

**Table 29 Intervals used for LOCF and as-observed analyses for laboratory tests and vital signs (Study M96-164)**

DB Nominal visit day	LOCF	Observed data interval
Study day 29	2-43	2-43
Study day 57	2-71	44-71
Study day 85	2-92	72-99
Study day 113	2-141	100-141
Study day 169	2-183	142-183

**Table 30 Intervals used for LOCF and as-observed analyses for trough FEV1 and Asthma QOL**

DB Nominal visit day	LOCF	Observed data interval
Study day 85	2-127	2-127
Study day 169	2-183	128-183

*Reviewer's comments: According to the original Abbott protocol, the sample size calculation and primary health outcome is based on the percentage of patients experiencing asthma exacerbation requiring hospitalization or ER visit, not the percentage of patients with ALT elevations as specified in the primary safety variable. The secondary outcome in the Abbott protocol is patient's self-reported quality of life. The CRTX report does not address why the primary outcome was changed.*

#### 10.2.11 Changes to protocol

##### Revision 1 (April 23, 1997). Approved after randomization of 820 patients.

- 1) Clarification when zileuton ER administration should occur relative to meals.
- 2) Bronchodilators not supplied by Abbott were not permitted.
- 3) Blind-breaking envelopes must be stored in a secured area.
- 4) Salmeterol and theophylline washout periods were relative to the onset of the 7-day screening period used to establish the AirWatch PEFr baseline rather than Study Day 1.
- 5) A patient diary would not be dispensed at the Month 6 visit.
- 6) Documentation of positive airway challenges within past year no longer acceptable as alternative to screening beta-agonist inhalation test.
- 7) PFT performed at least 15 minutes following nebulized treatment, not immediately afterwards.
- 8) Central laboratory name changed from ~~Abbott Laboratories~~ to ~~Abbott~~ laboratory Services.
- 9) ALT now the only LFT that could not be repeated at screening in order to gain entry into the study, rather than all LFTs.
- 10) A back-up phone number added to the ALT flowchart.
- 11) Clarification that plasma levels must have been drawn for all patients in the study, rather than those in the CR group only.
- 12) Clarification that patient diaries divided into 4 sections, not 2.
- 13) The CRC at ~~XXXXXX~~ was to use the last 4 digits of a patient's SSN rather than gender in order to identify patient.
- 14) Any unusual finding, not just unusual lab finding, during the study or within 30 days after drug discontinuation to be documented as an AE.
- 15) A title change and phone number clarification added to the Abbott monitors contact list.
- 16) Clarification of document retention in the protocol.

- 17) Appendix A revised to reflect all study inventory forms for the drug.
- 18) Concomitant Drug Restrictions list modified.
- 19) Definition for ER visit added to statistical analysis section.
- 20) Sample QOL forms modified to match validated version given to patients.
- 21) Visit procedures in Appendix E listed in order of performance.
- 22) AirWatch instructions added Dial-in instructions.
- 23) Correction of typographical errors.

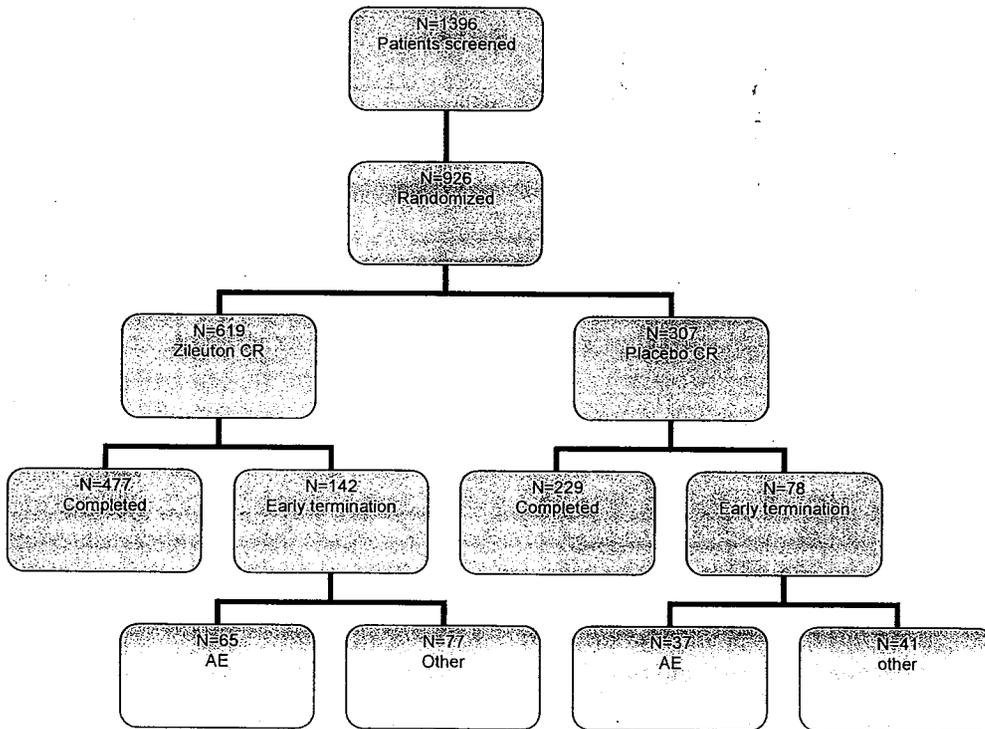
**10.2.12 Results**

**10.2.12.1 Study patients**

*10.2.12.1.1 Disposition*

Figure 3 and Table 31 summarize the disposition of patients in the study. Dropouts due to adverse events are reviewed in further detail under Safety Outcomes.

**Figure 3 Patient disposition for Study M96-464**



**Table 31 Summary of treatment exposure for Study M96-464**

Exposure	Zileuton ER		Placebo ER	
	N	%	N	%
Any	619	100	307	100
≥29 days	569	91.9	281	91.5
≥57 days	535	86.4	267	87.0
≥85 days	505	81.6	255	83.1
≥113 days	492	79.5	242	78.8
≥141 days	482	77.9	234	76.2
≥159 days	473	76.4	232	75.6

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Completers	477		229	
Mean days of exposure	168.8		168.7	
Range (days)	106-194		157-190	

Source: Volume 93, Statistical Table 14.1.2.1

### 10.2.12.1.2 Demographics/baseline characteristics (Full Analysis Set)

#### 10.2.12.1.2.1 Demographics

Patients in the zileuton ER and placebo groups were similar in terms of mean age, gender, and ethnicity. A slightly higher proportion of patients on the zileuton ER arm had a history of tobacco use at baseline. In terms of baseline asthma characteristics, the two groups were comparable as well. Approximately 50% of all subjects were taking inhaled corticosteroids at baseline and during the study. Results are summarized in the tables below.

Treatment group	N	Mean age (range)	Sex (% M)	Race	History of tobacco use
Zileuton ER	619	35.9 (12-83)	39.58%	B=38 (6.14%) W=532 (85.95%) O=49 (7.92%)	22.13%
Placebo ER	307	36.2 (12-81)	39.41%	B=21 (6.84%) W=262 (85.34%) O=24 (7.82%)	15.64%
<b>P-value</b>		0.753	0.961	0.919	0.02

Source: Volume 93, Statistical table 14.1.1.1

#### 10.2.12.1.2.2 Mean baseline asthma characteristics

	Zileuton ER (N=619)	Placebo ER (N=307)	P
Trough FEV1 (L)	2.52	2.52	0.932
% predicted FEV1	71.09	69.91	0.369
AM PEFr (L/min)	388.83	388.27	0.951
PM PEFr (L/min)	420.28	414.83	0.556
#occasions albuterol use/day	2.49	2.67	0.091
# puffs albuterol/day	4.57	5.09	0.018
QOL- overall score	4.66	4.62	0.554
Asthma severity*	Mild = 164 (33%) Mod = 204 (40%) Severe = 139 (27%)	Mild = 66 (26%) Mod = 118 (47%) Severe = 67 (27%)	0.50

\* Asthma severity: mild (FEV1 $\geq$ 80% predicted), moderate (FEV1 $>$ 60% and  $<$ 80%), and severe (FEV1 $\leq$ 60%)

*Reviewer's comments: Analysis using full and restricted analysis sets does not show any statistically significant differences between zileuton and placebo groups respectively in terms of baseline characteristics.*

#### 10.2.12.2 Protocol deviations

Protocol deviations were granted to particular study sites by medical monitors to allow certain patients to enroll who did not meet all study entrance criteria. The waivers were granted on a case-by-case basis to accommodate patients who were deemed to be appropriate study candidates but who fell slightly outside protocol requirements. Exceptions were recorded on the appropriate CRF.

One Investigator, Robert Fiddes, was excluded due to evidence of fraudulent data (no clear evidence that patients existed). Patient 10515/ was excluded after Abbott learned that the

patient had participated in both the efficacy (placebo ER) and long-term safety (zileuton ER) study simultaneously.

The blind was broken for one patient (2996) due to a positive pregnancy test. The patient was reported to have received placebo and she continued on to have a successful pregnancy.

### 10.2.12.3 Data sets analyzed

The sponsor's own audit of clinical study sites raised several concerns about data integrity. Of note, one of the clinical investigators, Dr. Robert Fiddes, has been subsequently debarred since the completion of Study M95-337, and another investigator, Dr. Thomas Edwards, has been placed on a restricted list. As a result and per discussion with the Division, the sponsor has generated full and restricted analysis sets for the two Phase 3 studies:

- 13) The **full analysis set for Study M96-464** comprises all randomized patients.
- 14) The **restricted analysis set for Study M96-464** excludes 9 clinical sites (N=75), as these sites either no longer exist or data is no longer available for audit.
- 15) Both restricted analysis sets also exclude one patient who simultaneously participated in both Study M95-337 and M96-464.

### 10.2.13 Safety outcomes

All safety analyses were performed using the full data analysis set. Since Study M96-464 has been designated as primarily a safety study, the safety results will be discussed first.

#### 10.2.13.1 Adverse events (AE)

##### 10.2.13.1.1 Dropouts due to AEs

**Table 34** summarizes the various AEs cited as reason for dropout from Study M96-464. Patients were permitted to cite more than reason for discontinuation. Sixty-five patients in the zileuton ER arm and 37 patients in the placebo ER arm discontinued due to an adverse event; the number and the percentage of patients who discontinued from the study early are given in the table. Comparison of zileuton ER to placebo is consistent with the AE profile described for the whole safety database and with AEs described in the zileuton IR label.

<b>Table 34 Study M96-464: Non-serious adverse events associated with dropouts (Number, %)</b>		
	<b>Zileuton ER (N=619)</b>	<b>Placebo ER (N=307)</b>
Total number of early dropouts	142 (22.9)	78 (25.4)
Dropouts due to AEs	65 (10.5)	37 (12.0)
Asthma exacerbation	13 (2.1)	12 (3.9)
Abdominal discomfort/pain	11 (1.8)	1 (0.3)
Nausea	7 (1.1)	4 (1.3)
Rash	6 (1.0)	2 (0.6)
Headache	4 (0.6)	2 (0.6)
Dizziness	3 (0.5)	0
Insomnia	3 (0.5)	0
Fatigue	2 (0.3)	3 (1.0)
Upper respiratory tract infection	2 (0.3)	1 (0.3)
Nasopharyngitis	2 (0.3)	0
Urticaria	2 (0.3)	0
LFT elevation	2 (0.3)	0
Leucopenia	2 (0.3)	0
Vomiting	2 (0.3)	0

Bronchitis	1 (0.2)	1 (0.3)
Sinusitis	1 (0.2)	0
Muscle cramp	1 (0.2)	0
Tachyarrhythmia	1 (0.2)	0
Depression	1 (0.2)	0
Constipation	1 (0.2)	0
Irregular menses	1 (0.2)	0
Hyperlipidemia	1 (0.2)	0
Tuberculosis	1 (0.2)	0
Diarrhea	1 (0.2)	0
Cheilitis/glossitis	1 (0.2)	0
Paresthesia	1 (0.2)	0
Acne	1 (0.2)	0
Lymphadenopathy	1 (0.2)	0
Anxiety	0	2 (0.6)
Palpitations	0	2 (0.6)
Thrombocytosis	0	1 (0.3)
Erectile dysfunction	0	1 (0.3)
Eczema	0	1 (0.3)
Irritable bowel syndrome	0	1 (0.3)
Anemia	0	1 (0.3)
Alopecia	0	1 (0.3)

#### 10.2.13.1.2 Common AEs

The overall incidence of AEs was similar in both treatment groups (86.9% to 84.7%) and is summarized in Table 35.

Table 35 Adverse events occurring in $\geq 3\%$ patients and more frequently in the zileuton ER vs. placebo arms [Study M96-464]		
Adverse Event (MedDRA SOC/PT)	Study M96-464	
	Zileuton ER (N=619)	Placebo ER (N=307)
	%	%
<b>Any adverse event</b>	86.9	84.7
<b>GI disorders</b>	31.2	20.8
Nausea	9.2	5.9
Diarrhea	5.3	2.3
Vomiting	5.0	2.0
Stomach discomfort	4.5	3.9
Dyspepsia	4.2	3.6
Toothache	3.7	2.3
<b>General disorders</b>	14.2	12.7
Fatigue	3.9	2.6
<b>Infections and infestations</b>	37.8	35.5
Nasopharyngitis	10.5	10.7
Sinusitis	9.2	7.5
Upper respiratory tract infection	8.6	7.2
Bronchitis	5.2	3.6
<b>Musculoskeletal and connective tissue disorders</b>	23.1	25.4
Back pain	8.1	10.1
Myalgia	6.9	4.6
Arthralgia	4.8	3.9
Neck pain	3.1	1.6
<b>Nervous system disorders</b>	31.5	23.5
Headache	23.4	20.8
Dizziness	4.7	1.6
<b>Psychiatric disorders</b>	9.9	4.9
Insomnia	5.5	2.0
<b>Respiratory, thoracic, and mediastinal disorders</b>	44.1	46.3
Asthma	33.1	37.8
Pharyngolaryngeal pain	5.7	5.2
Cough	3.2	2.3
<b>Skin and subcutaneous disorders</b>	9.9	8.8
Rash	3.2	2.3

NL: Not listed

(Source: Volume 93, Section 12.2, Table 21)

The most commonly reported AEs in the zileuton ER group were asthma exacerbation (33.1%), headache (23.4%), and nasopharyngitis (10.5%). A higher percentage of patients in the zileuton ER group (31.2%) compared to placebo (20.8%) reported gastrointestinal disorders. The incidence of nausea in the zileuton ER group (9.2%) was higher than placebo (5.9%), as was the incidence of diarrhea (5.3 vs. 2.3%) and vomiting (5.0 vs. 2.0%). Patients in the zileuton ER group also reported a higher incidence of nervous system disorders (31.5 vs. 23.5%, respectively) and psychiatric disorders (9.9 vs. 4.9%, respectively). The most commonly reported nervous system and psychiatric disorders included headache, dizziness, and insomnia.

*Reviewer's comments: Adverse events in the zileuton IR development program were coded using COSTART terms, precluding direct comparisons of event rates. Survey of the most commonly reported events, such as headache and various gastrointestinal complaints, suggests similar adverse event profiles for the CR and IR formulations.*

#### 10.2.13.1.3 Serious AEs

One death was reported in a patient who never received study drug. The study report describes 25 SAEs. Twenty SAEs involved 18 patients who received zileuton ER. These SAEs included 7 hospitalizations for asthma, 9 hospitalizations for other causes, and 4 patient-reported overdoses. Causes for the 9 hospitalizations not attributable to asthma included the following: revision of left hip prosthesis and subsequent close-reduction of left hip; right shoulder arthroscopy; rash and fever (presumed rickettsial infection); left tibia/fibula fracture; rule out ischemia for chest pain; pseudomonal pneumonia complicated by pneumothorax; cat bite infection, and perirectal abscess. Three of the overdose cases involved 1 additional dose of study drug on 1 study day; 1 patient took an extra dose for 4 study days. The 5 SAEs in the placebo group were hospitalizations for other causes.

#### 10.2.13.2 Liver enzyme monitoring

Liver enzymes were evaluated at screening, Day 1, Day 29 (Week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 169 (Week 24), and at the 30-day follow-up visit. Patients with elevations were rechecked at 4 week intervals until resolution. Liver enzymes  $\geq 3X$  ULN and total bilirubin  $\geq 1.5X$  ULN were considered as significant elevations and monitored.

LFT	Zileuton ER (N=619)		Placebo ER (N=307)	
	$\geq 3X$ to $<8X$ ULN N (%)	$\geq 8X$ ULN N (%)	$\geq 3X$ to $<8X$ ULN N (%)	$\geq 8X$ ULN N (%)
ALT	8 (1.3%)	3 (0.5%)	2 (0.6%)	0
AST	3 (0.5%)	1 (0.2%)	2 (0.6%)	0
GGT	5 (0.8%)	2 (0.3%)	0	0
Alk phos	2 (0.3%)	0	0	0
	$\geq 1.5X$ to $<3X$ ULN	$\geq 3X$ ULN	$\geq 1.5$ to $<3X$ ULN	$\geq 3X$ ULN
T bili	9 (1.4%)	0	7 (2.3%)	1 (0.3%)

\* The number of patients with liver enzyme elevations is shown in each column  
(Source: Volume 93, Section 12.3.1.3, Table 23)

An ALT elevation rate of 1.78% was observed. All ALT elevations observed resolved during treatment or after discontinuation. Demographic analysis of subjects with ALT elevations did not identify a particular risk profile in this study. The majority of elevations were reported within the first 3 months of treatment (9/11 zileuton ER patients; 81.8%). Patients with T bili elevations did not have an associated elevation of liver enzymes. Four cases in the zileuton ER group and 6 cases in the placebo groups were attributed to Gilbert's disease.

*Reviewer's comments: The frequency of LFT monitoring in the study was adequate and corresponded to the testing schedule recommended in the zileuton IR label: every month for the first 3 months and then every 2-3 months for the remainder of the first year. Patients with a significant elevation were monitored every 4 weeks until the enzymes returned to <1.5X ULN. The rate of ALT elevations is comparable to the rate reported in the placebo-controlled zileuton IR trials. In those trials, ALT elevations were observed in 1.9% of patients receiving zileuton IR versus 0.2% in the placebo group. In controlled and uncontrolled trials of zileuton IR in >5000 patients, an ALT elevation rate of 3.2% is reported.*

### **10.2.13.3 Other laboratory monitoring**

#### *10.2.13.3.1 Other chemistry variables and urinalysis*

No other clinically meaningful differences were assessed between treatment and placebo groups in regards to other serum chemistry values or urinalysis.

#### *10.2.13.3.2 Leukopenia and differential count changes*

Blood counts were evaluated at screening, Day 1, Day 29 (Week 4), Day 57 (Week 8), Day 85 (Week 12), Day 113 (Week 16), Day 169 (Week 24), and at the 30-day follow-up visit. More patients in the zileuton ER group developed a low WBC count ( $<3.0 \times 10^9/L$ ) than in the placebo group (2.6 vs. 1.7%). All cases in the zileuton ER group returned to within normal or baseline after study drug discontinuation, and none of the cases were deemed symptomatic. Of the 6 zileuton ER patients with leukopenia, 2 discontinued due to the lab abnormality, 2 discontinued due to another AE, and 2 completed the study. The applicant states that "there is no clear explanation for this finding." In addition, there was a statistically significant increase in % monocytes between zileuton ER and placebo groups at Study Day 57 (0.60 vs. 0.20;  $p=0.004$ ) and Study Day 85 (0.74 vs. 0.38;  $p=0.012$ ). Values at the final visit were similar to baseline values. More patients in the zileuton ER group were observed to have a relative decrease in neutrophil counts (3.4% vs. 2.4%) and relative increase in lymphocytes (2.6 vs. 1.7%). (Source Volume 93, Section 12.4.2.2)

*Reviewer's comment: Overall, the safety profile of zileuton ER appears comparable to zileuton IR. ALT elevations rates were similar to those reported in zileuton IR clinical trials. A higher rate of white cell count depression was noted in the zileuton ER group. The majority of white cell count decreases was small in magnitude, asymptomatic, and occurred in individuals with low or borderline values at baseline. Leukopenia is described in the product label for zileuton IR. The rates reported in this study are higher than those rates reported in the Adverse Reactions section of the zileuton IR label (1.0% zileuton IR vs. 0.6% placebo IR, respectively). However, leukopenia is defined using more stringent criteria ( $\leq 2.8 \times 10^9/L$ ) in the current label, which offsets this difference. The applicant does not postulate a mechanism for this observation and the known pharmacologic actions of the drug do not provide a ready explanation.*

A higher number of hospitalizations were observed in the zileuton ER group. Seven cases were attributable to asthma in contrast to zero hospitalizations for asthma in the placebo group ( $p=0.06$ ). Examination of baseline asthma severity and other efficacy variables does not explain why a higher rate of hospitalizations for asthma may have been observed for the zileuton ER group. Overall, more asthma exacerbations were noted in the placebo group, as might be expected presuming zileuton ER's efficacy. The other 9 hospitalizations were secondary to disparate causes which seem unlikely to be related to the zileuton ER.

## 10.2.14 Efficacy outcomes

### 10.2.14.1.1 Primary

Spirometry was performed at screening, Day 1, Day 85 (Week 12) and Day 169 (Week 24). The primary efficacy endpoint was mean change from trough baseline FEV1 and % change from baseline. The results are summarized in Table 37.

Trough FEV1	Zileuton ER (N=619)		Placebo ER (N=307)		P
	Mean baseline	Mean change	Mean baseline	Mean change	
DB Study Day 85	2.52	0.17	2.52	0.13	0.201
		8.62%		7.37%	0.470
DB Study Day 169	2.52	0.17	2.52	0.13	0.260
		8.79%		7.05%	0.316

(Source: Volume 93, Section 11.2.1.1)

- No significant differences were noted between zileuton ER and placebo groups in FEV1 change from baseline.
- Percentage of patients with a 12% or greater improvement in FEV1 was comparable in both treatment groups (~30%) at both Study Day 1 and 169.

*Reviewer's comments: Spirometry was performed only at two time points during the treatment period. As the data do not demonstrate a statistically significant benefit to zileuton ER at either time point, the adequacy of the efficacy measurement is somewhat moot.*

The applicant also provides FEV1 data stratified by asthma severity and inhaled corticosteroid use. Of note, the treatment groups were not stratified by asthma severity or inhaled corticosteroid use at baseline. No statistically significant differences are noted at Week 12 (Day 85) or at Week 24 (Day 169). The results are summarized in Table 38 and Table 39.

Asthma severity	Baseline FEV1		Mean change at Day 85		P	Mean change at Day 169		P
	Zileuton ER (N=619)	Placebo (N=307)	Zileuton ER (N=619)	Placebo (N=307)		Zileuton ER (N=619)	Placebo (N=307)	
Mild	3.17	3.26	+0.03	-0.02	0.280	+0.03	-0.01	0.446
Moderate	2.54	2.56	+0.19	+0.11	0.109	+0.19	+0.13	0.239
Severe	1.76	1.75	+0.34	+0.32	0.817	+0.34	+0.07	0.725

Asthma severity: mild (FEV1 $\geq$ 80% predicted), moderate (FEV1 $>$ 60% and  $<$ 80%), and severe (FEV1 $\leq$ 60%)

(Source: Volume 93, Section 11.2.1.3)

ICS use	Baseline FEV1		Mean change at Day 85		P	Mean change at Day 169		P
	Zileuton ER (N=619)	Placebo (N=307)	Zileuton ER (N=619)	Placebo (N=307)		Zileuton ER (N=619)	Placebo (N=307)	
No	2.64	2.71	0.20	0.19	0.776	0.22	0.23	0.820
Yes	2.42	2.35	0.16	0.07	0.078	0.14	0.05	0.077

(Source: Volume 93, Section 11.2.1.5)

*Reviewer's comments: No statistically significant differences were noted between treatment and placebo groups in terms of the primary efficacy variable. The applicant does not provide a possible explanation for these findings. Conceivably, in the context of routine asthma medication therapy, the treatment effect size of zileuton ER may be negligible or statistically significant. Alternatively, the decreased bioavailability of the ER formulation may have limited the efficacy, although it is worth noting that the to-be-marketed formulation has higher bioavailability than the formulation used in this study. Subgroup analysis by asthma severity and ICS use also did not reveal any significant differences.*

#### 10.2.14.1.2 Secondary

Results of various secondary endpoints are summarized in Table 40 and discussed in further detail below.

Efficacy endpoint	Zileuton ER (N=619)		Placebo (N=307)		P
	Mean baseline	Mean change	Mean baseline	Mean change	
AM PEFr (L/min)	388.83	55.41	388.27	30.38	<0.001
PM PEFr (L/min)	420.28	38.98	436.66	21.83	0.023
SABA use (occasions/day)	2.58	-0.19	2.71	-0.13	0.619
SABA use (puffs/day)	4.72	-0.30	5.23	-0.33	0.889
# patients $\geq 1$ exacerbation	213 (34.41%)		119 (38.76%)		0.168
Asthma QOL questionnaire	4.66	0.71	4.62	0.57	0.083

(Source: Volume 93, Section 11.2.2-11.2.5)

##### 10.2.14.1.2.1 PEFr

Both daily AM and PM PEFrs improved for all treatment arms through the course of the study. Statistically significant differences in AM PEFrs were noted between zileuton ER versus placebo for all time-points of the study; similar differences were noted in PM PEFrs but were not all statistically significant.

##### 10.2.14.1.2.2 SABA use

Beta-agonist use was recorded as number of occasions and number of puffs daily. At the majority of time-points in the study, rescue albuterol use was numerically lower in the zileuton ER group versus placebo, although none of these differences were statistically significant.

##### 10.2.14.1.2.3 Exacerbations

A comparable number of patients in each treatment group reported one or more exacerbations during the entire treatment period: zileuton ER [n=213 (34.47%)] and placebo [n=118 (38.76%)]; p=0.172. Percentage of patients experiencing at least one exacerbation requiring ER visit were 2.59% (zileuton ER) and 3.26% (placebo) [p=0.414]. In terms of hospitalizations for

asthma, 5 cases were reported in the zileuton ER group and none in placebo [p=0.162]. Time to first exacerbation and mean number of total exacerbations were also comparable between the treatment groups.

#### 10.2.14.1.2.4 QOL questionnaire

Domain-specific and overall QOL scores improved in both treatment groups. No statistically significant differences were noted between groups.

*Reviewer's comments: Patients in the zileuton ER group demonstrated improvement in AM and PM PEFrs compared to placebo; treatment effect sizes were modest (~25 and 17 L/min, respectively). Although no statistically significant differences between treatment groups were noted, most other secondary variable comparisons favored the zileuton ER group.*

*Hospitalizations for asthma are the exception, where 5 cases were reported for the zileuton ER group and none for placebo (p=0.162). Notably, hospitalizations for asthma was identified as the primary efficacy endpoint in the original Abbott study protocol, but is not presented as the primary endpoint in either the Abbott or CRTX final study report.*

#### 10.2.15 Study summary

Study M96-464 supports a safety profile for zileuton ER that is largely similar to the safety profile for the approved product, zileuton IR, over a 6-month period. The rate of liver function enzyme elevations which are the most notable adverse event described in the zileuton IR product label, were comparable to rates previously observed in controlled studies of zileuton IR.

Compared to the rates reported in the zileuton IR package insert, higher rates of asymptomatic leucopenia were also observed in this study. The difference appears to be secondary to a lower leucopenia cutoff ( $\leq 2.8 \times 10^9/L$  versus  $< 3.0 \times 10^9/L$ ) used in the original IR studies.

In terms of efficacy, zileuton ER did not demonstrate statistical superiority over placebo on its primary endpoint and the majority of the secondary endpoints, except for PEFrs. In general, the data favored zileuton ER over placebo numerically, if not statistically. The addition of usual asthma medications to the regimen may have masked any benefit attributable to zileuton ER, suggesting a limited therapeutic effect for the drug. Alternatively, reduced bioavailability of the controlled-release form may explain the lack of efficacy seen in this study, although it is worth noting that the to-be-marketed formulation has higher bioavailability than the Formulation H used in this study. The study provides supportive, but not sufficient, evidence of the efficacy of zileuton ER in the prophylaxis and chronic treatment of asthma.

### 10.3 Review of Individual Study Reports: Protocol Study M95-264

#### 10.3.1 Study administrative information

Study start date: November 1996

Study site: USA

Study report: CRTX Volume 36

#### 10.3.2 Objective/rationale

To compare the pharmacokinetics of zileuton ER (Formulation H used in the Phase 3 studies) to zileuton IR after multiple doses of each.

### 10.3.3 Study design

Phase 1, multiple-dose, randomized, open-label, 2-period, non-fasting, crossover, single-center study, with at least a 10-day washout interval between doses of successive periods.

### 10.3.4 Study population

24 healthy males (N=12) and females (N=12)

### 10.3.5 Study treatments

- 2 x 600mg zileuton ER tablets (1200 mg) q12h for 12 consecutive doses
- 1 x 600mg zileuton IR tablet (600 mg) q6h for 24 consecutive doses

Each dose administered with 180 ml of water. Each subject received 2400mg zileuton per 24-hour period.

### 10.3.6 Results

#### 10.3.6.1 Patient demographics and disposition

Twenty-three of 24 subjects enrolled completed both periods of the study. The ages ranged between 19 to 50 years (mean age = 35.8 years).

#### 10.3.6.2 PK

Blood samples were collected prior to the AM dose on Days 1 through 5 of each study period. Additional samples were collected at 5 minutes prior to the AM dose (0 hour) 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 7 AM dose on Day 6 in each study period. Samples were analyzed for zileuton and N-dehydrozileuton (A-66193).

##### 10.3.6.2.1 PK parameters of zileuton for subjects who completed the study (N=23)

24-hour PK parameters	1200 mg CR q12h	600 mg IR q6h
T <sub>max</sub> (hr)	2.6±2.0	1.7±0.5
C <sub>max</sub> (mcg/ml)	5.93±2.36	11.99±5.25
C <sub>min</sub>	0.62±0.46	1.13±0.87
C <sub>avg</sub>	2.48±0.97	4.55±2.52
Fl <sub>0-24</sub>	2.21±0.61	2.49±0.56
AUC <sub>0-24</sub> (mcg hr/mL)	59.5±23.2	109.2±60.5
β (hr <sup>-1</sup> )	0.218±0.081	0.357±0.052
T <sub>1/2</sub> (hr)	3.7±1.7	2.0±0.4
CL/F (ml/min)	766±267	434±155
Vd <sub>f</sub> /F (L)	253±163	72±21

##### 10.3.6.2.2 95% CI for the ratio of central values of C<sub>min</sub> and C<sub>max</sub>

	Test regimen	Reference regimen	Point estimate	*95% CI
C <sub>max</sub>	Zileuton ER	Zileuton IR	0.543	0.420-0.703
C <sub>min</sub>	Zileuton ER	Zileuton IR	0.499	0.429-0.581

\* antilogarithm of the difference of the least squares means for logarithms

##### 10.3.6.2.3 90% CI for the bioavailability of zileuton ER vs. zileuton IR

**Table 43 90% CI for the bioavailability of zileuton ER vs zileuton IR [Study M95-264]**

	Test regimen	Reference regimen	Point estimate	*95% CI
AUC <sub>0-24</sub> (mcg hr/mL)	Zileuton ER	Zileuton IR	0.560	0.503-0.622

#### 10.3.6.2.4 PK parameters of A-66193

Table 44, Table 45, and Table 46 summarize PK parameters for A-66193, a metabolite of zileuton. The concentration of A-66193 increases significantly with bowel transit time; hence more A-66193 is detected from zileuton ER compared to zileuton IR.

Table 44 PK parameters of A-66193 [Study M95-264]		
24-hour PK parameters	1200 mg CR q12h	600 mg IR q6h
T <sub>max</sub> (hr)	6.2±3.8	3.4±2.0
C <sub>max</sub> (mcg/ml)	7.44±7.57	1.11±0.76
C <sub>min</sub>	2.88±2.37	0.55±0.46
C <sub>avg</sub>	5.09±4.68	0.78±0.59
F <sub>0-24</sub>	0.89±0.39	0.82±0.53
AUC <sub>0-24</sub> (mcg hr/mL)	122.2±112.4	18.7±14.1
β (hr <sup>-1</sup> )	0.108±0.050	0.127±0.033
T <sub>1/2</sub> (hr)	8.0±4.1	5.9±0.1.7

**Table 45 95% CI for the ratio of central values of C<sub>min</sub> and C<sub>max</sub> for A-66193 [Study M95-264]**

	Test regimen	Reference regimen	Point estimate	*95% CI
C <sub>max</sub>	Zileuton ER	Zileuton IR	4.460	3.133-6.349
C <sub>min</sub>	Zileuton ER	Zileuton IR	5.760	4.175-7.947

\* antilogarithm of the difference of the least squares means for logarithms

**Table 46 90% CI for the bioavailability of A-66193 [Study M95-264]**

	Test regimen	Reference regimen	Point estimate	*95% CI
AUC <sub>0-24</sub> (mcg hr/mL)	Zileuton ER	Zileuton IR	5.77	4.440-7.500

#### 10.3.6.3 Safety

Eight subjects reported 18 AEs during the course of the study. The most commonly reported AE was headache (2 subjects, 8.3%). Two subjects had changes in laboratory values that were deemed clinically significant by the investigator.

#### 10.3.7 Study summary

Zileuton ER reaches T<sub>max</sub> more slowly as expected. Bioavailability of zileuton ER (Formulation H) is significantly reduced in comparison to the zileuton IR formulation, based on AUC<sub>0-24</sub> measurements. A-66193 metabolite levels are significantly higher after administration of the CR formulation, presumably secondary to longer gastrointestinal transit times.

## 10.4 Review of Individual Study Reports: Protocol Study M96-556

### 10.4.1 Study administrative information

Study start date: October 1996  
Study site: USA  
Study report: CRTX Volume 53

### 10.4.2 Objective/rationale

To evaluate the effect of food, high fat and low fat, on zileuton pharmacokinetics from a 600mg CR (Formulation H) tablet relative to zileuton IR (Zyflo).

### 10.4.3 Study design

Phase 1, single-dose, randomized, open-label, 4-period, fasting and non-fasting single-center study with a minimum of a 6-day washout interval between doses of successive periods.

### 10.4.4 Study population

Twenty-four healthy male (n=12) and female (n=12) subjects. All subjects completed all 4 periods of the study. The ages ranged from 19 to 45 years (mean = 33 years).

### 10.4.5 Study treatments

- 2 x 600mg zileuton ER tablets (1200 mg) administered as single dose under fasting conditions
- 2 x 600mg zileuton ER tablets (1200 mg) administered as single dose under non-fasting, high-fat conditions
- 2 x 600mg zileuton ER tablets (1200 mg) administered as single dose under non-fasting, low-fat conditions
- 1 x 600mg zileuton IR tablet (600 mg) administered as a single dose under fasting conditions, followed by a second dose at 6 hours

### 10.4.6 Results

#### 10.4.6.1 PK

Blood samples were collected prior to dosing (0 hour) 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 after dosing in each period. Plasma samples were analyzed for zileuton and N-dehydroxyzileuton (A-66193).

##### *10.4.6.1.1 PK parameters of zileuton*

Parameter	CR fasting	CR high-fat	CR low-fat	IR fasting
T <sub>max</sub> (h)	1.9±1.0	4.3±2.9	2.5±0.9	1.7±1.0
AUC <sub>0-last</sub> (µg.hr/ml)	29.36±10.25	41.98±14.29	30.45±13.52	51.91±16.73
C <sub>max</sub> (µg/ml)	4.39±1.76	5.22±2.16	4.73±1.30	6.68±2.60

#### 10.4.6.1.2 90% CI for the ratio of the CR formulation relative to the reference IR tablet

Parameter	Test	Reference	Point estimate	90% CI
C <sub>max</sub>	CR fasting	IR fasting	0.327	(0.286, 0.374)
C <sub>max</sub>	CR high-fat		0.397	(0.347, 0.454)
AUC <sub>0-∞</sub>	CR fasting		0.569	(0.530, 0.612)
AUC <sub>0-∞</sub>	CR high-fat		0.810	(0.754, 0.871)

#### 10.4.6.2 Safety

Seven subjects reported 10 AEs during the study. The most frequently reported AE was headache (n=3). All events resolved without treatment except for one patient who required treatment with a cool compress for headache. One subject experienced a 2.3-fold increase from baseline ALT.

#### 10.4.7 Study summary

Greater bioavailability of zileuton ER was observed under high-fat, fed conditions versus fasting (81% versus 57% of zileuton IR). Based on 90% CI for C<sub>max</sub> and AUC ratios, zileuton ER and zileuton IR are not equivalent. The bioavailability of zileuton ER is less than that of zileuton IR.

### 10.5 Review of Individual Study Reports: Protocol Study CTI-03-C05-102

#### 10.5.1 Study administrative information

Starting date: December 9, 2005

Study site: USA

Study report: CRTX Volume 59

#### 10.5.2 Objective/rationale

To compare the bioavailability after a single dose of zileuton ER 600 mg tablets (Formulation E21) administered under fasting and non-fasting conditions with that of zileuton IR under non-fasting conditions.

#### 10.5.3 Study design

Phase 1, randomized, single-center, single-dose, open-label, 3-period crossover study, with a minimum washout period of 6 days between periods.

### 10.5.4 Study population

Twenty-four healthy male (n=12) and female (n=12) subjects enrolled.

### 10.5.5 Study treatments

- 2 x 600mg zileuton ER tablets administered as a single dose under non-fasting conditions
- 2 x 600mg zileuton ER tablets administered as a single dose under fasting conditions
- 1 x 600mg zileuton IR tablet administered as a single dose under fasting conditions, followed by a second 600mg tablet at 6 hours

Each dose was administered with 180ml water. Each subject received 1200mg of zileuton per period.

### 10.5.6 Results

#### 10.5.6.1 Patient demographics and disposition

Twenty-three of 24 subjects enrolled completed all 3 periods and are included in the analysis. The mean age ranged from 20 to 55 years (mean 32.5 years).

#### 10.5.6.2 PK

Blood samples were collected prior to the AM dose on Days 1 through 5 of each study period. Additional samples were collected at 5 minutes prior to the AM dose (0 hour) 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 after dosing in each study period. Samples were analyzed for zileuton and N-dehydrozileuton (A-66193).

##### 10.5.6.2.1 PK parameters of zileuton [Item 8.7, Vol 73, P 100]

Parameters	Zileuton ER, fasting (N=23)	Zileuton ER, non-fasting (N=23)	Zileuton IR (N=23)
T <sub>max</sub> (h)	2.13±2.14	4.34±3.98	1.30±0.56
C <sub>max</sub> (mcg/ml)	3.11±0.87	3.67±1.46	5.57±1.82
AUC <sub>(0-∞)</sub> (mcg.hr/ml)	22.46±6.81	29.67±7.74	39.32±9.77
AUC <sub>(0-10)</sub> (mcg.hr/ml)	22.33±6.26	30.01±7.96	39.06±9.68
CL/F (ml/min)	956.27±236.71	714.26±195.54	542.64±133.04
T <sub>1/2</sub> (hr) <sup>a,b</sup>	-	-	2.24±0.47

<sup>a</sup> N=22 since elimination rate constant was not estimable after administration of regimen C for Subject 020

<sup>b</sup> Elimination rate constants could not be estimated for all subjects receiving CR formulations; elimination rate constants estimated from regimen C were used for all subjects

<sup>c</sup> After the first 600mg dose

##### 10.5.6.2.2 90% CI for the ratios of zileuton ER to zileuton IR under non-fasting conditions relative to fasted conditions

Table 50 90% CI for the ratios of zileuton ER (Formulation E21) to zileuton IR under fed and fasting conditions [Study CTI-03-C05-102]				
Parameter	Regimen		Ratio of means (N=24)	
	Test	Reference	Point estimate	90% CI
$C_{max}$ ( $\mu\text{g/ml}$ )	CR fast	IR fast	0.283	(0.248, 0.324)
$C_{min}$ ( $\mu\text{g/ml}$ )			0.562	(0.519, 0.609)
AUC ( $\mu\text{g hr/ml}$ )			0.567	(0.522, 0.615)
$C_{max}$ ( $\mu\text{g/ml}$ )	CR fed	IR fast	0.328	(0.287, 0.375)
$C_{min}$ ( $\mu\text{g/ml}$ )			0.751	(0.693, 0.814)
AUC ( $\mu\text{g hr/ml}$ )			0.761	(0.701, 0.826)
$C_{max}$ ( $\mu\text{g/ml}$ )	CR fed	CR fast	0.863	(0.775, 0.987)
$C_{min}$ ( $\mu\text{g/ml}$ )			0.749	(0.691, 0.811)
AUC ( $\mu\text{g hr/ml}$ )			0.745	(0.686, 0.808)

### 10.5.6.3 Safety

Adverse events were reported in all dosing periods: 3 subjects (13.0%) after zileuton ER non-fasting, 5 subjects (20.8%) after zileuton ER fasting, and 10 subjects (41.7%) after zileuton IR. The most common AE was headache. One SAE (severe slipped disc) was reported during the study. No deaths were reported, and no subjects discontinued from the study.

### 10.5.7 Study summary

The bioavailability of zileuton ER compared to zileuton IR increased from 57% to 76% when taken in conjunction with a meal, indicating a significant food effect. Ninety percent confidence intervals for  $C_{min}$ ,  $C_{max}$  and AUC fell outside of the range of 0.80 to 1.20, demonstrating the zileuton ER (Formulation E21) is not equivalent to (less than) the zileuton IR formulation.

## 10.6 Review of Individual Study Reports: Protocol Study CTI-03-C05-103

### 10.6.1 Study administrative information

Study dates: December 16, 2005

Study site: USA

Study report: Volume 64

### 10.6.2 Objective/rationale

To compare the bioavailability after multiple doses of zileuton ER 600 mg tablets (Formulation E21) administered under fasting and non-fasting conditions with that of zileuton IR under non-fasting conditions.

### 10.6.3 Study design

Phase 1, randomized, single-center, multiple-dose, 3-period crossover study.

#### 10.6.4 Study population

Thirty healthy male (n=18) and female (n=12) subjects enrolled.

#### 10.6.5 Study treatments

- 2 x 600mg zileuton ER tablets q12h for 12 consecutive doses under non-fasting conditions
- 2 x 600mg zileuton ER tablets q12h under fasting conditions
- 1 x 600mg zileuton IR tablet q6h under non-fasting conditions

Each dose administered with 180ml water. Each subject received 2400mg zileuton during each 24-hour period for 6 days.

#### 10.6.6 Results

##### 10.6.6.1 Patient demographics and disposition

Twenty-four of 30 subjects enrolled completed all 3 periods and are included in the analysis. The mean age ranged from 19 to 56 years (mean 33.5 years).

##### 10.6.6.2 PK

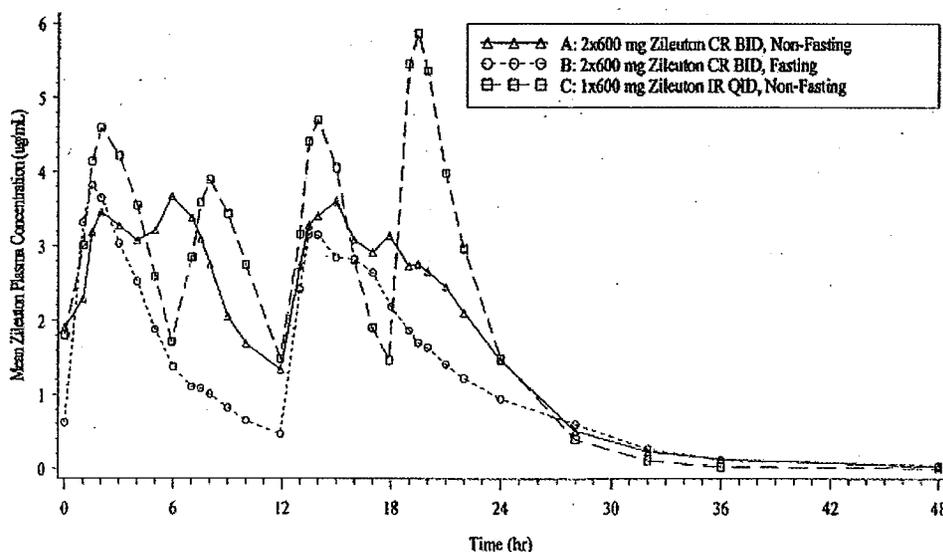
Blood samples were collected prior to the AM dose on Days 1 through 5 of each study period. Additional samples were collected at 5 minutes prior to the AM dose (0 hour) and at 1, 1.5, 2, 3, 4, 5, 6, 7, 7.5, 8, 9, 10, 12, 13, 13.5, 14, 15, 16, 17, 18, 19, 19.5, 20, 21, 22, 24, 28, 32, 36, and 48 hours after the 7 AM dose on Day 6 in each study period. Samples were analyzed for zileuton and N-dehydrozileuton (A-66193).

##### 10.6.6.2.1 PK parameters of zileuton [Item 8.7, Vol 73, P 105]

Parameters	Zileuton ER, non-fasting (N=24)	Zileuton ER, fasting (N=24)	Zileuton IR (N=24)
T <sub>max</sub> (h)	3.57±2.35	2.12±1.42	1.63±0.82
AUC (mcg.hr/ml)	63.99±15.95	44.85±12.59	77.42±21.36
C <sub>max</sub> (mcg/ml)	4.97±1.34	4.59±1.42	7.72±2.43
C <sub>min</sub> (mcg/ml)	1.00±0.45	0.37±0.17	0.99±0.38
C <sub>am</sub> trough (mcg/ml)	1.91±0.71	0.63±0.56	1.80±0.64
C <sub>avg</sub> (mcg/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±33.83
FI	1.50±0.33	2.27±0.34	2.19±0.83
T <sub>1/2</sub> (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

##### 10.6.6.2.2 Concentration-time profile for plasma zileuton

Figure 4 Concentration-time profile for plasma zileuton [Study CTI-03-C05-103]



10.6.6.2.3 90% CI for the ratios of zileuton ER to zileuton IR under non-fasting conditions relative to fasted conditions

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

10.6.6.3 Safety

Adverse events were reported in all dosing periods: 6 subjects (21.3%) after zileuton ER non-fasting, 5 subjects (17.9%) after zileuton ER fasting, and 9 subjects (33.3%) after zileuton IR. The most common AE was rash [3 subjects (zileuton IR)], followed by nasal congestion and pharyngolaryngeal pain [2 subjects (zileuton CR, non-fasting)]. No SAEs or deaths were reported. Three subjects discontinued due to AEs, 2 after receiving zileuton IR and 1 after receiving zileuton ER non-fasting.

### 10.6.7 Study summary

The bioavailability of zileuton ER compared to zileuton IR increased from 59% to 85% when taken in conjunction with a meal, indicating a significant food effect. Ninety percent confidence intervals for  $C_{max}$  and AUC fell outside of the range of 0.80 to 1.20, demonstrating the zileuton ER (Formulation E21) is not equivalent to the zileuton IR formulation. Overall, the bioavailability of zileuton ER (Formulation E21) is less than that of zileuton IR.

### 10.7 Line-by-Line Labeling Review

The proposed label was submitted in the new format. Recommended changes in the proposed labeling are shown below. Labeling discussions are pending at the time of this review.

12 Page(s) Withheld

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

✓ § 552(b)(4) Draft Labeling

       § 552(b)(5) Deliberative Process

Clinical Review  
Susan Limb, MD  
NDA 22-052, N000  
Zyflo XR, Zileuton Extended-release 600-mg Tablet

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## **11 REFERENCES**

No references are included in this review.

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## 1. GENERAL INFORMATION AND BACKGROUND

Zyflo (zileuton) is a leukotriene synthesis inhibitor that specifically blocks 5-lipoxygenase activity. Zyflo is currently approved for the prophylaxis and treatment of chronic asthma in adults and children ages 12 and older. The current formulation is a 600mg-tablet that is taken 4 times a day, with or without food. Previously, Abbott Laboratories, initiated a development plan for a controlled-release formulation, culminating in two Phase 3 studies with a specific zileuton CR formulation (Formulation H). Abbott later terminated its zileuton CR development program and did not file an NDA application. Subsequently, Critical Therapeutics acquired ownership of both Zyflo and zileuton CR. The new sponsor has modified Abbott's original Formulation H and developed a new controlled-release product, \_\_\_\_\_, which is to be administered as two 600-mg tablets twice daily, within one hour of a meal, for a total daily dosage of 2400mg. The controlled-release formulation features the Geomatrix system consisting of three layers: a fast release layer, a barrier layer, and a slow-release layer. The system allows for immediate release of approximately \_\_\_\_\_% of the dose, followed by \_\_\_\_\_ controlled release over a period of \_\_\_\_\_ hours.

The text from the proposed INDICATIONS AND USAGE section of the label follows: "\_\_\_\_\_ is indicated for the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older." The proposed indication is the same indication carried by the reference product, immediate-release zileuton (Zyflo).

The 505(b)(1) application is a paper submission.

## 2. CLINICAL DEVELOPMENT PROGRAM

The sponsor's drug development program relies on the Agency's previous findings of efficacy and safety of the approved reference product, zileuton immediate-release (Zyflo), and Phase 2 comparisons of bioavailability and bioequivalence of the new drug, zileuton controlled-release (\_\_\_\_\_), to the reference product. In addition, the sponsor has provided reports for a 12-week clinical efficacy study (M95-337) and a 6-month long-term safety study (M96-464) to support the efficacy and safety of the proposed product. These studies are described in more detail in a later section of this review.

Eleven bioavailability studies were performed, including the following 2 studies relating the proposed controlled-release formulation to the approved immediate-release product. These studies are reviewed in greater detail later in this document:

1. CTI-03-C04-102, a randomized, open-label, crossover single dose study (N=24) comparing zileuton immediate-release (IR) to zileuton controlled-release (CR) in fasting and non-fasting states.
2. CTI-03-C04-103, a randomized, open-label, crossover multiple dose (N=30) comparing zileuton IR to zileuton CR in fasting and non-fasting states.

The table below outlines key clinical pharmacology studies and the two Phase 3 trials in the clinical development program:

\* (600mg zileuton controlled-release tablets)

Table I Summary of Clinical Development Program for Zileuton CR						
Study No.	Description	Subjects	Design	Dose	Duration	Relevance
<b>Phase 1</b>						
6 exploratory PK studies conducted under original IR IND and determined administering zileuton in fed condition preferable						
M95-266	PK					older formulation
M95-264	PK – fed	24	SC, R, OL, 2 way XO	Zileuton CR H 1200mg Zileuton IR 600mg QID	6 days	Links P3 clinical formulation to IR
M96-556	PK – fed and fasting	24	SC, R, OL, 4-way XO	Zileuton CR H 1200mg (fasting) Zileuton CR H 1200mg (fed) Zileuton IR 600mg (fasting) 2 doses	Single dose	Links P3 clinical formulation to IR
M97-742	PK – fed (dissolution)	22	SC, R, OL, 4 way XO	Zileuton CR H (3 formulation with different dissolutions) 600mg Zileuton IR 600mg (fed)	Single dose	Links P3 clinical formulation to IR; dissolution
CTI-03-C04-101	PK – fed and fasting	11	SC, R, OL, 3-way XO with additional 4 <sup>th</sup> period	Zileuton CR S6 (fasting) 600mg Zileuton CR S6 (fed) Zileuton E21 (fasting) Zileuton E21 (fed) Zileuton IR 600mg (fasting)	Single dose	
CTI-03-C05-102	PK – fed and fasting	24	SC, R, OL, 3-way XO	Zileuton CR E21 (fasting) – 1200mg Zileuton CR E21 (fed) – 1200mg Zileuton IR (fasting) – 600mg (2 doses)	Single dose	BA between IR and to be marketed product
CTI-03-C05-103	PK – Fed and fasting	30	SC, R, OL, 3-way XO	Zileuton CR E21 (fasting) – 1200mg BID Zileuton CR E21 (fed) – 1200mg BID Zileuton IR (fed) – 600mg QID	6 days	BA between IR and to be marketed product
<b>Phase 3</b>						
M95-337A	Efficacy, Safety Fed conditions	591 subjects with asthma 12 yrs and older	MC, R, DB, PG, PC	Zileuton CR H 1200mg BID Zileuton CR placebo Zileuton IR 600mg QID Zileuton IR placebo  IR arm for benchmark for safety and efficacy – not necessary to power for equivalence	12 weeks	Pivotal - efficacy and safety info Abbott H formulation
M96-464A	Safety, Efficacy Fed conditions	926 subjects with asthma 12 yrs and older	MC, R, DB, PC, PG	Zileuton CR H 1200mg BID Placebo	6 months	Pivotal – safety and some efficacy info Abbott H formulation

### 3. FOREIGN MARKETING AND REGULATORY HISTORY

No application for approval for marketing of controlled-release zileuton has been made in any foreign country [Vol 2, P 337].

Zileuton IR 600mg QID has been approved for the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older in the United States since December 9, 1996 (NDA 20-471).

Six initial exploratory studies to develop a controlled-release formulation were performed under IND 30661 for zileuton IR. On March 1995, IR Abbott Laboratories in collaboration with Skye Pharma AG, Switzerland, submitted IND 47561 to develop a zileuton CR tablets. Abbott conducted several bioavailability studies as well as two Phase 3 studies in asthmatic patients using a zileuton CR tablet (Formulation H).

In December 2004, Critical Therapeutics (CRTX) acquired ownership of zileuton CR tablets and IND 47561 was transferred to CRTX on February 9, 2004 (S-047). In March 2004, CRTX also acquired ownership of zileuton IR (Zyflo), and NDA 20471 was transferred to CRTX on July 29, 2004.

A pre-NDA meeting was held with the sponsor on May 2, 2005 (Meeting minutes and Medical Officer Review, IND 47561). Several major issues were raised regarding the proposed drug product: 1) potential difficulty bridging the CRTX zileuton CR product to the former Abbott Formulation H product as Formulation H was no longer available, and 2) difficulty verifying data collected previously from pivotal phase 3 studies conducted by Abbott. As the studies had been conducted several years before, some study sites were no longer available for auditing and investigator debarments put data integrity into question.

In March 2005, CRTX also submitted a supplemental NDA to change manufacturing sites and the synthetic process for both the proposed drug substance and zileuton IR. The sNDA was approved on September 28, 2005.

#### **4. ITEMS REQUIRED FOR FILING AND REVIEWER COMMENTS (21 CFR 314.50)**

The following items were included in this submission:

- Form FDA 356h [Vol 1]
- Debarment certification [Vol 1 Item 16]
- Financial disclosure statement [Vol 1 Item 19]
- Statements of Good Clinical Practice [Item 8.2, Vol 73, P 11]
- Integrated Summary of Effectiveness (ISE) [Item 8.11, Vol 122, P 1]
  - Overview of clinical studies [Item 8.11, Vol 122, P 19]
  - Definition of ISE analysis populations [Item 8.11, Vol 122, P 22]
  - Design of controlled clinical studies [Item 8.11, Vol 122, P 24]
  - Statistical methodology [Item 8.11, Vol 122, P 27]
  - Patient enrollment. Study M95-337 and M96-464 [Item 8.11, Vol 122, P 28]
  - Study results [Item 8.11, Vol 122, P 29]
  - Evidence for an effective dosing regimen [Item 8.11, Vol 122, P 95]
  - Conclusions [Item 8.11, Vol 122, P 96]
- Integrated Summary of Safety (ISS) [Item 8.12, Vol 124, P1]:
  - Overview of clinical studies [Item 8.12, Vol 124, P 27]

- Definitions of ISS analysis populations [Item 8.12, Vol 124, P41]
- Methodology for evaluation of safety [Item 8.12, Vol 124, P47]
- Phase 3 integrated safety analysis [Item 8.12, Vol 124, P71]
- Phase I final formulations studies and phase I exploratory formulations [Item 8.12, Vol 124, P 155]
- Adverse events including laboratory abnormalities, from sources other than clinical studies [Item 8.12, Vol 124, P 173]
- Animal data [Item 8.12, Vol 124, P 174]
- Analysis of adverse effect dose-response information [Item 8.12, Vol 124, P 178]
- Drug-drug interactions [Item 8.12, Vol 124, P 180]
- Drug-demographic and drug-disease interactions [Item 8.12, Vol 124, P183]
- Pharmacologic properties other than the property of interest [Item 8.12, Vol 124, P 187]
- Long-term adverse events [Item 8.12, Vol 124, P189]
- Withdrawal effects [Item 124, Vol 124, P191]
- Review of the literature for safety information relevant to zileuton [Item 8.12.16, Vol 125]
- Proposed labeling and annotated labeling [Item 3.1, Vol 1].
- Integrated summary of benefits and risks [Item 8.13, Vol 133, P 1]
- Overdose and drug abuse information [Item 8.14, Vol 140, P 124]
- Case report tabulations [Item 11, Vols 207 and 253] and forms for patients with serious adverse events or discontinuing studies [located on Study Disks]
- Environmental assessment [Item 4R4P, Vol 3, P 308]
- Request for waiver and deferral of pediatric studies [Item 8.15, Vol 140, P 125]
- Pharmacokinetic studies in special populations (geriatric, pediatric, gender, race, body size, renal impairment, hepatic impairment) [Item 8.7, Vol 73, P 27]
- Pharmacovigilance and Risk Minimization Action Plan (for transaminitis, hepatic toxicity) [Item 8.13, Vol 140, P 88-123; Statistical plan Item 10.13.7, Vol 206, P 88-123]

*Reviewer's comment: Only brief summary of drug-demographic information included.*

## 5. CLINICAL STUDIES

The submission refers to 6 exploratory bioavailability studies of different controlled-release formulations of zileuton CR conducted by Abbott in Europe or under IND 30661. Under IND 47561, Abbott conducted a study examining bioavailability after single dose (M95-266), multiple doses (M95-264), and food effect following single dose (M96-556) of Formulation H (zileuton CR). Formulation H was also used in a biopharmaceutical study (M97-742) to establish correlation between in vitro and in vivo release. In addition, safety and efficacy of Formulation H were studied in 12-week clinical efficacy study (M95-337) and a 6-month long-term safety study (M96-464).

CRTX developed Formulation S6, identical to Abbott's Formulation H, and then Formulation E21 with a modified barrier layer to improve the consistency and dissolution profile of the tablet. CRTX has subsequently performed three bioavailability studies

using zileuton CR Formulation E21. Per the sponsor, CRTX, Formulation E21 and Abbott's Formulation H used in the Phase 3 studies have comparable dissolution profiles. Study CTI-03-C04-101 was a pilot bioavailability study examining in vivo release profiles of E21 compared to zileuton IR. Study CTI-03-C04-102 compared single-dose zileuton IR to zileuton CR in fasting and non-fasting states. Study CTI-03-C04-103 compared multiple doses of zileuton IR to zileuton CR in fasting and non-fasting states.

The clinical review of efficacy and safety of the proposed product will focus on the two Phase 3 trials, the single-dose and multiple-dose bioavailability studies of zileuton CR (CTI-03-C04-102 and CTI-03-C04-103), and previous safety information obtained from the approved reference product, zileuton IR. The study reports and synopses are appropriately indexed to allow review.

### 5.1 Study CTI-03-C04-102

Study CTI-03-C04-102 was a randomized, open-label, three-way crossover, single-center trial (N=24) comparing bioavailability of zileuton CR (Formulation E21) to zileuton IR (Zyflo) under fasting and non-fasting conditions. Single-dose (2 x 600mg tablets) zileuton CR was compared to two 600mg doses of zileuton IR administered 6 hours apart. The study concluded that mean  $T_{max}$  for zileuton CR was significantly longer than for zileuton IR; AUC and  $C_{max}$  were lower for zileuton CR than zileuton IR. The bioavailability of zileuton CR was increased after a high-fat meal compared to fasting states, as had been previously observed in Study M96-556, Abbott's Phase 3 study using Formulation H. Historical comparison of CRTX Formulation E21 to Abbott's Formulation H showed a lower mean  $C_{max}$  and AUC for Formulation E21. The sponsor reports that the lower bioavailability is secondary to temporal effects.

Subjects in this study were allocated to the following regimens:

- A: 2 zileuton CR 600mg tablets (E21); single dose under fasting conditions
- B: 2 zileuton CR 600mg tablets (E21); single dose under non-fasting conditions
- C: 1 zileuton IR 600mg tablet (Zyflo) ; two doses separated by 6 hours under fasting conditions

PK parameters [Item 8.7, Vol 73, P 100]

Parameters	Zileuton CR, fasting (N=23)	Zileuton CR, non-fasting (N=23)	Zileuton IR (N=23)
$T_{max}$ (h)	2.13±2.14	4.34±3.98	1.30±0.56
$C_{max}$ (mcg/ml)	3.11±0.87	3.67±1.46	5.57±1.82
AUC <sub>(0-t)</sub> (mcg.hr/ml)	22.46±6.81	29.67±7.74	39.32±9.77
AUC <sub>(0-inf)</sub> (mcg.hr/ml)	22.33±6.26	30.01±7.96	39.06±9.68
CL/F (ml/min)	956.27±236.71	714.26±195.54	542.64±133.04
$T_{1/2}$ (hr) <sup>a,b</sup>	-	-	2.24±0.47

<sup>a</sup> N=22 since elimination rate constant was not estimable after administration of regimen C for Subject 020

<sup>b</sup> Elimination rate constants could not be estimated for all subjects receiving CR formulations; elimination rate constants estimated from regimen C were used for all subjects

<sup>c</sup> After the first 600mg dose

### 5.2 Study CTI-03-C04-103

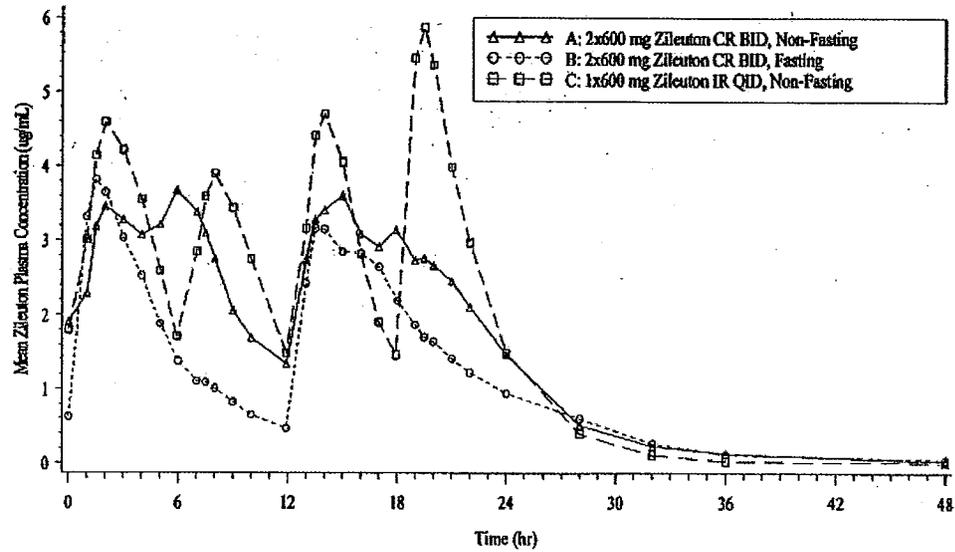
Study CTI-03-C04-103 was a randomized, open-label, three-way crossover, single-center trial (N=30) comparing bioavailability of multiple, repeated doses of zileuton CR (Formulation E21) to zileuton IR (Zyflo) under fasting and non-fasting conditions over 6 days. In this study, 1200mg (2 x 600mg tablets) zileuton CR were administered every 12 hours for 12 consecutive doses; 600mg zileuton IR were administered every 6 hours for 24 consecutive doses. As in the previous study, bioavailability for zileuton CR was increased in non-fasting conditions. According to the sponsor's report, zileuton CR demonstrated a stable controlled-release profile with no dose-dumping characteristics. After multiple doses, the mean  $T_{max}$ ,  $C_{max}$ ,  $C_{min}$ , and AUC values of an inactive metabolite, A-66193, were significantly higher after zileuton CR administration compared to IR. The safety of the inactive metabolite has been evaluated in previous animal studies, genotoxic studies, and a Phase 3 clinical study in patients with asthma.

Subjects were randomized to one of the following 3 regimens:

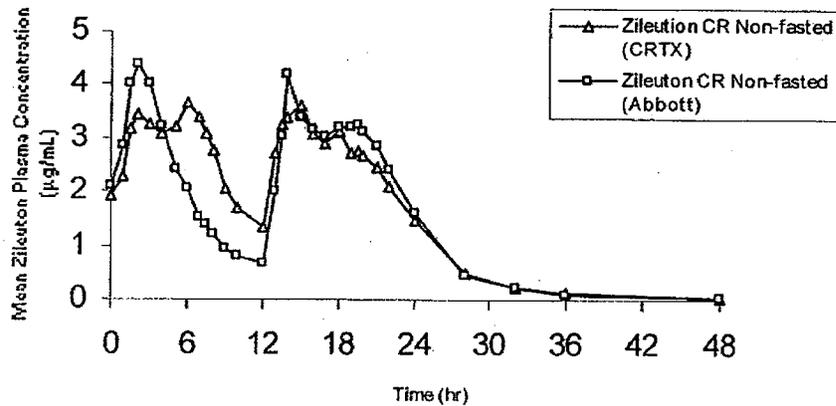
- A: 2 zileuton CR 600mg tablets (E21) Q12h for 12 consecutive doses (6 days) under non-fasting conditions
- B: 1 zileuton CR 600mg tablets (E21) Q12h for 12 consecutive doses under fasting conditions
- C: 1 zileuton IR 600mg tablet (Zyflo) Q6h for 24 consecutive doses under non-fasting conditions
- PK parameters [Item 8.7, Vol 73, P 105]

Parameters	Zileuton CR, non-fasting (N=24)	Zileuton CR, fasting (N=24)	Zileuton IR (N=24)
$T_{max}$ (h)	3.57±2.35	2.12±1.42	1.63±0.82
AUC (mcg.hr/ml)	63.99±15.95	44.85±12.59	77.42±21.36
$C_{max}$ (mcg/ml)	4.97±1.34	4.59±1.42	7.72±2.43
$C_{min}$ (mcg/ml)	1.00±0.45	0.37±0.17	0.99±0.38
$C_{am}$ trough (mcg/ml)	1.91±0.71	0.63±0.56	1.80±0.64
$C_{avg}$ (mcg/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±33.83
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

- Mean concentration-time profiles for plasma zileuton: zileuton CR (E21) in fasting and non-fasting states and zileuton IR [Item 8.7, Vol 73, P 105]



- Historical comparison of mean concentration-time profiles for plasma zileuton CR in non-fasted state: Formulation H (Abbott) versus Formulation E21 (CRTX) [Item 8.7, Vol 73, P 109]



Reviewer's comment: The data for the chart is derived from two separate studies superimposed on one another. Bioequivalence of Formulation E21 to Formulation H, the zileuton CR formulation used in the two Phase 3 trials, is established primarily through indirect, cross-study comparison. In general, preliminary review of the PK data suggests less exposure from the CRTX Formulation E21 compared to zileuton IR.

### 5.3 Study M95-337

Study M95-337 was a randomized, double-blind, placebo-controlled, multicenter, parallel group, 12-week efficacy study in subjects with asthma conducted by Abbott. Five-hundred ninety-one subjects, ages 12 to 81 years, were randomized to receive zileuton CR [Formulation H], active control (zileuton IR), or placebo (CR or IR placebo). Zileuton IR was included as a benchmark comparator to provide a link to two Phase 3

zileuton IR studies. After a 14-day run-in period, subjects were randomized into a double-blind, 12-week treatment period and were administered zileuton CR 1200mg (2 x 600mg tablets) BID, zileuton CR placebo BID, zileuton IR 600mg (1 x 600mg tablet) QID, or zileuton IR placebo QID. After completion of treatment, subjects were followed for an additional 2-week run-out period off study drug. The primary efficacy variable was trough FEV1. Secondary efficacy variables were AM and PM peak expiratory flow rates, beta-agonist use, daily and nocturnal symptom scores, acute exacerbations of asthma, and asthma quality-of-life (QOL) measures. Safety assessments included adverse event monitoring, clinical laboratory measurements, vital signs, and physical exams.

Results for the primary and secondary efficacy endpoints are summarized in the table below. Similar trends were observed from multiple analyses using the full and restricted data sets (see Section 7: DSI Review/Audit).

Primary and secondary efficacy endpoints for 12-week Study M95-337

Efficacy endpoint	2x600mg tablets BID		Placebo		P
	Mean baseline	Mean change	Mean baseline	Mean change	
Trough FEV1 (L)	2.17	0.39	2.2	0.27	0.021
AM PEFr (L/min)	369.73	58.45	353.86	43.36	0.147
PM PEFr (L/min)	397.92	56.24	386.8	36.95	0.083
SABA use (puffs/day)	5.99	-0.96	5.96	-0.31	0.009
Daily sx score (0-3)	1.42	-0.32	1.41	-0.29	0.585
Nocturnal sx score (0-3)	1.37	-0.42	1.32	-0.45	0.752
# patients ≥1 exacerbation	92 (46.23%)		105 (53.03%)		0.173
Asthma QOL questionnaire	4.02	0.86	4.06	0.68	0.102

The overall incidence of AEs was similar in all treatment groups. The rate of ALT elevations in subjects receiving zileuton CR (2.5%) was slightly higher than the rate observed in the zileuton IR group (2.1%) or the rate observed in previous zileuton IR placebo-controlled studies (1.9%). Based on these study results, the sponsor has concluded that zileuton CR has a similar efficacy and safety profile as zileuton IR.

5.4 Study M96-464

Study M96-464 was a randomized, double-blind, multicenter, parallel group, 6-month safety study. Nine-hundred twenty-six subjects, ages 12 to 83 years, received either zileuton CR [Formulation H] 1200mg BID or placebo in addition to their usual asthma care regimen. Subjects enrolled in the study were permitted to continue inhaled corticosteroids, cromolyn, short-acting beta-agonists, nasal steroids, and nedocromil. Theophylline, long-acting beta-agonists, and other leukotriene modifiers were not allowed. The primary endpoint was ALT elevations. Other safety endpoints included adverse events, other laboratory measurements, vital signs, and physical exams. Co-primary efficacy endpoints were trough FEV1 and PEFr; secondary efficacy endpoints included beta-agonist use, frequency of asthma exacerbations, time to first exacerbation, and asthma QOL measures. Results for major efficacy endpoints are summarized in the table below.

Primary and secondary efficacy endpoints for 6-month Study M96-464

Efficacy endpoint	2x600mg tablets BID		Placebo		P
	Mean baseline	Mean change	Mean baseline	Mean change	
Trough FEV1 (L)	2.52	0.17	2.52	0.13	0.260
AM PEFr (L/min)	388.83	55.41	388.27	30.38	<0.001
PM PEFr (L/min)	420.88	38.98	414.83	21.83	0.023
SABA use (puffs/day)	4.67	-0.23	5.09	-0.30	0.727
# patients $\geq$ 1 exacerbation	213 (34.41%)		119 (38.76%)		0.168
Asthma QOL questionnaire	4.66	0.71	4.62	0.57	0.083

Overall incidence of adverse events was 86.9% for zileuton CR and 84.7% for placebo). The most commonly reported AEs were asthma exacerbation, headache, and nasopharyngitis. The zileuton CR treatment group had a 50% higher incidence of reported GI disorders, including nausea (9.2 vs. 5.9%), diarrhea (5.3 vs. 2.3%), and vomiting (5.0 vs. 2.0%). The ALT elevation rate ( $\geq$ 3x upper limit of normal) was 1.78%, similar to the rate observed in zileuton IR placebo-controlled studies (1.9%). The ALT elevations occurred most often in the first 3 months of treatment. Leukopenia was also reported more frequently in the zileuton CR group compared to placebo (2.6 vs. 1.7%). Several cases were considered spurious lab findings or resolved while the subject remained on the drug. In 6 patients (1%), the leukopenia was attributed to zileuton CR. Two of these 6 stopped the study secondary to leukopenia, 2 discontinued the secondary to other AEs, and the final 2 completed the study. Five patients in the zileuton CR group required hospitalization for asthma and 16 patients required an ER visit; in comparison, 0 patients in the placebo group required hospitalization and 10 required ER care. These differences were not statistically significant. Based on these results, the sponsor has concluded that zileuton CR, when added to usual care, is generally well tolerated by patients for up to 6 months with a safety profile comparable to zileuton IR.

*Reviewer's comment: Per preliminary statistical review, the efficacy analyses may be significantly altered by multiplicity adjustment. Also, the statistical analysis plan (SAP) for the long-term safety study was not included in the NDA submission. In addition, ALT elevations are designated as the primary endpoint although the original sample size was calculated to compare rates of hospitalizations or ER visits due to asthma. Of note, there appear to be several data discrepancies. In Volume 93, P 147, the Safety Conclusions report 7 hospitalizations due to asthma in the zileuton CR group compared to N=5 reported elsewhere in the results. Also, Tables 14.2.B.11.4 and 14.2.C.6.4 report 2 versus 3 hospitalizations for Day 29.*

## 6. BRIEF REVIEW OF PROPOSED LABELING

Proposed package labeling has been included in this submission [Vol 1, Item 3.1, Labeling, P 37-59]. The sponsor seeks an indication for the prophylaxis and chronic treatment of asthma in adults and children ages 12 years and older. The proposed label is similar to that of Zyflo (zileuton IR) tablets.

1. The proposed label states that "the oral minimum lethal doses in mice and rats were 4000 and 1000 mg/kg, respectively." The Zyflo label states that "oral minimum doses in mice and rates were 500-4000 and 300-1000mg/kg in various preparations, respectively."
2. Under Clinical Studies, the proposed label summarize two clinical zileuton CR studies: ~~the following~~

3. ~~The following~~
4. The label should also state that ~~the product~~ should not be used in children under the age of 4 due to reduced hepatic metabolism and hematologic immaturity, as cited in the Pediatric Waiver request.

A more extensive review of the product label is to follow.

*Reviewer's comments: The proposed label follows the new content and format requirements. Additional discussion of label differences regarding non-clinical data is deferred to the Pharmacology/Toxicology team.*

## 7. DSI REVIEW/AUDIT

The sponsor's own audit of clinical study sites raised several concerns about data integrity. Of note, one of the clinical investigators, Dr. Robert Fiddes, has been subsequently debarred since the completion of Study M95-337, and another investigator, Dr. Thomas Edwards, has been placed on a restricted list. As a result and per discussion with the Division, the sponsor has generated full and restricted analysis sets for the two Phase 3 studies:

- 1) The **full analysis set for Study M95-337** comprises all patients randomized with the exception of patients enrolled by Dr. Fiddes (N=12) and Dr. Thomas Edwards (N=10).
- 2) The **restricted analysis set for Study M95-337** excludes an additional 6 clinical sites (N=57), as these sites either no longer exist or data is no longer available for audit.
- 3) The **full analysis set for Study M96-464** comprises all randomized patients.

- 4) **The restricted analysis set for Study M96-464** excludes 9 clinical sites (N=75), as these sites either no longer exist or data is no longer available for audit.

Both restricted analysis sets also exclude one patient who simultaneously participated in both Study M95-337 and M96-464. In addition, 3 sensitivity analysis sets have been defined and submitted for Study M96-337:

- 5) **Sensitivity analysis set 1** included all patients randomized into the treatment period at all study sites
- 6) **Sensitivity analysis set 2** excludes only patients enrolled by Dr. Thomas Edwards (N=10)
- 7) **Sensitivity analysis set 3** excludes only patients enrolled by Dr. Robert Fiddes (N=12)

*Reviewer's comments: Clinical review is hampered by missing source data from several study sites, including some sites which no longer exist. Preliminary statistical review does not suggest any treatment-center effect, however. The submission relies on indirect pharmacokinetic data linking the proposed controlled-release formulation (E21) to Formulation H used in the two Phase 3 studies, making bridging of the two products a significant review issue. The key pharmacokinetic studies sponsored by CRTX were conducted by ~~\_\_\_\_\_~~ and will be the focus of a DSI audit/review.*

## **7. PEDIATRIC WAIVER REQUEST [ITEM 8.15, VOL 140, P 125]**

The submission includes a request for full waiver of pediatric requirements for zileuton CR in neonates, infants, and children up to 4 years of age, citing unpredictable hepatic metabolism and hematologic immaturity in this age group. The sponsor has also requested a deferral of PREA requirements for zileuton CR in children ages 4 to 11 years on several grounds, including difficulty in developing a suitable controlled-release dosage form for patients in this age group. To date, completed Phase 3 trials have included children down to the age of 12. A pediatric PK study of the zileuton IR formulation has been completed in children ages 9 to 12 (Study M92-752, submitted under NDA 20-471).

## **8. SUMMARY**

This is a 45-day filing and planning review of an NDA for a controlled-release formulation of zileuton. The sponsor, Critical Therapeutics (CRTX), has developed a controlled-release 600-mg zileuton tablet for twice-daily use. The proposed indication is the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. Two pivotal bioavailability studies (CTI-03-C04-102 and CTI-03-C04-103) comparing the proposed product formulation (CRTX's Formulation E21) to the currently approved zileuton IR (Zyflo), are submitted in support of this application. The sponsor has also provided reports for a 12-week clinical efficacy study (M95-337) and a 6-month long-term safety study (M96-464) using an older controlled-release formulation (Abbott's Formulation H) to support the efficacy and safety of the proposed product.

Two bioavailability studies (M96-264 and M96-556) comparing Formulation H to zileuton IR are included to link the proposed Formulation E21 to Formulation H used in the two Phase 3 studies. These study reports are appropriately indexed and organized to allow review. The sponsor has provided an Integrated Summary of Efficacy, Integrated Summary of Safety, Integrated Summary of Benefits and Risks, copies of proposed labeling, and appropriate case report forms.

The submission is adequate to allow clinical review. The submission is fileable.

## 9. COMMENTS TO THE SPONSOR

The following comment will be conveyed to the sponsor in the 74-day filing letter regarding potential review issues:

- In the absence of direct pharmacokinetic comparisons of the proposed Formulation E21 to Abbott's Formulation H used in the Phase 3 safety and efficacy studies, the bridging between the two products will be a significant review issue.

The following information request will be conveyed to the sponsor in the 74-day filing letter:

- Clarify the following discrepancies in the data presented:
  1. In Volume 93, P 147, the Safety Conclusions report 7 hospitalizations due to asthma in the zileuton CR group compared to N=5 reported elsewhere in the results.
  2. Tables 14.2.B.11.4 and 14.2.C.6.4 report 2 versus 3 hospitalizations for Day 29.

## 10. TIME LINE FOR REVIEW

The timeline for review and processing of the NDA application is as follows:

**Table 2. Proposed schedule for review of NDA 25-052**

Milestone	Target Date for Completion
74-day Letter due date	October 13, 2006
Mid-cycle review meeting	December 15, 2006
Wrap-up meeting	March 15, 2007
Primary reviews due date	March 28, 2007
Internal labeling meeting	April 13, 2007
Labeling teleconference	May 1, 2007
PDUFA due date, 10 months	May 31, 2007

Reviewed by:

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Susan Limb, M.D.  
Medical Officer, Division of Pulmonary and Allergy Drug Products

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Sally Seymour, M.D.  
Acting Medical Team Leader, Division of Pulmonary and Allergy Drug Products

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I concur

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