CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-052

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

Statistical Review

NDA:	22,052
Drug Name :	[redacted](Zileuton controlled release) 600 mg tablets
Indications:	The prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older.
Applicant:	Critical Therapeutics, Inc.
Dates:	Paper and electronic submission dated 07/30/2006
Biometrics Division:	Division of Biometrics II (HFD-715)
Statistical reviewer:	James Gebert, Ph.D.
Concurring Reviewers:	Joy Mele, M.S., Acting Statistics Team Leader
	Thomas Permutt, Ph.D., Acting Division Director
Medical Division:	Division of Allergy and Pulmonary Products
	(HFD-570)
Clinical reviewer:	S. Limb, M.D.
Medical Team Leader:	S. Seymour, M.D.
Project manager:	A. Zeccola
Keywords:	Analysis of Covariance, Clinical Studies, NDA Review

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1. Executive Summary

1.1 Conclusions and Recommendations

Study M95-337 demonstrated that controlled release Zileuton was significantly better than Placebo for mean change and percent change in FEV_1 from baseline. There were only numerical trends favoring Zileuton CR in AM and PM PEFR. Study M96-464, which was mainly a safety study where Zileuton or Placebo was added to usual care, demonstrated efficacy for controlled release Zileuton for AM and PM PEFR but not for FEV_1.

1.2 Brief Overview of Clinical Studies

Zileuton is a 5-lipoxygenase inhibitor that is used for the treatment of Asthma. On December 9, 1996, Zileuton immediate release (IR) tablets, under the trade name Zyflo, was approved by the FDA for the prophylaxis and chronic treatment of asthma in adults and children 12 years of age and older. The original application of Zyflo was by Abbott Labs. Critical Therapeutics bought the rights of Zileuton from Abbott Labs. In the present submission, the sponsor presented the results of two Phase 3 studies of controlled release Zileuton. These studies had been conducted by Abbott with their version of controlled release Zileuton. For the same indication, the controlled release formulation would allow BID medication compared to QID IR Zileuton.

1.3 Statistical Issues and Findings

The sponsor did not indicate how multiplicity (changes from baseline and percent changes at various assessment times) would be handled. The protocol for Study M95-337, also, did not specify the primary efficacy variable. The sample size discussion in Study M95-337 concerned itself about detecting a difference in percent changes from baseline in FEV_1. It would be assumed therefore that percent change from baseline in FEV_1 would be considered the primary variable. The sponsor provided a one page discussion of the effects of using the Hochberg procedure on changes from baseline in FEV_1 and percent changes from baseline in FEV_1 at the various assessment times for Study M95-337. Using the Hochberg procedure for percent changes from baseline in FEV_1 only the comparison of Zileuton CR to placebo CR at the first on-treatment clinic visit (DB day 15) was significant. The use of the Hochberg procedure is somewhat questionable in this situation. The Hochberg procedure is usually used for different endpoints not different assessment times for the same endpoint. The Hochberg procedure is also too conservative for this situation.

This reviewer performed a repeated measures analysis on percent change from baseline in FEV_1 in Study M95-337. The significant difference of Zileuton CR from placebo in that analysis and the significant differences from placebo in the endpoint analysis and the observed cases analysis at Day 85 lead to the conclusion that Zileuton CR is effective. Although the repeated measures analysis is a *post hoc* analysis, it gives a global indication whether Zileuton was effective over the whole treatment period.

2. Introduction

s a controlled release version of Zyflo (Zileuton immediate release). The proposed dose is two 600 mg tablets BID whereas Zyflo is given as one 600 mg tablet QID. Therefore, the total daily dose of the two products is identical. The clinical efficacy studies of this submission were conducted by Abbott Labs. Critical Therapeutics Inc. bought the rights to Zyflo and Abbott's version of controlled release Zileuton from Abbott Labs. Abbott conducted the two Phase 3 studies in this submission with their version of

controlled release Zileuton. Abbott provided study reports for these studies. Abbott decided not to pursue an NDA for their Zileuton controlled release formulation. In preparations to file this NDA, Critical Therapeutics Inc. found that certain sites in Abbott's studies no longer existed or no longer had source documents that could be audited. In addition, there were two investigators whose data was suspect, one of whom has been debarred and the other who has been put on the restricted list. Thus they reanalyzed the data from these studies excluding these two investigators (plus one additional patient) and the data from the sites that could not be audited. Critical Therapeutics provided new study reports for these studies.

Critical Therapeutics met with the FDA by teleconference on May 2, 2005 about these studies and it was agreed that only the adverse event data and efficacy data from FEV_1 and PEFR would be supplied. At this teleconference the proposal by Critical Therapeutics to reanalyze the FEV_1 and PEFR data from these studies with only treatment and investigator in the model (deleting treatment by investigator interaction) was agreed to by the agency with the stipulation that the interaction effect should be explored.

Looking over the material supplied with the submission, this reviewer realized that there were no Statistical Analysis Plans for Studies M95-337 and M96-464. They were requested but Critical Therapeutics said they did not exist. Therefore, this reviewer did not have any documentation about how Abbott planned to address the multiplicity issues of multiple endpoints and multiple assessment times.

2.1 Overview

There were only two Phase 3 studies in this submission. Study M95-337 was an efficacy and safety study with a 12 week treatment period and M96-464 was a six month safety study. This review will only discuss these studies.

2.1.1 Study M95-337

This was a randomized, double-blind, multicenter, 16 week, placebo controlled parallel group study in adults and children 12 years of age and older with moderate asthma. The treatments were Zileuton CR tablets (2 x 600 mg tablets) BID, Placebo CR (2 tablets BID), Zileuton IR tablets (1 x 600 mg tablet QID) and Placebo IR (1 tablet QID). Some investigators had only CR subjects, some had only IR subjects, and some investigators had both CR and IR subjects. The 16 week study period was comprised of a 14-day SB 2-arm placebo lead- in period, either Placebo CR (2 tablets BID) or Placebo IR (1 tablet QID), followed by 12 weeks of DB dosing with either Zileuton CR 1200 mg BID or placebo BID (Arm A) or Zileuton IR 600 mg QID or placebo QID (Arm B), with a subsequent 2-week run-out period in which medication was not administered.

It was estimated that a sample size of 170 subjects per treatment group would have greater than 80% power to detect a difference of 8.5% for the percent change from baseline in FEV_1. Anticipating dropouts, the sponsor increased the Arm A subjects to 200 per treatment group. The sponsor targeted an enrollment of 100 subjects per treatment group in Arm B. This Arm B sample size was not chosen for the comparison of Zileuton CR and Zileuton IR or for the comparison of Zileuton IR and Placebo IR. [In the discussion of sample size, it can not be determined whether Abbott took the multiplicity of testing into consideration.]

Clinic visits for pulmonary function testing were at screening, Day 1, Week 1(Day 8), Week 2 (Day 15, Double-Blind Day 1), Week 4 (Day 29, Double-Blind Day 15), Week 6 (Day 43, Double-Blind Day 29), Week 10 (Day 71, Double-Blind Day 57), Week 14 (Day 99, Double-Blind Day 85) and Week 16 (Day 113, run-out). Pulmonary function testing was measured immediately prior to administrating of the morning dose at the study center. To enter the Double-Blind portion of the study, subjects were to have an FEV_1 of 40-75% of predicted normal and have demonstrated reversibility by demonstrating $\geq$15% increase in FEV_1 from best pre-bronchodilator value when tested at least 15 minutes after two puffs of inhaled albuterol. The Double-Blind Day 1 assessment of FEV_1 was the baseline value of FEV_1.

PEFR values (best of three) were collected by an electronic peak flow meter (AirWatch unit). The first (AM) measurement was performed just before the first daily dose of study drug; the second (PM) measurement was performed at approximately 2000 hours.

The primary assessment of efficacy was trough FEV_1 at clinic visits. In particular in each Arm (IR or CR) changes from baseline in FEV_1 and percent changes from baseline in FEV_1 were analyzed by the sponsor using an ANOVA with center and treatment as factors. [redacted]. Abbott's protocol did not discuss how the multiplicity of clinic visits (Double- Blind Days 15, 29, 57, and 85) and the multiplicity of endpoints (change from baseline in FEV_1 and percent change from baseline in FEV_1) would be handled. The sponsor provided the results of applying the Hochberg Procedure on the multiple assessment times in an appendix. In each Arm (IR or CR) centers with < 2 subjects in either treatment group were pooled into a single "site".

There were two important populations analyzed by the sponsor, the Full Analysis Set which excluded data from 2 sites (Dr. Robert Fiddes and Dr. Thomas Edwards) because of questionable reliability and the Restricted Analysis Set which also excluded sites that no longer existed or did not have data that could be audited. In addition one patient (Patient 10515) who participated in studies M95-337 and M96-464 concurrently was excluded from the Restricted Analysis Set.

The sponsor performed both LOCF and observed data analyses for FEV_1 and PEFR.

Data obtained more than three days after the end of double-blind study drug dosing were excluded from the analyses. Data obtained on study days following oral corticosteroids were also excluded from analyses. For trough FEV_1 two types of intervals were used for the analyses at double--blind visits: those based on "carry-forward" intervals, and those based on "observed data" intervals. Data was selected for analysis at a particular double-blind day visit by selecting data that best corresponded to the appropriate nominal visit day; i.e., the value that was closest to (in days) to the nominal visit day in absolute value, where if two values were of equal distance (in days) to the nominal day then the value following the nominal day was selected. These intervals and the corresponding nominal days are given below.

Nominal Day	"Carry Forward" Intervals (Double-Blind Days)	"Observed Data" Intervals (Double-Blind Days)
Double-Blind Day 15	2-22	2-22
29	2-43	23-43
57	2-71	44-71
85	2-92	72-92

The same observed data intervals were used for PEFR. The observed data analyses of PEFR were performed on the average of data obtained in that interval. The "Carry Forward" analyses for PEFR were performed by using the previous interval average for an interval that had no data within it.

2.1.2 Study M96-464

This was a long-term safety study of Zileuton CR plus usual care versus Placebo CR plus usual care in subjects with asthma. There was no IR Arm or placebo run-in period. The double blind period was six months with clinic visits at screening, Day 1, Day 29, Day 57, Day 85, Day 112, Day 169, and a 30 Day Follow Up. To enter the study subjects had to have 15% reversibility and an FEV_1 ≥40% of predicted normal value when taken ≥48 hours after the last theophylline use, ≥6 hours after the last short-acting beta-agonist, and ≥12 hours after the last long acting beta-agonist use. Subjects could be on stable doses of inhaled corticosteroids, nasal steroids, nedocromil, or cromolyn sodium.

Pulmonary function testing including FEV_1 was done at clinic visits on Days 1, 85, and 169 or early termination visit. The Day 1 assessment of FEV_1 is the baseline assessment. The morning PEFR was performed upon awakening, just before the daily dose of study drug. The evening measurement of PEFR

was performed between 1800 and 2000 hours. Patients were instructed to take these measurements at the same time of day throughout the study. The baseline measurement was the average of the 7 daily measures prior to Day 1.
The windows for FEV_1 were

Nominal Day	"Carry Forward" Intervals (Double-Blind Days)	"Observed Data" Intervals (Double-Blind Days)
Double-Blind Day 85	2-127	2-127
169	2-183	128-183

For PM PEFR values, intervals for bi-weekly averages were Days 1-14, 15-28.etc. (for AM PEFR values the intervals were 2-15, 16-29, etc.) Carry-forward analyses for these assessments were performed using the most recent 14 days for patients who terminate prior to completing a bi-weekly interval.

The protocol states that the primary safety variable will be the percentage of patients who experience an ALT elevation of ≥ 3 times the upper limit of normal within the 6-month study period.

The sample size calculations were based on the percentage of patients experiencing an asthma exacerbation resulting in a hospitalization or an ER visit within the 6-month study period as the endpoint. This sample size was chosen using the results from study M94-199 where the rates were 4.7% for Zileuton CR plus usual care and 8.7% for placebo plus usual care. A sample size of 600 Zileuton CR patients and 300 placebo patients was determined (providing 56% power at a 2-sided 0.05 level of significance).

Changes from baseline in FEV_1 and percent changes from baseline in FEV_1 were analyzed by the sponsor using an ANOVA with center and treatment as factors. [redacted] Abbott's protocol did not discuss how the multiplicity of clinic visits (Double- Blind Days 85 and 169) and the multiplicity of endpoints (change from baseline in FEV_1 and percent change from baseline in FEV_1) would be handled. The sponsor provided the results of applying the Hochberg Procedure on the multiple assessment times in an appendix. Centers with < 2 subjects in either treatment group were pooled into a single "site". Two-week intervals in AM and PM PEFR were analyzed by the sponsor using an ANOVA with center and treatment as factors [redacted]

Patients who contacted the Investigator with complaints of worsened asthma symptoms and who, upon subsequent questioning and/or physical examination exhibited one or more of the following criteria, were considered to have an acute exacerbation of asthma:

1. A decrease of $\geq 20\%$ from baseline (mean of the AirWatch AM PEFR values over the 7 days prior to Study Day 1) in AM PEFR for 4 out of 7 consecutive days.
2. Albuterol use ≥ 12 puffs per day for 3 out of 7 consecutive days.
3. A 100% increase of ICS use over baseline for 7 consecutive days.
4. An ER visit that required treatment beyond existing asthma therapy.
5. In-patient hospitalization for asthma.
6. Systemic steroids (oral, injected or intravenous) were required for treatment of asthma in the judgment of the Investigator, regardless of whether or not any of the above criteria were met.

2.2 Data Sources

The data and programs which after slight modification that run against that data are contained in Cdsesub1 n22052 N 000 2006-07-20 and Cdsesub1 n22052 N 000 2006-09-05.

3. Statistical Evaluation

3.1 Evaluation of Efficacy

3.1.1 Study M95-337

There were 613 subjects (206 Zileuton CR, 203 CR placebo, 101 Zileuton IR, and 103 IR placebo) randomized into the study at 76 investigative sites. Twenty-two subjects (from Dr. Edwards and Dr. Fiddes) were excluded from the analyses. This left 591 subjects in the Full Analysis Set (199 Zileuton CR, 198 CR Placebo, 97 Zileuton IR, and 97 IR Placebo). Of these 591 subjects, 449 (76%) completed the study [144 (72%) Zileuton CR, 143 (72%) CR Placebo, 82 (84%) Zileuton IR, and 80 (82%) IR Placebo]. The main reason for non-completion was Adverse Events (about 57% of non-completers). The Restricted Analysis Set contained 533 subjects (178 Zileuton CR, 177 CR Placebo, 91 Zileuton IR, and 87 IR Placebo).

The treatment groups in each Arm (CR and IR) were comparable in demographic and baseline pulmonary function.

The following table provides the means and p-values for the analysis of Zileuton CR and Placebo CR for the LOCF analyses of the Full Analysis Set and Restricted Analysis Set. [Subjects 10248, 10411, 10439 and 10714 had no day 15 evaluation of FEV_1.] For the Full Analysis Set without adjusting for multiplicity both changes from baseline in FEV_1 and percent changes from baseline in FEV_1 were significant at Days 15, 57, and 85. The Restricted Analysis Set confirmed the results of the Full Analysis Set. The sponsor mentions that using the Hochberg procedure for the Full Analysis Set that the results at Days 15, 57, and 85 were significant for mean changes in FEV_1 but only the Day 15 results were significant for percent changes in FEV_1. [This reviewer believes that the Hochberg procedure is too conservative in this situation where multiple time points of the same variable are being tested.]

Table 3.1 FEV_1 LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
DB Study Day 15				
N	189	186	168	168
Mean Baseline (L)	2.16	2.19	2.16	2.20
Visit Mean (L)	2.40	2.28	2.41	2.30
Mean Change from Baseline	0.23	0.09	0.25	0.10
Z-CR vs. PBO-CR, p-value	0.001		0.002	
Mean Percent Change from Baseline	13.10	3.90	14.08	4.42
Z-CR vs. PBO-CR, p-value	0.007		0.010	
DB Study Day 29				
N	192	187	171	169
Mean Baseline (L)	2.17	2.20	2.16	2.21
Visit Mean (L)	2.44	2.40	2.45	2.42
Mean Change from Baseline	0.27	0.21	0.29	0.21
Z-CR vs. PBO-CR, p-value	0.141		0.112	
Mean Percent Change from Baseline	15.01	9.48	15.78	9.63
Z-CR vs. PBO-CR, p-value	0.090		0.085	
DB Study Day 57				
N	192	187	171	169
Mean Baseline (L)	2.17	2.20	2.16	2.21

Visit Mean (L)	2.50	2.39	2.51	2.40
Mean Change from Baseline	0.33	0.20	0.35	0.19
Z-CR vs. PBO-CR, p-value	0.007		0.004	
Mean Percent Change from Baseline	17.38	9.67	18.29	9.53
Z-CR vs. PBO-CR, p-value	0.019		0.015	
DB Study Day 85				
N	192	187	171	169
Mean Baseline (L)	2.17	2.20	2.16	2.21
Visit Mean (L)	2.55	2.47	2.55	2.48
Mean Change from Baseline	0.39	0.27	0.39	0.27
Z-CR vs. PBO-CR, p-value	0.021		0.033	
Mean Percent Change from Baseline	20.77	12.73	21.06	12.69
Z-CR vs. PBO-CR, p-value	0.032		0.042	

The following table provides the means and p-values for the analysis of Zileuton CR and Placebo CR for the Observed Cases Analyses of the Full Analysis Set and Restricted Analysis Set. For the Full Analysis Set without adjusting for multiplicity, both changes from baseline in FEV_1 and percent changes from baseline in FEV_1 were significant at Days 15, 57, and 85. For the Full Analysis Set without adjusting for multiplicity, changes from baseline in FEV_1, but not percent changes from baseline in FEV_1, was significant at Day 29. The Restricted Analysis Set confirmed the results of the Full Analysis Set.

Table 3.2 FEV_1 Observed Cases Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
DB Study Day 15				
N	189	186	168	168
Mean Baseline (L)	2.16	2.19	2.16	2.20
Visit Mean (L)	2.40	2.28	2.41	2.30
Mean Change from Baseline	0.23	0.09	0.25	0.10
Z-CR vs. PBO-CR, p-value	0.001		0.002	
Mean Percent Change from Baseline	13.10	3.90	14.08	4.42
Z-CR vs. PBO-CR, p-value	0.007		0.010	
DB Study Day 29				
N	178	174	157	159
Mean Baseline (L)	2.18	2.17	2.18	2.18
Visit Mean (L)	2.46	2.37	2.47	2.38
Mean Change from Baseline	0.28	0.19	0.30	0.20
Z-CR vs. PBO-CR, p-value	0.041		0.038	
Mean Percent Change from Baseline	15.34	8.90	16.21	9.28
Z-CR vs. PBO-CR, p-value	0.061		0.065	
DB Study Day 57				
N	162	156	143	142
Mean Baseline (L)	2.19	2.20	2.18	2.20
Visit Mean (L)	2.57	2.39	2.58	2.39
Mean Change from Baseline	0.38	0.19	0.40	0.19
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	19.69	9.79	20.82	9.82
Z-CR vs. PBO-CR, p-value	0.008		0.008	
DB Study Day 85				

N	144	138	125	125
Mean Baseline (L)	2.20	2.19	2.20	2.19
Visit Mean (L)	2.67	2.51	2.67	2.52
Mean Change from Baseline	0.47	0.32	0.47	0.33
Z-CR vs. PBO-CR, p-value	0.009		0.019	
Mean Percent Change from Baseline	25.46	14.95	26.17	15.26
Z-CR vs. PBO-CR, p-value	0.029		0.041	

In order to see whether Zileuton CR showed overall efficacy, this reviewer did three sensitivity analyses. It was decided to use percent change from baseline in FEV_1 rather than change from baseline in FEV_1 because percent change showed less efficacy when the Hochberg procedure was used and the sponsor's sample size discussion mentioned percent change from baseline in FEV_1.

The first sensitivity analysis was on on-treatment averages of percent change from baseline in FEV_1. For each subject the mean of observed cases assessments at Days 15, 27, 57, and 85 were calculated. These mean percent changes in FEV_1 were analyzed by an analysis of variance with treatments and centers as factors. This analysis gave the following results. [Note that the Ns here are larger than the Day 15 Observed Cases Ns because 4 individuals did not have a Day 15 assessment of percent changers in FEV_1 from baseline but had assessments assigned to a later time point.]

Table 3.3 FEV_1 Percent Change from Baseline Averaged Over Days 15, 27, 57 and 85

	Zileuton CR	Placebo CR
N	192	187
Mean (SD)	17.38 (38.69)	9.59 (18.24)
Least squares mean (SE)	16.43 (2.34)	8.68 (2.36)
Difference	7.75 (1.48, 14.01)	
P-value	0.016	

A second sensitivity analysis of averaged percent changes in FEV_1 using subjects that had all four assessments yielded results consistent with those in Table 3.3.

The third sensitivity analysis was a repeated measures analysis using PROC Mixed with Unspecified Covariance structure on the observed cases assessments of percent changes from baseline in FEV_1.

Table 3.4 Repeated Measures Analysis of FEV_1 Percent Change from Baseline

	Zileuton CR	Placebo CR
N	192	187
Least squares mean (SE)	17.03 (2.38)	9.58 (2.37)
Difference	7.44 (1.11, 13.78)	
P-value	0.021	

All three sensitivity analyses lead to the conclusion that Zileuton CR was more effective than Placebo for percent change in FEV_1.

Not all sites in this study contained both a placebo CR and a placebo IR arm. This reviewer investigated whether the two placebo arms were comparable in order to justify comparing the Zileuton CR and IR arms head-to-head. The following table provides the comparison of the Placebo CR and Placebo IR means for changes from baseline in FEV_1 and percent changes from baseline in FEV_1 for the LOCF analysis of the Full Analysis Set and the Restricted Analysis Set The mean changes and mean percent changes of the placebo treatments were not appreciably different. As such the numerical comparison of Zileuton CR and Zileuton IR is reasonable.

Table 3.5 FEV_1 LOCF Results for Placebo CR and Placebo IR

	Full Analysis Set		Restricted Analysis Set	
	PBO-CR	PBO-IR	PBO-CR	PBO-IR
DB Study Day 15				
N	186	93	168	84
Mean Baseline (L)	2.19	2.17	2.20	2.20
Visit Mean (L)	2.28	2.32	2.30	2.34
Mean Change from Baseline	0.09	0.14	0.10	0.14
Mean Percent Change from Baseline	3.90	7.49	4.42	7.39
DB Study Day 29				
N	187	93	169	84
Mean Baseline (L)	2.20	2.17	2.21	2.20
Visit Mean (L)	2.40	2.27	2.42	2.31
Mean Change from Baseline	0.21	0.10	0.21	0.11
Mean Percent Change from Baseline	9.48	5.82	9.63	6.53
DB Study Day 57				
N	187	938	169	84
Mean Baseline (L)	2.20	2.17	2.21	2.20
Visit Mean (L)	2.39	2.40	2.40	2.41
Mean Change from Baseline	0.20	0.22	0.19	0.21
Mean Percent Change from Baseline	9.67	12.30	9.53	12.05
DB Study Day 85				
N	187	93	169	84
Mean Baseline (L)	2.20	2.17	2.21	2.20
Visit Mean (L)	2.47	2.45	2.48	2.48
Mean Change from Baseline	0.27	0.28	0.27	0.28
Mean Percent Change from Baseline	12.73	14.07	12.69	14.17

The following table provides the comparison of the Zileuton CR and Zileuton IR means for changes from baseline in FEV_1 and percent changes from baseline in FEV_1 for the LOCF analysis of the Full Analysis Set and the Restricted Analysis Set. For both mean changes from baseline in FEV_1 and percent changes from baseline in FEV_1 for the LOCF analysis of the Full Analysis Set and the Restricted Analysis Set, Zileuton CR was higher than Zileuton IR although these differences were small.

Table 3.6 FEV_1 LOCF Results for Zileuton CR and Zileuton IR

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	Z-IR	Z-CR	Z-IR
DB Study Day 15				
N	189	96	168	90
Mean Baseline (L)	2.16	2.13	2.16	2.10
Visit Mean (L)	2.40	2.31	2.41	2.27
Mean Change from Baseline	0.23	0.17	0.25	0.17
Mean Percent Change from Baseline	13.10	8.55	14.08	8.36
DB Study Day 29				
N	192	96	171	90
Mean Baseline (L)	2.17	2.13	2.16	2.10

Visit Mean (L)	2.44	2.36	2.45	2.32
Mean Change from Baseline	0.27	0.23	0.29	0.23
Mean Percent Change from Baseline	15.01	12.48	15.78	12.39
DB Study Day 57				
N	192	96	1.71	90
Mean Baseline (L)	2.17	2.13	2.16	2.10
Visit Mean (L)	2.50	2.44	2.51	2.40
Mean Change from Baseline	0.33	0.31	0.35	0.30
Mean Percent Change from Baseline	17.38	15.93	18.29	15.93
DB Study Day 85				
N	192	96	171	90
Mean Baseline (L)	2.17	2.13	2.16	2.10
Visit Mean (L)	2.55	2.51	2.55	2.48
Mean Change from Baseline	0.39	0.38	0.39	0.38
Mean Percent Change from Baseline	20.77	19.30	21.06	19.42

The table below provides the mean AM PEFR for the CR Arm for the Full Analysis Set and Restricted Analysis Set. No significant differences were seen.

Table 3.7 AM PEFR LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
DB Study Days 2-22				
N	193	192	172	172
Mean Baseline (L/min)	369.78	353.47	367.26	355.63
Interval Mean (L/min)	389.20	368.10	386.95	369.77
Mean Change from Baseline	19.42	14.63	19.69	14.15
Z-CR vs. PBO-CR, p-value	0.421		0.377	
Mean Percent Change from Baseline	5.91	4.10	6.05	4.06
Z-CR vs. PBO-CR, p-value	0.284		0.270	
DB Study Days 23-43				
N	193	192	172	172
Mean Baseline (L/min)	369.78	353.47	367.26	355.63
Interval Mean (L/min)	403.45	377.77	399.27	378.81
Mean Change from Baseline	33.67	24.30	32.01	23.18
Z-CR vs. PBO-CR, p-value	0.262		0.315	
Mean Percent Change from Baseline	10.49	7.32	10.02	7.15
Z-CR vs. PBO-CR, p-value	0.216		0.295	
DB Study Days 44-71				
N	193	193	172	173
Mean Baseline (L/min)	369.73	353.86	367.21	356.04
Interval Mean (L/min)	419.18	389.23	414.31	389.07
Mean Change from Baseline	49.45	35.37	47.10	33.03
Z-CR vs. PBO-CR, p-value	0.156		0.179	
Mean Percent Change from Baseline	15.36	11.02	14.78	10.64
Z-CR vs. PBO-CR, p-value	0.156		0.207	
DB Study Day 72-92				
N	193	193	172	173

Mean Baseline (L/min)	369.73	353.86	367.21	356.04
Interval Mean (L/min)	428.18	397.22	423.16	395.92
Mean Change from Baseline	58.45	43.36	55.95	39.88
Z-CR vs. PBO-CR, p-value	0.147		0.145	
Mean Percent Change from Baseline	17.93	13.61	17.25	12.98
Z-CR vs. PBO-CR, p-value	0.196		0.235	

The table below provides the mean PM PEFR for the CR Arm for the Full Analysis Set and Restricted Analysis Set. Again, no significant differences were seen.

Table 3.8 PM PEFR LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
DB Study Days 2-22				
N	193	193	172	173
Mean Baseline (L/min)	397.92	386.80	393.86	387.41
Interval Mean (L/min)	414.37	397.51	411.25	396.89
Mean Change from Baseline	16.45	10.72	17.39	9.48
Z-CR vs. PBO-CR, p-value	0.367		0.227	
Mean Percent Change from Baseline	4.521	2.76	4.87	2.52
Z-CR vs. PBO-CR, p-value	0.284		0.175	
DB Study Days 23-43				
N	193	193	172	173
Mean Baseline (L/min)	397.92	386.80	393.86	387.41
Interval Mean (L/min)	429.49	407.72	425.16	40718
Mean Change from Baseline	31.58	20.92	31.29	19.77
Z-CR vs. PBO-CR, p-value	0.217		0.198	
Mean Percent Change from Baseline	8.49	5.83	8.45	5.71
Z-CR vs. PBO-CR, p-value	0.256		0.267	
DB Study Days 44-71				
N	193	193	172	173
Mean Baseline (L/min)	397.92	386.80	393.86	387.41
Interval Mean (L/min)	443.33	419.19	437.95	417.65
Mean Change from Baseline	45.41	32.39	44.08	30.24
Z-CR vs. PBO-CR, p-value	0.186		0.177	
Mean Percent Change from Baseline	12.71	9.28	12.54	8.94
Z-CR vs. PBO-CR, p-value	0.216		0.222	
DB Study Day 72-92				
N	193	193	172	173
Mean Baseline (L/min)	397.92	386.80	393.86	387.41
Interval Mean (L/min)	454.16	423.75	448.48	420.82
Mean Change from Baseline	56.24	36.95	54.62	33.41
Z-CR vs. PBO-CR, p-value	0.083		0.069	
Mean Percent Change from Baseline	16.01	10.90	15.86	10.26
Z-CR vs. PBO-CR, p-value	0.107		0.097	

3.1.2 Study M96-464

There were 926 subjects (619 Zileuton CR and 307 Placebo) randomized into the trial at 88 investigative sites. Of these 926 subjects, 706 (76%) (477 Zileuton CR and 229 Placebo) completed the study. The main reason for non-completion was adverse events [102 subjects (46% of the dropouts), 65 Zileuton and 37 placebo]. The Full Analysis Set includes all 926 patients. The Restricted Analysis Set, which included 850 subjects (568 Zileuton CR and 282 Placebo), excluded patient 2742/ [redacted] (patient in both studies) and data from 9 additional sites which could not be audited. Patient 274[redacted] was on Zileuton CR during this study and on placebo CR in Study M95-337.

The treatment groups were comparable in demographic variables and baseline pulmonary function with the exception that the Zileuton group had a larger percentage of subjects with a history of tobacco use (22.13% versus 15.64%). The placebo group also had a higher daily use in number of puffs of beta-agonists 5.09 puffs versus 4.57 puffs at screening.

The following table provides the mean changes and percent changes from baseline in FEV_1 at clinic visits using LOCF rules. About 82% of both Zileuton and placebo patients in the Full Analysis Set had on-treatment assessment of FEV_1. No significant differences were observed between Zileuton and Placebo.

Table 3.9 FEV_1 LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
Study Day 85				
N	507	251	463	229
Mean Baseline (L)	2.52	2.52	2.51	2.50
Visit Mean (L)	2.70	2.64	2.69	2.62
Mean Change from Baseline	0.17	0.13	0.18	0.13
Z-CR vs. PBO-CR, p-value	0.201		0.181	
Mean Percent Change from Baseline	8.62	7.37	8.81	7.43
Z-CR vs. PBO-CR, p-value	0.470		0.454	
Study Day 169				
N	507	251	463	229
Mean Baseline (L)	2.52	2.52	2.51	2.50
Visit Mean (L)	2.70	2.65	2.68	2.63
Mean Change from Baseline	0.17	0.13	0.17	0.13
Z-CR vs. PBO-CR, p-value	0.260		0.295	
Mean Percent Change from Baseline	8.79	7.05	8.81	7.03
Z-CR vs. PBO-CR, p-value	0.316		0.35	

If a PROC MIXED repeated measures analysis is performed on observed mean changes in FEV_1 (the most significant of mean changes and percent changes) for the Full Analysis Set, the results are non-significant (mean diff in changes from baseline=0.04, p=0.20). Thus, mean changes from baseline in FEV_1 did not show efficacy using an overall test of efficacy.

The table below provides the mean AM changes from baseline PEFR and percent changes from baseline PEFR for the CR Comparison for the Full Analysis Set and Restricted Analysis Set using LOCF rules. The differences in mean changes from baseline and percent changes from baseline were significant for all two-week intervals. Although the sponsor has not adjusted for multiple testing, the results here would be significant with any reasonable multiple testing procedure.

Table 3.10 AM PEFR LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
Study Days 2-15				
N	605	296	555	272
Mean Baseline (L/min)	389.34	389.28	387.99	385.95
Interval Mean (L/min)	411.09	391.99	410.73	387.44
Mean Change from Baseline	21.76	2.71	22.74	1.48
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	5.71	0.54	6.00	0.19
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Study Days 16-29				
N	610	298	560	274
Mean Baseline (L/min)	388.86	388.46	387.47	385.07
Interval Mean (L/min)	415.89	396.40	415.26	392.17
Mean Change from Baseline	27.02	7.94	27.79	7.10
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	7.10	1.96	7.32	1.66
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Study Days 30-43				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	422.02	402.70	421.25	398.46
Mean Change from Baseline	33.19	14.43	33.81	13.59
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	8.83	3.77	8.98	3.56
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Study Day 44-57				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	427.77	407.79	426.85	403.29
Mean Change from Baseline	38.94	19.51	39.42	18.42
Z-CR vs. PBO-CR, p-value	0.002		0.001	
Mean Percent Change from Baseline	10.59	5.34	10.71	5.07
Z-CR vs. PBO-CR, p-value	0.003		0.002	
Study Days 58-71				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	432.15	410.00	430.94	405.17
Mean Change from Baseline	43.32	21.73	49.50	20.30
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	11.94	6.05	12.05	5.70
Z-CR vs. PBO-CR, p-value	0.002		0.001	
Study Days 72-85				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	434.38	413.00	433.16	407.83

Mean Change from Baseline	45.55	24.73	45.73	22.97
Z-CR vs. PBO-CR, p-value	0.002		0.001	
Mean Percent Change from Baseline	12.73	6.86	12.80	6.38
Z-CR vs. PBO-CR, p-value	0.003		0.002	
Study Days 86-99				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	436.70	416.27	436.54	411.72
Mean Change from Baseline	47.87	28.00	49.10	26.86
Z-CR vs. PBO-CR, p-value	0.004		0.002	
Mean Percent Change from Baseline	13.38	7.87	13.73	7.59
Z-CR vs. PBO-CR, p-value	0.006		0.003	
DB Study Day 100-113				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	438.73	419.46	437.89	414.42
Mean Change from Baseline	49.90	31.19	50.46	29.56
Z-CR vs. PBO-CR, p-value	0.008		0.005	
Mean Percent Change from Baseline	13.98	8.72	14.16	8.37
Z-CR vs. PBO-CR, p-value	0.011		0.007	
Study Days 114-127				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	439.45	420.42	438.74	414.94
Mean Change from Baseline	50.61	32.15	51.30	30.07
Z-CR vs. PBO-CR, p-value	0.010		0.004	
Mean Percent Change from Baseline	14.10	9.03	14.27	8.56
Z-CR vs. PBO-CR, p-value	0.014		0.008	
Study Days 128-141				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	440.07	420.31	439.89	414.92
Mean Change from Baseline	51.24	32.04	52.46	30.05
Z-CR vs. PBO-CR, p-value	0.008		0.003	
Mean Percent Change from Baseline	14.45	9.00	14.79	8.52
Z-CR vs. PBO-CR, p-value	0.009		0.004	
Study Days 142-155				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87
Interval Mean (L/min)	442.15	420.13	441.77	415.04
Mean Change from Baseline	53.32	31.86	54.34	30.17
Z-CR vs. PBO-CR, p-value	0.004		0.002	
Mean Percent Change from Baseline	15.13	9.10	15.38	8.74
Z-CR vs. PBO-CR, p-value	0.005		0.003	
Study Days 156-169				
N	612	298	562	274
Mean Baseline (L/min)	388.83	388.27	387.43	384.87

Interval Mean (L/min)	444.24	418.65	444.46	414.86
Mean Change from Baseline	55.41	30.38	57.03	29.99
Z-CR vs. PBO-CR, p-value	<0.001		<0.001	
Mean Percent Change from Baseline	15.62	8.67	16.07	8.67
Z-CR vs. PBO-CR, p-value	0.002		0.002	

The table below provides the mean PM changes from baseline PEFR and percent changes from baseline PEFR for the CR Comparison for the Full Analysis Set and Restricted Analysis Set using LOCF rules. The differences in mean changes from baseline and percent changes from baseline were significant in about half the two-week intervals. The sponsor in Appendix 2 of the Study report (Volume 165, page 327), states that no significant results were found for PM PEFR when the Hochberg procedure was used. This reviewer believes the Hochberg procedure is too conservative in this situation where multiple time points of the same variable are being tested. With so many significant results and many near-significant results, a judgment that PM PEFR showed efficacy is more appropriate.

Table 3.11 PM PEFR LOCF Results for Zileuton CR Compared to Placebo

	Full Analysis Set		Restricted Analysis Set	
	Z-CR	PBO-CR	Z-CR	PBO-CR
Study Days 1-14				
N	605	296	556	272
Mean Baseline (L/min)	420.88	415.80	420.29	412.16
Interval Mean (L/min)	435.71	420.64	434.83	415.01
Mean Change from Baseline	14.83	4.84	14.54	2.85
Z-CR vs. PBO-CR, p-value	0.013		0.005	
Mean Percent Change from Baseline	3.54	1.00	3.41	0.49
Z-CR vs. PBO-CR, p-value	0.009		0.004	
Study Days 15-28				
N	610	298	561	274
Mean Baseline (L/min)	420.32	415.02	419.67	411.33
Interval Mean (L/min)	435.63	419.19	434.44	414.57
Mean Change from Baseline	15.32	4.16	14.77	3.24
Z-CR vs. PBO-CR, p-value	0.035		0.038	
Mean Percent Change from Baseline	3.64	0.68	3.45	0.36
Z-CR vs. PBO-CR, p-value	0.022		0.022	
Study Days 29-42				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	443.98	426.83	442.92	422.05
Mean Change from Baseline	23.70	11.99	23.29	10.92
Z-CR vs. PBO-CR, p-value	0.043		0.039	
Mean Percent Change from Baseline	5.84	2.90	5.66	2.61
Z-CR vs. PBO-CR, p-value	0.039		0.037	
Study Day 43-56				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	446.84	428.94	446.20	424.48
Mean Change from Baseline	26.56	14.11	26.57	13.35
Z-CR vs. PBO-CR, p-value	0.051		0.046	
Mean Percent Change from Baseline	6.71	3.39	6.64	3.14

Z-CR vs. PBO-CR, p-value	0.040		0.037	
Study Days 57-70				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	451.09	432.62	450.30	428.29
Mean Change from Baseline	30.81	17.78	30.67	17.16
Z-CR vs. PBO-CR, p-value	0.052		0.055	
Mean Percent Change from Baseline	7.82	4.57	7.81	4.37
Z-CR vs. PBO-CR, p-value	0.058		0.056	
Study Days 71-84				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	453.21	433.35	452.56	428.12
Mean Change from Baseline	32.93	18.51	32.94	17.00
Z-CR vs. PBO-CR, p-value	0.036		0.027	
Mean Percent Change from Baseline	8.42	4.73	8.41	4.31
Z-CR vs. PBO-CR, p-value	0.038		0.028	
Study Days 85-98				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	454.64	435.78	454.51	431.50
Mean Change from Baseline	34.36	20.95	34.88	20.37
Z-CR vs. PBO-CR, p-value	0.054		0.047	
Mean Percent Change from Baseline	8.78	5.53	8.93	5.38
Z-CR vs. PBO-CR, p-value	0.067		0.057	
DB Study Day 99-112				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	455.65	438.24	455.44	432.67
Mean Change from Baseline	35.37	23.41	35.81	21.54
Z-CR vs. PBO-CR, p-value	0.095		0.056	
Mean Percent Change from Baseline	9.11	6.10	9.22	5.67
Z-CR vs. PBO-CR, p-value	0.104		0.066	
Study Days 113-126				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	457.03	437.96	456.11	432.52
Mean Change from Baseline	36.74	23.13	36.48	21.39
Z-CR vs. PBO-CR, p-value	0.061		0.047	
Mean Percent Change from Baseline	9.58	6.19	9.54	5.78
Z-CR vs. PBO-CR, p-value	0.074		0.059	
Study Days 127-140				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	458.76	438.91	457.88	433.90
Mean Change from Baseline	38.48	24.08	38.25	22.78
Z-CR vs. PBO-CR, p-value	0.049		0.042	

Mean Percent Change from Baseline	10.07	6.51	10.08	6.23
Z-CR vs. PBO-CR, p-value	0.062		0.055	
Study Days 141-154				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	459.05	438.37	458.36	433.13
Mean Change from Baseline	38.77	23.54	38.73	22.01
Z-CR vs. PBO-CR, p-value	0.043		0.033	
Mean Percent Change from Baseline	10.20	6.51	10.21	6.19
Z-CR vs. PBO-CR, p-value	0.059		0.051	
Study Days 155-168				
N	612	298	563	274
Mean Baseline (L/min)	420.28	414.83	419.63	411.12
Interval Mean (L/min)	459.26	436.66	458.61	431.58
Mean Change from Baseline	38.98	21.83	38.99	20.46
Z-CR vs. PBO-CR, p-value	0.023		0.019	
Mean Percent Change from Baseline	10.25	5.98	10.30	5.68
Z-CR vs. PBO-CR, p-value	0.031		0.026	

The sponsor reports the following percentages of Full Analysis Set subjects having an acute exacerbation of asthma requiring various methods of treatment.

Table 3.12 Number and Percentage of Full Analysis Set Subjects Having an Acute Exacerbation of Asthma Requiring Various Methods of Treatment

	Zileuton CR N=619	Placebo N=307	P-value
Alternative Treatment	16 (2.58 %)	10 (3.26 %)	0.408
ER visit	16 (2.58 %)	10 (3.26 %)	0.121
Hospitalization	5 (0.81%)	0 (0%)	0.155

The sponsor did not present the results of comparing Zileuton CR and placebo for the percentage of patients having an acute exacerbation of asthma requiring an ER visit or hospitalization. The differences in percentages would not be significant since the ER visit results favor Zileuton and the Hospitalization results favor Placebo.

3.2 Evaluation of Safety

For the complete evaluation of safety see the Medical officer review.

4. Findings in Special/Subgroup Populations

4.1 Gender, Race and Age

There were no subgroup analyses either by the sponsor or by Abbott in the submission for these demographic variables in the submission. A subset analysis by gender for Study M95-337 by this reviewer obtained the following mean percent changes from baseline in FEV_1. Zileuton CR was effective in both sexes.

Table 4.1 FEV_1 Results by Gender

	Females				Males			
	Zileuton CR		Placebo CR		Zileuton CR		Placebo CR	
	N	Mean	N	Mean	N	Mean	N	Mean
Day 15	93	12.53	102	5.87	96	12.40	84	-0.37
Day 29	94	15.77	103	9.97	98	11.26	84	5.55
Day 57	94	18.90	103	12.28	98	15.87	84	6.30
Day 85	94	19.63	103	12.57	98	18.24	84	9.97

A subset analysis by age categories for Study M95-337 by this reviewer obtained the following mean percent changes from baseline in FEV_1 for the age categories age≤ 18 years and age >18 years. There were very few subjects with age >65 years. Not much efficacy was seen in the subjects 18 years of age or younger. The sample sizes are small in that subset, however.

Table 4.2 FEV_1 Results by Age

	Age ≤ 18				Age>18			
	Zileuton CR		Placebo CR		Zileuton CR		Placebo CR	
	N	Mean	N	Mean	N	Mean	N	Mean
Day 15	14	6.40	17	3.77	175	13.88	169	3.83
Day 29	14	4.51	18	10.72	178	15.49	169	8.55
Day 57	14	2.61	18	7.34	178	18.61	169	9.62
Day 85	14	11.97	18	10.40	178	21.45	169	12.70

A subset analysis by race for Study M95-337 by this reviewer obtained the following mean percent changes from baseline in FEV_1 for the races categories Caucasian, Black, and Other. Although the numbers are small, efficacy was not seen in Blacks.

Table 4.3 FEV_1 Results by Race

	Caucasian				Black				Other			
	Zileuton CR		Placebo CR		Zileuton CR		Placebo CR		Zileuton CR		Placebo CR	
	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean	N	Mean
Day 15	153	12.97	162	0.98	18	9.03	16	19.95	16	12.15	7	5.94
Day 29	155	14.10	163	6.63	18	18.96	16	30.82	17	13.05	7	4.22
Day 57	155	16.59	163	7.21	18	26.51	16	29.48	17	18.51	7	17.53
Day 85	155	18.35	163	9.17	18	27.89	16	37.95	17	25.72	7	13.47

\4.2 Other Special/Subgroup Populations

The sponsor did provide a subset analysis by baseline Percent Predicted categories > 60- <80% predicted and ≤60% predicted. Efficacy was seen in both percent predicted categories.

Table 4.4 FEV_1 Results by Baseline Percent Predicted

	>60-<80% predicted FEV1				≤ 60% Predicted FEV1			
	Zileuton CR		Placebo CR		Zileuton CR		Placebo CR	
	N	Mean	N	Mean	N	Mean	N	Mean
Day 15	81	8.07	100	2.89	107	19.85	86	7.74
Day 29	83	10.21	101	6.81	108	20.38	86	13.85
Day 57	83	14.75	101	5.20	108	21.29	86	16.69
Day 85	83	13.85	101	7.02	108	26.96	86	21.26

5. Summary and Conclusions

5.1 Statistical Issues and Collective Evidence

The sponsor did not indicate how multiplicity (changes from baseline and percent changes at various assessment times would be handled). The sample size discussion in Study M95-337 is about detecting a difference in percent changes from baseline in FEV_1. It would be assumed therefore that percent change from baseline in FEV_1 would be considered the primary variable. The sponsor provided a one page discussion of the effects of using the Hochberg procedure on changes from baseline in FEV_1 and percent changes from baseline in FEV_1 at the various assessment times for Study M95-337. Using the Hochberg procedure for percent changes from baseline in FEV_1 only the comparison of Zileuton CR to placebo CR at the first on-treatment clinic visit (DB day 15) was significant. The use of the Hochberg procedure is somewhat questionable in this situation. The Hochberg procedure is usually used for different endpoints not different assessment times for the same endpoint. The Hochberg procedure is also too conservative for this situation.

This reviewer performed a repeated measures analysis on percent change from baseline in FEV_1 in Study M95-337. The significant difference of Zileuton CR from placebo in that analysis and the significant differences from placebo in the endpoint analysis and the observed cases analysis at Day 85 lead to the conclusion that Zileuton CR is effective. Although the repeated measures analysis is a *post hoc* analysis, it gives a global indication whether Zileuton was effective over the whole treatment period.

5.2 Conclusions and Recommendations

Study M95-337 demonstrated that controlled release Zileuton was significantly better than Placebo for mean change and percent change in FEV_1 from baseline. There were only numerical trends favoring Zileuton CR in AM and PM PEFR. Study M96-464, which was mainly a safety study where Zileuton or Placebo was added to usual care, demonstrated efficacy for controlled release Zileuton for AM and PM PEFR but not for FEV_1.

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