http://intranetapps.fda.gov/scripts/ob_apps/ob/eWork/uploads/eWork/2009/Keywords-in-DFS.htm

(b) (4)

Open-Label Treatment	Daily Dose			
	Visit 2	Visit 3	Visit 4	Visit 5
Kapvay®	0.1 mg	0.1 to 0.2 mg	0.1 to 0.3 mg	0.1 to 0.4 mg

Open-Label Treatment (fixed dose)	Daily Dose				
	Visit 6	Visit 7	Visit 8	Visit 9	RANDOMIZATION
Kapvay®	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	

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A responder was defined as a subject with ≥30% reduction from Baseline (Visit 2) in the ADHD

Double-Blind Treatment	Daily Dose			
	Visit 9[a]	Visit 10	Visit 11	Visits 12 to 19
Kapvay®	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg	0.1 mg, 0.2 mg, 0.3 mg, or 0.4 mg
Placebo	0.1 mg Kapvay® 0.2 mg Kapvay® 0.3 mg Kapvay® or Placebo	0.1 mg Kapvay® 0.2 mg Kapvay® or Placebo	0.1 mg Kapvay® or Placebo	Placebo

[a]The dosing for the randomized-withdrawal began the day after Visit 9.

Taper-down and Follow-up Treatment	Daily Dose				
	Visit 20[a]	Visit 21	Visit 22	Visit 23	Visit 24
Kapvay®	0.1 mg, 0.2 mg, 0.3 mg, or Placebo	0.1 mg, 0.2 mg, or Placebo	0.1 mg or Placebo	Follow-up period. No study drug administered	Final study evaluations
Placebo	Placebo	Placebo	Placebo	Follow-up period. No study drug administered	Final study evaluations

[a]The dosing for the taper-down started the day after Visit 20.

≥30% increase (worsening) in ADHD

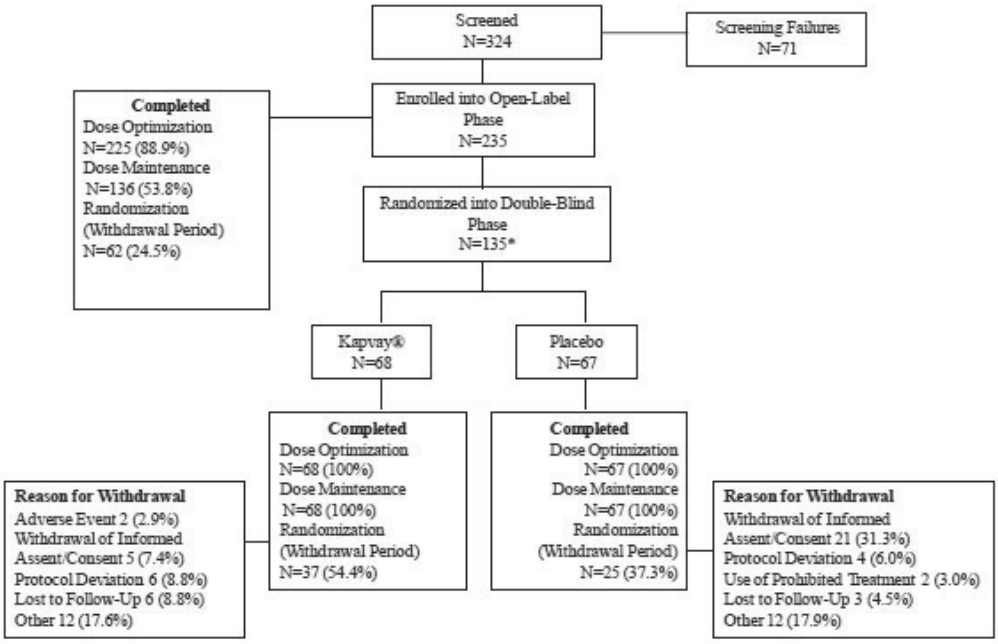
≥2 point increase (worsening) in CGI

		Period 1				Period 2			Period 3										Period 4				
	Scr[1]	BI[2]	Dose Optimization[3] Open-Label			Dose Maintenance[3] Open-Label			Randomized-Withdrawal[4] Double-Blind										Taper-down and Follow-up				
Treatment			Kapvay®			Kapvay®			Kapvay® or Placebo										Kapvay® or Placebo				f/u[5] (EIF[6])
Visit	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Day[7]	-30 to -1	1	8	15	22	29	43	57	71	78	85	92	99	113	127	141	169	197	225	253	260	267	274	281
Week		1	2	3	4	5	7	9	11	12	13	14	15	17	19	21	25	29	33	37	38	39	40	
ADHD-RS-IV	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
CGI-S	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
CGI-I			X	X	X	X	X	X																
WFIRS-P		X							X			X	X	X	X	X	X	X	X	X				
ESS-C		X							X			X	X	X	X	X	X	X	X	X				
C-SSRS	X								X			X				X		X		X				X
Concomitant Therapy	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Open-Label Study Drug Dispensed		X	X	X	X	X	X	X																
Responder Criteria Calculation[14]									X															
Randomization									X															
Double-Blind Study Drug Dispensed									X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Treatment Failure Calculation[15]										X	X	X	X	X	X	X	X	X	X	X				
Phone Contacts[16]																X	X	X	X					
Study Completion																								X

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4th edition; BMI = body mass index; CGI-I= Clinical Global Impression Improvement; CGI-S = Clinical Global Impression Severity; C-SSRS = Columbia Suicide Severity Rating Scale; ECG = electrocardiogram; ESS-C = Epworth Sleepiness Scale for Children; ETF = early termination follow-up visit; f/u = follow-up; hCG = human chorionic gonadotropin; MINI-kid = shorter version of the Kiddie-Schedule for Affective Disorders and Schizophrenia-Present & Lifetime; WFIRS-P = Weiss Functional Impairment Rating Scale-Parent

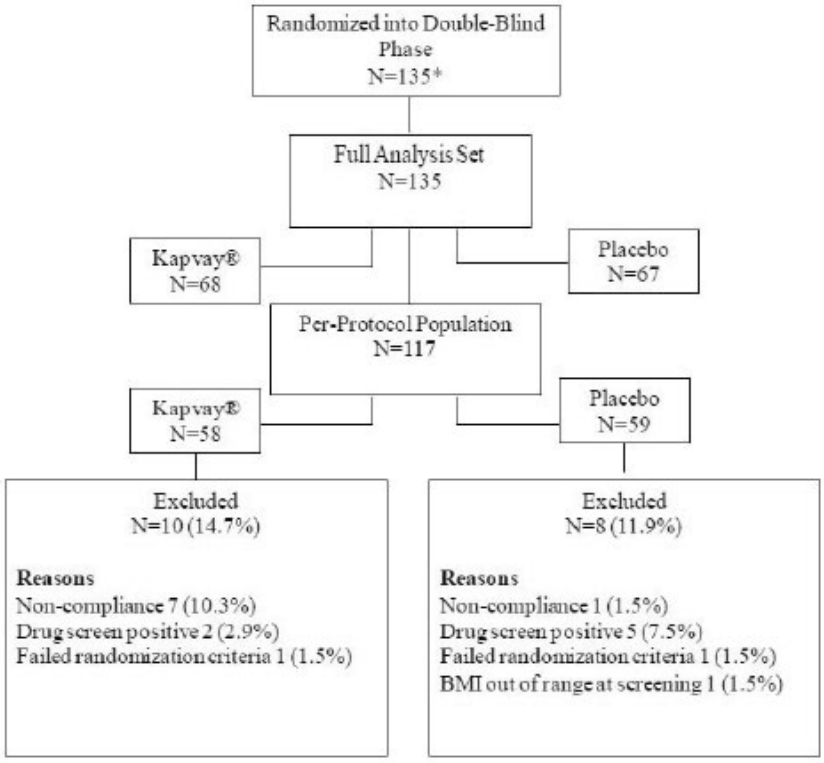
squared test at $\alpha=0.05$, and an equal treatment allocation

Reason for Withdrawal	Double-Blind Full Analysis Set		
	Kapvay® (n=68)	Placebo (n=67)	Overall (N=135)
Number of subjects withdrawn	31 (45.6%)	42 (62.7%)	73 (54.1%)
Adverse event	2 (2.9%)	0 (0%)	2 (1.5%)
Withdrawal of informed assent/consent	5 (7.4%)	21 (31.3%)	26 (19.3%)
Protocol deviation	6 (8.8%)	4 (6.0%)	10 (7.4%)
Use of prohibited treatment	0 (0%)	2 (3.0%)	2 (1.5%)
Lost to follow-up	6 (8.8%)	3 (4.5%)	9 (6.7%)
Other	12 (17.6%)	12 (17.9%)	24 (17.8%)



Source: Table 14.1.1.1

*Although 136 subjects were randomized, only 135 actually took randomized treatment and participated in the subsequent phases of the study.



BMI = body mass index
Source: Table 14.1.1.1, Appendix 16.2.2.1
*Although 136 subjects were randomized, only 135 actually took randomized treatment and participated in the subsequent phases of the study.

Table 8: Demographics Open-label and Double-blind Full Analysis Sets

Characteristic	Open-Label Full Analysis Set (N=253)	Double-Blind Full Analysis Set	
		Kapvay® (n=68)	Placebo (n=67)
Age at Screening (years)			
Mean (SD)	10.6 (2.93)	10.7 (2.77)	10.9 (2.98)
Gender			
Male	177 (70.0%)	43 (63.2%)	51 (76.1%)
Female	76 (30.0%)	25 (36.8%)	16 (23.9%)
Race			
White	166 (65.6%)	37 (54.4%)	50 (74.6%)
Black or African-American	67 (26.5%)	23 (33.8%)	14 (20.9%)
Asian	1 (0.4%)	1 (1.5%)	0 (0.0%)
American Indian or Alaska Native	1 (0.4%)	0 (0.0%)	0 (0.0%)
Native Hawaiian or Other Pacific Islander	1 (0.4%)	0 (0.0%)	0 (0.0%)
Mixed	17 (6.7%)	7 (10.3%)	3 (4.5%)
Ethnicity			
Not Hispanic or Latino	192 (75.9%)	56 (82.4%)	47 (70.1%)
Hispanic or Latino	61 (24.1%)	12 (17.6%)	20 (29.9%)
Weight (kg)			
Mean (SD)	40.86 (16.162)	40.49 (15.721)	41.61 (16.978)
Height (cm)			
Mean (SD)	144.80 (18.012)	145.64 (17.737)	145.45 (17.928)
BMI (kg/m^2)			
Mean (SD)	18.66 (3.275)	18.29 (2.921)	18.79 (3.485)

BMI = body mass index; SD = standard deviation

Source: table 11-2 in section 11.2.1 on p. 65 CSR

3.2.4 Results and Conclusions

3.2.4.1 Primary Endpoint – Primary Analysis

For the primary endpoint, there was a statistically significant difference in favor of Kapvay® in terms of the percentage of subjects determined as treatment failure for the double-blind FAS (p=0.0454). As summarized in the top portion of Table 9, a total of 31 (45.6%) subjects experienced treatment failure in the Kapvay® group compared to 42 (62.7%) subjects in the placebo group. In subjects between 6 and 12 years of age, 24 out of 53 (45.3%) subjects taking Kapvay® experienced treatment failure compared to 32 out of 49 (65.3%) subjects in the placebo group. In subjects between 13 and 17 years of age, 7 out of 15 (46.7%) subjects taking Kapvay® experienced treatment failure compared to 10 out of 18 (55.6%) subjects taking placebo. Refer to Table 12, Table 13 and Table 14 for a summary of these subgroup results.

[redacted] (b) (4)

Reason for Withdrawal	Double-Blind Full Analysis Set		p-value from CMH test stratified by age (6-12, 13-17)
	Kapvay®	Placebo	
Primary Analysis			
Number of subjects	68	67	
Number of treatment failures	31 (45.6%)	42 (62.7%)	0.0454*
Basis of Treatment Failure			
Clinical criteria[a,b]	11 (16.2%)	9 (13.4%)	
Lack of efficacy[c]	1 (1.5%)	3 (4.5%)	
Withdrawal of informed assent/consent	4 (5.9%)	20 (29.9%)	
Other early terminations	15 (22.1%)	10 (14.9%)	
Clinical Criteria or Lack of Efficacy			
Number of subjects	49	37	
Number of treatment failures	12 (24.5%)	12 (32.4%)	0.4077
Basis of Treatment Failure			
Clinical criteria[a,b]	11 (22.4%)	9 (24.3%)	
Lack of efficacy[c]	1 (2.0%)	3 (8.1%)	
Clinical Criteria, Lack of Efficacy, Withdrawal of Informed Assent/Consent			
Number of subjects	53	57	
Number of treatment failures	16 (30.2%)	32 (56.1%)	0.0056**
Basis of Treatment Failure			
Clinical criteria[a,b]	11 (20.8%)	9 (15.8%)	
Lack of efficacy[c]	1 (1.9%)	3 (5.3%)	
Withdrawal of informed assent/consent	4 (7.5%)	20 (35.1%)	

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4th edition; CGI-S = Clinical Global Impression-Severity; CMH = Cochran-Mantel Haenszel

[a]At the same 2 consecutive visits a (1) 30% or greater reduction in ADHD-RS-IV, and (2) 2-point or more increase in CGI-S.

[b]Subjects 503-002 (placebo) and 538-030 (Kapvay®) withdrew consent, but met the clinical criteria for treatment failure.

[c]Subjects 515-001, 518-011, and 521-001 (all placebo) discontinued the study due to treatment failure, but met only the criterion for ADHD-RS-IV.

*Significant at the 5% level.

**Significant at the 1% level.

Reason for Withdrawal	Double-Blind Per-Protocol Set		p-value from CMH test stratified by age (6-12, 13-17)
	Kapvay®	Placebo	
Primary Analysis			
Number of subjects	58	59	
Number of treatment failures	22 (37.9%)	35 (59.3%)	0.0216*
Basis of Treatment Failure			
Clinical criteria[a,b]	10 (17.2%)	8 (13.6%)	
Lack of efficacy[c]	1 (1.7%)	3 (5.1%)	
Withdrawal of informed assent/consent	3 (5.2%)	19 (32.2%)	
Other early terminations	8 (13.8%)	5 (8.5%)	
Clinical Criteria or Lack of Efficacy			
Number of subjects	47	35	
Number of treatment failures	11 (23.4%)	11 (31.4%)	0.4240
Basis of Treatment Failure			
Clinical criteria[a,b]	10 (21.3%)	8 (22.9%)	
Lack of efficacy[c]	1 (2.1%)	3 (8.6%)	
Clinical Criteria, Lack of Efficacy, Withdrawal of Informed Assent/Consent			
Number of subjects	50	54	
Number of treatment failures	14 (28.0%)	30 (55.6%)	0.0047**
Basis of Treatment Failure			
Clinical criteria[a,b]	10 (20.0%)	8 (14.8%)	
Lack of efficacy[c]	1 (2.0%)	3 (5.6%)	
Withdrawal of informed assent/consent	3 (6.0%)	19 (35.2%)	

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4th edition; CGI-S = Clinical Global Impression-Severity; CMH = Cochran-Mantel Haenszel

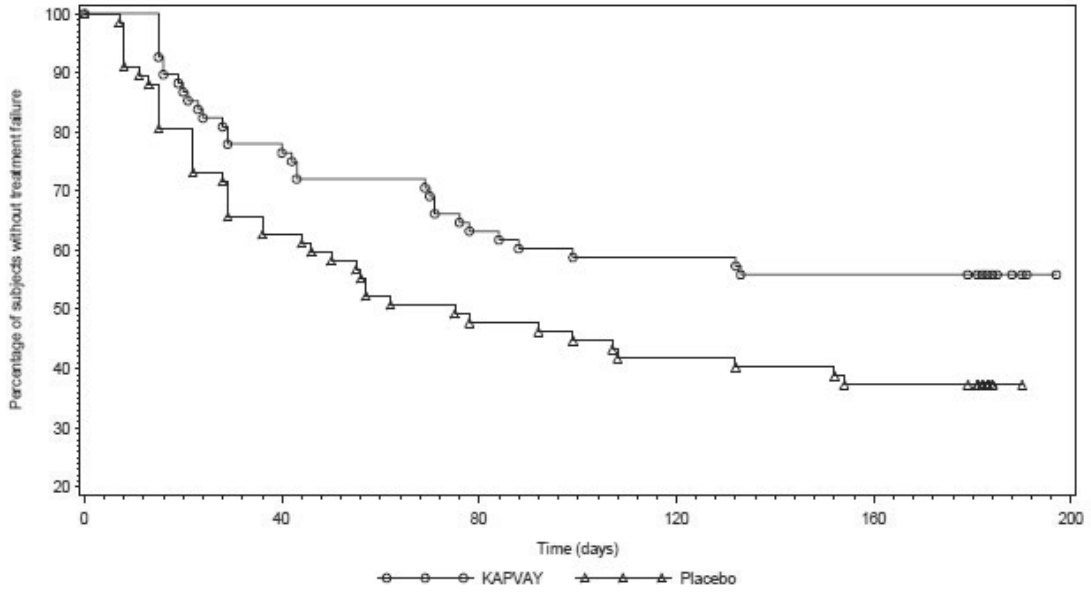
[a]At the same 2 consecutive visits a (1) 30% or greater reduction in ADHD-RS-IV, and a (2) 2-point or more increase in CGI-S.

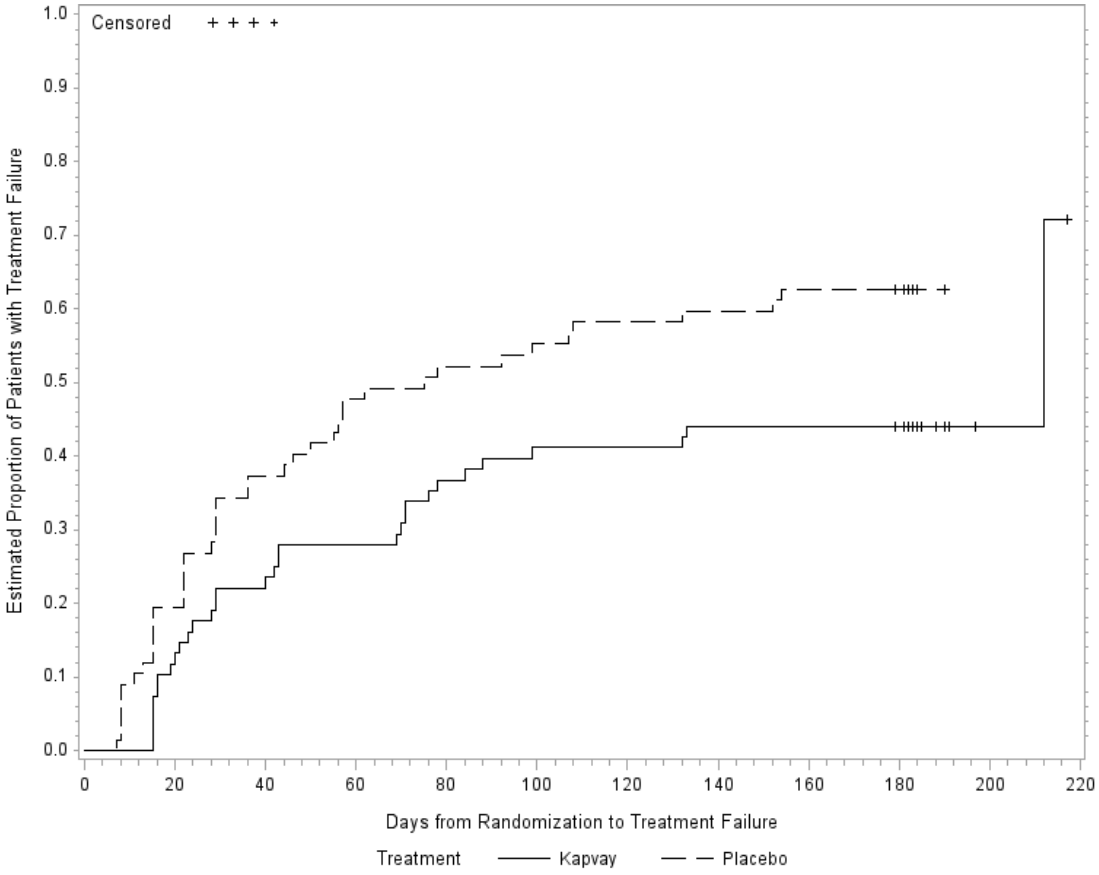
[b]Subject 503-002 (placebo) and Subject 538-030 (Kapvay®) withdrew consent, but met the clinical criteria for treatment failure.

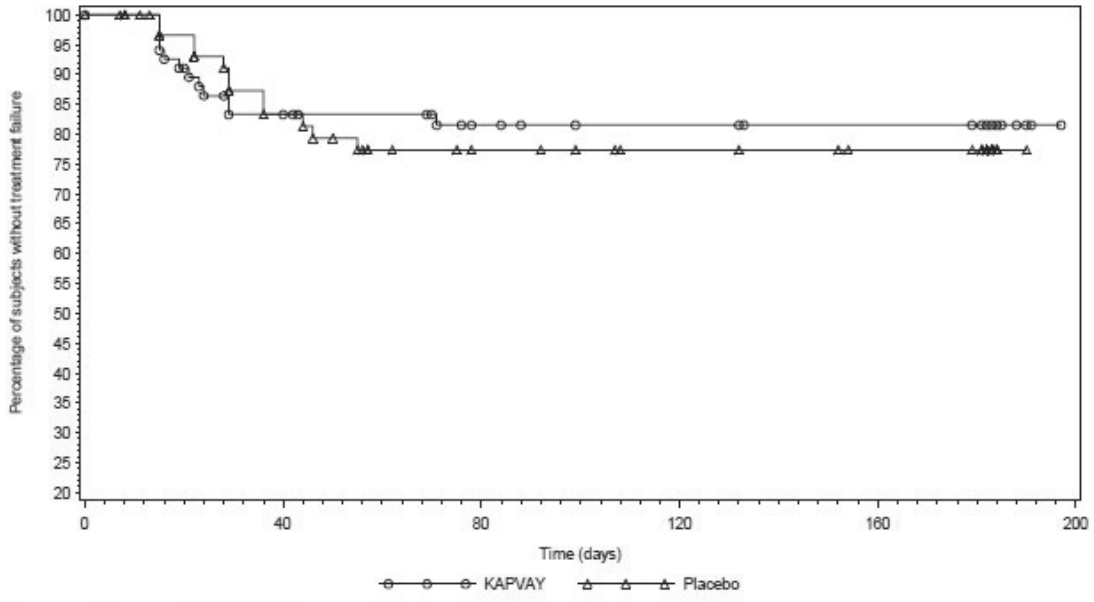
[c]Subjects 515-001, 518-011, and 521-001 (all placebo) discontinued the study due to treatment failure, but met only the criterion for ADHD-RS-IV.

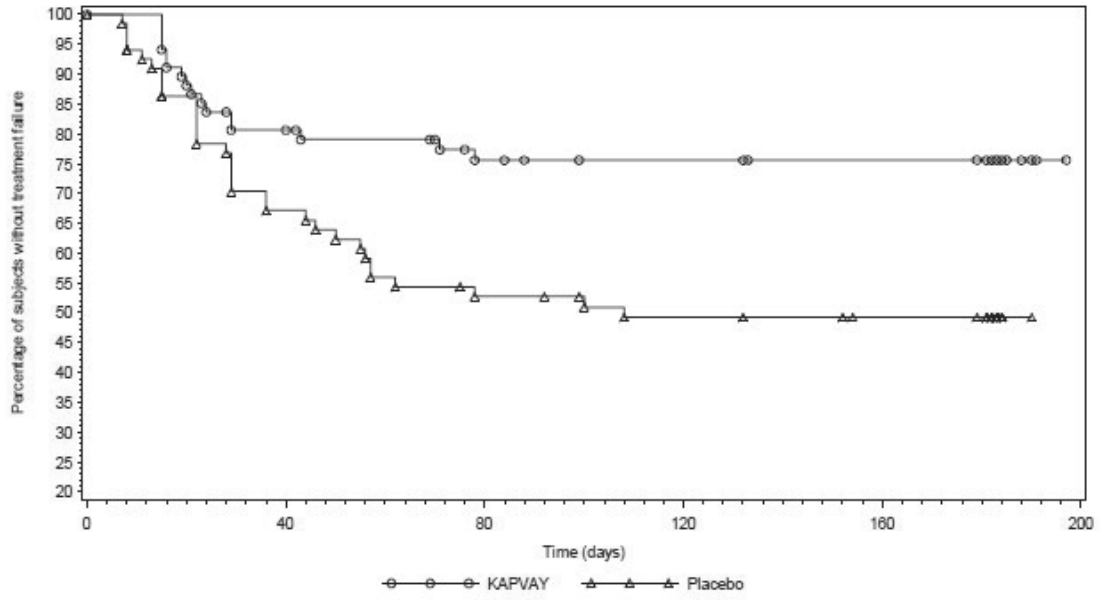
*Significant at the 5% level.

**Significant at the 1% level.


Percentage of subjects without treatment failure
100
90
80
70
60
50
40
30
20
0
40
80
120
160
200
Time (days)
KAPVAY
Placebo


Censored
Estimated Proportion of Patients with Treatment Failure
1.0
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0.0
0
20
40
60
80
100
120
140
160
180
200
220
Days from Randomization to Treatment Failure
Treatment
Kapvay
Placebo


Percentage of subjects without treatment failure
100
95
90
85
80
75
70
65
60
55
50
45
40
35
30
25
20
0
40
80
120
160
200
Time (days)
KAPVAY
Placebo



	Open-Label Full Analysis Set		Double-Blind Full Analysis Set KAPVAY		Double-Blind Full Analysis Set PLACEBO	
	Number of subjects reporting [1]	Number of reports	Number of subjects reporting [1]	Number of reports	Number of subjects reporting [1]	Number of reports
Number of Subjects with at least one TEAE	203(80.2)	641	34(50.0)	95	31(46.3)	78
Any Severe TEAE	15(5.9)	16	2(2.9)	2	0(0.0)	0
Any Serious TEAE	2(0.8)	2	0(0.0)	0	2(3.0)	2
Any TEAE leading to study discontinuation	16(6.3)	17	2(2.9)	2	0(0.0)	0
Any Treatment related AE [2]	179(70.8)	418	18(26.5)	37	12(17.9)	15

Source: Reviewer's table

Source: Reviewer's table

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/s/

YANG WANG

10/29/2014

This reviewer acknowledges Eiji Ishida for providing his expertise in verifying key information and conducting exploratory analyses.

PEILING YANG

10/29/2014

KOOROS MAHJOOB

10/29/2014

I concur with the review