus, stomach, small or large intestine in patients who already have a narrowing in any of these organs

Common side effects include:
- decreased appetite
- dry mouth
- trouble sleeping
- dizziness
- stomach ache
- increased sweating
- headache
- nausea
- anxiety
- weight loss
- irritability

Stimulants may impair the ability of you or your child to operate potentially hazardous machinery or vehicles. You or your child should exercise caution until you/your child is reasonably certain that CONCERTA® does not adversely affect your/your child's ability to engage in such activities.

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

How should I store CONCERTA®?
- Store CONCERTA® in a safe place at room temperature, 59 to 86° F (15 to 30° C). Protect from moisture.
- **Keep CONCERTA® and all medicines out of the reach of children.**

General information about CONCERTA®

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use CONCERTA® for a condition for which it was not prescribed. Do not give CONCERTA® to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about CONCERTA®. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about CONCERTA® that was written for healthcare professionals. For more information about CONCERTA® call 1-888-440-7903.

What are the ingredients in CONCERTA®?
Active Ingredient: methylphenidate HCl
Inactive Ingredients: butylated hydroxytoluene, carnuba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

Manufactured by
ALZA Corporation, Mountain View, CA 94043

Distributed and Marketed by
McNeil Pediatrics
Division of Ortho-McNeil-Janssen Inc., Titusville, NJ 08560

[ALZA logo] An ALZA OROS® Technology Product

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Revised: June 2008

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

SUMMARY REVIEW

M E M O R A N D U M **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 26, 2008

FROM: Thomas P. Laughren, M.D.
Director, Division of Psychiatry Products
HFD-130

SUBJECT: Recommendation for approval action for Concerta [OROS (methylphenidate) extended release tablets] for the treatment of attention deficit hyperactivity disorder (ADHD) in adults

TO: File NDA 21-121/S-017
[Note: This overview should be filed with the 8-31-07 original submission of this supplemental NDA.]

1.0 BACKGROUND

Concerta is an extended release formulation of methylphenidate that is already approved for the treatment of ADHD in children (up to 54 mg/day) and adolescents (up to 72 mg/day). This supplement was intended to support the treatment of Concerta in adults with ADHD up to doses of (b) (4) mg/day. The studies in support of this application were conducted under IND 54,575.

There has been concern about a risk of serious cardiovascular events with methylphenidate and other treatments for ADHD, including sudden death, stroke, and MI, particularly in patients with underlying risks for such events. These concerns are based entirely on spontaneous reports of such events in association with the use of these drugs. Nevertheless, these concerns led to very strong warning language in the labeling for these drugs that alerts prescribers to the possibility of such risks. Given this concern, the review of this supplement included particular focus on serious cardiovascular events. This supplement also included a PLR version of labeling that needed review.

The primary clinical reviewer for this application was Dr. Glenn Mannheim and the primary statistical reviewer was Dr. Julia Luan. A secondary review of this application was conducted by Dr. Mitch Mathis.

2.0 CHEMISTRY

There were no CMC issues that required review as part of this supplement other than the new labeling format and consideration for categorical exclusion. The CMC group recommended approval.

3.0 PHARMACOLOGY

There were no pharm/tox issues that required review as part of this supplement other than the new labeling format,. The pharm/tox group also recommended approval.

4.0 BIOPHARMACEUTICS

The biopharmaceutic issues included the new labeling format and several abuse potential studies that were evaluated by the pharmacometrics group within OCP. They generally agreed that the Concerta formulation shows less potential for drug abuse, based on "liking scores" in challenge studies, than comparable doses of immediate release methylphenidate. This is likely entirely explained by lower Cmaxes with the extended release formulation, and they suggested labeling language still acknowledging that all methylphenidate formulations have abuse potential. We also received a consultative review on this matter from CSS. They were generally less impressed with these findings than OCP. They also proposed language primarily emphasizing that all methylphenidate formulations have abuse potential.

5.0 CLINICAL DATA

5.1 Efficacy Data

Our efficacy review focused on 2 randomized, double-blind, placebo-controlled trials of Concerta in adults with ADHD (study 3002 and study 02-159):

-Study 3002: This was a 5-week fixed-dose study (18, 36, and 72 mg/day vs pbo), with about 100 patients per group. All 3 doses were superior to placebo and there was clear dose-response for efficacy (mean change from baseline on the CAARS was -76, -10.6, -11.5, and -13.7 for placebo, 18, 36, and 72, respectively).

> Comment: Dr. Mannheim argued that, based on these data, there is no support for doses beyond 36 mg/day. I disagree with this judgment, and instead, agree with Drs. Mathis and Luan that all 3 doses are supported, with an expectation for somewhat greater efficacy at the 72 mg/day dose compared to the lower doses.

-Study 02-159: This was a 7-week flexible-dose study (36-108 mg/day vs pbo), with about 115 patients per group. The Concerta group was superior to placebo (with mean changes from baseline on the AISRS of -6.8 and -10.9 for placebo and Concerta, respectively). The mean final dose for Concerta was 68 mg/day.

-Subgroup Analyses: Subgroup analyses based on gender, age, and race did not suggest any differences in efficacy based on different subgroups.

> Comment: Dr. Mannheim has recommended restricting use to patients ages 49 and less, presumably based on his view that there has not been adequate exposure experience in patients > 49. I disagree with restricting use on this basis. It is an entirely arbitrary distinction. I think current strong warning language in labeling is sufficient to alert prescribers to possible risks in adults who might be prescribed these drugs, and they can then decide, along with their patients, who should and who should not be prescribed such medications.

DSI found the data generated for this program to be acceptable.

-Efficacy Conclusions: I agree with Drs. Mathis and Luan that the sponsor has demonstrated efficacy for Concerta in the treatment of adult ADHD, with no restrictions on age as suggested by Dr. Mannheim. Flexible-dose studies are difficult to interpret with regard to dose recommendations because they are not informative about differences in efficacy at different doses. One might argue that a positive study for a particular dose range studied supports dosing in that range, assuming this range can be considered safe. In this instance, however, we have 1 fixed dose study that supports a possible advantage of a 72 mg/day dose over lower doses, but is uninformative about the 108 mg/day dose because it was not included in the design. If we had no concerns about safety, we might permit a recommendation of dosing up to 108 mg/day, based on the flexible dose study, but there is clear dose response for certain safety outcomes for this drug. Dr. Mathis has suggested a conservative approach of limiting the upper end of the recommended dosing range to 72 mg/day until it can be shown that a higher dose provides an efficacy advantage that outweighs the additional risk associated with a higher dose. I agree with this position.

5.2 Safety Data

The safety review for this product was based on the 2 adult double-blind efficacy studies, i.e., 3002 and 02-159, plus open label studies and abuse potential studies, yielding a total of n=1015 adult patients/subjects exposed to Concerta in this program. There were no deaths and a total of only 4 SAEs in the double-blind phases of the controlled trials:

> -One of these was a vertebrobasilar stroke from which the patient recovered. It should be noted that this patient had been on immediate release methylphenidate for 3 years prior to starting study 3002. His dose in study 3002 was 18 mg/day. The investigator did not consider the stroke drug-related.
>
> -Onset of depression; not considered drug-related by the investigator.
>
> -Migraine headache; not considered drug-related. Dr. Mannheim suggested that this might represent a "stroke," based on a report in the patient's record indicating a CT finding of "probable lacunar infarct in the caudate nucleus." However, a more accurate characterization of the patient's record indicated that this finding was described by the radiologist as an "old lesion, very likely a perinatal lesion."
>
> -Worsening of anxiety; unknown relationship to drug.

The focus of the safety review was on cardiovascular events, because this has been a concern for drugs in this class. The review revealed that there was the expected modest increase in blood pressure and heart rate. Some ECG data were also collected, however, the only finding was the expected modest tachycardia. The sponsor also assessed the adverse event data for a relationship between pre-existing cardiovascular risk status and treatment-emergent cardiovascular events, and found no relationship.

Dr. Mannheim identified 13 patients (11 patients on Concerta and 2 on placebo) with non-specific ECG changes in the context of study 02-159 that he considered as potentially representative of cardiac ischemia. [Note: ECGs were not routinely obtained in study 3002.] However, as noted in Dr. Mathis's review, none of these instances was associated with relevant clinical symptoms, none had associated reports of cardiac enzyme changes, and none of the patients had adverse cardiac outcomes. We also had Dr. Stephan Grant, a cardiologist from the cardiorenal division, evaluate the 13 sets of ECGs in question. He found that none of the 13 ECG series could be confirmed as representative of cardiac ischemia or other serious cardiac events, and in fact, he considered 12 to be essentially normal ECGs. For the one patient having an abnormal ECG, this finding was present at baseline and showed no evolutionary changes upon exposure to Concerta.

Despite the negative assessment of this supplement regarding cardiovascular risk, Dr. Mannheim has recommended that the sponsor be required to conduct a large, randomized, placebo-controlled trial to better define cardiovascular risk for this drug, as a condition for approval, i.e., it would need to be completed prior to approval.

> Comment: Dr. Mathis has argued against this requirement, and I agree. A very large retrospective cohort study that is being funded jointly by FDA and AHRQ is currently well-along, and should be capable of yielding some useful information about cardiovascular risk associated with the use of drugs in this class in both adults and children. The study proposed by Dr. Mannheim is simply not feasible. It would need to involve hundreds of thousands of patients, would need a placebo arm, and would take years to complete. In the meantime, the labels for Concerta and other drugs in this class already have very strong warning language that alerts prescribers to possible cardiovascular risks. Thus, I do not agree with the need for the study proposed by Dr. Mannheim, and I will not suggest it to the sponsor.

The safety review of this supplement otherwise found Concerta to be reasonably well-tolerated in the adult population and it had the usual and expected profile of common adverse events, vital signs changes, and weight changes that are recognized for this drug. As noted under the efficacy discussion, Dr. Mannheim has recommended restricting use to patients ages 49 and less, presumably based on his view that there has not been adequate exposure experience in patients > 49. As I noted under that section of this memo, I disagree with restricting use on this basis. The only approach to obtaining an adequate exposure to detect the kinds of events Dr. Mannheim is concerned about (i.e., sudden deaths and other catastrophic cardiovascular adverse events) is to observe a very large population of exposed patients. This is being accomplished in an ongoing retrospective cohort study being funded by FDA and AHRQ. I disagree that this needs to be done before taking an action on this supplement. As I have noted, current strong warning language in labeling is sufficient, in my view, to alert prescribers to possible risks in adults who

might be prescribed these drugs, and prescribers can then decide, along with their patients, who should and who should not be prescribed such medications.

6.0 FOREIGN REGULATORY ACTIONS

To my knowledge, Concerta is not approved anywhere at this time for the treatment of adult ADHD.

7.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

We did not to take this application to the PDAC.

8.0 LABELING AND APPROVAL LETTER

8.1 Labeling

Our review of labeling included consideration of the new PLR formatting, and we made a number of modifications to the sponsor's proposed labeling. We have now reached agreement with the sponsor on final labeling.

> Comment: Dr. Mannheim has recommended that, if this extension of the ADHD claim to adults were to be approved, the warning language regarding cardiovascular risk be elevated to a black box warning. In my view, the current warning language is sufficient to alert prescribers to any potential risk. My view is consistent with the view of the Pediatric Advisory Committee that considered this issue in March, 2006.

8.2 Approval Letter

The approval letter includes our agreed upon final labeling. There were no phase 4 commitments or requirements.

9.0 CONCLUSIONS AND RECOMMENDATIONS

I believe that the sponsor has submitted sufficient data to support the conclusion that Concerta is effective and acceptably safe in the treatment of adult ADHD. We have reached agreement on final labeling, and I will issue the attached approval letter along with the agreed upon final labeling.

APPEARS THIS WAY ON ORIGINAL

cc:
Orig NDA 21-121/S-017
HFD-130
HFD-130/TLaughren/MMathis/NKhin/GMannheim/JCliatt

DOC: Concerta_Adult ADHD_Laughren_AP Memo.doc

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
6/26/2008 09:06:58 AM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

OFFICER/EMPLOYEE LIST

Officer/Employee List
Application: NDA 21-121/017; Concerta

The following officers or employees of FDA participated in the decision to approve this application and consented to be identified:

Ikram Elayam
Thomas Laughren
Glenn Mannheim
Mitchell Mathis
Peiling Yang

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

CROSS DISCIPLINE TEAM LEADER REVIEW

M E M O R A N D U M

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

DATE: 5 June 2008

FROM: Mitchell V. Mathis, M.D.
Deputy Director
Division of Psychiatry Products, HFD-130

TO: File NDA 21-121 S-017

SUBJECT: Recommendation of Approval Action for Concerta [OROS (methylphenidate HCl)] Extended Release Tablets for the Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (18 years and older)

1 BACKGROUND AND REGULATORY HISTORY

Concerta is a central nervous system stimulant; it is an extended-release form of methylphenidate HCl. It is an approved product for the treatment of ADHD in children 6 - 12 years old (August 2000) and adolescents aged 13-17 years (October 2004). Concerta is approved in doses up to 54 mg/day in children and up to 72 mg/day in adolescents. The purpose of the current supplement is to examine Concerta for safety and efficacy in adults (up to age 65) with ADHD; the program was developed under IND 54,575.

Attention Deficit Hyperactivity Disorder (ADHD) is a psychiatric disorder that begins in childhood with approximately 50% of patients requiring treatment into adulthood. A recent U.S. National Comorbidity Survey estimated the prevalence of ADHD in adults to be approximately 4%. Adults with ADHD have, by definition, social and occupational dysfunction from the disorder. Stimulant therapy is the mainstay of pharmacologic treatment, and methylphenidate is the most commonly prescribed and most studied of the stimulant medications.

Concerta has been formulated to deliver therapeutic doses of methylphenidate over a 12-hour interval, which is a significant improvement in terms of patient satisfaction and compliance compared to the older immediate-release formulations.

This NDA has been reviewed by Glenn Mannheim, M.D. (clinical), Peter Lee, Ph.D. and Kofi Kumi, Ph.D. (clinical pharmacology and biopharmaceutics), Julia Luan, Ph.D. (statistics), Nallaperum Chidabaram (Chemistry), and Susan Thompson, M.D. (DSI).

The Cardiology team (Stephen Grant, M.D.) was consulted to review several ECGs from the controlled trial database.

2 CHEMISTRY

The chemists recommend an APPROVAL action. All CMC issues have been resolved and there are no deficiencies to be communicated to the sponsor.

3 PHARMACOLOGY/TOXICOLOGY

This approved product has previously been evaluated by the Pharmacologists/Toxicologists and there are no outstanding issues or concerns. Labeling comments have been provided by the team.

4 CLINICAL PHARMACOLOGY

Drs. Kumi and Lee have noted in their review that at comparable dose levels (54 mg Concerta versus 50 mg Ritalin, and 108 mg Concerta versus 90 mg Ritalin), the abuse potential (drug-liking score) is lower for Concerta than for Ritalin. He points out that this is due to the extended-release formulation and that there is no statistical difference in the primary abuse potential. The pharmacokinetics of methylphenidate after administration of Concerta is linear between 54 mg and 144 mg. No Phase IV commitments were recommended and labeling comments have been provided.

5 CLINICAL DATA

5.1 Overview of Studies

The sponsor presented the results of two randomized, placebo-controlled, double-blind trials in adults with ADHD.

- Study 42603ATT3002 (Study 3002) was a 5-week fixed dose study examining doses of 18 mg/day, 36 mg/day, 72 mg/day, and placebo; this study was continued as a 7-week, open-label, flexible-dose (18 mg/day – 90 mg/day) extension. Approximately 400 patients were randomized for study 3002.
- Study 02-159 was a 7-week flexible dose (36 mg/day – 108 mg/day or placebo) study. Patients were titrated to an individualized effective and tolerated dose where they were maintained for at least 2 weeks. Approximately 230 patients were randomized for study 02-159.

There were three open-label studies involving over 600 patients (approximately 500 of whom were followed for up to one year) given doses of 18 mg/day to 108 mg/day.

5.2 Efficacy Findings

Study 3002

The pre-specified primary endpoint in this study was change in total score of the investigator-rated Conner's Adult ADHD Rating Scale (CAARS). There were several secondary endpoints identified (see Dr. Luan's review), but none was identified as a key secondary endpoint. There were 402 patients randomized to placebo or one of three fixed dose groups and 365 (91%) completed the double-blind (5-week) phase of the study. The analysis used the ANCOVA model and was based on the ITT population using the LOCF approach to impute missing data. The results for total score are provided below.

CAARS Total Score: Actual Values and Change from Baseline to Double-Blind End Point – LOCF (Study 3002: *Intent to Treat / Double-Blind*)

	Placebo	PR OROS MPH		
		18 mg	36 mg	72 mg
Baseline	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Median	38.0	35.0	38.0	36.0
Range	24 – 51	24 – 53	25 – 51	24 – 52
Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Median	29.0	24.0	26.0	22.0
Range	4 – 50	4 – 51	4 – 52	1 – 50
Change From Baseline to Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Median	-6.0	-10.0	-10.0	-13.0
Range	-45 – 8	-35 – 16	-37 – 8	-40 – 8
p-value[a] (comparison versus placebo)		0.0146	0.0131	<0.0001

[a] Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure;
N = number of subjects with data
Source: Attachment 17, Attachment 18

Efficacy Conclusions from Study 3002

Concerta is clearly more effective a producing meaningful changes in the symptoms of adult ADHD than placebo. Furthermore, it is evident from the data that doses up to 72 mg/day offer additional benefit over lower doses. Dr. Mannheim comments in his review that these data only support an approvable action for doses no greater than 36 mg/day, but it is clear to me that doses of up to 72 mg/day (the maximum dose approved for adolescents) offer additional efficacy in adults. I don't agree that the dose should be restricted to less than 72 mg/day based upon efficacy data from this study. In fact, from the data presented above, it seems that there is improvement in symptoms of ADHD in adults with increasing dose (18 mg/day and 36 mg/day, while effective, were not as effective as 72 mg/day).

Dr. Luan examined the CAARS Hyperactivity/Impulsivity and Inattention subscales (measures of the distinctive forms of the disease as defined by DSM-IV) and points out in her review (page 13), "For both subscales and at all time points, the largest decrease from baseline was consistently observed in the 72 mg PR OROS methylphenidate [Concerta] group."

In conclusion, this fixed-dose study supports the use of up to 72 mg/day in adults with ADHD.

Study 02-159

The pre-specified primary endpoint in this study was change from baseline in the Adult ADHD Investigator Symptom Rating Score (AISRS) as assessed by the investigator at the Final Visit (Week 7). There were several secondary endpoints identified (see Dr. Luan's review), but none was identified as a key secondary endpoint. There were 229 patients randomized to placebo or to a titration schedule and 161 (70%) completed the double-blind (5-week) phase of the study. The

analysis used the ANCOVA model and was based on the ITT population using the LOCF approach to impute missing data. The results for total score are presented below.

AISRS Total Score and Change From Baseline at Final Visit (LOCF)[a] (ITT)

Statistic	All CONCERTA	Placebo	p-Value[b]
Baseline			
N	110	116	
Mean (SD)	38.6 (6.85)	38.1 (7.31)	
Median	38.5	38.0	
Range (min, max)	(24, 54)	(24, 54)	
Final Visit (LOCF)			
N	110	116	
Mean (SD)	27.6 (13.17)	31.3 (12.38)	
Median	26.5	33.0	
Range (min, max)	(0, 52)	(3, 54)	
Change from Baseline:			
N	110	116	
Mean (SD)	-10.9 (11.75)	-6.8 (11.45)	
Median	-9.0	-3.0	
Range (min, max)	(-48, 13)	(-38, 12)	
95% CI	(-13.2, -8.7)	(-8.9, -4.7)	
LSMean (SEM)	-10.6 (1.09)	-6.8 (1.06)	0.012

a: AISRS total score ranges from 0 to 54 with higher scores indicating more severe ADHD. Change from baseline is the value at the visit minus the baseline value. A negative change from baseline indicates an improvement.

b: p-Value from test for significant treatment difference from ANCOVA model with change from baseline as the dependent variable, site and treatment (All CONCERTA, placebo) as factors, and baseline value as covariate.

Abbreviation: CI - confidence interval

Note: For AISRS Total Score, subjects who lacked post-baseline data had their baseline values carried forward to Final Visit (LOCF).

Source: Table 9-1 of sponsor's clinical study report as duplicated in Dr. Luan's Review

The mean final dose for the All Concerta group was 67.7 mg. The descriptive statistics for change from baseline in AISRS score by titration visit and dose group are presented in Table 9-2 of the sponsor's study report for Study 02-159. The last visit information from that table is presented below.

Table 9-2: AISRS Total Score and Change From Baseline by Visit - Intent-to-Treat Population

Statistic[a]	CONCERTA 36 mg	CONCERTA 54 mg	CONCERTA 72 mg	CONCERTA 90 mg	CONCERTA 108 mg	All CONCERTA	Placebo	p-Value[b]
Final Visit (LOCF)								
N	36	17	20	14	23	110	116	
Mean (SD)	26.8 (13.91)	25.4 (11.56)	22.2 (14.28)	28.2 (12.18)	35.0 (10.07)	27.6 (13.17)	31.3 (12.38)	
Median	26.0	26.0	16.5	26.0	35.0	26.5	33.0	
Range (min, max)	(0, 52)	(5, 43)	(3, 49)	(8, 51)	(13, 47)	(0, 52)	(3, 54)	
Change from Baseline:								
N	36	17	20	14	23	110	116	
Mean (SD)	-12.1 (13.41)	-11.3 (10.62)	-15.0 (12.14)	-11.3 (10.62)	-5.1 (8.31)	-10.9 (11.75)	-6.8 (11.45)	
Median	-8.5	-8.0	-16.5	-11.5	-5.0	-9.0	-3.0	
Range (min, max)	(-48, 7)	(-38, 2)	(-33, 7)	(-32, 5)	(-21, 13)	(-48, 13)	(-38, 12)	
95% CI	(-16.7, -7.6)	(-16.8, -5.8)	(-20.7, -9.3)	(-17.4, -5.2)	(-8.7, -1.5)	(-13.2, -8.7)	(-8.9, -4.7)	
LSMean (SEM)						-10.6 (1.09)	-6.8 (1.06)	0.012

a: AISRS total score ranges from 0 to 54 with higher scores indicating more severe ADHD. Change from baseline is the value at the visit minus the baseline value. A negative change from baseline indicates an improvement.

b: p-Value from test for significant treatment difference from ANCOVA model with change from baseline as the dependent variable, pooled site and treatment (All CONCERTA, placebo) as factors, and baseline value as covariate. Nominal p-Value with no adjustment for multiple testing.

Abbreviation: CI - confidence interval

Note: For AISRS Total Score, subjects who lacked post-baseline data had their baseline values carried forward to Final Visit (LOCF).

Source: Sponsor's Clinical Study Report Table 9-2

Although a flexible dose titration study, patients were maintained at their optimum (final) dose for at least two weeks. The change from baseline in the AISRS score for the 108 mg group was numerically smaller than that of the 72 mg group (-15 for 72 mg/day and -5 for 108 mg/day) and there was no overlap in the confidence intervals.

Efficacy Conclusions from Study 02-159

The results of this flexible-dose study provide replication of the positive result seen in the fixed dose study discussed above. The dose range here was broad and included doses above what is approved for adolescents (maximum dose 72 mg/day).

While all dose groups were effective, there is not clear evidence that doses above 72 mg/day provided any additional benefit and there are dose-related adverse reactions associated with Concerta (see below).

5.3 Subgroup Analyses

Study 3002

CAARS total scores by subgroup for change from baseline to double-blind endpoint are presented below.

Descriptive Statistics for Change from Baseline to Double-Blind Endpoint (LOCF) in CAARS Total Score, by Age Group, Gender and Race (ITT)

Treatment Group	Subgroup	N	Mean	Std Dev	Median
MPH 18mg OD	Female	43	-8.6	9.77	-8
	Male	56	-12.16	10.59	-12.5
MPH 36mg OD	Female	55	-10.93	9.74	-11
	Male	46	-12.11	10.3	-10
MPH 72mg OD	Female	46	-12.68	9.61	-13.5
	Male	53	-14.53	12.29	-13
PLACEBO	Female	36	-7	8.22	-6
	Male	59	-7.98	10.9	-6

MPH 18mg OD	Aged 18-25	52	-10.87	10.89	-12
	Aged 36-49	37	-9.84	9.43	-9
	Aged 50-65	10	-12.2	11.5	-11
MPH 36mg OD	Aged 18-25	55	-10.68	9.96	-8
	Aged 36-49	40	-13.08	10.36	-13.5
	Aged 50-65	6	-8	6.03	-6.5
MPH 72mg OD	Aged 18-25	57	-12.35	10.89	-13
	Aged 36-49	36	-15.67	11.63	-15.5
	Aged 50-65	6	-14.17	9.87	-12
PLACEBO	Aged 18-25	49	-7.47	9.94	-6
	Aged 36-49	41	-7.44	10	-6
	Aged 50-65	5	-10.4	11.13	-11
MPH 18mg OD	White	98	-10.63	10.39	-11
	other	1	-9	.	-9
MPH 36mg OD	Black or African Heritage	1	-9	.	-9
	White	98	-11.55	10.07	-10
	other	2	-8.5	9.19	-8.5
MPH 72mg OD	White	96	-13.47	11.02	-13
	other	3	-20	14.73	-23
PLACEBO	Black or African Heritage	1	-11	-	-11
	White	93	-7.65	10	-6
	other	1	0	-	0

The point estimates of treatment effect are similar among the various demographic groups analyzed.

Study 02-159

AISRS total scores by subgroup for change from baseline to double-blind endpoint are presented below.

Descriptive Statistics for Change from Baseline to Final Visit (LOCF) in the AISRS Total Score, by Age Group, Gender and Race (ITT)

Subgroup	All CONCERTA				Placebo			
	n	mean	Std Dev	median	n	mean	Std Dev	median
Female	47	-10.66	11.43	-8	52	-6.79	12.21	-1.50
Male	63	-11.16	12.08	-11	64	-6.88	10.89	-3.50
Age 18-35	42	-11.31	12.68	-9.00	47	-7.72	11.22	-3.00
Age 36-49	40	-10.60	10.09	-8.50	4	-6.25	11.82	-3.00
Age 50-65	28	-10.89	12.90	-9.00	21	-6.19	11.52	-4.00
African-American	7	-8.43	14.91	-2.00	6	-2.67	5.35	0.00
Caucasian	96	-11.48	11.78	-11.00	99	-7.37	11.98	-3.00
Other	7	-6.14	7.15	-5.00	11	-4.27	8.14	-1.00

The point estimates of treatment effect are similar among the various subgroups analyzed.

Comment on Clinical Review: Dr. Mannheim has made the recommendation that the data do not support use in patients greater than 49 years old. I disagree with this recommendation because I

believe that there is clear evidence from the studies submitted that patients up to age 65 with ADHD benefit from Concerta. While I acknowledge that we have fewer patients represented in these studies in this older age group, we do have enough data to determine that the drug is efficacious up to age 65. In fact, the efficacy results are similar among adults of all ages. We should not restrict treatment based upon age because the data do not support such a restriction.

5.4 Efficacy Conclusions

It is clear from the data presented by the sponsor that Concerta is efficacious in the acute treatment of adults with ADHD. The sponsor has submitted the results of two trials with similar positive results. Both trials support a dose of up to 72 mg/day, but there is not clear evidence from the flexible dose study of up to 108 mg/day that doses above 72 mg/day add any additional benefit and we know that there are dose-related side effects with Concerta.

6.0 SAFETY

Dr. Mannheim reviewed the integrated safety database for the Concerta development program which consisted of the two double-blind studies submitted for the pivotal efficacy claim as well as several open-label studies. Central nervous system stimulants, including Concerta, are expected to have predictable effects upon the cardiovascular and nervous systems (including psychiatric symptoms), and this expectation is borne out in the data from the Concerta development program. Table 14 from the sponsor's SCS (page 49—reproduced below) summarizes the pooled data for adverse events in the two double-blind trials.

Table 14: Summary of All Adverse Events by Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set)

Parameter	All CONCERTA N=415 n (%)	Placebo N=212 n (%)
Subjects with adverse events	330 (79.5)	137 (64.6)
Subjects with serious adverse events	4 (1.0)	0 (0.0)
Subjects who discontinued due to adverse events	29 (7.0)	7 (3.3)
Deaths	0 (0.0)	0 (0.0)

Cross-reference: Appendix 3.1.

As of 21 February 2007, the combined exposure to Concerta in the double-blind and open-label studies was 1,015 subjects receiving at least one dose (282 person-years).

6.1 Deaths

There were no deaths during the Concerta development program.

6.2 Serious Adverse Events

There were 4 serious adverse events identified in study 3002, there were none in study 02-159.

Study 3002
The sponsor identified 4 serious adverse events as shown in table 37 of their Study Report reproduced below.

Table 37: Serious Adverse Events During Double-Blind
(Study 42603ATT3002: *All Subjects / Double-Blind)*

Treatment Subject No.	Age (yrs) Gender	Preferred Term [Verbatim Term]	Day of SAE Onset in Trial*	Dosage Group in DB phase	Action Taken	Relationship to Study Drug	Outcome (Duration)	Total Days of Therapy in DB/OL
Double-Blind								
OROS methylphenidate								
A10253	59 male	**Cerebrovascular accident** [vertebrobasilare stroke]	22	18 mg	Temporary stop	Doubtful	Recovered (17 days)	38/22
A10472	21 male	**Depression** [depressive disorder]	NAV	72 mg	None	Possible	Not yet recovered (NAV)	35/51
A10801	34 female	**Migraine** [abortive migraine attack]	32	72 mg	None	Doubtful	Recovered (2 days)	34/49
A10885	43 female	**Anxiety disorder** [reactivation of anxiety disorder]	17	18 mg	None	None	Recovered (5 days)	37/50

Source: Attachment 44, Attachment 45 and Attachment 46
NAV: not available
DB: Double-Blind; OL: Open-Label
* number of days since first medication intake in double-blind phase at time of onset of SAE

Discussion of SAEs
Case A10253: This patient had a vertebrobasilare stroke by ultrasound while on drug, but the relationship to drug is not clear. The clinical data collected for this patient are sparse. It does seem that he had had increased blood pressure to 148/77 (baseline was 127/71) at some time during the course of this event, but the records also indicate that he was restarted on Concerta after the event because his stroke was not considered to be drug-related. It should be noted that this patient had been on immediate-release methylphenidate 40 mg/day for the three years prior to the study with evidently no problems related to the drug.

Case A10472: Depression a common disorder and is likely unrelated to study drug. Stimulants, including methylphenidate are often used in practice to treat depression, so the relationship to drug here is not clear.

Case A10801: Headaches are very common and this patient recovered in 2 days. The sponsor has identified headaches as an adverse reaction to Concerta in labeling. Dr. Mannheim has some concern that this case may represent a stroke secondary to a CT scan demonstrating "a probable lacunar (11mm) infarct in caudate nucleus…" This case was interpreted by a radiologist who described this as an "old lesion, very likely a perinatal lesion." From the evidence presented by the sponsor, this cannot reasonably be classified as a new cerebrovascular event. Headaches are prominently identified in labeling as a common adverse reaction.

Case A10885: Exacerbation of anxiety with stimulants is an expected adverse reaction and is prominently described in labeling.

Study 02-159
There were no deaths or serious adverse events reported in this study.

6.3 Cardiovascular Risk Assessment

The sponsor identified cardiovascular adverse events expected from stimulant medications in the development program for Concerta. These include a modest increase in blood pressure, tachycardia, and palpitations. ECG data were collected in Study 02-159 at screening, baseline, after each upward dose titration, and at the Final Visit. Except for an expected increase in heart rate, no abnormalities were noted in any of multiple cardiac interval assessments, specifically, there was no change in QT or QTc intervals. There were no serious treatment-emergent cardiac adverse events reported by the sponsor.

The sponsor (CSS page 48) examined the incidence of adverse events based upon cardiovascular risk status of patients and found that there was no relationship between pre-existing cardiovascular risk status and adverse cardiovascular events.

Dr. Mannheim has identified 13 cases of non-specific ECG changes, which he discusses in his review as being potentially related to cardiac ischemia; four of these cases are grouped as "possible ischemic events" on page 72 of his review. None of these cases is conclusive for myocardial damage; there was no clinical correlation with symptoms, no cardiac enzyme levels were reported as abnormal, and none of these patients had adverse cardiac outcomes. I reviewed these cases with Dr. Mannheim and we agreed that none of these could be classified with certainty as cardiac adverse events.

We asked the Division of Cardiorenal Products (DCRP) to evaluate the ECGs in question. Dr. Stephen Grant, a cardiologist from DCRP, confirmed that the non-specific changes identified by Dr. Mannheim could not be classified with certainty as ischemic or other serious cardiac events. In fact, 12 of the 13 ECGs were read by Dr. Grant as "normal" and none had changes specific to cardiac ischemia developing during the trial (serial ECGs were available). Despite the fact that no cases of cardiac ischemia were identified in the controlled trial database, it should be noted that concerning cases have been identified from post-marketing data on Concerta, and the labeling reflects this in the first WARNING which states, "Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs and usual doses for ADHD."

Dr. Mannheim has made several recommendations for further study of cardiovascular events in his review. He has suggested that a large randomized trial be conducted as a condition for approval in adults. While I agree that the data from a large randomized trial would help us to better quantify the risk of cardiovascular events with Concerta and other stimulants, I don't believe we need the results of a large randomized trial to adequately label Concerta for use in the adult population. We have accepted that the expected cardiovascular side effects of Concerta may increase the cardiovascular risk in some patients, and we have labeled the product accordingly with a strong statement in WARNINGS and PRECAUTIONS. I also agree with Dr. Mannheim that the large cohort study currently being conducted under the auspices of AHRQ—examining cardiovascular endpoints in stimulant treatment of ADHD—will be useful in confirming our understanding of cardiovascular risks associated with stimulants. The data from this study may well be the most definitive we will have on this topic since a large randomized trial would have practical and ethical limitations. At any rate, we know the risk exists and we have carefully and prominently labeled it, so no further action is indicated with regard to cardiovascular risk assessment at this time.

In summary, there are expected cardiovascular risks with all stimulants, and Concerta has these same expected cardiovascular risks. The labeling for Concerta adequately warns physicians of this risk to adults taking the drug for ADHD and no further action is indicated at this time regarding cardiovascular risk and Concerta.

6.4 Dropouts

Dr. Mannheim has pointed out in his review that overall there was a low rate of discontinuation due to adverse events in the pooled data from double-blind studies 3002 and 02-159. There were 69 subjects (16.6%) withdrawn from the drug-treated groups, primarily for adverse events (7%); 3% of placebo-treated patients withdrew for adverse events. The majority of adverse events resulting in discontinuation were known adverse reactions associated with stimulants: anxiety/nervousness, irritability/agitation, gastrointestinal complaints, and increased blood pressure. See Dr. Mannheim's review for a more detailed discussion (pages 34-40).

6.5 Common Adverse Reactions

Table 16 from the sponsor's CSS (pages 51-52) details the adverse events seen in the two double-blind studies used to establish efficacy. From the table, there are several adverse events which are likely adverse reactions to the drug including decreased appetite, dry mouth, nausea, headache, tachycardia, palpitations, vertigo, insomnia, hyperhidrosis, and anxiety/agitation/irritability. These are expected reactions to stimulant medications and are described in labeling.

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Table 16: Number (%) of Subjects With Adverse Events Where CONCERTA is Greater Than or Equal to 1% and Greater Than Placebo by System Organ Class, MedDRA Preferred Term and Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set)

System or Organ Class[a] MedDRA Preferred Term[a]	All CONCERTA N=415 n (%)	Placebo N=212 n (%)
Any adverse event	330 (79.5)	137 (64.6)
Cardiac disorders	**33 (8.0)**	**3 (1.4)**
Palpitations	13 (3.1)	2 (0.9)
Tachycardia	20 (4.8)	0 (0.0)
Ear and labyrinth disorders	**14 (3.4)**	**3 (1.4)**
Vertigo	7 (1.7)	0 (0.0)
Eye disorders	**24 (5.8)**	**5 (2.4)**
Vision blurred	7 (1.7)	1 (0.5)
Gastrointestinal disorders	**135 (32.5)**	**43 (20.3)**
Constipation	6 (1.4)	2 (0.9)
Dry mouth	58 (14.0)	8 (3.8)
Dyspepsia	9 (2.2)	2 (0.9)
Nausea	53 (12.8)	7 (3.3)
Vomiting	7 (1.7)	1 (0.5)
General disorders and administration site conditions	**63 (15.2)**	**22 (10.4)**
Irritability	24 (5.8)	3 (1.4)
Thirst	5 (1.2)	1 (0.5)
Infections and infestations	**55 (13.3)**	**22 (10.4)**
Influenza[b]	8 (1.9)	4 (1.9)
Upper respiratory tract infection	9 (2.2)	2 (0.9)
Investigations	**60 (14.5)**	**23 (10.8)**
Weight decreased	27 (6.5)	7 (3.3)
Metabolism and nutrition disorders	**116 (28.0)**	**21 (9.9)**
Anorexia	7 (1.7)	0 (0.0)
Decreased appetite	105 (25.3)	14 (6.6)
Musculoskeletal and connective tissue disorders	**37 (8.9)**	**17 (8.0)**
Muscle tightness	8 (1.9)	0 (0.0)
Nervous system disorders	**147 (35.4)**	**58 (27.4)**
Dizziness	28 (6.7)	11 (5.2)
Headache	92 (22.2)	33 (15.6)
Paresthesia	5 (1.2)	0 (0.0)
Sedation	5 (1.2)	0 (0.0)
Tension headache	5 (1.2)	1 (0.5)
Tremor	11 (2.7)	1 (0.5)
Psychiatric disorders	**150 (36.1)**	**37 (17.5)**
Affect lability	6 (1.4)	2 (0.9)
Aggression	7 (1.7)	1 (0.5)
Agitation	9 (2.2)	1 (0.5)
Anxiety	34 (8.2)	5 (2.4)
Bruxism	7 (1.7)	1 (0.5)
Confusional state	5 (1.2)	1 (0.5)
Depressed mood	16 (3.9)	3 (1.4)

(Continued)

Table 16: Number (%) of Subjects with Adverse Events where CONCERTA is Greater Than or Equal to 1% and Greater Than Placebo by System Organ Class, MedDRA Preferred Term and Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set) (Continued)

System or Organ Class [a] MedDRA Preferred Term[a]	All CONCERTA N=415 n (%)	Placebo N-212 n (%)
Psychiatric disorders (Continued)		
Depression	7 (1.7)	2 (0.9)
Initial insomnia	18 (4.3)	6 (2.8)
Insomnia	51 (12.3)	13 (6.1)
Libido decreased	7 (1.7)	1 (0.5)
Nervousness	13 (3.1)	1 (0.5)
Restlessness	13 (3.1)	0 (0.0)
Tension	5 (1.2)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	**19 (4.6)**	**12 (5.7)**
Pharyngolaryngeal pain	7 (1.7)	3 (1.4)
Skin and subcutaneous tissue disorders	**30 (7.2)**	**6 (2.8)**
Hyperhidrosis	21 (5.1)	2 (0.9)

[a] Subjects counted only once within each system organ class and MedDRA preferred term.
[b] Source table in cross-reference is rounded; based on incidence without rounding, the incidence of influenza is higher in the CONCERTA-treated subjects than in the placebo-treated subjects.
Note: Adverse events were included only if the percentage was ≥1% without rounding.

Dose-related Adverse Events

Table 36 (below) is taken from the sponsor's study report of study 3002. From this fixed-dose study it is possible to attribute dose-relatedness to adverse events. From the table, many of the known adverse events of stimulants appear to be dose-related and include palpitations, tachycardia, dry mouth, nausea, decreased appetite and weight, insomnia, tremor, anxiety, nervousness/restlessness, and irritability. No unexpected adverse events were identified.

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Table 36: Treatment-Emergent Adverse Events During Double-Blind Phase Occurring in >2% of Subjects Receiving PR OROS MPH, by Preferred Term

(Study 42603ATT3002: *All Subjects / Double-Blind*)

Body System Preferred Term n (%)	Placebo (N=96)	PR OROS MPH 18 mg (N=101)	PR OROS MPH 36 mg (N=102)	PR OROS MPH 72 mg (N=102)	PR OROS MPH All (N=305)
Any AE	**63 (65.6)**	**76 (75.2)**	**77 (75.5)**	**84 (82.4)**	**237 (77.7)**
Cardiac Disorders	**0**	**5 (5.0)**	**10 (9.8)**	**13 (12.7)**	**28 (9.2)**
Palpitations	0	2 (2.0)	5 (4.9)	5 (4.9)	12 (3.9)
Tachycardia	0	4 (4.0)	5 (4.9)	8 (7.8)	17 (5.6)
Ear and Labyrinth Disorders	**0**	**3 (3.0)**	**4 (3.9)**	**5 (4.9)**	**12 (3.9)**
Vertigo	0	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Gastro-Intestinal Disorders	**18 (18.8)**	**25 (24.8)**	**32 (31.4)**	**40 (39.2)**	**97 (31.8)**
Abdominal pain upper	5 (5.2)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Diarrhea	5 (5.2)	3 (3.0)	1 (1.0)	4 (3.9)	8 (2.6)
Dry mouth	2 (2.1)	8 (7.9)	7 (6.9)	21 (20.6)	36 (11.8)
Nausea	4 (4.2)	8 (7.9)	16 (15.7)	15 (14.7)	39 (12.8)
General Disorders and Administration Site Conditions	**11 (11.5)**	**10 (9.9)**	**9 (8.8)**	**10 (9.8)**	**29 (9.5)**
Fatigue	6 (6.3)	4 (4.0)	4 (3.9)	6 (5.9)	14 (4.6)
Infections and Infestations	**12 (12.5)**	**10 (9.9)**	**12 (11.8)**	**7 (6.9)**	**29 (9.5)**
Influenza	3 (3.1)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Nasopharyngitis	9 (9.4)	7 (6.9)	8 (7.8)	4 (3.9)	19 (6.2)
Investigations	**8 (8.3)**	**9 (8.9)**	**12 (11.8)**	**12 (11.8)**	**33 (10.8)**
Weight decreased	5 (5.2)	3 (3.0)	8 (7.8)	11 (10.8)	22 (7.2)
Metabolism and Nutrition Disorders	**9 (9.4)**	**22 (21.8)**	**24 (23.5)**	**36 (35.3)**	**82 (26.9)**
Decreased appetite	7 (7.3)	20 (19.8)	22 (21.6)	35 (34.3)	77 (25.2)
Nervous System Disorders	**34 (35.4)**	**42 (41.6)**	**39 (38.2)**	**47 (46.1)**	**128 (42.0)**
Dizziness	7 (7.3)	6 (5.9)	10 (9.8)	9 (8.8)	25 (8.2)
Headache	17 (17.7)	26 (25.7)	21 (20.6)	17 (16.7)	64 (21.0)
Initial insomnia	2 (2.1)	3 (3.0)	2 (2.0)	5 (4.9)	10 (3.3)
Insomnia	7 (7.3)	12 (11.9)	12 (11.8)	17 (16.7)	41 (13.4)
Tremor	1 (1.0)	1 (1.0)	1 (1.0)	7 (6.9)	9 (3.0)
Psychiatric Disorders	**6 (6.3)**	**18 (17.8)**	**24 (23.5)**	**40 (39.2)**	**82 (26.9)**
Aggression	1 (1.0)	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Anxiety	1 (1.0)	3 (3.0)	5 (4.9)	8 (7.8)	16 (5.2)
Depressed mood	1 (1.0)	6 (5.9)	3 (2.9)	5 (4.9)	14 (4.6)
Depression	1 (1.0)	0	3 (2.9)	4 (3.9)	7 (2.3)
Irritability	1 (1.0)	4 (4.0)	4 (3.9)	9 (8.8)	17 (5.6)
Nervousness	1 (1.0)	0	3 (2.9)	8 (7.8)	11 (3.6)
Restlessness	0	0	2 (2.0)	6 (5.9)	8 (2.6)
Skin and Subcutaneous Tissue Disorders	**3 (3.1)**	**9 (8.9)**	**5 (4.9)**	**10 (9.8)**	**24 (7.9)**
Hyperhidrosis	1 (1.0)	5 (5.0)	3 (2.9)	8 (7.8)	16 (5.2)

Source: Attachment 38

6.6 Vital Signs

Concerta was associated with modest increases in blood pressure and pulse, which is consistent with the known effects of stimulants and with what is known from the experience in the pediatric population. The blood pressure readings were recorded in different positions in the two double-blind studies, and so are reported separately.

For study 3002, the mean increases in standing systolic and diastolic blood pressures from baseline to Final Visit on drug were 0.9 and 0.8 mmHg versus 1.1 and -1.8 mmHg for placebo, respectively. The mean change in standing pulse rate from baseline to Final Visit was 6.2 bpm for the all three Concerta treatment groups versus 2.7 bpm for the placebo group.

For study 02-159, the mean change on Concerta from baseline to Final Visit for systolic and diastolic blood pressure was -1.2 mmHg 1.1 mmHg versus -0.5 and 0.4 mmHg for placebo, respectively. The mean change in pulse was 3.6 bpm for drug versus -1.6 bpm for the placebo group.

The sponsor conducted an analysis of blood pressure and pulse of potentially clinical significance for subjects with known cardiovascular risk factors and compared these to changes in blood pressure and pulse in patients without cardiovascular risk factors. This analysis did not identify an association of pre-existing cardiovascular risk factors and potentially clinically significant vital sign changes. The details of this analysis can be found in the Summary of Clinical Safety pages 138-139/2058. Increases in blood pressure and tachycardia are well known adverse reactions associated with stimulants and are prominently labeled.

Changes in Body Weight

The mean change in body weight from baseline to Final Visit during double-blind treatment (pooled results) with Concerta was approximately -1.5 kg compared to an increase of 0.3 kg in the placebo group. During the open-label treatment, the mean decrease in body weight was -2.0 kg, which is consistent with the adverse reactions of decreased appetite. This is a well known adverse reaction with stimulants and is prominently labeled.

Summary of Vital Signs Findings

Concerta causes modest increases in blood pressure and heart rate. Patients lose a small amount of weight when treated with Concerta.

6.7 ECG

ECGs were collected at screening, baseline, each titration visit and at Final Visit for study 02-159. With the exception of increased heart rate, no other ECG interval measurements showed a greater post-baseline change in patients receiving Concerta compared to patients receiving placebo; specifically, there was no evidence of increase in the QT interval (see discussion above under Cardiovascular Risk Assessment).

6.8 Laboratory Values from Double-Blind Studies Analysis Set

As noted in Dr. Mannheim's review (page 47), there were no trends in abnormal laboratory values reported by the sponsor and no markedly abnormal values seen in the double-blind studies excepting a greater decrease in total cholesterol in Concerta versus placebo (-7.5 mg/dL vs. -1.0 mg/dL) and LDL (-7.9 mg/dL for Concerta vs. -2.8 mg/dL for placebo).

6.9 Safety Conclusions

Exposure to Concerta from the Summary of Clinical Safety was 282 person-years in 5 double-blind and open-label studies in patients with ADHD. There were 1015 adult subjects in these studies with a mean age of 36.7 years. Mean duration of treatment was 101.4 days (43.5 days during double-blind studies and 98.8 days during open-label studies). Concerta was generally well tolerated during the short-term (5-7 weeks) double-blind studies. Longer-term open-label studies (including one with duration of 9 months and another with duration of 12 months) suggest that the incidence of adverse events does not increase over time.

Concerta has a predictable profile of adverse events and some of these are dose-related (see discussion above). Concerta is a stimulant, and as such may produce predictable cardiovascular changes including modest increases in heart rate and blood pressure. ECGs were obtained during the development program and except for heart rate, had no clear pattern of abnormalities associated with drug treatment.

Psychiatric adverse events were also more common in Concerta treated patients, primarily increased anxiety/nervousness, which would be expected from this class of medications.

There were no concerning changes in mean serum chemistry or hematology laboratory values and no potentially clinically significant outlier values of concern to the primary medical reviewer.

7.0 Postmarketing Experience

The sponsor has certified that for the life of the product through 28 February 2007 there have been 889 spontaneous case reports for Concerta involving adults, 180 (20%) of which were considered serious. The majority of these spontaneously reported events are consistent with what is known from the pediatric experience and no new safety concerns were identified in adults.

8.0 Literature Review

The sponsor conducted a comprehensive literature search through 21 February 2007 for Concerta used in adults. A total of 44 publications were identified and reviewed for relevant clinical efficacy and safety data. The sponsor's conclusions were that there is a consistent demonstration of efficacy and no concerning safety findings.

6.0 PSYCHOPHARMACOLOGICAL DRUGS ADVISORY COMMITTEE (PDAC) MEETING

This NDA was not presented to the PDAC.

7.0 PREA

I have recommended that the (b) (4) mg/day dose not be approved due to no clear evidence of additional efficacy above 72 mg/day and the known drug-related side effects of stimulants. If this recommendation is accepted by the Director, then this application does not trigger PREA because there would be no new dosage (from what is already approved in children and adolescents), the route of administration would remain unchanged from that previously approved, and this drug has already been approved in children and adolescents and is therefore adequately labeled for the pediatric population.

7.0 DSI INSPECTIONS

Clinical investigator sites from both pivotal studies were inspected by DSI and it was determined that the data generated to support this application were acceptable.

8.0 ACTION LETTER

We should explain that the efficacy data do not support using doses higher than 72 mg/day in adults.

9.0 DMETS

Concerta is an approved and established trade name and input from DMETS was not required.

10.0 PHASE 4 COMMITMENTS

The team has not identified any Phase 4 Commitments.

11.0 CONCLUSION AND RECOMMENDATION

It is clear from the data presented by the sponsor that Concerta is efficacious in the acute treatment of adults with ADHD. The sponsor has submitted the results of two trials with similar positive

results. Both trials support a dose of up to 72 mg/day, but it is not clear that doses above 72 mg/day add any additional benefit.

Concerta has a predictable profile of adverse events and some of these are dose-related (see discussion above). Concerta is a stimulant and as such may produce predictable cardiovascular changes including modest increases in heart rate and blood pressure. ECGs were obtained during the development program and excepting for heart rate, had no clear pattern of abnormalities are associated with drug treatment.

Psychiatric adverse events were also more common in Concerta treated patients, primarily increased anxiety/nervousness, which would be expected from this class of medications.

There were no concerning changes in mean serum chemistry or hematology laboratory values and no potentially clinically significant outlier values of concern.

The recommended final action is APPROVAL.

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

/s/

Mitchell Mathis
6/5/2008 03:40:43 PM
MEDICAL OFFICER
CDTL Memo

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	Supplemental, Clinical and Safety Data
Submission Number	21, 121
Submission Code	SE5-017
IND Number	54, 575
Letter Date	August 31, 2007
Stamp Date	August 31, 2007
Amendments Stamp Date	• December 06, 2007: Revised Labeling • December 21, 2007: CRF's, ECG's, Patient Profiles, 4-Month Safety Update • February 08, 2008: Modified Narratives, Cardiovascular AE Information, HAM-A and HAM-D for Psychiatric AE's, Data Quality Assessment • February 29, 2008: HAM-A and HAM-D Outlier Analysis, Headache, Concurrent Medications With Cardiovascular AE's Analysis • March 13, 2008: Final Clinical Study Report for Study 12-304, Long-Term Safety Study
PDUFA Goal Date	June 05, 2008
Reviewer Name	Glenn B. Mannheim, MD
Review Completion Date	April 14, 2008
Established Name	Methylphenidate HCl
Code Name	OROS (methylphenidate HCl)
Trade Name	Concerta
Therapeutic Class	Stimulants
Applicant	Johnson & Johnson Pharmaceutical Research & Development, L.L.C.
Priority Designation	Standard
Formulation	Extended Release Tablets: 18, 27, 36, or 54 mg
Proposed Dosing Regimen	18-(b) (4) mg
Intended Population	• Adults: ≥ 18 years

Table of Contents

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

Based upon the information reviewed to date, parts of which came late in the review cycle, it is recommended that the Division take an "approvable action"; however, this reviewer has residual concerns about cardiovascular safety. To mitigate some of these concerns and to satisfy Sec. 505 of the FDC Act mandating an application "include *all tests reasonably applicable* to show" that the "*drug is safe and effective* under...proposed labeling", the following is recommended:

- The use of Concerta for doses *no greater than 54 mg* in adults between 18-49 years, which is what is probably supported by the available data (if one just uses the fixed dose study it would be 36 mg) reviewed to date (refer to efficacy conclusions and recommendations);
- Consider requiring, a new Phase 3, fixed dose study to adequately identify the safe and effective dose for subjects older than 49 years;
- Consideration should be given to requiring a large, randomized *simple safety trial* to look at cardiovascular events (e.g. stroke, myocardial infarction and sudden death) and making it *a condition for approval. A phase 4 commitment for such a study should not suffice* since a good percentage of phase 4 commitments do not get done[1], and when they do get done, many years may have elapsed; and a large number of adults are currently being and will be treated with methylphenidates and other ADHD drugs. The February 2006 AC Meeting suggested that on the order of 1 million prescriptions for ADHD products per month are dispensed to patients over 18 years. Further, one might argue that FDA and AHRQ currently have a large cohort study looking at cardiovascular endpoints (possibly with data by the summer 2009), and doing such a study would be redundant. Information to be gained from a large simple trial which would not be obtained from the current study are: as a result of randomization, a large simple trial would give a more appropriate reference group (adults with ADHD) compared to non stimulant users without ADHD in the observational study; and, 2) the simple trial would provide information on the early period after starting stimulants (e.g. time to event) which will not be readily available form the observational study. The observation in Study 42603ATT3002 (3002) of *an event rate in excess of the background* [2 events/ 30 person years (Concerta) vs. 150/10,000 person years (background)] is of real concern and should with the recent findings by Gould [2] provide an impetus for making such an action a condition for approval.
- The Agency and Sponsor(s) should consider doing a pooled analysis across the entire ADHD program in adults.
- Consideration should be given to having the current labeling modified, preferably to a black box, consistent with my earlier recommendations[3], and probably should reflect some of the following :

1 Report on the Performance of Drug and Biologics Firms in Conducting Postmarketing Commitment Studies: 04/15/2008

2.Gould MS, ET. al. Sudden Death and use of Stimulant medications in Youth; NEJM (Under Review, 2008)

3 s (b) (4)

- Stimulants are associated with sudden cardiac death in healthy, asymptomatic children without structural heart disease (Gould et. al.);
- There is probably a small, but real risk of death, associated with the use of stimulants so that the user needs to carefully balance risks and benefits;
- Patients with co-morbid risk factors of age, hypertension, obesity, physical inactivity, high cholesterol and low high-density lipoprotein (HDL), hypertriglycidemia, diabetes mellitus, coagulation abnormalities are at independent risk for having cardiovascular event and strokes (Framingham Heart Study) that little is known about the interaction of stimulant use on patients with these different risks (discussed further in reference below)[4] but that there likely may be an additive risk in adults taking stimulants with any of these risk factors;
- The role of structural heart disease in sudden death is at best uncertain, presumably is not good, and could even possibly be a secondary rather than a primary event, however, we have no data on long-term safety and the long-term effect on the heart;
- No information is available about the role of exercise and chronic stimulant use because it has largely been unstudied;
- Patients may be at increased risk of strokes or having other cerebrovascular events;
- And, consistent with the American Academy of Neurology, the American Stroke Association and others, the medication guides should be upgraded to instruct the consumer on the warning signs of a stroke, reversible ischemic neurological deficit (RIND) and what to do, should you get any of these symptoms.

1.2 Summary of Clinical Findings

1.2.1 BRIEF OVERVIEW OF CLINICAL PROGRAM

The present sNDA consists of two (2) Phase III double blind trials in adults with ADHD:

- Study 42603ATT3002 (3002), a 5 week, *fixed dose* Concerta study [18 mg (n=101), 36 mg (n=102), 72 mg (n=102)] or Placebo (n=96)] was performed in the European Union;
- *Study 02-159* was a 7 week, dose-*titration study* [36, 54, 72, 90, or 108 mg] in 226 adults assigned to either placebo (n=116), or Concerta (n=110) was performed in the United States.

The following open-label studies were also submitted:

4 The current review of cardiovascular adverse events of interest in the double-blind studies by the sponsor suggest increased risk of tachycardia and palpations on Concerta compared to placebo, the implications of which are uncertain [Concerta Module 2.7 Clinical Summary 2.7.4 Clinical Summary: pgs. 72-74) discussed further in the Section entitled "Other Assessments/Analysis of Adverse Events by Cardiovascular Risk Status (CRS)"]. Further analyses are provided by the sponsor in the Response to FDA-74 Day Letter-Additional Analyses February 2008, Sec. 4.3, relating to the long-term open label study, states that "subjects experiencing cardiovascular adverse events of interest in this long-term open-label safety study, did demonstrate a consistent modest increase in blood pressure and pulse that was apparent after 1 week of exposure and throughout the course of the study".

- *Study 12-304* was a US *dose titration* study (36-108 mg/day) conducted in about 550 subjects [84 (15 %) from Study 02-159 (double-blind)]; 466 (85 %) de-novo] for up to one year;
- *Study C-99-018-00* was a *dose-titration, cohort* study (18 mg, 36 mg, or 54 mg) performed in a community setting involving 136 subjects (18-66 yrs) for up to 9 months;
- *Study CON-CAN-4* was a *Canadian, pilot dose-titration* study (18 mg, 36 mg, 54 mg or 72 mg) involving 32 subjects (19-54 yrs) treated for about 1 month.

1.2.2 EFFICACY

Study 42603ATT3002 (3002), a 5 week, double-blind, *fixed dose* Concerta study [18 mg (n=101), 36 mg (n=102), 72 mg (n=102)] or Placebo (n=96)] support an approvable action for Concerta for doses *no greater than 36 mg* in adults between 18-49 years. Further support is given by Study 02-159, the 7 week *dose-titration* study (Concerta, n=110; placebo, n=116), which if considering an average dose might suggest a dose of 54 mg, Further discussion about the basis for these recommendations is provided [Efficacy Conclusion(s) and Recommendation(s)].

1.2.3 SAFETY

- There was an imbalance of cerebrovascular events in the double blind portion of Study 42603ATT3002 (3002), with 2 out of 304 subjects exposed to Concerta having evidence of a cerebrovascular event and 0 out of 96 subjects exposed to placebo, not having such an event. The open-label portion of this trial also had 1 event suggestive of a cerebrovascular event (RIND) associated with a blood pressure of 170/117 mm Hg, supine and 184/103 mm Hg standing. A possible event suggestive of an event which occurred in another subject was later denied by the sponsor. The rate observed in this double-blind study was 2 events in about 30 person years of exposure, which is considerably higher than the background rate of 150/10,000 person years, which was presented at the February 2006 DSaRM (referenced to Heart disease and stroke statistics-2004 update. American Heart Association; US census data, 2000).
- Other cerebrovascular events have been identified in other adult ADHD trials. To date, there have been 5 drugs which submitted NDA's examining the use of stimulants in adult ADHD. There has been 1 additional trial with atomoxetine which his been classified a non-stimulant, but which has many properties similar to the stimulants. The totality of subjects exposed in all these trials have been about 2235 (drug) and 1087 (placebo). There have been 3 and 5 events, respectively in all the double blind and open label cases. Two (2) of these events are those identified in Study 42603ATT3002 (3002).
- Based on the selection criteria used to select cardiovascular events of interest, correlating them with adverse events , vital sign and ECG's, there appeared to be an imbalance of such events in the double blind Study 02-159 (Concerta: 11/113 [9.7 %], Placebo: 2/116 [1.7 %]). The significance and impact of this imbalance is also uncertain and may need further exploration (s). Additional cases were identified in the open-label exposure but since no control is available and historical controls seem to vary widely, limited interpretations are possible. The open-label experience may give some credence to the controlled study, and which in totality may need further evaluation and explanation, but suggests rigorous caution be applied.

1.2.4 DOSING REGIMEN AND ADMINISTRATION

The sponsor has placed the following language in the proposed labeling:

"For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed (b) (4) mg/day for adults."

The sponsor defines adults as up to 65.

In this reviewer's opinion, the data does not support that, but would support the use of Concerta for doses no greater than 36 mg (fixed dose study) and probably up to 54 mg (flexible dose study). It does not support the safe and effective use in subjects greater than 49 years as a result of insufficient exposure in that age group.

1.2.4 SPECIAL POPULATIONS

In this reviewer's opinion there has been inadequate exposure of subject's greater than 49 years of age to adequately assess the safe and effective use of Concerta in this population.

2 INTRODUCTION AND BACKGROUND

Concerta [OROS (racemic methylphenidate HCL) Extended-Release Tablets] is currently approved for children, 6-12 years of age, for the indication of ADHD at doses of 18, 27, 36 and 54 mg on August 1, 2000. Approval for doses up to 72 mg for ADHD in adolescents (13-17 years) was given on October 21, 2004 (S-008).

The current supplemental NDA (21-121 SE5-017) hopes to extend this indication to adults (18-65 years) with a maximum, allowable dose of (b) (4) . The present sNDA consists of two (2) Phase III trials in adults with ADHD [Study 02-159 and Study 42603ATT3002 (3002)] and a one-year open label study [Study 12-304]. The one-year open label experience is partially supplemented by a 9 month open-label study [Study C-99-018-00], a 38 day open-label study [CON-CAN-4] and a 5 week double-blind SSRI/SNRI augmentation in major depressive disorder (MDD) [Study CON-CAN-3].

Brief summaries of these trials are listed below.

Double-Blind Studies in Adult ADHD:

- *Study 02-159*, a US study, was a 7 week randomized, placebo-controlled, double-blind, parallel-group, *dose-titration study* [36, 54, 72, 90, or 108 mg] in 226 adults (18 - 65 yrs) randomly assigned to one of two groups: placebo (n=116), or Concerta (n=110).

- *Study 42603ATT3002 (3002)*, a European Study, was a randomized, placebo-controlled, double-blind, parallel-group, five-week *fixed dose-response study*, involving 4 doses [18, 36, or, 72 mg; or, placebo (PBO)], followed by a seven-week open-label flexible dose (18 to 90 mg) phase in 401 subjects (18-65 yrs) with adult ADHD. The 401 subjects were randomized in the double blind portion of the study into the PBO (n=96), 18 mg (n=101), 36 mg (n=102), and 72 mg (n=102).

Open Label Studies in Adult ADHD:

- *Study 12-304* was a US *open-label, doses titration* study (36-108 mg/day) conducted in about 550 subjects [84 (15 %) from Study 02-159 (double-blind)]; 466 (85 %) de-novo] for up to one year.

- *Study C-99-018-00* was an *open-label, dose-titration, cohort* study (18 mg, 36 mg, or 54 mg) performed in a community setting involving 136 subjects (18-66 yrs) for up to 9 months.

- *CON-CAN-4* was an *open-label, Canadian, pilot dose-titration* study (18 mg, 36 mg, 54 mg or 72 mg) involving 32 subjects (19-54 yrs) treated for about 1 month.

Other Clinical Study:

- CON-CAN-3 was *a multicenter, Canadian, double-blind, randomized, placebo-controlled* study using Concerta (18-54 mg/day) as an *adjunctive therapy* to adults with MDD for 5 weeks.

2.1 Product Information

Concerta [OROS (racemic methylphenidate HCL) Extended-Release Tablets] is a central nervous system stimulant currently approved for children, 6-12 years of age, for the indication of ADHD at doses of 18, 27, 36 and 54 mg on August 1, 2000. Approval for doses up to 72 mg for ADHD in adolescents (13-17 years) was given on October 21, 2004 (S-008).

The proposed supplemental indication is for the use of Concerta for adult ADHD (18-65 years of age) and with a starting dose of 18 or 36 mg/day to be titrated up to (b) (4) day based on clinical response.

2.2 Currently Available Treatment for Indications

The following drugs are currently approved in the United States for the treatment of adult ADHD: Focalin XR (Dexmethylphenidate HCl: NDA 21802), Adderall XR (Amphetamine, Mixed Salts: NDA 21-303/S005, 006), Vyvanse (Lisdexamfetamine: N 021977/SE5 001) and Strattera (atomoxetine: NDA 21-411).

2.3 Availability of Proposed Active Ingredient in the United States

Concerta is available in the Unites States as are other methylphenidate products. Major safety concerns are associated with it use. It currently carries a black box for drug dependence, and contains warnings and precautions about cardiovascular, psychiatric risks, growth suppression,

2.4 Important Issues with Pharmacologically Related Products

There have been reports of sudden death, myocardial infarction, stroke, hypertension, and other cardiovascular related events associated with the use of stimulants. Much of this experience was pediatric occurring largely prior to the commercial availability of Adderall XR in 2004 and is summarized in the post-marketing safety review of that year[5]. There has been no updated review of AERS data to assess the marketed safety experiences for stimulant therapy in the adult populations [e.g. death, sudden death, cardiovascular SAEs (including stroke)] in the 4 years since that review. Short-term use with stimulants have been associated with 5 mm Hg increases in systolic blood pressure, which over the long-term has been associated with an increase in mortality. The impact of co-morbid risk factors of age, hypertension, obesity, physical inactivity,

5 Gelperin K, ET. al. Review of AERS data for marketed safety experience during stimulant therapy: death, sudden death, cardiovascular SAEs (including stroke). 04/27/2004.

high cholesterol and low high-density lipoprotein (HDL), hypertriglycidemia, diabetes mellitus, coagulation abnormalities on cardiovascular events and strokes have largely been known from the Framingham Heart Study, but little is known about the interaction of stimulant use on patients with different risks. Furthermore, there is no information on the long-term effects of stimulant therapy on the heart, despite the observation of structural heart changes in animal studies and in stimulant abuse.

There was discussion of these issues by two FDA Advisory Committees in 2006 with differing recommendations. The data presented at the February 2006 AC Meeting suggested that on the order of 1 million prescriptions for ADHD products per month are dispensed to patients over 18 years, many of which are for methylphenidate-containing products. Hence, the public health burden of cardiovascular risks for adults using methylphenidate could be large.

FDA placed a class warning on all stimulants in 2006, which consisted of a warning and precaution for serious cardiovascular and psychiatric, with emphasis on pre-existing structural cardiac abnormalities or other serious heart problems. Medication guides warning of these same issues were created. FDA and AHRQ co-sponsored a large observational study of cardiovascular events in children and adults with ADHD.

The Columbia University Case Control Study (Gould MS, et. al. In Press, 2008) has recently shown an association between methylphenidate use and sudden pediatric death which is independent of heart disease.

2.5 Regulatory Activity

The following meetings took place between the sponsor (J&J) and FDA on the indicated dates with the following relevant decisions reviewed which relate to clinical issues in this sNDA:

2.5.1 2/04/2002: CONCERTA ADOLESCENT AND ADULT DEVELOPMENT PROGRAM:

- Study 02-159, the Phase 3 flexible dose study: "the Division's preferred design would be a traditional parallel group, fixed dose study, a design that *would be capable of assessing dose response and thus could determine the optimum dose for adults.*" "..it was also pointed out by FDA *that adults may have different vulnerabilities for adverse drug reactions than pediatric patients (e.g., hypertension), and therefore safety data in adults at the proposed dosages will be needed.*
- Preferred Patient Population: FDA expressed a preference for a 50/50 mix reflective of actual population practice and said patients with medical co- morbidities, as previously mentioned, such as, hypertension should also be included in the mix and concurrent medications are acceptable. It was also agreed that strict exclusion criteria for comorbid conditions or concomitant psychiatric medications would be undesirable and would limit the external validity of the adult trial; it is anticipated that up to 40% of adult subjects will have a psychiatric comorbidity.'

2.5.2 07/12/2005: CONCERTA ADULT DEVELOPMENT PROGRAM:

- Study 02-159, the Phase 3 flexible dose study, was described as a *fixed dose study* at (36, 72, and 108) and placebo and 12-304, the open-label study was planned as a randomized study at 72 or 108 mg.

- FDA "found the design of the studies acceptable. but expressed our concern that there would be essentially no experience in older patients (>55) and those with comorbidity, in particular cardiovascular. We noted that study *02-160 suggested a clear exposure response relationship for increased BP and HR, both of which are recognized risks in patients with cardiovascular disease. The sponsor agreed to consider expanding the heterogeneity of patients* in study 304, and also to *explore the literature and other sources of information to try to better understand possible risks of this drug in vulnerable adult patients*. We noted that this would be an important issue to address in the NDA."

- Further, "we asked the sponsor to structure the adverse event section of the study report in such a way to facilitate exploration and understanding of adverse event findings. For example, we noted a clear dose response relationship for HA, and noted that it would be useful to try to correlate HA incidence with increases in BP."

- In response to a discussion of the adequacy of Study 02-160 (Open-label, Dose Escalation, Multiple Dose Pharmacokinetic Study in Adults) we stated that the study provided important information but "we asked the sponsor to better explore the risks of Concerta in adult patients who might be expected to be at risk for cardiovascular events, both through studies 02-159 and 12-304, and also through other sources. *We noted that the PK/PD analysis to be conducted in protocol 02-159 (although it is not planned in detail in the protocol) should focus on the dose selection to get the optimal dose for balancing the benefit and risk.*"

2.5.3 03/13/2007: TYPE B, PRE-SNDA

- Study 3002 was a randomized, placebo-controlled, 5-week, parallel group, *fixed dose* study (18, 36, 72 mg/day vs. placebo); and Study 02-159 was a randomized, placebo-controlled, 7-week, parallel group, *flexible-dose* (36 to 108 mg/day vs. placebo). "..if there are reasonable numbers of cardiovascular adverse events, these adverse events should also be classified by the presence or absence of cardiovascular risk factors (e.g. history of CV disease, active smoking, and hyperlipidemia, history of diabetes mellitus, hypertension, family history, exercise, diet, and BMI > 30 kg/m2.) with the number of subjects with the following possible ischemic events: coronary (chest pain, angina, treatment emergent ECG changes, enzyme elevation, etc.), cerebrovascular (paresthesia, numbness, weakness, cranial nerve abnormality, etc)., and other ischemic event (gastro-intestinal, as with colitis, or, peripheral extremities as with Raynaud's, etc), and, vital sign changes (SBP > 140 mmHg , DBP > 90 mmHg, HR > 110 BPM). *The safety data should also be sub-grouped by dose, and gender. Exposure should be provided by the number of subjects, gender, and person time.*"

- A *history of cardiovascular risk was systematically collected only in two studies (02-159 and 12-304).* This included collection of general cardiovascular history, smoking status, BMI, history of diabetes mellitus and hypertension. Lipid profiles were also collected.

- The Sponsor proposes to use *"HR>100 bpm"* as the threshold level to declare *tachycardia.*

2.5.4 10/24/2007: FILING MEETING

The Division sent a fileable action letter on 11/09/2007. In that letter multiple, potential review issues were identified which are summarized.

- Study 02-159: Missing multiple CRF's, need of patient profiles, absence of multiple ECG's in subjects identified as having Cardiovascular Adverse Events of Interest, need for work-ups for subjects with serious adverse events, data missing in many case narratives requiring many to be re-done, results of the HAM-A and HAM-D and study and outlier analysis, and correlations of abnormal ECG's and clinical signs and symptoms.

- Study 3002: data missing in many case narratives requiring many to be re-done, need for supporting clinical data and ancillary studies for specific subjects with significant adverse events, copies of hospital records and imaging studies for multiple subjects, and dataset verification.

- Study 12-304: absence of multiple ECG's and CRF's in subjects identified having Cardiovascular Adverse Events of Interest, data missing in many case narratives requiring many to be re-done.

- Unable to Locate or Missing Data Previously Requested in pre-NDA Meeting consisting of an analysis of analyzing the cardiovascular safety data for subjects with cardiovascular events of interest by the following identifiable cardiovascular risk factors: history of cardiovascular disease, active smoking, history or presence of hypertension, history or presence of hyperlipidemia, presence of elevated CRP, history or presence of diabetes mellitus, obesity (BMI > 30 kg/m2 at baseline), and age ($\geq$ 50 years at baseline).

    - Need for classification of headaches by headache history, headache type, hypertension, etc.

    - Analyzing subjects with cardiovascular adverse events of interest by concurrent medications and concurrent use with Concerta.

    - Need for structured product labeling (SPL) format

The Division sent a modified fileable action letter on 12/13/2007.

2.5.5 12-06-07 SPONSOR'S SUBMISSION

- Revised labeling submitted.

2.5.6 12-21-2007 SPONSOR'S RESPONSE AND SUBMISSIONS

- CRF's, cardiologist interpretation of ECG's and patient profiles provided. Narratives deferred to February 2008. Discharge summaries, hospital records and imaging studies would not be provided as a result of J&J's interpretation of privacy laws in Europe and EU Directive 95/46/EC.

- 4-Month Safety Update provided with addition of dyskinesia in adverse reactions in postmaketing experience and addition of depressed mood due discontinuation as a result of adverse reactions.

2.5.7 02-08-2008 SPONSOR'S RESPONSE AND SUBMISSIONS

- Modified narratives were submitted. Partial information of cardiovascular adverse events of interest received with discharge summaries being deferred to February 28, 2008. Responds to questions posed by the Division in an email dated February 1, 2008, regarding CRFs and ECGs from studies 12-304, 02-159 and 02-160, and questions on the conduct of a definitive QT study and definitions of cardiovascular adverse events. HAM-A and HAM-D scores at baseline and end of study are included for psychiatric adverse events.

- Reinterpretation of EU Directive 95/46/EC will allow sponsor to supply the requested information. The written response to the queries along with any relevant source documentation such as clinic notes, hospital records and ancillary test results are provided in this submission.

- Provides assurance that data quality control measures have been effective.

2.5.8 02-29-2008 SPONSOR'S SUBMISSIONS

- Revised labeling, HAM-A/HAM-D outlier analysis for Study 02-159, headache analysis for all integrated double blind studies [3002 (DB portion) and 02-159 and concurrent medication analysis for subjects who reported a cardiovascular adverse event of special interest provided.

2.5.9 03-13-2008 SPONSOR'S SUBMISSIONS

- Provides Final Clinical Study Report for Study 12-304, Long-Term Safety Study

2.6 Other Relevant Background Information

There has been international concern about the cardiovascular and psychiatric risks associated with stimulants, as well as the risk of sudden death.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 Biometrics

The Division of Biometrics I (HFD-710) finds that based on, the 5-week fixed dose, European Union (EU) study 42603ATT3002 (3002) "once daily dosages of oral CONCERTA® 18, 36 and 72 mg are effective for the treatment adult ADHD, as assessed by change from baseline in sum of inattention and hyperactivity/impulsivity subscale score of CAARS". They further find that Study 02-159, the 5-week United States, dose titration (36 to 108 mg/day) showed "a therapeutic advantage of CONCERTA® over placebo for the treatment of adult ADHD in terms of the change from baseline in the AISRS total score."

3.2 Good Clinical Practice Branch/DSI

The Division of Scientific Investigations (DSI), Good Clinical Practice Branch I, was asked to visit Site 118 [Angela Pinheiro, M.D., Summit Research Network, Inc., Farmington, MI] as a result of excessive enrollment with discontinuations resulting in adverse event for studies 02-159 (n=12) and 12-304 (n=13).

DSI was also asked to visit Site 107 [Donald J. Garcia, Jr, M.D., FutureSearch Trials, Austin, TX] as a result of excessive enrollment with discontinuations resulting in adverse event for studies 02-159 (n=12) and less so for study 12-304 (n=2). *The formal results of the audit from this site are still pending at the time of this review.* However, an e-mail received on 04/25/2008 indicates that there are no significant issues to report.

3.3 Cardiovascular and Renal Products/HFD-110

The Division of Cardiovascular and Renal Product, was asked to review the clinical history and ECGs of the cases identified from the Phase III double-blind study (02-159) and provide input on whether or not the adverse events could be considered cardiac in origin and to provide there best diagnosis for each case; and to suggest the best approach to classifying these cases for purposes of pooling them across studies so that we can make meaningful drug to placebo comparisons. *This consult is still outstanding at the time of this review.*

3.4 Biopharm/HFD 860, Pharmacometrics/HFD 850

Dr. Peter I. Lee of Pharmacology, Pharmacometrics (HFD 850) reviewed the exposure-abuse potential for this submission and presented his findings to the Division on March 10, 2008.

Formal consult(s) could not be identified at the time of this review. Notes from Dr. Lee's presentation indicates that the proposed labeling language, largely based on Studies 12-005 and 12-007, do not clearly support the Sponsor's Claim (below from labeling) because the blood levels at the different measuring times are not equal (based on differences in dosing being between Concerta and immediate-release methylphenidate). Concerta's proposed labeling (below) would essentially be a marketing claim (b) (4)
(b) (4)

Proposed Labeling

(b) (4)

(b) (4)

Reviewer's Comments: Review of the other stimulants (Adderall XR, Daytrana, Focalin XR, Ritalin XR, Dexedrine and Desoxyn) and non-stimulant (atomoxetine) to not show a similar claim. The drug abuse and dependence identified in most of these other labels largely are limited to statements about the potential for abuse; it being a Schedule II Controlled Substance; the development of tolerance; the association of psychosis or death with abuse or excessive doses; and, the contraindication in those with a history of abuse; etc.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY SOURCES OF CLINICAL DATA

The safety and efficacy of Concerta in ADHD population is based on the double-blind Studies *42603ATT3002* and 02-159 which were fixed and dose-titration studies respectively. Supplemental safety information was obtained from the following open-label Studies; 12-304, a year study; 02-160, a dose escalation multiple dose pharmacokinetic study; C-99-018-00, a 9 month dose titration, cohort study; CON-CAN-4, a 1 month, pilot dose titration study; and the following double-blind study CON-CAN-3, a 5 week adjunctive study in MDD.

4.1 Tables of Clinical Studies

A tabular listing of all double blind and open label studies is presented in the section entitled "Study type and design/patient enumeration".

4.2 Review Strategy

All relevant Clinical Study Reports were reviewed. Adverse events resulting in discontinuation and cardiovascular adverse events of interest were reviewed. Cases of interest were identified and the CRF's for many of these cases was then reviewed to construct timelines for the adverse

events for these cases. ECG's, when available, were then correlated in time, in relation to the adverse events and dose titration, when done. From these cases, several potentially significant adverse events groupings were identified (cardiovascular, cerebrovascular, psychiatric and other). Many of these cases required supplemental medical information and ECG's, and sometimes clarification, in order to determine the cases significance.

4.3 Data Quality and Integrity

Given that one of the pivotal trials was at multiple countries and languages in the EU, it was difficult to have sites audited for Study 3002. Two sites (# 118 and 107) in the US were chosen for audit based on the high enrollment number and adverse event discontinuations. Results of the DSI inspections are described in the section entitled "Significant Findings from Other Review Disciplines". Narratives relating to discontinuation were reviewed and compared to CRF's for multiple subjects for studies 3002, 02-159 and 12-304. Discrepancies noted resulted in the request for much supplemental information. Some protocol violations were identified.

4. Compliance with Good Clinical Practices

Possible protocol violations were identified for Study 12-304 for various Cardiovascular Cases of Interest audited against CRF's and ECG's. Several subjects were identified with protocol violations, others with missing CRF pages, others with missing CRF's for time periods relating to potentially significant adverse events, etc. Similarly, various narratives for Study 3002 was compared to the CRF's and identified various discrepancies requiring multiple information requests which impacted this sNDA timeline. These issues were presented in a mid-cycle review meeting and were to be referred to DSI for further investigation.

4.5 Financial Disclosures

The sponsor submitted appropriate financial disclosures for the attached investigators for the different trials. There appears to be no obvious conflicts of interest.

5 CLINICAL PHARMACOLOGY

Dr. Peter I. Lee of Pharmacology, Pharmacometrics (HFD 850) reviewed the exposure-abuse potential for this submission and presented his findings to the Division on March 10, 2008. *Formal consult(s) could not be identified at the time of this review.* It is briefly discussed above in Section 3.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Review of Efficacy for Study 42603ATT3002 (3002)

6.1.1 STUDY 3002

This was one of two (2) phase 3 pivotal efficacy trials submitted in support of this sNDA to evaluate the safety and efficacy of Concerta in adults with ADHD. It consisted of a 5 week, randomized double-blind, placebo control phase (with a 1 week titration for the 72 mg group) which was followed by a 7 week, open-label-extension phase. It was conducted at 48 investigative sites in the European Union (EU)[6] over about a 14 month period from 04/07/2005 to 08/01/2006, by the investigators/sites identified in the Appendix. Also in the Appendix is a Table which summarizes this study.

6.1.2 OBJECTIVE(S)

The primary objective of the double-blind portion of this study was to evaluate the efficacy and safety of 3 *fixed Concerta doses* (18, 36 and 72 mg/day) compared to placebo in adults subjects with Attention Deficit Hyperactivity Disorder (ADHD). The primary efficacy was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated Conners Adult ADHD Rating Scale (CAARS) from baseline to the end of the double-blind phase.

6.1.3 POPULATION

The subjects were 401 adults (18-65 yrs of age) with DSM-IV defined ADHD confirmed by the Conners' Adult ADHD Diagnostic Interview for DSM-IV, a baseline CAARS total score $\geq$ 24, and had to have some DSM-IV symptoms present prior to 7 years. At the time of study entry, subjects had to report a history of ADHD symptomatology from childhood to adulthood, with some symptoms having been present prior to 7 years of age. Subjects with a history[7] of hyperthyroidism, myocardial infarction or stroke in the prior 6 months; those with a history of seizures, glaucoma or uncontrolled hypertension; those with angina pectoris or cardiac arrhythmias; or those with any serious illnesses (e.g. liver or renal insufficiency, significant cardiac, vascular, pulmonary, gastrointestinal, endocrine, neurological, psychiatric or metabolic disturbances); and, or unstable psychiatric conditions were excluded. Subjects on tricyclic antidepressants, SSRI's, other stimulants, MAOI's, and alpha-2 adrenergic receptor agonists were disallowed. Sponsor's Schedule of Events [identified by the Sponsor as Table 8 in the Clinical Study (pg. 39)] is pasted in the Appendix of this review.

6 The study was conducted in Great Britain, Germany, Denmark, Norway, Sweden, Finland, Czech Republic, Greece, France, Netherlands, Spain, Portugal, and Switzerland.

7 Clinical Study Report 42603ATT3002: pgs. 28-29

6.1.4 DESIGN

This was an international, multicenter, double-blind, randomized, placebo controlled, parallel group, dose-response study of 5 wks duration (with a 1 week titration for the 72 mg group) followed by a 7 week, open-label extension phase. An international open-label extension study of 52 weeks followed. Subjects were randomized into one of four treatment groups to receive 18, 36 or 72 mg of Concerta, or placebo for the double-blind phase. There was no 54 mg dose group in the double-blind phase of this study. Subjects who complete the double blind period or those who discontinued study medication due to poor tolerability after at least 7 days were eligible to enter a 7-week open-label extension with Concerta doses ranging from 36 to 90 mg (except for the subjects treated at German and Spanish centers as indicated below[8]). Dose titration to 54 mg, an intermediate dose not used in the double-blind phase, but was possible in the open-label phase.

The primary efficacy criterion was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of an investigator-rated CAARS[9] from baseline to the last post-randomization assessment in the double-blind phase (end of 5 weeks or earlier).

6.1.5 STUDY SUBJECTS

The 401 subjects in the double blind portion of the study were randomized into the following groups of either Concerta [18 mg (n=101), 36 mg (n=102), 72 mg (n=102)] or Placebo (n=96). The composition of the subjects studied were 54.4 % male, 97.5% Caucasians with a mean age of 34 years (range 18 to 63). *The majority of subjects exposed to study drug were less than 49 years of age (n=367) compared to the 50-65 year age groups (n=30).* The subjects mean weight was 77.8 kg (42-151 kg), mean age at first ADHD diagnosis (29.9 yrs) with various ADHD subtypes [combined (70.8 %), predominantly inattentive (24.2 %), predominantly hyperactive-impulsive (16 %) and NOS 1 (1 %)]. *The majority of subjects were stimulant naïve with 13 % having been on prior stimulants*[10]. Concurrent mood and anxiety disorders were reported for 12% of all subjects and 30 % reported a history of such disorders[11]. Thirty- seven (37; 10 %) of all subjects[12] were on anti-depressants [18 mg (11, 11.6%), 36 mg (9, 9.5 %), 72 mg (11, 12.6 %) and Placebo (6, 6.5 %)] during this portion of the trial.

Of the 401 subjects[13], the Sponsor defined 394 subjects as the *"intent to treat population"*

8 German: starting dose changed from 36 to 18 mg/d, and subjects dropping out of the double-blind phase from poor tolerability, would not be allowed to enter the open-label period; Spanish Sites: subjects dropping out of the double-blind phase from poor tolerability, would not be allowed to enter the open-label period.

9 Conners' Adult ADHD Rating Scale (CAARS): clinician administered 18 item scale corresponding to 18 DSM-IV symptoms for ADHD, with each item rated on a 4-point scale (0 = never, 1 = a little, 2 = often; 3 = frequently) derived from Conners' ADHD rating scale (CARS) and using subscales more to adult behavior.

10 Clinical Study Report 42603ATT3002: Attachment 12, Previous Therapies, Tabulation, pg. 219.

11 Clinical Study Report 42603ATT3002: Sec. 4.2: Demographic and Baseline Characteristics, pg. 58.

12 Clinical Study Report 42603ATT3002: Attachment 14, Concomitant Therapies, Tabulation, pg. 264.

13 Clinical Study Report 42603ATT3002: Sec. 4: Subject and Treatment Information Double-Blind Phase, pg. 52.

defined as those "who used the trial medication at least once and who had a least one post- baseline efficacy assessment during the double-blind treatment" in the following groups: Concerta [18 mg (n=99), 36 mg (n=101), 72 mg (n=99)] or Placebo (n=95). The Sponsor states that 23 of these subjects had "a major protocol violation during any of the screening or double-blind visits resulting in a *'per protocol/double-blind'* population of 371 subjects." These differences are indicated in a table from the Sponsor indicating the number of subjects in each treatment group which is pasted in the Appendix.

6.1.6 ASSESSMENTS

Safety evaluations included laboratory evaluations[14], pregnancy testing, vital signs[15], body weight and adverse events at the intervals identified in Sponsor's Schedule of Events pasted in the Appendix of this review. ECG's were not performed at any visits for this study. A physical examination was only performed at screening, not repeated at any subsequent visits, except where a "clinically significant abnormality persisting at the end of the study was followed by the investigator until resolution or until reaching a clinically stable end point."[16]

6.1.7 SUBJECTS DISPOSITION

Of the 401 subjects who were randomized and treated in the double blind phase, the number of subjects whom discontinued from the study consisted of 6 subjects in the Placebo group and 30 subjects in the Concerta groups [18 mg (n=6), 36 mg (n=10) and 72 mg (n=14). Subject disposition[17] for the double-blind phase is shown in sponsor's Figure 2 pasted in the Appendix of this review. Median treatment duration was the same (35 days) for the Placebo and Concerta Groups (Clinical Study Report, pg. 62). The Sponsor identifies twelve (12) adverse events resulting in discontinuations during the double blind phase with most occurring in the high (72 mg, n=8) and intermediate (36 mg, n=3) dose compared to the low (18 mg, n=1) dose groups[18]. In addition to the twelve (12) adverse events, eight (8) additional subject's meeting the regulatory definition of "serious adverse event" (Clinical Study Report, pg. 2488), of which, four (4) occurred or had *its onset* during the double-blind portion of the study (18 mg, n=2; 72 mg, n=2) which are itemized in the reference below[19], and which are summarized in the Summary of

14 *Hematology*: Hb, HCT, RBC, WBC with differential, platelet and reticulocyte count. *Chemistry:* BUN, creatinine, glucose (non-fasting), LFT's, CPK, albumin, uric acid, TP, and TSH. Cholesterol and triglycerides were assessed only for Swedish subjects.

15 SBP, DBP and HR after being supine over 5 minutes followed by repeat after 2 minutes standing.

16 Clinical Study Report 42603ATT3002: Physical Examination, pg. 43.

17 Clinical Study Report 42603ATT3002: Fig. 2: Subject Disposition in the Double-Blind Phase, pg. 54.

18 Clinical Study Report 42603ATT3002: Attachment 79: Clinical Narratives, pg. 2488.

19 Regulatory defined cases of serious adverse events occurring in Clinical Study 42603ATT3002: double-blind: 18 mg (A10253), 72 mg (A10801); double-blind to open-label and, or, immediate post-study: 18 mg (A 10885 with positive re-challenge in open label at 54 mg), 72 mg (A10472, A 10801). Additional serious adverse events occurring during the open-label or immediate post-study period were: 36 mg (A11086), 54 mg (A11006) and 72 mg (A10368).

Narratives for Discontinuations from Clinical Study 42603ATT3002 which is included in the Appendix of this review. Three (3) additional "serious adverse events" occurred during the open-label and are also referenced below.

The mean duration of drug exposure[20] during the double-blind portion of the study was 33.9 days ranging between 34.5 (18 mg) to 32.8 (72 mg) days. The mean duration of drug exposure for the open-label portion of this study "was 47.6 (9.13) days, with an average daily dose (excluding zero doses) of 47.5 (13.93) mg and a mean (SD) maximum dose of 57.6 (18.11) mg daily. Mean (SD) last dose was 52.6 (19.29) mg."

Description of the adverse events leading to discontinuation and treatment emergent adverse events are presented in detail in another section of this review.

6.1.8 ANALYSIS PLAN

The primary efficacy analysis "was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated CAARS from baseline to the last post-randomization assessment in the double-blind treatment period. The change from baseline score at each visit and at end point was analyzed using an ANCOVA model. The last-observation-carried-forward (LOCF) method was used."[21]

Further review and discussion of the statistical analysis plan are given and described in Dr. Jingyu Luan's review[22] from the Division of Biometrics of the Office of Biostatistics.

6.1.9 RESULTS

Sponsor's Table 20 (Clinical Study Report, pg. 64) showing baseline, end-point and changes in CAARS total score is pasted below. Statistical superiority to placebo is shown for the 18 mg, 36 mg and 72 mg Concerta groups.

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20 Clinical Study Report 42603ATT3002: Sec. 4.6, Extent of Exposure, pg. 62; Sec.7.6, Extent of Exposure, pg. 105.

21 Clinical Study Report 42603ATT3002: Sec. 3.11.2.1.1 Primary End Point in Double-Blind Phase, pg. 45.

22 Luan, J/ HFD-710: NDA 21-121 SE5-017, Statistical Review and Evaluation, 03/26/2008.

Table 20: CAARS Total Score: Actual Values and Change From Baseline to Double-Blind End Point -- LOCF
(Study 42603ATT3002: *Intent to Treat / Double-Blind*)

	Placebo	PR OROS MPH 18 mg	PR OROS MPH 36 mg	PR OROS MPH 72 mg
Baseline	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Median	38.0	35.0	38.0	36.0
Range	24 – 51	24 – 53	25 – 51	24 – 52
Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Median	29.0	24.0	26.0	22.0
Range	4 – 50	4 – 51	4 – 52	1 – 50
Change From Baseline to Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Median	-6.0	-10.0	-10.0	-13.0
Range	-45 – 8	-35 – 16	-37 – 8	-40 – 8
p-value[a] (comparison versus placebo)		0.0146	0.0131	<0.0001

[a] Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure;
N = number of subjects with data
Source: Attachment 17, Attachment 18

6.1.10 CONCLUSION(S)

Superior efficacy on the CAARS totals score [change from baseline to the double-blind endpoint] was shown for all three doses studied: 18 mg, 36 mg and 72 mg. The majority of adverse events leading to discontinuation and serious adverse events occurred in the higher (72 mg, n=11) compared to the lower dose groups (18 mg, n=3; 36 mg, n=3). This would seem to indicate that Concerta doses greater that 36 mg may be associated with increased adverse events without improving efficacy. Unfortunately, the 54 mg dose group was not evaluated in this study, making its utility for this age group difficult to determine. To few subjects were exposed to study drug in the 50-65 year age groups compared to the 18-49 year age groups (30 vs. 367) to adequately assess its safe and efficacious use in this age group in this, the single fixed dose study. Given, increased cardiovascular risks associated with the 50-65 year age groups, a recommendation for the safe use in subjects greater than 49 years cannot be made based on this study. Similarly, doses greater than 36 mg cannot be made based upon a small increase in efficacy compared to a large increase in adverse dropouts.

We do not know from this study if the dose response would be different from chronic users 87 % of the subjects were stimulant naïve.

6.1.11 RECOMMENDATION(S)

Study 42603ATT3002 (3002) would seem to support an approvable action for Concerta for doses no greater than 36 mg in adult, stimulant naïve, subjects between 18-49 years.

6.2 Review of Efficacy for Study 02-159

6.2.1 STUDY 02-159

This was one (1) of the two (2) phase 3 pivotal, randomized double-blind, placebo controlled efficacy trials submitted in support of this sNDA whose purpose(s) were to evaluate the safety and efficacy of Concerta in adults with ADHD. It was *a 7 week dose-titration study* using doses ranging from 36-108 mg per day and which was conducted at 27 investigative sites in the US over the 6.5 month period from 05/08/2006 to 11/21/2006, by the investigators/sites identified in the Appendix.

6.2.2 OBJECTIVE(S)

The primary objective of this study was to evaluate the efficacy and safety of Concerta at five doses (36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day) compared to placebo in adults with Attention Deficit Hyperactivity Disorder (ADHD).

6.2.3 POPULATION

The subjects were adults (18-65 yrs of age) with DSM-IV defined ADHD[23] with a Baseline confirmed Adult ADHD Clinical Diagnostic Scale V 1.2 (ACDS)[24] diagnosis (after a 1-2 week washout period on no medication), a Baseline confirmed Adult ADHD Investigator Symptom Rating Scale (AISRS)[25] score $\geq$ 24 (after a 1-2 week washout period), a Baseline Global Assessment of Functioning (GAF) score of 41-60 (after a 1-2 week washout period on no medication); whose Screening weight was $\geq$ 45.4 kg (100 lbs); who had a negative urine drug test at Screening and Baseline[26]; who did not have any coexisting medical condition, structural cardiac abnormality (assessed by history, physical examination, and/or ECG); who did not have a history of myocardial infarction or ischemia, cerebrovascular accident or transient ischemic attack, cardiomyopathy, serious cardiac problems or clinically significant arrhythmia or

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23 Investigator determined diagnosis of ADHD (Any type: Combined, Predominantly Inattentive, or Predominantly Hyperactive-Impulsive) as defined by DSM-IV criteria based on subjects describing a course of ADHD symptomatology from childhood to adulthood, with symptoms present before age 7 years and continuing to meeting full DSM-IV criteria at the time of assessment;

24 Adult ADHD Clinical Diagnostic scale V 1.2 (ACDS) at Baseline [ACDS questions about "the past 12 months" referred specifically to *periods in the past 12 months when the subject was not on medication, including the 1 to 2 week washout period*].

25 Adult ADHD Investigator Symptom Rating Scale (AISRS) score ≥ 24 at Baseline [scores after 1-2 weeks with no medication for ADHD].

26 Drugs of abuse (amphetamines, barbiturates, benzodiazepines, cannabinoids, cocaine and opioids), unless the positive result(s) were attributed by the investigator to a concomitant medication taken by the subject (e.g., subject provided a current prescription for a benzodiazepine, cannabinoid, or opioid or subject was receiving stimulant therapy at screening). Subject must have washed-out from stimulant therapy before the Baseline Visit.

cardiovascular disease (e.g., coronary artery disease); who did not have potentially clinically important ECG abnormalities; who did not have a blood pressure measurement > 140 mmHg systolic or 90 mm Hg diastolic at Screening or Baseline or pulse > 100 bpm (average of triplicate measurements); who did not have diagnosis of or a family history of Tourette's syndrome, or motor or vocal tics; who did not have marked anxiety, tension or agitation or a Baseline HAM-A score ≥ 21; who did not have moderate severity or depression with a Baseline HAM-D score ≥ 17; who did not have any of the following co-morbid psychiatric diagnoses: bipolar disorder; who did not have a history of drug or alcohol abuse/dependence with 6 mths prior to Screening; and who did not have suicidal ideation or behavior in the past year. Additional Inclusion and Exclusion Criteria were used.

6.2.4 DESIGN

This was a 7 week randomized, placebo-controlled, double-blind, parallel-group, *dose-titration study* in *226 adults* with ADHD (18 - 65 yrs) randomly assigned to one of two groups: placebo (n=116), or CONCERTA (n=110). Subjects was initiated at 36 mg and were titrated in 18 mg increments on a weekly basis to either 36, 54, 72, 90, or 108 mg once daily) based on a 30% improvement in baseline Adult ADHD Investigator Symptom Rating Scale (AISRS) score and a Clinical Global Impression (CGI) of much improved or very much improved (2) or titration to the maximum dose of 108 mg (35 day titration period with minimum of 16 days at maximum dose). Downward titration by 18 mg occurred for a limiting AE, a resting heart rate >100 bpm, systolic blood pressure >140 mmHg, or diastolic blood pressure >90 mmHg (average of triplicate measurements), or at the discretion of the investigator. Once a subject was down-titrated that dose could not be up-titrated again during the study.

The primary efficacy variable was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit (two weeks after Titration Visit 5) or the last score provided during the study.

Sponsor's Schedule of Events (identified by the Sponsor as Table 7-4) is pasted in the Appendix of this review. Also pasted in the Appendix is Sponsor's Summary Table for Study 02-159.

6.2.5 STUDY SUBJECTS[27]

Of the 229 subjects in this study, 113 were randomized to Concerta and 116 were randomized to placebo. The composition of the subjects studied were 56.8% male, 86 % Caucasians with a mean age of 39.2 years (range 18 to 65). *Eighty two (82 %) of the subjects on were less than 49 years of age.* .The subjects mean weight was 84 kg (48-150 kg), mean age at first ADHD diagnosis (29.1 yrs) with various ADHD subtypes [combined (79.9 %), predominantly inattentive (19.2 %) and predominantly hyperactive-impulsive (0.9%). Many of the subjects were stimulant naïve (64.6 %) with 35.4 % having been on prior stimulants. Only 7 % (n=16) of the subjects were currently taking ADHD medications. Concurrent depression and anxiety was

27Clinical Study Report 42603ATT3002: Tables 8-5, Demographic and Baseline Characteristics by Treatment Group-All Randomized Patients; Table 8.6, Demographic and Baseline Characteristics by Treatment Group-Intent to Treat Population; Table 8-7, Psychiatric History by Treatment Group, All Randomized Patients: pgs: 76 -81.

reported for 5.2 % and3.9 % of the subjects, respectively. Fifteen (15) of all subjects were on selective serotonin uptake inhibitors [Concerta: 5, 4.5 %, Placebo: 10, 8.6 %] at the time of study entry. Of the 229 *all randomized patients* (Concerta: n= 113, Placebo: n=116), there were 226 patients in *the intent to treat and safety groups* (Concerta: n= 110, Placebo: n=116).

6.2.6 ASSESSMENTS

Safety evaluations included fasting laboratory evaluations[28], urine pregnancy testing, urine drug screen, vital signs[29], screening height on a stadiometer, body weight on same scale, and adverse events at the intervals identified in Sponsor's Schedule of Events pasted in the Appendix of this review. ECG's[30] were performed at screening, baseline and with each upward dose titration. A physical examination was performed at screening and repeated at the final visit. HAM-A's and HAM-D's were performed at baseline and end of study. The primary efficacy assessment was the Adult ADHD Investigator Symptom Rating Scale (AISRS).

6.2.7 SUBJECTS DISPOSITION

Of the 229 subjects in this study, 113 were randomized to Concerta and 116 were randomized to placebo. There were 71 subjects in the Concerta and 90 subjects in the placebo groups who completed the study. Overall 37.2% (42/113) of the subjects in the Concerta and 22.4% (26/116) in the placebo groups withdrew from the study. Subjects on Concerta withdrew earlier than those on placebo (14.2 % vs. 5.2 %) particularly because of adverse events. Half of the subjects (21/42, 50 %) in the Concerta group who terminated early withdrew at a final dose of 36 mg; further down-titration was not allowed in this study. The sponsor identified[31] 16 and 6 subjects, respectively, in the Concerta (16/35, 46 %) and placebo (6/26, 23 %) groups, who withdrew because of adverse events. Subjects classified by the sponsor as having cardiovascular adverse events of interest[32] were slightly more in subjects on Concerta (19/113, 16.8 %) compared to subjects on placebo (15/116, 12.9 %). Adverse events resulting in discontinuation and cardiovascular adverse events of interest are summarized in the Narratives for Discontinuations for Clinical Study 02-159 which is included in the Appendix of this review. Subject disposition[33] and Disposition of Subjects by Final Dose[34] of those subjects who discontinued prematurely are shown by the sponsor in Figure 8-1 and Table 8-1, respectively, which are pasted in the Appendix of this review. Mean duration of exposure was 38.9 days for Concerta and 42.6

28 Hematology: CBC with differential, and platelet count. Chemistry: BUN, creatinine, glucose, LFT's, albumin, total protein, alkaline phosphatase; lipid profile [cholesterol, HDL, LDL, VLDL, triglycerides, lipoprotein (a)], TSH; T4; and C-reactive protein.

29 Triplicate pulse and blood pressure were to be measured in the sitting position after being seated for 3 minutes between each measurement, at the same time of day

30 The sponsor had ECGs interpreted at a central diagnostic company. Subjects with ECG abnormalities at screening or baseline deemed clinically important were excluded.

31 Sponsor's Table 8-2, Clinical Study Report 02-159, pg. 72 indicates that 13 subjects on Concerta withdrew to an adverse event. However, Table 10-12, Clinical Study Report 02-159, pg. 179 indicates that 16 subjects withdrew because of adverse events.

32 Safety Update: pg. 687-699; Cardiovascular Adverse Events of Interest included cardiac disorders, chest discomfort, blood pressure increase, specific ECG abnormalities, syncope, respiratory disorders and vascular disorders.

33 Clinical Study Report 02-159: Fig. 8-1: Disposition of Subjects, pg. 69.

34 Clinical Study Report 02-159: Table 8-1: Disposition of Subjects by Final Dose-All Randomized Subjects, pg. 71.

daysfor placebo. The mean final dose for the Concerta group was 67.7 mg. The Number of Responders by Dose Based on the AISRS Total Score and the CGI and the Duration of exposure by Treatment Group is shown in sponsor's Tables 9-20 and 10-1, which are pasted in the Appendix. Description of the adverse events leading to discontinuation and treatment emergent adverse events are presented in another section of this review.

6.2.8 ANALYSIS PLAN

The primary efficacy analysis "was the change from baseline in the AISRS (Adult ADHD Investigator Symptom Rating Score) total score as assessed by the investigator at the Final Visit/Two Week Efficacy Assessment Visit. A total AISRS score was calculated by adding the score (0 to 3) for each of 18 items, thus giving a total score ranging from 0 to 54. A reduction in score represented an improvement. The two treatment groups (All CONCERTA®, placebo) were compared using analysis of covariance (ANCOVA) with change from baseline as the dependent variable; study site and treatment as factors; and baseline score as the covariate. Sites with fewer than eight subjects were combined. The primary efficacy analysis was based on the ITT population using the LOCF approach."

Further review and discussion of the statistical analysis plan are given and described in Dr. Jingyu Luan's review[35] from the Division of Biometrics of the Office of Biostatistics.

6.2.9 RESULTS

Sponsor's Table 9-1 (Clinical Study Report, pg. 90) showing baseline, end-point and changes in AISRS total score is pasted below. Subjects treated with Concerta had a statistical significant improvement in the AISRS total score, from baseline to endpoint, compared to subjects receiving placebo (p=0.012).

35 Luan, J/ HFD-710: NDA 21-121 SE5-017, Statistical Review and Evaluation, 03/26/2008.

Table 9-1: AISRS Total Score and Change From Baseline at Final Visit (LOCF),[a] Intent-to-Treat Population

Statistic	All CONCERTA	Placebo	p-Value[b]
Baseline			
N	110	116	
Mean (SD)	38.6 (6.85)	38.1 (7.31)	
Median	38.5	38.0	
Range (min, max)	(24, 54)	(24, 54)	
Final Visit (LOCF)			
N	110	116	
Mean (SD)	27.6 (13.17)	31.3 (12.38)	
Median	26.5	33.0	
Range (min, max)	(0, 52)	(3, 54)	
Change from Baseline:			
N	110	116	
Mean (SD)	-10.9 (11.75)	-6.8 (11.45)	
Median	-9.0	-3.0	
Range (min, max)	(-48, 13)	(-38, 12)	
95% CI	(-13.2, -8.7)	(-8.9, -4.7)	
LSMean (SEM)	-10.6 (1.09)	-6.8 (1.06)	0.012

a: AISRS total score ranges from 0 to 54 with higher scores indicating more severe ADHD. Change from baseline is the value at the visit minus the baseline value. A negative change from baseline indicates an improvement.

b: p-Value from test for significant treatment difference from ANCOVA model with change from baseline as the dependent variable, site and treatment (All CONCERTA, placebo) as factors, and baseline value as covariate.

Abbreviation: CI - confidence interval

Note: For AISRS Total Score, subjects who lacked post-baseline data had their baseline values carried forward to Final Visit (LOCF).

6.2.10 CONCLUSION(S)

Statistical superiority on the AISRS total score (baseline to endpoint) was shown for subjects receiving Concerta compared to those receiving placebo in this *7 week dose-titration study (*36-108 mg per day) in 229 subjects (Concerta: 113, placebo: 116). Adverse events leading to discontinuation occurred more frequently [Concerta: 37.2% (42/113); placebo: 22.4% (26/116)], 2.8 times earlier [Concerta: 14.2 %; placebo: 5.2 %] and in 50 % [Concerta: 50 % (21/42)] of those on Concerta discontinuing at the lowest downward titrated dose of 36 mg. Limitations inherent in a flexible dose study make it largely unusable in assessing dose response, especially as it applies to *determining the optimum dose for adults older than 49 years, the group with the*

greatest cardiovascular risks, a problem defined in meetings with the sponsor on 02/04/200 and 07/12/2005. As with the fixed dose study (3002), insufficient subjects were exposed to study drug in the 50-65 year age groups compared to the 18-49 year age groups (18 % vs. 82 %) to adequately assess its safety and ultimately to give recommendations for the safe use of Concerta in subjects greater than 49 years of age.

A sufficient sampling of stimulant naïve (64.6 %) and prior stimulant users were present in this sample of subjects as compared to Study 3002.

6.2.11 RECOMMENDATION(S)

Study 02-159 further supports an approvable action for Concerta in subjects between 18-49 years. The fact that it is a flexible dose study makes it largely unusable in assessing dose response and in determining the optimum dose for adults. An average dose would not address differential risk and age.

6.3 Efficacy Conclusion(s) and Recommendation(s)

Study 42603ATT3002 (3002), a 5 week, double-blind, *fixed dose* Concerta study [18 mg (n=101), 36 mg (n=102), 72 mg (n=102)] or Placebo (n=96)] support an approvable action for Concerta for doses *no greater than 36 mg* in adult, stimulant naïve, subjects between 18-49 years. If one considered the average dose of about 67.7 mg used in Study 02-159, the 7 week, double-blind, *dose-titration* study, *one might argue for a higher dose of 54-72 mg*, but again, this would not address the clear under-exposure of the above 49 year age group, to safely recommend this group to the doses (18-(b) (4) mg) and ages (18-65) desired by the sponsor.

These recommendations are based on the facts that *the single fixed dose study (3002)* showed about a 3.6 increase in adverse event discontinuations in the higher, 72 mg dose, compared to the lower, 18 mg and 36 mg doses; there was a small increase in efficacy compared to a large increase in adverse dropouts with the 72 mg dose; and, the intermediate dose (54 mg) was not studied. Unfortunately, to few subjects were exposed in the 50-65 year age groups compared to the 18-49 year age groups (30 vs. 367) to adequately assess the safe and efficacious use in this more, vulnerable age group. *Study 02-159* confirmed efficacy, but being *a flexible dose study* becomes unusable in assessing dose response and in determining the optimum dose for adults, especially those older than 49 years, a population with the greater cardiovascular risks, a problem stated in meetings with the sponsor on 02/04/200 and 07/12/2005. This study also had insufficient subjects exposed to study drug in the 50-65 year age groups compared to the 18-49 year age groups (18 % vs. 82 %) to adequately assess its safety and ultimately give recommendations for the safe of Concerta in subjects greater than 49 years. The fact that 50 % (21/42) of subjects on Concerta discontinued with adverse events in the lowest downward dose of 36 mg suggests that assessing dose response for the 18 mg group may be of benefit.

Further studies may be needed in subjects above 49 years.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

This evaluation of the safety of Concerta is based upon review of the two double-blind placebo controls, the long term and the shorter term open labels. Serious adverse events, adverse events resulting in discontinuation, treatment emergent adverse events were reviewed. Cardiovascular events of interest were correlated with vital sign and ECG changes.

7.1.1 DEATHS

No deaths occurred in any of the studies, except for Subject A10802 in Study 3002, electing to have an abortion while becoming pregnant on 36 mg of Concerta during the open-label portion of the study.

7.1.2 OTHER SERIOUS ADVERSE EVENTS

More detailed description of some of these serious adverse events and other adverse events leading to discontinuation are given in greater detail in the Appendix of this review [Narratives for Discontinuations Clinical Study 42603ATT3002, Narratives for Discontinuations Clinical Study 12-304; Narratives for Subjects with Cardiovascular Adverse Events of Interest].

7.1.1.1 Study 42603att3002 Serious Adverse Events

The sponsor identified 4 subjects having serious adverse events in the double blind portion of this trial which the Sponsor summarizes in Table 37, pasted below:

Table 37: Serious Adverse Events During Double-Blind
(Study 42603ATT3002: *All Subjects / Double-Blind)*

Treatment Subject No.	Age (yrs) Gender	Preferred Term [Verbatim Term]	Day of SAE Onset in Trial*	Dosage Group in DB phase	Action Taken	Relationship to Study Drug	Outcome (Duration)	Total Days of Therapy in DB/OL
Double-Blind								
OROS methylphenidate								
A10253	59 male	**Cerebrovascular accident** [vertebrobasilare stroke]	22	18 mg	Temporary stop	Doubtful	Recovered (17 days)	38/22
A10472	21 male	**Depression** [depressive disorder]	NAV	72 mg	None	Possible	Not yet recovered (NAV)	35/51
A10801	34 female	**Migraine** [abortive migraine attack]	32	72 mg	None	Doubtful	Recovered (2 days)	34/49
A10885	43 female	**Anxiety disorder** [reactivation of anxiety disorder]	17	18 mg	None	None	Recovered (5 days)	37/50

Source: Attachment 44, Attachment 45 and Attachment 46
NAV: not available
DB: Double-Blind; OL: Open-Label

Brief Description of Above SAE Relating to Study 42603att3002

A10253, Germany, was a 59 year old male, previously treated with methylphenidate (20-40 mg q.d.) whom develops symptoms of vertebrobasilare insufficiency, 10 days after starting on 18 mg of Concerta during the double blind portion of the trial. This culminates in a vertebrobasilare stroke 10 days later for which he is hospitalized and for which he had residual sequelae. In the revised narrative submitted by the sponsor in February 2008, it states that the subjects developed "symptoms of recurring acute dizziness which ago in combination with an acute twist of his hand while jogging and which was followed by spinal column stretching exercise."

A10801, Sweden, was a 34 year old female, stimulant naïve, and about 1 month later, becomes hospitalized with *mild abortive migraine attack, vertigo and an unspecified visual disorder. The original CRF's indicated that the subject had a history of inactive migraine ("normal to currently active"/CRF; no medications/attacks previous year/Remarks on pg. 68 of CRF) without other medical problems.* The sponsor has classified this case, above, as a migraine. However, the sponsor states that the CCT showed a *probable lacunar infarct* (11 mm) *in caudate nucleus* with slight expansion of the frontal horn of the right lateral ventricle. In the revised narrative submitted by the sponsor in February 2008, it states that the subject *usually developed* unilateral migraine with an aura; however, this time she had the acute onset of dizziness followed by headache. The sponsor states that a radiologist interpreted the finding as an "old lesion, very likely a perinatal lesion."

Reviewer Comment: As it relates to the above two (2) cases (A10253, A10801), regard-less of the exact mechanism or timing of these strokes, or, if the drug was the cause of these events,

there seems to be *an imbalance of subjects on drug compared to placebo having these kind of events* in Study 3002. Other possible cerebrovascular events, not classified as serious are identified below, under the section "Dropouts and Other Significant Adverse Events" and the sub-section "Other Possible Cerebrovascular Events Occurring in Study 3002".

A 10472, Netherlands, was a 21 year old male, stimulant naïve, randomized to 72 mg of Concerta, and who developed a depressive disorder. Later randomized to open label on 03/30/06 for which he was placed on venlafaxine on 05/21/06, and for which he developed suicidality on 05/31/06, while in the open label. The sponsor states "the investigator reported this adverse event as serious since medically significant." In the revised narrative submitted by the sponsor in February 2008, it states that the subject has prior suicidal attempts and has "chronic suicidal thought and a history of acting impulsively on these thoughts."

Reviewer Comment: It is unclear *why this case was classified as a serious adverse event* for the double blind trial since it occurred during the open label portion of the trial. In addition, the subject developed *recurrence of chronic suicidality.*

A10885, Switzerland, was a 43 year old female with a history of depression and anxiety on citalopram, who was treated with 18 mg of Concerta during the double blind trial, and 18 days alter starting was hospitalized for about 2-3 days because of anxiety and depressive thoughts. She was treated with lorazepam while hospitalized. About 2-3 days later, she was re-started on Concerta, and had a "*reactivation of anxiety disorder*, with *continua*tion of depressive thoughts." She was re-admitted to a psychiatric hospital; this time diagnosed with adjustment disorder and subsequently completed her participation in the double blind trial. She was randomized to the open label trial and developed restlessness and anxiety treated with bromazepam and citalopram. In the revised narrative submitted by the sponsor in February 2008, it states that the subject reported '"suicidal thoughts" but no "acute suicidal tendencies"' during the first hospitalization. During the re-hospitalization, "suicidal ideation did recur".

Reviewer Comment: In spite of there, possibly being a *protocol violation* with this case (concomitant mediation), it would appear that this *case has been misclassified* and should be re-classified as suicidality.

Serious Adverse Events Occurring During Open Label or Immediate Post-Open Label Portion in Study 42603att3002

A11006, Finland, was a 27 year old female who had a history of panic disorder treated with 72 mg of Concerta during the double-blind portion and 54 mg in the open label portion when 1 day after study completion developed increased anxiety requiring psychiatric hospitalization. A10368, Germany, was a 46 year old male who was on 72 mg of Concerta during the open label portion of the trial and was hospitalized for foreign body in the urethra.

A11086, Germany, was a 40 year old male, treated with 18 mg of Concerta during the double blind portion of the trial, and was titrated to 36 mg during the open label portion. The subject developed headache and *hypertension* (170/100) and was hospitalized for "acute psychological stress", and was placed on enalapril. In the revised narrative and supporting documents,

submitted by the sponsor in February 2008, it states that "the patient was not hospitalized in our hospital.." and was seen for "high blood pressure" (CRF, pg. 265-266).

Reviewer Comment: This may be another *case of mis-coding.*

A10788, Sweden, was a 27 year old male with baseline, borderline hypertension *((145/90 mm Hg: supine; 145/95 mm Hg, standing)* and a *rapid heart rate* (pulse: *92 bp*m, standing). The subject was treated with Concerta 72 mg during the double blind. *Borderline hypertension (145/90 mm Hg: supine; 145/95 mm Hg, standing)* and a *rapid heart rate* (pulse: *92 bp*m, standing) were present at screen/baseline with *both increasing by visit 4 (150/90 mm Hg: supine; 155/95 mm Hg, standing; 100 bpm standing).* During the open label portion of the trial (72 mg Concerta) *the blood pressure worsened 160-165/90 mm Hg: supine; 130-150/100 mm Hg:* standing). The CRF indicates that the subject awoke on 07/24/05, six days after the last dose in open label with *"a severe headache for which he was hospitalized for < 12 hours"*. No information is provided about the work-up at the hospital. However, the sponsors vignette indicates that *a diagnosis of temporal arteritis was made. The basis and the work-up for this diagnosis are not provided.* In the revised narrative submitted by the sponsor in February 2008, it states that the investigator stated that there was "no basis for the diagnosis of "temporal arteritis" and "that must be some mistake if the patient got that diagnosis". The patient has a long history (since youth) of 2 to 3 times per year of attacks of headache, localized over the temporal lobe and the eye on the same side...According to the investigator, the headache that led to hospitalization may have been more intense than previous episodes. CT and laboratory results taken at the hospital were normal, with the exception of mild hyperlipidemia. Diagnosis was suspect Horton's syndrome." As an explanation for not recording the adverse of hypertension, the investigator reported "These small changes in blood pressure measurements were not recorded as adverse events. Since the subject had documented pre-existing hypertension and the values recorded in the trial are in the same range as the blood pressure recorded prior to the study medication administration, elevated blood pressure need not be reported as an adverse event if the investigator did not believe the study values were clinically different than the pre-study values."

Reviewer Comment: The explanation that is given for *mis-coding* this case as temporal arteritis seems reasonable to this reviewer. However, *not coding adverse events* occurring during a trial, even if present in smaller magnitude at baseline, raise serious questions about the integrity of the database.

7.1.1.2 Study 02-159 Serious Adverse Events

No treatment emergent serious adverse events were reported.

7.1.3 DROPOUTS AND OTHER SIGNIFICANT ADVERSE EVENTS

7.1.1.3 Double Blind Analysis Set (Studies 3002 and 02-159)

Overall, there was a low rate of discontinuations due to adverse events in the double-blind studies. Of the 415 subjects on Concerta, 29 (7.0%) discontinued vs. 7 (3.3%) on placebo. The following subjects on Concerta had anxiety (n=7), irritability (n=6), increased blood pressure (n=4), and nervousness (n=3).

For Study 02-159, the sponsor states that 16 (14.5 %) and 6 (5.2 %) subjects on Concerta and placebo discontinued because of adverse events. A summary of the adverse events resulting in discontinuation are given in the table entitled "Cases from Double-Blind Study 02-159", with adverse events resulting in discontinuation being underlined. Also on that list are cardiovascular and psychiatric cases of interest.

7.1.1.4 Overall profile of dropouts

For Study 3002, treatment emergent adverse events occurred in 75-82 % of the Concerta compared to 66 % of the placebo subjects during the double blind portion of the study. The proportion of subjects reporting at least one treatment-emergent adverse event was highest in the 72 mg group (82%). "One (1%) subject in the placebo group permanently discontinued study drug in the open-label phase due to at least one adverse event that emerged in the double-blind phase. Study drug discontinuation due to an adverse event emerging in the double-blind phase was observed in 1 (1%), 4 (4%) and 8 subjects (8%) of the 18 mg, 36 mg and 72 mg Concerta group, respectively. One subject in the 36 mg Concerta group discontinued trial medication in the open-label phase because of an adverse event that started during the double-blind phase." [36] A > 2 % Table of Treatment Emergent Adverse Events is pasted in the Appendix.

The sponsor reports[37] the most common treatment adverse events for all subjects in the the double-blind portion of this study. "The most frequently reported adverse events reported by 5 % or 2 % of all subjects treated with Concerta were decreased appetite (25% vs. 7% PBO), headache (21% vs. 18%), insomnia (13% vs. 7%), nausea (13% vs. 4%), dry mouth (12% vs. 2%), dizziness (8% vs. 7%), weight loss (7% vs. 5%), nasopharyngitis (6% vs. 9%), tachycardia (6% vs. 0%), irritability (6% vs. 1%), anxiety (5% vs. 1%) and hyperhidrosis (5% vs. 1%).

For Study 02-159, a numerical summary of all treatment emergent adverse events is shown by the sponsor in Table 10-3 which is pasted below.

36 CSR 42603att3002, Sec. 6.2.1: Summary of All Adverse Events: pgs. 83-84

37 Clinical Study Report, 42603att3002: Sec. 6.2.2 Common Treatment Emergent Adverse Events: pgs. 84-86.

Table 10-3: Summary of All Treatment Emergent Adverse Events - Safety Population

Evaluation	All CONCERTA N=110	Placebo N=116
Subjects with adverse events, n (%)	93 (84.5)	74 (63.8)
Subjects with serious adverse events, n (%)	0 (0.0)	0 (0.0)
Subjects who discontinued due to adverse events, n (%)	16 (14.5)	6 (5.2)
Deaths, n (%)	0 (0.0)	0 (0.0)

Adverse events that were reported in at least 20% of Concerta were reported more frequently than in placebo subjects included decreased appetite (25.5%, 6.0%), headache (25.5%. 13.8%), and dry mouth (20.0%, 5.2%). Those reported in at least 10% but less than 20% of Concerta subjects reported more frequently than placebo subjects included anxiety (16.4%, 3.4%), nausea (12.7%, 2.6%), and increased blood pressure (10%, 5.2%). Irritability, increased heart rate increased, muscle tightness, bruxism, initial insomnia, and insomnia occurred in ≥ 5% but less than 10% of Concerta subjects and were more frequently than placebo. *Those adverse events on Concerta with an incidence ≥ 1% and more than twice that in the placebo group were* tachycardia, blurred vision, dry mouth, dyspepsia, nausea, feeling jittery, irritability, upper respiratory tract infection, weight decreased, decreased appetite, affect liability, anxiety, bruxism, initial insomnia, libido decreased, and hyperhidrosis. This is shown in the sponsor's 1% table pasted in the Appendix.

7.1.1.5 Adverse events associated with dropouts

For Study 02-159, Sponsors Table 11, listing the number and percent of subjects who withdrew because of an adverse event by treatment group, MedDRA is pasted below.

Table 10-11: Number and Percent of Subjects Who Withdrew Because of an Adverse Even by Treatment Group, System Organ Class and MedDRA Preferred Term - Safety Populatio

System Organ Class MedDRA Preferred Term	All CONCERTA N=110 n (%)	Placebo N=116 n (%)
Any adverse event that led to withdrawal	16 (14.5)	6 (5.2)
Cardiac Disorders	1 (0.9)	0 (0.0)
Tachycardia	1 (0.9)	0 (0.0)
Gastrointestinal Disorders	1 (0.9)	0 (0.0)
Stomach Discomfort	1 (0.9)	0 (0.0)
General Disorders and Administration Site Conditions	3 (2.7)	0 (0.0)
Irritability	3 (2.7)	0 (0.0)
Investigations	5 (4.5)	3 (2.6)
Blood Pressure Increased	4 (3.6)	2 (1.7)
Electrocardiogram Abnormal	0 (0.0)	1 (0.9)
Electrocardiogram QRS Complex Prolonged	1 (0.9)	0 (0.0)
Nervous System Disorders	1 (0.9)	0 (0.0)
Dyskinesia	1 (0.9)	0 (0.0)
Psychiatric Disorders	5 (4.5)	3 (2.6)
Agitation	1 (0.9)	0 (0.0)
Anxiety	3 (2.7)	0 (0.0)
Depressed Mood	0 (0.0)	2 (1.7)
Depression	0 (0.0)	1 (0.9)
Mood Altered	1 (0.9)	0 (0.0)
Panic Attack	1 (0.9)	0 (0.0)
Thinking Abnormal	1 (0.9)	0 (0.0)
Skin and Subcutaneous Tissue Disorders	1 (0.9)	0 (0.0)
Hyperhidrosis	1 (0.9)	0 (0.0)
Vascular Disorders	1 (0.9)	0 (0.0)
Hypertension	1 (0.9)	0 (0.0)

For Study 3002, Sponsors Table 38 showing $\geq$ 2 % of subjects who discontinued during the double blind because of an adverse event. A listing, entitled "Narratives for Each Individual Subject Who Discontinued Clinical Study 42602ATT3202" of each individual subjects with the adverse event resulting in discontinuation has been placed in the Appendix.

Table 38: Adverse Events Emerging During Double-Blind With Action Taken Permanently Stopped Trial Medication, Reported by ≥2 Subjects in the Overall Group
(Study 42603ATT3002: *All Subjects / Double-Blind*)

		PR OROS MPH			
Body System Preferred Term n (%)	Placebo (N=96)	18 mg (N=101)	36 mg (N=102)	72 mg (N=102)	Overall (N=401)
Any AE in this category	**1 (1.0)**	**1 (1.0)**	**4[b] (3.9)**	**8 (7.8)**	**14 (3.5)**
Nervous System Disorders	**0**	**0**	**1 (1.0)**	**4 (3.9)**	**5 (1.2)**
Insomnia	0	0	0	2 (2.0)	2 (0.5)
Tremor	0	0	0	2 (2.0)	2 (0.5)
Psychiatric Disorders	**0**	**0**	**4 (3.9)**	**7 (6.9)**	**11 (2.7)**
Anxiety	0	0	1 (1.0)	3 (2.9)	4 (1.0)
Irritability	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Nervousness	0	0	1 (1.0)	2 (2.0)	3 (0.7)
Restlessness	0	0	0	2 (2.0)	2 (0.5)
Vascular Disorders	**1 (1.0)**	**0**	**0**	**1 (1.0)**	**2 (0.5)**
Hypertension	1[a] (1.0)	0	0	1 (1.0)	2 (0.5)

[a] subject A11047 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.
[b] subject 10871 discontinued trial medication in the open-label phase because of an adverse event that emerged during the double-blind phase.
Source: Attachment 47

A table combining both adverse events resulting in discontinuation n for both Studies 3002 and 02-159 is pasted below.

Number and Percent of Subjects Who Withdrew Because of an Adverse Event by System Organ Class, MedDRA Preferred Term and Treatment Group - Double-Blind Safety Population

System Organ Class[a] MedDRA Preferred Term[a]	All CONCERTA N=416 n (%)	Placebo N=212 n (%)
Any adverse event	29 (7.0)	7 (3.3)
Cardiac disorders	3 (0.7)	0 (0.0)
Palpitations	1 (0.2)	0 (0.0)
Tachycardia	2 (0.5)	0 (0.0)
Ear and labyrinth disorders	1 (0.2)	0 (0.0)
Tinnitus	1 (0.2)	0 (0.0)
Eye disorders	2 (0.5)	0 (0.0)
Accommodation disorder	1 (0.2)	0 (0.0)
Vision blurred	1 (0.2)	0 (0.0)
Gastrointestinal disorders	5 (1.2)	0 (0.0)
Abdominal pain	1 (0.2)	0 (0.0)
Dry mouth	1 (0.2)	0 (0.0)
Eructation	1 (0.2)	0 (0.0)
Nausea	1 (0.2)	0 (0.0)
Stomach discomfort	1 (0.2)	0 (0.0)
Vomiting	1 (0.2)	0 (0.0)
General disorders and administration site conditions	6 (1.4)	0 (0.0)
Fatigue	1 (0.2)	0 (0.0)
Irritability	6 (1.4)	0 (0.0)

a: Subjects counted only once within each system organ class and MedDRA preferred term

7.1.1.6 Other significant adverse events

7.1.1.6.1 Study 42603att3002 Significant Adverse Events

Other Possible Cerebrovascular Events Occurring In Study 42603att3002

The following other cases were reported by the sponsor during the open label portions of this trial which are relevant to the issue of cerebrovascular events, suggested by the two index, serious adverse events, reported above for Study 3002.

A11047, Finland, was a 29 year old female, stimulant naïve, with a history of asthma on various medications, gestational diabetes who was found to be *hypertensive at screening* [165/109 supine, 142/94 standing]. She was on placebo during the double blind phase of the study from 12/21/05-02/01/06 during which time, she had flu with fever and stomachache for unclear duration. Supine blood pressures during this time ranged from 132-143/89-97. From 02/02-02/28/06, the subject was enrolled in the open label portion of the trial. During the open label

portion of the trial, she was on Concerta 36 mg for 9 days, which was increased to 54 mg, and the subject then developed *dizziness, headache, nausea, palpitations* (decrease dose to 36 mg), paresthesia *of the right arm, in the context of worsening high blood pressure* (170/117 mm Hg: supine; 184/103 standing-End of open label.)

Reviewer Comment: One cannot say with any certainty that the subject did or did not have a reversible ischemic neurologic deficit.

A10788 is described above, in the sub-section, entitled "Serious Adverse Events Occurring during Open Label Portion in Study 3002".

A10123, France, was a 45 year old male, stimulant naïve, treated with 36 mg of Concerta during the double blind portion of the trial. After 28 days on Concerta, in the open label portion of the trial the subject developed persistent symptoms of vertigo, hypoacusia, tinnitus and nystagmus. Review of the CRF indicates that an MRI was apparently performed on 01/25/06, and the note on the remark page of the CRF's (page 63), dated 04/26/06, states "MRI Cerebral and focused on internal auditory meatus not involving recent accidental ischemia." In the revised narrative submitted by the sponsor in February 2008, it states that a "the MRI report indicated no evidence of cerebral ischemic damage".

Reviewer Comment: The explanation given seems acceptable.

Some Other Adverse Events of Note Resulting in Discontinuation in Study 42603att3002

A10771, Sweden, was a 45 year old female treated with 36 mg Concerta during the double blind which was increased to 54 mg during the open label portion when she developed dizziness, suicidal thoughts and depression, which resulted in a dose decrease to 36 mg, and finally stopping with resolution of the suicidality (positive dechallenge).

A10804, Sweden, was a 46 year old male, stimulant naïve, with a history of depression on venlafaxine, who was on Concerta 36 mg during the double blind portion of the trial when she developed delusions of reference; polyuria, polydypsia; concentrations, memory and uneasiness, symptoms of depression and diarrhea; borderline hypertension (150/90) and borderline, standing tachycardia (100) [not listed as AE's in original narrative] with the delusions of reference continuing the open label phase of the trial. She continued on Concerta 36 mg during the open label trial and because of the persisting delusions of reference, the Concerta was stopped resulting in resolution of these symptoms. In the revised narrative and supporting documents, submitted by the sponsor in February 2008, it states that "the subject reported increased internal excitement and a feeling of people showing a keen interest in him" as delusion of reference. Further information is supplied that the subject had a "history of polysubstance dependence... including amphetamine dependence of substance-induced psychosis."

Reviewer Comment: This may *possibly be a protocol violation* depending on the interval of abusing agents and would contradict the initial history suggesting that the subject was stimulant naïve.

7.1.1.6.2 Study 02-159 Significant Adverse Events

Cardiovascular cases of potential significance are discussed in the Electrocardiograms (ECGs) Section/Additional analyses and explorations and whose cases are described in the Appendix. An additional summary is also included in the Appendix describing these cases and other significant adverse events.

Also refer to the section entitled Special Safety Studies which briefly describes the findings of three (3) additional analyses performed at FDA's request which involve Study 02-159: a HAM-A/HAM-D Outlier, Cardiovascular Risk Status (CRS), and Headaches, which are discussed in the Conclusion(s).

7.1.4 OTHER SEARCH STRATEGIES

Refer to the Section entitled ECG/Additional Analyses and Exploration for further discussion about ascertainment of cardiovascular cases of interest from Study 02-159.

7.1.5 COMMON ADVERSE EVENTS

The following pooled double blind analysis sets for both double-blind studies 3002 and 02-159 are pasted below for the listed categories:

All Adverse Events by Treatment Group

Table 14: Summary of All Adverse Events by Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set)

Parameter	All CONCERTA N=415 n (%)	Placebo N=212 n (%)
Subjects with adverse events	330 (79.5)	137 (64.6)
Subjects with serious adverse events	4 (1.0)	0 (0.0)
Subjects who discontinued due to adverse events	29 (7.0)	7 (3.3)
Deaths	0 (0.0)	0 (0.0)

Cross-reference: Appendix 3.1.

Over-All Incidence (≥ 1 %)

Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set)

System or Organ Class[a] MedDRA Preferred Term[a]	All CONCERTA N=415 n (%)	Placebo N=212 n (%)
Any adverse event	330 (79.5)	137 (64.6)
Cardiac disorders	**33 (8.0)**	**3 (1.4)**
Palpitations	13 (3.1)	2 (0.9)
Tachycardia	20 (4.8)	0 (0.0)
Ear and labyrinth disorders	**14 (3.4)**	**3 (1.4)**
Vertigo	7 (1.7)	0 (0.0)
Eye disorders	**24 (5.8)**	**5 (2.4)**
Vision blurred	7 (1.7)	1 (0.5)
Gastrointestinal disorders	**135 (32.5)**	**43 (20.3)**
Constipation	6 (1.4)	2 (0.9)
Dry mouth	58 (14.0)	8 (3.8)
Dyspepsia	9 (2.2)	2 (0.9)
Nausea	53 (12.8)	7 (3.3)
Vomiting	7 (1.7)	1 (0.5)
General disorders and administration site conditions	**63 (15.2)**	**22 (10.4)**
Irritability	24 (5.8)	3 (1.4)
Thirst	5 (1.2)	1 (0.5)
Infections and infestations	**55 (13.3)**	**22 (10.4)**
Influenza[b]	8 (1.9)	4 (1.9)
Upper respiratory tract infection	9 (2.2)	2 (0.9)
Investigations	**60 (14.5)**	**23 (10.8)**
Weight decreased	27 (6.5)	7 (3.3)
Metabolism and nutrition disorders	**116 (28.0)**	**21 (9.9)**
Anorexia	7 (1.7)	0 (0.0)
Decreased appetite	105 (25.3)	14 (6.6)
Musculoskeletal and connective tissue disorders	**37 (8.9)**	**17 (8.0)**
Muscle tightness	8 (1.9)	0 (0.0)
Nervous system disorders	**147 (35.4)**	**58 (27.4)**
Dizziness	28 (6.7)	11 (5.2)
Headache	92 (22.2)	33 (15.6)
Paresthesia	5 (1.2)	0 (0.0)
Sedation	5 (1.2)	0 (0.0)
Tension headache	5 (1.2)	1 (0.5)
Tremor	11 (2.7)	1 (0.5)
Psychiatric disorders	**150 (36.1)**	**37 (17.5)**
Affect lability	6 (1.4)	2 (0.9)
Aggression	7 (1.7)	1 (0.5)
Agitation	9 (2.2)	1 (0.5)
Anxiety	34 (8.2)	5 (2.4)
Bruxism	7 (1.7)	1 (0.5)
Confusional state	5 (1.2)	1 (0.5)
Depressed mood	16 (3.9)	3 (1.4)

Psychiatric disorders (Continued)		
Depression	7 (1.7)	2 (0.9)
Initial insomnia	18 (4.3)	6 (2.8)
Insomnia	51 (12.3)	13 (6.1)
Libido decreased	7 (1.7)	1 (0.5)
Nervousness	13 (3.1)	1 (0.5)
Restlessness	13 (3.1)	0 (0.0)
Tension	5 (1.2)	1 (0.5)
Respiratory, thoracic, and mediastinal disorders	**19 (4.6)**	**12 (5.7)**
Pharyngolaryngeal pain	7 (1.7)	3 (1.4)
Skin and subcutaneous tissue disorders	**30 (7.2)**	**6 (2.8)**
Hyperhidrosis	21 (5.1)	2 (0.9)

[a] Subjects counted only once within each system organ class and MedDRA preferred term.
[b] Source table in cross-reference is rounded; based on incidence without rounding, the incidence of influenza is higher in the CONCERTA-treated subjects than in the placebo-treated subjects.
Note: Adverse events were included only if the percentage was ≥1% without rounding.

For Concerta compared to placebo, the following are the most notable: decreased appetite (25.3% vs. 6.6%), dry mouth (14.0% vs. 3.8%), nausea (12.8% vs. 3.3%), headache (22.2 % vs. 15.6 %) tachycardia (4.8% vs. 0 %) and palpitations (3.1% vs. 0.9%).

7.1.1.7 Incidence of common adverse events

The most notable adverse events for Concerta compared to placebo in pooled data sets for the double-blind trials are decreased appetite (25.3% vs. 6.6%), dry mouth (14.0% vs. 3.8%), nausea (12.8% vs. 3.3%), headache (22.2 % vs. 15.6 %) tachycardia (4.8% vs. 0 %) and palpitations (3.1% vs. 0.9%).

The most frequently reported adverse events were headache (20.0%), decreased appetite (17.9%), and insomnia (15.3%) in a ≥ 2 % pooled incidence table for open label studies (3002 OL, 12-304, C-99-018-00 and CON-CAN-4).

7.1.1.7.1 Double Blind Study 42603att3002

The sponsor states "treatment-emergent adverse events reported per body system and those reported by more than **2% of all subjects** who received Concerta during the double-blind" treatment is pasted below in the subsection entitled "Common adverse event tables". However, the description in the clinical study report indicates "that these are the most frequently reported adverse events (reported by **>5% of the subjects**)".

Reviewer Comment(s): It is not clear if the table or the description refers to 2 % or 5 % of adverse events.

The sponsor reports[38] the most common treatment adverse events for all subjects in the the double-blind portion of this study. "The most frequently reported adverse events reported by 5 % or 2 % of all subjects treated with Concerta were decreased appetite (25% vs. 7% PBO), headache (21% vs. 18%), insomnia (13% vs. 7%), nausea (13% vs. 4%), dry mouth (12% vs. 2%), dizziness (8% vs. 7%), weight loss (7% vs. 5%), nasopharyngitis (6% vs. 9%), tachycardia (6% vs. 0%), irritability (6% vs. 1%), anxiety (5% vs. 1%) and hyperhidrosis (5% vs. 1%). A trend towards dose-relatedness was present for decreased appetite (34% in 72 mg vs. 22% in 36 and 20% in 18 mg and 7% in PBO) and dry mouth (21% in 72 mg vs. 7% in 36 mg and 8% in 18 mg and 2% in PBO). Weight decreased by11% in the 72 mg group, 8% in the 36 mg group, 3% in the 18 mg and 5% in the PBO group. Irritability was reported by 9 % of the subjects in the 72 mg group vs. 4% in both the 36 mg and 18 mg group and 1% in PBO. Anxiety was reported by 8% of the subjects in the 72 mg group, 5% in the 36 mg group and 3% in the 18 mg group and 1% in PBO.

A similar but less pronounced trend towards dose-relatedness was present for tachycardia (8% in the 72 mg, 5% in the 36 mg, 4% in the 18 mg groups and none in the PBO), insomnia (17% in the 72 mg, 12% with both 18 mg and 36 mg and 7% in PBO), nausea (15% in 72 mg vs. 16% in 36 mg, 8% in the 18 mg and 4% in PBO) and dizziness (9% in 72 mg vs. 10% in 36 mg and 6% in the 18 mg groups and 7% in PBO).

A trend towards dose-relatedness was present for psychiatric disorders (18%, 24% and 39% of the subjects in 18 mg, 36 mg and 72 mg groups, respectively vs. 6% in the PBO group), gastrointestinal disorders (25%, 31% and 39% vs. 19% in the PBO group), metabolism and nutrition disorders (22%, 24% and 35% vs. 9% in the PBO group) and cardiac disorders (5%, 10% and 13% vs. 0% in the PBO group).

The most common treatment emergent adverse events were: severe decreased appetite with 2-7 kg body weight loss (72 mg, n=3), severe weight loss (36 mg, n=1) without decreased appetite, severe nausea (72 mg, n=3; 36 mg, n=1) vs. PBO (n=1), severe headache (72 mg, n=4; 36 mg, n=1), severe insomnia (72 mg, n=2; 36 mg, n=2) vs. PBO (n=1), severe dry mouth (72 mg, n=2), severe irritability (72 mg, n=3), severe anxiety (72 mg, n=1) , severe dizziness (72 mg, n=1) .

"In total, severe treatment-emergent adverse event were reported for 34 subjects (11%) treated with Concerta. The number of subjects with at least one adverse event, assessed by the investigator as severe, was higher in the 72 mg Concerta group (20% of the subjects) compared to the other treatment groups, with a dose-related increase in incidence across Concerta (4% in the 18 mg group and 10% in the 36 mg group). This proportion was 4% in the placebo group."

38 Clinical Study Report, 42603att3002: Sec. 6.2.2 Common Treatment Emergent Adverse Events: pgs. 84-86.

APPEARS THIS WAY ON ORIGINAL

7.1.1.8 Common adverse event tables

7.1.1.8.1 Study 42603att3002

APPEARS THIS WAY ON ORIGINAL

Table 36: Treatment-Emergent Adverse Events During Double-Blind Phase Occurring in ≥2% of Subjects Receiving PR OROS MPH, by Preferred Term
(Study 42603ATT3002: *All Subjects / Double-Blind*)

Body System Preferred Term n (%)	Placebo (N=96)	PR OROS MPH 18 mg (N=101)	PR OROS MPH 36 mg (N=102)	PR OROS MPH 72 mg (N=102)	All (N=305)
Any AE	**63 (65.6)**	**76 (75.2)**	**77 (75.5)**	**84 (82.4)**	**237 (77.7)**
Cardiac Disorders	**0**	**5 (5.0)**	**10 (9.8)**	**13 (12.7)**	**28 (9.2)**
Palpitations	0	2 (2.0)	5 (4.9)	5 (4.9)	12 (3.9)
Tachycardia	0	4 (4.0)	5 (4.9)	8 (7.8)	17 (5.6)
Ear and Labyrinth Disorders	**0**	**3 (3.0)**	**4 (3.9)**	**5 (4.9)**	**12 (3.9)**
Vertigo	0	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Gastro-Intestinal Disorders	**18 (18.8)**	**25 (24.8)**	**32 (31.4)**	**40 (39.2)**	**97 (31.8)**
Abdominal pain upper	5 (5.2)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Diarrhea	5 (5.2)	3 (3.0)	1 (1.0)	4 (3.9)	8 (2.6)
Dry mouth	2 (2.1)	8 (7.9)	7 (6.9)	21 (20.6)	36 (11.8)
Nausea	4 (4.2)	8 (7.9)	16 (15.7)	15 (14.7)	39 (12.8)
General Disorders and Administration Site Conditions	**11 (11.5)**	**10 (9.9)**	**9 (8.8)**	**10 (9.8)**	**29 (9.5)**
Fatigue	6 (6.3)	4 (4.0)	4 (3.9)	6 (5.9)	14 (4.6)
Infections and Infestations	**12 (12.5)**	**10 (9.9)**	**12 (11.8)**	**7 (6.9)**	**29 (9.5)**
Influenza	3 (3.1)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Nasopharyngitis	9 (9.4)	7 (6.9)	8 (7.8)	4 (3.9)	19 (6.2)
Investigations	**8 (8.3)**	**9 (8.9)**	**12 (11.8)**	**12 (11.8)**	**33 (10.8)**
Weight decreased	5 (5.2)	3 (3.0)	8 (7.8)	11 (10.8)	22 (7.2)
Metabolism and Nutrition Disorders	**9 (9.4)**	**22 (21.8)**	**24 (23.5)**	**36 (35.3)**	**82 (26.9)**
Decreased appetite	7 (7.3)	20 (19.8)	22 (21.6)	35 (34.3)	77 (25.2)
Nervous System Disorders	**34 (35.4)**	**42 (41.6)**	**39 (38.2)**	**47 (46.1)**	**128 (42.0)**
Dizziness	7 (7.3)	6 (5.9)	10 (9.8)	9 (8.8)	25 (8.2)
Headache	17 (17.7)	26 (25.7)	21 (20.6)	17 (16.7)	64 (21.0)
Initial insomnia	2 (2.1)	3 (3.0)	2 (2.0)	5 (4.9)	10 (3.3)
Insomnia	7 (7.3)	12 (11.9)	12 (11.8)	17 (16.7)	41 (13.4)
Tremor	1 (1.0)	1 (1.0)	1 (1.0)	7 (6.9)	9 (3.0)
Psychiatric Disorders	**6 (6.3)**	**18 (17.8)**	**24 (23.5)**	**40 (39.2)**	**82 (26.9)**
Aggression	1 (1.0)	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Anxiety	1 (1.0)	3 (3.0)	5 (4.9)	8 (7.8)	16 (5.2)
Depressed mood	1 (1.0)	6 (5.9)	3 (2.9)	5 (4.9)	14 (4.6)
Depression	1 (1.0)	0	3 (2.9)	4 (3.9)	7 (2.3)
Irritability	1 (1.0)	4 (4.0)	4 (3.9)	9 (8.8)	17 (5.6)
Nervousness	1 (1.0)	0	3 (2.9)	8 (7.8)	11 (3.6)
Restlessness	0	0	2 (2.0)	6 (5.9)	8 (2.6)
Skin and Subcutaneous Tissue Disorders	**3 (3.1)**	**9 (8.9)**	**5 (4.9)**	**10 (9.8)**	**24 (7.9)**
Hyperhidrosis	1 (1.0)	5 (5.0)	3 (2.9)	8 (7.8)	16 (5.2)

Source: Attachment 38

7.1.1.8.2 Study 02-159

Table 10-7: Number and Percent of Subjects With Adverse Events where CONCERTA Incidence ≥1% and >Placebo by System Organ Class and MedDRA Preferred Term - Safety Population

System Organ Class MedDRA Preferred Term	All CONCERTA N=110 n (%)	Placebo N=116 n (%)
Any adverse event	93 (84.5)	74 (63.8)
Cardiac Disorders	5 (4.5)	3 (2.6)
Tachycardia	3 (2.7)	0 (0.0)
Eye Disorders	6 (5.5)	1 (0.9)
Vision Blurred	3 (2.7)	1 (0.9)
Gastrointestinal Disorders	38 (34.5)	25 (21.6)
Abdominal Pain Upper	2 (1.8)	2 (1.7)
Constipation	2 (1.8)	1 (0.9)
Dry Mouth	22 (20.0)	6 (5.2)
Dyspepsia	3 (2.7)	1 (0.9)
Nausea	14 (12.7)	3 (2.6)
Vomiting	2 (1.8)	1 (0.9)
General Disorders and Administration Site Conditions	18 (16.4)	8 (6.9)
Chest Discomfort	2 (1.8)	2 (1.7)
Feeling Jittery	4 (3.6)	1 (0.9)
Irritability	7 (6.4)	2 (1.7)
Infections and Infestations	9 (8.2)	8 (6.9)
Upper Respiratory Tract Infection	4 (3.6)	2 (1.7)
Investigations	27 (24.5)	15 (12.9)
Blood Pressure Increased	11 (10.0)	6 (5.2)
Heart Rate Increased	8 (7.3)	5 (4.3)
Weight Decreased	5 (4.5)	2 (1.7)
Metabolism and Nutrition Disorders	33 (30.0)	12 (10.3)
Anorexia	4 (3.6)	0 (0.0)
Decreased Appetite	28 (25.5)	7 (6.0)
Musculoskeletal and Connective Tissue Disorders	13 (11.8)	10 (8.6)
Muscle Tightness	7 (6.4)	0 (0.0)
Pain in Extremity	2 (1.8)	2 (1.7)
Nervous System Disorders	42 (38.2)	29 (25.0)
Dysgeusia	2 (1.8)	0 (0.0)
Headache	28 (25.5)	16 (13.8)
Lethargy	2 (1.8)	1 (0.9)
Poor Quality Sleep	2 (1.8)	0 (0.0)
Tremor	2 (1.8)	0 (0.0)
Psychiatric Disorders	44 (40.0)	23 (19.8)
Affect Lability	3 (2.7)	1 (0.9)
Agitation	5 (4.5)	0 (0.0)
Anger	3 (2.7)	0 (0.0)
Anxiety	18 (16.4)	4 (3.4)
Bruxism	7 (6.4)	1 (0.9)

Table 10-7: Number and Percent of Subjects With Adverse Events where CONCERTA Incidence ≥1% and >Placebo by System Organ Class and MedDRA Preferred Term - Safety Population

System Organ Class MedDRA Preferred Term	All CONCERTA N=110 n (%)	Placebo N=116 n (%)
Depressed Mood	2 (1.8)	2 (1.7)
Initial Insomnia	8 (7.3)	4 (3.4)
Insomnia	10 (9.1)	6 (5.2)
Libido Decreased	3 (2.7)	1 (0.9)
Nervousness	2 (1.8)	0 (0.0)
Restlessness	5 (4.5)	0 (0.0)
Tension	2 (1.8)	1 (0.9)
Thinking Abnormal	2 (1.8)	0 (0.0)
Reproductive System and Breast Disorders	3 (2.7)	3 (2.6)
Erectile Dysfunction	2 (1.8)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	7 (6.4)	8 (6.9)
Cough	2 (1.8)	1 (0.9)
Sinus Congestion	2 (1.8)	2 (1.7)
Skin and Subcutaneous Tissue Disorders	7 (6.4)	3 (2.6)
Hyperhidrosis	5 (4.5)	1 (0.9)

7.1.7 LABORATORY FINDINGS

7.1.1.9 Study 42603att3002

No trend in laboratory values was reported by the sponsor. The sponsor further states that "no markedly abnormal values were determined in this study" (Clinical Study Report, pg. 93)

7.1.1.10 Study 02-159

Subjects taking Concerta had a greater decrease in total cholesterol compared to placebo (-7.5 mg/dL vs. -1.0 mg/dL) and LDL (-7.8 mg/dL vs. -2.8 mg/dL), while subjects taking placebo tended to have a greater increase in triglycerides compared with Concerta (12.6 mg/dL vs. 2.9 mg/dL).

7.1.8 VITAL SIGNS

7.1.1.11 Overview of vital signs testing in the development program

7.1.1.11.1 Blood Pressure, Heart Rate, Weight for Study 42603att3002

"For both standing diastolic and systolic blood pressure, the mean increase vs. baseline reached statistical significance ($p<0.05$) at Week 1 in the 72 mg group (mean increase of 2.0 mmHg for standing DBP and 4.0 mmHg for standing and supine SBP) but not at later time points. Pulse

showed a small but statistically significant increase in beats per minute for all three treatment groups vs. baseline ($p<0.05$) (range of the mean change 2.0 –10.6 bpm)."[39]

Table 40: Mean Changes From Baseline for Vital Signs Parameters During Double-Blind (Study 42603ATT3002: *All Subjects / Double-Blind*)

	Placebo (N=96)			PR OROS MPH 18 mg (N=100)			PR OROS MPH 36 mg (N=102)			PR OROS MPH 72 mg (N=101)		
Parameter (units)												
Timepoint	W1	W3	W5	W1	W3	W5	W1	W3	W5	W1	W3	W5
DBP (mmHg)												
Standing	-1.4	-0.8	-1.8	-0.1	0.3	-0.7	1.9	**2.3**	1.7	**2.0**	1.9	1.6
Supine	-1.6	-1.9	-1.7	0.7	1.3	0.3	-0.5	0.1	-0.6	1.7	1.2	0.7
SBP (mmHg)												
Standing	0.8	1.2	1.1	0.8	-0.6	0.1	-0.2	-0.6	0.4	**4.0**	-0.1	2.2
Supine	0.4	-0.4	-0.3	-1.5	-1.0	0.2	0.1	2.0	-0.1	**4.0**	2.2	0.5
Pulse (bpm)												
Standing	2.1	**3.7**	2.7	**2.9**	**2.7**	**3.9**	**5.3**	**5.7**	**5.2**	**8.1**	**10.6**	**9.8**
Supine	**2.1**	1.7	**2.4**	**2.0**	**3.7**	**3.9**	**4.6**	**4.5**	**3.0**	**7.1**	**9.1**	**9.6**

W1: Week 1; W3: Week 3; W5: Week 5; bpm: beats per minute
Bold: Statistically significant change at 0.05 level versus baseline (two-sided paired T-test)
Source: Attachment 49

A statistically significant decrease versus baseline in mean body weight was observed in the three active treatment groups. Mean decrease was 0.9, 1.1 and 1.9 kg in the 18 mg, 36 mg and 72 mg Concerta groups. A statistically significant mean weight increase of 0.4 kg versus baseline occurred in the placebo group.

7.1.1.11.2 Blood Pressure, Heart Rate, Weight for Study 02-159

For Concerta compared to placebo, "the mean change from baseline to LOCF in systolic blood pressure was -1.2 mmHg (8.92) and -0.5 mmHg (9.72), diastolic blood pressure was +1.1 mmHg (6.72) and +0.4 mmHg (7.43), and pulse was +3.6 bpm (9.78) and -1.6 bpm (8.33), respectively".[40] For pulse, the mean change from baseline to LOCF was +3.6 bpm (9.78) for Concerta compared to –1.6 bpm (8.33) placebo. The mean change in weight from baseline to LOCF was -2.2 kg (2.33) in the Concerta compared to +0.2 kg (1.74) in placebo.

39 Clinical Study Report Study 42603att3002, pg. 94

40 Clinical Study Report 02-159, pg. 196

7.1.9 ELECTROCARDIOGRAMS (ECGS)

7.1.1.12 Overview of ECG testing in the development program, including brief review of preclinical results

7.1.1.12.1 ECG's for Study 42603att3002

No electrocardiograms were obtained at baseline or end of study, hence cardiovascular abnormalities could not be adequately evaluated. Furthermore, there apparently was individual, investigator difference in the coding of adverse events (e.g. a subject with borderline, baseline hypertension who has mild increases in blood pressure associated with other events). Hence, the occurrence of certain cardiovascular events may not have been adequately characterized (e.g. palpitations, recurrent syncope, etc).).

7.1.1.12.2 ECG's for Study 02-159

ECGs were performed at screening, baseline, each titration visit, and at the end of the double-blind phase of Study 02-159. ECGs were read by a central diagnostic company. Fridericia's correction was used.

7.1.1.13 Standard analyses and explorations of ECG data

With the exception of an increase in heart rate (mean maximum increase 12.1 bpm on Concerta vs. 7 bpm on PBO), none of the ECG interval assessments showed a greater post-baseline change in the Concerta compared to placebo. There sponsor found no evidence of a drug-induced lengthening of the QT or corrected QT interval (mean maximum QTcB of 19.3 msec on Concerta vs. 17.4 msec on placebo).

In Study 02-159, the sponsor identified 15 subjects on placebo with cardiovascular adverse events of interest and 19 subjects treated with Concerta.

Sponsor's Table 43 (CSR) of potentially clinical important post baseline ECG measurement is pasted in the Appendix of this review.

7.1.1.14 Additional analyses and explorations

For Study 02-159, the sponsor identified subjects with cardiovascular adverse events of interest (Concerta: 19; Placebo: 15). These cases and subjects with adverse events leading to discontinuation were reviewed in detail for the presence of absence of possible cardiovascular symptoms of concern (e.g. chest pain or discomfort, electrographic evidence of ischemia or myocardial infarction, dizziness, syncope, palpitations, QT prolongation and, or arrhythmia, etc) in the subject narratives. CRF's for these subjects was then reviewed to allow for temporal reconciliation of the adverse events(s) with vital sign and ECG changes. In addition, cases on the sponsor's listing for ECG changes during the trial were reviewed to identify potentially

significant ECG changes which may have occurred. Possible contributory factors (e.g. smoking, obesity, and probable metabolic syndrome, concurrent medications were identified in each CRF and a summary was constructed for each subject of interest. Those subjects with new adverse events or new ECG changes which were not present at baseline and, or, which occurred with dose titration were classified as probable drug related cardiovascular adverse events. This was only done for those studies where ECG's were performed at regular intervals associated with dose titration. Cases were then discussed with some members of the Cardio-Renal Division to determine the appropriateness as a possible Case of Interest. This resulted in the following cases (Concerta: 11/113 [9.7 %], PBO: 2/116 [1.7 %]) which was submitted for consultation to the Cardio-Renal to better assess the significance of the ECG's and, of the events. A brief summary of the selected cases is presented in the Appendix.

7.1.10 SPECIAL SAFETY STUDIES

7.1.1.15 Analysis of Adverse Events by Cardiovascular Risk Status (CRS)

CRS Status[41] defined as the presence at screening and, or baseline of previous cardiovascular medical history, baseline systolic blood pressure >140 mmHg, baseline diastolic blood pressure >90 mmHg, baseline pulse >100 bpm, baseline BMI >30 kg/m2, baseline total cholesterol ≥200 mg/dL, baseline HDL for males ≤44 mg/dL, baseline HDL for females ≤49 mg/dL, history of diabetes, and current smoker status.

In the double blind studies 3002 and 02-159, CRS was identified in 203 of 415 (48.9 %) on Concerta compared to 134 of 212 (63.2 %) of placebo identified no clear patterns of increased cardiovascular risk (CR) or possible cardiovascular related adverse vents in Concerta subjects with or without CR versus placebo with or without CR risk except for tachycardia and palpitations.

Sponsor's Table 25 showing the number of subjects reporting cardiovascular related adverse events by cardiovascular risk status for the double blind studies is pasted in the Appendix.

In an additional analysis, looking at the long term open label safety experience(s) in the 1 year, open label study, 12-304, a subset of subjects experiencing cardiovascular adverse events of interest while taking Concerta and at least 1 concomitant medication known to increase blood pressure or pulse, did demonstrate" a consistent modest increase in blood pressure and pulse that was apparent after 1 week of exposure and throughout the course of the study". However, the sensitivity of this analysis is limited and may need further exploration(s).

7.1.1.16 Headache Analysis

Since headaches occurred in >1 % of subjects treated with Concerta in the Two (2) Placebo Controlled Trials, the sponsor was asked to examine all subjects in this

41 Concerta Module 2.7 Clinical Summary 2.7.4 Clinical Summary: pgs. 72-74.

submission who developed this symptom based on the presence or absence of a baseline history of headache and by headache type (e.g., migraine, tension), of hypertension, etc. This was submitted in the February 2008 Response to FDA-74 Day Letter-Additional Analyses (pgs. 20-45). A preliminary review of the sponsor's findings discussions and conclusions indicate that a history of a headache did not increase the percentage of subjects reporting a headache as an adverse event for placebo (18.0% history, 17.9% no history), but did for Concerta (33.7% history, 22.0% no history).

This analysis found a pronounced higher reporting of headaches among those with a history of headache who were treated with Concert vs. placebo.

Further exploration(s) of these findings are needed.

7.1.1.17 Study 02-159: HAM-A/HAM-D Outlier Analysis

These tests were performed at baseline and at the final visit in Study 02-159. No group differences were identified. An outlier analysis[42] was done determine if a subset of subjects who participated in Study 02-159 experienced changes in HAM-A or HAM-D scores during the study that differed from the changes observed in the overall study population, since both anxiety and MDD have previously been identified as adverse events during Concerta and other MPH's.

"A greater percentage of subjects with sub clinical levels of anxiety at study initiation developed a clinically relevant level of anxiety (as measured by HAM-A scores) when randomly assigned to CONCERTA treatment compared with placebo treatment, 9.5% vs. 4.6%, respectively. Likewise, a greater percentage of subjects with sub clinical levels of depression at study initiation developed a clinically relevant level of depressive symptoms (as measured by HAM-D scores) when randomly assigned to CONCERTA treatment compared with placebo treatment, 10.5% vs. 6.5%, respectively."

Further exploration(s) of these findings are needed.

42 CONCERTA: Response to FDA Day-74 Letter - Additional Analyses February 2008, pgs, 10-19.

WITHDRAWAL PHENOMENA AND/OR ABUSE POTENTIAL

The reader should refer to the section entitled "Significant Findings from Other Review Disciplines" discussing a presentation of Dr. Lee of Pharmacometrics who reviewed the exposure-abuse potential for this submission and presented his findings to the Division on March 10, 2008.

Adequacy of Patient Exposure and Safety Assessments

The following is based on the Summary of Clinical Safety with data up to the 02/21/2008 cut-off date.

Double-Blind Studies

- 415 subjects received at least 1 dose of Concerta in the double-blind studies (3002 DB and 02-159)

Open Label Studies

- 896 subjects received Concerta in the open-label portion of Studies 3002OL, 12-304, C-99-018-00, and CON-CAN-4.

DESCRIPTION OF PRIMARY CLINICAL DATA SOURCES (POPULATIONS EXPOSED AND EXTENT OF EXPOSURE) USED TO EVALUATE SAFETY

7.1.1.18 Study type and design/patient enumeration

Table of Studies[43]

Table 1: Table of Studies
(All Studies Contributing Data to the Summary of Clinical Safety)

Protocol Number	Study Design/Number of Subjects
PHASE 3 DOUBLE-BLIND STUDIES IN SUBJECTS WITH ADHD	
3002 Double Blind Phase	A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Safety and Efficacy of Prolonged Release (PR) OROS® Methylphenidate (18, 36 and 72 mg per day), with Open- Label Extension, in Adults with Attention Deficit/Hyperactivity Disorder No. Subjects Evaluable for Safety: 401 Treated with CONCERTA: 305
02-159	A Placebo-Controlled, Double-Blind, Parallel Group, Dose Titration Study to Evaluate the Efficacy and Safety of CONCERTA® in Adults With Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day No. Subjects Evaluable for Safety: 226 Treated with CONCERTA: 110

43 Module 2.7 Clinical Summary, 2.7.4 Clinical Safety, pgs. 28-29

PHASE 3 OPEN-LABEL STUDIES IN SUBJECTS WITH ADHD	
3002 Open-Label Phase	A Multicentre, Randomized, Double-Blind, Placebo-Controlled, Parallel Group, Dose-Response Study to Evaluate Safety and Efficacy of Prolonged Release (PR) OROS® Methylphenidate (18, 36 and 72 mg per day), with Open- Label Extension, in Adults with Attention Deficit/Hyperactivity Disorder No. Subjects Evaluable for Safety: 370
12-304 Interim Analysis	An Open-Label, Dose Titration, Long-Term Safety Study to Evaluate CONCERTA® at Doses of 36 mg, 54 mg, 72 mg, 90 mg, and 108 mg per day in Adults with Attention Deficit Hyperactivity Disorder No. Subjects Evaluable for Safety: 358
C-99-018-00 Adult Cohort	Open-Label Study to Evaluate Subject Use and Safety of OROS® Methylphenidate HCl in Patients With ADHD in a Community Setting No. Subjects Evaluable for Safety: 136
CON-CAN-4	An Open-Label Study Evaluating the Safety and Effectiveness of OROS® Methylphenidate (CONCERTA®) in Adults with Attention Deficit Hyperactivity Disorder No. Subjects Evaluable for Safety: 32
PHASE 3 DOUBLE-BLIND STUDY IN SUBJECTS WITH MAJOR DEPRESSIVE DISORDER (Additional Safety Information in Adults Who Have Received CONCERTA)	
CON-CAN-3	A Double-Blind, Randomized Trial to Evaluate the Safety, Tolerability and Efficacy of CONCERTA® Augmentation of SSRI/SNRI Monotherapy in Adult Patients with Major Depressive Disorder No. Subjects Evaluable for Safety: 145 Treated with CONCERTA: 73

Note: The number of subjects listed in the table is the number who enrolled and took at least 1 dose of study medication.

Table 1: Table of Studies (Continued)
(All Studies Contributing Data to the Summary of Clinical Safety)

Protocol Number	Study Design/Number of Subjects
	PHARMACOKINETIC/PHARMACODYNAMIC STUDIES
02-160	An Open-Label, Dose Escalation, Multiple Dose Pharmacokinetic Study of CONCERTA® in Healthy Adults No. Subjects Evaluable for Safety: 27
12-004	The Pharmacokinetics of CONCERTA® (Methylphenidate HCl) in Crushed and Whole Form, and RITALIN® in Crushed Form Dosed to Healthy Subjects No. Subjects Evaluable for Safety: 19
12-005	A Double-Blind, Randomized, Crossover Study to Evaluate the Abuse Potential of a Single Oral Dose of OROS® Methylphenidate Hydrochloride Extended-Release Tablets (CONCERTA®) as Compared to Immediate Release Methylphenidate Hydrochloride Tablets (RITALIN®) and Placebo in Subjects with a History of Recreational Stimulant Use No. Subjects Evaluable for Safety: 49
12-007	A Double-Blind, Randomized, Crossover Study to Assess the Abuse Potential of Oral Doses of OROS® Methylphenidate Hydrochloride Extended-Release Tablets (CONCERTA®) as Compared to Immediate Release Methylphenidate Hydrochloride Tablets (RITALIN®) and Placebo in Healthy Normal Subjects No. Subjects Evaluable for Safety: 53
12-302	A Double-Blind, Randomized, Placebo-Controlled, Crossover Study of Single Doses of OROS® Methylphenidate Hydrochloride (CONCERTA®) and Immediate Release Methylphenidate Hydrochloride (RITALIN®) in Adults with Substance Abuse No. Subjects Evaluable for Safety: 18

Note: The number of subjects listed in the table is the number who enrolled and took at least 1 dose of study medication.

7.1.1.19 Demographics

7.1.1.19.1 Double Blind

Table 9: Demographic and Baseline Characteristics by Treatment Group
(Pooled Double-Blind Studies 3002 and 02-159: Safety Analysis Set)

Demographic Characteristic	All CONCERTA N=415	Placebo N=212	Total N=627
Gender, n (%)			
Male	222 (53.5)	123 (58.0)	345 (55.0)
Female	193 (46.5)	89 (42.0)	282 (45.0)
Age (years)			
N	415	212	627
Mean (SD)	35.5 (11.25)	36.5 (10.77)	35.8 (11.09)
Median	35.0	36.5	36.0
Range (min, max)	18, 65	18, 64	18, 65
Age group, n (%)			
18 to 35	211 (50.8)	97 (45.8)	308 (49.1)
36 to 49	154 (37.1)	89 (42.0)	243 (38.8)
50 to 66	50 (12.0)	26 (12.3)	76 (12.1)
Race, n (%)			
White or Caucasian	393 (94.7)	193 (91.0)	586 (93.5)
Black/African American	9 (2.2)	7 (3.3)	16 (2.6)
Asian	3 (0.7)	4 (1.9)	7 (1.1)
American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.5)	1 (0.2)
Other	10 (2.4)	7 (3.3)	17 (2.7)
BMI (kg/m^2)			

Open-Label

Table 10: Demographic and Baseline Characteristics
(Pooled Open-Label Studies 3002, 12-304, C-99-018-00, and CON-CAN-4: Sa

Demographic Characteristic	All CONCERTA N=896
Gender, n (%)	
Male	492 (54.9)
Female	404 (45.1)
Age (years)	
N	896
Mean (SD)	36.6 (11.04)
Median	37.0
Range (min, max)	18, 66
Age group, n (%)	
18 to 35	419 (46.8)
36 to 49	359 (40.1)
50 to 66	118 (13.2)
Race, n (%)	
White or Caucasian	841 (93.9)
Black/African American	26 (2.9)
Asian	8 (0.9)
American Indian/Alaska Native	0 (0.0)
Native Hawaiian/Other Pacific Islander	1 (0.1)
Other	20 (2.2)

Overall

Table 11: Demographic and Baseline Characteristics: Overall CONCERTA Safety Population

Demographic Characteristic	All CONCERTA N=1015
Gender, n (%)	
Male	563 (55.5)
Female	452 (44.5)
Age (years)	
N	1015
Mean (SD)	36.7 (11.22)
Median	37.0
Range (min, max)	18, 66
Age group, n (%)	
18 to 35	477 (47.0)
36 to 49	396 (39.0)
50 to 66	142 (14.0)
Race, n (%)	
White or Caucasian	946 (93.2)
Black/African American	32 (3.2)
Asian	11 (1.1)
American Indian/Alaska Native	0 (0.0)
Native Hawaiian/Other Pacific Islander	1 (0.1)
Other	25 (2.5)

7.1.1.20 Extent of exposure (dose/duration)

Double-Blind Studies
The mean duration of exposure were 34.5 days for Concerta and 38.5 days for placebo with the majority being exposed for at least 29 days [Concerta (85.2 %), PBO (86.4 %]. The higher doses (90 and 108 mg) were exposed for a maximum of 29 and 25 days, while the 36-mg dose group was for at least 50 days.

Open Label Studies
The mean duration of exposure was 98.8 days with a maximum exposure of 333 days. The largest proportion (420 subjects; 46.9%) of subjects was exposed for 31-60 days, followed by 195 subjects (21.8%) exposed for 18-270 days. Twenty-three point four percent (23.4%) of subjects exposed for at least 6 months received the 108-mg per day dose. A total of 29.2% were exposed for at least 6 months and no subjects in any dose were exposed for a year.

The mean maximum daily dose was 62.2 mg and the mean final daily dose was 56.9 mg. Duration ranged from 1 to 329 days. The mean length of time at the maximum daily dose was 64.1 days and the final daily dose, 72.1 days. The mean dose with the longest cumulative duration was 55.3 mg per day and the mean length of time at this dose was 76.6 days.

Overall Concerta Population

The mean duration of exposure in the overall CONCERTA population was 101.4 days. The overall duration exposure by age[44] was 120.36 person years (18-35 years), 115.17 person years (36-49 years) and 46.14 person years (50-66 years).

DESCRIPTION OF SECONDARY CLINICAL DATA SOURCES USED TO EVALUATE SAFETY

An initial review prior to the filing review identified various deficiencies which suggested that cardiovascular events might be occurring above what has been seen with earlier trials in adults with stimulants, necessitating that the sponsor produce provide supporting clinical data and ancillary studies for specific subjects with significant adverse events, copies of hospital records and imaging studies for multiple subjects, multiple CRF's, with further description of the narratives. The reader should refer to the section entitled "Regulatory Activity, 10/24/2007: Filing Meeting" for further details.

7.1.1.21 Other studies

Some data inconsistencies and unclear primary data were identified in the initial review of the adverse events resulting in discontinuation and cardiovascular events of interest which were provided by the sponsor.

7.1.1.22 Postmarketing experience

The sponsor's postmaketing review concluded that "the safety profile of Concerta use in adults is consistent with the known experience in the pediatric population"[45] in a review from approval to 02/28/2007. The sponsor states "There were 889 spontaneous case reports for CONCERTA involving adults. One hundred eighty (180; 20%) of these involved serious adverse events and 709 involved non-serious adverse events. There were 15 adverse reactions that were reported disproportionately more frequently in adults compared to children/adolescents. Of these, an analysis of incidence and prevalence data for *angina pectoris, blood pressure increased, chest discomfort, fatigue, hot flush, hyperhidrosis, hypertension, mania, overdose, sedation, and somnolence* suggested that the disproportionally higher reporting in adults was likely *attributable to population risk rather than specific drug risk. Background data were not available for palpitations, euphoric mood, nervousness or tension.* It is plausible that reporting bias or co-

44 Module 2.7 Clinical Summary, 2.7.4 Clinical Safety, Appendix 2.5.2, Overall Duration of Exposure by Subgroup-Overall Concerta, pg. 308

45 Module 2.7 Clinical Summary, 2.7.4 Clinical Safety, Sec. 8. Postmarketing Data and Literature Review, 8.1 Postmarketing Data, , pg. 134

morbidities with a higher prevalence in adults contributed to disproportional reporting for these adverse reactions."

The source data has not been reviewed at the time of this review.

7.1.1.23 Literature

The sponsor conducted a literature review of the use of Concerta for the treatment of ADHD in adults[46] up to 02/21/2007 and identified 7 publications containing safety data (3 open label studies and 4 placebo control studies). "Overall, data were reported for more than 777 adult subjects with ADHD, of which at least 387 received Concerta.. The adverse events that were most frequently reported were s*leep disturbances, decreased appetite, dry mouth and headache.* A statistically significant *increase in heart rate* (4.5 to 8.7 bpm) and/or *blood pressure* (3.5 bpm systolic, 4.0 bpm diastolic) was reported in 4 articles. In one article, statistically significant reductions from baseline in systolic and diastolic blood pressure were observed at end point."

"There was no statistically significant correlation between the dose of Concerta and systolic blood pressure, diastolic blood pressure, heart rate, PR interval, QRS interval, or QTc interval. A *statistically significant prolongation (5.1 ms) in QTc interval* was reported in a small open-label study of adults with late-onset ADHD (n=36). *No subject in that study had a QTc interval greater than 460 ms.* A randomized, placebo-controlled study in adults with ADHD reported *a 1.9 ms prolongation in Concerta -treated subjects* and a QTc shortening of 1.2 ms in placebo-treated subjects. *The maximum QTc value observed in this study was 488 ms.* A third study, a double blind, placebo-controlled study of adults with ADHD (n=41), reported *no significant difference in QTc interval* in Concerta – or placebo-treated subjects and there were no clinically significant outliers in QTc intervals (>460 ms). *QT correction methods were not described* in any publications in which QT intervals were reported."

The source papers have not been reviewed at the time of this review.

ADEQUACY OF OVERALL CLINICAL EXPERIENCE

Study 42603ATT3002 (3002), the single, double blind, *fixed dose* failed to use and intermediate dose of 54 mg and used to few subjects older than 49 years (n=30) to adequately assess it safety in the 50-65 year age group, a population with the greater cardiovascular risks, a need previously stated in meetings with the sponsor on 02/04/200 and 07/12/2005. Doses of 54 mg probably are safe; however, one cannot assume this from the second, double blind, dose-titration study (02-159). Similarly, Study 42603ATT3002 (3002) did not use ECG's at baseline or endpoint, making it impossible to determine the significance of certain cardiovascular adverse events.

46 Module 2.7 Clinical Summary, 2.7.4 Clinical Safety, Sec. 8. Postmarketing Data and Literature Review, 8.1 Postmarketing Data, , pg. 134

ADEQUACY OF ROUTINE CLINICAL TESTING

As indicated above, Study 42603ATT3002 (3002) did not use ECG's at baseline or endpoint, making it impossible to determine the significance of certain cardiovascular adverse events. Furthermore, investigator determine inclusion of specific adverse events (e.g. increased in blood pressure) make the data set of Study 42603ATT3002 (3002) less secure.

ADEQUACY OF EVALUATION FOR POTENTIAL ADVERSE EVENTS FOR ANY NEW DRUG AND PARTICULARLY FOR DRUGS IN THE CLASS REPRESENTED BY THE NEW DRUG; RECOMMENDATIONS FOR FURTHER STUDY

No definite QT study has been done to date. Extrapolation of a lack of QT prolongation is based on a QT study performed in adults of a methylphenidate isomer (Focalin XR, dexmethylphenidate HCl ER, NDA 21-278).

ASSESSMENT OF QUALITY AND COMPLETENESS OF DATA

A significant effort was made by the sponsor to provide the supplemental information requested in order to address various concerns. A portion of these materials was received late in the review cycle. Ideally there would have been more time to review these materials.

In the 02/28/08 the sponsor response to a request on clarification of the definitions used to define an adverse event as tachycardia, or, systolic or diastolic hypertension for all clinical studies submitted is potentially concerning. It may mean that the adverse events may have been under-reported in double-blind, Study 3002, the fixed dose study and the combined common adverse event table with double-blind, Study 02-159.

The sponsor's response is indicated below:

J&JPRD Response February 8, 2008:

Five clinical studies evaluating CONCERTA in adults with ADHD were submitted in Module 5.3.5 of S-017 (sequence 0000). These are Studies 02-159, 42603ATT3002, 12-304, C-99-018 and CON-CAN-4.

In Studies 02-159 and 12-304, the definition used for tachycardia was heart rate >100 bpm, Systolic blood pressure was considered clinically significant if it was > 140 mmHg, Diastolic blood pressure was considered clinically significant if it was > 90 mmHg. Hypertension was defined as systolic blood pressure

>140 mmHg on 3 separate occasions or diastolic blood pressure > 90 mmHG on 3 separate occasions, or both.

In Studies 42603ATT3002, C-99-018 and CON-CAN-4, criteria for diastolic hypertension, systolic hypertension, hypertension or tachycardia to be considered as an adverse event were not specifically specified. Therefore, the default definition would be that terms should be reported as an adverse event if they are considered clinically significant by the investigator.

A similar response is provided in a revised narrative with a serious adverse event (A10788 in Study 3002) and is copied below.

*pressure measurement in this trial were significant. These small changes in blood pressure measurements were not recorded as adverse events. Since the subject had documented pre-existing hypertension and the values recorded in the trial are in the same range as the blood pressure recorded prior to the study medication administration, elevated blood pressure need not be reported as an adverse event if the investigator did not believe the study values were clinically different than the pre-study values.**

8 ADDITIONAL CLINICAL ISSUES

The following have been reviewed in brief and are discussed in the relevant sections of this review. Unfortunately, they came late in the review cycle, so no definitive statement(s) can be made about the impact, if any, that it may have on subsequent labeling:

1) Data inconsistencies in the data set and the method chosen for reporting adverse events, as previously identified, especially as it applies to Study 3002, may affect the common adverse event table and drafting of the SPL;
2) Cardiology Consult with complete assessment of the cardiovascular risk is still pending;
3) HAM-A/HAM-D outlier analysis for Study 02-159;
4) Headache analysis for all integrated double blind studies [3002 and 02-159];
5) Concurrent medication and co-morbidity analysis for subjects who were reported to have a cardiovascular adverse event of special interest;
6) Post-marketing review of relevant adverse events;
7) And, review of the Structured Product Labeling (SPL)

Other clinical issues are described in the section entitled "Executive Summary, Recommendations on Regulatory Action".

8.1 Dosing Regimen and Administration

As discussed in Sec. 1.2.4, Dosing Regimen, the sponsor has placed the following language in the proposed labeling:

"For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed (b) (4) mg/day for adults."

The sponsor defines adults as up to 65.

In this reviewer's opinion, the data does not support that, but would support the use of Concerta for doses no greater than 36 mg (fixed dose study) and probably up to 54 mg (flexible dose study). It does not support the safe and effective use in subjects greater than 49 years as a result of insufficient exposure in that age group.

8.2 Special Populations

In this reviewer's opinion, based upon the materials reviewed to date, there has been inadequate exposure for subjects above 49 years to make an assessment of safety, a group with greatest co-morbid risk factors for cardiovascular events, strokes and death. Please refer to the section entitled "Efficacy Conclusion(s) and Recommendation(s)".

8.3 Postmarketing Risk Management Plan

Various risk management strategies are discussed in Sec. 1.1, Recommendations on Regulatory Action. Administration consideration needs to be given to determine if there is agreement with any of these recommendations, and if so, when in the cycle they should be: pre-approval, post-approval, or as part of a risk management plan.

9 OVERALL ASSESSMENT

9.1 Conclusions

Study 42603ATT3002 (3002), a 5 week, double-blind, *fixed dose* Concerta study [18 mg (n=101), 36 mg (n=102), 72 mg (n=102)] or Placebo (n=96)] support an approvable action for Concerta for doses *no greater than 36 mg* in adults between 18-49 years. Further support is given by Study 02-159, the 7 week *dose-titration* study (Concerta, n=110; placebo, n=116), which if considering an average dose might suggest a higher dose of 54 mg,

On face, considering the most common treatment emergent adverse event, the safety profile does not appear to be remarkable. The blood pressure changes also appear unremarkable. However, Study 3002 has an imbalance between drug and placebo for cerebrovascular events, perhaps a chance occurrence related to an antecedent or unrelated event, but an imbalance, nonetheless. There were no events with in placebo. The rate observed in this single study is above background (2/30 person years compared to 150/10,000 person years). Another cerebrovascular event is present in this open-label portion of the same study suggesting that this may not be a random event. Other cases have been seen in other adult

stimulant trials which may be also a chance and may be totally unrelated to stimulants, but which give further credence to this being a real observation.

Adjudicating the sponsor's cases for selective cardiovascular events of interest in Study 02-159, then correlating them with extracted history, adverse events, vital sign changes and ECG's and looking for ECG's suggestive of ischemic changes, there again appears to be an imbalance (Concerta: 11/113 [9.7 %], Placebo: 2/116 [1.7 %]). It is possible that this could be selection bias because this reviewer was not blinded but the selection criteria and various cases were discussed with different members of the Cardio-Renal Team prior to being included. It is also possible that this could be the result of lead placement error, but again, it then should have been equal between groups. The reasons for these observations are unclear and are awaiting Cardio Renal input.

These combined cardio-cerebrovascular observations should be carefully explored, especially given the recent observation of stimulants being associated with sudden cardiac death in healthy, asymptomatic children without structural heart disease. Given the many co-morbidities in the intended population we need to understand both the short and long-term impacts of the use of stimulants in the adult population, especially given the lack of any clear biological marker for ADHD, the known mis-use by students and de-conditioned middle aged adults looking for performance enhancers.

The headache analysis found a pronounced higher reporting of headaches among those with a history of headache treated with Concerta (33.7% history, 22.0% no history) compared to placebo (18.0% history, 17.9% no history). The implications of this need to be carefully explored both as it may relate to cerebrovascular risks (if any), patient management, and or, labeling recommendations.

The HAM-A or HAM-D outlier analysis found that subjects with sub-clinical anxiety and depression developed clinically relevant levels of anxiety and depression at the end of the study. The implications of this need to be carefully explored both as it may relate to patient management, and or, labeling recommendations.

Recommendation on Regulatory Action

These are described in the Executive Summary.

10 APPENDICES

Review of 02-159

LIST OF PRINCIPAL INVESTIGATORS IN STUDY 02-159

Lenard Adler, MD (101) (5)	Veterans Administration, New York Harbor Health Care System 423 East 23rd Street, Room 17025W New York, NY 10010
Joseph Biederman, MD (102) (13)	Mass. General Hospital 185 Alewife Brook Parkway, Suite 2000 Boston, MA 02138
John Burnside, MD (103) (6)	ADHD Clinic of San Antonio 13535 Jones Maltsberger Road San Antonio, TX 78247
Andrew Cutler, MD (104) (8)	Florida Clinical Research Center, LLC 3914 S. R. 64 East Bradenton, FL 34208
Bernadette D'Souza, MD (105) (11)	Midwest Clinical Research, LLC 627 Edwin C. Moses Boulevard East Medical Plaza, Suite 3G Dayton, OH 45408
Beal Essink, MD (106) (11)	Oregon Center for Clinical Investigations, Inc. (OCCI, Inc.) 2230 Northwest Pettygrove Street, Suite 120 Portland, OR 97210
Donald Garcia, Jr, MD (107) (12)	FutureSearch Trials 4200 Marathon Boulevard, Suite 200 Austin, TX 78756
Michael Greenbaum, MD (108) (9)	Capstone Clinical Research 1117 South Milwaukee Avenue, Suite B-7 Libertyville, IL 60048
James Grimm, MD (109) (7)	Oregon Center for Clinical Investigations, Inc. 572 West 11th Avenue Eugene, OR 97401
C. Gualtieri, MD (110) (8)	North Carolina Neuropsychiatry PA 1829 East Franklin Street 400-500 Franklin Square Chapel Hill, NC 27514
Daniel Lieberman, MD (112) (7)	George Washington University 2300 K Street Northwest Warwick Building, Suite 205 Washington, DC 20037
David Marks, MD Jorge Porras, MD (113) (5)	Optimum Health Services a Division of eStudy Site 7200 Parkway Drive, Suite 116 Le Mesa, CA 91942
Gregory Mattingly, MD (114) (8)	Saint Charles Psychiatric Associates 330 First Capitol Drive, Suite 390 Saint Charles, MO 63301

Kamalesh Pai, MD (117) (10)	Clinical Neuroscience Solutions, Inc. 6867 Southpoint Drive North, Suite 101 Jacksonville, FL 32216
Angela Pinheiro, MD (118) (12)	Summit Research Network, Inc. 23700 Orchard Lake Road, Suite M Farmington, MI 48336
Neil Pugach, MD (119) (7)	Brighton Research Group, LLC 780 Lynnhaven Parkway, Suite 285 Virgina Beach, VA 23452
Leon Rosenberg, MD (120) (9)	Center for Emotional Fitness 1 Utah Avenue Cherry Hill, NJ 08002
Keith Saylor, MD (122) (8)	NeuroScience Inc. 106 Elden Street, Suite 17 Herndon, VA 20170
Scott Segal, MD (123) (6)	Segal Institute for Clinical Research 1065 Northeast 125th Street, Suite 417 North Miami, FL 33161
Mary Shemo, MD (124) (3)	Psychiatric Alliance of the Blue Ridge 2496 Old Ivy Road 2nd Floor, Suite 400 Charlottesville, VA 22903
Jerry Steiert, MD (125) (12)	Summit Research Network, LLC 901 Boren Avenue, Suite 1800 Seattle, WA 98104
Jay Tarnow, MD (126) (6)	Tarnow and Associates, PA, dba Tarnow Center for S Management 1001 West Loop South, Suite 215 Houston, TX 77027
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Richard Weisler, MD (128) (12)	Richard H. Weisler, MD, PA 700 Spring Forest Road, Suite 125 Raleigh, NC 27609
Timothy Wigal, MD (129) (7)	University of California 19722 MacArthur Boulevard Irvine, CA 92612
Joel Young, MD (130) (8)	Rochester Center for Behavioral Medicine 441 South Livernois, Suite 205 Rochester Hills, MI 48307
John Zajecka, MD (131) (9)	Psychiatric Medicine Associates 9669 North Kenton, Suite 209 Skokie, IL 60076

SCHEDULE OF EVENTS FOR STUDY 02-159

Table 7-4: Conduct of the Study

Activity	Screening	Baseline Visit (Off any ADHD meds for 1-2 weeks)	Titration Visits 1-5	Final Visit/2 Week Efficacy Assessment Visit or Early Termination Visit
Informed Consent	X			
Medical History including psychiatric history	X			
Physical Exam/Height[a]	X			X[a]
Weight	X	X	X	X
Vital signs (BP/pulse[b]/respirations)	X	X	X	X
ADHD diagnosis ACDS		X		
HAM-A		X		X
HAM-D		X		X
ECG[c]	X	X	X[c]	X
Urine drug screen	X	X		X
Urine pregnancy test	X	X		X
Lab Tests—fasting blood draw	X			X
Adult ADHD Investigator Symptom Rating Scale (AISRS)		X	X	X
Global Assessment of Functioning (GAF)		X		
Randomization		X		
Dispense Study Drug		X	X	
Return Study Drug			X	X
Monitor Dosing Compliance			X	X
Global Assessment of Effectiveness (GAE)			X	X
CAARS—S:S		X	X	X
Q-LES-Q-SF		X		X
CGI Severity of Illness		X	X	X
CGI Improvement			X	X
ADHD Impact Module for Adults™ (AIM-A)		X		X
Sheehan Disability Scale		X		X
Concomitant Medications	X	X	X	X
Adverse Event Assessment		X	X	X
Review Subject Diary			X	X
Collect Subject Diary				X

Note: The window for study visits was +/- 2 days.
a. Height at Screening Visit only.
b: Triplicate pulse and blood pressure were measured in the sitting position, ideally at the same time of day.
c: ECG was to be performed after each upward dose titration.

SUMMARY TABLE FOR STUDY 02-159

Protocol Number Study Identifier[a] Principal Investigator (Country) Start/End Dates	Study Description/Design	Subjects Evaluated[b] Sex (M/F) Age (yr): median [mean] (range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report (CRFs and CRT) or Publication
02-159 EDMS-PSDB-6481513 L. Adler (US) Start: 8 May 05 End: 21 Nov 06	R, DB, PC, PG, DT flexible-dose study to evaluate the efficacy and safety of CONCERTA in adults with ADHD	226 127M/99F 38.5 [39.0] (18-65) 195/13/18	Titration Phase (5 weeks): Subjects were randomized in 1:1 ratio to CONCERTA or placebo, initiating treatment with 36 mg/day with incremental increases of 18 mg every 7 days until their individualized dose was achieved or to a maximum dose of 108 mg/day. Maintenance Phase (2 weeks). Subjects were maintained on their individualized dose *Batch nos:* *CONCERTA 36 mg: 0541990* *CONCERTA 54 mg: 0541991* *Placebo: 0517770*	Completed Clinical Study Report Mod5.3.5.1\02-159 (CRF) (CRT)
Other Clinical Studies in Adults With ADHD				
42603ATT3002 Open-Label Phase (Open label phase of Study 42603ATT3002 is included with the double-blind phase. See full study description under the previous heading, Controlled Clinical Studies Relevant to Adults With ADHD: Key Efficacy Trials)				

Key: ADHD = Attention Deficit Hyperactivity Disorder; B=Black; CO = crossover, CRF = case report form; DB = double-blind; DR = dose response; DT = dose titration; F=female; M=male; O=other;
OL = open-label, PC = placebo-controlled, PG = parallel group, R = randomized; US=United States; W=white

[a] Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) is a global organization that includes, but is not limited to Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Janssen-Cilag International N.V., McNeil Pediatrics Division of McNeil-PPC, Inc.; ALZA Corporation, Janssen-Ortho Inc., and McNeil Consumer and Specialty Pharmaceuticals Division of McNeil-PPC, Inc.

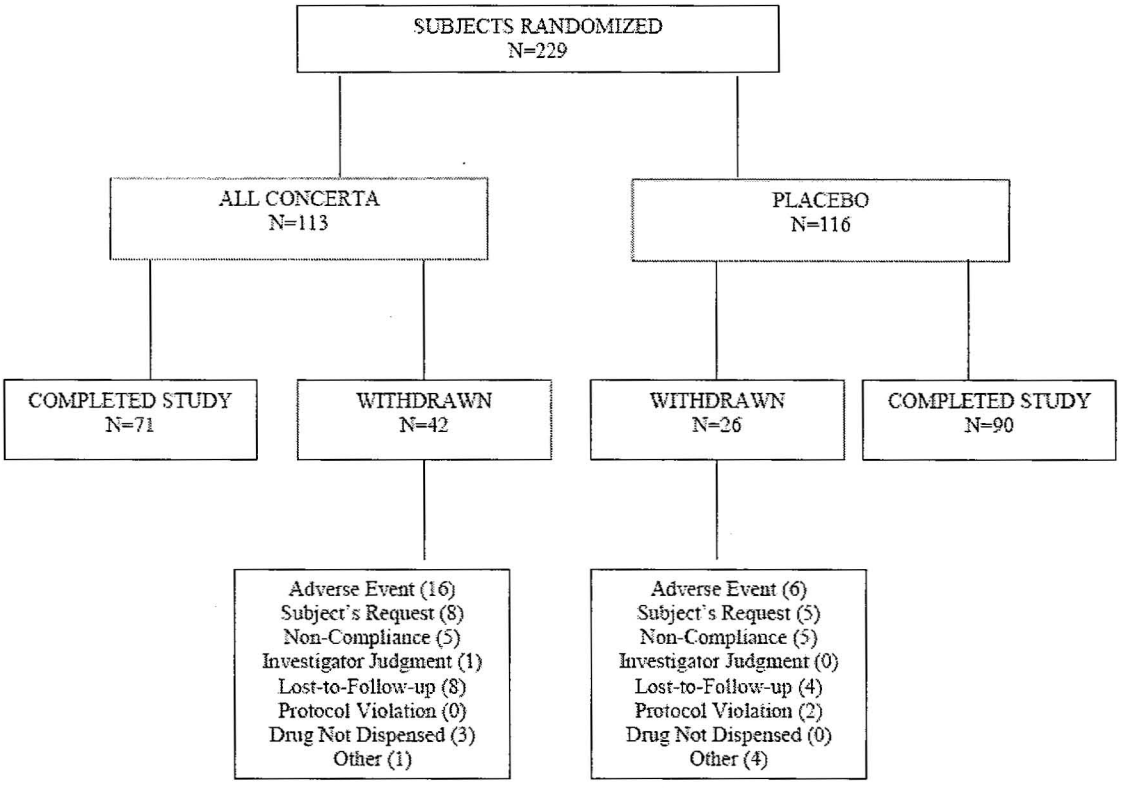
[b] Number of subjects evaluated for safety.

[c] 'Black or African heritage' is included in 'Other'

[d] Asian is included with "Other"

SUBJECT DISPOSITION FOR STUDY 02-159

Figure 8-1: Disposition of Subjects



Subjects Completing the Study, N=161

SUBJECT DISPOSITION BY FINAL DOSE FOR STUDY 02-159

Table 8-1: Disposition of Subjects by Final Dose - All Randomized Subjects

Outcome	CONCERTA 36 mg N=39 n (%)[a]	CONCERTA 54 mg N=16 n (%)	CONCERTA 72 mg N=19 n (%)	CONCERTA 90 mg N=16 n (%)	CONCERTA 108 mg N=23 n (%)	All CONCERTA N=113 n (%)	Placebo N=116 n (%)
Completed Study	18 (46.2)	8 (50.0)	16 (84.2)	11 (68.8)	18 (78.3)	71 (62.8)	90 (77.6)
Withdrawn[b]	21 (53.8)	8 (50.0)	3 (15.8)	5 (31.3)	5 (21.7)	42 (37.2)	26 (22.4)
Withdrawn due to an Adverse Event	6 (15.4)	5 (31.3)	1 (5.3)	2 (12.5)	2 (8.7)	16 (14.2)	6 (5.2)
Withdrawn at Subject's Request	4 (10.3)	2 (12.5)	1 (5.3)	1 (6.3)	0 (0.0)	8 (7.1)	5 (4.3)
Non-compliance or Uncooperativeness	2 (5.1)	1 (6.3)	1 (5.3)	1 (6.3)	0 (0.0)	5 (4.4)	5 (4.3)
Withdrawn due to investigator's judgment	1 (2.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.9)	0 (0.0)
Lost to Follow-up	5 (12.8)	0 (0.0)	0 (0.0)	1 (6.3)	2 (8.7)	8 (7.1)	4 (3.4)
Protocol Violation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (1.7)
Drug not Dispensed (Randomized in error)[c]	3 (7.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (2.7)	0 (0.0)
Other[d]	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (4.3)	1 (0.9)	4 (3.4)

a: Percentages are based upon the total number of subjects randomized with that final dose.
b: Subjects were counted once, under their primary reason for withdrawal.
c: Subjects randomized in error and not dispensed drug are counted under the Concerta 36mg column.
d: All subjects withdrew due to lack of efficacy.

DURATION OF EXPOSURE BY TREATMENT GROUP - SAFETY POPULATION

Table 10-1: Duration of Exposure by Treatment Group - Safety Population

Duration (Days)	CONCERTA 36mg N=110 n (%)	CONCERTA 54mg N=78 n (%)	CONCERTA 72mg N=60 n (%)	CONCERTA 90mg N=45 n (%)	CONCERTA 108mg N=29 n (%)	All CONCERTA N=110 n (%)	Placebo N=116 n (%)
< 7[a]	21 (19.1)	10 (12.8)	8 (13.3)	10 (22.2)	2 (6.9)	10 (9.1)	3 (2.6)
7 to < 14	64 (58.2)	58 (74.4)	34 (56.7)	24 (53.3)	9 (31.0)	6 (5.5)	5 (4.3)
14 to < 21	2 (1.8)	1 (1.3)	2 (3.3)	2 (4.4)	2 (6.9)	4 (3.6)	5 (4.3)
21 to < 28	3 (2.7)	1 (1.3)	2 (3.3)	7 (15.6)	16 (55.2)	8 (7.3)	9 (7.8)
28 to < 35	1 (0.9)	0 (0.0)	4 (6.7)	2 (4.4)	0 (0.0)	1 (0.9)	1 (0.9)
35 to < 42	1 (0.9)	4 (5.1)	10 (16.7)	0 (0.0)	0 (0.0)	9 (8.2)	4 (3.4)
42 to < 49	3 (2.7)	4 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	7 (6.4)	22 (19.0)
>= 49	15 (13.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	65 (59.1)	67 (57.8)
Mean Duration (SD)	14.8 (16.56)	10.9 (10.72)	14.4 (11.52)	10.5 (7.61)	16.1 (6.76)	38.9 (17.23)	42.6 (14.06)
Range (min, max)	(1, 66)	(2, 46)	(6, 40)	(1, 29)	(5, 25)	(1, 66)	(1, 62)

a: Duration was set to one day if the subject had no post-baseline visit and date of last dose was unknown.

NUMBER OF RESPONDERS BY DOSE BASED ON THE AISRS TOTAL SCORE AND CGI

Table 9-20: Number (%) of Responders by Dose Based on the AISRS Total Score and the CGI - Improvement Scale
(Study 02-159; Intent-to-treat Population)

	CONCERTA		Placebo	
Dose Level (mg/day)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)	No. Subjects Evaluated at This Dose	First Responded at This Dose n (%)
36	103	21 (20.4)	115	9 (7.8)
54	78	11 (14.1)	103	11 (10.7)
72	59	12 (20.3)	85	6 (7.1)
90	44	8 (18.2)	71	1 (1.4)
108	29	5 (17.2)	67	3 (4.5)

SUBJECTS WITH ADVERSE EVENTS ≥ 1% FOR STUDY 02-159

Table 10-7: Number and Percent of Subjects With Adverse Events where CONCERTA Incidence ≥1% and >Placebo by System Organ Class and MedDRA Preferred Term - Saf Population

System Organ Class MedDRA Preferred Term	All CONCERTA N=110 n (%)	Placebo N=116 n (%)
Any adverse event	93 (84.5)	74 (63.8)
Cardiac Disorders	5 (4.5)	3 (2.6)
Tachycardia	3 (2.7)	0 (0.0)
Eye Disorders	6 (5.5)	1 (0.9)
Vision Blurred	3 (2.7)	1 (0.9)
Gastrointestinal Disorders	38 (34.5)	25 (21.6)
Abdominal Pain Upper	2 (1.8)	2 (1.7)
Constipation	2 (1.8)	1 (0.9)
Dry Mouth	22 (20.0)	6 (5.2)
Dyspepsia	3 (2.7)	1 (0.9)
Nausea	14 (12.7)	3 (2.6)
Vomiting	2 (1.8)	1 (0.9)
General Disorders and Administration Site Conditions	18 (16.4)	8 (6.9)
Chest Discomfort	2 (1.8)	2 (1.7)
Feeling Jittery	4 (3.6)	1 (0.9)
Irritability	7 (6.4)	2 (1.7)
Infections and Infestations	9 (8.2)	8 (6.9)
Upper Respiratory Tract Infection	4 (3.6)	2 (1.7)
Investigations	27 (24.5)	15 (12.9)
Blood Pressure Increased	11 (10.0)	6 (5.2)
Heart Rate Increased	8 (7.3)	5 (4.3)
Weight Decreased	5 (4.5)	2 (1.7)
Metabolism and Nutrition Disorders	33 (30.0)	12 (10.3)
Anorexia	4 (3.6)	0 (0.0)
Decreased Appetite	28 (25.5)	7 (6.0)
Musculoskeletal and Connective Tissue Disorders	13 (11.8)	10 (8.6)
Muscle Tightness	7 (6.4)	0 (0.0)
Pain in Extremity	2 (1.8)	2 (1.7)
Nervous System Disorders	42 (38.2)	29 (25.0)
Dysgeusia	2 (1.8)	0 (0.0)
Headache	28 (25.5)	16 (13.8)
Lethargy	2 (1.8)	1 (0.9)
Poor Quality Sleep	2 (1.8)	0 (0.0)
Tremor	2 (1.8)	0 (0.0)
Psychiatric Disorders	44 (40.0)	23 (19.8)
Affect Lability	3 (2.7)	1 (0.9)
Agitation	5 (4.5)	0 (0.0)
Anger	3 (2.7)	0 (0.0)
Anxiety	18 (16.4)	4 (3.4)
Bruxism	7 (6.4)	1 (0.9)

Depressed Mood	2 (1.8)	2 (1.7)
Initial Insomnia	8 (7.3)	4 (3.4)
Insomnia	10 (9.1)	6 (5.2)
Libido Decreased	3 (2.7)	1 (0.9)
Nervousness	2 (1.8)	0 (0.0)
Restlessness	5 (4.5)	0 (0.0)
Tension	2 (1.8)	1 (0.9)
Thinking Abnormal	2 (1.8)	0 (0.0)
Reproductive System and Breast Disorders	3 (2.7)	3 (2.6)
Erectile Dysfunction	2 (1.8)	0 (0.0)
Respiratory, Thoracic and Mediastinal Disorders	7 (6.4)	8 (6.9)
Cough	2 (1.8)	1 (0.9)
Sinus Congestion	2 (1.8)	2 (1.7)
Skin and Subcutaneous Tissue Disorders	7 (6.4)	3 (2.6)
Hyperhidrosis	5 (4.5)	1 (0.9)

CASES FROM DOUBLE-BLIND STUDY 02-159

ECG Event/Subject No.	ECG	Trial
Possible Ischemic Events		
(b) (6)	w/ ECG's showing premature ventricular systoles (Screen, Titration 1, 2, Last Dose), non-specific T abnormality (c/w pos. inf infarct; Titration 2)	02-159
(b) (6) Doubtful	54 yo female w/ Baseline ECG showing minor ST depression, non-specific ST abnormality with ECG at increased dose (72 mg) showing: ST Depression -.1 Mv. or More Negative T Non-Specific ST-T Abnormality or Ischemia	02-159
(b) (6) Doubtful	31 yo male with Screening ECG showing sinus bradycardia with ECG change at increased dose (54 mg) showing: Borderline Q or Qs in 2 Leads of 2,3,avf Possible Inferior Infarct	02-159
(b) (6) Comment: No ECG's done on Titrations 3, 4, 5; ECG missing from Final Visit (09/26/06)	61 yo female with AE's of insomnia, decreased appetite, headache; w baseline ECG showing a depressed ST/ischemia with ECG at increased dose (54 mg) showing Borderline Q or Qs in 2 Leads of 2,3,avf Possible Inferior Infarct	02-159
(b) (6) Doubtful	60 yo male with Baseline, slight left axis deviation, and with Titration 2 (Placebo) shows abnormal Q or Qs in 2 Leads of 2,3,avf Consistent with Inferior Infarct, Age Undetermined	02-159
Electrical Blocks: Does Concerta affect Na Channels?		
(b) (6)	QRS going from 90 (Baseline) to 107 (Titration 1) to 121 (Titration 2) w/ development of intraventricular block. QRS normalized w/drug being stopped to 84.	02-159
ST Changes		
(b) (6)	ST depression on 07/21 (non-scheduled visit) which resolved on 07/24)	02-159
	w/normal ECG 's (Baseline, Titration 2-4) then non-specific ST depression (Titration 1)	02-159
	w/normal screen ECG, then baseline + other	02-159

	visits showing non-specific ST abnormality	
Sinus Tachycardia		
(b) (6)	w/ normal ECG's except for Titration 5 (sinus tachycardia)	02-159
	w/ ECG showing sinus tachycardia on 08/07 + preventricular systoles on 08/21	02-159
Other Cases of Interest		
(b) (6)	Dizziness associated w/ECG (Screen) showing non-specific T abn, sinus bradycardia w poor ant. R. progression (Baseline), missing ECG's (Titration 2-5)	02-159
	Increased heart rate, chest pain, out of breath w/ ECG's showing ST, J point elevation (Baseline), then normal (End of Study)	02-159

STUDY 02-159, POTENTIALLY CLINICAL IMPORTANT POST BASELINE ECG MEASURES

Table 43: Postbaseline ECG Measurements of Potential Clinical Importance
(Study 02-159: Safety Population)

Parameter Criterion	All CONCERTA N = 102	Placebo N = 115
PR (ms), n (%)		
Maximum ≥220 ms	0 (0.0)	0 (0.0)
Maximum increase >25%	1 (1.0)	3 (2.6)
QRS (ms), n (%)		
Maximum >120 ms	1 (1.0)	1 (0.9)
Maximum increase >25%	8 (7.8)	12 (10.4)
Pulse (bpm), n (%)		
Maximum >100 bpm	5 (4.9)	1 (0.9)
Maximum increase >25%	32 (31.4)	16 (13.9)
Minimum <50 bpm	5 (4.9)	9 (7.8)
Maximum decrease >25%	2 (2.0)	2 (1.7)
QT (ms), n (%)		
Maximum >480 to ≤500 ms	0 (0.0)	1 (0.9)
Maximum >500 ms	0 (0.0)	0 (0.0)
Maximum increase >30 to ≤60 ms	12 (11.8)	28 (24.3)
Maximum increase >60 ms	1 (1.0)	2 (1.7)
QTc (Bazett) (ms), n (%)		
Maximum >480 to ≤500 ms	0 (0.0)	0 (0.0)
Maximum >500 ms	0 (0.0)	0 (0.0)
Maximum increase >30 to ≤60 ms	29 (28.4)	27 (23.5)
Maximum increase >60 ms	2 (2.0)	1 (0.9)
QTc (Fridericia) (ms), n (%)		
Maximum >480 to ≤500 ms	0 (0.0)	0 (0.0)
Maximum >500 ms	0 (0.0)	0 (0.0)
Maximum increase >30 to ≤60 ms	10 (9.8)	18 (15.7)
Maximum increase >60 ms	0 (0.0)	1 (0.9)
T-wave morphology, n (%)		
Other than normal	17 (16.7)	29 (25.2)
U-wave morphology, n (%)		
U-waves present	0 (0.0)	0 (0.0)

Cross-reference: Mod5.3.5.1\02-159\Table10-25.

NARRATIVES FOR DISCONTINUATIONS CLINICAL STUDY 02-159

Subject	Age	Sex	AE Dose	Fin Dose	Events	Relevant PMHX/Meds
SUBJECTS TREATED WITH PLACEBO DURING THE DOUBLE-BLIND PHASE (N=6)						
(b) (6) CRF	42	M	PBO	PBO	Depressed mood	Bradycardia, headache, alcohol dependence/ fat burning caffeine pill
(b) (6) CRF	22	F	PBO	PBO	Worsening sadness	H/O previous substance abuse
(b) (6) CRF(REV) ECG Rcvd	39	M	PBO	PBO	Decreased libido, heart palpitations, depression w/ ECG's showing non-specific T wave abn at Baseline and End of Study	H/O previous substance abuse
(b) (6)	43	M	PBO	PBO	Diastolic HTN, moderate	Gastric ulcer, migraines

CRF CRF(REV) ECG Rcvd					increased BP; w/normal baseline and End of Study ECG and Screen, Titration 1, 2 showing left axis deviation	
(b) (6) CRF(REV-) ECG Rcvd pprofile- (b) (6)	49	M	PBO	PBO	Baseline: 07/18-07/27, Final. *High blood pressur*e (BP: 152/84: Final: 07/27): w/ normal ECG	Asthma, hypercholesterolemia/ Vytorin, Pulmicort, Zyrtec-D, and Vicodin ES.
(b) (6) (b) (6) CRF(REV) ECG Rcvd CC pprofile- (b) (6) (b) (6)	37	M	PBO	PBO	Baseline: 06/21-07/20, Final. Sleep difficulty [06/07-?]; Bell's palsy (txed w prednisone [06/22-06/27], acyclovir [06/22-06/29], Vicodin) [06/22-06/29]; increased heart rate (102 bpm: Titration 1, 06/29); *abnormal ECG with possible MI* [06/21-07/13]; headache [07/06-?]; w/ ECG's showing premature ventricular systoles (Screen, Titration 1, 2, Last Dose), non-specific T abnormality (c/w pos. inf infarct; Titration 2)	H/O headaches on 222-Canadian aspirin, acetaminophen; dizziness, and anxiety; stimulant naïve; concomitant medications: prednisone, vicodin and acyclovir for Bell's palsy; moderate obesity (276.2 lb); non-smoker; stimulant naive
Subjects With Cardiovascular Adverse Events of Interest (N=15)						
(b) (6) CRF(REV) ECG Rcvd	64	M	PBO	PBO	Cold sweats, insomnia, somnolence, elevated BP, vomiting, herpes outbreak, weight gain w/ ECG normal at baseline, then sinus bradycardia at Titration 1, non-specific ST-T abnormalities at Titration 4 w/ normal subsequent ECG's	EBV, herpes, hyperlipidemia, elevated FBS, smoker,
(b) (6) CRF(REV) ECG Rcvd	37	F	PBO	PBO	Increased HR (08/14-17), breathless feeling (08/14-17), hyper-alert, arm pain (09/01-2) w/ ECG normal at baseline, then? left atrial or ventricular disease at Visit 3 w/ normal subsequent ECG's	Heart murmur, heartburn, elevated lipoprotein A, optical migraines during pregnancy
(b) (6) CRF(REV) ECG Rcvd	38		PBO	PBO	Dizziness, initial insomnia, premature atrial complexes w/ECG's showing non-specific T abn at Baseline + End of Study and non-specific ST abn at Titration 2	Hypercholesterolemia, tension-migraine headaches, peptic ulcer disease, GERD, smoking history/Excedrine Migraine, albuterol, loratadine (Claritin)
(b) (6) CRF(REV) ECG Rcvd	41	M	PBO	PBO SW	Increase BP [07/11/06-?] + respiration [07/11/06-?] w/ECG normal at baseline, then non-specific ST-T abn at Titration 1, then subsequent normal ECG?	Ginkgo biloba
(b) (6) CRF(REV) ECG Rcvd	48	F	PBO	PBO	Drowsiness, headache, tension, insomnia, elevated BPP, tightening of chest, anxiety (txed w Xanax), nausea w/ normal ECG sinus bradycardia at baseline and end of study, then non-specific T abn at Titration 4 Heart palpitations	Adrenal complex nutritional supplement
(b) (6) CRF(REV) ECG Rcvd	27	M	PBO	PBO	Dry mouth, decreased appetite; increased sweating [07/05-23]; upset stomach, dizziness [07/18-	MDD, Claritin for seasonal allergies; stimulant naive

					19]; chest pain [08/05/06]; w/ ECG at baseline showing sinus bradycardia which was normal at End of Study	
(b) (6) CRF(REV) ECG Rcvd	23	M	PBO	PBO	Dry mouth; upset stomach [08/11/06]; chest tightness [08/25-26] w/normal baseline and End of Study ECG, and possible intraventricular block at Titration 1	Eczema, cluster migraines/ketoconazole
(b) (6) CRF's Missing CRF(REV) ECG Rcvd 118-020	23	M	PBO	PBO	Increased systolic BP + pulse; normal baseline and End of Study ECG w/ poss. RVH (screen study)	Occasional headaches, insomnia stimulant naive
(b) (6) CRF(REV) ECG Rcvd	44	F	PBO	PBO	Diastolic HTN, moderate increased BP Diarrhea; muscle tenderness (06/01-21); joint aches (07/05-06); chest pain (07/13-15); *elevated BP* (07/17-?) w/normal ECG's	Headache, migraines; stimulant naive
(b) (6) CRF(REV) ECG Rcvd	22	F	PBO	PBO	Bruxing, sore throat, decreased appetite, headache [07/19-21], nasal congestion, *heart palpitations* [08/02-03]; w/ ECG showing atypical T waves [negative T waves V 1, 2] (baseline, Titration 1, 5)	Obesity
(b) (6) CRF (REV-ECG Rcvd (b) (6)	42	M	PBO	PBO	Baseline: 07/10-08/21, Final. Shortness of breath txed w/Sudafed; w/normal ECG except for sinus bradycardia (Baseline)	Non-smoker; obesity (231 lb); Strattera
(b) (6) CRF					High blood pressure	
(b) (6) CRF CRF(REV) ECG Rcvd CC	37	M	PBO	PBO	Sleep difficulty [06/07-?]; Bell's palsy (txed w prednisone, acyclovir, Vicodin) [06/21-?], *abnormal ECG with possible MI* [06/21-07/13]; headache [07/06-?]; w/ ECG's showing premature ventricular systoles (Screen, Titration 1, 2, Last Dose), non-specific T abnormality (c/w pos. inf infarct: Titration 2)	moderate obesity, headaches, dizziness, and anxiety/ 222-Canadian aspirin; stimulant naïve; concomitant medications: prednisone, vicodin and acyclovir for Bell's palsy;
SUBJECTS TREATED WITH CONCERTA DURING THE DOUBLE-BLIND PHASE (N=17)						
(b) (6) CRF	51	M	Not listed (NL)	72	GERD prior to baseline, hospitalized; decreased appetite, headache, elevated HR, tinnitus, nausea, insomnia, dry mouth	H/O tinnitus, GERD
(b) (6) CRF	35	F	54	54	Grinding teeth; increased agitation, irritability, + anxiety	H/O sinus infection, increased ALT, GGT, ankle swelling, headaches
(b) (6) CRF	40	M	NL	72	Metallic taste, dry mouth, increased energy, jaw tension, tachycardia (dec dose), hand trembling	
(b) (6) CRF	23	M	NL	54	Anxiety, increased sweating, dry mouth	Eczema/ Airborne Cold Remedy
(b) (6) CRF	54	M	NL	108	Panic attack	H/O Heartburn, headaches, sleep apnea, MDD/Ranitidine, Reglan, Xanax, Prilosec

(b) (6) CRF	54	M	NL	NL	Nausea, decreased appetite, stomach discomfort, dizziness blurred vision eye hemorrhage	H/O hyperlipidemia, insomnia/Trazadone, Zocor, Flonase
(b) (6) CRF CRF(REV) ECG Rcvd	49	M	NL, 54	36	Headache, diarrhea (decr dose), increased BP w/ baseline and end of study ECG showing sinus bradycardia	H/O IBS, anemia
(b) (6) CRF	56	F	NL	NL	Increased mood lability, tension, agitation, anxiety, jaw clenching, headache, dry mouth, tongue blister, loss of appetite	H/O acid reflux/Pepcid, Claritin
(b) (6) CRF(REV) ECG Rcvd Only Baseline, End of Study CC	20	M	NL	36	Increased irritability (07/22-28); anxiety (07/24-28), fidgeting (07/23-28), dry mouth, out of breath (07/24-29); increased sweating (07/25-28); nausea, vomiting (07/25/06); increased heart rate (07/24-28), chest pain (07/25-27) + blurred vision (07/25-?): w/ ECG's showing ST, J point elevation (Baseline), then normal (End of Study)	H/O surgically removed, neonatal underdeveloped intestines; prev. txed w Strattera (on concomitant med sheet), Adderall (on prior med sheet)
(b) (6) CRF(REV) ECG Rcvd Only Baseline, End of Study BP Not Correct	23	F	? 36	36	Stomachache, headache, (07/20-26); dry mouth, increased BP (avg BP > 140/90) [07/26-08/16] w/ECG at baseline and End of Study normal	H/O headaches, allergy related asthma/Zyrtec, Singulair, Alesse; stimulant naive
(b) (6) CRF (REV) ECG Rcvd	26	M	?54	36	Nausea (07/18-19: 07/25), scintillating scotoma (07/21-22), mild *hypertension* (dec dose from 54 mg) [07/31-09/05]/ w normal baseline ECG, then non-specific ST abn w/ Titrations 1 and 2, then ECG normalizes w/ dose reduction	H/O headaches/Orthro Evra; smoker (5 Pack Yrs): Strattera (previous tx)
(b) (6) CRF(REV) ECG Rcvd CC	23	F	36	36	*Prolonged QRS interval* (05/30-06/06) w/ QRS going from 90 (Baseline) to 107 (Titration 1) to 121 (Titration 2) w/ development of intraventricular block. QRS normalized w/drug being stopped.	On Birth Control Patch: H/O intermittent headaches; stimulant naive
(b) (6) CRF	43	M	NL	90	Nausea, irritability	H/O sleep apnea
124-004 CRF (REV-) ECG Rcvd CC (?)	23	M	NL	36	Baseline: 06/20-07/17, Final. Headache (06/21-06/27); stomach fullness (07/21-07/24): increased wakefulness (07/06-07/17); increased BP (07/13-?) [BP: 140/104: Titration 1: 06/27, 145/104: Titration 2: 07/13] and increased heart rate [HR: 106 bpm: Titration 1: 06/27]; w/ normal ECG's	H/O asthma; obesity (227 lb); stimulant naïve
(b) (6) CRF	23	M	NL	36	Headache, stomach fullness, increased wakefulness; *increased BP*	H/O asthma, obesity
(b) (6) CRF's Not Recvd ECG Rcvd	50	M	NL	54	Baseline: 06/13- 07/12, ECG Dates. Dry mouth, nasal congestion txed w Claritin; *increased BP;*	H/O hyperlipidemia, headaches/Valerian

CC (?)					w/ECG being normal except for sinus bradycardia (Screen) and left atrial enlargement (Titration 2: 07/06)	
(b) (6) CRF	59	F	NL	108	Dull headache, insomnia, emotional lability, dry mouth, dysphagia, oral dyskinesia	Desipramine
(b) (6) CRF(REV) pprofile- (b) (6)	31	M	NL	90	Headache (08/22-08/24, 09/14/06), hot flashes (08/22-08/24); decreased appetite, increased diaphoresis (08/23-09/16); racing thoughts + anxiety (09/12-?)	H/O asthma/Albuterol; stimulant naive
Subjects With Cardiovascular Events of Special Interest (N=19)						
(b) (6) CRF(REV) ECG Rcvd	20	M	36	36	Increased talking (1 d), chest (9/29-10/15/06; intermittent, mild) + neck tightness (neck tension: 10-05-27/06; intermittent, mild), decreased appetite, abdominal warmth (10/27-?), headache (10/28/06)	H/O pancreatitis secondary to ERCP, histoplasmosis Screen: 0920 Baseline: 09/28 Titration 1: 10/05 Titration 2: 10/12 Titration 3: 10/19 Titration 4: 10/26 Titration 5: 11/20 2 wk Efficacy/Final Visit: 11/16
(b) (6) CRF (REV) CC	65	F	NL	108 LOE	Dry mouth, grinding teeth, nausea (07/9-08/01/06) ; agitation, , early insomnia; increase BP (on 72 mg) (07/19-24/06) assoc w/ minor ST depression 0n 07/21 (non-scheduled visit) which resolved on 07/24) Increased BP	H/O migraines; prev. txed w/ Strattera
(b) (6) CRF(REV) CC	44	F	NL	36	Stomachache (06/09), initial insomnia, elevated BP (06/14-27/06) [06/27/07: non-scheduled visit], dizziness (06/25) [06/25/07: non-scheduled visit]; w/ECG (Screen) showing non-specific T abn, sinus bradycardia w poor ant. R. progression (Baseline), missing ECG's (Titration 2-5)	H/O allergies + HTN/Atenolol, Diovan, Allegra; stimulant-naive No ECG's done for Titration Days 2-5 ? Reason is uncertain.
(b) (6) CRF CRF(REV) ECG Rcvd CC	20	M	NL	36	Increased irritability, anxiety, fidgeting, dry mouth, *out of breath*; increased sweating, nausea, vomiting, *chest pain* + blurred vision	H/O surgically removed, neonatal underdeveloped intestines; prev. txed w Strattera
(b) (6) CRF CRF(REV) ECG Rcv	23	F	? 36	36	Stomachache, headache, (07/20-26); dry mouth, *increased BP (avg BP > 140/90)* [07/26-08/16] w/ECG at baseline and End of Study normal	H/O headaches, allergy related asthma/Zyrtec, Singulair, Alesse; stimulant naive
(b) (6) CRF's Missing CRF (REV)	41	M	NL	54	Decreased appetite; headaches (08/19-); heart palpitations (08/24-09/07/06), agitation (72 mg, dec dose) [08/24-09/15/06]; [non-scheduled visit: 09/07, 09/15: ?]	H/O rosacea Prev tx w/ Adderall, Strattera
(b) (6) CRF (REV)	26	M	?54	36	Nausea (07/18-19; 07/25), scintillating scotoma (07/21-22),	H/O headaches/Orthro Evra; smoker (5 Pack Yrs); Strattera (previous tx)

					mild *hypertension* (dec dose from 54 mg) [07/31-09/05]	
(b) (6) CRF (REV) ECG Rcvd CC	45	F	NL	90	Decreased appetite; anxiety (08/02-19/06); blurred vision (08/08-25), indigestion (08/09-13); moderate elevated BP (dec dose from 108 mg); w/normal ECG 's (Baseline, Titration 2-4) then non-specific ST depression (Titration 1)	H/O oral herpes, IBS, arthralgia, headache, MDD/Valtrex, Aleve; prev. Txed w/Ritalin
(b) (6) CRF CRF(REV) ECG Rcvd CC	23	F	36	36	*Prolonged QRS interval* (05/30-06/06) w/ QRS going from 90 (Baseline) to 107 (Titration 1) to 121 (Titration 2) w/ development of intraventricular block. QRS normalized w/drug being stopped to 84.	On Birth Control Patch: H/O intermittent headaches; stimulant naive
(b) (6) CRF (REV) ECG Rev CC (?)	38	M	36	90	Chest tightness (07/20-08/03/06); headache (07/20-08/03/06); reduced appetite, weight loss; emotional (teary-eyed, cried easily) [08/26]; w/ normal ECG's except for Titration 5 (sinus tachycardia) [103 bpm]	H/O false pos hepatitis, substance abuse (cocaine: 1 gm/d X 2-3 yrs; none in past yr); smoker X 20 yrs
(b) (6) CRF (REV) ECG Rev	56	M	NL	108	Mild elevated BP (on 54 mg) [10/12/06]; headaches [10/18/06]; psychosocial stressors; w/ normal ECG's	H/O anxiety episode
(b) (6) CRF ECG Rev					Increased BP	
(b) (6) CRF					Increased BP	
(b) (6) CRF (REV) ECG REV CC	63	M	NL	36	Baseline: 07/25-09/14, Final. Mild high BP (dec dose from 54 mg) [08/08-17] w/ ECG's showing baseline premature ventricular systoles then non-specific ST abnormalities from Titration 1 to End of Study	H/O acne rosacea; allergic rhinitis on diphenhydramine; smoked x 13 yrs; prior Ritalin
(b) (6) CRF (REV) ECG Rcvd CC	41	F	NL	108	Baseline: 07/24-09/11, Final. HR > 100 bpm [08/07-14]; DBP > 90 mm Hg (on 72 mg) [08/14-21] w/ ECG showing sinus tachycardia on 08/07 + preventricular systoles on 08/21	H/O occasional insomnia/Tylenol PM; gestational DM 8 yrs prior; Adderall XR 20 mg
(b) (6) CRF (REV) ECG REV pprofile- (b) (6)	31	M	36	36	Baseline: 07/31-09/19, Final. Increased anger (08/10-25); fatigue (08/12-25) assoc. w/ ECG showing sinus bradycardia; elevated BP (08/14-21)	H/O being overweight (215 lb)t; stimulant naive
(b) (6) CRF (REV) ECG REV CC pprofile- (b) (6)	39	F	NL	54	Baseline: 05/25-07/13, Final. Headaches (05/23-24); heart flutter (06/09-10), muscle aches (06/26-27); dry mouth w/normal screen ECG, then baseline + other visits showing non-specific ST abnormality (? day of first dose)	H/O heart murmur dxed @ 25 w recent cardiac w/u w/ neg. results, occasional bradycardia, water retention, premenstrual dysphoric disorder on Zoloft, Dyazide; stimulant naive
(b) (6) CRF (REV)	58	F	NL	90	Baseline: 06/14-08/03, Final. Decreased sleep; moderate high	H/O sarcoid in lymphatic system, pulmonary sarcoidosis, chronic obesity,

ECG REV CC					BP (dec dose) w/ baseline and final ECG showing non-specific ECG abnormality [07/20-08/03]; 8 lb wt. loss	gastric by-pass in 2002, headache, diabetes type II on metformin. Glipiside ER, (oral hypoglycemic agent); stimulant naive
Subjects With Psychiatric Adverse Events of Interest (N=5)						
(b) (6) CRF's Missing CRF (REV) No ECG	19	F	NL	108	Allergic skin rx (txed w Benadryl) [09/05-10/15; 10/23-25], hives [10/22-23]; decreased appetite; anxiety [09/30-?]; sad + angry mood [10/22-?]; initial insomnia; increased headaches [10/04-10/10]; dry mouth; URI (txed w Sudafed + amoxicillin); hives (txed w Benadryl); nausea; muscle tension [10/22-?]; 10 lb wt loss	H/O eczema, recurrent strept throats, IMN, hyperlipidemia, headaches/NuvaRing; stimulant naive
(b) (6) CRF's Missing CRF (REV) No ECG	36	M	NL	72	Decreased appetite; weight loss (18 lbs. 8.1 kg); diaphoresis [06/09-?]; persistent rash on torso [06/13-29] leg cramps [06/14/19]; racing thoughts (on 90 mg) [06/30-07/08] Racing thoughts; anxiety	H/O poylsubstance abuse (1986-1999), headaches/Adderall XR [stopped 05/30/06] (prev. med), Claritin, Nasacort, Flonase
(b) (6) CRF						
(b) (6) CRF's Missing CRF (Rev)	31	M	36	36	Increased anger (08/10-25); fatigue (08/12-25) assoc. w/ ECG showing sinus bradycardia; elevated BP (08/14-21)	H/O being overweight; stimulant naive
(b) (6) CRF's Missing CRF (REV)	23	M	36	36	Insomnia; short-tempered (07/18-26); decreased appetite; anxiety episode (08/22, 08/24); 7 lb wt. loss	Stimulant naive
(b) (6) CRF's Missing CRF	65	F	NL	108 LOE	Dry mouth, grinding teeth, nausea; agitation, , early insomnia; increase BP (on 72 mg)	H/O migraines
(b) (6) CRF's Missing	41	M	PBO	PBO SW	Increase BP + respiration	Ginkgo biloba
Abn ECGs, No AE						
(b) (6) CRF (Rev)	54	F			54 yo female with no adverse events except dry mouth and tooth pain during the trial/ Baseline ECG showing minor ST depression, non-specific ST abnormality with ECG at increased dose (72 mg) showing: ST Depression -.1 Mv. or More Negative T Non-Specific ST-T Abnormality or Ischemia	H/O fibromyalgia; non-smoker; joint pains on Advil; previously on Cylert; borderline obesity (194 lbs)
(b) (6) CRF (Rev)	31	M			No adverse events occurred during the trial except for appetite loss; Screening ECG showing sinus bradycardia with ECG change at increased dose (54 mg) showing: Borderline Q or Qs in 2 Leads of 2,3,avf Possible Inferior Infarct	Non-smoker; stimulant naïve; no-concurrent medications; borderline obesity (194 lbs)
(b) (6) CRF (Rev) Comment:	61	F			Baseline: 08/06-Final: 09/26 Early insomnia (08/09-?); middle insomnia (08/28-09/13);	H/O post-menopausal; irritable bowel; acid reflux on famotidine; diarrhea on loperamide; allergies on Lodrane, Singulair,

			No ECG's done on Titrations 3, 4, 5; ECG missing from Final Visit (09/26/06)	decreased appetite (08/12-?); headache (09/02-09/03); Baseline ECG showing a depressed ST/ ischemia with ECG at increased dose (54 mg) showing Borderline Q or Qs in 2 Leads of 2, 3, avf Possible Inferior Infarct	Rhineocort; arthritis on diclofenac; insomnia on Ambien; Smoked 2 PPY; borderline obesity (217 lbs)
(b) (6) CRF (Rev)	60	M	No adverse events; baseline, slight left axis deviation, and with Titration 2 (Placebo) shows abnormal Q or Qs in 2 Leads of 2,3,avf Consistent with Inferior Infarct, Age Undetermined	H/O hypothyroidism on levothyroxine; hyperlipidemia on lovastatin; smoking 6 PPY; Adderall XR

Notes:
LTFU=Lost to follow-up
NCD= Noncompliant Dismissal
LOE=Lack of Efficacy
SW=withdrawn at subject's request
IW= Investigator Withdrawn
Refused to Return=RTR

Review of 42603ATT3002 (3002)

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SUMMARY TABLE FOR STUDY 42603ATT3002 (3002)

Protocol Number/ Study Identifier[a] Principal Investigator (Country) Start/End Dates	Study Description/Design	Subjects Evaluated[b] Sex (M/F) Age (yr): median [mean] (range) Race: W/B/O	Treatment Regimen/Duration Route of Administration Batch/Formulation Numbers	Study Status Type of Report Location of Study Report (CRFs and CRT) or Publication
Controlled Clinical Studies Relevant to Adults With ADHD: Key Efficacy Trials				
42603ATT3002 EDMS-PSDB-5043916 (International) Start: 07 Apr 05 End: 01 Aug 06	R, DB, PC, PG, DR study to evaluate the efficacy and safety of 3 fixed doses of CONCERTA in adults with ADHD	401 218M/183F 34.0 [34.0] (18-53) 391/Not available[c]/10	DB, PC Phase (5 weeks), 4 treatment groups: A) 18 mg/day B) 36 mg/day C) 36 mg/day x 4 days, 54 mg/day x3 days, then 72 mg/day D) placebo OL Extension Phase (7 weeks) Treatment initiated at 36 mg/day except for subjects treated at German centers, who were given a starting dose of 18 mg/day, increased in 18 mg/day increments to a maximum of 90 mg/day. *Batch/Lot nos:* *Double-Blind* *CONCERTA 18 mg 0609478/0410815* *CONCERTA 18 mg 0609478/0413539* *CONCERTA 36 mg 0609477/0413562* *CONCERTA 36 mg 0609477/0309360* *Placebo 0613063/12150.1* *Open-Label:* *CONCERTA 18 mg 0609478/0410815* *CONCERTA 18 mg 0609478/0309369* *CONCERTA 36 mg 0609477/0413562* *CONCERTA 36 mg 0609477/0413973* *CONCERTA 36 mg 0609477/0521184* *CONCERTA 54 mg 0609958/0413349* *CONCERTA 54 mg 0614353/0433317* *CONCERTA 54 mg 0609989/0329864* *CONCERTA 54 mg 0609989/0333909*	Completed Clinical Study Report Mod5.3.5.3\42603ATT3002 (CRF) (CRT)

Key: ADHD = Attention Deficit Hyperactivity Disorder; B=black; CO = crossover, CRF = case report form; DB = double-blind, DR = dose response, DT = dose titration, F=female, M=male; O=other;
OL = open-label, PC = placebo-controlled, PG= parallel group, R. = randomized; US=United States; W=white

[a] Johnson & Johnson Pharmaceutical Research & Development (J&JPRD) is a global organization that includes, but is not limited to Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Janssen-Cilag International N.V., McNeil Pediatrics Division of McNeil-PPC, Inc.; ALZA Corporation, Janssen-Ortho Inc., and McNeil Consumer and Specialty Pharmaceuticals Division of McNeil-PPC, Inc.

[b] Number of subjects evaluated for safety.

[c] Black or African heritage' is included in'Other'

[d] Asian is included with "Other"

SCHEDULE OF EVENTS FOR STUDY 42603ATT3002 (3002)

Table 8: Time and Events Schedule

	Screening[a]	Baseline[b]	Double-Blind Phase			Open-Label Extension			Post-Study Visit[c]
Visit	1	2[d]	3[e]	4[e]	5[e]	6[e]	7[e]	8[e]	9[e]
Week	-2 to 0		1[f]	3[g]	5[g,h]	6[g]	8[g]	12[g,h]	13[g]
Day			7	21	35	42	56	84	91
Informed consent	X								
Medical, psychiatric, medication history	X								
ADHD diagnosis (DSM–IV) and type of ADHD	X								
Current education and employment status	X								
SCID	X								
DSM-IV assessment of substance use disorder	X	X			X			X	
Inclusion/exclusion criteria	X	X			X[i]				
Physical examination	X								
Height	X								
Body weight	X	X			X			X	
Vital signs	X	X	X	X	X	X	X	X	X
Clinical laboratory tests	X	X			X			X	X
Pregnancy test in females[j]	X	X			X			X	X
Conners' Adult ADHD Rating Scale	X	X	X	X	X	X	X	X	X
CGI-S		X			X			X	X
CGI-C					X			X	X
Conners' Self-Report Short Version		X			X			X	
SDS		X			X			X	
Q-LES-Q		X			X			X	
GAE					X			X	
Randomization to treatment group[k]		X							
Dispense study drug[l]		X	X	X	X	X	X		
Study drug accountability			X	X	X	X	X	X	
Dosing compliance			X	X	X	X	X	X	
Concomitant medication review		X	X	X	X	X	X	X	X
Adverse event monitoring[m]	X	X	X	X	X	X	X	X	X

[a] Screening period for up to 14 days. When tapering off from fluoxetine or MAO inhibitors was required, a maximum screening period of 4 weeks was allowed.

[b] For subjects who did not require tapering and discontinuation of current medications, baseline procedures could be performed on the same day as screening, so long as all procedures – except randomization – were completed and the subject satisfied inclusion and exclusion criteria prior to randomization. Eligible subjects could be randomized only when laboratory results had been reviewed and approved by an investigator. The maximum time allowed between combined screening and baseline assessments and randomization/dispensing of medication was 7 calendar days.

[c] For those subjects not continuing into the open-label extension, the post-study visit was scheduled one week after the final dose of study drug.

[d] First dose of study medication was taken Day 1, the morning after randomization and receipt of medication. Prior to randomization, the investigator had to have received the laboratory results and approved the subject's entry into the double-blind phase. Study medication was to be taken before 10:00 a.m., if possible.

[e] Visit scheduled for end of respective week.

[f] This visit could take place ± 1 day around the indicated day.

[g] This visit could take place ± 2 days around the indicated day.

[h] End-of-phase procedures also had to be performed for all subjects who withdrew prematurely from the double-blind phase or open-label extension.

[i] Review of inclusion and exclusion criteria to determine subject's eligibility to continue into open-label extension. Exception: previous treatment with MPH or PR OROS methylphenidate and no minimum CAARS score required.

[j] Urine pregnancy test.

(Footnotes continue on next page)

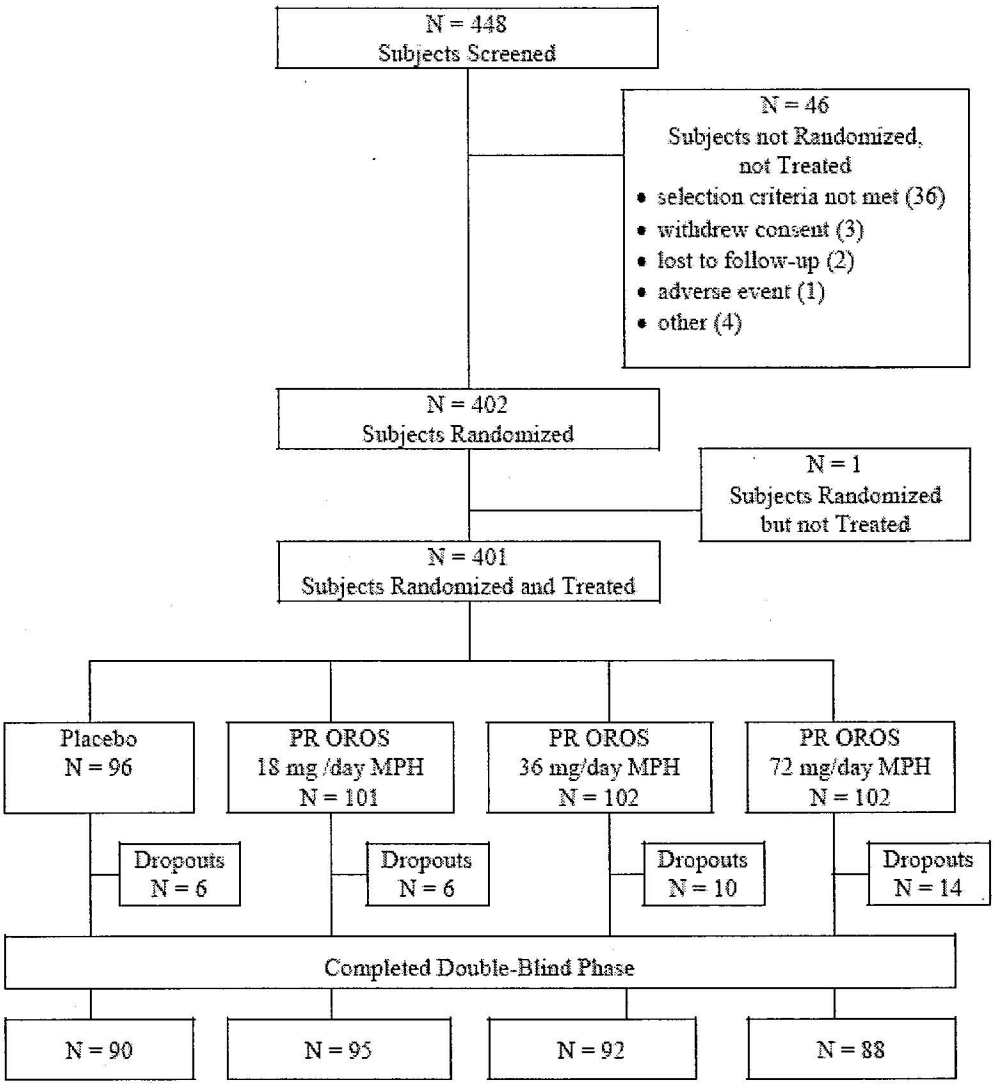
[k] Contact IVRS for randomization.

[l] Drug was dispensed according to IVRS guidelines.

[m] Monitoring for adverse events started after the Informed Consent Form was signed and the first study-related procedure was performed, and continued until the last study-related procedure was performed.

DOUBLE-BLIND PHASE, SUBJECT DISPOSITION FOR STUDY 42603ATT3002 (3002)

Figure 2: Subject Disposition in the Double-Blind Phase



Source: Attachment 1, Attachment 5, Attachment 6
N = number of subjects

SPONSOR'S TABLE OF NUMBER OF SUBJECTS RANDOMLY ASSIGNED TO EACH TREATMENT GROUP DURING THE DOUBLE-BLIND PHASE FOR STUDY 42603ATT3002 (3002)

(Study 42603ATT3002: *All Subjects / Double-Blind*)

		PR OROS MPH			
	Placebo (N=96) n (%)	18 mg (N=101) n (%)	36 mg (N=102) n (%)	72 mg (N=103) n (%)	Total (N=402) n (%)
All randomized subjects	96 (100.0)	101 (100.0)	102 (100.0)	103 (100.0)	402 (100.0)
All subjects population	96 (100.0)	101 (100.0)	102 (100.0)	102 (99.0)	401 (99.8)
Intent-to-treat population	95 (98.9)	99 (99.0)	101 (99.0)	99 (96.1)	394 (98.0)
Per-protocol population	90 (93.8)	94 (93.1)	94 (92.2)	93 (90.3)	371 (92.3)

Source: Attachment 1
N = number of subjects with data; n = number of subjects with observation

TABLE > 2 % OF TREATMENT EMERGENT ADVERSE EVENT FOR STUDY 42603ATT3002 (3002)

Table 36: Treatment-Emergent Adverse Events During Double-Blind Phase Occurring in >2% of Subjects Receiving PR OROS MPH, by Preferred Term
(Study 42603ATT3002: *All Subjects / Double-Blind*)

		PR OROS MPH			
Body System Preferred Term n (%)	Placebo (N=96)	18 mg (N=101)	36 mg (N=102)	72 mg (N=102)	All (N=305)
Any AE	**63 (65.6)**	**76 (75.2)**	**77 (75.5)**	**84 (82.4)**	**237 (77.7)**
Cardiac Disorders	**0**	**5 (5.0)**	**10 (9.8)**	**13 (12.7)**	**28 (9.2)**
Palpitations	0	2 (2.0)	5 (4.9)	5 (4.9)	12 (3.9)
Tachycardia	0	4 (4.0)	5 (4.9)	8 (7.8)	17 (5.6)
Ear and Labyrinth Disorders	**0**	**3 (3.0)**	**4 (3.9)**	**5 (4.9)**	**12 (3.9)**
Vertigo	0	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Gastro-Intestinal Disorders	**18 (18.8)**	**25 (24.8)**	**32 (31.4)**	**40 (39.2)**	**97 (31.8)**
Abdominal pain upper	5 (5.2)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Diarrhea	5 (5.2)	3 (3.0)	1 (1.0)	4 (3.9)	8 (2.6)
Dry mouth	2 (2.1)	8 (7.9)	7 (6.9)	21 (20.6)	36 (11.8)
Nausea	4 (4.2)	8 (7.9)	16 (15.7)	15 (14.7)	39 (12.8)
General Disorders and Administration Site Conditions	**11 (11.5)**	**10 (9.9)**	**9 (8.8)**	**10 (9.8)**	**29 (9.5)**
Fatigue	6 (6.3)	4 (4.0)	4 (3.9)	6 (5.9)	14 (4.6)
Infections and Infestations	**12 (12.5)**	**10 (9.9)**	**12 (11.8)**	**7 (6.9)**	**29 (9.5)**
Influenza	3 (3.1)	4 (4.0)	2 (2.0)	2 (2.0)	8 (2.6)
Nasopharyngitis	9 (9.4)	7 (6.9)	8 (7.8)	4 (3.9)	19 (6.2)
Investigations	**8 (8.3)**	**9 (8.9)**	**12 (11.8)**	**12 (11.8)**	**33 (10.8)**
Weight decreased	5 (5.2)	3 (3.0)	8 (7.8)	11 (10.8)	22 (7.2)
Metabolism and Nutrition Disorders	**9 (9.4)**	**22 (21.8)**	**24 (23.5)**	**36 (35.3)**	**82 (26.9)**
Decreased appetite	7 (7.3)	20 (19.8)	22 (21.6)	35 (34.3)	77 (25.2)
Nervous System Disorders	**34 (35.4)**	**42 (41.6)**	**39 (38.2)**	**47 (46.1)**	**128 (42.0)**
Dizziness	7 (7.3)	6 (5.9)	10 (9.8)	9 (8.8)	25 (8.2)
Headache	17 (17.7)	26 (25.7)	21 (20.6)	17 (16.7)	64 (21.0)
Initial insomnia	2 (2.1)	3 (3.0)	2 (2.0)	5 (4.9)	10 (3.3)
Insomnia	7 (7.3)	12 (11.9)	12 (11.8)	17 (16.7)	41 (13.4)
Tremor	1 (1.0)	1 (1.0)	1 (1.0)	7 (6.9)	9 (3.0)
Psychiatric Disorders	**6 (6.3)**	**18 (17.8)**	**24 (23.5)**	**40 (39.2)**	**82 (26.9)**
Aggression	1 (1.0)	2 (2.0)	3 (2.9)	2 (2.0)	7 (2.3)
Anxiety	1 (1.0)	3 (3.0)	5 (4.9)	8 (7.8)	16 (5.2)
Depressed mood	1 (1.0)	6 (5.9)	3 (2.9)	5 (4.9)	14 (4.6)
Depression	1 (1.0)	0	3 (2.9)	4 (3.9)	7 (2.3)
Irritability	1 (1.0)	4 (4.0)	4 (3.9)	9 (8.8)	17 (5.6)
Nervousness	1 (1.0)	0	3 (2.9)	8 (7.8)	11 (3.6)
Restlessness	0	0	2 (2.0)	6 (5.9)	8 (2.6)
Skin and Subcutaneous Tissue Disorders	**3 (3.1)**	**9 (8.9)**	**5 (4.9)**	**10 (9.8)**	**24 (7.9)**
Hyperhidrosis	1 (1.0)	5 (5.0)	3 (2.9)	8 (7.8)	16 (5.2)

NARRATIVES FOR DISCONTINUATIONS CLINICAL STUDY 42603ATT3002 (BLUE FONT: REGULATORY SERIOUS ADVERSE EVENTSL RED FONT: ADVERSE EVENTS OF POTENTIAL CONCERN)

Subject	Age	Sex	AE Dose	Fin Dose	Events	Relevant PMHX
Treated With Placebo During Double-Blind Phase + PR OROS methylphenidate During Open-Label Phase (n=5)						
A10282 Germany	39	F	18 36 54	54	*Depressed mood; lethargy* (54 mg), *fatigue; insomnia; headache; decreased appetite*	Previous ADHD treatment included caffeine
A10327 Germany	27	M	18 36	36	*Sinusitis* (tx w grippostad-Dextromethorphan, paracetamol, ethanol); *fever; GI discomfort*	No previous ADHD treatment
A10802 Sweden	24	F	36	36	*Pregnancy* (tx w abortion)	No previous ADHD treatment
A11047 ** Finland	29	F	36 54 18	18	9 days on 36 mg in OL, increased to 54 mg, then: *Dizziness; headache; nausea; palpitations* (Decrease dose to 36 mg); *paresthesia right arm; worsening of high blood pressure* (170/117 mm Hg: supine; 184/103 standing-End of OL)	No previous ADHD treatment; H/O Hypertension (165/109 mmHg: supine; 142/94 mmHg: standing; screening); without H/O stimulants CRF's Reviewed Note: On 2/23, the subject developed *feelings of paresthesia in the right arm (left arm crossed out) which apparently persisted*, and the dose was decreased to 18 mg on 02/23 and stayed in that dose until 02/28/06. On 03/02/06, at Visit 8 (Day 84), *the supine blood pressure was 170/117 and the standing blood pressure was 184/103.* The subject discontinued from the trial on 03/02/06 for the hypertension and was seen at a post-study visit on 03/08/06 when the *supine blood pressure was* 143/93 *and the standing blood pressure was* 141/95

Reviewer Comments: (b) (6) indicates that the subject was a 29 year old female with a history of asthma [on Terbutaline sulfate (Bricanyl) and Budesonid (Pulmicort)], allergies [on Pseudo-ephedri-hydrochloride, akrivastine (Dunct) and Mometaconfoae (Nasonex)], current sinusitis [on Zithromax] and gestational diabetes who was found to be *hypertensive at screening* [165/109 supine, 142/94 standing]. She was on Concerta in the double blind phase of the study from 12/21/05-02/01/06 during which time, she had flu with fever and stomachache for unclear duration. Supine blood pressures during this time ranged from 132-143/89-97. From 02/02-02/28/06, the subject was enrolled in the open label portion of the trial. At a dose of 36 mg, the subject developed a *disoriented feeling* lasting 5 days with *dizziness* beginning after 3 days and persisting for unclear duration. During this time *the supine blood pressure went from132/86 to 172/107*. The dose was increased to 54 mg on 02/10/06, and the subject then developed *palpitations, headache and nausea*. The dose was held 02/13/06, and restarted on 02/14/06 at 18 mg, held again on 02/15/06, then restarted again at 36 mg on 02/16 and remained at that dose until 02/19/06. The basis for the dose adjustment is not apparent since there are no vital signs or CRF notes between Visits 6 (02/09/06) and

Visits 7 (02/22/06). On 02/18/06 the subject developed *cramping feelings in the legs* which apparently persisted. The dose was held from 02/20-21 for unclear reasons (not listed in CRF). Supine blood pressure on Visit 7 (Day 56) on 02/22/06 was 137/97, and the dose was restarted at 36 mg. On 2/23, the subject developed *feelings of paresthesia in the right arm (left arm crossed out) which apparently persisted for at least more than 1 week (03/?/06)*, and the dose was decreased to 18 mg on 02/23 and stayed in that dose until 02/28/06. On 03/02/06, at Visit 8 (Day 84), *the supine blood pressure was 170/117 and the standing blood pressure was 184/103*. The subject discontinued from the trial on 03/02/06 for the hypertension and was seen at a post-study visit on 03/08/06 when the *supine blood pressure was* 143/93 *and the standing blood pressure was* 141/95.

Serious Adverse Events (n=1)

A10368 Germany OL, 72	46	M	18 36 54 72	72	Hospitalized for *foreign body in the urethra*	No previous ADHD treatment

Treated With PR OROS methylphenidate 18 mg Daily During the Double-Blind Phase; Discontinued During Open Label Phase (n=5)

A10061** Denmark CV ?	53	M	18 DB 36(OL) 18(OL)	18	OL started at 36 mg developed *stomach pain-abdominal pain*, drug stopped 2 days, then restarted at 18 mg; *tachycardia; decreased appetite; fatigue*	No previous ADHD treatment CRF's Reviewed
A10287 Germany	19	F	18 DB 18(OL) 36(OL)		*Loss of appetite, weight loss* 8.8 lbs)	No previous ADHD treatment
A10701 Portugal	41	F	18 DB 36(OL)		*Headache; nausea*	Previous treatment/Escitalopram (D/C 15 days before baseline)
A10791** Sweden CV w pos rechallenge. dechallenge	39	F	18 DB 36(OL)		*Syncope* (36 mg: drug stopped); resumed 2 days later (54 mg) with *recurrence of syncope* (drug stopped);	No previous ADHD treatment
A10970 Great Britain CV	36	F	18 DB 36(OL) 54(OL) 72(OL)		*Raised blood pressure*	H/O stable, mixed-anxiety depressive disorder/Venlafaxine 150 mg p.o.,q.d.; no previous ADHD treatment

Treated With PR OROS methylphenidate 18 mg Daily During the Double-Blind Phase; Discontinued During Double Blind Phase (n=4)

A11027 Finland	34	F	18 DB		*Nausea, vomiting; sweating; dry mouth*	No previous ADHD treatment

Treated With PR OROS methylphenidate 18 mg Daily During the Double-Blind Phase; Discontinued During Double Blind Phase: Serious Adverse Events (n=3)

A10253** Germany DB, 18	59	M	18 (DB) 36 (OL)		DB, 10/12-11/21/05: 10/25-11/05/05: on drug 10 d developed *vertebrobasilare insufficiency* (10/25), then *vertebrobasilare stroke* (10 days later) (Stop drug)-hospitalized X 16 days (tx w pantoprazole [PPI to tx GERD], heparin + phenprocoumon (anti-	Previous treatment/MPH (20-40mg) (D/C 30 days before baseline) CRF's Reviewed Note: On 12/17/05, he was reported to have *an increase of fat, and his body weight increased from 61 kg (11/21/05) to 70 kg (+ 9 kg).* No basis is identified as to the basis for this *large weight*

		coagulant); Exam: mild *swaying vertigo, blurred vision*. CCT (Initial): right *PICA infarction*; CT Angiography: right PICA; MRI: *bilateral PICA arteries infarctions (right > left* due to occlusion of the right); Doppler U/S: functional occlusion of the right vertebral artery due to dissection close to subclavian artery (?-note unclear); subject recovered without sequelae except for *reduction in physical tolerance (post-traumatic neurasthenia), cognitive disorder + intermittent vertigo*; concurrent events at SAE were: *sweating, sleep disturbance, ALT + GLT increased*	*gain.* The vignette indicates that his *ALT and GLT were increased* but the amount and timing of this increase is not specified.
			Dates: 10/15/2005: 18 mg 10/25/05: VBI 11/05/05: VB Stroke; D/C Drug (18 mg) *11/05-11/21/05:* Hospitalized -11/06/05: Restart Drug 11/22/05: OL (18 mg) *11/30-12/08/05:* Rehabilitation Hospital -12/02, 04, 07, 10/05: (36 mg) 12/13/05: OL discontinued because of recognition of using an exclusionary drug: (b) (6) phenprocoumon

Reviewer Comments: [redacted] indicates that the subject was a 59 year old WM whom had no concurrent medical problems except for psoriasis upon entering into the study. He had prior psychiatric problems (dissociative episodes). He had been on MPH 20-40 mg q.d. for 3.25 years, the basis of which is uncertain, given that his ADHD was first diagnosed at study entry. Baseline vital signs were unremarkable (supine pulse: 59; supine blood pressure: 127/71; weight: 63 kg). He was in the double blind portion for the trial from 10/12-11/21/05. From 10/25-11/05/05, he is said to have developed vertebrobasilare insufficiency, the basis of which is uncertain, given that the symptoms and signs are not identified in the CRF's. During this time he had a slight increase (+ 30) in his standing systolic blood pressure (118/75 to 148/77). He was hospitalized for on 11/05, and was diagnosed as having a vertebrobasilare stroke. The CRF's indicate that he had clinic visits on 11/21 (2 weeks after hospitalization). The vignettes (not the CRF's) indicate that on exam (date of exam uncertain), he had mild *swaying vertigo, blurred vision*; and that he had *bilateral PICA arteries infarctions (right > left* due to occlusion of the right) with a Doppler Ultrasound showing functional occlusion of the right vertebral artery due to dissection close to subclavian artery (?-vignette unclear). The vignette indicates that the subject recovered without sequelae except for *reduction in physical tolerance (post-traumatic neurasthenia), cognitive disorder* and *intermittent vertigo* (date of this determination is uncertain). He entered the open label portion of the trial from 11/22-12/13/05 during which time he remained at a fluctuating dose of 18-36 mg. Standing systolic blood pressure remained elevated (151/76) on 11/21/05. He was *sweating* (10/21-11/03/05). A sleep disturbance began on 11/24/05 while on 18 mg of drug and continued during the trial. *Post-traumatic neurasthenia*, described in the vignette, as a *reduction in physical tolerance.* On 12/17/05, he was reported to have

an increase of fat, and his body weight increased from 61 kg (11/21/05) to 70 kg (+ 9 kg). No basis is identified as to the basis for this *large weight gain.* The vignette indicates that his *ALT and GLT were increased* but the amount and timing of this increase is not specified.

A10885 Switzerland DB, 18 with pos. rechal DB, 18 OL , 54	43	F	**18(DB)** 36(OL) 54(OL)	54	11/29-12/15/05 (17 days): 18 mg DB: *anxiety disorder, depressive thoughts* caused subject to request admission to psychiatry polyclinic -12/16: lorazepam 1 mg -12/17: lorazepam, 2.5 mg -12/18: no Oros given -12/19: restarted OROS resulting in *reactivation of anxiety disorder*, with *continua*tion of depressive thoughts -12/20: admitted to psychiatry clinic for further stabilization, *diagnosed with adjustment disorder* -01/04/06: completed DB phase -1/05-26/06 (22 days): OL (36 mg): *restlessness* (dose increase 54 mg); 1/31-02/14/06: bromazepam for *anxiety* prophylaxis Started pre-trial-02/08/06: 30 mg qd 02/09/06: citalopram: 20 mg q d) for *MDD + anxiety*	H/O MDD, anxiety/Citalopram; no previous ADHD treatment Note: Protocol violation with concomitant medication
A11086** Germany OL, 36	40	M	18(DB) 18(OL) 36(OL)		11/10-12/14/05: 18 mg (DB) 12/15-22/05: 18 mg (OL) 12/22/05: 36 mg (OL) 01/13/05-02/03/06: hospital for *acute psychological stress; hypertonia [tx w/enalapril- (Vasotec) used to treat HTN]* -02/01: Oros stopped 02/08/06: acute psychological stress resolved , Hypertonia (?): not resolved	No previous ADHD treatment

<u>Treated With PR OROS methylphenidate 36 mg Daily During the Double-Blind Phase (n= 10; with n=3, discontinuing in the DB, n=5, discontinuing in the OL, and n=2 discontinuing in both DB + OL)</u>

A10034 Czech Republic	48	F	36(DB) 36(OL) 54(OL) 36(OL)		On 36 ng X 7 d, then 54 gm X 1 d, then *stomachache, nervosity, tremor of hands* (decrease dose 36 mg, then stopped drug after 5 days)	No previous ADHD treatment
A10074 Denmark	32	F	36(DB) 36(OL)		10/08-11/11/05: 36 mg (DB); -10/21-11/12/05: *sadness* 11/12-11/19/05: 36 mg (OL) -11/13: *depression*	H/O MDD, anxiety; no previous ADHD treatment

					-11/22: sadness	
A10123** France	45	M	36(DB) 36(OL) 18(OL) 36(OL)		11/10-12/14/05: 36 mg (DB); 12/15- :36 (OL) -12/22-01/04/06: decrease dose to 18 mg (reason uncertain) -01/05: 36 mg -01/11: 28 d OL: *rhinitis, vertigo* (tx w Betahistine: anti-vertgio; +, predni-solone-rhinitis) -01/21: *right hypoacousia* (hearing loss ?), *nystagmus*, tinnitus -11/12: Oros stopped -01/21: ethonolamine (anti-histamine) for *hypoacusia* + nystagmus; +, trimetazidine (angina pectoris, or, to preserve energy metabolism exposed to hypoxia or ischemia) for *vertigo, tinnitus* Ongoing: *nystagmus, right hypoacusia + rhinitis*	No previous ADHD treatment CRF's Reviewed Note: The following symptoms are reported to have an onset on 01/20/06 and which apparently persisted: *vertigo, hypoacusia, tinnitus and nystagmus*. An MRI was apparently performed on 01/25/06, and the note on the remark page of the CRF's (page 63), dated 04/26/06, states *"MRI Cerebral and focused on internal auditory meatus not involving recent accidental ischemia."*
A10408 ** Greece	30	M	36(DB)	36	11/01-11/05/05: 36 mg (DB), stopped OROS for: *-Abdominal cramps; anorexia; increased anxiety; hot flashes; sweating; tachycardia; tension headache; difficulty in visual focusing; weight loss* (all AEs reported as being present on 11/01)	H/O panic disorder w/ anxiety disorder (at screen/alprazolam; no previous ADHD treatment
A10698 Portugal	38	F	36(DB)	36	09/26-10/17/05: 36 mg (DB), stopped OROS for: *irritability, nervousness*	H/O ADHD/Paroxetine
A10771** Sweden Positive dechallenge	45	F	36(DB) 36(OL) 54(OL) 36(OL)	36	04/15-05/19/05: 36 mg (DB) 05/20-06/10/05:36 mg (OL) 06/10: dose incr 54 mg 06/12: *dizziness* (decr 36 mg) 06/26: *suicidal thoughts + depression* 06/27-28: Hold OROS 06/27: suicidal thoughts: resolve 06/29: *dizziness* resolved; 36 mg started 06/30: Stop OROS for: *depression* (tx w Paroxetine) 07/14: *depression* resolve *-sensitivity (?) + grey teeth*	H/O anxiety, depressive episodes; no previous ADHD treatment
A10804** Sweden Positive dechallenge	46	M	36(DB) 36(OL)		09/09-09/15/05: 36 mg (DB), stopped OROS for: 09/13: *delusion of reference* (tx w ? X 7 d)	No previous ADHD treatment CRF's Reviewed

					09/16-19/05: 36 mg OL (stop OROS) for ongoing *delusion of reference* *09/22: delusion of reference resolved* *09/23: OL resumed*	

Reviewer Comments: (b) (6) indicates that the subject was a 46 year old male with a history of depression who was *on venlafaxine* (150 mg qd) since 08/2004, and who *continued on venlafaxine* during the double blind and part of the open label portions of the trial (10/26/2005). Sponsor's narrative indicates that the subject developed *delusions of reference from 09/13-22/2005*, and that no other adverse events occurred. Review of the CRF's indicate that *additional adverse events occurred at the end of the double blind phase (09/16/2005) and continued into the open label phase (09/22-11/10/2005)*. These adverse events *consisted of* dry mouth and perspiration (09/13/05-?); *polyuria, polydypsia* (09/13/05-09/22/05); *problems of concentration, memory and uneasiness, symptoms of depression* and diarrhea (09/16-09/22/2005); *paresthesia and delusions of reference (09/19-09/22/2005)*, and loss of libido (09/19-?). Review of the CRF vital signs indicates supine and standing borderline hypertension (150/90) and borderline, standing tachycardia (100) on days 8 and 11 of the double blind portion of the trial, respectively (not listed as AE's).

A10807 Sweden	20	M	36(DB) 36(OL) 54(OL)	54	11/16-12/21/05: 36 mg (DB) 12/22-12/30/05: 36 mg (OL), dose incr to 54 mg 01/13: *weight loss* 6.6 lbs, *insomnia* (OROS stopped)	No previous ADHD treatment
A10871 Switzerland	30	M	36(DB) 36(OL)	36	04/21-05/30/05: 36 mg (DB) -baseline *aggression* -05/24: *aggression* worsens 05/31-06/08: 36 mg (OL), *aggression*	No previous ADHD treatment
A10940 Finland	25	F	36(DB) 36(OL)	36	09/27-11/02/05: 36 mg (DB) 11/03-11/21/05: 36 mg -11/18-11/30/05: *tachycardia* (OROS stopped)	No previous ADHD treatment
Treated With PR OROS methylphenidate 72 mg Daily During the Double-Blind Phase (n=11 ; with n=8, discontinuing in the DB with n=1 being a SAE, n=1, discontinuing in the OL, and n=2 discontinuing in both DB + OL)						
A10172 Germany	42	F	72(DB)1 8(OL) 36(OL) 54(OL) 72(OL) 36(OL)	36	10/05-11/08/05: 72 mg (DB) 11/09-11/16/05: 18 mg (OL) 11/16-11/23/05: 36 mg (OL) 11/23-11/30/05: 54 mg (OL) 11/30-12/01/05: 72 mg (OL) -reduce dose to 36 mg (? reason) 12/01-12/12/05: 36 mg OL -12/11: *depressed mood* (OROS stopped) 12/13: tx w sertraline	H/O MDD; no previous ADHD treatment
A10180 Germany	24	M	72	72	10/03-11/08/05: 72 mg (DB), ORO stopped for: *Increased rebound phenomenon (?), increased nervosity, inner tremor*	No previous ADHD treatment/Concerta (18 mg) (09-11/10/05 ?: conflicting dates with dose of double blind treatment?
A10194** Germany	45	W	72	72	08/03-08/07/05: 72 mg (DB), ORO stopped for: *anxiety; increased arterial hypertension (130/90: standing, 130/85: sitting); sleep disorder, insomnia restlessness; paralysis of*	H/O arterial hypertension/captropril; no previous ADHD treatment

					accommodation; subjective visual field constriction; tension headache	CRF's Reviewed
A10270 Germany	35	M	72	72	09/03-10/20/05: 72 mg (DB), ORO stopped for: *10/07-10/28/05: depression*	No previous ADHD treatment
A10288 Germany CV	38	M	72	72	06/07-06/18/05: 72 mg (DB), ORO stopped for: *anxiety; dry mouth; sleep disorder; nervousness; palpitations; dizziness* 06/18-06/19/05: *paralysis of accommodation* *Tinnitus* persisting	No previous ADHD treatment CRF's Reviewed
A10296** Germany	22	M	72	72	07/06-07/25/05: 72 mg (DB), ORO stopped for: *tiredness; severe indifference; irritability; insomnia; depressed mood; increased sweating; tachycardia*	No previous ADHD treatment
A10298 Germany CV	33	F	72	72	12/07-12/16/05: 72 mg (DB), ORO stopped for: 12/07-12/16/05: headaches 12/12/05: *palpitations* 12/15:05: *Anxiety-panic, inner restlessness, shakiness, tremor*	H/O unknown cardiovascular problems; no previous ADHD treatment
A10627 Norway	39	F	72	72	12/08-12/13/05: 72 mg (DB), ORO stopped for: Eructation, burning sensation epigastrium, vomiting, nausea, dry mouth, headache, vertigo, diarrhea (stop OROS)	H/O hiatus hernia, eructation (reflux esophagitis), MDD/fluoxetine (stopped 3 wks before baseline)
A10650 Norway CV	37	M	72(DB) 36(OL) 72(OL)	72	11/22-12/29/05: 72 mg (DB), 12/30/05-01/24/06: OL ORO (72mg) stopped for: *Impotency (01/19-01/29); unwell in stomach (11/25/06); tachycardia (11/28-?); increased BP (125/100: Day 7, 11/28) and increased HR (100-112 bpm: Day 7, 11/28)*	H/O reactive depression, social phobia; no previous ADHD treatment
A10694 Portugal	43	F	72(DB) 36(OL)	36	01/03-01/23/06: 72 mg (DB), ORO stopped for: *Anxiety, hyperfocus of attention, irritability, motor agitation* (tx w alprazolam for *anxiety*) 01/26-01/27/06: OL (36 mg) *Anxiety, hyperfocus of attention, irritability, motor*	No previous ADHD treatment

					agitation (tx w alprazolam for *anxiety*)	
Serious Adverse Events (n=1)						
A10472 Netherlands DB + OL: 72	21	M	72(DB) 36(OL) 54(OL) 72(OL)	?	02/23-03/29/06: 72 mg (DB), developed: *Depressive disorder* 03/30-?/06: OL -05/21/06 (tx w venlafaxine) *05/31: depressive disorder w suicidal thoughts (pg. 54)*	H/O essential tremor (both hands), fatigue; no previous ADHD treatment
Serious Adverse Events During Post-Study Period (n=3; with 3 occurring in the OL)						
A10788** Sweden DB to OL to post-study, 72	27	M	72(DB) 36(OL) 54(OL) 72(OL) 90(OL)	90	04/26-05/30/05: 72 mg (DB) -Borderline *hypertension*, not coded (150/90) 05/31-7/18/05: OL -07/24: *severe headache, temporal arteritis*-hospitalized -07/25: borderline *hypertension*: 160/90 ? investigator states severe headache prior to study enrollment thought to be *Horton's syndrome* (episodic vascular headaches usually related to blood pressure; or, excruciating headache usually over one eye and on the forehead; one-sided headache) CCT (? Date): negative -07/20-22: *insomnia* + other *ADHD symptoms* 06/07: borderline *hypertension* (not coded): 165/90	H/O PTSD, insomnia, panic disorder/zolpidem (Ambien), venlafaxine, mirtazapine (Remeron); no previous ADHD treatment CRF's reviewed.

Reviewer Comments: [redacted] (b) (6) indicates that the subject was a 27 year old male with a history of ENT allergies, rhinitis, conjunctivitis, back pain, eczema, mild panic disorders and PTSD who was on and remained on the following medications during the trial: Remeron, Effexor, Stilnet (?zolpidem), and Claritin. *The CRF's indicates the following additional adverse events (not identified in the sponsor's vignette) identified at screening based upon laboratory abnormalities: hypertriglycidemia, hypercholesterolemia, high ALT and GT (however, these numbers are not given in the CRF's).* The subject was treated with Concerta 72 mg during the double blind. *Borderline hypertension (145/90 mm Hg: supine; 145/95 mm Hg, standing)* and a *rapid heart rate* (pulse: *92 bpm*, standing) were present at screen/baseline with *both increasing by visit 4 (150/90 mm Hg: supine; 155/95 mm Hg, standing; 100 bpm standing).* During the open label portion of the trial (72 mg Concerta) *the blood pressure worsened 160-165/90 mm Hg: supine; 130-150/100 mm Hg:* standing). The CRF indicates that the subject awoke on 07/24/05, six days after the last dose in open label with *"a severe headache for which he was hospitalized for < 12 hours"*. No information is provided about the work-up at the hospital. However, the sponsors vignette indicates that *a diagnosis of temporal arteritis was made. The basis and the work-up for this diagnosis are not provided.* The sponsor states in the vignette that there was a severe headache prior to study enrollment and that the investigator thought *that the subject had a Horton's syndrome. No information is provided about the basis for the investigator's determination of this headache type.* The concomitant medications used during this study were protocol violations (? check). *Hypertension and tachycardia are not listed as adverse events.*

A10801** Sweden DB, 72	34	F	72(DB) 36(OL) 54(OL)	?	06/16-07/19/05: 72 mg (DB) 06/16-07/06/05: *fatigue* 07/17: *mild abortive migraine*	H/O migraine; no previous ADHD treatment

			36(OL)	*attack, vertigo, visual disorder* (hospitalized) CCT: *probable lacunar infarct* (11 mm) *in caudate nucleus* with slight expansion of the frontal horn of the right lateral ventricle 07/20-09/06/05: OL	CRF's reviewed.

(b) (6) indicates that the subject was a 34 year old female with a history of inactive migraine ("normal to currently active"/CRF; no medications/attacks previous year/Remarks on pg. 68 of CRF) without other medical problems, was on no other concurrent medications, and whom was stimulant naive. Past medical history was remarkable for unspecified alcohol, or, substance abuse, which she stopped 10 yrs prior when she became pregnant. She reportedly had an *abortive migraine* on 07/17/05 during the double blind portion of the trial on a dose of Concerta 72 mg. The vignette submitted by the sponsor indicates that there was *vertigo* and an *unspecified visual disorder* associated with the episode. This information could not be identified in the CRFs. *A description of the event is not contained in the CRF's, except Remarks dated 2 days after the event (07/19/05) where it is noted "got hospitalized, CAT revealed old small lesion nothing current." Information contained in the sponsor's vignette indicates "CCT: probable lacunar infarct (11 mm) in caudate nucleus with slight expansion of the frontal horn of the right lateral ventricle". However, this information is not contained in the CRF's. V.S.'s 2 days after the event (Visit 5) showed a resting pulse of 74 and a supine PB of 110/80.*

A11006 Finland OL to Post-Study, 54	27	F	72(DB) 36(OL) 54(OL)	11/08-12/13/05: 72 mg (DB) 12/14/05-02/02/06: OL -02/07/06: increased anxiety (hospitalized in psychiatric hospital)	H/O headache, MDD, panic disorder/citalopram (until 5 wks before baseline), diazepam

Review of 12-304

NARRATIVES FOR DISCONTINUATIONS CLINICAL STUDY 12-304 (N=98); NARRATIVES FOR SUBJECTS WITH CARDIOVASCULAR ADVERSE EVENTS OF INTEREST (N=82)

Subject	Age	Sex	AE Dose	Fin Dose	Events	Relevant PMHX/Meds
Narratives for Subjects With Serious Adverse Events (N=6)						
(b) (6) CRF (REV) No ECG	44	M	36-72	54	Baseline: 08/03- Mth 6, 01/29/07. Nausea, Insomnia, fatigue, dry cough (08/21-09/15), exercise induced asthma (08/21-09/15)- hospitalized for asthma, txed with Albuterol; acid reflux; moderate flu on Z-Pac; mild elevated ALT (09/31/07-?)	H/O occasional mild heart palpitations, hepatitis w jaundice, PPD positive, Raynaud's syndrome, occasional headaches/Airborne multivitamin, acyclovir; exercise induced asthma on Albuterol; anxiety on Zoloft; Strattera
(b) (6) CRF (REV-) No ECG	42	M	36-72	72	Baseline 06/07-01/08/07, Mth 7) Fatigue (06/06-07/03); bee stings (txed with epinephrine, prednisone, Benadryl) [07/01-07/08]; jitteriness (07/04); rhinitis (09/01-09/08); migraine headaches (11/27, 12/07, 12/21, 12/23, 12/26); diarrhea + vomiting (txed w Imodium); back	H/O GERD on Prevacid; migraine on Atenolol, Imitrex; sleep apnea on CPAP; MDD on Zoloft; rhinitis on Allegra; non-smoker; Adderall XR

					strain	
(b) (6) CRF (REV) No ECG Comment: Pg. 37: Pt. withdrew from study because of subdural (11/02)	57	M	36-108	108	Baseline: 08/23-11/28. Final. Decrease appetite; subdural hematoma + abrasions from MVA [11/02] (hospitalized); 23 lb wt. loss over 3 mths	H/O asthma on Advair; Adderall; obesity (215 lbs)
(b) (6) CRF (REV) No ECG Comment: Pg. 27: Withdrew at pt's request Review lab	29	M	36-54	54 SW	Baseline: 09/05-09/13 (Titrat 1). Sinusitis; severe dehydration (09/13-09/14) with DKA (09/13-09/14) (hospitalized); 5 lb wt. loss over 2 week	H/O type 2 diabetes on insulin pump, Humalogin; non-smoker; obesity (211 lbs); stimulant naive
(b) (6) CRF (REV) ECG **CC (?)** Comment: Protocol Violation Hospital records to confirm date of hospitalization during time when in study	47	M	36-36	36	Difficulty urinating (06/14-?); 10 days prior to baseline, hospitalized with persistent MDD (06/02-?), suicidal ideation (06/02-?) + alcoholism (06/02-?); moderate elevated systolic + diastolic BP + pulse (06/22-?); w/ ECG showing borderline LVH (Baseline)	H/O insomnia, **alcoholism, substance abuse**, MDD, anxiety, suicide attempt, recent 15 lb weight loss/on Citalopram 40 mg, Symbyax 5/20 mg, Trazadone 100 mg ,Celebrex, Ritalin QD; smoker X 30 yrs. on
(b) (6) CRF (REV) **CC** Comment: Protocol Violation Urine Drug Screen positive for canabinoids (pg. 24) Hospital records Needed No ECG's submitted	57	F	36-54	54	Headache (08/17); anxiety (08/28-09/12), agitation (08/28-09/12); muscle tenderness (08/28-09/12), heartburn (09/09-09/10), chest pains due to anxiety (09/10-09/11), severe chest pains (hospitalized)	H/O allergic rhinitis/Allegra; stimulant naive

Narratives for Subjects Who Discontinued due to Adverse Events (N=92)

(b) (6) CRF (REV-) No ECG	54	M	36-90	90	Baseline: 07/17-08/18. Final. Weight loss (14 lbs over 1 mth); irritability, agitation (08/10-08/13); jaw tightness (08/10-08/13) (reduce dose)	H/O GERD on Prilosec; hyperlipidemia; non-smoker; Atomoxetine
(b) (6) CRF (REV-) No ECG	18	M	36-54	54	Baseline: 10/06-10/27, Final Headache (10/07); anxiety (10/07)	H/O dyspnea on exertion; stimulant naïve
(b) (6) CRF (REV-) No ECG	24	M	36-72	72	Blurred vision (long distance); uncomfortable increased energy; fatigue	H/O IMN; non-smoker; stimulant naïve
(b) (6) CRF (REV-)	47	F	36	36	Baseline: 07/28-08/02. Final. Jitteriness; jaw tightness, neck	H/O **poylsubstance abuse**/MPH (last dose 4 days before baseline), Klonopin; smoker

No ECG Comments: Stopped shortly after Baseline					tension; headache	15 PPY; Ritali, Ritalin LA
(b) (6) CRF (REV-) ECG	32	F	36-54	36	Baseline: 08/14. Chest discomfort; musculoskeletal (08/08-09/06): persistent moderate headache (08/24-?): anxious feeling; irritable mood; daytime fatigue; w/ normal ECG's	H/O remote MDD, GAD, social anxiety, ODD, alcohol abuse; mild specific phobia; MPH 10 mg qid, Wellbutrin
(b) (6) CRF (REV-) ECG Comments: On drug from 09/13-09/17	30	F	36-36	36	Baseline: 09/13. Shortness of breath (09/14-09/18); insomnia (09/13-09/18): nervousness (09/14-09/18); nausea (09/13-09/18); w/normal ECG's	H/O MDD: Strattera
(b) (6) CRF (REV) ECG **CC**	65	M	36-90	72	Baseline: 08/08-Final, 11/14. Dizziness (08/08-11/10); dyspepsia (08/08-11/10); severe headaches (08/30-10/04, 11/07-11/11); fatigue (08/30-09/30); lightheaded-ness (09/03-11/10); moderate worsening hypertension (10/04-10/20): w/ premature ventricular systoles (Titration 2) + non-specific T abnormalities (Titration 4) [assoc/ w/ lightheadedness]	H/O HTN, tinnitus, hypercholesterolemia, type 2 diabetes, erectile dysfunction /Diovan (ACE inhibitor for HTN), glipizide (oral hypoglycemia agent) metformin, Vytorin (ezetimibe and simvastatin); Ritalin
(b) (6) CRF (REV-) No ECG Comment: Protocol Violation	48	F	36-90	54	Dry mouth; chronic back pain worsening (txed w prednisone); headache (08/29/06, 09/05-?); restlessness (09/01-?); insomnia; *paranoia* (09/01-?); 13 lb (5.9 kg) weight gain	H/O hyperthyroidism, insomnia/Fosamax (alendronate-osteoporosis, Restoril, depression on Lexapro; chronic lumbar back pain on Lortab (acetaminophen and hydrocodone), prednisone;Nuva Ring (oral contraceptive); *positive Baseline, Final Visit urine drug screen for benzodiazepine, opioids;* stimulant naive
(b) (6) CRF (REV-) No ECG CC (?) Comment: Stopped shortly after Titration 1	31	F	36	36	Nausea(08/18-08/26); worsening headaches (08/18-08/26); agitation (08/18-08/26)	H/O increased PR interval (ECG 06/09/06), headaches; stimulant naive
(b) (6) CRF (REV-) CC (?) No ECG Comment: Unscheduled ECG was done 09/28. Review ECG's and lab.	28	M	36-54	54	Baseline: 08/30-Final, 10/12. Worsening of headaches (08/31-09/02); insomnia; irritability (09/14-09/25, 09/28-10/02); jitteriness (09/15-10/02); restlessness (09/28-10/01); increased appetite; moderate memory impairment (09/28-10/03)	H/O hyperlipidemia, hypothyroidism, headaches, kidney stones; stimulant naïve Unscheduled Vist
(b) (6) NO CRF No ECG	29	M	NL	NL	URI; tension headaches; initial insomnia; euphoria; anxiety dry mouth; increased appetite	H/O migraines
(b) (6) CRF (REV-) ECG Comment: Stopped shortly	22	F	36	36	Nervousness; sweaty palms (09/11-09/16); increased energy (09/11-09/16); dry mouth; palpitations (09/11-09/16); increased pulse rate (106 bpm-Final Visit)[09/15-	Stimulant naive

after Baseline [9/08-09/15]					09/16]; mild elevated ALT (09/11-10/03): w/ screening ECG showing aberrant ventricular conduction	
(b) (6) CRF (REV-) ECG	43	M	36-72	72	Elevated heart rate; tachy-cardia (10/25); increased blood pressure [158/86] (dec dose), hypertension; deceased appetite; sweating; jitteriness; cold symptoms; w/ECG showing sinus tachycardia (10/25)	H/O heart murmur, nausea (resolved AE from Study 02-159), diarrhea (resolved AE from Study 02-159); obese (271 lbs): stimulant naive
(b) (6) CRF (REV-) ECG	50	M	36-72	36	Baseline: 08/24-Final, 12/14. Decreased appetite; dry mouth; difficulty breathing (09/03-10/01); p.m. fatigue; sweaty palms (dec dose), clammy palms [10/25-12/06]; mild systolic hypertension: w/ normal ECG's except for sinus bradycardia (Baseline, Final)	H/O dry mouth (resolved AE from Study 02-159), cold symptoms (resolved AE from Study 02-159), arterial malformation of brain; stimulant naïve; smoker 8PPY:
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Titration 1 [07/28-8/03]	45	M	36-36	36	Baseline: 07/27-Final, 08/23. Blurred vision (07/29-08/12); low libido (07/29-08/12); irritability (07/29-08/12)	H/O back pain on **hydrocodone; former alcohol dependence**; non-smoker; stimulant naïve 07/27 204
(b) (6) No CRF No ECG Comment: Review ECG	59	F	NL	NL	Constipation; nasal congestion, cough, sinus + ear + urinary tract infections, laryngitis; gum pains; anxiety; insomnia; *increased heart rate*; ulcers in upper intestine (tx w Protonix);	H/O psoriasis, intermittent migraines/Topamax
(b) (6) No CRF No ECG	24	M	NL	NL	Decreased appetite; insomnia; severe weight loss	H/O **former alcoholism**, muscular-skeletal swelling/**oxycodone, Versed (midazolam), fentanyl (opioid agonist)**, cephalexin, **propofol (sedative-hypnotic agent)**
(b) (6) CRF (REV) ECG CC	46	M	36-54	36	Baseline: 08/01-Final, 08/23. Headache (08/12); *elevated blood pressure* (08/22-23); *mild elevated QRS interval* (08/22); w/ ECG showing intraventricular block (Titration 2)	H/O MDD, heartburn, hyper-triglyceridemia/Zoloft, gemfibrozil (lipid lowering); dextroampheta-mine (stopped 08/05); *positive urine drug screen* for amphetamines on no prior stimulants
(b) (6) CRF (REV-) ECG Comment: Withdrew after baseline.	56	M	36-36	36	Baseline: 08/14-Final, 08/28. *Elevated blood pressure* (08/22-?), tachycardia [HR: 100 bpm, Final, 08/28)] (SBP 143) w/ obesity (233 lbs); w/ normal ECG's	H/O seasonal allergies on Sudafed; stimulant naïve; obesity (233 lbs)
(b) (6) CRF (REV-) No ECG Comment: Withdrew after baseline. Uncertain length of time on drug.	27	F	36	NL	Baseline: 08/28-Final, 09/07. Headache; *dizziness*; loss of appetite; euphoria	H/O Borderline anemia; stimulant naive
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Baseline	44	F	36	36	Baseline: 07/28-Final, 08/07. Lack of energy; persistent headaches	Non-smoker; Adderall

[07/29-08/05] (b) (6) CRF (REV-) Comment: Protocol Violation Substance abuse	46	M	36-90	54	Decreased appetite; insomnia; daytime sedation (06/10-09/04); blurred vision (07/15-09/02)	H/O back pain; stimulant naïve; *urine drug screen positive for canabinoids (Months 3)*
(b) (6) No CRF No ECG	35	F	NL	NL	Decreased appetite; anxiety; moderate weight loss	H/O migraine headaches on Excedrin
(b) (6) CRF (REV-) No ECG Comments: Normotensive during events Check lab, Review ECG	54	F	36-72	54	Baseline: 06/16-07/07. Lethargy (06/30-07/10); reduced appetite; muscle tension (07-07/09); *left arm numbness (07/07)*; dosed 72 to 54 mg (07/06)	Smoker 2PPY: Strattera
(b) (6) CRF (REV-) No ECG	42	M	36-90	72	Insomnia; dry mouth; nauseas; vomiting w + without bright red blood; sedation (dose reduce)	H/O gastric ulcer, headaches, head injury, Brights Disease/ *on Viocodin*; obesity (222 lbs): stimulant naive
(b) (6) CRF (REV-) No ECG Comment: Review ECG Stopped shortly after Baseline.	26	F	36	36	Baseline: 08/09-08/12; Final, 08/31. Increased heart rate (08/10-08/13); *dizziness* (08/10-08/13); decreased appetite (08/10-08/13); insomnia (08/10-08/13)	H/O bronchitis, occasional headaches, post-partum MDD: on Celexa for anxiety; monocycline for acne; stimulant naïve; non-smoker;
(b) (6) CRF (REV-) No ECG	31	F	36	72	Baseline: 08/16-Final, 09/06. Middle insomnia; blurred vision (08/17-09/05); decreased appetite; increased heart rate (08/21-08/24); anxiety (09/01-09/05); inattention (09/01-09/05)	Stimulant naive
(b) (6) No CRF No ECG	28	F	NL	NL	Moodiness; anxiety	
(b) (6) CRF (REV-) No ECG	48	F	36-90	90	Baseline: 09/11-Final, 10/25. Headache (09/12/06); nausea; dry mouth; sinus congestion	H/O hypertension on Vasotec; Strattera
(b) (6) CRF (REV-) No ECG	44	M	36-108	108	Baseline: 06/12-08/16. Muscle aches (08/09-08/15); sinusitis; gastroenteritis; agitation (07/13-07/23)	H/O Redman allergic reaction (vancomycin rx), hearing loss, tinnitus, vascular aneurysm (2004)/ASA; stimulant naive
(b) (6) No CRF No ECG	43	M	NL	NL	Headaches; stomach cramps; decreased appetite; anxiety attacks	
(b) (6) No CRF's ECG CC Comment: Review lab.	55	M	NL	NL	Stomach virus + URI; diastolic BP > 90 mmHg (reduce med), systolic blood pressure > 140 mm Hg; w/ ECG's showing sinus bradycardia (Baseline)+ non-specific T abn (07/07, 08/17) and possible ischemia (08/17)	H/O hypertension, low testosterone/Atenolol, hydrochlorothiazide, Diovan (ACE Inhibitor), Focalin, testosterone

(b) (6) No CRF's No ECG	45	M	NL	NL	Dry mouth; mood lability	On simvastatin
(b) (6) CRF (REV-) No ECG	36	F	36-54	36	Dry mouth; fatigue; headache; irritability; *discontinued for severe mood lability(10/12-10/26)*; exercise induced shortness of breath; decreased appetite	H/O musculoskeletal pain; stimulant naive
(b) (6) No CRF's No ECG	61	F	NL	NL	Insomnia; decreased appetite	H/O MDD, moodiness, hormone replacement therapy
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Baseline [09/16/06]	23	M	36	36	Decreased appetite; anxiety; confusion (09/16-09/17); sore joints	Stimulant naive
(b) (6) No CRF's No ECG	37	M	NL	NL	Anxiety	H/O tachycardia, headaches, poor sleep, jitteriness, edginess, irritability
(b) (6) CRF (REV-) ECG	58	F	36	36	Baseline: 08/14-08/31. Decreased sleep; *high blood pressure* (SBP 154: Titrat 1); w/normal ECG's	H/O lymphatic sarcoid, pulmonary sarcoidosis, chronic obesity (283 lbs), gastric bypass surgery, type 2 diabetes, headaches, decreased sleep; stimulant naive
(b) (6)	29	F	NL	NL	Anxiety; tiredness	H/O ulcerative colitis, high platelet count, anemia panic attacks, anxiety/prednisone, Imuran asacol-sulfasalazine
(b) (6) CRF (REV-) ECG CC	33	M	36-72	72	Increased diastolic (DBP: 90-Titrat 2) + systolic (SBP: 156-Titrat 1) blood pressure; morning sleepiness; URI; w/ ECG's showing non-specific ST abnormality (Baseline, Final) w premature atrial systoles w/ later increased ST-T depression (09/22)	H/O esophageal reflux, heartburn, headaches, insomnia, frequent sinus infections/Benadryl; obese (254 lbs): Ritalin, Concerta, Strattera
(b) (6) CRF (REV-) No ECG Comment: Review ECG	36	F	36-108	90	Baseline: 05/26-Final, 09/20. *Decreased exercise tolerance* [07/30] (dose reduce); insomnia (tx w lorazepam); pharyngitis: 9 lb wt loss over 4 mths	H/O recurrent oral herpes, sinus headaches, sleep difficulties/ Keflex, Tylenol PM, Ritalin, Zorivax; stimulant naive (pg. 22) but concomitant meds lists prior use of Ritalin
(b) (6) CRF (REV-) ECG CC Comment: Pg. 15 Stopped shortly after Baseline [06/9-06/14] Pg. 17: "two episodes of tachycardia lasting over 2 min"	38	M	36	36	Baseline: 06/07-Final, 06/14. Tachycardia (76-82 bpm: Final Visit)[06/09-06/12]; elevated diastolic blood pressure [06/14-06/26] w/ ECG's showing non-specific T abnormality (Baseline, Final]	H/O headaches; smoker 11PPY; obese (239 lbs); stimulant naive
(b) (6) CRF (REV-) ECG Comment: ? Protocol	33	M	36	72	Baseline: 05/30-Final, 06/22. Elevated diastolic blood pressure (DBP: 99: Titration 2); tachycardia (111 bpm : Titration 2); w/ ECG showing sinus tachycardia (106/min) [06/130	MPH on Screening ; *positive drug screen for amphetamine; prior Adderall on Concurrent medications*

(b) (6) CRF (REV-) No ECG	42	F	36-90	72	Baseline: 05/26-Final, 12/15. Decreased appetite; fever, swollen lymph nodes; constipation, nauseas, epigastric burning; weight loss (9 lbs over 4.5 mths); increased pulse rate	H/O hypothyroidism, Hodgkin's Lymphoma, headaches, insomnia, anxiety on Lexapro; hypothyroidism on Synthroid, prior *hydrocodone for back pain*, Allegra; stimulant naïve
(b) (6) CRF (REV) No ECG CC (?) Comment: Review ECG	40	F	36-108	72	Insomnia; numbness (back, shoulder, upper arms) [07/30-?]; tense feeling (08/03-08/28), jitteriness; tachycardia [120 bpm: Mth 2] (dose reduce); dizziness; sinus infection; weight loss of 12.5 lbs (5.7 kg) over 2 mths	H/O hypercholesterolemia, asthma on albuterol; estradiol; stimulant naïve
(b) (6) CRF (REV) ECG Not Submitted CC	41	F	36	36	Baseline: 06/15-Final, 06/29 *Moderate abnormal ECG* [ECG possible anteroseptal infarct] (06/15-06/29)	H/O muscular pain in chest; obesity (285 lbs); stimulant naive
(b) (6) CRF (REV-) No ECG	50	M	36-90	90	Jitteriness, anxiety; insomnia	H/O hypercholesterolemia; stimulant naïve
(b) (6) CRF (REV-) No ECG	38	F	36	36	Increased pulse rate; nervousness; insomnia; nausea	H/O hypothyroidism on Synthroid; stimulant naïve
(b) (6) CRF (REV-) No ECG Comment: Review ECG	27	F	36	36	Cold symptoms; unknown pain (tx Tylenol w codeine-?); persistent tachycardia (HR: 121: Mth 1)	H/O tinnitus, hearing loss; smoker 10 m PPY: Cylert, Ritalin
(b) (6) CRF (REV-) No ECG Comment: Review ECG	39	F	36-72	72	Cold; sleep disturbance; tachycardia (102 bpm: Mth 1)	H/O Chronic back pain; Ritalin, Focalin
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Baseline [05/30-06/01]	46	F	36	36	Insomnia; nervousness; restlessness, frenzied feeling; decreased appetite; constipation	H/O MDD on Lexapro; night sweats, night time awakening; allergies on Flonase, Claritin, Sudafed; Ritalin; Adderall XR
(b) (6) CRF (REV-) ECG Comments: Protocol Violation	54	F	36	72	Baseline: 08/15-Final, 09/12. Increased blood pressure (SBP: 142. Titration 1 w/ SBP 144 Screening); anxiety; insomnia, nightmares; decreased appetite; hot flashes; w/ normal ECG's	H/O insomnia on Ambien, Fernhrt; baseline drug screen positive for benzodiazepines on no concomitant benzodiazepines; stimulant naïve
(b) (6) CRF (REV-) No ECG	35	F	36	36	Headaches; anxiety; dry mouth; stomach pain	H/O tension headache; asthma on Albuterol; stimulant naïve
(b) (6) CRF (REV-) No ECG	28	F	36-54	NL	Intermittent headaches; severe hyperactivity (dose reduce); hyperfocused	H/O finger lesions (possible Raynaud's); Strattera, Adderall
(b) (6) CRF (REV-) No ECG	52	F	36-90	72	Dry mouth	H/O migraines/Excedrin Migraine, Imitrex; Adderall XR
(b) (6) CRF (REV) ECG	33	F	36	36	Baseline: 05/16-Last Dose, 05/19. Abnormal ECG (First Degree AV Block, prolonged PR Interval)	H/O lumbar spine stiffness; txed w/ MPH, Concerta

CC (?) Comment: Appears to be screening failure. Uncertain if subject received first dose.						
(b) (6) CRF (REV-) No ECG Comment: Unscheduled ECG 09/13 Check ECG	19	M	36-72	72	Baseline: 08/14-Final, 11/14. Decreased appetite; muscular pain (both shoulders) [08/28-09/01]; irritability (08/30-?); headache (09/06/06); hand tremors (09/18-?):	Stimulant naïve
(b) (6) CRF (REV-) No ECG Comment: Review lab.	57	M	36-108	108	Subdural hematoma (11/02) w/ last visit prior to SDH (Mth 2: 02/10) w/ tx (11/18) w/ Final Visit (11/28)	H/O asthma; Adderall
(b) (6) CRF (REV-) No ECG Comment: Under Hx.	24	M	36-90	90	Baseline: 09/18-Final, 11/06. Cold, flu (10/02-10/09); intermittent headaches (10/02-11/03); nausea (10/02-11/03); decreased appetite	Stimulant naïve Comment: Second Pharmacy given to patient for Titration 3 visit. Pharmacy card # (b) (6) Second Pharmacy card given to patient for TV4 # (b) (6)
(b) (6) CRF (REV-) No ECG Comment: Review ECG	28	M	36-54	36	Baseline: 08/22-Final, 09/21. Elevated pulse (Pulse: 110 bpm: Titration 2) [09/07-?]	H/O situational MDD on Lexapro; Concerta (past)
(b) (6) CRF (REV-) No ECG Comment: Unscheduled ECG: 09/19	40	M	36-108	72	Irritability; insomnia; depressed mood; elevated SBP (141: Mth 3)	H/O migraines, high lipoprotein; smoker 10 PPY
(b) (6) CRF (REV-) ECG	23	M	36	36	Irritability; increased blood pressure (SBP: 150, Final Visit); w/ normal ECG's	Concerta
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Baseline [08/04-08/08]	36	M	36	36	Baseline: 08/03-Final, 08/10. Anxiety (08/04-08/09); paranoia (08/04-08/09); insomnia (08/09); decreased appetite	Adderall, Strattera
(b) (6) CRF (REV-) ECG CC?	41	F	36-54	54	Restless sleep; decreased appetite; alopecia (07/16-07/30); lightheadedness (10/15-?); palpitations (08/19-08/25); insomnia; tachycardia (HR: 98: Mth 5, 11/13); 10 lb wt. loss over 7 mths; w/ normal ECG	H/O Headaches; Strattera
(b) (6) CRF (REV-) ECG	59	F	36-36	36	Nervousness; insomnia; elevated blood pressure (SBP: 161: 07/28); decreased appetite; 4 lb wt. loss over	Stimulant naïve

					5.5 wks; w/ ECG showing shortened PR interval w/ accelerated AV conduction (Baseline) 6/30 w/ normal subsequent studies; 4 lb wt. loss over 5.5 wks	
(b) (6) CRF (REV-) No ECG Comment: Review labs, ECG	19	F	36-54	54	Baseline on 09/29 then, fever (10/04-10/05); sleep difficulties(10/08-10/23); headache (10/09-10/23); blurry vision (10/10-10/23); 2.4 lb wt. loss over 3.5 weeks	H/O Gastroesophageal reflux on Prevacid; asthma on Advair, albuterol; MDD on Lexapro; Cyclessa (birth control); stimulant naïve
(b) (6) CRF (REV) ECG CC Comment: The occurrence of the tachycardia on other days and the ECG abnormalities, and the weight loss was not mentioned in the narrative	27	F	36-54	54	*Tachycardia* (09/12-09/20); *stress* (09/12-09/20), *anxiety* (02/18/07); *palpitations* (02/18/07). Tachycardia was also present mth 3 (11/13) [97-99]. Mth 4 (12/13) [102]. Mth 5 (01/11) [95-99]. ECG's were normal except for the Final ECG (02/23) showing a broad QRS, intraventricular block. There was a 14 lb wt. loss over 5 mths.	H/O allergies on Claritin-D, Flonase; Ortho Tr-Cyclen Low; Concerta (prior), Wellbutrin, Strattera
(b) (6) CRF (REV-) No ECG Comment: Review labs, ECG	42	F	36-36	36	Baseline was on 08/16/06. Poison ivy (tx prednisone); blurred vision (08/18-?), dry eyes (12/02-?); headache (08/30/06); anxiety attacks (09/10-?); carpal tunnel syndrome (11/01/06); stiffness of fingers + neck (09/05-?); insomnia (09/04-?) 4 lb wt. loss over 6 mths	Strattera
(b) (6) CRF (REV-) No ECG Comment: Stopped shortly after Baseline [08/16-08/24]	41	M	36-36	36	Baseline (08/16). Aggression (08/18/06); 3 lb wt loss over 8 days Comments: Pg. 17: "Subject had one single episode of moderate aggression that was possibly related to study drug."	H/O headaches; wt (231 lbs): stimulant naïve
(b) (6) CRF (REV-) No ECG	43	M	36-54	36	Exacerbation of rosacea (dose reduce) [10/13-10/18]	H/O basal cell Ca, ressected; stimulant naïve 08/01 181
(b) (6) CRF (REV-) No ECG Comment: Txed 09/29-10/09. Sponsor's comments indicate "took meds 10/7-10/9."	44	M	36-54	54	Irritability (10/02-10/03); headache (10/03-10/04); distressing thoughts + sensations (10/10-10/11)	**H/O poly-substance abuse (alcohol, cocaine, heroin, marijuana)**, elevated thyroid; Ritalin, Strattera 216 09/29
(b) (6) CRF (REV) ECG CC	25	M	36-54	54	Baseline (07/26) *Lightheadedness* (07/27-08/09, 08/16-08/17); *palpitations* (07/28, 08/04); headaches (07/29); nervousness (07/28-08/01, 08/03-08/09), anxiety (08/09-08/18); decreased appetite; dry mouth, gingivitis; w/ECG's	H/O hypothyroidism, headaches; Ritalin

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/s/

Glenn Mannheim
4/29/2008 06:10:22 PM
MEDICAL OFFICER

Mitchell Mathis
6/5/2008 03:17:25 PM
MEDICAL OFFICER
See my Memo to File

Review and Evaluation of Information
NDA 21-121 SE5-017

Sponsor:	Johnson and Johnson Pharmaceutical Research and Development; Alza
Drug:	OROS® (methylphenidate HCL) Extended-Release Tablets
Material Submitted:	SNDA Application for Adult ADHD
Related NDA's:	# 21-121: Approved for ADHD in children (6 -12 years): 08/2000.
Approved Doses:	18, 27, 36 and 54 mg
Correspondence Date:	08/31/2007
Pre-NDA Meeting:	03/13/2007
Filing Meeting:	10/24/2007

I. Studies Submitted

The sponsor has submitted the following two (2) Phase III trials in adults with ADHD:

Study 02-159: A Placebo-Controlled, Double-Blind, Parallel-Group, Dose-Titration Study to Evaluate the Efficacy and Safety of CONCERTA® in Adults With Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day

- This was a 7 week randomized, placebo-controlled, double-blind, parallel-group, ***dose-titration study*** in ***226 adults*** with ADHD (18 - 65 yrs) randomly assigned to one of two groups: placebo (n=116), or CONCERTA (n=110). Subjects were titrated in 18 mg increments on a weekly basis to either 36, 54, 72, 90, or 108 mg once daily) based on a 30% improvement in baseline Adult ADHD Investigator Symptom Rating Scale (AISRS) score and a Clinical Global Impression (CGI) of much improved or very much improved (2) or titration to the maximum dose of 108 mg (35 day titration period with minimum of 16 days at maximum dose). The primary efficacy variable was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit (two weeks after Titration Visit 5) or the last score provided during the study.

  71 subjects on Concerta (65 %) completed the study compared to 90 on placebo (78 %). The number of subjects withdrawing on Concerta was 42 vs. 26 on placebo, with adverse events resulting in discontinuations in 16/42 (30 %) of Concerta subjects vs. 6/26 (23 %) on PBO, with one

additional subject having a serious adverse event prior to baseline. There were 34 cardiovascular adverse events of interest (Drug: 19; PBO: 15) and 5 psychiatric adverse events of interest (Drug: 5). The disposition of subjects by final dose is shown below:

Table 8-1: Disposition of Subjects by Final Dose - All Randomized Subjects

Outcome	CONCERTA 36 mg N=39 n (%)[a]	CONCERTA 54 mg N=16 n (%)	CONCERTA 72 mg N=19 n (%)	CONCERTA 90 mg N=16 n (%)	CONCERTA 108 mg N=23 n (%)	All CONCERTA N=113 n (%)	Placebo N=116 n (%)
Completed Study	18 (46.2)	8 (50.0)	16 (84.2)	11 (68.8)	18 (78.3)	71 (62.8)	90 (77.6)
Withdrawn[b]	21 (53.8)	8 (50.0)	3 (15.8)	5 (31.3)	5 (21.7)	42 (37.2)	26 (22.4)
Withdrawn due to an Adverse Event	6 (15.4)	5 (31.3)	1 (5.3)	2 (12.5)	2 (8.7)	16 (14.2)	6 (5.2)

Sponsor's Figure of Subject Disposition is included in the Appendix.

Identifiable deficiencies are identified in the next section.

Study 42603ATT3002 (3002): This was a randomized, placebo-controlled, double-blind, parallel-group, five-week ***fixed dose***-response study, involving 4 doses (18, 36, or, 72 mg; or, PBO), followed by a seven-week open-label flexible dose (18 to 90 mg) phase in 401 subjects (18-65 yrs) with adult ADHD. The 401 subjects were randomized in the double blind portion of the study into the PBO (n=96), 18 mg (n=101), 36 mg (n=102), and 72 mg (n=102).There were 34 AE resulting in discontinuation, of which, 8 were serious. Of these, 15 occurred during the double blind, and 19 occurred during the open label phases of the trial. The primary efficacy criterion was the change in the sum of the inattention and hyperactivity/ impulsivity subscale scores of the investigator-rated Conners' Adult ADHD Self-Report Short Version (CAAS) from baseline at the end of the double-blind phase (end of 5 weeks or last post-baseline assessment). Doses for the 7 week, open-label extension were 18-90 mg.

In addition the above two (2) phase 3 studies; the sponsor has submitted the following open-label experience(s):

Study 12-304: This is the one-year open label study which was to include subjects who have successfully completed Study 02-159 and new subjects, who were washed out from their previous ADHD medication and titrated to an effective dose of drug (36-108 mg). It was to consist of 560 subjects. The study began on 05/08/2006 with 02/21/2007, as an

interim cut-off. An interim analysis is provided for all subjects enrolled from 05/08-09/08/2006, the first 4 months of the study, or who discontinued the study before 12/20/2006 (7 months). Sponsor's figure 1 (Disposition of Subjects) is pasted in the Appendix of this review. It indicates. There have been a total of 358 subjects who have received Concerta with 161 subjects on-going. To date, there have been 98 discontinuations due to adverse events, of which 6 were serious AE's.

Study C-99-018-00 (submitted and reviewed in S-008, approved October 21, 2004) was an open-label 9 mth study at doses of 18, 36, or, 54 mg of drug in 136 patients older than 18 years (18-35 yrs: 58; 36-49 yrs: 57; and 50-66 yrs: 21). There were 15 adverse events resulting in discontinuation.

Study CON-CAN-4 was a 30 day open label pilot study in 32 adults (19-54 yrs, mean 36 yrs) with ADHD receiving doses from 18-72 mg and which was conducted in Canada.

The following post-marketing analysis of information was submitted:

Cumulative Review of Spontaneous Adverse Events in Adults Receiving Concerta Through 28 February 2007

II. Identifiable Deficiencies

Study 02-159:

In accordance with CFR 314.50(f)(3) please submit to the Division, the following "additional case report forms.. needed to conduct a proper review of the application":

Page 2468 of your Clinical Study Report identifies Case Report Forms available on request (Appendix). Case Report Forms were submitted for some of these cases, however, the cases identified in yellow highlight could not be located. Please submit.

All subjects identified in your submission with cardiovascular and psychiatric events of special interest, are to include case report forms. As part of the cardiovascular CRF's [e.g's: 30-009 (abnormal ECG with possible MI), 106-016 (premature atrial complexes), tightening of the chest (110-015); sweating, chest pain

(110-011), prolonged QRS interval (120-004) etc.] attach copies of all ECG tracings for all visits, to which should be attached a copy of your cardiologist's interpretation for each individual ECG. If any work-up was done for any adverse event (either at the study site) or by outside medical practitioner provide copies and results of studies and work-up which was performed.

Many narratives for subjects with discontinuations, cardiovascular adverse events of interest and special interest are difficult to interpret and should be modified as follows as it relates to the description of the following adverse events:

- blood pressure (e.g. elevated, increased, increased systolic and, or, diastolic, or, mild diastolic blood pressure greater than 90, etc) with and without modifiers (e.g. mild or moderate, etc)should include baseline blood pressures and other vital signs, and actual blood pressures and vital signs at the time of the adverse event, and changes from baseline;

-heart rate and, or, pulse (e.g. increased), mild heart rate greater than 100, tachycardia, etc. should include baseline heart rate and other vital signs, and actual heart rate changes at the time of the adverse event;

-palpitations (mild), heart flutter (mild) should include the actual symptom, diagnosis and any studies done, and the results of those studies;

-abnormal ECG, mild premature atrial complexes, moderate QRS interval, etc. should include the specific ECG abnormalities, changes from baseline, and the cardiologist's interpretation of the ECG study;

-breathless feeling, increased respiration, shortness of breath (mild, moderate), etc., should include baseline and respiratory rate at the time of the event, and change in respiratory rate, and any associate symptoms, and, or work-up performed to evaluate those symptoms;

-tightening, tightness of the chest (mild, moderate), chest tightness with neck tension, intermittent chest pain, chest pain (mild, moderate), arm pain, stomachache, muscle aches etc., provide a precise description of the symptoms

(anatomical location, presence or absence of radiation, duration, etc) and associated signs (e.g. diaphoresis) and vital signs, and include any work-up and results, by the study site or outside provider;

-dizziness should include a clear description of the event (e.g. duration), presence or absence of other associated symptoms or findings (e.g. nystagmus, etc) and vital signs at, or near the time of the event;

-headache: mild, moderate; if possible, provide a description of the event, history of prior headache, differences in headache characteristics, changes in vital signs at or near the time of the event (e.g. increased heart rate or blood pressure);

-vision: blurred, eye hemorrhage, scintillating scotoma, provide a more accurate description and work-up performed;

For all narratives with elevated or abnormal laboratory tests (e.g. hyperlipidemia, high cholesterol, elevated fasting blood sugar, elevated ALT, GGT, etc) identify the lab value obtained, and the normal range for the patient age and sex).

For all narratives which state weight gain or loss, describe the baseline weight and changes at the time of the adverse event. For adverse events using the term decreased appetite, identify whether or not there was weight gain or loss associated with that event.

For all narratives with skin rashes (e.g. hives) describe the characteristics, location and associated symptoms with the rash.

For all narratives with psychiatric adverse events of interest, provide the subjects baseline and end of study Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D).

The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered at the Baseline Visit to identify significant psychiatric co-morbidities that would exclude the subject. Your schedule of events (Table 7-4) indicates these tests were repeated at the Final or Early Termination Visit. These results could not be identified in the Clinical Study Report.

Provide the results of the secondary efficacy analysis for the Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) and include an outlier analysis.

For all narratives, identify whether the subject had or had not prior treatment with stimulants, the titration schedule for that subject, and the dose at which each adverse event occurred, and what if any actions were taken.

Table 12-40, entitled lists subjects with an abnormal ECG finding in the safety population. Identify whether there was they any clinical correlations at or near the time of these abnormal findings, and if so, where a description of these events can be found?

Page 2471 of your Clinical Study Report identifies Patient Profiles available on request (Appendix). Please submit.

Study 42603ATT3002 (3002):

For the following subject vignettes, please describe or provide the following information:

A10282: the vital signs at time of, or around about the onset of headache, fatigue, and lethargy and the presence of weight loss, if any, with the decreased appetite;

A11047, please provide the interval examinations (office notes) between visit 6 and 7. The basis for the dose adjustment is not apparent since there are no vital signs or CRF notes between Visits 6 (02/09/06) and Visits 7 (02/22/06) when the subject developed adverse events and there was dose adjustment. Provide interval physical and neurological examinations, if done (at the study site), or, by a private practioner during the open label and within several weeks of discontinuation from the study. Provide any work-up or studies done to characterize the subject's paresthesias.

A10061 identify the laboratory studies and the results for the symptoms of stomach-abdominal pain. Provide vital signs temporally associated with these symptoms and ECG's around the time of the tachycardia? Provide interval vital signs.

A10701 provide the vital signs, laboratory studies, and, or other information available at baseline and in relationship

to the adverse vents of headache and nausea. If any additional studies were done to evaluate please provide.

A10791 provide vital signs, laboratory studies, and, or other information available at baseline and surrounding the adverse events of recurrent syncope.

A10253 provide translated copies of the following hospital records: admission, discharge summaries, consultant reports, ancillary testing done, and copies of the scans.

A10885 provide translated copies of hospital records: admission, discharge summaries, consultant reports, and any ancillary testing which was done.

A11086 provide translated copies of hospital records: admission, discharge summaries, consultant reports, and any ancillary testing which was done. Did the subject develop hypertonia, as stated? If so, what were the symptoms? Provide vital signs, laboratory studies, and, or other information available at baseline and in relationship to the adverse events.

A10034 identifies a subject with an episode of hypertension who developed persistent vertigo, hypoacusia, tinnitus and nystagmus for which an MRI was apparently performed on 01/25/06. Provide a translated copy of the imaging report and the scan. If you have consultant reports or any other ancillary testing which may have been performed, please provide.

A10123 identifies a subject with an episode of hypertension who developed persistent vertigo, hypoacusia, tinnitus and nystagmus for which an MRI was apparently performed on 01/25/06. Provide a translated copy of the imaging report and the scan. If you have consultant reports or any other ancillary testing which may have been performed, please provide.

A10804’s CRF’s only describe the adverse event of delusion of reference; however, the CRF’s indicate the following additional adverse events: dry mouth, polyuria, polydypsia, perspiration, and problems concentration, problems with memory, depression, uneasiness, paresthesias, diarrhea and loss of libido. Redo this CRF with a complete listing of the adverse events, and provide assurance that all adverse events have been recorded. Provide vital signs, laboratory

studies, and, or other information available at baseline and in relationship to the adverse events, and provide a copy of any work-up performed to further characterize these adverse events.

A10940 describes the adverse events of tachycardia, but fails to provide baseline vital signs, and vital signs occurring at the time of the adverse events. Provide copies of baseline and ECG's occurring at the time of the event(s).

A10180 describes the adverse event of increased rebound phenomenon. What is it, and how was it characterized and evaluated? Provide pertinent information.

A10194 indicates that the subject developed a tension headache, visual field constriction (subjective), paralysis of accommodation (the term, reduced visual acuity was crossed out), and increased arterial hypertension (130/90 mm Hg: standing at V5). No information is contained in these CRF's about the basis for the determination of paralysis of accommodation and visual field constriction, and what diagnostic procedures were done, if any. The CRF's indicate that the subject withdrew informed consent, a fact not noted in the vignette. Provide all vital signs for each visit, lab studies, etc. at the time of each adverse event.

A10296 indicates that the subject developed tachycardia. Indicate the dates for this adverse event, baseline and event related vital signs, and changes in heart rate which occurred.

A10298 indicates that the subject developed palpitations, Identify vital sign and ECG changes, if any which occurred at the time of this adverse event.

Review concomitant medications allowed. Psychiatric hospitalization discharge summary. Discuss disallowing patients who received periodic psychiatric hospitalizations.

A10650 indicates that the subject developed erectile dysfunction for which he left the study. However, review of the CRF's indicates that following additional adverse events: tachycardia, hypertension, weight loss, nausea and upset stomach. This vignette should be re-submitted. Vital signs and, or abnormal laboratory studies including ECG

occurring around the time of each adverse event should be noted. All adverse events should be noted in the final adverse event tabulations. The sponsor should provide a review of the post-marketing AERS cases of sexual dysfunction, to which, the term should include impotence.

A10472 indicates that the subject developed depression for which he was treated with venlafaxine. Review of the CRF indicates that the depression occurred with suicidal thoughts, and that additional adverse consisting of decreased appetite and sweating were present. This vignette should be re-submitted with corrected information. Additional information about the suicidality should be provided.

A10788 indicates that the subject developed hypertension, severe headache and was hospitalized and diagnosed with a temporal arteritis. Provide translated copies of the hospital admission note, discharge summary, and any diagnostic testing performed. What was the basis for the diagnosis of temporal arteritis? What is the basis for the investigator's determination that the subject had Horton's syndrome at the time of enrollment? The CRF's indicates the following additional adverse events (not identified in the vignette) were identified at screening based upon laboratory abnormalities: hypetriglycidemia, hyper-cholesterolemia, high ALT and GT (however, these numbers are not given in the CRF's). Additionally, the CRF's indicates that a worsening blood pressure occurred with a rapid heart rate. These events are not identified in the vignette. A complete vignette with all the supporting information and all the additional information requested should be provided.

A10801 indicates that the subject had an abortive migraine, developed vertigo and an unspecified visual disorder. Information about vertigo and an unspecified visual disorder could not be identified in the CRF's. A description of the event is not contained in the CRF's, except for remarks dated 2 days after the event ([redacted] (b) (6)) where it is noted "got hospitalized, CAT revealed old small lesion nothing current." Information contained in the sponsor's vignette indicates "CCT: probable lacunar infarct (11 mm) in caudate nucleus with slight expansion of the frontal horn of the right lateral ventricle". However, this information is not contained in the CRF's. The sponsor should provide a translated copy of the imaging study

report with a copy of the scan. Copies of any consultative reports or ancillary studies done in relation to these adverse events should be provided. A complete vignette with all the supporting information should be provided by the sponsor.

A11006 provide translated copies of the hospital admitting and discharge summaries.

Study 12-304:

The sponsor stated in the 03/13/2007 pre-sNDA meeting that this study would consist of 560 subjects and that there would be 200 subjects exposed for at least 6 months. The current submission is 358 subjects with 161 subjects still in the study at 4 months. It seems a little short of the defined exposures. Subjects from Study 02-159 were to be washed out and titrated to a new effective dose in this study. No information could be identified in the CSR of the number of subjects who continued on from study 02-159.

CRF's could not be located for the following 19 subjects who discontinued from the study for different reasons. A majority of them have cardiovascular symptoms of concern. In accordance with CFR 314.50(f) (3) please submit to the Division, the following "additional case report forms.. needed to conduct a proper review of the application". In addition, provide copies of all ECG tracings for these subjects including the cardiologist's interpretations. Narratives on these subjects should be re-submitted indicating titration schedule and dose at the time of the adverse events, baseline and vital signs in relation to the adverse event, baseline laboratory and laboratory studies done at the time of the adverse event(s), ancillary testing done to further evaluate the adverse event(s), and if hospitalized or seen by a specialist or other practioner, a copy of hospital admission, discharge, consultant notes, and, or, hospital studies done, or, practioner notes or consultants obtained.

Narratives with Subject Discontinuing for Different Reasons (N=19)

LOE=Lack of Efficacy (N=5)

102-109** CRF's Missing	20	F	NL	NL LOE	Increased heart rate; temporal perception distortion; chest (muscular) + shoulder + stomach + jaw + pharyngeal discomfort (dose decr) ; headache; increased energy; decreased appetite; jitteriness; nausea; dizziness	H/O remote alcohol abuse/Levora (oral contraception)/Yasmin
102-112** CRF's Missing	28	M	NL	NL LOE	Headache; episodes of chest muscle discomfort; uncomfortable increased energy with coffee; dry mouth	H/O shoulder discomfort (rare), headaches
106-104** CRF's Missing	51	F	NL	NL LOE	Premature ventricular contractions; dry mouth; decreased libido; persistent orange discoloration of hands; insomnia; URI (tx w/ Zithromax); dry mouth	H/O smoker (20 PPY)l seasonal allergies, mitral valve prolapse; systolic ejection murmur, chronic sinusitis, obesity, GERD/Premarin, Cozaar (ACE antagonist), Nexium, Claritin (loratadine)
219-106** CRF's Missing	60	M		LOE	Dizziness, lightheadedness; mild elevated QRS interval (dose reduc); headache	H/O hypercholesterolemia/Lipitor, Lexapro
226-123** CRF's Missing	37	F		LOE	*Dizziness*; sinus congestion (tx w Z-Pac); *muscle weakness (work-up done); increased pulse (dose reduce); mild chest tightness (ischemia)* (evaluation done); anxiety	H/O seasonal allergies, sinusitis, headaches, anxiety/Celexa

NCD= Noncompliant Dismissal (N=2)

109-106** CRF's Missing	39	F	NL	NL NCD	Nausea; poor appetite; *muscular chest tightness*; body tremor episodes; URI	H/O smoker (17 PPY), recurrent sinusitis Hepatitis C, genital herpes, insomnia, previous polysubstance abuse/Isotonix (vitamins).Trazadone
214-100** CRF's Missing	53	M		NCD	*Chest muscle tightness*; severe headache	H/O low WBC

LTFU=Lost to Follow-Up (N=6)

118-007** CRF's	60	F	NL	NL LTFU	*Increased blood pressure* (dose reduc); URI (tx w	H/O increased CRP-HS, hypertension, hiatal hernia,

Missing					Sudafed); *depressed mood*	headaches/Zoloft, Diovan (ace inhibitor), Prilosec
119-103** CRF's Missing	24	M	NL	NL LTFU	Jitteriness; *tightening of the throat*	
203-110** CRF's Missing	44	M		LTFU	*Jaw clenching*; lethargy (dose reduc); irritability; *elevated diastolic blood pressure*	H/O sleep apnea
208-101** CRF's Missing	31	F		LTFU	Decreased appetite; anxiety; *fatigue*; vomiting; insomnia; headaches; *elevated blood pressure*; *palpitations*; recurrent URI with sinusitis, bronchitis (tx w Drixoral, Theraflu-Chlorpheniramine, Dextromethorphan hydrobromide, Pseudo-ephedrine hydrochloride), Dayquil (Acetaminophen, Dextromethorphan HBr Phenylephrine Nyquil, Zicam)	H/O psoriasis/taclonex cream
214-104** CRF's Missing	30	M		LTFU	Insomnia; *chest muscle tightness*	H/O seasonal allergies, seboriasis, high VLDL
221-103 CRF's Missing	26	M		LTFU	*Increased pulse;* right flank pain (tx w Dilaudid), renal calculi excretion w resolution of flank pain); initial insomnia; nausea (tx w phenergan); *diastolic blood pressure increase (94 mm Hg)* (dose reduce); *shortness of breath; palpitations; lightheadness*; rash (tx w Benadryl); restlessness	H/O URI, back pain/Tylenol # 3
SW=Withdrawn At Subject's Request (N=6)						
131-100** CRF's Missing	48	F		SW	*Hypertension* (dose reduce, tx w hydrochlorothiazide + benazepril (lotensin))	H/O eczema/Ortho Tri-Cyclen Lo
131-103 CRF's Missing	53	F		SW	Dry mouth; restlessness; *racing feeling*; severe decreased sleep; depression; worsening of asthma; decreased appetite	H/O allergies, hyperlipidemia, asthma/Claritin-D, Advair, Lipitor

210-102** CRF's Missing	19	F	SW	Rhinitis; moderate *cardiac awareness*; *headache*; restlessness (dose reduce)	H/O allergic rhinitis, irregular menstrual periods/Zyrtec, Microgestin
219-101** CRF's Missing	61	F	RTR SW	*Stomachache; heart pounding*; fatigue; cough (tx w Zyrtec), cold	H/O sarcoidosis, sleeping difficulty/Ambien, Lexapro, Cortisone
226-110** CRF's Missing	46	M	SW vs. IW	*Headache; backache; mild abnormal QTC ECG*	

Definition of Abbreviations: LTFU=Lost to follow-up; NCD= Noncompliant Dismissal; LOE=Lack of Efficacy; SW=withdrawn at subject's request; IW= Investigator Withdrawn; Refused to Return=RTR

All CRF's for Study 12-304 should be resubmitted with the following additional information for each subject: the drug titration schedule and dose at the time of each adverse event; baseline vital signs and available, vital signs occurring at, or, proximal to the time of each adverse event; baseline and abnormal laboratory studies for each subject identified as having an adverse event of laboratory studies (e.g. elevated ALT, GTT should be substituted with the abnormal values, the normal range, and the change from baseline); and all laboratory or ancillary studies done to evaluate the adverse events; ECG's should be appended to the CRF's of all subjects with cardio-vascular adverse events of interest with a copy of the cardiologists interpretation appended to each report.

III. Recommendations

1. A non-fileable action is recommended based upon the deficiencies identified above which relate to the following:

- The number of remaining subjects in Study 12-304, is 161 at 4 months, short of the 200 subjects which the sponsor stated would be exposed at 6 months.

- Subject narratives are lacking interpretable information and CRF's are missing for subjects with potentially significant adverse events preventing adequate review of this sNDA [314.50(f)(3)].

2. Should a decision be made to file this sNDA, Advisory Committee Recommendations input is recommended as it relates to the safe use of stimulants in the adult population. This is based upon a preliminary review of

the adverse events resulting in discontinuations in this submission has identified serious adverse events (strokes in 2 subjects, a possible TIA in another subject, and a case of temporal arteritis). To date, there have been 4-5 cerebrovascular events only occurring in subjects on stimulants (double-blind and, or open-label) but not on placebo in the following adult stimulant sNDA: N 21-303 S005, (b) (4) Adderall XR; (b) (4); and the current submission NDA 21-121 SE5-017. This imbalance in adverse events may not be too dissimilar to the experience with Zelnorm (Tegaserod) which required a meta-analysis to identify the occurrence of coronary ischemic events. A consult from OSE on this issue is requested.

3. An updated review of AERS data for marketed safety experiences for stimulant therapy in the adult populations [e.g. death, sudden death, cardiovascular SAEs (including stroke)] from DRE's review(Gelperin, 04/27/2004 is recommended. There has been 3.5 years of subsequent exposure in the adult population to stimulants. A consult from OSE should be obtained.

4. A consult is requested from OSE as it relates to the sponsors review, entitled: Cumulative Review of Spontaneous Adverse Events in Adults Receiving Concerta through 28 February 2007.

5. A consult is requested from the cardio-renal group as it relates to the interpretation of the cardiovascular adverse events of interest identified by the sponsor.

6. In an attempt to provide adequate labeling for this heterogenic population with various medical co-morbidities, the cardiovascular safety data for this sNDA should be analyzed by the sponsor and by HFD's 120-130 Safety Group by the following identifiable cardiovascular risk factors: history of cardiovascular disease, active smoking, history or presence of hypertension, history or presence of hyperlipidemia, presence of elevated CRP, history or presence of diabetes mellitus, obesity (BMI > 30 kg/m^2 at baseline), and age (≥ 50 years at baseline).

7. Since asthma medications (e.g. Salbutamol) have been associated with increased heart rate and blood pressure, the sponsor should examine changes in vital signs and

adverse events based on the use or lack of use of these medications in this sNDA.

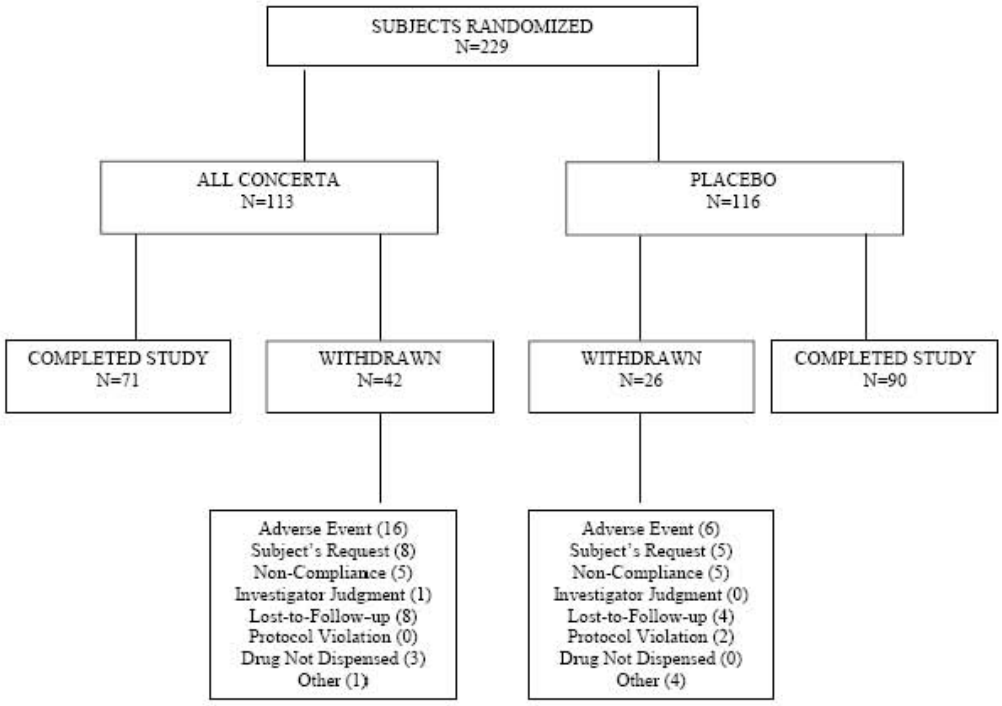
Glenn B. Mannheim, M.D.
October 23, 2007

cc: NDA 21-121 SE5-017
HFD 130
HFD 130/
J Cliatt
G Mannheim
N Khin
T Laughren

Appendix:

1. Study 02-159: Disposition of Study Subjects

Figure 8-1: Disposition of Subjects



Subjects Completing the Study, N=161

2. Listing of Subjects for Whom Case Report Forms are Available

Case report forms are not provided here but are available upon request for subjects who experienced serious adverse events, discontinued due to adverse events and for subjects treated with CONCERTA who reported a cardiovascular or psychiatric adverse event of special interest. No subjects died during this study. The following table provides a list of subjects for whom case report forms are available.

Listing of Subjects for Whom Case Report Forms are Available

Subject ID	Reason
101-001	Discontinued Due to AE
101-007	Psychiatric AE of Interest
102-004	Discontinued Due to AE
102-006	Discontinued Due to AE
102-009	Discontinued Due to AE
102-014	Discontinued Due to AE
102-015	Cardiovascular AE of Interest
103-009	Discontinued Due to AE
105-007	Discontinued Due to AE
107-001	Cardiovascular AE of Interest
107-004	Discontinued Due to AE, Cardiovascular AE of Interest
107-017	Discontinued Due to AE
108-002	Cardiovascular AE of Interest
108-007	Serious AE
109-006	Discontinued Due to AE
110-011	Discontinued Due to AE, Cardiovascular AE of Interest
110-012	Discontinued Due to AE, Cardiovascular AE of Interest
112-001	Cardiovascular AE of Interest
117-007	Discontinued Due to AE, Cardiovascular AE of Interest
118-017	Cardiovascular AE of Interest
118-020	Discontinued Due to AE
120-004	Discontinued Due to AE
122-004	Cardiovascular AE of Interest
122-006	Discontinued Due to AE
122-008	Cardiovascular AE of Interest
124-004	Discontinued Due to AE, Cardiovascular AE of Interest
125-001	Discontinued Due to AE, Cardiovascular AE of Interest
125-006	Cardiovascular AE of Interest
126-009	Discontinued Due to AE, Cardiovascular AE of Interest
127-006	Psychiatric AE of Interest
127-007	Discontinued Due to AE
127-016	Discontinued Due to AE, Psychiatric AE of Interest
128-012	Cardiovascular AE of Interest, Psychiatric AE of Interest
129-005	Psychiatric AE of Interest
129-008	Discontinued Due to AE
130-002	Cardiovascular AE of Interest
130-008	Cardiovascular AE of Interest
130-009	Discontinued Due to AE

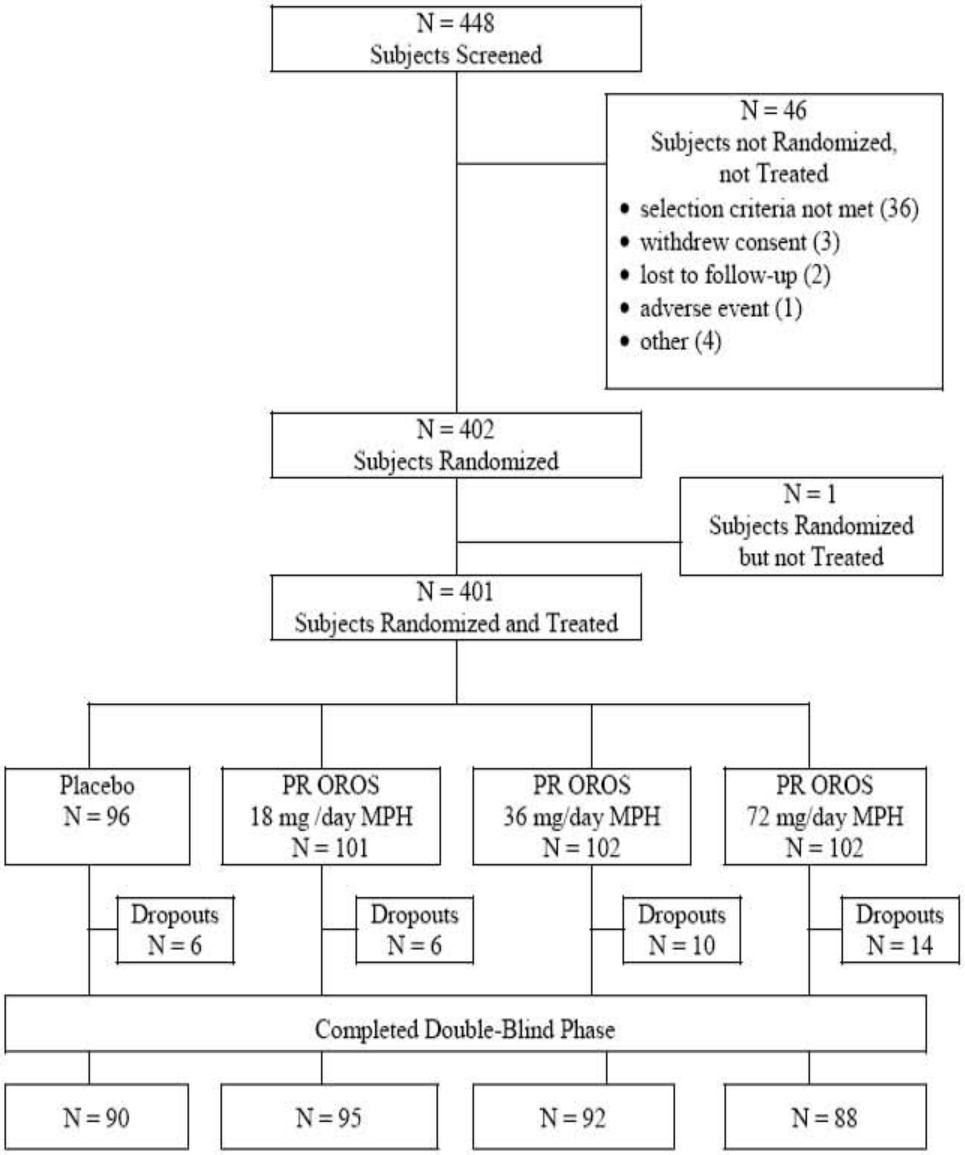
3. Listing of Subjects for Whom Patient Profiles are Available

Listing of Subjects for Whom Patient Profiles are Available

Subject ID	Reason
127-007	Discontinued Due to AE
127-016	Discontinued Due to AE, Psychiatric AE of Interest
128-003	Cardiovascular AE of Interest
128-012	Cardiovascular AE of Interest, Psychiatric AE of Interest
129-005	Psychiatric AE of Interest
129-008	Discontinued Due to AE
130-002	Cardiovascular AE of Interest
130-008	Cardiovascular AE of Interest
130-009	Discontinued Due to AE

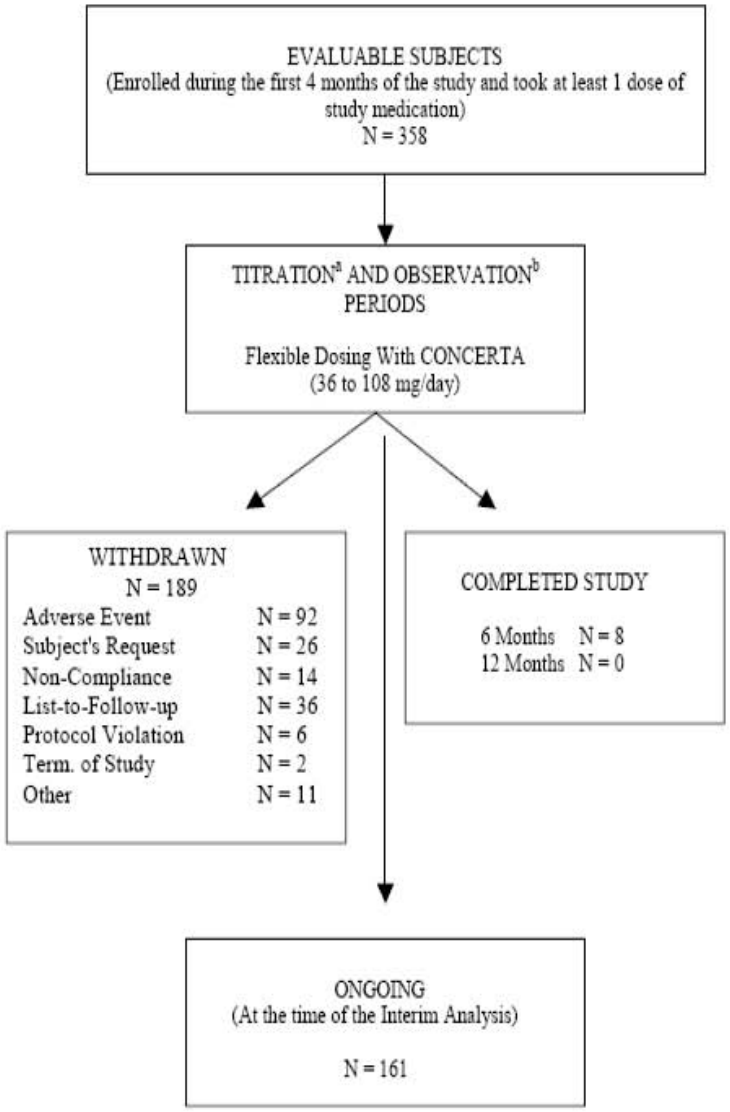
4. Study 3002: Disposition of Study Subjects in the Double-Blind Phase

Figure 2: Subject Disposition in the Double-Blind Phase



5. Study 012-304: Disposition of Study Subjects

Figure 1: Disposition of Subjects
(Study 12-304: All Evaluable Subjects)



[a] **Titration Period**: All subjects initiated treatment with 36 mg of CONCERTA per day. The dose was titrated up in 18 mg increments every 7 (±2) days. Titration stopped once there was a 30% improvement on the AISRS and a CGI-I score of 1 or 2. The maximum dose was 108 mg. This dose was then the individualized dose. Titration downward was required for resting heart rate > 100 beats per minute (bpm), systolic BP > 140 mmHg, or diastolic BP > 90 mmHg (average of triplicate measurements). If a limiting AE occurred, the dose was titrated down by 18 mg. Any subject unable to tolerate the 36-mg dose was discontinued from the study at the investigator's discretion.

[b] **Observation Period**: Subjects who tolerated their individualized dose generally continued at the same dose for the duration of the study. If a subject did not tolerate an increase, they returned to the previous dose. An investigator could increase (up to 108 mg) or decrease (down to 36 mg) a subject's dose by 18 mg if deemed clinically necessary. Titration downward was required for resting heart rate > than 100 bpm, systolic BP > 140 mmHg, or diastolic BP > 90 mmHg (average of triplicate measurements). Down-titration of a CONCERTA dose for AEs was at the discretion of the investigator.

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

/s/

Glenn Mannheim
10/23/2007 11:13:31 PM
MEDICAL OFFICER

Ni Aye Khin
10/26/2007 12:19:25 PM
MEDICAL OFFICER
The issues identifed by Dr. Mannheim in this review were discussed at the filing meeting on 10/24/2007. I disagree with his recommendation that this sNDA be considered non-fileable. See memo to file for additional comments.

Memorandum

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
DIVISION OF CARDIOVASCULAR AND RENAL PRODUCTS

Date: May 21, 2008

From: Stephen M. Grant, M.D.
Clinical Reviewer
Division of Cardiovascular and Renal Products /CDER

Through: Norman Stockbridge, M.D., Ph.D.
Division Director
Division of Cardiovascular and Renal Products /CDER

To: Nicholette Hemingway
Regulatory Project Manager
Division of Psychiatry Products

Subject: DCRP consult to evaluate abnormal ECGs from adult subjects in a clinical study of extended release tablet formulation of methylphenidate

This memo responds to your consult to us requesting we review ECGs acquired from 13 subjects enrolled in a trial of extended release tablet formulation of methylphenidate (CONCERTA®) submitted to support an efficacy supplement to NDA 21-121. We understand that these ECGs were interpreted as abnormal by the sponsor and you lack appropriate expertise to evaluate the significance of these abnormalities. You have requested we review the ECGs to assess whether the abnormalities warrant further evaluation. We received and reviewed the following materials:

- Your consult dated 04 Mar 2007
- 81 separate ECG tracings in PDF format from 13 separate subjects listed by subject number.

Background

CONCERTA® is a central nervous system stimulant approved for the treatment of attention deficit hyperactivity disorder (ADHD) in children and adolescents. The current PI states "Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD…. Stimulant medications cause a modest increase in average blood pressure (about 2-4 mmHg) and average heart rate (about 3-6 bpm) and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing

hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia."

Johnson & Johnson Pharmaceutical Research and Development has submitted an efficacy supplement to NDA 21-121 for use of CONCERTA® in the treatment of ADHD in adults. To support the application, the sponsor presents data from study 02-159, a flexible dosage, R DB PC in which adults with ADHD were titrated to an effective and tolerable dose over 5 weeks and then maintained at the dose for at least two weeks. Patients with structural heart disease were not eligible to enroll. The protocol stipulated acquisition of ECGs at the screening, baseline, after each upward dose titration, and at the final visit/two week efficacy visit.

Limitations

Patients who have cardiac disease may not have any electrocardiographic changes or nonspecific electrocardiographic changes so lack of evolutionary ECG changes does not rule out interval myocardial infarction, cardiomyopathy, or other cardiac disease. Similarly, some abnormalities on ECGs may indicate cardiac disease (e.g. possible MI) but also may be due to other causes. Therefore, if there is a concern about CONCERTA® increasing the frequency of cardiac disease, other trial data or post-marketing data may need to be examined for a clearer picture of the possible association.

While this reviewer previously was a practicing board-certified cardiologist who interpreted ECGs, he does not have additional special expertise in the interpretations of ECGs. Further the ECGs were interpreted from each subject in the order they were obtained without any "negative' or "positive" controls (e.g., serial ECGs from healthy patients and patients who have had interval MI) so the specificity and sensitivity of the findings detailed below are unknown.

ECG Readings

107-001 (7 ECGs dated 15 Jun 2006 to 31 Jul 2006): Initial and all subsequent ECGs are normal.

108-002 (4 ECGs dated 01 Jun 2006 to 27 Jul 2006): Sinus bradycardia on initial ECG without other abnormalities. No evolutionary changes noted on subsequent ECGs.

110-011 (3 ECGs dated 11 Jul 2006 to 25 Jul 2006): Initial and all subsequent ECGs are normal.

108-002 (4 ECGs dated 12 Jul 2006 to 05 Sep 2006): Initial ECG is normal. ECG dated 24 Jul 2006 demonstrates sinus tachycardia with nonspecific ST segment and T wave abnormalities. All subsequent ECGs normal.

120-004 (5 ECGs dated 09 May 2006 to 05 Jun 2006): Initial and all subsequent ECGs are normal.

122-044 (8 ECGs dated 13 Jul 2006 to 06 Sep 2006): Initial and all subsequent ECGs are normal except mild sinus tachycardia noted on ECG of 24 Aug 2006.

126-009 (8 ECGs dated 17 Jul 2006 to 11 Sep 2006): Initial and all subsequent ECGs are normal. A premature ventricular beat is noted on the ECG dated 21 Aug 2006; in the absence of structural heart disease this finding is not significant.

130-002 (5 ECGs dated 12 May 2006 to 13 Jul 2006): Initial and all subsequent ECGs are normal.

130-009 (6 ECGs dated 07 Jun 2006 to 20 Jul 2006): Initial ECG has 2 premature ventricular beats; otherwise normal. Some subsequent ECGs also have premature ventricular beats without

evolutionary changes.

128-016 (6 ECGs dated 16 Aug 2006 to 11 Oct 2006): Initial and all subsequent ECGs are normal.

114-011 (7 ECGs dated 15 Jun 2006 to 02 Aug 2006): Initial and all subsequent ECGs have nonspecific ST segment and T wave abnormalities without evolutionary changes.

117-006 (8 ECGs dated 22 Jun 2006 to 10 Aug 2006): Initial and all subsequent ECGs are normal.

128-014 (6 ECGs dated 27 Jul 2006 to 22 Aug 2006): Initial ECG has small Q-waves in leads 3 and aVF (can not rule out inferior myocardial infarction) and inverted T waves in all precordial leads. No evolutionary changes noted on subsequent ECGs.

DCRP COMMENTS:

Most of the abnormalities noted on the ECGs submitted for review are nonspecific and would not warrant further evaluation in the absence of signs or symptoms of cardiac disease. The only subject with definite ECG abnormalities was subject 128-014. Assuming the first ECG is at from screening or at baseline, there are no evolutionary changes in subsequent ECGs obtained after exposure to CONCERTA®.

Therefore, our review of these ECGs does not identify any definite abnormalities that developed during the course of the trial so none of them alone warrant further investigation.

Thank you for requesting our input into the development of this product under IND. We welcome more discussion with you now and in the future.

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/s/

Stephen Grant
5/21/2008 10:28:48 AM
MEDICAL OFFICER

Norman Stockbridge
5/21/2008 08:34:13 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

CHEMISTRY REVIEW(S)

Division of Post Approval Marketing Evaluation IV
Chemist Review of Supplement

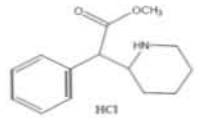
1. Division of Post Approval Marketing IV
2. NDA Number: 21121
3. Supplement Numbers: SE5 017
Letter Date: August 29, 2007
Stamp Date: August 29, 2007
5. Received by Chemist: May 8, 2008

6. Applicant Name and Address: Johnson &Johnson
1125 Trenton-Harbourton Road
PO Box 200
Titusville, NJ 08560

7. Name of the Drug: Concerta® Extended Release Tablets
[OROS® methylphenidate HCl]

8. Nonproprietary name: 2-piperidine acetic acid, α–phenyl-, methyl ester, hydrochloride (b) (4) (±)

Chemical Formula: $C_{14}H_{19}NO_2 \cdot HCl$
Molecular Weight: 269.77
CAS Registry Number: CAS-298-59-9



10: Dosage Form: tablets
11. Potency: 54 mg

12. Pharmacological Category: attention deficit disorder (ADHD)
13. How Dispensed: XXX (RX) _____(OTC)
14. Records and Reports current XXX (yes) _____(No)
15. Related IND/NDA/DMF: _____(yes) XXX__ (No)

16. **Comments**: This PA Supplement provides for a new indication for the approved Concerta ® extended release tablets, for the treatment of Attention Deficit Hyperactivity Disorder in adults (18 years or older). This indication will be supported by the currently approved marketed strengths (18mg, 27mg, 36mg and 54mg). There are no changes proposed to the CMC for this drug product and no changes to the CMC sections of the labeling. A claim for categorical exclusion for an environmental assessment is requested under 21 CRF 25.31[b], since less than 1 ppb (EIC = (b) (4)) is expected to enter the environment, as a result of the new indication for this drug product.

17. Recommendation: *From a CMC standpoint, approval of this PA supplement is recommended.*

_____

19. Reviewer Name Julia C. Pinto, Ph.D., Chemist

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

/s/

Julia Pinto
5/21/2008 05:02:20 PM
CHEMIST

Jim Vidra
5/21/2008 05:13:58 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

PHARMACOLOGY REVIEW(S)

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

PHARMACOLOGY/TOXICOLOGY REVIEW AND EVALUATION

NDA NUMBER: 21121

SERIAL NUMBER: SE5 (017)

DATE RECEIVED BY CENTER: August 29, 2007

PRODUCT: Methylphenidate hydrochloride

INTENDED CLINICAL POPULATION: Adults

SPONSOR: Johnson and Johnson Pharmaceutical Research and Development on behalf of ALZA Corporation

DOCUMENTS REVIEWED: all submitted documents

REVIEW DIVISION: Division of Psychiatry Products (DPP)

PHARM/TOX REVIEWER: Ikram Elayan

PHARM/TOX SUPERVISOR: Barry Rosloff

DIVISION DIRECTOR: Thomas Laughren

PROJECT MANAGER: Nicholette Hemingway

Date of review submission to Division File System (DFS): 6/19/08

TABLE OF CONTENTS

EXECUTIVE SUMMARY

I. Recommendations

A. Recommendation on approvability: approvable

B. Recommendation for nonclinical studies: no studies recommended

C. Recommendations on labeling:

The findings from a study in which lactating females were treated orally with a single dose of radiolabeled methylphenidate indicated that radioactivity was observed in the milk. The ratio of radioactivity in milk compared to that in the plasma was increased with time and was ~1.45 at 24h. It should be pointed out that data from only 3 animals were used in this study and that total radioactivity rather than the levels of the parent were evaluated in this study.

The following is to be added to the labeling:

Section 8.3:

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

In addition, in Section 8.1 under Pregnancy, the fold difference in plasma concentration of methylphenidate and its metabolite PPAA in rats in relation to humans is to be changed to take into consideration the different plasma concentrations in adults, adolescents, and children at the MRHD for each group. The value in the current labeling (2) represent the difference in levels between children and animals and the change proposed (1-2) will include the difference compared to adolescents (~1) and adults (~1.5). (See **note** below for calculations to obtain these values)

Labeling change Section 8.1:

A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of CONCERTA® on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of CONCERTA® based on the AUC.

Note: these values proposed in the labeling were calculated based on the sum of plasma levels of methylphenidate and its metabolite PPAA in adults at a dose of 108 mg, adolescents at a dose of 72 mg and were compared to levels in pregnant rats treated with 30 mg/kg/day:

	AUC (ng.h/ml) **Adults** (Dose 108 mg)	AUC(ng.h/ml) **Adolescents** (Dose 72 mg)	AUC (ng.h/ml) **Rats** (Dose 30 mg/kg)
Methylphenidate Day 1 (human) or 6 (rat)	293	185	833
Methylphenidate Day 4 (human) or 17 (rat)	291		1277
PPAA Day 1 (human) or 6 (rat)	16766	10708	8155
PPAA Day 4 (human) or 17 (rat)	16465		11550
Average parent	292	185	1055
Average metabolite	16616	10708	9853
Total (parent + metabolite	16908	10893	10908

II. Summary of nonclinical findings

A. Brief overview of nonclinical findings:

Safety pharmacology studies were conducted to evaluate the effect of the drug on the cardiovascular system (CVS), central nervous system (CNS), and the respiratory system (RS).

In the evaluation of the effect on the CVS, two in vitro studies were conducted, one using HERG channels and the other using isolated guinea pig papillary muscles. In these studies, the test article at doses up to 1 µg/ml (which is ~ 30 times the estimated maximum plasma concentration in humans of 30 ng/ml) had no effect on the rapidly activating delayed rectifier potassium current (I_{kr}) or on the resting membrane potential, action potential amplitude, maximum rising velocity, and action potential duration at

30%, 60%, and 90% repolarization. In addition, in an in vivo study in which beagle dogs were treated with a single oral dose of the test article at 0, 3, 10, and 30 mg/kg there was an increase in blood pressure and heart rate at 30 mg/kg but there was no effect on the duration of ECG complexes and no cause of arrhythmia at doses up to 30 mg/kg using telemetric evaluation for 24h.

For the evaluation of the effect on the CNS, two studies were conducted. One study was to evaluate the effect of a single oral dose methylphenidate (10, 30, or 100 mg/kg) on the induction of convulsions due to pentylenetetrazole (PTZ) or electric shock in mice. The second study evaluated its effect on CNS using the functional observation battery test (FOB) in rats treated with a single oral dose of 3, 10, 30, and 100 mg/kg. In the first study, the results indicated that methylphenidate has a convulsion potentiation action at 30 and 100 mg/kg and no anticonvulsant effect at any dose. In the second study, the effects as assessed by the FOB test indicated a tendency of excitement at ≥ 10 mg/kg, an increased rearing count at 10 and 30 mg/kg, increased arousal level, number of unit areas crossed, body temperature and stereotypy at 30 and 100 mg/kg. An increase in visual and touch response was also seen at 100 mg/kg.

In a study to evaluate the effect on the respiratory system, male rats were treated with a single oral dose of 3, 10, and 30 mg/kg. The data indicated that methylphenidate affects the respiratory system at doses of 10 mg/kg and more as observed by an increase in respiratory rate and minute volume, an effect that could not be completely explained by the influence of increased activity.

In a study conducted to evaluate the abuse/misuse of Concerta, beagle dogs were treated with intravenous bolus injection (1 mg/kg) of Concerta, Ritalin or vehicle (ethanol, 40% v/v) for 14 days. It should be noted that tablets of both Concerta (containing the OROS system) and Ritalin were crushed and used to prepare the dosing formulation. In the Concerta treated group, one male died and one female was euthanized shortly after dosing on the first day. The dose was lowered for animals treated with Concerta to 0.5 mg/kg, and one male died in response to treatment. In response to these deaths, no further treatment with Concerta was attempted while animals treated with Ritalin or vehicle continued to be treated to the end of the study with no deaths. The sponsor concluded that these data indicate that intravenous administration of Concerta would be considered a poor choice for human abuse/misuse.

Two TK studies were conducted: one in juvenile rats and one in lactating females.

In the juvenile rat study, rats (4 weeks old) were treated with a single dose of radiolableled methylphenidate either by oral gavage (5 mg/kg) or I.P. administration (0.2 or 1 mg/kg) and blood and plasma levels were evaluated. The ratio of AUC of plasma concentration of the unchanged compound to plasma concentration of total radioactivity after oral administration was approximately 0.02, and the ratio of Cmax was approximately 0.05. In response to I.P. administration, the ratio of AUC of plasma concentrations of the unchanged compound to plasma concentrations of radioactivity was ~ 0.03, and the ratio of Cmax was ~ 0.08.

Lactating females were treated with a single dose of 5 mg/kg radiolableled methylphenidate orally by gavage. Plasma and milk concentration of radioactivity were determined at 15 min, 1, 2, 4, 8, and 24h. The ratio of the concentration of radioactivity in breast milk to plasma was 0.53 at 15 min after dosing, 0.86-1.07 between 1 and 4 h after dosing and 1.24-1.45 between 8 and 24h after dosing. It should be noted that data from only 3 animals were utilized. In addition, total radioactivity was evaluated; therefore, it could not be determined how much of this radioactivity represents the parent.

B. Pharmacologic activity:

No studies were submitted; however, studies related to the pharmacological activity of methylphenidate were reviewed within the original submission of the NDA.

C. Nonclinical safety issues relevant to clinical use

The studies reviewed here did not indicate any major CVS findings that are of concern. As clear from the studies conducted, there was no effect on the HERG channels current up to a concentration of 1 μg/ml (which is ~ 30 times the estimated maximum plasma concentration in humans of 30 ng/ml) and the other CVS effects observed are already known effects of methylphenidate (increases in blood pressure and heart rate).

As for the CNS, induction of convulsions by methylphenidate is probably an expected effect of a stimulant and that should be taken into consideration clinically when administered with other stimulants that might have convulsive effects. The effect was seen at doses of 30 mg/kg and higher and there was no anticonvulsant effect for methylphenidate at any of the tested doses. The increase in activity and stereotypy in treated animals are already known effects of methylphenidate.

The effect on the respiratory system included an increase in respiratory rate and minute volume which could not be explained by the influence of increased activity.

In evaluating the abuse/misuse of this form of methylphenidate (within the OROS system in Concerta), the data indicated that intravenous administration of methylphenidate as found in Concerta with alcohol (40% v/v) would be considered a poor choice for human abuse/misuse due to deaths observed in animals treated with crushed Concerta tablets dissolved in alcohol (40% v/v).

The release of methylphenidate and/or its metabolites in milk should be considered based on the findings reported here in which total radioactivity in milk of lactating female rats, relative to levels in plasma, was found to increase with time up to 24h after treatment.

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

NDA number: 21-121
Review number:
Sequence number/date/type of submission: SE5 (017), August 29, 2007
Information to sponsor: Yes ( ) No (X)
Sponsor and/or agent: Johnson and Johnson Pharmaceutical Research and Development on behalf of ALZA Corporation
Manufacturer for drug substance: Alza Corporation
Vacaville, California
And
Janssen Cilag Manufacturing LLC
Gurabo
Puerto Rico
Reviewer name: Ikram Elayan
Division name: DPP
HFD #: 130
Review completion date:

Drug:

Trade name: Concerta

Generic name: Concerta

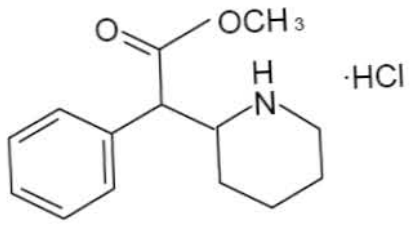
Code name: NA

Chemical name: methylphenidate HCl, d,l-methyl-α-phenyl-2-piperidineacetate hydrochloride.

CAS registry number:

Molecular formula/molecular weight: $C_{14}H_{19}NO_2.HCl$/ MW 269

Structure:



Relevant INDs/NDAs/DMFs:

Drug class: a central nervous system stimulant

Intended clinical population: adults with ADHD (doses ranging from 18 mg to (b) (4) mg per day)

Clinical formulation: extended release tablets

Route of administration: oral

Disclaimer: Tabular and graphical information are constructed by the reviewer unless cited otherwise.

Studies reviewed within this submission: six safety pharmacology studies were submitted to the NDA for adolescents (and also as part of the Japanese requirement) were also submitted here. These studies include CNS safety studies (2 studies), CVS safety studies (2 in vitro studies and 1 in vivo study in conscious dogs) and a respiratory study. These studies will not be reviewed in detail; however, a summary of the findings will be presented. In addition, a pharmacokinetic study (in pregnant or nursing animals) will be reviewed and the findings will be described in the labeling if applicable. A toxicology study to assess the abuse/misuse potential in support of DEA submission (February 20, 2004) is also submitted here. This study will be briefly summarized here.

Studies not reviewed within this submission: **none**

2.6.2 PHARMACOLOGY

2.6.2.1 Brief summary

2.6.2.2 Primary pharmacodynamics

Mechanism of action: mechanism of action of the drug was discussed in the original submission to this NDA (21-121) and is not discussed in here.

Drug activity related to proposed indication:

2.6.2.3 Secondary pharmacodynamics

2.6.2.4 Safety pharmacology

Neurological effects:

In male mice treated with single oral dose of methylphenidate chloride at doses of 10, 30, or 100 mg/kg/day 15 min before induction of convulsions with pentylenetetrazole (PTZ, 80 mg/kg, s.c.) or electroshock (25 mA). There was a convulsion potentiation action effect at 30 and 100 mg/kg which resulted an increase in the rate of occurrence of

pentylenetetrazole-induced convulsions in a dose dependent manner (a rate of 80% and 100% at the respective doses with the test article compared to 50% in the presence of PTZ alone) and there were no anticonvulsant effect at any of the tested doses. While the rate of mortality was zero in the presence of PTZ alone, the rate of morality increased to 20% in the 100 mg/kg treated group. In the group treated with the electric shock (25 mA), the rate of occurrence of convulsions was 100% and mortality was 0% in animals treated with electric shock alone and with each dosage group of methylphenidate hydrochloride, the rate of occurrence of convulsions was 100% and the mortality was 10% and 20%, respectively. There was no anticonvulsant effect for the test article at any of the tested doses in the electric. **Based on the previous results, methylphenidate is considered to have a convulsion evoking action effect at dosages of ≥ 30 mg, and no anticonvulsant effect at the tested dosages (10-100 mg/kg) with convulsions induced by either pentylenetetrazole or electric shock.**

In male rats (8/group) treated with single oral dose of methylphenidate hydrochloride at 3, 10, or 100 mg/kg the effect on the CNS as assed by the Functional Observation Battery (FOB) test (before dosing, 0.5, 1, and 4h post dosing) the following effects were observed: there was a tendency of excitement at ≥ 10 mg/kg and an increase in rearing counts at 10 and 30 mg/kg, increased number of unit areas crossed, arousal level, body temperature and stereotypy at 30 and 100 mg/kg. An increase in visual and touch response was also seen at 100 mg/kg. **From the previous findings it is evident that a single dose of methylphenidate hydrochloride is considered to have effects on the central nervous system of rats at ≥ 10 mg/kg as evaluated by the FOB test.**

Cardiovascular effects:

In an in vitro study, methylphenidate at a concentrations of 0.1, 0.3, and 1 µg/ml had no inhibitory effects on the rapidly activating delayed rectifier potassium current (I_{kr}) using human hERG channels transfected in human embryonic kidney (HEK)-293 cells as assessed by the patch clamp method. The positive control E-4031 at a concentration of 10 ng/ml resulted in a 33% inhibition relative to the control. The sponsor indicated that the concentration of methylphenidate in this study (1 µg/ml) is 30 times the estimated maximum plasma concentration in humans (30 ng/ml). The following table provided by the sponsor summarizes the results:

Table 1. Effects of methylphenidate hydrochloride on I_{Kr} in hERG-transfected HEK-293 cells

	Negative control[a]	Methylphenidate hydrochloride			Positive Control[b]
Concentration (µg/mL):	0	0.1	0.3	1	10 ng/mL
Inhibition Rate (%)[c]:	3.5 ± 5.1	-1.4 ± 5.1	-1.2 ± 1.9	0.6 ± 7.0	33.8 ± 16.6**

[a] Negative (vehicle) control = distilled water

[b] Positive control = E-4031

[c] Values are the mean ± standard deviation for 5 cells.

No significant differences were found between the control and methylphenidate hydrochloride-treated groups by Dunnett's test.

**p<0.01, significantly different from the control by Student's t-test.

Similarly, there was no effect of 0.1, 0.3, and 1 µg/ml on action potential parameters in papillary muscle isolated from the right ventricle of guinea pigs. Methylphenidate had no effect on resting membrane potential, action potential amplitude, maximum rising velocity, or action potential duration at 30%, 60%, and 90% repolarization. The following table summarizes the results of this study as provided by the sponsor:

Table 2. Effects of methylphenidate hydrochloride on the action potential of guinea pig papillary muscles

	Negative control[a]		Methylphenidate hydrochloride						Positive Control[b]	
Concentration (µg/mL):	0		0.1		0.3		1		10	
Parameter	pre	30 min	pre	30 min	pre	30 min	pre	30 min	pre	30 min
RMP (mV)	-92.70	-92.85	-92.43	-92.53	-93.35	-93.55	-92.06	-92.26	-92.79	-92.72
APA (mV)	136.07	136.19	135.53	135.00	136.84	136.52	135.00	134.35	135.54	135.18
dV/dt max (V/sec)	249.49	246.80	240.29	240.98	254.85	257.11	238.25	234.86	214.50	209.00
APD_{30} (msec)	119.41	119.75	119.77	120.10	117.66	118.62	118.82	118.82	118.12	125.46
APD_{60} (msec)	157.39	157.62	156.54	157.34	154.17	154.83	156.70	157.11	154.11	175.21**
APD_{90} (msec)	178.76	178.66	179.19	179.20	178.84	178.81	179.18	179.35	178.09	204.48**

[a] Negative (vehicle) control = distilled water
[b] Positive control = sotalol
[c] Values are the mean for 5 muscles.
Methylphenidate hydrochloride had no significant (Dunnett's test) effect on action potential parameters compared to the negative control. The positive control prolonged APD, with statistically significant increases in APD_{60} and APD_{90}.
**$p<0.01$, significantly different from the control by Student's t-test.

APA = action potential amplitude; APD = action potential duration; APD_{30} = APD at 30% repolarization; APD_{60} = APD at 60% repolarization; APD_{90} = APD at 90% repolarization; dV/dt max = maximum rising velocity; pre = pre-application of test substance; RMP = resting membrane potential

In an in vivo study in which conscious beagle dogs (4 males) treated with a single oral (gavage) dose of 0, 3, 10 or 30 mg/kg increases in blood pressure and heart rate were seen at 30 mg/kg but there was no effect on the duration of ECG complexes and did not cause arrhythmia at doses up to 30 mg/kg (telemetric evaluation for 24h). The results are summarized in the following table as provided by the sponsor:

Table 3. Cardiovascular Effects in Male Dogs After a Single Oral Dose of Methylphenidate Hydrochloride

	0 mg/kg	3 mg/kg	10 mg/kg	30 mg/kg
MBP[a] (mmHg)				
predose	92	93	98	99
postdose	0-4h 84 to 94	0.5h 106	0.5h 108	0-2h 123 to 124
	7-24h 89 to 97	0.5-24h 89 to 95	0.5-24h 87 to 101	3-4h 116
				7-24h 97 to 98
SBP (mmHg)				
predose	131	131	138	140
0-2h	120 to 131	129 to 144	135 to 148	159 to 164
3-4h	132	127	131	156
7-24h	128 to 137	133 to 134	128 to 137	140 to 141
DBP (mmHg)				
predose	73	73	78	79
0-2h	65 to 75	75 to 87	78 to 88	103 to 105
3-4h	73	70	71	96
7-24h	69 to 76	73 to 75	67 to 77	76 to 77
Heart Rate (beats/min)				
predose	99	91	98	95
0-4h	94 to 117	87 to 124	93 to 107	114 to 142
7-24h	86	82 to 85	83 to 88	90 to 92
ECG				
Duration of Complex	NA	No effect[b]	No effect[b]	↓ QT interval at 1h but no effect on QTcF
Arrhythmia[c]	NA	No effect	No effect	No effect

[a] Blood pressure (systolic, diastolic, and mean) and heart rate were recorded via telemetry for 20-second periods at 5-minute intervals from 1 hour before dosing to 24 hours after dosing.

[b] No difference from the control group in the duration of PR, QT, and RR intervals, QRS width, and QTcF.

[c] 1 or 2 animals from the 0, 10, and 30 mg/kg groups had premature ventricular contractions and second-degree atrio-ventricular block of 1 to 8 beats before dosing, but no increase in incidence of these changes was observed after dosing.

↓ = decrease; DBP = diastolic blood pressure; MBP = mean blood pressure; QTcF = QT interval corrected for heart rate using Fridericia's formula; SBP = systolic blood pressure

Pulmonary effects:

In a study that evaluated the respiratory system under unrestricted conditions, male rats (6/group) were treated with a single oral dose methylphenidate hydrochloride at 3, 10, or 30 mg/kg (the 30 mg/kg dose was considered adequate for evaluating the respiratory system as a high dose since the 100 mg/kg dose was associated with stereotypy and self biting, therefore, the 100 mg/kg was considered to be excessively high for the examination of effect on the respiratory system). Under these conditions, there was no effect at the 3 mg/kg dose but there were increases in respiratory rate and minute volume at ≥ 10 mg/kg and tidal volume at 30 mg/kg. These data were evaluated without excluding the effect of the test article on body movement. However, when the data were evaluated to exclude the effect of the test article on body movement (by measuring these values only when the animals were motionless, as much as possible), there was no change observed in the 3 mg/kg group, no change observed in the tidal volume and minute volume at 10 mg/kg but there was an increase in respiratory rate, at the 30 mg/kg group, there was no change in the tidal volume but there was an increase in respiratory rate and minute volume. For all the observed effect on the respiratory system, the effect was not observed 4h after treatment. **The data indicate that methylphenidate affects the**

respiratory system at doses ≥10 mg/kg as observed in an increase in respiratory rate and minute volume, an effect that could not be completely explained by the influence of the increased activity.

Renal effects: no studies were submitted

Gastrointestinal effects: no studies were submitted

Abuse liability:

The sponsor indicated that extensive non-clinical evaluation of methylphenidate hydrochloride was previously conducted to support marketing approval of Concerta (NDA 2121 and NDA 21-121/S-008). However, in support of a DEA submission dated 20 February 2004 that requested a change in the scheduling of Concerta, an additional toxicology study was conducted in beagle dogs to assess the abuse/misuse potential of pulverized Concerta mixed with alcohol when administered IV. This study is briefly summarized and discussed here by the reviewer:

Beagle dogs (4/sex/group) were treated with a single intravenous bolus injection (1mg/kg) over a duration of ~15 sec via the cephalic vein of pulverized Concerta (using the 27 mg OROS tablets, long acting methylphenidate by using the **O**smotically controlled-**R**elease **O**ral delivering **S**ystem) or Ritalin (using the 10 mg immediate release tablets) in a 40% v/v ethanol solution at 1 mg/kg/day for 14 days or with the vehicle. The sponsor indicated that crushing the Concerta tablets prior to soaking was difficult and required significant mechanical force and resulted in large fragments and that all extracts of Concerta were more cloudy and viscous than Ritalin samples (all the procedures were done under aseptic techniques). Furthermore, since the OROS systems (present in Concerta) contain (b) (4) by design, this contributed to more viscous and turbid solutions than from the immediate release methylphenidate tablets (the mixture was stirred overnight).

In the Concerta-treated group, one male died and one female was euthanized moribund shortly after dosing (15 min and 4 min, respectively), therefore, no further dogs in this group were dosed on Day 0. The Concerta dose was decreased to 0.5 mg/kg/day on Day 1, and the one male that was treated with this dose was euthanized moribund after 6 min from dosing. Accordingly, the sponsor terminated the administration of Concerta to the whole group that was designated for Concerta for humane reasons (animals were returned to the Testing Facility's stock colony). There was no histological findings for the dogs that died (all findings were considered to be background lesions that can occur in dogs) and therefore the cause of death could not be determined by the histopathological evaluation. Some of the clinical signs observed prior to death in these animals included involuntary head movements, involuntary defecation, vocalization, shallow breathing, labored breathing, rigidity, lateral recumbency, no capillary refill, dilated pupils, and lack of papillary reflex. Gross necropsy findings included dark red areas on the heart, wet matting on the haricoat, mottled lung, reddened small intestine, abnormal content in

trachea, reddened aortic valve cusps and atrioventricular valve, subcutaneous hemorrhage at the injection site, dark red lung, and abnormal content in the lung.

There were no deaths in the vehicle and Ritalin treated animals and all survived the 2-week treatment period. Some of the clinical signs seen in Ritalin treated animals were only transient and they were associated with predicted signs observed with Ritalin treatment (salivation, wobbly gait, vocalization, relaxed posture, rapid breathing, and increased activity) that lasted up to 1.5 h after treatment and there were no histopathological findings in these animals. In addition, the localized injection site lesions observed in the control and Ritalin treated animals were considered to be background lesions that occur with repeat-dose IV administration with ethanol with no treatment-related lesions observed microscopically.

From the presented data it was evident that IV administration of Concerta (0.5 and 1 mg/kg) dissolve in alcohol in dogs was associated with death after a single dose and that a similar effect was not seen with Ritalin administered with the same route and the same vehicle (1 mg/kg/day) for 14-days. The sponsor stated that although the cause of death in Concerta-treated dogs was not determined based on histopathological examination, it is likely that the deaths were not due to methylphenidate since no death was observed with Ritalin treatment and it is likely to be due to the OROS system rather than methylphenidate since all animals treated with methylphenidate survived the 14-day treatment.

Therefore, the sponsor concluded that the intravenous abuse of methylphenidate as contained in Concerta is not feasible, and renders Concerta a poor choice among psychostimulants for human abuse/misuse.

Other:

2.6.2.5 Pharmacodynamic drug interactions

No studies were submitted.

2.6.3 PHARMACOLOGY TABULATED SUMMARY

No studies were submitted.

2.6.4 PHARMACOKINETICS/TOXICOKINETICS

2.6.4.1 Brief summary:

The sponsor indicated that the following studies were requested by the Japanese authorities: a PK study in juvenile rats treated with a single dose of methylphenidate either orally or by I.P. administration, and another study in which the excretion of the test article into breast milk in rats was studied.

2.6.4.2 Methods of Analysis

N/A

2.6.4.3 Absorption

2.6.4.4 Distribution

2.6.4.5 Metabolism

2.6.4.6 Excretion

2.6.4.7 Pharmacokinetic drug interactions

2.6.4.8 Other Pharmacokinetic Studies

In **the juvenile animals TK study**, male Sprague Dawley rats (4 weeks old) were treated with a single dose of radiolabeled methylphenidate either by oral gavage (5 mg/kg) or I.P. (0.2 and 1 mg/kg). Blood samples were collected via the abdominal vena cava at 5, 10, 15, 30 minutes, 1, 1.5, 2, 4, 6, 8, and 24 h after the oral administration (3 animals/time point), and at 5, 15 minutes, 1, 2, 4, 8, and 24h (3 animals/time point) in the I.P. treated groups.

Results:

Blood and plasma concentrations profile of radioactivity and plasma concentrations profile of the unchanged compound after the single oral dose are shown in the following figure and table as provided by the sponsor:

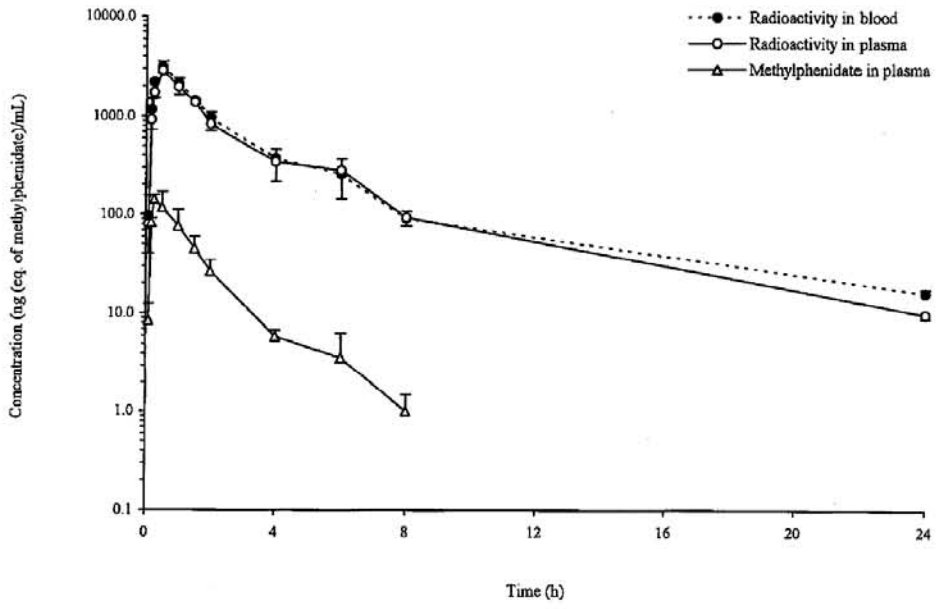


Figure 2 Concentration of radioactivity in blood and plasma, and concentration of methylphenidate in plasma after single oral administration of [^{14}C]methylphenidate to young male rats at 5 mg/kg

Each value represents the mean + (or –) S.D. of three rats.

Table II Concentration of radioactivity in blood and plasma, concentration of methylphenidate in plasma, and percentage fraction of radioactivity in blood cells after single oral administration of [^{14}C]methylphenidate to young male rats at 5 mg/kg

Time	Concentration (ng (eq. of methylphenidate)/mL)			Percentage fraction in blood cells (%)
	Radioactivity in blood	Radioactivity in plasma	Methylphenidate in plasma	
5 min	97.6 ± 58.4	79.4 ± 39.0	8.5 ± 3.9	46.4 ± 6.0
10 min	1155.2 ± 345.8	924.1 ± 195.5	83.2 ± 8.4	48.8 ± 5.0
15 min	2191.9 ± 104.5	1727.3 ± 184.0	142.1 ± 16.3	49.9 ± 4.8
30 min	3121.8 ± 413.3	2865.9 ± 157.2	118.2 ± 50.8	40.8 ± 5.4
1 h	2142.0 ± 246.0	1957.8 ± 316.7	77.0 ± 34.9	41.5 ± 7.7
1.5 h	1428.7 ± 39.2	1378.8 ± 60.3	45.4 ± 14.4	38.2 ± 3.3
2 h	967.8 ± 129.1	833.1 ± 121.8	26.5 ± 8.2	45.8 ± 1.8
4 h	370.1 ± 96.2	342.7 ± 126.3	5.9 ± 0.9	41.1 ± 6.5
6 h	255.5 ± 109.3	281.7 ± 136.9	3.6 ± 2.7	28.6 ± 4.6
8 h	91.0 ± 17.1	93.7 ± 16.0	1.0 ± 0.5	32.2 ± 2.1
24 h	15.7 ± 1.6	9.7 ± 0.8	N.D.	58.2 ± 5.9

Each value represents the mean ± S.D. of three rats.
N.D. : not detected

Plasma concentrations profile of radioactivity and the unchanged compound after single I.P. administration is shown in the following figure and table as summarized by the sponsor:

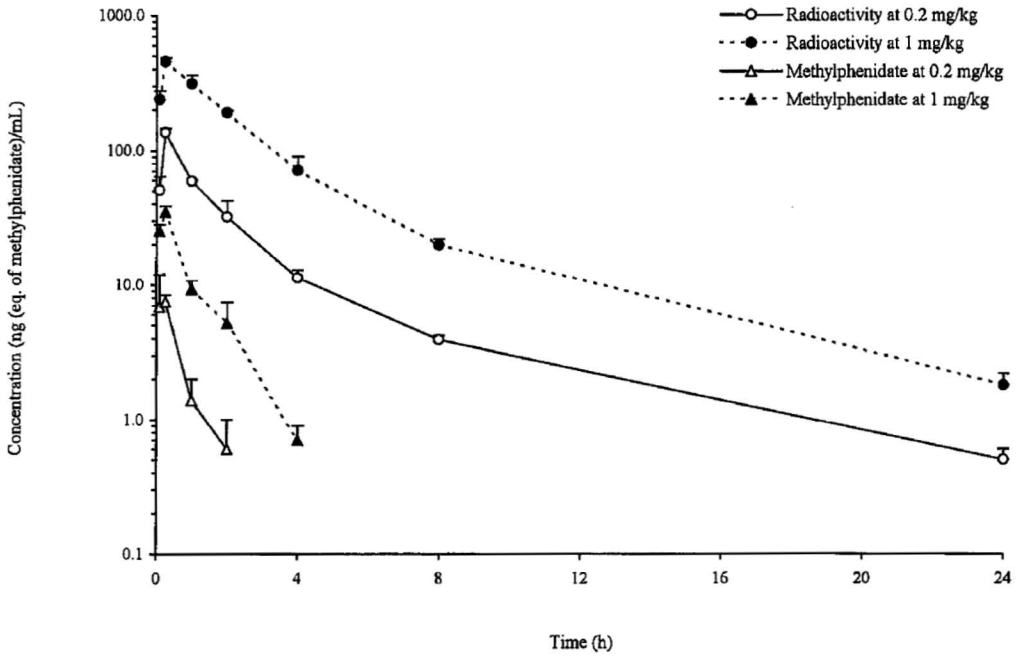


Figure 3 Concentration of radioactivity and methylphenidate in plasma after single intraperitoneal administration of [^{14}C]methylphenidate to young male rats at 0.2 or 1 mg/kg

Each value represents the mean + S.D. of three rats.

Table III Concentration of radioactivity and methylphenidate in plasma after single intraperitoneal administration of [^{14}C]methylphenidate to young male rats at 0.2 or 1 mg/kg

Time	Concentration (ng (eq. of methylphenidate)/mL)			
	0.2 mg/kg		1 mg/kg	
	Radioactivity	Methylphenidate	Radioactivity	Methylphenidate
5 min	50.9 ± 12.7	6.9 ± 5.1	240.7 ± 38.0	25.2 ± 3.1
15 min	137.1 ± 8.5	7.5 ± 0.9	454.3 ± 30.5	35.0 ± 3.7
1 h	58.9 ± 1.6	1.4 ± 0.6	313.2 ± 45.6	9.3 ± 1.5
2 h	32.1 ± 10.2	0.6 ± 0.4	190.9 ± 7.6	5.2 ± 2.2
4 h	11.3 ± 1.6	N.D.	71.1 ± 19.5	0.7 ± 0.2
8 h	3.9 ± 0.3	N.D.	19.8 ± 2.2	N.D.
24 h	0.5 ± 0.1	–	1.8 ± 0.4	–

Each value represents the mean ± S.D. of three rats.
N.D. : not detected, – : not measured

The PK parameters in each dosing group are summarized in the following table as provided by the sponsor:

Table IV Pharmacokinetic parameters of radioactivity in blood and plasma, and methylphenidate in plasma after single oral or intraperitoneal administration of [^{14}C]methylphenidate to young male rats

Parameter		5 mg/kg p.o.			0.2 mg/kg i.p.		1 mg/kg i.p.	
		Radioactivity in blood	Radioactivity in plasma	Methylphenidate in plasma	Radioactivity in plasma	Methylphenidate in plasma	Radioactivity in plasma	Methylphenidate in plasma
C_{max}	(ng (eq.)/mL)	3121.8	2865.9	142.1	137.1	7.5	454.3	35.0
t_{max}	(h)	0.5	0.5	0.25	0.25	0.25	0.25	0.25
$t_{1/2}$ (4 – 24 h)	(h)	4.6	4.0	–	4.7	–	4.0	–
$t_{1/2}$ (C_{max} – t)	(h)	–	–	1.1	–	0.49	–	0.70
AUC_{0-t}	(µg (eq.)·h/mL)	6.83	6.32	0.190	0.246	0.006	1.22	0.036
$AUC_{0-\infty}$	(µg (eq.)·h/mL)	6.93	6.38	0.191	0.249	0.006	1.23	0.037
CL_{tot}/F	(L/h/kg)	0.623	0.677	22.6	0.694	27.7	0.701	23.7

Each value obtained from the mean of three rats.

It should be noted that the ratio of AUC of plasma concentration of the unchanged compound to plasma concentration of the radioactivity after oral administration was approximately 0.02, and the ratio of Cmax was approximately 0.05. In response to I.P. administration, the ratio of AUC of plasma concentrations of the unchanged compound to plasma concentrations of radioactivity was ~ 0.03, and the ratio of Cmax was ~ 0.08.

In the study investigating the **excretion of radioactivity in rat breast milk**, Sprague Dawley females (n=5, 1 lactating rat/8 infant rats) were treated orally by gavage with a single dose of 5 mg/kg radiolabeled methylphenidate 12 days after parturition. Plasma and milk concentration of radioactivity was determined at 15 minutes, 1, 2, 4, 8 and 24h. Oxytocin (1 U/ml/kg) was intraperitoneally administered 15 min before dosing at each time point to promote the secretion of breast milk, and animals were mildly anesthetized at the time of milk sampling. Blood samples were obtained via the caudal vein.

Results: it should be pointed out that results were obtained from only 3 animals (sponsor did not specify reasons, but at least in one animal, milk secretion could not be achieved). The concentration ratio of radioactivity between breast milk and plasma in lactating rats was calculated as following: concentration of radioactivity in breast milk/concentration of activity in plasma.

Breast milk and plasma concentrations profile of radioactivity after single oral administration of radiolabeled methylphenidate are summarized in the following figure and table as provided by the sponsor:

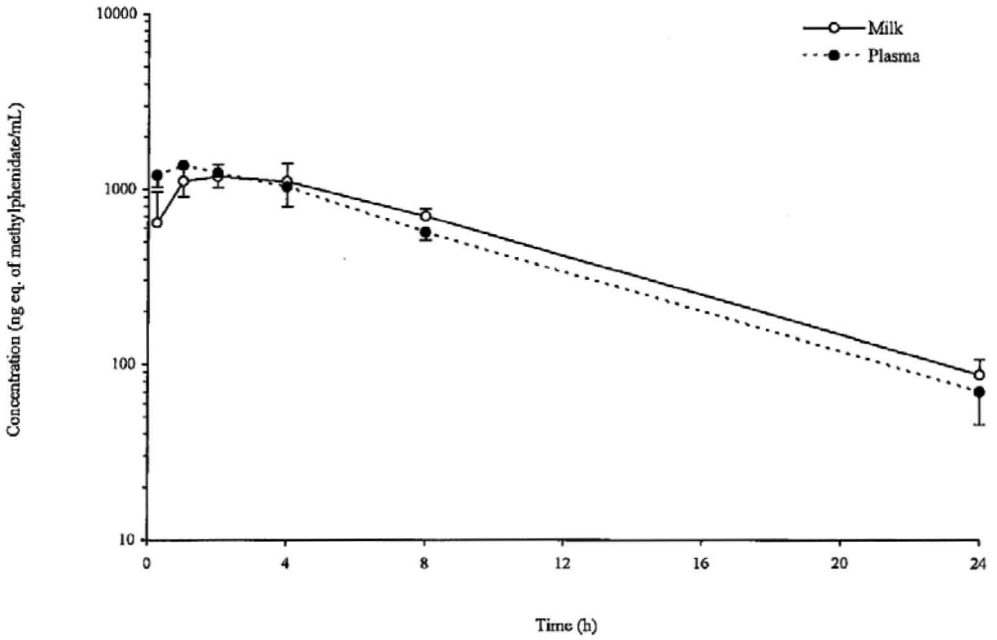


Figure 4 Concentration of radioactivity in milk and plasma after single oral administration of [^{14}C]methylphenidate to pregnant rats at 5 mg/kg

Each value represents the mean + (or –) S.D. of three rats.

Table V Concentration of radioactivity in milk and plasma after single oral administration of [^{14}C]methylphenidate to pregnant rats at 5 mg/kg

Time	Concentration (ng eq. of methylphenidate/mL)		Milk/Plasma
	Milk	Plasma	
15 min	643.7 ± 320.3	1199.0 ± 175.9	0.53 ± 0.20
1 h	1109.1 ± 247.7	1357.0 ± 451.7	0.86 ± 0.29
2 h	1179.2 ± 197.8	1231.0 ± 216.1	0.96 ± 0.09
4 h	1107.1 ± 292.2	1033.8 ± 236.2	1.07 ± 0.04
8 h	702.9 ± 72.2	568.3 ± 54.4	1.24 ± 0.04
24 h	87.4 ± 19.0	69.8 ± 24.8	1.45 ± 0.88

Each value represents the mean ± S.D. of three rats.

The PK parameters are summarized in the following table as provided by the sponsor:

Table VI Pharmacokinetic parameters of radioactivity in milk and plasma after single oral administration of [^{14}C]methylphenidate to pregnant rats at 5 mg/kg

Parameter		Milk	Plasma
C_{max}	(ng eq./mL)	1254.7 ± 224.9	1455.5 ± 381.4
t_{max}	(h)	2.3 ± 1.5	1.1 ± 0.9
$t_{1/2}$ (4 – 24 h)	(h)	5.4 ± 0.2	5.2 ± 1.0
AUC_{0-t}	(μg eq.·h/mL)	14.1 ± 2.0	13.0 ± 1.8
$AUC_{0-\infty}$	(μg eq.·h/mL)	14.8 ± 2.2	13.6 ± 1.6
CL_{tot}/F	(L/h/kg)	0.296 ± 0.041	0.322 ± 0.035

Each value represents the mean ± S.D. of three rats.

The ratio of the concentration of radioactivity in breast milk to plasma was 0.53 at 15 min after dosing, 0.86-1.07 between 1 and 4 h after dosing and 1.24-1.45 between 8 and 24h after dosing.

As obvious from the data from the lactating animals only total radioactivity was evaluated and there was no evaluation of the levels of the parent alone.

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

/s/

Ikram Elayan
6/19/2008 04:49:06 PM
PHARMACOLOGIST

Barry Rosloff
6/19/2008 05:00:33 PM
PHARMACOLOGIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

STATISTICAL REVIEW(S)

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

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA /Serial Number:	21-121/SE5-017
Drug Name:	CONCERTA®
Indication:	Adult Attention Deficit Hyperactivity Disorder (ADHD)
Applicant:	Johnson & Johnson Pharmaceutical Research & Development
Date of Submission:	08/31/2007
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Jingyu (Julia) Luan, Ph.D. (HFD-710)
Concurrent Reviewer:	Peiling Yang, Ph.D. (HFD -710)
	H.M. James Hung, Ph.D. (HFD -710)
Medical Division:	Division of Psychiatry Products (HFD -130)
Medical Officer:	Glenn Mannheim, M.D. (HFD -130)
Project Manager:	Nicholette Hemingway (HFD -130)

Key Words: Adult ADHD, Analysis of Covariance, Dunnett's procedure

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on Study 42603ATT3002, there is evidence that once daily dosages of oral CONCERTA® 18, 36 and 72 mg are effective for the treatment adult ADHD, as assessed by change from baseline in sum of inattention and hyperactivity/impulsivity subscale score of CAARS. Study 02-159 also displays a therapeutic advantage of CONCERTA® over placebo for the treatment of adult ADHD in terms of the change from baseline in the AISRS total score.

1.2 Brief Overview of Clinical Studies

This submission includes two pivotal efficacy studies, Study 42603ATT3002 (hereafter referred to as Study 3002) conducted in Europe and Study 02-159 conducted in United States.

Both Study 3002 and Study 02-159 were randomized, double-blind and placebo-controlled studies while Study 3002 was a 5-week fixed-dose study (18, 36, and 72 mg/day) followed by a 7-week, open-label, flexible-dose (18 to 90 mg/day) extension and Study 02-159 utilized a dose titration design. In Study 02-159, adults with ADHD were titrated to an individualized effective and tolerated dose over the dose range of 36 to 108 mg/day over a 5-week period and were maintained at this dose for a minimum of 2 additional weeks. Approximately 400 and 230 subjects were randomized into Study 3002 and Study 02-159, respectively.

1.3 Statistical Issues and Findings

For Study 3002, the primary efficacy parameter was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores (i.e., the total score) of the investigator-rated CAARS from baseline to the end of the double-blind phase. This primary efficacy parameter was analyzed using an ANCOVA model. The model included treatment, country and gender as factors and baseline score as a covariate. Dunnett's procedure was used to adjust for multiple comparisons of the 3 CONCERTA® dosages versus placebo. It appeared that superior effect was shown in patients treated with CONCERTA® 18 mg, 36 mg and 72 mg in comparison with patients treated with placebo. "Gender" is typically not included as a factor in primary efficacy analysis. However, based on this reviewer's analysis, the analysis results are consistent with or without "gender" as a factor in the ANCOVA model.

For Study 02-159, the primary endpoint was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit. The two treatment groups were compared using ANCOVA with change from baseline as the dependent variable; study site and treatment (All CONCERTA®, placebo) as factors; and baseline score as the covariate. It appeared that subjects treated with CONCERTA® displayed a therapeutic advantage in terms of change in AISRS total score than those treated with placebo. *In sponsor's primary efficacy analysis, the baseline observation was carried forward (BOCF) to Final Visit for subjects with no post-baseline evaluation. However, patients without post-baseline assessment are typically excluded from*

primary efficacy analysis. Based on this reviewer's analysis, for this study, since only 8 patients (2 in Placebo group, 6 in All CONCERTA group) did not have post-baseline score, the analysis results are consistent with or without these 8 subjects.

2 INTRODUCTION

2.1 Overview

Attention Deficit Hyperactivity Disorder (ADHD) is a disorder that begins in childhood, and studies suggest that between 30% and 60% of children who have been given a diagnosis of ADHD continue to manifest symptoms into adulthood. Data on the prevalence of ADHD in adults are limited, but recently the U.S. National Comorbidity Survey Replication estimated it to be approximately 4%. Adults with ADHD tend to have lower socioeconomic status, less educational and employment success, impaired interpersonal skills, and higher rates of separation/divorce.

Stimulant therapy is the mainstay of pharmacologic treatment for ADHD. Methylphenidate (MPH) is the most commonly prescribed and frequently studied stimulant medication for the treatment of ADHD. Methylphenidate is available as immediate release and sustained release formulations. An extended-release formulation of MPH, that utilizes ALZA Corporation's OROS® Push-Pull™ technology (hereafter referred to as CONCERTA® tablets), has been developed to deliver MPH over a 12-hour interval. CONCERTA® has been approved in the U.S. for the treatment of ADHD in children (6 to 12 years) and in adolescents (13 to 17 years). CONCERTA® is also approved in several other countries for the treatment of ADHD in children and adolescents.

The clinical development program evaluating the efficacy of CONCERTA® in the treatment of adult ADHD includes Study 3002 conducted in Europe and Study 02-159 conducted in United States.

Both Study 3002 and Study 02-159 were randomized, double-blind and placebo-controlled studies while Study 3002 was a 5-week fixed-dose study (18, 36, and 72 mg/day) followed by a 7-week, open-label, flexible-dose (18 to 90 mg/day) extension and Study 02-159 utilized a dose titration design. In Study 02-159, adults with ADHD were titrated to an individualized effective and tolerated dose over the dose range of 36 to 108 mg/day over a 5-week period and were maintained at this dose for a minimum of 2 additional weeks. Approximately 400 and 230 subjects were randomized into Study 3002 and Study 02-159, respectively.

2.2 Data Sources

The sponsor's electronic submission was stored in the directory of \\Cdsesub1\evsprod\NDA021121\0000 of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The efficacy of CONCERTA® for the treatment of adult ADHD was evaluated in two pivotal studies, Study 3002 and Study 02-159.

3.1.1 STUDY 42603ATT3002 (STUDY 3002)

3.1.1.1 Study Objectives

This study consists of **double-blind phase** and **open-label extension phase.**

The primary objective of the **double-blind phase** of this study was to evaluate the efficacy and safety of 3 fixed dosages of CONCERTA® (PR OROS methylphenidate) (18, 36 and 72 mg/day) compared with placebo in adult subjects with ADHD.

The primary objective of the **open-label extension** was to assess safety and tolerability of PR OROS methylphenidate in a flexible dose regimen (18-90 mg/day) in adult subjects diagnosed with ADHD.

3.1.1.2 Study Design

This was an international, multicenter, double-blind, randomized, placebo-controlled, parallel group, dose-response study followed by a 7-week open-label extension phase. During the 5-week double-blind phase, subjects were randomized into one of 4 treatment groups to receive once daily dosages of oral CONCERTA® 18, 36 or 72 mg, or placebo. Approximately 400 subjects from 13 countries in Europe were randomized in the double-blind phase of this study.

3.1.1.3 Efficacy Measures

The primary efficacy parameter was defined as the change in the sum of the inattention and hyperactivity/impulsivity subscale scores (i.e., the total score) of the investigator-rated Conners' Adult ADHD Rating Scale (CAARS) from baseline to the end of the double-blind phase (end of 5 weeks or last post-baseline assessment).

The secondary efficacy parameters include changes from baseline to the end of the treatment in:

- Clinical Global Impression-Severity of Illness Subscale (CGI-S) and Clinical Global Impression-Global Change Subscale (CGI-C)
- Conners' Adult ADHD Self-Report Short Version (CAARS-S:S)
- Sheehan's Disability Scale (SDS)
- Global Assessment of Effectiveness (GAE)

3.1.1.4 Statistical Analysis Plan

The primary efficacy parameter, change from Baseline in Sum of Inattention and Hyperactivity/Impulsivity Subscale Scores of CAARS, will be analyzed using an ANCOVA model. The model will include treatment, country and gender as factors and baseline sum of the inattention and hyperactivity/impulsivity subscale scores of the investigator-rated CAARS as a covariate. Dunnett's procedure will be used to adjust for multiple comparisons of the 3 PR OROS methylphenidate dosages versus placebo. The primary efficacy analysis will be conducted on ITT population and the last-observation-carried-forward (LOCF) method will be used to impute missing data.

CGI-S will be analyzed by ANOVA on the ranks of change from baseline with treatment and investigator as factors. CAARS-S:S, SDS and GAE will be analyzed using ANOVA with treatment and investigator as factors and the baseline score as covariate.

3.1.1.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

Patient disposition is summarized in Figure 1. Overall, 365 (91%) subjects completed the double-blind phase. The main reason for trial discontinuation during the double-blind phase was "adverse events" (3% - 12 subjects). All trial discontinuations due to adverse events were reported in the PR OROS methylphenidate groups, with the majority (8% - 8 subjects) in the highest dose group.

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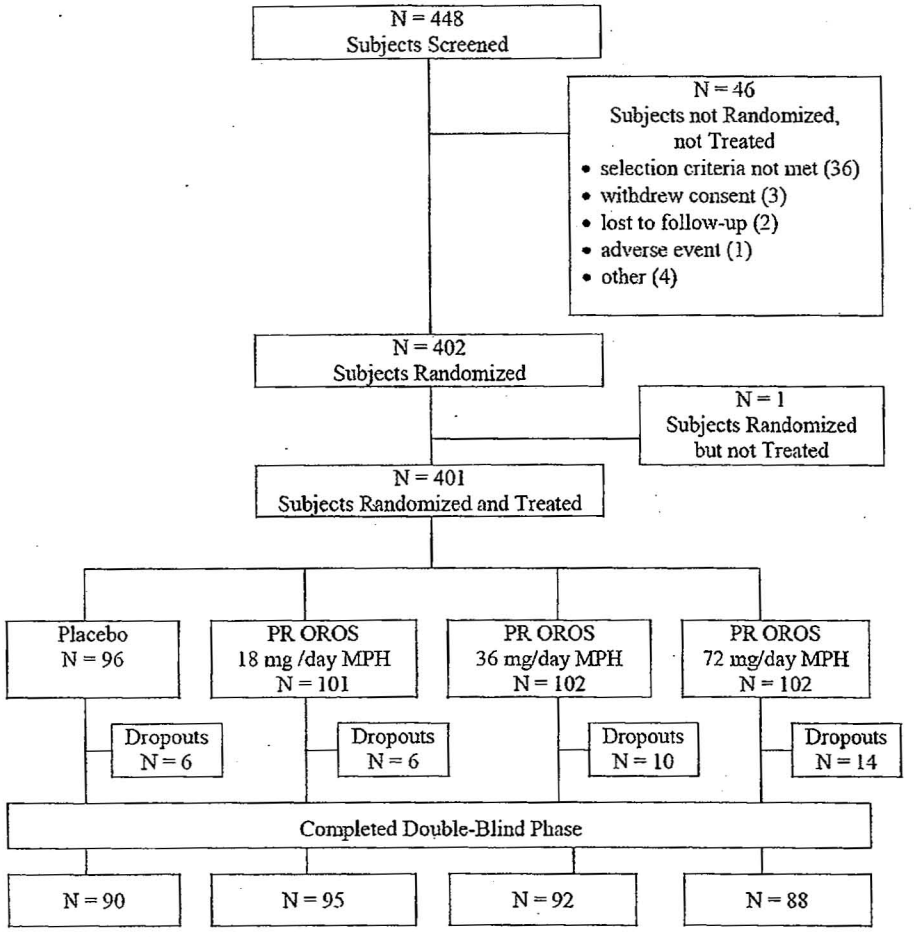
Figure 1 Subject Disposition in the Double-Blind Phase



Source: Attachment 1, Attachment 5, Attachment 6
N = number of subjects

Source: Figure 2 of Sponsor's Clinical Study Report

Demographic and Baseline Characteristics

Demographic and baseline characteristics of the "all subjects / double-blind" population are summarized in Table 1.

Table 1 Demographic Data and Baseline Characteristics (Study 3002: All Subjects / Double-Blind)

		PR OROS MPH			
	Placebo (N=96)	18 mg (N=101)	36 mg (N=102)	72 mg (N=102)	Total (N=401)
Age (years)					
N	96	101	102	102	401
Mean (SD)	34.5 (9.64)	34.2 (10.67)	33.8 (10.39)	33.6 (10.33)	34.0 (10.24)
Median	35.0	35.0	34.0	33.0	34.0
Range	18 - 57	18 - 60	18 - 60	18 - 63	18 - 63
Sex, n (%)					
N	96	101	102	102	401
Male	59 (61.5)	58 (57.4)	46 (45.1)	55 (53.9)	218 (54.4)
Female	37 (38.5)	43 (42.6)	56 (54.9)	47 (46.1)	183 (45.6)
Race, n (%)					
N	96	101	102	102	401
Caucasian	94 (97.9)	100 (99.0)	98 (96.1)	99 (97.1)	391 (97.5)
Other[a]	2 (2.1)	1 (1.0)	4 (3.9)	3 (2.9)	10 (2.5)
Weight (kg)					
N	95	100	102	102	399
Mean (SD)	79.6 (18.09)	78.3 (16.83)	75.7 (18.09)	77.7 (15.22)	77.8 (17.07)
Median	77.0	77.0	72.0	78.0	77.0
Range	48 - 147	50 - 151	44 - 135	42 - 117	42 - 151
Height (cm)					
N	96	100	102	102	400
Mean (SD)	175.8 (9.49)	172.9 (10.19)	172.3 (9.02)	173.2 (10.13)	173.5 (9.77)
Median	175.0	172.0	172.0	173.0	173.0
Range	155 - 198	145 - 194	151 - 192	149 - 198	145 - 198
BMI (kg/m^2)					
N	95	99	102	102	398
Mean (SD)	25.7 (5.37)	26.1 (5.06)	25.4 (5.47)	25.8 (3.97)	25.8 (4.98)
Median	24.5	24.9	24.7	25.1	24.9
Range	17.0 - 45.9	18.1 - 47.1	15.8 - 45.6	16.8 - 39.5	15.8 - 47.1
Child bearing potential					
N	37	43	55	47	182
Yes	33 (89.2)	39 (90.7)	45 (81.8)	44 (93.6)	161 (88.5)
No	4 (10.8)	4 (9.3)	10 (18.2)	3 (6.4)	21 (11.5)
Educational degree					
N	96	101	102	102	401
High school	32 (33.3)	22 (21.8)	27 (26.5)	29 (28.4)	110 (27.4)
Primary school	16 (16.7)	16 (15.8)	18 (17.6)	11 (10.8)	61 (15.2)
Secondary school	33 (34.4)	43 (42.6)	40 (39.2)	42 (41.2)	158 (39.4)
University	15 (15.6)	20 (19.8)	17 (16.7)	20 (19.6)	72 (18.0)
Still completing education					
N	96	101	102	101	400
Yes	30 (31.3)	27 (26.7)	26 (25.5)	29 (28.7)	112 (28.0)
No	66 (68.8)	74 (73.3)	76 (74.5)	72 (71.3)	288 (72.0)

[a] Other is defined as 'Black or African heritage', 'Hispanic' and 'Other'
N = number of subjects with data; n = number of subjects with observation
Source: Attachment 7

Source: Table 11 of sponsor's Clinical Study Report

The treatment groups of the double-blind phase appeared generally similar with respect to demographic data and baseline characteristics.

3.1.1.6 Sponsor's Primary Efficacy Results

The investigator-rated CAARS comprises 18 items, each corresponding to the 18 DSM-IV symptoms for ADHD. It is rated on a 4-point scale 0 = Not at all, never; 1 = Just a little, once in a while; 2 = Pretty much, often; 3 = Very much, very frequently. The scores of the individual items are summarized using two subscale scores (hyperactivity/impulsivity subscale and inattention subscale) and a total score, which is obtained by making the sum of the subscales.

The primary efficacy parameter was defined as the change in the sum of the inattention and hyperactivity/impulsivity subscale scores (i.e., the total score) of the investigator-rated CAARS from baseline to the end of the double-blind phase (end of 5 weeks or last post-baseline assessment).

The primary efficacy parameter was analyzed using an ANCOVA model. The model included treatment, country and gender as factors and baseline score as a covariate. Dunnett's procedure was used to adjust for multiple comparisons of the 3 CONCERTA® dosages versus placebo. The primary efficacy analysis was conducted on ITT population and the last-observation-carried-forward (LOCF) method was used to impute missing data.

Actual scores at baseline and end point, and changes from baseline to end point (LOCF) for the CAARS total score are presented in Table 2.

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Table 2 CAARS Total Score: Actual Values and Change from Baseline to Double-Blind End Point – LOCF (Study 3002: *Intent to Treat / Double-Blind*)

	Placebo	PR OROS MPH		
		18 mg	36 mg	72 mg
Baseline	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	37.2 (7.09)	35.6 (6.91)	37.3 (6.88)	36.6 (6.58)
Median	38.0	35.0	38.0	36.0
Range	24 – 51	24 – 53	25 – 51	24 – 52
Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	29.6 (10.60)	25.0 (10.43)	25.8 (10.88)	22.9 (10.95)
Median	29.0	24.0	26.0	22.0
Range	4 – 50	4 – 51	4 – 52	1 – 50
Change From Baseline to Double-Blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	-7.6 (9.93)	-10.6 (10.34)	-11.5 (9.97)	-13.7 (11.11)
Median	-6.0	-10.0	-10.0	-13.0
Range	-45 – 8	-35 – 16	-37 – 8	-40 – 8
p-value[a] (comparison versus placebo)		0.0146	0.0131	<0.0001

[a] Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure;
N = number of subjects with data
Source: Attachment 17, Attachment 18

Source: Table 20 of sponsor's Clinical Study Report

It appeared that superior effect was shown in patients treated with CONCERTA® 18 mg, 36 mg and 72 mg in comparison with patients treated with placebo, as assessed by the change from baseline to double-blind end point in CAARS total score.

Reviewer's Comments:

"Gender" is typically not included as a factor in primary efficacy analysis. However, based on this reviewer's analysis, the analysis results are consistent with or without "gender" as a factor in the ANCOVA model.

3.1.1.7 Sponsor's Secondary Efficacy Results

CAARS Hyperactivity/Impulsivity Subscale and Inattention Subscale

Changes from baseline for the hyperactivity/impulsivity and inattention subscale scores are shown in Table 3 and Table 4, respectively.

Table 3 CAARS Hyperactivity/Impulsivity Subscale Scores: Actual Values and Changes from Baseline during the Double-Blind Phase -- Observed Case (Study 3002: *Intent to Treat / Double-Blind*)

	Placebo	PR OROS MPH		
		18 mg	36 mg	72 mg
Baseline	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	17.2 (5.48)	16.4 (5.08)	17.4 (4.84)	16.8 (5.05)
Week 1	(N=94)	(N=98)	(N=101)	(N=99)
Mean (SD)	14.7 (5.81)	12.9 (5.30)	13.7 (5.44)	12.8 (5.44)
Mean Change From Baseline (SD)	-2.5 (3.99)	-3.5 (4.80)	-3.7 (4.83)	-3.9 (4.73)
p-value[a] (comparison versus placebo)		0.0464	0.0773	0.0134
Week 3	(N=92)	(N=98)	(N=92)	(N=95)
Mean (SD)	13.4 (5.77)	12.1 (4.96)	12.8 (5.25)	11.1 (5.30)
Mean Change From Baseline (SD)	-3.7 (5.18)	-4.3 (5.19)	-4.6 (5.02)	-5.7 (6.12)
p-value[a] (comparison versus placebo)		0.3208	0.4201	0.0023
Week 5	(N=88)	(N=92)	(N=88)	(N=86)
Mean (SD)	12.9 (6.42)	11.7 (5.73)	12.4 (6.06)	10.7 (5.61)
Mean Change From Baseline (SD)	-4.2 (5.46)	-4.6 (5.65)	-5.2 (5.06)	-5.9 (6.10)
p-value[a] (comparison versus placebo)		0.4967	0.5368	0.0193
Double-blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	13.2 (6.43)	11.8 (5.61)	12.5 (5.92)	10.7 (5.73)
Mean Change From Baseline (SD)	-3.9 (5.46)	-4.7 (5.54)	-4.9 (5.04)	-6.0 (6.18)
p-value[a] (comparison versus placebo)		0.2721	0.4056	0.0033

[a] Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure

N = number of subjects with data

Source: Attachment 17, Attachment 18

Source: Table 24 of sponsor's Clinical Study Report

Table 4 CAARS Inattention Subscale Scores: Actual Values and Changes from Baseline during the Double-Blind Phase -- Observed Case (Study 3002: *Intent to Treat / Double-Blind*)

		PR OROS MPH		
	Placebo	18 mg	36 mg	72 mg
Baseline	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	20.1 (4.29)	19.2 (4.45)	19.9 (4.12)	19.8 (3.60)
Week 1	(N=94)	(N=98)	(N=101)	(N=99)
Mean (SD)	17.0 (4.98)	14.7 (5.21)	14.4 (5.45)	14.2 (5.39)
Mean Change From Baseline (SD)	-3.1 (3.76)	-4.5 (4.94)	-5.5 (5.09)	-5.6 (5.04)
p-value[a] (comparison versus placebo)		0.0102	0.0001	0.0001
Week 3	(N=92)	(N=98)	(N=92)	(N=95)
Mean (SD)	16.2 (5.90)	13.8 (5.42)	13.3 (5.74)	12.2 (6.12)
Mean Change From Baseline (SD)	-3.8 (4.82)	-5.3 (5.09)	-6.6 (5.74)	-7.6 (6.15)
p-value[a] (comparison versus placebo)		0.0300	0.0004	< 0.0001
Week 5	(N=88)	(N=92)	(N=88)	(N=86)
Mean (SD)	16.2 (6.08)	13.3 (6.04)	12.9 (6.42)	12.2 (6.11)
Mean Change From Baseline (SD)	-3.7 (5.28)	-5.9 (5.86)	-7.2 (5.90)	-7.7 (6.21)
p-value[a] (comparison versus placebo)		0.0031	0.0001	< 0.0001
Double-blind End Point	(N=95)	(N=99)	(N=101)	(N=99)
Mean (SD)	16.4 (5.99)	13.2 (5.89)	13.4 (6.36)	12.2 (6.11)
Mean Change From Baseline (SD)	-3.7 (5.23)	-5.9 (5.76)	-6.5 (5.92)	-7.6 (6.29)
p-value[a] (comparison versus placebo)		0.0014	0.0004	< 0.0001

[a] Comparison between each dose group and placebo adjusted for multiplicity using Dunnett's procedure

N = number of subjects with data

Source: Attachment 17, Attachment 18

Source: Table 25 of sponsor's Clinical Study Report

It seems that baseline scores were comparable across treatment groups for both subscales, respectively. However, baseline scores for the inattention subscale (range: 19.2 – 20.1) were numerically higher than those for the hyperactivity/impulsivity subscale (range: 16.4 – 17.4) in all treatment groups. For both subscales and at all time points, the largest decrease from baseline was consistently observed in the 72 mg PR OROS methylphenidate group.

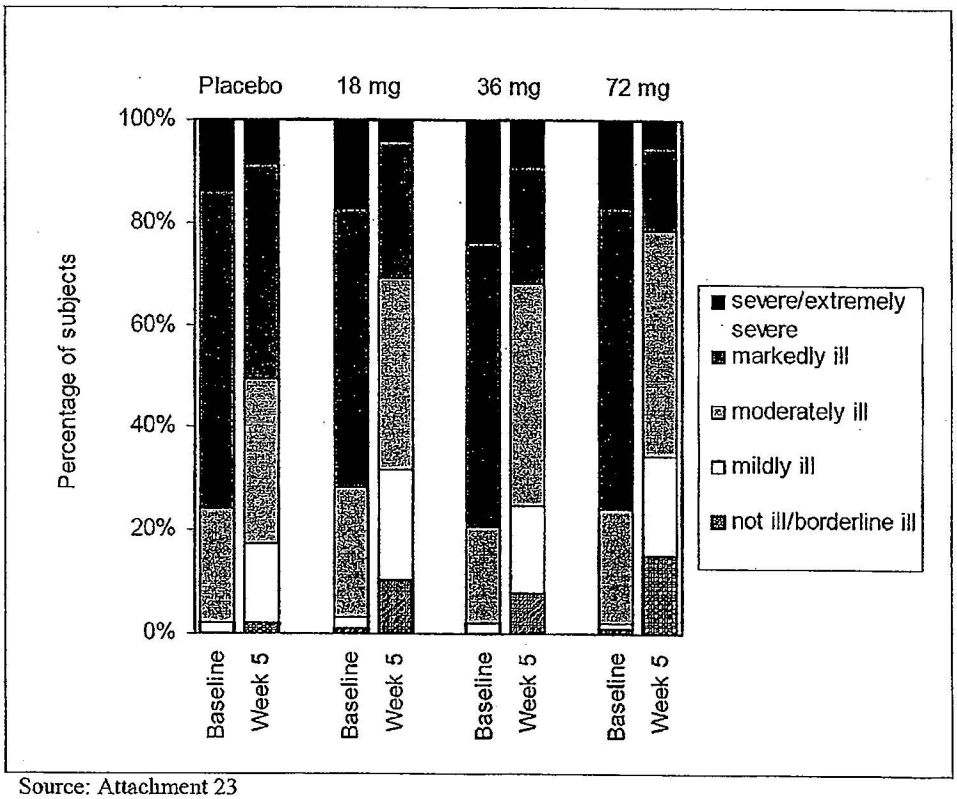
Reviewer's Comments:

The p-values in the two tables above were adjusted for the comparisons between each dose group and placebo for a specific time point, but not adjusted for all comparisons across time points.

Clinical Global Impression – Severity (CGI-S)

The investigator-rated CGI-S scale is used to evaluate the severity of a subject's illness on a 7-point scale ranging from 1 (not ill) to 7 (extremely severe). The distribution of CGI-S scores at baseline and Week 5 is shown graphically in Figure 2.

Figure 2 CGI-S: Percentage of Subjects by Severity at Baseline and Week 5 (end of the Double-Blind Phase) (Study 3002: *Intent to Treat / Double-Blind*)



Source: Attachment 23

Source: Figure 3 of sponsor's Clinical Study Report

At baseline, 72% to 79% of subjects in the four treatment groups were considered markedly to extremely ill. At Week 5, the proportion of subjects who were considered markedly to extremely ill had decreased to 21%-32% in the PR OROS methylphenidate groups compared to 51% in the placebo group.

3.1.2 STUDY 02-159

3.1.2.1 Study Objectives

The primary objective of this study was to evaluate the efficacy and safety of CONCERTA® extended-release tablets at five dose levels (36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day) compared to placebo in adults with ADHD.

3.1.2.2 Study Design

This was a randomized, placebo-controlled, double-blind, parallel-group, dose-titration study conducted in the US at 27 investigative sites. A total of 229 adult subjects were enrolled. Treatment schedule for this study is summarized in Table 5.

Table 5 Treatment Schedule for Study 02-159

Visit	Screening Visit[a]	Baseline Visit	Titration Visit 1[b]	Titration Visit 2[b]	Titration Visit 3[b]	Titration Visit 4[b]	Titration Visit 5[b]	Final Visit/ 2 Week Efficacy Assessment
Study Day	Day -14 to -7	Day[a] 0	Day 7 +/-2 days	Day 14 +/- 2 days	Day 21 +/-2 days	Day 28 +/- 2 days	Day 35 +/- 2 days	Day 49 +/- 2 days
Dose Evaluation	Washout from ADHD medication 7-14 days as needed		36 mg Placebo	54 mg Placebo	72 mg Placebo	90 mg Placebo	108 mg Placebo	Individualized Dose

a: Subjects that were being treated for ADHD at screening had to washout from all ADHD medication for seven to 14 days. Subjects on atomoxetine HCl returned for Baseline within a 10 to 14 day window.
b: Doses were titrated until the individualized dose was achieved. All visits were required, even if a subject had achieved an individualized dose.

Source: Table 7-1 of sponsor's Clinical Study Report

3.1.2.3 Efficacy Measures

Primary Measures:

- Change from baseline in the AISRS (Adult ADHD Investigator Symptom Rating Score) total score as assessed by the investigator at the Final Visit/Two Week Efficacy Assessment Visit.

Selected Secondary Measures:

- Global Improvement subscale of the Clinical Global Impression (CGI-I)
- Response defined as a subject who has a 30% improvement (without rounding) in the AISRS score from baseline and has a CGI-I of ≤ 2 (either very much improved or much improved)
- Change from baseline of the Severity of Illness subscale of the (CGI-S)

- Change from baseline in total score of the Conners' Adult ADHD Rating Scale – Self-Report: Short Version (CAARS-S:S)
- Change from baseline in the ADHD Impact Module for Adults (AIM-ATM)
- Change from baseline in the Sheehan Disability Scale at the end of the study.

3.1.2.4 Statistical Analysis Plan

The primary endpoint was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit/Two Week Efficacy Assessment Visit. A total AISRS score was calculated by adding the score (0 to 3) for each of 18 items, thus giving a total score ranging from 0 to 54. A reduction in score represented an improvement. The two treatment groups (All CONCERTA®, placebo) were compared using analysis of covariance (ANCOVA) with change from baseline as the dependent variable; study site and treatment as factors; and baseline score as the covariate. Sites with fewer than eight subjects were combined. The primary efficacy analysis was based on the ITT population using the LOCF approach.

Continuous secondary endpoints were analyzed using ANCOVA similarly as the primary endpoint. Responder analysis was performed using a Cochran-Mantel-Haenszel test comparing responder status (responder versus non-responder) by treatment (All CONCERTA®, placebo) stratified by site.

Selected secondary endpoints were analyzed sequentially and were considered statistically significant at the 0.05 level only if the endpoint was individually significant at the 0.05 level and previous endpoints in the hierarchy were significant at the 0.05 level, including the primary endpoint. If the primary endpoint was statistically significant, the selected secondary endpoints were assessed in the following order:

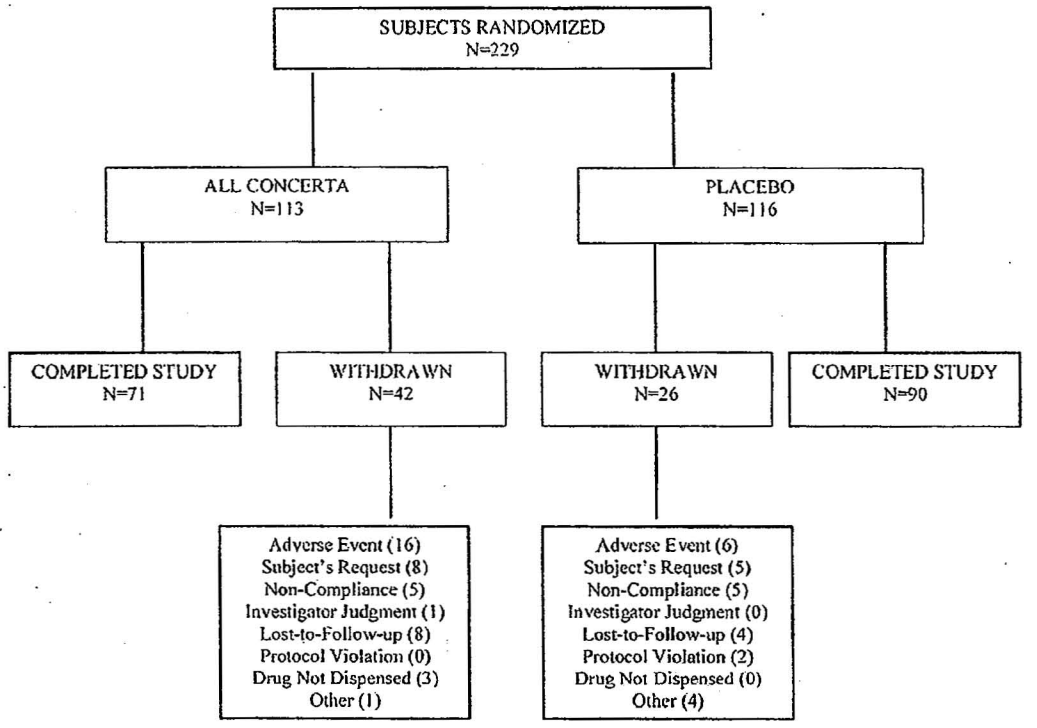
- CGI-I (last score provided during the study)
- CAARS-S:S total score change from baseline (last score provided during the study)
- Response defined as a subject who had a 30% improvement (without rounding) in the AISRS score from baseline and has a CGI-I of much improved or very much improved (last score provided during study)
- Sheehan Disability Scale change from baseline score for the "work" question
- CGI-S last score provided during the study
- AIM-A work/home/school domain (change from baseline)

3.1.2.5 Patient Disposition, Demographic and Baseline Characteristics

Patient Disposition

A total of 348 subjects were screened for study entry, 229 subjects were randomized and 161 subjects completed the study. Figure 3 summarizes the status of subjects in the study.

Figure 3 Disposition of Subjects



Source: Figure 8-1 of sponsor's Clinical Study Report

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Demographic and Other Baseline Characteristics

Demographic and baseline characteristics for the All Randomized Population are presented by treatment group in Table 6. In general, the treatment groups appeared similar with respect to demographic and baseline characteristics.

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Table 6 Demographic and Baseline Characteristics by Treatment Group – All Randomized Subjects

Characteristic	All CONCERTA N=113	Placebo N=116	Total N=229
Gender, n (%)			
Male	66 (58.4)	64 (55.2)	130 (56.8)
Female	47 (41.6)	52 (44.8)	99 (43.2)
Age, years			
N	113	116	229
Mean (SD)	40.2 (12.38)	38.2 (11.40)	39.2 (11.91)
Median	40.0	38.0	39.0
Range (min, max)	(18, 65)	(19, 64)	(18, 65)
Age Group, years, n (%)			
18 to 35	42 (37.2)	47 (40.5)	89 (38.9)
36 to 49	41 (36.3)	48 (41.4)	89 (38.9)
50 to 65	30 (26.5)	21 (18.1)	51 (22.3)
Race, n (%)			
White or Caucasian	98 (86.7)	99 (85.3)	197 (86.0)
Black/African American	8 (7.1)	6 (5.2)	14 (6.1)
Asian	3 (2.7)	4 (3.4)	7 (3.1)
American Indian/Alaska Native	0 (0.0)	0 (0.0)	0 (0.0)
Native Hawaiian/Other Pacific Islander	0 (0.0)	1 (0.9)	1 (0.4)
Other	4 (3.5)	6 (5.2)	10 (4.4)
Ethnicity, n (%)			
Hispanic or Latino	13 (11.5)	14 (12.1)	27 (11.8)
Non Hispanic	100 (88.5)	102 (87.9)	202 (88.2)
Weight, kg			
N	113	116	229
Mean (SD)	82.92 (17.926)	85.14 (17.822)	84.05 (17.869)
Median	81.20	84.55	83.00
Range (min, max)	(47.6, 150.1)	(48.1, 148.8)	(47.6, 150.1)
Height, cm			
N	113	116	229
Mean (SD)	171.44 (9.468)	171.76 (9.565)	171.60 (9.497)
Median	170.20	172.70	171.40
Range (min, max)	(147.3, 191.8)	(149.9, 194.3)	(147.3, 194.3)
BMI, kg/m^2			
N	113	116	229
Mean (SD)	28.27 (6.243)	28.81 (5.435)	28.54 (5.841)
Median	27.40	28.25	27.80
Range (min, max)	(17.9, 58.6)	(19.0, 51.4)	(17.9, 58.6)
Smoking status, n (%)			
None	71 (62.8)	76 (65.5)	147 (64.2)
Former	24 (21.2)	26 (22.4)	50 (21.8)
Current	18 (15.9)	14 (12.1)	32 (14.0)
Pack Years (Former/Current)			
N	41	40	81
Mean (SD)	12.1 (16.19)	9.4 (10.65)	10.8 (13.72)
Median	5.0	5.5	5.0
Range (min, max)	(0, 80)	(0, 42)	(0, 80)
Years since quitting			
N	24	26	50
Mean (SD)	9.5 (10.74)	8.7 (10.17)	9.1 (10.35)
Median	4.5	5.5	5.0
Range (min, max)	(0, 38)	(0, 38)	(0, 38)
ADHD subtype, n (%)			
Inattentive	23 (20.4)	21 (18.1)	44 (19.2)
Hyperactive-Impulsive	1 (0.9)	1 (0.9)	2 (0.9)
Combined	89 (78.8)	94 (81.0)	183 (79.9)
Global Assessment of Functioning (GAF)			
N	113	116	229
Mean (SD)	53.2 (4.02)	53.0 (4.23)	53.1 (4.12)
Median	52.0	54.0	54.0
Range (min, max)	(41, 65)	(42, 60)	(41, 65)

Source: Table 8-5 of sponsor's Clinical Study Report

3.1.2.6 Sponsor's Primary Efficacy Results

The primary endpoint of the study was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit. The primary efficacy analysis was based on the ITT analysis set using the LOCF approach. The baseline observation was carried forward (BOCF) to Final Visit for subjects with no post-baseline evaluation. The two treatment groups were compared using ANCOVA with change from baseline as the dependent variable; study site and treatment (All CONCERTA®, placebo) as factors; and baseline score as the covariate. A decrease from baseline in the observed weekly AISRS score indicated improvement in ADHD symptoms. Statistical testing was performed on the All CONCERTA® group versus the placebo group. The results were presented in Table 7.

Table 7 AISRS Total Score and Change From Baseline at Final Visit (LOCF)[a] (ITT)

Statistic	All CONCERTA	Placebo	p-Value[b]
Baseline			
N	110	116	
Mean (SD)	38.6 (6.85)	38.1 (7.31)	
Median	38.5	38.0	
Range (min, max)	(24, 54)	(24, 54)	
Final Visit (LOCF)			
N	110	116	
Mean (SD)	27.6 (13.17)	31.3 (12.38)	
Median	26.5	33.0	
Range (min, max)	(0, 52)	(3, 54)	
Change from Baseline:			
N	110	116	
Mean (SD)	-10.9 (11.75)	-6.8 (11.45)	
Median	-9.0	-3.0	
Range (min, max)	(-48, 13)	(-38, 12)	
95% CI	(-13.2, -8.7)	(-8.9, -4.7)	
LSMean (SEM)	-10.6 (1.09)	-6.8 (1.06)	0.012

a: AISRS total score ranges from 0 to 54 with higher scores indicating more severe ADHD. Change from baseline is the value at the visit minus the baseline value. A negative change from baseline indicates an improvement.

b: p-Value from test for significant treatment difference from ANCOVA model with change from baseline as the dependent variable, site and treatment (All CONCERTA, placebo) as factors, and baseline value as covariate.

Abbreviation: CI - confidence interval

Note: For AISRS Total Score, subjects who lacked post-baseline data had their baseline values carried forward to Final Visit (LOCF).

Source: Table 9-1 of sponsor's clinical study report

It seems that subjects treated with CONCERTA® displayed a therapeutic advantage in terms of change in AISRS total score than those treated with placebo (p=0.012).

Reviewer's Comments:

In sponsor's primary efficacy analysis, the baseline observation was carried forward (BOCF) to Final Visit for subjects with no post-baseline evaluation. However, patients without post-baseline assessment are typically excluded from primary efficacy analysis. Based on this reviewer's analysis, for this study, since only 8 patients (2 in Placebo group, 6 in All CONCERTA group) did not have post-baseline score, the analysis results are consistent with or without these 8 subjects.

3.1.2.7 Sponsor's Secondary Efficacy Analysis

Table 8 presents baseline scores and Table 9 presents the summary and analysis of the efficacy endpoints including the primary endpoint and secondary efficacy endpoints at Final Visit (LOCF) for the ITT Population. The secondary endpoints were analyzed sequentially. Details regarding this testing procedure were presented in Section 3.1.2.4.

Table 8 Primary and Secondary Baseline Scores by Treatment Group - Intent-to-Treat

Variable	All CONCERTA	Placebo
Primary		
AISRS Total Score		
N	110	116
Mean (SD)	38.6 (6.85)	38.1 (7.31)
Median	38.5	38.0
Range (min, max)	(24, 54)	(24, 54)
Secondary		
CAARS-S:S Total Score		
N	109	116
Mean (SD)	50.4 (10.32)	49.4 (10.73)
Median	50.0	50.0
Range (min, max)	(29, 72)	(19, 71)
Sheehan Disability Scale - Work		
N	106	109
Mean (SD)	6.7 (2.21)	6.6 (2.19)
Median	7.0	7.0
Range (min, max)	(1, 10)	(0, 10)
CGI-Severity		
N	110	116
Mean (SD)	4.7 (0.63)	4.6 (0.60)
Median	5.0	5.0
Range (min, max)	(4, 7)	(4, 7)
AIM-A: Work/Home/School Domain		
N	110	116
Mean (SD)	30.2 (18.31)	31.5 (16.66)
Median	28.8	32.5
Range (min, max)	(0, 75)	(0, 78)

Source: Table 9-6 of sponsor's Clinical Study Report

Table 9 Summary of Efficacy Endpoints at Final Visit (LOCF), Intent-to-Treat Population

Variable[a]	All CONCERTA	Placebo	p-Value[b]
Primary			
AISRS: Change from Baseline			
N	110	116	
LSMean ± SEM	-10.6 ± 1.09	-6.8 ± 1.06	0.012
Secondary			
CGI-Improvement:			
N	103	115	
LSMean ± SEM	3.0 ± 0.11	3.4 ± 0.11	0.008
CAARS-S:S Total Score: Change from baseline			
N	102	115	
LSMean ± SEM	-12.7 ± 1.45	-8.3 ± 1.37	0.029
Responder defined as:			
Subjects with 30% improvement in AISRS Score and a CGI-Improvement rating of much or very much improved, % (n/N)	36.9 (38/103)	20.9 (24/115)	0.009
Sheehan Disability Scale - Work: Change from baseline			
N	90	99	
LSMean ± SEM	-1.3 ± 0.25	-1.0 ± 0.24	0.397
CGI-Severity: Change from baseline			
N	103	115	
LSMean ± SEM	-0.9 ± 0.11	-0.5 ± 0.10	Not Tested[c]
AIM-A: Work/Home/School Domain: Change from baseline			
N	94	107	
LSMean ± SEM	16.5 ± 2.37	8.6 ± 2.24	Not Tested[c]

a: Lower values indicate greater improvement for AISRS, CGI-Improvement, CAARS-S:S Total Score, Sheehan Disability Score- Work, and CGI-Severity. Higher values indicate greater effectiveness for AIM-A Work/Home/School Domain.

b: Tests for significant treatment differences for AISRS total score, CAARS-S:S Total Score, Sheehan Disability Score - Work, CGI-Severity, and AIM-A Work/Home/School Domain with ANCOVA model. Tests for significant treatment differences for CGI-Improvement with ANOVA model. Tests for significant treatment differences for responder analysis with Cochran-Mantel-Haenszel row means score.

c: Formal testing was not performed due to multiple-testing hierarchy. Nominal p-values: CGI-Severity nominal p-value = 0.009, AIM-A Work/Home/School Domain nominal p-value = 0.016.

Note: The number of subjects reported for each variable is not the same because the baseline value was carried forward to final visit only for the AISRS score.

Source: Table 9-7 of sponsor's Clinical Study Report

Based on the results of the pre-specified sequential testing procedure, it appeared that subjects treated with CONCERTA® showed superior effects in CGI-I score, CAARS-S:S total score, and

responder analysis. Responder is defined as subjects with both a 30% improvement in AISRS score and a CGI-I rating of much or very much improved.

3.1.3 REVIEWER'S ANALYSIS

This reviewer agrees with sponsor's primary efficacy analysis results. Please refer to ***Reviewer's Comments*** in Section 3.1.1.6, 3.1.1.7, and 3.1.2.6 for comments/additional analyses.

3.2 Evaluation of Safety

Please refer to Dr. Mannheim's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

4.1.1 STUDY 3002

Table 10 presents the summary statistics for change from baseline to double-blind endpoint in CAARS total score by subgroups.

Table 10 Descriptive Statistics for Change from Baseline to Double-Blind Endpoint (LOCF) in CAARS Total Score, by Age Group, Gender and Race (ITT)

Treatment Group	Subgroup	N	Mean	Std Dev	Median
MPH 18mg OD	Female	43	-8.6	9.77	-8
	Male	56	-12.16	10.59	-12.5
MPH 36mg OD	Female	55	-10.93	9.74	-11
	Male	46	-12.11	10.3	-10
MPH 72mg OD	Female	46	-12.68	9.61	-13.5
	Male	53	-14.53	12.29	-13
PLACEBO	Female	36	-7	8.22	-6
	Male	59	-7.98	10.9	-6
MPH 18mg OD	Aged 18-25	52	-10.87	10.89	-12
	Aged 36-49	37	-9.84	9.43	-9
	Aged 50-65	10	-12.2	11.5	-11
MPH 36mg OD	Aged 18-25	55	-10.68	9.96	-8
	Aged 36-49	40	-13.08	10.36	-13.5
	Aged 50-65	6	-8	6.03	-6.5
MPH 72mg OD	Aged 18-25	57	-12.35	10.89	-13

PLACEBO	Aged 36-49	36	-15.67	11.63	-15.5
	Aged 50-65	6	-14.17	9.87	-12
	Aged 18-25	49	-7.47	9.94	-6
	Aged 36-49	41	-7.44	10	-6
	Aged 50-65	5	-10.4	11.13	-11
MPH 18mg OD	White	98	-10.63	10.39	-11
	other	1	-9	.	-9
MPH 36mg OD	Black or African Heritage	1	-9	.	-9
	White	98	-11.55	10.07	-10
	other	2	-8.5	9.19	-8.5
MPH 72mg OD	White	96	-13.47	11.02	-13
	other	3	-20	14.73	-23
PLACEBO	Black or African Heritage	1	-11	-	-11
	White	93	-7.65	10	-6
	other	1	0	-	0

Source: Reviewer's Analysis

It seems that that the point estimates of treatment effect are in the same direction across the patient subgroups investigated.

4.1.2 STUDY 02-159

The change from baseline to final visit in the AISRS total score is summarized by subgroups and treatment group in Table 11.

Table 11 Descriptive Statistics for Change from Baseline to Final Visit (LOCF) in the AISRS Total Score, by Age Group, Gender and Race (ITT)

Subgroup	All CONCERTA				Placebo			
	n	mean	Std Dev	median	n	mean	Std Dev	median
Female	47	-10.66	11.43	-8	52	-6.79	12.21	-1.50
Male	63	-11.16	12.08	-11	64	-6.88	10.89	-3.50
Age 18-35	42	-11.31	12.68	-9.00	47	-7.72	11.22	-3.00
Age 36-49	40	-10.60	10.09	-8.50	4	-6.25	11.82	-3.00
Age 50-65	28	-10.89	12.90	-9.00	21	-6.19	11.52	-4.00
African-American	7	-8.43	14.91	-2.00	6	-2.67	5.35	0.00
Caucasian	96	-11.48	11.78	-11.00	99	-7.37	11.98	-3.00
Other	7	-6.14	7.15	-5.00	11	-4.27	8.14	-1.00

Source: Reviewer's Analysis

It appears that the point estimates of treatment effect are in the same direction across the patient subgroups investigated.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

For Study 3002, the primary efficacy parameter was the change in the sum of the inattention and hyperactivity/impulsivity subscale scores (i.e., the total score) of the investigator-rated CAARS from baseline to the end of the double-blind phase. This primary efficacy parameter was analyzed using an ANCOVA model. The model included treatment, country and gender as factors and baseline score as a covariate. Dunnett's procedure was used to adjust for multiple comparisons of the 3 CONCERTA® dosages versus placebo. It appeared that superior effect was shown in patients treated with CONCERTA® 18 mg, 36 mg and 72 mg in comparison with patients treated with placebo. "Gender" is typically not included as a factor in primary efficacy analysis. However, based on this reviewer's analysis, the analysis results are consistent with or without "gender" as a factor in the ANCOVA model.

For Study 02-159, the primary endpoint was the change from baseline in the AISRS total score as assessed by the investigator at the Final Visit. The two treatment groups were compared using ANCOVA with change from baseline as the dependent variable; study site and treatment (All CONCERTA®, placebo) as factors; and baseline score as the covariate. It appeared that subjects treated with CONCERTA® displayed a therapeutic advantage in terms of change in AISRS total score than those treated with placebo. *In sponsor's primary efficacy analysis, the baseline observation was carried forward (BOCF) to Final Visit for subjects with no post-baseline evaluation. However, patients without post-baseline assessment are typically excluded from primary efficacy analysis. Based on this reviewer's analysis, for this study, since only 8 patients (2 in Placebo group, 6 in All CONCERTA group) did not have post-baseline score, the analysis results are consistent with or without these 8 subjects.*

5.2 Conclusions and Recommendations

Based on Study 42603ATT3002, there is evidence that once daily dosages of oral CONCERTA® 18, 36 and 72 mg are effective for the treatment adult ADHD, as assessed by change from baseline in sum of inattention and hyperactivity/impulsivity subscale score of CAARS. Study 02-159 also displays a therapeutic advantage of CONCERTA® over placebo for the treatment of adult ADHD in terms of the change from baseline in the AISRS total score.

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Jingyu Luan
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Peiling Yang
3/26/2008 04:31:31 PM
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James Hung
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21121
Drug:	Methylphenidate HCl
Trade Name:	Concerta® Extended Release (OROS® methylphenidate HCl)
Strengths:	18 and 36 mg
Sponsor:	Johnson and Johnson
Indication:	Treatment of Attention Deficit Hyperactivity Disorder (ADHD) in Adults
Type of Submission:	Efficacy Supplement (New Population)
Submission Date:	8/29/07, 12/6/07
OND Division:	DPP (HFD-130)
OCP Division:	DCP1
PM Reviewer:	Peter Lee, Ph.D.
PM Secondary Reviewer:	Joga Gobburu, Ph.D.
Reviewer:	Kofi A. Kumi, Ph.D.
Team Leader:	Raman Baweja, Ph.D.

Table of Contents

APPEARS THIS WAY ON ORIGINAL

1. Executive Summary

1.1 Recommendations

The Office of Clinical Pharmacology (OCP) has reviewed the data submitted to the Clinical Pharmacology and Biopharmaceutics sections of NDA 21-121 SE017 and finds the data acceptable. The following are OCP recommendations:

At comparable dose levels (54 mg Concerta vs 50 mg Ritalin, and 108 mg Concerta vs 90 mg Ritalin), the abuse potential (VAS drug liking score) is lower for Concerta than for Ritalin, due to the lower drug concentration that can be achieved with the extended-release formulation.

For formulations of Concerta and Ritalin that produce similar range of drug concentration (108 mg Concerta vs 60 mg Ritalin), there is no statistical difference in the primary abuse potential.

The drug concentration (e.g. Cmax) following 144 mg Concerta is at the similar level as that of 90 mg Ritalin. However, the abuse potential of 144 mg Concerta has not been investigated.

Systemic exposures for methylphenidate were greater for the Ritalin immediate release treatment compared to either crushed or whole Concerta treatments, even when exposures were adjusted for dose.

The pharmacokinetics of methylphenidate after administration of Concerta is linear between 54 to 144 mg and is similar to that observed for lower doses up to 72 mg.

1.2 Phase IV Recommendation

There are no Phase IV commitment recommended

1.3 Summary of Clinical Pharmacology and Biopharmaceutics

Background: Methylphenidate is a stimulant commonly used to treat Attention Deficit Hyperactivity Disorder (ADHD). Concerta is a once-a-day, controlled-release, oral methylphenidate HCl formulation that uses the patented OROS® technology. Concerta was approved under NDA 21-121 for the treatment of ADHD in children (6 to 12 years) at doses ranging from 18 to 54 mg/day. Concerta was also approved (NDA 21-121 S008) for the treatment of ADHD in adolescents (13 to 17 years) at doses ranging from 18 mg to 72 mg/day. This supplemental New Drug Application (sNDA) is for the use of Concerta in the treatment of ADHD in adults, at doses ranging from 18 mg to (b) (4) mg per day. This sNDA contains safety and efficacy data from 2 key placebo-controlled Phase 3 trials in adults with ADHD (Protocols 42603ATT3002 and 02-159). The use of Concerta in Adults will be supported with approved and currently marketed dosage strengths. There are new pharmacokinetic data from single and multiple doses of Concerta in adults up to doses of 144 mg/day, included in this application. Additionally, the sNDA includes pharmacokinetic (PK) and pharmacodynamic (PD) data related to abuse potential of Concerta. The sponsor cross referenced the studies in Adults describing the human pharmacokinetics and bioavailability in Adults submitted to the original application.

Therapeutic Indication and Dosage Regimen in Adults: Concerta is indicated for the treatment of ADHD in adults, at doses ranging from 18 to (b) (4) mg per day.

Exposure-Response

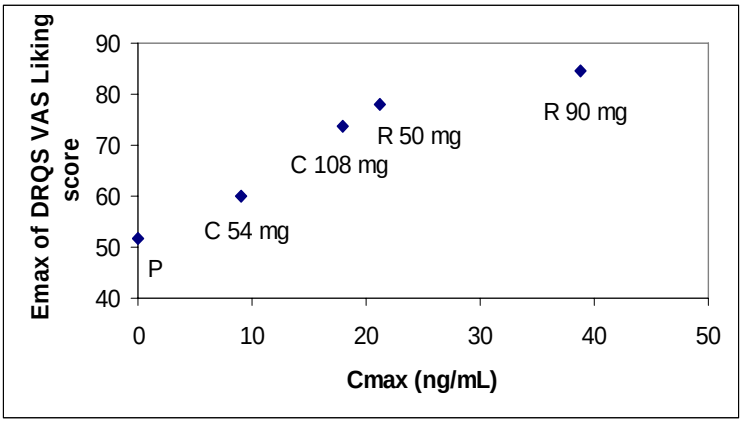
The sponsor conducted 3 clinical studies (12-005, 12-007, 12-302) to compare the abuse potential of Concerta, an extended-release formulation, and that of Ritalin, an immediate-release formulation of the same active ingredient (methylphenidate HCl). The three abuse potential studies were conducted in different patient populations with various experiences of substance abuse. The dose range of Concerta and Ritalin were also different among the three studies. The OCP review of abuse potential of Concerta was conducted by Dr. Peter Lee of the Pharmacometrics group.

At comparable dose levels (54 mg Concerta vs 50 mg Ritalin, and 108 mg Concerta vs 90 mg Ritalin), the abuse potential (VAS drug liking score) is lower for Concerta than for Ritalin, due to the lower drug concentration that can be achieved with the extended-release formulation.

For formulations of Concerta and Ritalin that produce similar range of drug concentration (108 mg Concerta vs 60 mg Ritalin), there is no statistical difference in the primary abuse potential.

The drug concentration (e.g. Cmax) following 144 mg Concerta is at a similar level as that of 90 mg Ritalin. However, the abuse potential of 144 mg Concerta has not been investigated. The drug label proposed by the sponsor recommends up to (b) (4) mg daily.

Fig 1: PK-PD relationship between the mean values of Cmax vs Emax from study 12-007. (C: Concerta, R: Ritalin)



Pharmacokinetics of Methylphenidate in Adults

Methylphenidate exhibits linear and dose-proportional pharmacokinetics for doses in the range of 54 to 144 mg. At doses of 54 to 144 mg, the pharmacokinetics of methylphenidate were similar to those observed previously for lower doses (doses up to 72 mg).

Bioavailability and Bioequivalence

The sponsor conducted a study to determine the pharmacokinetics of methylphenidate from single oral doses of crushed and whole Concerta® Tablets and crushed Ritalin® Tablets in healthy subjects.

Systemic exposures of methylphenidate were greater for Ritalin immediate release treatment compared to either Concerta when crushed or taken whole. Post hoc relative bioavailability analysis of the two crushed tablet dosing regimens revealed that the crushed Concerta treatment was not bioequivalent to the crushed Ritalin treatment. The crushed Concerta tablet resulted in mean peak methylphenidate concentrations that were on average approximately 20% lower than the crushed Ritalin tablet when adjusted for the actual dose the subject received.

2. Question Based Review

The QBR section of the review has used a deductive approach (i.e. starts with conclusions followed with supportive details) as instructed by CDER Review Template MaPP 4000.4.

2.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology and biopharmaceutics of this drug?

The sponsor submitted data in this supplemental New Drug Application (sNDA) to support the use of Concerta for the treatment of ADHD in adults (18 years and older). In August, 2000, Concerta was approved under NDA 21-121 for the treatment of ADHD in children (6 to 12 years) at doses ranging from 18 mg to 54 mg/day. In October, 2004 (S-008), Concerta was approved for the treatment of ADHD in adolescents (13 to 17 years) at doses ranging from 18 mg to 72 mg/day. This sNDA cross-referenced the original Concerta NDA (treatment in children) and the supplement 008 (treatment of ADHD in adolescents). This indication for adults will be supported with currently approved and marketed dosage strengths and does not include any new formulation or strength.

2.2. General Clinical Pharmacology and Biopharmaceutics

2.2.1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Efficacy results of 2 placebo-controlled, Phase 3 clinical trials in adults (18 to 65 years) with ADHD (DSM-IV criteria) were submitted in this Application. Study 42603ATT3002 was a randomized, double-blind, placebo-controlled, 5-week fixed-dose (18, 36 and 72 mg/day) study followed by a 7-week, open-label, flexible-dose (18 to 90 mg/day) extension. According to the sponsor, this study provided a benefit-risk assessment of Concerta for the treatment of adults with ADHD at fixed doses of 18, 36, 72 mg/day. The second randomized, double-blind, placebo-

controlled trial included in this application, Study 02-159, utilized a dose titration design. In Study 02-159, adults with ADHD were titrated to an individualized effective and tolerated dose over a dose range of 36 to 108 mg/day (36, 54, 72, 90 or 108 mg/day) over a 5-week period and were maintained at this dose for a minimum of 2 additional weeks. A series of four clinical pharmacokinetic-pharmacodynamic studies were conducted to evaluate different aspects of abuse liability that might be related to Concerta.

2.2.2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes, the active moieties in the plasma have been adequately identified and measured.

2.2.3. Exposure- Response

The review of the abuse potential of Concerta was conducted by Dr. Peter Lee of the Pharmacometric group in OCP.

2.2.3.1. What are the designs of the three abuse potential studies?

Three studies were conducted to investigate abuse potential of Concerta vs Ritalin. Study 12-302 has a smaller subject number of 18. Study 12-005 includes 49 healthy adults with a history of recreational stimulant use, and study 12-007 includes, a different population, 55 healthy adults with a history of light (occasional) stimulant use. The two larger studies are considered for the analyses of abuse potential by the sponsor and in this review. In addition, Study 02-160 contains pharmacokinetics information of a wider range of doses of Concerta, which were not studied in 12-005 and 12-007. The additional PK information are used as part of the PK-PD analyses in this review.

2.2.3.2. What are the endpoints used in the two "pivotal" abuse potential studies, 12-005 and 12-007?

The primary endpoint for abuse potential in both 12-005 and 12-007 is the DQRS-VAS Liking scale score. Additional endpoints including ARCI and SDVP were also measured in the studies. Multiple time points of these endpoints were measured after dosing, so that the maximum effect (E_{max}, *defined as the maximum effect within 24 hour post dosing*) and the area under the effect curve (AUE) can be estimated.

2.2.3.3 How are the abuse potentials compared between Concerta and Ritalin based on the PK-PD relationship?

Since the doses of Concerta and Ritalin studied and compared in 12-005 and 12-007 are not identical, and the pharmacokinetic profiles of the two formulations (extended-release for Concerta and immediate-release for Ritalin) are very different, it is important to examine the abuse potential based on concentration-response relationship. In addition, the highest tolerable doses for the two formulations may also be different due to the difference in pharmacokinetic profile, such as in the Cmax values. Figure 2 shows that Cmax of Concerta is relatively lower than that of Ritalin at comparable dose amounts. This may explain the lower abuse potential

effects between 54 mg Concerta and 50 mg Ritalin, and between 108 mg Concerta and 90 mg Ritalin in study 12-007. On the other hand, 108 mg Concerta and 60 mg Ritalin have similar Cmax range (Figure 2) and there was no statistical difference in the primary endpoint of abuse potential effect between the two formulations in study 12-005. The PK-PD plot of Cmax vs Emax (Figure 3) also indicates consistent trend between the PK and PD parameters regardless of the formulation (Concerta or Ritalin).

Figure 2. Comparison of Cmax between Concerta and Ritalin at various dose levels based on Studies 005, 007 and 160. (C: Concerta, R: Ritalin)

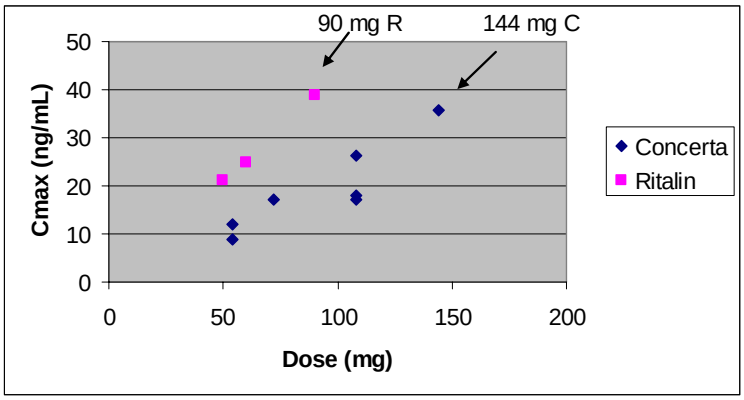
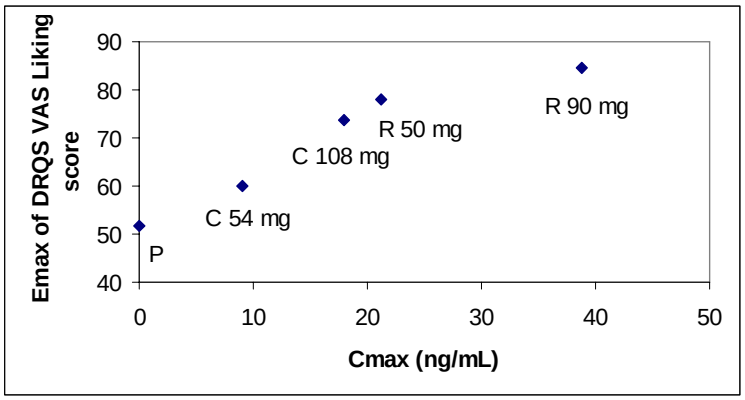


Figure 3. PK-PD relationship between the mean values of Cmax vs Emax from study 12-007. (C: Concerta, R: Ritalin)



2.2.4. What is the pharmacokinetics of methylphenidate after administration of high doses of Concerta® (54, 72, 108 and 144 mg) in healthy adults?

Methylphenidate exhibits linear and dose-proportional pharmacokinetics for doses in the range of 54 to 144 mg in adults. There was minimal accumulation upon once-daily multiple dosing. This is similar to the observation for lower doses (18 to 72 mg/day) in pediatric and adolescent subjects.

The sponsor conducted a study to determine the pharmacokinetics of high doses of Concerta® (54, 72, 108 and 144 mg) in healthy adults. The study was an open-label, four-period, dose-escalation, multiple-dose design. Study personnel administered the Concerta (methylphenidate HCl) dose to subjects each morning for four days. All subjects received sequentially increasing doses during four periods separated by three-days washout. In each study period, subjects were dosed once daily for four days in order to reach steady state concentrations of methylphenidate. The following table contains descriptive pharmacokinetic parameters for methyphenidate on day 1 and day 4. And the figures show the methylphenidate concentrations increase dose proportionally between 54 and 144 mg.

Table 1: Methylphenidate Pharmacokinetic Parameters (Mean, SD, %CV) for Subjects Who Completed All Four Treatments (N=25)

	DAY 1					
	C_{MAX} (ng/mL)	T_{MAX}[a] (h)	AUC_{INF} (ng-h/mL)	K_{EL} (1/h)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{TAU}/ AUC_{INF})
Treatment A (54 mg)	12.03 (3.54) 29.4%	6 (1-10) 31.5%	130 (32.4) 24.9%	0.199 (0.033) 16.4%	3.58 (0.629) 17.6%	1.082[c] 1.021, 1.142
Treatment B (72 mg)	17.12 (5.80) 33.9%	6 (5-10) 26.0%	196 (65.7) 33.5%	0.200 (0.034) 17.1%	3.57 (0.617) 17.3%	0.961 0.925, 0.998
Treatment C (108 mg)	26.26 (6.38) 24.3%	6 (5-12) 25.8%	293[c] (76.5) 26.1%	0.198[c] (0.031) 15.8%	3.59[c] (0.544) 15.2%	1.066[c] 0.971, 1.042
Treatment D (144 mg)	35.83 (9.72) 27.1%	6 (1-12) 35.9%	381[d] (104.5) 27.4%	0.195[d] (0.032) 16.4%	3.65[d] (0.598) 16.4%	1.081[d] 1.018, 1.144
	DAY 4					
	C_{MAX} (ng/mL)	T_{MAX}[a] (h)	AUC_{TAU} (ng-h/mL)	K_{EL} (1/h)	$T_{½}$ (h)	$C_{MIN,SS}$ (ng/mL)
Treatment A (54 mg)	12.45 (2.84) 22.8%	6 (1-10) 35.5%	139[c] (33.6) 24.1%	0.199 (0.033) 16.3%	3.60 (0.844) 23.5%	0.496 (0.305) 61.5%
Treatment B (72 mg)	16.12 (4.60) 28. 6%	6 (5-8) 15.4%	185 (49.0) 26.4%	0.194 (0.029) 15.1%	3.63 (0.49) 13.4%	0.807 (0.428) 53.1%
Treatment C (108 mg)	25.96 (6.99) 26.9%	6 (5-10) 19.2%	291 (71.1) 24.4%	0.197 (0.030) 15.2%	3.60 (0.56) 15.5%	1.228 (0.607) 49.4%
Treatment D (144 mg)	36.94 (11.31) 30.6%	6 (1-8) 30.8%	419 (137.0) 32.7%	0.207 (0.033) 15.7%	3.42 (0.50) 14.5%	1.731 (0.894) 51.6%

a: median and range are listed; b: mean and 95% confidence interval are listed;
c: N = 24; d: N = 23

Table 2: Statistical Analysis of Log Transformed PK Parameters for Methylphenidate

Contrast PK Parameter		Day 1 Ratio (%)	Day 1 90 % confidence Lower	Day 1 90 % confidence Upper	Day 4 Ratio (%)	Day 4 90 % confidence Lower	Day 4 90 % confidence Upper
CMAX	72/54	106.72	93.96	121.20	96.21	85.43	108.36
	108/54	110.62	97.40	125.64	103.60	91.84	116.48
	144/54	112.30	98.87	127.54	109.60	97.32	123.43
	108/72	103.66	91.27	117.73	107.50	95.45	121.07
	144/72	105.23	92.65	119.51	113.91	101.15	128.29
	144/108	101.51	89.38	115.29	105.96	94.09	119.34
AUCINF[a]	72/54	111.59	99.12	125.62	100.01	89.08	112.28
	108/54	112.41	99.73	126.70	104.94	93.47	117.81
	144/54	109.44	96.97	123.52	110.63	98.55	124.20
	108/72	100.74	89.37	113.54	104.93	93.58	117.66
	144/72	98.08	86.90	110.70	110.62	98.66	124.04
	144/108	97.36	86.16	110.02	105.43	94.02	118.22

[a] AUC_{tau} for Day 4

Fig 4: Methylphenidate Dose-Proportionality of AUCinf on Day 1

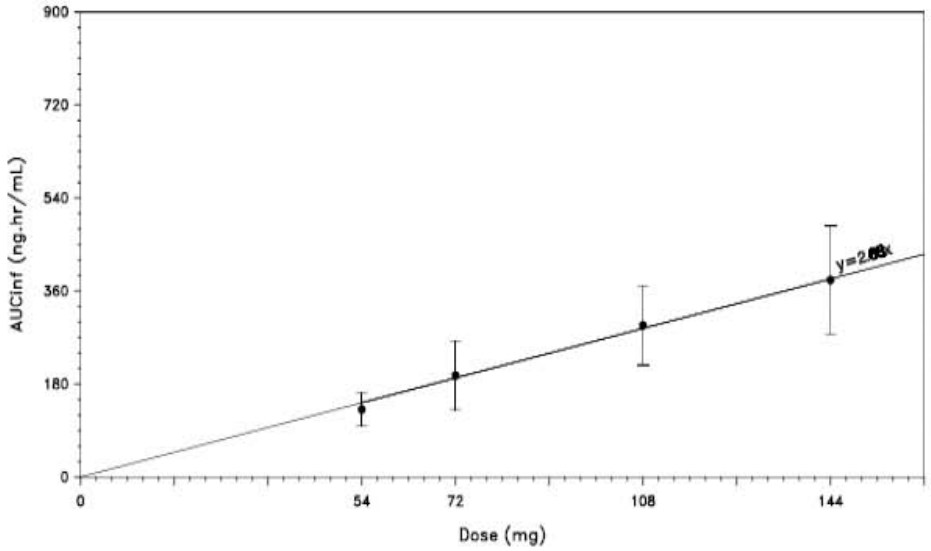
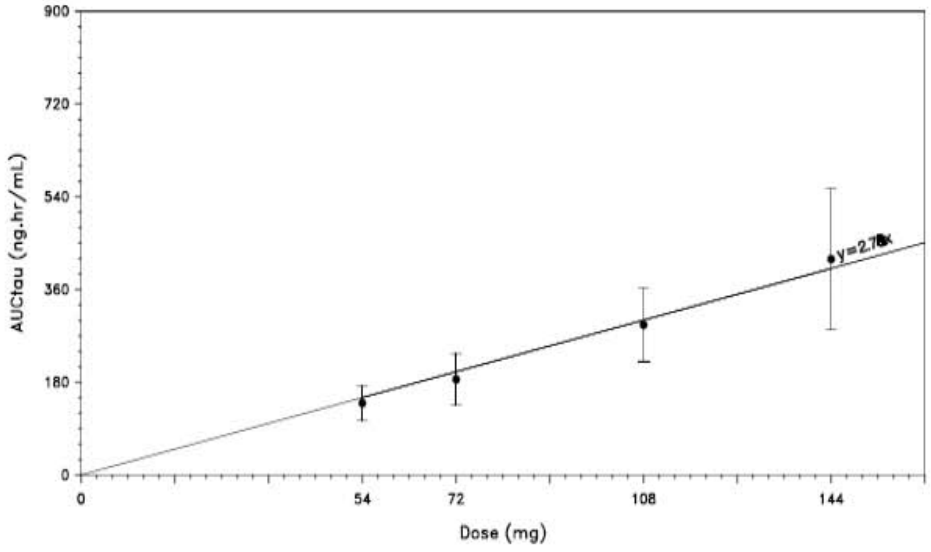


Fig 5: Methylphenidate Dose-Proportionality of AUCtau on Day 4



2.2.5 Are the Pharmacokinetics of methylphenidate similar after administration of Concerta to Pediatric, Adolescents and Adult Subjects?

The pharmacokinetics of methylphenidate was similar between adolescents and adults. Body weight was found to have a significant effect on CL/F, Vd/F and T ½ Total MPH and for CL/F and V/F of *d*-MPH. The effect of body weight on half-life was not significant for *d*-MPH.

A cross-study analysis was performed to evaluate the effect of demographics across a wide range of ages and doses. Data from studies used in previously submitted cross-study analysis that included children, adolescents and adults up to doses of 72 mg/day were also included. This analyses evaluated the effects of demographic variables of weight and age group on the pharmacokinetics parameters of *d*- and Total methylphenidate. For children (6-12), the PK parameters were estimated from Ritalin 5 mg three times a day (TID) administration. For adolescents and adults, the PK parameters were estimated after administration of Concerta at various doses, ranging from 18 to 144 mg. Data from studies measuring the same analyte were pooled together. A total of 190 subjects contributed to the evaluation of Total MPH and a total of 185 subjects contributed to the evaluation of *d*-MPH. The following table contains descriptive statistics of pharmacokinetic parameters by age group

Age did not have a statistically significant effect on body-weight normalized oral clearance, neither for Total MPH nor for *d*-MPH. However, there was a statistically significant effect of age on V/F/WT and T1/2 for Total MPH. For these parameters, children aged 6-12 years had statistically significant lower values than for adults and adolescents, while values were statistically not significantly different for adolescents and adults aged 18-35 years and 36-55 years. As body weight increased, CL/F, V/F, and T1/2 increased for Total MPH, CL/F, V/F increased for *d*-MPH.

Table 3: Descriptive Statistics of Pharmacokinetic Parameters by Age-Group

Analyte	PK Parameter	Statistics	Children (6-12 years)[a]	Adolescent (13-17 years)[b]	Adult (18-35 years)[b]	Adult (36-55 years)[b]
Total MPH	CL/F (L/h)	N	31	26	291	88
		Mean	242.55	384.03	440.60	497.35
		(SD)	(68.1)	(108.67)	(127.96)	(178.94)
	V/F (L)	Mean	653.19	2088.05	2303.35	2506.33
		(SD)	(158.98)	(698.79)	(756.3)	(966.41)
	$T_{1/2}$ (h)	Mean	1.92	3.84	3.63	3.52
		(SD)	(0.36)	(1.34)	(0.56)	(0.61)
	CL/F/WT (L/h/kg)	Mean	6.58	6.60	5.85	6.56
		(SD)	(2.02)	(1.88)	(1.98)	(2.77)
	V/F/WT (L/kg)	Mean	17.72	36.06	30.35	32.92
		(SD)	(4.63)	(13.7)	(10.59)	(14.28)
d-MPH	CL/F (L/h)	N	NA	26	202	70
		Mean	NA	195.76	265.66	265.49
		(SD)		(54.89)	(84.94)	(96.1)
	V/F (L)	Mean	NA	1100.82	1433.13	1549.97
		(SD)		(448.51)	(453.55)	(547.34)
	$T_{1/2}$ (h)	Mean	NA	3.99	3.82	4.20
		(SD)		(1.85)	(0.69)	(1.10)
	CL/F/WT (L/h/kg)	Mean	NA	3.36	3.82	3.50
		(SD)		(0.94)	(1.19)	(1.30)
	V/F/WT (L/kg)	Mean	NA	19.05	20.53	20.36
		(SD)		(8.80)	(6.24)	(7.17)

[a] CL/F, V/F, and T1/2 values are from RITALIN (immediate release methylphenidate) dosed three times on one day to mimic CONCERTA (see text for further explanation)

[b] CONCERTA data

N = Number of Observations; NA = Data not available

Fig 6: Plot of PK Parameters Versus Body Weight

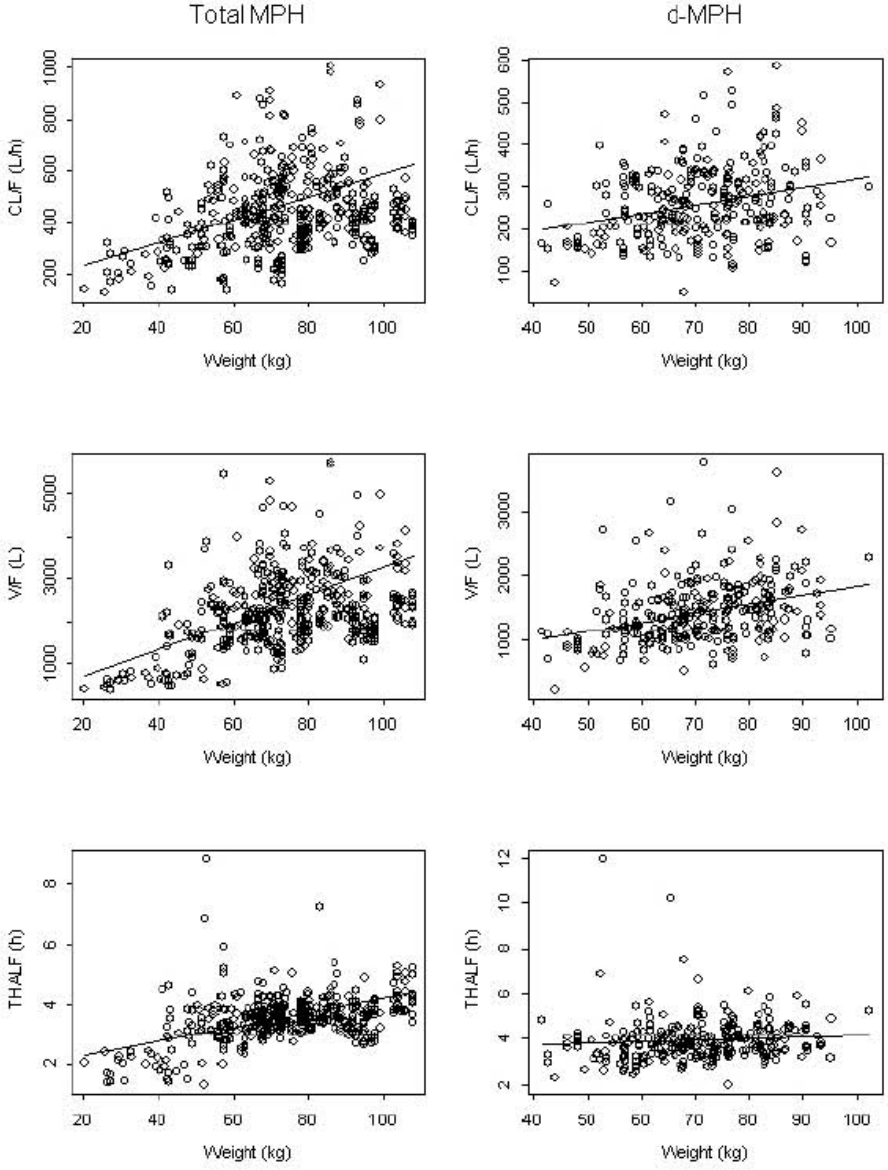


Table 4: Estimated Intercept and Slope, Test Statistics and P-Value for the Evaluation of the Effect of Body Weight

Analyte	Parameter	Intercept	Estimated Slope for Weight	SE of Estimated Slope	Degrees of Freedom	Test Statistic (t)	p-value for Significance of Slope
Total MPH	CL/F (L/h)	145.53	4.42	0.576	197	7.68	<0.001
	V/F (L)	71.11	31.97	3.246	194	9.85	<0.001
	$T_{1/2}$ (h)	1.81	0.02	0.003	171	7.80	<0.001
d-MPH	CL/F (L/h)	110.90	2.08	0.502	186	4.14	<0.001
	V/F (L)	461.48	13.69	2.747	183	4.98	<0.001
	$T_{1/2}$ (L)	3.48	0.01	0.006	171	1.03	0.306

2.2.6 Are the pharmacokinetics of Concerta® (Methylphenidate HCl) in crushed and whole form, and Ritalin® in crushed form dosed to healthy subjects similar?

Systemic exposures for methylphenidate were greater for the Ritalin immediate release treatment compared to either crushed or whole Concerta treatments, even when exposures were adjusted for dose. Crushed Concerta treatment was not bioequivalent to the crushed Ritalin treatment. The crushed Concerta tablet resulted in mean peak d-threomethylphenidate concentrations that were on average approximately 20% lower than the crushed Ritalin tablet when adjusted for dose.

The sponsor conducted a study to determine the pharmacokinetics of methylphenidate from single oral doses of crushed and whole Concerta® Tablets and crushed Ritalin® Tablets in healthy subjects. The study was a single-dose, open-label, three-treatment crossover design. Subjects were fasted overnight for at least 10 hours prior to receiving drug in each treatment period. They received one of the three treatments, designated A through C, each period: 1) One intact (whole) Concerta Tablet, 18 mg 2) One Concerta Tablet, 18 mg, crushed. 3) One Ritalin Tablet, 20 mg, crushed. Each subject consumed 4 ounces of apple sauce with the dose and drank 180 mL of water. Table 5 contains the statistical analysis comparing the different treatments in the study.

Fig 7: Mean (SD) Plasma d-Threo-Methylphenidate Concentrations versus Time Following Single Doses to Healthy Adults

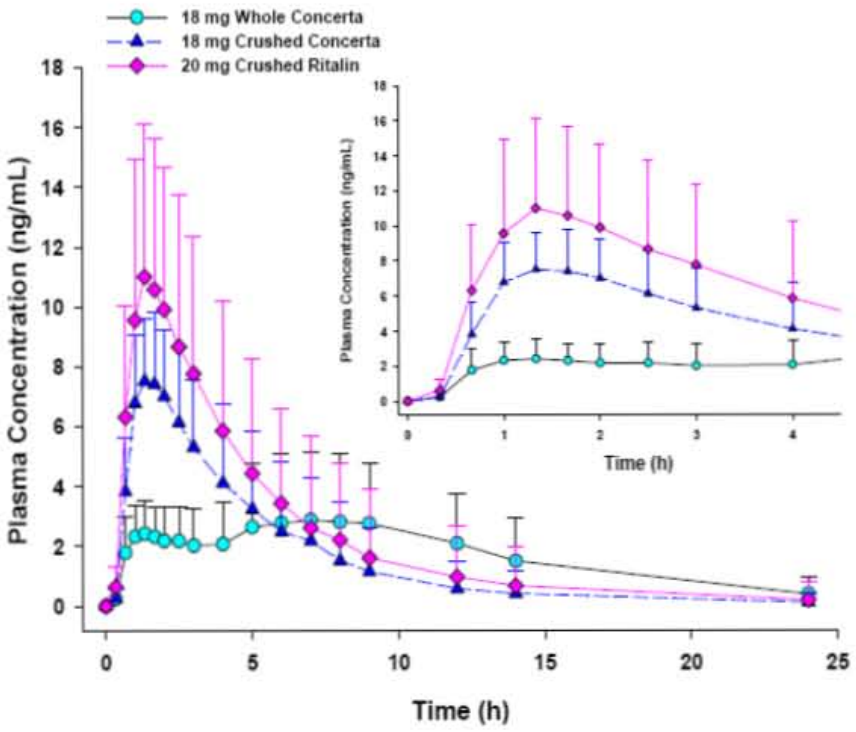


Table 5: Summary of Post hoc Statistical Analysis for Relative Bioavailability of d-Threo-Methylphenidate Following Single Doses of 18 mg Crushed Concerta Tablet Relative to 20 mg Crushed Ritalin Tablet to Healthy Adults (N = 18)

Pharmacokinetic Parameter	Ratio[a] (%)	90% Confidence Intervals	p value
CMAX/Dose (ng/mL/mg)	81.46	(74.75, 88.78)	0.0008
CMAX (ng/mL)	72.68	(66.68, 79.22)	< 0.0001
AUC_{0-2h}/Dose (ng.h/mL/mg)	80.13	(71.10, 90.31)	0.0054
AUC_{0-2h} (ng.h/mL)	71.49	(63.41, 80.61)	0.0002
AUCMEDIAN/Dose (ng.h/mL/mg)	79.29	(66.33, 94.78)	0.0376

A: Ratio between adjusted geometric means (Test/Reference).

2.3. Analytical Methods

2.3.1 What bioanalytical methods are used to assess concentrations?

Although methylphenidate is a racemic mixture of *d*- and *l*- forms, plasma concentrations of the *l*-isomer are approximately 40-fold less than the plasma concentrations of the *d*-isomer. Total methylphenidate, d-methylphenidate and the major metabolite, α-phenyl piperidine acetic acid (PPA), concentrations were measured using a validated liquid chromatographic assay with mass spectrometry (LC/MS/MS). In process controls for each study are included in the individual study report. The analytical method was reviewed in the original application and is acceptable.

3. Detailed Labeling Recommendations

OCP Labeling recommendations are included in the proposed draft label in Appendix. OCP edits are noted as "Track Changes" in the proposed draft label

4. Appendices

Proposed Draft Labeling with OCP edits
Clinical Pharmacology and Biopharmaceutics Individual Study Reviews
Consult Review (Pharmacometric Review)

34 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

4.2. Clinical Pharmacology and Biopharmaceutics Individual Study Reviews

4.2.1. Title (Protocol 02-160): An Open-label, Dose Escalation, Multiple Dose Pharmacokinetic Study of Concerta® in Healthy Adults

Objective: To determine the pharmacokinetics and safety of high doses of Concerta® (54, 72, 108 and 144 mg) in healthy adults so that dose levels between 1 and 2 mg/kg can be achieved to manage ADHD symptoms.

Study Design: This study had an open-label, four-period, dose-escalation, multiple-dose design. A total of 27 healthy adults were enrolled in the study. They ranged in age from 20 to 50 years, and all were non-smokers. The mean ± SD age was 28.9 ± 8.46 years. They included one African American, two Hispanic, two Native American, and 22 Caucasian subjects. On the day before each period, subjects reported to the clinical site and participated in a supervised overnight fast. Study personnel administered the Concerta (methylphenidate HCl) dose each morning for four days. All subjects were to receive sequentially increasing doses during four periods separated by three-days washout. In each study period, subjects were dosed once daily for four days in order to reach steady state concentrations of methylphenidate. One pre-dose and fourteen post-dose blood samples (4 mL) were collected on Days 1 and 4. They were collected before dosing and at 0.5, 1, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14 and 24 hours after the dose on Days 1 and 4. Subjects remained sequestered at the clinical site until after the last blood sample was collected on Day 5. There was a wash-out period of three days between the treatments.

The four treatments were:

Treatment A: A dose of 54 mg methylphenidate HCl (one 54-mg CONCERTA OROS® tablet) was swallowed with 240 mL of water each morning for four days.

Treatment B: A dose of 72 mg methylphenidate HCl CONCERTA (two 36-mg CONCERTA OROS tablets) was swallowed with 240 mL of water each morning for four days.

Treatment C: A dose of 108 mg methylphenidate HCl CONCERTA (two 54-mg CONCERTA OROS tablets) was swallowed with 240 mL of water each morning for four days.

Treatment D: A dose of 144 mg methylphenidate HCl (two 54-mg and one 36-mg CONCERTA OROS tablets) was swallowed with 240 mL of water each morning for four days.

Doses of 1 to 2 mg/kg may be effective for therapeutic management of ADHD in adults. The 54- mg dose was selected as a reference because this is the highest strength currently approved for treatment of ADHD in children. The 72, 108 and 144 mg doses were selected because they provide dose levels in the 1 to 2 mg/kg target dose window for the treatment of ADHD in a wide range of adult weights. Study personnel at the clinical site administered the assigned doses to the subjects beginning around 8 AM on Days 1 through 4 of each period. Each dose was administered following an overnight fast of at least eight hours.

Analytical method: Although methylphenidate is a racemic mixture of *d*- and *l*- forms, plasma concentrations of the *l*-isomer are approximately 40-fold less than the plasma concentrations of the *d*-isomer. Hence, total methylphenidate concentrations were measured in this study.

Plasma samples were analyzed for methylphenidate and the major metabolite, α-phenyl piperidine acetic acid (PPA) using a validated liquid chromatographic assay with mass spectrometry (LC/MS/MS). The lower limit of quantification (LLOQ) of methylphenidate and PPA in 100 µL of extracted plasma was 0.100 ng/mL and 2.00 ng/mL respectively. The standard curve was linear from 0.100 to 50.0 ng/mL for methylphenidate, and 2.00 to 1000 ng/mL for PPA. Accuracy of the methylphenidate assay over a range of 0.100 to 37.5 ng/mL and PPA assay over a range of 2.0 to 750 ng/mL was measured as the percent difference from theoretical concentrations of the quality control pools. The percent difference from theoretical for 0.100, 0.250, 0.50 and 37.5 ng/mL was –2.97, 0.312, 1.56 and 1.47% respectively. The percent difference from theoretical for 2.00, 5.00, 50.0 and 750 ng/mL was –2.97, 0.312, 1.56 and 1.47% respectively. The coefficients of variation were 4.14, 2.46, 1.73, and 1.41% for methylphenidate and 2.97, 1.71, 1.31 and 0.98% for PPA respectively. Recoveries of methylphenidate from QC samples at three nominal concentrations of 0.250, 2.50, and 37.5 ng/mL were 94.0, 90.2, and 87.6%, respectively. Recoveries of PPA from QC samples at three nominal concentrations of 5.00, 50.0, and 750.0 ng/mL were 60.1, 56.3 and 60.4%, respectively.

Data Analysis: Pharmacokinetic parameters were determined from plasma concentration-time data by non-compartmental methods for methylphenidate and PPA. Dose proportionality of log transformed dose-normalized AUC and Cmax was assessed with Schuirmann's two one-sided 90% confidence interval method. An analysis of variance model with subject (random factor) and dose as factors was used and all treatment pairs were compared. This was done for methylphenidate and PPA on Day 1 and Day 4. Additionally, dose proportionality was evaluated by a no intercept linear regression of AUC on absolute dose and dose expressed in mg/kg for both methylphenidate and PPA.

Results

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The mean concentration time profile for methylphenidate after normalizing to 54 mg.

Figure 1

Methylphenidate Concentration Profiles With Doses Normalized to 54 mg on Day 1
Subjects Who Completed All Dose Periods

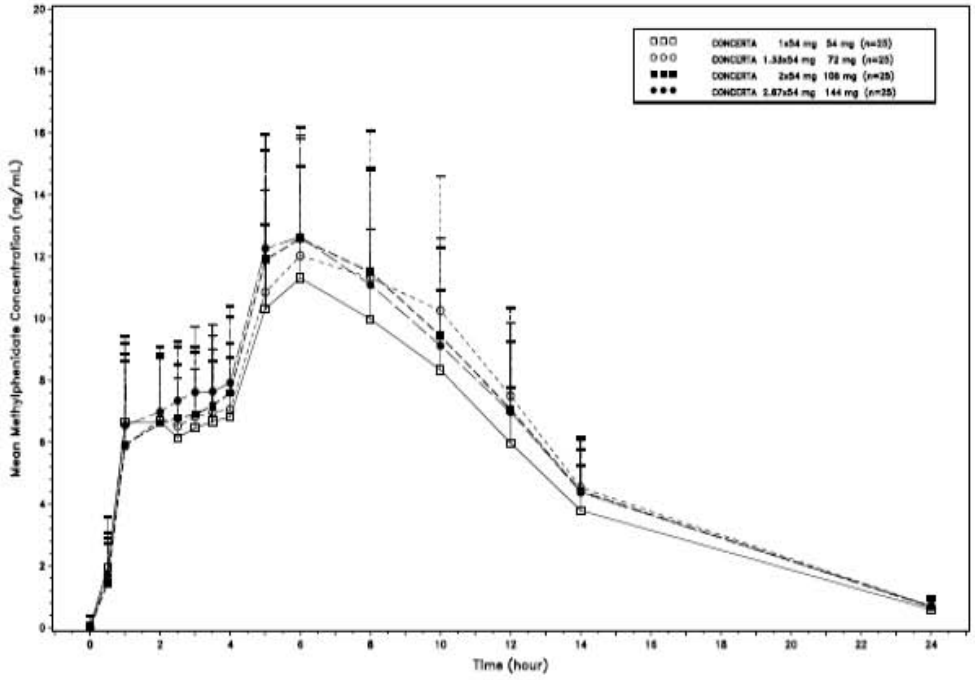
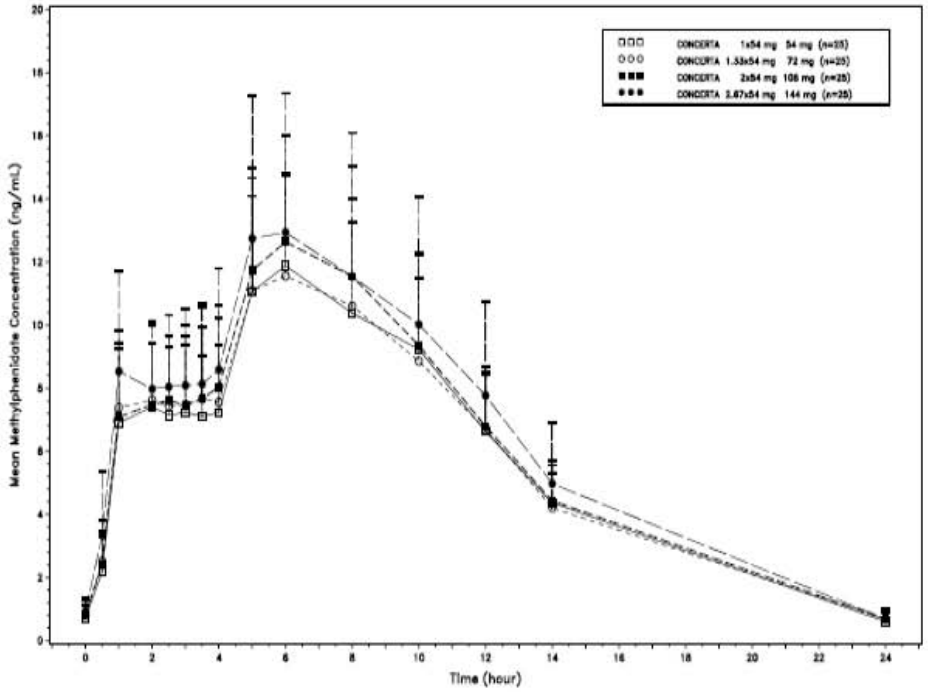


Figure 4
Methylphenidate Concentration Profiles With Doses Normalized to 54 mg on Day 4
Subjects Who Completed All Dose Periods



Following oral administration of Concerta (methylphenidate HCl), plasma concentrations increased rapidly during the first hour, followed by a slower increase in plasma concentration. Thereafter, there was a gradual decline in plasma concentrations. The dose-normalized plasma concentration profiles were superimposable.

The estimated mean (SD) pharmacokinetic parameters for methylphenidate are summarized in the following table.

Methylphenidate Pharmacokinetic Parameters (Mean, SD, %CV) for Subjects Who Completed All Four Treatments

DAY 1

	C_{MAX} (ng/mL)	T_{MAX}[a] (h)	AUC_{INF} (ng-h/mL)	K_{EL} (1/h)	$T_{½}$ (h)	Exposure Ratio[b] (AUC_{TAU}/ AUC_{INF})
Treatment A (54 mg)	12.03 (3.54) 29.4%	6 (1-10) 31.5%	130 (32.4) 24.9%	0.199 (0.033) 16.4%	3.58 (0.629) 17.6%	1.082[c] 1.021, 1.142
Treatment B (72 mg)	17.12 (5.80) 33.9%	6 (5-10) 26.0%	196 (65.7) 33.5%	0.200 (0.034) 17.1%	3.57 (0.617) 17.3%	0.961 0.925, 0.998
Treatment C (108 mg)	26.26 (6.38) 24.3%	6 (5-12) 25.8%	293[c] (76.5) 26.1%	0.198[c] (0.031) 15.8%	3.59[c] (0.544) 15.2%	1.066[c] 0.971, 1.042
Treatment D (144 mg)	35.83 (9.72) 27.1%	6 (1-12) 35.9%	381[d] (104.5) 27.4%	0.195[d] (0.032) 16.4%	3.65[d] (0.598) 16.4%	1.081[d] 1.018, 1.144

DAY 4

	C_{MAX} (ng/mL)	T_{MAX}[a] (h)	AUC_{TAU} (ng-h/mL)	K_{EL} (1/h)	$T_{½}$ (h)	$C_{MIN,SS}$ (ng/mL)
Treatment A (54 mg)	12.45 (2.84) 22.8%	6 (1-10) 35.5%	139[c] (33.6) 24.1%	0.199 (0.033) 16.3%	3.60 (0.844) 23.5%	0.496 (0.305) 61.5%
Treatment B (72 mg)	16.12 (4.60) 28. 6%	6 (5-8) 15.4%	185 (49.0) 26.4%	0.194 (0.029) 15.1%	3.63 (0.49) 13.4%	0.807 (0.428) 53.1%
Treatment C (108 mg)	25.96 (6.99) 26.9%	6 (5-10) 19.2%	291 (71.1) 24.4%	0.197 (0.030) 15.2%	3.60 (0.56) 15.5%	1.228 (0.607) 49.4%
Treatment D (144 mg)	36.94 (11.31) 30.6%	6 (1-8) 30.8%	419 (137.0) 32.7%	0.207 (0.033) 15.7%	3.42 (0.50) 14.5%	1.731 (0.894) 51.6%

a: median and range are listed; b: mean and 95% confidence interval are listed;
c: N = 24; d: N = 23

When the AUC ratios were compared, there was no difference in the ratio of AUCs on Day 4 to Day 1 and in general the ratios were close to 1.0. Mean Cmax and AUC increased approximately proportionally with dose.

Statistical Analysis of Log Transformed PK Parameters for Methylphenidate

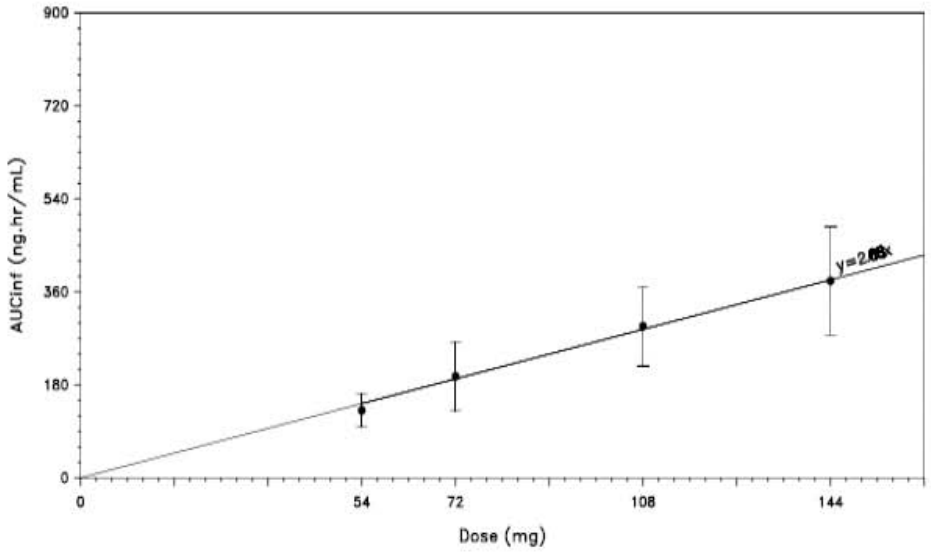
Contrast PK Parameter		Day 1 Ratio (%)	Day 1 90 % confidence Lower	Day 1 90 % confidence Upper	Day 4 Ratio (%)	Day 4 90 % confidence Lower	Day 4 90 % confidence Upper
CMAX	72/54	106.72	93.96	121.20	96.21	85.43	108.36
	108/54	110.62	97.40	125.64	103.60	91.84	116.48
	144/54	112.30	98.87	127.54	109.60	97.32	123.43
	108/72	103.66	91.27	117.73	107.50	95.45	121.07
	144/72	105.23	92.65	119.51	113.91	101.15	128.29
	144/108	101.51	89.38	115.29	105.96	94.09	119.34
AUCINF[a]	72/54	111.59	99.12	125.62	100.01	89.08	112.28
	108/54	112.41	99.73	126.70	104.94	93.47	117.81
	144/54	109.44	96.97	123.52	110.63	98.55	124.20
	108/72	100.74	89.37	113.54	104.93	93.58	117.66
	144/72	98.08	86.90	110.70	110.62	98.66	124.04
	144/108	97.36	86.16	110.02	105.43	94.02	118.22

[a] AUC_{tau} for Day 4

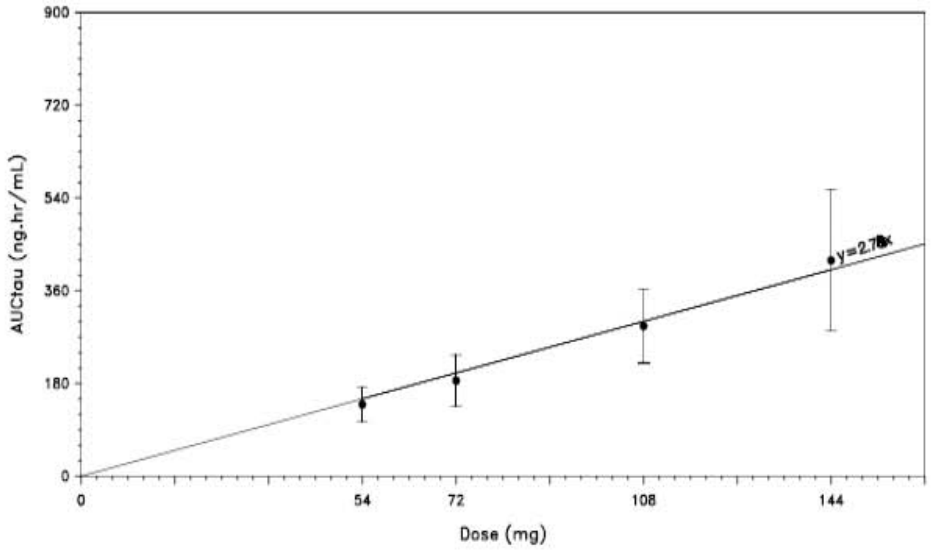
For methylphenidate, the 90% CI for the normalized Cmax and AUC were contained within the confidence limits of 80% to 125% except 4 out of 12 comparisons on Day 1 and 1 out of 12 upper limits on Day 4. The upper limits of 90% CI for those not contained within the limits were higher than 125%.

For PPA the 90% CI for the dose-normalized pharmacokinetic parameters (AUC and CMAX) fell within the bioequivalence criteria of 80 to 125% on both days of sampling (Day 1 and Day 4).

Methylphenidate Dose-Proportionality of AUCtau on Day 1



Methylphenidate Dose-Proportionality of AUCtau on Day 4

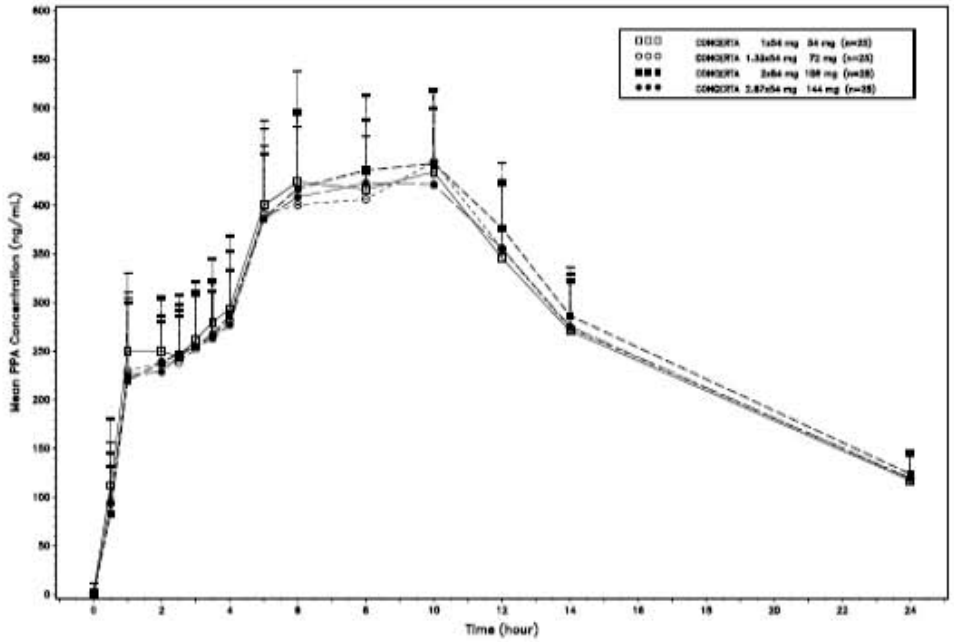


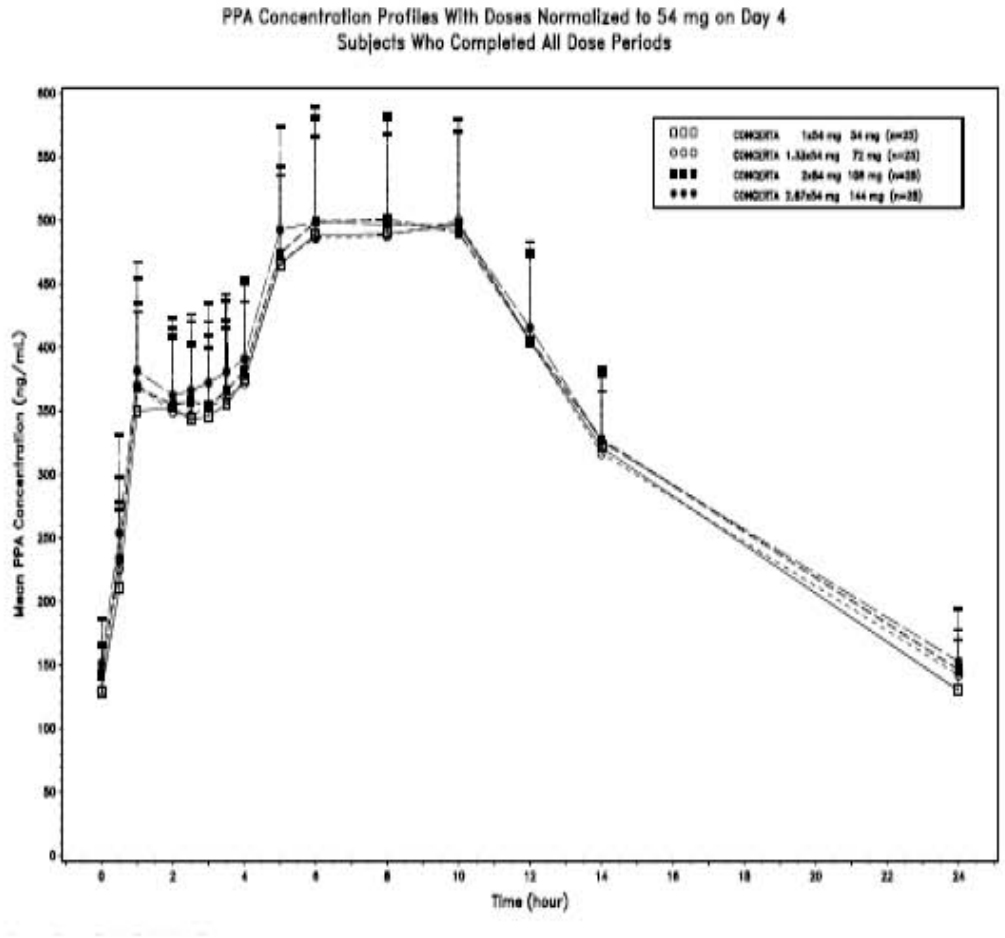
A regression model without intercept was used to assess the dose effect of AUC for methylphenidate. A proportional increase in the AUC values was observed suggesting Concerta (methylphenidate HCl) follows linear and dose-proportional pharmacokinetics.

α-Phenylpiperidine Acetic Acid (PPA) Pharmacokinetics

The dose normalized mean pharmacokinetic parameters for PPA are provided in the following figure.

Figure 6
PPA Concentration Profiles With Doses Normalized to 54 mg on Day 1
Subjects Who Completed All Dose Periods





Following oral administration of Concerta, mean plasma concentrations of PPA increased rapidly during the first hour followed by a slower increase. The dose normalized plasma concentration profiles for all treatments were superimposable suggesting dose proportionality. The estimated mean pharmacokinetic parameter values of PPA for all doses of Concerta are provided in the following table.

PPA Pharmacokinetic Parameters (Mean, SD, %CV) for Subjects Who Completed All Four Treatments (N = 25)

	DAY 1					
	CMAX (ng/mL)	TMAX[a] (h)	AUC_{INF} (ng-h/mL)	KEL (1/h)	T½ (h)	Exposure Ratio[b] ($AUCtau/AUC_{INF}$)
Treatment A (54 mg)	477 (108.1) 22.7%	8 (5-10) 25.5%	8068 (1405) 17.4%	0.088 (0.014) 15.4%	8.04 (1.29) 16.1%	1.001[c] 0.962, 1.039
Treatment B (72 mg)	609 (95.8) 15.8%	10 (5-10) 23.5%	10713 (1634) 15.3%	0.089 (0.014) 16.0%	8.01 (1.29) 161%	1.012 0.985, 1.038
Treatment C (108 mg)	937 (144.1) 15.4%	10 (5-12) 27.2%	16766[d] (2399) 14.3%	0.088[d] (0.014) 16.3%	8.09[d] (1.17) 14.5%	0.999[d] 0.956, 1.041
Treatment D (144 mg)	1220 (211.9) 17.4%	8 (5-12) 23.6%	21429[d] (3071) 14.3%	0.087[d] (0.013) 15.0%	8.16[d] (1.32) 16.2%	1.051[d] 1.000, 1.102
	DAY 4					
	CMAX (ng/mL)	TMAX[a] (h)	AUCTAU (ng-h/mL)	KEL (1/h)	T½ (h)	CMIN,SS (ng/mL)
Treatment A (54 mg)	536 (84.7) 15.8%	8 (5-12) 26.0%	7941[c] (1172) 14.8%	0.087[c] (0.015) 16.9%	8.23[c] (2.04) 24.8%	120 (45.1) 37. 6%
Treatment B (72 mg)	706 (106.3) 15.1%	8 (5-12) 28.3%	10788 (1446) 13.4%	0.086[c] (0.012) 14.0%	8.22[c] (1.03) 12.6%	167 (45.3) 27.1%
Treatment C (108 mg)	1061 (164.7) 15.5%	8 (5-12) 26.2%	16465 (2497) 15.2%	0.084[c] (0.013) 15.5%	8.45[c] (1.21) 14.4%	271 (81.2) 30.0%
Treatment D (144 mg)	1430 (216.0) 15.1%	8 (1-12) 36.6%	22288 (3092) 13.9%	0.081[e] (0.016) 19.4%	9.06[e] (2.79) 30.8%	379 (99.8) 26.4%

a: median and range are listed; b: mean and 95% confidence interval are listed;
c: N = 24; d: N = 22; e: N = 23.

When the AUC ratios were compared, in general the ratios were close to one suggesting no accumulation and dose proportionality. Mean Cmax and AUC increased proportionally with dose. The mean ratios of AUC values on Day 1 and Day 4 were comparable across doses indicating that there were no differences in metabolism of methylphenidate with dose after single dose or after repeat dosing.

PPA to Methylphenidate (MP) AUC Ratios (Mean, SD, 95% CI)

Ratio	Dose 54 mg	72 mg	108 mg	144 mg
PPA AUC_{INF}/ MP AUC_{INF} (Day 1)	65.66 (20.55) 57.18, 74.15	59.49 (19.48) 51.45, 67.53	61.41 (17.86) 53.49, 69.33	60.11 (18.54) 51.89, 68.33
PPA AUC_{tau}/ MP AUC_{tau} (Day 4)	59.78 (15.29) 53.32, 66.23	61.62 (16.45) 54.83, 68.41	59.42 (15.80) 52.90, 65.94	57.64 (16.68) 50.76, 64.53

Safety Summary

The sponsor reported that over the course of the study, 156 adverse events were reported by 19 of the 27 subjects. The number of adverse events reported with each dose is 29 with the 54-mg dose, 13 with the 72-mg dose, 62 with the 108-mg dose, and 52 with the 144-mg dose. The incidence was approximately 52% with the 54-mg dose, 33% with the 72-mg dose, 56% with the 108-mg dose, and 58% with the 144-mg dose. Twelve adverse events were moderate in intensity; the remaining adverse events (144) were mild in intensity. The more common adverse events (when all doses are considered) include headache (40.7% of subjects), anorexia (29.6%), dizziness (22.2%), dry mouth (22.2%), and nausea (22.2%). The incidence of anorexia and dry mouth was greater with the two higher doses than with the two lower doses. The percentage of subjects reporting nausea was highest with the 108-mg and the 54-mg doses (18.5% and 11.1%, respectively). The incidence of headache and dizziness appears to increase with increasing dose The sponsor reported that there was a mean decrease in weight during each treatment period

The sponsor reported that after accounting for circadian rhythm, a dose - related drug effect on Heart rate mesor (HRm) and amplitude for all doses was statistically significant. The sponsor reported that the data showed that increasing doses of methylphenidate increase the mean daily heart rate and the swing in heart rate, but have no effect on the periodicity except at the highest dose of 144 mg daily (Refer to medical review).

Conclusions: At doses of 54 to 144 mg, the pharmacokinetics of methylphenidate and PPA were similar to those observed previously for lower doses. Methylphenidate exhibits linear and dose-proportional pharmacokinetics for doses in the range of 54 to 144 mg. The metabolism of methylphenidate (PPA (metabolite)/MPH (parent)) was similar across doses.

Reviewer Comments: The reviewer agrees with the conclusions.

Attachments

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	11.90	15.90	22.50	28.10
26	13.40	19.70	29.90	45.10
27	11.70	18.40	33.70	40.60
Cmax (ng/mL)				
n	25	25	25	25
Mean	12.032	17.120	26.260	35.828
SD	3.5402	5.8039	6.3770	9.7242
SE	0.7080	1.1608	1.2754	1.9448
CV (%)	29.42	33.90	24.28	27.14
Median	11.800	15.800	25.100	35.200
Min, Max	6.28, 21.80	11.10, 37.80	17.80, 42.30	21.90, 63.30
Geometric Mean	11.552	16.397	25.559	34.634
Mean (ln)	2.447	2.797	3.241	3.545
SD (ln)	0.2937	0.2856	0.2362	0.2646

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	120.15	172.58	233.70	286.31
26	175.60	246.57	367.37	425.35
27	179.25	236.25	305.94	459.00
AUCt (ng·hr/mL)				
n	25	25	25	25
Mean	127.307	191.319	285.820	382.896
SD	31.5275	64.1867	72.5130	107.8611
SE	6.3055	12.8373	14.5026	21.5722
CV (%)	24.76	33.55	25.37	28.17
Median	123.760	182.006	274.085	358.555
Min, Max	74.94, 201.41	116.17, 405.91	179.34, 493.12	240.42, 724.44
Geometric Mean	123.584	183.233	277.761	370.125
Mean (ln)	4.817	5.211	5.627	5.914
SD (ln)	0.2504	0.2870	0.2411	0.2602

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	121.17	174.47	236.39	290.02
26	181.09	253.92	381.46	439.31
27	186.46	242.92	313.76	471.54
AUCinf (ng·hr/mL)				
n	25	25	24	23
Mean	130.568	196.352	293.536	381.076
SD	32.4399	65.6940	76.4778	104.5189
SE	6.4880	13.1388	15.6110	21.7937
CV (%)	24.85	33.46	26.05	27.43
Median	125.039	189.409	284.171	371.320
Min, Max	76.56, 204.96	118.66, 415.25	183.07, 507.50	246.10, 743.44
Geometric Mean	126.743	188.067	284.872	369.460
Mean (ln)	4.842	5.237	5.652	5.912
SD (ln)	0.2502	0.2866	0.2473	0.2471

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	4.59	4.25	4.66	5.07
26	3.04	2.89	2.89	3.38
27	3.71	3.70	4.41	3.87
Clearance (L/hr/kg)				
n	25	25	24	23
Mean	5.278	4.797	4.728	4.795
SD	1.4804	1.4964	1.3162	1.2667
SE	0.2961	0.2993	0.2687	0.2641
CV (%)	28.05	31.19	27.84	26.42
Median	5.116	4.610	4.553	4.516
Min, Max	3.04, 8.37	2.44, 7.82	2.89, 7.16	2.65, 7.77

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	5.00	5.00	5.00	6.00
26	6.00	10.00	5.00	5.00
27	10.00	10.00	6.00	8.00
Tmax (hr)				
n	25	25	25	25
Mean	6.040	6.720	6.280	6.240
SD	1.9035	1.7445	1.6207	2.2413
SE	0.3807	0.3489	0.3241	0.4483
CV (%)	31.51	25.96	25.81	35.92
Median	6.000	6.000	6.000	6.000
Min, Max	1.00, 10.00	5.00, 10.00	5.00, 12.00	1.00, 12.00

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 8
Methylphenidate PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	2.67	2.82	2.90	2.90
26	3.82	3.67	4.17	3.98
27	3.81	3.58	3.82	3.71
T1/2 (hr)				
n	25	25	24	23
Mean	3.583	3.566	3.585	3.646
SD	0.6288	0.6165	0.5440	0.5979
SE	0.1258	0.1233	0.1111	0.1247
CV (%)	17.55	17.29	15.18	16.40
Median	3.551	3.583	3.572	3.683
Min, Max	2.63, 5.18	2.52, 4.97	2.40, 5.04	2.57, 4.89

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 9
Methylphenidate PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	13.70	14.90	22.90	31.80
26	15.30	19.10	30.00	45.20
27	10.60	15.40	20.50	44.80
Cmax (ng/mL)				
n	25	25	25	25
Mean	12.454	16.118	25.956	36.944
SD	2.8444	4.6027	6.9856	11.3079
SE	0.5689	0.9205	1.3971	2.2616
CV (%)	22.84	28.56	26.91	30.61
Median	12.500	15.300	23.700	31.900
Min, Max	8.82, 18.50	9.44, 28.00	16.50, 44.10	22.40, 76.50
Geometric Mean	12.158	15.556	25.147	35.575
Mean (ln)	2.498	2.744	3.225	3.572
SD (ln)	0.2229	0.2666	0.2511	0.2710

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 9
Methylphenidate PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	0.31	0.11	0.53	0.22
26	1.08	1.41	2.22	2.67
27	0.90	1.30	1.71	1.98
Cmin (ng/mL)				
n	25	25	25	25
Mean	0.496	0.807	1.228	1.731
SD	0.3054	0.4282	0.6067	0.8937
SE	0.0611	0.0856	0.1213	0.1787
CV (%)	61.54	53.07	49.39	51.63
Median	0.464	0.800	1.100	1.580
Min, Max	0.00, 1.08	0.11, 1.65	0.18, 2.22	0.18, 4.04
Geometric Mean	0.508	0.675	1.045	1.431
Mean (ln)	-0.678	-0.394	0.044	0.359
SD (ln)	0.4792	0.6738	0.6465	0.7369

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 9
Methylphenidate PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	130.71	155.19	233.07	306.38
26	189.21	236.26	368.19	522.00
27	153.04	201.09	291.76	498.36
AUCtau (ng·hr/mL)				
n	24	25	25	25
Mean	139.264	185.465	291.557	418.652
SD	33.6103	49.0365	71.1264	137.0226
SE	6.8607	9.8073	14.2253	27.4045
CV (%)	24.13	26.44	24.40	32.73
Median	131.926	173.860	275.454	405.048
Min, Max	88.60, 229.69	111.10, 333.63	199.42, 470.90	202.93, 890.51
Geometric Mean	135.826	180.101	284.201	399.942
Mean (ln)	4.911	5.194	5.650	5.991
SD (ln)	0.2232	0.2413	0.2255	0.3049

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 9
Methylphenidate PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	4.26	4.78	4.73	4.80
26	2.91	3.11	2.99	2.84
27	4.52	4.48	4.75	3.66
Clearance (L/hr/kg)				
n	24	25	25	25
Mean	4.812	4.936	4.695	4.551
SD	1.1890	1.2690	1.1908	1.7719
SE	0.2427	0.2538	0.2382	0.3544
CV (%)	24.71	25.71	25.36	38.94
Median	4.588	4.687	4.735	4.208
Min, Max	2.91, 7.75	3.04, 7.61	2.99, 7.21	2.22, 11.26

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 9
Methylphenidate PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	2.89	2.91	3.05	2.72
26	3.83	4.09	4.13	3.80
27	3.70	3.75	3.76	3.38
T1/2 (hr)				
n	25	25	25	25
Mean	3.597	3.633	3.596	3.415
SD	0.8436	0.4855	0.5586	0.4958
SE	0.1687	0.0971	0.1117	0.0992
CV (%)	23.45	13.36	15.53	14.52
Median	3.556	3.751	3.656	3.395
Min, Max	2.56, 7.22	2.63, 4.41	2.53, 5.26	2.31, 4.42

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 10
PPA PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	550.00	682.00	981.00	1230.00
26	417.00	638.00	896.00	1050.00
27	475.00	646.00	996.00	1050.00
Cmax (ng/mL)				
n	25	25	25	25
Mean	477.160	608.680	937.120	1220.240
SD	108.0724	95.8474	144.1172	211.8632
SE	21.6145	19.1695	28.8234	42.3726
CV (%)	22.65	15.75	15.38	17.36
Median	474.000	597.000	936.000	1190.000
Min, Max	342.00, 743.00	483.00, 868.00	726.00, 1270.00	916.00, 1650.00
Geometric Mean	466.212	601.869	926.895	1203.080
Mean (ln)	6.145	6.400	6.832	7.093
SD (ln)	0.2167	0.1513	0.1519	0.1709

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 10
PPA PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	7595.75	10176.33	15193.46	17955.50
26	6581.43	8793.00	13855.80	15710.90
27	7540.00	9635.50	14290.25	18285.55
AUCt (ng·hr/mL)				
n	25	25	25	25
Mean	6686.038	8838.956	13686.980	17661.841
SD	1182.1533	1344.1315	2058.4855	2712.3905
SE	236.4307	268.8263	411.6971	542.4781
CV (%)	17.68	15.21	15.04	15.36
Median	6628.250	8793.000	13855.800	17606.000
Min, Max	4687.53, 8796.00	6642.75, 11976.55	10775.50, 17563.55	13835.55, 23164.00
Geometric Mean	6585.859	8742.924	13538.869	17465.801
Mean (ln)	8.793	9.076	9.513	9.768
SD (ln)	0.1779	0.1517	0.1509	0.1520

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 10
PPA PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	8533.64	11465.37	17706.21	20588.18
26	8132.19	10687.87	16203.36	20428.81
27	9539.06	11873.59	17855.68	22904.52
AUCinf (ng·hr/mL)				
n	25	25	22	22
Mean	8068.186	10713.248	16765.770	21428.909
SD	1404.7123	1634.0246	2399.4286	3071.3819
SE	280.9425	326.8049	511.5599	654.8208
CV (%)	17.41	15.25	14.31	14.33
Median	7781.144	10580.311	16825.341	20696.307
Min, Max	5319.92, 10368.41	7659.77, 14214.87	12773.23, 22626.92	16340.96, 27467.92
Geometric Mean	7949.943	10593.120	16605.679	21224.450
Mean (ln)	8.981	9.268	9.718	9.963
SD (ln)	0.1772	0.1552	0.1417	0.1417

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 10
PPA PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	10.00	8.00	10.00	6.00
26	10.00	10.00	10.00	5.00
27	10.00	10.00	6.00	8.00
Tmax (hr)				
n	25	25	25	25
Mean	7.960	8.440	8.560	8.560
SD	2.0306	1.9807	2.3288	2.0224
SE	0.4061	0.3961	0.4658	0.4045
CV (%)	25.51	23.47	27.21	23.63
Median	8.000	10.000	10.000	8.000
Min, Max	5.00, 10.00	5.00, 10.00	5.00, 12.00	5.00, 12.00

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 10
PPA PK Parameters by Treatment on Day 1

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	6.25	6.29	7.17	6.52
26	8.40	7.82	9.78	9.67
27	8.35	8.16	8.92	8.56
T1/2 (hr)				
n	25	25	22	22
Mean	8.036	8.008	8.094	8.156
SD	1.2934	1.2879	1.1709	1.3232
SE	0.2587	0.2576	0.2496	0.2821
CV (%)	16.09	16.08	14.47	16.22
Median	7.964	7.945	8.372	8.175
Min, Max	5.74, 11.73	5.77, 10.72	5.49, 9.97	6.20, 12.08

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 11
PPA PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	644.00	723.00	999.00	1390.00
26	501.00	686.00	1030.00	1310.00
27	572.00	770.00	1140.00	1720.00
Cmax (ng/mL)				
n	25	25	25	25
Mean	536.440	706.040	1061.200	1429.600
SD	84.7226	106.3185	164.7329	215.9954
SE	16.9445	21.2637	32.9466	43.1991
CV (%)	15.79	15.06	15.52	15.11
Median	524.000	723.000	1050.000	1440.000
Min, Max	374.00, 696.00	491.00, 979.00	743.00, 1350.00	1070.00, 1920.00
Geometric Mean	529.959	698.238	1048.714	1414.031
Mean (ln)	6.273	6.549	6.955	7.254
SD (ln)	0.1596	0.1520	0.1583	0.1513

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

PPA PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	123.00	65.90	179.00	147.00
26	155.00	196.00	335.00	394.00
27	176.00	211.00	361.00	505.00
Cmin (ng/mL)				
n	25	25	25	25
Mean	120.124	167.096	271.048	378.640
SD	45.1129	45.2660	81.2417	99.7810
SE	9.0226	9.0532	16.2483	19.9562
CV (%)	37.56	27.09	29.97	26.35
Median	125.000	177.000	270.000	389.000
Min, Max	0.00, 189.00	53.50, 236.00	91.20, 466.00	147.00, 550.00
Geometric Mean	118.269	158.971	257.722	363.115
Mean (ln)	4.773	5.069	5.552	5.895
SD (ln)	0.3668	0.3553	0.3417	0.3167

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

PPA PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	9297.00	10845.73	15703.50	21083.25
26	8110.25	10770.95	16511.50	20999.37
27	9351.75	11864.50	18834.75	26860.75
AUCtau (ng·hr/mL)				
n	24	25	25	25
Mean	7940.743	10788.149	16465.902	22288.062
SD	1171.6040	1446.2498	2497.2460	3091.6193
SE	239.1527	289.2500	499.4492	618.3239
CV (%)	14.75	13.41	15.17	13.87
Median	7817.875	10770.950	16223.250	22130.750
Min, Max	6106.10, 9924.75	8003.25, 13176.00	11722.05, 21691.25	15858.80, 28738.00
Geometric Mean	7856.069	10692.737	16281.097	22078.510
Mean (ln)	8.969	9.277	9.698	10.002
SD (ln)	0.1494	0.1377	0.1554	0.1411

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 11
PPA PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	6.00	6.00	6.00	8.00
26	10.00	10.00	10.00	5.05
27	10.00	12.00	10.00	10.00
Tmax (hr)				
n	25	25	25	25
Mean	8.120	7.680	7.640	7.642
SD	2.1079	2.1741	1.9975	2.7951
SE	0.4216	0.4348	0.3995	0.5590
CV (%)	25.96	28.31	26.15	36.58
Median	8.000	8.000	8.000	8.000
Min, Max	5.00, 12.00	5.00, 12.00	5.00, 12.00	1.00, 12.00

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 11
PPA PK Parameters by Treatment on Day 4

PK Parameter/ Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
25	6.53	6.86	6.53	6.62
26	9.00	9.22	10.29	9.05
27	8.25		8.03	20.62
T1/2 (hr)				
n	24	24	24	23
Mean	8.230	8.223	8.449	9.056
SD	2.0391	1.0323	1.2135	2.7917
SE	0.4162	0.2107	0.2477	0.5821
CV (%)	24.78	12.55	14.36	30.83
Median	8.135	8.265	8.538	8.571
Min, Max	6.15, 16.74	5.78, 9.87	6.05, 10.29	6.47, 20.62

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 12
Day 4 AUCtau/Day 1 AUCinf Ratio for Total Methylphenidate Exposure by Treatment
All Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
21	1.36	0.80	1.07	
22	1.11	0.87		
23	1.07	0.99	0.97	1.15
24	1.04	0.91	1.08	1.24
25	1.08	0.89	0.99	1.06
26	1.05	0.93	0.97	1.19
27	0.82	0.83	0.93	1.06
n	24	25	24	23
Mean	1.082	0.961	1.006	1.081
SD	0.1436	0.0887	0.0836	0.1462
SE	0.0293	0.0177	0.0171	0.0305
95% CI	1.021, 1.142	0.925, 0.998	0.971, 1.042	1.018, 1.144
CV (%)	13.28	9.23	8.31	13.53
Median	1.075	0.950	0.991	1.059
Min, Max	0.82, 1.36	0.80, 1.14	0.77, 1.17	0.61, 1.32
Geometric Mean	1.072	0.958	1.003	1.070
Mean (ln)	0.070	-0.043	0.003	0.067
SD (ln)	0.1345	0.0921	0.0856	0.1540

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 12.1
Day 4 AUCtau/Day 1 AUCinf Ratio for Total Methylphenidate Exposure by Treatment
Male Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
n	18	18	17	16
Mean	1.103	0.951	0.997	1.125
SD	0.1430	0.0825	0.0885	0.1049
SE	0.0337	0.0194	0.0215	0.0262
95% CI	1.032, 1.174	0.910, 0.992	0.952, 1.043	1.070, 1.181
CV (%)	12.96	8.68	8.88	9.32
Median	1.082	0.960	0.985	1.134
Min, Max	0.82, 1.36	0.80, 1.08	0.77, 1.15	0.94, 1.32
Geometric Mean	1.095	0.947	0.993	1.121
Mean (ln)	0.090	-0.054	-0.007	0.114
SD (ln)	0.1321	0.0879	0.0927	0.0938

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 12.2
Day 4 AUCtau/Day 1 AUCinf Ratio for Total Methylphenidate Exposure by Treatment
Female Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
1	0.99	1.14	1.04	0.61
3		0.95	1.00	1.21
4	1.07	1.11	1.06	0.95
6	0.86	0.92	0.96	1.00
13	1.22	0.89	0.99	1.06
16	0.89	1.03	1.17	0.97
25	1.08	0.89	0.99	1.06
n	6	7	7	7
Mean	1.016	0.989	1.029	0.979
SD	0.1360	0.1045	0.0711	0.1627
SE	0.0555	0.0395	0.0269	0.0690
95% CI	0.873, 1.159	0.892, 1.086	0.963, 1.095	0.810, 1.148
CV (%)	13.39	10.57	6.91	16.67
Median	1.029	0.950	1.002	0.996
Min, Max	0.86, 1.22	0.89, 1.14	0.96, 1.17	0.61, 1.21
Geometric Mean	1.009	0.985	1.027	0.961
Mean (ln)	0.009	-0.016	0.027	-0.039
SD (ln)	0.1337	0.1039	0.0662	0.2143

Table 13
Day 4 AUCtau/Day 1 AUCinf Ratio for Total PPA Exposure by Treatment
All Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
21	1.11	1.13	1.00	
22	1.07	1.00		
23	1.05	1.08	1.07	1.14
24	0.96	1.00	1.09	1.14
25	1.09	0.95	0.89	1.02
26	1.00	1.01	0.91	1.03
27	0.98	1.00	1.06	1.17
n	24	25	22	22
Mean	1.001	1.012	0.999	1.051
SD	0.0910	0.0647	0.0963	0.1152
SE	0.0186	0.0129	0.0205	0.0246
95% CI	0.962, 1.039	0.985, 1.038	0.956, 1.041	1.000, 1.102
CV (%)	9.10	6.40	9.65	10.96
Median	1.001	1.008	1.018	1.049
Min, Max	0.83, 1.19	0.88, 1.13	0.74, 1.14	0.66, 1.19
Geometric Mean	0.997	1.009	0.994	1.044
Mean (ln)	-0.003	0.009	-0.006	0.043
SD (ln)	0.0917	0.0647	0.1014	0.1245

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 13.1
Day 4 AUCtau/Day 1 AUCinf Ratio for Total PPA Exposure by Treatment
Male Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
n	18	18	16	16
Mean	1.016	1.019	0.995	1.090
SD	0.0900	0.0633	0.1054	0.0726
SE	0.0212	0.0149	0.0263	0.0182
95% CI	0.972, 1.061	0.987, 1.050	0.939, 1.052	1.051, 1.129
CV (%)	8.85	6.22	10.59	6.66
Median	1.024	1.004	1.011	1.100
Min, Max	0.83, 1.19	0.88, 1.13	0.74, 1.14	0.94, 1.19
Geometric Mean	1.013	1.017	0.990	1.088
Mean (ln)	0.012	0.017	-0.010	0.084
SD (ln)	0.0896	0.0627	0.1116	0.0676

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 14
Day 1 PPA AUCinf/Day 1 Methylphenidate AUCinf Ratio by Treatment on Day 1
All Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
21	44.08	25.48	39.79	
22	65.25	61.79	63.21	
23	49.26	42.10	40.91	41.85
24	54.82	52.79	50.03	56.30
25	70.43	65.72	74.90	70.99
26	44.91	42.09	47.72	46.50
27	51.16	48.88	56.91	48.57
n	25	25	22	22
Mean	65.666	59.489	61.413	60.108
SD	20.5521	19.4782	17.8607	18.5376
SE	4.1104	3.8956	3.8079	3.9522
95% CI	57.182, 74.149	51.449, 67.530	53.494, 69.331	51.889, 68.327
CV (%)	31.30	32.74	29.08	30.84
Median	61.840	56.416	56.423	55.868
Min, Max	31.16, 117.27	25.48, 103.36	31.39, 107.73	27.10, 108.25
Geometric Mean	62.722	56.315	59.017	57.447
Mean (ln)	4.139	4.031	4.078	4.051
SD (ln)	0.3099	0.3466	0.2900	0.3109

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 14.1
Day 1 PPA AUCinf/Day 1 Methylphenidate AUCinf Ratio by Treatment on Day 1
Male Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
n	18	18	16	16
Mean	64.813	57.114	59.685	59.437
SD	23.2914	21.3665	19.5858	20.9654
SE	5.4898	5.0361	4.8965	5.2414
95% CI	53.231, 76.396	46.488, 67.739	49.248, 70.121	48.265, 70.609
CV (%)	35.94	37.41	32.82	35.27
Median	56.061	51.840	55.309	54.531
Min, Max	31.16, 117.27	25.48, 103.36	31.39, 107.73	27.10, 108.25
Geometric Mean	61.181	53.437	56.912	56.159
Mean (ln)	4.114	3.979	4.042	4.028
SD (ln)	0.3468	0.3797	0.3162	0.3487

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 14.2
Day 1 PPA AUCinf/Day 1 Methylphenidate AUCinf Ratio by Treatment on Day 1
Female Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
1	76.69	76.50	74.91	72.34
3	75.89	71.17	62.79	64.72
4	81.36	82.11	79.97	66.67
6	57.26	65.30		
13	66.07	45.89	52.66	50.12
16	47.33	52.52	50.90	46.54
25	70.43	65.72	74.90	70.99
n	7	7	6	6
Mean	67.859	65.598	66.020	61.896
SD	12.0298	12.7922	12.4085	10.9258
SE	4.5468	4.8350	5.0658	4.4604
95% CI	56.733, 78.984	53.767, 77.429	52.998, 79.042	50.430, 73.362
CV (%)	17.73	19.50	18.80	17.65
Median	70.427	65.715	68.844	65.695
Min, Max	47.33, 81.36	45.89, 82.11	50.90, 79.97	46.54, 72.34
Geometric Mean	66.868	64.448	65.018	61.028
Mean (ln)	4.203	4.166	4.175	4.111
SD (ln)	0.1913	0.2065	0.1941	0.1874

Table 15
Day 4 PPA AUCtau/Day 4 Methylphenidate AUCtau Ratio by Treatment on Day 4
All Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
21	36.13	35.72	37.20	42.85
22	65.63	70.95		
23	48.37	45.82	45.51	41.49
24	50.61	57.84	50.64	51.85
25	71.13	69.89	67.38	68.81
26	42.86	45.59	44.85	40.23
27	61.11	59.00	64.56	53.90
n	24	25	25	25
Mean	59.775	61.621	59.421	57.643
SD	15.2915	16.4468	15.8006	16.6801
SE	3.1214	3.2894	3.1601	3.3360
95% CI	53.318, 66.232	54.832, 68.410	52.899, 65.943	50.758, 64.528
CV (%)	25.58	26.69	26.59	28.94
Median	57.887	61.420	61.983	52.729
Min, Max	30.52, 90.36	29.45, 97.01	24.89, 105.68	24.74, 90.52
Geometric Mean	57.842	59.380	57.278	55.211
Mean (ln)	4.058	4.084	4.048	4.011
SD (ln)	0.2666	0.2867	0.2862	0.3080

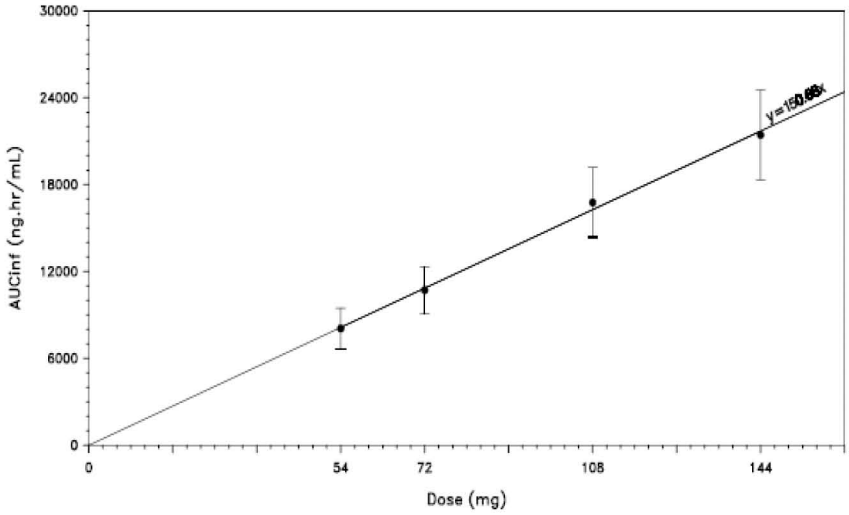
Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

Table 15.1
Day 4 PPA AUCtau/Day 4 Methylphenidate AUCtau Ratio by Treatment on Day 4
Male Subjects

Subject No.	CONCERTA 1x54 mg 54 mg	CONCERTA 1.33x54 mg 72 mg	CONCERTA 2x54 mg 108 mg	CONCERTA 2.67x54 mg 144 mg
n	18	18	18	18
Mean	58.854	60.097	57.625	55.907
SD	16.6795	18.3901	17.5822	17.9285
SE	3.9314	4.3346	4.1442	4.2258
95% CI	50.560, 67.149	50.951, 69.242	48.881, 66.368	46.991, 64.822
CV (%)	28.34	30.60	30.51	32.07
Median	57.701	59.362	59.434	52.485
Min, Max	30.52, 90.36	29.45, 97.01	24.89, 105.68	24.74, 90.52
Geometric Mean	56.596	57.375	55.061	53.141
Mean (ln)	4.036	4.050	4.008	3.973
SD (ln)	0.2916	0.3206	0.3180	0.3347

Note: Subjects 12 and 22 did not complete all dose periods and, therefore, data for these subjects are not included in the computation of summary statistics.

PPA Dose–Proportionality of AUCinf on Day 1
Subjects Who Completed All Dose Periods



PPA Dose–Proportionality of AUCtau on Day 4
Subjects Who Completed All Dose Periods

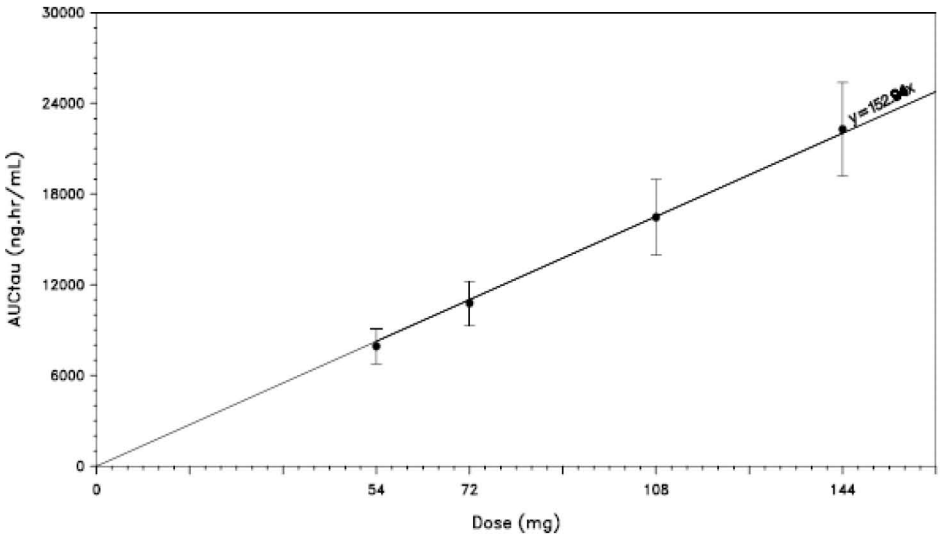
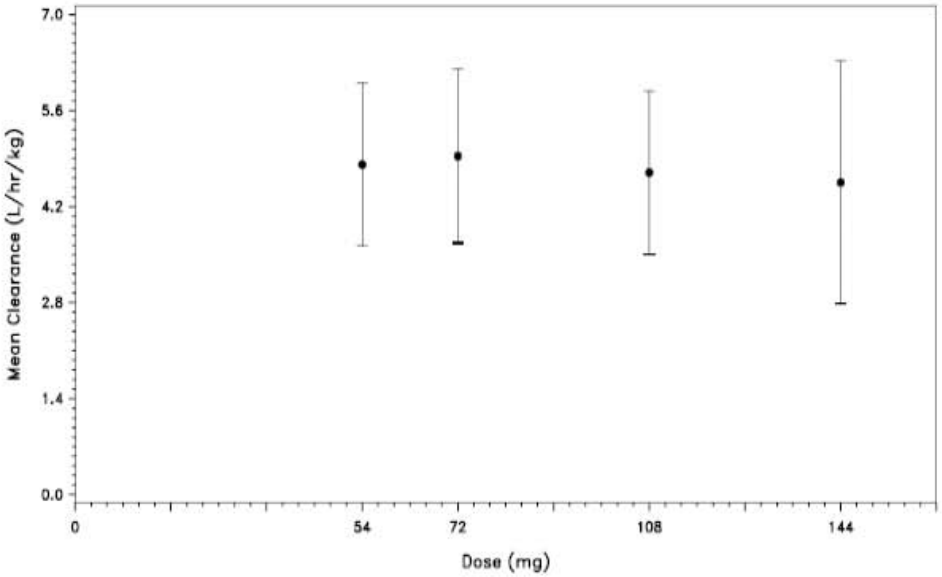


Figure 26
Mean Methylphenidate Clearance on Day 4 by Dose
Subjects Who Completed All Dose Periods



4.2.2. Title (Protocol No 12-004): The Pharmacokinetics of CONCERTA® (Methylphenidate HCl) in Crushed and Whole Form, and RITALIN® In Crushed Form Dosed to Healthy Subjects.

Objective: To determine the pharmacokinetics of methylphenidate from single oral doses of crushed and whole Concerta® Tablets and crushed Ritalin® Tablets in healthy subjects.

Study Design: This study was a single-dose, open-label, three-treatment crossover design. Nineteen healthy male and female subjects, ages 18 through 51 years, were enrolled in the study. The mean age and weight were 29.8 ± 11.2 years and 168.6 ± 22.8 Ibs, respectively. Subjects were fasted overnight for at least 10 hours prior to receiving drug in each treatment period. They received one of the three treatments, designated A through C, each period:

A: One intact (whole) Concerta Tablet, 18 mg, was swallowed with 180 mL of water. Each subject then consumed 4 ounces of apple sauce.
B: One Concerta Tablet, 18 mg, was crushed and swallowed with 4 ounces of Apple sauce. Each subject then consumed 180 mL of water.
C: One Ritalin IR Tablet, 20 mg, was crushed and swallowed with 4 ounces of Apple sauce. Each subject then consumed 180 mL of water.

The lot number for Concerta tablets used in this study was 0412541 and for Ritalin, it was 022J2045. Serial blood samples were collected at 0 (predose), 20, 40, 60, 80, 100, 120 minutes, and at 2.5, 3, 4, 5, 6, 7, 8, 9, 12, 14, and 24 hours following each dose. Dosing in each treatment period was separated by at least 72 hours. Subjects remained at the clinical study site until after the 24-h blood collection for each period. Safety assessments included adverse events monitoring throughout the study, and vital signs, clinical chemistry and hematology testing at study completion.

Analytical Method: Plasma samples were quantified for *d*- and *l*- threo-methylphenidate (MPH) using a validated LC/MS/MS assay. The LC/MS/MS method was linear for *d*-threo-methylphenidate over the range of 0.05 to 50.0 ng/mL, and for *l*- threo-methylphenidate over the range of 0.01 to 10.0 ng/mL. The Lower Limit of Quantification (LLOQ) in 0.2 mL of Extracted Plasma of *D*-Threo-Methylphenidate nominally was 0.05 ng/ml, and of *L*-Threo-Methylphenidate was 0.01 ng/ml. Accuracy of the assay for *d*-threo-methylphenidate over a range of 0.05 to 50.0 ng/mL was demonstrated by coefficients of variation that ranged from –5.63 to 1.67% for the means at each concentration of the standard curve. Accuracy of the assay for *l*-threo-methylphenidate over a range of 0.01 to 10.0 ng/mL was demonstrated by coefficients of variation that ranged from –2.04 to 0.414% for the means at each concentration of the standard curve. Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of *d*-threo-methylphenidate at 0.0500, 0.150, 1.75, and 37.5 ng/mL. The coefficients of variation were 4.65, 2.59, 2.34, and 1.98% for the limit of-quantitation, low, medium, and high control samples, respectively. Precision of the method was demonstrated by the assay of pooled QC samples at nominal concentrations of *l*-threo-methylphenidate at 0.01, 0.03, 0.35, and 7.5 ng/mL. The coefficients of variation were 9.78, 6.30, 2.44, and 1.46% for the limit-of-quantitation, low, medium, and high control samples, respectively.

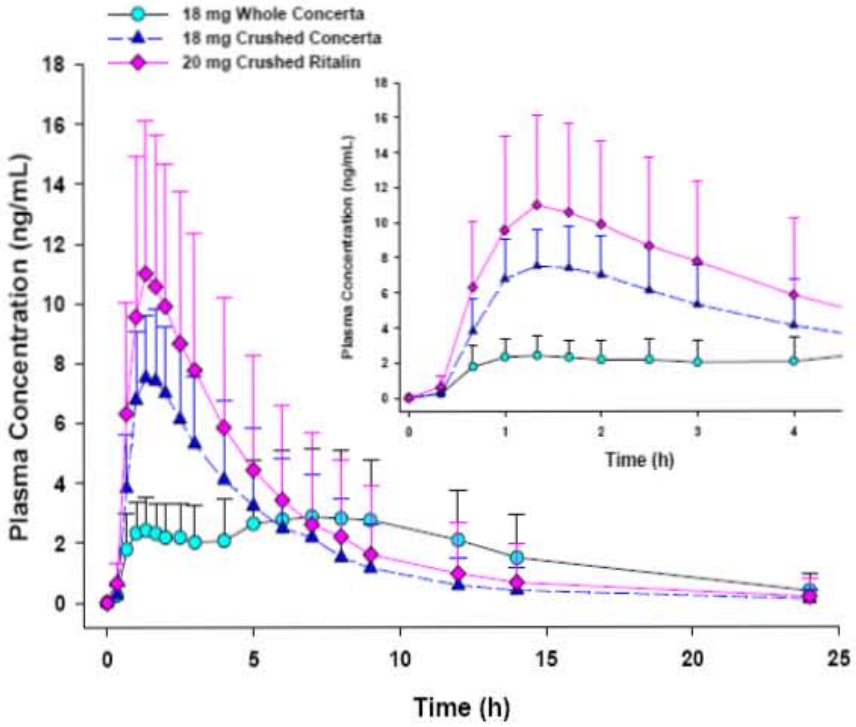
Data Analysis: Pharmacokinetic parameters were computed using non-compartmental methods.

A post hoc evaluation of the relative bioavailability of *d*-threo-methylphenidate from an 18 mg crushed Concerta tablet (test treatment) versus a 20 mg crushed Ritalin tablet (reference treatment) was conducted. The endpoints included in this analysis were Cmax, AUC0-2h, AUCmedian, Cmax/Dose, AUC0-2h/Dose and AUCmedian/Dose. Following ln transformation, the individual values for each of the listed pharmacokinetic parameters were analyzed by ANOVA using a mixed effects model containing fixed effects for sequence, period, and treatment and a random effect for subjects (within sequence). The point estimates and 90% confidence intervals of the ratios for the ln transformed values of Cmax, AUC0-2h, AUCmedian, Cmax/Dose, AUC0-2h/Dose and AUCmedian/Dose were determined.

Pharmacokinetic Results: The actual doses of *d*-threo-methylphenidate administered as crushed tablets (Treatments B and C) ranged from 8.4 to 8.9 mg for Concerta and 9.5 to 9.9 mg for the Ritalin.

The plasma concentration time profile of *d*-threo-methylphenidate from whole Concerta is provided in the following figure

Mean (SD) Plasma d-Threo-Methylphenidate Concentrations versus Time Following Single Doses to Healthy Adults



D-threo-methylphenidate was rapidly absorbed from the crushed Concerta tablet (Treatment B) and the crushed Ritalin tablet (Treatment C) with a median Tmax of

about 1.33 hours. The terminal plasma concentration-time profiles for the two treatments paralleled one another and declined in a mono-exponential manner. There were large inter-individual differences observed for the *d*-threo-methylphenidate concentration-time profiles within each treatment group. The summary statistics for Cmax, Tmax, AUC0-2h and AUCT for the 17 subjects (excluding subject 17) are presented in the following table. And summary table of these same key parameters with data from all subjects (n=18) completing the study is also presented for comparison.

Descriptive Statistics for d-Threo-Methylphenidate Pharmacokinetic Parameters Following Single Doses of 18 mg Concerta Tablet Whole or Crushed or 20 mg Ritalin Tablet Crushed to Healthy Adults (N=17)

	18 mg Whole CONCERTA (Treatment A)	18 mg Crushed CONCERTA (Treatment B)	20 mg Crushed RITALIN (Treatment C)
C_{MAX} (ng/mL)	3.55 (2.25)	8.17 (2.59)	11.6 (5.01)
T_{MAX}* (h)	6.00 (0.66 - 12.00)	1.33 (0.66 - 2.50)	1.33 (1.00 - 3.00)
AUC_{0-2h} (ng.h/mL)	3.39 (1.56)	9.79 (2.76)	14.4 (6.76)
AUC_T (ng.h/mL)	39.7 (31.0)	37.1 (24.3)	54.5 (48.5)

*median (range)

Descriptive Statistics for d-Threo-Methylphenidate Pharmacokinetic Parameters Following Single Doses of 18 mg Concerta Tablet Whole or Crushed or 20 mg Ritalin Tablet Crushed to Healthy Adults (N=18)

	18 mg Whole CONCERTA (Treatment A)	18 mg Crushed CONCERTA (Treatment B)	20 mg Crushed RITALIN (Treatment C)
C_{MAX} (ng/mL)	4.28 (3.79)	8.07 (2.56)	11.5 (4.90)
T_{MAX}* (h)	5.50 (0.66 - 12.00)	1.33 (0.66 - 2.50)	1.33 (1.00 - 3.00)
AUC_{0-2h} (ng.h/mL)	3.58 (1.71)	9.62 (2.78)	14.1 (6.63)
AUC_T (ng.h/mL)	39.7 (30.1)	37.0 (23.6)	54.1 (47.1)

*median (range)

Compared to the crushed Ritalin tablet, the crushed Concerta tablet appeared to result in lower peak concentrations and systemic exposures (Cmax and AUC parameters, respectively) of *d*-threo-methylphenidate, even when these parameters were adjusted for dose. Based on a post hoc statistical evaluation, the dose normalized pharmacokinetics parameters for *d*-threo-methylphenidate from crushed Concerta were not considered bioequivalent to those from crushed Ritalin. The 90% confidence intervals were not contained within the 80 to 125% range. Thus the two treatments could not be determined to be bioequivalent with or without dose normalization. In addition, the ratios and the 90% CIs for Cmax, AUC0-2h, AUCmedian/Dose, and AUCmedian did not fall within the 80 – 125 range. This indicates that the dose normalized pharmacokinetics parameters that determine early exposure (Cmax, AUC0-2h) were different for crushed Concerta and crushed Ritalin.

Summary of Post hoc Statistical Analysis for Relative Bioavailability of d-Threo-Methylphenidate Following Single Doses of 18 mg Crushed Concerta Tablet Relative to 20 mg Crushed Ritalin Tablet to Healthy Adults (N = 18)

Pharmacokinetic Parameter	Ratio[a] (%)	90% Confidence Intervals	p value
CMAX/Dose (ng/mL/mg)	81.46	(74.75, 88.78)	0.0008
CMAX (ng/mL)	72.68	(66.68, 79.22)	< 0.0001
AUC_{0-2h}/Dose (ng.h/mL/mg)	80.13	(71.10, 90.31)	0.0054
AUC_{0-2h} (ng.h/mL)	71.49	(63.41, 80.61)	0.0002
AUCMEDIAN/Dose (ng.h/mL/mg)	79.29	(66.33, 94.78)	0.0376

A: Ratio between adjusted geometric means (Test/Reference).

Safety Summary: The sponsor reported that 8 of 19 subjects (42.1%) experienced 21 adverse events, most of which were regarded as not related to study drug. The most frequently reported adverse event was nausea (N=5). The sponsor reported that all adverse events recorded during the study were considered to be mild except for one event of moderate viral illness, which was considered unrelated to the study drug by the investigator. Two subjects (ID 2 and ID 12) experienced elevated total bilirubin at screening that did not resolve upon repeat testing but were considered mild and not clinically significant by the investigator. The drugs were well tolerated and there were no serious adverse events in this study.

Summary: Overall, systemic exposures for *d*-threo-methylphenidate were greater for the Ritalin immediate release treatment compared to either of the Concerta treatments, even when exposures were adjusted for dose. The post hoc relative bioavailability analysis of the two crushed tablet dosing regimens revealed that the crushed Concerta treatment was not bioequivalent to the crushed Ritalin treatment. The crushed Concerta tablet resulted in mean peak d-threomethylphenidate concentrations (Cmax) that were on average approximately 20% lower than the crushed Ritalin tablet when adjusted for the actual dose the subject received. In addition, d-threo-methylphenidate mean dose-adjusted exposures over the initial absorption phase (AUC0-2h and AUCmedian) were also approximately 20% less than the exposures observed for the Ritalin treatment.

Reviewer comments: The reviewer agrees that when Concerta ER and Ritalin IR are administered in the crushed form, the formulations are not bioequivalent. Dose normalized concentrations were lower for Concerta as compared to Ritalin.

APPEARS THIS WAY ON ORIGINAL

Attachments

Figure 9-2. Mean (SD) Plasma *d*-Threo-Methylphenidate CMAX Following Single Doses to Healthy Adults (N=17)

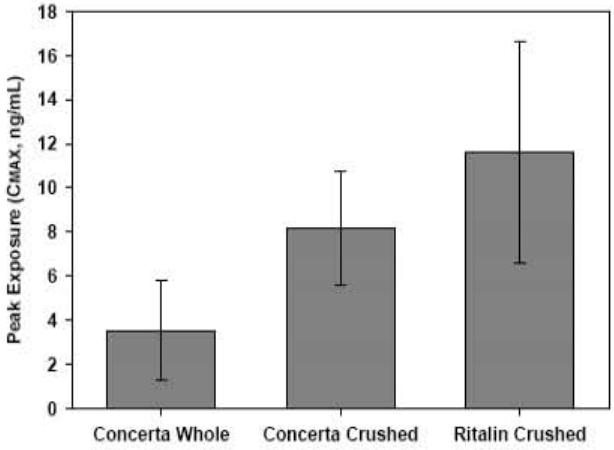


Figure 9-3. Mean (SD) Plasma *d*-Threo-Methylphenidate $AUC_{0\text{-}2h}$ Following Single Doses to Healthy Adults (N=17)

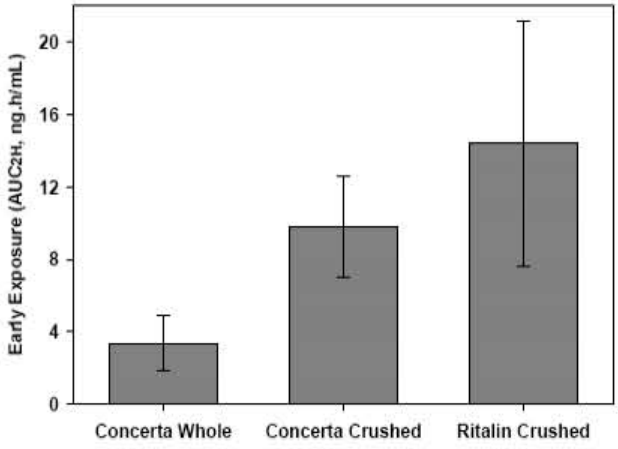


Table 9. PK Parameters: Individual Listings and Summary Statistics for Treatment A (18 mg CONCERTA Tablet Whole.)

Subject Number	TMAX (h)	CMAX (ng/mL)	CMAX/Dose (ng/mL/mg)	AUC2H (h*ng/mL)	AUC2H/Dose (h*ng/mL/mg)	AUCMEDIAN (h*ng/mL)	AUCMEDIAN/Dose (h*ng/mL/mg)	AUCT (h*ng/mL)
1	1.66	3.05	0.34	3.97	0.44	10.09	1.12	28.19
2	6.00	1.90	0.21	1.99	0.22	7.53	0.84	27.77
3	0.66	5.26	0.58	5.83	0.65	12.47	1.39	34.34
4	5.00	5.36	0.60	5.31	0.59	19.40	2.16	39.10
6	1.00	1.71	0.19	2.32	0.26	6.78	0.75	21.74
7	8.00	2.77	0.31	2.61	0.29	8.09	0.90	32.24
8	5.00	3.95	0.44	1.52	0.17	10.08	1.12	38.22
9	12.00	3.25	0.36	3.66	0.41	10.82	1.20	41.00
10	9.00	2.71	0.30	2.91	0.32	8.87	0.99	35.94
11	8.00	3.19	0.35	2.98	0.33	10.78	1.20	34.53
12	9.00	2.61	0.29	3.57	0.40	9.48	1.05	36.94
13	5.00	2.56	0.28	2.97	0.33	10.14	1.13	30.21
14	6.00	2.36	0.26	2.05	0.23	7.32	0.81	23.17
15	8.00	11.30	1.26	7.59	0.84	33.63	3.74	158.14
16	1.00	2.38	0.26	3.13	0.35	8.44	0.94	29.46
17	1.00	16.70	1.86	6.76	0.75	12.87	1.43	39.80
18	8.00	2.10	0.23	2.18	0.24	6.62	0.74	29.69
105	2.50	3.81	0.42	3.02	0.34	10.42	1.16	33.94
N	18	18	18	18	18	18	18	18
Mean	5.38	4.28	0.48	3.58	0.40	11.32	1.26	39.69
SD	3.44	3.79	0.42	1.71	0.19	6.30	0.70	30.06
CV%	64	89	89	48	48	56	56	76
Min	0.66	1.71	0.19	1.52	0.17	6.62	0.74	21.74
Median	5.50	2.91	0.32	3.00	0.33	10.09	1.12	34.14
Max	12.00	16.70	1.86	7.59	0.84	33.63	3.74	158.14
Geo Mean	3.93	3.45	0.38	3.25	0.36	10.35	1.15	35.21

AUCMEDIAN=AUC(0-5.5h)

Table 9 contd. PK Parameters: Individual Listings and Summary Statistics for Treatment A (18 mg CONCERTA Tablet Whole.)

Subject Number	AUCT/Dose (h*ng/mL/mg)	AUCINF (h*ng/mL)	AUCINF/Dose (h*ng/mL/mg)	AUC %Extrap	Half-life (h)	CL/F (L/h)	Vz/F (L)	CMAX/AUCINF (1/h)
1	3.13	30.06	3.34	6.24	5.25	299.36	2265.31	0.10
2	3.09	31.05	3.45	10.54	6.10	289.89	2549.68	0.06
3	3.82	35.37	3.93	2.93	3.68	254.44	1352.02	0.15
4	4.34	42.10	4.68	7.13	10.20	213.76	3146.59	0.13
6	2.42	22.95	2.55	5.28	4.69	392.21	2653.08	0.07
7	3.58	33.48	3.72	3.72	3.92	268.80	1519.90	0.08
8	4.25	39.85	4.43	4.10	4.34	225.84	1414.61	0.10
9	4.56	43.04	4.78	4.73	3.84	209.13	1157.65	0.08
10	3.99	37.99	4.22	5.40	4.27	236.87	1458.87	0.07
11	3.84	35.42	3.94	2.51	3.69	254.10	1350.96	0.09
12	4.10	40.02	4.45	7.71	5.10	224.88	1655.19	0.07
13	3.36	31.26	3.47	3.35	4.10	287.90	1703.39	0.08
14	2.57	23.66	2.63	2.08	3.60	380.39	1975.46	0.10
15	17.57	185.80	20.64	14.89	7.46	48.44	521.36	0.06
16	3.27	30.96	3.44	4.86	4.26	290.68	1785.16	0.08
17	4.42	42.32	4.70	5.96	4.60	212.66	1411.66	0.39
18	3.30	31.22	3.47	4.89	4.12	288.27	1712.48	0.07
105	3.77	34.46	3.83	1.49	3.16	261.20	1189.00	0.11
N	18	18	18	18	18	18	18	18
Mean	4.41	42.83	4.76	5.43	4.80	257.71	1712.35	0.11
SD	3.34	36.16	4.02	3.22	1.69	73.42	621.56	0.08
CV%	76	84	84	59	35	29	36	71
Min	2.42	22.95	2.55	1.49	3.16	48.44	521.36	0.06
Median	3.79	34.91	3.88	4.87	4.26	257.82	1587.54	0.08
Max	17.57	185.80	20.64	14.89	10.20	392.21	3146.59	0.39
Geo Mean	3.91	37.26	4.14	4.69	4.59	241.58	1600.80	0.09

Table 10. PK Parameters: Individual Listings and Summary Statistics for Treatment B (18 mg CONCERTA Tablet Crushed.)

Subject Number	TMAX (h)	CMAX (ng/mL)	CMAX/Dose (ng/mL/mg)	AUC2H (h*ng/mL)	AUC2H/Dose (h*ng/mL/mg)	AUCMEDIAN (h*ng/mL)	AUCMEDIAN/Dose (h*ng/mL/mg)	AUCT (h*ng/mL)
1	1.33	7.98	0.90	9.43	1.06	4.51	0.51	29.72
2	2.00	5.13	0.58	5.49	0.62	2.35	0.26	26.98
3	1.00	9.57	1.14	11.97	1.43	6.31	0.75	31.71
4	1.00	13.30	1.55	16.66	1.94	9.09	1.06	48.51
6	0.66	7.49	0.85	9.47	1.08	5.80	0.66	24.32
7	1.33	5.09	0.58	6.01	0.68	2.65	0.30	26.07
8	1.66	8.22	0.94	9.80	1.13	4.51	0.52	34.90
9	1.66	8.27	0.94	10.11	1.15	5.01	0.57	34.86
10	1.33	6.93	0.79	8.51	0.97	4.08	0.46	30.73
11	1.00	9.22	1.07	10.95	1.27	5.72	0.67	31.12
12	1.33	7.62	0.88	10.52	1.21	5.46	0.63	33.65
13	1.33	7.27	0.85	8.69	1.01	4.38	0.51	26.49
14	1.33	8.21	0.95	9.36	1.09	4.17	0.48	34.39
15	2.50	14.90	1.73	14.26	1.66	5.39	0.63	128.40
16	1.33	8.00	0.93	10.40	1.21	6.04	0.70	38.34
17	2.00	6.29	0.71	6.67	0.76	2.85	0.32	34.86
18	2.00	6.31	0.73	7.63	0.89	3.62	0.42	23.59
105	1.00	5.41	0.62	7.17	0.82	3.83	0.44	22.73
N	18	18	18	18	18	18	18	18
Mean	1.43	8.07	0.93	9.62	1.11	4.77	0.55	36.97
SD	0.46	2.56	0.30	2.78	0.33	1.59	0.19	23.61
CV%	32	32	33	29	30	33	34	64
Min	0.66	5.09	0.58	5.49	0.62	2.35	0.26	22.73
Median	1.33	7.80	0.89	9.45	1.08	4.51	0.51	31.41
Max	2.50	14.90	1.73	16.66	1.94	9.09	1.06	128.40
Geo Mean	1.36	7.75	0.89	9.26	1.07	4.53	0.52	33.59

AUCMEDIAN = AUC(0-1.33h)

Table 10 contd. PK Parameters: Individual Listings and Summary Statistics for Treatment B (18 mg CONCERTA Tablet Crushed.)

Subject Number	AUCT/Dose (h*ng/mL/mg)	AUCINF (h*ng/mL)	AUCINF/Dose (h*ng/mL/mg)	AUC %Extrap	Half-life (h)	CL/F (L/h)	Vz/F (L)	CMAX/AUCINF (1/h)
1	3.34	30.62	3.44	0.26	2.73	290.66	1146.72	2.94
2	3.26	29.36	3.30	0.17	4.18	303.12	1828.99	1.29
3	3.78	32.46	3.86	0.29	2.66	258.80	992.04	2.31
4	5.64	48.78	5.67	0.27	3.61	176.29	919.28	0.55
6	2.76	24.79	2.82	0.30	2.68	355.04	1371.51	1.89
7	3.19	28.35	3.22	0.18	3.77	310.43	1686.34	0.98
8	4.01	36.18	4.16	0.23	2.75	240.43	952.20	3.55
9	3.96	35.85	4.07	0.23	2.74	245.48	970.89	2.76
10	3.49	31.50	3.58	0.22	2.58	279.40	1040.60	2.44
11	3.62	31.82	3.70	0.29	2.56	270.30	997.07	2.18
12	3.87	34.51	3.97	0.22	2.80	252.13	1019.45	2.47
13	3.08	26.92	3.13	0.27	2.22	319.46	1023.52	1.58
14	4.00	35.16	4.09	0.23	2.40	244.59	848.37	2.19
15	14.93	139.26	16.19	0.11	5.66	61.75	504.20	7.80
16	4.46	39.01	4.54	0.21	2.51	220.44	797.79	1.72
17	3.96	35.23	4.00	0.18	4.02	249.80	1447.26	1.05
18	2.74	23.93	2.78	0.26	2.17	359.40	1126.86	1.43
105	2.61	23.39	2.69	0.23	3.01	372.02	1616.69	2.79
N	18	18	18	18	18	18	18	18
Mean	4.26	38.17	4.40	0.23	3.06	267.20	1127.21	2.33
SD	2.76	25.95	3.03	0.05	0.88	72.26	338.25	1.57
CV%	65	68	69	21	29	27	30	67
Min	2.61	23.39	2.69	0.11	2.17	61.75	504.20	0.55
Median	3.70	32.14	3.78	0.23	2.74	264.55	1021.49	2.18
Max	14.93	139.26	16.19	0.30	5.66	372.02	1828.99	7.80
Geo Mean	3.86	34.40	3.96	0.23	2.96	252.73	1079.81	1.98

Table 11. PK Parameters: Individual Listings and Summary Statistics for Treatment C (20 mg RITALIN Tablet Crushed.)

Subject Number	TMAX (h)	CMAX (ng/mL)	CMAX/Dose (ng/mL/mg)	AUC2H (h*ng/mL)	AUC2H/Dose (h*ng/mL/mg)	AUCMEDIAN (h*ng/mL)	AUCMEDIAN/Dose (h*ng/mL/mg)	AUCT (h*ng/mL)
1	1.33	10.40	1.06	15.31	1.56	8.51	0.87	42.25
2	1.33	9.37	0.97	10.56	1.09	5.21	0.54	39.38
3	1.33	14.10	1.42	18.99	1.92	10.78	1.09	44.26
4	1.33	17.20	1.77	16.95	1.75	6.08	0.63	64.16
5	2.50	7.51	0.78	4.88	0.51	1.13	0.12	36.55
6	1.00	7.79	0.80	9.84	1.01	5.20	0.54	27.20
7	1.66	8.15	0.84	9.75	1.01	4.62	0.48	43.69
8	1.33	13.00	1.33	14.85	1.52	6.65	0.68	60.73
9	1.00	13.00	1.35	18.00	1.88	10.29	1.07	51.36
10	3.00	7.56	0.77	7.55	0.77	2.99	0.31	39.10
11	1.00	12.90	1.33	15.81	1.63	8.10	0.84	49.02
12	1.00	12.90	1.32	15.03	1.53	8.21	0.84	48.82
13	1.00	12.30	1.24	16.82	1.70	10.01	1.01	45.54
14	1.33	9.18	0.94	11.46	1.17	5.56	0.57	38.70
15	2.50	26.80	2.73	35.62	3.63	17.90	1.83	238.45
16	1.00	11.10	1.16	14.14	1.47	8.20	0.85	38.26
17	2.00	9.05	0.92	10.11	1.03	4.42	0.45	47.40
18	2.00	5.84	0.61	6.31	0.66	2.73	0.29	27.82
105	1.66	5.54	0.57	7.12	0.73	3.44	0.35	27.69
N	19	19	19	19	19	19	19	19
Mean	1.54	11.25	1.15	13.64	1.40	6.84	0.70	53.18
SD	0.60	4.85	0.49	6.79	0.69	3.82	0.39	45.94
CV%	39	43	43	50	49	56	55	86
Min	1.00	5.54	0.57	4.88	0.51	1.13	0.12	27.20
Median	1.33	10.40	1.06	14.14	1.47	6.08	0.63	43.69
Max	3.00	26.80	2.73	35.62	3.63	17.90	1.83	238.45
Geo Mean	1.45	10.46	1.07	12.31	1.26	5.84	0.60	45.74

AUCMEDIAN = AUC(0-1.33h)

Table 11 contd. PK Parameters: Individual Listings and Summary Statistics for Treatment C (20 mg RITALIN Tablet Crushed.)

Subject Number	AUCT/Dose (h*ng/mL/mg)	AUCINF (h*ng/mL)	AUCINF/Dose (h*ng/mL/mg)	AUC %Extrap	Half-life (h)	CL/F (L/h)	Vz/F (L)	CMAX/AUCINF (1/h)
1	4.31	43.37	4.43	2.58	2.59	225.977	8447.962	0.24
2	4.06	39.76	4.10	0.96	3.78	243.937	13302.52	0.24
3	4.47	44.79	4.52	1.17	2.66	221.047	8479.152	0.31
4	6.61	64.53	6.65	0.57	3.27	150.329	7084.926	0.27
5	3.81	36.91	3.85	0.97	3.56	260.072	13369.34	0.20
6	2.80	27.73	2.86	1.92	2.16	349.741	10903.9	0.28
7	4.50	43.86	4.52	0.40	2.38	221.143	7601.581	0.19
8	6.20	61.11	6.24	0.63	3.41	160.366	7898.09	0.21
9	5.35	52.55	5.47	2.27	2.57	182.671	6779.147	0.25
10	3.99	40.24	4.11	2.82	2.49	243.552	8745.339	0.19
11	5.05	49.60	5.11	1.18	4.88	195.566	13762.4	0.26
12	4.98	49.18	5.02	0.73	4.06	199.269	11662.07	0.26
13	4.60	46.39	4.69	1.82	2.32	213.417	7155.605	0.27
14	3.95	39.73	4.05	2.59	2.42	246.663	8617.639	0.23
15	24.33	263.65	26.90	9.56	7.13	37.1703	3823.941	0.10
16	3.99	38.96	4.06	1.80	2.27	246.385	8070.314	0.28
17	4.84	48.67	4.97	2.61	5.53	201.353	16060.43	0.19
18	2.93	28.15	2.96	1.19	1.96	337.441	9561.462	0.21
105	2.83	28.50	2.91	2.84	2.55	343.903	12651.51	0.19
N	19	19	19	19	19	19	19	19
Mean	5.45	55.14	5.65	2.03	3.26	225.26	9683.02	0.23
SD	4.68	51.45	5.24	2.00	1.34	72.37	3066.34	0.05
CV%	86	93	93	98	41	32	32	21
Min	2.80	27.73	2.86	0.40	1.96	37.17	3823.94	0.10
Median	4.47	43.86	4.52	1.80	2.59	221.14	8617.64	0.24
Max	24.33	263.65	26.90	9.56	7.13	349.74	16060.43	0.31
[illegible]	4.70	46.70	4.80	1.53	3.06	208.48	9206.48	0.22

Table 12. Results for Post Hoc Relative Bioavailability Analysis Comparing the Test Treatment B (18 mg crushed Concerta tablet) versus the Reference Treatment C (20 mg crushed Ritalin tablet).

BE Parameter Output	CMAX/Dose	CMAX	AUC2H/Dose	AUC2H	AUCMEDIAN/Dose	AUCMEDIAN
Units	ng/mL/mg	ng/mL	ng*h/mL/mg	ng*h/mL	ng*h/mL/mg	ng*h/mL
Form Var	Treatment	Treatment	Treatment	Treatment	Treatment	Treatment
Form Reference	C	C	C	C	C	C
Reference LSM	0.0895	2.3681	0.2848	2.5615	-0.4208	1.8558
Reference LSM SE	0.0758	0.0753	0.0787	0.0782	0.0933	0.0929
Reference Geometric LSM	1.0938	10.6558	1.3295	12.9548	0.6565	6.3970
Test	B	B	B	B	B	B
Test LSM	-0.1156	2.0470	0.0633	2.2259	-0.6529	1.5097
Test LSM SE	0.0758	0.0753	0.0787	0.0782	0.0933	0.0929
Test Geometric LSM	0.8908	7.7445	1.0653	9.2615	0.5206	4.5255
Difference	-0.2051	-0.3191	-0.2215	-0.3356	-0.2320	-0.3461
Difference SE	0.0491	0.0491	0.0682	0.0685	0.1018	0.1021
Difference DF	15.0357	15.0390	15.0614	15.0688	15.1364	15.1499
Ratio[%Ref]	81.46	72.68	80.13	71.49	79.29	70.74
90% LCI	74.75	66.68	71.10	63.41	66.33	59.15
90% UCI	88.78	79.22	90.31	80.61	94.78	84.60
Alternative Hypothesis p-value	0.3588	0.9652	0.4907	0.9394	0.5340	0.8765
Power	0.9932	0.9931	0.9263	0.9238	0.6671	0.6652
p-value for Treatment effect	0.0008	0.0000	0.0054	0.0002	0.0376	0.0040
p-value for Sequence effect	0.0844	0.0831	0.0581	0.0569	0.0845	0.0832
p-value for Period 1 effect	0.2551	0.2283	0.1870	0.1704	0.2896	0.2529
p-value for Period 2 effect	0.5001	0.4926	0.2163	0.2130	0.1629	0.1606

4.2. Pharmacometric Review

PHARMACOMETRIC REVIEW

NDA:	21121
Drug name:	Concerta (Methylphenidate HCl)
Indication:	ADHD in Adults
Proposed Regimen (Sponsor):	18 – (b) (4) mg once daily
Applicant:	J&J
OCP Reviewer	Kofi Kumi, PhD
PM Associate Director:	Peter Lee, Ph.D.
Type of Submission:	NDA
Submission Date:	2007
PDUFA Date:	June 29, 2008

TABLE OF CONTENTS

18 INTRODUCTION

Concerta is currently approved for ADHD in the pediatric populations (children and adolescents). With this new submission, the sponsor is now seeking the same indication, ADHD, in adults. In addition to efficacy, safety, and typical clinical pharmacology studies, the sponsor also conducted 3 clinical studies to compare the abuse potential of Concerta, an extended-release formulation, and that of Ritalin, an immediate-release formulation of the same active ingredient (methylphenidate HCl). The three abuse potential studies were conducted in different patient populations with various experiences of substance abuse. The dose range of Concerta and Ritalin were also different among the three studies. In addition, the amount of methylphenidate HCl dose in the two formulations, Concerta and Ritalin, were also different in the individual studies. The main objective of this review is to determine the abusive potential between the two formulations, given the difference in study design and dose among the three studies.

19 AIM OF THE REVIEW

There are two specific aims of the following review:

1. Determine difference in abusive potential between the two formulations by a direct comparison between the doses investigated in the individual studies.
2. Compare the abuse potential between the two formulations at similar drug concentration ranges utilizing the PK-PD relationship.

20 QUESTION BASED REVIEW

What are the designs of the three abuse potential studies ?

Three studies were conducted to investigate abuse potential of Concerta vs Ritalin (Table 1). Study 12-302 has a smaller subject number of 18. Study 12-005 includes 49 healthy adults with a history of recreational stimulant use, and study 12-007 includes, a different population, 55 healthy adults with a history of light (occasional) stimulant use. The two larger studies are considered for the analyses of abuse potential by the sponsor and in this review. The doses of Concerta and Ritalin given in the two studies are listed in Table 1.

In addition, Study 02-160 contains pharmacokinetics information of a wider range of doses of Concerta, which were not studied in 12-005 and 12-007. The additional PK information are used as part of the PK-PD analyses in this review.

Table 1. Summary of clinical pharmacology studies

Study	Study Design / Subject Population	Objectives	Treatments/dosing	Location of Report
02-160	Open-label, fixed-sequence, single- and multiple dose pharmacokinetics and safety study / 27 (20 M/7 F) Healthy adults	To assess single- and multiple-dose pharmacokinetics and safety of high doses of CONCERTA	CONCERTA 54 mg, 72 mg, 108 mg, 144 mg / oral dosing once daily for four days	Mod5.3.3.1\02-160 Healthy Subject PK and Initial Tolerability Study Reports
12-004	Open-label, single-dose, randomized, crossover pharmacokinetic study / 19 (14 M/5 F) Healthy adults	To determine the pharmacokinetics of methylphenidate from whole and crushed CONCERTA Tablets and crushed RITALIN tablets	CONCERTA 18 mg (whole and crushed), RITALIN 20 mg (crushed) / oral single dose	Mod5.3.3.1\12-004 Healthy Subject PK and Initial Tolerability Study Reports
12-302	Double-blind, randomized, placebo-controlled, crossover study / 18 (16 M/2 F) Healthy adults with a recent history of substance abuse	To assess the abuse potential of CONCERTA as compared to RITALIN and placebo	RITALIN 60 mg; placebo; CONCERTA 108 mg / oral single dose	Mod5.3.4.1\12-302 Healthy Subject PD and PK/PD Study Reports
12-005	Double blind, placebo-controlled, randomized, crossover study / 49 (37 M/12 F) Healthy adults with a history of recreational stimulant use	To evaluate the abuse potential of CONCERTA as compared to RITALIN and placebo; and to assess the pharmacokinetic-pharmacodynamic relationships (PK-PD) of methylphenidate when dosed as CONCERTA and RITALIN	RITALIN 60 mg; placebo; CONCERTA 108 mg / oral single dose	Mod5.3.4.1\12-005 Healthy Subject PD and PK/PD Study Reports
12-007	Double-blind, placebo-controlled, randomized, crossover study with a qualifying and a treatment phase / 55 (42 M/ 13 F) Healthy normal adults with a history of light (occasional) stimulant drug use	To assess abuse potential of CONCERTA as compared to RITALIN and placebo at comparable doses.	RITALIN 50 and 90 mg; placebo; CONCERTA 54 and 108 mg / oral single dose	Mod5.3.4.1\12-007 Healthy Subject PD and PK/PD Study Reports

What are the endpoints used in the two "pivotal" abuse potential studies, 12-005 and 12-007 ?

The primary endpoint for abuse potential in both 12-005 and 12-007 is the DQRS-VAS Liking scale score. Additional endpoints including ARCI and SDVP were also measured in the studies. Multiple time points of these endpoints were measured after dosing, so that the maximum effect (E_{max}, *defined as the maximum effect within 24 hour post dosing*) and the area under the effect curve (AUE) can be estimated. Additional details regarding the endpoint measures are described below for the 2 studies.

Study 12-005

The primary endpoint was the maximum value (E_{MAX}) of Liking as scored by a subject's response to question 2 on the DRQS-VAS. Additional evaluations from DRQS-VAS included:

- TE_{MAX} and $AUE_{0\text{-}MTEMAX}$ for Liking
- $AUE_{0\text{-}TEMAX}$ for Drug Dislike
- E_{MAX} and $AUE_{0\text{-}TEMAX}$ for Drug Effect (Feel Drug Effect)
- Mean Liking score at each time point

In addition, mean (SD) and 95% confidence intervals of SDVP were calculated for each treatment. For the Cole/ARCI subscales (MBG, A, LSD, BG, PCAG, Sedation–Motor, Sedation–Mental, Unpleasantness–Physical, and Unpleasantness–Dysphoria scales), individual and mean data from the ARCI responses were summarized for each time-point for all subjects.

Study 12-007

The Liking score, the subject's response to the question on the DRQS-VAS ("Do you like the drug effect you are feeling now?"), was considered as one of the primary measures of abuse liability. The subject's responses to the other questions of the DRQS-VAS were secondary pharmacologic measures related to abuse potential.

In addition, the ARCI, the MBG, and the Cole/ARCI scales were measured.

How are primary endpoint of abuse potential different or similar between various Concerta and Ritalin doses studied in 12-005 and 12-007 by direct comparison ?

Study 12-005

The comparisons of key abuse potential endpoints between Concerta and Ritalin at the doses studied are listed in Table 2. There is no statistically significant difference between the two formulations (108 mg Concerta and 60 mg Ritalin) in the primary endpoint E_{max} of Linking score or other parameters derived from the Liking scores, e.g. $AUE_{0\text{-}TEMAX}$, 1-hr score, and 2-hr score. However, there is a numerical difference (2-fold) especially in $AUE_{0\text{-}TEMAX}$ between the two formulations. There is no statistical or much numerical difference in TE_{max} between the two formulations (Table 2).

The mean time course of DRQS-VAS drug liking score after single doses of both formulations also shows consistent difference in the primary endpoint throughout the 24-hr post-dosing period as shown in Figure 1. The difference in DRQS-VAS drug liking score between the two formulations are slightly more pronounced during the first 3 hours after dosing, especially around TE_{max}.

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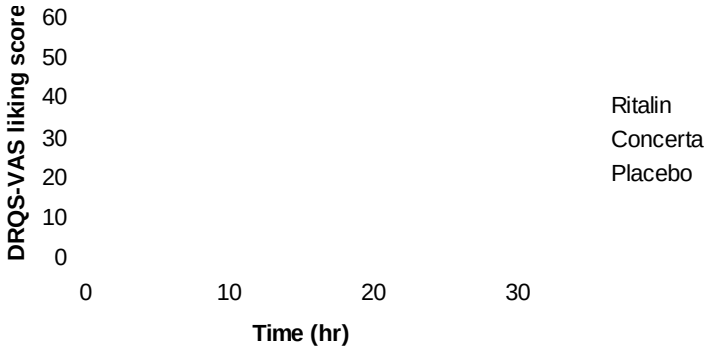
Table 2. Key Positive Effects Measures for Placebo, CONCERTA and RITALIN in study 12-005

Positive Effects Measure	Placebo	CONCERTA 108 mg N=40	RITALIN 60 mg N=40
VAS Liking			
E_{MAX}, Geometric mean (%CV)	13.7 (1326)*	46.8 (132.7)	56.6 (125.1)
TE_{MAX} (hours), Mean (SD)	3.4 (3.81)	4.2 (5.68)	3.0 (5.10)
$AUE_{0\text{-}MTEMAX}$[a], Geometric mean (%CV)	13.5 (3222)*	32.6 (724.3)	68.1 (232.6)
1-hour score, Mean (SD)	31.0 (29.82)*	43.8 (32.59)	55.3 (29.02)
2-hour score, Mean (SD)	35.6 (30.99)*	42.8 (27.76)	54.4 (27.41)
Cole/ARCI – Stimulation Euphoria			
1-hour score, Mean (SD)	4.9 (6.63)*	10.2 (10.42)*	14.2 (11.93)
2-hour score, Mean (SD)	5.4 (7.22)*	9.4 (8.06)*	15.5 (11.62)
Cole/ARCI - Abuse Potential			
1-hour score, Mean (SD)	2.0 (2.97)*	4.6 (4.41)	5.4 (3.93)
2-hour score, Mean (SD)	2.2 (2.97)*	3.7 (4.00)	4.0 (4.91)
ARCI Amphetamine			
1-hour score, Mean (SD)	4.9 (4.90)*	8.8 (7.05)*	10.9 (7.62)
2-hour score, Mean (SD)	5.2 (5.07)*	8.9 (5.94)*	11.8 (7.34)
ARCI Morphine Benzedrine group			
2-hour score, Mean (SD)	6.1 (7.98)*	10.7 (9.20)*	16.7 (12.37)
Subjective Drug Value Procedure			
Subjective drug value ($)[b], Mean (SD)	6.39 (15.52)	6.49 (13.33)	7.85 (14.42)

a: Calculated from the median TE_{MAX} of RITALIN
b: Canadian dollars (At the time of the study, the exchange value of the local, Canadian dollar was approximately $0.80 to 0.83 in U.S. dollars)
* - Significantly different from RITALIN (P<0.05)

Figure 1.

Mean time course of DRQS-VAS drug liking scores in study 12-005



Study 12-007

The comparisons of abuse potential effects between Concerta (54 and 108 mg) and Ritalin (50 and 90 mg) are listed in Table 3. The statistical analysis results (p-values) were shown between 54 mg Concerta and 50 mg Ritalin, between 108 mg Concerta and 90 mg Ritalin, and between both doses of Ritalin and placebo. Most parameters derived from the primary endpoint VAS Drug Liking score with the exception of $AUE_{0\text{-}24h}$ show statistical difference for all comparisons between respective Concerta and Ritalin formulations.

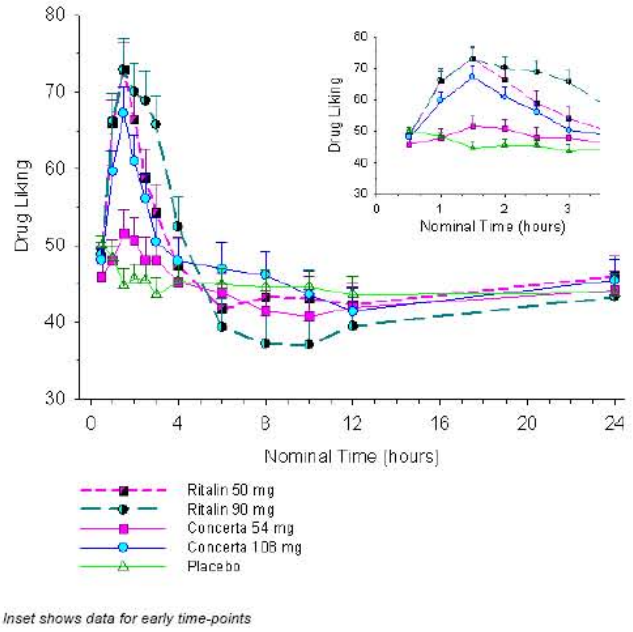
The time course of VAS Drug Liking score after the single dose of respective formulations also shows consistent difference numerically between Concerta and Ritalin (Figure 2). The difference is particularly pronounced between 54 mg Concerta and 50 mg Ritalin during the first 3 hours post-dosing.

Table 3. Abuse potential effects (Mean and SD) for Placebo, CONCERTA 54 and 108 mg, and RITALIN 50 and 90 mg: Primary dependent variables in study 12-007

Subjective Measure	Mean (SD)	Placebo	CONCERTA 54 mg	CONCERTA 108 mg	RITALIN 50 mg	RITALIN 90 mg
VAS Drug Liking ('at this moment')	$AUE_{0\text{-}1h}$	24.5 (4.2)	23.4 (8.5)[a]	26.9 (5.6)	28.6 (6.7)*	28.8 (7.0)*
	$AUE_{0\text{-}2h}$	70.4 (15.3)	74.0 (26.3)[a]	90.7 (23.4)*	98.2 (27.2)*	99.5 (30.5)*
	$AUE_{0\text{-}3h}$	115.5 (27.1)	122.6 (42.2)[a]	146.6 (41.4)*[b]	157.9 (49.1)*	167.8 50.2)*
	$AUE_{0\text{-}24h}$	1040.9 (349.3)	1024.6 (371.2)	1079.2 (392.7)	1083.4 (407.1)	1042.2 (411.6)
	EMAX	51.7 (9.6)	60.0 (16.8)*[a]	73.8 (20.0)*[b]	78.1 (19.9)*	84.7 (17.1)*
Overall Drug Liking	12 h	40.4 (18.3)	43.0 (22.1)[a]	48.7 (30.5)	53.4 (30.7)*	50.6 (30.7)*
	24 h	38.2 (21.6)	42.1 (24.2)[a]	44.3 (30.9)	53.0 (25.0)*	48.0 (30.1)*
	EMAX	42.7 (17.8)	46.3 (21.5)[a]	53.3 (31.4)*	58.2 (27.4)*	56.6 (29.1)*
ARCI MBG	$AUE_{0\text{-}1h}$	6.7 (6.8)	6.9 7.8)[a]	8.4 (7.1)*[b]	9.9 (7.8)*	10.9 (7.4)*
	$AUE_{0\text{-}2h}$	12.2 (12.5)	19.1 (18.2)*[a]	27.3 (17.7)*[b]	33.6 (20.2)*	37.2 (17.6)*
	$AUE_{0\text{-}3h}$	17.5 (18.5)	29.4 (28.2)*[a]	42.8 (28.4)*[b]	52.5 (33.2)*	62.3 (29.6)*
	$AUE_{0\text{-}24h}$	129.4 (159.9)	157.3 (161.8)[a]	221.9 (188.9)*	216.5 (190.5)*	246.6 (190.7)*
	EMAX	9.4 (9.8)	17.4 (14.4)*[a]	24.0 (14.5)*[b]	28.8 (14.7)*	33.8 (11.6)*

a: 'At this moment'
* Significantly different from placebo ($p<0.05$)
[a] Significant difference between CONCERTA 54 mg and RITALIN 50 mg ($p<0.05$)
[b] Significant difference between CONCERTA 108 mg and RITALIN 90 mg ($p<0.05$)

Figure 2. Mean (SD) time course of DRQS-VAS drug liking scores in study 12-007



4How are the abuse potentials compared between Concerta and Ritalin based on the PK-PD relationship ?

Since the doses of Concerta and Ritalin studied and compared in 12-005 and 12-007 are not identical, and the pharmacokinetic profiles of the two formulations (extended-release for Concerta and immediate-release for Ritalin) are very different, it is important to examine the abuse potential based on concentration-response relationship. In addition, the highest tolerable doses for the two formulations may also be different due to the difference in pharmacokinetic profile, such as in the Cmax values. Figure 3 shows that Cmax of Concerta is relatively lower than that of Ritalin at comparable dose amounts. This may explain the lower abuse potential effects between 54 mg Concerta and 50 mg Ritalin, and between 108 mg Concerta and 90 mg Ritalin in study 12-007. On the other hand, 108 mg Concerta and 60 mg Ritalin have similar Cmax range (Figure 3) and there was no statistical difference in the primary endpoint of abuse potential effect between the two formulations in study 12-005. The PK-PD plot of Cmax vs Emax (Figure 4) also indicates consistent trend between the PK and PD parameters regardless of the formulation (Concerta or Ritalin).

Figure 3. Comparison of Cmax between Concerta and Ritalin at various dose levels based on Studies 005, 007 and 160. (C: Concerta, R: Ritalin)

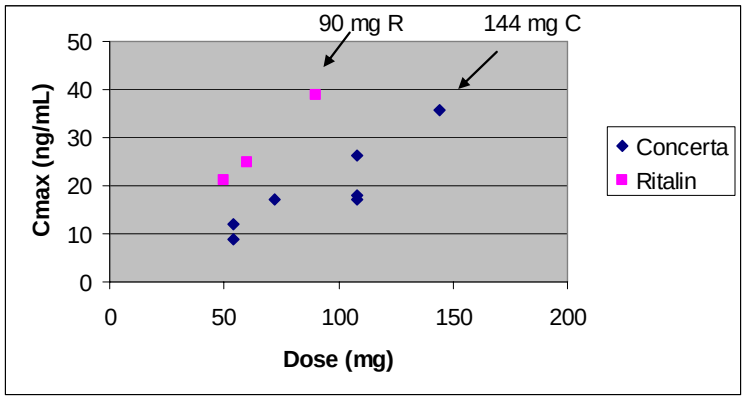
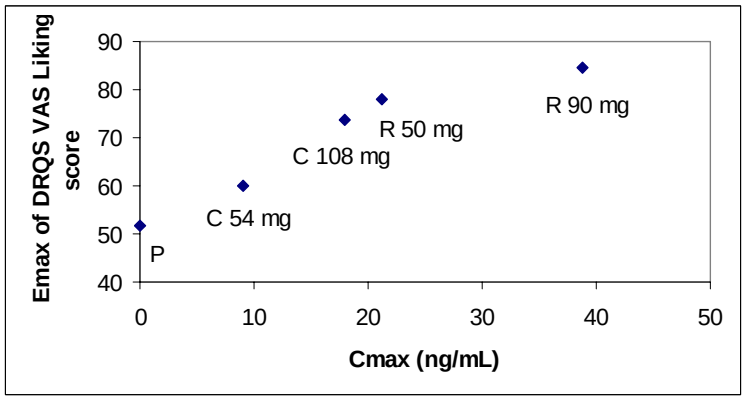


Figure 4. PK-PD relationship between the mean values of Cmax vs Emax from study 12-007. (C: Concerta, R: Ritalin)



21 CONCLUSION

1) At comparable dose levels (54 mg Concerta vs 50 mg Ritalin, and 108 mg Concerta vs 90 mg Ritalin), the abuse potential (VAS drug liking score) is lower for Concerta than for Ritalin, due to the lower drug concentration that can be achieved with the extended-release formulation.
2) For formulations of Concerta and Ritalin that produce similar range of drug concentration (108 mg Concerta vs 60 mg Ritalin), there is no statistically difference in the primary abuse potential.
3) The drug concentration (e.g. Cmax) following 144 mg Concerta is at the similar level as that of 90 mg Ritalin. (b) (4) .

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

/s/

Kofi Kumi
5/8/2008 01:40:31 PM
BIOPHARMACEUTICS

Ider P. Lee
5/8/2008 01:52:38 PM
UNKNOWN

Jogarao Gobburu
5/8/2008 07:46:42 PM
BIOPHARMACEUTICS

Raman Baweja
5/9/2008 01:44:00 PM
BIOPHARMACEUTICS

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

OTHER REVIEW(S)

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-121 Supplement # 017 Efficacy Supplement Type SE- 5

Proprietary Name: Concerta Extended-Release Tablets
Established Name: methylphenidate
Strengths: 18 mg, 27 mg, 36 mg, 54 mg

Applicant: Johnson & Johnson
Agent for Applicant (if applicable): Ann Jenkins-Frison

Date of Application: August 29, 2007
Date of Receipt: August 29, 2007
Date clock started after UN:
Date of Filing Meeting:
Filing Date: October 28, 2007
Action Goal Date (optional): User Fee Goal Date: June 29, 2008

Indication(s) requested: treatment of ADHD in adults (18 years and older)

Type of Original NDA: (b)(1) ☐ (b)(2) ☐
AND (if applicable)
Type of Supplement: (b)(1) ☒ (b)(2) ☐

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.) 3
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 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:

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, 3 Years 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 ☐
N/A

- 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: 54,575

- 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-NDA Meeting(s)? Date(s) P-sNDA March 13, 2007 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:

- 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?
  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? YES ☐ NO ☐

ATTACHMENT

MEMO OF FILING MEETING

DATE: March 24, 2009

NDA #: 21-121

DRUG NAMES: Concerta Extended-Release Tablet

APPLICANT: Johnson & Johnson

BACKGROUND: CONCERTA® [OROS® (methylphenidate HCl)] Extended-Release Tablets is currently approved for children (6-12 years of age), and adolescents (13-17 years of age) (approvals granted August 1 2000, and October 21, 2004, respectively).

The sponsor submitted a supplemental new drug application on August 29, 2007, for new indication for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adults (18 years and older).

ATTENDEES:

ASSIGNED REVIEWERS (including those not present at filing meeting) : Thomas Laughren, Mitchell Mathis, Ni Khin, Glenn Mannheim, Jingyu Luan, Peiling Yang, James Hung, Kofi Kumi, Ider Lee, Jogarao Gobburu, Raman Baweja, Stephen Grant, Norman Stockbridge, Ikram Elayan, Barry Rossloff, Julia Pinto, James Vidra, Katherine Bonson, Michael Klein, Susan Thompson, Tejashri Purohit-Sheth, Nicholette Hemingway, Janet Cliatt

Discipline/Organization	**Reviewer**
Medical:	Ni Aye Khin
Secondary Medical:	Glenn Mannheim
Statistical:	Jingyu Luan
Pharmacology:	Ikram Elayan
Statistical Pharmacology:	
Chemistry:	Julia Pinto
Environmental Assessment (if needed):	
Biopharmaceutical:	Kofi Kumi
Microbiology, sterility:	
Microbiology, clinical (for antimicrobial products only):	
DSI:	Susan Thompson
OPS:	
Regulatory Project Management:	Nicholette Hemingway
Other Consults:	DCRP: Stephen Grant

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):

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.

Sandy Chang (current RPM) ***Note: The filing checklist was not completed by the original RPM who has since left the Agency. This checklist is being completed based upon the history in DFS and to complete the package.

Regulatory Project Manager

Appendix A to NDA Regulatory Filing Review

NOTE: The term "original application" or "original NDA" as used in this appendix denotes the NDA submitted. It does not refer to the reference drug product or "reference listed drug."

An original application is likely to be a 505(b)(2) application if:

(1) it relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application,
(2) it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval, or
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies),

(2) No additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application, and.

(3) All other “criteria” are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the

original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2),

(2) The applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement, or

(3) The applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's Office of Regulatory Policy representative.

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/s/

ShinYe Chang

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CSO

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
CONTROLLED SUBSTANCE STAFF

Date: **June 6, 2008**

To: **Thomas Laughren, M.D., Director**
Division of Psychiatry Products

Through: **Michael Klein, Ph.D., Acting Director**
Controlled Substance Staff

From: **Katherine Bonson, Ph.D., Pharmacologist**
Controlled Substance Staff

Subject: **Concerta Extended Release (methylphenidate hydrochloride)**
Labeling Recommendations
NDA 21-121
Indication: Treatment of Adult Attention Deficit and Hyperactivity Disorder (18, 27, 36 and 54 mg)
Sponsor: Johnson and Johnson Pharmaceutical Research and Development, on behalf of ALZA Corporation

Background:

This CSS consult responds to a request from the Division of Psychiatry Products to recommend appropriate labeling of Concerta extended release (ER) tablets regarding three new human abuse potential studies that were submitted to NDA 21-121.

The present NDA is an efficacy supplement to evaluate the use of Concerta ER for the treatment of adult ADHD using the same formulation and proposed dosage forms (18, 27, 36 and 54 mg) as those in the currently marketed Concerta ER. The proposed daily doses for adults range from 18 to (b) (4) mg.

Concerta ER (methylphenidate hydrochloride in an OROS formulation) was approved in 2000 for the treatment of ADHD in children at doses of 18, 27, 36 and 54 mg. In 2004, the approved indication was expanded to include treatment of ADHD in adolescents at doses of 18, 27, 36, 54 and 72 mg. The API in Concerta ER is methylphenidate, a Schedule II substance under the Controlled Substances Act (CSA). Thus, Concerta ER is a Schedule II drug product.

Conclusions and Recommendations

1. Methylphenidate is a Schedule II substance under the Controlled Substances Act (CSA). Thus, any product containing methylphenidate, such as Concerta ER, is Schedule II.

2. In 2004, the previous manufacturer of Concerta ER (McNeil Consumer and Specialty Pharmaceuticals) submitted a petition to the Drug Enforcement Administration (DEA) requesting that their drug product be rescheduled from Schedule II to Schedule III. In 2007, DEA forwarded this petition to HHS, requesting a scientific and medical analysis of the abuse potential of Concerta ER. CSS is conducting this scientific and medical analysis on behalf of HHS in a separate recommendation. Thus, a final scheduling recommendation decision by HHS is pending.

3. Three human abuse potential studies (Studies # 12-302, 12-005, 12-007) conducted with Concerta ER were submitted in the present efficacy supplement. Each study had a double-blind, randomized, crossover, placebo-controlled design that compared subjective responses to Concerta ER, IR methylphenidate and placebo in individuals with a history of stimulant use. The results of these studies are summarized below and in Table 1:

* In two of three human abuse potential studies (Studies #12-005 and #12-007), there was a statistically significant increase in subjective responses measuring rewarding effects to the positive control IR methylphenidate (50, 60 and 90 mg) compared to placebo, validating the studies. The third study (Study #12-302) did not show a statistically significant difference between IR methylphenidate (60 mg) and placebo on subjective measures of reward and is considered invalid.

* In Study 12-005, 108 mg Concerta ER produced increases in subjective responses that were statistically similar to 60 mg IR methylphenidate on the primary measure of Drug Response Questionnaire-Subjective (DRQS)-Drug Liking as well as on the scale Addiction Research Center Inventory (ARCI)/Cole Abuse Potential. Concerta ER produced subjective responses that were statistically less than 60 mg IR methylphenidate on four scales (ARCI/Cole Stimulation-Euphoria, ARCI-Euphoria, ACRI-Amphetamine, ARCI-Benzedrine). Statistical tests on Concerta ER results were only conducted in relation to IR methylphenidate, but not in relation to the difference between Concerta ER and placebo. The data from this study suggest that Concerta ER produces some rewarding effects in humans that are indistinguishable from IR methylphenidate.

* In Study 12-007, two doses of Concerta ER (54 and 108 mg) produced statistically significant increases in subjective responses compared to placebo on 9 scales (DRQS-Drug Liking, DRQS-Overall Drug Liking, DRQS-Good Effects, DRQS-High, DRQS-Take Drug Again, ARCI/Euphoria, ARCI/Amphetamine, ARCI/Cole Stimulation-Euphoria, ARCI/Cole Stimulation-Motor). Statistical tests on Concerta ER results were only conducted in relation to placebo, but not in relation to the difference between Concerta ER and IR methylphenidate. The data from this study show that Concerta ER produces subjective effects indicative of abuse potential.

Table 1: Human Abuse Potential Studies with Concerta ER

Study Number	12-302	12-005	12-007
Subjects	Adults meeting DSM-IV criteria for substance abuse, who regularly used stimulants such as amphetamine or cocaine for at least one month and had used stimulants within the past 30 days prior to study participation	Adults with a history of cocaine, amphetamine, methamphetamine, MDMA or methyl-phenidate use on at least 10 occasions in the past 5 years and at least once in the past year	Adults who had a single nonmedical use of a stimulant in the past 12 months, without any other drug history required
Number of Subjects	N = 17	N = 49	N = 49
Drug Dosing	Single, oral doses of Concerta ER (108 mg), immediate-release methylphenidate (60 mg) and placebo	Single, oral doses of Concerta ER (108 mg), immediate-release methylphenidate (60 mg) and placebo	Single, oral doses of Concerta ER (54 and 108 mg), immediate-release methylphenidate (50 and 90 mg) and placebo
Study Validated?	No	Yes	Yes
Study Results	n/a	Concerta ER produced increases on positive subjective scales (DRQS-Drug Liking, ARCI/Cole Abuse Potential) that were statistically indistinguishable from immediate-release methylphenidate. No information was provided regarding statistical differences between Concerta ER and placebo.	Both doses of Concerta ER produced statistically significant increases in subjective responses compared to placebo on 9 scales (DRQS-Drug Liking, DRQS-Overall Drug Liking, DRQS-Good Effects, DRQS-High, DRQS-Take Drug Again, ARCI/Euphoria, ARCI/Amphetamine, ARCI/Cole Stimulation-Motor, ARCI/Cole Stimulation-Euphoria).

4. CSS has evaluated the label text proposed by the Sponsor and recommends inclusion of the results from the two validated human abuse potential studies submitted in the NDA in the labeling. Below is a proposed revised label text to Section 9.4 of the Drug Abuse and Dependence section:

Section 9: Drug Abuse and Dependence

9.4 Human Data

In two placebo-controlled human abuse potential studies, oral doses of CONCERTA were compared to oral doses of immediate-release methylphenidate in individuals with a history of recreational stimulant use to assess relative abuse

potential. Both studies were validated by statistical differentiation between immediate-release methylphenidate and placebo on the primary subjective measure of Drug Liking.

In one study, CONCERTA (108 mg) produced increases in subjective responses on two scales (Drug Liking, Abuse Potential) that were statistically indistinguishable from immediate-release methylphenidate (60 mg). In the other study, CONCERTA (54 and 108 mg) produced statistically significant increases in subjective responses compared to placebo on nine scales (Drug Liking, Overall Drug Liking, Good Effects, High, Take Drug Again, Euphoria, Amphetamine, Stimulation-Euphoria, and Stimulation-Motor).

5. CSS recommends that the information proposed by the Sponsor for *Section 12.4 Studies Pertinent to the Drug Abuse Potential of CONCERTA* of the label be removed from the Clinical Pharmacology section because it is redundant with information proposed (above) for inclusion in *Section 9.4 Human Data of Drug Abuse and Dependence*.

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/s/

Katherine Bonson
6/6/2008 03:34:26 PM
PHARMACOLOGIST

Michael Klein
6/6/2008 03:45:40 PM
PHARMACOLOGIST
Acting Director - Controlled Substance Staff

M E M O R A N D U M

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

CLINICAL INSPECTION SUMMARY

DATE: May 7, 2008

TO: Nicholette Y. Hemingway, M.P.H., Regulatory Management Officer
Glenn Mannheim, M.D., Medical Officer
Division of Psychiatry

FROM: Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, M.D.
Acting Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: 21-121

APPLICANT: Johnson and Johnson Pharmaceutical Research & Development, L.L.C

DRUG: Concerta (methylphenidate HCl)

NME: No

THERAPEUTIC CLASSIFICATION: Standard Review

INDICATIONS: Treatment of adults with Attention Deficit Hyperactivity Disorder (ADHD)

CONSULTATION REQUEST DATE: November 28, 2007

DIVISION ACTION GOAL DATE: April 29, 2008

PDUFA DATE: June 5, 2008

I. BACKGROUND: Johnson and Johnson submitted a supplemental New Drug Application (NDA 21-121) for Concerta (methyphenidate HCl) on October 29, 2007 for the treatment of adults with ADHD. Concerta extended release tablets are a long-acting form of

methylphenidate designed for once daily dosing. Previous studies have demonstrated the safety and efficacy of Concerta in the treatment of ADHD in children 6- to 12-years old and in adolescents 13- to 18-years of age. Concerta was first approved in the United States in August of 2000 for the treatment of ADHD in children, and for the treatment of adolescents with ADHD in doses up to 72 mg in October of 2004. These studies were initially conducted by McNeil Consumer & Specialty Pharmaceuticals, and later by Johnson and Johnson.

Two pivotal studies were supported in support of this supplemental NDA, and both were selected for audit. These studies are summarized below.

Protocol #02-159: "A Placebo-controlled, Double-blind, Parallel-group, Dose-titration Study to Evaluate the Efficacy and Safety of CONCERTA® in Adults with Attention Deficit Hyperactivity Disorder at Doses of 36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day"

This is a randomized, placebo-controlled, double-blind, parallel-group, dose-titration study. This Phase 3 study enrolled adults (age 18 to 65 years at screening) who described a chronic course of ADHD from childhood to adulthood with the diagnosis of ADHD established at screening through clinical evaluation by the investigator. The objective of the study was to evaluate the efficacy and safety of Concerta Extended Release Tablets at five dose levels (36 mg, 54 mg, 72 mg, 90 mg, or 108 mg per day) compared to placebo. After written Informed Consent was obtained, subjects were randomized using an IVRS system, and they were assigned randomization numbers and the material number of the dosing package to be dispensed. All subjects initiated treatment with 36 mg and continued with incremental increases of 18 mg of Concerta every seven days ($\pm$ 2 days) until a final individualized dose was achieved based on improvement of ADHD symptoms or the maximum dose of 180 mg was achieved. If a limiting adverse event occurred (resting heart rate >100 bpm, systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg) the dose was to be titrated downward by 18 mg. The dose could also be titrated downward at the investigator's discretion. The dose could only be titrated downward once and was not be titrated back up for the duration of the study. Subjects were to remain on the final individualized dose for five Titration Visits and a Final Visit at 2 weeks after Titration Visit 5. The primary efficacy variable was the change from baseline in the Adult ADHD Investigator Symptom Rating Scale *(*AISRS) total score as assessed by the investigator at the end of treatment or the last score provided during the study. The titration period of the study lasted up to 35 days; subjects could be on study drug for a maximum of 51 days.

Protocol #12-304: "An Open-label, Dose-titration, Long-term Safety Study to Evaluate Concerta at Doses of 36 mg, 54 mg, 72 mg, 90 mg, & 108 mg per day in Adults with Attention Deficit Hyperactivity Disorder"

This is a multi-center, open-label, dose-titration, long-term safety Phase 3 study in adult subjects who have been diagnosed with ADHD. Subjects were age 18 to 65 years at screening. The primary objective of this study was to evaluate the safety of Concerta extended release tablets at doses of 36 mg, 54 mg, 72 mg, 90 mg, and 108 mg per day in adults with ADHD. After written Informed Consent was obtained, the subjects received a prescription for Concerta

at the baseline visit. All subjects initiated treatment with 36 mg of Concerta per day. The dose was titrated up in 18 mg increments every 7 days (± 2 days); there was to be one Baseline visit and five Titration visits. Subjects were then followed monthly, with a Final or Early Termination Visit, as appropriate. Titration was stopped once there was a 30% improvement on the AISRS and a Clinical Impression Improvement Score of 1 or 2. The maximum dose was 108 mg. If a limiting adverse event occurred (resting heart rate >100 bpm, systolic blood pressure >140 mm Hg, or diastolic blood pressure >90 mm Hg), the dose was titrated down by 18 mg. The dose could also be titrated downward at the discretion of the investigator. This dose was then the final individualized dose. No statistical testing of efficacy was planned for this safety study. The plan was to enroll 450 subjects; approximately 250 subjects were to be enrolled for one year and the next approximately 200 were to be enrolled for six months.

Of the 27 sites for Study 02-159 and 54 sites for Study 12-304, 2 were chosen for DSI audit: site 118 (Angela Pinheiro, M.D.) and site 107 (Dr. Donald J. Garcia, M.D.) These two sites were chosen for inspection because they enrolled a high number of subjects for this application and because they both also had high discontinuation rates due to adverse events.

II. INSPECTION RESULTS (by Site):

Name of CI City, State or Country	**Protocol # and # of Subjects:**	**Insp. Date**	**EIR Receipt Date**	**Final Classification**
Angela L. Pinheiro, M.D. Farmington, MI Site 118	Protocol 02-159: 12 enrolled, 12 audited Protocol 12-304: 15 enrolled, 15 audited	3/11/08 – 3/14/08	4/14/08	NAI
Donald Garcia, Jr. M.D. Austin, TX Site 107	Protocol 02-159: 12 enrolled, 14 audited Protocol 12-304: 17 enrolled, 16 audited	3/4/06 – 3/10/08	Pending	Pending – Preliminary NAI

Key to Classifications
NAI = No deviation from regulations.
VAI-No Response Requested= Deviations(s) from regulations.
VAI-R = Response Requested = Deviation(s) from regulations.
OAI = Significant deviations from regulations.
Pending = Preliminary classification based on information in 483; EIR has not been received from the field and complete review of EIR is pending.

1. Angela L. Pinheiro, M.D.
23700 Orchard Lake Road, Suite M
Summit Research Network, Inc.
Farmington, MI 48336

   a. **What was inspected**: This inspection was conducted in accordance with Compliance Program 7348.811 between March 11 and March 14, 2008. A total of 22 subjects were screened with 10 screening failures and 12 subjects enrolled for Study 02-159. There were 22 subjects screened with 15 subjects enrolled for Study

12-304, including 5 who rolled-over from the Study 02-159. All Informed Consent forms were verified, and all subject files were reviewed and compared to the Case Report forms and line data submission from the NDA. Particular attention was paid to the primary efficacy measure, discontinued subjects, and adverse events. There were no limitations to the inspection.

b. General observations/commentary: Generally, the investigator was felt to have executed the study adequately. The documentation was in good order and was described as very detailed. No Form 483 was issued. There were three instances of dosing errors:

- The dose for Subject 007 (Study 12-304) should have been decreased due to an elevated blood pressure of 147/87. It was instead increased from 54 mg to 72 mg rather than being decreased to 36 mg. The error was noted the following day, and the subject was called and instructed to decrease the dose. A Subject Waiver Request was written on 11/15/06; the monitor approved the protocol violation and approved the subject to continue on the study. In addition, the subject took Sudafed for 3 days without the approval of the study site; this violation was acknowledged by the monitor.

- Subject 005 (Study 12-304) took 5 doses of her daughter's prescribed medication at 72 mg instead of the study dose of 90 mg qd. A dosing error also occurred for this subject– a prescription was accidentally written for 54 mg instead of 72 mg as reported in the records. The error was corrected before the medication was dispensed.

- Subject 012 (Study 02-159) had a decrease in dose from 90 mg to 72 mg on 7/13/06 due to agitation and loss of appetite. On 7/24/06 the subject reported continued agitation. Although the physician planned no change in dose, the IVRS fax reported "This subject has been up titrated", with the dose increased to 90 mg. Additional protocol violations in this subject were return visits out of window (7/11/06 by 1 day and 7/24/06 by 5 days), and the subject mistakenly discarding empty drug packaging. The subject did not return for follow-up visits and was lost to follow-up.

Comparison of the Protocol Deviations reported in the NDA submission to the medical records found many discrepancies in that the NDA submission did not report many of the deviations that were reported from the site to the sponsor. Many of the reports are documented on Waiver forms or Medical Review forms instead of Deviation forms. However, even deviations reported on the deviation forms were not always included in the NDA. The deviations were acknowledged and approved by the sponsor's reviewer on the Waiver Requests and emails from the monitor. None of the three dosing errors or other violations above were reflected as protocol violations in the NDA, although the sponsor was notified of all three. The remaining examples of protocol violations reported by the investigator to the sponsor but not reported in the NDA are given below.

- There were no protocol violations in the sponsor's NDA submission for Subject 109 (Study 12-304). However, the subject repeatedly missed doses of study medication, with a 64% compliance rate noted at the Month 7 visit. The subject also returned for a visit one day outside the study window; this was documented on a Subject Waiver Request. The reports were acknowledged by the monitor as protocol violations and emails clarified the points.

- There were no protocol violations in the sponsor's NDA submission for Subject 013 (Study 12-304). However, a Significant Protocol Deviation form showed that an incorrect (previous) version of the Informed Consent Document was used to enroll the subject on 8/4/06. In addition, a Subject Waiver Request was written to report out-of-window visits (by 3 to 4 days) for Titration Visits 3 and 4.

- Subjects 007, 010, 013, and 016 had abnormal laboratory values at the final visit for Study 02-159 and were rolled over into Study 12-304. The deviations were not reported in the NDA submission line-data for any of the subjects. These subjects were followed for the duration of the second study.

- Subject 010 completed study 02-159 dosing from 5/31/06 to 7/27/06. He reported the adverse event of erectile dysfunction on 7/20/06. He was enrolled into Study 12-304 on 8/4/06, but did not take the initial doses of the study drug due to the adverse event of erectile dysfunction until the return visit on 8/10/06. A Subject Waiver Request was completed and approved by the monitor to continue the subject on the study.

- There were no protocol violations reported for subject 015 in Study 02-159. A Subject Waiver Request was written to report that Titration Visit 2 took place one day out of window for the protocol. The reviewers acknowledged the protocol deviation. The Waiver Request was completed on the wrong form (for Study 12-304 instead of Study 02-159).

- The NDA submission reported a protocol violation of less than 80% compliance for subject 107 in Study 12-304. However, a Significant Protocol Deviation Form was completed stating that the subject took a Tylenol #3 with codeine one day prior to enrollment; the urine drug screen was positive. A verbal waiver was obtained to continue the subject in the study. (The Note to File contained an incorrect identification number (007 rather than 107). A Subject Waiver Request was submitted to continue the subject on the study with a phone report of adverse events (lethargy, hip pain, decreased appetite) and decrease of dose; the subject discontinued the study 3 days after that phone report due to left arm numbness and muscle tightness. The NDA contained the adverse events and early withdrawal of the subject, but not the other protocol deviations.

- A Significant Protocol Deviation Form reported that Subjects 010, 016, 020, 106, 107, and 114 did not fast for their final labs; several subjects terminated the study early. The deviations were not reported in the NDA submission line-data listings for these subjects.

- There were no protocol violations reported in the NDA submission for Subject 003 (Study 12-304). There are several Subject Waiver Requests which were submitted and acknowledged by the sponsor as protocol deviations; approval was given to continue the subject in the study. The subject started his initial dose one day early on 7/20/06. H returned 1 week late for Titration Visits 3 and 4 and 12 days late for Titration Visit 5. This subject also missed 4 doses of study medication on 8/13 – 8/16/06, 10/12 - 10/15/06, and 11/18 – 11/20/06.

Dr. Pinheiro's site was noted by the Division of Psychiatry to have a high rate of subject discontinuation due to adverse events. Of 12 subjects enrolled in Study 02-159 at this site, 1 subject was lost to follow-up at Week 8 and 1 subject withdrew early due to an adverse event (increased blood pressure). Of 15 subjects enrolled in Study 12-304, 3 subjects were lost to follow-up, 1

withdrew consent, and 5 withdrew due to adverse events (decreased appetite, decreased weight, generally intolerant, vomiting, irritability).

c. Assessment of data integrity: The data from Dr. Pinheiro's site collected according to the two protocols described above appears acceptable for both studies in support of NDA 21-121. The three dosing errors described above are unlikely to affect data integrity or patient safety. The Review Division will need to evaluate the clinical significance of the sponsor's failure to reflect in the NDA all protocol violations reported by Dr. Pinheiro's site and will need to consider requesting that the Sponsor clarify the discrepancies.

2. Donald Garcia Jr., M.D.
4200 Marathon Boulevard
FutureSearch Trials
Austin, TX 78756

a. What was inspected: This inspection was conducted in accordance with Compliance Program 7348.811 between March 4 and March 10, 2008. For Study 02-159, a total of 17 subjects were screened with 5 screening failures and 12 subjects enrolled. There were 25 subjects screened with 17 subjects enrolled for Study 12-304. The audit included comparison of the source documentation of CRFs with data listings (primary efficacy measure, discontinued patients, and adverse events) provided in the NDA. The complete EIR was not available at the time this CIS was written. The observations noted are based on preliminary communications with the FDA field investigator.

b. General observations/commentary: Generally, the investigator was felt to have executed the study adequately. Records were well organized. All data provided with the assignment was compared to the source documents, and no discrepancies were found. No Form 483 was issued. Particular attention was paid to the reasons for subject discontinuation, since there was a high discontinuation rate at Dr. Garcia's site. Review of Study 02-159 showed that 3 of 9 subjects who discontinued the study did so because of adverse events (dry mouth/grinding teeth, elevated blood pressure, increased mood lability), while 6 were discontinued due to loss to follow-up. For Study 12-304, 2 of 19 discontinuations were due to adverse events (tachycardia, feeling jittery), while 17 were due to loss to follow-up. The only item discussed with Dr. Garcia at the conclusion of the inspection was an ECG which was not done for Subject 007 at the final visit as called for in the Study 02-159 protocol.

c. Assessment of data integrity: The data from Dr. Garcia's site collected according to the two protocols described above appears acceptable for both studies in support of the supplement to NDA 21-121.

IV. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the two sites inspected adhered to the applicable regulations and good clinical practices governing the conduct of clinical investigations The few regulatory violations documented are unlikely to affect data integrity or the outcome of the study. Many subjects from these two sites who did not complete the study were lost to follow-up rather than discontinuing due to adverse events. In general, for both sites the studies appear to have been conducted adequately, and the data generated by the sites may be used in support of the indication. For Dr. Pinheiro's site, the major concern identified is the failure of the Sponsor to include protocol violations reported by the site in the NDA submission. These omissions appear to be the sole responsibility of the sponsor, as Dr. Pinheiro's site reported the identified omissions appropriately to the sponsor. The Review Division will need to evaluate the clinical significance of the failure to reflect all protocol violations reported by Dr. Pinheiro's site 118 in the Concerta sNDA and will need to consider requesting that the Sponsor clarify the discrepancies.

For Dr. Garcia's site, the observations above are based on communications with the field investigator. DSI will generate an inspection summary addendum if the conclusions change significantly upon receipt and review of the pending complete EIRs and the supporting inspection evidence and exhibits.

{See appended electronic signature page}

Susan D. Thompson, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.
Acting Branch Chief
Good Clinical Practice Branch II
Division of Scientific Investigations
Office of Compliance

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/s/

Susan Thompson
5/8/2008 12:31:21 PM
MEDICAL OFFICER

Tejashri Purohit-Sheth
5/8/2008 12:33:06 PM
MEDICAL OFFICER

M E M O R A N D U M

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

DATE: October 26, 2007

FROM: Ni A. Khin, M.D.
Team Leader
Division of Psychiatry Products, HFD-130

TO: File NDA 21,121/SE5-017 (This memo should be filed with the sNDA submission dated 8/31/07)

SUBJECT: Additional comments and recommendations in response to Dr. Mannheim's initial clinical filing review dated 10/24/2007

This memo is in response to Dr. Mannheim's recommendation of non-fileable action of above referenced sNDA. The sponsor submitted this supplemental NDA for concerta in the treatment of ADHD in adults. In this submission, the sponsor included results from two phase 3 placebo-controlled, double blind studies (02-159 and 42603ATT3002) and open-label safety data from 3 studies (12-304, C-99-018-00, and CON-CAN-4). Concerta (methylphenidate extended release OROS tablets) has been marketed for the treatment of ADHD in children and adolescents.

On 10/24/07, the review team held a filing meeting. During the meeting, all other disciplines found no filing issues except Dr. Mannheim recommended that we should refuse to file (RTF) this sNDA. It was discussed that, the RTF issues of missing CRFs, the number of subjects in study 12-304 and inadequate subjects' narratives as perceived by Dr. Mannheim, did not constitute a basis for non-filing of this application under applicable CFR and current CDER RTF policy. Yet, Dr. Mannheim has also written an initial clinical review (dated 10/24/07) in which he continues to argue for refusing to file this sNDA based upon the followings:

- The number of remaining subjects in Study 12-304, is 161 at 4 months, short of the 200 subjects which the sponsor stated would be exposed at 6 months.
- Subject narratives are lacking interpretable information and CRF's are missing for subjects with potentially significant adverse events preventing adequate review of this sNDA [314.50(f)(3)].

While I note Dr. Mannheim's focus was just on number of subjects and exposure (161 subjects at 4 months) in one study 12-304 as the sponsor stated during the pre-NDA meeting that they expect to have enrollment of 200 subjects for 6 months in this study. In this submission, the sponsor's clinical study report of study 12-304, table 14, duration of exposure notes 148 subjects for 6 months. However, in the integrated safety summary, the sponsor has provided duration of exposure for all evaluable subjects (N=896) for 3 pooled open label studies that there were 195 subjects exposed for at least 6 months and 42 subjects for 9-12 months. I believe these numbers seem sufficient to make an adequate safety evaluation for the purposes of this sNDA.

Dr. Mannheim's citation and interpretation of 21 CFR 314.50(f)(3) along with repeated referral in his review as "missing CRFs" could not be regarded as missing as the sponsor did provide CRFs for

deaths and AE dropouts in accordance with the CFR requirements. The items (such as CRFs from cases with CV events and amendment to case narratives with clinically useful information) that Dr. Mannheim insists to have for his review would not materially interfere with clinical review of the remainder of the application. Current RTF policy clearly states that "the RTF is not an appropriate vehicle for dealing with complex and close judgments on such matters as balancing of risks and benefits…"

In addition, Dr. Mannheim in his initial RTF review recommends the need for an input from PDAC advisory committee regarding the cerebrovascular events. He also requests for consultation to the OSE for the AERS data and the Division of Cardio-Renal Products regarding the cardiovascular adverse events of interest. As needed, we may set up a separate meeting to further discuss these issues once Dr. Mannheim commences his full clinical review and provide detailed justification for such recommendations.

Cc:
HFD-130/Laughren/Mathis/Mannheim/Cliatt

File: N21121/Memo_102007

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

/s/

Ni Aye Khin
10/26/2007 01:47:03 PM
MEDICAL OFFICER

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-121/S-017

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/2010
See OMB Statement on Page 3.

NDA NUMBER
21-121

NAME OF APPLICANT / NDA HOLDER
Ortho-McNeil-Janssen Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME
CONCERTA

ACTIVE INGREDIENT(S)	STRENGTH(S)
Methylphenidate HCl	18, 27, 36, 54 mg
DOSAGE FORM	APPROVAL DATE OF NDA OR SUPPLEMENT
Tablets	6/27/2008

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
6,930,129	8/16/2005	7/31/2017

d. Name of Patent Owner	Address *(of Patent Owner)*	
ALZA Corporation	1900 Charleston Road	
	City/State Mountain View, CA	
	ZIP Code 94043	FAX Number *(if available)* (650) 564-7070
	Telephone Number (650) 564-5000	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☒ Yes	☐ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☒ No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patient. For each approved method of use claimed by the patient, provide the following information:

4.1	Does the patent claim one or more approved methods of using the approved drug product?	☒ Yes	☐ No
4.2	Patent Claim Number(s) *(as listed in the patent)* SEE ATTACHED APPENDIX	Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product? ☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* SEE ATTACHED APPENDIX	

4.2b If the answer to **4.2** is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: (Submit the description of the approved indication or method of use that you propose FDA include as *the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

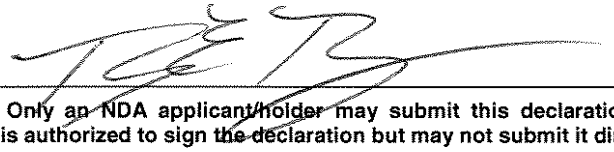
☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*



Date Signed

7-21-08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Timothy E. Tracy, Esq.	
Address Johnson & Johnson One Johnson & Johnson Plaza	City/State New Brunswick, NJ
ZIP Code 08933	Telephone Number (732) 524-6586
FAX Number *(if available)* (732) 524-2138	E-Mail Address *(if available)* TTracy@corus.jnj.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.htm.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

APPENDIX

4. Method of Use - 1 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **1**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** Absorption Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 2 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* 2	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 3 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **4**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 4 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **5**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** Absorption Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 5 of 8

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?

☒ Yes ☐ No

4.2 Patent Claim Number *(as listed in the Patent)* **6**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** Absorption Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 6 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **8**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 7 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **9**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 8 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **10**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. CONCERTA® also contains the following inert ingredients: butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin. **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation or Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/2010
See OMB Statement on Page 3.

NDA NUMBER
21-121

NAME OF APPLICANT / NDA HOLDER
Ortho-McNeil-Janssen Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME CONCERTA	
ACTIVE INGREDIENT(S) Methylphenidate HCl	STRENGTH(S) 18, 27, 36, 54 mg
DOSAGE FORM Tablets	APPROVAL DATE OF NDA OR SUPPLEMENT 6/27/2008

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number 6,919,373	b. Issue Date of Patent 07/19/2005	c. Expiration Date of Patent 07/31/2017
d. Name of Patent Owner ALZA Corporation	Address *(of Patent Owner)* 1900 Charleston Road	
	City/State Mountain View, CA	
	ZIP Code 94043	FAX Number *(if available)* (650) 564-7070
	Telephone Number (650) 564-5000	E-Mail Address *(if available)*
e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States) ☞	Address *(of agent or representative named in 1.e.)*	
	City/State	
	ZIP Code	FAX Number *(if available)*
	Telephone Number	E-Mail Address *(if available)*

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☒ Yes	☐ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☒ No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1	Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement?	☐ Yes	☒ No
2.2	Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA?	☐ Yes	☒ No
2.3	If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4	Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5	Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.)	☐ Yes	☒ No
2.6	Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7	If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- **the answers to 2.1 and 2.2 are "No," or,**
- **the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,**
- **the answer to 2.3 is "Yes" and there is no response to 2.4, or,**
- **the answer to 2.5 or 2.6 is "Yes."**
- **the answer to 2.7 is "No."**

3. Drug Product (Composition/Formulation)

3.1	Does the patent claim the approved drug product as defined in 21 CFR 314.3?	☐ Yes	☒ No
3.2	Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3	If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- **the answer to question 3.1 is "No," or,**
- **the answer to question 3.2 is "Yes," or,**
- **the answer to question 3.3 is "No."**

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patient. For each approved method of use claimed by the patient, provide the following information:

4.1	Does the patent claim one or more approved methods of using the approved drug product?	☒ Yes	☐ No
4.2	Patent Claim Number(s) *(as listed in the patent)* SEE ATTACHED APPENDIX	Does (Do) the patent claim(s) referenced in **4.2** claim an approved method of use of the approved drug product? ☒ Yes	☐ No
4.2a	If the answer to **4.2** is "Yes," identify the use with specific reference to the approved labeling for the drug product.	Use: *(Submit indication or method of use information as identified specifically in the approved labeling.)* SEE ATTACHED APPENDIX	

4.2b If the answer to **4.2** is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.	Use: (Submit the description of the approved indication or method of use that you propose FDA include as *the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)*

FDA will not list the patent in the Orange Book as claiming the method of use if:

- **the answer to question 4.1 or 4.2 is "No," or**
- **if the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.**

5. No Relevant Patents

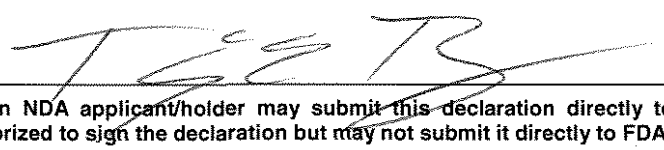
For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.

☐ Yes

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
	7-21-08

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☒ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☐ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Timothy E. Tracy, Esq.	
Address Johnson & Johnson One Johnson & Johnson Plaza	City/State New Brunswick, NJ
ZIP Code 08933	Telephone Number (732) 524-6586
FAX Number *(if available)* (732) 524-2138	E-Mail Address *(if available)* TTracy@corus.jnj.com

INFORMATION AND INSTRUCTIONS FOR FORM 3542

PATENT INFORMATION SUBMITTED UPON AND AFTER APPROVAL OF AN NDA OR SUPPLEMENT

General Information

- To submit patent information to the agency the appropriate patent declaration form must be used. Two forms are available for patent submissions. The approval status of your New Drug Application will determine which form you should use.
- Form 3542a should be used when submitting patent information with original NDA submissions, NDA amendments and NDA supplements prior to approval.
- Form 3542 should be used after NDA or supplement approval. This form is to be submitted within 30 days after approval of an application. This form should also be used to submit patent information relating to an approved supplement under 21 CFR 314.53(d) to change the formulation, add a new indication or other condition of use, change the strength, or to make any other patented change regarding the drug, drug product, or any method of use. Form 3542 is also to be used for patents issued after drug approval. Patents issued after drug approval are required to be submitted within 30 days of patent issuance for the patent to be considered "timely filed."
- Only information from form 3542 will be used for Orange Book publication purposes.
- Forms should be submitted as described in 21 CFR 314.53. Sending an additional copy of form 3542 to the Orange Book Staff will expedite patent publication in the Orange Book. The Orange Book Staff address (as of April 2007) is: Orange Book Staff, Office of Generic Drugs OGD/HFD-610, 7500 Standish Place, Rockville, MD 20855.
- The receipt date is the date that the patent information is date stamped in the central document room. Patents are considered listed on the date received.
- Additional copies of these forms may be downloaded from the Internet at: *http://www.fda.gov/opacom/morechoices/fdaforms/fdaforms.htm.*

First Section

Complete all items in this section.

1. General Section

Complete all items in this section with reference to the patent itself.

1c) Include patent expiration date, including any Hatch-Waxman patent extension already **granted**. Do not include any applicable pediatric exclusivity. The agency will include pediatric exclusivities where applicable upon publication.

1d) Include full address of patent owner. If patent owner resides outside the U.S. indicate the country in the zip code block.

1e) Answer this question if applicable. If patent owner and NDA applicant/holder reside in the United States, leave space blank.

2. Drug Substance (Active Ingredient)

Complete all items in this section if the patent claims the drug substance that is the subject of the approved NDA or supplement.

2.4) Name the polymorphic form of the drug identified by the patent.

2.5) A patent for a metabolite of the approved active ingredient may not be listed. If the patent claims an approved method of using the approved drug product to administer the metabolite, the patent may be listed as a method of use patent depending on the responses to section 4 of this form.

2.7) Answer this question only if the patent is a product-by-process patent.

3. Drug Product (Composition/Formulation)

Complete all items in this section if the patent claims the drug product that is the subject of the approved NDA or supplement.

3.3) An answer to this question is required only if the referenced patent is a product-by-process patent.

4. Method of Use

Complete all items in this section if the patent claims one or more methods of use of the drug product that is the subject of the approved NDA or supplement.

4.2) For each approved use of the drug claimed by the patent, identify by number the claim(s) in the patent that claim the approved use of the drug. An applicant may list together multiple patent claim numbers and information for each approved method of use, if applicable. However, each approved method of use must be separately listed within this section of the form.

4.2a) Specify the part of the approved drug labeling that is claimed by the patent.

4.2b) The answer to this question will be what FDA uses to create a "use-code" for Orange Book publication. The use code designates a method of use patent that claims the approved indication or use of a drug product. Each approved use claimed by the patent should be separately identified in this section and contain adequate information to assist 505(b)(2) and ANDA applicants in determining whether a listed method of use patent claims a use for which the 505(b)(2) or ANDA applicant is not seeking approval. Use a maximum of 240 characters for each "use code."

5. No Relevant Patents

Complete this section only if applicable.

6. Declaration Certification

Complete all items in this section.

6.2) Authorized signature. Check one of the four boxes that best describes the authorized signature.

APPENDIX

4. Method of Use - 1 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* 1	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA®

APPENDIX

4. Method of Use - 2 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **2**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 3 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **3**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 4 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* 4	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 5 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **5**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 6 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **6**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 7 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* 7	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

APPENDIX

4. Method of Use - 8 of 8	
Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:	
4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	
4.2 Patent Claim Number *(as listed in the Patent)* **8**	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No
4.2a If the answer to **4.2** is "Yes", identify with specificity the use with reference to the proposed labeling for the drug product.	Use: *(Submit indication of method of use information as identified specifically in the approved labeling).* INDICATION AND USAGE CONCERTA® is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. **DESCRIPTION** CONCERTA® is a central nervous system (CNS) stimulant. CONCERTA® is available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. **SYSTEM COMPONENTS AND PERFORMANCE** Furthermore, the drug release rate from the system increases with time over a period of 6 to 7 hours due to the drug concentration gradient incorporated into the two drug layers of CONCERTA® **PHARMACOKINETICS** <u>Absorption</u> Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours after which a gradual decrease begins.

EXCLUSIVITY SUMMARY

NDA # 21-121 SUPPL # SE5-017 HFD # 130

Trade Name Concerta Extended-Release Tablets

Generic Name methylphenidate

Applicant Name Johnson & Johnson

Approval Date, If Known 6-27-08

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:

N/A

d) Did the applicant request exclusivity?

YES ☒ NO ☐

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

3 years

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

YES ☒ NO ☐

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?

No

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# 21-121 Concerta (methylphenidate) Tablets

NDA#

NDA#

2. Combination product.

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

YES ☐ NO ☐

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

NDA#

NDA#

NDA#

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

Study 02-159 & Study 3002

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

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Investigation #1 YES ☐ NO ☒

Investigation #2 YES ☐ NO ☒

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

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

Study 02-159 & Study 3002

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

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

Investigation #1		!
		!
IND # 54,575	YES ☒	! NO ☐
		! Explain:

Investigation #2		!
		!
IND # 54,575	YES ☒	! NO ☐
		! Explain:

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

Investigation #1	!
	!
YES ☐	! NO ☐
Explain:	! Explain:

Investigation #2	!
	!
YES ☐	! NO ☐
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:

==========

Name of person completing form: Paul David
Title: CPMS
Date: 9-25-08

Name of Office/Division Director signing form: Thomas Laughren, MD
Title: DPP Division Director

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

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
9/25/2008 02:58:26 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 21-121 | Supplement Number: 017 | NDA Supplement Type (e.g. SE5): SE-5

Division Name: Division of Psychiatry Products | PDUFA Goal Date: June 29, 2008 | Stamp Date: 8/29/2007

Proprietary Name: Concerta Extended-Release Tablet

Established/Generic Name: methylphenidate

Dosage Form: extended-release tablet

Applicant/Sponsor: Johnson & Johnson

Indication(s) *previously approved* (please complete this question for supplements and Type 6 NDAs only):
(1) ADHD in children 6-12 years old
(2) ADHD in adolescents 13-17 years old
(3) _____
(4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1
(Attach a completed Pediatric Page for each indication in current application.)

Indication: ADHD in adults (18 years and older)

Q1: Is this application in response to a PREA PMR? Yes ☐ Continue
No ☒ Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

☐ Yes. Please proceed to Section D.

☐ No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW ☐ active ingredient(s) (includes new combination); ☐ indication(s); ☐ dosage form; ☐ dosing regimen; or ☐ route of administration?*

(b) ☒ No. PREA does not apply. **Skip to signature block.**

**** Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.***

Q3: Does this indication have orphan designation?

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

☐ No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

☐ Yes: (Complete Section A.)

☐ No: Please check all that apply:

☐ Partial Waiver for selected pediatric subpopulations (Complete Sections B)

☐ Deferred for some or all pediatric subpopulations (Complete Sections C)

☐ Completed for some or all pediatric subpopulations (Complete Sections D)

☐ Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)

☐ Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____
- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

☐ Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

				Reason (see below for further detail):			
		minimum	maximum	Not feasible[#]	Not meaningful therapeutic benefit[*]	Ineffective or unsafe[†]	Formulation failed[Δ]
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- ☐ Necessary studies would be impossible or highly impracticable because:
  - ☐ Disease/condition does not exist in children
  - ☐ Too few children with disease/condition to study
  - ☐ Other (e.g., patients geographically dispersed): _____

***** Not meaningful therapeutic benefit:

- ☐ Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of

pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- ☐ Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- ☐ Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- ☐ Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)*

☐ Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):				**Reason for Deferral**			**Applicant Certification †**
Population		minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐	☐	☐
☐	All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐	☐	☐
	Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	Yes ☐	No ☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes ☐	No ☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	Other	__ yr. __ mo.	__ yr. __ mo.
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
☐	Neonate	__ wk. __ mo.	__ wk. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	Other	__ yr. __ mo.	__ yr. __ mo.	☐	☐
☐	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	☐	☐

Are the indicated age ranges (above) based on weight (kg)? ☐ No; ☐ Yes.

Are the indicated age ranges (above) based on Tanner Stage? ☐ No; ☐ Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

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

/s/

ShinYe Chang

3/24/2009 03:42:19 PM

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # 21-121 NDA Supplement # 017
BLA # BLA STN #

If NDA, Efficacy Supplement Type: SE-5

Proprietary Name: Concerta Extended-Release Tablets
Established/Proper Name: methylphenidate
Dosage Form: extended-release tablet

Applicant: Johnson & Johnson
Agent for Applicant (if applicable): Ann Jenkins-Frison

RPM: Shin-Ye Chang

Division: Psychiatry Products

NDAs:
NDA Application Type: 505(b)(1) 505(b)(2)
Efficacy Supplement: 505(b)(1) 505(b)(2)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):

(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). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, check here and explain:

Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.

No changes Updated
Date of check:

If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

- ❖ User Fee Goal Date — June 29, 2008
  Action Goal Date (if different)
- ❖ Actions

• Proposed action	AP TA AE NA CR
• Previous actions *(specify type and date for each action taken)*	None

- ❖ Promotional Materials *(accelerated approvals only)*
  Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain — Received

[1] The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application[2] Characteristics

Review priority: Standard Priority
Chemical classification (new NDAs only):

Fast Track
Rolling Review
Orphan drug designation

Rx-to-OTC full switch
Rx-to-OTC partial switch
Direct-to-OTC

NDAs: Subpart H
Accelerated approval (21 CFR 314.510)
Restricted distribution (21 CFR 314.520)
Subpart I
Approval based on animal studies

BLAs: Subpart E
Accelerated approval (21 CFR 601.41)
Restricted distribution (21 CFR 601.42)
Subpart H
Approval based on animal studies

Submitted in response to a PMR
Submitted in response to a PMC

Comments:

❖ Date reviewed by PeRC *(required for approvals only)*
If PeRC review not necessary, explain: sponsor asking for adult indication.

❖ BLAs only: *RMS-BLA Product Information Sheet for TBP* has been completed and forwarded to OBPS/DRM *(approvals only)* — Yes, date

❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)* — Yes No

❖ Public communications *(approvals only)*

• Office of Executive Programs (OEP) liaison has been notified of action	Yes No
• Press Office notified of action (by OEP)	Yes No
• Indicate what types (if any) of information dissemination are anticipated	None HHS Press Release FDA Talk Paper CDER Q&As Other

[2] All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity

• Is approval of this application blocked by any type of exclusivity?	No Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	No Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	No Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	No Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	No Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)*	No Yes If yes, NDA # and date 10-year limitation expires:

❖ Patent Information (NDAs only)

• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	Verified Not applicable because drug is an old antibiotic.
• Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) Verified 21 CFR 314.50(i)(1) (ii) (iii)
• [505(b)(2) applications] If the application includes a **paragraph III** certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	No paragraph III certification Date patent will expire
• [505(b)(2) applications] For **each paragraph IV** certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	N/A (no paragraph IV certification) Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

  Answer the following questions for **each** paragraph IV certification:

  (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? Yes No

  (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).

  *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*

  (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? Yes No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.*

  *If "**No**," continue with question (3).*

  (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant? Yes No

  (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).

  *If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*

  (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? Yes No

  *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

  *If "**No**," continue with question (5).*

(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).	Yes	No

*If "**No**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (*Summary Reviews*).*

*If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.*

CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist[3]	March 24, 2009

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	Included
Documentation of consent/non-consent by officers/employees	Included

Action Letters

❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Approved June 27, 2008

Labeling

❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	September 7, 2006
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	August 29, 2007
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use *(write submission/communication date at upper right of first page of each piece)*	Medication Guide Patient Package Insert Instructions for Use None

[3] Fill in blanks with dates of reviews, letters, etc.

• Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
• Original applicant-proposed labeling	
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date at upper right of first page of each submission)*	
• Most-recent division proposal for (only if generated after latest applicant submission)	
• Most recent applicant-proposed labeling	
❖ Labeling reviews *(indicate dates of reviews and meetings)*	RPM DMEDP DRISK DDMAC CSS Other reviews
❖ Proprietary Name • Review(s) *(indicate date(s))* • Acceptability/non-acceptability letter(s) *(indicate date(s))*	

Administrative / Regulatory Documents

❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)*	March 24, 2009
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	Included
❖ Application Integrity Policy (AIP) Status and Related Documents www fda.gov/ora/compliance_ref/aip_page html	
• Applicant in on the AIP	Yes No
• This application is on the AIP	Yes No
o If yes, Center Director's Exception for Review memo *(indicate date)*	
o If yes, OC clearance for approval *(indicate date of clearance communication)*	Not an AP action
❖ Pediatric Page *(approvals only, must be reviewed by PERC before finalized)*	Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent *(include certification)*	Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	None
• Outgoing communications *(if located elsewhere in package, state where located)*	
• Incoming submissions/communications	
❖ Postmarketing Commitment (PMC) Studies	None
• Outgoing Agency request for postmarketing commitments *(if located elsewhere in package, state where located)*	

[4] Filing reviews for other disciplines should be filed behind the discipline tab.

• Incoming submission documenting commitment	
❖ Outgoing communications *(letters (except previous action letters), emails, faxes, telecons)*	See Section O
❖ Internal memoranda, telecons, etc.	
❖ Minutes of Meetings	
• PeRC *(indicate date; approvals only)*	Not applicable
• Pre-Approval Safety Conference *(indicate date; approvals only)*	Not applicable
• Regulatory Briefing *(indicate date)*	No mtg
• Pre-NDA/BLA meeting *(indicate date)*	No mtg March 13, 2007
• EOP2 meeting *(indicate date)*	No mtg
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting(s)	No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	

Decisional and Summary Memos

❖ Office Director Decisional Memo *(indicate date for each review)*	None
Division Director Summary Review *(indicate date for each review)*	None June 26, 2008
Cross-Discipline Team Leader Review *(indicate date for each review)*	None June 5, 2008

Clinical Information[5]

❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	October 26, 2007
• Clinical review(s) *(indicate date for each review)*	April 29, 2009; October 23, 2007
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	None
❖ Safety update review(s) *(indicate location/date if incorporated into another review)*	
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	
❖ Clinical reviews from other clinical areas/divisions/Centers *(indicate date of each review)*	None DCRP May 21, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	Not needed June 6, 2008
❖ Risk Management • Review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)* • REMS Memo *(indicate date)* • REMS Document and Supporting Statement *(indicate date(s) of submission(s))*	None
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	None requested May 8, 2008

Clinical Microbiology None

❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	None

[5] Filing reviews should be filed with the discipline reviews.

Clinical Microbiology Review(s) *(indicate date for each review)*	None
Biostatistics	None
❖ Statistical Division Director Review(s) *(indicate date for each review)*	None
Statistical Team Leader Review(s) *(indicate date for each review)*	None
Statistical Review(s) *(indicate date for each review)*	None March 26, 2008
Clinical Pharmacology	None
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	None
Clinical Pharmacology review(s) *(indicate date for each review)*	None May 8, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	None
Nonclinical	None
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	None
• Supervisory Review(s) *(indicate date for each review)*	None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	None June 19, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	No carc
❖ ECAC/CAC report/memo of meeting	None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	None requested
CMC/Quality	None
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	None
• CMC/product quality review(s) *(indicate date for each review)*	None
• BLAs only: Facility information review(s) *(indicate dates)*	None
❖ Microbiology Reviews • NDAs: Microbiology reviews (sterility & pyrogenicity) *(indicate date of each review)* • BLAs: Sterility assurance, product quality microbiology *(indicate date of each review)*	Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	None May 21, 2008
❖ Environmental Assessment (check one) (original and supplemental applications)	
Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	5-21-08
Review & FONSI *(indicate date of review)*	
Review & Environmental Impact Statement *(indicate date of each review)*	

❖ NDAs: Methods Validation	Completed Requested Not yet requested Not needed
❖ Facilities Review/Inspection	
• NDAs: Facilities inspections (include EER printout) *(date completed must be within 2 years of action date)*	Date completed: Acceptable Withhold recommendation
• BLAs: o TBP-EER	Date completed: Acceptable Withhold recommendation
o Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) *(date completed must be within 60 days prior to AP)*	Date completed: Requested Accepted Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

(1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
(2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
(3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations(see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy 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).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

(1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
(2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
(3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

(1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
(2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
(3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

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

/s/

ShinYe Chang

3/24/2009 03:36:23 PM

Cliatt, Janet

From: Cliatt, Janet
Sent: Thursday, December 13, 2007 1:06 PM
To: 'Jenkins-Frison, Ann [MCCUS]'
Cc: 'Foy, Suzanne [PRDGB]'
Subject: RE: NDA 21-121/S017 Filing Communication dated 11/9/07; response 12/04/07 email

Attachments: IR Concerta 12-12-07.pdf

Dear Ann, upon further consideration of our email request dated 12/6/07, I'm sending you the original detailed list as a starting document and used track changes to clearly indicate the changes for your consideration.

IR Concerta
L2-12-07.pdf (103 ..

~ Janet

From: Cliatt, Janet
Sent: Friday, December 07, 2007 4:10 PM
To: 'Jenkins-Frison, Ann [MCCUS]'
Subject: NDA 21-121/S017 Filing Communication dated 11/9/07; response 12/04/07 email

Dear Ann,

Division Management would like to re-examine the request for clinical data communicated to you in the filing letter. We would like to determine if the information requested can be limited to essential safety data. I should be able to give you an update next week.

LCDR Janet Cliatt, MT., CLS (NCA)
Regulatory Project Manager
Division of Psychiatry Products/HFD-130
Food and Drug Administration

10903 New Hampshire Avenue, Building 22, Room 4123
Silver Spring, Maryland 20993-0002

Phone: 301-796-0240
Fax: 301-796-9838
janet.cliatt@fda.hhs.gov

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-121/S-017

Johnson and Johnson Pharmaceutical Research &
Development, L.L.C
Attention: Ann Jenkins-Frison
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Jenkins-Frison:

Please refer to your August 29, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Concerta (methylphenidate HCL) Extended Release Tablets.

Reference is also made to the Agency's November 9, 2007, letter notifying you that this application was filed. That letter included a detailed list of requests for additional information, and we understand that you are planning a response to these requests. Upon further consideration of our requests, we wish to slightly modify this list, mostly for clarification and elimination of several requests that are not critical to a response. In order to best communicate these changes, we have used the original detailed list as a starting document and used track changes to clearly indicate the changes. As a general qualification, we would note that we understand that for some of these requests the requested information is not available or accessible. In those instances, it would suffice to simply state that fact. If needed, we would be happy to further discuss these requests with you.

Clinical

Study 02-159

1. Please provide the Case Report Forms (CRFs) for the following 25 subjects: 101-007; 102-015; 107-001; 108-002; 112-001; 118-017;122-004;122-008; 125-006;126-009;127-006;128-012; 129-005; 130-008;101-004;102-005;106-016;107-002;110-006; 110-015;113-007;120-008;124-007;128-003;130-002.

2. Please provide patient profiles as page 2471 of your Clinical Study Report notes these are available on request for the subjects listed: 127-007; 127-016; 128-003; 128-012; 129-005; 129-008; 130-002; 130-008; 130-009.

3. For all subjects whom you have identified as having Cardiovascular Adverse Events of Interest (Table 12-33, pgs. 685-686, Clinical Study Report), please provide copies of all ECG

~~tracings with an attached copy of~~ your cardiologist's interpretation of any ECG changes if available. If any work-up was done for any adverse event either at the study site or by outside medical practitioner, or, at hospital (discharge summaries, consultant report), please also provide copies and results from any of these studies.

4. Many case narratives for subjects with discontinuations, cardiovascular adverse events of interest and special interest are difficult to interpret since clinically useful information is lacking. We request that these narratives should be modified as it relates to the description of the following adverse events:

   a) Blood pressure: Any cases of elevated BP with and without modifiers (e.g. mild, moderate) should include baseline blood pressures and other vital sign measures, and actual blood pressures and vital signs at, or proximal to the time of the adverse event, and changes from baseline.

   b) Heart rate and/or pulse: Cases with increased heart rate should include baseline heart rate and other vital sign measurements, and actual heart rate changes at the time of the adverse event.

   c) Abnormal ECGs: for example, premature atrial complexes, moderate QRS interval should include specific ECG abnormalities, changes from baseline, and the cardiologist's interpretation of the ECG, if any.

   d) Cases with possible cardiac or respiratory events such as palpitations/heart flutter, tightness of chest, chest pain, shortness of breath, neck tension, arm pain should include the precise description of actual symptom, any associated signs and symptoms (eg. diaphoresis), diagnosis and vital sign measurement at baseline and at the time of event, mention if any laboratory, imaging or other workup was done, and the results of those tests. If an outside work-up was done to evaluate these symptoms, information should be provided about the nature of that workup, and, all results which are available regarding that assessment work-up should be provided.

   d) Cases presented with neurological or opthamological symptoms such as dizziness, headaches, blurred vision, eye hemorrhage, scintillating scotoma should include a clear description of the event (e.g. duration), presence or absence of other associated symptoms or findings (e.g. nystagmus, etc) and vital signs at, or near the time of the event; any findings on exam, and the results of any work-up performed. If the subject had a headache, you should include whether the subject had a history of headaches and any differences in headache characteristics which may have occurred. If an outside work-up was done to evaluate any of the neurological symptoms, information should be provided about the nature and extend of that work-up, and, all results which are available regarding that assessment, or, work-up should be provided.

   e) For all narratives with elevated or abnormal laboratory tests (e.g. hyperlipidemia, high cholesterol, elevated fasting blood sugar, elevated ALT, GGT, etc), identify the lab value

obtained and provide the normal range.

f) For all narratives which state weight gain or loss, describe the baseline weight and changes at the time of the adverse event. For adverse events using the term decreased appetite, identify whether or not there was weight gain or loss associated with that event.

g) For all narratives with skin rashes (e.g. hives) describe the characteristics, location and associated symptoms with the rash.

h) For all narratives with psychiatric adverse events of interest, provide the subjects baseline and end of study Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D), if any.

i) For all narratives, identify whether the subject had or had not prior treatment with stimulants, the titration schedule for that subject, and the dose at which each adverse event occurred, and what if any actions were taken.

k) The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered at the Baseline Visit to identify significant psychiatric co-morbidities that would exclude the subject. Your schedule of events (Table 7-4) indicates these tests were repeated at the Final or Early Termination Visit. These results could not be identified in the Clinical Study Report. Provide the results of the analysis and include an outlier analysis.

l) Table 12-40, entitled lists subjects with an abnormal ECG finding in the safety population. Identify whether there was they any clinical correlations at or near the time of these abnormal findings, and if so, where a description of these events can be found?

Study 42603ATT3002 (3002)

1. The following subjects identified below experienced adverse events (AE) during the study and were judged by you to require narrative summaries. Each of these subject narratives should be modified with the vital signs (baseline and onset of AE), laboratory studies, reports on any ECG findings, ~~and~~reports for~~, or~~ any electrodiagnostic or any ancillary studies (at the time of the event with a baseline comparison, if available), details of any physical examinations, dose adjustments and/or other clinically relevant information available at baseline and in relationship to the adverse events. We request that you provide a complete vignette with all the supporting information (copies of clinic notes, consultant reports, test reports, work-ups if available) for these subjects.

A10282: headache, fatigue, and lethargy and weight loss with the decreased appetite

A11047: paraesthesia between visit 6 and 7 (in this case, we also ask that you provide the interval examinations (office notes) between visit 6 and 7. The basis for the dose adjustment is not apparent since there are no vital signs or CRF notes between Visits 6 (02/09/06) and Visits 7 (02/22/06) when the subject developed adverse events and there was dose adjustment.

A10061: tachycardia and stomach-abdominal pain

A10701: headache and nausea

A10791: recurrent syncope

A11086: hospitalized for hypertonia. In this case, we also ask did the subject develop hypertonia, as stated? If so, what were the symptoms?

A10123: an episode of hypertension who developed persistent vertigo, hypoacusia, tinnitus and nystagmus for which an MRI was apparently performed on 01/25/06.

A10804: delusion of reference. A10804's narrative indicates that the subject only developed delusions of reference from 09/13-22/2005, and that no other adverse events occurred. Review of the CRF's indicate that additional adverse events occurred at the end of the double blind phase (09/16/2005) and continued into the open label phase (09/22-11/10/2005). These adverse events consisted of dry mouth and perspiration (09/13/05-?); polyuria, polydypsia (09/13/05-09/22/05); problems of concentration, memory and uneasiness, symptoms of depression and diarrhea (09/16-09/22/2005); paresthesia and delusions of reference (09/19-09/22/2005), and loss of libido (09/19-?). Redo this narrative with a complete listing of the adverse events.

A10940: tachycardia

A10180: increased rebound phenomenon. What is increased rebound phenomenon? How was it characterized and evaluated? Provide pertinent information.

A10194: developed a tension headache, visual field constriction (subjective), paralysis of accommodation (the term, reduced visual acuity was crossed out), and increased arterial hypertension (130/90 mm Hg: standing at V5). No information is contained in the CRF about the basis for the determination of paralysis of accommodation and visual field constriction, and what diagnostic procedures were done, if any.

A10296: tachycardia.

A10298: palpitations.

A10650: tachycardia, hypertension, weight loss, nausea and upset stomach. He also developed erectile dysfunction for which he left the study.

A10472: developed depression for which he was treated with venlafaxine. Review of the CRF indicates that the depression occurred with suicidal thoughts. Additional information about the suicidality should be provided.

A10788: developed hypertension, severe headache, was hospitalized and diagnosed with a temporal arteritis. Additionally, the re-written narrative should answer the following questions: What was the basis for the diagnosis of temporal arteritis? What is the basis for the investigator's determination that the subject had Horton's syndrome at the time of enrollment? The narrative should include information on the following additional adverse events identified in the CRF: the screening laboratory abnormalities [hypertriglycidemia, hypercholesterolemia, elevated liver enzymes] and any changes that may have occurred during the conduct of the trial; and increasing blood pressure and heart rate in relation to all the adverse events.

A10801: migraine, developed vertigo and an unspecified visual disorder. CT showed probable lacunar infarct (11 mm) in caudate nucleus with slight expansion of the frontal horn of the right lateral ventricle. You should provide a complete description of the migraine history, the abortive migraine episode, the vertigo and characteristics of the visual disorder.

2. Please provide translated copies of ~~the~~ hospitalization records, specifically, admission and discharge summaries, consultative, testing reports, for ~~radiology (~~ MRI or CT scans~~),~~ and any ~~/or,~~ other ancillary testing reports, if available, for the following subjects, : A11006; A10253; A10885; A11086; A10788; A10801. In addition to the above, provide copies of the reports for ~~imaging (~~CCT and/or MRI~~)~~ studies performed on the following subjects: A10801, A10123, and A10253.

3. Please provide assurance that all adverse events noted in the CRFs of the following subjects have been recorded in the dataset and these AEs are reflected in the proposed labeling: A10804; A10650; A10472; A10788 and A10801. Please provide further assurance that no other such cases are present in this sNDA submission.

Study 12-304:

1. Please provide CRFs for subjects who experienced cardiovascular adverse events of interest in this study, identified on pages 515-518 of Interim Clinical Study Report 12-304, and which were not previously submitted. In addition, provide copies of the cardiologist's interpretation all any ECG tracings for these subjects ~~with attachment of the cardiologist's interpretation~~, if available.

2. Please provide the CRF for subject 131-103 who had a psychiatric adverse event of interest.

3. In addition, please include copies of the cardiologist's interpretation of any ECG findings~~reports with attachment of the cardiologist's interpretation,~~ for the following subjects: 112-101; 127-013; 210-103; 214-100; 222-109.

4. Narratives on all subjects previously submitted for Study 12-304 should be modified and re-submitted with inclusion of the following information in the narratives:
   a) titration schedule and dose at the time of the adverse events;
   b) baseline and vital signs occurring at, or, proximal to the time of each adverse event;

c) baseline and abnormal laboratory studies for each subject identified as having an adverse event of laboratory studies (e.g. elevated ALT, GTT should be substituted with the abnormal values, the normal range, and the change from baseline)
d) other ancillary testing done to further evaluate the adverse event(s);
e) if hospitalized or seen by a specialist or other practioner, a copy of hospital admission, discharge, consultant or practioner notes, and/or any other tests done.

As discussed during the pre-NDA meeting, please analyze the cardiovascular safety data for subjects in all studies for this sNDA with cardiovascular events of interest by the following identifiable cardiovascular risk factors: history of cardiovascular disease, active smoking, history or presence of hypertension, history or presence of hyperlipidemia, presence of elevated CRP, history or presence of diabetes mellitus, obesity (BMI > 30 kg/m^2 at baseline), and age (≥ 50 years at baseline). If you have already done this analysis, please identify the location in the submission.

Since headaches seem to occur in >1 % of subjects treated with Concerta in the 2 Placebo Controlled Trials, please examine all subjects in this submission who developed this symptom based on the presence or absence of a baseline history of headache and by headache type (e.g., migraine, tension), of hypertension, etc. How many subjects developed new onset headache and how many subjects developed worsening of pre-existing headaches? For all subjects who developed this adverse event, describe vital sign changes proximal or at the time of the headache. Describe the natural course of this adverse event? If you have already done this analysis, please identify the location in the submission.

For all subjects identified as having cardiovascular adverse events of interest, examine concurrent medications use (e.g., Salbutamol) to identify if there is any risk associated with using such medications concurrently with Concerta. For example, since asthma medications (e.g., Salbutamol) have been associated with increased heart rate and blood pressure; examine changes in vital signs and adverse events based on the use or lack of use of these medications in this sNDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Finally, we note that this submission provides the first conversion of your package insert to the PLR Content and Format Requirements. Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to review your submitted PLR labeling to verify that none of these deficiencies are in the PLR labeling submitted on August 29, 2007. If you find that there are deficiencies in the PLR labeling, please amend your application with revised labeling to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address: http://www.fda.gov/cder/regulatory/physLabel/default.htm. We request that you complete this PLR labeling review and respond to us with any necessary revisions to labeling within 30 days of receipt of this letter. We consider this a separate request from the filing review issues listed in this letter, and it may be addressed separately.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 796-0240

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

Common Proposed Labeling Deficiencies
Identify and Correct before Labeling Content Review Begins

Highlights:

• Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.
[See 21 CFR 201.57(d)(6) and Implementation Guidance]
• The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
• The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]
• The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
• The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
• For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
• The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

• Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
• A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.
[See 21 CFR 201.57 (a)(11)].
• Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
[See comment #34 Preamble]
• The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
• A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at

the time of submission and will be edited to the month/year of application or supplement approval.
• A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Contents:
• The wording of the headings and sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]
• The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
• Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
• Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
• When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):
• Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
• Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products Content and Format," available at hhttp://www.fda.gov/cder/guidance.
• The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
[See Implementation Guidance]

• Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
• Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
• The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
• There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
• The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
• Regarding information at the end of the labeling, company website addresses are not encouraged. Delete from package insert labeling. The same applies to PPI and MG.
• If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
• Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Created: J. Delasko, SEALD Team, 1/29/07
Revised: R. Anderson, SEALD Team, 3/1/07

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/s/

Thomas Laughren

12/13/2007 07:59:58 AM

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/s/

Janet Cliatt

2/11/2008 02:44:58 PM

CSO

Cliatt, Janet

From: Cliatt, Janet
Sent: Tuesday, December 04, 2007 2:29 PM
To: 'Jenkins-Frison, Ann [MCCUS]'
Subject: RE: NDA 21-121/S-017 Filing Communication dated 11/9/2007

Dear Ann

Sending Questions 1-3 for Studies 12-304 (pp. 5) and Study 02-159 (pp. 1) by end week of December is fine. However, we will need a response to Questions 4 (Study 02-159, pp. 2-3; Study 12-304, p. 5) and Questions 1-3 (Study 42603ATT3002, pp 3-5) much earlier than the proposed last week of February (2nd week of January). We would like PDF ECG's with attached interpretations from your cardiologists, as previously requested. Identify the location of the results for HAM-A and HAM-D (including outlier analysis) . We are referencing Table 12-44 (not, Table-33), entitled "Subjects for Whom Narratives are Provided" which is located on pages 685-685 of Clinical Study Report 02-159.

From: Jenkins-Frison, Ann [MCCUS] [mailto:AJenkin2@MCCUS.JNJ.com]
Sent: Friday, November 16, 2007 3:35 PM
To: Cliatt, Janet
Subject: NDA 21-121/S-017 Filing Communication dated 11/9/2007

Hi Janet:

RE: NDA 21-121/S-017 for CONCERTA adult indication.

As promised by Suzanne Foy, this e-mail is follow-up to the telephone conversation you had with her, in my absence, on Wednesday, November 14, 2007 regarding the "Filing Communication" Letter dated 11/9/2007 for NDA 21-121/S-017. Below are proposed timings for our response to this letter and 2 requests for clarification of 2 questions in this letter.

#1. Proposed Tentative Timeline for Responses
We propose the following tentative timeline for providing the requested information to FDA. Provide responses for all items, with the exception of Study 02-159 (Question 4) on pp. 2-3, Study 42603ATT3002 (Questions 1, 2, 3) on pp. 3-5, and Study 12-304 (Question 4) on p. 5, by the 3rd week of December, 2007. Responses for the exceptions noted above to be provided by last week in February, 2008.

#2. Request for Clarification of Study 02-159, Question 3 (copies of ECGs) on p. 1
We believe the FDA has access to the central ECG database at Mortara where our ECG data was uploaded. Does the Medical Reviewer have access to this database to allow him to review any of the ECGs from Studies 02-159 and 12-304? If not, we can provide the requested ECG tracings as digitized PDF files. Is this acceptable?

Also, please confirm that you intended to reference Table 12-44, entitled, "Subjects for Whom Narratives are Provided," located on pp. 685-686 of the clinical study report and not Table 12-33, entitled, "Summary of Serum Chemistry Laboratory Results over Time by Treatment Group - Safety Population," located on p. 463 of the CSR.

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We further presume that letter k is requesting an analysis of HAM-A and HAM-D scores for the entire safety population. Such an analysis is included in the current sNDA package and we will specify the location in our official response. Please confirm that this is acceptable.

Looking forward to your response. I can be reached at 215-273-8948.

Regards.

Ann Jenkins-Frison
Global Regulatory Affairs
J&JPRD

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/s/

Janet Cliatt
2/11/2008 02:27:36 PM
CSO

feedback email 12-4-07

Cliatt, Janet

From: Jenkins-Frison, Ann [MCCUS] [AJenkin2@MCCUS.JNJ.com]

Sent: Wednesday, November 07, 2007 10:17 AM

To: Cliatt, Janet

Cc: Foy, Suzanne [PRDGB]; Grundy, Christine [PRDUS]

Subject: NDA 21-121/S-017 - Concerta [OROS (methylphidate HCl) Extended-release Tablets

Good Morning LCDR Cliatt:
I have question for you about the safety updates to the CONCERTA adult indication sNDA (NDA 21-121/S-017).

In accordance with 21 CFR 314.50(d)(5)(vi)(b), we plan to submit a 4-month safety update. I've heard from my colleagues that DPP also requests a 7-month safety update.

I couldn't find anything in regulation or guidance regarding a 7-mos. safety update. Nor, in my past experience have I encountered this.

Can you please let me know if the 7-mos. safety update submission is standard or is it only requested under certain circumstances, ie., for NCEs?

Also, how far in advance will the Division notify us that the 7-mos. safety update will be required? Any other information or guidance re: safety updates that you can provide will be helpful. Thank you for providing clarity to this situation.

Please note, I will be out of the office, Thurs., Nov. 8, 2007 through Wed., Nov. 14, 2007. During my absence, I will not have access to e-mail or voice-mail, so please copy Suzanne Foy, 44 7796 930221 and Christine Grundy, (609) 730-2203 (names in cc line of this message) on all correspondence to me.

FYI-Suzanne is located in the U.K., and there is a 5-hour time difference for her (she's 5 hours ahead of us). Should you need to telephone, I've provided their numbers above.

Once again, thank you for your assistance.
Regards.
Ann Jenkins-Frison
J&JPRD

Cliatt, Janet

From: Jenkins-Frison, Ann [MCCUS] [AJenkin2@MCCUS.JNJ.com]
Sent: Friday, November 16, 2007 3:35 PM
To: Cliatt, Janet
Subject: NDA 21-121/S-017 Filing Communication dated 11/9/2007

Hi Janet:

RE: NDA 21-121/S-017 for CONCERTA adult indication.

As promised by Suzanne Foy, this e-mail is follow-up to the telephone conversation you had with her, in my absence, on Wednesday, November 14, 2007 regarding the "Filing Communication" Letter dated 11/9/2007 for NDA 21-121/S-017. Below are proposed timings for our response to this letter and 2 requests for clarification of 2 questions in this letter.

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We propose the following tentative timeline for providing the requested information to FDA. Provide responses for all items, with the exception of Study 02-159 (Question 4) on pp. 2-3, Study 42603ATT3002 (Questions 1, 2, 3) on pp. 3-5, and Study 12-304 (Question 4) on p. 5, by the 3rd week of December, 2007. Responses for the exceptions noted above to be provided by last week in February, 2008.

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Looking forward to your response. I can be reached at 215-273-8948.
Regards.
Ann Jenkins-Frison
Global Regulatory Affairs
J&JPRD

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/s/

Janet Cliatt
2/11/2008 02:22:47 PM
CSO

email correspondance- safety clarif

Cliatt, Janet

From: Cliatt, Janet
Sent: Friday, February 01, 2008 10:51 AM
To: 'Jenkins-Frison, Ann [PRDUS]'
Subject: 21-121/017 questions pertaining to your supplemental

Attachments: Inforeq 01-29-08_GM_NK_MMedits.doc

Good Morning Ann,

We have the following requests and questions pertaining to your supplemental NDA (S-017). If the information requested below is included in your submission, please indicate where it may be found. Please incorporate the requested information below in your response to some of the items requested in the 74 day letter by February 8, 2008, if possible.

Inforeq
9-08_GM_NK_MMec

Janet

LCDR Janet Cliatt, MT., CLS (NCA)
Regulatory Project Manager
Division of Psychiatry Products/HFD-130
Food and Drug Administration

10903 New Hampshire Avenue, Building 22, Room 4123
Silver Spring, Maryland 20993-0002

Phone: 301-796-0240
Fax: 301-796-9838
janet.cliatt@fda.hhs.gov

Study 12-304

CRFs: We are unable to locate the CRFs of 118-003 and 126-105, please provide them.

ECGs: We are unable to locate the safety information on subjects 216-114, 227-119, and 114-004. No ECGs could be identified at the ECG Warehouse for these serious adverse events. Please provide scanned ECGs with a cardiologist's interpretation, if available, for all visits for these subjects. Please let us know if ECG Data for the 4 month safety Update has been provided to the ECG Warehouse for all subjects.

Specific Hospital Records and Consultative Reports: Please provide copies of hospitalization records (specifically admission note and discharge summaries) and any consultative or cardiac testing reports for 3 subjects who had serious adverse events: 216-114, 227-119 and 114-004.

Study 02-159

CRFs: Provide CRF's for subjects 114-011, 117-006, 128-014 and 128-016.

ECGs: We note that subject 114-004 was enrolled in both Studies 12-304 and 02-159. In addition to the ECG for this subject for study 12-304, we would also like them for Study 02-159. Please provide all scanned ECGs with the cardiologist's interpretation, if available, for subjects: 114-011, 117-006, 128-014 and 128-016.

Study 02-160

ECG: Provide scanned ECGs with the cardiologist's interpretation for subjects 01012 and 01022, if available.

Additional Questions:

1. Has a definitive QT study ever been performed for Concerta? If so, please provide a submission date and number to the Concerta IND or NDA.

2. Please clarify the definitions you used to define an adverse event as tachycardia, or, systolic or diastolic hypertension for all clinical studies submitted.

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/s/

Janet Cliatt
2/1/2008 03:16:04 PM
CSO

Cliatt, Janet

From: Foy, Suzanne [PRDGB] [SFoy@prdgb.JNJ.com]
Sent: Monday, December 10, 2007 8:10 AM
To: Cliatt, Janet
Subject: RE: NDA 21-121/S017 Filing Communication dated 11/9/07; response 12/04/07 email

Thank you Janet,

I appreciate you forwarding this to me.

Kind regards,

Suzanne

-----Original Message-----
From: Cliatt, Janet [mailto:Janet.Cliatt@fda.hhs.gov]
Sent: 10 December 2007 12:12
To: Foy, Suzanne [PRDGB]
Subject: FW: NDA 21-121/S017 Filing Communication dated 11/9/07; response 12/04/07 email

Good Morning Suzanne,

Fyi-
Janet

From: Cliatt, Janet
Sent: Friday, December 07, 2007 4:10 PM
To: 'Jenkins-Frison, Ann [MCCUS]'
Subject: NDA 21-121/S017 Filing Communication dated 11/9/07; response 12/04/07 email

Dear Ann,

Division Management would like to re-examine the request for clinical data communicated to you in the filing letter. We would like to determine if the information requested can be limited to essential safety data. I should be able to give you an update next week.

LCDR Janet Cliatt, MT., CLS (NCA)
Regulatory Project Manager
Division of Psychiatry Products/HFD-130
Food and Drug Administration
10903 New Hampshire Avenue, Building 22, Room 4123
Silver Spring, Maryland 20993-0002
Phone: 301-796-0240
Fax: 301-796-9838
janet.cliatt@fda.hhs.gov

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/s/

Janet Cliatt

12/20/2007 12:16:07 PM

CSO

Cliatt, Janet

From: Cliatt, Janet
Sent: Thursday, December 20, 2007 9:21 AM
To: 'Jenkins-Frison, Ann [MCCUS]'
Subject: RE: NDA 21-121/S-017 Filing Communication dated 11/9/2007. Response to 12/4/07 e-mail.

Good Morning Ann,
As a follow-up to our telephone conversation on Monday 12/17/07 requesting the Division to re-evaluate Johnson and Johnson's request to submit the modified narratives the last week of February, 2008 rather than the second (2nd) week of January, 2008, we would like to get your response to all requested information for Study 02-159 (double-blind study), and Study 42603ATT3002 (both double-blind and open label extension phase) earlier than your proposed time line of last week in February. We request that you submit the requested information for these two studies to us by end of first week in February (i.e. February 8, 2008). The remaining materials for study 12-304 (open label study) and additional analyses could be submitted by February 29, 2008.
Regards,
~Janet

From: Jenkins-Frison, Ann [MCCUS] [mailto:AJenkin2@MCCUS.JNJ.com]
Sent: Thursday, December 06, 2007 12:24 PM
To: Cliatt, Janet
Cc: Foy, Suzanne [PRDGB]
Subject: RE: NDA 21-121/S-017 Filing Communication dated 11/9/2007. Response to 12/4/07 e-mail.

Hi Janet:
In addition to the voice-mail I left you this morning to send the 11/9/07 Filing Communication as a WORD doc, please see the response below to your 12/4/07 email.

RE: NDA 21-121/S-017 Filing Communication, dated 11/9/07. Response to 12/4/07 e-mail (below).

> We respectfully request the Division to re-consider our timeline proposal to submit the Study 02-159 (Question 4) on pp. 2-3, Study 42603ATT3002 (Questions 1, 2, 3) on pp. 3-5, and Study 12-304 (Question 4) on p. 5 (i.e., revised narratives) by the last week in February, 2008. After careful consideration of all factors, this date was considered to be the earliest we can provide a complete and thorough response in accordance with the Division's request. We are cognizant of the Division's request to avoid submitting the response in "bits and pieces", which has been stressed to us on several occasions.
>
> The re-writing of the narratives requires considerable time to completely incorporate the descriptions listed in the Filing Communication. In order to revise the patient narratives to include additional data, direct queries to some investigational sites is required. Study 3002 was conducted in Europe. Moreover, some of the additional information requested (e.g, reports from physicians outside of the clinical trial) was not collected for the clinical trial. The process of collecting this information involves requesting outside records from the clinical trial investigator who must then contact the subject to get written permission to contact these physicians, contacting the other physicians, collecting the records and sending them on to us. We then need to have these translated when necessary to prepare the documents for electronic submission.

The winter holiday season will further impede the process since many centers and businesses will close for 2 weeks around this time.

The responses to the Filing Communication also directly coincides with the 4-month Safety Update which, by regulation 21 CFR 314.50(d)(5)(vi)(b), is required to be submitted by December 29, 2007, and must be prioritized.

Once again, we stress, our proposed timeline for submitting the aforementioned information the last week in February, 2008 will enable us to provide a complete and thorough response in the most timely manner.

As time is critical and limited, please relay your decision on this matter to us by Friday, December 7, 2007. Please copy Suzanne Foy (see cc: list on this e-mail) on your response as I will be out of the office. If you require further clarification, you may reach me at 215-273-8948 or Suzanne at 011-44-7796-930221 by telephone. Please be aware, Suzanne is located in the U.K. and there is a 5 hour time difference (5 hours ahead of EST).

Looking forward to hearing from you.

Regards.

amj-f

P.S. Please let me know when FDA will be closed for the Christmas holiday and if you will be unavailable any days in addition to your office closing. If so, I'll need an alternate contact. Likewise, I'll advise you of our coverage schedule during the holidays.

-----Original Message-----
From: Cliatt, Janet [mailto:Janet.Cliatt@fda.hhs.gov]
Sent: Tuesday, December 04, 2007 2:29 PM
To: Jenkins-Frison, Ann [MCCUS]
Subject: RE: NDA 21-121/S-017 Filing Communication dated 11/9/2007

Dear Ann

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From: Jenkins-Frison, Ann [MCCUS] [mailto:AJenkin2@MCCUS.JNJ.com]
Sent: Friday, November 16, 2007 3:35 PM
To: Cliatt, Janet
Subject: NDA 21-121/S-017 Filing Communication dated 11/9/2007

Hi Janet:

RE: NDA 21-121/S-017 for CONCERTA adult indication.

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Regards.

Ann Jenkins-Frison
Global Regulatory Affairs
J&JPRD

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/s/

Janet Cliatt

12/20/2007 10:07:22 AM

CSO

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-121/S-017

Johnson and Johnson Pharmaceutical Research &
Development, L.L.C
Attention: Ann Jenkins-Frison
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Jenkins-Frison:

Please refer to your August 29, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Concerta (methylphenidate HCL) Extended Release Tablets.

Reference is also made to the Agency's November 9, 2007, letter notifying you that this application was filed. That letter included a detailed list of requests for additional information, and we understand that you are planning a response to these requests. Upon further consideration of our requests, we wish to slightly modify this list, mostly for clarification and elimination of several requests that are not critical to a response. In order to best communicate these changes, we have used the original detailed list as a starting document and used track changes to clearly indicate the changes. As a general qualification, we would note that we understand that for some of these requests the requested information is not available or accessible. In those instances, it would suffice to simply state that fact. If needed, we would be happy to further discuss these requests with you.

Clinical

Study 02-159

1. Please provide the Case Report Forms (CRFs) for the following 25 subjects: 101-007; 102-015; 107-001; 108-002; 112-001; 118-017;122-004;122-008; 125-006;126-009;127-006;128-012; 129-005; 130-008;101-004;102-005;106-016;107-002;110-006; 110-015;113-007;120-008;124-007;128-003;130-002.

2. Please provide patient profiles as page 2471 of your Clinical Study Report notes these are available on request for the subjects listed: 127-007; 127-016; 128-003; 128-012; 129-005; 129-008; 130-002; 130-008; 130-009.

3. For all subjects whom you have identified as having Cardiovascular Adverse Events of Interest (Table 12-33, pgs. 685-686, Clinical Study Report), please provide copies of all ECG

~~tracings with an attached copy of~~ your cardiologist's interpretation of any ECG changes if available. If any work-up was done for any adverse event either at the study site or by outside medical practitioner, or, at hospital (discharge summaries, consultant report), please also provide copies and results from any of these studies.

4. Many case narratives for subjects with discontinuations, cardiovascular adverse events of interest and special interest are difficult to interpret since clinically useful information is lacking. We request that these narratives should be modified as it relates to the description of the following adverse events:

   a) Blood pressure: Any cases of elevated BP with and without modifiers (e.g. mild, moderate) should include baseline blood pressures and other vital sign measures, and actual blood pressures and vital signs at, or proximal to the time of the adverse event, and changes from baseline.

   b) Heart rate and/or pulse: Cases with increased heart rate should include baseline heart rate and other vital sign measurements, and actual heart rate changes at the time of the adverse event.

   c) Abnormal ECGs: for example, premature atrial complexes, moderate QRS interval should include specific ECG abnormalities, changes from baseline, and the cardiologist's interpretation of the ECG, if any.

   d) Cases with possible cardiac or respiratory events such as palpitations/heart flutter, tightness of chest, chest pain, shortness of breath, neck tension, arm pain should include the precise description of actual symptom, any associated signs and symptoms (eg. diaphoresis), diagnosis and vital sign measurement at baseline and at the time of event, mention if any laboratory, imaging or other workup was done, and the results of those tests. If an outside work-up was done to evaluate these symptoms, information should be provided about the nature of that workup, and, all results which are available regarding that assessment work-up should be provided.

   d) Cases presented with neurological or opthamological symptoms such as dizziness, headaches, blurred vision, eye hemorrhage, scintillating scotoma should include a clear description of the event (e.g. duration), presence or absence of other associated symptoms or findings (e.g. nystagmus, etc) and vital signs at, or near the time of the event; any findings on exam, and the results of any work-up performed. If the subject had a headache, you should include whether the subject had a history of headaches and any differences in headache characteristics which may have occurred. If an outside work-up was done to evaluate any of the neurological symptoms, information should be provided about the nature and extend of that work-up, and, all results which are available regarding that assessment, or, work-up should be provided.

   e) For all narratives with elevated or abnormal laboratory tests (e.g. hyperlipidemia, high cholesterol, elevated fasting blood sugar, elevated ALT, GGT, etc), identify the lab value

obtained and provide the normal range.

f) For all narratives which state weight gain or loss, describe the baseline weight and changes at the time of the adverse event. For adverse events using the term decreased appetite, identify whether or not there was weight gain or loss associated with that event.

g) For all narratives with skin rashes (e.g. hives) describe the characteristics, location and associated symptoms with the rash.

h) For all narratives with psychiatric adverse events of interest, provide the subjects baseline and end of study Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D), if any.

i) For all narratives, identify whether the subject had or had not prior treatment with stimulants, the titration schedule for that subject, and the dose at which each adverse event occurred, and what if any actions were taken.

k) The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered at the Baseline Visit to identify significant psychiatric co-morbidities that would exclude the subject. Your schedule of events (Table 7-4) indicates these tests were repeated at the Final or Early Termination Visit. These results could not be identified in the Clinical Study Report. Provide the results of the analysis and include an outlier analysis.

l) Table 12-40, entitled lists subjects with an abnormal ECG finding in the safety population. Identify whether there was they any clinical correlations at or near the time of these abnormal findings, and if so, where a description of these events can be found?

Study 42603ATT3002 (3002)

1. The following subjects identified below experienced adverse events (AE) during the study and were judged by you to require narrative summaries. Each of these subject narratives should be modified with the vital signs (baseline and onset of AE), laboratory studies, reports on any ECG findings, ~~and~~reports for~~, or~~ any electrodiagnostic or any ancillary studies (at the time of the event with a baseline comparison, if available), details of any physical examinations, dose adjustments and/or other clinically relevant information available at baseline and in relationship to the adverse events. We request that you provide a complete vignette with all the supporting information (copies of clinic notes, consultant reports, test reports, work-ups if available) for these subjects.

A10282: headache, fatigue, and lethargy and weight loss with the decreased appetite

A11047: paraesthesia between visit 6 and 7 (in this case, we also ask that you provide the interval examinations (office notes) between visit 6 and 7. The basis for the dose adjustment is not apparent since there are no vital signs or CRF notes between Visits 6 (02/09/06) and Visits 7 (02/22/06) when the subject developed adverse events and there was dose adjustment.

A10061: tachycardia and stomach-abdominal pain

A10701: headache and nausea

A10791: recurrent syncope

A11086: hospitalized for hypertonia. In this case, we also ask did the subject develop hypertonia, as stated? If so, what were the symptoms?

A10123: an episode of hypertension who developed persistent vertigo, hypoacusia, tinnitus and nystagmus for which an MRI was apparently performed on 01/25/06.

A10804: delusion of reference. A10804's narrative indicates that the subject only developed delusions of reference from 09/13-22/2005, and that no other adverse events occurred. Review of the CRF's indicate that additional adverse events occurred at the end of the double blind phase (09/16/2005) and continued into the open label phase (09/22-11/10/2005). These adverse events consisted of dry mouth and perspiration (09/13/05-?); polyuria, polydypsia (09/13/05-09/22/05); problems of concentration, memory and uneasiness, symptoms of depression and diarrhea (09/16-09/22/2005); paresthesia and delusions of reference (09/19-09/22/2005), and loss of libido (09/19-?). Redo this narrative with a complete listing of the adverse events.

A10940: tachycardia

A10180: increased rebound phenomenon. What is increased rebound phenomenon? How was it characterized and evaluated? Provide pertinent information.

A10194: developed a tension headache, visual field constriction (subjective), paralysis of accommodation (the term, reduced visual acuity was crossed out), and increased arterial hypertension (130/90 mm Hg: standing at V5). No information is contained in the CRF about the basis for the determination of paralysis of accommodation and visual field constriction, and what diagnostic procedures were done, if any.

A10296: tachycardia.

A10298: palpitations.

A10650: tachycardia, hypertension, weight loss, nausea and upset stomach. He also developed erectile dysfunction for which he left the study.

A10472: developed depression for which he was treated with venlafaxine. Review of the CRF indicates that the depression occurred with suicidal thoughts. Additional information about the suicidality should be provided.

A10788: developed hypertension, severe headache, was hospitalized and diagnosed with a temporal arteritis. Additionally, the re-written narrative should answer the following questions: What was the basis for the diagnosis of temporal arteritis? What is the basis for the investigator's determination that the subject had Horton's syndrome at the time of enrollment? The narrative should include information on the following additional adverse events identified in the CRF: the screening laboratory abnormalities [hypertriglycidemia, hypercholesterolemia, elevated liver enzymes] and any changes that may have occurred during the conduct of the trial; and increasing blood pressure and heart rate in relation to all the adverse events.

A10801: migraine, developed vertigo and an unspecified visual disorder. CT showed probable lacunar infarct (11 mm) in caudate nucleus with slight expansion of the frontal horn of the right lateral ventricle. You should provide a complete description of the migraine history, the abortive migraine episode, the vertigo and characteristics of the visual disorder.

2. Please provide translated copies of ~~the~~ hospitalization records, specifically, admission and discharge summaries, consultative, testing reports, for ~~radiology (~~ MRI or CT scans~~),~~ and any ~~/or,~~ other ancillary testing reports, if available, for the following subjects, : A11006; A10253; A10885; A11086; A10788; A10801. In addition to the above, provide copies of the reports for ~~imaging (~~CCT and/or MRI~~)~~ studies performed on the following subjects: A10801, A10123, and A10253.

3. Please provide assurance that all adverse events noted in the CRFs of the following subjects have been recorded in the dataset and these AEs are reflected in the proposed labeling: A10804; A10650; A10472; A10788 and A10801. Please provide further assurance that no other such cases are present in this sNDA submission.

Study 12-304:

1. Please provide CRFs for subjects who experienced cardiovascular adverse events of interest in this study, identified on pages 515-518 of Interim Clinical Study Report 12-304, and which were not previously submitted. In addition, provide copies of the cardiologist's interpretation all any ECG tracings for these subjects ~~with attachment of the cardiologist's interpretation~~, if available.

2. Please provide the CRF for subject 131-103 who had a psychiatric adverse event of interest.

3. In addition, please include copies of the cardiologist's interpretation of any ECG findings~~reports with attachment of the cardiologist's interpretation,~~ for the following subjects: 112-101; 127-013; 210-103; 214-100; 222-109.

4. Narratives on all subjects previously submitted for Study 12-304 should be modified and re-submitted with inclusion of the following information in the narratives:
   a) titration schedule and dose at the time of the adverse events;
   b) baseline and vital signs occurring at, or, proximal to the time of each adverse event;

c) baseline and abnormal laboratory studies for each subject identified as having an adverse event of laboratory studies (e.g. elevated ALT, GTT should be substituted with the abnormal values, the normal range, and the change from baseline)
d) other ancillary testing done to further evaluate the adverse event(s);
e) if hospitalized or seen by a specialist or other practioner, a copy of hospital admission, discharge, consultant or practioner notes, and/or any other tests done.

As discussed during the pre-NDA meeting, please analyze the cardiovascular safety data for subjects in all studies for this sNDA with cardiovascular events of interest by the following identifiable cardiovascular risk factors: history of cardiovascular disease, active smoking, history or presence of hypertension, history or presence of hyperlipidemia, presence of elevated CRP, history or presence of diabetes mellitus, obesity (BMI > 30 kg/m^2 at baseline), and age (≥ 50 years at baseline). If you have already done this analysis, please identify the location in the submission.

Since headaches seem to occur in >1 % of subjects treated with Concerta in the 2 Placebo Controlled Trials, please examine all subjects in this submission who developed this symptom based on the presence or absence of a baseline history of headache and by headache type (e.g., migraine, tension), of hypertension, etc. How many subjects developed new onset headache and how many subjects developed worsening of pre-existing headaches? For all subjects who developed this adverse event, describe vital sign changes proximal or at the time of the headache. Describe the natural course of this adverse event? If you have already done this analysis, please identify the location in the submission.

For all subjects identified as having cardiovascular adverse events of interest, examine concurrent medications use (e.g., Salbutamol) to identify if there is any risk associated with using such medications concurrently with Concerta. For example, since asthma medications (e.g., Salbutamol) have been associated with increased heart rate and blood pressure; examine changes in vital signs and adverse events based on the use or lack of use of these medications in this sNDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Finally, we note that this submission provides the first conversion of your package insert to the PLR Content and Format Requirements. Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to review your submitted PLR labeling to verify that none of these deficiencies are in the PLR labeling submitted on August 29, 2007. If you find that there are deficiencies in the PLR labeling, please amend your application with revised labeling to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are also encouraged to review our PLR guidance documents located at the following internet address: http://www.fda.gov/cder/regulatory/physLabel/default.htm. We request that you complete this PLR labeling review and respond to us with any necessary revisions to labeling within 30 days of receipt of this letter. We consider this a separate request from the filing review issues listed in this letter, and it may be addressed separately.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 796-0240

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

Common Proposed Labeling Deficiencies
Identify and Correct before Labeling Content Review Begins

Highlights:

• Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.
[See 21 CFR 201.57(d)(6) and Implementation Guidance]
• The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
• The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]
• The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
• The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
• For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
• The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

• Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
• A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.
[See 21 CFR 201.57 (a)(11)].
• Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
[See comment #34 Preamble]
• The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
• A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at

the time of submission and will be edited to the month/year of application or supplement approval.
• A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Contents:
• The wording of the headings and sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]
• The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
• Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
• Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
• When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):
• Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
• Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.
• The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
[See Implementation Guidance]

• Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
• Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
• The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
• There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
• The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
• Regarding information at the end of the labeling, company website addresses are not encouraged. Delete from package insert labeling. The same applies to PPI and MG.
• If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
• Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Created: J. Delasko, SEALD Team, 1/29/07
Revised: R. Anderson, SEALD Team, 3/1/07

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/s/

Thomas Laughren

12/13/2007 07:59:58 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 21-121/S-017

Johnson and Johnson Pharmaceutical Research &
Development, L.L.C
Attention: Ann Jenkins-Frison
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Jenkins-Frison:

Please refer to your August 29, 2007 supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Concerta (methylphenidate HCL) Extended Release Tablets.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on October 24, 2007 in accordance with 21 CFR 314.101(a).

During our filing review of your application, we identified the following potential review issues:

Clinical

Study 02-159

1. Please provide the Case Report Forms (CRFs) for the following 25 subjects: 101-007; 102-015; 107-001; 108-002; 112-001; 118-017;122-004;122-008; 125-006;126-009;127-006;128-012; 129-005; 130-008;101-004;102-005;106-016;107-002;110-006; 110-015;113-007;120-008;124-007;128-003;130-002.

2. Please provide patient profiles as page 2471 of your Clinical Study Report notes these are available on request for the subjects listed: 127-007; 127-016; 128-003; 128-012; 129-005; 129-008; 130-002; 130-008; 130-009.

3. For all subjects whom you have identified as having Cardiovascular Adverse Events of Interest (Table 12-33, pgs. 685-686, Clinical Study Report), please provide copies of all ECG tracings with an attached copy of your cardiologist's interpretation if available. If any work-up was done for any adverse event either at the study site or by outside medical practitioner, or, at hospital (discharge summaries, consultant report), please also provide copies and results from any of these studies.

4. Many case narratives for subjects with discontinuations, cardiovascular adverse events of interest and special interest are difficult to interpret since clinically useful information is lacking. We request that these narratives should be modified as it relates to the description of the following adverse events:

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   b) Heart rate and/or pulse: Cases with increased heart rate should include baseline heart rate and other vital sign measurements, and actual heart rate changes at the time of the adverse event.

   c) Abnormal ECGs: for example, premature atrial complexes, moderate QRS interval should include specific ECG abnormalities, changes from baseline, and the cardiologist's interpretation of the ECG, if any.

   d) Cases with possible cardiac or respiratory events such as palpitations/heart flutter, tightness of chest, chest pain, shortness of breath, neck tension, arm pain should include the precise description of actual symptom, any associated signs and symptoms (eg. diaphoresis), diagnosis and vital sign measurement at baseline and at the time of event, mention if any laboratory, imaging or other workup was done, and the results of those tests. If an outside work-up was done to evaluate these symptoms, information should be provided about the nature of that workup, and, all results which are available regarding that assessment work-up should be provided.

   d) Cases presented with neurological or opthamological symptoms such as dizziness, headaches, blurred vision, eye hemorrhage, scintillating scotoma should include a clear description of the event (e.g. duration), presence or absence of other associated symptoms or findings (e.g. nystagmus, etc) and vital signs at, or near the time of the event; any findings on exam, and the results of any work-up performed. If the subject had a headache, you should include whether the subject had a history of headaches and any differences in headache characteristics which may have occurred. If an outside work-up was done to evaluate any of the neurological symptoms, information should be provided about the nature and extend of that work-up, and, all results which are available regarding that assessment, or, work-up should be provided.

   e) For all narratives with elevated or abnormal laboratory tests (e.g. hyperlipidemia, high cholesterol, elevated fasting blood sugar, elevated ALT, GGT, etc), identify the lab value obtained and provide the normal range.

f) For all narratives which state weight gain or loss, describe the baseline weight and changes at the time of the adverse event. For adverse events using the term decreased appetite, identify whether or not there was weight gain or loss associated with that event.

g) For all narratives with skin rashes (e.g. hives) describe the characteristics, location and associated symptoms with the rash.

h) For all narratives with psychiatric adverse events of interest, provide the subjects baseline and end of study Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D), if any.

i) For all narratives, identify whether the subject had or had not prior treatment with stimulants, the titration schedule for that subject, and the dose at which each adverse event occurred, and what if any actions were taken.

k) The Hamilton Anxiety Rating Scale (HAM-A) and the Hamilton Depression Rating Scale (HAM-D) were administered at the Baseline Visit to identify significant psychiatric co-morbidities that would exclude the subject. Your schedule of events (Table 7-4) indicates these tests were repeated at the Final or Early Termination Visit. These results could not be identified in the Clinical Study Report. Provide the results of the analysis and include an outlier analysis.

l) Table 12-40, entitled lists subjects with an abnormal ECG finding in the safety population. Identify whether there was they any clinical correlations at or near the time of these abnormal findings, and if so, where a description of these events can be found?

Study 42603ATT3002 (3002)

1. The following subjects identified below experienced adverse events (AE) during the study. Each of these subject narratives should be modified with the vital signs (baseline and onset of AE), laboratory studies, ECG and, or any electrodiagnostic or any ancillary studies (at the time of the event with a baseline comparison, if available), any examination, dose adjustment and/or other clinically relevant information available at baseline and in relationship to the adverse events. We request that you provide a complete vignette with all the supporting information (copies of clinic notes, consultant reports, test reports, work-ups if available) for these subjects.

A10282: headache, fatigue, and lethargy and weight loss with the decreased appetite

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A10061: tachycardia and stomach-abdominal pain

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A10940: tachycardia

A10180: increased rebound phenomenon. What is increased rebound phenomenon? How was it characterized and evaluated? Provide pertinent information.

A10194: developed a tension headache, visual field constriction (subjective), paralysis of accommodation (the term, reduced visual acuity was crossed out), and increased arterial hypertension (130/90 mm Hg: standing at V5). No information is contained in the CRF about the basis for the determination of paralysis of accommodation and visual field constriction, and what diagnostic procedures were done, if any.

A10296: tachycardia.

A10298: palpitations.

A10650: tachycardia, hypertension, weight loss, nausea and upset stomach. He also developed erectile dysfunction for which he left the study.

A10472: developed depression for which he was treated with venlafaxine. Review of the CRF indicates that the depression occurred with suicidal thoughts. Additional information about the suicidality should be provided.

A10788: developed hypertension, severe headache, was hospitalized and diagnosed with a temporal arteritis. Additionally, the re-written narrative should answer the following questions: What was the basis for the diagnosis of temporal arteritis? What is the basis for the investigator's determination that the subject had Horton's syndrome at the time of enrollment? The narrative

should include information on the following additional adverse events identified in the CRF: the screening laboratory abnormalities [hypertriglycidemia, hypercholesterolemia, elevated liver enzymes] and any changes that may have occurred during the conduct of the trial; and increasing blood pressure and heart rate in relation to all the adverse events.

A10801: migraine, developed vertigo and an unspecified visual disorder. CT showed probable lacunar infarct (11 mm) in caudate nucleus with slight expansion of the frontal horn of the right lateral ventricle. You should provide a complete description of the migraine history, the abortive migraine episode, the vertigo and characteristics of the visual disorder.

2. Please provide translated copies of the hospitalization records, specifically, admission and discharge summaries, consultative, testing reports, radiology (MRI or CT scans), and/or, other ancillary testing reports, if available for the following subjects, : A11006; A10253; A10885; A11086; A10788; A10801. In addition to the above, provide copies of the imaging (CCT and/or MRI) studies performed on the following subjects: A10801, A10123, and A10253.

3. Please provide assurance that all adverse events noted in the CRFs of the following subjects have been recorded in the dataset and these AEs are reflected in the proposed labeling: A10804; A10650; A10472; A10788 and A10801. Please provide further assurance that no other such cases are present in this sNDA submission.

Study 12-304:

1. Please provide CRFs for subjects who experienced cardiovascular adverse events of interest in this study, identified on pages 515-518 of Interim Clinical Study Report 12-304, and which were not previously submitted. In addition, provide copies of all ECG tracings for these subjects with attachment of the cardiologist's interpretation, if available.

2. Please provide the CRF for subject 131-103 who had a psychiatric adverse event of interest.

3. In addition, please include ECG reports with attachment of the cardiologist's interpretation, for the following subjects: 112-101; 127-013; 210-103; 214-100; 222-109.

4. Narratives on all subjects previously submitted for Study 12-304 should be modified and re-submitted with inclusion of the following information in the narratives:
   a) titration schedule and dose at the time of the adverse events;
   b) baseline and vital signs occurring at, or, proximal to the time of each adverse event;
   c) baseline and abnormal laboratory studies for each subject identified as having an adverse event of laboratory studies (e.g. elevated ALT, GTT should be substituted with the abnormal values, the normal range, and the change from baseline)
   d) other ancillary testing done to further evaluate the adverse event(s);
   e) if hospitalized or seen by a specialist or other practioner, a copy of hospital admission, discharge, consultant or practioner notes, and/or any other tests done.

As discussed during the pre-NDA meeting, please analyze the cardiovascular safety data for subjects in all studies for this sNDA with cardiovascular events of interest by the following identifiable cardiovascular risk factors: history of cardiovascular disease, active smoking, history or presence of hypertension, history or presence of hyperlipidemia, presence of elevated CRP, history or presence of diabetes mellitus, obesity (BMI > 30 kg/m^2 at baseline), and age (≥ 50 years at baseline). If you have already done this analysis, please identify the location in the submission.

Since headaches seem to occur in >1 % of subjects treated with Concerta in the 2 Placebo Controlled Trials, please examine all subjects in this submission who developed this symptom based on the presence or absence of a baseline history of headache and by headache type (e.g., migraine, tension), of hypertension, etc. How many subjects developed new onset headache and how many subjects developed worsening of pre-existing headaches? For all subjects who developed this adverse event, describe vital sign changes proximal or at the time of the headache. Describe the natural course of this adverse event? If you have already done this analysis, please identify the location in the submission.

For all subjects identified as having cardiovascular adverse events of interest, examine concurrent medications use (e.g., Salbutamol) to identify if there is any risk associated with using such medications concurrently with Concerta. For example, since asthma medications (e.g., Salbutamol) have been associated with increased heart rate and blood pressure; examine changes in vital signs and adverse events based on the use or lack of use of these medications in this sNDA.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at http://www.fda.gov/oc/datacouncil/spl.html. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

Finally, we note that this submission provides the first conversion of your package insert to the PLR Content and Format Requirements. Our Study Endpoints and Label Development (SEALD) Team have created (attached) a list of the most frequently encountered PLR format/content deficiencies. We are asking you to review your submitted PLR labeling to verify that none of these deficiencies are in the PLR labeling submitted on August 29, 2007. If you find that there are deficiencies in the PLR labeling, please amend your application with revised labeling to correct these deficiencies. Additionally, please note that this is not an exhaustive list and you are

also encouraged to review our PLR guidance documents located at the following internet address: http://www.fda.gov/cder/regulatory/physLabel/default.htm. We request that you complete this PLR labeling review and respond to us with any necessary revisions to labeling within 30 days of receipt of this letter. We consider this a separate request from the filing review issues listed in this letter, and it may be addressed separately.

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 796-0240

Sincerely,

{See appended electronic signature page}

Thomas Laughren, M.D.
Director
Division of Psychiatry Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Attachment

Common Proposed Labeling Deficiencies
Identify and Correct before Labeling Content Review Begins

Highlights:

• Type size for all labeling information, headings, and subheadings must be a minimum of 8 points, except for trade labeling. This also applies to Contents and the FPI.
[See 21 CFR 201.57(d)(6) and Implementation Guidance]
• The Highlights must be limited in length to one-half page, in 8 point type, two-column format. [See 21 CFR 201.57(d)(8)]
• The highlights limitation statement must read as follows: These highlights do not include all the information needed to use [insert name of drug product] safely and effectively. See full prescribing information for [insert name of drug product].
[See 21 CFR 201.57(a)(1)]
• The drug name must be followed by the drug's dosage form, route of administration, and controlled substance symbol. [See 21 CFR 201.57(a)(2)]
• The boxed warning is not to exceed a length of 20 lines, requires a heading, must be contained within a box and bolded, and must have the verbatim statement "See full prescribing information for complete boxed warning." Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format (e.g., Imdicon and Fantom) and 21 CFR 201.57(a)(4).
• For recent major changes, the corresponding new or modified text in the Full Prescribing Information (FPI) must be marked with a vertical line ("margin mark") on the left edge. [See 21 CFR 201.57(d)(9) and Implementation Guidance].
• The new rule [21 CFR 201.57(a)(6)] requires that if a product is a member of an established pharmacologic class, the following statement must appear under the Indications and Usage heading in the Highlights:

"(Drug/Biologic Product) is a (name of class) indicated for (indication(s))."

Please propose an established pharmacologic class that is scientifically valid AND clinically meaningful to practitioners or a rationale for why pharmacologic class should be omitted from the Highlights.

• Refer to 21 CFR 201.57 (a)(11) regarding what information to include under the Adverse Reactions heading in Highlights. Remember to list the criteria used to determine inclusion (e.g., incidence rate).
• A general customer service email address or a general link to a company website cannot be used to meet the requirement to have adverse reactions reporting contact information in Highlights. It would not provide a structured format for reporting.
[See 21 CFR 201.57 (a)(11)].
• Do not include the pregnancy category (e.g., A, B, C, D, X) in Highlights.
[See comment #34 Preamble]
• The Patient Counseling Information statement must appear in Highlights and must read See 17 for PATIENT COUNSELING INFORMATION. [See 21 CFR 201.57(a)(14)]
• A revision date (i.e., Revised: month/year) must appear at the end of Highlights. [See 21 CFR 201.57(a)(15)]. For a new NDA, BLA, or supplement, the revision date should be left blank at

the time of submission and will be edited to the month/year of application or supplement approval.
• A horizontal line must separate the Highlights, Contents, and FPI.
[See 21 CFR 201.57(d)(2)]

Contents:
• The wording of the headings and sub-headings used in the Contents must match the headings and sub-headings used in the FPI. [See 21 CFR 201.57(b)]
• The Contents section headings must be in bold type. The Contents subsection headings must be indented and not bolded. [See 21 CFR 201.57(d)(10)]
• Create subsection headings that identify the content. Avoid using the word General, Other, or Miscellaneous as the title for a subsection heading.
• Only section and subsection headings should appear in Contents. Headings within a subsection must not be included in the Contents.
• When a subsection is omitted, the numbering does not change.
[See 21 CFR 201.56(d)(1)] For example, under Use in Specific Populations, subsection 8.2 (Labor and Delivery) is omitted. It must read as follows:

8.1 Pregnancy
8.3 Nursing Mothers (not 8.2)
8.4 Pediatric Use (not 8.3)
8.5 Geriatric Use (not 8.4)

• When a section or subsection is omitted from the FPI, the section or subsection must also be omitted from the Contents. The heading "Full Prescribing Information: Contents" must be followed by an asterisk and the following statement must appear at the end of the Contents: "*Sections or subsections omitted from the Full Prescribing Information are not listed."

Full Prescribing Information (FPI):
• Only section and subsection headings should be numbered. Do not number headings within a subsection (e.g., 12.2.1 Central Nervous System). Use headings without numbering (e.g., Central Nervous System).
• Other than the required bolding [See 21 CFR 201.57(d)(1), (d)(5), and (d)(10)], use bold print sparingly. Use another method for emphasis such as italics or underline.
Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Do not refer to adverse reactions as "adverse events." Please refer to the "Guidance for Industry: Adverse Reactions Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format," available at hhtp://www.fda.gov/cder/guidance.
• The preferred presentation of cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. For example, *[see Use in Specific Populations (8.4)]* not See *Pediatric Use (8.4)*. The cross-reference should be in brackets. Because cross-references are embedded in the text in the FPI, the use of italics to achieve emphasis is encouraged. Do not use all capital letters or bold print.
[See Implementation Guidance]

• Include only references that are important to the prescriber. [See 21 CFR 201.57(c)(16)]
• Patient Counseling Information must follow after How Supplied/Storage and Handling section. [See 21 CFR 201.56(d)(1)] This section must not be written for the patient but rather for the prescriber so that important information is conveyed to the patient to use the drug safely and effectively. [See 21 CFR 201.57 (c)(18)]
• The Patient Counseling Information section must reference any FDA-approved patient labeling or Medication Guide. [See 21 CFR 201.57(c)(18)] The reference [See FDA- Approved Patient Labeling] or [See Medication Guide] should appear at the beginning of the Patient Counseling Information section to give it more prominence.
• There is no requirement that the Patient Package Insert (PPI) or Medication Guide (MG) be a subsection under the Patient Counseling Information section. If the PPI or MG is reprinted at the end of the labeling, include it as a subsection. However, if the PPI or MG is attached (but intended to be detached) or is a separate document, it does not have to be a subsection, as long as the PPI or MG is referenced in the Patient Counseling Information section.
• The manufacturer information (See 21 CFR 201.1 for drugs and 21 CFR 610 – Subpart G for biologics) should be located after the Patient Counseling Information section, at the end of the labeling.
• Regarding information at the end of the labeling, company website addresses are not encouraged. Delete from package insert labeling. The same applies to PPI and MG.
• If the "Rx only" statement appears at the end of the labeling, delete it. This statement is not required for package insert labeling, only container labels and carton labeling. [See Guidance for Industry: Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 – Elimination of Certain Labeling Requirements]. The same applies to PPI and MG.
• Refer to http://www.fda.gov/cder/regulatory/physLabel/default.htm for fictitious examples of labeling in the new format.
• Refer to the Institute of Safe Medication Practices' website (http://www.ismp.org/Tools/abbreviationslist.pdf) for a list of error-prone abbreviations, symbols, and dose designations.

Created: J. Delasko, SEALD Team, 1/29/07
Revised: R. Anderson, SEALD Team, 3/1/07

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
11/9/2007 09:39:49 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-121/S-017

PRIOR APPROVAL SUPPLEMENT

Johnson and Johnson Pharmaceutical Research &
Development, L.L.C
Attention: Ann Jenkins-Frison,
Associate Director, Regulatory Affairs
1125 Trenton-Harbourton Road
Titusville, NJ 08560-0200

Dear Ms. Jenkins-Frison:

We have received your supplemental drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Concerta (methylphenidate HCL) Extended Release Tablets

Review Priority Classification: Standard

Date of Application: August 29, 2007

Date of Receipt: August 29, 2007

Our Reference Number: NDA 21-121/S-017

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on October 28, 2007 in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be June 29, 2008.

Please cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Psychiatry Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call LCDR Janet Cliatt, Regulatory Project Manager, at (301) 796-0240

Sincerely,

{See appended electronic signature page}

CAPT Paul A. David, R.Ph.
Chief, Project Management Staff
Division of Psychiatry Products/HFD-130
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

Paul David

10/9/2007 11:30:30 AM