REVIEW AND EVALUATION OFLINICAL DATA

APPLICATION INFORMATION

NDA 21-121
SPONSOR: McNeil Consumer Healthcare
Date Submitted: September 5, 2003
User Fee Date: March 5, 2004

DRUG NAME

Generic Name: methylphenidate HCl
Trade Name: CONCERTA®

DRUG CATEGORIZATION

Pharmacological class: Psychostimulant
Indication: Attention Deficit Disorder
Dosage Forms: 18 mg, 36 mg, 54 mg extended release tablets
Route: Oral

REVIEWER INFORMATION

Medical Officer: Roberta L. Glass, M.D.
Review Completion Date: February 25, 2004

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Executive Summary

I. Recommendations

A. Recommendation on Approvability

Although the efficacy data supports the effectiveness of Concerta™ 72 mg, there is insufficient patient exposure and safety data to safely approve this higher dose of this stimulant medication for treatment of ADHD in adolescents. This recommendation is given in light of the fact that ADHD is recognized as a chronic illness, often requiring treatment for more than two years. It is recommended that the sponsor conduct further studies to increase the safety exposure by number of patients exposed and length of exposure time before this higher dosage is approved as a labeling change. It is also recommended that the sponsor provide further details of safety data from the submitted studies including narratives of abnormal labs, details of ECG findings, and data sets for further assessment of growth data.

B. Recommendation on Phase 4 Studies and Risk Management Steps

It is recommended that the sponsor further explore efficacy findings in the subgroups of females and non-Caucasians, as both of these groups are under-represented and have questionable efficacy results in the data reviewed.

Given that clinical starting doses for pediatric medications are often are calculated by mg/kg/day, it would be helpful if the sponsor would conduct a study with dosing by mg/kg/day groups rather than having patients randomized to fixed dose groups.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Concerta™, a controlled release form of methylphenidate is a psychostimulant labeled for the treatment of ADHD; it is also a Category II controlled substance. Concerta™, has been available for marketing since August, 2000. The current submission was submitted to fulfill the terms of the Revised Pediatric Written Request issued to the sponsor on 9/2/03. This submission was intended to support labeling changes including an increase in the maximum dosage to Concerta™ 75 mg daily and proposed modification of safety information.

B. Efficacy

The results of the two week placebo controlled portion of Study 01-146 support the claim that the dose of Concerta™ 72 mg daily is effective in treating ADHD in adolescent patients. However, in the combined Concerta™ treatment groups, effectiveness was primarily observed in Caucasian males. Females patients did not show as much improvement as male patients, and, in the sponsor's analysis, females did not demonstrate a statistically significant change from baseline compared to placebo. Results from this study do not support the effectiveness of Concerta™ in non-Caucasian populations.

C. Safety

In total, the dose of Concerta™ 72 mg daily was tested in 90 patients exposed for less than 90 days, and 7 patients exposed from 90 to 180 days. There were no patients exposed to the 72 mg dose for greater than 180 days.

In the two week placebo controlled portion of Study 01-146, there were dose dependent increases in systolic and diastolic blood pressure with the highest changes observed in the Concerta 72 mg group. A dose dependent decrease in body weight was also observed in this two week time period.

The sponsor's calculation of z-scores for the two open label studies submitted (maximum dose of 54 mg daily) suggested that there was a decrease of 6 percentiles in weight and a decrease of 0.8 percentile in height for children (mean duration was 10.4 months). Z-scores for adolescents suggested that there was little effect on height or weight for adolescents.

D. Dosing

Study 01-146 was the only study formally assessing Concerta™ 72 mg daily in adolescents. The other two studies submitted had a maximum dose of Concerta™ 54 mg daily by protocol; however, there were 13 patients (of n=1514 or 0.8%) who received a dosing of ≥ 72 mg Concerta™; eleven of these patients were aged 5-13 (mean exposure of 3.3 days).

E. Special Populations

From the data presented, it appears that girls did not have as robust a response to Concerta™ than observed in boys. For the efficacy evaluation, girls made up 20.5% of the population assessed; however, it could be argued that this percentage is reflective of the clinical presentation as the majority of patients diagnosed with ADHD are male.

The efficacy results for non-Caucasians did not show a statistical significance. The sponsor suggests that the non-Caucasian population was too small to show a difference. Certainly, non-Caucasians were under-represented in the efficacy portion as only 14.5% of patients were African –American and 11.4% were "other."

Sub-group analyses were not submitted for safety data.

Clinical Review

I. Introduction and Background

A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication, Dose, Regimens, Age Groups

The sponsor is proposing to increase the maximum dose to Concerta™ 72 mg daily for the adolescents for the treatment of ADHD. The current maximum dosage for all patients is Concerta™ 54 mg daily.

B. State of Armamentarium for Indication

Psychostimulants have been used with increasing frequency in the treatment of Attention Deficit/Hyperactivity Disorders (ADHD) over the past thirty years. Various formulations have been marketed for the indication of ADHD using the following three basic compounds: methylphenidate (e.g. Ritalin, Ritalin SR, Metadate ER, Concerta), dextroamphetamine (e.g. Dexedrine, Adderall), and pemoline (Cylert). Pemoline is a Category IV controlled substance, while the methylphenidate and the dextroamphetamine derivatives are a Category II controlled substance.

More recently, atomoxetine, a norepinephrine reuptake inhibitor, has been marketed and labeled as a non-stimulant ADHD drug and is not a controlled substance.

C. Important Milestones in Product Development

In August 2000, Concerta was approved for marketing for the indication of ADHD originally at the doses of 18 and 36 mg tablets to be administered once daily. At the current time, Concerta is labeled for dosing of up to a maximum of 54 mg with approved and marketed tablets of 18, 27, 36 and 54 mg tablets.

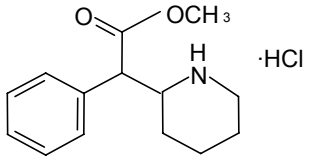
D. Other Relevant Information

The original ownership of IND 54, 575 for Concerta (OROS or methylphenidate HCl) Extended-Release tablet was transferred from ALZA Corporation to McNeil Consumer & Specialty Pharmaceuticals as of November 4, 2002. Agent rights for the NDA 21-121 CONCERTA Extended-release Tablets [OROS (methylphenidate HCl)] were transferred to McNeil as of May 1, 2003, but ALZA continues to have ownership of the NDA.

II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

A. Chemistry

The chemical structure for methlyphenidate is the following:



The chemical name is methyl α-phenyl-2-piperidineacetate hydrochloride. The study drug contains the enantiomeric forms of both the *d-threo* and the *l-threo* isomers of methylphenidate hydrochloride. The Concerta form of methylphenidate is designed to have an extended release mechanism (for further details, please see original NDA review by Andrew Mosholder, M.D. of 3/23/2002).

B. Animal Pharmacology and Toxicology

The sponsor submitted two new oral toxicity and toxicokinectic studies in beagle dogs. The results showed that the maximum tolerated dose was 216 mg/day. At doses of 72, 144, 216 mg/day for 30 consecutive days, the following reversible toxicological effects were identified: hyperactivity, salivation, decreased body weight gain, and decreased food consumption. These same effects were also observed at 216 mg/day dose, except that the body weight effects were not reversible at this higher dose. The sponsor concluded that the no-observable-adverse-effect-level (NOAEL) in dogs after 30 days was 144 mg/day (mean daily doses were 20.1 and 23.9 mg/kg in male and female dogs, respectively).

III. Human Pharmacokinetics and Pharmacodynamics

For complete details, please refer to the FDA Clinical Pharmacology and Biopharmaceutics review by Veneeta Tandon, PhD.

This submission included a 6 day multiple dose pharmacokinetic study (Study 12-001) conducted in 26 healthy adolescents (13-17 y.o.) diagnosed with ADHD. Findings demonstrated that the pharmacokinetics of methylphenidate were observed to be linear in doses up to 72 mg. Compared to children (6-12 y.o.), there appeared to be a 58% increase of oral clearance in adolescents, and 104% increase in clearance in adults. It appears that body weight had a significant effect on the clearance of this form of methylphenidate. It was also concluded that the metabolism of methylphenidate in adolescents appears to be similar to that in adults.

IV. Description of Clinical Data and Sources

A. Overall Data

The sources of data in this review are the clinical trials submitted by the sponsor. Also of relevance is the sponsor's summary of post marketing data.

B. Tables Listing the Clinical Trials

Table 1 (below) summarizes the studies described in this supplement, as well as on-going studies.

Table 1 Table of all studies included in the current submission and ongoing studies of NDA 21-121

	DESIGN/DURATION	DEMOGRAPHICS	DOSE / % PT. COMPLETED
Clinical Pharmacology Studies			
Protocol 12-001	Open label PK study /6 days	N=26 Ages: 13-16 y.o. 73% M; 27% F C 77%, 15%A, 8% O	18, 27, 36, 54, 72 mg (qd x 6 days)
Protocol 01-148	Effect of Diet on Bioavailability and pk of Concerta and AdderallXR in healthy adults	N=38 Ages 19-46 46%M; 54%F C 62%, 10%A, 28% O	36 mg Concerta 20 mg Adderall XR
Efficacy and Safety Study (one phase is controlled)			
Protocol 01-146	Titration Phase/1-4 weeks *Placebo Controlled Phase/ 2 weeks* Open Label Phase/ 8 weeks	N=220 *N=177 randomized* N=171: open label Ages: 13-18 yo 75%M; 25%F %C; 10%A; 15% O	18 mg: 4 (80% 36 mg: 22 (88%) 54 mg: 20 (83%) 72 mg: 25 (75.8%)
Completed Open Label Studies			
Protocol 98-012	One year open label safety study in patients with ADHD/ 12 to 21 months	N=432 (Part I: 1st 12 months) n=278 (Part II) Ages: 6-13 (mean 9) 83% M, 17%F	18 , 36 , 54 mg Concerta (Drug holiday for approx. 22%)
Protocol 99-018	Open label safety study in ADHD patients in community setting (9 months).	N=1082 Ages: 5-66 y.o; (mean 14.2 y) 6-12: n=682 13-17: n=264 ≥18: n=136	18, 36, 54 mg

	DESIGN/DURATION	DEMOGRAPHICS	DOSE / % PT. COMPLETED
		77% M , 23% F; 90%C, 6 % A, 4% O	
Ongoing Studies			
Protocol C-2000-045	Open label safety study in ADHD patients	N=106	18, 36, 54 mg Concerta
Protocol 02-160	Open label pharmacokinetic, dose escalation study in healthy adults	N=27 Ages: 20-50 y.o. (mean: 28.9 y.o.) 74%M, 26% F 81%C, 4%A, 15% O	54, 72, 108, 144 mg Concerta

C. Postmarketing Experience

In an FDA review dated 12/24/02 (by Dr. Andrew Mosholder), there was one case (Mfr. Control No. 10739, pg 182-3) in which a literature case was reported of a 3 y.o. boy who underwent treatment for renal calculi. A flat plate radiograph of the abdomen appeared to show a number of residual stones; however, a subsequent spiral CT scan of the abdomen showed that these were actually Concerta tablets in the GI tract. This finding suggests that the Concerta tablets can be radio-opaque. Dr. Mosholder suggested that it would be helpful to have this information in labeling so that treating physicians evaluating patients being treated with Concerta. The sponsor should confirm if the tablets are radio-opaque, and, if so, propose appropriate labeling changes.

In the current submission, the sponsor states that a total of 994 spontaneous adverse event reports (2,168 total events) have been reported which included 7 reports of death and an additional 97 serious reports. The sponsor states that the most commonly reported individual adverse events were the following: therapeutic response decreased (144), insomnia (113), anorexia (101), abdominal pain (92) and headache (90). Although it is difficult to attribute the cause of any of the reported deaths to Concerta, for the sake of completion, this review includes the following table which summarizes the postmarketing deaths reported in this NDA.

Table 2 Post-marketing deaths reported while patients taking Concerta

Patient	Brief Description of Event
ALZ-10502 13 y.o. male	Had a possible overdose with toxic level of methylphenidate of 280 ng/mL (therapeutic range 3.7-6.8 ng/mL),. Autopsy included pulmonary edema and congestion, moderate cardiac ventricular dilation without LV hypertrophy, 370 g heart with no embolus, coronary artery disease, thrombosis, infarction, fibrosis, contusion or defects. Bicuspid aortic valve was noted. The 2380 g liver showed hepatic steatosis. Was taking 54 mg Concerta daily (previously treated with bupropion for 3-4 years) .
ALZ-10130 14 y.o. male	Committed suicide 3 weeks after initiating therapy with Concerta 35 mg daily; concomitant treatment with sertraline. Reported history of depression and familial history of suicide.
NSADSS2002030267 9 y.o. female	Died of cardiopulmonary arrest after developing flu symptoms and acute sinusitis with vomiting. Autopsy report had methylpenidate level of 156 ng/mL (therapeutic range 3.7-6.8 ng/mL), and the blood glucose level was over 402 mg/dl (normal random glucose 70-125 mg/dL). Had history of asthma and chronic otitis media with concomitant medications includeing loratadine (Claritin) and fluticasone (Flovent).
NSADSS2002046188 13 y.o. male	Sudden cardiac death. Was taking Concerta 36 mg for 8 motnhs. Had two previous syncopal episodes (one prior to Concerta treatment and one while on Concerta with unremarkable ECG during episode on

Patient	Brief Description of Event
	Concerta).
NSADSS2002032843 42 y.o. male	Suicide. Had bupropion level of 2800 ng/mL
NSADSS2002032842 42 y.o. female	Found unresponsive with unsuccessful recitations efforts. Patient reportd to be taking bupropion SR, methylphenidate, chlordiazepoxide/clindinium, montelukast and levothyroxine.

Otherwise, the events reported have been previously described in labeling.

D. Literature Review

The sponsor conducted a literature search for Concerta and provided a summary of the available literature. From their summary, there did not appear to be any unexpected events, and the safety findings described are consistent with the current labeling.

V. Clinical Review Methods

A. How the Review was Conducted

For the purpose of evaluating efficacy, there was only one study which included a placebo controlled portion (Study 01-146). Therefore, the efficacy section will only discuss the two week placebo controlled portion of Study 01-146.

Because the most significant labeling change which the sponsor has requested in this submission is to increase the maximum dose in labeling to 72 mg Concerta™ daily (currently labeled for a maximum of 54 mg daily), the main focus for the safety review will also be Study 01-146 (the only study submitted which included a dosing of 72 mg Concerta™ daily). Relevant information to this higher dosing in the open label studies will be discussed.

Because Study 98-012 was the only study in which laboratory studies were conducted, the laboratory section of this review will discuss only this study. Also, z-scores were calculated for the open label studies 98-012 and 99-018 only (not for Study 01-146) and is discussed in the Vital Signs section of the Safety Review (below).

B. Overview of Materials Consulted in Review

Original NDA Submission: Submissions of the following dates: 9/5/03, 9/15/03, 9/23/03, 10/13/03, 2/4/04, 2/15/04, 2/16, 04, 2/9/04)
Statistical Review by Fanhui Kong, Ph.D. (draft)
Office of Clinical Pharmacology and Biopharmaceutics Review by Veneeta Tandon, Ph.D. (2/12/04)

C. Overview of Methods Used to Evaluate Data Quality and Integrity

A review from the Division of Scientific Investigations is pending at the time of this review.

D. Evaluation of Financial Disclosure

The sponsor submitted a certification of Financial Interests and Arrangements of Clinical Investigators. The Executive Director of Regulatory Affairs signed the Form 3454 testifying that, to her knowledge, there was no financial arrangement made with investigators that could affect the outcome of the studies as

defined in 21 CFR 54.2 (a), and that no listed investigator (attached to the form) was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f). The Executive Director of Regulatory Affairs also signed Form 3455 which discusses that (b) (6) received "significant payments" from the originator sponsor on Concerta, ALZA, to fund clinical trials and fees as a consultant; the sponsor did not disclose the amount of the funds. The sponsor references Study (b) (6) as the study that Dr. (b) (6) was a principal investigator, and conclude Dr. (b) (6) compensation did not influence the outcome of study (b) (6). It is unlikely that Dr. (b) (6) compensation could have affected the overall safety outcomes of the study, especially given that he was in charge of 1 of (b) (6) sites.

VI. Integrated Review of Efficacy

A. Brief Statement of Conclusions

The results of the two week placebo controlled portion of Study 01-146 support the claim that the dose of Concerta 72 mg daily is effective in treating ADHD in the adolescent patients. However, the data brings up questions regarding the effectiveness of Concerta in the subgroups of girls and non-Caucasians.

B. General Approach to Review of the Efficacy of the Drug

Of the studies submitted, Study 01-146 was the only study with a placebo controlled portion; therefore, this is the only study that will be reviewed for the purposes of efficacy. There were only two weeks of the placebo controlled phase of this study, and the baseline values were obtained at the beginning of the titration phase which took place 1 to 4 weeks prior to randomization. The efficacy instrument used was the ADHD Rating Scale using investigator evaluation. Efficacy was assessed by looking at the change from baseline to the end of the randomized double-blind phase of the ADHD Rating Scale.

This review will refer to the statistical review of Fanhui Kong, PhD, FDA statistician.

C. Detailed Review of Trials

Study 01-146

Investigators/Location

This study was conducted at 15 centers in the USA with 15 principal investigators involved in this study. Please refer to the sponsor's study report of Protocol 01-146 Section 4 for a full listing of all principal investigators.

Study Plan

Objective(s)/Rationale

The objective of this study was to evaluate the safety and efficacy of Concerta™ (up to 72 mg daily) in treating adolescents (aged 13-18 y.o.) diagnosed with Attention Deficit Hyperactivity Disorder (ADHD).

Population

Patients chosen for this study were physically healthy adolescents, aged 13-18, diagnosed with ADHD according to the DSM-IV criteria. Required for participation was a score of 41-70 in the Children's Global Assessment Scale. Excluded form the study were patients with a history of non-response to methylphenidate, marked anxiety/tension/or agitation, glaucoma, seizure disorder, psychotic disorder,

Tourette's disorder (or family history of Tourette's), mental retardation, significant learning disorder and bipolar disorder. If a behavior medication program was in place at time of study initiation, then it was allowed to continue unchanged during the study, but no new behavioral modification program could be initiated during the study. Sexually active females were required to use medically accepted forms of birth control.

Prohibited concomitant medications included clonidine, other alpha-2 adrenergic receptor agonists, tricyclic antidepressants, SSRIs, theophylline, coumadin, anticonvulsants, soporifics, and medications to treat an anxiety or mood disorder.

Design

This study was a 15 site, four phase study (up to 14 weeks) with a 2 week double blind, placebo controlled portion in patients aged 13 to 18 y.o. diagnosed with ADHD according to DSM-IV criteria. After screening (Phase 1), patients began an open-label titration phase (Phase 2) and were treated with the starting dose of 18 mg per day and then titrated in 18 mg increments approximately every 7 days to a maximum of 72 mg/day depending on improvement of ADHD symptoms; doses in this phase were 18, 36, 54, or 72 mg daily. It is unclear from the protocol how long Phase 2 was, but there appeared to be weekly visits until the individualize treatment dose was achieved (the study report states that the titration phase could be up to four weeks).

After the titration phase, patients then entered Phase 3 (the two week placebo controlled phase) and were randomized to either a placebo group or the Concerta™ group (at the individualize dose achieved in Phase 2). Upon completion of Phase 3 or early termination of Phase 3 (due to poor efficacy results), patients could then enter Phase 4, an open label 8-week follow up period at the doses identified in Phase 2 of the study; during Phase 4, patients were assessed at Weeks 4 and 8.

Doses were administered in the morning; the protocol dose not state if doses were given in the fasting or fed state.

Screening included a history and physical, ECG, urine drug screen, and urine pregnancy test. Vital signs and urine drug screens were repeated at each visit. Assessment instruments used during the study included K-SADS (to confirm the clinical diagnosis of ADHD), C-GAS, ADHD Rating Scale (parent and investigator), Child Conflict Index (Parent), Conners-Wells' Self Report Scale (subject), Global Assessment of Effectiveness (investigator), and the CGI (investigator).

Analysis Plan

The primary efficacy variable was the change from baseline in the ADHD Rating Scale assessed by the investigator using analysis of covariance models with treatment and study site as factors and the corresponding baseline total score as a covariate. Treatment-by-site interaction was examined at the significance level of alpha=0.10. Change from baseline in the mean of the last week of the CGI was to be analyzed using either ANCOVA (if normality assumptions are not violated) or the Wilcoxon rank sum test. Treatment effect was to be analyzed using the GAS and CGI and the Cochran-Mantel-Haenszel correlation statistic stratified by study site at the end of the randomized double-blind phase.

The efficacy endpoints are based on the intent-to-treat approach which would include all randomized patients who have at least one post-randomization assessment of the ADHD Rating Scale.

Study Conduct/Efficacy Outcome

Patient Disposition

Of the 220 patients who entered Phase 2 (the titration phase), 177 patients were randomized to enter Phase 3 (double blind placebo controlled phase), and 171 patients entered Phase 4 (open label phase). In the double blind placebo controlled phase (Phase 3), 87 patients received study drug and 90 patients were in the placebo group. Reasons given for patients not continuing onto Phase 3 included adverse events (n=4), lost to follow-up (n=2), protocol violation (n=6), and other, not specified (n=2).

In the placebo controlled portion of the study (Phase 3), 62 of 90 patients in the placebo group, and 71 of the 87 patients assigned to Concerta™ group completed the study. Reasons for early withdrawal included the following: adverse events, lack of efficacy, protocol violation, and lost to follow up. Table 3 (below) elaborates on the percentages of patients who dropped out for each reason within the Concerta™ groups and placebo group. As can be seen in Table 3, there were 33 patients randomized to the 72 mg dose, of which 25 (or 76%) patients completed this portion of the study and 8 patients (or 24%) withdrew due to lack of efficacy.

Of the study drug dosing groups, it is noted that the withdrawal rate due to lack of efficacy was highest in the 72 mg dose, perhaps suggesting that patients who would not benefit from Concerta were unnecessarily titrated to this higher dose. An explanation for the high withdrawal rate due to lack of efficacy in the placebo group could be due to a withdrawal phenomenon.

Table 3 Reasons for withdrawal during the placebo controlled portion (Phase 3) of Study 01146

Reasons for Withdrawal	Placebo N=90 (%)	Concerta™ N=87			
		18 mg N=5 (%)	36 mg N=25 (%)	54 mg N=24 (%)	72 mg N=33 (%)
Adverse events	1 (1)	0	0	0	0
Lack of efficacy	23 (26)	1 (20)	1 (4)	4 (17)	8 (24)
Protocol violation*	2 (2)	0	2 (8)	0	0
Lost to follow up	2 (2)	0	0	0	0
Total withdrawal	_____	1 (20)	3 (12)	4 (17)	8 (24)
Total completed		4 (80)	22 (88)	20 (83)	25 (76)
Total withdrawal	28 (31)	16 (18)			
Total completed	62 (69)	71 (82)			

*For details, please refer to the sponsor's table 8-1 in the study report

Demographics /Group Comparability

The majority of the patients in this study were Caucasian males comprised of 141 boys (80.6%) and 34 girls (19.4%) with a mean age of 14.6 years (range 13 to 18 years). The population consisted of 131 (74.9%) Caucasians, 24 (13.7%) African-Americans, and 20 (11.4%) "other." In the double blind portion of the trial there was a statistically significant difference in the gender of the placebo group versus the Concerta groups (for the Intent to Treat: p=0.0431; for All Subjects: p=0.0287). In the intent to treat population, there were more males in the placebo group (n=77 or 86.5%) than in the Concerta groups (n=64 or 74.4%); conversely, there were fewer females in the placebo group (n=12 or 13.5%) than in the Concerta groups (n=34 or 19.4%). Otherwise, there were no significant baseline differences identified in race, age, weight, and height.

Concomitant Medications

Concomitant medications used with greatest frequency included acetaminophen, ibuprofen, benadryl (for allergies), Claritin, and albuterol. Of note, one patient (Subject 13007) in the placebo group was reported to taking Adderall 10 mg for ADHD. Otherwise, there were no notable differences between treatment groups in terms of concomitant medications.

Efficacy Results

For the primary efficacy variable, the sponsor reported a statistically significant difference when comparing the pooled Concerta groups and placebo with a p-value=0.001 (please see Table 4 below). In his statistical review, Dr. Kong confirmed that there was a statistically significant difference comparing the pooled Concerta treatment groups with the placebo group, and went further to separate out the treatment effects by dose. As can be seen in Table 5 (below), the treatment effect was primarily coming from the higher dose groups (54 and 72 mg/day); however, as pointed out by Dr. Kong, the 18 mg dose group had too small a sample (n=4) to provide reliable results.

Table 4 Mean Change from Baseline to end of placebo controlled portion of study (excerpt from sponsor's table)

			CONCERTA					
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value[a]
Baseline	N	89	4	25	24	33	86	
	Mean	30.99	25.50	30.28	32.88	32.27	31.55	
	SD	9.64	7.05	8.29	9.54	10.31	9.42	
	Min, Max	10,54	18,32	18,47	11,52	8,54	8,54	
End of RDB[b]	N	89	4	25	24	33	86	
	Mean	21.40	8.00	17.96	16.25	16.91	16.62	
	SD	13.44	1.83	10.30	11.45	11.76	11.03	
	Min, Max	1,54	6,10	0,44	3,44	0,46	0,46	
Change from Baseline at End of RDB[b]	N	89	4	25	24	33	86	
	Mean	-9.58	-17.50	-12.32	-16.63	-15.36	-14.93	0.0010
	SD	9.73	8.81	9.93	10.12	11.91	10.72	
	Min, Max	-34,9	-25,-8	-33,7	-41,6	-37,9	-41,9	

a: ANCOVA models with treatment (placebo or Any CONCERTA) and site as factors and the corresponding baseline total score as a covariate.
b: Last observation carried forward at the end of randomized double-blind phase.

Table 5 Change of ADHD Total Score at the end of Double blind Phase by dose group (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Dose Group	Treatment Group	Placebo Group	Trt_effect	p-Value
18 mg/day (SD)	-17.5 (8.81) n=4	-9.58 (9.73) n=89	-7.92 (9.70)	0.11
36 mg/day (SD)	-12.32 (9.93) n=25	-9.58 (9.73) n=89	-2.74 (9.77)	0.22
54 mg/day (SD)	-16.63 (10.12) n=24	-9.58 (9.73) n=89	-7.04 (9.81)	0.002
72 mg/day (SD)	-15.36 (11.91) n=33	-9.58 (9.73) n=89	-5.78 (10.36)	0.007

A point of concern was that there was no wash out period between the titration phase and the placebo controlled phase; this could have created a confounding variable of a withdrawal or rebound phenomenon (which could resemble symptoms of ADHD) for patients who were randomized to the placebo group during the placebo controlled portion of the study. In order to look at this question more carefully, Dr. Kong looked at the efficacy results at the end of Weeks 1 and 2 of the study. His findings suggest that there was a rebound effect as evidenced by the fact that the magnitude of change in the placebo group ADHD Rating Scores were significantly greater than magnitude of change in the Concerta™ group when comparing the end of Week 1 and Week 2 (see Table 6 below). It is noted that a treatment effect was observed at the end of both weeks ($p<0.0001$); however, it is also noted that there was a high drop out in the placebo group that could have been due to a withdrawal reaction, providing a confounding variable.

Table 6 The Change from baseline of ADHD Total Score by week of treatment in the placebo controlled portion of Study 01-146 (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Treatment Group	End of Titration	First Week of RDB	Second Week of RDB
Concerta	-20.88 (7.56) n=86	-15.38 (10.47) n=86	-16.25 (10.14) N=72
Placebo	-20.36 (8.21) n=89	-8.97 (10.01) n=89	-12.19 (8.36) N=63

In their subgroup analysis, the sponsor provided data suggesting that Concerta was not as effective in females patients compared to male patients. From Table 7 below, it appears that statistical significance was not demonstrated for females when comparing the Concerta™ treatment group with the placebo group. Also numerically, it appears that the female patients did not have as much improvement as the male patients in their ADHD Rating Scale at the end of the placebo controlled phase.

Also from Table 7, it appears that the treatment effect was primarily in Caucasians and not in the African-American and other race groups. The sponsor argues that the number in the non-Caucasian groups are too small to place any significance on these findings.

Dr. Kong, FDA statistician, concluded that there was a treatment effect observed in both the male and female group (See Table 8 below). However, based on the effect of change of ADHD Total Score, there did not appear to be a treatment effect in a pooled Non-Caucasian group (See Table 9).

Table 7 Mean change from baseline of the ADHD Rating Scale (Investigator) at the end of the placebo controlled portion of Study 01-146 separated by Gender and Race (sponsor's table)

		CONCERTA					
	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value[a]
Change from Baseline at End of RDB[b], Mean±SD (N)							
Male	-10.36±9.51 (77)	-18.50±9.19 (2)	-13.74±10.37 (19)	-17.61±10.05 (18)	-15.60±11.66 (25)	-15.70±10.66 (64)	0.0010
Female	-4.58±10.03 (12)	-16.50±12.02 (2)	-7.83±7.39 (6)	-13.67±10.63 (6)	-14.63±13.46 (8)	-12.68±10.82 (22)	0.5240
Caucasian	-8.61±10.08 (67)	-15.00±8.89 (3)	-12.71±8.40 (17)	-16.94±10.95 (18)	-15.27±11.75 (26)	-15.05±10.49 (64)	0.0008
African-American	-14.00±7.20 (15)	(0)	-4.00±13.04 (4)	-9.00± NA (1)	-24.25±3.20 (4)	-13.56±13.15 (9)	0.2672
Other Race	-9.43±9.57 (7)	-25.00± NA (1)	-19.00±9.49 (4)	-17.00±8.00 (5)	-4.33±13.65 (3)	-15.31±10.89 (13)	0.0766

a: ANCOVA models with treatment (placebo or Any CONCERTA) and site as factors and the corresponding baseline total score as a covariate.
b: Last observation carried forward at the end of randomized double-blind phase.
Abbreviations: RDB=randomized double-blind phase

Table 8 Treatment effect on Change of ADHD Total Score according to Gender at the end of placebo controlled phase of Study 01-146 (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Sex	Therapy	Patient	Change	Trt effect	p-Value
Male	**Any Concerta**	64	-15.70	-5.34	0.002
	Placebo	77	-10.36		
Female	**Any Concerta**	22	-12.68	-8.1	0.04
	Placebo	12	-4.58		

Table 9 Treatment effect on the change of ADHD Total Score according to Race Group at the end of the placebo controlled phase of Study 01-146 (table extracted from FDA statistical review by Fanhui Kong, PhD.)

Race	Therapy	Patient	Change	Trt_effect	t-Value
Caucasian	**Any Concerta**	64	-15.05	-6.44	0.0005
	Placebo	67	-8.61		
Noncaucasian	**Any Concerta**	22	-14.59	-2.05	0.5
	Placebo	22	-12.55		

Conclusions and Discussion

The results of the two week placebo controlled portion of Study 01-146 support the claim that the dose of Concerta 72 mg daily is effective in treating ADHD in the adolescent patients. However, in the combined Concerta treatment groups, effectiveness was primarily observed in Caucasian males. Females patients did not show as much improvement as male patients, and, in the sponsor's analysis, females did not demonstrate a statistically significant change from baseline compared to placebo. Results from this study do not support the effectiveness of Concerta in non-Caucasian populations.

A flaw in the design of this study was the absence of a washout period between the titration phase and the placebo controlled phase; therefore, patients randomized to placebo were abruptly withdrawn from Concerta. The FDA statistical review suggested that there was evidence of a rebound phenomenon (see analysis section above). This may have been the explanation for a high drop out rate in the placebo group.

Another complication of the protocol is a blinding issue; patients who were dosed to receive 72 mg of Concerta™ were required to take two 36 mg tablets. It is unclear if all patients were given two tablets, or if the placebo patients received two tablets. The result could have been that patients taking two tablets could easily be identified as patients on treatment drug during the placebo controlled portion of the study.

Unfortunately there were only two weeks of the placebo controlled phase of this study, and one could question whether or not this is an adequate time period to assess efficacy for this drug to treat the disorder of ADHD, as clinical trials for this indication are usually a minimum of three to four weeks. It is noted that there was a titration phase prior to the placebo controlled phase of the study, and that this added an exposure time for patients assigned to drug treatment in the placebo controlled portion of the study.

To summarize, keeping in mind the design flaws discussed above, this study supports the efficacy claims of Concerta 72 mg daily. However, the data brings up questions of the effectiveness of Concerta in the subgroups of girls and non-Caucasians.

VII. Integrated Review of Safety

With the exception of a two week period in Study 01-146, the data in this submission was collected in open label studies. This poses a serious limitation to the interpretation of safety data, as much of the data obtained in open label studies is not able to be interpreted without a control group.

Most tables referred to in this section will be included in the Appendix A.

A. Brief Statement of Conclusions

In the two week placebo controlled portion of Study 01-146, there were dose dependent increases in systolic and diastolic blood pressure with the highest changes observed in the Concerta 72 mg group. A dose dependent decrease in body weight was also observed in this two week time period.

The sponsor's calculation of z-scores for the two open label studies (maximum dose of 54 mg daily) suggested that there was a decrease of 6 percentiles in weight and a decrease of 0.8 percentile in height for children (mean duration was 10.4 months). Z-scores for adolescents suggested that there was little effect on height or weight for adolescents.

B. Background and Methodology

The main issue in this supplement is whether the sponsor has provided sufficient data to support the increase in the maximum dose of Concerta to 72 mg daily. Therefore, the main focus for the safety review will be Study 01-146 which is the only study submitted which included a dosing of 72 mg Concerta™ daily and had a placebo controlled portion. Relevant information to this higher dosing in the open label studies will be discussed.

Because Study 98-012 was the only study in which laboratory studies were conducted, the laboratory section of this review will discuss only this study. Also, the sponsor calculated z-scores for the open label studies 98-012 and 99-018 only (not for Study 01-146); this topic is discussed in the Vital Signs section of the Safety Review.

All studies in this submission were conducted in the USA.

C. Description of Patient Exposure (i.e., number of patients at given duration, dose, demographic, distribution, country)

Study 01-146 was the only study formally assessing Concerta 72 mg daily. As can be seen in Table A-1 (in the appendix), a total of 84 patients were exposed to Concerta 72 mg of which 90% were treated for less than 12 weeks. The sponsor did not provide an exposure period in terms of patient-time. A very rough estimate of exposure time could range from a minimum of 9 patient years to a maximum of 15 patient years using information from Table A-1.

As can be seen from Table A-2, the majority of patients exposed to Concerta 72 mg in Study 01-146 were Caucasian males with a mean age of 14.9 years. For details regarding the demographics for Study 01-146, please refer to the demographics section in the efficacy review (above).

For the pooled studies 98-012 and C-99-018, the protocol set the maximum dose at Concerta 54 mg. However, there were 13 patients (of n=1514 or 0.8%) who received a dosing of ≥ 72 mg Concerta; eleven of these patients were aged 5-13 (mean exposure of 3.3 days), one patient was aged 13-17 (for 22 days), and there was one adult (for one day); for details, please refer to Table A-3 (appendix).

Table A-4 summarizes the dosing for the all three protocols combined (i.e. Studies 01-146, 98-012, and 99-018). It is noted that for the dose of 72 mg or greater, the exposure was very low with 90 patients exposed for less than 90 days, and only 7 patients were exposed for 180 days or less. There were no patients exposed to the 72 mg dose for greater than 180 days.

D. Death/Other serious adverse events

There were no deaths reported in the studies in this submission.

The Tables A-5 and A-6 summarize the serious adverse events occurring in the safety data base for this submission (i.e. Studies 01-146, 98-012 and 99-018). It is difficult to determine the causality of these events, and whether or not Concerta was a contributing factor.

E. Assessment of Dropouts (will only discuss 01-146 unless there are unusual events in the other data banks)

1. Overall pattern of dropouts

In the placebo controlled portion of the study (Phase 3), 62 of 90 patients in the placebo group, and 71 of the 87 patients assigned to Concerta™ group completed the study. Reasons for early withdrawal included the following: adverse events, lack of efficacy, protocol violation, and lost to follow up. As can be seen in Table 10 (below), the highest rate of withdrawal occurred due to lack of efficacy observed in the placebo and the 72 mg groups. There was only one patient who withdrew due to an adverse event in this placebo controlled portion of study 01-146.

Table 10 Summary of drop outs for placebo controlled portion (Phase 3) of Study 01-146

Reasons for Withdrawal	Placebo N=90 (%)	Concerta™ N=87			
		18 mg N=5 (%)	36 mg N=25 (%)	54 mg N=24 (%)	72 mg N=33 (%)
Adverse events	1 (1)	0	0	0	0
Lack of efficacy	23 (26)	1 (20)	1 (4)	4 (17)	8 (24)

Protocol violation*	2 (2)	0	2 (8)	0	0
Lost to follow up	2 (2)	0	0	0	0
Total withdrawal	_____	1 (20)	3 (12)	4 (17)	8 (24)
Total completed		4 (80)	22 (88)	20 (83)	25 (76)
Total withdrawal	28 (31)	16 (18)			
Total completed	62 (69)	71 (82)			

*For details, please refer to the sponsor's Table 8-1 in the study report

2. Adverse Events Associated with Dropouts

The only patient who withdrew due to an adverse event in the placebo controlled portion of Study 01-146 was Subject # 1012, a 15 year old Caucasian male randomized to placebo who discontinued on Day 2 of the placebo controlled portion due to increased mood irritability. One possibility is that this patient was experiencing a withdrawal phenomenon from the abrupt completion of Concerta treatment to begin the placebo controlled portion of the study.

Table A-7 summarizes the withdrawals due to adverse events for the open label sections of Study 01-146. There were no unexpected events reported that have not been previously described in labeling.

Please see the sponsor's ISS Table 5-28 for a complete listing of patients who withdrew from Studies 98-012 and 99-018. Generally, these events were consistent with the current labeling. Of note was Patient # 015204, a 47 y.o. Caucasian male who experienced "erectile difficulty" on Day 32 while taking the dose of 36 mg Concerta.

F. Other safety findings

1. Adverse Event Incidence

In order to better characterize the safety of this drug in the higher dose of 72 mg, it would be most helpful to examine the adverse events profile generated in the two week placebo controlled portion of Study 01-146.

As can be seen from Table A-8, the sponsor's 1% table, there appears to be a statistical significance of digestive system events (p=0.009) and a significant difference for the incidence in insomnia (p=0.056) when comparing the placebo and Concerta groups. It is noted that the finding of insomnia and digestive symptoms did not occur with a higher incidence in the 72 mg group compared to lower dose groups. The most commonly reported adverse events during this phase of the study were headaches and accidental injury.

2. Laboratory Findings

Post baseline laboratory values were collected by protocol only in Study 98-012 (at baseline, 6 and 12 months). Unfortunately, there is no placebo control group to add perspective; this lack of a placebo control makes the findings difficult to interpret.

In the ISS, the sponsor submitted summary results for the following select laboratory tests: WBC, platelet count, hemoglobin, AST an ALT. Table A-9 describes the number laboratory test results that were outside the normal range in Study 98-012.

Six patients had abnormal laboratory values reported as adverse events; two patients with albuminuria, one patient with albuminuria and glycosuria, and one patient with leukopenia, increased creatinine, and abnormal liver function tests. Details for these patients were not located in the original submission.

It is also noted that the mean change from baseline for all laboratory values was not appreciable or indicative of a signal for concern (for details, please refer to the study report for Study 98-012 Table 11.1.5-30).

3. Vital Signs

Vitals signs including systolic/diastolic blood pressures and pulse were collected at each visit; weight and height were recorded at 4 week intervals in Studies 01-146, 98-019 and for the first 3 months of Study 99-018.

In order to establish a comparator control, it is most helpful to look in more depth at the placebo controlled portion of Study 01-146. Please refer to Tables A-10, A-11 and A-12 which describe the changes in systolic, diastolic and pulse rate comparing baseline (obtained at the beginning of the titration phase) and the reading at the end of the placebo controlled phase.

As can be seen from Table A-10, the mean change from baseline for systolic blood pressure in the Concerta 72 mg group was higher than any other group (increased 2.39 bpm), and there appears to be a dose dependent increase in the mean change from baseline with the 54 mg group demonstrating a similar increase to placebo (0.71 vs 0.73).

Again, there appears to be a dose dependent increase when looking at the mean change in diastolic pressure as seen in Table A-11. Both the 54 mg and 72 mg Concerta groups demonstrated the greatest mean increase in change from baseline (at 2.13 mmHg and 4 mmHg, respectively) compared to placebo (1.36 mmHg).

As seen in Table A-12, pulse rates were increased at a statistically significant level for the Concerta groups combined compared to placebo when comparing the mean change from baseline at the end of the double blind phase ($p=0.0261$). There is a dose dependent increase in mean blood pressure observed up to the Concerta 54 mg group, and in this data set, a dip in mean pulse rate in the 72 mg group comparable to the 18 mg group dose group.

Body Weight and Height

Body Weight was measured at 4 week intervals in Studies 01-146, 98-019 and for the first 3 months of Study 99-018. Table A-13 demonstrates that there was a statistically significant decrease in the mean change from baseline of body weight when comparing all Concerta groups with placebo ($p <0.001$) in the two week placebo controlled portion of Study 01-146. These changes appear to be dose dependent, with the highest change from baseline being the 72 mg Concerta group (-4.41 compared to placebo mean change of -0.02).

As would be expected, because of the time period of 3-4 weeks, there was no change from baseline in height observed in the placebo controlled portion of study 01-146 (see Table A-14).

Z-Scores

Another perspective of growth can be obtained by analyzing the height and weight growth chart using the value of **z-scores**. (The following explanation of z-scores was obtained from an FDA review by Gerard Boehm, MD, MPH: NDA 19839: 9/3/03) The z-score is defined as the number of standard deviations from the population mean for a specific patient's weight based on gender and age. This analysis uses population data from CDC growth charts and allows a determination about whether study subjects are growing along their predicted growth curve. No change in mean z-score would indicate that subjects are

growing as predicted by data from age adjusted peers. Decreases in mean z-score would indicate that subjects are lagging behind in growth.

Z-scores for Study 0-0146 were not able to be located in the ISS of this submission.

The sponsor separated out the two age groups of children (5-12 y.o.) and adolescents (13-17 y.o.) for the pooled data of Study 98-019 and Study 99-018.

Weight

As can be seen from Table A-15, for the children age group, the mean baseline weight z-score was +0.06 (or mean percentile of 52.4 with n=1097). At the end of the study (using last observation carried forward analysis), the mean z-score was -0.09 (i.e. a mean percentile of 46.4). This data shows that, as a group, children exposed to Concerta in this safety data base had a mean **decrease of 6 percentiles in weight**; further suggesting that Concerta does have an effect on the weight growth of children.

For **adolescents (**see Table A-16), the mean baseline **weight z-score** was 0.30 (i.e. a mean percentile of 61.8 with n=269). At the end of the study (using LOCF analysis), the mean z-score was 0.31 (i.e. a mean percentile of 62.2 with n=266). These findings may suggest that, in this data base, there was little effect on weight for adolescents when exposed to Concerta (assuming that they were compliant with treatment).

Height

As can be seen in Table A-17, the mean baseline **height** z-score for **children** was -0.04 (i.e. a mean percentile of 48.4 with n=1108). At the end of the studies (using an LOCF analysis), the mean z-score was -0.06 (or a mean percentile of 47.6 with n=1097). These finding suggest that the mean height decreased by 0.8 percentile, suggesting that there was a slight effect on height for the longer term use of Concerta.

For adolescents height (see Table A-18), at baseline the height z-score was 0.00 (or a mean percentile of 50 with n=269). At the end of the study (using an LOCF analysis), the mean z-score was +0.05 (or mean percentile of 52.0 with n=266). This finding might suggest that adolescent patients taking Concerta had a slight increase in 2.0 percentile in height compared to established national standards.

Comments on weight and height z-score analysis

Although the mean duration of treatment with Concerta for children was calculated at 10.4 month (315.6 days), and the mean duration for Concerta for adolescents was 7.5 months (229.3 days), it is difficult to make clear interpretations from this data. It would appear that one flaw with this analysis is that there was a last observation carried forward analysis with no built in method to assess at what point patients withdrew. Therefore, it is difficult to make conclusions based on time of exposure, as it would appear that the analysis did not take this into account.

It would also be helpful to have an independent FDA review of this growth data. In addition, it would be helpful to calculate z-scores for Study 0-0146, to be able to assess effects of the higher dose groups (such as 72 mg dose).

4. ECGs

ECGs were performed during Study 01-146 at the screening visit, the end of the two week placebo controlled phase, and at the end of the open label follow-up phase. The only data in this submission was the percent of normal and abnormal ECG readings (See tables 10-34 and 10-35 in the ISS) and a line listing of abnormal ECGs. For a full line listing of abnormal ECGs in Study 01-146, please see Table A-19. The

sponsor included a cardiologist's consult; it appears that the cardiologist only evaluated the ECGs determined to be abnormal (it is unclear if these were originally machine read or read by a physician/technician). The sponsor's cardiology consultant stated that all of the ECGs he reviewed were "normal or … compatible with a normal variant."

Because there is so little ECG data from patients on methylphenidate or its derivatives (a MedLine search revealed no literature on this topic), this ECG data merits a closer look. It would be most helpful if the sponsor could re-evaluate this data assessing the mean changes of cardiac intervals, especially the QTc, to allow for some measure to assess the potential for any cardiac event (e.g. ventricular arrthymias).

5. Withdrawal reactions and abuse potential

There was no new data included in this submission.

6. Human Reproduction Data

There was no new data included in this submission.

7. Overdose experience

There was no new data included in this submission.

G. Adequacy of Safety Testing (adequacy of patient exposure and assessments)

The sponsor did not provide an exposure time for the Concerta 72 mg daily dosing. It appears that the exposure was very low for this higher dose with 90 patients exposed for less than 90 days, and only 7 patients were exposed for up to 180 days. There were no patients exposed to 72 mg daily dose for greater than 180. This is a seen as a severe limitation, as ADHD has been recognized as a long term illness often requiring years of treatment.

It is also noted that non-Caucasian and females are under-represented in this NDA data base.

H. Summarize Critical Safety Findings and Limitations of Data

In the two week placebo controlled portion of Study 01-146, there were dose dependent increases in systolic and diastolic blood pressure with the highest changes observed in the Concerta 72 mg group. A dose dependent decrease in body weight was also observed in this two week time period.

Unfortunately, z-scores were not calculated for Study 01-146 to assess the effects of Concerta 72 mg daily. The sponsor's calculation of z-scores for the two open label studies (maximum dose of 54 mg daily) suggested that there was a decrease of 6 percentiles in weight and a decrease of 0.8 percentile in height for children (mean duration was 10.4 months). Z-scores for adolescents suggested that there was little effect on height or weight for adolescents.

VIII. Dosing, Regimen, and Administration Issues

It is interesting to note that although the protocol set the maximum dose of Concerta at 54 mg, there were 13 patients who received a dosing of $\geq$ 72 mg Concerta; eleven of these patients were aged 5-13 (mean exposure of 3.3 days). It is concerning that the sponsor allowed the dosing to reach this level. It would seem these children were titrated to the highest dose because there was poor efficacy at lower doses, and, in all likelihood, this medication was not helpful for them, as evidenced by the low exposure time. It is concerning that these younger children were unnecessarily exposed to these higher doses.

IX. Use in Special Populations

A. Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation

From the efficacy data presented, it appears that girls did not have as robust a response to Concerta than was seen in boys. For the efficacy evaluation, girls made up 20.5% of the population assessed; however, it could be argued that this percentage is reflective of the clinical presentation as the majority of patients diagnosed with ADHD are male.

B. Evaluation Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy

The efficacy results for non-Caucasians did not show a statistical significance. The sponsor suggests that the non-Caucasian population was too small to show a difference. Certainly, non-Caucasians were under-represented in the efficacy portion as only 14.5% of patients were African –American and 11.4% were "other."

C. Evaluation of Pediatric Program

Efficacy and safety were only assessed in the adolescent age group for the higher dose of Concerta 72 mg daily.

X. Conclusions and Recommendations

Efficacy

The results of the two week placebo controlled portion of Study 01-146 support the claim that the dose of Concerta 72 mg daily is effective in adolescents. However, in the analysis pooling of all Concerta treatment groups, it appears that effectiveness was demonstrated primarily in Caucasian males. Females patients did not show as much improvement as male patients, and in the sponsor's analysis, females did not demonstrate a statistically significant change from baseline compared to placebo. Results from this study do not support the effectiveness of Concerta in non-Caucasian populations.

Safety

In the entire safety data base, there were 97 patients exposed to this higher dose of Concerta 72 mg of which 92 percent were exposed for less than 3 months; there were no patients exposed to the 72 mg dose for greater than 180 days. This become a major concern given that many individuals diagnosed with ADHD require long term treatment that could extend for years; therefore, it is important to establish a better safety profile for longer term use of this higher dose.

From the two week placebo controlled portion of Study 01-146, there was evidence of dose dependent increases in both systolic and diastolic blood pressure; there was also a statistically significant dose dependent weight loss observed in this short two week period.

Because most of the safety data was collected in open label studies, it makes the interpretation of findings difficult without a comparator control. Also, the majority of the safety data bank was based on studies that did not include the higher dose of Concerta 72 mg daily, but had a maximum dose of Concerta 54 mg. Using the analysis of z-scores to assess weight and height (based on established national standards), the sponsor concluded that, in the pooled safety data of the two open label studies only, children demonstrated a decrease in weight (by 6 percentiles) and, to a lesser extent, a decrease in height (< 1 percentile).

According to the sponsor's z-score analysis, there was a not an appreciable difference seen in adolescents for weight, and even a slight increase in height (2 percentiles).

As seen in the open label studies, there is a concern that younger children will be exposed to this higher dose of Concerta 72 mg, not just the adolescents. This makes it even more important for at least a sound safety profile in the population that it will be labeled for, especially given that there may be off-label use in the younger population.

Labeling

The following comments are based on the sponsor's proposed labeling

1. Under **Clinical Studies** Section

   a. In the subsection labeled "Children" (p. 5): it is misleading to refer to the laboratory investigators as "laboratory schoolteachers." Subjects enrolled in these studies are primarily not there to learn, but rather to be observed.

   b. In the subsection labeled "Adolescents" (p.6):
   - the first line should emphasize that this study contained only a two week placebo controlled portion.
   - The reference to a maximum mg/kg/day is misleading. The patients were dosed according to clinical improvement (titrated by a fixed mg dosing) and limiting adverse events, not by mg/kg/day.
   - (b) (4)

2. Under **Long Term Use** Section (p.7)

   The effectiveness of Concerta for long term use, i.e. for more than 4 weeks, has still not been systematically evaluated in controlled trials. (b) (4)

   (b) (4)

3. Under **Long-Term Suppression of** Growth Section (p.9)

   For the same reasons discussed in item 2 above , the paragraph on Long-Term Suppression of Growth should be kept. It should also be kept in mind that medications used for the treatment of ADHD may be used for many years, beyond the maximum of 24 months studied in these open label studies that were submitted.

4. Under **Adverse Reaction** Section (p.12)

   The sponsor has identified the patient exposure as (b) (4) This may be misleading suggesting that all of these ages have been adequately studied in controlled trials for safety and effectiveness. It would be more true to the data, if the sponsor listed ages that were included in placebo-controlled studies, and otherwise use general terms like "children", "adolescents" or "adults" to refer to adverse event exposure data.

5. Under **Adverse Findings in Clinical Trials** Section (p.13)

The description of the two open label studies is too detailed for this section, (b) (4) It is recommended that the labeling state "in uncontrolled studies up to 24 months with Concerta……"

6. Under the **Treatment-Emergent Adverse Events** Section (p.13)

It is recommended that the sponsor's proposed labeling be amended to reflect the incidence of 1% or more of adverse events. Please see Table A-8 (appendix) which is the 1% table from the placebo controlled portion of Study 01-146.

Table 5 is misleading, and it is recommended that if a 1% table be used, it should emphasize that the data was obtained during a 2-week placebo controlled portion of Study 01-146 rather (b) (4)

[Last paragraph on of this section on p. 15]: the sponsor's proposed labeling is misleading, suggesting that there (b) (4)

7. Under **Tics** Section (p.15):

It is recommended that the labeling retain the information regarding specifically children and the incidence of tics. It must be kept in mind that the pooling of Studies 5 and 6, although weighted towards children, included a significant number of adults and adolescents.

8. Under **Dosage and Administration** Section (p.16):

The sponsor's additional comment of "Based on an assessment of clinical benefit and tolerability, doses may be increased at weekly intervals for patients who have not achieved an optimal response at a lower dose," may unnecessarily encourage an increase in dosage when a lower dosage would be adequate as the phrase "optimal response" is quite vague; it recommended that language state "if needed for clinical response, titration to higher doses should occur weekly."

(b) (4). It is recommended that the sponsor present the maximum dosing in text form and emphasize that the labeling for the maximum dosing is for adolescents. If a table is used, it should also include the minimum dosing recommended.

A. Recommendations

It is recommended that the sponsor clarify the exposure data for this higher dose of Concerta 72 mg. It is also recommended that they conduct further studies to expand the safety exposure data by number of patients and length of time before this higher dosage is approved as a labeling change.

The following are additional recommendations for further safety review of the submitted studies:

1. Since there is such a sparse amount of literature on ECG changes with methylphenidate exposure, it is recommended that FDA further analyze this data the ECG data. Please see details for the requests to the sponsor in Appendix B.

2. It is recommended that there be an independent FDA review of the growth data. In addition, it would be helpful to calculate z-scores for Study 0-0146, to be able to assess effects of the higher dose groups (such as 72 mg dose). Please see details for the requests to the sponsor in Appendix C.

3. It is recommended that the sponsor submit detailed narratives of the six patients in Study 98-012 who had abnormal laboratory values including any follow-up history and laboratory values.

4. Because of a post-marketing report of a Concerta tablet being radio-opaque (see Post Marketing Section above), it is recommended that the sponsor confirm if Concerta tablets are radio-opague, and, if so, propose appropriate labeling changes

Appendices

Appendix A
Tables for the Safety Review Section

Table A-1 Summary of over all duration of exposure to Concerta or Placebo in all phases of Study 01-146 (excerpt from sponsor's table).

		CONCERTA[a, b]				
Duration, n	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA
Up to 2 weeks	73	203	144	88	22	15
>2 weeks-8 weeks	17	2	10	5	13	44
>8 weeks-12 weeks	0	6	34	36	41	73
>12 weeks-20 weeks	0	4	4	8	8	84

a: Subjects were titrated upward to an effective CONCERTA dose during the titration phase, and therefore may be counted in more than one dose group.

Table A-2 Demographic Summary for All patients at the Beginning the Titration Phase of Study 01-146 (excerpt from sponsor's table)

	CONCERTA				
Characteristic	18 mg (N=27)	36 mg (N=53)	54 mg (N=55)	72 mg (N=85)	Any CONCERTA (N=220)
Gender					
Male	21 (77.8%)	42 (79.2%)	46 (83.6%)	66 (77.6%)	175 (79.5%)
Female	6 (22.2%)	11 (20.8%)	9 (16.4%)	19 (22.4%)	45 (20.5%)
Race					
Caucasian	22 (81.5%)	39 (73.6%)	38 (69.1%)	64 (75.3%)	163 (74.1%)
African-American	3 (11.1%)	6 (11.3%)	9 (16.4%)	14 (16.5%)	32 (14.5%)
Other	2 (7.4%)	8 (15.1%)	8 (14.5%)	7 (8.2%)	25 (11.4%)
Age (y)					
Mean (SD)	14.8 (1.8)	14.5 (1.4)	14.5 (1.5)	14.9 (1.6)	14.7 (1.5)
Range	13.0-18.0	13.0-18.0	13.0-18.0	13.0-18.0	13.0-18.0

Note: Patients were titrated upward to an effective Concerta Dose during the titration phase, and may be counted in more than one dose group.

Table A-3 Summary of exposure in Studies 98-012 and 99-018 (excerpt from sponsor's table)

	CONCERTA				
Duration[a] of Treatment (days)	18 mg (N=777)	36 mg (N=1103)	54 mg (N=777)	>= 72 mg (N=13)	Any Dose (N=1514)
Children (5 - 12 years)					
N	568	809	552	11	1109
Mean	102.6	196.4	240.7	3.3	315.6
SD	146.5	184.3	204.8	5.6	219.7
Median	35.0	168.0	219.5	1.0	273.0
Min, Max	1, 793	1, 805	1, 855	1, 20	2, 856
Adolescents (13 - 17 years)					
N	115	191	145	1	269
Mean	54.8	148.5	186.0	22.0	229.3
SD	79.0	117.7	107.0	-	101.7
Median	27.0	167.0	226.0	22.0	267.0
Min, Max	1, 292	2, 703	1, 612	22, 22	3, 703
Adults (>= 18 years)					
N	94	103	80	1	136
Mean	55.9	94.7	156.2	1.0	202.2
SD	83.3	99.7	101.8	-	100.2
Median	22.5	46.0	188.0	1.0	255.5
Min, Max	1, 298	1, 295	1, 329	1, 1	1, 333

a: The date of the last dose - the date of the first + 1 for a specific dose group. A subject may have more than 1 time of a specific dose and durations were summed for this specific dose group. In Studies C-98-012 and C-99-018, subjects were permitted to change CONCERTA dose as needed clinically. Subjects therefore may be counted in more than one dose group.

A-4 Duration of Exposure for Studies 0-146, 98-012, and 99-018 (excerpt from sponsor's table)

	CONCERTA[a]				
Duration of Treatment	18 mg (N=992)	36 mg (N=1295)	54 mg (N=914)	>=72 mg (N=97)	Any Dose (N=1730)
Less than 90 days	779 (78.5%)	658 (50.8%)	362 (39.6%)	90 (92.8%)	425 (24.6%)
90 to < 180 days	63 (6.4%)	131 (10.1%)	104 (11.4%)	7 (7.2%)	170 (9.8%)
180 to < 360 days	118 (11.9%)	393 (30.3%)	340 (37.2%)	0 (0.0%)	845 (48.8%)
360 days or more	32 (3.2%)	113 (8.7%)	108 (11.8%)	0 (0.0%)	290 (16.8%)

a: In Studies C-98-012 and C-99-018, subjects were permitted to change CONCERTA dose as needed clinically. In Study 01-146, subjects were titrated upward to an effective CONCERTA dose during the titration phase. Subjects therefore may be counted in more than one dose group.

Table A-5 Summary of nonfatal serious adverse events occurring in the Studies 01-146

Patient	Serious Adverse Event
Study 01-146	
1022 13 y.o. female	Day 13 of 72 mg Cellulitis secondary to a bug bite
2024 16 y,o, female	Day 1 of 18 mg: depressed mood Day 3 of 18 mg: suicidal ideation Symptoms resolved after withdrawal from the study

Table A-6 Summary of nonfatal serious adverse events occurring in the Studies 98-012 and 99-018, open label studies.

Patient	Serious Adverse Event
C98012-019015 10 y.o. male	Day 291 at 54 mg Headache, fever and vomiting. Hospitalized and diagnosed with viral syndrome.
C98012-019047 14 y.o. male	Day 532 at 18 mg Diabetic Ketoacidosis (1st episode); continued Concerta after hospitalization
C98012-019192 12 y.o. male	Day 168 on 54 mg Violent threat (threatened family members with a knife; continued Concerta after hospitalization)
C98012-19213 10 y.o. male	Day 109 on 36 mg Tracheitis
C98012-29121 10 y.o. male	Day 66 18 mg Hospitalized for viral infection
C98012-169025: 8 y.o. male	Day 75 on 18 mg Adenoiditis and Tonsilitis
C98012-169024 13 y.o. male	Day 75 on 18 mg Adenoiditis and Tonsilitis
C98012-169005 7 y.o. male	Day 207 on 36 mg Broken leg after motor vehicle accident
C98012-39011 9 y.o.	Day 13 on 18 mg Viral menigitis
C99018-11407 51 y.o. male	Day 195, 54 mg Broken Ribs and pneumothorax after accidental falling off ladder
C99-018-12208 7 y.o. male	Day 262, 36 mg Bacterial pneumonia
C99018-13804 9 y.o. male	Day 202, 54 mg Acute appendicitis
C99018-14405 14 y.o.male	Day 262, 18 mg Diabetes mellitus (new onset)
C99018-17803 16 y.o. female	Day 82, 36 mg Elective bilateral uretheral reimplantation
C99018-18605 11 y.o. male	Day 73, 36 mg Appendicitis Day 88, 36 mg: Gastroenteritis

Patient	Serious Adverse Event
C99018-19607 14 y.o. male	Day 213, 54 mg, On drug holiday for 3 weeks prior to event Depression with suicidal
C99018-20607 10 y.o. female	Day 135, 36 mg Appendicitis

Note: Because there were some inconsistencies between these narratives from Appendix B of the ISS and Summary Table 5-26 in the ISS, this table is based on the narratives from Appendix B of the ISS

Table A-7 Withdrawals due to adverse events in the titration phase and open label phase of study 01-146 (excerpt from sponsor's table)

Subject ID (01146-)	Age/Gender/ Race	Relative Days[a]	CONCERTA Dose/Exposure mg (mg/kg)	Adverse Experience
1015	14 y / M / C	55[b]	72 mg (1.215)	Headache
		14	36 mg (0.608)	Irritability
2003	17 y / M / A	21	72 mg (1.184)	Feeling Dehydrated
		21	72 mg (1.184)	Lethargy
3021	13 y / M / C	1	18 mg (0.298)	Lethargy
		1	18 mg (0.298)	Increased Anger
4001	15 y / F / C	16	54 mg (1.025)	Joint Pain
		15	54 mg (1.025)	Lethargy
		15	54 mg (1.025)	Upset Stomach
		20	54 mg (1.025)	Headache
12006	14 y / F / C	8	36 mg (0.762)	Dizziness
		8	36 mg (0.762)	Shaky Hands
12015	18 y / F / O	4	18 mg (0.412)	Weight Loss (Lost 4lbs)
		4	18 mg (0.412)	Anxiety
		4	18 mg (0.412)	Mild Depression
12024	16 y / F / C	1	18 mg (0.235)	Depressed Mood
		3	18 mg (0.235)	Suicidal Ideation
13008	15 y / M / C	2	18 mg (0.300)	Hallucinations (Visual)
		2	18 mg (0.300)	Light-Headedness
1004	14 y / M / C	2	72 mg (0.985)	Overfocusing
2001	13 y / M / C	7	72 mg (1.101)	Mild Depression
2009	16 y / M / C	1	54 mg (0.725)	Decreased Appetite
		1	54 mg (0.725)	Depressed Feeling
4007	17 y / M / A	7	72 mg (1.079)	Appetite Decrease
5001	14 y / F / C	13	72 mg (1.002)	Irritability
6006	13 y / M / C	33	36 mg (0.886)	Loss Of Appetite
		1	36 mg (0.886)	Malaise
6011	16 y / M / C	3	72 mg (0.620)	Elevated Blood Pressure
7005	14 y / M / C	29	36 mg (0.637)	Anorexia
7007	14 y / M / C	1	18 mg (0.209)	Worsening Of Symptoms Of Depression
10009	13 y / M / C	28	72 mg (0.909)	Weight Changes (Inc)
		28	72 mg (0.909)	Irritability
		28	72 mg (0.909)	Mood Swings
		28	72 mg (0.909)	Aggression
13001	14 y / M / H	49	36 mg (0.595)	Vomiting
13002[b]	13 y / M / C	1	54 mg (1.166)	Headache

Table A-8 Adverse Events in controlled portion of Study 01-146 occurring in at least 1% of Concerta patients.

Body System	Placebo (N=90) n (%)	CONCERTA 18 mg (N=5) n (%)	CONCERTA 36 mg (N=25) n (%)	CONCERTA 54 mg (N=24) n (%)	CONCERTA 72 mg (N=33) n (%)	CONCERTA Any CONCERTA (N=87) n (%)	p-Value[a]
Any adverse event	27 (30.0%)	3 (60.0%)	10 (40.0%)	10 (41.7%)	14 (42.4%)	37 (42.5%)	0.088
Body as a whole	20 (22.2%)	2 (40.0%)	6 (24.0%)	5 (20.8%)	8 (24.2%)	21 (24.1%)	0.859
Abdominal pain	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (3.0%)	2 (2.3%)	1.000
Accidental injury	3 (3.3%)	0 (0.0%)	2 (8.0%)	1 (4.2%)	2 (6.1%)	5 (5.7%)	0.492
Allergic reaction	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Asthenia	2 (2.2%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	0 (0.0%)	2 (2.3%)	1.000
Chest pain	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Fever	0 (0.0%)	1 (20.0%)	0 (0.0%)	2 (8.3%)	0 (0.0%)	3 (3.4%)	0.117
Flu syndrome	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Headache	7 (7.8%)	1 (20.0%)	3 (12.0%)	1 (4.2%)	3 (9.1%)	8 (9.2%)	0.792
Pain	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	1.000
Digestive system	2 (2.2%)	0 (0.0%)	5 (20.0%)	3 (12.5%)	3 (9.1%)	11 (12.6%)	0.009
Anorexia	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.2%)	0 (0.0%)	2 (2.3%)	0.240
Diarrhea	0 (0.0%)	0 (0.0%)	1 (4.0%)	1 (4.2%)	0 (0.0%)	2 (2.3%)	0.240
Dyspepsia	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Gastrointestinal disorder	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Increased appetite	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	0.492
Nausea	2 (2.2%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	1.000
Tooth caries	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	0.492
Vomiting	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	1 (3.0%)	3 (3.4%)	0.117
Musculoskeletal system	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Myalgia	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	0 (0.0%)	1 (1.1%)	0.492
Nervous system	7 (7.8%)	1 (20.0%)	0 (0.0%)	4 (16.7%)	3 (9.1%)	8 (9.2%)	0.792
Agitation	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	0.492
Anxiety	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (1.1%)	0.492
Dizziness	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	0.492
Insomnia	0 (0.0%)	1 (20.0%)	0 (0.0%)	3 (12.5%)	0 (0.0%)	4 (4.6%)	0.056
Neurosis	1 (1.1%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (1.1%)	1.000
Tremor	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	0.492
Respiratory system	3 (3.3%)	1 (20.0%)	0 (0.0%)	1 (4.2%)	3 (9.1%)	5 (5.7%)	0.492
Pharyngitis	1 (1.1%)	1 (20.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	2 (2.3%)	0.617
Rhinitis	2 (2.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (9.1%)	3 (3.4%)	0.679
Urogenital system	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.0%)	2 (2.3%)	0.240
Dysmenorrhea	0 (0.0%)	0 (0.0%)	1 (4.0%)	0 (0.0%)	1 (3.0%)	2 (2.3%)	0.240

[a]: Fisher's-Exact Test: Any CONCERTA vs Placebo at Onset of AE

Table A-9 Summary of out-of-reference range post-treatment laboratory test for children and adolescents in Study 98-012.

	At Baseline N=428	Month 6 N=335	Month 12 N=285	Completion/ Termination N=235
WBC				
# (%) within reference range	401 (93.7%)	302 (90.1%)	268 (94.0%)	215 (91.5%)
# (%) below reference range	26 (6.1%)	33 (9.9%)	14 (4.9)	17 (7.2)
# (%) above reference range	1 (0.2)	0	3 (1.1)	3 (1.3)
Platelet Count				
# (%) **within** reference range	413 (96.5)	315 (94)	267 (94)	228 (97)
# (%) **below** reference range	0	0	0	0
# (%) **above** reference range	15 (3.5)	20 (6.0)	17 (6.0)	7 (3.0)
Hemoglobin				
# (%) **within** reference range	415 (97)	321 (95.8)	267 (93.7)	225 (95.7)
# (%) **below** reference range	13 (3.0)	14 (4.2)	18 (6.3)	10 (4.3)
# (%) a**bove** reference range	0	0	0	0
AST (SGOT)				
# (%) **within** reference range	416 (97.2)	315 (94.6)	271 (95.1)	224 (96.6)
# (%) **below** reference range	0	0	0	0
# (%) a**bove** reference range	12 (2.8)	18 (5.4)	14 (4.9)	8 (3.4)
ALT (SGPT)				
# (%) **within** reference range	422 (98.6)	327 (98.2)	282 (98.9)	226 (97.4)
# (%) **below** reference range	1 (0.2)	1 (0.3)	0	1 (0.4)
# (%) a**bove** reference range	5 (1.2)	5 (1.5)	3 (1.1)	5 (2.2)

Table A-10 Changes in systolic blood pressure comparing baseline and the end of placebo controlled portion of Study 01-146 (excerpt from sponsor's table)

			CONCERTA				
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA
Baseline	N	90	5	24	24	33	86
	Mean	112.56	116.00	111.29	111.00	113.58	112.36
	SD	9.95	12.06	8.92	8.51	12.43	10.41
	Min, Max	84, 143	107, 134	94, 135	93, 132	76, 132	76, 135
End of Randomized Double-Blind Phase[a]	N	89	5	25	24	33	87
	Mean	113.29	105.80	112.04	111.71	115.97	113.08
	SD	9.14	6.91	10.31	10.46	10.55	10.47
	Min, Max	91, 133	98, 117	92, 136	91, 132	91, 136	91, 136
Change from Baseline at End of Randomized Double-Blind Phase[a]	N	89	5	24	24	33	86
	Mean	0.73	-10.20	0.58	0.71	2.39	0.69
	SD	9.75	10.89	9.32	9.58	8.08	9.30
	Min, Max	-32, 26	-29, -3	-22, 17	-17, 21	-16, 15	-29, 21
Distribution of Change at End of Randomized Double-Blind Phase[a]	≤0	42 (47.2%)	5 (100%)	11 (45.8%)	14 (58.3%)	15 (45.5%)	45 (52.3%)
	1 - 4	15 (16.9%)	0 (0.0%)	3 (12.5%)	1 (4.2%)	2 (6.1%)	6 (7.0%)
	5 - 8	19 (21.3%)	0 (0.0%)	6 (25.0%)	3 (12.5%)	9 (27.3%)	18 (20.9%)
	9 - 12	5 (5.6%)	0 (0.0%)	2 (8.3%)	5 (20.8%)	4 (12.1%)	11 (12.8%)
	13 - 16	3 (3.4%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	3 (9.1%)	4 (4.7%)
	17 - 20	3 (3.4%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	0 (0.0%)	1 (1.2%)
	21 - 26	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	0 (0.0%)	1 (1.2%)

Table A-11 Changes in diastolic blood pressure comparing baseline and the end of placebo controlled portion of Study 01-146 (excerpt from sponsor's table)

			CONCERTA				
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA
Baseline	N	90	5	24	24	33	86
	Mean	61.66	61.00	61.08	62.42	61.18	61.49
	SD	7.95	4.30	6.69	7.33	8.94	7.61
	Min, Max	45, 82	57, 68	51, 76	51, 80	44, 81	44, 81
End of Randomized Double-Blind Phase[a]	N	89	5	25	24	33	87
	Mean	63.02	60.40	62.96	64.54	65.18	64.09
	SD	6.91	5.41	8.28	8.47	9.41	8.62
	Min, Max	46, 85	55, 68	42, 80	52, 82	46, 84	42, 84
Change from Baseline at End of Double-Blind Phase[a]	N	89	5	24	24	33	86
	Mean	1.36	-0.60	1.92	2.13	4.00	2.63
	SD	6.82	7.40	8.17	8.77	9.40	8.73
	Min, Max	-13, 17	-10, 7	-19, 16	-17, 18	-14, 26	-19, 26
Distribution of Change at End of Randomized Double-Blind Phase[a]	≤0	41 (46.1%)	3 (60.0%)	8 (33.3%)	12 (50.0%)	12 (36.4%)	35 (40.7%)
	1 - 4	18 (20.2%)	0 (0.0%)	6 (25.0%)	3 (12.5%)	7 (21.2%)	16 (18.6%)
	5 - 8	19 (21.3%)	2 (40.0%)	6 (25.0%)	2 (8.3%)	5 (15.2%)	15 (17.4%)
	9 - 12	7 (7.9%)	0 (0.0%)	3 (12.5%)	4 (16.7%)	4 (12.1%)	11 (12.8%)
	13 - 16	2 (2.2%)	0 (0.0%)	1 (4.2%)	2 (8.3%)	2 (6.1%)	5 (5.8%)
	17 - 20	2 (2.2%)	0 (0.0%)	0 (0.0%)	1 (4.2%)	1 (3.0%)	2 (2.3%)
	21 - 26	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	2 (6.1%)	2 (2.3%)

Table A-12 Changes in pulse comparing baseline and the end of placebo controlled portion of Study 01-146 (excerpt from sponsor's table)

			CONCERTA					
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value
Baseline	N	90	5	24	24	33	86	
	Mean	74.74	71.60	75.46	79.58	76.45	76.77	
	SD	9.17	5.50	11.87	14.36	8.14	11.17	
	Min, Max	56, 96	67, 80	59, 96	53, 123	58, 96	53, 123	
End of Randomized Double-Blind Phase[a]	N	89	5	25	24	33	87	
	Mean	77.43	75.60	82.08	86.42	80.85	82.44	
	SD	11.78	11.37	9.81	13.76	11.19	11.76	
	Min, Max	56, 110	63, 94	65, 105	57, 119	57, 100	57, 119	
Change from Baseline at End of Randomized Double-Blind Phase[a]	N	89	5	24	24	33	86	
	Mean	2.82	4.00	5.67	6.83	4.39	5.41	0.0261[b]
	SD	11.00	9.82	10.54	12.06	12.27	11.48	
	Min, Max	-22, 30	-4, 20	-11, 28	-14, 29	-21, 28	-21, 29	
Distribution of Change at End of Randomized Double-Blind Phase[a]	≤1	44 (49.4%)	2 (40.0%)	8 (33.3%)	7 (29.2%)	12 (36.4%)	29 (33.7%)	
	2 - 6	18 (20.2%)	2 (40.0%)	9 (37.5%)	6 (25.0%)	7 (21.2%)	24 (27.9%)	
	7 - 11	10 (11.2%)	0 (0.0%)	0 (0.0%)	2 (8.3%)	4 (12.1%)	6 (7.0%)	
	12 - 16	8 (9.0%)	0 (0.0%)	2 (8.3%)	4 (16.7%)	6 (18.2%)	12 (14.0%)	
	17 - 21	2 (2.2%)	1 (20.0%)	3 (12.5%)	2 (8.3%)	1 (3.0%)	7 (8.1%)	
	22 - 26	2 (2.2%)	0 (0.0%)	1 (4.2%)	1 (4.2%)	1 (3.0%)	3 (3.5%)	
	27 - 30	5 (5.6%)	0 (0.0%)	1 (4.2%)	2 (8.3%)	2 (6.1%)	5 (5.8%)	0.1387[c]

Table A-13 Changes in weight comparing baseline and the end of placebo controlled portion of Study 01-146 (excerpt from sponsor's table).

			CONCERTA					
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value
Baseline	N	90	5	25	24	33	87	
	Mean	144.81	147.84	140.03	142.78	152.21	145.86	
	SD	40.58	11.39	38.64	28.90	37.95	34.79	
	Min, Max	77, 284	131, 162	75, 256	88, 199	112, 274	75, 274	
End of Randomized Double-Blind Phase[a]	N	88	5	25	24	33	87	
	Mean	144.78	146.60	138.65	138.12	147.80	142.43	
	SD	41.19	10.30	38.87	28.20	38.76	34.92	
	Min, Max	76, 287	130, 157	75, 257	88, 196	107, 271	75, 271	
Change from Baseline at End of Randomized Double-Blind Phase[a]	N	88	5	25	24	33	87	
	Mean	-0.02	-1.24	-1.38	-4.66	-4.41	-3.43	<0.0001[b]
	SD	3.29	2.37	2.53	4.03	4.70	4.11	
	Min, Max	-6, 12	-5, 0	-7, 3	-13, 2	-12, 9	-13, 9	
Distribution of Change at End of Randomized Double-Blind Phase[a]	≥-13.0 to ≤-7.0	0 (0.0%)	0 (0.0%)	1 (4.0 %)	5 (20.8%)	11 (33.3%)	17 (19.5%)	
	>-7.0 to ≤-2.0	25 (28.4%)	1 (20.0%)	10 (40.0%)	12 (50.0%)	13 (39.4%)	36 (41.4%)	
	>-2.0 to ≤3.0	51 (58.0%)	4 (80.0%)	14 (56.0%)	6 (25.0%)	7 (21.2%)	31 (35.6%)	
	>3.0 to ≤8.0	9 (10.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	
	>8.0 to ≤12.0	3 (3.4 %)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	1 (1.1%)	<0.0001[c]

Table A-14 Change in Height (in inches) from baseline at the end of the double blind phase Study 01-146 (excerpt from sponsor's table)

			CONCERTA					
	Statistics	Placebo	18 mg	36 mg	54 mg	72 mg	Any CONCERTA	p-Value[a]
Baseline	N	90	5	25	24	33	87	
	Mean	66.03	66.50	65.79	65.87	67.10	66.35	
	SD	3.79	5.04	4.04	3.66	3.43	3.75	
	Min, Max	56, 74	62, 74	59, 72	59, 73	61, 74	59, 74	
End of Randomized Double-Blind Phase[b]	N	88	5	25	24	33	87	
	Mean	66.07	66.40	65.91	66.04	67.05	66.40	
	SD	3.81	5.16	4.00	3.69	3.43	3.74	
	Min, Max	56, 74	61, 74	59, 72	59, 73	61, 74	59, 74	
Change from Baseline at End of Randomized Double-Blind Phase[b]	N	88	5	25	24	33	87	
	Mean	0.09	-0.10	0.12	0.17	-0.05	0.06	0.5216
	SD	0.41	0.22	0.39	0.49	0.36	0.41	
	Min, Max	-2, 1	-1, 0	-1, 1	-1, 2	-1, 1	-1, 2	

Table A-15 Summary of weight and corresponding z-scores for children (5-12) in Studies 98-012 and 99-018 (excerpt from sponsor's table)**.**

Measurement	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	End of Study[a]
Absolute Weight (kg)										
N	1107	1090	991	917	846	764	281	246	88	1097
Mean	34.19	34.10	34.15	34.18	35.09	35.89	36.18	38.50	41.03	37.02
SD	10.69	10.78	10.86	10.88	11.66	11.43	11.46	12.34	12.34	12.17
Median	31.78	31.65	31.40	31.55	32.27	33.07	33.70	34.80	38.50	34.05
Maximum	97.38	90.35	98.06	101.24	103.97	88.40	90.30	95.90	83.00	105.33
Minimum	14.76	14.98	14.53	14.76	14.98	15.44	20.00	20.80	22.40	15.44
Weight Percentile Change										
N		1088	989	915	844	764	280	245	88	1095
Mean		-2.23	-3.31	-4.39	-4.57	-4.52	-7.07	-7.07	-7.24	-3.92
SD		7.56	8.17	9.40	11.01	12.00	12.30	12.97	16.39	12.08
Median		-1.46	-2.15	-3.15	-3.52	-3.09	-5.36	-5.39	-5.00	-2.42
Maximum		70.17	69.15	90.37	80.63	42.90	45.89	33.00	34.20	50.48
Minimum		-53.52	-51.78	-56.74	-58.46	-66.16	-65.89	-56.97	-68.44	-68.44
Standardized Weight (Z-score)										
N	1107	1090	991	917	846	764	281	246	88	1097
Mean	0.06	-0.02	-0.06	-0.11	-0.14	-0.13	-0.08	-0.05	-0.08	-0.09
SD	1.09	1.11	1.10	1.10	1.10	1.08	1.11	1.13	1.06	1.12
Median	0.03	-0.07	-0.10	-0.13	-0.17	-0.16	-0.14	-0.14	-0.07	-0.12
Maximum	3.40	3.64	3.05	3.12	3.16	2.84	2.80	2.88	2.54	3.64
Minimum	-3.98	-3.99	-4.61	-4.50	-4.21	-4.10	-3.12	-3.17	-3.27	-4.10
Change from Baseline (Z-score)										
N		1088	989	915	844	764	280	245	88	1095
Mean		-0.08	-0.12	-0.16	-0.17	-0.17	-0.26	-0.25	-0.24	-0.15
SD		0.32	0.30	0.34	0.40	0.41	0.40	0.42	0.52	0.43
Median		-0.07	-0.11	-0.15	-0.17	-0.17	-0.25	-0.26	-0.22	-0.12
Maximum		3.09	3.21	3.59	3.18	1.56	1.62	1.13	1.04	3.09
Minimum		-2.99	-2.61	-3.14	-3.26	-3.32	-2.42	-2.10	-2.02	-3.32

Table A-16 Summary of weight and corresponding z-scores for adolescents in Studies 98-012 and 99-018 (excerpt from sponsor's table)**.**

Measurement	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	End of Study[a]
Absolute Weight (kg)										
N	269	265	238	230	213	193	4	4	1	266
Mean	60.35	60.13	60.63	61.23	62.34	63.86	53.43	58.80	59.60	63.15
SD	16.78	16.67	16.77	16.66	16.83	17.00	11.54	10.07	NA	16.41
Median	58.11	58.57	59.14	59.93	59.93	61.83	50.55	55.60	59.60	60.84
Maximum	119.86	118.95	122.13	123.49	118.58	121.22	69.80	73.40	59.60	123.49
Minimum	29.96	20.88	32.23	32.23	33.60	34.28	42.80	50.60	59.60	33.82
Weight Percentile Change										
N		265	238	230	213	193	4	4	1	266
Mean		-0.98	-1.20	-0.93	-0.20	0.10	-8.07	1.66	-4.32	0.52
SD		6.32	5.57	6.39	8.35	8.82	8.86	7.67	NA	8.27
Median		-0.40	-0.41	-0.24	0.03	0.06	-9.88	3.71	-4.32	0.15
Maximum		18.44	16.72	29.22	28.00	28.06	3.55	8.53	4.32	29.22
Minimum		-72.37	-18.48	-18.56	-23.64	-29.27	-16.05	-9.31	-4.32	-29.27
Standardized Weight (Z-score)										
N	269	265	238	230	213	193	4	4	1	266
Mean	0.30	0.23	0.26	0.27	0.28	0.34	-0.01	0.27	0.29	0.31
SD	1.17	1.28	1.16	1.16	1.18	1.17	1.01	0.78	NA	1.14
Median	0.32	0.29	0.32	0.33	0.29	0.31	-0.22	-0.01	0.29	0.29
Maximum	2.97	2.93	2.98	2.94	2.93	2.87	1.37	1.41	0.29	2.87
Minimum	-2.63	-8.39	-2.63	-2.47	-2.47	-2.49	-1.00	-0.30	0.29	-2.49
Change from Baseline (Z-score)										
N		265	238	230	213	193	4	4	1	266
Mean		-0.06	-0.05	-0.03	-0.00	0.01	-0.21	0.08	-0.12	0.02
SD		0.57	0.19	0.22	0.29	0.31	0.30	0.23	NA	0.29
Median		-0.03	-0.04	-0.03	0.00	0.01	-0.29	0.16	-0.12	0.01
Maximum		0.47	0.42	0.82	0.99	0.99	0.20	0.24	0.12	0.99
Minimum		-8.99	-0.58	-1.10	-0.91	-0.90	-0.46	-0.24	-0.12	-0.90

a: Last measure after the first dose of the study medication during the study.

Table A-17 Summary of height and corresponding z-scores for children (5-12) in Studies 98-012 and 99-018 (excerpt from sponsor's table).

Measurement	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	End of Study[a]
Absolute Height (cm)										
N	1108	1087	988	915	843	768	282	246	87	1097
Mean	137.52	138.11	138.57	139.00	140.33	141.62	141.52	144.46	148.29	142.61
SD	11.69	11.71	11.96	12.07	12.49	12.50	11.99	12.35	11.97	12.84
Median	137.16	137.50	138.42	138.43	139.60	140.80	140.20	142.50	146.60	141.99
Maximum	180.00	181.00	182.00	182.50	182.63	184.60	171.40	177.00	172.90	185.00
Minimum	102.87	104.14	104.14	104.14	105.92	105.41	115.40	117.00	126.00	105.41
Height Percentile Change										
N		1086	988	915	843	768	282	246	87	1096
Mean		0.19	0.26	0.14	-0.35	-0.47	-2.06	-2.18	0.81	-0.69
SD		6.72	8.03	7.82	9.08	9.87	9.25	11.44	13.39	10.90
Median		-0.18	-0.17	-0.11	-0.21	-0.43	-1.47	-1.93	0.13	-0.74
Maximum		55.79	69.22	64.64	63.92	62.78	30.83	33.71	42.76	62.78
Minimum		-60.81	-71.87	-59.16	-71.67	-34.57	-34.34	-37.33	-28.26	-71.67
Standardized Height (Z-score)										
N	1108	1087	988	915	843	768	282	246	87	1097
Mean	-0.04	-0.04	-0.04	-0.04	-0.05	-0.06	-0.06	-0.05	-0.07	-0.06
SD	1.02	1.00	1.02	1.02	1.05	1.03	1.02	1.04	0.91	1.02
Median	-0.05	-0.05	-0.07	-0.06	-0.12	-0.08	-0.09	-0.04	-0.04	-0.07
Maximum	3.29	3.36	3.29	3.23	6.41	3.30	3.30	3.61	2.16	4.18
Minimum	-3.57	-3.62	-3.56	-3.58	-3.69	-3.54	-3.58	-3.59	-2.59	-3.53
Change from Baseline (Z-score)										
N		1086	988	915	843	768	282	246	87	1096
Mean		0.01	0.01	0.00	-0.00	-0.02	-0.07	-0.08	0.03	-0.02
SD		0.23	0.28	0.27	0.38	0.34	0.30	0.37	0.41	0.38
Median		-0.01	-0.01	-0.01	-0.02	-0.03	-0.08	-0.10	0.01	-0.04
Maximum		2.26	2.41	1.93	5.83	2.16	0.90	0.99	1.23	3.43
Minimum		-1.98	-2.36	-1.93	-2.31	-1.07	-0.89	-1.10	-0.76	-2.36

Table A-18 Summary of height and corresponding z-scores for adolescents (aged) in Studies 98-012 and 99-018 (excerpt from sponsor's table).

Measurement	Baseline	Month 1	Month 2	Month 3	Month 6	Month 9	Month 12	Month 18	Month 24	End of Study[a]
Absolute Height (cm)										
N	269	265	238	229	213	193	4	4	1	266
Mean	165.99	166.70	167.28	167.87	168.48	169.44	166.80	171.35	177.20	168.88
SD	11.20	10.85	10.75	10.69	10.76	10.71	2.94	4.10	NA	10.68
Median	166.37	167.00	167.64	168.40	168.91	170.18	167.65	171.85	177.20	170.18
Maximum	197.61	197.61	198.88	198.88	200.66	201.42	169.10	175.50	177.20	201.42
Minimum	128.50	139.70	138.43	140.97	141.48	142.75	162.80	166.20	177.20	138.43
Height Percentile Change										
N		265	238	229	213	193	4	4	1	266
Mean		0.69	0.98	1.63	0.88	1.41	3.01	8.90	13.24	1.31
SD		7.70	7.37	8.53	9.06	11.33	11.36	11.34	NA	10.76
Median		-0.14	-0.07	0.03	-0.15	0.00	-0.26	5.78	13.24	0.00
Maximum		83.32	85.29	83.26	81.54	82.10	19.35	23.94	13.24	82.10
Minimum		-55.47	-12.59	-13.09	-28.56	-79.51	-6.79	0.09	13.24	-79.51
Standardized Height (Z-score)										
N	269	265	238	229	213	193	4	4	1	266
Mean	-0.00	0.03	0.06	0.08	0.06	0.11	0.17	0.35	0.93	0.05
SD	1.17	1.14	1.12	1.13	1.16	1.14	0.48	0.60	NA	1.14
Median	0.05	0.09	0.11	0.12	0.06	0.19	0.23	0.45	0.93	0.11
Maximum	4.24	4.19	4.33	4.28	4.38	4.38	0.62	0.86	0.93	4.38
Minimum	-4.65	-3.24	-3.00	-3.02	-3.03	-2.76	-0.38	-0.34	0.93	-3.24
Change from Baseline (Z-score)										
N		265	238	229	213	193	4	4	1	266
Mean		0.03	0.05	0.07	0.04	0.06	0.07	0.25	0.43	0.05
SD		0.43	0.41	0.43	0.46	0.56	0.32	0.30	NA	0.53
Median		-0.01	-0.00	0.00	-0.02	0.00	-0.01	0.18	0.43	0.00
Maximum		5.62	5.70	5.62	5.55	5.57	0.52	0.63	0.43	5.57
Minimum		-3.38	-0.82	-0.56	-0.78	-3.28	-0.22	0.00	0.43	-3.38

Table A-19 Line listings of abnormal ECGs in Study 01-146 (excerpt from sponsor's table)

Subject ID	Treatment (Placebo or CONCERTA)	Visit[a]	ECG Date	Comments
Subjects Receiving Placebo During the Double-Blind Phase				
1001	--	Screening	28MAR2002	sinus rhythm premature systoles probably supraventricular poor anterior r progression
	Placebo	Double-Blind[b]	19APR2002	left atrial abnormality; horizontal axis incomplete right bundlebranch block, christa pattern
	36 mg	Open-Label[b]	18JUN2002	left atrial abnormality; poor anterior r progression
1003	--	Screening	23APR2002	poor anterior r progression
	Placebo	Double-Blind	03JUN2002	sinus bradycardia, high chest lead placement; poor anterior r progression
1004	--	Screening	02APR2002	sinus rhythm, vertical axis, possible rvh
	Placebo	Double-Blind	21MAY2002	sinus arrythmia; vertical axis; possible rvh
	72 mg	Open-Label	18JUN2002	vertical axis, possible rvh
3018	--	Screening	06JUN2002	low heart rate-poor anterior r progression
	Placebo	Double-Blind	17JUL2002	non-specific t abnormality
	54 mg	Open-Label	11SEP2002	abnormal sinus bradycardia
5002	Placebo	Double-Blind	24MAY2002	low t wave anterolateral t wave inversion
5010	--	Screening	04JUN2002	rate less than sixty/ncs
6011	72 mg	Open-Label	05AUG2002	sinus rhythm
6012	--	Screening	07JUN2002	sinus bradycardia
	Placebo	Double-Blind	29JUL2002	rate
6013	--	Screening	21JUN2002	normal except for rate age 14
	54 mg	Open-Label	27SEP2002	sinus bradycardia, premature systoles, atrial worsened, atrial ectopy present
8006	--	Screening	17APR2002	st abnormalities
12021	Placebo	Double-Blind	11JUN2002	waiting for consultation report
12033	54 mg	Open-Label	08OCT2002	could be a normal variant but it needs to be r/o lvh and poor anterior r progression
13002	--	Screening	03APR2002	abnormal because of rhythm
13012	54 mg	Open-Label	24JUL2002	abnormal b/c of rhythm
13013	--	Screening	16APR2002	because of rhythm
13014	--	Screening	16APR2002	abnormal because of rhythm
14002	72 mg	Open-Label	24JUL2002	sinus bradycardia, incomplete right bundle branch block, crista pattern. probably due to leads
14006	Placebo	Double-Blind	28MAY2002	slight left axis deviation, dr. abe bartell deemed not clinically significant
	54 mg	Open-Label	29JUL2002	sinus rhythm slight left axis deviation
14013	--	Screening	02JUL2002	normal except rhythm for age 14
	Placebo	Double-Blind	24JUL2002	sinus arrythmia and bigeminy
	36 mg	Open-Label	23SEP2002	sinus rhythm, borderline qt interval
13009	--	Screening	12APR2002	abnormal for age 14
Subjects Receiving CONCERTA During the Double-Blind Phase				
1007	--	Screening	04APR2002	sinus rhythm, vertical axis, rvh or conduction anomaly
	36 mg	Double-Blind	10MAY2002	vertical axis, possible rvh

5005	36 mg	Double-Blind	03MAY2002	minor st depression
8001	36 mg	Open-Label	29JUL2002	sinus rhythm, incomplete right bundle, branch block, poor anterior r progression, no change
14008	36 mg	Open-Label	12AUG2002	sinus ar
1014	--	Screening	11APR2002	poor anterior r progression
6005	-- 54 mg	Screening Open-Label	26MAR2002 28JUN2002	sinus arrhythmia sinus bradycardia - worsen and slow rate
10007	54 mg	Open-Label	26JUL2002	low or negative t wavesw, non-specific t abnormality
13010	54 mg	Double-Blind	28MAY2002	because of rhythm
1021	72 mg	Open-Label	17SEP2002	slightly taller t-waves-could be posterior ischemia or hyperkalemia worsened
6001	72 mg	Open-Label	03JUL2002	sinus rhythm, possible lvh
8011	72 mg	Open-Label	22AUG2002	rate over 100, longer qtc, faster rate, no clinical sx or hx
10001	-- 72 mg	Screening Double-Blind	27MAR2002 15MAY2002	sinus rhythm, incomplete right bundle branch block, abnormal, possibly significant incomplete right bundle branch blodck, abnormal for age 13
13015	--	Screening	16APR2002	abnormal rad
14005	72 mg	Double-Blind	04JUN2002	non specific t abnormality; pediatrician consulted and deemed results not clinically significant
14009	-- 72 mg	Screening Open-Label	19APR2002 26JUL2002	non specific t abnormality; interpreted as not normal by pediatrician poor anterior r progression, taller t waves
15009	72 mg	Open-Label	26JUL2002	non specific t wave abnormality

Appendix B

DETAILS FOR FURTHER DATA REQUEST FOR ECG (as specified by Dr. Judith Racoosin, FDA Safety Team Leader)

ECG Issue

1. For each of the studies (clinical pharmacology and phase II/III) in which ECGs were collected, provide the following information:
   - How many baseline ECGs were performed?
   - On which visit days were ECGs performed?
   - Were ECGs timed to correlate with Tmax, or another specific time point following dose administration?
   - Describe the method by which the ECGs were read (e.g., (automated vs. manual; if manual, hand-held calipers vs. digitized; centralized vs. at each center)
   - Describe who did the ECG reading (e.g., site investigator read, site cardiologist read, central cardiologist read, etc.).
   - What method was used to correct the QT interval for heart rate?

2. If the Bazett's correction was used originally, please repeat the analyses using the Fridericia correction and provide these results. Alternatively, submit analyses that used the baseline or placebo ECG data to generate the appropriate correction factor. (See attached divisional recommendations).

3. Mean change from baseline for HR, PR interval, QRS interval, QT interval, and QTc interval (using the correction approaches above) should be presented by treatment group.

4. An outlier analysis for QTc (using the correction approaches above) should be provided. The data presentation should follow the guidelines described below[1]:

Categorical analyses of QT/QTc interval data are based on the number and percentage of patients meeting or exceeding some predefined upper limit value. Clinically noteworthy QT/QTc interval signals may be defined in terms of absolute QT/QTc intervals or changes from baseline. Absolute interval signals are QT/QTc interval readings in excess of some specified threshold value. Separate analyses should be provided for patients with normal and elevated baseline QT/QTc intervals.

Consensus within the scientific community concerning the choice of upper limit values for absolute interval signals and change from baseline signals does not exist. While lower limits increase the false-positive rate, higher limits increase the risk of failing to detect a signal.

Multiple analyses using different signal values are a reasonable approach to this controversy:

- Absolute QT/QTc interval signals of interest include the following:
  - QT/QTc ≥ 450 msec for males.
  - QT/QTc ≥ 470 msec for females.
  - QT/QTc ≥ 500 msec (for all patients).

- Change from baseline signals of interest include the following:
  - QT/QTc interval increases from baseline ≥ 30 msec.
  - QT/QTc interval increases from baseline ≥ 60 msec.

5. If plasma level data is available for the four studies in which ECGs were measured at Cmax, a QTc-plasma level relationship should be evaluated.

[1] Derived from CDER's "The Clinical Evaluation of QT/QTc Interval Prolongation and Proarrhythmic Potential for Non-arrhythmic Drugs: Preliminary Concept Paper", November 2002.

6. Please submit electronic datasets with the PR, QRS, QT, QTc (for whichever correction factors were used), and the RR intervals for each ECG measured in the trials. Each row (one row per ECG) should also include the patient ID, trial number, center number, treatment assignment, and study day the ECG was measured.

Appendix C

DETAILS FOR FURTHER DATA REQUEST FOR GROWTH DATA (as specified by Dr. Judith Racoosin, FDA Safety Team Leader)

- Please provide details on how the weight and height measurements were done (e.g., was the measurement schedule and methodology standardized, were study staff were trained in the measurement procedures, etc?)

- For placebo controlled trials, please provide an analysis of mean height and weight changes from baseline for Concerta compared to placebo using data from the placebo controlled portion of Study 01-146.

- Please provide outlier analyses that identify the percentage of pediatric subjects that lost at least 3.5% of their body weight for Concerta compared to placebo for the placebo controlled portion of Study 01-146.

Investigators have used growth curve data to assess growth in placebo-controlled and open label studies, in some cases by using z-scores. A z-score is the number of standard deviations that one is from their gender/age standardized mean. Investigators determine each subject's z-score at the beginning and then at the end of the observation period. If the mean change in the z-score is negative, then the group did not grow as expected based on normal population data.

- Please provide an analysis of mean height and weight z-score changes from baseline for Concerta compared to placebo for the placebo controlled portion of Study 01-146.

- Please provide an analysis of mean height and weight z-score changes from baseline for patients treated with open label Concerta. Repeat this analysis stratified on age (<12 years and ≥12 to 17 years) and on treatment arm in the preceding controlled trial.

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

/s/

Roberta Glass
2/25/04 03:19:52 PM
MEDICAL OFFICER

Paul Andreason
2/27/04 03:41:23 PM
MEDICAL OFFICER
I recommend an Approvable Action on sNDA 21-121 SE1-08.
See my memo to the file dated Feb
27, 2004.