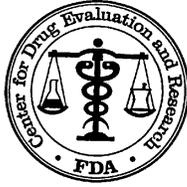


**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202971Orig1s000

STATISTICAL REVIEW(S)



U.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 AND EVALUATION

CLINICAL STUDIES

NDA (Serial) Number: 202,971/O-1 (SN 0000/SDN 1, SN 0006/SDN 7)

Drug Name: Aripiprazole (Abilify)

Indication: Schizophrenia

Applicant: Otsuka Pharmaceutical Development & Commercialization, Inc.

Submission Date: 9-26-2011

Review Priority: Standard

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1. EXECUTIVE SUMMARY

The sponsor's findings on aripiprazole IM depot (400 mg or 300 mg) were confirmed by the reviewer to be statistically significantly superior to placebo (log-rank test p-value < .0001) in reducing the time to exacerbation of psychotic symptoms/impending relapse in schizophrenic patients. The result of the Chi-square test on the percentage of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria was also statistically significant.

The effect on the Black/African American sub-population may not be conclusive because of the lack of representation.

2. INTRODUCTION

2.1 Overview

Aripiprazole has been approved as oral formulations for several antipsychotic indications. It has also been approved as an injection for acute treatment of agitation associated with schizophrenia or bipolar disorder. In this application, the sponsor is seeking for approval as an extended-release-suspension injection for the maintenance treatment of schizophrenia in adults based on one pivotal efficacy study 31-07-246.

Study 31-07-246 is a 52-week, double-blind, placebo-controlled maintenance trial in adult patients who met DMS-IV-TR criteria for schizophrenia. This trial included an oral conversion phase for patients on antipsychotic medications other than aripiprazole, an oral aripiprazole stabilization phase, a minimum 12-week aripiprazole extended release suspension for injection stabilization phase, and a randomized placebo-controlled phase to observe for impending relapse.

The trial design included 2 prespecified interim analyses for efficacy in order to minimize continued exposure to placebo and the risk of relapse; one was to occur after accrual of 50% of the 125 targeted events (63 events) and the second was to occur after 75% accrual of the events (94 events). A Data Monitoring Committee (DMC) was responsible for ongoing safety monitoring and evaluation of efficacy from the prespecified interim analyses.

The sponsor has determined that Dr. Kashfi's site (Site 046) had significant compliance issues that were detected during the sponsor oversight visit for Trial 31-08-248, after completion of Trial 31-07-246. Thus the sponsor has performed additional analysis of the primary efficacy endpoint excluding the subjects from Site 046 (7 subjects).

2.2 Data Sources

The sponsor's submitted data and program listings are available in the following directory of the CDER' electronic document room (EDR):

<\\Cdseub1\evsprod\NDA202971\0000\m5\datasets\31-07-246>

3. STATISTICAL EVALUATION

3.1 Data and Analysis Quality

This reviewer was able to reproduce most of the primary analysis dataset from the raw data; however, the primary efficacy endpoint (time from randomization to impending relapse) was neither derived nor described in the `define.pdf` file for the data set. Nevertheless, the date of the impending relapse and the date of the relapse were available. These two variables are practically

identical, except two observations (subject screening numbers S0228 and S0371) for which impending relapse was documented, but no actual relapse was recorded:

Table 1. Summary of the patients with impending relapse but no actual relapse.

Subject Screening #	Subject #	Center #	Impending relapse date	Time to relapse	Relapse date
S0228	5094	037	June 14, 2010	271	NA
S0371	6007	038	Nov 23, 2009	41	NA

Source: computed by the reviewer.

3.2 Evaluation of Efficacy

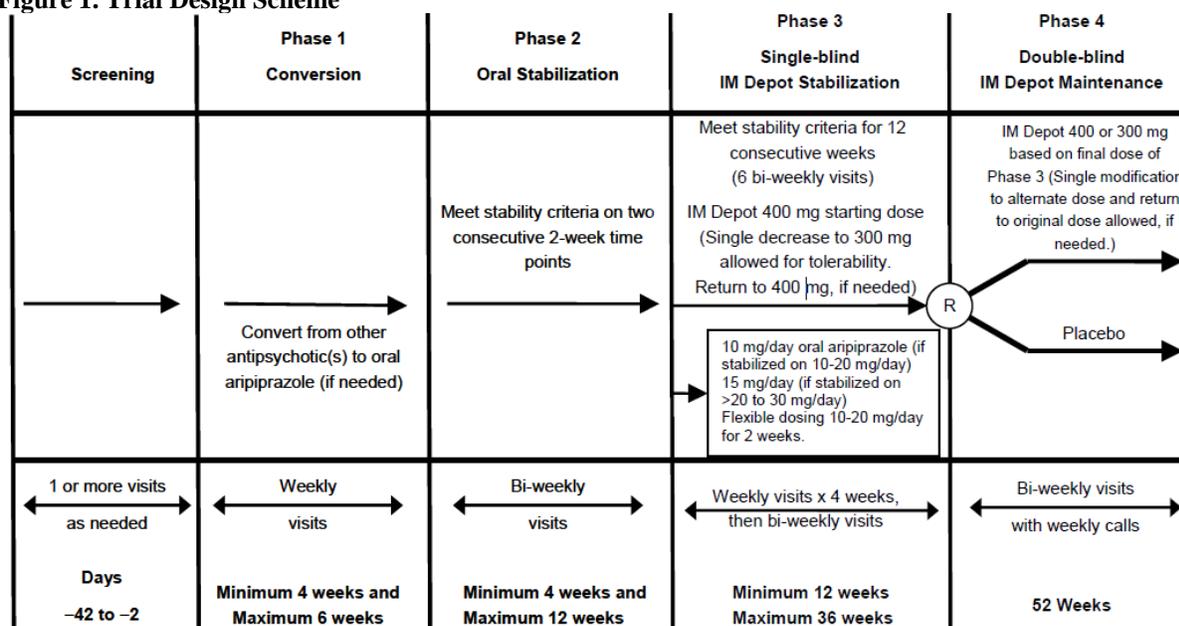
Objectives

The primary objective was to evaluate the efficacy of aripiprazole intramuscular (IM) depot (300 or 400 mg) compared with placebo IM depot, as measured by time to exacerbation of psychotic symptoms/impending relapse, in schizophrenic patients who have maintained stability on aripiprazole IM depot for at least 12 weeks.

Study Design and Endpoints

This was a randomized, double-blind, placebo-controlled trial consisting of a screening phase and 4 treatment phases: (1) Conversion, (2) Oral Stabilization, (3) IM Depot Stabilization, and (4) Double-blind Placebo-controlled. Referred in the protocol numerically, i.e., Phase 1, 2, 3, and 4, respectively (see Figure 1).

Figure 1. Trial Design Scheme



Source: Protocol 31-07-246 (pg. 45), IND 67,380.

The trial design includes 2 prespecified interim analyses for efficacy in order to minimize continued exposure to placebo and the risk of relapse: the first interim analysis was planned after accrual of 50% of the 125 targeted events (63 events) and the second interim analysis was planned after 75% accrual of the events (94 events). A Data Monitoring Committee (DMC) was responsible for ongoing safety monitoring and evaluation of efficacy from the prespecified interim analyses.

The **primary efficacy endpoint** of this study is the time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 4, defined as meeting ANY or ALL of the following four criteria:

- 1) CGI-Improvement of ≥ 5 (minimally worse) AND
 - a) an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 with an absolute increase of ≥ 2 on that specific item since randomizationOR
 - b) an increase on any of the following individual PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 and an absolute increase of ≥ 4 on the combined four PANSS items (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) since randomization.
- OR
- 2) Hospitalization due to worsening of psychotic symptoms (including partial hospitalization programs), but excluding hospitalization for psychosocial reasons
- OR
- 3) CGI-SS of 4 (severely suicidal) or 5 (attempted suicide) on Part 1 and/or 6 (much worse) or 7 (very much worse) on Part 2
- OR
- 4) Violent behavior resulting in clinically significant selfinjury, injury to another person, or property damage.

The **key secondary efficacy endpoint** was defined as percentage of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria.

Application of Subimpending Relapse Criteria: The criteria were applied to define a subimpending event as an approach to assess the robustness of analysis results from the primary endpoint; it led to an event for some censored subjects (based on the primary endpoint) who at the time of discontinuation were close to meeting the impending relapse criteria. The subimpending relapse criteria are defined as follows:

- (a) CGI-I I score of > 5 (minimally worse)
AND
an increase on any of the following individual PANSS items score (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 ;
- OR
- (b) CGI-SS score of 3 (moderately suicidal) on Part 1.

These subimpending relapse criteria were applied to all subjects who discontinued (rather than the sponsor discounted trial) and did not meet the exacerbation of psychotic symptoms/impending relapse criteria. In this sensitivity analysis, all discontinued subjects who met the subimpending relapse criteria were considered as having events on one day after the discontinuation date in addition to subjects who met the impending relapse criteria. The log-rank test was applied for final analysis.

The original version of the protocol was issued on April 30, 2008. It was amended twice: first time on July 24, 2008 (Amendment 1) and then on November 18, 2009 (Amendment 2). The Amendment 2 revised the statistical analysis methods, by clarifying the sequential testing procedure used for the key secondary efficacy endpoints in Phase 4 in order to keep the overall experimentwise Type I Error at 0.05.

Patient Disposition, Demographic and Baseline Characteristics

The dataset from the first interim analysis includes 64 events, because the last two had occurred on the same day (June 8, 2010). Because of the positive result of the first interim analysis, the trial was terminated early with the last subject discontinued from the Double-blind, Placebo-controlled Phase on 24 August 2010. Since there were 16 additional impending relapse events after the interim look, it led to a total of 80 impending relapse events in the data set for the final analysis. Table 2 describes all types of the dataset used in the study:

Table 2. Summary of the analyses datasets.

	Planned # of events	Observed # of events	Randomized # of subjects
First Interim Analysis Dataset*	63	64	344
Second Interim Analysis Dataset	94	NA	NA
Final Analysis Dataset	125	80	403

Source: computed by the reviewer.

There were 2 subjects (07246-022-0158 and 07246-004-0063) unblinded during the trial at the site level. Neither of these 2 subjects experienced an impending relapse event.

Another 2 subjects (07246-029-0248 and 07246-029-0185) were entered into more than one trial with aripiprazole and received extra doses of aripiprazole IM depot during the double-blind, placebo controlled phase. Neither of these 2 subjects experienced an impending relapse event as they were discontinued from the trial as soon as their double trial entry was identified.

The sponsor also reported one subject (07246-061-0411) who was enrolled in more than one trial, but discontinued due to the lack of efficacy with AE, but not due to the violation (no overlap in dates or dosings).

* Since the study was terminated prior to conducting second interim analysis, for simplicity the in this review we will refer to ‘the first interim analysis’ as just ‘the interim analysis’.

Table 3. Demographic characteristics in the randomized, double-blind phase 4 (Final Analysis Set, 80 Events)

Demographic Characteristic	Aripiprazole IM Depot (N=269)	Placebo (N=134)	Total (N=403)
Sex n (%)			
Male	162 (60.2)	79 (59.0)	241 (59.8)
Female	107 (39.8)	55 (41.0)	162 (40.2)
Age (years)			
Mean (SD)	40.1 (11.0)	41.7 (10.5)	40.6 (10.8)
Min – Max	18 – 60	20 – 61	18 – 61
< 45 n (%)	158 (58.7)	82 (61.2)	240 (59.6)
≥ 45 n (%)	111 (41.3)	52 (38.8)	163 (40.4)
Weight (kg)			
Mean (SD)	80.6 (20.4)	84.8 (23.3)	82.0 (21.4)
Min – Max	43.2 – 178.2	43.3 – 178.4	43.2 – 178.4
Height (cm)			
Mean (SD)	169.5 (9.9)	169.6 (10.8)	169.5 (10.2)
Min – Max	140.0 – 206.0	133.0 – 190.0	133.0 – 206.0
BMI (kg/m ²)			
Mean (SD)	28.1 (6.9)	29.5 (7.5)	28.5 (7.1)
Min – Max	15.7 – 58.2	16.9 – 53.3	15.7 – 58.2
BMI n (%)			
< 18.5 (kg/m ²)	6 (2.2)	2 (1.5)	8 (2.0)
18.5 to < 25 (kg/m ²)	96 (35.7)	42 (31.3)	138 (34.2)
25 to < 30 (kg/m ²)	81 (30.1)	39 (29.1)	120 (29.8)
≥ 30 (kg/m ²)	86 (32.0)	51 (38.1)	137 (34.0)
Race n (%)			
Caucasian	152 (56.5)	92 (68.7)	244 (60.5)
Black or African American	59 (21.9)	22 (16.4)	81 (20.1)
Asian	45 (16.7)	13 (9.7)	58 (14.4)
Other	13 (4.8)	7 (5.2)	20 (5.0)
Ethnicity n (%)			
Hispanic or Latino	29 (10.8)	18 (13.4)	47 (11.7)
Not Hispanic or Latino	239 (88.8)	116 (86.6)	355 (88.1)
Unknown	1 (0.4)	0 (0.0)	1 (0.2)
Region n (%)			
US	122 (45.4)	61 (45.5)	183 (45.4)
Non-US	147 (54.6)	73 (54.5)	20 (54.6)
Last dose in Phase 3* n (%)			
400 mg	246 (91.4)	123 (91.8)	369 (91.6)
300 mg	23 (8.6)	11 (8.2)	34 (8.4)

Source: Clinical Study Report 31-07-246, pg. 196, Table 8.2.4-1.

*From IM depot study medication records.

Table 4. Patients disposition in the randomized to phase 4 (interim analysis, 64 events, all sites included)

	Aripiprazole	Placebo	Total
Screened			971
Randomized by the cut-off date 06/08/2010	230	114	344
Terminated study early n (%)	57 (24.78)	62 (54.39)	119 (34.59)
Lost to follow-up	6 (2.61)	3 (2.63)	9 (2.62)
Sponsor discontinued study	0 (0)	0 (0)	0 (0)
Subject met withdrawal criteria	3 (1.30)	2 (1.75)	5 (1.45)
Withdrawn by investigator	6 (2.61)	6 (5.26)	12 (3.49)
Subject withdrew consent to participate	12 (5.22)	4 (3.51)	16 (4.65)
Protocol deviation	1 (0.43)	0 (0)	1 (0.29)
Adverse event without impending relapse	7 (3.04)	5 (4.39)	12 (3.49)
Lack of efficacy with adverse event	9 (3.91)	11 (9.65)	20 (5.81)
Lack of efficacy without adverse event	13 (5.65)	31 (27.19)	44 (12.79)
Completed treatment n (%)	173 (75.22)	52 (45.61)	225 (65.41)

Source: computed by the reviewer.

Table 5. Patients disposition in the randomized to phase 4 (final analysis, 80 events, all sites included)

	Aripiprazole	Placebo	Total
Screened			971
Randomized by the cut-off date 08/24/2010	269	134	403
Terminated study early n (%)	246 (91.45)	131 (97.76)	377 (93.55)
Lost to follow-up	5 (1.86)	3 (2.24)	8 (1.99)
Sponsor discontinued study	179 (66.54)	58 (43.28)	237 (58.81)
Subject met withdrawal criteria	2 (0.74)	2 (1.49)	4 (0.99)
Withdrawn by investigator	8 (2.97)	6 (4.48)	14 (3.47)
Subject withdrew consent to participate	14 (5.20)	4 (2.99)	18 (4.47)
Protocol deviation	2 (0.74)	0 (0)	2 (0.50)
Adverse event without impending relapse	9 (3.35)	5 (3.73)	14 (3.47)
Lack of efficacy with adverse event	11 (4.09)	13 (9.70)	24 (5.96)
Lack of efficacy without adverse event	16 (5.95)	40 (29.85)	56 (13.90)
Completed treatment n (%)	23 (8.55)	3 (2.24)	26 (6.45)

Source: computed by the reviewer.

Statistical Methodologies

The primary endpoint compares the efficacy of aripiprazole IM depot (400 mg or 300 mg) with that of placebo IM depot with regard to time to exacerbation of psychotic symptoms/impending relapse. This was analyzed using a *log-rank test* comparing the two treatment groups (aripiprazole IM depot 400 mg or 300 mg versus placebo IM depot) at an overall nominal significance level of 0.05 (two-sided) following a group sequential procedure. *Interim analyses* were planned to be performed at approximately 50% and 75% of event accrual time points using Haybittle-Peto group sequential boundaries and an alpha level of 0.001 at each of the two interim looks. The second interim analysis (at 75% of events) was planned to be performed only if the first interim analysis is not positive. The alpha level for the final analysis will be 0.0498.

Additionally, a 95% confidence interval for the hazard ratio (aripiprazole vs. placebo IM depot) will be provided using the Cox Proportional Hazard model with terms for treatment in the model.

For sensitivity analyses of the primary efficacy endpoint to deal with discontinued patients, the sponsor adopted 4 different approaches (see Appendix A). The obtained datasets were analyzed using log-rank test.

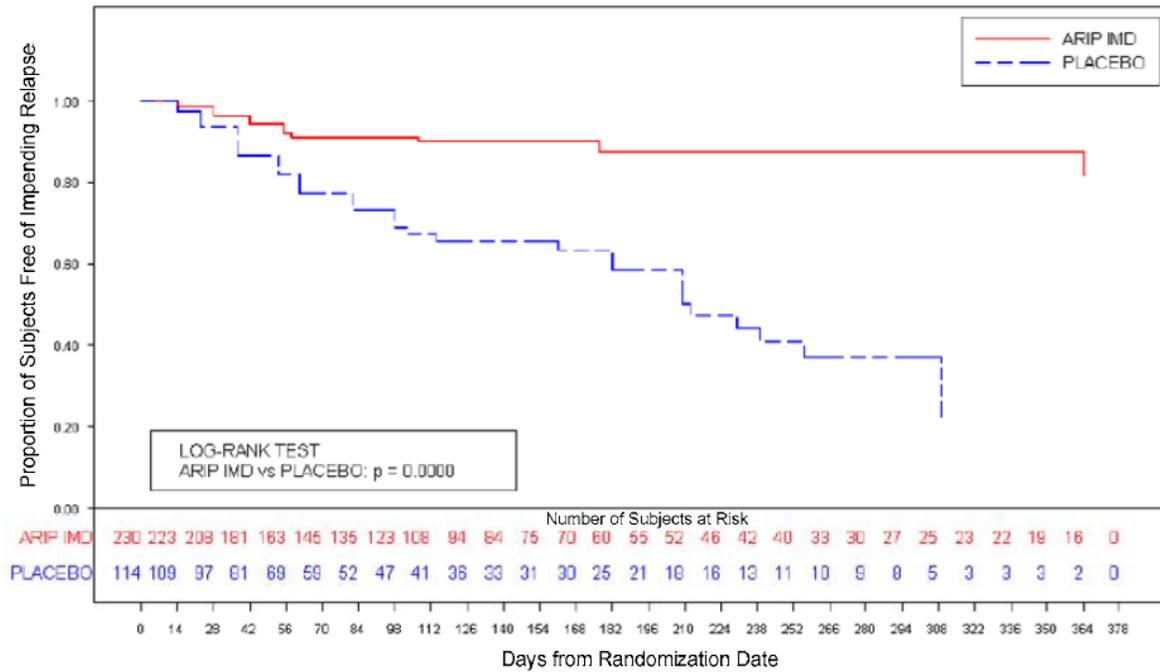
The key secondary endpoint is the proportion of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria. The primary analysis for this key secondary endpoint is based on the *Chi-square test* with the 0.05 level of significance.

Sponsor's Efficacy Results and Conclusions

Based on the interim analysis of the efficacy data, the sponsor was informed of the DMC recommendation to terminate the trial early. It was concluded that time to impending relapse was statistically significantly shorter for subjects randomized to placebo compared with subjects randomized to aripiprazole IM depot in the Double-blind Phase 4 (log-rank test p-value < 0.0001). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole comparison was 4.72 (95% CI = 2.81 – 7.94), thus subjects in the placebo group have 4.72 times the chance of experiencing impending relapse compared to the aripiprazole group. The hazard ratio from the Cox proportional hazard model for the aripiprazole to placebo comparison was 0.212 (95% CI = 0.126 – 0.357).

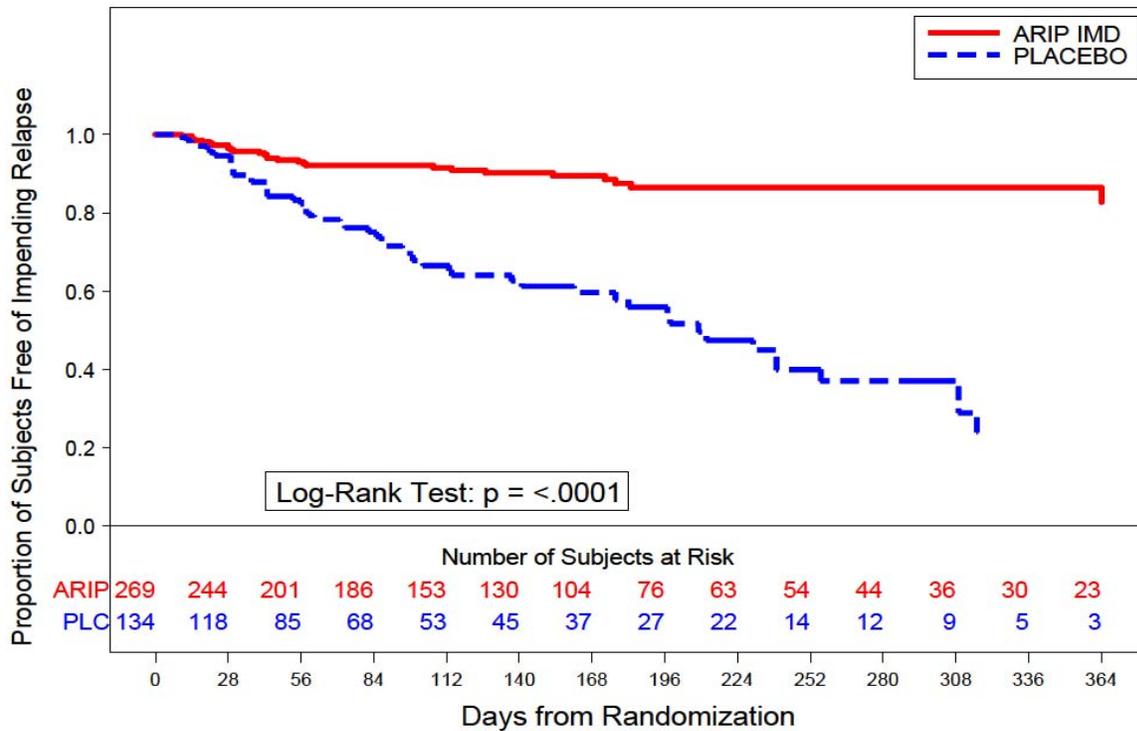
The final efficacy analysis included 403 randomized subjects and 80 impending relapse events. The results from the final analysis were consistent with the interim analysis results in showing that the time to impending relapse was statistically significantly shorter for subjects in the placebo group compared with subjects in the aripiprazole group (hazard ratio = 5.03, p < 0.0001; log-rank test). The hazard ratio from the Cox proportional hazard model for the placebo to aripiprazole comparison was 5.029 (95% CI = 3.154, 8.018), thus subjects in the placebo group have 5.03 times bigger chance of experiencing impending relapse compared to the aripiprazole group. The hazard ratio from the Cox proportional hazard model for the aripiprazole to placebo comparison was 0.199 (95% CI = 0.125, 0.317). Kaplan-Meier estimates of the reliability (survival) functions for the interim and final analyses are shown in the Figure 2 and Figure 3.

Figure 2. Kaplan-Meier Plot of Time to Impending Relapse (Interim Analysis, 64 Events)



Source: computed by the sponsor.

Figure 3. Kaplan-Meier Plot of Time to Impending Relapse (Final Analysis Set, 80 Events)



Source: computed by the sponsor.

The key secondary endpoint (percentage of subjects meeting the exacerbation of psychotic symptoms/impending relapse criteria) was computed by the sponsor without taking into account censoring, thus the values are different from the Kaplan-Meier plots. The values of the key secondary endpoint computed using full analysis dataset are consistent with the values based on interim analysis data (see Table 6 and Table 7).

Table 6. Subjects' disposition in the interim and full analysis datasets (all sites included).

n (%)	Interim analysis dataset			Full analysis dataset		
	Relapsed	Censored	Total	Relapsed	Censored	Total
Aripiprazole	22 (9.57)	208 (90.43)	230	27 (10.04)	242 (89.96)	269
Placebo	42 (36.84)	72 (63.16)	114	53 (39.55)	81 (60.45)	134
Total	64 (18.60)	280 (81.40)	344	80 (19.85)	323 (80.15)	403

Source: computed by the reviewer.

Table 7. Summary of subjects' exacerbation of psychotic symptoms/impending relapse criteria (all sites included).

Impending Relapse Criteria	Aripiprazole IM Depot		Placebo		p-value
	Subjects in the arm	Subjects who met criteria	Subjects in the arm	Subjects who met criteria	
Interim Dataset					
At least one criterion	230	22 (9.6%)	114	42 (36.8%)	<.0001
CGI-I + PANSS	230	16 (7.0%)	114	36 (31.6%)	
Hospitalization	230	5 (2.2%)	114	4 (3.5%)	
CGI-SS	230	1 (0.4%)	114	1 (0.9%)	
Violent behavior	230	1 (0.4%)	114	3 (2.6%)	
Final Dataset					
At least one criterion	269	27 (10.0%)	134	53 (39.6%)	<.0001
CGI-I + PANSS	269	20 (7.4%)	134	46 (36.3%)	
Hospitalization	269	7 (2.6%)	134	5 (3.7%)	
CGI-SS	269	1 (0.4%)	134	1 (0.8%)	
Violent behavior	269	1(0.4%)	134	4 (3.0%)	

Source: Clinical study report 31-07-246, pg 210, Table 9.4-1.

The results of the sponsor-performed sensitivity analyses (4 different approaches) to assess the robustness of the primary endpoint and/or the impact of dropout are summarized in Table 8.

Table 8. Summary of the Sensitivity Analyses for the interim and final datasets (all sites included).

Criteria	p-value (interim dataset)	p-value (final dataset)
Application of sub-impending Relapse Criteria	<.0001	<.0001
Randomly Selected 20% of Discontinued Subjects from the Aripiprazole IM Depot Groups as Events	<.0001	<.0001
Discontinuations as Events (regardless of treatment group)	<.0001	<.0001

Multiple Imputation Method		
$\theta = 0.950$	<.0001	<.0001
$\theta = 0.975$	<.0001	<.0001
$\theta = 1.000$	<.0001	<.0001
$\theta = 1.025$	<.0001	<.0001
$\theta = 1.050$	<.0001	<.0001

Source: Clinical study report 31-07-249, pg 209, Table 9.3-2.

During the quality assurance audit performed by the Quality Management department of Otsuka America Pharmaceutical, Inc., after completion of Trial 31-07-246, the site 046 was detected to have significant compliance issues. Of particular concern were issues suggesting possible falsification of data by the study coordinator. A total of 13 subjects had been enrolled at Site 046 and received treatment in the Conversion (n = 5), Oral Stabilization (n = 13), IM Depot Stabilization (n = 9), and Double-blind, Placebo-controlled Phases (n=7). The sponsor has performed the analyses of the primary efficacy endpoint excluding the data from the study site 046. The results of the log-rank test remained consistent (see Table 9).

Table 9. Hazard ratio estimation and analysis summary for the final analysis set excluding site 046.

	Randomized n	Relapsed n (%)	Arip/Placebo Hazard Rate (95% CI)	Placebo/Arip Hazard Rate (95% CI)	Log-rank Test p-value
Aripiprazole	263	26 (9.89)	0.195	5.116	<0.0001
Placebo	133	53 (39.85)	(0.122, 0.313)	(3.190, 8.205)	

Source: Clinical Study report 31-07-246, pg 1839, CT-26.1

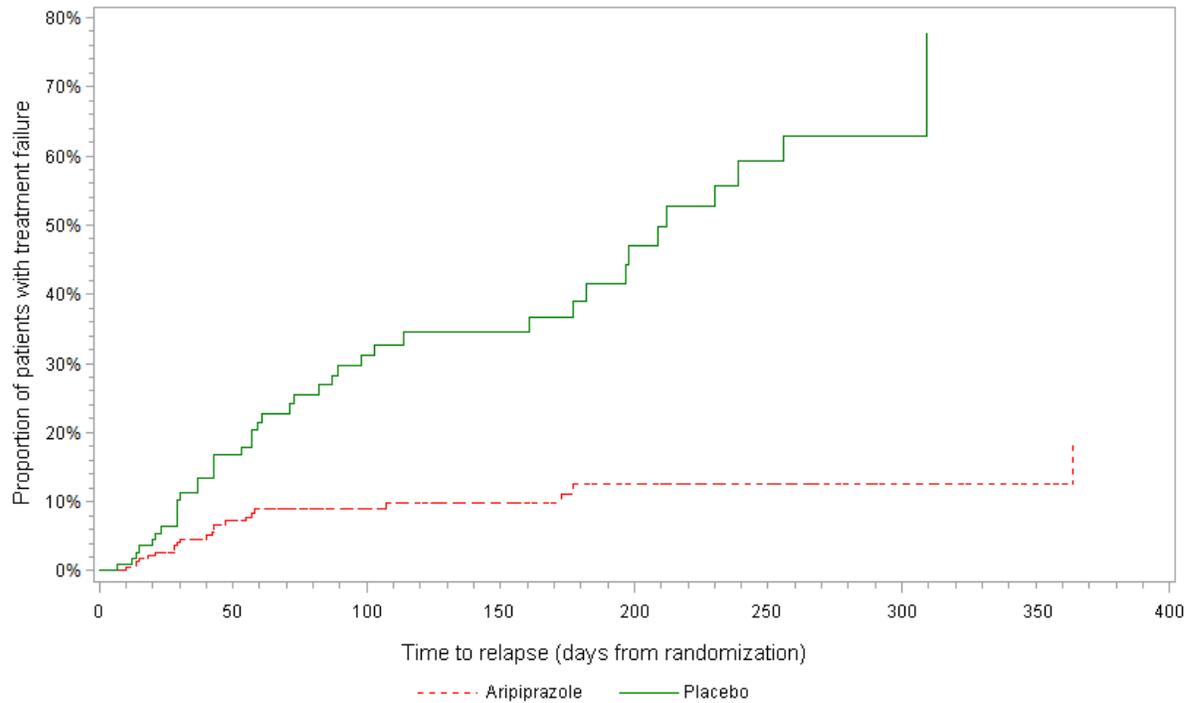
Reviewer's Results and Comments

This reviewer confirmed the sponsor's analysis results for the primary and key secondary efficacy endpoints. The results were highly statistically significant (p-value <0.0001) showing the statistically significant difference between the active drug and placebo.

The primary analysis is typically performed on the pre-specified intent-to-treat analysis set regardless of protocol violations. The practice of removing one site from the primary analysis set, particularly after trial completion, raises some concerns and needs to be avoided unless with persuasive justifications. In this trial, the results are not impacted by removing this site. Hence, this reviewer recommends that the labeling description be based on the pre-specified analysis set (i.e., all sites should be included).

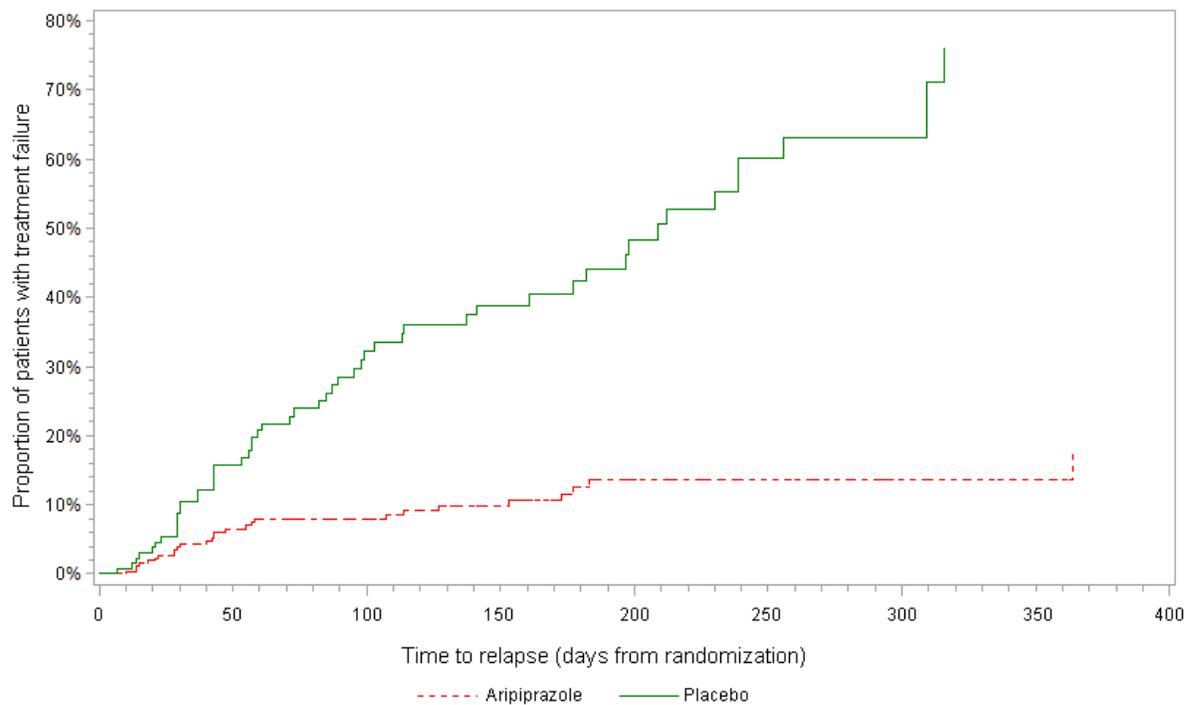
The plots of the cumulative proportion of the treatment failure over time are provided in Figure 4 (interim analysis) and Figure 5 (final analysis set) respectively. The plots display the proportions of patients in each treatment arm who had a treatment failure by a given day after randomization. Both plots appear to support the efficacy of the aripiprazole compared to placebo.

Figure 4. Cumulative Kaplan-Meier Plot of Time to Impending Relapse (Interim Analysis, 64 Events)



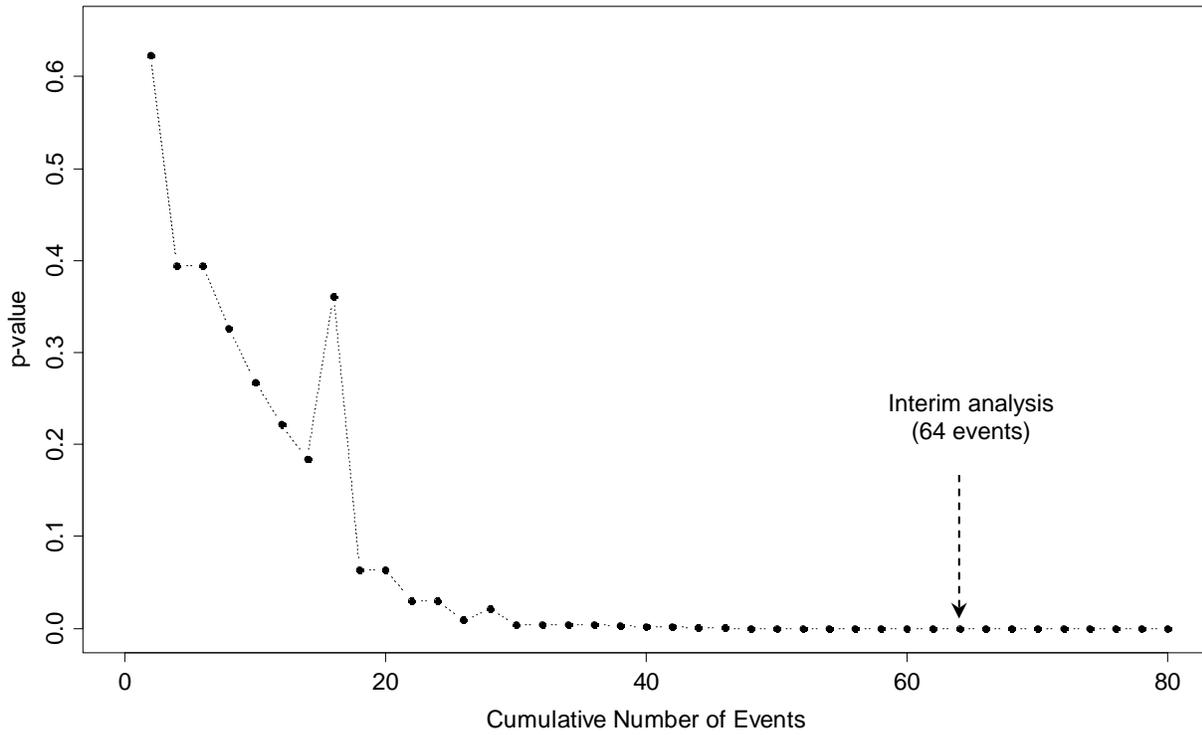
Source: computed by the reviewer

Figure 5. Cumulative Kaplan-Meier Plot of Time to Impending Relapse (Final Analysis Set, 80 Events)



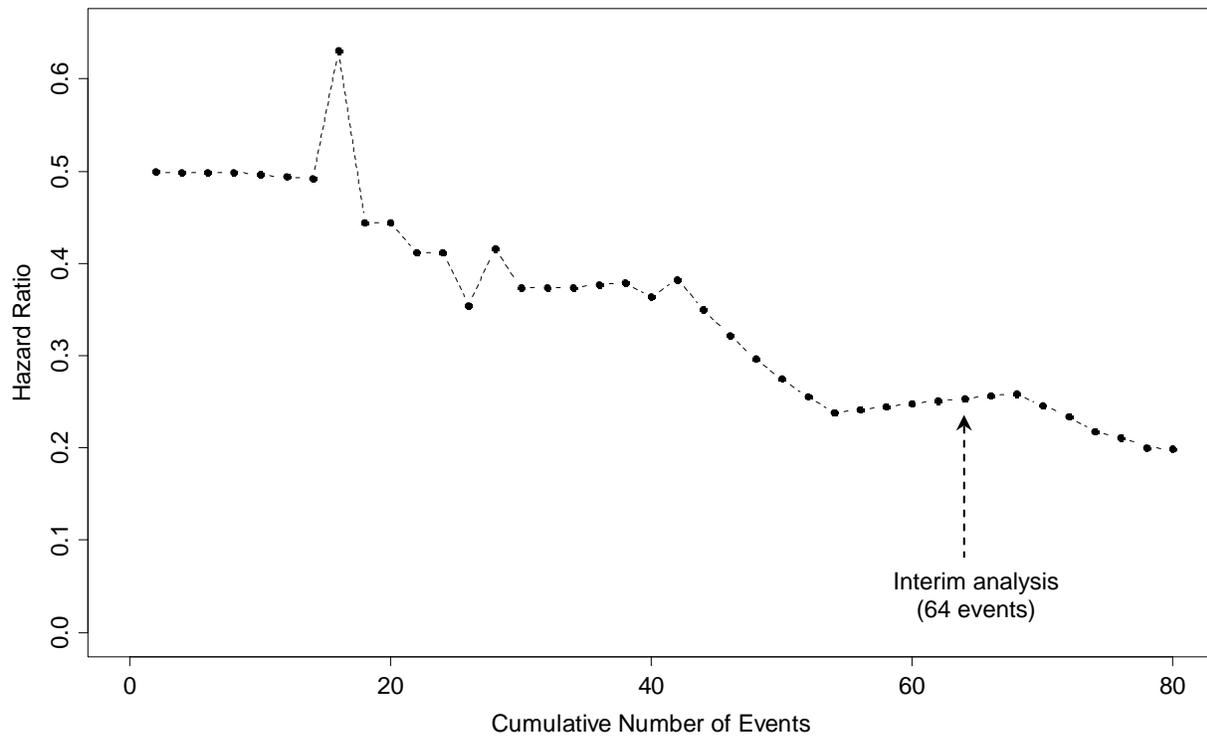
Source: computed by the reviewer

Figure 6. P-value plot computed for a different number of cumulative events (Full Analysis Set).



Source: computed by the reviewer

Figure 7. Hazard ratio plot computed for a different number of cumulative events (Full Analysis Set).



Source: computed by the reviewer

Since the trial was stopped at 50% information time with a positive effect, the result could be a random high outcome. The reviewer has plotted the estimates of the p-values and hazard ratios computed for a different number of events (from 2 to 64 with 2 events increments). The Figure 6 and Figure 7 show the converging trends of the estimates.

Evaluation of Safety

The evaluation of safety was not performed and reported here. Please refer to the clinical review for the safety evaluation and report.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

This section contains the reviewer’s results of the exploratory analysis using Cox-proportional hazard model on the time from randomization to exacerbation of psychotic symptoms/impending relapse in Phase 4 for the interim population subgroups (see Table 10). The data were grouped by gender, race, ethnicity, region (US vs. non-US), and drug dose. The subgroup analysis stratified by age was omitted because the entire population was under the age of 65.

Table 10. Cox-proportional hazard analysis of the time to treatment failure by subgroups (interim dataset).

	n	Hazard Ratio (Arip/Placebo)	95% conf. interval
ITT	344	0.213	0.127–0.359
Gender			
Male	206	0.203	0.104–0.394
Female	138	0.256	0.112–0.587
Race			
Caucasians	204	0.184	0.098–0.345
Black/African American	78	1.462	0.171–12.514
Asian	43	0.356	0.060–2.135
Ethnicity			
Hispanic/Latino	48	0.968	0.257–3.653
Not Hispanic or Latino	295	0.170	0.096–0.303
Region			
US	175	0.241	0.129–0.449
Non-US	169	0.170	0.066–0.440
Last Dose in Phase 3			
400 mg	311	0.194	0.112–0.335
300 mg	33	0.489	0.069–3.476

Source: computed by the reviewer.

The results suggest consistent trends in favor of Aripiprazole in various subgroups except the Black/African American. However, the variability was quite large in this relatively small subgroup. It is uncertain whether the observed outcomes were mainly due to the chance or were clinically relevant. An additional descriptive analysis for the Black/African American subgroup was performed. Subjects disposition for both the interim and full analysis dataset is presented in Table 11. The demographic characteristics of the subgroup are summarized in Table 12.

Table 11. Subjects' disposition in the interim and full analysis datasets (Black/African American subgroup).

n (%)	Interim analysis dataset			Full analysis dataset		
	Relapsed	Censored	Total	Relapsed	Censored	Total
Aripiprazole	5 (8.62)	53 (91.38)	58	5 (8.47)	54 (91.53)	59
Placebo	2 (10.00)	18 (90.00)	20	2 (9.09)	20 (90.91)	22
Total	7 (8.97)	71 (91.03)	78	7 (8.64)	74 (91.36)	81

Source: computed by the reviewer.

Table 12. Demographic characteristics in Black/African American subgroup (Final Analysis Set)

Demographic Characteristic	Aripiprazole IM Depot (N=59)	Placebo (N=22)	Total (N=81)
Sex n (%)			
Male	34	14	48
Female	25	8	33
Age (years)			
Mean (SD)	43.58 (9.47)	42.68 (9.81)	43.33 (9.51)
Min – Max	20 – 60	21 – 58	20 – 60
BMI (kg/m ²)			
Mean (SD)	32.12 (8.56)	33.68 (9.25)	32.54 (8.72)
Min – Max	18.00 – 58.20	20.60 – 53.30	18.00 – 58.20
BMI n (%)			
< 18.5 (kg/m ²)	1	0	1
18.5 to < 25 (kg/m ²)	11	5	16
25 to < 30 (kg/m ²)	17	4	21
≥ 30 (kg/m ²)	30	13	43
Region n (%)			
US	59	22	81
Non-US	0	0	0
Last Phase 3 Dose n (%)			
400 mg	57	21	78
300 mg	2	1	3

Source: computed by the reviewer.

A major difference of the Black/African American demographic characteristics compared to the entire sample (Table 3) is that all the subjects in this subgroup belong to the US region, and demonstrate clear tendency towards obesity. This, in addition to the limited size, might be a sign

that the subgroup data are not presentable enough, and that no statistical inference regarding the efficacy endpoints should be drawn from the subgroup on its own.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The reviewer confirms sponsor's findings that aripiprazole IM depot (400 mg or 300 mg) was statistically significantly superior to placebo (log-rank test p-value less than .0001) in reducing the time to exacerbation of psychotic symptoms/impending relapse in schizophrenic patients. The result of the Chi-square test on the percentage of subjects meeting exacerbation of psychotic symptoms/impending relapse criteria was also statistically significant.

The effect on the Black/African American sub-population may not be conclusive because of the lack of representation.

5.2 Conclusions and Recommendations

The statistical results of the study provide adequate evidence that aripiprazole intramuscular depot (400 mg or 300 mg) reduces the time to exacerbation of psychotic symptoms/impending relapse compared with placebo in schizophrenic patients who have maintained stability on aripiprazole IM depot for at least 12 weeks.

APPENDIX A

Description of the Sensitivity Analyses:

1. *Application of Subimpending Relapse Criteria.* The idea of this approach is to consider the censored subjects who at the time of discontinuation were close to meeting the impending relapse criteria as having events on one day after the discontinuation date in addition to subjects who met the impending relapse criteria. The subimpending relapse criteria are defined as follows: (a) CGI-I I score of > 5 (minimally worse) AND an increase on any of the following individual PANSS items score (conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content) to a score > 4 ; OR (b) CGI-SS score of 3 (moderately suicidal) on Part 1.
2. *Randomly Selected Discontinued Subjects as Events:* This sensitivity analysis was conducted by considering 20% of randomly selected discontinued subjects (other than subjects discontinued because of trial termination by the sponsor) in the Double-blind, Phase 4 on aripiprazole treatment without meeting the exacerbation of psychotic symptoms/impending relapse criteria as having the impending relapse at one day after the discontinuation date.
3. *Discontinuations as Events:* This approach considers all discontinued subjects (other than subjects discontinued because of trial termination by the sponsor) in the Double-blind, Placebo-controlled Phase without meeting the exacerbation of psychotic symptoms/impending relapse criteria as having the impending relapse at one day after the discontinuation date.
4. *Multiple Imputation Method:* This method was used for the discontinued subjects (other than subjects discontinued when the sponsor terminated the trial) who did not meet exacerbation of psychotic symptoms/impending relapse criteria. The censoring time of a subject was imputed based on computation of conditional probability from the Kaplan-Meier curve per treatment group based on 5 θ levels, where θ is the hazard ratio for the extent of a higher failure rate for censored subjects in the time after censoring than applies to noncensored subjects during such time intervals. Ten imputations were done for each θ level. The statistics for multiple imputation were computed for each θ level. The censoring time of a subject was imputed based on the conditional probability (given the censoring time) that the subject would have experienced the event had the subject continued in the trial. The conditional probability was computed based on the observed Kaplan-Meier curves. The probability model was parameterized by θ . A value of $\theta = 1$ would represent the case where a censored subject was equally likely to have an event as a noncensored subject; whereas a value of $\theta > 1$ would represent the situation where a censored subject would have a higher probability of an event relative to a noncensored subject, and vice versa. The values of θ used in the imputations were 0.95, 0.975, 1.0, 1.025, and 1.05. Ten imputations were made for each value of θ , and the final result (combining the results of the 10 imputations) was obtained by the method of Rubin.

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06/04/2012

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

NDA Number: 202971 Applicant: Otsuka Pharmaceutical Stamp Date: 09/26/2011

**Drug Name: Aripiprazole NDA/BLA Type: O-1
(Abilify)**

On **initial** overview of the NDA/BLA application for RTF:

	Content Parameter	Yes	No	NA	Comments
1	Index is sufficient to locate necessary reports, tables, data, etc.	√			
2	ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.)	√			ISE not available
3	Safety and efficacy were investigated for gender, racial, and geriatric subgroups investigated (if applicable).	√			
4	Data sets in EDR are accessible and do they conform to applicable guidances (e.g., existence of <code>define.pdf</code> file for data sets).	√			The primary efficacy variable was not derived

IS THE STATISTICAL SECTION OF THE APPLICATION FILEABLE? Yes

If the NDA/BLA is not fileable from the statistical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Content Parameter (possible review concerns for 74-day letter)	Yes	No	NA	Comment
Designs utilized are appropriate for the indications requested.	√			
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	√			
Interim analyses (if present) were pre-specified in the protocol and appropriate adjustments in significance level made. DSMB meeting minutes and data are available.	√			
Appropriate references for novel statistical methodology (if present) are included.			√	
Safety data organized to permit analyses across clinical trials in the NDA/BLA.			√	
Investigation of effect of dropouts on statistical analyses as described by applicant appears adequate.	√			

STATISTICS FILING CHECKLIST FOR A NEW NDA/BLA

Andrejus Parfionovas 11/21/2011

Reviewing Statistician Date

Peiling Yang

Supervisor/Team Leader Date

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

/s/

ANDREJUS PARFIONOVAS
11/28/2011

PEILING YANG
11/28/2011