

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-052

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

CLINICAL PHARMACOLOGY REVIEW

NDA 22-052:	Submission Date: July 30, 2006
Brand Name:	— 'XR tablet
Generic Name:	Zileuton Controlled Release tablet
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.
OCP Division:	DCP 2
OND Division:	DPADP
Sponsor:	Critical Therapeutics (CRTX), Inc.
Submission Type:	Original (S000)
Formulation; Strength(s):	Zileuton 600 mg CR tablet
Indication:	Prophylaxis and chronic treatment of asthma at a dosage regimen of 1200 mg twice daily for adults and children 12 years of age and older.

TABLE OF CONTENTS

ITEM	PAGE NUMBER
1. Executive Summary	2
1.1 Recommendation	2
1.2 Phase 4 Commitment	2
1.3 Summary of Clinical Pharmacology and Biopharmaceuticals Findings	2
2. Question-Based Review	6
2.1 General attribute of Zileuton	6
2.2 General Clinical Pharmacology	7
2.5 General Biopharmaceutics	8
2.6 Analytical Section	22
3. Labeling Recommendation	22
4. Appendix	
4.1 Proposed labeling	24
4.2 Individual studies	34
4.3 OCP filing/Review Form	53

1. EXECUTIVE SUMMARY

1. **Recommendation:** The Office of Clinical Pharmacology (OCP/Division of clinical pharmacology 2 OCP2)) has reviewed the clinical pharmacology studies submitted to NDA 22-052, and found them acceptable. DSI audit was requested but was not performed (due to the budget issue).

1.2 **Phase 4 Commitment:** None.

1.3 Summary of clinical Pharmacology and Biopharmaceutics Findings

Abbott initiated the development of zileuton controlled-release (CR) tablets (“Formulation H”) and conducted pivotal BA studies, multiple-dose (M95-264) and a food effect/single-dose study (M96-556) as well as two Phase III studies, a 12-week clinical efficacy study (M95-337) and a 6-month long term safety study (M96-464) with Formulation H CR tablets. However, Abbott never filed an NDA application for CR tablets. Abbott also developed immediate-release (IR) formulation of zileuton tablets (Zyflo®), and this was approved in 1996.

Subsequently, Critical Therapeutics, Inc. (CRTX) acquired ownership of both Zyflo® and zileuton CR tablets. CRTX had modified Abbott’s Formulation H (which is no longer available) and developed a new CR tablet (to-be marketed Formulation, E21), and performed two (definitive) BA studies; a single-dose/food effect (CTI-03-C05-102) and a multiple-dose study (CTI-03-C05-103) which were designed similarly to M96-556 and M95-264, respectively, to allow the comparison of the study results between these studies. The two studies (CTI-03-C05-102 and CTI-03-C05-103) conducted by CRTX along with two studies conducted by Abbott (M96-556 and M95-264) are summarized below.

Study CTI-03-C05-102 (single dose): PK of zileuton from the test product zileuton (_____) CR tablets (2 x 600 mg) under fasted (Regimen A) and fed (Regimen B) conditions were compared to the reference product, Zyflo® IR tablets (1 x 600 mg every 6 hrs, 2 doses) under fasted (Regimen C) condition in a 3-way crossover study in healthy volunteers. The results are summarized in Table 1.

Table 1. Summary of mean (±SD) Ziluton PK parameters (Study CTI-03-C05-102)

Parameters	Regimen A (n=23)	Regimen B (n=23)	Regimen C (n=23)
T _{max} (h)	2.13 ± 2.14	4.34 ± 3.98	1.30 ± 0.56 ^c
C _{max} (µg/mL)	3.11 ± 0.87	3.67 ± 1.46	5.57 ± 1.82 ^c
AUC _(0-∞) (µg·hr/mL)	22.46 ± 6.81	29.67 ± 7.74	39.32 ± 9.77
AUC _(0-inf) (µg·hr/mL) ^a	22.33 ± 6.26	30.01 ± 7.96	39.06 ± 9.68
CL/F (mL/min) ^a	956.27 ± 236.71	714.26 ± 195.54	542.64 ± 133.04
t _{1/2} (hr) ^{a, b}	-	-	2.24 ± 0.47

^a n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020.

^b Elimination rate constants could not be estimated for all subjects from the CR regimens; therefore, the elimination rate constants estimated from Regimen C were used for all subjects.

^c After the first 600 mg dose

Note: C_{max} after the 2nd dose IR was 8.1 µg/mL

Food caused increase in C_{max}, AUC_t and AUC_{inf} by 18%, 32% and 34% respectively, and T_{max} by almost 2-fold. Increased bioavailability of the CR tablets after a high fat meal compared to fasted condition was statistically significant.

Mean AUC and Cmax values were lower after administration of the CR formulation (under fasted and fed conditions) than after administration of the IR formulation (under fasted condition): Cmax and AUC ratios of CR fasted conditions to IR were 39% (3.1 *vs.* 8.1 $\mu\text{g/mL}$) and 57% (22.5 *vs.* 39 $\mu\text{g}\cdot\text{hr/mL}$), respectively. Similarly, Cmax and AUC ratios of CR under fed conditions to IR were 46% (3.7 *vs.* 8.1 $\mu\text{g/mL}$) and 76% (30 *vs.* 39 $\mu\text{g}\cdot\text{hr/mL}$), respectively.

Comparison with Study M96-556

Study M96-556 had same design as Study CTI-03-C05-102, except that there were 4 treatment groups (Regimens A-D). PK results are summarized in Table 2.

Table 2. Summary of mean (\pm SD) Zileuton PK parameters (n=24) (Study M96-556)

Zileuton PK Parameters	Regimen A 1200 mg CR Fasting	Regimen B 1200 mg CR High Fat Non-Fasting	Regimen C 1200 mg CR Low Fat Non-Fasting	Regimen D 1200 mg IR Fasting
T_{max} (hr)	1.9 \pm 1.0	4.3 \pm 2.9 [†]	2.5 \pm 0.9	1.7 \pm 1.0 [†]
C_{max} ($\mu\text{g/mL}$)	4.39 \pm 1.76	5.22 \pm 2.16 [†]	4.73 \pm 1.30	6.68 \pm 2.60 [†]
$AUC_{0-12\text{hr}}$ ($\mu\text{g}\cdot\text{hr/mL}$)	29.36 \pm 10.25	41.98 \pm 14.29 [†]	30.45 \pm 13.52	51.91 \pm 16.73
$AUC_{0-\infty}$ ($\mu\text{g}\cdot\text{hr/mL}$)	29.82 \pm 10.27	42.42 \pm 14.41 [†]	30.82 \pm 13.64	52.07 \pm 16.73
CL/F (mL/min)	748 \pm 265	525 \pm 179	773 \pm 345	423 \pm 136
$t_{1/2}$ (hr)				2.6 \pm 0.7

[†]After the first 600 mg dose.

Note: Cmax after the 2nd dose IR was 10.5 $\mu\text{g/mL}$

Food (high fat, Regiment B) caused increase in Cmax and AUC by 19% and 42% respectively, and Tmax by approximately 2-fold. The increased bioavailability of the CR tablets after a high fat meal was statistically significant.

The mean ratio of zileuton $AUC_{0-\infty}$ values after administration of the CR tablets under fasted conditions and with a high fat meal to IR were 57% (90% CI = 0.53-0.61) and 81% (90% CI = 0.75-0.87), respectively. Mean ratio of zileuton Cmax values after administration of zileuton CR formulation under fasted conditions and with a high fat meal to IR were 42% (4.4 *vs.* 10.5 $\mu\text{g/mL}$) and 50% (5.2 *vs.* 10.5 $\mu\text{g/mL}$), respectively.

Summary of zileuton PK comparison between Studies CTI-03-C05-102 and M96-556 are as follows (Table 3):

- Mean $AUC_{0-\infty}$ after administration of the CR tablets under fasted conditions and with a high fat meal were about 57% and 76%, respectively of the mean $AUC_{0-\infty}$ after administration of the IR tablets under fasted conditions in Study CTI-03-C05-102, while these values were 57% and 81%, respectively in Study M96-556.
- Mean zileuton Cmax values after administration of zileuton CR formulation under fasted conditions and with a high fat meal were 39% and 46%, respectively of the mean Cmax administration of zileuton IR formulation administered under fasted conditions in Study CTI-03-C05-102, while these values were 42% and 50%, respectively in Study M96-556.
- None of the 90% CIs were within the equivalence range of 0.8 and 1.25 however, overall, the results showed similar BA between these two studies.

Table 3. 90% CIs of the Ratios of Mean Zileuton PK parameters

Parameters	Test	Reference	CRTX Ratio of Means (Test/Reference) (n = 23)		Abbott Ratio of Means (Test/Reference) (n = 24)	
			Point Estimate	90% CI	Point Estimate	90% CI
C _{max} (µg/mL)	A	C/D	0.39		0.42	
AUC _{0-t} (µg.h/mL)	A	C/D	0.56	(0.52, 0.61)		
AUC _{0-∞} (µg.h/mL)	A	C/D	0.57	(0.52, 0.62)	0.57	(0.53, 0.61)
C _{max} (µg/mL)	B	C/D	0.46		0.50	
AUC _{0-t} (µg.h/mL)	B	C/D	0.75	(0.69, 0.81)		
AUC _{0-∞} (µg.h/mL)	B	C/D	0.76	(0.70, 0.83)	0.81	(0.75, 0.87)

A=CR Fasted; B=CR with High Fat Meal; C=IR Fasted (CRTX reference); D=IR Fasted (Abbott reference)

C_{max} from Regimen C and Regimen D was obtained by 2 x C_{max} after the first dose.

Source: Statistical Tables 14.2.3.1, 14.2.3.2 and 14.2.3.3 (CTI-03-C05-102 study)

Appendix E.5R, Amendment to the Drug Metabolism Report for Abbott M96-556 study

Study CTI-03-C05-103 (steady state): PK of zileuton from the test product ~~CR tablets~~ CR tablets under fed (Regimen A) and fasted (Regimen B) conditions were compared to the reference product, Zylflo® IR tablets under fed (Regimen C) condition in a 3-way crossover study in healthy volunteers. All subjects received treatment drugs for 6 days. The results are summarized in Table 4.

Table 4. Mean (±SD) Ziluton PK parameters at steady state (Study CTI-03-C05-103)

Parameters	Regimen A	Regimen B	Regimen C
	2 x 600 mg CR Every 12 hours Non-Fasting (n=24)	2 x 600 mg CR Every 12 hours Fasting (n=24)	1 x 600 mg IR Every 6 hours Non-Fasting (n=24)
T _{max} (hr)	3.57±2.35	2.12±1.42	1.63±0.82
AUC (µg·hr/mL)	63.99±15.95	44.85±12.59	77.42±21.36
C _{max} (µg/mL)	4.97±1.34	4.59±1.42	7.72±2.43
C _{min} (µg/mL)	1.00±0.45	0.37±0.17	0.99±0.38
C _{min trough} (µg/mL)	1.91±0.71	0.63±0.56	1.80±0.64
C _{avg} (µg/mL)	2.67±0.67	1.87±0.53	3.23±0.89
CL/F (mL/min)	668.7±195.95	968.8±316.37	607.4±433.83
FI	1.50±0.33	2.27±0.34	2.19±0.83
t _{1/2} (hr)	3.19±1.24*	4.05±1.94*	2.23±0.53
Beta (1/hr)	0.24±0.07*	0.21±0.09*	0.32±0.06

* n=19 for Regimen A and n=20 for Regimen B since elimination rate constant was not estimable for some of the subjects.

Source: Statistical Tables 14.2.2.1.2, 14.2.2.2.2, 14.2.2.3.2, 14.2.1.1.4, 14.2.1.2.4 and 14.2.1.3.4.

Food caused statistically significant increase in AUC₀₋₂₄ and C_{min} by 44% and 170% respectively, but no effect on C_{max}. T_{max} was delayed by almost 2-fold.

The point estimates (90% CI) for C_{max}, C_{min} and AUC₀₋₂₄ of CR (fasted) to IR (fed) were 0.60 (0.55-0.62), 0.39 (0.33-0.46) and 0.59 (0.54-0.64), respectively. The point estimates (90% CI) for C_{max} and AUC₀₋₂₄ of CR to IR both under both fed conditions were 0.65 (0.60-0.71) and 0.85 (0.78-0.92), respectively, however C_{min} was equivalent [1.05 (0.88-1.25)].

Comparison with Study M95-264

Study M96-556 had same design as Study CTI-03-C05-103, except that there were 2 treatment groups, CR (Regimen A) *vs.* IR (Regimen B), both under fed conditions. PK results are summarized in Table 5.

Table 5. Summary of mean (\pm SD) Zileuton PK parameters (n = 24) (Study M95-264)

24-Hour Zileuton PK Parameters	Regimen A 1200 mg CR every 12 hours	Regimen B 600 mg IR every 6 hours
T _{max} (hr)	2.6 \pm 2.0*	1.7 \pm 0.5
C _{max} (μ g/mL)	5.93 \pm 2.36*	11.99 \pm 5.25
C _{min} (μ g/mL)	0.62 \pm 0.46*	1.13 \pm 0.87
C _{avg} (μ g/mL) [†]	2.48 \pm 0.97	4.55 \pm 2.52
FI ₀₋₂₄	2.21 \pm 0.61*	2.49 \pm 0.56
AUC ₀₋₂₄ (μ g \cdot hr/mL)	59.5 \pm 23.2*	109.2 \pm 60.5
β (hr ⁻¹)	0.218 \pm 0.081*	0.357 \pm 0.052
t _{1/2} (hr) [†]	3.7 \pm 1.7	2.0 \pm 0.4
CL/F (mL/min) [†]	766 \pm 267	434 \pm 155
Vd ₀ /F (L) [†]	253 \pm 163	72 \pm 21

*Statistically significantly different from Regimen B.

[†]Parameter not tested statistically.

The mean zileuton C_{max}, C_{min} and AUC₀₋₂₄ after administration of the CR tablet formulation (1200 mg q12h) was 51%, 45% and 54%, respectively lower than those after administration of a 600 mg IR tablet q6h (p<0.05). The mean zileuton T_{max} after administration of the CR tablet was significantly longer than the corresponding value after administration of the IR tablet formulation (2.6 *vs.* 1.7 hr).

For comparison, the 90% CIs of the ratios of means from Study CTI-03-C05-103 (CRTX) and Study M95-264 (Abbott) are presented in Table 6.

Table 6. 90% CIs of the Ratios of Mean Zileuton PK parameters

Parameters			CRTX Ratio of Means (Test/Reference) (n = 23)		Abbott Ratio of Means (Test/Reference) (n = 24)	
	Test	Reference	Point Estimate	90% CI	Point Estimate	90% CI
C _{max} (μ g/mL)	CR	IR	0.650	(0.595, 0.710)	0.499	(0.429, 0.581)
C _{min} (μ g/mL)	CR	IR	1.046	(0.879, 1.245)	0.543	(0.420, 0.703)
AUC ₀₋₂₄ (μ g \cdot h/mL)	CR	IR	0.846	(0.781, 0.915)	0.560	(0.503, 0.622)

Source: Statistical Tables: 14.2.3.1, 14.2.3.2, 14.2.3.3 (CTI-03-C05-103; Appendix C, Amendment to the Drug Metabolism Report for Abbott M95-264 study)

As shown in Table 6, in Study M95-264, steady state C_{max}, C_{min} and AUC₀₋₂₄ from zileuton CR tablets were approximately 50% of those from zileuton IR tablets. In Study CTI-03-C05-103, C_{max} and AUC from zileuton CR tablets were 65% and 85% of those from zileuton IR tablets, while C_{min} was similar. Therefore, bioavailability after CR formulation E21 compared to IR formulation in Study CTI-03-C05-103 was higher compared to that after CR formulation H compared to IR formulation in Study M95-264. In addition, the results (higher C_{min} and smaller FI) indicated an improved controlled-release profile with the zileuton CR formulation E21 compared to that CR formulation H.

Pharmacokinetics (from IR product): After oral administration IR zileuton, a mean T_{max} was 1.72 (± 0.94) (+S.D.) hours. The mean zileuton peak level (C_{max}) and the mean systemic exposure (AUC), normalized for a 600 mg dose, were 4.98 pg/mL and 19.2 pg. hr/mL, respectively. The PK of zileuton up to 2400 mg/day was linear. The average zileuton half-life is approximately 2.5 hours.

The apparent volume of distribution of zileuton is approximately 90 L. The plasma protein binding of zileuton in humans is high averaging 93%, with most of the binding associated with albumin, with minor binding to α_1 -acid glycoproteine.

Zileuton is extensively metabolized by the liver. The major urinary metabolites in humans (approximately 80 - 90% of the dose) are zileuton glucuronides. The urinary excretion of the inactive N-dehydroxylated metabolite (A-66193) and unchanged zileuton each accounted for less than 0.5% of the dose. The inactive metabolite A-66193 has been shown to be formed by the gastrointestinal microflora prior to the absorption of zileuton and its formation increases with delayed absorption of zileuton. In vitro studies utilizing human liver microsomes have shown that zileuton and A-66193 can be oxidatively metabolized by the cytochrome P450 isoenzymes CYP1A2, 2C9 and 3A4.

In cirrhotic patients with mild to moderate hepatic impairment the systemic exposure for zileuton was doubled and the apparent plasma clearance was reduced by half as compared to that in healthy subjects. Zileuton tablets are contraindicated in patients with active liver disease or unexplained transaminase elevations. Renal impairment did not affect the PK of zileuton accordingly, no dosage adjustments are necessary in this population.

Indication and Dosage: Prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older at a dosage regimen of two 600 mg CR tablets twice daily, within one hour after morning and evening meals. Hepatic transaminase should **be evaluated prior to initiation of** ~~zileuton~~ and periodically during treatment.

2.5. General Biopharmaceutics

2.5.1. What is the relative bioavailability of the proposed to-be-marketed formulation following single dose administration to the IR formulation (CTI-03-C05-102)? How different is the PK profile of zileuton CR tablets from this study compared to that from the study conducted by Abbott (M96-556)?

Study CTI-03-C05-102 was a single-dose, randomized, open-label, 3-period, crossover design, with a minimum of a 6-day washout interval between periods. Twenty-four healthy male (n=12) and female (n=12) subjects enrolled in this study. The objective of this study was to compare the bioavailability of zileuton CR 600 mg tablets (E21 Formulation) administered under fasted and fed (high fat meal) conditions with that of zileuton IR 600 mg tablets (Zyflo[®]) under fasted condition. The following regimens were used in this study:

- **TRT A:** Two 600 mg CR zileuton tablets under fasting condition; Lot #: 3049002R.
- **TRT B:** Two 600 mg CR zileuton tablets under fed condition; Lot #: 3049002R.
- **TRT C:** One 600 mg IR zileuton tablet (Zyflo[®]) **administered at Time "0" and a second tablet administered at "6 hours" under fasting conditions;** Lot #: 07104AF21.

Blood samples were collected at prior to dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 12, 14, 16, 20, 24, 28, and 36 hours post-dosing in each period. The plasma samples were analyzed for zileuton and

A-66193 with a validated LC-MS/MS assay at ~~.....~~. The LLQ was ~~.....~~ $\mu\text{g/mL}$ for each analyte.

An analysis of variance (ANOVA) model was performed on the natural logarithmic transformations of C_{max} and AUC for zileuton and inactive metabolite A-66193. The relative bioavailability of the CR tablets versus the IR tablets and CR tablets under fasted versus CR tablets under fed conditions (food effect) were assessed by the 2 one-sided test procedure via 90% CI of the ratios of the treatment geometric least-squares (LS) means for each comparison (Regimen A/Regimen B, Regimen A/Regimen C, and Regimen B/Regimen C).

Results

Disposition of subjects: One subject withdrew prematurely (received Regimens A and C only), and twenty-three subjects completed all 3 study periods and were included in the BA analyses.

Demographics: Subjects' ages ranged 20-55 years (mean of 32.5 years), heights ranged 157-191 cm (mean of 171.1 cm), and their weights ranged 54-91 kg (mean of 71.7 kg), respectively.

Pharmacokinetics:

Zileuton: Mean plasma concentration-time profiles of zileuton are shown in Figure 1. Mean PK parameters per regimen are summarized in Table 8, and statistical BE analysis for zileuton are presented in Tables 9-10.

Figure 1. Mean zileuton Plasma Concentration versus Time profiles by Treatment

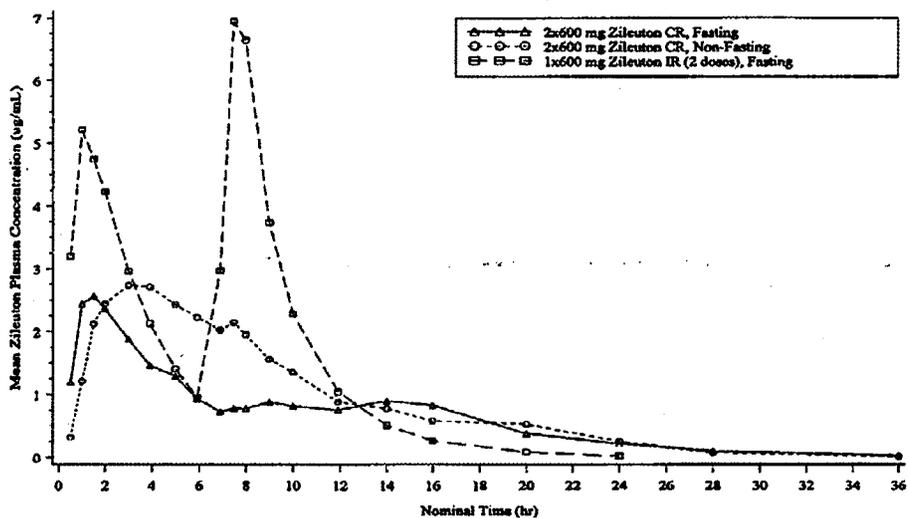


Table 8. Summary of mean (\pm SD) Ziluton PK parameters

Parameters	Regimen A	Regimen B	Regimen C
	2 x 600 mg CR Fasting (n=23)	2 x 600 mg CR Non-Fasting (n=23)	1 x 600 mg IR (2 Doses) Fasting (n=23)
T _{max} (hr)	2.13 \pm 2.14	4.34 \pm 3.98	1.30 \pm 0.56
C _{max} (μ g/mL)	3.11 \pm 0.87	3.67 \pm 1.46	5.57 \pm 1.82 ^c
AUC _(0-t) (μ g \cdot hr/mL)	22.46 \pm 6.81	29.67 \pm 7.74	39.32 \pm 9.77
AUC _(0-inf) (μ g \cdot hr/mL) ^a	22.33 \pm 6.26	30.01 \pm 7.96	39.06 \pm 9.68
CL/F (mL/min) ^a	956.27 \pm 236.71	714.26 \pm 195.54	542.64 \pm 133.04
T _{1/2} (hr) ^{a, b}	-	-	2.24 \pm 0.47

^a n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020.

^b Elimination rate constants could not be estimated for all subjects from the CR regimens; therefore, the elimination rate constants estimated from Regimen C were used for all subjects.

^c After the first 600 mg dose

Source: Statistical Tables 14.2.2.1.2, 14.2.2.2.2 and 14.2.2.3.2

Food effect of CR formulation: Food caused increase in C_{max}, AUC_t and AUC_{inf} by 18%, 32% and 34% respectively, and T_{max} by almost 2-fold (Table 8). The increased bioavailability of the CR tablets after a high fat meal was statistically significant (Table 9).

Table 9. Statistical Analysis of zileuton CR tablet under fasted (A) vs. fed (B) conditions

Parameters	Regimen		Ratio of Means (Fasting/Non-Fasting)	
	Fasting	Non-Fasting	Point Estimate ^a	90% CI
C _{max} (μ g/mL)	A	B	0.863	(0.755, 0.987)
AUC _(0-t) (μ g \cdot hr/mL)	A	B	0.749	(0.691, 0.811)
AUC _(0-inf) (μ g \cdot hr/mL)	A	B	0.745 ^b	(0.686, 0.808)

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

^b n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020. Hence, AUC_(0-inf) could not be calculated for this subject.

Table 10. Statistical Analysis of zileuton CR tablets under fasted (A) and fed (B) conditions vs. IR tablets under fasted condition (C)

Parameters	Test	Reference	CRTX Ratio of Means (Test/Reference) (n = 23)	
			Point Estimate	90% CI
C _{max} (μ g/mL)	A	C	0.39	
AUC _{0-t} (μ g.h/mL)	A	C	0.56	(0.52, 0.61)
AUC _{0-∞} (μ g.h/mL)	A	C	0.57	(0.52, 0.62)
C _{max} (μ g/mL)	B	C	0.46	
AUC _{0-t} (μ g.h/mL)	B	C	0.75	(0.69, 0.81)
AUC _{0-∞} (μ g.h/mL)	B	C	0.76	(0.70, 0.83)

A=CR Fasted; B=CR with High Fat Meal; C=IR Fasted

Source: Statistical Tables 14.2.3.1, 14.2.3.2 and 14.2.3.3 (CTI-03-C05-102 study)

BA comparison CR vs. IR tablets (Tables 8 and 10): Mean AUC and C_{max} values were lower after administration of the CR formulation (under fasted and fed conditions) than after administration of the IR formulation (under fasted condition): C_{max} ratio of CR to IR was 39% (fasted) and 46% (fed).

Similarly, AUC_{0-inf} ratio of CR to IR was 57% (fasted) and 76% (fed).

Results from this study are summarized as follows:

- For the CR formulation, food increased zileuton C_{max}, AUC_t and AUC_∞ 18%, 32% and 34%, respectively. T_{max} was almost doubled (2.13 vs. 4.34 hr) in the presence of food.
- The mean zileuton C_{max} values after administration of CR tablets under fasted conditions and with a high fat meal were about 39% and 46%, respectively of the mean zileuton C_{max} after administration of IR tablets under fasted conditions. Similarly, the mean zileuton AUC_∞ values after administration of CR tablets under fasted conditions and with a high fat meal were about 57% and 76%, respectively of the mean zileuton AUC_∞ after administration of IR tablets under fasted conditions. None of the CIs were within the range of 0.80 and 1.25; therefore, the CR formulation (both fasted and fed) is not equivalent to the IR formulation under fasted condition.

Metabolite A-66193: The key PK parameters of metabolite A-66193 are summarized in Table 11.

Table 11. Mean (±SD) PK parameters of A-66193

Parameters	Regimen A	Regimen B	Regimen C
	2 x 600 mg CR Fasting (n=19)	2 x 600 mg CR Non-fasting (n=19)	1 x 600 mg IR (2 Doses) Fasting (n=19)
T _{max} (hr)	24.63 ± 3.34	25.47 ± 4.46	19.48 ± 4.85
C _{max} (µg/mL)	2.31 ± 1.54	0.91 ± 0.73	0.43 ± 0.40 ^b
AUC _(0-t) (µg·hr/mL)	45.81 ± 26.87 ^a	23.77 ± 15.83 ^a	8.06 ± 7.13 ^a

^a n=14 for Regimen A; n=8 for Regimen B; n=12 for Regimen C; AUC was not calculated for subjects who had more than two thirds of the metabolite concentrations below the lower limit of quantification.

^b After the first 600 mg dose

Source: Statistical Tables 14.2.6.1.2, 14.2.6.2.2 and 14.2.6.3.2

The appearance of metabolite A-66193 was highly variable among subjects after administration of the CR formulation or the IR formulation. There were 4 subjects (Nos. 014, 015, 017 and 018) who did not have any measurable A-66193 after administration of CR formulation with a high fat meal as well as after administration of IR formulation under fasted conditions. Times for the first measurable concentrations of A-66193 ranged from 5 to 24 hours for CR and IR formulation under fasted conditions and from 8 to 28 hours for CR formulation under fed conditions. The mean T_{max} values for A-66193 were ~5 hrs longer after administration of the CR formulation than after administration of the IR formulation under fasted conditions. The mean values for A-66193 C_{max} and AUC_{0-t} were higher after administration of the CR formulation than after administration of the IR formulation. For the CR formulation, the values of C_{max} and AUC_{0-t} were larger for the fasted than for the fed condition. The inactive metabolite A-66193 has been shown to be formed by the micro flora in the GI tract (NDA 20-471). A larger portion of the zileuton CR dose was converted to A-66193 under fasted conditions, and resulted in lower zileuton AUC.

A-66193 PK results from Study CTI-03-C05-102 are summarized as follows:

- Mean AUC_{0-t} after administration of the CR tablets under fasted conditions and with a high fat meal were about 5.7- and 3.0-fold, respectively of the mean AUC_{0-t} after administration of the IR tablets under fasted conditions.
- Mean C_{max} values after administration of CR formulation under fasted conditions and with a high fat meal were about 5.4- and 2.1-fold, respectively of the mean C_{max} administration of IR formulation administered under fasted conditions.

Historical Comparison with Study M96-556

In Study M96-556, PK of zileuton CR tablets vs. IR tablets and food effect of CR tablets were assessed like in Study CTI-03-C05-102.

Study M96-556 utilized 4 arms as follows:

- **TRT A:** Two 600 mg CR zileuton tablets under fasted condition; Lot #: 17-434-AR-04.
- **TRT B:** Two 600 mg CR zileuton tablets under high-fat fed condition; Lot #: 17-434-AR-04.
- **TRT C:** Two 600 mg CR zileuton tablets under low-fat fed condition; Lot #: 17-434-AR-04.
- **TRT D:** One 600 mg IR zileuton tablet (Zyflo®) administered at Time "0" and a second tablet administered at "6 hours" under fasted conditions; Lot #: 01-087-AR-03.

Blood samples were collected at 0 hr (prior to dosing) and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 12, 14, 16, 20, 24, 28, 36, and 48 hours post-dosing in each period. The plasma samples were analyzed for zileuton and A-66193 with a validated HPLC assay at [redacted]. The LLQ was [redacted] mL for each analyte.

Subject demographics. Twenty-four healthy male (n=12) and female (n=12) subjects participated in the study. All subjects completed all 4 periods of the study. Their ages ranged from 19 to 45 years (mean of 33 years), their heights ranged from 152.4 to 190.5 cm (mean of 169.9 cm), and their weights ranged from 54.4 to 88 kg (mean of 71), respectively.

Pharmacokinetic Results

Zileuton: Mean plasma concentration-time profiles of zileuton are shown in Figure 2. The PK parameters of zileuton and statistical analysis after administration of each of the 4 study regimens are summarized in Tables 12-14.

Figure 2. Mean zileuton Plasma Concentration versus Time profiles by Treatment

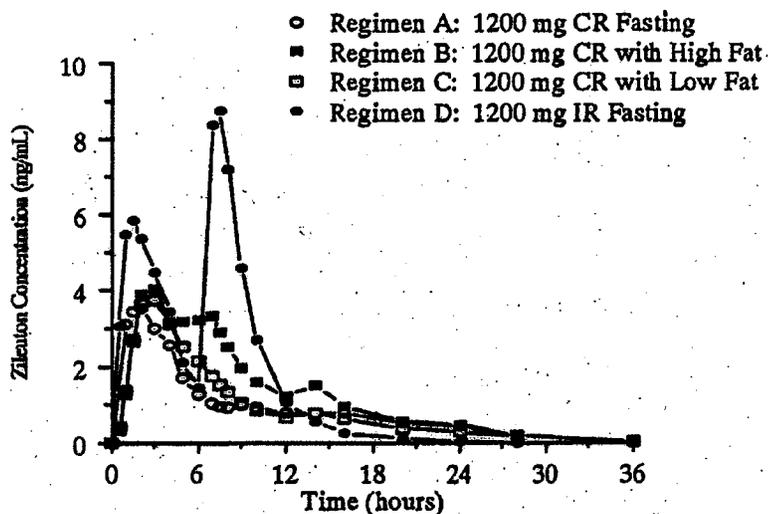


Table 12. Summary of mean (\pm SD) Zileuton PK parameters (Study M96-556)

Zileuton PK Parameters	Regimen A 1200 mg CR Fasting	Regimen B 1200 mg CR High Fat Non-Fasting	Regimen C 1200 mg CR Low Fat Non-Fasting	Regimen D 1200 mg IR Fasting
T_{max} (hr)	1.9 \pm 1.0	4.3 \pm 2.9 [†]	2.5 \pm 0.9	1.7 \pm 1.0 [†]
C_{max} (μ g/mL)	4.39 \pm 1.76	5.22 \pm 2.16 [†]	4.73 \pm 1.30	6.68 \pm 2.60 [†]
AUC_{0-last} (μ g \cdot hr/mL)	29.36 \pm 10.25	41.98 \pm 14.29 [†]	30.45 \pm 13.52	51.91 \pm 16.73
$AUC_{0-\infty}$ (μ g \cdot hr/mL)	29.82 \pm 10.27	42.42 \pm 14.41 [†]	30.82 \pm 13.64	52.07 \pm 16.73
CL/F (mL/min)	748 \pm 265	525 \pm 179	773 \pm 345	423 \pm 136
$t_{1/2}$ (hr)				2.6 \pm 0.7

[†]After the first 600 mg dose.

Table 13. Statistical Analysis of zileuton CR tablets under high fat meals (B) and low fat meals (C) *vs.* CR tablet under fasted conditions (A)

Parameter	Formulation		Ratio of Means	
	Test	Reference	Point Estimate [†]	95% Confidence Interval
C_{max}	B	A	1.211	1.032 – 1.422
C_{max}	C	A	1.135	0.996 – 1.332
$AUC_{0-\infty}$	B	A	1.424	1.306 – 1.553
$AUC_{0-\infty}$	C	A	1.000	0.917 – 1.091

[†]Antilogarithm of the difference of the least squares means for logarithms.

Food effect of CR formulation (Tables 12-13): Food (high fat, Regiment B) caused increase in C_{max} and AUC by 19% and 42% respectively, and T_{max} by approximately 2-fold. The increased bioavailability of the CR tablets after a high fat meal was statistically significant.

Table 14. Statistical Analysis of zileuton CR tablets under fasted (A) and fed (B) conditions *vs.* IR tablets under fasted condition (D)

Parameters	Test	Reference	Abbott Ratio of Means (Test/Reference) (n = 24)	
			Point Estimate	90% CI
C_{max} (μ g/mL)	A	D	0.42	
$AUC_{0-\infty}$ (μ g.h/mL)	A	D	0.57	(0.53, 0.61)
C_{max} (μ g/mL)	B	D	0.50	
$AUC_{0-\infty}$ (μ g.h/mL)	B	D	0.81	(0.75, 0.87)

A=CR Fasted; B=CR with High Fat Meal; D=IR Fasted

Source: Appendix E.5R, Amendment to the Drug Metabolism Report

BA comparison CR vs. IR tablets (Tables 12 and 14): The mean zileuton AUC_{∞} values after administration of the CR tablets under fasted conditions and with a high fat meal were about 57% (90% CI = 0.53-0.61) and 81% (90% CI = 0.75-0.87), respectively of the mean zileuton AUC_{∞} after administration of the IR tablets under fasted conditions. Mean zileuton C_{max} values after administration of zileuton CR formulation under fasted conditions and with a high fat meal were 42% (4.4 *vs.* 10.5 μ g/mL) and 50% (5.2 *vs.* 10.5 μ g/mL), respectively of the mean C_{max} administration of zileuton IR formulation administered under fasted conditions.

Comparison between Study CTI-03-C05-102 and M96-556 are presented in Table 15.

Table 15. 90% CIs of the Ratios of Mean Zileuton PK parameters

Parameters	Test	Reference	CRTX Ratio of Means (Test/Reference) (n = 23)		Abbott Ratio of Means (Test/Reference) (n = 24)	
			Point Estimate	90% CI	Point Estimate	90% CI
C _{max} (µg/mL)	A	C/D	0.39		0.46	
AUC _{0-t} (µg.h/mL)	A	C/D	0.56	(0.52, 0.61)		
AUC _{0-∞} (µg.h/mL)	A	C/D	0.57	(0.52, 0.62)	0.57	(0.53, 0.61)
C _{max} (µg/mL)	B	C/D	0.46		0.50	
AUC _{0-t} (µg.h/mL)	B	C/D	0.75	(0.69, 0.81)		
AUC _{0-∞} (µg.h/mL)	B	C/D	0.76	(0.70, 0.83)	0.81	(0.75, 0.87)

Note: A=CR Fasted; B=CR with High Fat Meal; C=IR Fasted (CRTX reference); D=IR Fasted (Abbott reference)

Source: Statistical Tables 14.2.3.1, 14.2.3.2 and 14.2.3.3 (CTI-03-C05-102 study)

Appendix E.5R, Amendment to the Drug Metabolism Report for Abbott M96-556 study

Comparison of zileuton PK between Study CTI-03-C05-102 and Study M96-556 are summarized as follows (Table 15) :

- Mean AUC_{0-∞} after administration of the CR tablets under fasted conditions and with a high fat meal were about 57% and 76%, respectively of the mean AUC_{0-∞} after administration of the IR tablets under fasting conditions in Study CTI-03-C05-102, while these values were 57% and 81%, respectively in Study M96-556.
- Mean zileuton C_{max} values after administration of zileuton CR formulation under fasting conditions and with a high fat meal were 39% and 46%, respectively of the mean C_{max} administration of zileuton IR formulation administered under fasting conditions in Study CTI-03-C05-102, while these values were 42% and 50%, respectively in Study M96-556.
- PK parameter after CR tablets were not equivalent to IR tablets however, overall, the results showed similar PK profiles following CR tablets between these two studies.

Metabolite A-66193: The key PK parameters of metabolite A-66193 are summarized in Table 16.

Table 16. Mean (±SD) PK parameters of A-66193 (Study M96-556)

Abbott-66193 Parameters	Regimen A	Regimen B	Regimen C	Regimen D
	1200 mg CR Tablet Fasting	1200 mg CR Tablet High Fat Nonfast- ing	1200 mg CR Tablet Low Fat Nonfast- ing	1200 mg IR Tab- let Fasting
T _{max} (hr)	23.1 ± 7.4	26.8 ± 4.3	25.6 ± 8.6	16.8 ± 7.1
C _{max} (µg/mL)	1.59 ± 1.35	0.67 ± 0.67	1.26 ± 1.13	0.332 ± 0.537
AUC ₀₋₄₈ (µg·hr/mL)	24.88 ± 23.52	10.20 ± 11.31	21.12 ± 21.35	5.19 ± 9.07

The appearance of metabolite A-66193 was highly variable among subjects after administration of both the CR and the IR formulations similar to Study CTI-03-C05-102. The mean values for A-66193 C_{max} and AUC₀₋₄₈ were higher after administration of the CR formulation than after administration of the IR formulation. For the CR formulation, the values of C_{max} and AUC₀₋₄₈ were larger for the fasting than for the fed condition. A larger portion of the zileuton CR dose was converted to the metabolite under fasted conditions, resulting in lower AUC values for zileuton.

A-66193 PK results from Study M96-556 are summarized as follows:

- Mean AUC after administration of the CR tablets under fasted conditions and with a high fat meal were about 4.8- and 2.0-fold, respectively of the mean AUC after administration of the IR tablets under fasted conditions.
- Mean Cmax values after administration of CR formulation under fasted conditions and with a high fat meal were about 4.8- and 2.0-fold, respectively of the mean Cmax administration of IR formulation administered under fasted conditions.

Comparison of A-66193 PK between Study M96-556 and Study CTI-03-C05-102 and are summarized as follows:

- Mean AUC after administration of the CR tablets under fasted conditions and with a high fat meal were about 4.8- and 2.0-fold, respectively of the mean AUC after administration of the IR tablets under fasted conditions in Study M96-556, while these values were about 5.7- and 3-fold, respectively in Study CTI-03-C05-102.
- Mean Cmax values after administration of CR formulation under fasting conditions and with a high fat meal were about 4.8- and 2.0-fold, respectively of the mean Cmax administration of IR formulation administered under fasting conditions in Study M96-556, while these values were about 5.4- and 2.1-fold, respectively in Study CTI-03-C05-102.

Overall, the PK results from Study CTI-03-C05-102 were similar to those from Study M96-556.

2.5.2. What is the relative bioavailability of the proposed to-be-marketed formulation following multiple-dose administration (CTI-03-C05-103) to the IR formulation? How different is the PK profile of zileuton CR tablets from this study compared to that from the study conducted by Abbott (M95-264)?

Study **CTI-03-C05-103** was a multiple-dose, randomized, open-label, 3-period, complete crossover, with a minimum of a 10-day washout between each period. Thirty healthy male (n=18) and female (n=12) subjects enrolled in this study. The objective of this study was to compare the bioavailability of zileuton CR 600 mg tablets (E21 Formulation) administered under fasted and fed (high fat meal) conditions with that of zileuton IR 600 mg tablets (Zyflo[®]) under fasted conditions. The following regimens were used in this study:

- **TRT A:** Two 600 mg CR zileuton tablets q12h for 12 consecutive doses (6 days) under fed conditions; Lot #: 3049002R.
- **TRT B:** Two 600 mg CR zileuton tablets q12h for 12 consecutive doses (6 days) under fast conditions; Lot #: 3049002R.
- **TRT C:** One 600 mg IR zileuton tablet (Zyflo[®]) administered q6h for 24 consecutive doses (6 days) under fed conditions; Lot #: 07104AF21.

Blood samples were collected prior to morning dose (trough blood samples) on Days 1 through 5 of each study period. Blood samples were also collected prior to morning dosing (0 hr) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 12, 13, 13.5, 14, 15, 16, 17, 18, 19, 19.5, 20, 21, 22, 24, 28, 32, 36, and 48 hours after the morning dose on Day 6 in each period. The plasma samples were analyzed for zileuton and A-66193 with a validated LC-MS/MS assay with LLQ of ~~0.1~~ ^{0.5} µg/mL for each analyte.

Pharmacokinetic parameters at steady-state were calculated with non-compartmental methods after dosing on Day 6 (AUC₀₋₂₄, Cmax, Cmin, Cavg, fluctuation index (FI), Tmax, apparent total body clearance (CL/F), and t_{1/2}), and these PK parameters were summarized with descriptive statistics.

An ANOVA model was performed on the natural logarithmic transformations (ln) of Cmax and AUC for both zileuton and metabolite A-66193, and generated 90% CI of the ratios of the treatment geometric least-squares (LS) means for each comparison.

Results

Disposition of subjects: All 30 subjects were included in the safety population, 24 subjects were included in the PK population because 6 subjects did not complete all scheduled doses.

Demographics of PK population: Their ages ranged from 19 to 56 years (mean of 34.6 years), heights ranged from 156 to 183 cm (mean of 171.2 cm), and weights ranged from 58.9 to 96.3 kg (mean of 78 kg), respectively.

Pharmacokinetics:

Zileuton: Mean plasma concentration-time profiles of zileuton are shown in Figure 3. Mean PK parameters and statistical BE analysis for zileuton are presented in Tables 17-18.

Figure 3. Mean zileuton Plasma Concentration versus Time profiles by Treatment (Day 6)

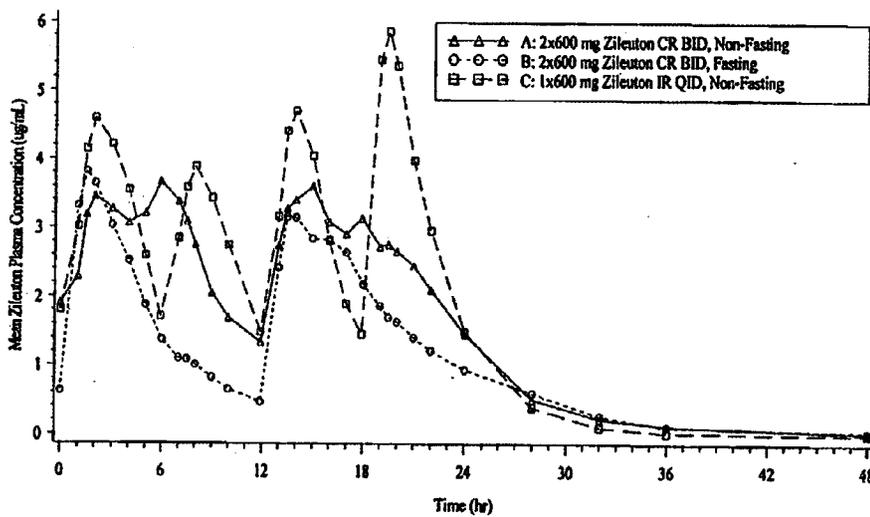


Table 17. Summary of mean (\pm SD) Zileuton PK parameters (Day 6)

Parameters	Regimen A 2 x 600 mg CR Every 12 hours Non-Fasting (n=24)	Regimen B 2 x 600 mg CR Every 12 hours Fasting (n=24)	Regimen C 1 x 600 mg IR Every 6 hours Non-Fasting (n=24)
T _{max} (hr)	3.57±2.35	2.12±1.42	1.63±0.82
AUC (µg·hr/mL)	63.99±15.95	44.85±12.59	77.42±21.36
C _{max} (µg/mL)	4.97±1.34	4.59±1.42	7.72±2.43
C _{min} (µg/mL)	1.00±0.45	0.37±0.17	0.99±0.38
C _{min trough} (µg/mL)	1.91±0.71	0.63±0.56	1.80±0.64
C _{avg} (µg/mL)	2.67±0.67	1.87±0.53	3.23±0.89
CL/F (mL/min)	668.7±195.95	968.8±316.37	607.4±433.83
FI	1.50±0.33	2.27±0.34	2.19±0.83
t _{1/2} (hr)	3.19±1.24 ^a	4.05±1.94 ^a	2.23±0.53
Beta (1/hr)	0.24±0.07 ^a	0.21±0.09 ^a	0.32±0.06

^a n=19 for Regimen A and n=20 for Regimen B since elimination rate constant was not estimable for some of the subjects.

Source: Statistical Tables 14.2.2.1.2, 14.2.2.2.2, 14.2.2.3.2, 14.2.1.1.4, 14.2.1.2.4 and 14.2.1.3.4.

The results of this study showed that zileuton CR tablets demonstrated a controlled-release profile, with reduced fluctuations between C_{max} and C_{min} and no dose-dumping characteristics. Under fed conditions, the bioavailability of zileuton CR based on AUC₀₋₂₄ and C_{max} values was lower than those of zileuton IR but equivalent based on C_{min} values. The bioavailability of zileuton CR was markedly increased, and absorption was delayed, when it was administered under fed conditions.

Food effect of CR formulation (Tables 17 and 18): Food caused statistically significant increase in C_{min} and AUC₀₋₂₄, by 170% and 44% respectively, but no effect on C_{max}. T_{max} was increased by almost 2-fold.

BA comparison CR vs. IR tablets (Tables 17 and 18): Mean C_{max}, C_{min} and AUC values were lower after administration of the CR formulation than after administration of the IR formulation: ratios for C_{max}, C_{min} and AUC₀₋₂₄ of CR (fasted) to IR (fed) were 60%, 39% and 59%, respectively. Similarly, ratios for C_{max} and AUC₀₋₂₄ of CR to IR both under fed conditions were 65% and 85%, respectively, however C_{min} was equivalent.

Results from this study are summarized as follows:

- For the CR formulation, food increased zileuton AUC and C_{min} by 44% and 170%, respectively, but no significant change in C_{max}. T_{max} was almost doubled (2.12 *vs.* 3.57 hr) in the presence of food.
- Mean C_{max}, C_{min} and AUC values of zileuton CR under fasted conditions were 60%, 39% and 59%, respectively of those of zileuton IR under fed conditions.
- Mean C_{max} and AUC values of zileuton CR were 65% and 85% of those of zileuton IR both under fed conditions. C_{min} values were similar between these two formulations.
- Zileuton CR tablets demonstrated a controlled-release profile, with reduced fluctuations between C_{max} and C_{min} and no dose-dumping characteristics.

Table 18. Statistical Analysis of zileuton

Parameters	Regimen		Ratio of Means (Test/Reference) (n=24)	
	Test	Reference	Point Estimate ^a	90% CI
C _{max} (µg/mL)*	CR fed	IR fed	0.650	(0.595, 0.710)
C _{min} (µg/mL)	CR fed	IR fed	1.046	(0.879, 1.245)
AUC (µg•hr/mL)	CR fed	IR fed	0.846	(0.781, 0.915)
C _{max} (µg/mL)*	CR fast	IR fed	0.597	(0.546, 0.652)
C _{min} (µg/mL)	CR fast	IR fed	0.389	(0.327, 0.463)
AUC (µg•hr/mL)	CR fast	IR fed	0.588	(0.543, 0.637)
C _{max} (µg/mL)*	CR fed	CR fast	1.089	(0.997, 1.190)
C _{min} (µg/mL)	CR fed	CR fast	2.688	(2.259, 3.199)
AUC (µg•hr/mL)	CR fed	CR fast	1.438	(1.328, 1.557)

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

* Carryover effect was tested using the ANOVA model with effects for subject, period, treatment regimen and first-order carryover. The carryover effect was found significant for this parameter (p < 0.100).

Metabolite A-66193: The PK parameters of metabolite A-66193 are summarized in Table 19.

Table 19. Mean (±SD) PK parameters of A-66193

Parameters	Regimen A 2 x 600 mg CR Every 12 hours Non-Fasting (n=22)	Regimen B 2 x 600 mg CR Every 12 hour Fasting (n=22)	Regimen C 1 x 600 mg IR Every 6 hours Non-Fasting (n=22)
T _{max} (hr)	6.40±3.79	7.84±2.64	3.66±2.01
C _{max} (µg/mL)	4.89±3.44	8.89±4.61	1.19±0.98
C _{min} (µg/mL)	2.82±2.79	4.70±2.86	0.64±0.43
AUC (µg•hr/mL)	93.11±73.95	162.78±85.41	19.62±12.21
t _{1/2} (hr) ^a	8.87±3.62	7.31±2.47	6.44±1.45

^a n=19 for Regimen A and for Regimen B, and n=20 for Regimen C, since the elimination rate constant was not estimable for some of the subjects.

In general, the mean C_{max} and AUC for metabolite A-66193 after administration of the CR tablets were significantly higher than those after administration of the IR tablets. The mean C_{max} values for metabolite A-66193 after administration of CR tablets under fed and fasted conditions were about 4-fold and 7.5-fold higher, respectively, than the mean C_{max} after administration of IR tablets under fed conditions. The mean AUC values for metabolite A-66193 after administration of the CR tablets under

fed and fasted conditions were about 4.7-fold and 8.3-fold higher, respectively, than the mean AUC after administration of the IR tablets under fed conditions. Both the C_{max} and AUC values for metabolite A-661 93 after administration of the CR tablets under fed conditions were only 57% of the values observed after administration of the CR tablets under fasted conditions, indicating that a smaller fraction of zileuton CR is converted to the inactive metabolite when administered under fed conditions.

Historical Comparison with Study M95-264

Study CTI-03-C05-103 was designed similar to Study M95-264 in order to compare the results between these studies (BA comparison between CR and IR tablets); if the results are similar, this suggests that Formulation E21 (CRTX) and Formulation H (Abbott) are similar.

Study M95-264 was a multiple-dose, randomized, open-label, 2-period, crossover study, with at least a 10-day washout interval between the treatments in 24 healthy adult male and female subjects. The objective of this study was to compare the PK of a zileuton CR formulation to a zileuton IR formulation both under fed conditions. The following regimens were used in this study:

- **TRT A:** 2 x 600 mg Zileuton CR tablets q12h for 12 consecutive doses; Lot #: 17-434-AR-04.
- **TRT B:** 1 x 600 mg Zileuton IR tablet q6h for 24 consecutive doses; Lot #: 01-087-AR-03.

Blood sampling schemes and data analysis were handled the same as in Study CTI-03-C05-103.

Subject demographics: All twenty-three subjects, except one subject (subject #16 prematurely discontinued), completed the study. Their ages ranged from 19 to 50 years (mean of 35.8 years), their heights ranged from 147.3 to 180.3 cm (mean of 165.7 cm), and their weights ranged from 55.3 to 83.5 kg (mean of 69.3), respectively.

Pharmacokinetic Results:

Zileuton: Mean plasma concentration-time profiles of zileuton are shown in Figure 4. The PK parameters of zileuton after administration of each study regimens are summarized in Table 20.

Figure 4. Mean Zileuton Concentrations in Plasma on Study Day 6 after Multiple Oral Doses of CR or IR Zileuton Tablets in Study M95-264

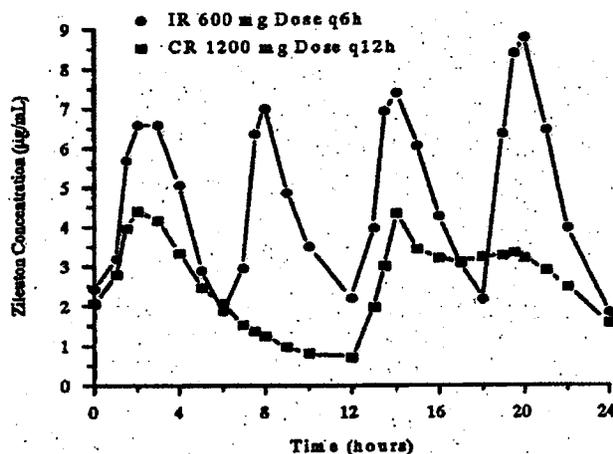


Table 20. Summary of mean (\pm SD) Zileuton PK parameters (n = 23)

24-Hour Zileuton PK Parameters	Regimen A	Regimen B
	1200 mg CR every 12 hours	600 mg IR every 6 hours
T_{max} (hr)	2.6 \pm 2.0*	1.7 \pm 0.5
C_{max} (μ g/mL)	5.93 \pm 2.36*	11.99 \pm 5.25
C_{min} (μ g/mL)	0.62 \pm 0.46*	1.13 \pm 0.87
C_{avr} (μ g/mL) [†]	2.48 \pm 0.97	4.55 \pm 2.52
FI_{0-24}	2.21 \pm 0.61*	2.49 \pm 0.56
AUC_{0-24} (μ g \cdot hr/mL)	59.5 \pm 23.2*	109.2 \pm 60.5
β (hr^{-1})	0.218 \pm 0.081*	0.357 \pm 0.052
$t_{1/2}$ (hr) [†]	3.7 \pm 1.7	2.0 \pm 0.4
CL/F (mL/min) [†]	766 \pm 267	434 \pm 155
Vd_p/F (L) [†]	253 \pm 163	72 \pm 21

*Statistically significantly different from Regimen B.

[†]Parameter not tested statistically.

The mean zileuton C_{max} and AUC after administration of the CR tablet formulation (1200 mg q12h) was 51% and 54%, respectively lower than those after administration of a 600 mg IR tablet q6h ($p < 0.05$). The mean zileuton T_{max} after administration of the CR tablet formulation was significantly longer than the corresponding value after administration of the IR tablet formulation (2.6 vs. 1.7 hr).

For comparison, the 90% CIs of the ratios of means from Study CTI-03-C05-103 and Study M95-264 are presented in Table 21.

Table 21. 90% CIs of the Ratios of Mean Zileuton PK parameters

Parameters	Regimen		CRTX Ratio of Means (Test/Reference) (n=24)		Abbott Ratio of Means (Test/Reference) (n=23)	
	Test	Reference	Point Estimate ^a	90% CI	Point Estimate ^a	90% CI
	C_{max} (μ g/mL)*	CR fed	IR fed	0.650	(0.595, 0.710)	0.499
C_{min} (μ g/mL)	CR fed	IR fed	1.046	(0.879, 1.245)	0.543	(0.420, 0.703)
AUC (μ g \cdot hr/mL)	CR fed	IR fed	0.846	(0.781, 0.915)	0.560	(0.503, 0.622)

Note: CRTX = CTI-03-C05-103; Abbott = M95-264

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

* Carryover effect was tested using the ANOVA model with effects for subject, period, treatment regimen and first-order carryover. The carryover effect was found significant for this parameter ($p < 0.100$).

Source: Statistical Tables 14.2.3.1, 14.2.3.2, and 14.2.3.3 (CTI-03-C05-103 study); Appendix C, Amendment to the Drug Metabolism Report for Abbott M95-264 study.

As shown in Table 21, in Study M95-264, steady state C_{max} , C_{min} and AUC from zileuton CR tablets were approximately 50% of those from zileuton IR tablets. In Study CTI-03-C05-103, C_{max} and AUC from zileuton CR tablets were 65% and 85% of those from zileuton IR tablets, while C_{min} was similar. Therefore, bioavailability after CR formulation E21 in Study CTI-03-C05-103 was higher compared to

that after CR formulation H in Study M95-264. In addition, the results (higher C_{min}, smaller FI) indicated an improved extended-release profile with the zileuton CR formulation E21 compared to that CR formulation H.

Metabolite A-66193: The PK parameters of metabolite A-66193 are summarized in Table 22.

Table 22. Mean (±SD) PK parameters of A-66193 (Study M95-264)

24-Hour A-66193 PK Parameters	Regimen A 1200 mg CR every 12 hours	Regimen B 600 mg IR every 6 hours
T _{max} (hr)	6.2±3.8*	3.4±2.0
C _{max} (µg/mL)	7.44±7.57*	1.11±0.76
C _{min} (µg/mL)	2.88±2.37*	0.55±0.46
C _{AVR} (µg/mL) [†]	5.09±4.68	0.78±0.59
FI ₀₋₂₄	0.89±0.39	0.82±0.53
AUC ₀₋₂₄ (µg·hr/mL)	122.2±112.4*	18.7±14.1
B (hr ⁻¹)	0.108±0.050	0.127±0.033
t _{1/2} (hr) [†]	8.0±4.1	5.9±1.7

*Statistically significantly different from Regimen B.

[†]Parameter not tested statistically.

The PK parameters of A-66193 were quite variable among subjects after administration of either the CR tablet or the IR tablet formulations. The mean T_{max}, C_{max}, C_{min}, and AUC₀₋₂₄ values for A-66193 were statistically significantly higher after administration of the CR tablet formulation compared to the corresponding values after administration of the IR tablet formulation. The mean A-66193 AUC₀₋₂₄ and C_{max} after administration of the CR tablet formulation were almost 7-fold higher than those after administration of the IR tablet formulation.

For comparison, the 90% CIs of the ratios of means obtained from Study CTI-03-C05-103 and Study M95-264 are presented Table 23.

Table 23. 90% or 95% CIs of the Ratios of Mean A-66193 PK parameters

Parameters	Regimen		CRTX Ratio of Means (Test/Reference) (n=22)		Abbott Ratio of Means (Test/Reference) (n=23)	
	Test	Reference	Point Estimate ^a	90% CI	Point Estimate ^a	CI
C _{max} (µg/mL)	CR fed	IR fed	4.41	(3.54, 5.50)	5.76	(4.18, 7.95) ^b
C _{min} (µg/mL)	CR fed	IR fed	4.26	(3.29, 5.52)	4.46	(3.13, 6.35) ^b
AUC (µg·hr/mL)	CR fed	IR fed	4.73	(3.85, 5.81)	5.77	(4.44, 7.50) ^c

Note: CRTX = CTI-03-C05-103; Abbott = M95-264

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

^b 95% CI

^c 90% CI

Source: Statistical Tables 14.2.8.1, 14.2.8.2 and 14.2.8.3 (CTI-03-C05-103 study); Appendix C, Amendment to the Drug Metabolism Report for Abbott M95-264 study.

11 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

 § 552(b)(5) Deliberative Process

4.2. Individual Studies (Synopsis)

NAME OF COMPANY Critical Therapeutics, Inc. 60 Westview Street Lexington, MA 02421-3108 NAME OF FINISHED PRODUCT Zileuton CR Tablets NAME OF ACTIVE INGREDIENT Zileuton	SUMMARY TABLE Referring to Part of the Dossier: Volume: Page: Reference:	FOR NATIONAL AUTHORITY USE ONLY
TITLE: A Randomized, Single-Center, Single-Dose, 3-Period Cross-Over, Definitive Study Of The Bioavailability Of Zileuton Controlled-release (CR) Tablets (E21) Compared To Zileuton Immediate-release (IR) Tablets Under Fasting And Non-Fasting Conditions		
PROTOCOL NUMBER: CTI-03-C05-102		
STUDY PERIOD: Date of first enrollment: 9 December, 2005 Date of last completed: 9 January, 2006	Phase of Development: Phase I	
INVESTIGATORS: _____ MD		
STUDY CENTER: _____		
OBJECTIVES: To compare the bioavailability of zileuton CR 600 mg tablets (E21; Formulation 1) administered under fasting and non-fasting conditions (i.e., after a high-fat meal) with that of zileuton IR 600 mg tablets (Zyflo [®] ; Formulation 2) under fasting conditions.		
STUDY DESIGN: This was a Phase I, randomized, single-center, single-dose, 3-period cross-over, definitive study of the bioavailability of zileuton CR tablets (E21; Formulation 1) administered under fasting and non-fasting conditions (i.e., after a high-fat meal) compared to zileuton IR tablets (Zyflo [®] ; Formulation 2) administered under fasting conditions in 24 healthy adult subjects. Healthy subjects were evaluated for safety and pharmacokinetics (PK) of the study drug formulations.		
NUMBER OF SUBJECTS: 24 planned; 24 randomized; 24 analyzed for safety; 23 analyzed for bioavailability		
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION: Healthy male and female subjects between 19 – 60 years of age with a body mass index (BMI) between 18 - 30 kg/m ² . Subjects were to have liver function tests (LFTs) within normal limits and were to have been non-nicotine users. Females of childbearing potential were to have a negative pregnancy test and were to have been practicing effective birth control. All medications (except those for birth control) were to be discontinued ≥1 week prior to study drug dosing. Subjects were to be excluded if they had any uncontrolled systemic disease, any hypersensitivity to any of the components in zileuton, any significant drug sensitivity, history of alcohol or substance abuse, active liver disease, positive serology for hepatitis B or C or human immunodeficiency virus (HIV) within 28 days prior to study drug dosing, history of or current immunosuppressive condition, history of malignancy (other than squamous or basal cell carcinoma of the skin), and if they required any medication on a regular basis.		

TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, AND LOT NUMBER(S):
Regimen A: 2 zileuton CR 600 mg tablets (E21; Formulation 1) administered as a single-dose at Time "0" under fasting conditions; Lot number: 3049002R.
Regimen B: 2 zileuton CR 600 mg tablets (E21; Formulation 1) administered as a single-dose at Time "0" under non-fasting conditions (i.e., after a high-fat meal); Lot number: 3049002R.
Regimen C: 1 zileuton IR 600 mg tablet (Zyflo®; Formulation 2) administered at Time "0" and a second tablet administered at "6 hours" under fasting conditions; Lot number: 07104AF21.

CRITERIA FOR EVALUATION:

Bioavailability:

Pharmacokinetic parameters included area under the concentration versus time curve [$AUC_{(0-t)}$ and $AUC_{(0-inf)}$], maximum observed concentration (C_{max}), time to maximum observed concentration (T_{max}), apparent total body clearance (CL/F) and elimination half-life ($t_{1/2}$).

Safety:

Monitoring of adverse events (AEs), monitoring of concomitant medications, physical examinations, vital signs, and clinical laboratory measurements (chemistry, hematology, and urinalysis).

STATISTICAL METHODS:

Bioavailability:

- The PK parameters C_{max} , T_{max} , and AUC of zileuton and metabolite A-66193 (N-dehydroxy zileuton) were calculated using a non-compartmental method for each treatment regimen, and summarized with descriptive statistics. The parameters CL/F and $t_{1/2}$ of zileuton were also calculated and descriptively summarized.
- An analysis of variance (ANOVA) model was performed on the natural logarithmic transformations (ln) of the C_{max} and AUC for both zileuton and metabolite A-66193. Carryover effects were to be tested. In cases when carryover effects were non-significant, a reduced ANOVA model with effects for subject, period and treatment regimen was applied for the treatment comparisons of interest (Regimen A versus Regimen B, Regimen A versus Regimen C, and Regimen B versus Regimen C). The relative bioavailabilities of the CR tablets versus the IR tablets were assessed by the 2 1-sided test procedure via 90% confidence intervals (CI) of the ratios of the treatment geometric least-squares (LS) means for each comparison (Regimen A/Regimen B, Regimen A/Regimen C, and Regimen B/Regimen C). These 90% CI were obtained within the framework of the reduced ANOVA model for $\ln(C_{max})$ and $\ln(AUC)$.
- For the purpose of historical comparison, mean $\ln(C_{max})$ and mean $\ln(AUC)$ obtained from CRTX zileuton CR formulation were compared to the zileuton CR data from a similarly designed Abbott Laboratories (Abbott) study (Study M96-556) using both 90% and 95% CI. These parameters were considered similar to those obtained from the Abbott CR data if the CI for the ratio of the mean values of the 2 formulations ($C_{max} \text{ CRTX CR}/C_{max} \text{ Abbott CR}$ and $AUC \text{ CRTX CR}/AUC \text{ Abbott CR}$) contained the value of 1.

Safety:

- Adverse event incidences were descriptively summarized by Medical Dictionary for Drug Regulatory Affairs (MedDRA) system organ class and preferred term for each regimen. Each AE was assigned to the last treatment regimen received prior to the start of the event. Discontinuations due to AEs, drug-related AEs, and serious AEs (SAEs) were summarized. Incidences of AEs by maximum severity as well as by maximum relationship to study drug were also provided.

- Changes from baseline to the final assessment in clinical chemistry, hematology and urinalysis were descriptively summarized. Shift tables in categories derived from the laboratory standard ranges and incidences of clinically significant abnormal values were also provided.
- Clinical safety was also addressed by summarizing changes from screening to final assessment in physical examination findings as well as changes from baseline to final assessment in vital signs.

BIOAVAILABILITY RESULTS:

The pharmacokinetic parameters of zileuton after administration of each of the 3 study regimens are summarized in the following table (mean ± standard deviation [SD]):

Parameters	Regimen A (n=23)	Regimen B (n=23)	Regimen C (n=23)
T _{max} (h)	2.13 ± 2.14	4.34 ± 3.98	1.30 ± 0.56
C _{max} (µg/mL)	3.11 ± 0.87	3.67 ± 1.46	5.57 ± 1.82 ^c
AUC _(0-t) (µg•hr/mL)	22.46 ± 6.81	29.67 ± 7.74	39.32 ± 9.77
AUC _(0-inf) (µg•hr/mL) ^a	22.33 ± 6.26	30.01 ± 7.96	39.06 ± 9.68
CL/F (mL/min) ^a	956.27 ± 236.71	714.26 ± 195.54	542.64 ± 133.04
t _{1/2} (hr) ^{a, b}	-	-	2.24 ± 0.47

^a n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020.

^b Elimination rate constants could not be estimated for all subjects from the CR regimens; therefore, the elimination rate constants estimated from Regimen C were used for all subjects.

^c After the first 600 mg dose

For the 2 1-sided tests procedure based on analysis of ln(C_{max}) and ln(AUC) of zileuton, the 90% confidence interval for the ratios of the CR formulation relative to that of the IR formulation under fasting conditions are shown below:

Parameters	Regimen		Ratio of Means (Test/Reference)	
	Test	Reference	Point Estimate ^a	90% CI
C _{max} (µg/mL)	A	C	0.283	(0.248, 0.324)
AUC _(0-t) (µg•hr/mL)	A	C	0.562	(0.519, 0.609)
AUC _(0-inf) (µg•hr/mL)	A	C	0.567 ^b	(0.522, 0.615)
C _{max} (µg/mL)	B	C	0.328	(0.287, 0.375)
AUC _(0-t) (µg•hr/mL)	B	C	0.751	(0.693, 0.814)
AUC _(0-inf) (µg•hr/mL)	B	C	0.761 ^b	(0.701, 0.826)

Note: from Regimen C was dose-normalized in these analyses.

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

^b n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020. Hence, AUC_(0-inf) could not be calculated for this subject.

The 90% confidence intervals for the ratio of $\ln(C_{max})$ and $\ln(AUC)$ for the CR formulation under fasting condition relative to the CR formulation with a high fat meal are shown below:

Parameters	Regimen		Ratio of Means (Fasting/Non-Fasting)	
	Fasting	Non-Fasting	Point Estimate ^a	90% CI
C_{max} ($\mu\text{g/mL}$)	A	B	0.863	(0.755, 0.987)
$AUC_{(0-t)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	A	B	0.749	(0.691, 0.811)
$AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	A	B	0.745 ^b	(0.686, 0.808)

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

^b n=22 since elimination rate constant was not estimable after administration of Regimen C for Subject 020. Hence, $AUC_{(0-inf)}$ could not be calculated for this subject.

Mean AUC values were lower after administration of the CR formulation than after administration of the IR formulation (administered under fasting conditions). Based on the 90% CIs, the CR formulation (fasting or non-fasting) is not equivalent to the IR formulation (fasting) with respect to zileuton AUC. The AUC ratio of CR to IR increased when zileuton CR was taken with a high fat meal (AUC ratio of CR to IR: 57% fasting and 76% non-fasting). As expected, mean C_{max} values after zileuton CR under fasting and non-fasting conditions were much lower than those after zileuton IR under fasting condition (C_{max} ratio of CR to IR: 28% fasting and 33% non-fasting).

For the CR formulation, the mean T_{max} and AUC values were much higher under non-fasting conditions than under fasting conditions while the mean C_{max} did not change much between the 2 conditions ($AUC_{(0-inf)}$ increased by 34%, $AUC_{(0-t)}$ increased by 32%, C_{max} increased by 18% and T_{max} increased by almost 2-fold). These results show that administration of the CR formulation with a high fat meal resulted in a large increase in the extent and a decrease in the rate of absorption of zileuton CR. The increased bioavailability of the current CR formulation (E21) after a high fat meal confirms the significant food effect observed with the Abbott CR formulation.

For historical comparisons, mean $\ln(C_{max})$ values and mean $\ln(AUC)$ values obtained from CRTX zileuton CR formulation were compared to the Abbott zileuton CR data from Study M96-556, using both 90% and 95% confidence intervals for fasting conditions and for non-fasting conditions. Results were summarized below:

Parameters	Condition	Ratio of Means (CRTX/Abbott)		
		Point Estimate ^a	90% CI	95% CI
C_{max} ($\mu\text{g/mL}$)	Fasting	0.744	(0.618, 0.896)	(0.596, 0.929)
$AUC_{(0-t)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	Fasting	0.777	(0.666, 0.906)	(0.646, 0.935)
$AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	Fasting	0.764	(0.657, 0.889)	(0.638, 0.916)
C_{max} ($\mu\text{g/mL}$)	Non-Fasting	0.707	(0.592, 0.843)	(0.572, 0.874)
$AUC_{(0-t)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	Non-Fasting	0.721	(0.622, 0.837)	(0.603, 0.863)
$AUC_{(0-inf)}$ ($\mu\text{g}\cdot\text{hr/mL}$)	Non-Fasting	0.721	(0.620, 0.839)	(0.601, 0.865)

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

The mean AUC and C_{max} values of the CR formulation from the current study were generally lower than those of the CR formulation from the Abbott M96-556 study (AUC_(0-inf) ratio of CRTX to Abbott: 76% fasting and 72% non-fasting; C_{max} ratio of CRTX to Abbott: 71% fasting and 74% non-fasting). In order to understand this difference in bioavailability of the CR formulations used in these 2 studies, a post hoc historical comparison was also performed on the IR formulation. The historical comparison performed for zileuton IR also indicates that based on the AUC values, the bioavailability of the IR formulation under fasting conditions from the current study is less than that from the Abbott M96-556 study (AUC ratio of CRTX to Abbott: 77%; C_{max} ratio of CRTX to Abbott: 86%). These results are suggestive of a possible temporal effect on the bioavailability results of both CR and IR formulations.

Post hoc comparisons with 2 other previous studies (Abbott M97-742 and CRTX pilot study CTI-03-C04-101) were performed to investigate the possible temporal effects of the historical comparisons. In general, these comparisons showed that the PK parameters of the CR formulation from the current study are similar to those from the 2 selected studies. These results also support that the lower bioavailability observed in the current study as compared to the Abbott M96-556 study is mostly explained by a temporal effect with the historical comparisons rather than a difference in zileuton CR formulation performance.

The appearance of metabolite A-66193 was highly variable among subjects after administration of the CR formulation or the IR formulation. The mean T_{max} values for A-66193 were notably longer after administration of the CR formulation than after administration of the IR formulation under fasting conditions. The mean values for A-66193 C_{max} and AUC_(0-t) were higher after administration of the CR formulation than after administration of the IR formulation.

CONCLUSIONS:

Mean zileuton AUC values after administration of the CR tablets were lower than mean zileuton AUC values after administration of the IR tablets (administered under fasting conditions). Based on the 90% CIs, the CR formulation (fasting or non-fasting) is not equivalent to the IR formulation (fasting) with respect to zileuton AUC. The AUC ratio of CR to IR increased when zileuton CR was taken with a high fat meal (AUC ratio of CR to IR: 57% fasting and 76% non-fasting). As expected, the mean zileuton C_{max} values after administration of the CR tablets were lower than mean zileuton C_{max} values after administration of the IR tablets under fasting conditions (C_{max} ratio of CR to IR: 28% fasting and 33% non-fasting). Similar trends have been reported by Abbott in the Food Effect Study M96-556.

Administration of the CR formulation with a high-fat meal resulted in a large increase in the extent and a decrease in the rate of absorption of zileuton CR. The increased extent is apparent by a 34% higher mean $AUC_{(0-inf)}$, a 32% higher mean $AUC_{(0-t)}$ and a 18% higher mean C_{max} , resulting from administration with a high fat meal than the respective mean values, resulting from administration under fasting conditions. Mean T_{max} also increased almost 2 fold with food, providing further evidence of a decreased rate. Again, similar trends have been reported by Abbott in Study M96-556 indicating that food improves the bioavailability of zileuton CR.

For both fasting conditions and with a high fat meal, the CR formulation generally resulted in a lower mean C_{max} and AUC in the current study than those reported in Abbott M96-556 study (AUC ratio of CRTX to Abbott: 76% fasting and 72% high fat meal; C_{max} ratio of CRTX and Abbott: 74% fasting and 71% high fat meal). Based on the 90% and 95% CIs, the PK parameters of the CR formulation in the current study are not similar to those from the Abbott M95-556 study. To investigate a possible temporal effect of the historical comparison, a post hoc comparison was performed for zileuton IR in the current study versus Abbott M96-556 study. Results indicated that based on AUC values, the bioavailability of the IR formulation from the current study is also less than that from the Abbott M96-556 study. This is suggestive of a possible temporal effect.

Additional post hoc historical comparisons with previous PK studies showed that the PK parameters of the current study were consistent with estimates reported in previous studies while those of both zileuton IR and CR from Study M96-556 appear to be higher than estimates reported in previous studies.

The appearance of metabolite A-66193 was highly variable among subjects after administration of both the CR formulation and the IR formulation

TITLE: A Randomized, Single-Center, Multiple-Dose, 3-Period Cross Over, Definitive Study of the Bioavailability of Zileuton Controlled-release (CR) Tablets (E21) Compared to Zileuton Immediate-release (IR) Tablets Under Fasting and Non-Fasting Conditions	
PROTOCOL NUMBER: CTI-03-C05-103	
STUDY PERIOD: Date of first enrollment: December 16, 2005 Date of last completed: January 30, 2006	Phase of Development: Phase I
INVESTIGATORS: MD	
STUDY CENTERS:	
OBJECTIVES: To compare the bioavailability after multiple doses of zileuton CR 600 mg tablets (E21; Formulation 1) administered under fasting and non-fasting conditions (i.e., 30 minutes after a meal) with that of zileuton IR 600 mg tablets (Zyflo [®] ; Formulation 2) under non-fasting conditions.	
STUDY DESIGN: This was a Phase I, randomized, single-center, multiple-dose, 3-period cross-over, definitive study of the bioavailability of zileuton CR tablets (E21; Formulation 1) administered under fasting and non-fasting conditions (i.e., 30 minutes after a meal), compared to zileuton IR tablets (Zyflo [®] ; Formulation 2) administered under non-fasting conditions in 30 healthy adult subjects. Healthy subjects were evaluated for safety and pharmacokinetics (PK) of the study drug formulations.	
NUMBER OF SUBJECTS: 30 planned; 30 randomized; 30 analyzed for safety; 24 analyzed for bioavailability.	
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION/EXCLUSION: Healthy male and female subjects between 19-60 years of age with a body mass index (BMI) between 18-30 kg/m ² . Subjects were to have liver function tests (LFTs) within normal limits and were to have been non-nicotine users. Females of childbearing potential were to have a negative pregnancy test and were to have been practicing effective birth control. All medications (except those for birth control) were to be discontinued ≥1 week prior to study drug dosing. Subjects were to be excluded if they had any uncontrolled systemic disease, any hypersensitivity to any of the components in zileuton, any significant drug sensitivity, history of alcohol or substance abuse, active liver disease, positive serology for hepatitis B or C or human immunodeficiency virus (HIV) within 28 days prior to study drug dosing, history of or current immunosuppressive condition, history of malignancy (other than squamous or basal cell carcinoma of the skin), and if they required any medication on a regular basis.	
TEST PRODUCTS, DOSE AND MODE OF ADMINISTRATION, AND LOT NUMBER(S): Regimen A: 2 zileuton CR 600 mg tablets (E21; Formulation 1) administered every 12 hours at 7:00 a.m. and again at 7:00 p.m. for 12 consecutive doses (6 days) under non-fasting conditions (i.e., 30 minutes after a meal); Lot number: 3049002R. Regimen B: 2 zileuton CR 600 mg tablets (E21; Formulation 1) administered every 12 hours at 6:00 a.m. and again at 6:00 p.m. for 12 consecutive doses (6 days) under fasting conditions (i.e., 3 hours before a meal); Lot number: 3049002R Regimen C: 1 zileuton IR 600 mg tablet (Zyflo [®] ; Formulation 2) administered every 6 hours at 7:00 a.m.,	

1:00 p.m., 7:00 p.m., and 1:00 a.m. for 24 consecutive doses (6 days) under non-fasting conditions (i.e., 30 minutes after a meal except for the 1:00 a.m. dose); Lot number: 07104AF21.

DURATION OF TREATMENT:

Zileuton CR 600 mg tablets were administered as 2 x 600 mg tablets every 12 hours for 12 consecutive doses (6 days), and zileuton IR 600 mg tablets were administered as 1 tablet every 6 hours for 24 consecutive doses (6 days). Subjects were confined for approximately 7½ days during each of the 3 dosing periods. There was a minimum of 10 days washout between each period.

CRITERIA FOR EVALUATION:

Bioavailability:

Pharmacokinetic parameters at steady state were calculated with non-compartmental methods from the 0 - 24 hour period after dosing on Day 6. They included area under the concentration versus time curve (AUC_{0-24}), maximum observed concentration (C_{max}), minimum observed concentration (C_{min}), the average plasma concentration (C_{avg}), fluctuation index (FI), time to maximum observed concentration (T_{max}), apparent total body clearance (CL/F), and elimination half-life ($t_{1/2}$).

Safety:

Monitoring of adverse events (AEs), monitoring of concomitant medications, physical examinations, vital signs, and clinical laboratory measurements (chemistry, hematology, and urinalysis).

STATISTICAL METHODS:

Bioavailability:

- The PK parameters AUC, C_{max} , C_{min} , T_{max} , and $t_{1/2}$ of zileuton and metabolite A-66193 (N-dehydroxy zileuton) were calculated based on the PK samples from the 0 to 24-hour period on Day 6 using a non-compartmental method for each treatment regimen, and summarized with descriptive statistics. The parameters C_{avg} , FI, and CL/F of zileuton were also calculated and descriptively summarized.
- An analysis of variance (ANOVA) was performed on the natural logarithmic transformations (\ln) of the C_{min} , C_{max} and AUC for both zileuton and metabolite A-66193. Carryover effects were to be tested. In cases when carryover effects were non-significant, a reduced ANOVA model with effects for subject, period and treatment regimen was applied for the treatment comparisons of interest (Regimen A versus Regimen B, Regimen A versus Regimen C, and Regimen B versus Regimen C). The relative bioavailabilities of the CR tablets versus the IR tablets were assessed by the 2 1-sided test procedure via 90% confidence intervals (CI) of the ratios of the treatment geometric least square (LS) means for each comparison (Regimen A/Regimen B, Regimen A/Regimen C, and Regimen B/Regimen C). These 90% CI were obtained within the framework of the reduced ANOVA model for $\ln(C_{min})$, $\ln(C_{max})$, and $\ln(AUC)$.
- For the purpose of historical comparison, mean $\ln(C_{min})$, mean $\ln(C_{max})$ and mean $\ln(AUC)$ obtained from CRTX zileuton CR formulation were compared to the zileuton CR data from a similarly designed Abbott Laboratories (Abbott) study (Study M95-264) using both 90% and 95% CI. These parameters were considered similar to those obtained from the Abbott CR data if the CI for the ratio of the mean values of the 2 formulations contained the value of 1.
- The PK parameters AUC, C_{max} , C_{min} , T_{max} , C_{avg} , and FI of zileuton were also calculated and descriptively summarized for other specified intervals (i.e., 0-12 and 12-24 for CR regimens; 0-6, 6-12, 12-18 and 18-24 for IR regimen).

BIOAVAILABILITY RESULTS:

The pharmacokinetic parameters of zileuton after administration of each of the 3 study regimens for 6 days are summarized in the following table (mean \pm standard deviation [SD]):

Parameters	Regimen A (n=24)	Regimen B (n=24)	Regimen C (n=24)
T_{max} (hr)	3.57 \pm 2.35	2.12 \pm 1.42	1.63 \pm 0.82
AUC ($\mu\text{g}\cdot\text{hr}/\text{mL}$)	63.99 \pm 15.95	44.85 \pm 12.59	77.42 \pm 21.36
C_{max} ($\mu\text{g}/\text{mL}$)	4.97 \pm 1.34	4.59 \pm 1.42	7.72 \pm 2.43
C_{min} ($\mu\text{g}/\text{mL}$)	1.00 \pm 0.45	0.37 \pm 0.17	0.99 \pm 0.38
C_{avg} ($\mu\text{g}/\text{mL}$)	2.67 \pm 0.67	1.87 \pm 0.53	3.23 \pm 0.89
CL/F (mL/min)	668.7 \pm 195.95	968.8 \pm 316.37	607.4 \pm 433.83
FI	1.50 \pm 0.33	2.27 \pm 0.34	2.19 \pm 0.83
$t_{1/2}$ (hr)	3.19 \pm 1.24 ^a	4.05 \pm 1.94 ^a	2.23 \pm 0.53
Beta (1/hr)	0.24 \pm 0.07 ^a	0.21 \pm 0.09 ^a	0.32 \pm 0.06

^a n=19 for Regimen A and n=20 for Regimen B since elimination rate constant was not estimable for some of the subjects.

Under non-fasting conditions, the absorption profile after 6 days of treatment with zileuton CR tablets demonstrated a successful controlled-release profile, with reduced fluctuations between C_{max} and C_{min} and no dose-dumping characteristics. As expected with a controlled-release formulation, the mean zileuton C_{max} values after administration of the CR tablets were lower than after administration of the IR tablets. The mean zileuton C_{max} after administration of CR tablets under non-fasting conditions (4.97 $\mu\text{g}/\text{mL}$) was 65% of the C_{max} following zileuton IR treatment (7.72 $\mu\text{g}/\text{mL}$), while the C_{min} for zileuton CR treatment under non-fasting conditions (1.00 $\mu\text{g}/\text{mL}$) was 105% of the C_{min} following zileuton IR treatment (0.99 $\mu\text{g}/\text{mL}$). Trough zileuton plasma concentrations (prior to morning dose on Days 2 to 6) were similar between zileuton CR in the non-fasting state (range 1.72-2.33 $\mu\text{g}/\text{mL}$) and zileuton IR in the non-fasting state (range 1.77-1.97 $\mu\text{g}/\text{mL}$), and appeared generally lower with zileuton CR in the fasting state (range 0.63-1.44 $\mu\text{g}/\text{mL}$). The time to maximum zileuton plasma levels (T_{max}) was increased greater than 2-fold following treatment with the zileuton CR formulation under non-fasting conditions compared to the

zileuton IR formulation, consistent with a controlled-release delivery.

The mean terminal half-life of zileuton was 3.19 hours following 6 days of zileuton CR in the non-fasted state, 4.05 hours following zileuton CR in the fasted state, and 2.23 hours following zileuton IR in the non-fasted state. As expected, the CR formulation demonstrated a longer half-life than the IR formulation in this study. The mean half-life value for the IR formulation was consistent with estimates reported in previous studies.

For the 2 1-sided tests procedure based on analysis of $\ln(C_{max})$, $\ln(C_{min})$, and $\ln(AUC)$ of zileuton, the 90% CI for the ratios of the CR formulation under both non-fasting and fasting conditions relative to that of the IR formulation under non-fasting conditions, as well as the CR formulation under non-fasting conditions relative to that under fasting conditions, are shown below:

Parameters	Regimen		Ratio of Means (Test/Reference) (n=24)	
	Test	Reference	Point Estimate ^a	90% CI
C_{max} ($\mu\text{g/mL}$)*	CR fed	IR fed	0.650	(0.595, 0.710)
C_{min} ($\mu\text{g/mL}$)	CR fed	IR fed	1.046	(0.879, 1.245)
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	CR fed	IR fed	0.846	(0.781, 0.915)
C_{max} ($\mu\text{g/mL}$)*	CR fast	IR fed	0.597	(0.546, 0.652)
C_{min} ($\mu\text{g/mL}$)	CR fast	IR fed	0.389	(0.327, 0.463)
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	CR fast	IR fed	0.588	(0.543, 0.637)
C_{max} ($\mu\text{g/mL}$)*	CR fed	CR fast	1.089	(0.997, 1.190)
C_{min} ($\mu\text{g/mL}$)	CR fed	CR fast	2.688	(2.259, 3.199)
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	CR fed	CR fast	1.438	(1.328, 1.557)

^a The point estimate is the ratio of means which was derived by exponentiating the difference in least square means of the log transformed parameters.

* Carryover effect was tested using the ANOVA model with effects for subject, period, treatment regimen and first-order carryover. The carryover effect was significant for this parameter ($p < 0.100$).

The bioavailability (AUC) of zileuton CR under non-fasting conditions was 85% of that of zileuton IR under non-fasting conditions, but under fasting conditions was only 59% of that of zileuton IR under non-fasting conditions. The CI for the ratio of mean C_{min} of the CR formulation compared to the IR formulation, both under non-fasting conditions, was within the range of 0.80 and 1.25. Therefore, under non-fasting conditions, the CR formulation is equivalent to the IR formulation in terms of C_{min} .

None of the other CI for ratio of means of zileuton CR compared to zileuton IR were contained within the range of 0.80 and 1.25; therefore, the CR formulation (both non-fasting and fasting) is not equivalent to the IR formulation under non-fasting conditions with respect to zileuton C_{max} and AUC, although AUC was

markedly increased under non-fasting conditions compared to fasted conditions.

The bioavailability of zileuton CR was markedly increased under non-fasting conditions compared to fasting conditions. The AUC was increased by 43%, and C_{min} was increased by 170%, with similar C_{max} values for the two treatment regimens. This resulted in smaller fluctuations between C_{max} and C_{min} following treatment with zileuton under non-fasting conditions compared with fasting conditions. T_{max} was quite variable for zileuton CR under non-fasting conditions, but in general, absorption of the CR formulation appeared to be delayed by food. These results confirm a significant food effect observed in Study M95-264 with the Abbott CR formulation, and support the administration of the CR tablet following a meal.

For historical comparison, mean $\ln(C_{max})$, mean $\ln(C_{min})$ and mean $\ln(AUC)$ values obtained from the CRTX zileuton CR formulation under non-fasting conditions on Day 6 were compared to the Abbott zileuton CR data under non-fasting conditions from Study M95-264, using both 90% and 95% CI. Results are summarized below.

Parameters	Condition	Ratio of Means (CRTX/Abbott)		
		Point Estimate ^a	90% CI	95% CI
C_{max} (µg/mL)	Non-Fasting	0.864	(0.733, 1.018)	(0.709, 1.052)
C_{min} (µg/mL)	Non-Fasting	1.804	(1.385, 2.350)	(1.314, 2.477)
AUC (µg•hr/mL)	Non-Fasting	1.115	(0.952, 1.304)	(0.923, 1.346)

Note: CRTX = CTI-03-C05-103; Abbott = M95-264

^a The point estimate is the ratio of means which was derived by exponentiating the difference in means of the log transformed parameters.

Historical comparison of the zileuton CR formulation E21 in this CRTX study with Abbott multiple-dose study M95-264, both under non-fasting conditions, showed a similar C_{max} and AUC, but the mean C_{min} value was 180% of that seen in the Abbott study. These results indicate an improved sustained-release profile with the zileuton CR E21 formulation administered under non-fasting conditions. Fluctuation between C_{max} and C_{min} was smaller with the zileuton E21 formulation, and the C_{min} value of 1.00 µg/mL was similar to that after treatment with zileuton IR (0.99 µg/mL), and well above the IC_{50} (0.47 µg/mL) for *ex vivo* inhibition of LTB_4 biosynthesis.

The pharmacokinetic parameters of metabolite A-66193 after administration of each of the 3 study regimens for 6 days are summarized in the following table (mean ± SD):

Parameters	Regimen A	Regimen B	Regimen C
	2 x 600 mg CR Every 12 hours Non-Fasting (n=22)	2 x 600 mg CR Every 12 hours Fasting (n=22)	1 x 600 mg IR Every 6 hours Non-Fasting (n=22)
T _{max} (hr)	6.40±3.79	7.84±2.64	3.66±2.01
C _{max} (µg/mL)	4.89±3.44	8.89±4.61	1.19±0.98
C _{min} (µg/mL)	2.82±2.79	4.70±2.86	0.64±0.43
AUC (µg•hr/mL)	93.11±73.95	162.78±85.41	19.62±12.21
t _{1/2} ^a	8.87±3.62	7.31±2.47	6.44±1.45
Beta (1/hr) ^a	0.09±0.03	0.11±0.04	0.11±0.02

^a n=19 for Regimen A and for Regimen B, and n=20 for Regimen C, since the elimination rate constant was not estimable for some of the subjects.

The mean T_{max}, C_{max}, C_{min}, and AUC for the inactive metabolite, A-66193 were significantly higher after zileuton CR administration (both non-fasted and fasted conditions), compared to zileuton IR under non-fasted conditions. The mean elimination t_{1/2} of A-66193 was 8.87 hours after zileuton CR non-fasted, 7.31 hours after zileuton CR fasted, and 6.44 hours following zileuton IR non-fasted. Trough plasma concentration of A-66193 before the morning dose indicated that steady-state was achieved by Day 3 and levels remain constant throughout Day 6.

The total exposure (AUC) to A-66193 following zileuton CR administration under non-fasted conditions was almost 5-fold higher than after zileuton IR under non-fasted conditions. Following zileuton CR under fasted conditions, the total exposure to A-66193 was almost 9-fold higher than after zileuton IR under non-fasted conditions. A much higher fraction of the zileuton CR dose is converted to A-66193 under fasted conditions than under non-fasted conditions, resulting in lower AUC values for zileuton.

CONCLUSIONS:

In summary, results of this study showed that zileuton CR tablets demonstrated a successful controlled-release profile, with reduced fluctuations between C_{max} and C_{min} and no dose-dumping characteristics. Under non-fasting conditions, the bioavailability of zileuton CR based on AUC and C_{max} values was lower than that of zileuton IR, but was equivalent based on C_{min} values. The bioavailability of zileuton CR was markedly increased, and absorption was delayed, when it was administered under non-fasting conditions, confirming a food effect seen in previous studies and supporting the recommendation to administer zileuton CR after a meal. The sustained-release profile of the zileuton CR E21 formulation was improved over that of the formulation used in the Abbott studies. Fluctuation between C_{max} and C_{min} was smaller with the zileuton E21 formulation, and the mean C_{min} value of 1.00 µg/mL was similar to that after treatment with zileuton IR, and well above the IC₅₀ (0.47 µg/mL) for LTB₄ inhibition. The total exposure (AUC) to A-66193 following zileuton CR administration under non-fasting conditions was almost 5-fold higher than after zileuton IR under non-fasting conditions. Following zileuton CR under fasting conditions, the total exposure to A-66193 was almost 9-fold higher than after zileuton IR under non-fasting conditions. A similar or higher exposure to A-66193 was observed in the Abbott multiple-dose study M95-264. *In vitro* genotoxicity studies and numerous animal studies confirmed the safety of A-66193 at or above the maximum anticipated exposure to this metabolite in humans given the zileuton CR formulation.

Study Number: M96-556

Title: The Effect of Food on the Pharmacokinetics of a Zileuton (Abbott-64077) Controlled-Release Tablet Formulation

Objectives: The objective of this Phase I study was to evaluate the effect of food, high fat and low fat, on zileuton pharmacokinetics from a 600 mg controlled-release (CR) tablet formulation. In addition, the pharmacokinetics of zileuton after administration of the 600 mg CR tablet formulation under fasting conditions were compared to the pharmacokinetics of the 600 mg immediate-release (IR) tablet administered under fasting conditions.

Study Design: This was a Phase I, single-dose, randomized, open-label, four-period, fasting and nonfasting, complete-crossover, single-center study, with a minimum of a 6 day washout interval between doses of successive periods.

Subjects: Twenty-four healthy male (n=12) and female (n=12) subjects participated in the study. All subjects completed all four periods of the study. Their ages ranged from 19 to 45 years, (mean 33 years), their heights ranged from 152.4 to 190.5 centimeters (mean, 169.9 centimeters) and their weights ranged from 54.4 to 88.0 kilograms (mean, 71.0 kilograms), respectively.

Formulations: Formulation 1: 600 mg of zileuton formulation CR tablet, Bulk NPRO 7224R, Bulk lot 17-434-AR-04, Finishing NPRO 8425, finishing subplot 21-531-S2. Potency: ~~label claim.~~

Formulation 2: 600 mg of zileuton formulation IR tablet, Bulk NPRO 6751N, Bulk lot 01-087-AR-03, Finishing NPRO 8425, finishing subplot 21-532-S2. Potency: ~~label claim.~~

Dosage: The subjects received a single 1200 mg dose of the CR tablet formulation (two 600 mg tablets) in each of three periods and two single doses, separated by 6 hours, of 600 mg of the IR tablet formulation in the remaining period.

Results

Pharmacokinetics: The pharmacokinetic parameters of zileuton after administration of each of the four study regimens are summarized in the following table (mean \pm SD):

Zileuton Pharmacokinetic Parameters	Regimen A 1200 mg CR Fasting	Regimen B 1200 mg CR High Fat Nonfasting	Regimen C 1200 mg CR Low Fat Nonfasting	Regimen D 1200 mg IR Fasting
T_{max} (hr)	1.9 \pm 1.0	4.3 \pm 2.9 †	2.5 \pm 0.9	1.7 \pm 1.0 à
C_{max} (μ g/mL)	4.39 \pm 1.76 *	5.22 \pm 2.16 †	4.73 \pm 1.30	6.68 \pm 2.60 à
AUC_{0-last} (μ g \cdot hr/mL)	29.36 \pm 10.25 *	41.98 \pm 14.29 †	30.45 \pm 13.52	51.91 \pm 16.73
$AUC_{0-\infty}$ (μ g \cdot hr/mL)	29.82 \pm 10.27 *	42.42 \pm 14.41 †	30.82 \pm 13.64	52.07 \pm 12.73
CL/F (mL/min) ⁺	748 \pm 265	525 \pm 179	773 \pm 345	423 \pm 136
$t_{1/2}$ (hr) [†]	-	-	-	2.6 \pm 0.7

CR: Controlled-Release; IR: Immediate-Release

* Statistically significantly different from Regimen D;

† Statistically significantly different from Regimen A;

à After the first 600 mg dose;

+ Parameter not test statistically.

For the two one-sided tests procedure based on analysis of $\ln(C_{max})$ and $\ln(AUC_{0-\infty})$ of zileuton, the 90% confidence intervals for the ratio of the CR tablet formulation (Regimen A) relative to that of the reference IR tablet formulation (Regimen D) are shown below:

Parameter	Formulation		C_{max} Ratio	
	Test	Reference	Point Estimate [†]	90% Confidence Interval
C_{max}	A	D	0.410	0.364 - 0.461
$AUC_{0-\infty}$	A	D	0.569	0.530 - 0.612

[†] Antilogarithm of the difference of the least squares means for logarithms.

The 95% confidence intervals for the ratio of $\ln(C_{max})$ and $\ln(AUC_{0-\infty})$ for the CR tablet given with a high fat meal (Regimen B) or a low fat meal (Regimen C) relative to the CR tablet given under fasting conditions (Regimen A) are shown below.

Parameter	Formulation		C_{max} Ratio	
	Test	Reference	Point Estimate [†]	95% Confidence Interval
C_{max}	B	A	1.211	1.052 - 1.394
C_{max}	C	A	1.135	0.986 - 1.306
$AUC_{0-\infty}$	B	A	1.424	1.306 - 1.533
$AUC_{0-\infty}$	C	A	1.000	0.917 - 1.091

[†] Antilogarithm of the difference of the least squares means for logarithms.

The individual key pharmacokinetic parameters for Abbott-66193, after administration of each of the four study regimens, are summarized in the following table (mean \pm SD):

Abbott-66193 Parameters	Regimen A 1200 mg CR Tablet Fasting	Regimen B 1200 mg CR Tablet High Fat Nonfasting	Regimen C 1200 mg CR Tablet Low Fat Nonfasting	Regimen D 1200 mg IR Tablet Fasting
T_{max} (hr)	23.1 \pm 7.4	26.8 \pm 4.3	25.6 \pm 8.6	16.8 \pm 7.1
C_{max} (μ g/mL)	1.59 \pm 1.35	0.67 \pm 0.67	1.26 \pm 1.13	0.332 \pm 0.537
AUC_{0-48} (μ g \cdot hr/mL)	24.88 \pm 23.52	10.20 \pm 11.31	21.12 \pm 21.35	5.19 \pm 9.07

CR: Controlled-Release; IR: Immediate-Release

Conclusions:

The CR formulation was not found to be equivalent to the IR formulation under fasting conditions with respect to zileuton $AUC_{0-\infty}$. The mean values of zileuton C_{max} , $AUC_{0-\infty}$ and T_{max} were statistically significantly different when the CR formulation was administered with a high fat meal compared to administration of the CR formulation under fasting conditions but were not statistically significantly different when the CR formulation was administered with a low fat meal compared to administration of the CR formulation under fasting conditions. The zileuton 600 mg formulation used in this study was generally well tolerated by the subjects.

Figure 1. Mean Zileuton Concentrations ($\mu\text{g/mL}$) in Plasma in Study M96-556 - Linear Scale

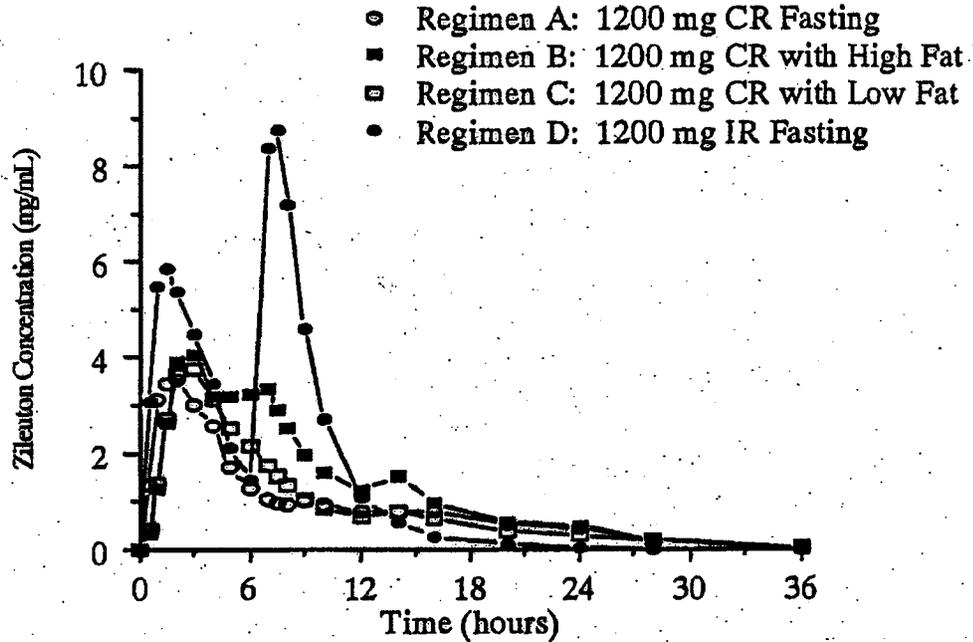
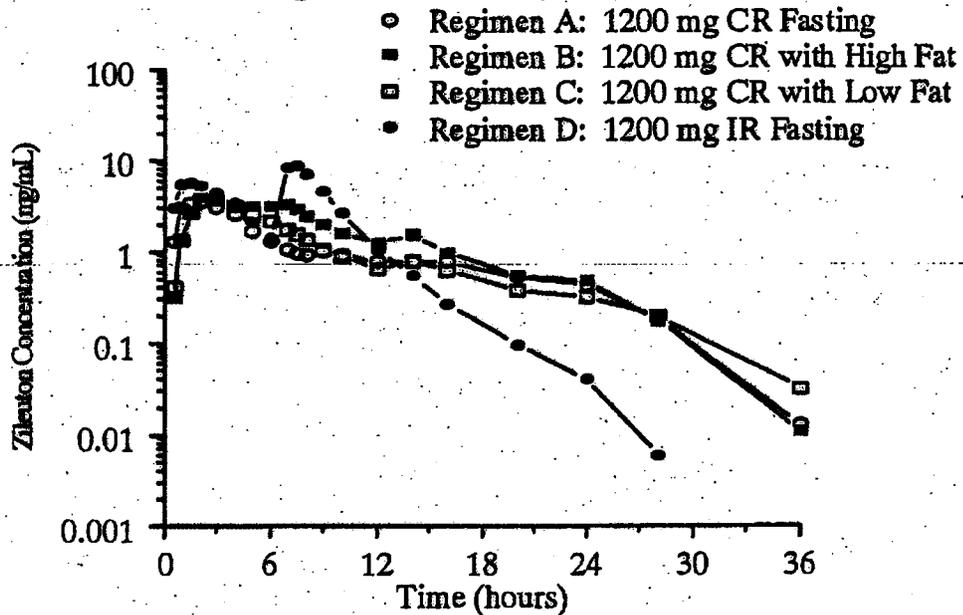


Figure 2. Mean Zileuton Concentrations ($\mu\text{g/mL}$) in Plasma in Study M96-556 - Log-Linear Scale



Study Number: M95-264

Title: Comparison of the Pharmacokinetics of a Zileuton Controlled-Release Tablet Formulation to a Zileuton Immediate-Release Tablet Formulation Following Multiple Doses

Objectives: The objective of this study was to compare the pharmacokinetics of a zileuton controlled-release (CR) formulation to a zileuton immediate-release (IR) formulation after administration of multiple doses of each.

Study Design: This was a Phase I, multiple-dose, randomized, open-label, two-period, nonfasting, complete-crossover, single-center study, with at least a 10 day washout interval between doses of successive periods.

Subjects: Twenty-four healthy male (n=12) and female (n=12) subjects participated in the study. Twenty-three completed both periods of the study. The ages of the 24 participants ranged from 19 to 50 years, (mean 35.8 years), their heights ranged from 147.3 to 180.3 centimeters (mean, 165.7 centimeters) and their weights ranged from 55.3 to 83.5 kilograms (mean, 69.3 kilograms), respectively.

Regimens:

A: Two 600 mg zileuton CR tablets (1200 mg) q12h for 12 consecutive doses.

B: One 600 mg zileuton IR tablet (600 mg) q6h for 24 consecutive doses.

Formulations:

A: Zileuton CR tablets, Bulk NPRO 7224R, Bulk lot 17-434-AR-04. Finishing NPRO 8448, Finishing lot 22-654-S2. Potency: ~~meets~~ label claim.

B: Zileuton IR tablets, Bulk NPRO 6751N, Bulk lot 01-087-AR-03. Finishing NPRO 8448, Finishing lot 22-655-S2. Potency: ~~meets~~ label claim.

Dosage:

Each subject received a total of 2400 mg zileuton during each 24-hour period for six consecutive days during each of the two study periods. Each dose was given with 180 mL of water.

Results**Pharmacokinetics:**

The pharmacokinetic parameters of zileuton for the subjects who completed the study ($n = 23$) are summarized in the following table (mean \pm SD):

24-hour Zileuton Pharmacokinetic Parameters	Regimen A 1200 mg CR every 12 hours	Regimen B 600 mg IR every 6 hours
T_{max} (hr)	$2.6 \pm 2.0^*$	1.7 ± 0.5
C_{max} ($\mu\text{g/mL}$)	$5.93 \pm 2.36^*$	11.99 ± 5.25
C_{min} ($\mu\text{g/mL}$)	$0.62 \pm 0.46^*$	1.13 ± 0.87
C_{avg} ($\mu\text{g/mL}$) ⁺	2.48 ± 0.97	4.55 ± 2.52
Fl_{0-24}	$2.21 \pm 0.61^*$	2.49 ± 0.56
AUC_{0-24} ($\mu\text{g}\cdot\text{hr/mL}$)	$59.5 \pm 23.2^*$	109.2 ± 60.5
β (hr^{-1})	$0.218 \pm 0.081^*$	0.357 ± 0.052
$t_{1/2}$ (hr) ⁺	3.7 ± 1.7	2.0 ± 0.4
CL/F (mL/min) ⁺	766 ± 267	434 ± 155
Vd_p/F (L) ⁺	253 ± 163	72 ± 21

CR: Controlled-Release; IR: Immediate-Release

* Statistically significantly different from Regimen B

+ Parameter not tested statistically.

The 95% confidence intervals for the ratios of central values of C_{min} and C_{max} for the CR tablet formulation (Regimen A) relative to that of the reference IR tablet formulation (Regimen B) are shown below:

24-Hour Parameter	Regimen		Ratio of Central Values	
	Test	Reference	Point Estimate [†]	95% Confidence Interval
C_{min}	A	B	0.543	0.420 - 0.703
C_{max}	A	B	0.499	0.429 - 0.581

[†] Antilogarithm of the difference of the least squares means for logarithms.

For the two one-sided tests procedure based on analysis of $\ln(\text{AUC}_{0-24})$ of zileuton, the 90% confidence interval for the bioavailability of the CR tablet formulation (Regimen A) relative to that of the reference IR tablet formulation (Regimen B) is shown below:

Parameter	Regimen		Relative Bioavailability	
	Test	Reference	Point Estimate [†]	90% Confidence Interval
AUC_{0-24}	A	B	0.560	0.503 - 0.622

[†] Antilogarithm of the difference of the least squares means for logarithms.

Conclusion:

The results of this study show that the mean zileuton T_{\max} after administration of the CR tablet formulation was significantly higher than the corresponding value after administration of the IR tablet formulation. The mean zileuton C_{\max} after q12h administration of the CR tablet formulation (1200 mg) was 51% lower than the mean zileuton C_{\max} after administration of a 600 mg IR tablet q6h ($p < 0.05$). Therefore, the CR tablet formulation appears to be successful in delivering zileuton at a slower release rate than the IR formulation. The lower FI and C_{avg} values after administration of the CR formulation also suggest that the CR tablet formulation does not exhibit dose-dumping characteristics. However, it should be noted that the mean zileuton AUC_{0-24} after administration of the CR tablet formulation (Regimen A) was only 54% of the mean AUC_{0-24} after administration of the IR tablet formulation (Regimen B).

4.3. OCP filing

Office of Clinical Pharmacology New Drug Application Filing and Review Form				
General Information About the Submission				
	Information		Information	
NDA Number	22-052	Brand Name	CR tablet	
OCP Division (I, II, III, IV,V)	DCP-II	Generic Name	Zileuton	
Medical Division	DNCE	Drug Class	Inhibitor of 5-lipoxygenase	
OCPB Reviewer	Shinja Kim	Indication(s)	Asthma	
OCPB Team Leader	Emmanuel Fadiran	Dosage Form	600 mg Controlled-release (CR) Tablet	
		Dosing Regimen	2 tablets BID Q12h for ≥12 years of age	
Date of Submission	7/30/06	Route of Administration	Oral	
Estimated Due Date of OCPB Review	3/30/07	Sponsor	Critical Therapeutics	
PDUFA Due Date	5/30/07	Priority Classification	3 S	
Division Due Date	3/30/07			
3 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			
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:				
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:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				

Data rich:			
Data sparse:			
II. Biopharmaceutics			
Absolute bioavailability:			
Relative bioavailability -			
solution as reference:			
alternate formulation as reference:			
Bioequivalence studies -			
traditional design; single / multi dose:	x	5	
replicate design; single / multi dose:			
Food-drug interaction studies:	x	2	
Dissolution:	x		
(IVIVC):			
Bio-wavier request based on BCS			
BCS class			
III. Other CPB Studies			
Genotype/phenotype studies:			
Chronopharmacokinetics			
Pediatric development plan			
Literature References			
Total Number of Studies		5	
Filability and QBR comments			
	"X" if yes	Comments	
Application filable?	x		
Comments sent to firm?			
QBR questions (key issues to be considered)	<ul style="list-style-type: none"> • Is formulation used in the bio-study identical to the to-be-marketed formulation? • Is the tested formulation bioequivalent to the reference (innovator) product? • What bioanalytical methods are used to assess concentrations of active moieties? 		

Background:

Zileuton immediate-release (IR) tablet (Zyflo[®] FilmTab[®]) was approved in December, 1996. The recommended dose was one 600 mg tablet QID that could be taken with meals and at bedtime. An important precaution for Zyflo[®] was elevation of liver enzyme levels. Abbott filed IND 47,561 in early 1995 to develop a CR tablet formulation of zileuton to offer twice-a-day dosing to patients, as 1200 mg BID, and conducted two Phase 3 studies (M95-337 and M96-464) and PK studies (M95-264, M96-556, M97-742) using "formulation H". However, Abbott never filed an NDA. Then, in 2003, Abbott discontinued Zyflo[®] FilmTab[®](IR) due to sluggish sales.

In December, 2003, CRTX acquired full ownership of zileuton CR and in March, 2004, acquired ownership of Zyflo FilmTab. The applicable IND's and NDA were also transferred to CRTX. Supplies of the Abbott CR product, used in Phase 3 studies and the PK studies (above mentioned studies), no longer existed. Thus, CRTX manufactured its own CR formulation ("S6" formulation) and conducted a bioavailability study (CTI-03-C04-101) comparing CRTX CR product to the Abbott IR product, which is still exists and which would provide a link to the Abbott ER product.

CRTX contends that the S6 formulation is “the same as” Abbott’s Formula H. However, it was manufactured in a different facility with some change to the support layer of the tablet. The Sponsor introduces yet another formulation, “E21,” and conducted 2 PK studies (CTI-03-C05-102 and CTI-03-C05-103). These 2 PK studies are designed similar to studies M96-264 and M96-556 to link the Formulation E21 to Formulation H. However, this is a ‘cross-study’ comparison (not the direct comparison).

The Division agreed to accept CTI-03-C05-102 and CTI-03-C05-103, however, warned to the sponsor not including S6 in the BA/BE study is risky since there is no bench mark to the formulation that was used to conduct the clinical studies.

Although, this NDA is filable, linking the studies conducted using formulations H to E21 will be a problematic and is the most important aspect of review.

Conclusion: This NDA is filable.

Request for DSI audit: Bio-analyses for studies CTI-03-C05-102 and CTI-03-C05-103 (and CTI-03-C04-101) were performed by the laboratory, and the name and address are shown below:

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

/s/

Shinja Kim
3/26/2007 01:54:28 PM
BIOPHARMACEUTICS

Emmanuel Fadiran
3/26/2007 04:50:14 PM
BIOPHARMACEUTICS
I concur.

CLINICAL PHARMACOLOGY TEAM LEADER'S MEMO

NDA 22-052:	Submission Date: July 30, 2006
Brand Name:	Xyflo™ XR tablet
Generic Name:	Zileuton Controlled Release tablet
Reviewer:	Shinja Kim, Ph.D.
Team Leader:	Emmanuel Fadiran, Ph. D.
OCP Division:	DCP 2
OND Division:	DPADP
Sponsor:	Critical Therapeutics (CRTX), Inc.
Submission Type:	Original (S000)
Formulation; Strength(s):	Zileuton 600 mg CR tablet
Indication:	Prophylaxis and chronic treatment of asthma at a dosage regimen of 1200 mg twice daily for adults and children 12 years of age and older.
Memo date:	April 6, 2007

This is a clinical pharmacology team leader's memo on NDA 22-052 for Xyflo XR (Zileuton Controlled Release) tablet by CTRX. The NDA was submitted to the Agency on July 30, 2006 and the original clinical pharmacology review (CP review dated March 26, 2007) by Dr. Shinja Kim recommended that the clinical pharmacology studies were acceptable subject to a favorable DSI report. This memo will focus on the comparison of the multiple PK dose study conducted by CTRX using formulation E21 (Study CTI-03-C05-103) to that conducted by Abbott Laboratories (Study M95-264) using Formulation H which was used for the clinical efficacy study M95-337 and then provide the clinical pharmacology rationale for the approval of the NDA based on favorable efficacy findings from Study M95-337. For the review of the single dose studies (CTI-03-C05-102 by CTRX and M96-556 by Abbott) and other related biopharmaceutics issues in the submission please refer to Dr. Kim's CP review.

Study CTI-03-C05-103 was a multiple-dose, randomized, open-label, 3-period, complete crossover, with a minimum of a 10-day washout between each period in 24 healthy subjects. The objective of this study was to compare the bioavailability of zileuton CR 600 mg tablets (Formulation E21) administered under fasted and fed (high fat meal) conditions with that of zileuton IR 600 mg tablets (Zyflo®) under fed conditions using the following treatments:

- **TRT A:** Two 600 mg CR zileuton tablets q12h for 12 consecutive doses (6 days) under fed conditions
- **TRT B:** Two 600 mg CR zileuton tablets q12h for 12 consecutive doses (6 days) under fast conditions
- **TRT C:** One 600 mg IR zileuton tablet (Zyflo®) administered q6h for 24 consecutive doses (6 days) under fed conditions

Blood samples were collected prior to morning dose (trough blood samples) on Days 1 through 5 of each study period and up to 48 hours after the morning dose on Day 6 in each period. The

plasma samples were analyzed for zileuton and metabolite A-66193 with a validated LC-MS/MS assay with LLQ of $0.5 \mu\text{g/mL}$ for each analyte.

Table 1 shows the summary of zileuton pharmacokinetic parameters at steady-state while Figure 1 shows the mean concentration-time profiles for each treatment.

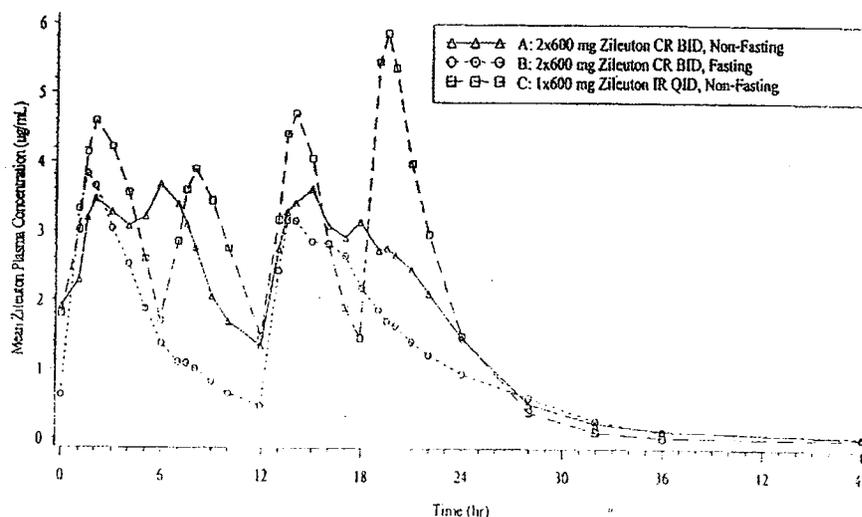
Table 1. Mean (\pm SD) Zileuton PK parameters at steady state (Study CTI-03-C05-103)

Parameters	Regimen A 2 x 600 mg CR Every 12 hours Non-Fasting (n=24)	Regimen B 2 x 600 mg CR Every 12 hours Fasting (n=24)	Regimen C 1 x 600 mg IR Every 6 hours Non-Fasting (n=24)
T_{max} (hr)	3.57 \pm 2.35	2.12 \pm 1.42	1.63 \pm 0.82
AUC ($\mu\text{g}\cdot\text{hr/mL}$)	63.99 \pm 15.95	44.85 \pm 12.59	77.42 \pm 21.36
C_{max} ($\mu\text{g/mL}$)	4.97 \pm 1.34	4.59 \pm 1.42	7.72 \pm 2.43
C_{min} ($\mu\text{g/mL}$)	1.00 \pm 0.45	0.37 \pm 0.17	0.99 \pm 0.38
$C_{\text{min trough}}$ ($\mu\text{g/mL}$)	1.91 \pm 0.71	0.63 \pm 0.56	1.80 \pm 0.64
$C_{24\text{h}}$ ($\mu\text{g/mL}$)	2.67 \pm 0.67	1.87 \pm 0.53	3.23 \pm 0.89
CL/F (mL/min)	668.7 \pm 195.95	968.8 \pm 316.37	607.4 \pm 433.83
FI	1.50 \pm 0.33	2.27 \pm 0.34	2.19 \pm 0.83
$t_{1/2}$ (hr)	3.19 \pm 1.24 ^a	4.05 \pm 1.94 ^a	2.23 \pm 0.53
Beta (1/hr)	0.24 \pm 0.07 ^a	0.21 \pm 0.09 ^a	0.32 \pm 0.06

^a n=19 for Regimen A and n=20 for Regimen B since elimination rate constant was not estimable for some of the subjects.

Source: Statistical Tables 14.2.2.1.2, 14.2.2.2.2, 14.2.2.3.2, 14.2.1.1.4, 14.2.1.2.4 and 14.2.1.3.4.

Figure 1. Mean Zileuton Concentrations in Plasma on Study Day 6 after Multiple Oral Doses of CR or IR Zileuton Tablets in Study CTI-03-C05-103



Study M95-264 was a multiple-dose, randomized, open-label, 2-period, crossover study, with at least a 10-day washout interval between the treatments in 23 healthy subjects. The objective of this study was to compare the PK of a zileuton CR formulation (Formulation H) to a zileuton IR formulation (Zyflo[®]) both under fed conditions.

The following regimens were used in this study:

- **TRT A:** 2 x 600 mg Zileuton CR tablets q12h for 12 consecutive doses
- **TRT B:** 1 x 600 mg Zileuton IR tablet q6h for 24 consecutive doses

Blood sampling schemes and data analysis were as described for Study CTI-03-C05-103.

Table 2 shows the summary of zileuton pharmacokinetic parameters at steady-state were calculated with non-compartmental methods while Figure 2 shows the mean concentration-time profiles for each treatment.

Table 2. Summary of mean (\pm SD) Ziluton PK parameters (n = 24) (Study M95-264)

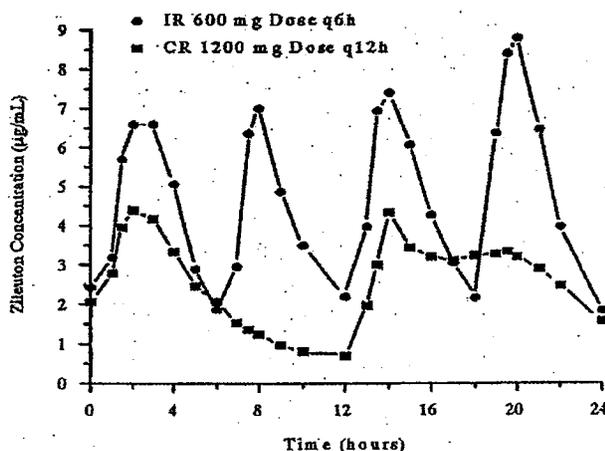
24-Hour Zileuton PK Parameters	Regimen A 1200 mg CR every 12 hours	Regimen B 600 mg IR every 6 hours
T _{max} (hr)	2.6 \pm 2.0*	1.7 \pm 0.5
C _{max} (μ g/mL)	5.93 \pm 2.36*	11.99 \pm 5.25
C _{min} (μ g/mL)	0.62 \pm 0.46*	1.13 \pm 0.87
C _{avg} (μ g/mL) [†]	2.48 \pm 0.97	4.55 \pm 2.52
FI ₀₋₂₄	2.21 \pm 0.61*	2.49 \pm 0.56
AUC ₀₋₂₄ (μ g \cdot hr/mL)	59.5 \pm 23.2*	109.2 \pm 60.5
B (hr ⁻¹)	0.218 \pm 0.081*	0.357 \pm 0.052
t _{1/2} (hr) [†]	3.7 \pm 1.7	2.0 \pm 0.4
CL/F (mL/min) [†]	766 \pm 267	434 \pm 155
Vd _B /F (L) [†]	253 \pm 163	72 \pm 21

*Statistically significantly different from Regimen B.

[†]Parameter not tested statistically.

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Figure 2. Mean Zileuton Concentrations in Plasma on Study Day 6 after Multiple Oral Doses of CR or IR Zileuton Tablets in Study M95-264



A comparison of the relative bioavailability with respect to Cmax, Cmin and AUC of the CR formulations to the IR formulation under fed conditions is summarized in Table 3.

Table 3. Comparison of Mean Zileuton PK parameters

Parameters	Test	Reference	CRTX Ratio of Means (Test/Reference) (n = 24)		Abbott Ratio of Means (Test/Reference) (n = 23)	
			Point Estimate	90% CI	Point Estimate	90% CI
Cmax (µg/mL)	CR	IR	0.650	(0.595, 0.710)	0.499	(0.429, 0.581)
Cmin (µg/mL)	CR	IR	1.046	(0.879, 1.245)	0.543	(0.420, 0.703)
AUC ₀₋₂₄ (µg.h/mL)	CR	IR	0.846	(0.781, 0.915)	0.560	(0.503, 0.622)

Discussion & Recommendation: The systemic exposure from Abbott Formulation H with respect to Cmax, Cmin and AUC was approximately 50% of those from zileuton IR tablets (Table 3). In contrast, the systemic exposure from CRTX Formulation E21 with respect to Cmax, Cmin and AUC were 65%, 105% and 85% of those from zileuton IR tablets (Table 3). In addition, the higher Cmin (1.0 compared to 0.62), smaller Fluctuation Index, FI (1.5 compared to 2.2) indicate an improved extended-release profile with the CRTX Formulation E21 compared to Abbott Formulation H. The Cmin from Formulation E21 is also similar to that from the IR formulation indicating similar effect at trough from both formulations. Therefore, systemic exposure from Formulation E21 as well as the product performance are much better than those from Formulation H. There is no safety concern from approval of Formulation E21 since the

systemic exposure measures (Cmax and AUC) from this formulation are lower than those from the IR formulation and efficacy will be better than that of Formulation H which was used for the successful clinical study M95-337. Therefore, based on observed systemic exposure to zileuton at steady state, Formulation E21 would be expected to perform much better than Formulation H and is therefore recommended for approval based on the improved systemic exposure from Formulation E21 and the results of the successful clinical Study M95-337 that used Formulation H.

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