CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

20-936/S001

Trade Name: Paxil CR

Generic Name: (paroxetine hydrochloride)

Sponsor: SmithKline Beecham Pharmaceuticals

Approval Date: July 2, 1999

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S001

CONTENTS

Reviews / Information Included in this NDA Review.

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

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S001

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-936/S-001

SmithKline Beecham Pharmaceuticals
Attention: Thomas F. Kline
Manager, U.S. Regulatory Affairs
1250 South Collegeville Road, P.O. Box 5089
Collegeville, Pennsylvania 19426

JUL -2 1999

Dear Mr. Kline:

Please refer to your supplemental New Drug Application dated March 1, and received March 2, 1999, submitted pursuant to section 505(b) of the Federal Food, Drug, and Cosmetic Act for Paxil CR (paroxetine hydrochloride) Controlled-Release 12.5 mg and 25 mg Tablets.

This supplemental application provides for the following: 1) an alternate site of drug product manufacture for both the 12.5 mg and 25 mg tablets at the SmithKline Beecham, Cidra, Puerto Rico facility, and 2) data supporting a "new commercial image" for both the 12.5 mg and 25 mg tablets.

We have completed the review of this supplemental application, and we are only approving the alternate site of drug product manufacture change which is effective as of the date on this letter.

The following comments provide additional information regarding our review of your application.

1. As stated above, the addition of your facility in Cidra Puerto Rico as an alternate site of drug product manufacture (original image) is approved. Please note that the shelf-life of the drug product at this time may not exceed 24 months. You may extend the expiry period in the future as acceptable long-term stability data (i.e., (b) (4) %RH) becomes available.

2. Your application additionally provides for a change in tablet color, i.e., a "new commercial image". We note that, for all batches of "new commercial image" tablets discussed in the supplement, the proposed additional color coating process was performed at (b) (4) (b) (4) commercial Image" tablets is not approved. Any new submission seeking approval of this process should include the following:

a. batch records demonstrating complete manufacture at the proposed site(s),

b. comparative dissolution profiles (to currently approved tablets) in various media with f2 calculations submitted for review by the office of new Drug Chemistry and the Office of Clinical Pharmacology and Biopharmaceutics,

c. release testing results, and

d. stability testing results.

3. We note that the existing commercial image tablets start out with an initial hardness of about (b) (4) (b) (4) (b) (4) We recommend that you address these discrepancies more thoroughly in future submissions concerning the new commercial image.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Paul David, R.Ph., Regulatory Project Manager, at (301) 594-5530.

Sincerely,

9/11/99

Russell Katz, M.D.
Acting Director
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Archival NDA 20-936
HFD-120/Div. File
HFD-120/PDavid
HFD-120/RKatz/TLaughren/GDubitsky
HFD-120/RSeevers/RLostritto
HFD-860/CSahajwalla/RYuan
HFD-810/DNDC Division Director
DISTRICT OFFICE
February 2, 1999
filename: SCM001.AP1

APPROVAL (AP)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S001

CHEMISTRY REVIEW(S)

12.1

CHEMIST'S REVIEW

1. ORGANIZATION HFD-120 DNDP		2. NDA NUMBER 20-936 JUL - 1 1999
3. NAME AND ADDRESS OF APPLICANT *(City and State)* SmithKline Beecham, Collegeville, PA		4. AF NUMBER 5. SUPPLEMENT (S) NUMBER(S) DATES(S) SCM-001 3/02/99 (CDER Date) (subject of this review)
6. NAME OF DRUG Paxil® Controlled Release Tablets	7. NONPROPRIETARY NAME paroxetine HCl hemihydrate	
8. SUPPLEMENT PROVIDES FOR: an alternate site of drug product manufacture, release testing and stability testing at the applicant's Cidra, Puerto Rico facility; and the addition (b) (4) (b) (4)		9. AMENDMENTS DATES
10. PHARMACOLOGICAL CATEGORY antidepressant	11. HOW DISPENSED RX X OTC _____	12. RELATED IND/NDA/DMF (b) (4)
13. DOSAGE FORM(S) oral modified release tablets	14. POTENCY 12.5 mg and 25 mg tablet strengths	
15. CHEMICAL NAME AND STRUCTURE See USAN (1996) page.		16. RECORDS AND REPORTS CURRENT YES_____NO_____ REVIEWED YES_____NO_____

17. COMMENTS

cc:
Orig. NDA # 20-936
HFD-120/Div. File
HFD-120/RLostritto
HFD-120/RSeevers
HFD-120/PDavid
HFD-120/CSahajwalla
R/D Init. by: RTS 7/1/99
F/T by: RTLostritto
doc # n20936.s01

18. CONCLUSIONS AND RECOMMENDATIONS **It is recommended that this supplement be approved for the site change only (with 24 month expiration period) and that the addition of a final color coating is not approvable.** (b) (4) (b) (4) (b) (4) **Please see the attached draft letter comments which are to be sent to the applicant in a letter.**

19. REVIEWER

NAME	SIGNATURE	DATE COMPLETED
Richard T. Lostritto, Ph.D.	RTLostritto 7/01/99	07/01/99

DISTRIBUTION ORIGINAL JACKET ___ DIVISION FILE ___ REVIEWER ___ CSO ___ TEAM LEADER ___

14 Page(s) Withheld

J § 552(b)(4) Trade Secret / Confidential

_____ § 552(b)(4) Draft Labeling

_____ § 552(b)(5) Deliberative Process

Withheld Track Number: Chemistry-20-936/S001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S001

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

COMPLETED JUN 16 1999

JUN 15 1999

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA 20-936
Paxil CR® (Paroxetine hydrochloride)
(12.5 and 25 mg controlled-release tablets)

Type of submission: SCM-001 (site change)
Submission Date: March 1, 1999

Sponsor: Smithkline Beecham

INDICATION: Antidepressant

REVIEWER: Rae Yuan, Ph.D. Draft Date: 6/10/99

The sponsor seeks approval for paxil CR 12.5- and 25-mg tablets manufactured at Cidra, PR facility. Reference is made to NDA 20-936 for paxil CR 12.5- and 25-mg tablets manufactured at Crawley, UK, approved for the treatment of depression. In the original application (NDA 20-936), the sponsor conducted a study in 40 healthy volunteers but failed to demonstrate the bioequivalence for the tablets manufactured at these two sites. The failure was believed to be due to the larger-than-expected within individual variation (~40%). The present submission consists of data from two bioequivalence studies (n=80 each) conducted as a replicate design: Study 569 and 579 compare, respectively, 12.5 mg and 25 mg tablets developed at Cidra manufacturing site to the ones at Crawley site. In addition to BE studies, the sponsor also conducted a dissolution profile comparison and showed that the dissolution profiles were comparable for the products at two site at each dosage strength (see Attachment A).

Study Design: It was an open, randomized, replicate, two-treatment, four period crossover study in 80 healthy volunteers. Each volunteer received a single dose of paxil CR (2x 12.5 mg in study 569 and 25 mg in study 579) manufactured at each site on two separate occasions. A period of 7-10 days separated each treatment. Subjects were randomized to one of the two treatment sequences (ABBA and BAAB, A was the Cidra arm and B was the Crawley arm) and were dosed with the drug under fasted state. On each dosing occasion, blood samples were collected at predose, 2, 3, 4, 5, 6, 8, 10, 12, 15, 18, 24, 32, 48, 72, 96 and 120 hr after dosing. The geometric means of the replicate $AUC_{0\text{-}inf}$ and Cmax of each subject were calculated. Log_e transformed $AUC_{0\text{-}inf}$ and Cmax were analyzied by ANOVA appropriate to the study design with terms for sequence, subject within sequence, period, formulation, and formulation by subject within sequence interaction. The point estimates and associated 90% confidence interval were computed.

Results:

Study 569 (See the Attachment B):

(1) Seventy-four of the 80 subjects (23 females and 57 males) provided evaluable pharmacokinetic (PK) data for both formulations for at least one occasion. Six subjects withdrew due to the deviation from the protocol after first dosing, 4 from Cidra arm and 2 from Crawley arm. For the remaining subjects, the PK parameters were calculated as geometric means of the 2 replicated occasions for subjects who provided reliable PK parameters of the same formulation twice. As a result, Cmax and Tmax values were derivable for all dosing occasions in all 74 subjects, while accurate geometric means of $AUC_{0-\infty}$ was generated in only 67 subjects. For the remaining 7 subjects, plasma concentrations were notably low throughout the study, making it difficult to derive accurate estimation of the rate of elimination (thereby to derive accurate $AUC_{0-\infty}$). However, because each of these subjects provided one reliable $AUC_{0-\infty}$ from the replicate dose of the same formulation, the sponsor used that $AUC_{0-\infty}$ value in the final statistical analysis.

(2) Based on the data from 74 subjects, statistical comparison of Cidra and Crawley arms, with respect to $AUC_{0-\infty}$ (0.84-0.98) and Cmax (0.85-0.99), are within acceptable BE criteria for 90% confidence interval limit. Within subject variation are as follow:

	Cidra	**Crawley**
AUC	42%	43%
Cmax	41%	47%.

(3) Period effects (p=0.0117) were detected in the analysis of $AUC_{0-\infty}$. Adjustment for these period differences was made in the comparison between the formulations, and did not impact the statistical inference.

(4) Similar number of adverse effects were observed for products from Cidra and Crawley sites.

Study 579 (See the Attachment C):

(1) Sixty-nine of the 80 subjects (41 females and 39 males) provided evaluable pharmacokinetic (PK) data for both formulations for at least one occasion. For the 11 subjects who withdrew, 5 were due to the deviation from the protocol, 3 due to treatment-related adverse effects (1 suffered from dizziness, nausea and vomitting in Cidra arm; 2 suffered from dizziness, nausea, or erythema in Crawley arm) and 1 due to the treatment-unrelated serious adverse experience (in Cidra arm). Two subjects in Cidra arm withdrew with no explanation. However, 6 of the withdrawn subjects completed 2 dosing sessions. Thus, 75 subjects were evaluated for PK analysis as described for study 569.

(2) Based on the data from 75 subjects, statistical comparison of Cidra and Crawley arms, with respect to $AUC_{0-\infty}$ (0.84-1.01) and Cmax (0.85-1.03), are within acceptable BE criteria for 90% confidence interval limit. Within subject variation are as follow:

	Cidra	**Crawley**
AUC	59%	36%
Cmax	62%	41%.

(3) Period effects (p=0.0117) were detected in the analysis of $AUC_{0-\infty}$. Adjustment for these period differences was made in the comparison between formulations and did not impact the statistical inference.

(4) Similar number of adverse effects was observed for products from Cidra and Crawley sites.

COMMENTS:

1. Of all the evaluable profiles, 19% subjects had extrapolated AUC >20% of $AUC_{0-\infty}$ (ranges 20-40%) in study 569 and 22% subjects in study 579 (ranges 20-56%). A comparable large inter-subject variation (CV: ~200%) was observed for both formulations in both studies. Since paroxetine is metabolized by CYP2D6, a polymorphic enzyme in the population, the subjects with large extrapolated AUC could be the poor metabolizers thus contributed to the large variation in paroxetine PK parameters.

2. In spite of the large variation, the point estimates of PK parameters among the studied subjects indicated that the two manufacturing sites were equivalent. The reviewer conducted additional analysis on the individual data of all subjects from study 569 and the data extracted from individuals with half-life less than 30 hr in the same study (see attachment D). The analysis on data from all individuals showed that (1) the point estimates of Cidra versus Crawley for AUC and Cmax are 0.98 and 0.92, respectively; (2) the 90% confidence intervals of the products from the two sites are 84.9-98.7 for AUC and 84.3-98.6 for Cmax. The analysis on data from individuals with half-life less than 30 hr showed that (1) the point estimates of Cidra versus Crawley for AUC and Cmax are 0.91 and 0.89, respectively; (2) the 90% confidence intervals of the products from the two sites are 83.8-98.6 for AUC and 81.6-97.1 for Cmax.

RECOMMENDATION:

The sponsor has adequately demonstrated bioequivalency of 12.5- and 25-mg tablets manufactured at Cidra and Crawley sites. This reviewer supports the approval of 12.5 and 25 mg Paxil CR tablets manufactured at Cidra, PR site.

Rae Yuan, Ph.D.

Team Leader: Chandra Sahajwalla 6/15/99

Date of Signature: 6/15/99
Office of Clinical Pharmacology and Biopharmaceutics/Division I
CC list: HFD-120; CSO; HFD-860 (Yuan, Sahajwalla, Methu); CDR (Biopharmaceutic Review)

4.A.2.10 Table 8 Unit Formula of Paroxetine CR Tablets

Formula Code Ingredients	12.5 mg DY Quantity (mg/tablet)	25 mg DT Quantity (mg/tablet)
Active layer Paroxetine Hydrochloride, hemihydrate	(b) (4)	(b) (4)
Enteric coat	(b) (4)	

- Equivalent to either 12.5 mg or 25 mg respectively, of Paroxetine as the free base equivalent, based on a potency of (b) (4)%
- Total is equivalent to an increase tablet core weight of (b) (4)%

Figure 1: Dissolution Profiles for the Paroxetine Geomatrix® New Commercial Image Controlled Release 12.5 mg Tablets vs. Existing Commercial Image 12.5 mg Tablets

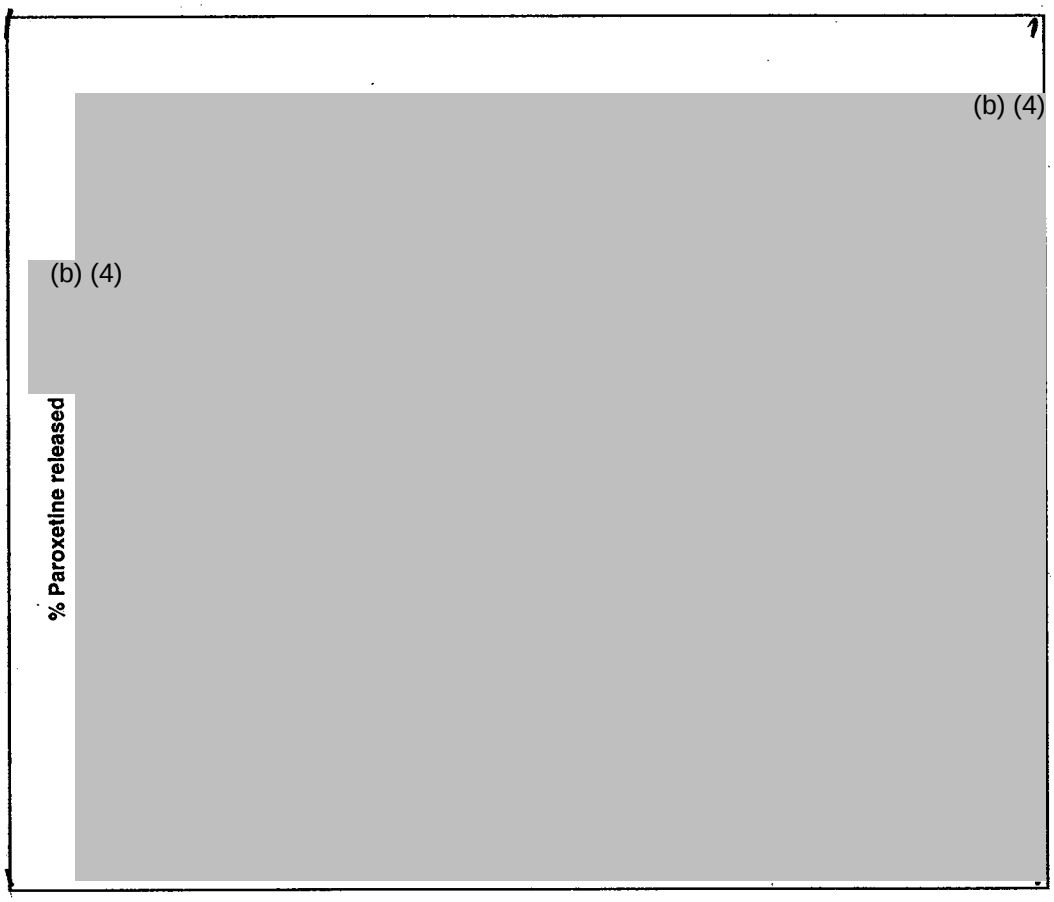
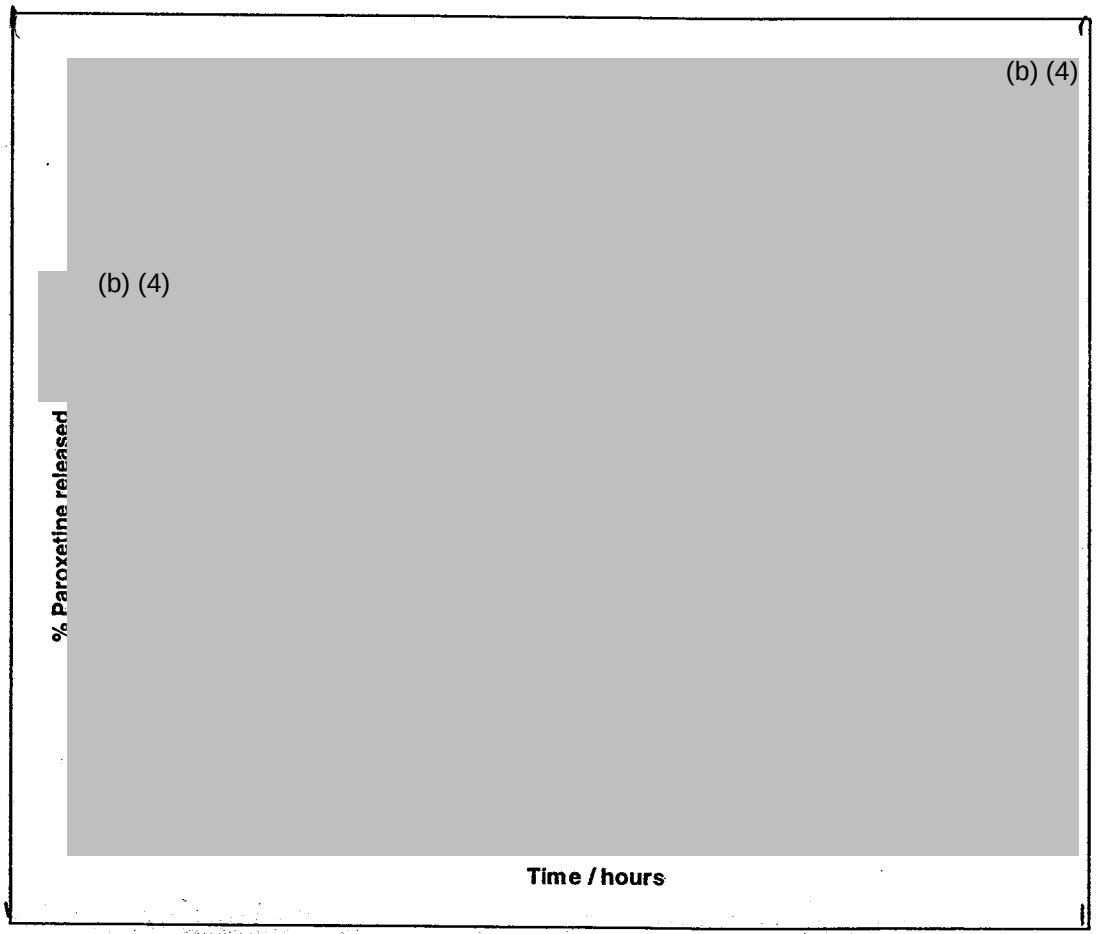


Figure 2: Dissolution Profiles for the Paroxetine Geomatrix® New Commercial Image Controlled Release 25 mg Tablets vs. Existing Commercial Image 25 mg Tablets



2.2 Calculation of f2 Similarity Factor for the Dissolution Comparisons

All of the results from the dissolution profiles obtained from the paroxetine 'Geomatrix'® NCI CR tablets were compared those from the original tablets using the following SUPAC equation, that defines a similarity factor (f_2)[12] :

$$f_2 = 50 \text{ LOG } \{[1 + 1/n \Sigma^{n}_{t=1} (R_t - T_t)^2]^{-0.5} \text{ x } 100\}$$

where R_t and T_t are percent dissolved at each time point for the Reference and Test profiles respectively. An f_2 value between 50 and 100 confirms that the two dissolution profiles are equivalent.

Samples were analysed and the results were used to determine the SUPAC f_2 similarity factor for the cross-validation between the paroxetine 'Geomatrix'® NCI CR tablets versus the 'Geomatrix'® CR tablets.

Table 10: f_2 Similarity Factors for the (b)(4) Dissolution Method		
	(b) (4)	**f_2**
12.5 mg		84
25 mg		75
37.5 mg		81
50 mg		61

Comparison of the profiles using the SUPAC similarity factor (f_2) demonstrate that the profiles obtained are equivalent as f_2 values are within the range of 50 and 100.

---

12 Guidance for Industry, SUPAC MR : Modified Release Solid Oral Dosage Forms, Scale-Up and Postapproval Changes : Chemistry, Manufacturing and Controls : In-Vitro Dissolution Testing and In-Vivo Bioequivalence Documentation, issued 6/10/97.

Parameter [n = 74]	Cmax (ng/mL)	Tmax (h)	AUC(0-inf) (ng.h/mL)	T½ (h)
Cidra dose 1 (2 x 12.5 mg)	4.38 (5.77)	8.0 (4.0 - 24.0)	164 * (314)	16.8 * (11.6)
Cidra dose 2 (2 x 12.5 mg)	4.45 (4.84)	8.0 (6.0 - 24.0)	178 ** (344)	16.7 ** (13.2)
Cidra 'combined'	**4.27**	**8.0**	**164**	**16.6**
Crawley dose 1 (2 x 12.5 mg)	4.65 (5.57)	8.0 (4.0 - 24.0)	184 * (368)	16.8 * (12.0)
Crawley dose 2 (2 x 12.5 mg)	4.71 (5.27)	10.0 (6.0 - 32.0)	200 (395)	16.5 (13.6)
Crawley 'combined'	**4.54**	**9.0**	**185**	**16.5**

* n = 71 ** n = 73

'combined' values (n=74 throughout) calculated from the following values for each formulation:
Cmax and AUC(0-inf): geometric mean of two values where available, or a single value when only one dosing session gave evaluable AUC(0-inf) data
Tmax and T½: arithmetic mean of two values where available, or a single value when only one dosing session gave evaluable T½ data

In seven subjects, notable for their low concentrations throughout the study, the terminal elimination phase could not be adequately delineated on one of the four dosing occasions. However, as these seven subjects provided reliable AUC(0-inf) data for each of the other three doses, including at least one dose of each formulation, they were included in the statistical analyses.

The results of the statistical analyses (based on all 74 completing subjects) are summarised in the Table below:

Parameter	n	Comparison	Ratio *	90% confidence interval
AUC(0-inf)	74	Cidra:Crawley	0.91	(0.84, 0.98)
Cmax	74	Cidra:Crawley	0.92	(0.85, 0.99)
Parameter	**n**	**Comparison**	**Median difference**	**95% confidence interval**
Tmax	74	Cidra–Crawley	0.00 h	(–0.50, 0.50)

* presented as the ratio of adjusted geometric means

For Cmax and AUC(0-inf), the 90% confidence intervals were completely contained within the predefined equivalence range (0.80, 1.25). Values of Tmax were very similar for both formulations.

The within-subject coefficients of variation by formulation for AUC(0-inf) and Cmax, 41.7% and 40.4%, respectively, for Cidra tablets and 43.4% and 46.7%, respectively, for Crawley tablets, were similar.

Table 10.10 Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	
								(b) (4)

Subject 021 completed only one treatment session; values in brackets excluded from summary statistics (Tables 10.14 and 10.15)

* Ratio = Cidra geometric mean/Crawley geometric mean

Table 10.10 (contd)
Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	
								(b) (4)

* Ratio = Cidra geometric mean/Crawley geometric mean
Subject 044 withdrew during the first session

Table 10.10 (contd)
Maximum observed plasma concentrations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	
								(b) (4)

Subjects 058, 059 and 066 completed only one treatment session; values in brackets excluded from summary statistics (Tables 10.14 and 10.15)
Subject 060 withdrew during the first session
* Ratio = Cidra geometric mean/Crawley geometric mean

Table 10.12 Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR
(25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio *
		1	2	1	2	Cidra	Crawley	

(b) (4)

Subject 021 completed only one treatment session; values in brackets excluded from summary statistics (Tables 10.14 and 10.15)
*Ratio = Cidra geometric mean/geometric Crawley mean
ND - AUC(0-inf) not determined (terminal phase inadequately delineated)

Table 10.12 (contd)

Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio *
		1	2	1	2	Cidra	Crawley	

(b) (4)

* Ratio = Cidra geometric mean/Crawley geometric mean
ND - AUC(0-inf) not determined (terminal phase inadequately delineated)
Subject 044 withdrew during the first session

Table 10.12 (contd)

Areas under the plasma concentration-time curves of paroxetine (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio *
		1	2	1	2	Cidra	Crawley	

(b) (4)

Subjects 058, 059 and 066 completed only one treatment session; values in brackets excluded from summary statistics (Tables 10.14 and 10.15)

* Ratio = Cidra geometric mean/Crawley geometric mean

ND - AUC(0-inf) not determined (terminal phase inadequately delineated)

Subject 060 withdrew during the first session

Table 10.14 Descriptive summary statistics of paroxetine pharmacokinetic parameters by formulation in healthy subjects after single oral administration of paroxetine-CR
(25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Parameter	Formula	n	Mean	S.D.	Min	Median	Max
AUC(0-inf)	A	74	164.12	321.33	6.17	40.50	1739.53
AUC(0-inf)	B	74	184.75	371.11	4.60	47.62	1735.52
Cmax	A	74	4.265	4.945	0.531	2.415	24.099
Cmax	B	74	4.540	5.279	0.347	2.599	29.459
Tmax	A	74	9.24	2.84	5.00	8.00	19.50
Tmax	B	74	9.34	2.78	6.00	9.00	22.00
T1/2	A	74	16.58	11.80	4.89	12.61	63.13
T1/2	B	74	16.52	12.20	5.23	12.33	58.18

Parameter	Formula	n	Geometric Mean	CV_b(%)
AUC(0-inf)	A	74	53.07	238.01
AUC(0-inf)	B	74	58.35	244.47
Cmax	A	74	2.594	124.77
Cmax	B	74	2.831	121.26

A = Cidra B = Crawley

Summary statistics for AUC(0-inf) and Cmax are based on the geometric mean of two values where available, or on a single value when only one dosing session gave evaluable AUC(0-inf) data.
Summary statistics for Tmax and T½ are based on the arithmetic mean of two values where available, or on a single value when only one dosing session gave evaluable T½ data.

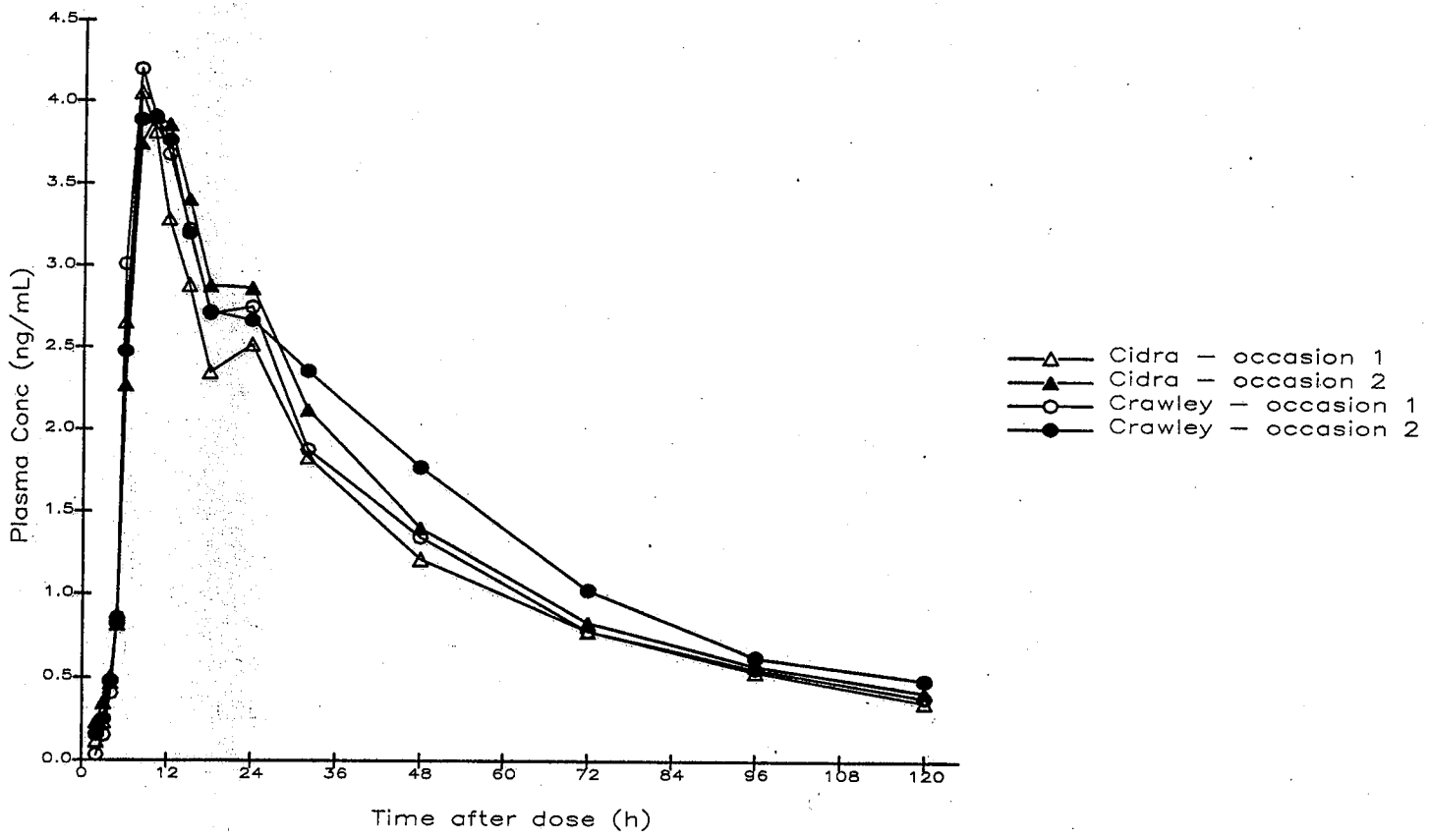
Table 10.15 Descriptive summary statistics of paroxetine pharmacokinetic parameters by formulation and administration in healthy subjects after single oral administration of paroxetine-CR (25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Parameter	Formula	Admin	n	Mean	S.D.	Min	Median	Max
AUC(0-inf)	A	1	71	163.56	313.66	6.61	33.99	1562.78
AUC(0-inf)	A	2	73	178.48	343.57	4.86	44.97	1936.28
AUC(0-inf)	B	1	71	184.43	368.37	3.23	46.99	1635.06
AUC(0-inf)	B	2	74	199.56	394.57	4.49	54.86	2011.67
Cmax	A	1	74	4.377	5.774	0.520	2.054	35.755
Cmax	A	2	74	4.447	4.844	0.385	2.585	22.462
Cmax	B	1	74	4.645	5.573	0.275	2.569	29.036
Cmax	B	2	74	4.708	5.265	0.402	2.950	29.889
Tmax	A	1	74	8.74	3.12	4.00	8.00	24.00
Tmax	A	2	74	9.74	3.67	6.00	8.00	24.00
Tmax	B	1	74	9.01	3.45	4.00	8.00	24.00
Tmax	B	2	74	9.66	3.78	6.00	10.00	32.00
T1/2	A	1	71	16.76	11.57	6.26	12.45	64.37
T1/2	A	2	73	16.67	13.21	4.16	12.73	75.91
T1/2	B	1	71	16.83	12.04	5.22	12.81	67.73
T1/2	B	2	74	16.49	13.63	4.08	12.27	69.25

Parameter	Formula	Admin	n	Geometric Mean	CV_b(%)
AUC(0-inf)	A	1	71	49.78	256.93
AUC(0-inf)	A	2	73	58.58	251.25
AUC(0-inf)	B	1	71	59.05	237.28
AUC(0-inf)	B	2	74	61.12	270.72
Cmax	A	1	74	2.482	135.55
Cmax	A	2	74	2.712	129.65
Cmax	B	1	74	2.738	135.36
Cmax	B	2	74	2.926	127.46

A = Cidra
B = Crawley
Admin 1 = first dosing session
Admin 2 = second dosing session

Figure 11.1 Mean plasma concentrations of paroxetine (ng/mL) in healthy subjects after single oral administration of paroxetine-CR
(25 mg, as 2 x 12.5 mg tablets) on four occasions; replicate design, each formulation
(Cidra and Crawley tablets) administered twice



Pharmacokinetics

Sixty-nine of the 80 subjects recruited completed all four dosing sessions and a further six completed two sessions. These 75 subjects, having received each formulation at least once, constitute the evaluable data set.

For both formulations, a consistent lag time (generally 3 to 5 hours) was observed in most subjects before any significant rise in concentration occurred. Tmax values were typically in the range 6 to 15 hours. The pharmacokinetic parameters, based on evaluable data from 75 subjects, are summarised below (arithmetic means and SD for dose 1 and dose 2 data, except medians and ranges for Tmax values; geometric means for 'combined' data):

Parameter [n = 75]	Cmax (ng/mL)	Tmax (h)	AUC(0-inf) (ng.h/mL)	T½ (h)
Cidra dose 1 (25 mg)	5.21 (6.40)	8.0 (6.0–24.0)	223** (508)	17.1 (12.3)
Cidra dose 2* (25 mg)	5.12 (5.57)	8.0 (5.0–49.3)	195 (364)	16.8 (12.1)
Cidra 'combined'	**4.87**	**9.0**	**197**	**16.8**
Crawley dose 1 (25 mg)	5.24 (5.62)	10.0 (6.0–24.0)	214*** (432)	17.0 ## (11.2)
Crawley dose 2* (25 mg)	5.09 (4.92)	10.0 (6.0–32.0)	205 # (375)	16.9 (11.8)
Crawley 'combined'	**4.96**	**9.0**	**198**	**16.7**

* n = 69 ** n = 73 ***n = 72 # n = 68 ## n = 74

'combined' values (n=75 throughout) calculated as follows:
Cmax and AUC(0–inf): geometric mean of two values where available, or a single value when only one dosing session gave evaluable AUC(0–inf) data
Tmax and T½: arithmetic mean of two values where available, or a single value when only one dosing session gave evaluable T½ data

The results of the analyses including all 75 evaluable subjects are summarised below:

Parameter	Comparison	Ratio *	90% confidence interval
AUC(0–inf)	Cidra:Crawley	0.92	(0.84, 1.01)
Cmax	Cidra:Crawley	0.94	(0.86, 1.03)
Parameter	**Comparison**	**Median difference**	**95% confidence interval**
Tmax	Cidra–Crawley	–0.47 h	(–1.00, 0.00)

* presented as the ratio of adjusted geometric means

Table 10.19

Maximum observed plasma concentations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	
								(b) (4)

* Ratio = Cidra geometric mean/Crawley geometric mean
Subject 026 withdrew after Session 2

Table 10.19 (cont.)

Maximum observed plasma concentations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	

(b) (4)

[redacted]

* Ratio = Cidra geometric mean/Crawley geometric mean

Subject 046 withdrew after Session 1 but data were not evaluable

Subject 052 withdrew after Session 2 Subject 054 withdrew after Session 1

Bracketed values excluded from summary statistics (Tables 10.25 and 10.26)

Table 10.19 (cont.)

Maximum observed plasma concentations of paroxetine (Cmax, ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	

(b) (4)

* Ratio = Cidra geometric mean/Crawley geometric mean
Subjects 055, 075 and 076 withdrew after Session 1
Subjects 061, 064, 065 and 066 withdrew after Session 2
Bracketed values excluded from summary statistics (Tables 10.25 and 10.26)

Table 10.22

Areas under the plasma concentration-time curves of paroxetine extrapolated to infinite time (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	

(b) (4)

[redacted]

* Ratio = Cidra geometric mean/Crawley geometric mean
NE – AUC(0-inf) not evaluable (>40% extrapolated area)
Subject 026 withdrew after Session 2

Table 10.22 (cont.)

Areas under the plasma concentration-time curves of paroxetine extrapolated to infinite time (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	

(b) (4)

Ratio = Cidra geometric mean/Crawley geometric mean

ND – not determined (terminal elimination phase could not be delineated)

NE – AUC(0-inf) not evaluable (>40% extrapolated area)

Subject 046 withdrew after Session 1 but data were not evaluable

Subject 052 withdrew after Session 2 Subject 054 withdrew after Session 1

Bracketed values excluded from summary statistics (Tables 10.25 and 10.26)

Table 10.22 (cont.)

Areas under the plasma concentration-time curves of paroxetine extrapolated to infinite time (AUC(0-inf), ng.h/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)		Geometric mean		Ratio*
		1	2	1	2	Cidra	Crawley	

(b) (4)

* Ratio = Cidra geometric mean/Crawley geometric mean
ND – not determined (terminal elimination phase could not be delineated)
Subjects 055, 075 and 076 withdrew after Session 1
Subjects 061, 064, 065 and 066 withdrew after Session 2
Bracketed values excluded from summary statistics (Tables 10.25 and 10.26)

Table 10.23

Extrapolated fraction of total areas under the plasma concentration versus time curves of paroxetine in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)	
		1	2	1	2

(b) (4)

$$\text{Extrapolated fraction} = \frac{AUC(0-inf) - AUC(0-t)}{AUC(0-inf)} \times 100\%$$

Bolded values = extrapolated fraction of AUC(0-inf) >40%

Subject 026 withdrew after Session 2

Table 10.23 (cont.)
Extrapolated fraction of total areas under the plasma concentration versus time curves of paroxetine in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)	
		1	2	1	2

(b) (4)

[redacted]

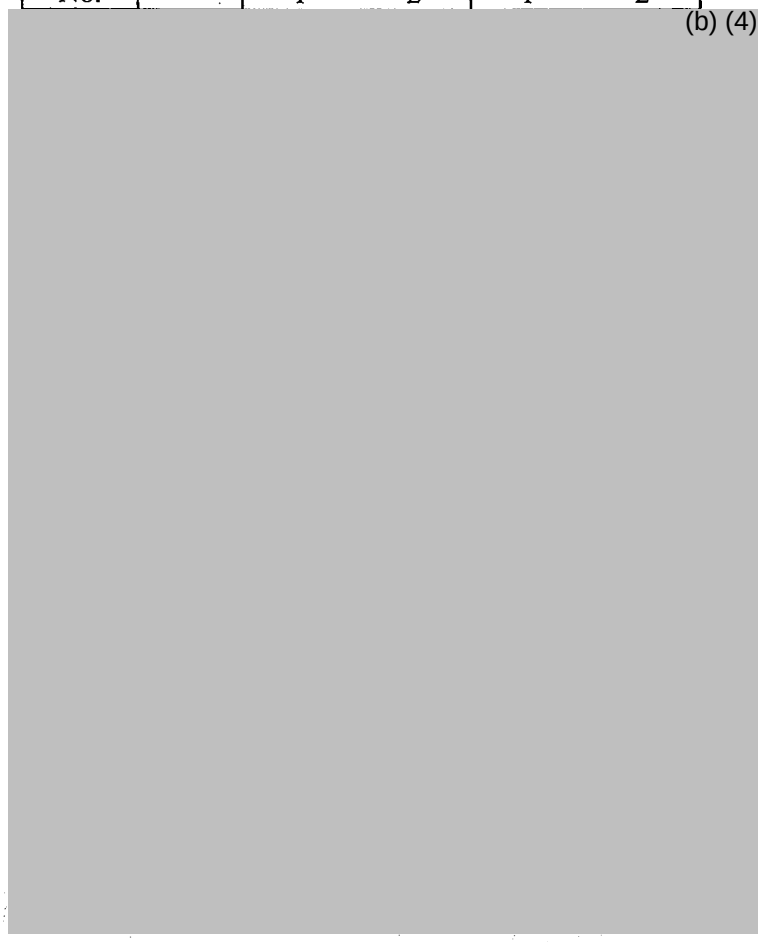
$$\text{Extrapolated fraction} = \frac{AUC(0-inf) - AUC(0-t)}{AUC(0-inf)} \times 100\%$$

Bolded values = extrapolated fraction of AUC(0-inf) >40%
ND – not determined (terminal elimination phase could not be delineated)
Subject 046 withdrew after Session 1 but data were not evaluable
Subject 052 withdrew after Session 2 Subject 054 withdrew after Session 1

Table 10.23 (cont.)
Extrapolated fraction of total areas under the plasma concentration versus time curves of paroxetine in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Subject No.	Seq.	Cidra (A)		Crawley (B)	
		1	2	1	2

(b) (4)



$$\text{Extrapolated fraction} = \frac{AUC(0-inf) - AUC(0-t)}{AUC(0-inf)} \times 100\%$$

Subjects 055, 075 and 076 withdrew after Session 1
Subjects 061, 064, 065 and 066 withdrew after Session 2

Table 10.25

Descriptive summary statistics of paroxetine pharmacokinetic parameters by formulation in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Parameter	Formula	n	Mean	S.D.	Min	Median	Max
AUC(0-inf)	A	75	197.37	404.854	5.20	54.40	2113.43
AUC(0-inf)	B	75	198.03	390.422	5.85	59.46	1993.59
AUC(0-t)	A	75	163.84	304.593	3.72	51.39	1511.49
AUC(0-t)	B	75	166.91	297.207	4.43	52.37	1337.34
Cmax	A	75	4.871	5.6340	0.382	2.755	29.152
Cmax	B	75	4.964	5.0950	0.404	3.154	22.304
Thalf	A	75	16.79	11.861	5.20	13.15	64.72
Thalf	B	75	16.70	11.019	5.01	12.65	63.62
Tmax	A	75	9.68	3.390	5.50	9.00	28.63
Tmax	B	75	10.03	3.381	6.00	9.00	28.00

Parameter	Formula	n	Geometric Mean	CV(%)
AUC(0-inf)	A	75	60.41	265.75
AUC(0-inf)	B	75	65.82	255.67
AUC(0-t)	A	75	52.81	281.35
AUC(0-t)	B	75	57.47	274.69
Cmax	A	75	2.821	144.78
Cmax	B	75	3.007	141.14

A = Cidra B = Crawley

Summary statistics by formulation were calculated based on average values for 2 periods (within-subject) where available, or single values where not. For the log-transformed parameters (AUC(0-inf), AUC(0-t) and Cmax), data were averaged on the log-scale (geometric mean). Data for all subjects contributing to the comparison of interest were included.

Table 10.26

Descriptive summary statistics of paroxetine pharmacokinetic parameters by formulation and administration in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

Parameter	Formula	Admin	n	Mean	S.D.	Min	Median	Max
AUC(0-inf)	A	1	73	223.36	507.934	4.32	51.70	3276.44
AUC(0-inf)	A	2	69	195.10	363.751	5.48	61.28	1826.55
AUC(0-inf)	B	1	72	213.82	432.290	5.17	63.64	2234.02
AUC(0-inf)	B	2	68	205.45	374.883	4.59	75.68	1779.04
AUC(0-t)	A	1	75	178.87	362.236	3.00	44.85	2101.81
AUC(0-t)	A	2	69	163.32	278.228	3.73	56.42	1394.31
AUC(0-t)	B	1	75	173.33	323.779	4.14	54.86	1583.99
AUC(0-t)	B	2	69	171.59	283.118	3.70	70.49	1192.93
Cmax	A	1	75	5.210	6.3981	0.358	2.496	32.227
Cmax	A	2	69	5.119	5.5723	0.435	2.940	26.371
Cmax	B	1	75	5.240	5.6225	0.408	2.773	22.696
Cmax	B	2	69	5.087	4.9153	0.312	3.343	21.918
Thalf	A	1	75	17.09	12.302	5.20	13.03	74.54
Thalf	A	2	69	16.84	12.096	5.48	12.76	63.32
Thalf	B	1	74	16.95	11.173	5.01	13.21	57.86
Thalf	B	2	69	16.89	11.772	5.99	13.04	72.15
Tmax	A	1	75	9.22	2.904	6.00	8.00	24.00
Tmax	A	2	69	10.29	5.719	5.00	8.02	49.25
Tmax	B	1	75	9.88	3.292	6.00	10.00	24.00
Tmax	B	2	69	10.31	4.102	6.00	10.00	32.00

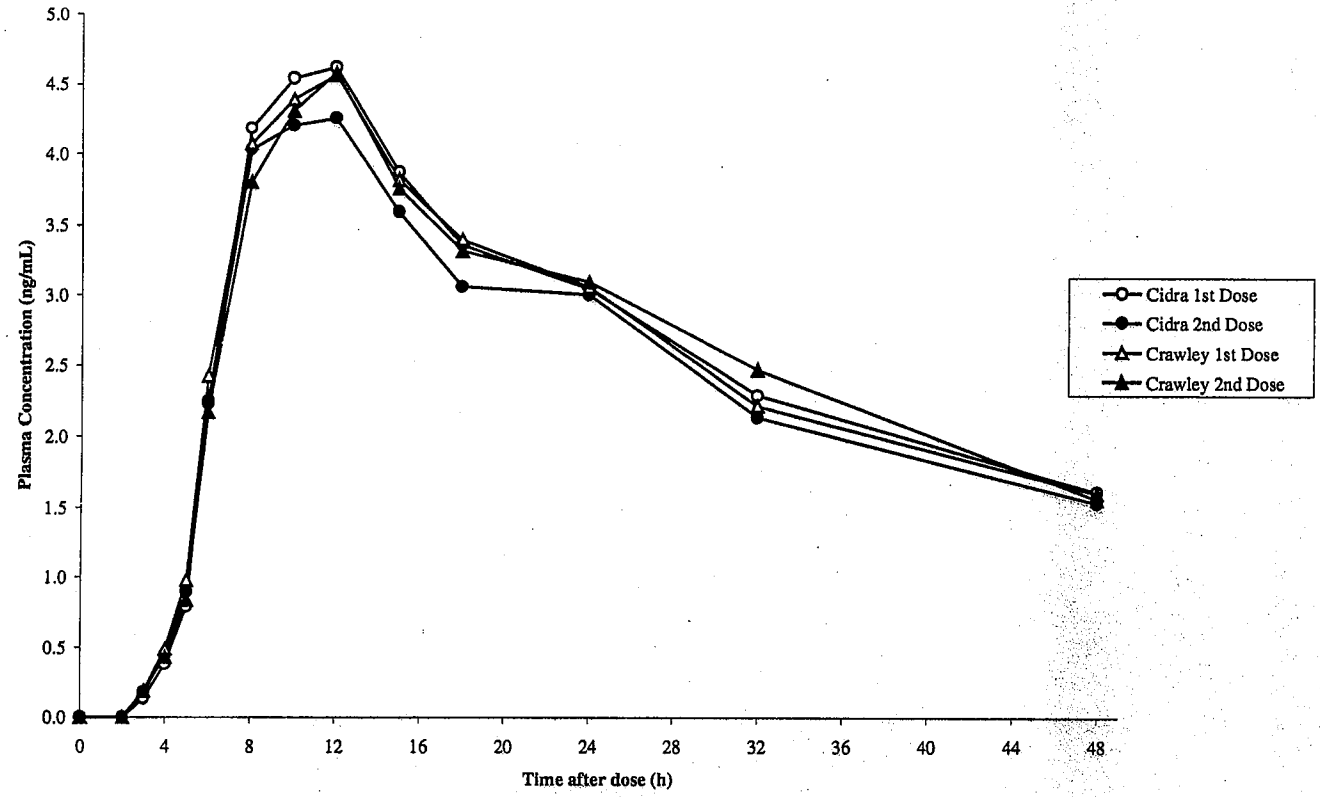
Parameter	Formula & Admin	n	Geometric Mean	CV(%)
AUC(0-inf)	A 1	73	60.63	302.47
AUC(0-inf)	A 2	69	64.81	263.18
AUC(0-inf)	B 1	72	69.24	257.37
AUC(0-inf)	B 2	68	71.68	262.88
AUC(0-t)	A 1	75	50.81	324.36
AUC(0-t)	A 2	69	56.60	281.65
AUC(0-t)	B 1	75	56.44	284.61
AUC(0-t)	B 2	69	62.18	281.27
Cmax	A 1	75	2.729	170.16
Cmax	A 2	69	2.967	149.42
Cmax	B 1	75	3.047	148.01
Cmax	B 2	69	3.109	147.15

A = Cidra B = Crawley

Admin 1 = first dosing session Admin 2 = second dosing session

Figure 11.1
Mean plasma concentrations of paroxetine (ng/mL) in healthy subjects after single oral administration of paroxetine-CR (25 mg) on four occasions; replicate design, each formulation (Cidra and Crawley tablets) administered twice

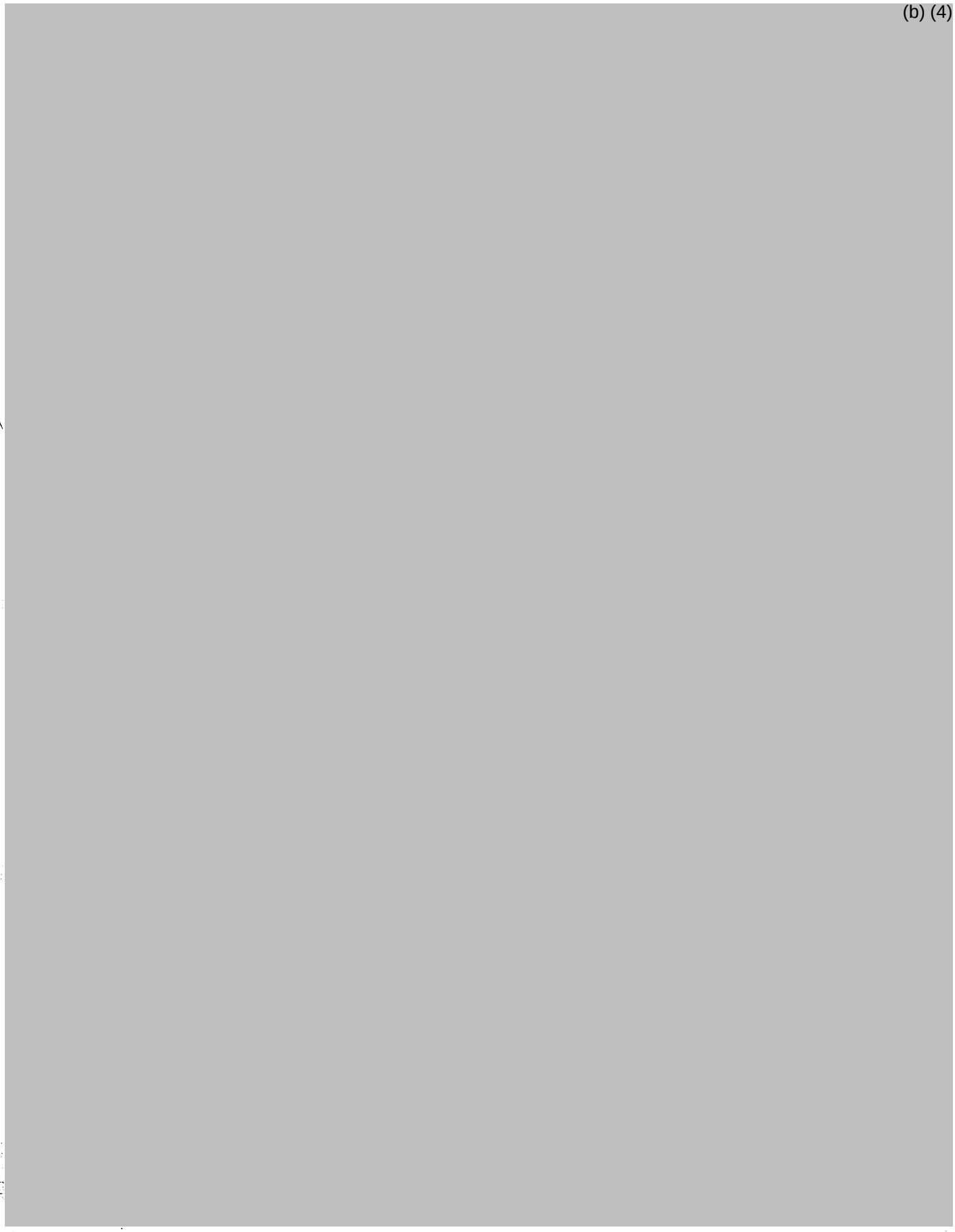
(data plotted up to 48 hours only)



Attachment D

AUC From All Subjects

(b) (4)

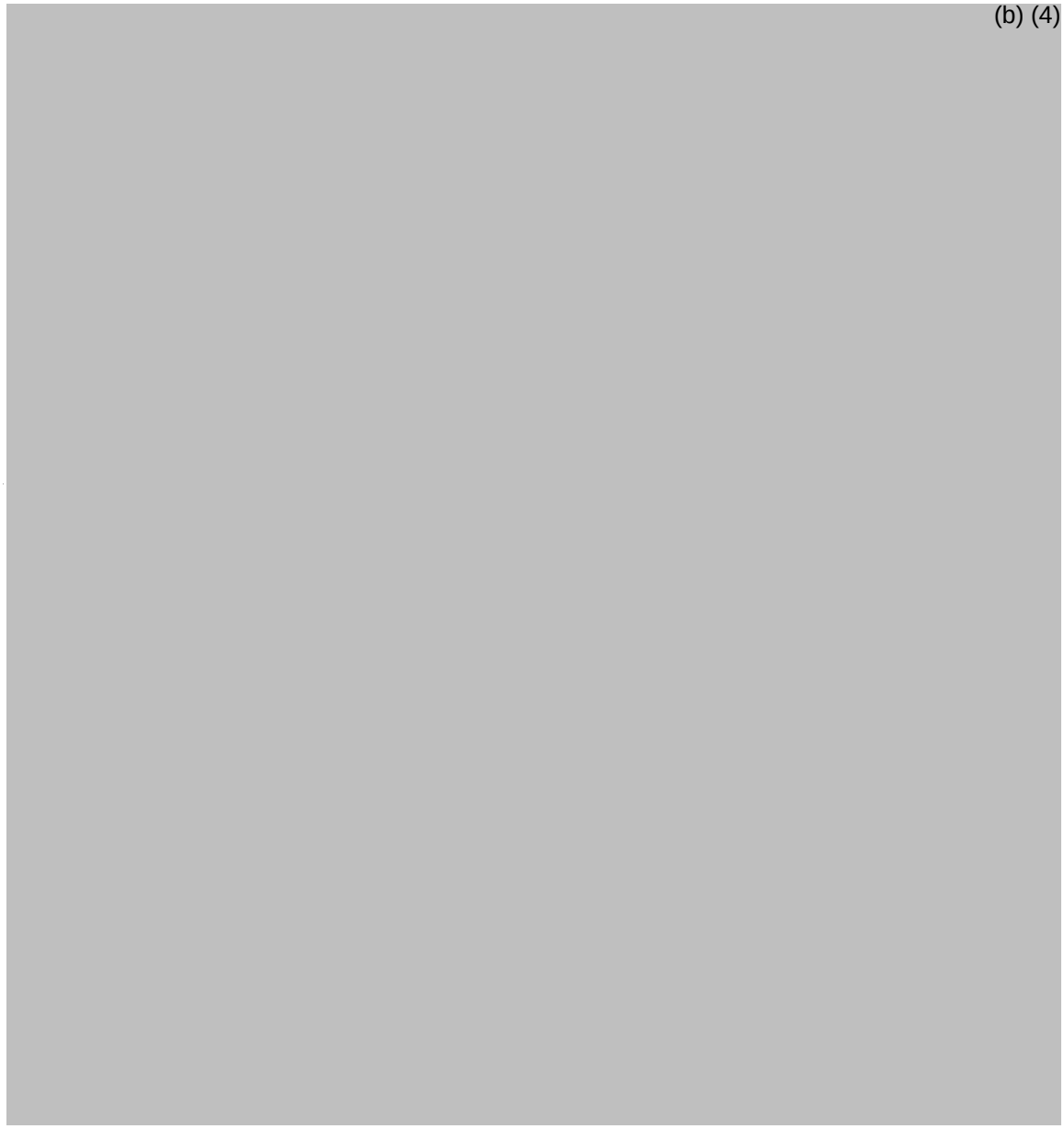


AUC From All Subjects

(b) (4)

AUC From All Subjects

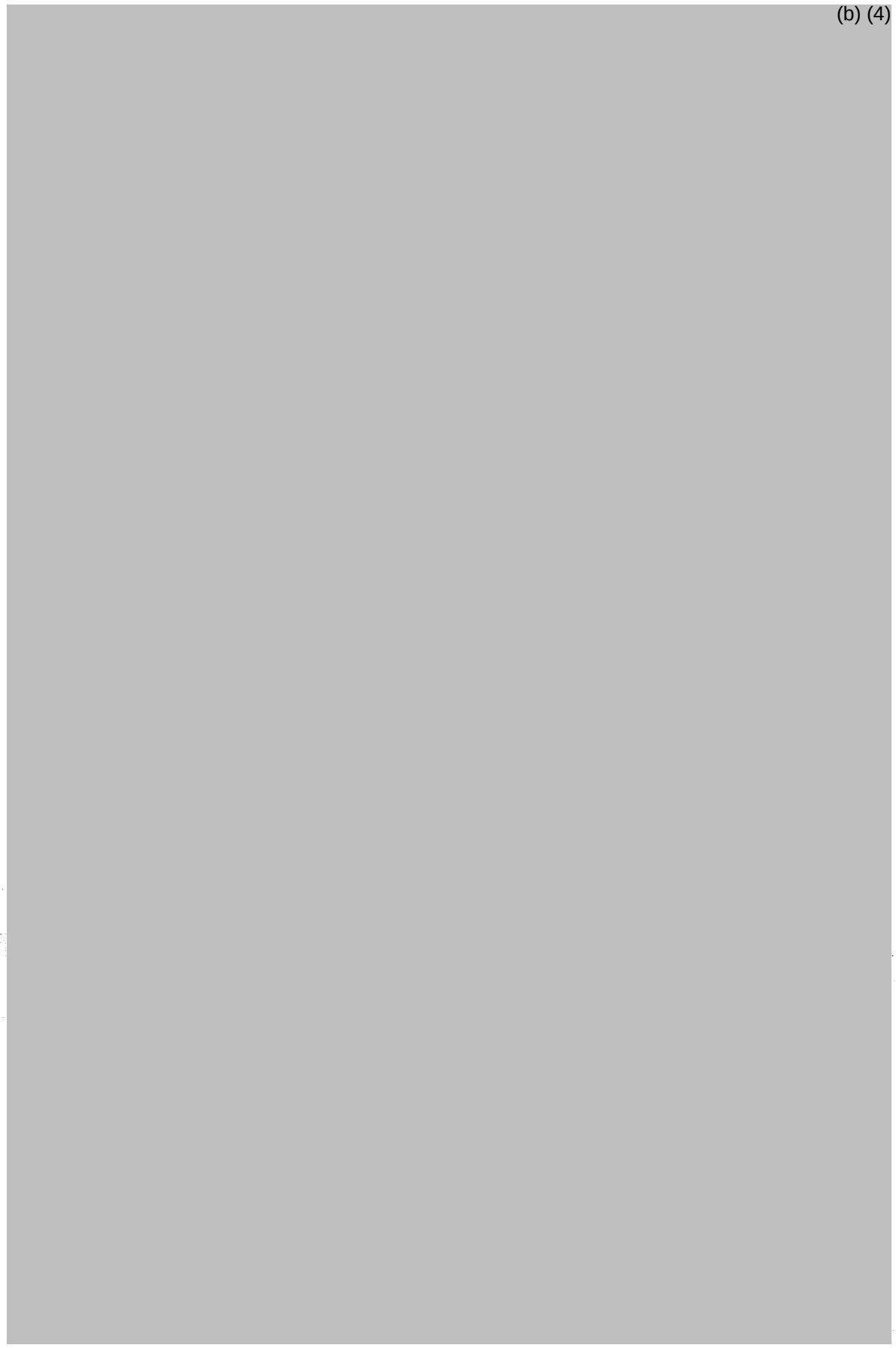
(b) (4)



90% C.I. Using Randy Program:
84.95-98.72

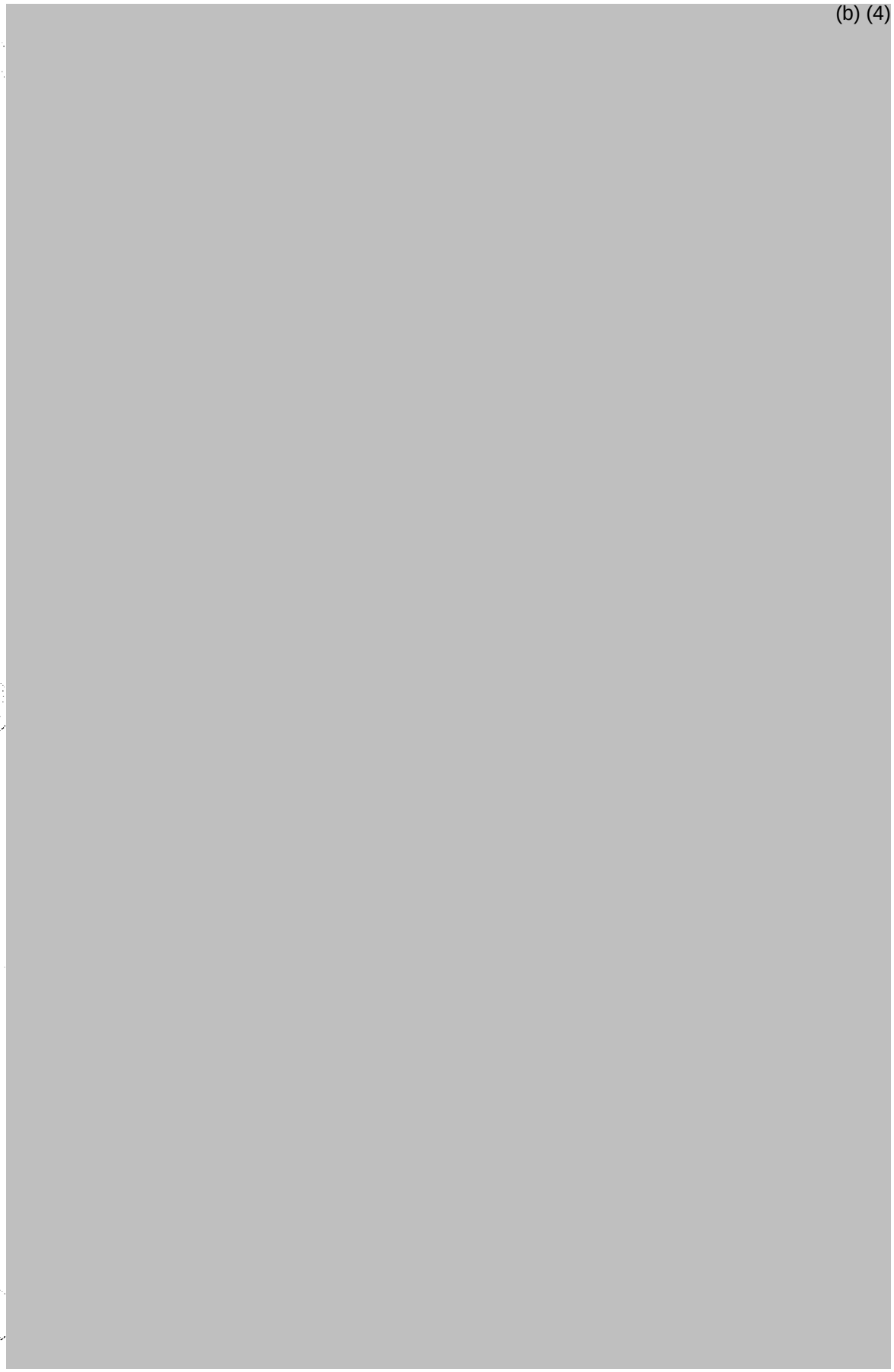
Cmax From All Subjects

(b) (4)



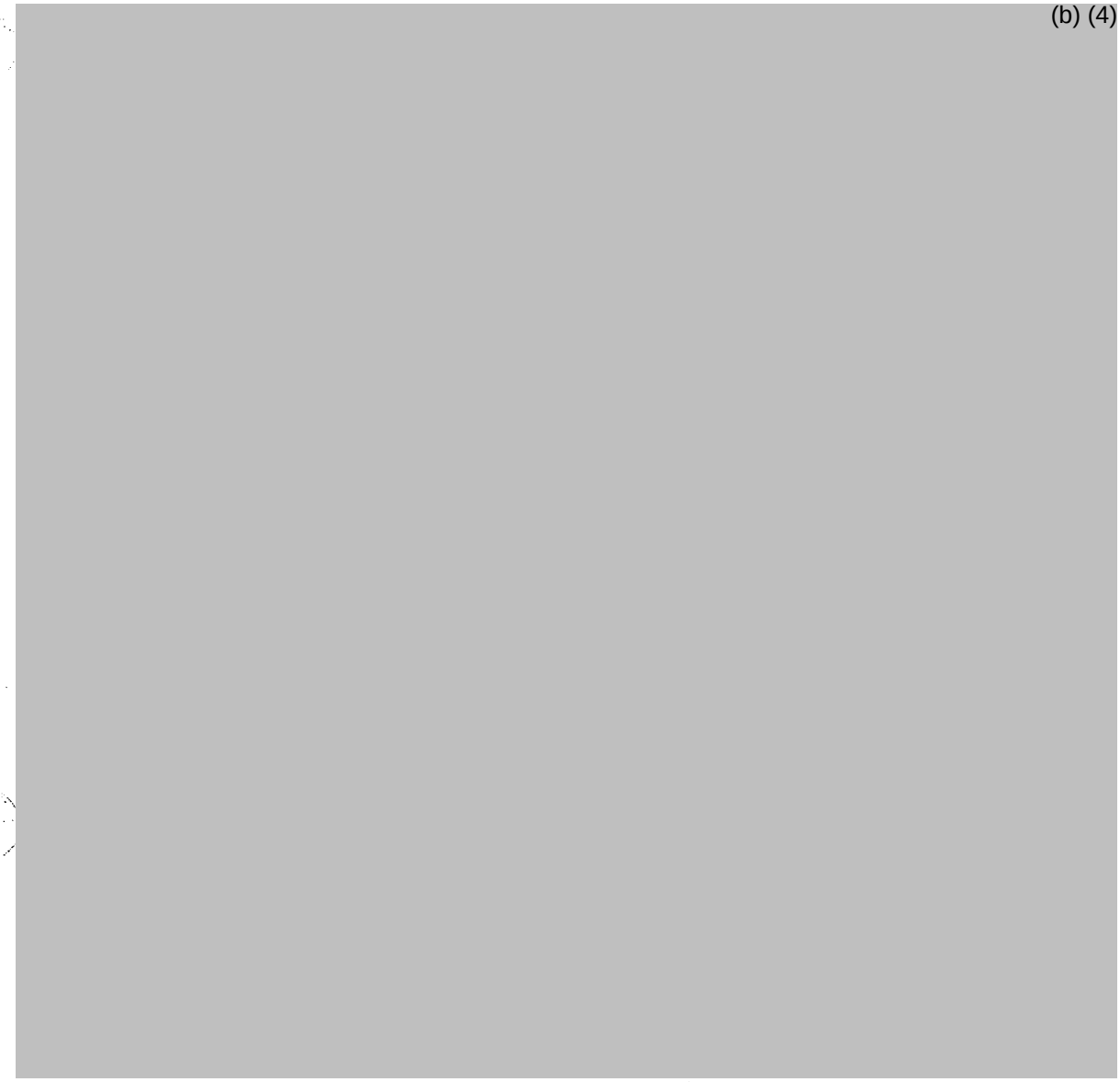
Cmax From All Subjects

(b) (4)



Cmax From All Subjects

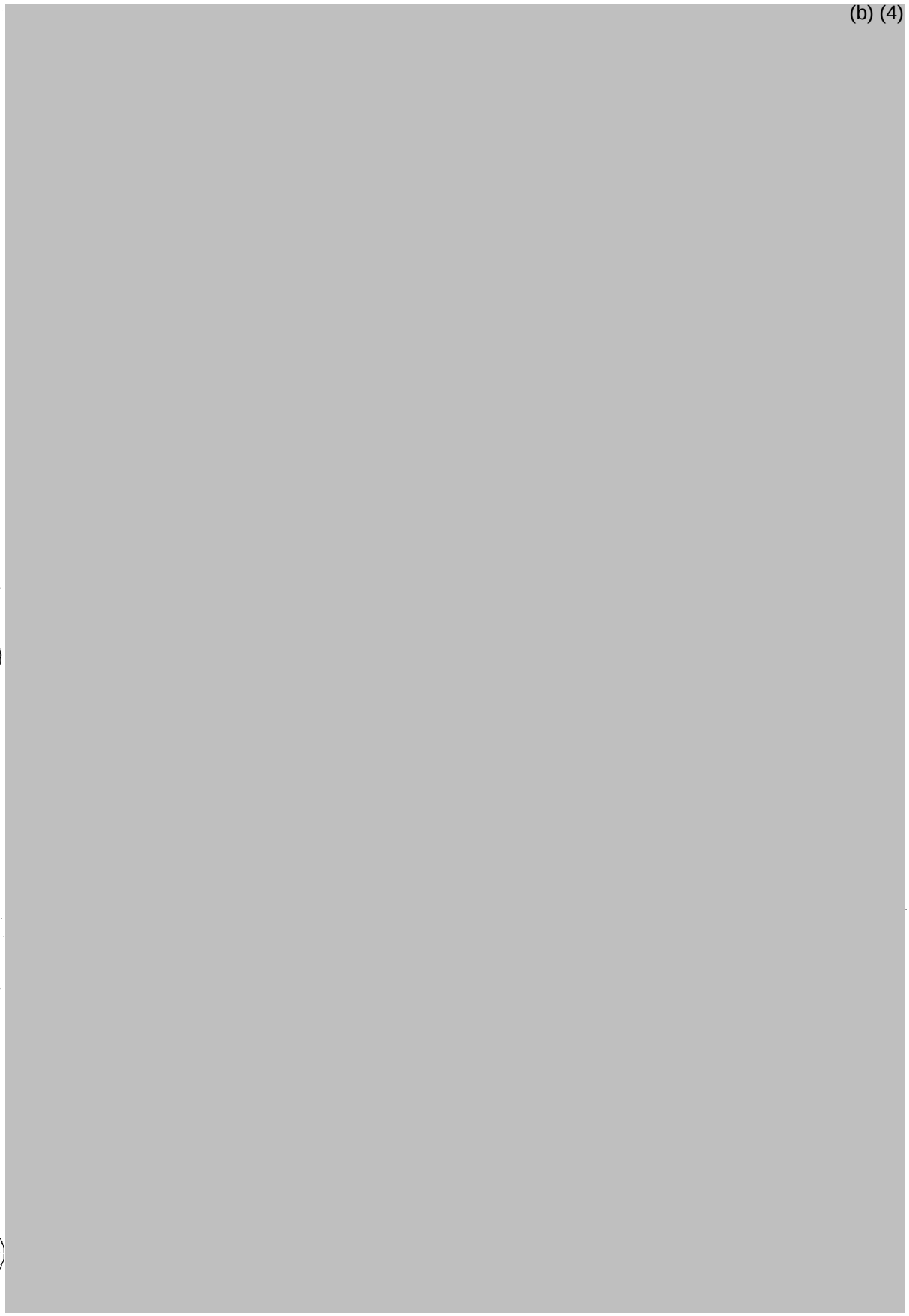
(b) (4)



90% C.I. Using Randy Program:
84.3-98.6

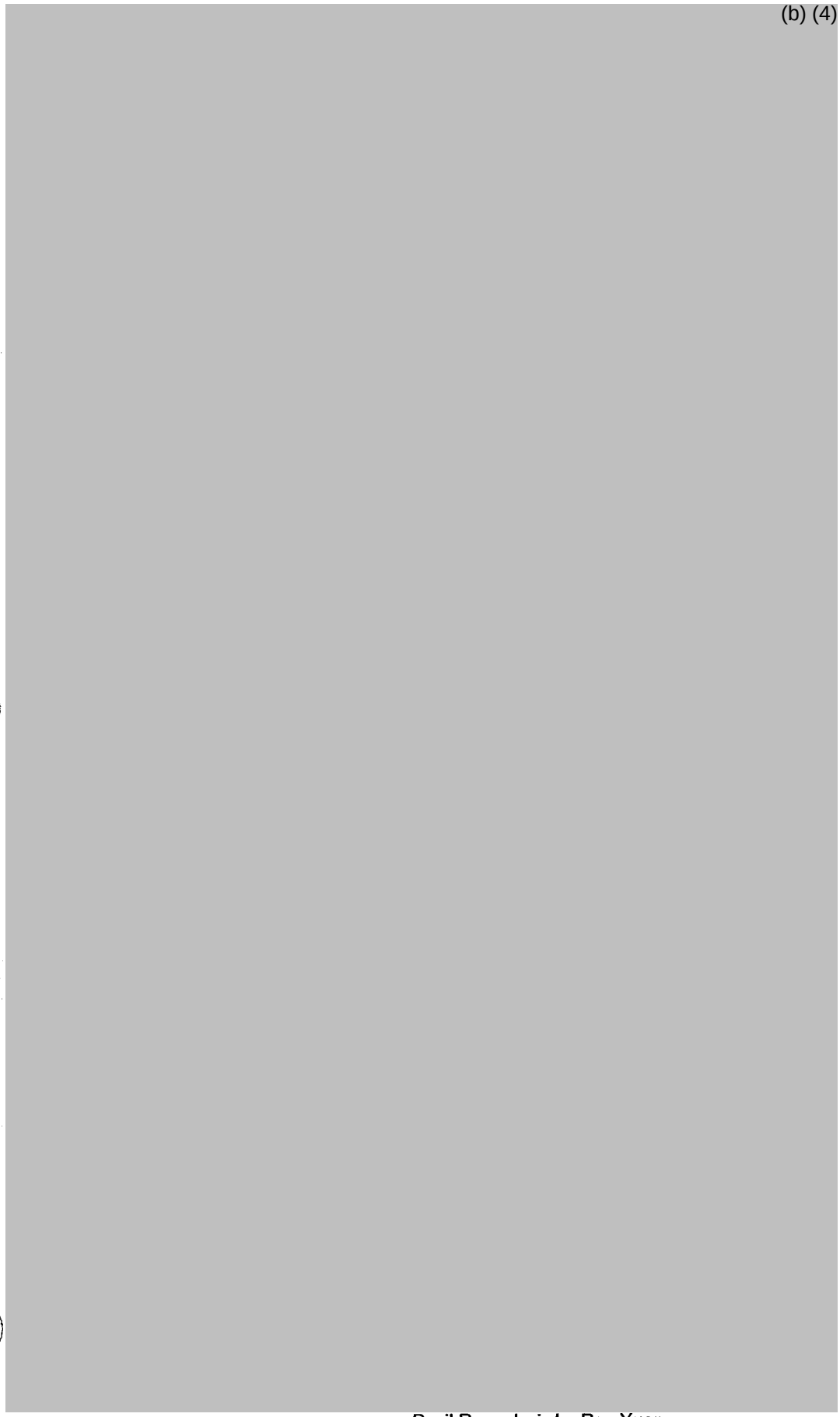
Cmax From Individuals With t1/2 <30 hr

(b) (4)



Cmax From Individuals With t1/2 <30 hr

(b) (4)



Paxil Reanalysis by Rae Yuan

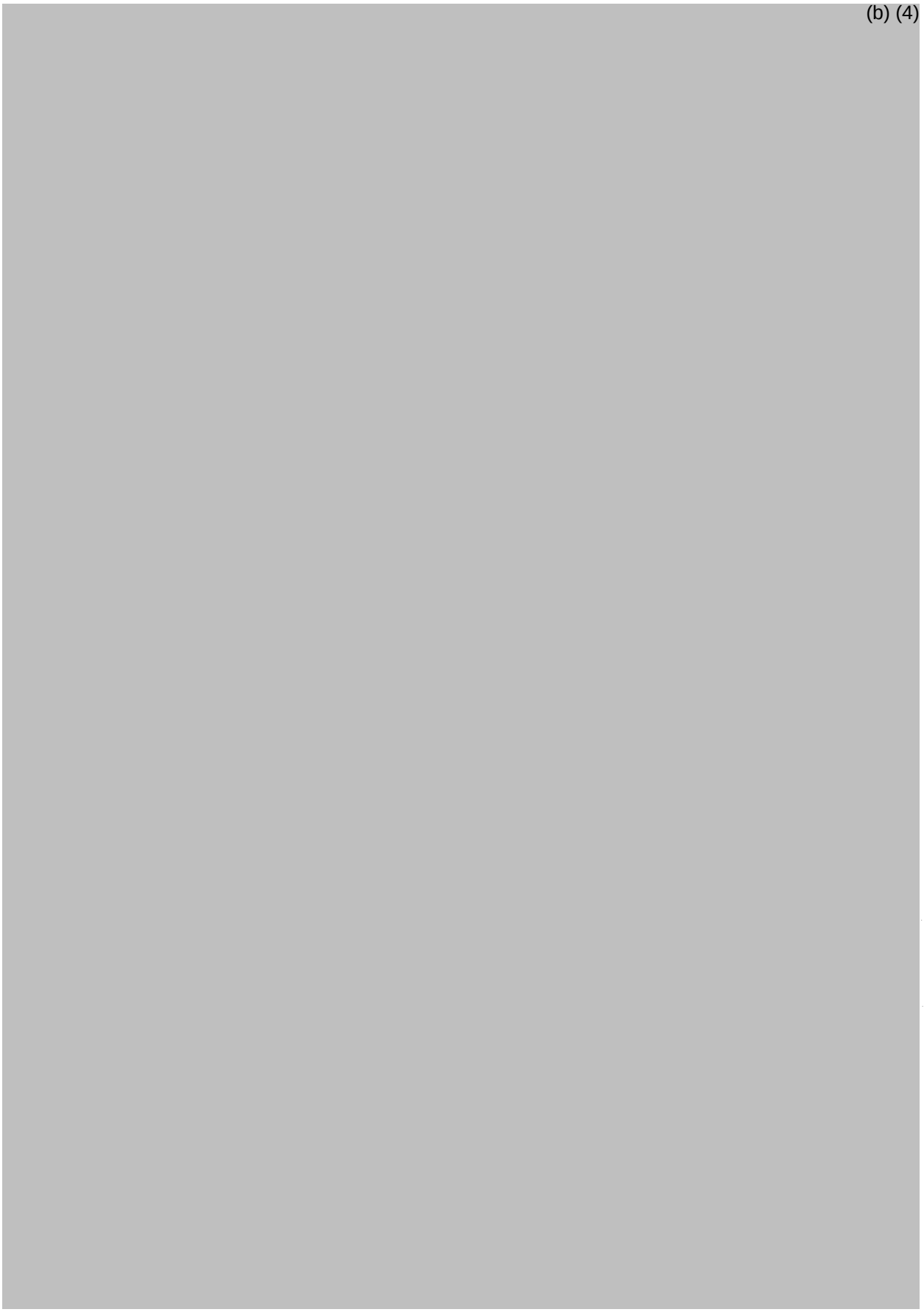
Cmax From Individuals With t1/2 <30 hr

(b) (4)

90% C.I. Using Randy Program:
81.6-97.1

AUC From Individuals With t1/2 <30 hr

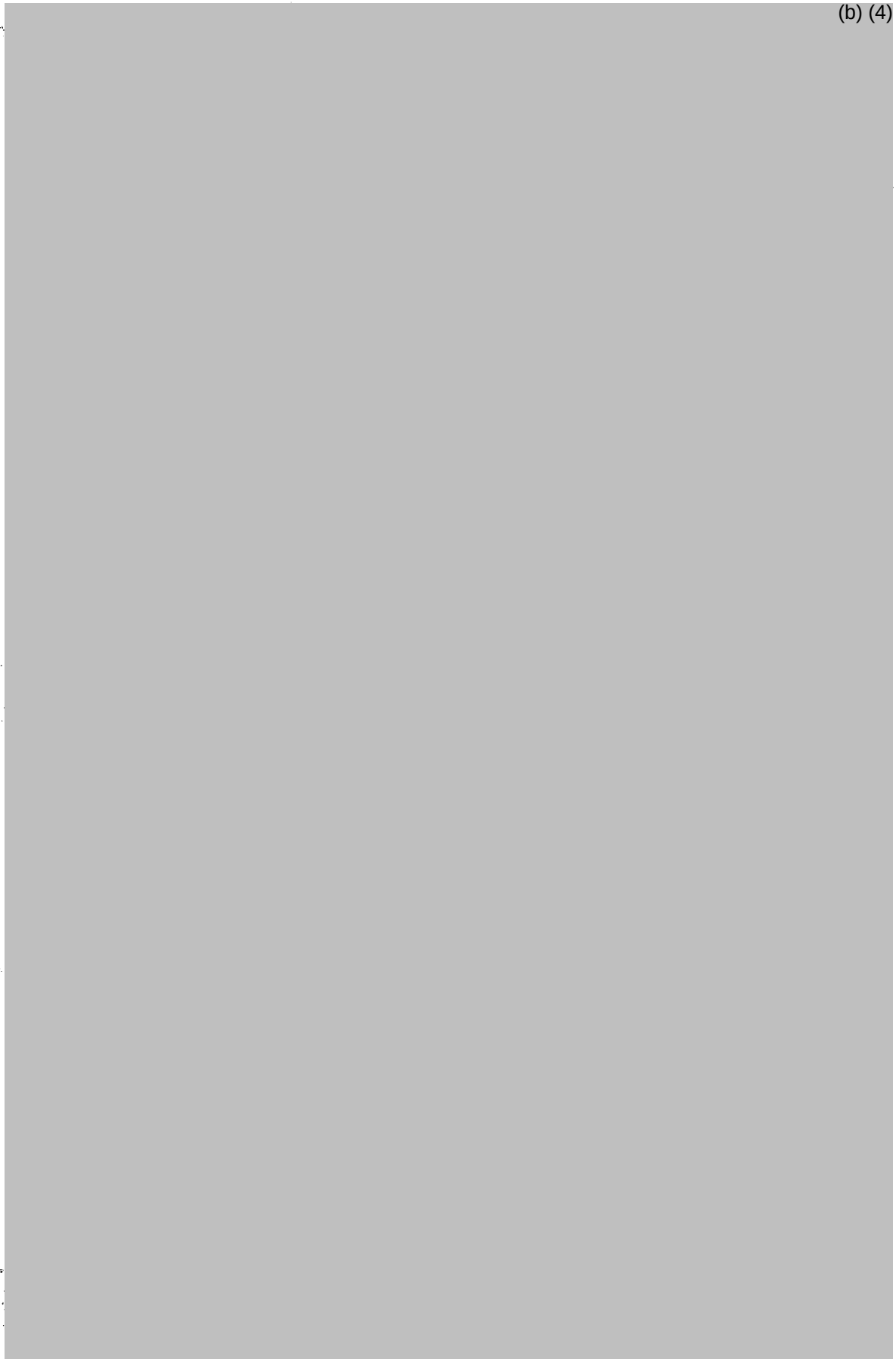
(b) (4)



Paxil Reanalysis by Rae Yuan

AUC From Individuals With t1/2 <30 hr

(b) (4)



AUC From Individuals With t1/2 <30 hr

(b) (4)

90% C.I. Using Randy Program:
83.8-99.6

[redacted] data were taken from individuals with t1/2 ranging from 4-30 hr
Mean ± SD of the group is 12.89± 4.89 hr for cidra, and 12.97 ± 4.90 for crawley

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

20-936/S001

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

12.1

MEMO OF TELEPHONE CALL

Date: September 14, 1999
NDA: 20-936
Drug: Paxil (paroxetine hydrochloride) Controlled-Release Tablets
Indication: Depression
Firm: SmithKline Beecham
Contact: Deborah Zuber, Regulatory Affairs
Phone #: (610) 917-6884

At the request of Dr. Seevers, I contacted Ms. Zuber in reference to a fax from SKB soliciting advice on the color coating requirements for their 2 approved strengths (12.5 mg and 25 mg tablets). (b) (4) They wish to manufacture (b) (4) strengths with the new commercial image (coating) at their Cidra, PR facility (see attached fax dated 8-10-99).

1. SKB is proposing to generate comparative dissolution profiles using 3 media of Stage II testing (b) (4) tablets) on their original coated tablet and their new commercial image tablet for both the 12.5 and 25 mg strengths. This data will be generated using only 1 batch of original coated tablet and 1 batch of new commercial coated tablet. F2 calculations will be completed for all of this data. This is acceptable to the Agency.

2. SKB proposes, when they submit the (b) (4)
(b) (4)

3. (b) (4)
(b) (4)

Ms. Zuber thanked me for the information, and she acknowledged understanding of the above.

Paul A. David, R.Ph.
Regulatory Project Manager

NDA ORIG 20-936
DIV FILE
HFD-120/RKatz/TLaughren/GDubitsky
HFD-120/PDavid
HFD-120/RSeevers/RLostritto
HFD-860/VJTammara/RYuan
DOC #PAXIL\CR\9-14-99 TELECON ZUBER.DOC

SB

SmithKline Beecham
Pharmaceuticals

To:	**Mr. Paul David** Regulatory Project Manager Division of Neuropharmacological Drug Products Food and Drug Administration	**Fax: (301) 594-2859**
From:	**Deborah E Zuber** Assistant Director U.S. Regulatory Affairs 1250 South Collegeville Road Collegeville, PA 19426-0989	**Tel: (610) 917-6884** **Fax: (610) 917-4704**
DATE:	August 10, 1999	
NO. OF PAGES:	2 (Including Cover Sheet)	
SUBJECT:	**NDA 20-936** **Paxil® (paroxetine hydrochloride) Controlled Release Tablets**	

Dear David:

As discussed in our telephone discussion on August 9, 1999, this fax provides a request for guidance on the mandate to generate comparative dissolution profile data in accordance with SUPAC-MR for the additional colored film coat on the Paxil® CR Tablets, 12.5 mg and 25 mg, manufactured at Cidra, PR facility.

(b) (4)

An FDA decision is respectfully requested.

Sincerely,

Deborah E. Zuber

Deborah E. Zuber
Assistant Director
N.A. Regulatory Affairs

MEMORANDUM

DATE: July 2, 1999

FROM: Acting Director
Division of Neuropharmacological Drug Products/HFD-120

TO: File, NDA 20-936/S-001

SUBJECT: Approval Action for NDA 20-936/S-001, Site Change for Paxil CR 12.5 and 25 mg Tablets.

On 3/1/99, SmithKline Beecham Pharmaceuticals submitted this supplement for a change in manufacture of Paxil CR 12.5 and 25 mg tablets. Specifically, the sponsor proposed a new cite of manufacture (Puerto Rico; the product is currently approved for production only in the UK) and a change in the color. In support of these changes, 2 large bioequivalence studies were performed comparing the product produced in Puerto Rico and the approved UK produced product. Dr. Yuan of OCPB has concluded that the 2 products are bioequivalent.

Dr. Lostritto, reviewing chemist, has concluded that the new color change is unacceptable (b) (4) (b) (4) He recommends that, (b) (4) (b) (4) dissolution testing of new color product produced at the manufacturing sites be compared to old color product before the new color product be approved.

A number of issues need to be addressed.

First, although not discussed in the reviews, it should be noted that the bioequivalence studies reviewed by Dr. Yuan were performed, as best we can tell, with product produced in Puerto Rico with the **old color** (based on a review of the batch records performed by Drs. Yuan and Lostritto on 7/2/99).

Second, Dr. Lostritto has, as noted earlier, recommended that submission of the appropriate dissolution data are critical to an assessment of the new color product (b) (4) (b) (4)

I have spoken with Drs. Yuan and Lostritto today (7/2/99) and we are in agreement that Dr. Lostritto's recommendations regarding the additional data necessary for approval of the new color product are appropriate. In part, Dr. Lostritto's recommendations are based on an earlier letter sent by the Division to the sponsor's IND (b) (4) in which this general approach for approval of a color change was agreed to.

Finally, the letter I will issue approves the site change, but only for the old color product manufactured there. I recognize that this is not exactly what the submission proposes

(again, it asks for approval for the new color product manufactured at the new site), but this is all the submitted data support. While one could argue that a Not Approval letter should issue, I believe that approving a portion of what the sponsor requests is perfectly appropriate. The fact that the bioequivalence studies were performed with the old color product produced at the new site lends support to this approach.

ACTION

Based on the above considerations, I will issue the attached letter which approves the site change for the product with the old color, and which details the additional data that will support ultimate approval of the new color.

Russell Katz, M.D.

Cc:
NDA 20-936/S-001
HFD-120
HFD-120/Katz/Laughren/Lostritto/Seevers/David
HFD-860/Yuan/Sahajwalla

M E M O R A N D U M

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

DATE: July 2, 1999

FROM: Thomas P. Laughren, M.D.
Team Leader, Psychiatric Drug Products
Division of Neuropharmacological Drug Products
HFD-120

SUBJECT: Recommendation for Approval Action for Site Change for Paxil CR (paroxetine) 12.5 & 25 mg strength tablets

TO: File NDA 20-936/S-001
[Note: This memo should be filed with the 3-1-99 original submission.]

Paxil CR is an approved drug product, for the treatment of depression, currently available in 12.5 and 25 mg tablet strengths. This supplement provides for (1) an alternate drug product manufacturing site (Cidra, PR), and (2) data supporting a change in tablet color.

The original NDA for Paxil CR in depression included bioequivalence data for the 2 sites in question (Crawley, UK & Cidra, PR), but failed to show bioequivalence, apparently due to larger-than-expected individual variation. This supplement (S-001) included data from 2 bioequivalence studies involving drug product from these same 2 sites in 80 volunteers (Study 569:2X12.5 & Study 579:25). The results of this study were reviewed by Rae Yuan, Ph.D., who concluded that the requirements for bioequivalence were met (review signed 6-15-99).

S-001 also included dissolution data for tablets produced with a different coloring technique (b) (4) (b) (4) (b) (4) approach, and argue that the comparsion must include dissolution data for product from both commercial sites, using both the original and the new method, as well as release testing results and stability results. Thus, they recommend that the new color coating step not be approved.

Recommendation

I recommend that the attached approval letter, approving only the site change for the original image, may issue.

cc:
Orig NDA 20-936/S-001
HFD-120/DivFile
HFD-120/TLaughren/RKatz/PDavid

DOC: NDA20936.01

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

42.1

NDA 20-936/S-001

Smithkline Beecham Pharmaceuticals
1250 S. Collegeville Road
P.O. Box 5089
Collegeville, PA 19426

MAR 11 1999

Attention: Deborah E. Zuber, Assistant Director

Dear Ms. Zuber:

We acknowledge receipt of your supplemental application for the following:

Name of Drug: Paxil CR Tablets

NDA Number: 20-936

Supplement Number: S-001

Date of Supplement: March 1, 1999

Date of Receipt: March 3, 1999

Unless we find the application not acceptable for filing, this application will be filed under Section 505(b)(1) of the Act on May 2, 1999 in accordance with 21 CFR 314.101(a).

All communications concerning this NDA should be addressed as follows:

Center for Drug Evaluation and Research
Division of Neuropharmacological Drug Products, HFD-120
Office of Drug Evaluation I
Attention: Document Control Room 4008
5600 Fishers Lane
Rockville, MD 20857

Sincerely,

John S. Purvis
Chief, Project Management Staff
Division of Neuropharmacological Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-936/001
HFD-120/Div. Files
HFD-120/CSO/David

filename: C:\WPWIN61\TEMPLATE\FDA\20-936.001

SUPPLEMENT ACKNOWLEDGEMENT

SmithKline Beecham

ORIGINAL

CENTER FOR DRUG EVALUATION AND RESEARCH

March 1, 1999 MAR 0 3 1999

RECEIVED HFD-120

NDA 20-936
Paxil® (paroxetine hydrochloride) Controlled Release Tablets

Russell Katz, M.D., Acting Director
Division of Neuropharmacological
Drug Products (HFN-120, Room 10B-45)
Center for Drug Evaluation and Research
Office of Drug Evaluation I
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

NDA SUPPLEMENT

CENTER FOR DRUG REC'D MAR 0 2 1999 HFD-570 EVALUATION AND RESEARCH

NDA NO. 20-936 REF NO. Scm-06

NDA SUPPL FOR Manufact

NDA SUPPLEMENT

Re: Prior Approval Supplemental NDA
Drug Product Manufacturing Site Transfer

Dear Dr. Katz:

Reference is made to the approved New Drug Application NDA 20-936 for Paxil® (paroxetine HC1) Controlled Release Tablets approved February 16, 1999 for the 12.5 mg and 25 mg Tablets. This supplemental NDA provides for an alternate site of drug product manufacture at SmithKline Beecham, Cidra, PR facility.

This submission includes Chemistry, Manufacturing, and Controls data located in Items 4.A.2, 4.B, and 4.C, for drug product batches manufactured at an alternate manufacturing site, SmithKline Beecham, Cidra, PR facility together with supporting bioequivalence data from two (2) clinical studies linking the 12.5 mg tablets and the 25 mg tablets from both manufacturing sites, SB Cidra and SB Crawley.

The following two (2) clinical studies are provided in Item 6.3 of this supplement.

- Clinical Protocol 29060/569, "A single dose, four period crossover study to demonstrate bioequivalence between 2 x 12.5 mg controlled release paroxetine tablets manufactured at Crawley and Cidra." Study Report No. 29060/569 BRL-029060/RSD-100RB2/1

- Clinical Protocol 29060/579, "A single dose, four period crossover study to demonstrate bioequivalence between 25 mg controlled release paroxetine tablets manufactured at Crawley and Cidra." Study Report No. 29060/579 BRL-029060/RSD-100TRD/1

1250 S. Collegeville Road, PO Box 5089, Collegeville, PA 19426-0989. Telephone (610) 917 7000. Fax (610) 917 7707.

In addition, Item 4.A.2 contains data for "new commercial image" tablets (12.5 mg is a

(b) (4)

[redacted]

Also included with this submission are three (3) copies of the Methods Validation Package for the FDA Laboratories.

A Field copy of this submission has been sent to the FDA San Juan District Office as per the regulations.

Annotated draft labeling has also been provided in this submission to reflect the

(b) (4)

[redacted]

film-coated tablets.

Should you have any questions or need additional information, please do not hesitate to contact me at (610) 917-6884.

Sincerely,

[redacted]

Deborah E. Zuber
Assistant Director
NA Regulatory Affairs

[redacted]