Clinical Pharmacology/Biopharmaceutics Review

PRODUCT (Generic Name):	Methylphenidate HCl
PRODUCT (Brand Name):	CONCERTA
DOSAGE FORM:	Extended Release Tablets
DOSAGE STRENGTHS:	18, 27, 36 and 54 mg
NDA:	21,121 (SE1-008)
NDA TYPE:	Supplement for ADHD in adolescents in response to FDA Pediatric Written Request Letter
SUBMISSION DATE:	9/5/03, 9/15/03, 10/13/03
SPONSOR:	McNeil
REVIEWER:	Veneeta Tandon, Ph.D.
TEAM LEADER:	Ramana Uppoor, Ph.D.
OCPB DIVISION:	DPE I, HFD 860
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TABLE OF CONTENTS

EXECUTIVE SUMMARY

CONCERTA is currently indicated in the United States for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) with a maximum daily dose of 54 mg in children ages 6-12 years. This sNDA provides support to change the current CONCERTA prescription labeling information to include an indication for treatment in adolescents age 13-17 years, to include once-daily dosage of up to 72 mg/day for adolescents, and to update various sections of the labeling with data included in this submission.

This sNDA includes a multiple dose pharmacokinetic study in adolescents with doses up to 72 mg, one randomized controlled clinical study of CONCERTA to assess safety and efficacy in doses up to 72mg/day in adolescents with ADHD and two long term safety studies at doses up to 54 mg.

The multiple dose pharmacokinetic study (Study 12-001) of a 6 day duration was conducted in 26 healthy adolescents with ADHD (ages 13-17), consisting of 19 males and 7 females. The number of subjects enrolled at the 18, 27, 36, 54 and 72 mg doses were 1, 1, 10, 8 and 6 respectively. Doses were chosen based on the dose prescribed by the subject's personal physician.

The overall conclusions from the pharmacokinetic study in adolescents were:

? The plasma concentration-time profiles of d- and total methylphenidate in adolescents were similar to the unique ascending profiles observed in previous studies with CONCERTA® in adults and children. These profiles showed the rapid increase in concentrations over the first hour due to the immediate-release overcoat followed by gradual ascending concentrations over the next six hours due to the OROS ® osmotic core.
? The pharmacokinetics of methylphenidate in adolescents were linear with dose up to 72 mg.
? In cross study comparisons the CL/F of total methylphenidate in children, adolescents and adults were 243, 384 and 497 L/h respectively, showing an increase of 58% in adolescents and 104% in adults compared to children. The weight normalized CL/F in these populations were 6.58, 6.60 and 7.31 L/h/kg respectively.
? In the covariate analyses using pooled data from children, adolescents, and adults (historical studies), there were some statistically significant findings. Body weight had a significant effect on CL/F and Vz/F for both d- and total methylphenidate. A 10 kg increase in weight resulted in a 66.9 L/h increase in CL/F for total methylphenidate and a 22.4 L/h increase in CL/F for d-methylphenidate. A 10 kg increase in weight resulted in a 441 L increase in Vz/F for total methylphenidate and a 104 L increase in Vz/F for d-methylphenidate.

? The effect of age using pooled data from children, adolescents, and adults was investigated on weight-normalized CL/F and Vz/F so as not to confound the effect of age with differences in body size. There was a statistically significant age effect on these weight-normalized CL/F and Vz/F and T½ for total methylphenidate, which included data for children, adolescents, and adults. However, there was no significant age effect on any parameter for d-methylphenidate, which included data for only adolescents and adults. This analysis showed that the weight-normalized CL/F for total methylphenidate increased slightly with age. A 10-year increase in age resulted in a 0.6 L/h/kg increase in weight-normalized CL/F for total methylphenidate.
A 10-year increase in age resulted in a 5.7 L/kg increase in weight-normalized Vz/F for total methylphenidate.

RECOMMENDATION

From a Clinical Pharmacology/Biopharmaceutics perspective this sNDA is acceptable with the labeling changes suggested on page 3. Please convey the labeling changes to the sponsor.

The sponsor's proposed dosing recommendations for the adolescent population are acceptable from a pharmacokinetics perspective provided the 72 mg dose is evaluated to be safe by the Medical Reviewer from a clinical perspective in an adequate number of subjects.

Veneeta Tandon, Ph.D.
Pharmacokineticist
Division of Pharmaceutical Evaluation I

Team Leader: Ramana Uppoor, Ph.D._____

LABELING RECOMMENDATIONS

The following labeling recommendation as shown by underline and strikeout should be conveyed to the sponsor:

Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of CONCERTA® plasma methylphenidate concentrations increase rapidly reaching an initial maximum at about 1 hour followed by gradual ascending concentrations over the next 5 to 9 hours (b) (4). Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 to 10 hours.

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

FIGURE 1

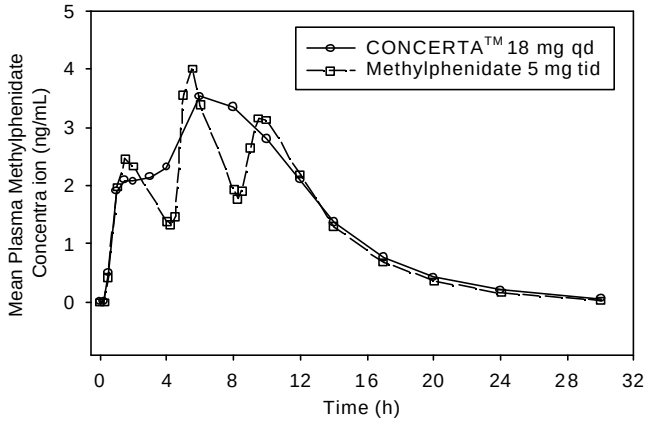


Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of CONCERTA® 18 mg qd and immediate-release methylphenidate 5 mg tid administered every 4 hours.

The mean pharmacokinetic parameters in 36 adults following the administration of CONCERTA® 18 mg qd and methylphenidate 5 mg tid are summarized in Table 1.

TABLE 1
Mean ± SD Pharmacokinetic Parameters

Parameters	CONCERTA® (18 mg qd) (n=36)	Methylphenidate (5 mg tid) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0

T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng?h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

No differences in the pharmacokinetics of CONCERTA® were noted following single and repeated once-daily dosing indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of CONCERTA® 18 mg.

Dose Proportionality

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

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

Distribution

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

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to a-phenyl-piperidine acetic acid (PPA) which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® qd as evaluated by metabolism to PPA is similar to that of methylphenidate tid. The metabolism of single and repeated once daily doses of CONCERTA® is similar.

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

Food Effects

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

Special Populations

Gender

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

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

Age
Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

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

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

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

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

CONCERTA® must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed (see PRECAUTIONS: Information for Patients).

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.

Patient Age	Maximum Dosage
Children 6-12 years of age	54 mg/day
Adolescents 13-18 years of age	72 mg/day

(In the Table above, add a column indicating the starting dose for children and adolescents)

Patients New to Methylphenidate
The recommended starting dose of CONCERTA® for patients who are not currently taking methylphenidate, or for patients who are on stimulants other than methylphenidate, is 18 mg once daily.

Patients Currently Using Methylphenidate
The recommended dose of CONCERTA® for patients who are currently taking methylphenidate bid, or tid, at doses of 10 to 45 mg/day is provided in Table 6. Dosing recommendations are based on current dose regimen and clinical judgment.

TABLE 6
Recommended Dose Conversion from
Methylphenidate Regimens to CONCERTA®

Previous Methylphenidate Daily Dose	1.1.1.1 Recommended 1.1.1.2 CONCERTA® Starting Dose
5 mg Methylphenidate bid or tid	18 mg q am
10 mg Methylphenidate bid or tid	36 mg q am
15 mg Methylphenidate bid or tid	54 mg q am

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

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

Maintenance/Extended Treatment
There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with CONCERTA®. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods. (b) (4)

Nevertheless, the physician who elects to use CONCERTA® for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

OVERALL SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS

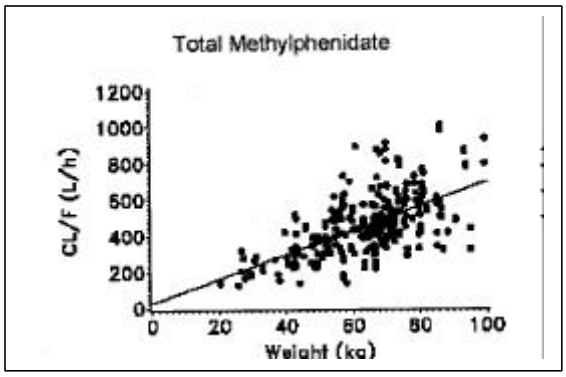
CONCERTA is currently indicated in the United States for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) with a maximum daily dose of 54 mg in children ages 6-12 years. This sNDA provides support to change the current CONCERTA prescription labeling information to include an indication for treatment in adolescents age 13-17 years, to include once-daily dosage of up to 72 mg/day for adolescents, and to update various sections of the labeling with data included in this submission.

This sNDA includes a multiple dose pharmacokinetic study in adolescents with doses up to 72 mg, one randomized controlled clinical study of CONCERTA to assess safety and efficacy at doses up to 72mg/day in adolescents with ADHD and two long term safety and effectiveness studies.

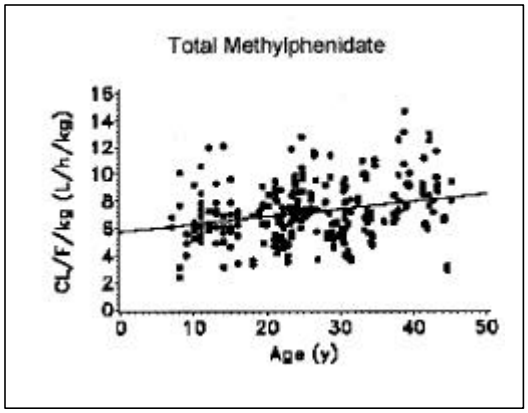
The multiple dose pharmacokinetic study (Study 12-001) of a 6 day duration was conducted in 26 healthy adolescents with ADHD (ages 13-17), consisting of 19 males and 7 females. The number of subjects enrolled at the 18, 27, 36, 54 and 72 mg doses were 1, 1, 10, 8 and 6 respectively. Doses were chosen based on the dose prescribed by the subject's personal physician.

The overall conclusions from the pharmacokinetic study in adolescents were:

- The plasma concentration-time profiles of d- and total methylphenidate in adolescents were similar to the unique ascending profiles observed in previous studies with CONCERTA® in adults and children. These profiles showed the rapid increase in concentrations over the first hour due to the immediate-release overcoat followed by gradual ascending concentrations over the next six hours due to the OROS ® osmotic core.
- The pharmacokinetics of methylphenidate in adolescents were linear with dose up to 72 mg.
- In cross study comparisons the CL/F of total methylphenidate in children, adolescents and adults were 243, 384 and 497 L/h respectively, showing an increase of 58% in adolescents and 104% in adults compared to children. The weight normalized CL/F in these populations were 6.58, 6.60 and 7.31 L/h/kg respectively (see Table on page 29).
- The metabolism of methylphenidate in adolescents appears similar to that in adults based on the methylphenidate-to-PPA AUCTAU ratios.
- In the covariate analyses using only adolescent data, there were no statistically significant findings of the effect of weight, age, or gender on CLss/F, Vz/F, and T½ for both d- and total methylphenidate.
- In the covariate analyses using pooled data from children, adolescents, and adults (historical studies), there were some statistically significant findings. Body weight had a significant effect on CL/F and Vz/F for both d- and total methylphenidate as seen in the figure below. A 10 kg increase in weight resulted in a 66.9 L/h increase in CL/F for total methylphenidate and a 22.4 L/h increase in CL/F for d-methylphenidate. A 10 kg increase in weight resulted in a 441 L increase in Vz/F for total methylphenidate and a 104 L increase in Vz/F for d-methylphenidate.



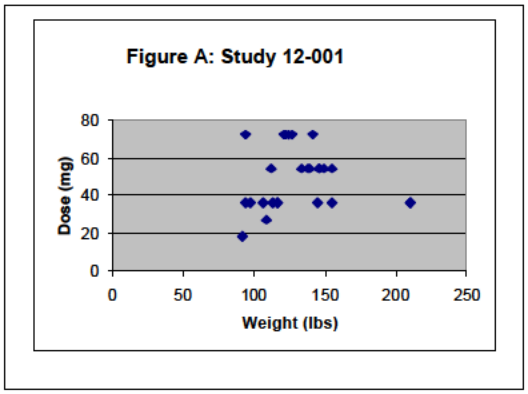
? The effect of age using pooled data from children, adolescents, and adults was investigated on weight-normalized CL/F and Vz/F so as not to confound the effect of age with differences in body size. There was a statistically significant age effect on these weight-normalized CL/F and Vz/F and T½ for total methylphenidate, which included data for children, adolescents, and adults. However, there was no significant age effect on any parameter for d-methylphenidate, which included data for only adolescents and adults. This analysis showed that the weight-normalized CL/F for total methylphenidate increased slightly with age as shown in the figure below. A 10-year increase in age resulted in a 0.6 L/h/kg increase in weight-normalized CL/F for total methylphenidate.
A 10-year increase in age resulted in a 5.7 L/kg increase in weight-normalized Vz/F for total methylphenidate.

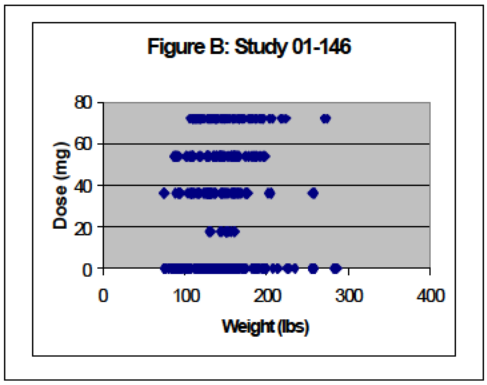


? There was no gender effect on any parameter for total methylphenidate, which included data for the three age groups. A gender effect was statistically significant on Vz/F and T½ for d-methylphenidate, which included data for adolescents and adults.

In cross study comparisons using AUCs and Cmax, the data suggested that both AUC and Cmax decreased with the increase of age. For details of this comparison see page 30 of the review. This also suggests that as the age or weight of the subjects increase, higher doses may be needed. This was also evident by the subjects enrolled in Study 12-001. Subjects received their doses as prescribed by their personal physicians. Only one subject was enrolled at the dose of 18 mg and one at the dose of 27 mg. Looking at the demographic information, it was observed that these two subjects were 13 year olds with body weight of 41.5 and 49.4 kg. In this study there were 3 more 13-year-olds enrolled with body weight of 48, 51 and 67 kg. These subjects were given 36 mg, 36 mg and 72 mg respectively. There did seem a trend that subjects with higher weight tended to receive higher doses, although there was overlap of doses within the same weight range as well.

The controlled clinical efficacy study 01-146 was conducted with an open label titration phase, where subjects initiated treatment with a dose of 18 mg/day. This dose was increased in 18 mg increments every week until an individualized dose was identified that produced the criteria for improvement in ADHD symptoms with tolerable safety for a given subject to a maximum of 72 mg/day. In the double blind phase, subjects completing the titration phase were randomized to receive their individualized CONCERTA dose or placebo. Given the titration design of the clinical efficacy study, a meaningful exposure response analysis cannot be obtained to elucidate the clinical significance of reduced exposure based on pharmacokinetic parameters and cannot corroborate the finding for the need for higher doses with the increase in body weight. Even looking at the doses received by these subjects in the two studies (Study 12-001 and Study 01-146) there seems to be a considerable overlap in the doses administered at similar weights as shown in the figures below.





Hence, increase of dose based on increase in body weight cannot be justified based on the results of the two studies, although the covariate analysis from the pharmacokinetic study 12-001 did suggest a statistically significant trend of increased CL/F with the increase in body weight. This analysis does suggest that some subjects with high body weight may need higher doses like 72 mg to achieve optimal efficacy provided the safety is not compromised.

The sponsor's proposed dosing recommendations for the adolescent population are acceptable from a pharmacokinetics perspective provided the 72 mg dose is evaluated to be safe by the Medical Reviewer from a clinical perspective in an adequate number of subjects.

BACKGROUND

CONCERTA brand extended-release methylphenidate hydrochloride is a once-daily oral dosage form utilizing ALZA's OROS drug-delivery technology. It was developed to meet the need for an effective product offering once-daily dosing, and is approved and marketed in the United States in 18 mg, 27 mg, 36 mg, and 54 mg dose strengths as CONCERTA (methylphenidate hydrochloride) Extended Release Tablets. FDA approved NDA 21-121 for prescription CONCERTA 18 mg and 36 mg Extended Release Tablets in August 2000, followed by the 54-mg tablet in December 2000, and the 27-mg tablet in April 2002.

Currently, CONCERTA is indicated in the United States for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) with a maximum daily dose of 54 mg in children ages 6-12 years. This sNDA submitted in response to a Written Request provides support to change the current CONCERTA prescription labeling information to include an indication for treatment in adolescents age 13-17 years, to include once-daily dosage of up to 72 mg/day for adolescents, and to update various sections of the labeling with data included in this submission.

The proposed 72-mg CONCERTA dose is intended to be prescribed for those adolescents with ADHD who do not derive adequate response with currently approved lower doses of CONCERTA of up to 54 mg.

The Pediatric Written Request requested pharmacokinetic, efficacy and safety studies in adolescents.

This sNDA consists of a multiple dose pharmacokinetic study in adolescents (Study 12-001). It also has a food effect study comparing CONCERTA to ADDERALL XR (Study 01-148). This study has been reviewed for completeness of information submitted, but does not have relevance to the current supplement. No labeling changes need to be made based on the results of this study.

APPENDIX I

INDIVIDUAL STUDY REVIEW

Study 12-001: Multiple-Dose Pharmacokinetics of CONCERTA ® (Methylphenidate HCl) in Healthy Adolescents with ADHD

Objective:

? The primary objective was to determine the steady-state pharmacokinetics of d- and l-methylphenidate from multiple doses of CONCERTA ® OROS ® Tablets in healthy adolescents with ADHD at their prescribed dose.
? A secondary objective was to compare methylphenidate pharmacokinetics in adolescents with those previously determined in children and adults.

Methodology:

The study had a multiple-dose, open-label, five-dose parallel design. Potential subjects already taking CONCERTA ® for treatment of ADHD were assessed for health at a screening visit. Those subjects who qualified for the study were instructed to take their medication once daily at the same time each day for five days (Days 1 to 5). On Day 6, they reported to one of two clinical centers in the morning, their vital signs were recorded, and the first blood sample was collected. Study personnel then administered the subject's prescribed dose of CONCERTA ® starting at approximately 8AM. The daily dose for any subject could be 18, 27, 36, and 54 mg, or higher if prescribed.

Study Population:

N=26 Healthy subjects with ADHD; male (N=19) and female (N=7), ages 13 through 17 years of age (13 years=7, 14 years=6, 15 years=7, 16 years=6, 17 years=0)

Duration of treatment:

Subjects received one dose of CONCERTA daily for six consecutive days.

Test regimen, dose and mode of administration, batch numbers:

One or two CONCERTA OROS Tablets, at the dose prescribed by the subject's personal physician, were taken at the same time each day for Days 1 to 5. On Day 6, the dose was swallowed with 240 mL of water at approximately 8 AM before breakfast.

18 mg Tablets, Lot 0216071
27 mg Tablets, Lot 0300414
36 mg Tablets, Lot 0218881
54 mg Tablets, Lot 0217377

Blood Samples:

Serial blood samples were collected after the morning dose on Day 6. Subjects at the CNS Research Institute had their last blood sample collected at 13 hours after the dose, were discharged, and returned the following morning, whereas subjects at Northwest Kinetics had their last blood sample at 14 hours because they were housed at the clinical center overnight. On Day 7 all subjects had a 24-hour blood sample collected, and exit vital signs measured. The subjects were allowed to resume taking their prescribed medication after the final blood draw. Plasma was harvested from the blood samples, and quantified for d- and l-methylphenidate and the major metabolite, d- and l-ritalinic acid (PPA), using validated assays.

Bioanalytical Methods:

Samples were analyzed for d- and l-methylphenidate and d- and l-ritalinic acid concentrations using validated assay methods.

D- & L- Methylphenidate

Method	High-performance liquid chromatography with mass spectrometry detection (LC/MS/MS) method
Linearity	linear for d-methylphenidate over the range 0.0500 to 50.0 ng/mL, and for l-methylphenidate over the range 0.0100 to 10.0 ng/mL.
Assay Specificity	No significant peaks interfered with those for either analyte or the internal standard in control blank plasma.
Assay Sensitivity	The lower limit of quantification (LLOQ) in 0.2 mL of extracted plasma of d-methylphenidate nominally was 0.0500 ng/mL, and of l-methylphenidate was 0.0100 ng/mL.
Accuracy	Accuracy of the assay for d-methylphenidate over a range of 0.0500 to 50.0 ng/mL was demonstrated by coefficients of variation that ranged from -5.7 to 1.6% for the means at each concentration of the standard curve with % deviation ranging from –5.73 to 1.46%. The % difference from theoretical for the QC samples at 0.0500, 0.150, 1.75, and 37.5 ng/mL were –3.06, -3.72, 1.50 and 1.62 % respectively with % CV less than 4.01% for all samples. Accuracy of the assay for l-methylphenidate over a range of 0.0100 to 10.0 ng/mL was demonstrated by coefficients of variation that ranged from -5.4 to 2.6% for the means at each concentration of the standard curve with % deviation ranging from –5.37 to 2.57%. The % difference from theoretical for the QC samples at 0.0100, 0.0300, 0.350, and 7.5 ng/mL were –3.04, -3.52, 2.09 and 0.697% respectively with % CV less than 10.1% for all.
Precision	Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of d-methylphenidate at 0.0500, 0.150, 1.75, and 37.5 ng/mL. The coefficients of variation were 3.1, 4.0, 2.8, and 2.0% for the limit-of-quantitation, low, medium, and high control samples, respectively. Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of l-methylphenidate at 0.0100, 0.0300, 0.350, and 7.5 ng/mL. The coefficients of variation were 10.1, 4.1, 2.8, and 1.7% for the limit-of-quantitation, low, medium, and high control samples, respectively.
Recovery	Recovery was determined during validation by comparing the d- and l-methylphenidate and internal standard analyte responses of extracted samples to those of external standards representing 100% recovery. Recoveries of d- methylphenidate from QC samples at low, medium, and high concentrations were 93.8, 93.2, and 86.7%,

respectively. Recoveries of l- methylphenidate from QC samples at low, medium, and high concentrations were 92.5, 95.0, and 90.9%, respectively.

D-& L-Ritalinic Acid (PPA)

Method	High-performance liquid chromatography with mass spectrometry detection (LC/MS/MS).
Linearity	linear for both d- and l-ritalinic acid over the range 1.00 to 1000 ng/mL.
Assay Specificity	No significant peaks interfered with those for either analyte or the internal standard in control blank plasma.
Assay Sensitivity	The lower limit of quantification (LLOQ) in 0.2 mL of extracted plasma of both d- and l-ritalinic acid nominally was 1.00 ng/mL.
Accuracy	Accuracy of the assay for d-ritalinic acid over a range of 1.00 to 1000 ng/mL was demonstrated by coefficients of variation that ranged from 1.2 to 5.2% for the means at each concentration of the standard curve with % deviation ranging from –1.82 to 4.83%. The % difference from theoretical for the QC samples at 1, 3, 35 and 750 ng/mL were –0.537, -1.21, -1.13, and –9.26% respectively with % CV less than 3.37% for all samples. Accuracy of the assay for l-ritalinic acid over a range of 1.00 to 1000 ng/mL was demonstrated by coefficients of variation that ranged from 1.3 to 3.3% for the means at each concentration of the standard curve with % deviation ranging from –1.23 to 2.27%. The % difference from theoretical for the QC samples at 1, 3, 35 and 750 ng/mL were –1.8, 0.648, -0.586 and –0.362% respectively with % CV less than 4.09 for all samples.
Precision	Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of d-ritalinic acid at 1.00, 3.00, 35.0, and 750 ng/mL. The coefficients of variation were 3.2, 3.4, 2.1, and 2.2% for the limit-of-quantitation, low, medium, and high control samples, respectively. Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of l-ritalinic acid at 1.00, 3.00, 35.0, and 750 ng/mL. The coefficients of variation were 6.0, 2.6, 2.5, and 1.4% for the limit-of-quantitation, low, medium, and high control samples, respectively.
Recovery	Recovery was determined during validation by comparing the d- and l-ritalinic acid and internal standard analyte responses of extracted samples to those of external standards representing 100% recovery. Recoveries of d-ritalinic acid from QC samples at low, medium, and high concentrations were 110, 111, and 109%, respectively.

Recoveries of l-ritalinic acid from QC samples at low, medium, and high concentrations were 106, 111, and 99.8%, respectively.

Criteria for Evaluation:

Pharmacokinetics: For d-, l-, and total methylphenidate (MPH) and d-, l-, and total PPA, the pharmacokinetic parameters of AUCTAU; CMAX; TMAX; KEL; T½; Vz/F; and CLSS/F were determined.

For the d- and l- isomers of both methylphenidate and PPA, CLss/F and Vz/F were computed with ½ CONCERTA ® Dose, because each isomer constitutes 50% of the racemic mixture. The effect of demographic variables (weight, age, and gender) on the following pharmacokinetic parameters of d- and total methylphenidate (CLss/F, Vz/F and T½) was assessed on data pooled from original NDA 21-121.

Statistical Methods:

The pharmacokinetic parameters d-, l-, and total MPH, and d-, l-, and total PPA in adolescents were summarized by descriptive statistics. The influence of covariates (weight, age, and gender) on CLss/F, Vz/F, and T½ was investigated for d- and total MPH. In addition, the individual results were pooled and reviewed in context with similar data available in children and adults.

Influence of Demographic Variables in this Study (McNeil Study 12-001)
The effects of weight, gender, and age were assessed in McNeil Study 12-001 for d- and total methylphenidate on the parameters CLss/F, Vz/F, and T½. The analyses did not include l-methylphenidate because it was not possible to calculate these parameters for 22 out of 26 subjects due to undetectable concentrations in the terminal phase. Both CLss/F and Vz/F were normalized by weight to assess an age effect. Regression analyses were used to assess the effect of weight and age on these pharmacokinetics parameters. A one-way ANOVA with gender as a factor was used to assess differences between genders.

Influence of Demographic Variables in Pooled ALZA and McNeil Studies

Total Methylphenidate
Data on total methylphenidate were pooled from ALZA Studies 97-033, 98-024, 98-025, 99-002, and 99-025 (NDA 21-121), and McNeil Study 12-001.

Study Number	NDA Volume	Age Group	Data Selected for the Pooled Analyses
C-97-033	NDA Vol 1.56	Children	Total methylphenidate (MPH) modeled values of CL/F, V/F, and T½ for Ritalin 5 mg TID (Normal and Fasted)
C-98-024	NDA Vol 1.61	Adults	Total MPH data for 18 mg OROS; 5 mg TID Ritalin
C-98-025	NDA Vol 1.64	Adults	d- MPH data for three OROS doses (18, 36, 54 mg)
C-99-002	NDA Vol 1.70	Adults	Total MPH data for 36 mg OROS (one 36 mg tablet and two 18 mg tablets, fasted)
C-99-025	SNDA[a] Vol 17.9	Adults	Total MPH data for 54 mg OROS (one 54 mg tablet and three 18 mg tablets, fasted)

a: Supplemental NDA submitted August 10, 2000

Parameter estimates of CL/F, Vz/F, and T½ for children and adolescents were obtained from steady-state methylphenidate concentrations after multiple doses, whereas estimates for adults were obtained after a single dose. Both sets of estimates are comparable, because methylphenidate exhibits linear pharmacokinetics over dose and time. In addition, CL/F, Vz/F, and T½ for CONCERTA ® in children ages 6 to 12 years were not available, because they could not be estimated in ALZA Study 97-033 due to sparse blood sampling and the unique concentration profile. However, in this same study, data from children taking Ritalin ® three times a day was modeled by the sponsor using population techniques to estimate the CL/F, Vz/F, and T½ for methylphenidate. Because these parameters are inherent characteristics of how a drug is handled by the body, they are expected to be the same for both Ritalin ® and CONCERTA ®, and data from ALZA Study 98-024 in adults confirmed this principle. Hence, the children's modeled CL/F, Vz/F, and T½ values with Ritalin ® from ALZA Study 97-033 were pooled with CONCERTA ® data from other studies and with Ritalin® data in adults from ALZA Study 98-024.

The effect of weight, gender, and age were assessed in the pooled data on the parameters CL/F, V/F, and T½. Both CL/F and V/F were normalized by weight for the assessment of an age effect. Regression analyses were used to assess effects of weight and age. A one-way ANOVA with gender as a factor was used to assess differences between genders.

D-Methylphenidate
Data on d-methylphenidate were pooled from ALZA Study 98-025 in adults and McNeil Study 12-001 in adolescents, and analyzed similarly to total methylphenidate. There were no d-methylphenidate data available in children, aged 6 to 12 years.

Safety:
Safety was assessed by reviewing vital signs, clinical laboratory test results, and the occurrence and seriousness of any adverse events.

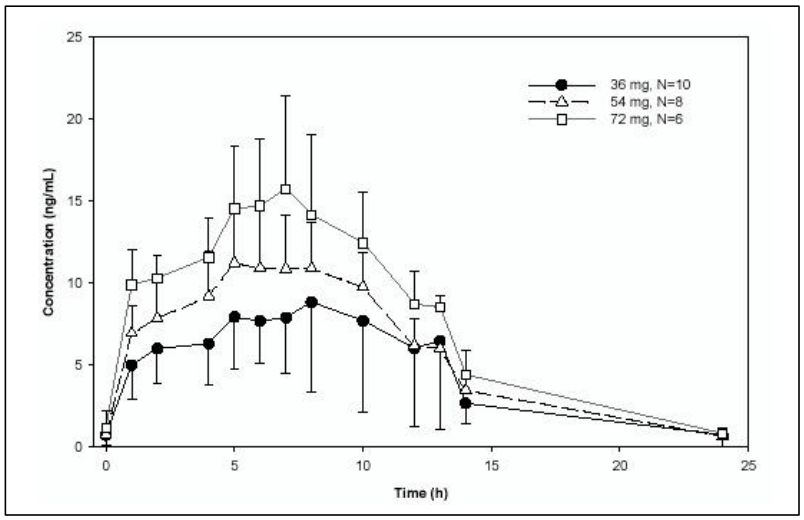
Pharmacokinetic Results:

D-, L-, and Total Methylphenidate Pharmacokinetics:

All subjects had quantifiable predose plasma concentrations of d-methylphenidate on Day 6, whereas all predose concentrations of l-methylphenidate were below the limit of quantification. These results are consistent with the multiple-dose study design and with previous CONCERTA ® pharmacokinetic data showing that l-methylphenidate concentrations

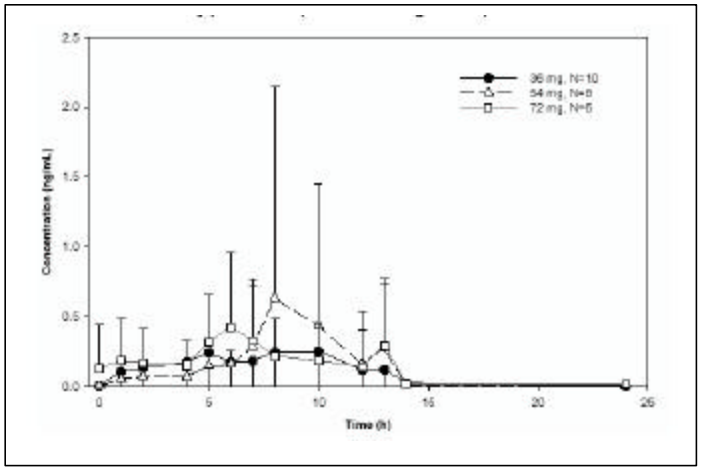
are generally 1/40 of d-methylphenidate. The mean ratio of CMAX to CMIN for d-methylphenidate was 20 or higher for all dose groups, using CMIN values at the predose or 24-h time points. Similarly, the mean ratio of CMAX to CMIN for total methylphenidate was 20 or higher for all dose groups.

Mean plasma concentration-time profiles for d- methylphenidate at 36, 54, and 72 mg CONCERTA ® are presented in the following Figure:



		d-Methylphenidate				
	Dose	18 mg (9 mg *d*-)	27 mg (13.5 mg *d*-)	36 mg (18 mg *d*-)	54 mg (27 mg *d*-)	72 mg (36 mg *d*-)
	N	1	1	10	8	6
CMAX (ng/mL)	Mean	3.97	8.60	9.5	12.2	17.6
	(sd)	.	.	(5.2)	(3.3)	(4.6)
	%cv	.	.	54.7	27.0	26.3
TMAX (h)	Mean	4	5	7.2	6.8	7.0
	(sd)	.	.	(1.6)	(1.7)	(1.8)
	%cv	.	.	22.5	24.7	25.6
AUCTAU (ng-h/mL)	Mean	54.9	89.7	110	137	182
	(sd)	.	.	(53.0)	(34.6)	(34.6)
	%cv	.	.	48.2	25.2	19.0
KEL (h^{-1})	Mean	0.143	0.262	0.186	0.194	0.199
	(sd)	.	.	(0.070)	(0.026)	(0.031)
	%cv	.	.	37.6	13.1	15.4
T½ (h)	Mean	4.84	2.65	4.60	3.62	3.55
	(sd)	.	.	(2.88)	(0.45)	(0.50)
	%cv	.	.	62.5	12.5	14.1
CLss/F (L/h)	Mean	164	151	189	208	203
	(sd)	.	.	(68.6)	(54.4)	(37.8)
	%cv	.	.	36.3	26.1	18.6
Vz/F (L)	Mean	1144	576	1221	1059	1037
	(sd)	.	.	(682)	(154)	(210)
	%cv	.	.	55.8	14.5	20.3

Mean (sd) Steady-State Concentration Time Profiles for *l*-Methylphenidate



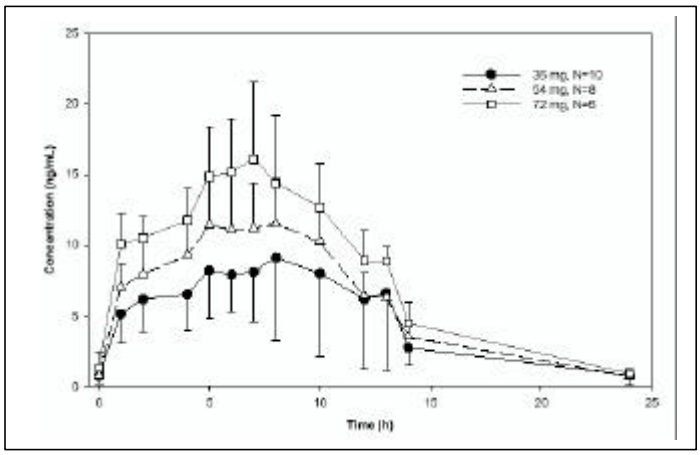
		***l*-Methylphenidate**				
	Dose	**18 mg (9 mg *l*-)**	**27 mg (13.5 mg *l*-)**	**36 mg (18 mg *l*-)**	**54 mg (27 mg *l*-)**	**72 mg (36 mg *l*-)**
	N	1	1	10	8	6
CMAX (ng/mL)	Mean	0.034	0.094	0.417	0.681	0.457
	(sd)	.	.	(0.47)	(1.50)	(0.52)
	%cv	.	.	112	220	113
TMAX (h)	Mean	2.00	5.00	6.5	5.8	5.7
	(sd)	.	.	(2.3)	(1.0)	(0.5)
	%cv	.	.	35.0	18.0	9.1
AUCTAU (ng-h/mL)	Mean	0.380	0.550	2.51	3.30	3.45
	(sd)	.	.	(3.12)	(6.34)	(5.16)
	%cv	.	.	125	192	150
KEL (h^{-1})	Mean	-[c]	-[c]	0.192[a]	0.378[b]	0.147[b]
	(sd)	.	.	(0.169)	.	.
	%cv	.	.	88.2	.	.
T½ (h)	Mean	-[c]	-[c]	5.93[a]	1.83[b]	4.73[b]
	(sd)	.	.	(5.23)	.	.
	%cv	.	.	88.2	.	.
CLss/F (L/h)	Mean	23699	24606	18179	35153	30368
	(sd)	.	.	(16087)	(33954)	(24044)
	%cv	.	.	88.5	96.6	79.2
Vz/F (L)	Mean	-[c]	-[c]	148427[a]	3777[b]	17697[b]
	(sd)	.	.	(202304)	.	.
	%cv	.	.	136	.	.

[a] N = 2; [b] N = 1; [c] Not estimated due to insufficient data

The plasma concentration-time profiles for l-methylphenidate generally paralleled those for d-methylphenidate with mean TMAX occurring at 5.7-6.5 h for the 36- to 72-mg doses, respectively. CMAX values of l-methylphenidate were less than 1.5 ng/mL for all subjects except Subject 1006 (54 mg dose), who had the highest CMAX concentration of

4.38 ng/mL. Due to undetectable plasma concentrations at the later time points (13 or 14 h and 24 h), the terminal elimination rate constant, half-life, and apparent volume of distribution could not be determined in 22 out of 26 subjects. In four subjects who had quantifiable plasma concentrations, the terminal half-life ranged from 1.8 -5.9 h. The AUCTAU and CLSS/F values were calculated and reported for all subjects; however, these estimates were based on the last quantifiable concentration that occurred mainly at 12 hours postdosing. The low plasma concentrations of l-methylphenidate are consistent with the stereospecific presystemic metabolism of methylphenidate.

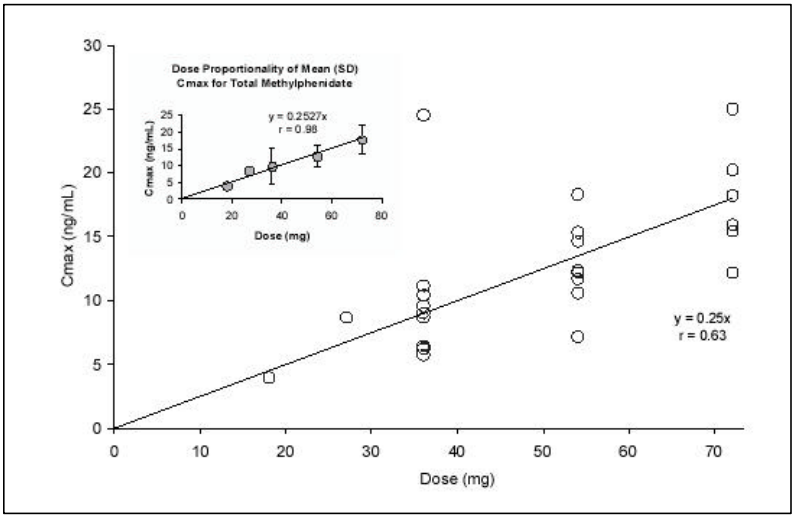
Mean (sd) Steady-State Concentration Time Profiles For Total-Methylphenidate

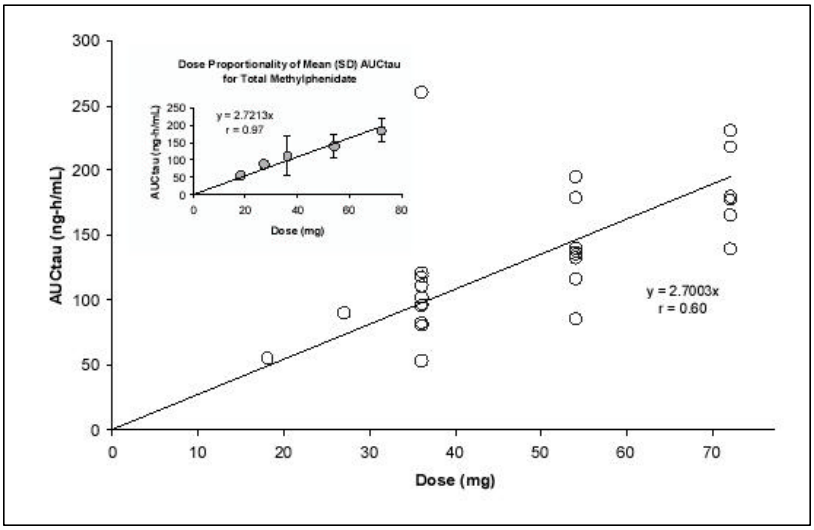


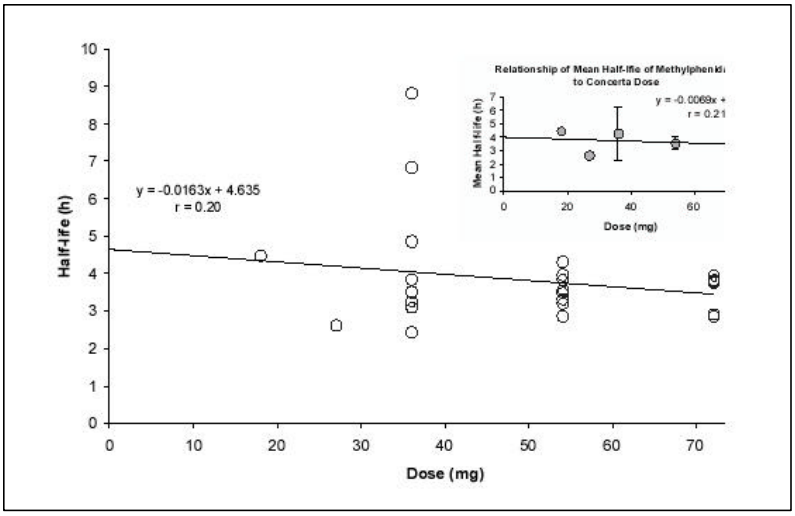
		Total Methylphenidate				
	Dose	**18 mg**	**27 mg**	**36 mg**	**54 mg**	**72 mg**
	N	1	1	10	8	6
CMAX (ng/mL)	Mean	4.00	8.69	9.9	12.8	17.8
	(sd)	.	.	(5.5)	(3.4)	(4.5)
	%cv	.	.	56.1	26.1	24.9
TMAX (h)	Mean	4.0	5.0	7.0	6.8	7.0
	(sd)	.	.	(2.1)	(1.7)	(1.8)
	%cv	.	.	30.1	24.7	25.6
AUCTAU (ng-h/mL)	Mean	55.3	90.2	112	141	186
	(sd)	.	.	(55.9)	(34.3)	(33.9)
	%cv	.	.	49.8	24.4	18.3
KEL (h^{-1})	Mean	0.154	0.262	0.186	0.197	0.200
	(sd)	.	.	(0.062)	(0.026)	(0.031)
	%cv	.	.	33.5	13.1	15.3
T½ (h)	Mean	4.49	2.64	4.29	3.58	3.54
	(sd)	.	.	(2.03)	(0.46)	(0.49)
	%cv	.	.	47.2	12.9	14.0
CLss/F (L/h)	Mean	326	299	372	406	399
	(sd)	.	.	(137)	(108)	(73.9)
	%cv	.	.	36.9	26.6	18.5
Vz/F (L)	Mean	2108	1142	2257	2040	2025
	(sd)	.	.	(1033)	(296)	(391)
	%cv	.	.	45.8	14.5	19.3

The time course of plasma concentrations for total methylphenidate was similar to that for d-methylphenidate: increased rapidly for the first hour followed by a slower ascending profile. On average, plasma concentrations for total methylphenidate peaked at 7 hours. These peak concentrations were followed by a gradual decline.

Dose Proportionality:





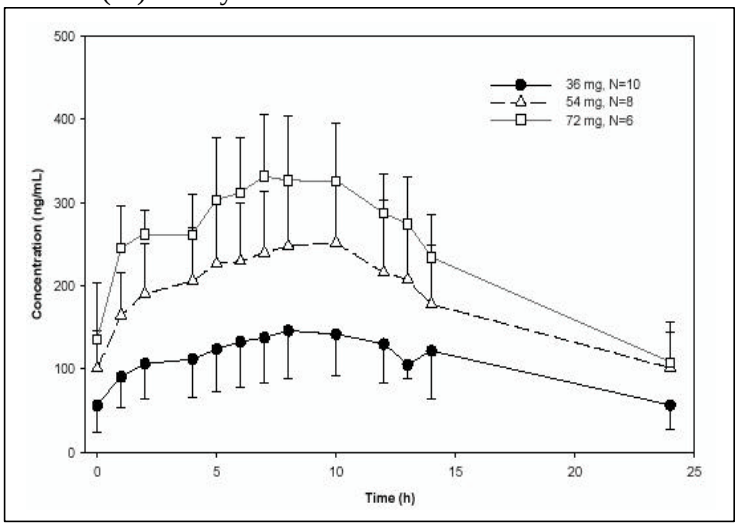


Linear regression shows that the Cmax and AUC increased proportionally with the increase in dose and the t1/2 remained unchanged.

D-, L-, and Total PPA Pharmacokinetics

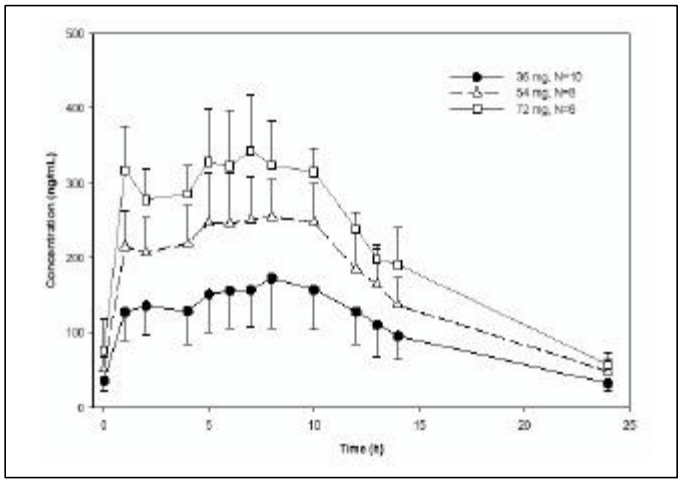
All subjects had quantifiable predose plasma concentrations of both d- and l-PPA. They ranged from 30 to 244 ng/mL for d-PPA and 16 to 84 ng/mL for l-PPA, although Subject 4 had a predose concentration of 159 ng/mL for the latter metabolite. The high plasma concentrations of d- and l-PPA are expected because these metabolites have longer half-lives than the respective parent isomers of methylphenidate.

Mean (sd) Steady-State Concentration Time Profiles for d-PPA



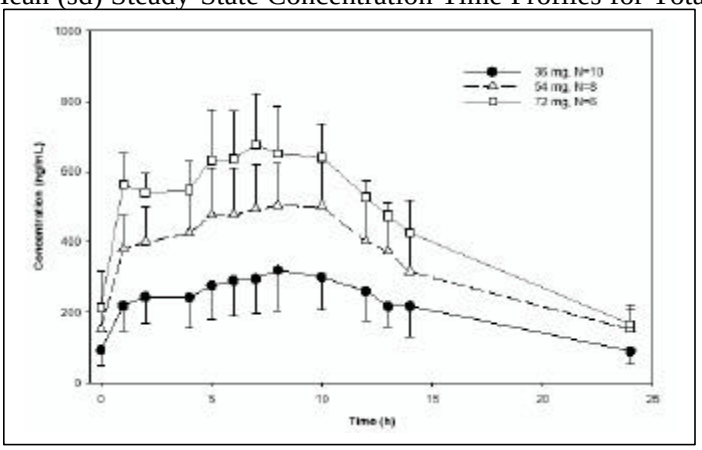
		d-PPA				
	Dose	18 mg (9 mg *d*-)	27 mg (13.5 mg *d*-)	36 mg (18 mg *d*-)	54 mg (27 mg *d*-)	72 mg (36 mg *d*-)
	N	1	1	10	8	6
CMAX (ng/mL)	Mean	79.3	140	154	263	354
	(sd)	.	.	(58.4)	(72.6)	(56.5)
	%cv	.	.	37.9	27.6	15.9
TMAX (h)	Mean	4.00	10.00	8.4	8.8	6.2
	(sd)	.	.	(2.3)	(1.4)	(2.3)
	%cv	.	.	27.6	15.9	37.6
AUCTAU (ng-h/mL)	Mean	1432	2072	2514	4394	5667
	(sd)	.	.	(963)	(1539)	(1088)
	%cv	.	.	38.3	35.0	19.2
KEL (h^{-1})	Mean	0.07	0.11	0.07	0.07	0.08
	(sd)	.	.	(0.02)	(0.02)	(0.02)
	%cv	.	.	23.6	23.1	26.3
T½ (h)	Mean	10.65	6.54	10.23	10.73	9.19
	(sd)	.	.	(2.44)	(2.73)	(2.39)
	%cv	.	.	23.9	25.4	26.0
CLss/F (L/h)	Mean	6.29	6.52	7.99	6.75	6.56
	(sd)	.	.	(2.52)	(2.00)	(1.29)
	%cv	.	.	31.6	29.6	19.7
Vz/F (L)	Mean	96.61	61.50	116	98.3	85.3
	(sd)	.	.	(41.3)	(14.7)	(20.6)
	%cv	.	.	35.6	15.0	24.1

Mean (sd) Steady-State Concentration Time Profiles for l-PPA



		l-PPA				
	Dose	**18 mg (9 mg *l*-)**	**27 mg (13.5 mg *l*-)**	**36 mg (18 mg *l*-)**	**54 mg (27 mg *l*-)**	**72 mg (36 mg *l*-)**
	N	1	1	10	8	6
CMAX (ng/mL)	Mean	101	131	186	272	397
	(sd)	.	.	(58.7)	(54.7)	(29.5)
	%cv	.	.	31.6	20.1	7.4
TMAX (h)	Mean	1.00	5.00	6.0	8.1	5.7
	(sd)	.	.	(2.8)	(1.6)	(2.5)
	%cv	.	.	47.1	20.2	44.2
AUCTAU (ng-h/mL)	Mean	1576	1582	2516	3888	5041
	(sd)	.	.	(685)	(908)	(575)
	%cv	.	.	27.3	23.4	11.4
KEL (h^{-1})	Mean	0.094	0.156	0.113	0.115	0.122
	(sd)	.	.	(0.027)	(0.011)	(0.017)
	%cv	.	.	23.9	9.2	14
T½ (h)	Mean	7.35	4.44	6.45	6.05	5.77
	(sd)	.	.	(1.50)	(0.56)	(0.77)
	%cv	.	.	23.3	9.2	13.4
CLss/F (L/h)	Mean	5.71	8.53	7.66	7.25	7.21
	(sd)	.	.	(2.10)	(1.50)	(0.74)
	%cv	.	.	27.5	20.7	10.3
Vz/F (L)	Mean	60.55	54.62	72.1	62.4	59.6
	(sd)	.	.	(26.2)	(10.3)	(7.0)
	%cv	.	.	36.3	16.5	11.7

Mean (sd) Steady-State Concentration Time Profiles for Total-PPA



		Total PPA				
	Dose	**18 mg**	**27 mg**	**36 mg**	**54 mg**	**72 mg**
	N	1	1	10	8	6
C_{MAX} (ng/mL)	Mean	179	254	335	532	746
	(sd)	.	.	(109)	(122)	(69)
	%cv	.	.	32.4	23	9.2
T_{MAX} (h)	Mean	2	5	8.0	8.1	5.8
	(sd)	.	.	(1.9)	(1.6)	(2.6)
	%cv	.	.	24.3	20.2	43.9
AUC_{TAU} (ng-h/mL)	Mean	3010	3657	5037	8294	10718
	(sd)	.	.	(1539)	(2428)	(1471)
	%cv	.	.	30.5	29.3	13.7
K_{EL} (h^{-1})	Mean	0.079	0.123	0.088	0.088	0.098
	(sd)	.	.	(0.021)	(0.014)	(0.018)
	%cv	.	.	23.9	15.9	18.7
T½ (h)	Mean	8.75	5.62	8.26	8.08	7.27
	(sd)	.	.	(1.87)	(1.37)	(1.32)
	%cv	.	.	22.7	17.0	18.2
CLss/F (L/h)	Mean	5.98	7.38	7.75	6.95	6.82
	(sd)	.	.	(2.24)	(1.73)	(0.89)
	%cv	.	.	28.9	24.9	13.1
Vz/F (L)	Mean	75.50	59.86	92.15	78.39	70.75
	(sd)	.	.	(32.22)	(11.62)	(11.36)
	%cv	.	.	35.0	14.8	16.1

Following oral administration of CONCERTA®, plasma concentrations of d-, l- and total PPA increased rapidly over the first hour then ascended more gradually thereafter. This unique profile reflects the methylphenidate release pattern of the overcoat layer and OROS® delivery system. Plasma concentrations reached a peak between four to eight hours after the dose, and then declined.

Parent-to-Metabolite AUCTAU Ratios

Mean AUCTAU ratios of parent to metabolite for d-, l-, and total methylphenidate to d-, l-, and total PPA, respectively, are summarized in the following Table. The ratios are similar for all dose levels, indicating that the metabolism of methylphenidate from CONCERTA ® is not dose dependent.

	Mean AUCTAU Ratios of MPH to PPA				
Dose (mg)	18	27	36	54	72
N	1	1	10	8	6
AUCTAU (*d*-MPH) / AUCTAU (*d*-PPA)	0.0384	0.0433	0.0475	0.0335	0.0328
AUCTAU (*l*-MPH) / AUCTAU (*l*-PPA)	0.0002	0.0003	0.0010	0.0010	0.0007
AUCTAU (Total-MPH) / AUCTAU (Total-PPA)	0.0184	0.0247	0.0229	0.0177	0.0175

The metabolism of methylphenidate in adolescents appears similar to that in adults based on the methylphenidate-to-PPA AUCTAU ratios. The mean parent to metabolite AUCTAU ratio in adults for total methylphenidate from Study 98-024 was 0.0190 after a 18 mg single dose compared to 0.0184 in adolescents from this study. This finding is consistent with methylphenidate being predominantly metabolized by esterases, which are not known to be different between adolescents and adults.

Isomer AUCTAU Ratios for Methylphenidate and PPA

Overall, plasma concentrations of l-methylphenidate were about 1/40 (or lower) than those of d-methylphenidate. Similarly, the mean AUCTAU ratios of l- to d-methylphenidate for the various doses were also about 1/40 or lower. The mean AUCTAU ratios of l- to d-PPA were close to unity and similar to the ratios in adults.

	Mean *l*- to *d*- AUCTAU Ratios				
Dose (mg)	18	27	36	54	72
N	1	1	10	8	6
AUCTAU (*l*-MPH) / AUCTAU (*d*-MPH)	0.0069	0.0061	0.0190	0.0262	0.0201
AUCTAU (*l*-PPA) / AUCTAU (*d*-PPA)	1.101	0.764	1.046	0.882	0.934

Covariate Analysis of PK Data Within Study 12-001

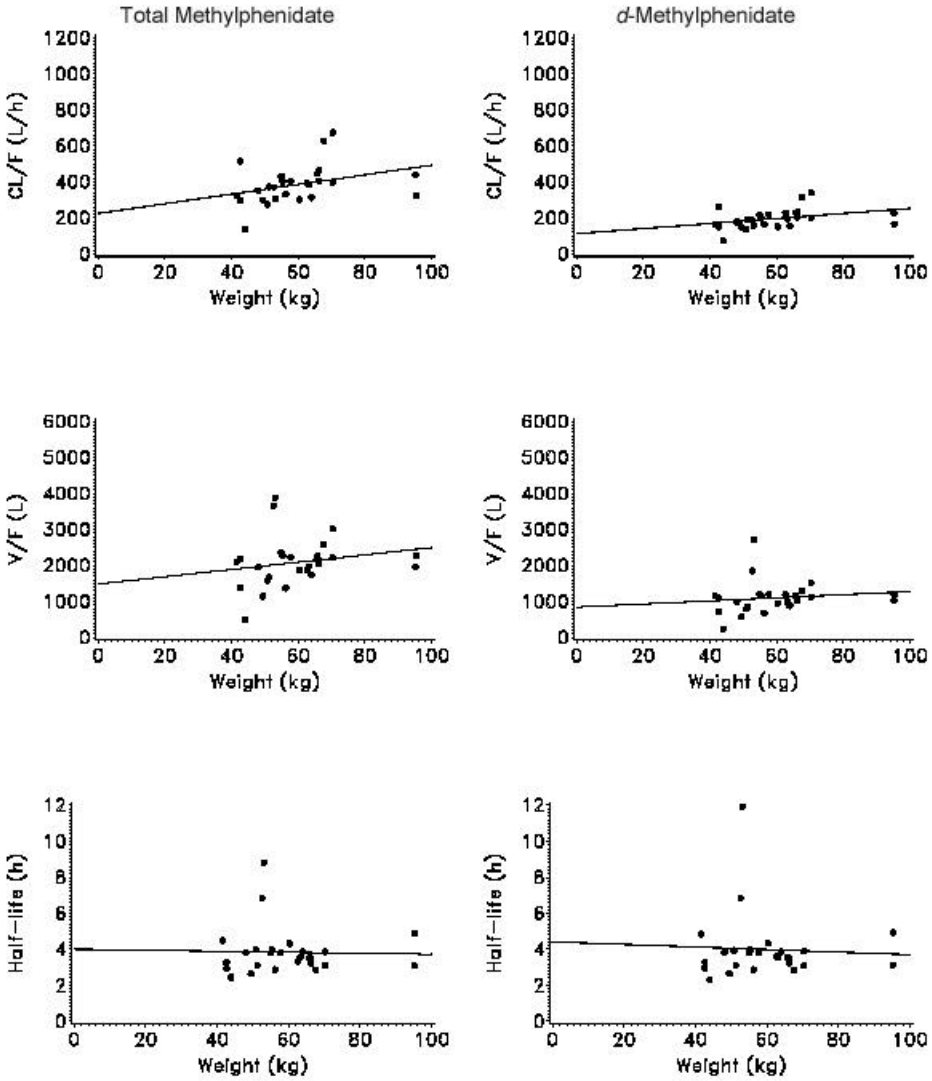
The effect of weight, age, and gender on key pharmacokinetic parameters (CLss/F, Vz/F and T½) for total and d-methylphenidate was investigated. Both CLss/F and Vz/F were normalized to body weight to investigate the effect of age.

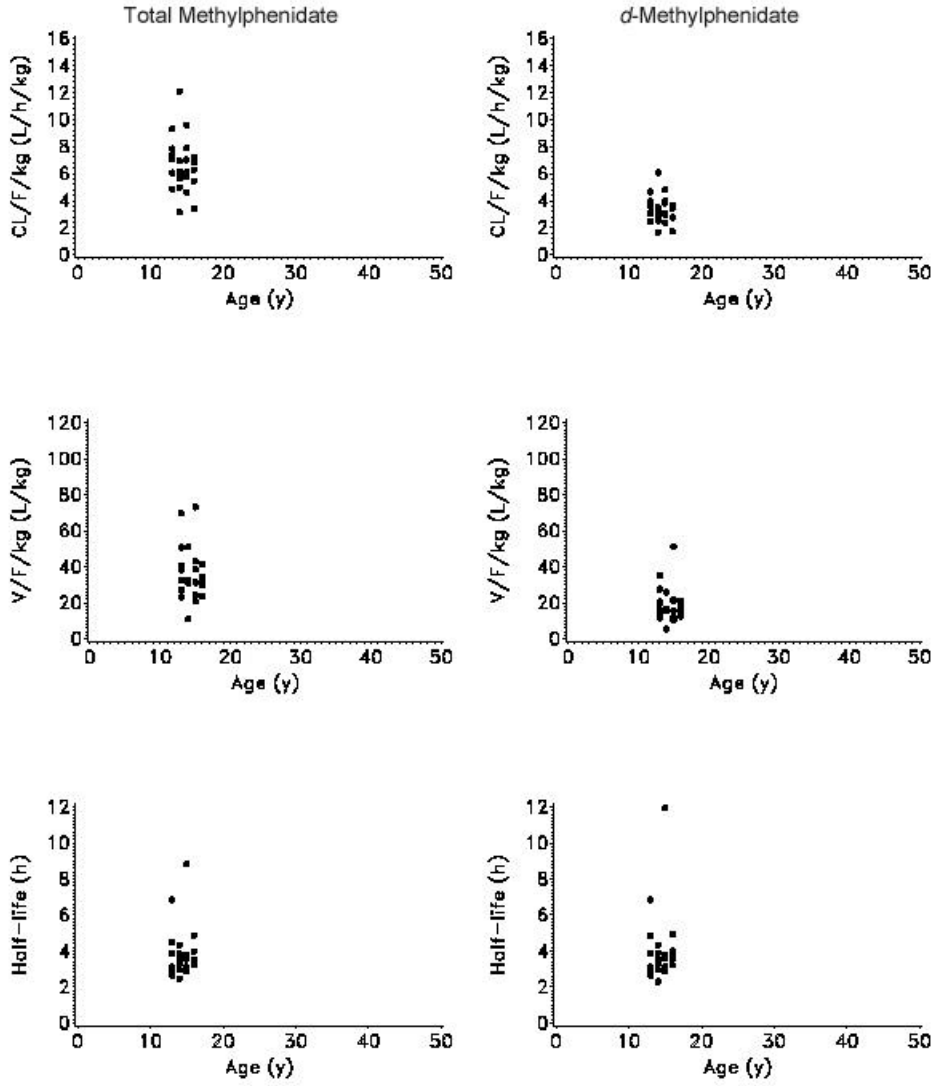
Results of the analyses with weight showed no significant effect on Vz/F and T½; although the effect of weight on CLss/F approached significance (p=0.09).

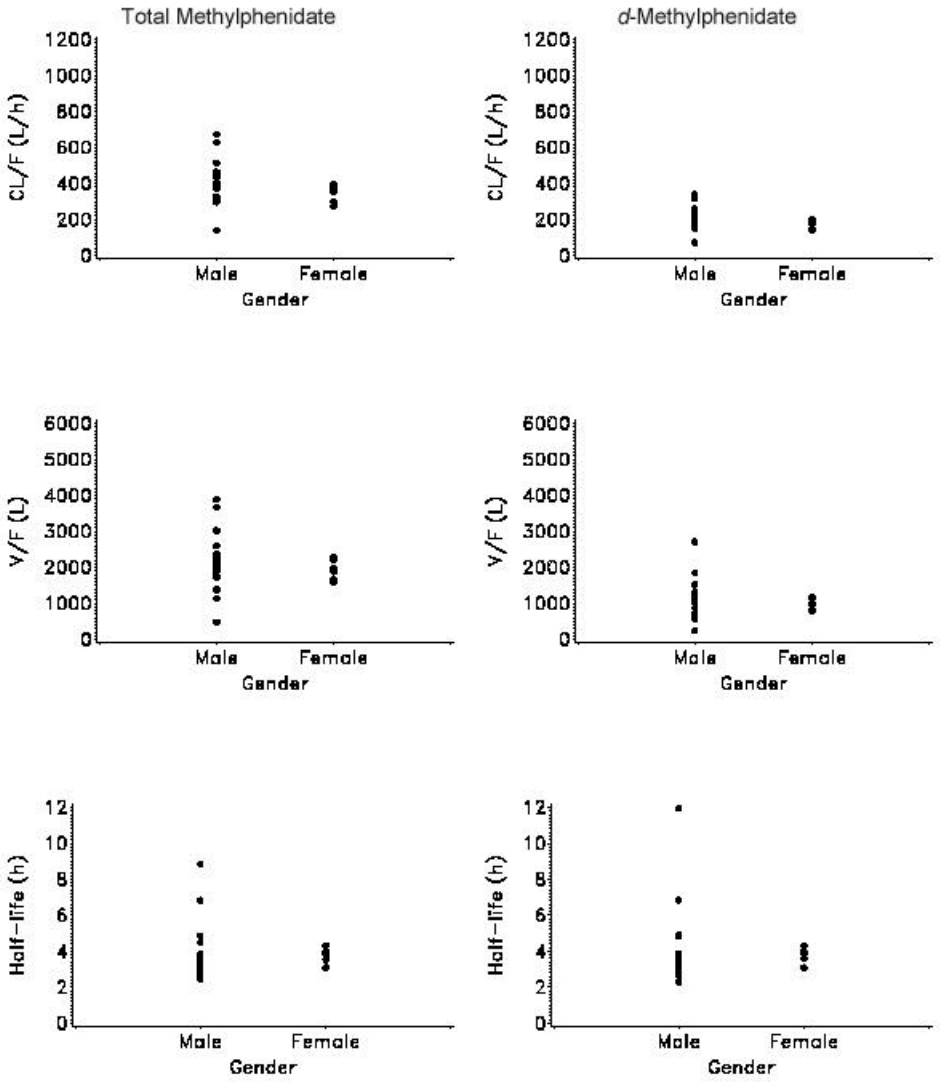
Similarly, results of the analyses with age (ages 13-17 years) showed no significant effect on weight- normalized CLss/F, weight-normalized Vz/F, and T½. Age explained no more than 3.4% of the variability on any parameter.

Finally, results of the analyses by gender showed no significant effect on CLss/F, Vz/F, and T½ ($p > 0.4172$).

The following figures show the individual parameters based on weight, age and gender for Study 12001




Total Methylphenidate
d-Methylphenidate
CL/F/kg (L/h/kg)
V/F/kg (L/kg)
Half-life (h)
Age (y)



Covariate Analysis of PK Data Across McNeil (Adolescent) and ALZA (Adult and children) Studies:

Data on total methylphenidate were pooled from ALZA Studies 97-033, 98-024, 98-025, 99-002, and 99-025 (NDA 21-121), and McNeil Study 12-001 in order to evaluate across a wide age range for potential effects of weight, age, and gender on key pharmacokinetic parameters. Estimates of CL/F, Vz/F, and T½ for children and adolescents were obtained from steady-state methylphenidate concentrations after multiple doses, whereas estimates for adults were obtained after a single dose. Both sets of estimates are comparable, because methylphenidate exhibits linear pharmacokinetics over dose and time and accumulation is low due to short half-life.

In addition, CL/F, Vz/F, and T½ in children ages 6 to 12 years were not available for

CONCERTA ® , because they could not be estimated in ALZA Study 97-033 due to sparse blood sampling and the unique concentration profile. However, in this same study, data from children taking Ritalin ® three times a day was modeled by the sponsor using population techniques to estimate the CL/F, Vz/F, and T½ for methylphenidate. According to the sponsor, because these parameters are inherent characteristics of how a drug is handled by the body, they are expected to be the same for both Ritalin ® and CONCERTA ®, and data from ALZA Study 98-024 in adults confirmed this principle. Hence, the children's modeled CL/F, Vz/F and T½ values with Ritalin ® from ALZA Study 97-033 were pooled with CONCERTA ® data from the studies listed above in adolescents and adults, and with Ritalin ® data in adults from ALZA Study 98-024. Overall, the pooled data used in these analyses provided insight into the effect of the demographics on CONCERTA ® pharmacokinetics across the three populations: children, adolescents, and adults.

Pharmacokinetic data for d-methylphenidate were only available from ALZA Study 98-025 in adults and McNeil Study 12-001 in adolescents. They were pooled and analyzed similarly to total methylphenidate. The following Table summarizes the mean parameters from pooled study data for total methylphenidate by the three age groups and for d-methylphenidate for adolescents and adults.

Mean (sd) Parameters By Age Group Using Pooled Historical Data

Pharmacokinetic Parameter	Children	Adolescents	Adults
Age Range (y)	6 to 12	13 to 17	18 and Over
Total Methylphenidate			
N	31	26	207
Cl/F (L/h)	243 (68)	384 (109)	497 (162)
V/F (L)	653 (159)	2088 (700)	2508 (909)
T½ (h)	1.92 (0.36)	3.84 (1.34)	3.52 (0.59)
Wt Normalized Cl/F (L/h/kg)	6.58 (2.02)	6.60 (1.88)	7.31 (2.16)
Wt Normalized V/F (L/kg)	17.7 (4.6)	36.1 (13.7)	36.7 (11.7)
d-Methylphenidate			
N		26	102
Cl/F (L/h)	--	196 (54.9)	254 (90.2)
V/F (L)	--	1101 (449)	1343 (376)
T½ (h)	--	3.99 (1.85)	3.82 (0.74)
Wt Normalized Cl/F (L/h/kg)	--	3.36 (0.94)	3.73 (1.24)
Wt Normalized V/F (L/kg)	--	19.0 (8.8)	19.7 (5.3)

The sponsor had used Ritalin? data and not CONCERTA? data to compare the pharmacokinetic parameters (Cl, Vd and t1/2) between the adolescents, children and adults. Although these

parameters are inherent characteristics of the drug and hence such comparisons should be acceptable, attempts have been made to compare other pharmacokinetic parameters (AUC, Cmax and Tmax) from the CONCERTA product between adolescents, children and adults at equivalent doses. The mean pharmacokinetic parameters from the ALZA studies in children and adults as taken from the review of N21-121, were compared to this study 12001 in adolescents for the following doses. The original NDA review did not report the standard deviations associated with the parameters and hence could not be reported here as well. Study 12001 was a multiple dose study where all subjects were given their doses for 6 consecutive days, where as studies in children and adult were single dose studies. A multiple dose study was not available for the 36 and 54 mg doses, but was available for the 18 mg dose. There was only one subject at the dose of 18 mg from Study 12001. The review of the original NDA 21-121 indicated that there was only 14% accumulation upon multiple dosing. Comparisons between multiple dose and single dose studies have been made here. Plasma samples were taken only up to 11.5 hours in children in Study 97-033, therefore for rough comparisons AUC0-12 was calculated from the adolescent study. These cross study comparisons should only be considered a crude methodology for comparing data. Since the sponsor had used Ritalin data to compare the CL, Vd and t1/2 between the adolescents, children and adults, the best that could be done with the CONCERTA formulation is tabulated below. Keeping the inherent limitation of this comparison in mind the pharmacokinetic parameters between the adolescents, children and adults seem to follow similar trends as observed for CL/F and Vz/F. The Cmax and AUC of total methylphenidate tended to decrease as age increased, which is consistent with the observed increase in CL with the increase of age.

Dose	Parameter	Children	Adolescents	Adults	Adults
		Study 97-033	Study 12-001	Study 99-002	Study 98-025
		SD	QD for 6 days	SD	SD
36 mg	Cmax (ng/ml)	11.3	9.9	6.20	7.28
	Tmax (h)	8.1	7.0	6.5	7.5
	AUC? (ng.h/ml)		112	66.9	80.66
	AUC0-12 (ng.h/ml)	87.7 (AUC0-11.5)	84		
	T1/2 (h)		4.29	3.5	
54 mg	Cmax (ng/ml)	15	12.8		10.52
	Tmax (h)	9.1	6.8		6.3
	AUC? (ng.h/ml)		141		118.8
	AUC0-12 (ng.h/ml)	121.5 (AUC0-11.5)	105		

Weight

A 10 kg increase in weight resulted in a 66.9 L/h increase in CL/F for total methylphenidate and a 22.4 L/h increase in CL/F for d-methylphenidate. These relationships were statistically significant (p?0.0001) and explained over 34% and 11% of the variability in CL/F for total and d-methylphenidate, respectively.

A 10 kg increase in weight resulted in a 441 L increase in Vz/F for total methylphenidate and a 104 L increase in Vz/F for d-methylphenidate. These relationships were statistically significant (p?0.0001) and explained over 42% and 11% of the variability in Vz/F for total

and d-methylphenidate, respectively.

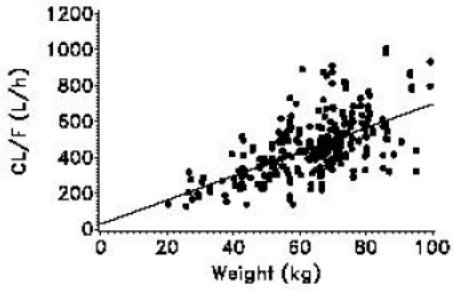
A 10 kg increase in weight resulted in a 0.25 h increase in T½ of total methylphenidate. This relationship was statistically significant ($p<0.0001$) and explained over 19% of the variability in T½ for total methylphenidate. There was no relationship between weight and T½ for d-methylphenidate.

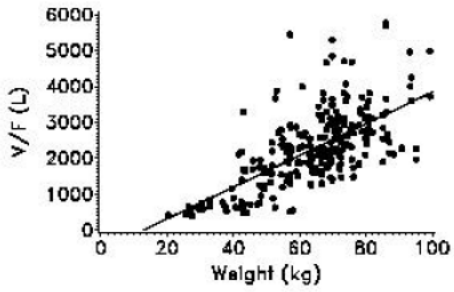
In summary, these analyses showed an effect of weight on CL/F, Vz/F, and T½ for total methylphenidate and an effect of weight on CL/F and Vz/F, but not T½ for d-methylphenidate.

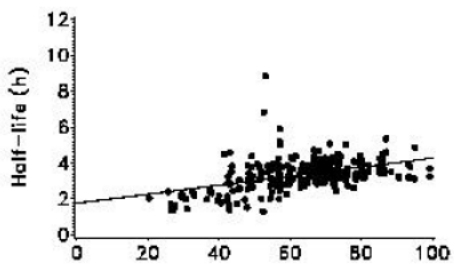
Analysis Results of Effect of Weight on Selected Pharmacokinetic Parameters for Total and d-Methylphenidate (Historical Data)

	CL/F (L/h)	Vz/F (L)	Half life (h)
Total Methylphenidate			
Intercept	27.91	-575.2	1.755
Slope	6.688	44.14	0.0252
p-value (slope)	<0.0001	<0.0001	<0.0001
R square	0.3464	0.4212	0.1944
d-Methylphenidate			
Intercept	92.08	598.8	3.916
Slope	2.241	10.37	-0.00086
p-value (slope)	0.0001	0.0001	0.9055
R square	0.1117	0.1129	0.0001

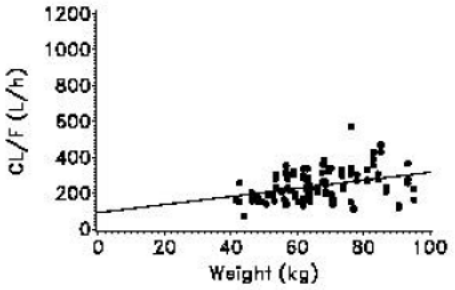
Total Methylphenidate

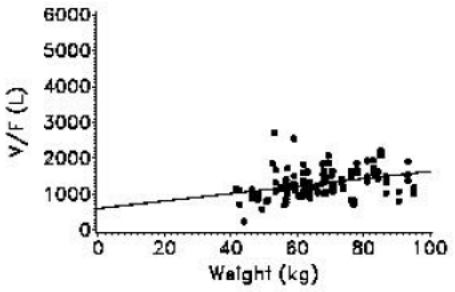


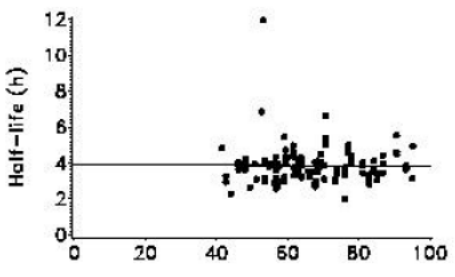




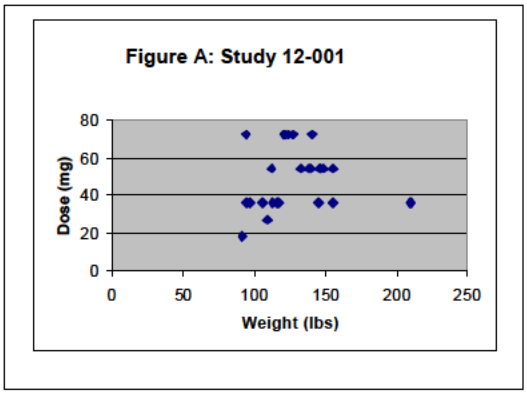
d-Methylphenidate

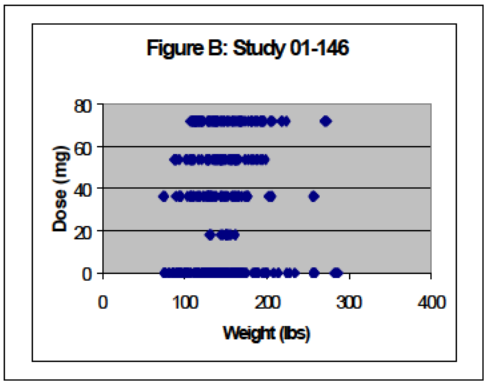






Based on these trends it appears that as the body weight increases, subjects may require higher doses. Trends towards this was somewhat evident from the pharmacokinetic study 12-001. In this study subjects received their doses as prescribed by their personal physicians. Only one subject was enrolled at the dose of 18 mg and one at the dose of 27 mg. Looking at the demographic information, it was observed that these two subjects were 13 year olds with body weight of 41.5 and 49.4 kg. In this study there were 3 more 13-year-olds enrolled with body weight of 48, 51 and 67 kg. These subjects were given 36 mg, 36 mg and 54 mg respectively. There did seem to be a trend. Subjects with higher weight tended to receive higher doses, although there was overlap of doses with the same weight range as well, as shown in the following figure A. The controlled clinical efficacy study (Study 01-146) for this submission was conducted with an open label titration phase, where subjects initiated treatment with a dose of 18 mg/day. This dose was increased in 18 mg increments every week until an individualized dose was identified that produced the criteria for improvement in ADHD symptoms with tolerable safety for a given subject to a maximum of 72 mg/day. In the double blind phase, subjects completing the titration phase were randomized to receive their individualized CONCERTA dose or placebo. The doses administered to the subjects in the double blind phase is shown in the following figure B. In this study as well only ~5% of the subjects stayed on the 18 mg dose, suggesting that most of the adolescents need higher doses.





Given the titration design of the clinical efficacy study, a meaningful exposure response analysis cannot be obtained to elucidate the clinical significance of reduced exposure based on pharmacokinetic parameters and cannot corroborate the need for higher doses with the increase in body weight. Even looking at the doses received by these subjects in the two studies there seems to be a considerable overlap in the doses administered at similar weights. This could be either due to sensitivity or tolerance to the drug. Hence, without the knowledge of exposure response relationships, any dosing recommendations based on weight is difficult to be established. Based on the criteria for improvement in the PD endpoint (?30% improvement in symptoms of ADHD from baseline), subjects with similar weight required doses in the range of 18-72 mg. Although dosing recommendations based on weight cannot be made, it could be that adolescents with higher bodyweight may need doses up to 72 mg, provided safety is not compromised with the use of higher doses.

Age

Both CL/F and Vz/F were normalized by weight so that the effect of age independent of the differences in body weight across ages could be assessed. Results of these analyses are listed in the following Table, and they show an effect of age ($p<0.0001$) on weight-normalized CL/F and Vz/F, and on T½ for total methylphenidate.

There was no significant effect of age on any parameter for d-methylphenidate, with less than 2% of the variability explained by age.

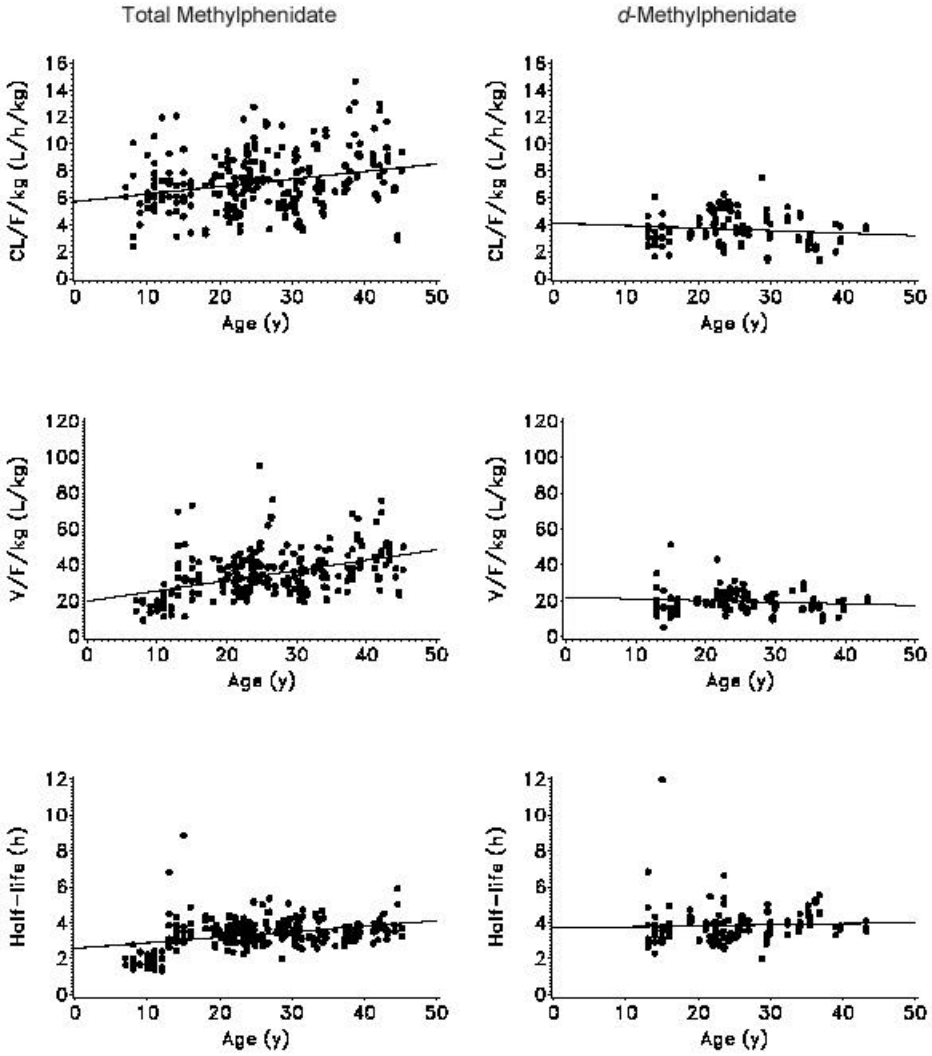
A 10-year increase in age resulted in a 0.6 L/h/kg increase in weight-normalized CL/F for total methylphenidate. This relationship was statistically significant ($p<0.0001$) but explained only 6.5% of the variability in weight-normalized CL/F for total methylphenidate.

A 10-year increase in age resulted in a 5.7 L/kg increase in weight-normalized Vz/F for total methylphenidate. This relationship was statistically significant ($p<0.0001$) and explained 19% of the variability in Vz/F for total methylphenidate.

A 10-year increase in age resulted in a 0.31 h increase in T½ of total methylphenidate. This relationship was statistically significant ($p<0.0001$) and explained 12% of the variability in T½ for total methylphenidate.

Analysis Results of Effect of Age on Weight-Normalized
Pharmacokinetic Parameters for Total and d-Methylphenidate (Historical Data)

	CL/F (L/h/kg)	Vz/F (L/kg)	Half life (h)
Total Methylphenidate			
Intercept	5.721	19.77	2.580
Slope	0.0559	0.5706	0.0307
p-value (slope)	<0.0001	<0.0001	<0.0001
R square	0.0653	0.1875	0.1201
d-Methylphenidate			
Intercept	4.123	21.86	3.701
Slope	-0.0185	-0.0897	0.0062
p-value (slope)	0.1656	0.1924	0.5998
R square	0.0152	0.0134	0.0022

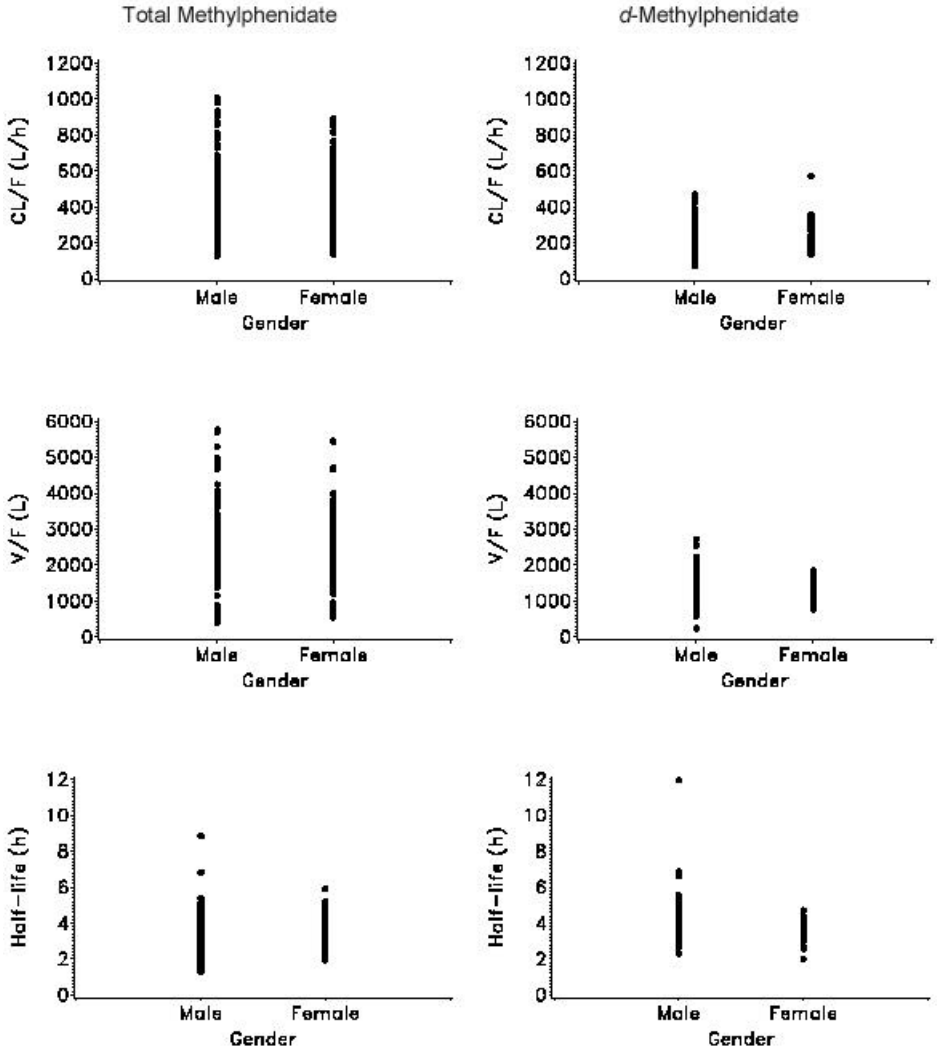


Gender

There were no statistically significant differences between genders in any of these parameters for total methylphenidate (p? 0.2106), but there were statistically significant differences between males and females for Vz/F and T½ for d-methylphenidate. For d-methylphenidate, males had a greater Vz/F and T½ than females. There was no significant difference between genders on CL/F for d-methylphenidate.

Analysis Results of Effect of Gender on Selected Pharmacokinetic Parameters for Total and d-Methylphenidate (Historical Data)

	CL/F (L/h)	Vz/F (L)	Half life (h)
Total Methylphenidate			
p-value (Gender)	0.7530	0.2106	0.7093
Mean			
Male (N=142)	458.83	2322.0	3.384
Female (N=122)	452.16	2163.3	3.434
d-Methylphenidate			
p-value (Gender)	0.4196	0.0066	0.0363
Mean			
Male (N=85)	246.75	1361.6	3.997
Female (N=43)	233.50	1159.0	3.584



Safety:

All 26 enrolled subjects completed the study per protocol. No subjects were withdrawn from the study for any reason. No clinically relevant changes in vital signs were observed in the study subjects from the time they were screened until they completed the study. In addition, no serious adverse events were reported. Eight of the 26 subjects reported a total of seven mild and three moderate adverse events during the study. None were categorized as related to study drug by the investigators.

OVERALL CONCLUSIONS

? The plasma concentration-time profiles of d- and total methylphenidate in adolescents were similar to the unique ascending profiles observed in previous studies with CONCERTA® in adults and children . Specifically, these profiles showed the rapid increase in concentrations over the first hour due to the immediate-release overcoat followed by gradual ascending concentrations over the next six hours due to the OROS ® osmotic core.

- The pharmacokinetics of methylphenidate in adolescents were linear with dose up to 72 mg.
- In cross study comparisons the CL/F of total methylphenidate in children, adolescents and adults were 243, 384 and 497 L/h respectively, showing an increase of 58% in adolescents and 104% in adults compared to children. The weight normalized CL/F in these populations were 6.58, 6.60 and 7.31 L/h/kg respectively (see Table on page 29).
- The metabolism of methylphenidate in adolescents appears similar to that in adults based on the methylphenidate-to-PPA AUCTAU ratios.
- In the covariate analyses using only adolescent data, there were no statistically significant findings of the effect of weight, age, or gender on CLss/F, Vz/F, and T½ for both d- and total methylphenidate.
- In the covariate analyses using pooled data from children, adolescents, and adults, there were some statistically significant findings. Body weight had a significant effect on CL/F and Vz/F for both d- and total methylphenidate.
- The effect of age using pooled data from children, adolescents, and adults was investigated on weight-normalized CL/F and Vz/F so as not to confound the effect of age with differences in body size. There was a statistically significant age effect on these weight-normalized CL/F and Vz/F and T½ for total methylphenidate, which included data for children, adolescents, and adults. However, there was no significant age effect on any parameter for d-methylphenidate, which included data for only adolescents and adults. This analysis showed that the weight-normalized CL/F for total methylphenidate increased slightly with age. Given the caveats of using pooled data across studies in these analyses and the magnitude of the effect on the weight-normalized parameters, the clinical relevance of these differences with age cannot be explained.
- There was no gender effect on any parameter for total methylphenidate, which included data for the three age groups. A gender effect was statistically significant on Vz/F and T½ for d-methylphenidate, which included data for adolescents and adults.
- Although there was a significant weight and age effect on the CL/F and Vz/F for total methylphenidate, dosing recommendation based on weight cannot be made due to lack of an established exposure-response relationship as well as due to confounding factors as tolerance or sensitivity which was evident based on the considerable overlap in the doses administered (18-72 mg) at similar body weights.

Study 01-148: Effect of diet on the bioavailability and pharmacokinetics of CONCERTA and ADDERALL XR in healthy adults

This study did not affect the labeling, but was reviewed for the sake of completeness of information provided to the Agency.
CONCERTA is a long-acting form of methylphenidate HCl designed for a 12-hour duration of effect utilizing OROS technology, and was approved in August 2000 for the treatment of ADHD. Some children do not respond to methylphenidate. Among the 30% to 40% of nonresponders, many may respond to other stimulant medications. An alternative stimulant therapy is the use of short-, intermediate-, and long-acting d-amphetamine. The latter two compounds are available as mixed amphetamine salts (b) (4) d-amphetamine and (b) (4) l-amphetamine). The McMaster report reviewed 22 studies and showed no differences comparing methylphenidate with dextroamphetamine or among different forms of these stimulants. The ADDERALL XR Capsule is the extended-release formulation of mixed amphetamine salts, and was approved in October 2001 for prescription use.

Objective:
The primary objective was to determine whether food alters the bioavailability and pharmacokinetic profile of each extended-release product.
The secondary objective was to determine whether the food effect on the rate of drug absorption from CONCERTA is less than that from ADDERALL XR.

Methodology:
This study had a single-dose, open-label, randomized, four-treatment, crossover design. Subjects each received four treatments, and the study periods were separated by a minimum of one week for drug washout. They reported to the clinical center the evening before each study period for a 10 hour supervised fast, and remained sequestered until after the last blood sample was collected 28 hours after dosing.

Study Population:
Thirty-six healthy male (17) and female (19) subjects, ages 18 through 50 years, completed the study and were included in the pharmacokinetic analysis.

Population and Size	Age (y)	Height (in)	Weight (lb)	Weight (kg)	Frame[a] (S / M/ L)	Race[b] (B / C / H / O)
17 Men	28.1	70.2	170.1	77.2	4/ 13/ 0	4/ 11/ 1/ 1
	(7.4)	(2.0)	(19.4)	(8.8)		
	20 to 46	66 to 73	143 to 208	65 to 94		
19 Women	30.4	65.1	143.4	65.0	3/ 13/ 3	0/ 13/ 6/ 0
	(8.3)	(2.2)	(21.4)	(9.7)		
	19 to 46	59 to 68	117 to 194	53 to 88		
36	29.3	67.5	156.0	70.8	7/ 26/ 3	4/ 24/ 7/ 1
Subjects	(7.9)	(3.3)	(24.3)	(11.0)		
	19 to 46	59 to 73	117 to 208	53 to 94		

Data are mean, sd, and range
a: S = Small, M = Medium, L = Large
b: B= Black, C= Caucasian, H= Hispanic, O= Other

Dosing and Administration:
Subjects received a single 36-mg dose of methylphenidate as one CONCERTA Tablet and a single 20-mg dose of mixed amphetamine salts as one ADDERALL XR Capsule according to a randomization schedule. Doses of each drug were administered both after an overnight fast and 15 minutes after a high-fat breakfast. Each treatment was separated by a one-week washout period.

Duration of treatment:
Subjects received one dose of methylphenidate during two study periods, and one dose of mixed amphetamine salts during two study periods. Each period had a two-day duration.

Test product, dose and mode of administration, batch number:
A: One CONCERTA Tablet, 36 mg, was swallowed with 240 mL of water. Subjects ate a high- fat breakfast 15 minutes before the dose. Lot 0111484
C: One ADDERALL XR Capsule, 20 mg, was swallowed with 240 mL of water. Subjects ate a high-fat breakfast 15 minutes before the dose. Lot 1E2232A

Reference product, dose and mode of administration, lot number:
B: One CONCERTA Tablet, 36 mg, was swallowed with 240 mL of water. Subjects fasted overnight before the dose. Lot 0111484
D: One ADDERALL XR Capsule, 20 mg, was swallowed with 240 mL of water. Subjects fasted overnight before the dose. Lot 1E2232A

Blood Samples:
Nineteen blood samples were withdrawn over 28 hours after each dose and, from these, plasma was harvested. They were collected before dosing and at 1, 2, 2.5, 3, 3.5, 4, 5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 12, 15, 24 and 28 hours after the dose.
Methylphenidate or amphetamine was quantified using validated assays.

Bioanalytical Methods:
Samples were analyzed for total methylphenidate and total amphetamine concentrations, as applicable, using validated assay methods.

Methylphenidate
Method: High-performance liquid chromatographic method with mass spectrometry detection (LC/MS/MS)
Linearity: linear over the range 0.25 to 25.0 ng/mL.
Accuracy : Accuracy of the assay over a range of 0.250 to 25.0 ng/mL was demonstrated by coefficients of variation that ranged from 1.8 to 5.5% for the means at each concentration of the standard curve with % deviation from –0.176 to 0.441. The % deviation from theoretical ranged from 8.25-10.4% on QC samples of 0.5, 2.5 and 20 mg/mL with % CV less than 5.38% for all samples.
Precision: Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of 0.250, 0.500, 2.50, and 20.0 ng/mL. The coefficients of variation were 4.1, 4.0, 5.3, and 2.9% for the limit-of-quantitation, low, medium, and high control samples, respectively.
Recovery: Recovery was determined during validation by comparing the methylphenidate and internal standard analyte responses of extracted samples to those of external standards representing 100% recovery. Recoveries of methylphenidate from QC samples at low, medium, and high concentrations were 83.9, 68.2, and 73.3%,

respectively. The corresponding recoveries of the internal standard were 79.8, 64.9, and 76.7%.

Stability: At –20?C for 259 days

Total Amphetamine

Method: Gas chromatography with nitrogen-phosphorous detection (GC) method

Linearity: linear over the range 0.25 to 50.0 ng/mL.

Accuracy: Accuracy of the assay over a range of 0.250 to 50.0 ng/mL was demonstrated by coefficient of variation that ranged from 3.6 to 8.6% for the means at each concentration of the standard curve with percent deviation from theoretical ranging from –1.77 to 2.43%. The % deviation from theoretical for the QC samples at 5, 6 and 40 ng/mL ranged from –1.68 to 5.99% with % CV less than 12.5 for all samples.

Precision: Precision of the method was demonstrated by the assay of pooled quality control (QC) samples at nominal concentrations of 0.250, 0.500, 6.00, and 40.0 ng/mL. The coefficients of variation were 5.5, 9.1, 10.1, and 4.1% for the limit-of-quantitation, low, medium, and high control samples, respectively.

Recovery: Recovery was determined during validation by comparing the amphetamine and internal standard analyte responses of extracted samples to those of external standards representing 100% recovery. Recoveries of amphetamine from QC samples at low, medium, and high concentrations were 74.1, 64.4, and 71.1%, respectively. The recovery of the internal standard was 70.3%.

Stability: At –20?C for 153 days

Criteria for Evaluation:

Pharmacokinetics: The pharmacokinetic parameters for methylphenidate and amphetamine in plasma were determined using noncompartmental methods. To determine food effects on the bioavailability of each extended-release dosage form, LCMAX, and LAUCINF were used. To determine the effect of food on the rate of absorption or early drug exposure, AUCp4h; AUCp6h; AUCp8h; and TMAX were used.

Safety:

Safety was assessed by reviewing vital signs, clinical laboratory test results, and the occurrence and seriousness of any adverse events.

Pharmacokinetic Results:

Mean pharmacokinetic profiles with and without food are shown in Figures 1-1 and 1-2 for methylphenidate and amphetamine, respectively.

Figure 1-1. Mean Pharmacokinetic Profiles for Methylphenidate (linear)

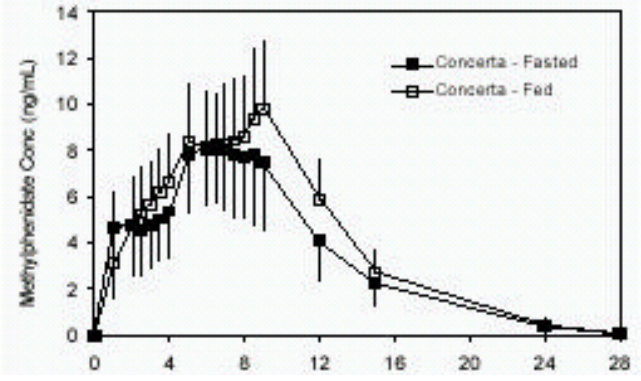
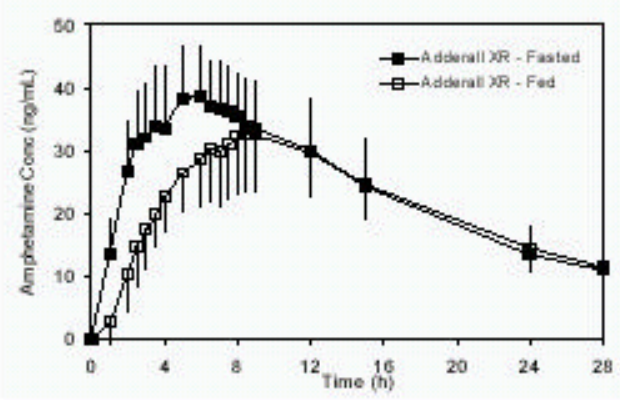


Figure 1-2. Mean Pharmacokinetic Profiles for Amphetamine (linear)



Food ingestion resulted in opposite shifts in the concentration-derived parameters (AUCs and CMAX) for the two stimulant drugs: the mean values increased for methylphenidate and decreased for amphetamine. Moreover the shifts in mean plasma concentrations occurred mainly over the first eight hours post-dosing for amphetamine and after this time for methylphenidate.

The pharmacokinetic parameters (mean, sd, CV%) for the four treatment groups are listed in the following Table.

Treatment	AUCp4h (ng·h/mL)	AUCp6h (ng·h/mL)	AUCp8h (ng·h/mL)	AUCT (ng·h/mL)	AUCINF (ng·h/mL)	CMAX (ng/mL)	TMAX (h)	kEL (1/h)	t½ (h)
CONCERTA® 36 mg Fed (Treatment A)	17.1	33.0	49.8	111	114	10.4	8.35	0.222	3.23
	(6.4)	(9.0)	(12.6)	(24.8)	(24.1)	(2.45)	(1.32)	(0.044)	(0.55)
	38%	27%	25%	23%	21%	24%	16%	20%	17%
CONCERTA® 36 mg Fasted (Treatment B)	16.6	30.9	46.6	90.8	93.6	8.82	6.46	0.203	3.59
	(5.74)	(10.0)	(14.6)	(31.9)	(31.7)	(2.76)	(1.99)	(0.050)	(0.78)
	35%	32%	31%	35%	34%	31%	31%	25%	22%
ADDERALL XR® 20 mg Fed (Treatment C)	42.3	94.6	156	591	789	36.9	8.36	0.063	11.6
	(15.3)	(22.2)	(34.0)	(98.0)	(141)	(7.93)	(2.39)	(0.014)	(2.60)
	36%	23%	22%	17%	18%	22%	29%	22%	23%
ADDERALL XR® 20 mg Fasted (Treatment D)	90.7	164	238	668	853	43.0	5.76	0.065	11.1
	(22.0)	(35.7)	(45.5)	(140)	(208)	(6.87)	(2.45)	(0.012)	(2.14)
	24%	22%	18%	21%	24%	16%	43%	19%	19%

Statistical comparisons of CONCERTA and ADDERALL XR on the effect of food on early drug exposure are listed in the following Tables. During the assessment of individual pharmacokinetic profiles and parameters, results for Subject 17 (fasted) were noted as markedly different from those for the other subjects. Both the profile and AUCINF were much lower than those expected for the 36-mg dose after fasting and the TMAX was early. Therefore, the statistical analysis was repeated without data for Subject 17, and the confidence interval results were then borderline for LCMAX, but still higher for LAUCINF.
For ADDERALL XR, results of the 90% confidence interval analysis for LAUCINF and LCMAX fell within the limits of 80 to 125% as previously reported. Because of the delayed absorption with food over the first eight hours, the measures for early drug exposure were below the lower limit.

Table 9-2. Statistical Analysis of *ln*-Transformed Methylphenidate Parameters for the 36 Completed Subjects

Parameter	CONCERTA Fed[a] (Treatment A)	CONCERTA Fasted[a] (Treatment B)	Ratio[b] of Fed to Fasted	Intrasubject cv (%)	90% Confidence Intervals
LAUCp4h (ng·h/mL)	16.1	15.6	103.0	24.2	93.7 to 113.3
LAUCp6h (ng·h/mL)	32.0	29.3	109.2	18.4	101.6 to 117.5
LAUCp8h (ng·h/mL)	48.4	44.0	109.9	19.0	102.0 to 118.5
LAUC$_{INF}$ (ng·h/mL)	111	87.2	127.1	23.1	116.1 to 139.2
LC$_{MAX}$ (ng/mL)	10.1	8.33	121.8	22.1	111.6 to 132.9

a: geometric mean data
b: ratio of least squares means

Table 9-3. Statistical Analysis of *ln*-Transformed Methylphenidate Parameters for 35 Subjects (Subject 17 Excluded)

Parameter	CONCERTA Fed[a] (Treatment A)	CONCERTA Fasted[a] (Treatment B)	Ratio[b] of Fed to Fasted	Intrasubject cv (%)	90% Confidence Intervals
LAUCp4h (ng·h/mL)	16.2	16.1	100.5	21.9	92.0 to 109.7
LAUCp6h (ng·h/mL)	32.3	30.5	106.0	13.2	100.5 to 111.8
LAUCp8h (ng·h/mL)	48.9	46.1	106.0	11.1	101.4 to 110.9
LAUC$_{INF}$ (ng·h/mL)	112	92.0	121.3	11.3	115.9 to 126.9
LC$_{MAX}$ (ng/mL)	10.2	8.71	117.3	15.4	110.3 to 124.8

a: geometric mean data
b: ratio of least squares means

Table 9-4. Statistical Analysis of *ln*-Transformed Amphetamine Parameters for the 36 Completed Subjects

Parameter	ADDERALL XR Fed[a] (Treatment C)	ADDERALL XR Fasted[a] (Treatment D)	Ratio[b] of Fed to Fasted	Intrasubject cv (%)	90% Confidence Intervals
LAUCp4h (ng·h/mL)	39.0	87.7	44.5	39.4	38.3 to 51.8
LAUCp6h (ng·h/mL)	92.0	160	57.4	21.8	52.7 to 62.6
LAUCp8h (ng·h/mL)	152	234	65.1	16.3	61.0 to 69.4
LAUCINF (ng·h/mL)	776	827	93.8	13.9	88.8 to 99.1
LCMAX (ng/mL)	36.0	42.4	84.9	11.6	81.0 to 88.9

a: geometric mean data
b: ratio of least squares means

Table 9-5. Statistical Analysis of *ln*-Transformed Amphetamine Parameters for 35 Subjects (Subject 17 Excluded)

Parameter	ADDERALL XR Fed[a] (Treatment C)	ADDERALL XR Fasted[a] (Treatment D)	Ratio[b] of Fed to Fasted	Intrasubject cv (%)	90% Confidence Intervals
LAUCp4h (ng·h/mL)	39.1	87.7	44.1	39.7	37.7 to 51.4
LAUCp6h (ng·h/mL)	92.6	162	57.1	21.9	52.3 to 62.3
LAUCp8h (ng·h/mL)	154	237	64.8	16.5	60.7 to 69.2
LAUCINF (ng·h/mL)	779	827	94.2	13.9	89.1 to 99.7
LCMAX (ng/mL)	36.6	43.0	85.1	11.7	81.1 to 89.2

a: geometric mean data
b: ratio of least squares means

Safety Results:
No serious adverse events occurred during this study. Twenty-four mild or moderate adverse events were reported in ten subjects during dosing with 36 mg of CONCERTA.
Eleven were categorized as possibly and seven as likely related to study drug by the investigator. The remaining six events were considered unrelated.
Thirty-three mild adverse events were reported in sixteen subjects during dosing with 20 mg of ADDERALL XR. Fourteen were categorized as possibly and six as likely related to study drug by the investigator, with the remaining 13 considered unrelated to study drug.

OVERALL CONCLUSIONS:

? Pharmacokinetic profiles and bioavailability measures, with and without food, were consistent with those previously reported for both CONCERTA and ADDERALL XR.
? Absorption of mixed amphetamine salts from ADDERALL XR with food led to significant decreases in early amphetamine exposure over the first eight hours after dosing. By contrast, early methylphenidate exposure from CONCERTA was unaffected by food.
? The products were well tolerated. No subjects withdrew because of an adverse event, and no serious events were reported.

APPENDIX II

SPONSOR'S PROPOSED LABELING

(With Changes to Original Label)

24 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

APPENDIX III

FILING AND REVIEW FORM

Office of Clinical Pharmacology and Biopharmaceutics

New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	**N21-121 (SE1-008)**	**Brand Name**	**CONCERTA**
OCPB Division (I, II, III)	**I**	**Generic Name**	**Methylphenidate**
Medical Division	**120**	**Drug Class**	**Piperidine derivative**
OCPB Reviewer	**Veneeta Tandon**	**Indication(s)**	**ADHD**
OCPB Team Leader	**Ramana Uppoor**	**Dosage Form**	**Extended release tablets**
		Dosing Regimen	**72 mg/day**
Date of Submission	**9/5/03**	**Route of Administration**	**Oral**
Estimated Due Date of OCPB Review	**2/5/04**	**Sponsor**	**McNeil**
PDUFA Due Date	**3/5/04**	**Priority Classification**	**S**
1.1.1.5 Division Due Date			

Background:

This is a supplement to include an indication for treatment of Attention Deficit Hyperactivity Disorder (ADHD) in adolescents, submitted in response to a pediatric written request letter issued by the Agency. CONCERTA is currently approved for in children up to the age of 12 years with maximum daily dose of 54 mg/day. This supplement includes once daily dosing up to 72 mg/day in adolescents.

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			Validation provided
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:	X	1		A five dose study
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				

geriatrics:				
renal impairment:				
hepatic impairment:				
AIDS patients				
PD:				
Phase 2:				
Phase 3:	X			Some dose response information is there and the need to do additional analysis will be evaluated at the time of the review
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:	X Regression analysis			From McNeil and Alza studies in children, adolescents and adults Covariate analysis to see effect of age, weight and gender
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:	X	1		Concerta food effect compared to Adderall XR food effect (amphetamine)
Dissolution:	X	1		For products used in the 2 PK studies submitted in this supplement.
(IVIVC):				
Bio-waiver request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		2	2	

Filability and QBR comments

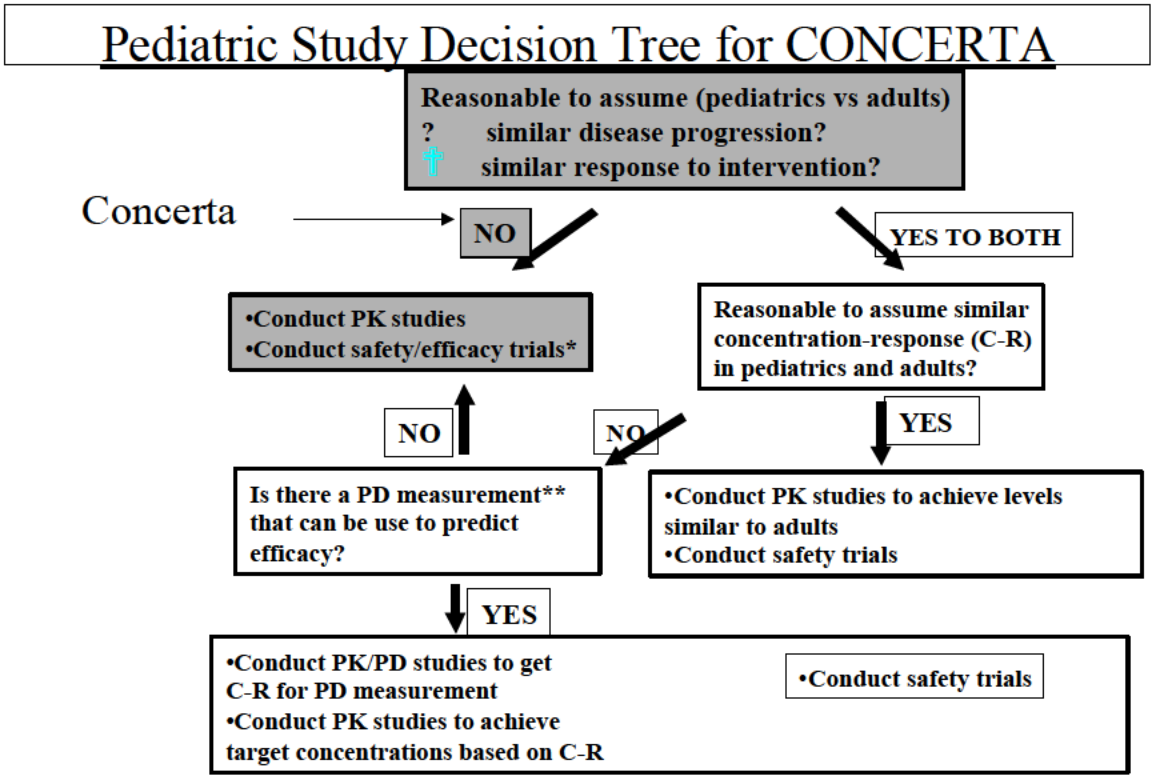
	"X" if yes	**Comments**
1 1.1.6		
1.1.1.7 Application filable ?	**X**	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
1.1.1.8 Comments sent to firm ?		Comments have been sent to firm (or attachment included). FDA letter date if applicable.
1.1.1.9		

QBR questions (key issues to be considered)	? **Are the analytical methods appropriately validated?** ? **Does the submitted data support the proposed label?** ? **Are the pharmacokinetics in adolescents similar to that in younger children ?**

Other comments or information not included above	**The PK study in adolescents reviewed from a filing point of view appeared to be sufficient to meet the terms of the PK study in the written request**
Primary reviewer Signature and Date	**Veneeta Tandon, Ph.D 10/14/03**
Secondary reviewer Signature and Date	**Ramana Uppoor, Ph.D 10/14/03**

APPENDIX IV

APPLICATION TO PEDIATRIC DECISION TREE



Pharmacokinetic and Clinical Efficacy and Safety Studies were done simultaneously.

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

/s/

Veneeta Tandon
2/12/04 04:45:34 PM
BIOPHARMACEUTICS

Ramana S. Uppoor
2/12/04 04:48:37 PM
BIOPHARMACEUTICS