

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:
21-479

STATISTICAL REVIEW(S)

MEMORANDUM

Date: June 6, 2003

From: Fanhui Kong (HFD-710)

To: File NDA 21479 (Serial number 108)

Subject: Regarding the discrepancy between the sponsor and the statistical reviewer in the efficacy results of Study 025

The p-values for the treatment effect on the primary endpoint as the average of Weeks 10 to 12 given by the statistical reviewer and the sponsor differ for the LOCF analysis in Study 025. The reviewer gave a p-value of 0.127 while the sponsor gave 0.896.

Given the primary endpoint to be the average of the last two visits (Weeks 10 and 12), the agency and sponsor differ in the interpretation of LOCF imputation. If a patient is missing in at least one of these two visits, the sponsor took the last available visit as the LOCF imputation while the agency insisted that the average of the last TWO available visits be regarded as the LOCF imputation. The results of the first submission were based upon the sponsor's interpretation. In January of 2003's re-submission of the analysis, the sponsor adopted the agency's interpretation of LOCF imputation. Their analysis gave a p-value of 0.583 for the treatment effect for the primary endpoint.

In search for the reasons of such differences, the agency clarified the unclear description of the efficacy data set in the submission and upon which recreated the analysis data set. This gave a p-value of 0.555. The agency also found some small errors in the creation of the analysis data set by the sponsor for the second submission which led to a small discrepancy of 0.028 in p-value between theirs and ours.

Cc: Dr. Katz (HFD-120)
Dr. Feeney (HFD-120)
Dr. Kapcala (HFD-120)
Ms. Wheelous, CSO (HFD-120)
Dr. George Chi (HFD-710)
Dr. Jin (HFD-710)

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

STATISTICAL REVIEW AND EVALUATION

Medical Division: Neuropharm Drug Products (HFD-120)

Biometrics Division: Division of Biometrics I (HFD-710)

NDA NUMBER: 21-479
DRUG NAME: Zydis selegiline
INDICATION: Parkinson' disease
SPONSOR: Elan Pharmaceuticals, Inc.
STATISTICAL REVIEWER: Fanhui Kong, Ph.D. (HFD-710)
DATE OF DOCUMENT: March 28, 2002

DISTRIBUTION:

HFD-120 Teresa Wheelous, Project Manager
Leonard Kapcala, M.D., Clinical Reviewer
John Feeney, M.D., Medical Team Leader
Russell Katz, M.D., Division Director
DFD-710 Kun Jin, Ph.D., Statistical Team Leader
George Chi, Ph.D., Division Director
HFD-700 Charles Anello, Sc.D., Deputy Director

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Statistical Review and Evaluation

1. Executive Summary

This submission consists of two Phase III, randomized, double-blind, parallel group multi-center studies comparing the efficacy and safety of Zydys selegiline 1.25 to 2.5 with placebo as an adjunct in the management of patients with Parkinson disease who are treated with Levodopa and exhibit deterioration in the quality of their response to this therapy. Both studies (Z/SEL/97/026, Z/SEL/97/025) were conducted at U.S. and Canada centers.

Both studies Z/SEL/97/025 and Z/SEL/97/026 were multicenter, randomized, double-blind, placebo-controlled, parallel-group comparisons of two treatments (Zydys selegiline 1.25 to 2.5 mg per day, placebo) in Parkinsonian patients receiving levodopa therapy, with or without a DOPA-decarboxylase inhibitor. In Study Z/SEL/97/025, a total of 150 patients were randomized and 148 were in the intent-to-treat population. In Study Z/SEL/97/026, a total of 155 patients were randomized and 140 were in the intent-to-treat population.

In this submission the primary endpoint was based on the reduction in percentage average daily "OFF" time during waking hours reported from patient/caregiver completed diary cards. Study Z/SEL/97/026 was positive with p-values below 0.001 in ITT-LOCF analysis. Study Z/SEL/97/025 was not statistically significant with a p-value of 0.467 in LOCF population.

2. Introduction

The current submission NDA 21-479 for Zydys selegiline consists of two phase-III studies to compare the efficacy and safety of Zydys selegiline with placebo as an adjunct in the management of patients with Parkinson being treated with Levodopa who exhibit deterioration in the quality of their response to this therapy.

Study Z/SEL/97/026 is a Phase III, randomized, double-blind, parallel-group study to compare the efficacy and safety of Zydys selegiline 1.25 to 2.5 mg QD with placebo as an adjunct in the management of Parkinsonian patients being treated with Levodopa who exhibit deterioration in the quality of their response to this therapy.

Study Z/SEL/97/025 is a Phase III, randomized, double-blind, parallel-group study to compare the efficacy and safety of Zydys selegiline 1.25 to 2.5 mg QD with placebo as an adjunct in the management of Parkinsonian patients being treated with Levodopa who exhibit deterioration in the quality of their response to this therapy.

In the LOCF analysis, Study 97/026 is positive in the primary endpoint of the reduction of Percent "OFF" time and therefore supports the conclusion that Zydys selegiline is more effective than placebo in improving clinical conditions of the patients with Parkinson disease who were treated with levodopa. Study 97/025 gives negative results in the same

primary endpoint, indicating that there is not enough evidence supporting the conclusion that Zydys selegiline is more effective than placebo as an adjunct in the management of patients with Parkinson disease who are treated with levodopa.

3 Study Z/SEL/97/026

The study period was between December 18, 1997 and October 15, 1999. The final protocol was signed off on March 5, 1999. The statistical analysis plan (SAP) for the study was finalized by the sponsor on December 22, 1999. There are five amendments in total to the original protocol. Significant changes were made in these amendments that include the change of primary endpoints and the analysis population. In the process, the sponsor has not always clearly identified which of the specific analysis data set (the OC or the LOCF of the ITT population) were planned for analysis of primary endpoint. In this submission the sponsor did not follow FDA's requirement on performing LOCF analysis. During the reviewing procedure, the medical and statistical reviewers contacted the sponsor through fax, telecons and communicated with them the requirement of FDA. For the primary endpoint defined as the average reduction of the percentage of "OFF" time reported by the patient at Week 10 and 12, there was a difference between the interpretation of LOCF of the agency and that of the sponsor. After the communication, the sponsor finally agreed to accept our interpretation and to create the LOCF data sets. So far the sponsor has not provided the requested data sets and the analysis reports. The reviewer conducted the LOCF analysis using the ITT data set provided by the sponsor for the statistical analyses of primary endpoint.

3.1 Study Objectives

The primary objective of this study was to compare the effectiveness and safety of Zydys selegine 1.25 to 2.5 mg per day with placebo as an adjunct in the management of Parkinsonian patients being treated with levodopa who exhibited deterioration in the quality of their response to this therapy

3.2 Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel group comparison of two treatments (Zydys selegiline 1.25 to 2.5 mg per day or placebo) in 142 patients with Parkinson's disease receiving levodopa therapy, with or without a DOPA-decarboxylase inhibitor. Two thirds of the patients were to be randomized to Zydys selegiline and one third to placebo.

The study comprised 2 periods and patients were expected to attend scheduled visits within ± 3 days of the stated visit days. Period 1 lasts 2 weeks in which patients continued to take their existing anti-parkinsonian medication. Their eligibility for randomization at Visit 3 (minimum average of 3 hours "OFF" time per day) was assessed by diary card completion. Period 2 lasts 12 weeks in which patients were randomized to receive either Zydys selegiline 1.25 mg per day or placebo. At Week 6, the patients' daily dose of Zydys

selegiline was increased to 2.5 mg per day or placebo equivalent (i.e., 2 tablets). The treatment is then maintained for the remaining 6 weeks of the study.

Throughout the study, symptoms of Parkinson's disease were rated using patient/caregiver completed diary cards to record "ON" and "OFF" times, the Clinical Global Impression Scale (CGI), the patient's Global Impression Scale (PGI) and the Motor and Activities of Daily Living (ADL) sub-scales of the Unified Parkinson's Disease Rating Scale (UPDRS).

In order to randomize 135 patients, it was anticipated that 155 patients would be recruited into the study with 103 to be randomized to Zydys selegiline and 52 to placebo to allow for patients who withdrew prior to Period 2. These patients were recruited from 16 centers in the United States.

3.3 Efficacy Measures

The primary efficacy measure of Zydys selegiline was based on the percentage reduction in total daily "OFF" time over 12 weeks on treatments during waking hours reported from patient/caregiver completed diary cards.

The secondary efficacy measures were based on the actual reduction in hours "OFF", the Unified Parkinson's Disease Rating Scale (UPDRS) (Motor sub-score for "OFF" and "ON", Activities of Daily Living [ADL] sub-score), the Clinical Global Impression Scale (CGI) and the patient's Global Impression Scale (PGI).

3.4 Statistical Analysis Plan

Intent-to-treat (ITT) population will be used to summarize data. The ITT population was defined as patients who were randomized to a treatment, received at least 1 dose of study medication, had baseline percent "OFF" time data collected, and had at least one set of "OFF" time data collected during treatment.

Endpoint was defined as the average reduction of the percentage of "OFF" time reported by the patients at Week 10 and 12 from the baseline "OFF" value. The patient's baseline "OFF" value was determined by averaging the percentage of "OFF" time reported by the patients at Week -2 and Week -1. Statistical tests for efficacy measures were two-sided and performed at the 0.05 level of significance. Tests of interaction were performed at the 0.1 significance level.

For both primary and secondary efficacy measures, descriptive data summaries are provided for each endpoint. Continuous endpoints were analyzed using analysis of covariance (ANCOVA) models with baseline score, treatment effects, center, treatment-by-center interactions as covariates. If the treatment-by-center interaction was not significant ($p \geq 0.1$), it was removed from the model. If this interaction term was significant, an assessment of its magnitude and direction was made. If the underlying assumptions of normality and homoscedasticity were found to have been violated (based

on examination of residuals), then the group medians were compared using ANCOVA on the ranks of the data.

However, the sponsor has not always clearly identified if the LOCF or OC dataset (that comprise the whole ITT population) were analyzed or were planned to be analyzed.

- The sponsor's original protocols for Phase 3, pivotal trials (studies Z/SEL/97/026 and Z/SEL/97/025) noted that the primary efficacy analysis would be conducted on the ITT patient population using the LOCF convention, thus the ITT-LOCF dataset. Specific wording on page 26 of the protocol noted: "The primary population for analysis of efficacy variables is defined as the intention-to-treat last observation carried forward (LOCF) data set."
- Protocol amendment # 2 (2/4/98) noted that the primary efficacy analysis was changed to analyze the ITT population instead of the LOCF data set. Specific wording on page 26 noted: "The primary population for analysis of efficacy variables is defined as the intention-to-treat population." This amendment further noted that a detailed plan of analysis would be prepared before the randomization code is broken and the analysis of the trial results begins.
- FDA faxed (10/15/99) comments to the sponsor regarding the sponsor's statistical analysis plan for studies Z/SEL/97/026 and Z/SEL/97/025. FDA pointed out that the ITT population should be included in the primary efficacy analysis and analyses of secondary efficacy variables. The fax further noted that "We recommend that the LOCF method be used for missing data when applicable."
- On 12/10/99 the sponsor submitted a revised statistical analysis plan along with responses to FDA comments communicated to the sponsor on 10/15/99. The sponsor provided the following response to FDA's recommendation (i.e. that the primary efficacy analysis and efficacy analyses of secondary variables utilize the ITT-LOCF data set).

"The ITT population will be changed to include all patients who have been randomized and have received at least one dose of study drug. Please note that this will result on a combined analysis of patients receiving 1.25 and 2.5 mg doses. Such an analysis was previously planned to be secondary in nature. This change has been incorporated into Section 3.1 on page 12."

- Section 3.1 of the statistical analysis plan describes analysis populations and the analysis strategy. The primary efficacy analysis is that performed on the primary efficacy parameter and considering an 'Intent-to-Treat' population (see LOCF-ITT population definition below) consisting of patients who were randomized, received at least one dose of study medication and completed a subsequent evaluation visit. Other efficacy analyses are described following definitions for the various patients populations considered."

The LOCF ITT population is described in section 3.1 as follows. "The term "LOCF ITT Population" will be used to refer to the ITT population in which the LOCF principal has been used in handling missing data. Toward the end of section 3.1 there is further mention of the LOCF ITT population and various efficacy analyses.

"Additional efficacy analyses are performed on the primary efficacy parameter considering the ITT completers population (with no imputation of missing data so that analyses are on the ITT completer only), the LOCF ITT population, and the PP population. All secondary efficacy analysis parameters are analyzed on the ITT completers population, the LOCF ITT population, and the PP population."

- During the 7/29/02 teleconference the sponsor was asked: "whether or not observed cases (OC) or Last Observation Carried Forward (LOCF) data sets were used in the efficacy analyses." The response further noted that the ITT population was defined in the analysis database that was used for the primary efficacy analysis. LOCF algorithms were implemented in the programming for data tables and were used to perform additional (secondary) efficacy analyses.
- On 11/6/02 teleconference the sponsor was found that they had a different interpretation of LOCF from that of the Agency. In the case of missing the endpoint measurements on Week 10, 12 or both, instead of taking the average of the last two measurements of the subject as the LOCF observation as interpreted by the agency, the sponsor took only the last one measurement as the LOCF observation. After FDA's insistence, the sponsor accepted the agency's interpretation on LOCF data set in the primary efficacy analyses and agreed to reanalyze the data set using the new interpretation. However, we haven't received their new analysis report yet.
- The last SAP amendment was made on December 22, 1999 in which some adjustment was made on how to analyze data if normality assumption failed.

3.5 Study Population

The target population for this study consisted of patients with Parkinson's disease who were being treated with levodopa and were exhibiting deterioration in the quality of their response to the therapy. Two-thirds of the patients were randomized to Zydys selegiline and one-third to placebo. Patients were recruited from 16 centers in the United States.

In total, 161 patients were enrolled and 142 patients entered randomized treatment in the study. Of these patients, 94 received Zydys selegiline and 48 received placebo. Seven patients in the Zydys selegiline group and 3 patients in the placebo group were discontinued from the study prematurely. ITT population included 140 patients, 94 of whom received Zydys selegiline and 46 received placebo. Two patients were excluded, of whom 1 was due to the lack of on-treatment efficacy data and the other was determined that his baseline efficacy data was not reliable. One hundred thirty-two patients completed the study.

For patient disposition (Table 3.5.1), selegiline group has protocol completed rate (93%) as compared to placebo (94%). The primary reasons for early discontinuation were “Adverse effects” and “Protocol deviation”. Selegiline group has a higher rate of “Adverse effects” while the placebo group has the same rate for “Adverse event” and “protocol deviation”.

Protocol deviation is moderate for this study. The related violation includes that some subjects were not visited at the prescribed window. This happened quite often and all visits outside the treatment window were listed in Table 5-1 of the New Drug Application Final Report I. 8 V. 31 P. 56 by the sponsor. Four patients in the Zydis selegiline group and 2 patients in the placebo group did not receive the increased dose as specified in the protocol. Treatment compliance is not of a great concern according to the sponsor’s report. One patient received more dosing (120%) than the specified dosing. One patient took only one dose of medication between Weeks 10 and 12.

Table 3.5.1 Reasons for Discontinuations from Study - All Randomized Subjects

Primary Reason for Discontinuation	Zydis selegiline		Placebo	
	(n=94)		(n=48)	
	n	(%)	n	(%)
Lack of Efficacy	1	(1)		
Adverse Event(s)	3	(3)	1	(2)
Protocol Violation	2	(2)	1	(2)
Lost to follow-up	1	(1)		
Other			1	(2)
TOTAL	7	(7.4)	3	(6.3)

Baseline patient characteristics including age, gender, race, height, weight and duration of illness appeared to be comparable across treatment groups. The only notable difference was in the average duration of Parkinson disease, with the Zydis selegiline treatment group reporting a slightly shorter duration (6.3 [\pm 4.5] years) than the placebo group (7.5 [\pm 5.1] years). This difference was not statistically significant ($p=0.167$). Baseline severity of illness based on both primary efficacy measure (Percentage “OFF” time) and secondary efficacy measures (Average “OFF” Time, CGI-S, CGI-I) appeared to be comparable across treatment groups.

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Table 3.5.2 Baseline Demographic Characteristics – ITT Population

VARIABLE	Zydis selegiline N=94	Placebo N=46
Age (yr)		
Mean (SD)	66.4 (9.3)	63.9 (11.1)
Min, Max	42.0, 85.0	38.0, 84.0
Gender		
Male	59 (62.8 %)	30 (65.2 %)
Female	35 (37.2 %)	16 (34.8 %)
Race		
Caucasian	86 (91.5 %)	43 (93.5 %)
Black	1 (1.1 %)	0 (0.0 %)
Oriental	2 (2.1 %)	0 (0.0 %)
Other	5 (5.3 %)	3 (6.5 %)
Height (kg)		
Mean (SD)	170.0 (11.9)	170.7 (10.3)
Min, Max	142.0, 193.0	142.0, 185.0
N	93	46
Weight(cm)		
Mean (SD)	75.3 (17.7)	78.1 (17.1)
Min, Max	40.9, 120.0	45.0, 127.7
N	93	46
Duration of Parkinson's Disease (yrs)		
Mean (SD)	6.3 (4.5)	7.5 (5.1)
Min, Max	0.5, 21.6	0.3, 19.0

Table 3.5.3 Baseline Efficacy Score - Baseline severity of Illness in ITT Population

Efficacy Parameters at Baseline	Zydis selegiline N = 94	Placebo N = 46	P-value
Percentage "OFF" Time			
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
Average "OFF" Time (hrs)			
Mean (SD)	6.9 (2.0)	7.0 (2.2)	
Min, Max	2.8, 11.5	3.4, 13.0	
CGI-S Score, Physician Rated			
Mean (SD)	3.70 (0.75)	3.93 (0.80)	0.094
CGI-I Score, Physician Rated			
Mean (SD)	3.97 (0.50)	4.09 (0.81)	0.338
N	93	46	

3.6 Sponsor's Efficacy Results

3.6.1 Primary Efficacy Results

Table 3.6.1 summarizes the primary efficacy analysis results. It gives the baseline and change from baseline to Weeks 10-12 in percent "OFF" time for the ITT population as reported on the patients' diary cards. "OFF" time is generally considered to be the time that a patient is not responding to levodopa, and is characterized by the appearance of

some or all of the patient's parkinsonian symptoms. Analysis of the ITT population treated with Zydys selegiline showed a statistically significant difference ($p < 0.001$) from the placebo group at the Average of Weeks 10-12 endpoint, with the difference favoring patients in the Zydys selegiline treatment group.

For both the primary and secondary analyses, the sponsor seems to have ambiguous idea of what is the appropriate data set in the ITT population to be analyzed. They did not point out whether the statistical analysis was performed using the OC data set or the LOCF data set. It seems to the reviewer that the sponsor has used the OC data set to obtain the results in Table 3.6.1.

Table 3.6.1 Reduction in Average Daily Percent "OFF" Time During Waking Hours from Baseline to Weeks 10-12---ITT Population

Primary Efficacy Parameters	Zydys selegiline (N=94)	Placebo (N=46)	P-value ^b
Baseline, Percentage "OFF" Time ^a			
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	87	44	
Mean (SD)	-13.1 (14.7)	-3.9 (10.5)	<0.001
95% Confidence Interval ^c	(-14.2, -4.7)		

^a Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1. ^b Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects). ^c Computed for difference between changes in Zydys selegiline and placebo values.

3.6.2 Secondary Efficacy Results

Table 3.6.2 summarizes the secondary efficacy analysis results for the ITT population. The reduction from baseline in the average number of daily "OFF" hours at Weeks 10-12 was greater for patients treated with Zydys selegiline than for patients treated with placebo ($p \leq 0.001$). Patients in the active treatment group had an average decrease of 2.2 (± 2.5) hours of daily "OFF" time at the Week 10-12 endpoint, compared to an average of 0.6 (± 1.6) hours in the placebo group at the same time points. A statistically significant different ($p = 0.026$) CGI-S scores were detected at Week 12. Physician-rated CGI-Improvement score which was used to measure a global improvement in condition from visit to visit improvement was not found to be statistically significant at Week 12 ($p = 0.362$). Patient-rated CGI-Improvement score was found to be statistically significant favoring the Zydys selegiline treatment group at Week 12 ($p = 0.029$). The UPDRS is a set of four subscales, which yield a combined score; in this study only the Motor and Activities of Daily Living subscales were employed to assess patient performance status. Each subscale is an ordinal scale that reflects increased severity of disease with increased scores, therefore, a lower score indicates less severe symptoms. A statistically significant difference ($p = 0.018$) in Motor "OFF" scores favoring Zydys selegiline treatment was

detected at Week 12. For other subscales, no statistically significant results were observed.

Table 3.6.2 Secondary Efficacy Measure at Endpoint - Intent-to-Treat Population

Secondary Efficacy Parameters At Endpoint	Zydis selegine (N=94) N (%)	Placebo (N=46) N (%)	P-value
Average "OFF" Time			
Mean change from baseline (SD)	-2.2 (2.5)	-0.6 (1.6)	<0.001
95% confidence interval	(-2.4, -0.8)		
N	87	44	
CGI-S Score –Physician Rated			
Mean score at baseline (SD)	3.70 (0.75)	3.93 (0.80)	0.094
N	94	46	
Mean score at Week 12 (SD)	3.18 (0.92)	3.53 (0.91)	0.026
N	82	43	
CGI-I Score –Physician Rated			
Mean score at baseline (SD)	3.97 (0.50)	4.09 (0.81)	0.338
N	93	46	
Mean score at Week 12 (SD)	3.50 (0.79)	3.63 (0.87)	0.362
N	82	43	
CGI-I Score –Patient Rated			
Mean score at Week 12 (SD)	3.01 (1.07)	3.47 (1.14)	0.029
N	82	43	
UPDRS Subscale and Condition			
ADL "ON" mean at Week 12 (SD)	6.0 (5.3)	6.9 (6.1)	0.282
N	81	43	
ADL "OFF" mean at Week 12 (SD)	14.6 (7.7)	16.2 (7.7)	0.668
N	81	43	
Motor "ON" mean at Week 12 (SD)	14.6 (8.3)	16.8 (10.8)	0.201
N	81	43	
Motor "OFF" mean at Week 12 (SD)	27.3 (12.4)	31.4 (12.5)	0.018
N	81	42	

(a) These are the least square adjusted means and standard errors. (b) The p-values are derived based on the least square adjusted means and standard errors.

3.7 Reviewer's Analysis

The reviewer replicated the sponsor's analyses according to the protocol. Using the ITT data set provided by the sponsor, the reviewer constructed the LOCF data set and performed the statistical analysis for the primary endpoint. The results are depicted in Table 3.7.1.

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Table 3.7.1 Reduction in Average Daily Percent “OFF” Time During Waking Hours from Baseline to Endpoint ---ITT LOCF Population

Primary Efficacy Parameters	Zydis selegiline (N=94)	Placebo (N=46)	P-value ^b
Baseline, Percentage “OFF” Time ^a			
Mean (SD)	41.5 (11.6)	42.1 (12.5)	
Min, Max	18.0, 68.8	20.7, 70.2	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	92	45	
Mean (SD)	-13.9 (15.2)	-5.1 (13.7)	0.0007
95% Confidence Interval ^c	(-14.1, -3.5)		

^a Percent “OFF” time of total waking hours for ITT population defined as an average of reported “OFF” time for Weeks -2 and -1. ^b Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects). ^c Computed for difference between changes in Zydis selegiline and placebo values.

The Shapiro-Wilks test indicates that the normality assumption holds for the primary endpoint of the reduction in the percent “OFF” time from baseline. Therefore the model assumption for statistical analysis reported in Table 3.7.1 are acceptable to the agency. To further see the robustness of results, the reviewer performed the Wilcoxon nonparametric test on the reduction from baseline of the percentage “OFF” time as well as the percentage change from baseline of the same variable, i.e., the reduction in percent “OFF” time from baseline divided by baseline. These tests give p-values 0.0007 and 0.0009. The Wilcoxon test suggests that the testing results in Table 3.7.1 are robust.

The information of each investigator is presented in the following table to check whether the significance result is mainly contributed by one investigator. In the following table, NSelegiline and NPlacebo are the number of patients in Zydis selegiline and Placebo groups, respectively. T is TTEST statistic performed on the difference of the mean reduction from baseline for unequal variances between two treatment groups.

Table 3.7.2 T Statistic by Investigator for the Average Reduction of Daily “OFF” Time

Obs	Invest	NSelegiline	NPlacebo	t-Value
01	104	12	7	-1.43
02	105	8	4	-1.09
03	108	10	5	-3.68
04	112	9	5	-0.75
05	115	8	3	-2.99
06	116	12	6	-0.58
07	118	9	4	0.75
08	G61	6	3	-0.37
09	G62	6	3	-3.33
10	G63	12	5	-0.16

Most of the clinic centers show that the Zydis selegiline reduces the daily “OFF” time compared to the placebo. Center 108 seems to have especially high significance level.

After removing this center, Wilcoxon test gives a p-value of 0.009 and t-test gives p-value of 0.013 for the significance test of the treatment effect of Zydys selegiline. So the significance of the treatment effect of Zydys selegiline in this study is not affected by a single investigator.

The following table gives t-test result for the treatment difference by sex. DIFF is the mean change from baseline to Weeks 10-12 on the percentage of "OFF" time. ZYDISDIFF is the difference between DIFF of Zydys selegiline and Placebo.

Table 3.7.3 Treatment Effect by Sex for the Reduction of Daily "OFF" Time

Sex	Therapy	Patient	DIFF	ZYDISDIFF	t-Value
Male	Zydys selegiline	58	-15.4	-10.8	-3.87
	Placebo	29	-4.7		
Female	Zydys selegiline	34	-11.3	-5.5	-1.02
	Placebo	16	-5.8		

The above table shows that Zydys selegiline has treatment effect in both male and female groups but it has statistical significant results only in the male group.

The following table gives t-test result for the treatment difference by age group. The median age is 66.5, so we separate the population into two age groups: above 66 years of age and not above 66 years of age. DIFF is the mean change from baseline to Weeks 10-12 on the percentage of "OFF" time. ZYDISDIFF is the difference between DIFF of Zydys selegiline and Placebo.

Table 3.7.4 Treatment Effect by Age Group for the Reduction of Daily "OFF" Time

Sex	Therapy	Patient	DIFF	ZYDISDIFF	t-Value
<=66 years	Zydys selegiline	45	-14.3	-7.6	-2.32 (p=0.024)
	Placebo	24	-6.7		
>66 years	Zydys selegiline	47	-13.5	-10.3	-2.38 (p=0.02)
	Placebo	21	-3.2		

So the treatment effect of Zydys selegiline in both age groups are statistically significant.

Given that Caucasians are 91.5% and 93.5% in the selegiline and placebo groups, we will not perform a group analysis for different racial groups.

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The study was performed between December 11, 1997 and November 24, 1999. The final protocol was signed off on March 5, 1999. The statistical analysis plan (SAP) for the study was finalized by the sponsor on December 22, 1999. Same amendments as Study 97/026 were made. Again the reviewer has the concern as in Study 97/026 on the data set used for the statistical analyses. These were discussed with the sponsor through fax, telecons. There were disagreements between the agency and the sponsor on the interpretation of LOCF imputation. The sponsor agreed to provide the required LOCF data set according to the interpretation of the agency together with the analysis report. However so far we haven't received any of these documents by the date this review is finished. So the reviewer constructed the LOCF data set using the ITT data set provided by the sponsor and performed the statistical analysis for the primary endpoint.

4.1 Study Objectives

Same as in Study 97/026, the objective of this study was to compare the efficacy and safety of Zydys selegiline (1.25 to 2.5 mg per day) with placebo as an adjunct in the management of Parkinsonian patients being treated with levodopa who exhibited deterioration in the quality of their response to this therapy.

4.2 Study Design

Same as Study 97/026, this was a multicenter, randomized, double-blind, placebo-controlled, parallel group study of two treatments (Zydis selegiline 1.25 to 2.5 mg per day or placebo) in patients with Parkinson's disease receiving levodopa therapy. Patients were randomly distributed in 2:1 into treatment or placebo groups.

Same as Study 97/026, this study consists of 2 periods. In the first period of 2 weeks patients continued their existing anti-parkinsonian medication. In the second period of 12 weeks they were randomized into either treatment or placebo group. In the treatment group, patients took Zydis selegiline 1.25 mg per day for the first 5 weeks and 2.5 mg per day for the last 7 weeks. Again, diary cards were administered to evaluate Parkinson's disease symptoms by recording "ON" and "OFF" times, the Clinical Global Impression Scale (CGI), the patient's Global Impression Scale (PGI) and the Motor and Activities of Daily Living (ADL) sub-scales of the Unified Parkinson's Disease Rating Scale (UPDRS). In order to randomize 135 patients, 155 patients would be recruited to allow for patients to withdraw prior to Period 2. These patients were recruited from 14 centers in the United States.

4.3 Efficacy Measures

The primary efficacy measure of Zydis selegiline was based on the percentage reduction in total daily "OFF" time over 12 weeks on treatment during waking hours reported from patient/caregiver completed diary cards.

The secondary efficacy measures were based on the actual reduction in hours "OFF", the Unified Parkinson's Disease Rating Scale (UPDRS) (Motor sub-score for "OFF" and "ON", Activities of Daily Living [ADL] sub-score), the Clinical Global Impression Scale (CGI) and the patient's Global Impression Scale (PGI).

4.4 Statistical Analysis Plan

The same statistical analysis plan as Study 97/026 was applicable for this study. The final revision of SAP was made on December 22, 1999. The agency had the same concerns as the above study regarding the appropriateness of the data sets used for statistical analysis. After various ways of communication and FDA's insist, the sponsor agreed to use LOCF data set along with our interpretation in the primary efficacy analyses. However, the agency has not received the data sets and the analysis report.

4.5 Study Population

The target population for this study consisted of patients with Parkinson's disease who were being treated with levodopa and were exhibiting deterioration in the quality of their response to the therapy. In total, 180 patients were enrolled and 150 patients were randomized. Of these patients, 100 received Zydys selegiline treatment and 50 received placebo. Eleven patients in the Zydys selegiline group and 5 patients in the placebo group were discontinued from the study prematurely. ITT population included 148 patients, 98 of whom received Zydys selegiline and 50 received placebo. One hundred thirty-four patients completed the study.

For patient disposition (Table 4.5.1), selegiline group has protocol completed rate (89%) as compared to placebo (90%). The primary reasons for early discontinuation were "Adverse effects" and "Others". Selegiline group has a higher rate of "Adverse effects" while the placebo group has the highest rate for "Others".

Protocol deviation is moderate for this study. The related violation includes that some subjects were not visited at the prescribed window. This happened quite often and all visits outside the treatment window were listed in Table 5-1 of the New Drug Application Final Report I.8 V.20 P.60 by the sponsor. One patient in the Zydys selegiline group did not receive the increased dose as specified in the protocol. Two patients were excluded from ITT population. One used prohibited medication and the other never returned for any post treatment evaluation. Some patients used prohibited concomitant medications. But this is not serious according to the sponsor.

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Table 4.5.1 Reasons for Discontinuations from Study - All Randomized Subjects

Primary Reason for Discontinuation	Zydis selegiline		Placebo	
	n	(%)	n	(%)
Lack of Efficacy			1	2%
Adverse Event(s)	7	7%		
Protocol Violation			1	2%
Lost to follow-up	1	1%		
Others	3	3%	3	6%
TOTAL	11	11%	5	10%

Baseline patient characteristics including age, gender, race, height, weight and duration of illness appeared to be comparable across treatment groups. The only notable difference was in the average duration of Parkinson Disease, with the Zydis selegiline treatment group reporting a slightly shorter duration (6.2 [\pm 4.5] years) than the placebo group (7.2 [\pm 5.5] years). This difference was not statistically significant ($p = 0.268$). Baseline severity of illness based on both primary efficacy measure (Percentage “OFF” time) and secondary efficacy measures (Average “OFF” Time, CGI-S, CGI-I) appeared to be comparable across treatment groups.

Table 4.5.2 Baseline Demographic Characteristics – ITT Population

VARIABLE	Zydis selegiline N=98	Placebo N=50
Age (yr)		
Mean (SD)	68.4 (9.0)	66.3 (10.6)
Min, Max	41.0, 93.0	39.0, 85.0
Gender		
Male	68 (69.4%)	36 (72.0%)
Female	30 (30.6%)	14 (28%)
Race		
Caucasian	93 (94.9%)	49 (98%)
Black	3 (3.1%)	0
Other	2 (2.0%)	1 (2.0%)
Height (kg)		
Mean (SD)	170.8 (8.9)	170.8 (19.9)
Min, Max	149.0, 188.0	151.0, 201.0
Weight(cm)		
N	97	49
Mean (SD)	77.6 (18.2)	79.4 (18.5)
Min, Max	43.6, 158.9	50.0, 129.4
Duration of Parkinson’s Disease (yrs)		
N	98	50
Mean (SD)	7.2 (5.5)	6.2 (4.5)
Min, Max	0.3, 32.7	0.4, 20.4

Table 4.5.3 Baseline Efficacy Score - Baseline severity of Illness in ITT Population

Efficacy Parameters at Baseline	Zydis selegiline N = 98	Placebo N = 50	P-value
Percentage "OFF" Time			
Mean (SD)	41.8 (14.1)	41.7 (12.9)	
Min, Max	18.6, 100.0	20.0, 72.4	
Average "OFF" Time (hrs)			
Mean (SD)	6.7 (2.3)	6.8 (2.2)	
Min, Max	3.1, 15.6	3.1, 12.0	
N	98	50	
CGI-S Score, Physician Rated			
Mean (SD)	3.79 (0.89)	3.57 (0.82)	0.075
N	98	49	
CGI-I Score, Physician Rated			
Mean (SD)	4.05 (0.70)	4.08 (0.65)	0.54
N	97	48	

4.6 Sponsor's Efficacy Results

4.6.1 Primary Efficacy Results

Table 4.6.1 summarizes the primary efficacy analysis results. It gives the baseline and change from baseline to Weeks 10-12 in Percent "OFF" time for the ITT population as reported on the patients' diary cards. "OFF" time is considered to be the time that a patient is not responding to levodopa. Analysis of the ITT population treated with active drug did not show a statistically significant difference (p=0.467) from the placebo group at the Average of Weeks 10-12 endpoint.

Table 4.6.1 Reduction in Average Daily Percent "OFF" Time During Waking Hours from Baseline to Weeks 10-12 —ITT Population

Primary Efficacy Parameters	Zydis selegiline (N=98)	Placebo (N=50)	P-value ^b
Baseline, Percentage "OFF" Time ^a			
Mean (SD)	41.8 (14.1)	41.7 (12.9)	
Min, Max	18.6, 100.0	20.0, 72.4	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	98	46	
Mean (SD)	-11.6 (17.5)	-9.8 (14.9)	0.467
95% Confidence Interval ^c	(-8.0, 3.7)		

^a Percent "OFF" time of total waking hours for ITT population defined as an average of reported "OFF" time for Weeks -2 and -1. ^b Comparison of treatment groups using ANOVA (with treatment, baseline, and center effects). ^c Computed for difference between changes in Zydis selegiline and placebo values.

4.6.2 Secondary Efficacy Results

Table 4.6.2 summarizes the secondary efficacy analysis results. These include the mean change from baseline of Average “OFF” Time, the mean change from baseline of Physician Rated CGI-S Score and Physician as well as Patient Rated CGI-I Score, and UPDRS Subscale and Condition Scores for the ITT population. No secondary endpoint was found to be statistically significant except the Patient-rated CGI-Improvement score, which favors the Zydys selegiline treatment group at Week 12 (p=0.02).

Table 4.6.2 Secondary Efficacy Measure at Endpoint - Intent-to-Treat Population

Secondary Efficacy Parameters At Endpoint	Zydys selegine (N=98) N (%)	Placebo (N=50) N (%)	P-value
Average “OFF” Time			
Mean change from baseline (SD)	-1.9 (2.7)	-1.6 (2.3)	0.588
95% confidence interval	(-1.2, 0.7)		
N	89	46	
CGI-S Score –Physician Rated			
Mean score at baseline (SD)	3.79 (0.89)	3.57 (0.82)	0.075
N	98	49	
Mean score at Week 12 (SD)	3.24 (1.07)	3.27 (1.01)	0.88
N	83	45	
CGI-I Score –Physician Rated			
Mean score at baseline (SD)	4.05 (0.70)	4.08 (0.65)	0.54
N	97	48	
Mean score at Week 12 (SD)	3.43 (0.83)	3.70 (0.79)	0.064
N	82	44	
CGI-I Score –Patient Rated			
Mean score at Week 12 (SD)	3.06 (1.23)	3.49 (1.25)	0.02
N	84	45	
UPDRS Subscale and Condition			
ADL “ON” mean at Week 12 (SD)	7.0 (6.2)	5.7 (5.0)	0.869
N	82	45	
ADL “OFF” mean at Week 12 (SD)	14.0 (7.3)	12.3 (5.7)	0.635
N	80	45	
Motor “ON” mean at Week 12 (SD)	15.5 (10.4)	13.5 (10.3)	0.306
N	82	45	
Motor “OFF” mean at Week 12 (SD)	27.4 (14.5)	25.0 (15.5)	0.892
N	77	44	

(a) These are the least square adjusted means and standard errors. (b) The p-values are derived based on the least square adjusted means and standard errors.

4.7 Reviewer’s Analysis

The reviewer replicated the sponsor’s analyses according to the protocol. Using the ITT data set provided by the sponsor, the reviewer constructed the LOCF data set and performed the statistical analysis for the primary endpoint. The results of the reviewer are depicted in the Table 4.7.1.

Table 4.7.1 Reduction in Average Daily Percent “OFF” Time During Waking Hours from Baseline to Weeks 10-12 —ITT LOCF Population

Primary Efficacy Parameters	Zydis selegiline (N=98)	Placebo (N=50)	P-value ^b
Baseline, Percentage “OFF” Time ^a			
Mean (SD)	41.8 (14.1)	41.7 (12.9)	0.98
Min, Max	18.6, 100.0	20.0, 72.4	
Average of Weeks 10-12 (%), (Dose=2.5 mg/day)			
N	93	48	
Mean (SD)	-12.1 (17.8)	-7.4 (18.1)	0.127
95% Confidence Interval ^c	(-11.0, 1.5)		

^a Percent “OFF” time of total waking hours for ITT population defined as an average of reported “OFF” time for Weeks -2 and -1. ^b Comparison of treatment groups using ANCOVA (with treatment, baseline, and center effects). ^c Computed for difference between changes in Zydis selegiline and placebo values.

The Shapiro-Wilks test indicates that the normality assumption holds for the primary endpoint of the reduction in daily percent “OFF” time from baseline. Therefore the model assumption to obtain the significance results in Table 4.7.1 is acceptable. To further see the robustness of results, the reviewer performed the Wilcoxon nonparametric test on the reduction from baseline of the daily percent “OFF” time. This test gives p-value 0.2062. This result of the Wilcoxon test further indicates that there is no statistical evidence in this study that supports the conclusion that Zydis selegiline improves patient’s condition over placebo by increasing daily percent “OFF” time.

At the same time, the ANCOVA indicates that there is no center effect. As a more detailed verification, Table 4.7.2 presents the reduction in percent “OFF” time made by each investigator. In the following table, NSelegiline and NPlacebo are the numbers of patients in Zydis selegiline and Placebo groups, respectively. T-value is TTEST statistic value performed on the difference of the mean reduction from baseline for unequal variances between two treatment groups.

Table 4.7.2 T Statistic by Investigator for the Reduction of Average Daily Percent “OFF” Time

Obs	Invest	Nselegiline	NPlacebo	DIFF	t-Value
01	002	24	12	3.7	0.51
02	011	22	10	-0.3	-0.04
03	018	8	6	-22.2	-2.78
04	019	8	5	-18.8	-1.54
05	G51	5	3	-6.3	-0.73
06	G52	7	3	-6.7	-0.68
07	G53	7	3	0.53	0.06
08	G54	12	6	-5.3	-0.54

Most of the clinic centers show that the Zydis selegiline reduces the daily “OFF” time compared to the placebo. Center 018 seems to have especially high reduction that is

statistically significant. However, because of the high variance, the overall reduction lacks statistical significance.

The following table gives the treatment difference by sex. DIFF is the mean reduction from baseline to Weeks 10-12 on daily percent “OFF” time. ZYDISDIFF is the difference between DIFF of Zydys selegiline and Placebo.

Table 4.7.3 Treatment Effect by Sex for the Reduction of Average Daily Percent “OFF” Time

Sex	Therapy	Patient	DIFF	ZYDISDIFF	t-Value
Male	Zydis selegiline	64	-10.4	-2.14	-0.62
	Placebo	34	-8.3		
Female	Zydis selegiline	29	-15.9	-10.72	-1.56
	Placebo	14	-5.1		

The above table shows that Zydis selegiline has some treatment effect in both male and female groups but it has a higher effect in female group. However, none of the groups is statistically significant.

5 Conclusion

The sponsor conducted two Phase III, placebo controlled clinical trials for the efficacy study of the Zydis selegiline for treating patients as an adjunct in the management of Parkinsonian patients being treated with levodopa who exhibited deterioration in the quality of their response to this therapy. In the planning of the study, the sponsor has modified the protocol several times. In the process, the sponsor has not always clearly identified study population (the OC or the LOCF of the ITT population) for the analysis of primary endpoint. This has caused confusions. They also had a different interpretation from the agency on the LOCF data set. After communication through email, fax and telecon, the sponsor accepted our interpretation and agreed to create the LOCF data sets. However, the agency has not received the new data sets and the related analysis reports at the time this review is finished. Using the ITT data sets provided by the sponsor, the reviewer conducted the LOCF analysis for the statistical analyses of primary endpoint.

In LOCF analysis, Study 97/026 was positive in the primary endpoints so it supported the conclusion that Zydis selegiline is more effective than placebo in improving patient’s percent “OFF” time. The normality assumption made by the sponsor on the primary endpoint was checked by the reviewer and was found to be acceptable. Further the Wilcoxon nonparametric test was also used to test the results. The results supported the conclusions regarding the efficacy of Zydis selegiline in reducing the daily percent “OFF” time, which was obtained under the normality assumption. However, in Study 97/025, the treatment was not found to be statistically significant so it did not support the conclusion that Zydis selegiline improves patient’s condition in reducing the daily percent “OFF” time more effectively than placebo.

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