

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-052

MEDICAL REVIEW

TEAM LEADER'S MEMORANDUM

Date: May 3, 2007

To: NDA 22-052

From: Sally Seymour, MD
Medical Team Leader, Division of Pulmonary and Allergy Products,
CDER, FDA

Product: Zyflo XR (zileuton) Extended Release Tablets 600mg

Applicant: Critical Therapeutics

I. Administrative and Introduction

Critical Therapeutics submitted a 505(b)(1) new drug application (NDA 22-052) on July 30, 2006, for zileuton extended release (ER) tablets 600mg for the prophylaxis and chronic treatment of asthma in adults and children 12 years and older. The PDUFA due date for this application is May 31, 2007. Critical Therapeutics currently has an immediate release zileuton product (Zyflo) approved for the same indication. Thus, this NDA is for a new formulation of zileuton.

The clinical development program for zileuton extended release tablets dates back to the mid 1990s, when Abbott Laboratories conducted a 12 week clinical efficacy study and a 6 month clinical safety study with zileuton ER (formulation H). However, Abbott never filed an NDA for extended release zileuton. In 2004, Critical Therapeutics acquired ownership of zileuton IR and ER tablets, including the data from the clinical trials conducted by Abbott. However, after acquiring ownership, Critical Therapeutics changed the zileuton ER formulation to formulation E21, which is the to-be-marketed formulation. To support this NDA, Critical Therapeutics performed two additional bioavailability studies with zileuton ER (formulation E21) and zileuton IR.

Based upon the information available, Critical Therapeutics has submitted the necessary CMC, non-clinical, clinical pharmacology, and clinical data necessary to support approval of this application. Pending agreed upon labeling, the recommendation for this NDA is **Approval**.

II. Chemistry, Manufacturing, and Controls, and Establishment Evaluation

The drug substance is zileuton, which is a synthetic 5-lipoxygenase inhibitor, and is the same as the drug substance in approved Zyflo (zileuton) Tablets (NDA 20-471). The drug product is a triple-layer tablet, consisting of a fast release (FR) layer, a barrier layer that slows the release of drug substance from the third slow release (SR) layer. Each tablet contains 600mg zileuton. The FR layer contains

The SR layer is

and contains

the barrier layer contains

Zyflo XR tablets are oblong, film-coated with one red layer between two white layers, and debossed on one side with "CT2".

The FR layer disintegrates within and contains of the drug substance (— ng), while the SR layer contains the remaining of the drug substance. The drug substance is manufactured at facilities in and . The EER status is acceptable.

Issues identified by the CMC reviewer included the dissolution profile of the two formulations and the concentration of — impurities. The dissolution test method used by Abbott for formulation H was different than the dissolution test method used by Critical Therapeutics for formulation E21. Thus, there was a difference in dissolution profiles between the products: — in 6 hours for formulation H vs. — for formulation E21. Another issue noted by the CMC reviewer was the presence of — impurities in the zileuton IR formulation at a — concentration in the ER formulation: —. Based upon a pharmacology/toxicology consult, the acceptance criteria for these impurities —.

The CMC reviewer has determined that the submitted CMC program is adequate and recommends an approvable action. The CMC reviewer generated comments and deficiencies have been conveyed to the Applicant. However, none of these issues should preclude approval of the application. The Applicant has responded adequately to address the comments/deficiencies.

III. Pharmacology and Toxicology

Critical Therapeutics cross-referenced the preclinical studies submitted to support zileuton IR in NDA# 20-471. The toxicology of zileuton has been evaluated extensively to support the NDA# 20-471 for zileuton IR. For the zileuton ER NDA, Critical Therapeutics submitted some additional pharmacology studies and genotoxicity studies with a major metabolite (A-66193).

The toxicology program for zileuton has been previously reviewed in detail for NDA# 20-471. The additional non-clinical studies submitted in this NDA were reviewed in detail in the PharmTox review by Dr. Wu. The genotoxicity studies with the major metabolite, A-66193, were negative. The PharmTox team has determined that the submitted pharmacology/toxicology program is adequate and recommends an approval action.

IV. Clinical Pharmacology

Critical Therapeutics cross-referenced the clinical pharmacology studies submitted to support zileuton IR in NDA# 20-471. In addition, Critical Therapeutics submitted the results of four pivotal bioavailability studies to support this application: two

bioavailability (BA) studies conducted by Abbott with zileuton ER formulation H and zileuton IR (Studies M95-264 and M96-556); and two bioavailability studies conducted by Critical Therapeutics with zileuton ER formulation E21 and zileuton IR (Studies CTI-03-C05-102 and CTI-03-C05-103). **Because Abbott's formulation H was no longer available, a bioavailability study comparing Abbott's and Critical Therapeutics' zileuton ER formulations was not conducted.** However, Abbott and Critical Therapeutics BA studies with the respective ER formulations included zileuton IR. Therefore, while a direct comparison of the BA of the two ER formulations in one study is not available, the relative BA of each ER formulation compared to the IR formulation allows comparison of the two ER formulations. The four pivotal clinical pharmacology studies are reviewed in **Dr. Kim's clinical pharmacology review. Dr. Kim found the studies to be acceptable to support approval.** A brief summary of pertinent findings is contained in the following paragraphs.

Single Dose PK Studies

Study M96-556 was a randomized, double-blind, 4-way crossover study of single dose zileuton ER (formulation H) under fasted and fed conditions and zileuton IR (two doses) under fasted and fed conditions in 24 healthy subjects. Study CTI-03-C05-102 was a randomized, double-blind, 3 way-crossover study of zileuton ER (formulation E21) under fasted and fed conditions compared to zileuton IR under fasted conditions in 23 healthy subjects. The results of both studies showed the following: 1) food increased the BA of the ER formulation compared to fasted condition; and 2) based upon Cmax and AUC, zileuton exposure was less with either ER formulation in both the fed and fasting conditions compared to the IR formulation.

However, it is important to understand how the relative BA of the to-be-marketed formulation (E21) and the IR formulation compares to the relative BA of the Abbott formulation H used in the clinical studies and the IR formulation. A cross study comparison of the ratio of the mean key PK parameters from Studies M96-556 and CTI-03-C05-102 from **Dr. Kim's review is shown in the table below.** The cross study comparison shows that the BA of formulation E21 compared to the IR zileuton was similar to the BA of formulation H compared to the IR formulation.

Ratio of Mean Zileuton PK Parameters with 90% Confidence Intervals Study M96-556 (Abbott) and CTI-03-C05-102 (Critical Therapeutics)						
Parameters	Test	Reference	Critical Therapeutics Zileuton ER (E21) Ratio of Means (Test/Reference) n=23		Abbott Zileuton ER (H) Ratio of Means (Test/Reference) n=24	
			Point Estimate	90% CI	Point Estimate	90% CI
C _{max} (mcg/mL)	A	C/D	0.39		0.42	
AUC ₀₋₄ (mcg.h/ml)	A	C/D	0.56	(0.52, 0.61)		
AUC _{0-∞} (mcg.h/ml)	A	C/D	0.57	(0.52, 0.62)	0.57	(0.53, 0.61)
C _{max} (mcg/mL)	B	C/D	0.46		0.50	
AUC ₀₋₄ (mcg.h/ml)	B	C/D	0.75	(0.69, 0.81)		
AUC _{0-∞} (mcg.h/ml)	B	C/D	0.76	(0.70, 0.83)	0.81	(0.75, 0.87)

A=CR Fasted; B=CR Fed; C=IR Fasted (Critical Therapeutics reference); D=IR fasted (Abbott reference)
Cmax from Regimen C and D was obtained by 2xCmax after the first dose

Steady State PK Studies

Study M96-264 was a 6-day, randomized, double-blind, 2-way crossover study of zileuton ER (formulation H) under fed condition and zileuton IR under fed condition in 24 healthy subjects. Study CTI-03-C05-103 was a 6-day, randomized, double-blind, 3 way-crossover study of steady state zileuton ER (formulation E21) under fasted and fed conditions compared to zileuton IR under fasted conditions in 24 healthy subjects. The results of both studies were similar to the single dose studies in that food increased the BA of the ER formulation compared to fasted condition and zileuton exposure was less with either ER formulation compared to the IR formulation. A cross study comparison of the ratio of the mean key PK parameters from **the steady state PK studies from Dr. Kim's** review is shown in the table below. The cross study comparison shows that the BA of formulation E21 compared to the IR formulation was higher than the BA of the formulation H compared to the IR formulation. In addition, the higher Cmin of the E21 formulation compared to the formulation H suggests an improved extended release profile with the E21 formulation.

Ratio of Mean Zileuton PK Parameters with 90% Confidence Intervals Study M96-264 (Abbott) and CTI-03-C05-103 (Critical Therapeutics)						
Parameters	Test	Reference	Critical Therapeutics Zileuton ER (E21) Ratio of Means (Test/Reference) n=23		Abbott Zileuton ER (H) Ratio of Means (Test/Reference) n=24	
			Point Estimate	90% CI	Point Estimate	90% CI
C _{max} (mcg/mL)	CR	IR	0.650	(0.595, 0.710)	0.499	(0.429, 0.581)
C _{min} (mcg/mL)	CR	IR	1.046	(0.879, 1.245)	0.543	(0.420, 0.703)
AUC ₀₋₂₄ (mcg.h/ml)	CR	IR	0.846	(0.781, 0.915)	0.560	(0.503, 0.622)

Taken together, the results of the four pivotal BA studies show that zileuton ER (H and E21) has less systemic exposure than zileuton IR, which supports the safety of the ER formulation. However, because of the lower exposure, efficacy of the zileuton ER formulation is called into question and clinical data are necessary to support the efficacy of zileuton ER. Two clinical studies were conducted with the Abbott formulation (H) and the results will be discussed in the next section. However, because clinical studies were not conducted with the to-be-marketed E21 formulation, it is important to note that based upon the observed systemic exposure to zileuton at steady state, the E21 formulation would be expected to perform better than formulation H.

V. Clinical and Statistical

A. Overview of the clinical program

A clinical program for this new ER formulation of zileuton was necessary because of the decreased systemic exposure of zileuton ER compared to zileuton IR. The clinical program consisted of a 12 week efficacy and safety study (M95-337A) and a 6 month safety study (M96-464A) in patients with asthma 12 years of age and older.

Detailed review of the clinical program can be found in **Dr. Limb's medical review** with detailed statistical analysis in **Dr. Gebert's statistical review**. The clinical and statistical teams concluded that the submitted studies support efficacy and safety of zileuton ER in patients 12 years and older. I concur with that conclusion. The clinical studies

mentioned above, which have direct bearing on the approvability decision of this application are briefly reviewed in the following sections.

B. Design and conduct of the pivotal efficacy and safety studies

1. Study M95-337A – 12 Week Efficacy and Safety Study

Study M95-337A was a 12-week, randomized, double-blind, placebo-controlled, parallel group study conducted in 79 study centers in the United States in patients with asthma 12 years of age and older. Patients had an FEV₁ percent predicted 40-75%, FEV₁ reversibility of 15%, and were taking no asthma medications except a short-acting bronchodilator. A 14 day placebo run-in period (Period I) was followed by a randomized 12 week treatment period (Period II) followed by a 2 week run-out period (Period III). Patients were randomized 2:2:1:1 to receive zileuton ER 1200 mg BID, zileuton ER placebo BID, zileuton IR 600 mg QID, and zileuton IR placebo QID. The intent of Study M95-337A was to establish the efficacy of zileuton ER.

The primary efficacy variable was FEV₁. Spirometry measurements included screening, treatment days 1, 15, 29, 57, and 85 (Week 12). The primary efficacy endpoint was the mean change in trough FEV₁ from baseline at 12 weeks for zileuton ER versus placebo. There was no pre-specified statistical analysis plan from Abbott and the Applicant did not adjust for multiplicity of time points assessed during the 12-week course of the study. Secondary endpoints included: peak expiratory flow rate (PEFR), beta agonist use, asthma symptoms (daily and nocturnal), asthma exacerbations, and the Asthma QOL questionnaire. The study was powered to detect an expected difference between zileuton ER and placebo ER of 8.5% percent change from baseline trough FEV₁ at 12 weeks with a two-sided alpha-level of 0.05. The study was not powered for comparison between zileuton ER and IR formulations.

Safety assessments included recording of adverse events, vital signs, and clinical laboratory measures. Five hundred ninety-one patients were randomized: 198 and 199 to the zileuton ER and zileuton ER placebo group, respectively and 97 to the zileuton IR and zileuton IR placebo groups each. Approximately 76% of the patients completed the study: 72% from each of the zileuton ER and placebo ER treatment groups and 82%-85% from the placebo IR and zileuton IR treatment groups.

2. Study M96-464A - 6 month safety study

Study M96-464A was a randomized, double-blind, placebo-controlled, parallel group, safety study conducted in 88 centers in the United States in patients 12 years of age and older with asthma. A 7-14 day screening period was followed by a randomized, double-blind 6 month treatment period. Patients were randomized 2:1 to either zileuton ER 1200mg BID or placebo BID taken orally within one hour of meals. Patients had an FEV₁ ≥40%, FEV₁ reversibility of 15%, and could be on other asthma medications except salmeterol, theophylline and systemic corticosteroids. Safety was assessed by recording of adverse events, vital signs, and clinical laboratory measures. The primary safety variable was the clinical laboratory test, ALT. Efficacy was also assessed by spirometry (treatment days 1, 85, and 169), PEFR, rescue albuterol use, asthma exacerbation, and the

Asthma QOL questionnaire. The study was powered (56%) to detect an expected difference of 4% in asthma exacerbations resulting in hospitalization or ER visit between zileuton ER and placebo with a two-sided alpha-level of 0.05. Nine hundred twenty-six patients were randomized: 619 to the zileuton ER group and 307 to the placebo ER group. Approximately 76% of patients completed the study: 77% in the zileuton ER group and 75% in the placebo group.

C. Efficacy Findings and Conclusions

Study M95-337A and the efficacy of the zileuton IR formulation support the efficacy of zileuton ER 1200mg BID in patients with asthma 12 years of age and older. Zileuton ER was statistically superior to placebo in the primary efficacy endpoint of change from baseline FEV₁ at 12 weeks as shown below. Although there was no pre-specified analysis plan to account for multiplicity, for the primary efficacy variable, zileuton ER was superior to placebo at the earlier timepoints. Zileuton IR was also included in the study as a benchmark. The results show that the change from baseline FEV₁ was similar between zileuton ER and the IR formulation; however, the study was not powered for a comparison between zileuton ER and zileuton IR. Secondary endpoints (PEFR, symptom scores, rescue medication use, exacerbations) were generally supportive of efficacy of zileuton ER.

Study M95-337 – Mean Change from Baseline Trough FEV ₁						
Study Day	Baseline (L)	Change from BL (L)	Baseline (L)	Change from BL (L)	Treatment group difference (L)	P value
	Zileuton ER N=199		Placebo ER N=198			
Day 15	2.16	0.23	2.19	0.09	0.14	0.001
Day 29	2.17	0.27	2.20	0.20	0.07	0.007
Day 57	2.17	0.33	2.20	0.20	0.13	0.007
Day 85	2.17	0.39	2.20	0.27	0.12	0.021
	Zileuton IR N=97		Placebo IR N=97			
Day 15	2.13	0.17	2.17	0.14	0.03	0.582
Day 29	2.13	0.23	2.17	0.10	0.13	0.027
Day 57	2.13	0.31	2.17	0.22	0.09	0.215
Day 85	2.13	0.38	2.17	0.28	0.10	0.188

While Study M96-464A was primarily a safety study, efficacy was assessed. The results show that there was a numerically greater improvement in trough FEV₁ in the zileuton ER group compared to the placebo group; however, the results were not statistically significant. Additional efficacy measures (PEFR, symptom scores, rescue medication use, exacerbations) also numerically favored the zileuton ER group and are supportive of efficacy of zileuton ER.

D. Safety findings and conclusions

The safety of zileuton ER in patients with asthma 12 years of age and older is supported by the submitted clinical studies and the safety database for the approved zileuton IR formulation because the systemic exposure of zileuton ER is less than zileuton IR. The clinical studies conducted to support this application included 818 subjects 12 years of

age and older who received zileuton ER 1200mg BID. The two clinical studies conducted by Abbott contributing clinical safety are the 12 week efficacy and safety study (M95-337A) and the 6 month safety study (M96-464A). In these studies, 199 patients 12 years and older received zileuton ER 1200mg BID for 12 weeks and 619 patients 12 years and older received zileuton ER 1200mg BID for 6 months. These exposure numbers are reasonable for safety assessment considering that zileuton ER is a change in formulation and safety is also supported by the zileuton IR safety database.

The safety findings in the 12 week study and 6 month study are similar, so the results are described together. In the controlled clinical studies, the safety profile of zileuton ER was generally consistent with the safety profile of zileuton IR. There was one death that occurred during screening for the 6 month safety study; however, this patient never received study drug. Serious adverse events occurred with similar incidence in the zileuton ER and placebo treatment groups. The most common serious adverse event was hospitalization due to asthma, which is not uncommon in this patient population. While there were more hospitalizations in the zileuton ER group than in the placebo group, there were more asthma exacerbations with discontinuations and more ER visits for asthma in the placebo group compared to the zileuton ER group. More patients discontinued due to adverse events from the placebo group (14%) compared to the zileuton ER group (12%). The common adverse events associated with zileuton ER were nasopharyngitis, sinusitis, upper respiratory tract infection, pharyngolaryngeal pain, nausea, and myalgia. Nausea and myalgia adverse events are consistent with the zileuton IR label. The upper respiratory adverse events are not uncommon in patients with asthma.

Review of vital signs and ECGs did not show any safety signals of concern. However, review of the laboratory data indicated that hepatotoxicity and low white blood cell counts are seen with zileuton ER. These findings are known potential adverse reactions with zileuton IR and are further described below.

Hepatotoxicity

Because hepatotoxicity is a known potential adverse reaction with zileuton IR, hepatic profiles were monitored closely in the zileuton ER program. The ALT is considered the most sensitive indicator of liver injury. In the clinical studies, the frequency of hepatotoxicity ($\geq 3X$ ULN of ALT) was 2% in the zileuton ER group compared to 0.4% in the placebo group. This is similar to the rate reported in the clinical studies with zileuton IR: 1.9% for zileuton IR and 0.2% for placebo. The majority of elevations were asymptomatic, although a few cases were associated with other adverse events, including right upper quadrant tenderness, rash, dark urine, fatigue, nausea, and diarrhea. Generally, these abnormalities occurred within the first month of use and resolved after discontinuation of the drug. Previous studies with zileuton IR suggested a slightly increased risk of LFT elevations in female patients ages 65 years and older, but this was not observed in the zileuton ER studies after stratification by age and gender. Information regarding the hepatotoxicity should be included in the product label along with a recommendation for monitoring as described in the zileuton IR product label.

Low white blood cell count

Low white blood cell count ($<3.0 \times 10^9/L$) was observed in 2.1% zileuton ER patients compared to 1.9% placebo ER placebo patients in the two clinical studies. In most cases, the leucopenia was clinically asymptomatic and resolved soon after discontinuation of the drug. Low white blood cell count ($\leq 2.8 \times 10^9/L$) is known to occur with zileuton IR as described in the Zyflo product label: 1% in zileuton treated patients compared to 0.6% in placebo treated patients. It should be noted that the definition of low white blood count was slightly different in the zileuton ER program compared to the zileuton IR program. When the zileuton ER data was reanalyzed with the $\leq 2.8 \times 10^9/L$ cutoff, the rate of low white blood cell count was 1.2%. The clinical significance of this finding of low white blood cell count is unknown as there were no clinical sequelae of the low white blood cell count noted; however, this information should be included in the product label.

Post-Marketing

The safety of zileuton ER is also supported by the post-marketing experience with the immediate release formulation. An FDA Office of Drug Safety (ODS) review dated August 5, 2003, concluded that the post-marketing safety profile of zileuton IR appeared consistent with adverse events listed in the label. From July 2004 until the 4th quarter of 2005, zileuton IR's sale was temporarily suspended during the transfer of the product from Abbott to CRTX. From the 4th quarter of 2005 to May 2006, no fatalities or SAEs have been reported. A review of the post-marketing data noted some cases of hepatotoxicity including death, life-threatening liver injury with recovery, symptomatic jaundice, hyperbilirubinemia, and elevations of ALT $> 8xULN$. The 3 deaths were medically complex and confounded by significant co-morbidities making it difficult to establish a causal relationship with zileuton IR. However, the post-marketing information regarding serious liver injury should be included in the label for both zileuton products.

Data Quality, Integrity, and Financial Disclosure

The Applicant conducted an audit of the clinical study sites, which raised concerns about data integrity. Two of the clinical investigators, Dr. Robert Fiddes and Dr. Thomas Edwards have been debarred and placed on a restricted list, respectively. In addition, because the studies were conducted years ago, nine clinical sites no longer existed or had data available for audit. These issues were known at the pre-NDA stage and sensitivity analyses were requested to assess the effects of the sites on the overall results of the development program. Because of the data integrity issues, the Division requested a DSI audit for _____ where a key clinical pharmacology study was conducted. However, on December 21, 2006, the Division received notice that an inspection could not be conducted. Since the development program included clinical studies, an audit of the pharmacokinetic data was not considered critical. According to the Applicant there are no financial conflicts for the two clinical studies and the two pivotal clinical pharmacology studies for this program.

Risk Management Program

Because of the hepatotoxicity associated with zileuton, the Applicant included a risk management and pharmacovigilance plan. The plan includes labeling, patient

educational materials, physician educational materials, a signal detection program, follow-up of individual safety reports, and a risk management team to monitor hepatotoxicity events.

Pediatric Considerations

Critical Therapeutics included children 12 years and older in the studies that were submitted with this application and requested a deferral for children 4 to 11 years of age and a waiver for children < 4 years of age. Typically, for an oral asthma controller medication, the Division has considered studies in children down to 6 months of age (e.g. montelukast). However, zileuton is eliminated via glucuronidation in the liver and the Applicant asserts that glucuronide formation reaches adult values between the third and fourth year and that metabolism in children < 4 years of age may be unpredictable and unsafe. In addition, zileuton is known to be associated with hepatotoxicity and there are alternative products available for asthma controller therapy in children between 12 months and 4 years of age, e.g. Pulmicort Respules and Singulair Oral Granules. Therefore, a waiver is recommended in children < 4 years of age. Pediatric studies in children 4 to 11 years of age are recommended for deferral.

Labeling

Critical Therapeutics submitted a label in the **new Physician's Labeling Rule** format that generally contains information consistent with the approved immediate release zileuton (Zyflo). The label was reviewed by various disciplines of this Division, and on consult by OSE and DDMAC. Various changes to different sections of the label are recommended to reflect the data accurately and truthfully and better communicate the findings to health care providers. Recommended changes to the label include the following: describing the adverse reactions for the 12 week and 6 month study separately; _____, and including a postmarketing experience section, which provides information regarding cases of severe hepatic injury. Labeling discussions are ongoing at the time of finalization of this review.

Product Name

Critical Therapeutics originally intended to use the name _____ for this product; however, during the review period, Critical Therapeutics changed the proposed trade name to Zyflo XR. The DMETS review of the proposed trade name, Zyflo XR, is pending at the time of finalization of this review.

Action

Critical Therapeutics has submitted substantial evidence demonstrating the efficacy of zileuton ER for the prophylaxis and chronic treatment of asthma in patients 12 years of age and older. Pending agreed upon labeling, the recommended action is **Approval**.

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/s/

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CLINICAL REVIEW

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Established Name Zileuton Extended-Release
(Proposed) Trade Name Zyflo XR
Therapeutic Class Leukotriene modifier
Applicant Critical Therapeutics

Priority Designation S

Formulation 600 mg extended-release tablet
Dosing Regimen 1200 mg PO BID
Indication Asthma
Intended Population Patients 12 years and older with
asthma

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1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The clinical recommendation for this application is **Approval**. The application contains adequate evidence of efficacy to support the proposed indication: “the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older.”

This is a 505(b)(1) application for Zileuton Extended Release (ER) for the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older. An immediate release (IR) formulation of zileuton is currently approved for the same indication. The zileuton ER development program included two clinical studies conducted by Abbott Laboratories with an older formulation of zileuton ER in addition to multiple pharmacokinetic studies comparing different formulations of zileuton ER and the immediate release zileuton. The pharmacokinetic studies demonstrated that all ER formulations had less bioavailability compared to the IR formulation; however, the to-be-marketed formulation’s bioavailability is more comparable to the IR formulation than previous formulations.

In addition to the pre-existing efficacy information available for the approved IR formulation, the clinical recommendation for an **Approval** action is based on the pharmacokinetic data, further supported by the results of the two Phase 3 clinical trials comparing an older formulation of zileuton ER to placebo in the treatment of asthma. The first study demonstrated a statistically significant benefit over placebo in trough FEV₁, the primary efficacy variable. The second study, a 6-month safety study, also included efficacy assessments. Although the results were generally supportive of the efficacy of zileuton ER, the efficacy results were not statistically significant compared to placebo. The lack of efficacy was likely attributable to key differences in study design.

The safety of zileuton ER is supported by the submitted clinical study data, the safety database to support approval of zileuton IR, postmarketing data for the approved zileuton IR, and published studies on the approved zileuton IR. Review of the safety data showed that zileuton ER is associated with hepatotoxicity and leucopenia, which are safety signals noted with zileuton IR and included in the zileuton IR product label. No new safety signals were identified. In addition, the systemic exposure of the to-be-marketed zileuton ER is slightly less than the systemic exposure of zileuton IR, which further supports the safety of zileuton ER.

Therefore, although the ER formulation is not bioequivalent to the IR formulation, the clinical trial data suggests that any pharmacokinetic differences are unlikely to be clinically relevant in regards to zileuton ER’s efficacy and safety in the treatment of asthma. As a result, the recommendation of the clinical review is **Approval**.

1.2 Recommendation on Postmarketing Actions

The recommendation for approval is for zileuton ER for patients 12 years of age and older. Because asthma/reactive airway disease may exist in children < 12 years of age, the Applicant will be required to explore the use of zileuton ER in children ages 4 to 11 to comply with PREA. A deferral for this age group at this time is acceptable. Because of the hepatotoxicity associated with zileuton and the fact that liver maturation may not be complete until around 4 years of age, clinical studies with zileuton in children < 4 years of age will not be required.

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

Zileuton is a leukotriene synthesis inhibitor that specifically blocks 5-lipoxygenase activity. Zileuton immediate-release (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 600 mg-tablet that is taken 4 times a day, with or without food. Previously, Abbott Laboratories initiated a development plan for an extended-release formulation, culminating in two Phase 3 studies with a specific zileuton ER formulation (Formulation H). Abbott later terminated its zileuton ER development program and did not file an NDA application. Subsequently, Critical Therapeutics acquired ownership of both Zyflo and zileuton ER. The new sponsor modified Abbott's original Formulation H and developed a new extended-release product (proposed tradename: ZyfloXR®) which is to be administered as two 600-mg tablets twice daily, within one hour of a meal, for a total daily dosage of 2400 mg. The proposed indication is "the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older," the same indication carried by the approved reference product, zileuton IR.

The Applicant's drug development program included two Phase 3 studies conducted by Abbott using Formulation H: a 12-week clinical efficacy study (M95-337; N=591) and a 6-month long-term safety study (M96-464; N=926). The two Phase 3 studies are the focus of the clinical review and are described in more detail in Section 6. Eight hundred eighteen patients are included in the safety database for zileuton ER, with exposure up to 6 months. In addition to the clinical study data, other pertinent clinical data sources included in this review are postmarketing data for the approved zileuton IR and published studies on the approved zileuton IR.

The sponsor's drug development program also relied on the Agency's previous findings of efficacy and safety of the approved reference product, zileuton IR, and Phase 2 comparisons of bioavailability of zileuton ER to the IR formulation. During the course of development, 11 bioavailability studies were performed, including two studies comparing the proposed extended-release formulation to the approved immediate-release product and two studies comparing Abbott's Formulation H used in the Phase 3 studies to the approved immediate-release product. The latter four pharmacokinetic studies are briefly reviewed in the Clinical Pharmacology section of this review.

1.3.2 Efficacy

The Applicant submitted reports for two Phase 3 efficacy and safety studies conducted by Abbott using zileuton ER Formulation H: Study M95-337, a 12-week clinical efficacy study and Study M96-464, a 6-month long-term safety study. No direct comparison between the to-be-marketed formulation and the formulation used (Formulation H) have been made as Formulation H no longer exists; however, review of pharmacokinetic data indicates that the to-be-marketed formulation has greater bioavailability and is more comparable to the IR formulation than the formulation used in the clinical studies. The pharmacokinetic data is reviewed in more detail in Section 5.

Study M95-337

Study M95-337 was a randomized, multi-center, double-blind, placebo-controlled trial of zileuton ER 1200 mg BID in the treatment of 591 patients with moderate asthma. The primary endpoint was mean percent change in trough FEV₁ from baseline at 12 weeks for zileuton ER versus placebo. Important secondary endpoints included AM and PM peak expiratory flow rates (PEFRs), rescue beta-agonist use, asthma symptom scores, asthma exacerbation rates, and quality-of-life questionnaires. Zileuton IR was included as an active comparator but statistical comparisons between zileuton ER and IR were not made. During the study, patients were permitted to use albuterol on an as-needed-basis. Other asthma medications, such as inhaled corticosteroids and leukotriene modifiers, were not permitted.

The results of Study M95-337 support the efficacy of zileuton ER 1200 mg BID in the treatment of asthma compared to placebo. In terms of the primary efficacy variable (trough FEV₁), the difference between zileuton ER and placebo ER in the mean percent change from baseline after 12 weeks was statistically significant in favor of zileuton ER: 20.77% vs. 12.73% (p=0.032), respectively. The mean change from baseline trough FEV₁ at 12 weeks was also statistically significant (0.39 L vs. 0.27 L; p=0.021). The treatment difference was 8% (120 ml). Time-points evaluated prior to 12 weeks also generally favored zileuton ER over placebo. Secondary efficacy data was generally supportive of zileuton ER's efficacy if not statistically significant, including PEFrs, symptom scores, exacerbations, and QOL questionnaire scores. Among the other efficacy variables examined, the results suggested a small but consistent reduction in beta-agonist use frequency and amount. Asthma severity subgroup analysis was unrevealing, limited by the uneven distribution of severity among treatment arms at randomization.

Study M96-464

Study M96-464 was a randomized, double-blind, placebo-controlled, 6-month efficacy and safety study of zileuton ER 1200 mg BID in the treatment of moderate asthma compared to placebo in 926 patients with asthma. In contrast to Study M95-337, patients in Study M96-464 were maintained on their usual asthma medication regimens, with the exception of salmeterol, theophylline, and systemic steroids. The CRTX study report describes Study M96-464 primarily as a safety study, and the primary endpoint was the percentage of patients who experienced an ALT elevation ≥ 3 x upper limit of normal within the 6-month study period. The main efficacy endpoint was mean change from baseline trough FEV₁ at 24 weeks and 12 weeks. Secondary outcomes included daily PEFr data, short-acting beta-agonist use, proportion of patients with one or more exacerbations due to asthma, and asthma quality-of-life questionnaire data. Of note, the sample size calculation in the original Abbott study protocol was based on rates of

hospitalization for asthma. This efficacy variable was ultimately not included as a major endpoint in the Critical Therapeutics analyses.

Zileuton ER did not demonstrate statistically significant superiority over placebo in terms of the primary efficacy endpoint but the results numerically favored zileuton ER. The mean change from baseline trough FEV1 for zileuton ER vs. placebo at 24 weeks was 0.17 L vs. 0.13 L ($p=0.260$), respectively, with a treatment difference of 40 ml. The mean percent change from baseline trough FEV1 was 9% vs. 7%, respectively ($p=0.316$). Similar results were noted at 12 weeks as well. Of note in this study, the number of patients experiencing hospitalization due to asthma was greater in the zileuton ER group compared to placebo (5 vs. 0 patients; $p=0.162$). Review of the case narratives did not provide an explanation for this imbalance, although overall, more asthma exacerbations were noted in the placebo group versus zileuton ER as anticipated. Other secondary endpoints were generally supportive of zileuton ER's efficacy, if not statistically significant. The addition of usual asthma medications to the regimen may have masked any benefit attributable to zileuton ER. While these data alone would ordinarily not be considered as adequate confirmation of efficacy, since zileuton ER is a change in formulation and efficacy was established in Study M95-337, Study M96-464 provides additional supplementary support for zileuton ER's efficacy in the proposed indication.

1.3.3 Safety

The safety profile of zileuton ER is supported by safety data from the two submitted clinical studies, the safety database of the approved zileuton IR, postmarketing data from zileuton IR, and published studies on zileuton IR. Safety was assessed in the two clinical studies with reports of adverse events, laboratory values, and vital signs. Eight hundred eighteen patients are included in the safety database for zileuton ER, with exposure up to 6 months. An additional 151 subjects who participated in pharmacokinetic studies were also reviewed but these exposures were limited to 1 week or less and many of these subjects received only a single dose. Overall, the safety of zileuton ER was comparable to the safety profile for zileuton IR. The most relevant safety issues associated with zileuton ER were liver function test (LFT) and white blood cell count abnormalities, both of which were noted in the zileuton IR development program and are described in the zileuton IR product label.

Liver function test elevations had been previously observed with the immediate-release formulation and a monitoring algorithm is provided in the approved product label. The rate of LFT elevations ($>3X$ the upper limit of normal) in the clinical studies in this application ($\sim 2\%$) was consistent with the rate described in placebo-controlled trials for zileuton IR. In general, the most common LFT abnormality was an elevation in ALT that occurred within the first month of treatment and resolved after discontinuation of the drug. The product label for zileuton ER proposes the same LFT monitoring algorithm as in the approved zileuton IR label. In addition, the Applicant proposes a risk management program and a pharmacovigilance program to decrease the risk of severe hepatic injury and to monitor for additional safety signals.

White blood cell (WBC) count abnormalities, primarily leucopenia ($<3.0 \times 10^9/L$), were also observed in 2.1% zileuton ER patients vs. 1.9% placebo ER patients in the two clinical studies. In most cases, the leucopenia was clinically asymptomatic and resolved soon after discontinuation of the drug. The rates of leucopenia in the two clinical studies are slightly higher

than those rates reported in the Adverse Reactions section of the zileuton IR label, 1.0% (zileuton IR) vs. 0.6% (placebo). However, leucopenia is defined using a lower cutoff point ($\leq 2.8 \times 10^9/L$) in the current zileuton IR label. Reclassification of the leucopenia noted in zileuton ER patients using the cutoff of $WBC \leq 2.8 \times 10^9/L$ reduces the observed rate to 1.2% in the two clinical studies with zileuton ER, which is comparable to the rate reported for zileuton IR. The Applicant proposed inclusion of the higher rates in the draft label for zileuton ER using the $< 3.0 \times 10^9/L$ cutoff. As the white cell count decreases were asymptomatic and generally mild, information in the label should be sufficient in terms of safety.

1.3.4 Dosing Regimen and Administration

The proposed dosing regimen is two 600-mg (1200 mg) zileuton ER tablets administered orally twice daily.

1.3.5 Drug-Drug Interactions

No formal drug interaction studies were conducted with zileuton ER. Prior drug interaction studies with zileuton IR have demonstrated decreased clearance of theophylline, warfarin, and propranolol. The product label for zileuton IR describes these drug interaction studies and similar precautions should be applied to zileuton ER administration when used concomitantly with any of these drugs. No significant interactions were found between zileuton IR and ethinyl estradiol or prednisone, two drugs metabolized by the cytochrome P450 system. No interactions have been found with digoxin, phenytoin, sulfasalazine, and naproxen. Review of adverse event reports does not reveal any apparent interactions between zileuton IR and beta-agonists or acetaminophen. The drug interaction studies that are described in the zileuton IR product label should be included in the zileuton ER label.

1.3.6 Special Populations

No formal studies in special populations have been conducted with zileuton ER. Review of data from the two Phase 3 studies does not indicate any differential efficacy of safety by gender and subgroup analyses by ethnicity and gender were limited by small patient numbers. The pharmacokinetics of zileuton IR in geriatric patients, patients with renal failure, and patients with hepatic impairment have been previously reported and should be included in the zileuton ER label. Based upon data with the IR formulation, patients with renal impairment do not need dose adjustment. Because of the hepatotoxicity associated with zileuton, zileuton ER is contraindicated in patients with active liver disease.

2 INTRODUCTION AND BACKGROUND

2.1 Product Information

The established name of the subject product of this application is Zileuton Extended-Release (ER) and the proposed trade name is Zyflo XR®. The established name will hereinafter be used in this review to refer to the product. Zileuton ER is supplied as an oblong, film-coated white tablet, debossed on one side with "CT2." In addition to 600 mg of the active ingredient, zileuton, the tablets also contain the following inactive ingredients: crospovidone, ferric oxide, glyceryl behenate, hydroxypropyl cellulose, hypromellose, magnesium stearate, mannitol, microcrystalline cellulose, povidone, pre-gelatinized starch, propylene glycol, sodium starch glycolate, and talc.

Zileuton ER is an extended-release formulation of the currently marketed Zyflo (zileuton IR). It is not a new molecular entity (NME). Zileuton is a leukotriene synthesis inhibitor that specifically blocks 5-lipoxygenase activity, the enzyme that catalyzes the formation of leukotrienes from arachadonic acid.

The proposed indication for zileuton ER is the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older, the same indication carried by the reference product, zileuton IR. The proposed dosing regimen is two 600-mg tablets (1200 mg) taken orally twice daily.

2.2 Currently Available Treatment for Indications

In addition to zileuton IR, other leukotriene inhibitors approved for the treatment of asthma include montelukast (Singulair) and zafirlukast (Accolate). Montelukast and zafirlukast are leukotriene receptor antagonists, while zileuton is a 5-lipoxygenase inhibitor. Other classes of drugs approved for the treatment of asthma include inhaled corticosteroids (ICS) and ICS combination products, long-acting and short-acting beta-agonists, inhaled cromolyn, theophylline, and anti-IgE therapy (omalizumab). According to NHLBI and GINA guidelines, ICS are first-line treatment for persistent asthma.

2.3 Availability of Proposed Active Ingredient in the United States

The active moiety is currently available in the United States as the immediate-release formulation (Zyflo). Zileuton was approved by the Agency on December 9, 1996 (NDA 20-471). As part of original approval, the applicant committed to post-marketing surveillance and a risk management program for liver enzyme elevations associated with zileuton. In March 2004, Critical Therapeutics (CRTX) acquired ownership of zileuton IR from Abbott Laboratories, and NDA 20471 was transferred to CRTX on July 29, 2004. Zileuton IR has never been withdrawn from the US market.

2.4 Important Issues With Pharmacologically Related Products

Zafirlukast was approved in the U.S. in September 1996. In 1997, the Precautions section of the product label was modified regarding an increased incidence of eosinophilic disorders such as Churg-Strauss syndrome associated with use of zafirlukast. In 2000 and 2004, the Precautions and Warnings sections of the label were further revised to address the risk of hepatotoxicity associated with the drug.

Montelukast was approved in the U.S. in February 1998. In December 1998, the Precautions section of the product label was modified to describe an increased incidence of Churg-Strauss syndrome and related eosinophilic conditions observed in the postmarketing period.

Eosinophilic disorders have not been observed with zileuton to date. Hepatotoxicity has been noted previously with zileuton and is covered in depth in Section 7 below. The product label for the approved zileuton IR includes warnings regarding hepatotoxicity and a recommended monitoring algorithm.

2.5 Presubmission Regulatory Activity

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 an extended-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 zileuton ER tablets. Abbott conducted several bioavailability studies as well as two Phase 3 studies in asthmatic patients using a zileuton ER tablet (Formulation H). Abbott did not submit an NDA for the zileuton ER product.

In December 2004, Critical Therapeutics (CRTX) acquired ownership of zileuton ER 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.

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. CRTX currently markets zileuton IR as Zyflo.

A pre-NDA meeting was held with CRTX on May 2, 2005 (Meeting minutes and Medical Officer Review, IND 47561). CRTX planned to submit the results of the two clinical studies conducted by Abbott in the mid-1990s to support an NDA with an older formulation of zileuton ER (Formulation H) and the results of some clinical pharmacology studies. Several major issues were raised regarding the development program: 1) potential difficulty bridging the proposed to be marketed CRTX zileuton ER product to the former Abbott Formulation H product as Formulation H was no longer available, and 2) difficulty verifying data collected from pivotal phase 3 studies conducted by Abbott almost 10 years previously. 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.

2.6 Other Relevant Background Information

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

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

The CMC reviewer's recommended action on this application is Approval. There are two CMC issues worth discussion – the dissolution profile and potential manufacturing issues with increased production.

The CMC review of this application has noted that the dissolution profile of the drug results in release of up to $\frac{1}{2}$ of the total drug by 6 hours, rather than attaining zero-order release over 8 to 10 hours as would be desirable for an extended-release product. As the overall drug exposure for zileuton ER appears to be less than the IR formulation, there are no clinical safety concerns expected with this dissolution profile.

The CMC review has also noted that several manufacturing problems were encountered during the $\frac{1}{2}$ scale-up; further increases in production may introduce new problems that prompt additional changes to the manufacturing process. Any new changes will need to be submitted for CMC review. The stability data submitted in this application support an expiry of 18 months.

3.2 Animal Pharmacology/Toxicology

The Pharmacology/Toxicology reviewer's recommended action on this application is Approval.

This application relied primarily on pharmacology and toxicology data submitted under NDA 20-471 for zileuton IR. New data submitted included qualification of impurities that are found in higher concentrations with the ER formulation compared to the IR formulation. No significant issues were noted in the Pharmacology/Toxicology review.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The primary source of clinical data for this review was the studies conducted by Abbott Laboratories, presented in the original Abbott and CRTX study reports. Data from postmarketing surveillance, literature reports referenced by the Applicant, and literature reports

collated from a PubMed literature performed by the reviewer were also used. IND and NDA data, including approved labeling for the IR formulation, were used as regulatory references.

4.2 Tables of Clinical Studies

Table 1 shows the main clinical studies presented by the Applicant in support of this application. The studies are organized by Phase. Studies M95-337 and M96-464 are the major efficacy (“pivotal”) studies in this application.

Table 1: Summary of Key Clinical Studies for Zileuton ER						
Study Number	Description	Subjects	Design	Dose*	Duration	Relevance
Phase 1						
M95-264	PK – fed	24	SC, R, OL, 2 way XO	Zileuton ER 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 ER H 1200mg (fasting) Zileuton ER H 1200mg (fed) Zileuton IR 600mg (fasting) 2 doses	Single dose	Links P3 clinical formulation to IR
CTI-03-C05-102	PK – fed and fasting	24	SC, R, OL, 3-way XO	Zileuton ER E21 (fasting) – 1200mg Zileuton ER 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 ER E21 (fasting) – 1200mg BID Zileuton ER E21 (fed) – 1200mg BID Zileuton IR (fed) – 600mg QID	6 days	BA between IR and to be marketed product
Phase 3						
M95-337A	Efficacy, Safety Fed conditions	591 subjects with asthma 12 yrs and older	MC, R, DB, PG, PC	Zileuton ER H 1200mg BID Zileuton ER 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 ER H 1200mg BID Placebo	6 months	Pivotal – safety and some efficacy info Abbott H formulation

* H – Abbott’s Formulation H zileuton ER; E21 – CRTX’s Formulation E21 zileuton ER

4.3 Review Strategy

The two Phase 3 studies and four pharmacokinetic studies presented in Table 1 were reviewed, with greater emphasis placed on the Phase 3 efficacy and safety studies, M95-337 and M96-464. The four pharmacokinetic studies were briefly reviewed to establish relative bioavailability of the ER product. Other pharmacokinetic studies conducted by Abbott Laboratories during the early development of an extended-release formulation were not reviewed, as these studies are not critical for linkage of the to-be-marketed formulation to the immediate-release formulation or the extended-release formulation used in the Phase 3 studies (Formulation H).

Reviews of the studies are based primarily on the CRTX study reports. The Abbott study reports and original protocols were also reviewed and used as cross-references. Notably, a prespecified Statistical Analysis Plan (SAP) was not available for either Phase 3 study. The Applicant’s summary data tables were reviewed in detail. Appendix tables and data listings were also

reviewed in varying amounts of detail, depending upon the endpoint and review issue. Case report forms (CRF) of patients with Serious Adverse Events (SAE) were reviewed.

The Applicant provided bibliographies within the study reports. These were reviewed to the extent of their relevance to the review.

Postmarketing safety data from zileuton IR was provided by the Applicant and was reviewed. A literature review was also performed by the Applicant and this reviewer to identify any new safety signals with zileuton.

4.4 Data Quality and Integrity

The Applicant'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. In addition, due to the extended time interval between conduct of the Phase 3 studies and submission of the NDA application, nine clinical sites no longer existed or had data available for audit. As a result of these issues and per discussion with the Division, the Applicant defined additional datasets for analysis excluding data from these sites. The 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 were 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)

The Division requested an audit by the Division of Scientific Investigations (DSI) for this NDA given the concerns about data integrity and the extended time interval that had elapsed between the conduct of the Phase 3 trials and the NDA submission. The clinical site recommended for audit, ~~_____~~ was the site responsible for the key pharmacokinetic studies sponsored by CRTX.

On December 21, 2006, the Division received notice from DSI that a site investigation could not be conducted due to budgetary constraints. As the results from the clinical trials provide confirmatory evidence of zileuton ER's efficacy, an audit of the pharmacokinetic data was considered less critical.

4.5 Compliance with Good Clinical Practices

With the exception of the two investigators who were subsequently debarred or placed on the restricted list, the studies were conducted in accordance with acceptable ethical standards. Study reports indicated that informed consent was obtained from all study participants. Analysis by treatment site does not indicate any systematic site-based bias.

4.6 Financial Disclosures

Based upon information provided to CRTX by Abbott, no disclosable financial arrangements occurred for Studies M95-337 and M96-464. CRTX certified that no disclosable financial arrangements occurred for Studies CTI-03-C05-102 and CTI-03-C05-103.

5 CLINICAL PHARMACOLOGY

Eleven pharmacokinetic studies were performed by Abbott in development of an extended-release zileuton formulation. Two of the studies, Studies M95-264 and M96-556, compare the pharmacokinetic profiles of zileuton IR and the extended-release formulation (Formulation H) used in the original Phase 3 studies. Two other studies, Studies CTI-03-C05-102 and CTI-03-C05-103, compare the pharmacokinetic profiles of zileuton IR and the to-be-marketed CRTX formulation (Formulation E21). This review briefly summarizes the findings of these four studies to establish an indirect link between the to-be-marketed formulation (Formulation E21) and the Phase 3 formulation (Formulation H).

5.1 Pharmacokinetics

Both the Abbott Formulation H and the CRTX Formulation E21 demonstrate decreased bioavailability compared to zileuton IR. Bioavailability is improved in the fed state as opposed to the fasting state. No direct comparative studies between Formulation H and E21 have been performed, as Formulation H is no longer available. Historical comparison suggests that E21 has greater bioavailability than Formulation H, although the reliability of such historical cross-study comparisons is somewhat limited. Results of the multiple-dose studies, Study M95-264 and Study CTI-03-C05-103, in the fed state are summarized below in Table 2. A detailed discussion of the pharmacokinetic results can be found in Dr. Shinja Kim's review.

24-hour PK parameters	Study M95-264 Formulation H (N=23)		Study CTI-03-C05-103 Formulation E21 (N=24)	
	1200 mg ER q12h	600 mg IR q6h	1200 mg ER q12 h	600 mg IR q12 h
T _{max} (hr)	2.6±2.0	1.7±0.5	3.57±2.35	1.63±0.82
C _{max} (mcg/ml)	5.93±2.36	11.99±5.25	4.97±1.34	7.72±2.43
C _{min} (units)	0.62±0.46	1.13±0.87	1.00±0.45	0.99±0.38
AUC ₀₋₂₄ (mcg hr/mL)	59.5±23.2	109.2±60.5	63.99±15.95	77.42±21.36

T_{1/2} (hr)	3.7±1.7	2.0±0.4	3.19±1.24	2.23±0.53
CL/F (ml/min)	766±267	434±155	668.7±195.95	607.4±33.83

Source: Volume 2, Section 3.6

Reviewer's comment: The decreased exposure of the zileuton ER formulation compared to the zileuton IR formulation does not raise any safety concerns; however, the decreased exposure does raise concerns about the efficacy of the zileuton ER formulation. Therefore, the clinical studies are necessary to establish the efficacy of zileuton ER.

No dedicated drug-drug, drug-demographic, or drug-disease interaction studies with zileuton ER were included in this application. This is acceptable because these studies were conducted with zileuton IR and the results of the interaction studies and special population studies with zileuton IR are summarized in the zileuton IR label. The information from the zileuton IR label should be included in the zileuton ER label.

5.2 Pharmacodynamics

No dedicated pharmacodynamic studies with zileuton ER were included in this application.

5.3 Exposure-Response Relationships

Dose selection was based on the recommended dosing for the approved zileuton IR product, 600 mg orally four times per day. Dose-ranging studies for zileuton ER were not included in this application.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The proposed indication for zileuton ER is "the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older," the same indication carried by the approved reference product, zileuton IR.

6.1.1 Methods

The efficacy review is based on the two, Phase 3 studies conducted by Abbott Laboratories, Study M95-337 and M96-464. Study M95-337 was a randomized, multi-center, double-blind, placebo-controlled 12-week trial of zileuton ER 1200 mg BID in the treatment of patients with moderate asthma. Study M96-464 was a randomized, double-blind, placebo-controlled, 6-month efficacy and safety study of zileuton ER 1200 mg BID in the treatment of moderate asthma compared to placebo. Detailed reviews of the individual studies are provided in the Appendix. The pharmacokinetic studies were briefly reviewed to establish a pharmacokinetic link to the approved product, zileuton IR, and for assessment of safety. These studies were discussed in Section 5, but are not included in the efficacy review. Unless otherwise specified, review of both efficacy and safety was based on the full data analysis sets for Studies M95-337 and M96-464,

described in Section 4.4. Analyses from the restricted data sets and sensitivity data sets were reviewed briefly for confirmation of the findings based on the full data sets.

6.1.2 General Discussion of Endpoints

The primary and secondary efficacy endpoints evaluated in Study M96-464 and Study M95-337 are consistent with endpoints suggested in the draft *Guidance for Industry: Clinical Development of Metered Dose Inhaler and Dry Powder Inhaler Drug Products for Pulmonary Indications*, which can be generalized to non-inhalational asthma drugs. In general, trough FEV1 is an acceptable, conventional primary efficacy endpoint for a drug of this class and the proposed indication. Secondary endpoints for both studies included daily PEFr data, rescue beta-agonist use, nocturnal awakenings, asthma exacerbations, symptom scores, and quality-of-life asthma questionnaire data. These other endpoints represented additional clinical indices for assessing the effectiveness of an asthma controller medication.

In Study M95-337, the primary efficacy endpoint was identified as the mean change AND % change in trough FEV1 from baseline at 12 weeks for zileuton ER versus placebo; the order of these endpoints was not specified, although they are closely related, and no adjustment was made for multiplicity of time points assessed during the 12-week course of the study. As the sample size calculation was based on % change in trough FEV1 from baseline FEV1 at 12 weeks, this endpoint was evaluated as the primary efficacy endpoint. The efficacy review took into account the multiple time points and a *post hoc* analysis performed by the FDA statistical review. A *post hoc* repeated measures analysis on % change from baseline in Study M95-337 was performed by Dr. James Gebert, statistical reviewer, to assess the effectiveness of zileuton ER over the whole treatment period. This analysis supported the efficacy of zileuton ER over multiple time points in the study.

Study M96-464 was presented as mainly a safety study, with the rate of ALT elevations specified as the primary endpoint. However, efficacy was assessed and the primary efficacy endpoint was identified as the mean change AND % change in trough FEV1 from baseline at 12 weeks and/or 24 weeks; the order and time point were not specified. Of note, Study M96-464's sample size calculation was based on the rate of hospitalizations for asthma, which differs from the primary efficacy endpoint in the Abbott or CRTX study reports.

Reviewer's comment: The discrepancy in specified and presented endpoints suggests a post hoc change in endpoints and possible introduction of bias in the analysis. This issue is somewhat a moot point as Study M96-464 does not demonstrate statistical superiority of zileuton ER over placebo in the primary efficacy endpoint at either 12 or 24 weeks, as will be discussed later in this review.

6.1.3 Study Design

6.1.3.1 Study M95-337

Study M95-337 was a 12-week, multicenter, randomized, double-blind, placebo-controlled study of patients with moderate asthma between the ages of 12 to 81 years. To be enrolled in the

study, patients had to have an FEV1 of 40-75% predicted, FEV1 reversibility of at least 15%, and take no other asthma medications except for a short-acting bronchodilator. After a 14-day, single-blind placebo run-in period (Period I), patients were randomized into a double-blind, 12-week treatment period (Period II) followed by a 2-week run-out period (Period III) off study medication. Patients were randomized 1:1:1:1 to receive zileuton ER 1200 mg BID, zileuton ER placebo BID, zileuton IR 600 mg QID, and zileuton IR placebo QID. The study included zileuton IR as a benchmark comparator. During the course of the study, patients underwent spirometry and other study evaluations at Screening, Day 1, Week 1 (Day 8), Week 2 (Day 15, Double-blind Day 1), Week 5 (DB Day 15), Week 6 (DB Day 29), Week 10 (DB Day 57), Week 14 (DB Day 85), and Week 16 (run-out). Pulmonary function testing was performed immediately prior to administration of the AM dose at the study site. Patients who discontinued the study due to adverse events were seen 26-34 days following discontinuation.

Dose selection was based on results of a prior dose-ranging study (M90-450) and two Phase 3 studies (M91-685 and M92-720) conducted with zileuton IR. The approved dose for zileuton IR is 600 mg orally four times per day; the selected zileuton ER dose approximates the IR dose although it is not exactly bioequivalent. The study design is consistent with guidelines published in the draft *Guidance for Industry: Clinical Development of Metered Dose Inhaler and Dry Powder Inhaler Drug Products for Pulmonary Indications* and includes appropriate controls, inclusion/exclusion criteria, and efficacy assessments for the proposed indication.

6.1.3.2 Study M96-464

Study M96-464 was a 6-month, multicenter, randomized, double-blind, placebo-controlled study of patients with moderate asthma between the ages of 12 to 81 years. To enter the study, subjects had to demonstrate 15% FEV1 reversibility and an FEV1 \geq 40% predicted at screening. In contrast to Study M95-337, patients were permitted to be on other asthma medications such as inhaled corticosteroids, with the exception of salmeterol, theophylline, and systemic steroids. After a 7-14 day run-in period, subjects were randomized 2:1 to receive zileuton ER or placebo ER; no active comparator was used in this study. Patients underwent spirometry and other study evaluations at Screening, Day 1, Day 85 (Week 12), and Day 169 (Week 24). Other study evaluations, including laboratory evaluations and screening for adverse events were performed 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. While the study design itself is acceptable to evaluate effectiveness of zileuton ER in the treatment of asthma, the concomitant use of other asthma medications makes direct comparisons between the two pivotal studies difficult.

6.1.4 Efficacy Findings

6.1.4.1 Patient populations and disposition

Table 3 shows the enrollment and patient disposition in each of the two efficacy studies.

Table 3 Enrollment and disposition in Phase 3 studies for zileuton ER		
	Study M95-337	Study M96-464

Disposition	Zileuton ER	Placebo ER	Zileuton IR	Placebo IR	Zileuton ER	Placebo ER
Randomized	199	198	97	97	619	307
Completed	144 (72%)	143 (72%)	82 (84%)	80 (82%)	477 (77%)	229 (75%)

Source: Volume 1.2, Section 3.9.3

A total of 818 patients received zileuton ER and 505 patients received placebo in the two Phase 3 studies for zileuton ER.

6.1.4.2 Baseline characteristics

The patient populations for the two studies were similar in terms of age (mean 33.3 to 35.3 years), gender (~50% male), and ethnicity (77.3 to 85.4% Caucasian). The studies' inclusion criteria for asthma severity were similar and were intended to define a patient population with moderate persistent asthma. Direct comparison of the study populations is difficult, since patients in Study M96-464 were permitted to use other asthma medications, including inhaled corticosteroids (ICS). Approximately 50% of the patients in Study M96-464 were taking concomitant ICS at enrollment and during the study. Based on spirometric parameters, PEFR data, and rescue beta-agonist usage at baseline, Study M95-337 had a higher proportion of patients with more severe disease compared to the patients in Study M96-464. However, the patients in Study M95-337 may have been under-treated at time of enrollment and had they been on ICS, the spirometry and other baseline asthma characteristics would be more similar to those observed in Study M96-464. On the other hand, the enrollment of a milder population in Study M96-464 cannot be ruled out entirely and may explain in part the lack of efficacy noted in that study; this issue is discussed in more detail in Section 6.1.4.3. Neither study stratified the randomization process by disease severity and in Study M95-337, a higher proportion of patients with baseline FEV₁ ≤60%, qualifying as severe, were randomized into the zileuton ER group over placebo (p=0.045). Within each study, treatment and placebo groups were otherwise relatively comparable. Table 4 summarizes the baseline asthma characteristics of the patients enrolled in both studies.

Table 4 Baseline asthma characteristics of patients enrolled in Study M95-337 and M96-464

Baseline characteristic	Study M96-464		Study M95-337			
	Zileuton ER (N=619)	Placebo ER (N=307)	Zileuton ER (N=199)	Placebo ER (N=198)	Zileuton IR (N=97)	Placebo IR (N=97)
Trough FEV ₁ (L)	2.52	2.52	2.17	2.20	2.13	2.17
% Predicted FEV ₁	71.09	69.91	57.68	59.42	58.12	58.19
AM PEFR (L/min)	388.83	388.27	369.73	353.86	365.54	365.24
PM PEFR (L/min)	420.28	414.83	397.92	386.80	399.51	398.93
# Occasions albuterol use/day	2.49	2.67	3.25	3.26	2.97	2.91
Asthma severity*	Mild = 164 (33%) Mod = 204 (40%) Severe = 139 (27%)	66 (26%) 118 (47%) 67 (27%)	1 (0.5%) 83 (43.2%) 108 (56.2%)	0 101 (54.0%) 86 (46.0%)	1 (1.0%) 37 (38.5%) 58 (60.4%)	3 (3.2%) 40 (43.0%) 50 (54%)

* Asthma severity: mild (FEV₁ ≥80% predicted), moderate (FEV₁ >60% and <80%), and severe (FEV₁ ≤60%)

6.1.4.3 Primary efficacy findings

As discussed in Section 6.1.2, the review of efficacy focuses on % change in trough FEV₁ from baseline at 12 weeks or 24 weeks as the primary efficacy endpoint for both Phase 3 studies using the Full Analysis Set. All data reported in the review refer to the Full Analysis Set. Efficacy findings were confirmed using the Restricted Analysis Set as a sensitivity analysis but the values

are not reported here. The definition of the different analysis datasets was discussed in Section 4. The major efficacy results are summarized in Table 5 and more detailed, individual study reviews are located in the Appendix.

6.1.4.3.1 Primary efficacy findings: Study M95-337

The results of Study M95-337 demonstrated that zileuton ER was statistically superior to placebo ER for mean change from baseline trough FEV₁ at 12 weeks and mean percent change from baseline trough FEV₁ at 12 weeks. In terms of the primary efficacy variable (trough FEV₁), the difference between zileuton ER and placebo ER in the mean percent change from baseline was statistically significant in favor of zileuton ER: +20.77 vs. +12.73% (p=0.032), respectively. The mean change from baseline trough FEV₁ at 12 weeks was also statistically significant (+0.39 L vs. +0.27 L; p=0.021). The treatment difference was 8.1% (~120 ml), which is comparable to the treatment difference observed in the original zileuton IR placebo-controlled trials (~130ml). In this study, zileuton ER and zileuton IR, the benchmark comparator, performed similarly. Responder analysis indicates that more subjects had ≥12% improvement in the zileuton ER group than placebo (63% vs. 50% at Study Day 85), further supporting efficacy.

The primary efficacy findings from both clinical studies are summarized in Table 5.

Table 5 Primary Efficacy Variables: Mean change in trough FEV ₁ from baseline and mean % change from baseline trough FEV ₁ at 12 weeks (Study M95-337) and at 6 months (Study M96-464)						
	Study M95-337				Study M96-464	
	Zileuton ER (N=199)	Placebo ER (N=198)	Zileuton IR (N=97)	Placebo IR (N=97)	Zileuton ER (N=619)	Placebo ER (N=307)
Baseline (L)	2.17	2.20	2.13	2.17	2.52	2.52
Trough FEV ₁ at end of study (L)	2.56	2.47	2.51	2.45	2.69	2.65
Mean change from baseline (L)	+0.39	+0.27	+0.38	+0.28	+0.17	+0.13
% Change from baseline	+20.8%	+12.7%	+19.3%	+12.9%	+8.8%	+7.0%
P-value	0.032		0.127		0.316	

As the original study reports did not account for multiplicity in endpoints or multiple assessments of the same variable made at different time points, three different sensitivity analyses were performed by the statistical reviewer, James Gebert, PhD., to assess the robustness of results: 1) on-treatment averages of % change from baseline FEV₁ over the different treatment phase study visits; 2) averaged % changes in FEV₁ from subjects who had participated in all four treatment study visits, and 3) a repeated measures analysis on the observed case assessments of percent changes from baseline FEV₁. According to the statistical reviewer, all three sensitivity analyses supported the finding that zileuton ER was more effective than placebo for % change in the trough FEV₁ from baseline at 12 weeks as well as at Weeks 5, 6, and 10. Details of the three sensitivity analyses are available in Dr. Gebert's statistical review.

Subgroup analysis by asthma severity (severity based on FEV₁) did not show any stratified improvement for the most severe group receiving zileuton ER compared to placebo. The uneven distribution of asthma severity among treatment arms may have confounded the results, although the other mean baseline asthma characteristics of the zileuton ER group versus the placebo ER group appeared comparable. Direct comparison between moderate-to-persistent and severe-persistent asthmatics' responses to study drug were not made. Overall, no conclusions about the efficacy of zileuton in certain disease subgroups can be made on the basis of the provided data.

No subgroup analyses by gender, age, or ethnicity were performed by the Applicant. Subgroup analyses performed by the statistical reviewer suggested lack of efficacy in patients ≤ 18 years of age and (N=14) and Blacks (N=18). The small number in each of these subsets limits the reliability of these analyses.

Reviewer's comment: Although the post hoc subgroup analysis is limited by the small number of patients of minority patients, the analysis suggested that Blacks actually did worse on zileuton ER compared to placebo. This issue should be considered in the review of future clinical studies and any post-marketing data.

6.1.4.3.2 Primary efficacy findings: Study M96-464

In contrast, Study M96-464 did not demonstrate that zileuton ER was statistically superior to placebo at 12 weeks or at 24 weeks in mean change from baseline trough FEV1 and mean percent change from baseline FEV1. Zileuton ER was numerically superior, but overall, performed comparably to placebo. Subgroup analysis by severity or by inhaled corticosteroid use did not indicate differential efficacy among groups.

Reviewer's comment: The addition of usual asthma medications to the regimen may have masked any benefit attributable to zileuton ER. Alternatively, reduced bioavailability of the ER formulation compared to the IR formulation may be partially responsible for the lack of efficacy seen in this study, although the pharmacokinetic comparison suggests that this scenario is unlikely. Also, patients enrolled in Study M96-464 overall may have had milder disease than patients in Study M95-337, making a treatment effect less discernible. The comparison of disease severity across studies is limited, however, by the concomitant use of other asthma medications in this study.

6.1.4.4 Secondary efficacy findings

Secondary efficacy data for both studies were generally supportive of the efficacy of zileuton ER. In Study M95-337, no statistically significant improvement in AM and PM PEFs was noted although the overall trends numerically favored zileuton ER over placebo. Among the other efficacy variables examined, the results suggested a small but consistent reduction in beta-agonist use frequency and amount. As for symptom scores, exacerbations, and QOL questionnaire scores, the results again were not statistically significant but the numerical values favored zileuton over placebo.

In Study M96-464 patients in the zileuton ER group demonstrated improvement in AM and PM PEFs compared to placebo, although treatment effect sizes were of arguable clinical significance (~25 and 17 L/min, respectively, at 24 weeks). Although most other secondary variable comparisons numerically favored the zileuton ER group, no statistically significant differences between treatment groups were noted. Hospitalizations for asthma were the exception, where 5 cases were reported for the zileuton ER group and none for placebo (p=0.162). 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 as noted previously. Hospitalizations for asthma will be discussed separately in Section 7.

Details of the secondary efficacy results are available in the individual study reports provided in the Appendix.

Reviewer's comment: The Applicant has proposed that the PEFR data for Study M96-464 provides evidence of efficacy, despite the failure of the study to meet its primary efficacy variable of trough FEV1. While PEFR data is supportive of efficacy, PEFR measurements tend to be less reliable and are generally insufficient as the main evidence of efficacy in an asthma trial.

6.1.5 Clinical Microbiology

Zileuton ER is not an antimicrobial drug product, and the application does not contain any clinical microbiology data.

6.1.6 Efficacy Conclusions

The Applicant has provided reports for two Phase 3 efficacy and safety studies conducted by Abbott using Formulation H: Study M95-337, a 12-week clinical efficacy study and Study M96-464, a 6-month long-term safety study. One of these two studies provides convincing evidence of zileuton ER's efficacy for the proposed indication, Study M95-337. Study M96-464 did not provide convincing evidence of the efficacy of zileuton ER, although results were generally supportive. It is unclear why study M96-464 did not establish the efficacy of zileuton ER; most likely, the inclusion of usual asthma medications in patients' regimens masked any benefit attributable to zileuton ER. Alternatively, patients enrolled in Study M96-464 overall may have had milder disease than patients in Study M95-337, making a treatment effect less discernible. The comparison of disease severity across studies is limited, however, by the concomitant use of other asthma medications in this study and different inclusion criteria regarding medication use at baseline.

Given the pharmacokinetic link to zileuton IR and the efficacy demonstrated in Study M95-337, and to a lesser degree, Study M96-464, the application demonstrates the efficacy of zileuton ER for the proposed indication of the prophylaxis and chronic treatment of asthma.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Safety was assessed in the clinical studies with reports of adverse events, laboratory values, and vital signs, in addition to data available from the zileuton IR clinical studies and postmarketing surveillance. Eight hundred eighteen patients with exposure to zileuton ER up to 6 months from the Phase 3 placebo-controlled trials are the primary focus of this Integrated Summary of Safety. An additional 151 subjects who participated in the Phase 1 pharmacokinetic studies were also reviewed; their exposures were limited to 1 week or less and many of these subjects received only a single dose. Where relevant, data from these additional subjects is also discussed although the information obtained from the Phase 1 studies is far more limited.

Table 6 summarizes the duration of exposure.

Table 6 Duration of exposure to Zileuton ER	
Number (%) of patients with exposure:	Zileuton ER (N=818)
≥ 29 days	749 (91.6)
≥ 57 days	693 (84.7)
≥ 85 days	556 (68.0)
≥ 113 days	492 (60.1)
≥ 141 days	482 (58.9)
≥ 159 days	473 (57.8)
Duration of exposure days for completers:	
N	621
Mean (SD)	149.2 (35.81)
Median	168.0
Minimum, Maximum	76, 194

Overall, the safety profile of zileuton ER was comparable to the safety profile for zileuton IR. The most relevant safety issues for this review were liver function test (LFT) and white blood cell count abnormalities.

7.1.1 Deaths

No deaths occurred during the course of the zileuton ER studies, with the exception of 1 patient who died prior to enrollment in Study M96-464 and never received study drug. During the screening visit, he developed cough and chest tightness and then subsequently became unconscious and apneic approximately 40 minutes after completing PFTs. The patient was transported to an emergency room where additional resuscitation measures were attempted but failed. The patient was deemed to have died from status asthmaticus.

7.1.2 Other Serious Adverse Events

A total of 42 non-fatal, serious adverse events (SAEs) were reported in the zileuton ER studies. One SAE was reported for a patient who developed a slipped disc requiring orthopedic repair during a Phase 1 study, CTI-03-C05-102. The remaining 41 SAEs were reported during the Phase 3 clinical trials. Of the 41, two occurred during the placebo, single-blind lead-in period of Study M95-337 and one occurred 155 days after the end of treatment in Study M96-464. Another 4 SAEs were reported for the placebo IR arm of Study M95-337.

In the Phase 3 studies, the incidence of SAEs in zileuton ER arms and placebo ER arms during treatment were comparable: 22 cases (2.6%) versus 12 (2.4%), respectively. The most common SAE in the zileuton ER group for both Phase 3 studies was hospitalization due to asthma (10/22 SAEs) Four out of the 22 were categorized as drug overdoses but did not require any medical intervention. Three of the overdose cases involved 1 additional dose of study drug on 1 study day; the fourth case involved 1 patient who took an extra dose for 4 study days. The remaining SAEs were hospitalizations for a wide range of causes: 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; pseudomonas pneumonia complicated by pneumothorax; cat bite infection; perirectal abscess; low back pain attributed to L4-5 central disk protrusion and possible spinal stenosis; hysterectomy for uterine

fibroids; removal of a right renal cyst; elective back surgery due to chronic back pain; pylorospasm; and atrial flutter/fibrillation. The various diagnoses do not suggest a common, drug-related adverse experience.

In the placebo ER group, 3 of the 12 SAEs were hospitalizations due to asthma exacerbations. In the remaining 9, the hospitalizations were due to a range of unrelated diagnoses. Overall, the rate of hospitalizations for asthma was greater for placebo than zileuton ER. However, review of the individual studies noted an imbalance of hospitalizations due to asthma compared to placebo in Study M96-464. In this study, 5 hospitalizations for asthma were reported for the zileuton ER arm compared to none in the placebo group. Examination of the case narratives and baseline demographic information for the study did not provide an explanation for this imbalance. Reassuringly, the rates of asthma exacerbations and emergency room visits were greater in the placebo arm compared to zileuton ER as anticipated in this study.

7.1.3 Dropouts and Other Significant Adverse Events

7.1.3.1 Overall profile of dropouts

	Zileuton ER (N=818)	Placebo ER (N=505)
<i>Completed study</i>	621 (75.9)	372 (73.7)
<i>Prematurely discontinued</i>	197 (24.1)	133 (26.3)
Adverse event	100 (12.2)	73 (14.4)
Personal reasons	31 (3.8)	16 (3.1)
Non-compliance	23 (2.8)	9 (1.8)
Withdrawal of consent	17 (2.1)	14 (2.8)
Lost to follow-up	12 (1.5)	9 (1.8)
Restricted medication	10 (1.2)	4 (0.8)
Lack of efficacy	7 (0.8)	13 (2.5)
Relocation	7 (0.8)	4 (0.8)
Pregnancy	2 (0.2)	3 (0.6)
Did not qualify	1 (0.1)	2 (0.4)
Sponsor request	1 (0.1)	0
Other†	3 (0.4)	2 (0.4)

*The number of patients in each category followed by the percentage of discontinued patients is provided in each column. Patients were permitted to cite more than reason for dropout.

† Some discontinuations were categorized as "other" by site investigators.

Table 7 summarizes reasons for early discontinuation from the two Phase 3 studies. The overall rate of discontinuation was comparable between zileuton ER and placebo arms, including discontinuations due to adverse events. More subjects in the placebo arm discontinued due to lack of efficacy, while more subjects in the zileuton ER arm discontinued due to non-compliance. Conceivably, non-compliance may have been related to unreported adverse events or drug intolerance but no conclusions can be drawn on the basis of the data provided.

7.1.3.2 Adverse events associated with dropouts

Non-serious adverse events cited as reasons for early termination are displayed in Table 8. In several cases, patients cited more than one reason for early withdrawal from the study. These data were collated by the reviewer from case narratives, as no summary information on specific

adverse events associated with dropouts was provided in the application. The terms used reflect the reasons cited in the case narratives and have not been classified using MedDRA preferred terms. A total of 197 patients in the zileuton ER arm and another 133 patients on placebo prematurely terminated from the study. Adverse event frequencies are presented as a percentage of the total number of early dropouts.

Number, %	Zileuton ER (N=818)	Placebo ER (N=505)
Total number of early terminations	197 (24.1)	133 (26.3)
Premature termination due to AE	100 (12.2)	73 (14.4)
Asthma exacerbation	29 (3.5)	34 (6.7)
Abdominal discomfort/pain	12 (1.5)	2 (0.4)
Nausea	8 (1.0)	4 (0.8)
Rash	6 (0.7)	3 (0.6)
Dizziness	5 (0.6)	2 (0.4)
Headache	4 (0.5)	3 (0.6)
Sinusitis	4 (0.5)	2 (0.4)
Urticaria	3 (0.4)	1 (0.2)
Upper respiratory tract infection	3 (0.4)	1 (0.2)
Insomnia	3 (0.4)	0
Nasopharyngitis	3 (0.4)	2 (0.4)
Fatigue	2 (0.2)	4 (0.8)
LFT elevation	2 (0.2)	2 (0.4)
Leucopenia	2 (0.2)	2 (0.4)
Bronchitis	2 (0.2)	2 (0.4)
Anxiety	2 (0.2)	2 (0.4)
Tachycardia	2 (0.2)	0
Chest discomfort	2 (0.2)	0
Vomiting	2 (0.2)	0
Mental impairment	1 (0.1)	1 (0.2)
Hypoglycemia	1 (0.1)	0
Acneiform dermatitis	1 (0.1)	0
Muscle cramp	1 (0.1)	0
Tachyarrhythmia	1 (0.1)	0
Depression	1 (0.1)	0
Constipation	1 (0.1)	0
Irregular menses	1 (0.1)	0
Hyperlipidemia	1 (0.1)	0
Tuberculosis	1 (0.1)	0
Diarrhea	1 (0.1)	0
Cheilitis/glossitis	1 (0.1)	0
Paresthesia	1 (0.1)	0
Acne	1 (0.1)	0
Lymphadenopathy	1 (0.1)	0
Ear pain	1 (0.1)	0
Palpitations	0	2 (0.4)
Pruritus	0	1 (0.2)
Thrombocytosis	0	1 (0.2)
Erectile dysfunction	0	1 (0.2)
Eczema	0	1 (0.2)
Irritable bowel syndrome	0	1 (0.2)
Anemia	0	1 (0.2)
Alopecia	0	1 (0.2)

In the Phase 3 trials, the most common adverse event associated with dropout in the zileuton arm was asthma exacerbation. Other cited non-serious adverse events included abdominal discomfort, nausea, and dizziness, consistent with adverse events listed on the approved zileuton IR label. Several cases of possible allergic reactions to zileuton ER were observed, including cases of acute onset urticaria after the first and later exposures.

Reviewer's comment: The most common adverse events cited as reason for dropout are consistent with AEs listed on the zileuton IR label and are likely treatment-related, e.g. abdominal discomfort, nausea, and dizziness. Other adverse events are more difficult to evaluate due to their rare nature and limited information provided in the case narratives. Liver enzyme elevation and leucopenia are discussed separately in Sections 7.1.7.2 and 7.1.7.5.

7.1.3.3 Other significant adverse events

Hepatic injury and leucopenia are known adverse events associated with zileuton IR. Liver enzyme elevations and white cell count associated with zileuton ER are discussed separately in Sections 7.1.7.2 and 7.1.7.5, respectively. No other significant adverse events are reported by the Applicant.

7.1.4 Other Search Strategies

Review of post-marketing data for zileuton IR since its approval did not indicate any new safety signals and is reviewed in more detail in Section 7.1.17. An electronic PubMed search [search terms: zileuton; search restrictions: human] yielded 256 literature reports and did not suggest any additional safety concerns not already described in the zileuton IR label.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were defined as any undesirable event such as signs, symptoms, or other findings experienced during a study or within 30 days after study drug discontinuation *OR* any event experienced with greater severity or frequency than documented in the patient's medical history. In Study M95-337, patients were instructed to contact the study site investigator with any adverse events as well as any complaints of worsening asthma symptoms. Patients also completed daily diaries and were instructed to describe any unusual or adverse experiences, including dates, duration, severity, and any treatment. Investigators reviewed these diaries and generated case report forms based on the information provided. Investigator review of the diary took place at Weeks 1, 2, 4, 6, 10, 14, and 16. In addition, investigators were instructed to monitor individual patients closely for evidence of drug intolerance and for the development of clinical or laboratory evidence of an AE at each study visit: Screening, Day 1, Weeks 1, 2, 4, 6, 10, 14, 16, and the 30-day follow-up visit. No formal checklist was used.

A similar approach was adopted for Study M96-464, with the exception that study visits occurred at longer intervals. Patient diaries were reviewed at Day 1, Month 1, 2, 3, 4, 6, and at the 30-day follow-up. Investigator clinical and laboratory monitoring for AEs was updated at those same study visits. No formal checklist was used.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

Adverse events were originally coded using COSTART preferred terms in the Abbott clinical database. AEs were subsequently recoded by CRTX using MedDRA, Version 7.1, preferred terms. The unique, reported terms were identified and compared with the MedDRA lower level term (LLT) using an autoencoder. If the terms matched exactly, the MedDRA LLT was assigned to the reported term. The MedDRA system organ class (SOC) and preferred term that linked to the LLT were reviewed to confirm that they were the appropriate choice for the reported term. All the remaining reported terms without an exact LLT match were manually assigned after review by the data manager. Upon completion of coding, two separate audits were performed by the Applicant to assess consistency in the recoding.

Preferred terms were examined for this review and spot-checked against case narratives, particularly for the SAEs. In general, the Applicant appears to have handled the recoding appropriately.

7.1.5.3 Incidence of common adverse events

The Applicant's report and display of AEs were consistent within each study report and in the Integrated Summary of Safety (ISS). The Applicant focused on all SAEs, AEs occurring in >3% of the zileuton ER arm, and AEs with lower incidence rates that occurred more frequently in the zileuton ER arm versus the placebo arm. The Applicant did not provide a summary table for subjects who discontinued the study due to non-serious AEs. To assess these events, the reviewer examined and tabulated the individual case narratives. Summary tables for all adverse events were provided in the Integrated Summary of Safety Appendix. The Applicant also included separated tabulation of events by investigator-determined relationship to the drug. For the most part, those presentations of events were not reviewed in depth.

In the ISS, the Applicant combined data from the two Phase 3 trials. Although the study designs differ, the dose regimens and recruitment criteria for the two studies were comparable and make this approach acceptable; safety data for the individual studies is provided in the respective study reports and reviewed in more detail in the Appendix of this review. Phase 1 data was presented separately and was not reviewed in depth, given the limited degree of exposure characterizing these earlier studies.

7.1.5.4 Common adverse event tables

Table 9 is collated from tables provided in the Applicant's ISS and ISS appendix regarding adverse events reported for at least 3% of patients in the zileuton ER group in the two Phase 3 studies.

Table 9 Adverse events reported for at least 3% of patients in the zileuton ER treatment arm and occurring more commonly in the zileuton ER group than placebo

SOC Preferred term	Number (%) patients	
	Zileuton ER N=818	Placebo ER N=505
Any adverse event	694 (84.8)	412 (81.6)
No adverse event	124 (15.2)	93 (18.4)
<i>Respiratory, thoracic, and mediastinal disorders</i>	386 (47.2)	265 (52.5)
Pharyngolaryngeal pain	45 (5.5)	24 (4.8)
<i>Infections and infestations</i>	283 (34.6)	160 (31.7)
Nasopharyngitis	75 (9.2)	45 (8.9)
URTI	62 (7.6)	34 (6.7)
Bronchitis	33 (4.0)	20 (4.0)
<i>Gastrointestinal disorders</i>	223 (27.3)	84 (16.6)
Nausea	67 (8.2)	21 (4.2)
Diarrhea	37 (4.5)	10 (2.0)
Vomiting	36 (4.4)	9 (1.8)
Stomach discomfort	32 (3.9)	16 (3.2)
Dyspepsia	29 (3.5)	12 (2.4)
Toothache	28 (3.4)	8 (1.6)
<i>Nervous system disorders</i>	223 (27.3)	97 (19.2)
Headache	164 (20.0)	85 (16.8)
Dizziness	34 (4.2)	8 (1.6)
<i>Musculoskeletal and connective tissue disorders</i>	166 (20.3)	101 (20.0)
Myalgia	48 (5.9)	18 (3.6)
<i>Skin and subcutaneous tissue disorders</i>	73 (8.9)	36 (7.1)
Rash	28 (3.4)	12 (2.4)
<i>Psychiatric disorders</i>	66 (8.1)	19 (3.8)
Insomnia	36 (4.4)	6 (1.2)

Source: Volume 124, Section 5.4.1.1 and Volume 128, Table 2.2.1.1

7.1.5.5 Identifying common and drug-related adverse events

A wide range of adverse events were reported for both the zileuton ER and placebo arms in Study M95-337 and Study M96-464. Comparison of incidence rates between arms and across the individual studies suggests that certain adverse events were likely treatment-related: several types of gastrointestinal complaints (nausea, diarrhea, vomiting, and dyspepsia), headache and dizziness, insomnia, and hepatotoxicity. The nature and frequency of these adverse events were generally consistent with those described in the zileuton IR label.

Stratification of these events by asthma severity, age, gender, ethnicity, and inhaled corticosteroid (Study M96-464 only) was performed. No clinically relevant age-related differences were noted although the number of very old and very young subjects was limited. Overall, more adverse events were reported by women than men, in particular nausea (11.4% vs. 4.1%). Females in general had a higher incidence of nausea than men in both zileuton ER and placebo arms. More Musculoskeletal and Connective Tissue Disorders were reported by men. No race-related treatment differences were noted, although again, the number of non-white study participants was limited. In Study M96-464, patients using ICS were more likely to report AEs in the Respiratory, Thoracic, and Mediastinal Disorders and conditions such as nasopharyngitis, sinusitis, upper respiratory tract infections; this disparity likely reflects a difference in baseline asthma disease severity or may be due in part to side effects associated with use of ICS.

Analysis of AEs by time interval presented by the Applicant shows that the incidence of AEs decreased over time for most of the AEs during each study. Two of the most common AEs,

headache and nausea, both decreased over the treatment duration from the initial study interval (DB Study days 1-14) to the end of each respective study.

7.1.5.6 Additional analyses and explorations

The adverse events that seem drug-related have been previously reported for zileuton and are included in the approved zileuton IR label. No new safety signals were identified in review of the zileuton ER safety database and additional analyses and explorations were not performed.

7.1.6 Less Common Adverse Events

The size of the safety database for the two clinical studies is unlikely to adequately evaluate less common adverse events. The majority of patients in the Phase 3 studies reported an adverse event (84.8% for zileuton ER; 81.6% for placebo). The frequency of uncommon events reflects that same trend. In the zileuton ER arm, one hundred sixty-seven different AEs were reported that each had an N=1 patient; another 52 AEs were reported that each had an N=2 patients. Evaluation of these rare events and their relationship to drug treatment is difficult. Events that occurred with <3% frequency but at least 0.5% more commonly in zileuton ER patients compared to placebo were examined to look for other possible treatment difference in uncommon events. Using this criterion, the following events were identified:

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Table 10 Uncommon adverse events occurring at least 0.5% more commonly in zileuton ER patients compared to placebo in the Phase 3 studies		
	Zileuton ER (N=818)	Placebo ER (N=505)
Fatigue	24 (2.9)	10 (2.0)
Cough	24 (2.9)	9 (1.8)
Neck pain	22 (2.7)	5 (1.0)
Viral infection	18 (2.2)	3 (0.6)
Muscle cramp	14 (1.7)	6 (1.2)
Dyspnea	14 (1.7)	4 (0.8)
Respiratory tract congestion	13 (1.6)	4 (0.8)
Hypersensitivity	13 (1.6)	3 (0.6)
Abnormal hepatic function	12 (1.5)	4 (0.8)
Anxiety	12 (1.5)	2 (0.4)
Depression	10 (1.2)	3 (0.6)
Chest discomfort	10 (1.2)	2 (0.4)
Flatulence	9 (1.1)	3 (0.6)
Abdominal discomfort	9 (1.1)	1 (0.2)
Abdominal pain	9 (1.1)	0
Tremor	8 (1.0)	2 (0.4)
Vaginal mycosis	7 (0.9%)	2 (0.4%)
Joint sprain	7 (0.9%)	2 (0.4%)
White blood cell count decrease	7 (0.9%)	1 (0.2%)
Otitis media	7 (0.9%)	0
Somnolence	6 (0.7%)	1 (0.2%)
Herpes simplex	6 (0.7%)	1 (0.2%)
Gingival pain	6 (0.7%)	0
Fungal infection	4 (0.5%)	0
Seasonal rhinitis	4 (0.5%)	0
Agitation	4 (0.5%)	0
Asthenia	4 (0.5%)	0
Eye pruritus	4 (0.5%)	0
Gastroenteritis	4 (0.5%)	0
Lethargy	4 (0.5%)	0
Lymphadenopathy	4 (0.5%)	0
Chills	4 (0.5%)	0

The following AEs were also noted to occur in the zileuton IR controlled trials and are likely to be treatment-related: hypersensitivity, low white blood cell count, and abnormal hepatic function. Leucopenia and LFT elevations are discussed in further detail in Section 7.1.7. Other less common adverse events that are mentioned in the zileuton IR label include lymphadenopathy, somnolence, and flatulent. The zileuton IR label also mentions vaginitis, pruritus, nervousness, and malaise, which may overlap with some of the reported less common AEs for zileuton ER. The other less common AEs do not appear to be serious and do not suggest any consistent pattern of body system involvement; their relationship to zileuton remains uncertain.

7.1.7 Laboratory Findings

7.1.7.1 Overview of laboratory testing in the development program

Routine laboratory testing was performed regularly during each study and as dictated by individual AEs. For Study M95-337, routine chemistries (including liver function tests), hematology, and urinalysis were performed at Screening, Day 1, Weeks 1, 2, 4, 6, 10, 14, 16, and the 30-day follow-up visit. A similar approach was adopted for Study M96-464, with the

exception that study visits occurred at longer intervals: Day 1, Month 1, 2, 3, 4, 6, and at the 30-day follow-up.

- Hematology: complete blood cell count with white cell count differential
- Hepatic chemistries: alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alkaline phosphatase (ALK PHOS), lactate dehydrogenase (LDH), and total bilirubin (TBILI)
- Renal and electrolytes: uric acid, blood urea nitrogen (BUN), creatinine, sodium, potassium, chloride, carbon dioxide, calcium, and inorganic phosphorus
- Metabolic: glucose, total protein, albumin, cholesterol, and triglycerides

Given the known risk for hepatic enzyme elevations associated with zileuton IR, a specific management algorithm was adopted for liver function tests and is described in further detail in Section 7.1.7.5.

A total of 774 zileuton ER patients and 478 placebo patients had baseline laboratory assessments and at least one post-baseline assessment. The assessment of laboratory values is based on these patients.

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

The two placebo-controlled Phase 3 studies were the primary basis for the review of drug-control comparisons of laboratory values, with particular attention paid to the 6-month Study M96-464. Longer term data on zileuton ER is not available.

7.1.7.3 Standard analyses and explorations of laboratory data

Laboratory test results are reviewed in Section 7.1.7.4, with the exception of liver enzyme abnormalities, which are discussed separately under Section 7.1.7.5.

7.1.7.3.1 *Analyses focused on measures of central tendency*

7.1.7.3.1.1 Hematology

Mean Hematology values were generally similar between zileuton ER and placebo groups and mean changes were small and not clinically significant.

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Table 11: Changes from baseline in hematology values*			
INDICES		Zileuton ER (N=774)	Placebo (N=447)
Hemoglobin (g/dl)	Mean (SD)	-0.19 (0.760)	-0.09 (0.763)
	Median	-0.20	-0.10
Hematocrit (%)	Mean (SD)	0.21 (2.886)	0.17 (2.765)
	Median	0.20	0.20
Platelets (x 10 ⁹ /L)	Mean (SD)	3.7 (38.20)	3.5 (38.21)
	Median	3.0	4.0
WBC (x 10 ⁹ /L)	Mean (SD)	-0.202 (1.7023)	-0.027 (1.9349)
	Median	-0.230	-0.060
Neutrophils (%)	Mean (SD)	1.35 (9.181)	1.18 (9.011)
	Median	1.40	1.00
Lymphocytes (%)	Mean (SD)	-0.87 (8.161)	-0.62 (8.192)
	Median	-1.00	-0.50
Monocytes (%)	Mean (SD)	0.15 (1.901)	0.13 (1.637)
	Median	0.10	0.20
Eosinophils (%)	Mean (SD)	-0.69 (3.015)	-0.65 (2.822)
	Median	-0.40	-0.50
Basophils (%)	Mean (SD)	0.02 (0.527)	-0.02 (0.440)
	Median	0	0

* Based on patients with baseline and follow-up laboratory values for comparison

Source: Volume 124, Table 5.6-1

7.1.7.3.1.2 Chemistry

With the exception of hepatic enzymes, discussed separately in Section 7.1.7.5, no clinically significant mean changes from baseline were noted for chemistry values.

Table 12: Changes from baseline in chemistry values*			
INDICES		Zileuton ER (N=774)	Placebo (N=447)
Uric acid (mg/dl)	Mean (SD)	-0.05 (0.738)	0.02 (0.729)
	Median	-0.10	0
BUN (mg/dl)	Mean (SD)	0.2 (3.32)	-0.1 (3.28)
	Median	0	0
Creatinine (mg/dl)	Mean (SD)	0.03 (0.111)	0 (0.117)
	Median	0	0
Sodium (meq/L)	Mean (SD)	1.4 (3.11)	1.4 (2.80)
	Median	1.0	1.0
Potassium (meq/L)	Mean (SD)	0 (0.408)	0.01 (0.374)
	Median	0	0
Chloride (meq/L)	Mean (SD)	0 (3.22)	-0.3 (3.11)
	Median	0	0
CO ₂ (meq/L)	Mean (SD)	0.9 (2.45)	1.1 (2.26)
	Median	1.0	1.0
Calcium (mg/dl)	Mean (SD)	-0.16 (0.398)	-0.13 (0.381)
	Median	-0.20	-0.10
Inorganic phosphorus (mg/dl)	Mean (SD)	0.09 (0.605)	0.03 (0.553)
	Median	0.10	0
Glucose (mg/dl)	Mean (SD)	3.1 (17.05)	2.8 (16.72)
	Median	2.0	3.0
Total protein (g/dl)	Mean (SD)	-0.09 (0.406)	-0.05 (0.430)
	Median	-0.10	0
Albumin (g/dl)	Mean (SD)	0.03 (0.264)	0 (0.275)
	Median	0	0
Cholesterol (mg/dl)	Mean (SD)	-1.2 (20.75)	-0.6 (22.26)
	Median	-1.0	-1.5
Triglycerides (mg/dl)	Mean (SD)	9.1 (62.64)	13.4 (72.46)
	Median	5.0	9.0

* Based on patients with baseline and follow-up laboratory values for comparison

Source: Volume 124, Table 5.6-5 and Table 5.6-8

7.1.7.3.2 Analyses focused on outliers or shifts from normal to abnormal

The limits used to determine extreme laboratory values were based on the Common Terminology Criteria for Adverse Events (CTCAE) v3.0, December 12, 2003.

7.1.7.3.2.1 Hematology

White blood cell count abnormalities, primarily leucopenia ($<3.0 \times 10^9/L$), were observed in 2.1% zileuton ER patients vs. 1.9% placebo ER placebo patients in the two clinical studies. In most cases, the leucopenia was clinically asymptomatic and resolved soon after discontinuation of the drug. The rates reported are slightly higher than those rates reported in the Adverse Reactions section of the zileuton IR label (1.0% vs. 0.6%, respectively). However, leucopenia is defined using more stringent criteria ($\leq 2.8 \times 10^9/L$) in the current zileuton IR label.

Reclassification of the zileuton ER patients using the more stringent cutoff reduces the observed rate to 1.2%, which is comparable to the rate reported for zileuton IR. The Applicant has proposed inclusion of the higher rates in the draft label for zileuton ER.

7.1.7.3.2.2 Chemistry

The proportion of patient with extreme renal or electrolyte abnormalities was $<1.5\%$ and no clinically significant differences were noted between zileuton ER and placebo groups. Similarly, no clinically significant differences were noted between treatment groups for metabolic evaluations. Hypertriglyceridemia (2.1% zileuton ER vs. 2.3% placebo) and hypercholesterolemia (0.8% vs. 0.6%, respectively) were the most commonly observed metabolic abnormalities.

7.1.7.3.3 Marked outliers and dropouts for laboratory abnormalities

In 11 of the 16 noted cases of leucopenia, the values normalized or returned to baseline by the final visit. Two patients on zileuton ER discontinued the study due to low WBC count. Patient 2567 had a WBC count of $3.53 \times 10^9/L$ at baseline, which dropped to $2.57 \times 10^9/L$ by Study Day 67. He subsequently dropped out of the study and by follow-up Day 50, his WBC count had normalized ($4.07 \times 10^9/L$). Patient 5149 dropped her WBC count from $3.68 \times 10^9/L$ to $2.78 \times 10^9/L$ and dropped out on Day 56; as of follow-up day 29, her WBC count remained low ($2.31 \times 10^9/L$). No other patients were discontinued for laboratory abnormalities, with the exception of LFT elevations, discussed in Section 7.1.7.5.

7.1.7.4 Additional analyses and explorations

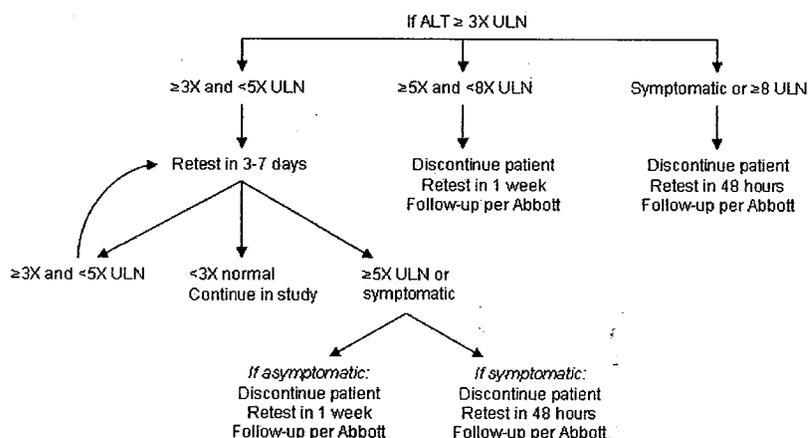
No formal dose-ranging study was performed for zileuton ER; the proposed 1200 mg BID regimen is based on the approved zileuton IR dose, 600 mg QID. In the zileuton IR Phase 3 studies, no relationship between zileuton blood levels and AEs were observed. Likewise, no drug-demographic, drug-disease, or drug-drug interaction studies were performed in the clinical development program for zileuton ER. Information on these interactions is extrapolated from previous zileuton IR studies.

7.1.7.5 Special assessments: Hepatotoxicity

7.1.7.5.1 LFT monitoring schedule

Hepatotoxicity is a known adverse event associated with zileuton IR. As a result, LFT monitoring received special attention in the Phase 3 zileuton ER studies. LFT elevations >5X ULN were reported as AEs. LFTs were routinely monitored on the same schedule as other laboratory assessments; abnormalities over a certain threshold triggered a monitoring algorithm in both studies:

Figure 1 Liver function test monitoring algorithm



7.1.7.5.2 Analysis by central tendency

The majority of patients did not demonstrate a clinically significant increase in their LFT values. Mean and median changes from baseline are presented in Table 13. There was a trend towards an increase in the mean ALT, AST, GGT, and LDH in the zileuton ER group compared to the placebo group.

Indices		Zileuton ER (N=774)	Placebo (N=447)
ALT (IU/L)	Mean (SD)	6.3 (60.75)	1.2 (12.89)
	Median	0	0
AST (IU/L)	Mean (SD)	1.8 (22.96)	-0.4 (7.77)
	Median	-1.0	0
GGT (IU/L)	Mean (SD)	4.4 (36.04)	1.2 (9.39)
	Median	1.0	0
Alk Phos (IU/L)	Mean (SD)	0.1 (34.21)	-3.0 (15.41)
	Median	-1.0	-2.0
LDH (IU/L)	Mean (SD)	4.4 (26.05)	1.5 (21.06)
	Median	2.5	1.0
TBILI (mg/L)	Mean (SD)	-0.01 (0.231)	-0.01 (0.240)
	Median	0	0

* Based on patients with baseline and follow-up laboratory values for comparison
Source: Volume 124, Table 5.5-1

7.1.7.5.3 Abnormal LFT values

The number and percentage of patients with LFT abnormal values in the Phase 3 studies for zileuton ER are shown in Table 14.

Table 14: Number and percentage of patients with LFT abnormalities in Phase 3 trials of zileuton ER							
Zileuton ER (N=818)							
	≤1X ULN*	>1-3X ULN	3-5X ULN	5-8X ULN	8->15X ULN	≥15X ULN	Missing
Alk phos	750 (91.7)	58 (7.1)	2 (0.2)	1 (0.1)	0	0	7 (0.9)
GGT	746 (91.2)	56 (6.8)	6 (0.7)	0	3 (0.4)	0	7 (0.9)
LDH	764 (93.4)	47 (5.7)	0	0	0	0	7 (0.9)
AST	710 (86.8)	94 (11.5)	2 (0.2)	2 (0.2)	3 (0.4)	0	7 (0.9)
ALT	667 (81.5)	128 (15.6)	5 (0.6)	5 (0.6)	4 (0.5)	2 (0.2)	7 (0.9)
Placebo (N=505)							
Alk phos	473 (93.7)	25 (5.0)	0	0	0	0	7 (1.4)
GGT	464 (91.9)	33 (6.5)	1 (0.2)	0	0	0	7 (1.4)
LDH	475 (94.1)	23 (4.6)	0	0	0	0	7 (1.4)
AST	448 (88.7)	45 (8.9)	3 (0.6)	2 (0.4)	0	0	7 (1.4)
ALT	422 (83.6)	73 (14.5)	2 (0.4)	1 (0.2)	0	0	7 (1.4)

*ULN: upper limit of normal

Source: Volume 124, Table 5.5-4

Most elevations were categorized as mild (>1X ULN to <1.5X ULN for TBILI and >1X ULN to <3X ULN for other LFTs). The rate of "significant" LFT elevations (≥3X ULN) in the clinical studies in this application, ~2%, was consistent with the rate described in placebo-controlled trials for zileuton IR. In general, the LFT abnormality was an elevation in ALT that occurred within the first month of treatment and resolved after discontinuation of the drug (<2X ULN). As shown in the table below, there were 16 zileuton ER patients with ALT >3xULN. All 16 zileuton ER patients with ALT >3xULN resolved off drug. The time to resolution varied from 4 to 101 days and did not correlate directly with the magnitude of the LFT elevation. The incidence of Tbili elevations was lower in the zileuton ER group (1.7%) compared to placebo (2.8%). The majority of elevations were asymptomatic, although a few cases were associated with other adverse events, including right upper quadrant tenderness, rash, dark urine, fatigue, nausea, and diarrhea. Whether these other symptoms resolved with normalization of the LFTs is not reported in the case narratives, but there does not appear to have been any long-term clinically relevant sequelae associated with the LFT abnormalities.

Previous studies with zileuton IR suggested a slightly increased risk of LFT elevations in female patients ages 65 years and older, but this result was not observed in the zileuton ER studies after stratification by age and gender. No differences by race were noted. Review of individual case narratives does not suggest other clinically relevant risk factors.

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7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Vital signs, including blood pressure, sitting pulse rate, respiratory rate, and body temperature were assessed at each study visit and were summarized by analysis group.

7.1.8.2 Selection of studies and analyses for overall drug-control comparisons

The two placebo-controlled Phase 3 studies were the primary basis for the review of drug-control comparisons of vital signs, with particular attention paid to the 6-month Study M96-464. Longer term data on zileuton ER is not available.

7.1.8.3 Standard analyses and explorations of vital signs data

7.1.8.3.1 Analyses focused on measures of central tendencies

Overall, no clinically significant differences were noted in changes from mean or median baseline vital sign measurements for the zileuton ER or placebo treatment groups. There did not appear to be any clinically significant drug-effect on vital signs.

7.1.8.3.2 Analyses focused on outliers or shifts from normal to abnormal

Extreme values were defined by the Applicant as follows: SBP < 80 or increase from baseline ≥ 40 mm Hg; DBP < 50 or increase from baseline ≥ 40 mm Hg; and pulse rate < 50 or > 120. The most common vital sign abnormality was an increase in DBP of at least 20 mm Hg from baseline. This abnormality was more frequently observed in the placebo group (6.9%) than in the zileuton ER arm (4.6%). The other abnormality observed was a low pulse rate, again more common in the placebo group (1.7%) compared to zileuton ER (0.9%). There did not appear to be any clinically significant drug-effect on vital signs.

7.1.8.3.3 Marked outliers and dropouts for vital sign abnormalities

No marked outliers are noted from either Phase 3 study and no patients were discontinued from the study due to a vital sign abnormality.

7.1.8.4 Additional analyses and explorations

No additional analyses or explorations were performed on the vital sign data.

7.1.9 Electrocardiograms (ECGs)

7.1.9.1 Overview of ECG testing in the development program, including brief review of preclinical results

A 12-lead ECG was performed at Screening for all patients and subsequently for cardiac-related signs or symptoms as determined by each investigator. The ECG results were reviewed by the

investigator. Any changes deemed by a consulting cardiologist to be outside “normal physiological variation” were considered clinically significant. Information on zileuton ER’s cardiac safety is also extrapolated from previous studies and post-marketing surveillance data available for zileuton IR.

7.1.9.2 Selection of studies and analyses for overall drug-control comparisons

The review is based on the two, placebo-controlled Phase 3 trials. No findings of clinical relevance were noted at screening or during treatment in the two studies. No systematic analyses or explorations of ECG were subsequently performed.

7.1.9.3 Standard analyses and explorations of ECG data

7.1.9.3.1 Analyses focused on measures of central tendency

No systematic analyses or explorations of ECG data were performed for this submission.

7.1.9.3.2 Analyses focused on outliers or shifts from normal to abnormal

No systematic analyses or explorations of ECG data were performed for this submission.

7.1.9.3.3 Marked outliers and dropouts for ECG abnormalities

No systematic analyses or explorations of ECG data were performed for this submission.

7.1.9.4 Additional analyses and explorations

No systematic analyses or explorations of ECG data were performed for this submission.

7.1.10 Immunogenicity

No immunogenicity studies are included in this submission, which is reasonable for this small molecule drug product.

7.1.11 Human Carcinogenicity

Long-term human carcinogenicity data is not available for zileuton ER. During the course of the 12-week and 6-month Phase 3 trials, no new diagnoses of tumor were made. Post-marketing data up to September 2006 for zileuton IR do not suggest any carcinogenic effects in humans.

7.1.12 Special Safety Studies

No special safety studies were conducted for zileuton ER.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

No special studies regarding withdrawal phenomena and/or abuse potential were conducted for zileuton ER or IR, as these issues were not considered to pertain to this class of drugs.

7.1.14 Human Reproduction and Pregnancy Data

No formal studies of zileuton ER or IR in pregnancy have been conducted. Two pregnancies were reported in Study M95-337 and 6 pregnancies in Study M96-464. The two patients in Study M95-337 had been randomized to placebo and did not receive zileuton. Both patients were terminated from the study. One patient (Patient 10005) underwent an elective abortion at 9 weeks; the other patient (Patient 10278) delivered a full term baby girl without complications. In Study M96-464, 1 of the 6 women was found to be pregnant after study completion and was still pregnant at the time of original study report. Her outcome is unknown. The other 5 patients were discontinued from the study. Of the two women randomized to the zileuton ER group, one patient (Patient 5266) delivered a full-term baby without complications while the other patient (Patient 6825) underwent elective abortion. The three other pregnant women in Study M96-464 had been randomized to the placebo arm. Patient 2966 delivered a baby boy by Cesarean section; the other two patients experienced spontaneous abortions.

On the basis of these inadvertent exposures, no specific safety signals were identified. Zileuton IR is Pregnancy Category C, and the Applicant proposes a similar rating for zileuton ER, which is appropriate given the available data.

7.1.15 Assessment of Effect on Growth

No pediatric studies were performed for zileuton ER and no assessment has been made of zileuton ER's effect on growth.

7.1.16 Overdose Experience

In the Phase 3 experience, there were 4 reported cases of drug "overdose." None of the cases required any medical intervention and did not appear to be clinically symptomatic. 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.

7.1.17 Post-marketing Experience

There is no postmarketing data available for zileuton ER. Zileuton ER has not been applied for approval in any countries outside of the United States. The Applicant has provided post-marketing safety data for zileuton IR updated to May 2006. Three deaths associated with hepatic injury have been reported since its approval in December 1996. The 3 cases were medically complex and characterized by significant co-morbidities, making assessment of zileuton's contribution to the case outcome difficult to discern. In at least 1 case, zileuton appears to have led to theophylline toxicity, which may have predisposed the patient to a series of events resulting in death. The other 2 cases do not appear to be directly related to zileuton. Other cases of major hepatocellular injury have been reported, including life-threatening liver injury with recovery (N=3), Hy's rule (N=3), symptomatic jaundice and hyperbilirubinemia (N=2), and an ALT >8X ULN (N=11). An FDA Office of Drug Safety (ODS) review (August 5, 2003) previously concluded that the post-marketing safety profile of zileuton IR appeared consistent with adverse events listed in the label. From July 2004 until the 4th quarter of 2005, zileuton

IR's sale was temporarily suspended during the transfer of the product from Abbott to CRTX. From the 4th quarter of 2005 to May 2006, no new fatalities or SAEs have been reported.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Study type and design/patient enumeration

The primary source of clinical data for the safety review was the Phase 3 studies conducted by Abbott. Phase 1 studies were reviewed briefly but their contribution to the safety database was limited, given the type of patients enrolled (healthy volunteers) and short durations of exposures (single-dose and multiple-dose studies up to 6 days). The safety data is supplemented by the known safety profile of zileuton IR.

Per patient data was available from hard copy patient data listings in the NDA, hard copy patient narratives in the NDA, electronic data sets provided for statistical review, and CRFs for patients who discontinued due to AEs in electronic .pdf files. Other CRFs were available on request.

Literature reports referenced by the Applicant were reviewed briefly. In addition, the reviewer performed an electronic PubMed search [search terms: zileuton; search restrictions: human] that yielded 256 literature reports; these articles were briefly reviewed and did not suggest any additional safety concerns not already described in the zileuton IR label.

Table 1 summarizes the study designs and subject enrollment of the two pharmacokinetic studies and the two Phase 3 studies relevant to this application. Additional detail of the individual studies can be found in the individual study reviews included in the Appendix.

7.2.1.2 Demographics

In general, the Phase 3 studies enrolled a wider age range of subjects and a higher percentage of non-White participants compared to Phase 1 studies. Demographic information for the clinical studies is summarized in Table 15.

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	Phase 3 trials		Phase 1 trials
	Zileuton ER (N=818)	Placebo ER (N=505)	N=151
Age, years			
Mean (SD)	35.3 (13.72)	35.4 (13.36)	35.1 (10.09)
Median	34.0	35.0	35
Range	12-83	12-81	18-56
Sex, n (%)			
Male	345 (42.2)	210 (41.6)	87 (57.6)
Female	473 (57.8)	295 (58.4)	64 (42.4)
Race, n (%)			
White	692 (84.6)	431 (85.3)	70 (46.4)
Black	58 (7.1)	41 (8.1)	30 (19.9)
Other	68 (8.3)	33 (6.5)	51 (33.8)

Source: Volume 124, Table 5.3-1 and Table 6.3-1

7.2.1.3 Extent of exposure (dose/duration)

All clinical studies included in this application used the same dose of zileuton ER, 1200 mg BID. Extent of exposure is summarized in Table 6 for the Phase 3 studies and in Table 1 for the Phase 1 studies.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

7.2.2.1 Other studies

No additional studies were reviewed for this application.

7.2.2.2 Postmarketing experience

Zileuton ER is not marketed elsewhere in the world and no post-marketing data is available. The Applicant has included post-marketing information on zileuton IR in the application. This information is reviewed in further detail in Section 7.1.17.

7.2.2.3 Literature

The Applicant provided 171 literature references, and for certain reports, full hard-copies of the articles regarding zileuton IR. In addition, the reviewer performed an electronic PubMed search [search terms: zileuton; search restrictions: human] that yielded 256 literature reports; these articles were briefly reviewed and did not suggest any additional safety concerns not already described in the zileuton IR label.

7.2.3 Adequacy of Overall Clinical Experience

Because the exposure of zileuton ER is less than the exposure of zileuton IR, we can rely on the safety database for zileuton IR to supplement the zileuton ER safety database. Therefore, adequate numbers of patients were included in the program to assess the safety of zileuton ER. The study designs, doses, and durations of exposure were adequate to assess safety for the

intended use. Although specific studies were not conducted to assess potential class effects and special populations, the existing safety database for zileuton IR compensates for this deficiency.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

The application largely references preclinical information previously reviewed in NDA 20-471 for zileuton IR. Specific to zileuton ER, the Applicant provided adequate qualifications for additional impurities associated with the ER formulation.

7.2.5 Adequacy of Routine Clinical Testing

Routine clinical testing for adverse effects was adequate. Patients were tested at screening, baseline, follow-up, and at appropriate, regular intervals during the treatment phases. Specific laboratory monitoring for hepatic injury are discussed in Section 7.2.7

7.2.6 Adequacy of Metabolic, Clearance, and Interaction Workup

In general, the pharmacokinetic evaluation of the to-be-marketed zileuton ER formulation (CRTX Formulation E21) was adequate and is discussed in more detail in Section 5 and Clinical Pharmacology review. Formal drug-drug-interaction studies were not conducted for zileuton ER but the Applicant references studies previously conducted with zileuton IR, which is an appropriate and acceptable reference.

7.2.7 Adequacy of Evaluation for Potential Adverse Events for Any New Drug and Particularly for Drugs in the Class Represented by the New Drug; Recommendations for Further Study

Hepatotoxicity is an established risk associated with use of zileuton IR, similar to other leukotriene modifiers. Liver function was monitored adequately in the clinical trials for zileuton ER, exceeded the monitoring frequency recommended in the zileuton IR product label. In addition, the Applicant has proposed a risk management program and pharmacovigilance program similar to the existing program for zileuton IR, which should provide additional safety information on potential hepatotoxicity in real-life use.

7.2.8 Assessment of Quality and Completeness of Data

The data and form of the data provided for the safety review are described in Section 7.2.1. Given the extended time period that has elapsed since the conduct of the original Abbott trials and that the Applicant acquired rights to the product after completion of the development program, the Applicant had limited control over the quality of data. Overall, the safety data appeared adequate and complete, although in certain instances the reviewer was required to tabulate the primary data e.g. adverse events associated with dropout. Laboratory data, particularly LFTs, were of particular interest in this review and this data appeared adequate and complete.

7.2.9 Additional Submissions, Including Safety Update

7.2.9.1 Responses to information requests

The primary source of data for the safety review was the information submitted by the Applicant in this application. No information requests were made regarding safety data.

7.2.9.2 Four-month safety update

A four-month safety update for zileuton IR was submitted (2 volumes) on November 16, 2006. The update included post-marketing line listings, as well as a finalized study report for an open-label safety study of zileuton IR in asthma (Study CTI-02-C04-001) that was completed in June 2004. The findings from the post-marketing surveillance are discussed in Section 7.1.17 and the results of Study CTI-02-C04-001 are consistent with the adverse event profile presented in the approved zileuton IR label.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

7.3.1 Hepatic injury

Hepatic injury has been previously established as an adverse event associated with zileuton IR. Data from the clinical program for zileuton ER suggests a similar hepatotoxicity profile, discussed in further detail in Section 7.1.7.5. The incidence rate of elevated liver function tests in patients treated with zileuton ER reported from the two Phase 3 trials was approximately 2%. Generally, these elevations occurred within the first month of use and resolved after discontinuation of the drug. Relevant information and a monitoring algorithm is recommended in the product labeling, in addition to a risk management program and pharmacovigilance program as previously discussed with the Applicant prior to the submission of this application.

7.3.2 White cell count decreases

As previously observed with zileuton IR, leucopenia ($<3.0 \times 10^9/L$) was observed in 2.1% zileuton ER patients and appears to be drug-related. Using an adjusted cutoff value, this rate approximates the rate observed in the controlled zileuton IR studies. As none of these cases were clinically symptomatic or significant and all resolved after discontinuation of the drug, this safety signal does not preclude approval of the drug. However, information regarding leucopenia should be included in the zileuton ER product label.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

7.4.1.1 Pooled data vs. individual study data

The Applicant pooled Phase 3 data for the ISS, providing safety assessments for the individual studies in the respective study reports. The two studies differed somewhat in terms of the study designs, so both pooled data and individual study data were examined for the purpose of this review. Incidence rates for LFT elevations, the primary concern, were comparable for the individual studies, as were incidence rates for adverse events occurring with >3% frequency. Therefore, the pooling of this data did not appear to hide any potential informative difference. For less common events, comparison of the pooled event rates between zileuton ER and placebo arms did not reveal additional safety signals. Phase 1 data was pooled separately but were of limited utility due to short durations of exposure.

7.4.1.2 Combining data

When data were combined, the numerators and denominators were simply combined.

7.4.2 Explorations for Predictive Factors

7.4.2.1 Explorations for dose dependency for adverse findings

No dose-exploration was performed for zileuton ER. Based on data from zileuton IR studies, there does not appear to be a consistent relationship between serum concentrations of zileuton and common adverse events.

7.4.2.2 Explorations for time dependency for adverse findings

Data from the clinical studies do not suggest a clear time dependency for adverse events, although it was noted that most hepatic enzyme elevations and white blood cell count decreases occurred during the first 3 months of use.

7.4.2.3 Explorations for drug-demographic interactions

Formal special population studies for zileuton ER were not conducted. When stratified by age, gender, and ethnicity, there appears to be an increased risk of liver enzyme elevations among older females. There were low numbers of very young and very old patients, as well as a small number of non-white study participants, limiting the strength of these observations.

7.4.2.4 Explorations for drug-disease interactions

The population enrolled in both studies was patients with mild to moderate asthma. Within this category, patients with more severe disease tended to report respiratory adverse events such as asthma exacerbations and cough, as might be expected, and do not appear to be drug-related. No other clinically significant drug-disease interactions are noted.

7.4.2.5 Explorations for drug-drug interactions

Formal drug-drug interaction studies were not performed for zileuton ER. Information on potential interactions is extrapolated from zileuton IR and is discussed in more detail in Section 8.2.

7.4.3 Causality Determination

Of the adverse events described, liver enzyme elevations and white blood cell count decreases appear to be drug-related and are consistent with the safety profile of zileuton IR. Gastrointestinal complaints, such as nausea and dyspepsia, are likely drug-related given the route of administration and the physical properties of the drug tablet. Other common adverse events, such as dizziness and headache, were consistently more common in zileuton ER groups compared to placebo, although the pathophysiology behind these reactions remains unclear. Among rare events, hypersensitivity reactions appear to be drug-related given their time-course. Other rare events are more difficult to assess and will require further study before any conclusions can be made.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dose of zileuton ER is 1600mg twice daily. The dosage and dosing regimen are based on the approved dosing regimen for zileuton IR. The application does not provide convincing evidence of efficacy for this dose using the zileuton ER formulation. Lack of efficacy may be due in part to lower bioavailability of the ER formulation compared to the IR formulation. Although bioavailability is improved in the presence of food, zileuton ER has a lower systemic exposure to zileuton than zileuton IR. Additional study of this zileuton ER dose is recommended to support efficacy. A higher dose or more frequent dosing is likely unfeasible, given the concern for hepatotoxicity and the practicality of administering an oral drug more than four times per day.

8.2 Drug-Drug Interactions

Information on drug-drug interactions is based on prior formal interaction studies and assessment of adverse events with the zileuton IR formulation. These data are summarized in the zileuton IR package insert. No new drug interaction studies were conducted with _____ for the submission of this NDA.

Zileuton undergoes extensive metabolism in the liver to form inactive zileuton (R+) and (S-) glucuronides. Common drugs sharing this metabolic pathway have been examined in formal drug-interaction studies. Theophylline, warfarin, and propranolol all require downward dose adjustment, along with clinical and laboratory monitoring as indicated. No significant interactions have been found with prednisone, ethinyl estradiol, digoxin, phenytoin, sulfasalazine, or naproxen. No formal studies have been performed with dihydropyridine, calcium channel blockers, or cyclosporine, all of which are metabolized by the hepatic enzyme, CYP3A4.

In placebo-controlled trials of zileuton IR, analysis of adverse events did not suggest any drug interactions with inhaled beta-agonists.

8.3 Special Populations

No formal studies in special populations have been conducted with zileuton ER. Review of data from the two Phase 3 studies does not indicate any differential efficacy of safety by gender or ethnicity. The pharmacokinetics of zileuton IR in geriatric patients, patients with renal failure, and patients with hepatic impairment have been previously reported and are described in the zileuton IR product label. Patients with renal impairment do not require dose adjustment and hepatic impairment is a contraindication for both zileuton formulations.

8.4 Pediatrics

The application includes a request for full waiver of pediatric requirements for zileuton ER in neonates, infants, and children up to 4 years of age, citing unpredictable hepatic metabolism and hematologic immaturity in this age group, which are safety concerns specific to this drug product. The sponsor has also requested a deferral of the Pediatric Research Equity Act (PREA) requirements for zileuton ER in children ages 4 to 11 years on several grounds, including difficulty in developing a suitable extended-release dosage form for patients in this age group. A waiver and deferral as requested are reasonable from a clinical standpoint.

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).

8.5 Advisory Committee Meeting

No Advisory Committee meeting related to this application was held or is planned.

8.6 Literature Review

The application includes a bibliography of 171 citations culled from literature searches using "zileuton" as the main search term and reprints of 35 citations deemed to be particularly relevant. All references are literature reports, including studies of zileuton-related hepatotoxicity. Those

were reviewed to the extent of their relevance to the evaluation of the application. The reviewer also performed an electronic PubMed search, yielding 256 literature reports [search terms: zileuton; search limit: human]. The majority of these reports overlapped with the 171 citations provided by the Applicant. These references did not yield any new safety signals and provided efficacy data of variable reliability for asthma and other off-label indications.

8.7 Postmarketing Risk Management Plan

8.7.1 Zileuton risk management plan

The Applicant included a risk management plan, Zileuton RiskMAP, in the application, to screen and prevent serious hepatic injury in the postmarketing period. The main components described in the plan are:

- Patient package inserts
- Patient educational materials to be distributed by client physicians
- Physician education materials with testing to document health care provider's knowledge and understanding of potential adverse effects
 - ACCME-approved zileuton monograph discussing potential hepatotoxicity
 - Direct distribution via the Applicant's Medical Affairs department with client physicians
 - Direct mailing program and distribution at major medical meetings
 - Pre-test and post-test with follow-up survey to assess impact of educational intervention
 - Results from a representative physician sample to be submitted to the Agency with PSUR compilations
 - Periodic random sampling of patient records to gauge liver enzyme screening practices

Reviewer's comment: The plan is consistent with the plan discussed at the pre-NDA meeting with the Applicant. As no new safety signals have been identified for the ER formulation following review of the NDA, the plan appears adequate.

8.7.2 Zileuton pharmacovigilance plan

The Zileuton RiskMAP will be conducted in conjunction with the *Zileuton Pharmacovigilance Plan (Zileuton PVP)*. The Zileuton PVP includes general pharmacovigilance activities and specific activities to monitor hepatotoxicity:

- Automated zileuton signal detection program using the Agency's Freedom of Information (FOI) database
- Triaging, processing, and follow-up of individual case safety reports (ICSRs)
- Regular searches of the medical literature for zileuton-related adverse events
- The Zileuton Risk Management Team aimed at monitoring hepatotoxic events specifically
- Specific questions relating to liver injury added to the spontaneous adverse event intake form

Reviewer's comment: The plan is consistent with the plan discussed at the pre-NDA meeting with the Applicant. As no new safety signals have been identified for the ER formulation following review of the NDA, the plan appears adequate.

8.8 Other Relevant Materials

Consultations were provided for this application by the Division of Drug Marketing, Advertising, and Communication (DDMAC); the Division of Medication Errors and Technical Support (DMETS), and Study Endpoints and Label Development group (SEALD). A consultation request was placed with the Division of Scientific Investigation (DSI) but was unable to be completed due to budgetary restrictions as discussed in Section 4.4.

The SEALD review was completed on September 28, 2006. The consult recommended several revisions to the proposed labeling, specifying formatting changes in detail. These comments were conveyed to the Applicant in the 74-day letter (October 12, 2006). The results of the DDMAC and DMETS consults are pending at the time of finalization of this review.

In addition, a previous review performed by the Office of Drug Safety (ODS; August 5, 2003) on postmarketing data for zileuton IR was referenced for the safety review of this application.

9 OVERALL ASSESSMENT

9.1 Conclusions

This review finds that the data submitted by the Applicant provides adequate evidence to support the indication proposed by the Applicant: "the prophylaxis and chronic treatment of asthma in adults and children ages 12 and older." Given the preexisting efficacy data available for zileuton IR and the pharmacokinetic link to zileuton IR, Study M95-337 provides the necessary confirmatory support of efficacy. Study M96-464 provides further supplementary support of efficacy.

Study M95-337, demonstrated a statistically and clinically significant improvement in trough FEV1, the primary endpoint. In this study, patients who received zileuton ER were observed to have a greater improvement from baseline trough FEV1 compared to patients in the placebo after 12 weeks of treatment (+0.39 ml vs. +0.27 ml; $p=0.021$). Secondary and other efficacy variables examined were generally supportive of zileuton ER's efficacy, if not statistically significant. Although no direct statistical comparisons were made between zileuton ER and zileuton IR, an active control, zileuton ER appeared to perform comparably to zileuton IR.

The 6-month study, Study M96-464, did not demonstrate a statistically significant difference from placebo in the primary endpoint, trough FEV1. As evidence of efficacy in this study, the Applicant relied on peak flow data. While these secondary data were generally supportive, peak flow data is not as reliable as spirometric data and is not sufficient evidence of efficacy. In addition, as there was no pre-specified statistical analysis plan and no adjustment for multiplicity

for the numerous secondary endpoints, the peak flow data is further devalued. However, if not statistically significant, the overall trend in the results favored zileuton ER over placebo for the primary and secondary endpoints, providing adjunct support of efficacy to this application.

Given the results of Study M95-337 and to a lesser degree, Study M96-464, this review concludes that the Applicant has demonstrated zileuton ER's efficacy for the proposed indication, the prophylaxis and chronic treatment of asthma in patients ages 12 years of age and older.

This review agrees with the Applicant's conclusion that the safety profile of zileuton ER appears comparable to zileuton IR. The rate of LFT elevations and general adverse event profile in the two Phase 3 studies corresponded to rates described in the zileuton IR product label. As the Applicant has proposed, a risk management program and a pharmacovigilance plan are appropriate post-marketing safety measures in addition to information provided on the product label.

9.2 Recommendation on Regulatory Action

From the clinical standpoint, the recommended action is **Approval**.

The data submitted in this application provides sufficient evidence of efficacy for the proposed indication. From a safety perspective, the submitted data indicate a safety profile similar to the approved product, zileuton IR. In addition, the safety is supported by the fact that there is less systemic exposure with the ER formulation compared to the IR formulation.

9.3 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

Given the risk of hepatotoxicity association with zileuton ER, post-marketing risk management and pharmacovigilance are appropriate measures to minimize the risk of major hepatic injury and to monitor for emerging safety signals. Review of the proposed Zileuton RiskMap and Zileuton PVP does not identify any major clinical issues at this time and is consistent with the plan discussed at the pre-NDA meeting with the Applicant.

9.3.2 Required Phase 4 Commitments

The Applicant will be required to explore the use of zileuton ER in children ages 4 to 11 to comply with PREA. A deferral for this age group at this time is acceptable.

9.3.3 Other Phase 4 Requests

No other Phase 4 requests are anticipated at this time.

10 APPENDICES

10.1 Review of Individual Study Reports: Protocol M95-337

Study M95-337: Phase 3 study of the efficacy of zileuton 1200mg BID, extended release (ER), and 600mg QID, immediate release (IR), and placebo in patients with moderate asthma

10.1.1 Study administrative information

- Protocol Issue Date: July 1996
- Protocol Amendment Dates: Revision 1 (October 22, 1996) and Revision 2 (January 14, 1997)
- Study Dates: November 25, 1996 to August 21, 1997
- Study Sites: 79 investigational sites located in the US
- Study Report Date: CRTX study report (January 31, 2006), original Abbott study report (June 1998)
- Source: Volume 74 (CRTX study report), Vol 77 (Abbott study report), Vol 81 (protocol and amendments)

Reviewer's comment: The CRTX study report (Volume 74) and the original protocol (Volume 81) were the basis for this review. Results presented in the CRTX study report were cross-checked with statistical tables provided in the appendix of the Abbott study report.

10.1.2 Objectives/Rationale

The primary objective was to compare safety and efficacy of zileuton ER to placebo. Zileuton IR tablets were included as a benchmark comparison with previous efficacy studies using the IR formulation.

10.1.3 Study design

Sixteen-week, randomized, double-blinded, placebo-controlled multicenter trial. After a single-blinded, 14-day placebo run-in period (Period I), subjects were randomized into a double-blind, 12-week treatment period (Period II) followed by a 2-week run-out period (Period III) off study medication. Patients who discontinued study due to AE were seen 26-34 days following discontinuation.

10.1.4 Study population

Subjects between ages 12 to 81 years of age with moderate asthma.

10.1.4.1 Inclusion criteria

10.1.4.1.1 Period I:

1. Ages 12 to 81 years of age.
2. FEV1 of 40-75% predicted when taken at least 48 hours after last theophylline use and at least 6 hours after short-acting beta-agonist use or 24 hours after long-acting beta-agonist use
3. FEV1 reversibility of at least 15% when tested 15 minutes after 2 puffs of albuterol

4. Adult weight within 30% acceptable range in Metropolitan Life actuary tables. Minimum weight of 90lbs. Patients 17 years and younger could not be morbidly obese.
5. Limited alcohol intake (no more than 2 oz alcohol per day, 2 x 12 oz beer per day, 2 x 4 oz wine per day, or 2 regular cocktails)
6. No chronic medications except oral/depot contraceptives, estrogen replacement, vitamins, diuretics for mild HTN or thyroid medication. Occasional nasal steroid and short courses of antibiotics for infections permitted.
7. No anti-asthma medications except short-acting bronchodilator.

10.1.1.1.1 Period II:

1. Negative urine pregnancy test.
2. Completion of patient diaries from Period I and $\geq 75\%$ study medication compliance.
3. FEV1 at end of Period I between 40-75% predicted and $\leq 10\%$ over baseline (Period I, Study Day 1).
4. Mean Daily Symptom Assessment Score (DSA) of at least 1 but not greater than 2.5 during Period I.
5. Beta-agonist use on average of at least 2 occasions per day during Period I.

10.1.1.2 Exclusion criteria

1. Pregnancy or breastfeeding.
2. Significant systemic disease
3. Clinically significant ECG abnormalities.
4. Clinically significant abnormalities on screening except those related to asthma.
5. History of elevated ALT $\geq 5x$ ULN. Patients with elevated TBili and documented Gilbert's disease permitted.
6. History of allergy or other significant adverse reactions to drugs similar to study medication
7. Tobacco use in prior 6 months. Ex-smokers must have ≤ 10 pack-year history of cigarette smoking.
8. Hospitalization for asthma within 6 months prior to screening.
9. Investigational drug within 30 days prior to study.

10.1.5 Study treatments

- 1200mg zileuton ER (600mg tablet) BID (7AM and 7PM, within 1 hour of meal)
- 600mg zileuton IR QID (7AM, 1PM, 6PM, and 11PM without regard to meals)
- Placebo zileuton ER BID
- Placebo zileuton IR QID

Dose selection based on results of dose-ranging study (M90-460) and two Phase 3 studies (M91-685 and M92-720) evaluating safety and efficacy of zileuton IR.

10.1.5 Randomization

Patients randomized in 2:1 ratio to CR:IR arms using computer-generated randomization schedules. Randomization did not include stratification for asthma severity. Study blind could be broken by Investigator or Abbott monitor if deemed to be in patient's best interest.

Period	Total N	Zileuton ER	CR placebo	Zileuton IR	IR placebo
I (placebo run-in)	786		523		263
II (treatment phase)	613	206	203	101	103
III (run-out)	464				

10.1.5 Study discontinuation

Patients had the right to withdraw from the study at any time. Study investigators could choose to discontinue a patient for any reason, including poor compliance or adverse events. In addition, the protocol specified 4 reasons for discontinuing a patient:

1. If steroids required for treatment of asthma, patient terminated and follow-up evaluation performed 1 month after study discontinuation.
2. If serum ALT reached 5X upper limit of normal, patient terminated and levels monitored weekly until normalization and then 4 weeks after normalization.
3. Clinically significant laboratory abnormalities as defined in table below:

Hematology	
<i>Hematocrit</i>	>10% below normal limit
<i>Hemoglobin</i>	>10% below normal limit
<i>Platelet count</i>	>20% below normal limit
<i>WBC count</i>	>20% below normal limit
Liver function tests	
<i>Alk phos</i>	>2X ULN (discontinue from study)
<i>AST</i>	>5X ULN (discontinue from study)
<i>Total bilirubin</i>	>2X ULN (discontinue from study)
Other tests	Investigator discretion

4. Positive pregnancy test. Pregnancy to be followed to completion with updates at least once per trimester and once after delivery.

10.1.5 Concomitant medications

The only asthma medication allowed during the study was short-acting beta-agonist (Ventolin) and was supplied to all patients. Patients were instructed to use the albuterol on an as-needed basis, recording each use in their diaries. Other chronic medications permitted included oral/depot contraceptives, estrogen replacement, vitamins, diuretics for mild hypertension, or thyroid medication. Occasional use of topical nasal steroids and short courses of oral antibiotics were also permitted, as was more regular use of nasal steroids or cromolyn if the dose had been stable for at least 6 weeks prior to enrollment or if used by the patient on a seasonal basis. Occasional decongestants, short-acting antihistamines, loratadine, or saline nasal irrigation were also permitted. Terfenadine and astemizole were not allowed. All medications used were to be recorded.

10.1.5 Study assessments and evaluations

10.1.6.1 Efficacy parameters

10.1.6.1.1 Primary efficacy variable: Trough FEV1

- Mean change from baseline and % change from baseline (order not specified)
- Baseline defined as trough FEV1 at the end of the placebo run-in phase (Period I)

- Albuterol held for ≥ 6 hours prior to testing

10.1.6.1.2 Secondary efficacy variable

PEFR

- Same time each AM (just before AM dose) and PM (~2200 hrs)
- Performed in triplicate
- Baseline defined as mean averaged over last 14 days of placebo run-in period
- AirWatch Unit electronic peak flow meter

10.1.6.2 Other efficacy variables

10.1.6.2.1 Beta-agonist use (number of occasions and puffs)

10.1.6.2.2 Daily and nocturnal symptoms

10.1.6.2.2.1 *Daily Symptom Assessment (DSA)*

Patients instructed to assess asthma symptoms during waking hours each evening:

- 0 = No symptoms at all; unrestricted activity
- 1 = Symptoms occurred, but with little or no discomfort; unrestricted activity
- 2 = symptoms occurred, sometimes annoying or affecting routine activity
- 3 = Symptoms severe, very little improvement after inhaler and required use of additional medication and/or doctor's visit

10.1.6.2.2.2 *Nocturnal Symptom Assessment (NSA)*

Patients to assess their sleep each morning upon waking:

- 0 = Slept well; no asthma symptoms
- 1 = spent restless night, may have awakened due to asthma; may have used inhaler
- 2 = awakened > 1 time due to asthma; inhaler used
- 3 = awake all night because of symptoms; inhaler used

10.1.6.2.3 Acute exacerbations of asthma

Patients meeting ≥ 1 of the following criteria:

- Decrease of $\geq 20\%$ from baseline AM PEFR (mean calculated from Period I; not used as criterion for Period I) on 4 of 7 consecutive days
- Decrease of $\geq 20\%$ from baseline FEV1 (during Period I, baseline defined as Study Day 1 measurement; during Period II, baseline defined as the measurement prior to dose on Study Day 15 (start of treatment period))
- ≥ 3 of 7 consecutive nights with awakening requiring albuterol use
- Albuterol use ≥ 12 puffs/day for 3 of 7 consecutive days

10.1.6.2.4 QOL measures

Self-administered questionnaire completed on Study Day 1, Day 43 (Period II day 29), and Day 99 (Period II day 85). Questionnaire addresses symptoms, activities, emotions, and environmental exposure, as well as overall quality of life.

10.1.5 Safety parameters

10.1.7.1 Adverse events

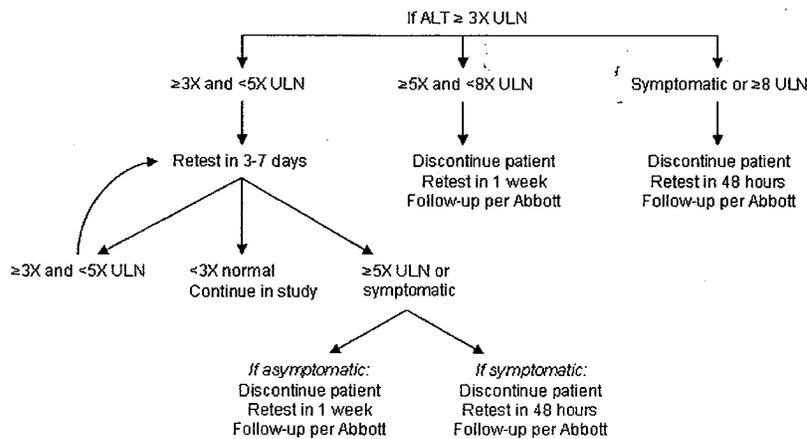
Defined as any untoward medical event not previously documented in patient's medical history or a worsening in severity of a pre-existing condition occurring during study or with 30 days of study discontinuation. AE considered to be serious if fatal, life-threatening, requiring hospitalization, prolonged hospitalization, severely or permanently disabling, associated with overdose, congenital anomaly, or cancer.

10.1.7.2 Change from baseline vital signs (BP, pulse, respiratory rate, and oral temperature)

10.1.7.3 Change from baseline hematology, chemistry, urinalysis labs

10.1.7.4 ALT elevations $\geq 3x$ ULN, number of days to onset and resolution

Figure 2 ALT elevation monitoring algorithm



10.1.5 Statistical plan

CRTX has stated that a pre-established, separate statistical analysis plan from Abbott does not exist except as specified in the protocol. The sample size was determined assuming an expected difference between zileuton ER and placebo ER of 8.5% percent change from baseline in FEV1. The difference is based on results from studies of zileuton IR compared to placebo (M91-685 and M92-720). The study was not powered for comparison between zileuton ER and IR formulations. Inferential treatment comparisons were declared statistically significant at the 5% level using 2-tailed tests.

In the original study report, Abbott tested treatment effects using ANOVA models that had a treatment-by-site interaction term. The term was removed from CRTX's analysis after discussion with the Division regarding potential for confounding treatment effect inferential tests. CRTX also employed Hochberg's procedure to assess impact of multiplicity on efficacy measurements.

Data that best corresponded to the nominal visit day from the appropriate interval was selected for all analyses. If 2 observations were the same number of days from the nominal visit day, then the observation following the visit day was selected for analysis. For the DB treatment period, data obtained more than 3 days after the end of dosing were not used for analyses.

DB Nominal visit day	LOCF	Observed data interval
Study day 15	2-22	2-22
Study day 29	2-43	23-43
Study day 57	2-71	44-71
Study day 85	2-92	72-92
Run-out/Study day 99	N/A	*

* Run-out analyses use data collected between 11 and 21 days after discontinuation of study drug.

10.1.5 Changes to protocol

10.1.9.1 Revision 1 (October 22, 1996)

These changes were approved prior to patient enrollment:

- 1) Up to 80 investigative sites instead of 75 sites.
- 2) Patients receiving CR formulation allowed to take study medication within 1 hour of meal rather than ½ hour.
- 3) A reference to study medication carton reference number added to the section referring to study drug labels.
- 4) The days of the study specified as Study Day 1, 8, 15, 29, 43, 71, 99, and 113 rather than Study Day 1, 7, 14, 28, 42, 70, 98, and 112.
- 5) Study Schematic changed to add 4 extra blood samples for patients receiving zileuton and placebo ER formulations for pharmacokinetic sampling.
- 6) A PEFR reading by spirometry added on Day 1 of lead-in period, designated as the Personal Best measurement to initiate the Air Watch device.
- 7) Multiple FEV1 measurements were to be captured using the Air Watch device during the lead-in period.
- 8) Schematic revised to clarify that on Study Day 29, patients to have study drug checked for compliance and re-dispensed for next dosing period.
- 9) The 4-hour fast requirement prior to blood sampling removed. An 8-hour fast prior to screening procedures added.
- 10) Blood samples for genetic polymorphism testing increased from 7-ml to 10-ml.
- 11) Patient randomization section modified to reflect use of the ~~randomization~~ CRC for drug assignment. The randomization script included in the protocol.
- 12) Clarification of dosing on the first day of the DB treatment period.
- 13) Protocol modified to request Investigators to contact the sponsor before dropping patients whose FEV1 values fell below 35%.
- 14) Study synopsis changed to clarify the sample size in the DB treatment period.

10.1.9.2 Revision 2 (January 14, 1997)

These changes approved after enrollment of 82 patients:

- 1) Additional allowed medications added to the patient inclusion criteria for Period I.
- 2) Urine pregnancy tests required at all study visits for all female patients except those with prior hysterectomy or post-menopausal for > 2 years

- 3) Study Schematic changes to reflect that Study Day 15 rather than Study Day 29 was the beginning of Period II.
- 4) Genetic polymorphism samples to be drawn at Study Day 15 rather than Study Day 29.
- 5) Additional details regarding bronchodilator reversibility testing added to pulmonary function testing section.
- 6) A new Personal Best PEFR was to be calculated on Study Day 15 based on values observed during the lead-in period. This value was used to assess subsequent PEFR performance for the remainder of the study.
- 7) A serum ALT that reached $\geq 3X$ ULN was not to be considered an AE and did not require completion of an AE form, but was to be monitored as per protocol. A serum ALT that reached $\geq 5X$ ULN was to be considered an AE. Any symptomatic serum ALT elevation was also to be recorded as an AE and be cause for early termination.
- 8) For asthma exacerbations in Period II, the baseline was defined as the measurement prior to dosing on Study Day 15, not on Day 28.
- 9) Claritin and Claritin-D added to list of allowed medications for symptomatic rhinitis.
- 10) Personnel changes made.
- 11) Concomitant drug restrictions list modified.
- 12) QOL forms changed to reference Protocol No. M95-337 and zileuton.
- 13) Informed consent form modified to eliminate reference to Abbott's Risk Management Department.
- 14) The SAE form, the Pregnancy Report Sheet, and the AirWatch instructions appendix were changed from stating Period II, Study Day 28 to Period II, Study Day 15.

10.1.5 Results

10.1.10.1 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:

- 8) 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).
- 9) 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.

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:

- 10) **Sensitivity analysis set 1** included all patients randomized into the treatment period at all study sites
- 11) **Sensitivity analysis set 2** excludes only patients enrolled by Dr. Thomas Edwards (N=10)

12) Sensitivity analysis set 3 excludes only patients enrolled by Dr. Robert Fiddes (N=12)

10.1.10.2 Protocol deviations

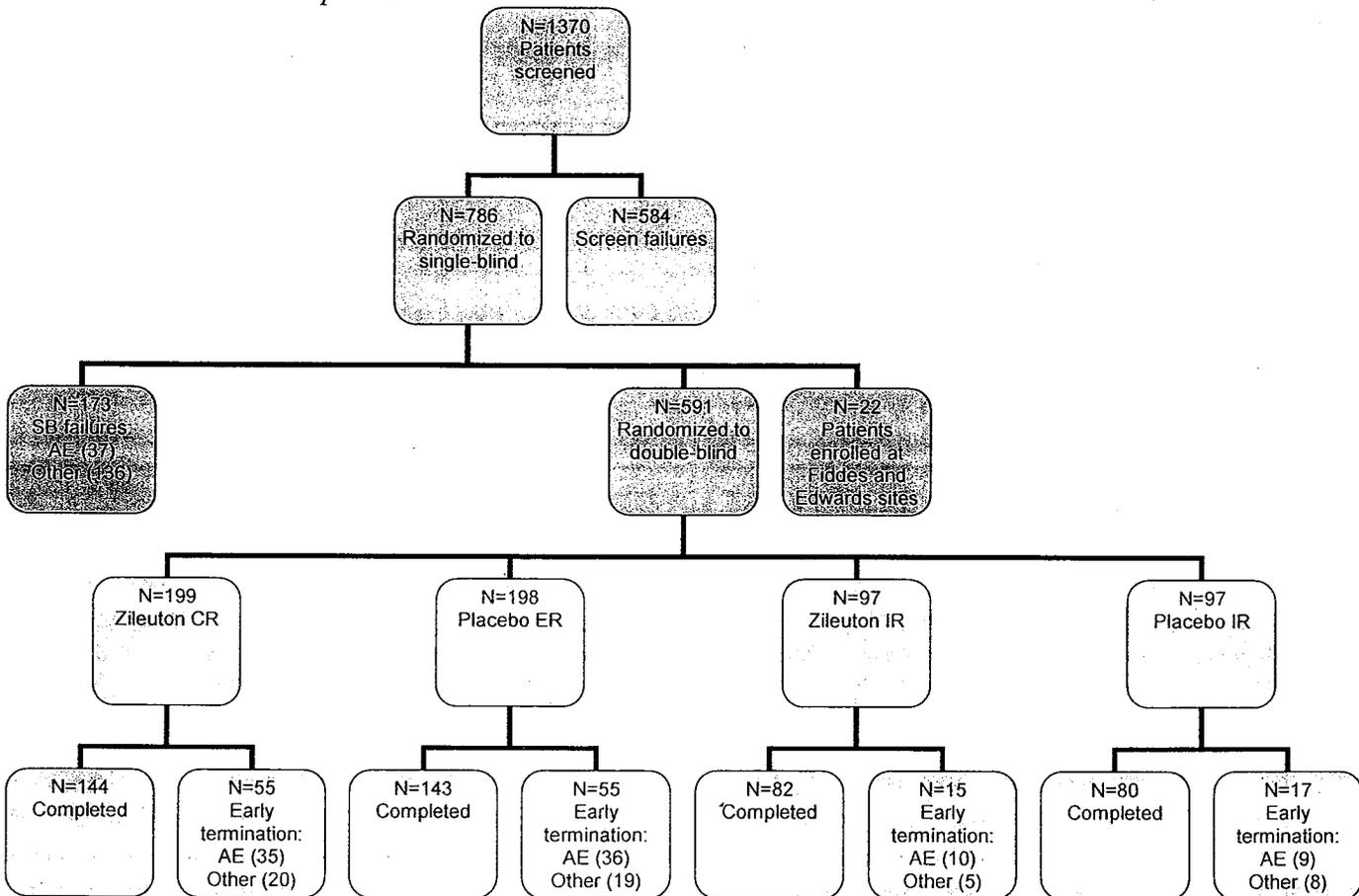
Protocol deviations were granted to particular study sites by medical monitors to allow certain patients to enroll who did not meet all study entrance criteria. The waivers were granted on a case-by-case basis to accommodate patients who were deemed to be appropriate study candidates but who fell slightly 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 105157 was excluded after Abbott learned that the patient had participated in both the efficacy (placebo ER) and long-term safety (zileuton ER) study simultaneously. Additional data sets were defined to address the above protocol deviations.

The blind was not broken for any patients in the study.

10.1.10.3 Study patients

10.1.10.3.1 Disposition



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10.1.10.3.2 Demographics/baseline characteristics(Full Analysis Set; see below)

10.1.10.3.2.1 Demographics

Treatment groups were comparable in terms of demographics and baseline asthma characteristics (Table 19 and Table 20). In general, the study participants were evenly divided by gender, were largely young adults, and predominantly Caucasian. Approximately 20-25% were tobacco users at time of enrollment. The majority of subjects displayed asthma characteristics consistent with moderate to severe persistent disease.

Treatment group	N	Mean age (range)	Sex (% M)	Race	History of tobacco use
Zileuton ER	199	33.3 (12-70)	50.25%	B=20 (10.05%) W=160 (80.4%) O=19 (9.55%)	21.12%
Placebo ER	198	34.1 (12-78)	44.95%	B=20 (10.10%) W=169 (85.35%) O=9 (4.55%)	25.25%
Zileuton IR	97	35.3 (12-81)	46.39%	B=13 (13.4%) W=80 (82.47%) O=4 (4.12%)	20.62%
Placebo IR	97	34.5 (12-74)	55.67%	B=9 (9.28%) W=75 (77.32%) O=13 (13.4%)	20.62%

10.1.10.3.2.2 Mean baseline asthma characteristics

	Zileuton ER (N=199)	Placebo ER (N=198)	P	Zileuton IR (N=97)	Placebo IR (N=97)	P
Trough FEV1 (L)	2.17	2.20	0.611	2.13	2.17	0.632
% predicted FEV1	57.68	59.42	0.087	58.12	58.19	0.965
Asthma severity*	Mild=1 (0.5%) Mod=83 (43.2%) Severe=108 (56.2%)	0 101 (54.0%) 86 (46.0%)	0.045	1 (1.0%) 37 (38.5%) 58 (60.4%)	3 (3.2%) 40 (43.0%) 50 (54%)	0.42
AM PEFR (L/min)	369.73	353.86	0.190	365.54	365.24	0.985
PM PEFR (L/min)	397.92	386.80	0.374	399.51	398.93	0.971
#occasions albuterol use/day	3.25	3.26	*	2.97	2.91	*
# puffs albuterol/day	5.99	5.96	*	5.67	5.37	*
DSA (Scale 0-3)	1.42	1.41	*	1.41	1.37	*
NSA (Scale 0-3)	1.37	1.32	*	1.32	1.37	*
QOL- overall score	4.02	4.06	*	4.12	4.07	*

* Asthma severity: mild (FEV1≥80% predicted), moderate (FEV1>60% and <80%), and severe (FEV1≤60%)

Reviewer's comments: Analysis using full and restricted analysis sets (see Section 10.1.10.3 for description of analysis sets) does not show any statistically significant differences between zileuton and placebo groups respectively. Zileuton IR to CR comparison not made. P-values are not reported for all data in the CRTX report to allow full comparison (marked as "*" in table).

10.1.10.4 Efficacy outcomes

10.1.10.4.1 Primary

Table 21. Study M95-337. Mean change from baseline trough FEV1 and % change from baseline: zileuton ER vs placebo ER

Study Day	Zileuton ER N=199		Placebo ER N=198		P
	Mean baseline	Mean change	Mean baseline	Mean change	
Day 15 (Week 2)	2.16	0.23 13.1%	2.19	0.09 3.9%	0.001 0.007
Day 29 (Week 4)	2.17	0.27 15.01%	2.20	0.20 9.48%	0.007 0.09
Day 57 (Week 8)	2.17	0.33 17.38%	2.20	0.20 9.67%	0.007 0.019
Day 85 (Week 12)	2.17	0.39 20.77%	2.2	0.27 12.73%	0.021 0.032

Table 22. Study M95-337. Mean change from baseline trough FEV1 and % change from baseline: zileuton IR vs placebo IR

Study Day	Zileuton IR N=97		Placebo IR N=97		P
	Mean baseline	Mean change	Mean baseline	Mean change	
Day 15 (Week 2)	2.13	0.17 8.55%	2.17	0.14 7.49%	0.582 0.670
Day 29 (Week 4)	2.13	0.23 12.48%	2.17	0.10 5.82%	0.027 0.018
Day 57 (Week 8)	2.13	0.31 15.93%	2.17	0.22 12.3%	0.215 0.265
Day 85 (Week 12)	2.13	0.38 19.3%	2.17	0.28 12.9%	0.188 0.127

- The study report states that more subjects had $\geq 12\%$ improvement in the zileuton ER group than placebo (63% vs. 50% at Study Day 85; $p=0.023$).
- Treatment groups were not stratified by asthma severity. More subjects with more severe asthma at baseline ($\leq 60\%$ predicted FEV1) were randomized to the zileuton ER group than to placebo (108 vs. 86; $p=0.045$).
- The sponsors have included analysis of mean change from baseline FEV1 and % change from baseline for patients with moderate asthma (FEV1 $>60\%$ to $<80\%$ predicted) and severe persistent asthma (FEV1 $\leq 60\%$). For patients with moderate asthma receiving zileuton ER, statistically significant improvements through various time-points compared to placebo are observed, as seen for the cohort as a whole. Statistically significant improvement is not observed for the severe-persistent group compared to placebo. The sponsor hypothesizes that this may be due to a large placebo response in the subjects with more severe disease. Direct comparison between moderate-to-persistent and severe-persistent subjects is not made.

Reviewer's comments: The difference between zileuton ER and placebo ER is modest; at the end of study treatment, trough FEV1 values differ by ~90 ml and the treatment difference was 8.4% (study powered to detect a difference of 8.5%). Zileuton ER performs similarly to the benchmark comparator, zileuton IR. The sponsor notes that FEV1 values observed for zileuton IR are comparable to those reported in the original zileuton IR pivotal studies (M91-685 and M92-720).

The uneven distribution of asthma severity among treatment arms may confound results, although the other mean baseline asthma characteristics of the zileuton ER group versus the

placebo ER group appear comparable. Direct comparison between moderate-to-persistent and severe-persistent asthmatics' responses to study drug are not made.

10.1.10.4.2 Secondary

Efficacy endpoint	Zileuton ER (N=199)		Placebo ER (N=198)		P
	Mean baseline	Mean change	Mean baseline	Mean change	
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 (occasions/day)	3.25	-0.54	3.26	-0.26	0.013
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

10.1.10.4.2.1 PEFr

Both AM and PM PEFrs improved for all treatment arms through the course of the study. No statistically significant differences were noted between zileuton ER versus placebo ER or zileuton IR versus placebo IR at any time-point of the study.

10.1.10.4.2.2 SABA use

Beta-agonist use was recorded as number of occasions and number of puffs daily. At all time-points in the study, beta-agonists were used less in number of occasions and puffs in the zileuton ER group versus placebo. The effect sizes were moderate (difference of "0.28 occasions" and "0.65 puffs"). The differences between zileuton IR and placebo IR were not as robust.

10.1.10.4.2.3 Daily symptom score

No statistically significant reductions in DSA score were noted between zileuton ER and placebo ER groups through the duration of the study ($p=0.055$ to 0.585). Similar results were observed for zileuton IR and placebo IR.

10.1.10.4.2.4 Nocturnal outcome score

No statistically significant reductions in NSA score were noted between zileuton ER and placebo ER groups through the duration of the study ($p=0.531$ to 0.936). Similar results were observed for zileuton IR and placebo IR.

10.1.10.4.2.5 Exacerbations

A comparable number of patients in each treatment group reported one or more exacerbations during the entire treatment period: zileuton ER [N=92 (46.2%)] and placebo ER [n=105 (53%)]; $p=0.173$. Significant differences were observed at shorter time intervals (up to Study Day 15, 29, and 57), but a significant difference was no longer observed by Study Day 85. Similar results were observed for zileuton IR and placebo IR, with approximately half of the subjects in each treatment arm experiencing an exacerbation by the end of the treatment period.

10.1.10.4.2.6 QOL questionnaire

No differences were noted in overall scores at Study Day 85 between zileuton ER and placebo IR (4.02 vs. 4.06; $p=0.10$). Statistically significant differences were observed for specific

questionnaire items at certain time-points (e.g. Study Day 29 – Activities score); but these differences were not consistently observed over the duration of the trial. The minimal important difference was previously defined as a 0.50 change in score. An increase in score of ≥ 0.50 was seen in all treatment arms of the study.

Reviewer's comments: The study did not meet the secondary efficacy endpoints of AM and PM PEFs. Among the other efficacy variables examined, the results suggest a small but consistent reduction in beta-agonist use frequency and amount. As for symptom scores, exacerbations, and QOL questionnaire scores, the results again are not statistically significant but the overall trends appear to favor zileuton over placebo. These results may be affected by appropriate adjustment for multiplicity.

10.1.5 Safety outcomes

All safety analysis was performed using the full data analysis set. Based on these results, the sponsor has concluded that zileuton ER, when added to usual care, is generally well tolerated by patients for up to 6 months with a safety profile comparable to zileuton IR.

10.1.11.1 Adverse events (AE)

10.1.11.1.1 Dropouts due to AEs

Table 24 summarizes dropouts due to non-serious AEs from Study M95-337. Patients were permitted to cite more than one AE as a reason for discontinuation. A total of 35 patients from the zileuton ER arm and 36 patients from the placebo ER arm dropped out due to adverse events; the number and the percentage of patients who terminated early are presented. 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.

Number (%)	Zileuton ER (N=199)	Placebo ER (N=198)
Total number of early dropouts	55 (27.6)	55 (27.8)
Dropouts due to AEs	35 (17.6)	36 (18.2)
Asthma exacerbation	16 (8.0)	22 (11.1)
Sinusitis	3 (1.5)	2 (1.0)
Insomnia	3 (1.5)	0
Dizziness	2 (1.0)	2 (1.0)
Anxiety	2 (1.0)	0
Tachycardia	2 (1.0)	0
Abdominal discomfort/pain	1 (0.5)	2 (1.0)
Nasopharyngitis	1 (0.5)	2 (1.0)
Urticaria	1 (0.5)	1 (0.5)
Nausea	1 (0.5)	0
Upper respiratory tract infection	1 (0.5)	0
Mental impairment	1 (0.5)	0
Hypoglycemia	1 (0.5)	0
Acneiform dermatitis	1 (0.5)	0
LFT elevation	0	2 (1.0)
Leucopenia	0	2 (1.0)
Bronchitis	0	2 (1.0)
Rash	0	1 (0.5)
Headache	0	1 (0.5)
Fatigue	0	1 (0.5)
Pruritus	0	1 (0.5)

10.1.11.1.2 Common AEs

The overall incidence of AEs was similar in all treatment groups; 75.3% to 78.4% of patients in each of the treatment arms reported at least one AE. No deaths were reported. The most commonly reported AEs ($\geq 3\%$ in zileuton ER patients) occurring more commonly in zileuton ER patients compared to placebo are presented in Table 25. Overall, a similar profile of AEs was observed in the zileuton IR group, and the AEs observed in Study M95-337 were generally consistent with AEs described in the zileuton IR product label.

	Zileuton ER (N=199) N (%)	Placebo ER (N=198) N (%)	Zileuton IR (N=97) N (%)	Zileuton IR (N=97) N (%)
Any AE	156 (78.4)	152 (76.8)	73 (75.3)	75 (77.3)
Sinusitis	13 (6.5)	8 (4.0)	2 (2.1)	4 (4.1)
Nausea	10 (5.0)	3 (1.5)	5 (5.2)	1 (1.0)
Pharyngolaryngeal pain	10 (5.0)	8 (4.0)	5 (5.2)	3 (3.1)
Back pain	8 (4.0)	7 (3.5)	1 (1.0)	1 (1.0)

10.1.11.1.3 Serious AEs

A total of 16 SAEs were reported during the study: zileuton ER (n=3), zileuton IR (n=0), placebo ER (n=7), and placebo IR (n=6). Ten of the 16 were hospitalizations related to asthma, including the 3 reports in the zileuton ER arm. The remaining 6 reports were hospitalizations for other causes: low back pain attributed to L4-5 central disk protrusion and possible spinal stenosis, hysterectomy for uterine fibroids, removal of a right renal cyst, elective back surgery due to chronic back pain, pylorospasm, and atrial flutter/fibrillation.

10.1.11.2 Liver enzyme monitoring

Liver function enzymes were checked at baseline and throughout the course of the study: Study Day 1, Day 15 (DB Study Day 1), Day 29 (DB Study Day 15), Day 43 (DB Study Day 29), Day 71 (DB Study Day 57), Day 99 (DB Study Day 85), Day 113, (DB Study Day 99, run-out), and at the 30-day follow-up if applicable.

LFT	Zileuton ER (N=199)		Zileuton IR (N=97)	
	$\geq 3X$ to $< 8X$ ULN	$\geq 8X$ ULN	$\geq 3X$ to $< 8X$ ULN	$\geq 8X$ ULN
ALT	2	3	1	1
AST	1	2	1	0
GGT	1	1	0	0
Alk phos	1	0	0	0
	$\geq 1.5X$ to $< 3X$ ULN	$\geq 3X$ ULN	≥ 1.5 to $< 3X$ ULN	$\geq 3X$ ULN
T bili	7	0	1	0

* The number of patients with liver enzyme elevations is shown in each column

The rate of ALT elevations in subjects receiving zileuton ER (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%). The ALT elevations occurred most often in the first 3 months of treatment, although in 2 of the 5 patients in the zileuton ER group, ALT elevations were detected at the run-out visit, 14 days after completion of study drug. The levels returned to $< 2X$

ULN or normal within 9 and 12 days, respectively. The other 3 subjects in this group were observed to return to <2X ULN within 15, 19, and 31 days after drug discontinuation. For the 2 zileuton IR patients, ALT levels returned to <2X ULN by 20 and 43 days.

Among the 7 zileuton ER patients with T bili elevations, one patient was suspected to have study-drug related hepatitis, with concomitant elevations in other hepatic enzymes (Patient 10769). Two were suspected of having Gilbert's disease. Three patients returned to normal or no more extreme than baseline by the end of the study. An additional 3 subjects experienced elevated T bili after completion of study treatment. The sponsors report that none were considered attributable to study drug and further information is not available.

10.1.11.3 Other laboratory monitoring

Laboratory chemistries and hematology counts were checked at baseline and throughout the course of the study: Study Day 1, Day 15 (DB Study Day 1), Day 29 (DB Study Day 15), Day 43 (DB Study Day 29), Day 71 (DB Study Day 57), Day 99 (DB Study Day 85), Day 113, (DB Study Day 99, run-out), and at the 30-day follow-up if applicable. Previous studies with the IR formulation had noted asymptomatic, decreased white blood cell counts. This drug effect is described in the current product label and the clinical relevance remains unknown. In Study M95-337, 4 patients (2.1%) and 2 patients (1.1%) developed low white blood cell counts ($\leq 3 \times 10^9/L$) during the treatment period, which was comparable to the rates reported in the IR studies. No clinically relevant changes from baseline or significant outliers were noted for other hematology indices or serum chemistries.

10.1.5 Study summary

Study M95-337 demonstrated a percent improvement in trough FEV1 at 12 weeks that was both statistically significant and clinically meaningful, albeit modest. The difference in mean trough FEV1 between zileuton ER and placebo ER groups is ~90 ml, and the treatment difference is 8.1% (study powered to detect a difference of 8.5%). The treatment difference is somewhat less than the treatment difference observed in the original zileuton IR placebo-controlled trials (~130ml); however, zileuton ER performed comparably to zileuton IR included in this study as a benchmark comparator. Analysis of the primary endpoint using mean change in FEV1 rather than % change yields similar efficacy results. Responder analysis indicates that more subjects had $\geq 12\%$ improvement in the zileuton ER group than placebo (63% vs. 50% at Study Day 85; $p=0.023$), further supporting efficacy.

As the original study reports did not account for multiplicity in endpoints or multiple assessments of the same variable made at different time points, three different sensitivity analyses were performed by the statistical reviewer, James Gebert, PhD., to assess the robustness of results: 1) on-treatment averages of % change from baseline over the different treatment phase study visits; 2) averaged % changes in FEV1 from subjects who had participated all treatment study visits, and 3) a repeated measures analysis on the observed case assessments. All three sensitivity analyses support the finding that zileuton ER was more effective than placebo for % change in the trough FEV1 from baseline at 12 weeks as well as at Weeks 5, 6, and 10. Details of the three sensitivity analyses are available in Dr. Gebert's statistical review.

Subgroup analysis by asthma severity (severity based on FEV1) shows less consistent results, with no statistically significant improvement observed for the severe group receiving zileuton ER compared to placebo. The uneven distribution of asthma severity among treatment arms may confound results, although the other mean baseline asthma characteristics of the zileuton ER group versus the placebo ER group appear comparable. Direct comparison between moderate-to-persistent and severe-persistent asthmatics' responses to study drug are not made. No subgroup analyses by gender, age, or ethnicity were performed. Overall, no conclusions about the efficacy of zileuton in certain disease subgroups can be made on the basis of the provided data.

In terms of safety, zileuton ER appears comparable to the already approved zileuton IR formulation. Hepatic abnormalities remain a concern and will require a risk management plan and medication guide in addition to appropriate labeling.

10.2 Review of Individual Study Reports: Protocol M96-464

Study M96-464: Long-term safety study of zileuton ER plus usual care versus placebo plus usual care in patients with asthma

10.2.1 Study administrative information

- Protocol Issue Date: January 15, 1997
- Protocol Amendment Date: April 23, 1997
- Study Dates: February 20, 1997 to October 21, 1997
- Study Sites: 88 investigational sites located in the US
- Study Report Date: CRTX study report (March 2, 2006), original Abbott study report (June 1998)
- Source: Volume 93 (CRTX study report), Vol. 95 (Abbott study report), Vol. 98 (protocol and amendments)

Reviewer's comments: This review of Study M96-464 is based primarily on the CRTX study report (Volume 93). The Abbott study report (Volume 95) was examined briefly for differences between the two study reports and to confirm baseline values in the analyses. Volume 98 was referenced for the original protocol and detailing listing of amendments.

10.2.2 Objectives/Rationale

To determine long-term safety and efficacy of zileuton ER tablets 1200mg (2 x 600 mg tablets) BID plus usual care compared with placebo plus usual care in patients with asthma.

10.2.3 Study design

A 6-month, Phase 3, randomized, double-blind, placebo-controlled, multicenter study in patients with asthma. The study consisted of a 7-14 day screening period followed by 6 months of treatment. Subjects were randomized to receive zileuton ER or placebo ER in a 2:1 ratio.

10.2.4 Study population

Subjects between ages 12 to 81 years of age with moderate asthma.

10.2.4.1 Inclusion criteria

1. Ages 12 years or older
2. FEV1 \geq 40% predicted when taken at least 48 hours after last theophylline use and at least 6 hours after short-acting beta-agonist use or 24 hours after long-acting beta-agonist use
3. FEV1 reversibility of at least 15% at screening or have had history of 15% reversibility within 1 year prior to study entry.
4. Adult weight within 30% acceptable range in Metropolitan Life actuary tables. Minimum weight of 90 lbs. Patients \leq 17 years could not be morbidly obese.
5. Limited alcohol intake (no more than 2 oz alcohol per day, 2 x 12 oz beer per day, 2 x 4 oz wine per day, or 2 regular cocktails)

10.2.4.2 Exclusion criteria

- 11 Pregnancy or breastfeeding.
- 12 Significant systemic disease
- 13 Clinically significant ECG abnormalities.
- 14 Clinically significant abnormalities on screening except those related to asthma.
- 15 History of elevated ALT \geq 5x ULN. Patients with elevated TBili and documented Gilbert's disease permitted.
- 16 History of allergy or other significant adverse reactions to drugs similar to study medication
- 17 Tobacco use in prior 6 months. Ex-smokers must have \leq 10 pack-year history of cigarette smoking.
- 18 Hospitalization for asthma within 6 months prior to screening.
- 19 Investigational drug within 30 days prior to study.

10.2.5 Study treatments

- 1200mg zileuton ER (2 x 600mg tablet) BID (7AM and 7PM, within 1 hour of meal)
- Placebo zileuton ER BID

Dose selection based on results of dose-ranging study (M90-460) and two Phase 3 studies (M91-685 and M92-720) evaluating safety and efficacy of zileuton IR. Zileuton IR was approved for the symptomatic treatment of asthma at a dose of 600mg four times daily.

10.2.6 Randomization

Patients randomized in 2:1 ratio to CR:placebo arms using computer-generated randomization schedules. Randomization did not include stratification for asthma severity. Study blind could be broken by Investigator or Abbott monitor if deemed to be in patient's best interest.

10.2.7 Study discontinuation

Patients had the right to withdraw from the study at any time. Study investigators could choose to discontinue a patient for any reason, including poor compliance or adverse events. In addition, the protocol specified 4 reasons for discontinuing a patient:

5. If patient experienced third asthma exacerbation during study requiring systemic steroids, Investigator required to contact Abbott medical monitor to discuss patient's continued participation in the study.

6. If serum ALT reached 5X upper limit of normal, patient terminated and levels monitored weekly until normalization and then 4 weeks after normalization.
7. Clinically significant laboratory abnormalities as defined in table below:

Table 27. Clinically significant laboratory abnormalities	
Hematology	
Hematocrit	>10% below normal limit
Hemoglobin	>10% below normal limit
Platelet count	>20% below normal limit
WBC count	>20% below normal limit
Liver function tests	
Alk phos	>2X ULN (discontinue from study)
AST	>5X ULN (discontinue from study)
Total bilirubin	>2X ULN (discontinue from study)
Other tests	Investigator discretion

8. Positive pregnancy test. Pregnancy to be followed to completion with updates at least once per trimester and once after delivery.

10.2.8 Concomitant medications

Patients permitted to continue usual asthma medications with the following exceptions: salmeterol, theophylline, and systemic steroids. Patients required to use albuterol (Ventolin) as needed provided by the sponsor. Patients taking ICS, nasal steroids, nedocromil, or cromolyn sodium must have been on a stable dose for ≥ 6 weeks prior to Study Day 1. If applicable, patients must have been on stable immunotherapy regimen for at least 3 months prior to Study Day 1 or discontinued at least 1 month prior. Short- and long-acting antihistamines (except terfenadine and astemizole), decongestants, and saline nasal irrigation permitted for treatment of rhinitis. Oral steroids (≤ 60 mg for 7 days) permitted for acute asthma exacerbations.

Reviewer's comment: The use of other asthma medications, including ICS, is a key difference in study design from the other main Phase 3 study, Study M95-337. The potential impact of this design difference is discussed later in the assessment of efficacy results and conclusions.

10.2.9 Study assessments and evaluations

10.2.9.1 Safety endpoints

10.2.9.1.1 Primary safety variable

Percentage of patients who experienced an ALT elevation ≥ 3 x upper limit of normal during the 6-month study period. Baseline defined as ALT value prior to dosing on Day 1. The numbers of days to resolution (< 2 X ULN and < 1.5 X ULN) were also calculated.

10.2.9.1.2 Adverse events

Defined as any untoward medical event not previously documented in patient's medical history or a worsening in severity of a pre-existing condition occurring during study or with 30 days of study discontinuation. AE considered to be serious if fatal, life-threatening, requiring hospitalization, prolonged hospitalization, severely or permanently disabling, associated with overdose, congenital anomaly, or cancer.

10.2.9.1.3 Change from baseline vital signs (BP, pulse, respiratory rate, and oral temperature)

10.2.9.1.4 Change from baseline hematology, chemistry, urinalysis labs. Baseline defined as those values prior to dosing on Day 1.

10.2.9.2 Efficacy parameters

10.2.9.2.1 FEV1

- Obtained at Screening and prior to dosing on Study Days 1, 85, and 169
- Baseline: Mean FEV1 recorded on AirWatch unit during last 7 days before Day 1.
- Albuterol held for ≥ 6 hours prior to testing

10.2.9.2.2 PEF

- Same time each AM (just before AM dose) and PM (1800-2000 hrs) before any inhaler use
- Performed in triplicate
- Baseline defined as mean averaged over last 7 days prior to Study Day 1
- AirWatch Unit electronic peak flow meter

10.2.9.2.3 Beta-agonist use (number of occasions and puffs)

10.2.9.2.4 Health outcome variables

10.2.9.2.4.1 Acute exacerbations of asthma

Patients meeting ≥ 1 of the following criteria:

- Decrease of $\geq 20\%$ from baseline AM PEF (mean calculated from Period I; not used as criterion for Period I) on 4 of 7 consecutive days
- ≥ 3 of 7 consecutive nights with awakening requiring albuterol
- 100% increase of ICS use over baseline for 7 consecutive days
- Albuterol use ≥ 12 puffs/day for 3 of 7 consecutive days
- ER visit requiring treatment beyond existing asthma therapy
- Inpatient hospitalization for asthma
- Systemic steroids required for treatment of asthma per discretion of the Investigator

Reviewer's comment: Acute asthma exacerbations are a potentially meaningful clinically endpoint, although no standard definition of asthma exacerbation exists. Based on the proposed criteria, subjects may qualify as having an exacerbation based on AM PEF data alone without clinical correlation. The clinical relevance of an "asymptomatic" exacerbation is questionable.

10.2.9.2.4.2 QOL measures

Self-administered. Juniper asthma quality of life (QOL) questionnaire completed on Study Day 1, 85, and 169. Questionnaire addresses symptoms, activities, emotions, and environmental exposure, as well as overall quality of life.

Study schematic

	Screening	Day 1	Day 29	Day 57	Day 85	Day 113	Day 169	30-day FU
Med Hx	X							
Physical exam		X					X	X [^]

ECG	X							
PFT	X	X			X		X	
Bronchodilator reversibility	X							
AirWatch PEFr personal best	X	X						
Transmit AirWatch PEFr data		X	X	X	X	X	X	
Vital signs	X	X	X	X	X	X	X	X
Baseline serum sample*	X							
Lab tests	X	X	X	X	X	X	X	X
Theophylline level	X	X						
Zileuton ER level			X	X	X	X	X	
Genetic polymorphism		X						
Urine pregnancy test	X	X	X	X	X	X	X	X
Asthma QOL questionnaire		X			X		X	
Phone visit ^o							X	
Investigator review of diary		X	X	X	X	X	X	X
AEs/concomitant meds		X	X	X	X	X	X	X
Inventory study drug			X	X	X	X	X	
Dispense patient diary	X	X	X	X	X	X	X	
Dispense study drug		X	X	X	X	X		

- * Stored for later testing to evaluate any pre-existing conditions
- ^ only performed if deemed necessary by investigator
- ° Performed for all patients who prematurely terminated to assess 1) ER visits, 2) hospitalizations, 3) use of systemic steroids at Month 6

10.2.10 Statistical plan

CRTX has stated that a pre-established, separate statistical analysis plan from Abbott does not exist except as specified in the protocol. A sample size of 600 (zileuton ER) and 300 (placebo) was determined assuming a 4% difference in rate of asthma exacerbations resulting in hospitalization or ER visit (providing 56% power at the two-sided 0.05 levels of significance). Kaplan-Meier survival curves were designated for analysis of exacerbation rates. Patients who terminated early without having had an exacerbation were to be considered censored observations.

In the original protocol, the secondary health outcome specified is change in patient's self-reported quality of life from baseline on Days 85 and 169, analyzed by two-way ANOVA. Patients with fewer than 75% of the questions answered were to be excluded.

Changes from baseline FEV1 and percent changes on Days 85 and 169 were to be analyzed using two-way ANOVA.

In the original study report, Abbott tested treatment effects using ANOVA models that had a treatment-by-site interaction term. The term was removed from CRTX's analysis after discussion with the Division regarding potential for confounding treatment effect inferential tests.

Data that best corresponded to the nominal visit day from the appropriate interval was selected for all analyses. If 2 observations were the same number of days from the nominal visit day, then the observation following the visit day was selected for analysis. For the DB treatment period, data obtained more than 3 days after the end of dosing were not used for analyses. All data were to be determined as "evaluable" or "unevaluable" by the project team prior to breaking the blind, with analyses planned for both evaluable data and intent-to-treat data.