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[REDACTED]

[REDACTED]

(b) (4)



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

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Open-Label Treatment (fixed dose)	Daily Dose				R A N D O M I Z A T I O N
	Visit 6	Visit 7	Visit 8	Visit 9	
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  $\geq 30\%$  reduction from Baseline (Visit 3) in the ADHD

Double-Blind Treatment	Daily Dose			
	Visit 9 <sup>a</sup>	Visit 10	Visit 11	Visits 12 to 19
Kapvay <sup>®</sup>	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 <sup>®</sup> 0.2 mg Kapvay <sup>®</sup> 0.3 mg Kapvay <sup>®</sup> or Placebo	0.1 mg Kapvay <sup>®</sup> 0.2 mg Kapvay <sup>®</sup> or Placebo	0.1 mg Kapvay <sup>®</sup> or Placebo	Placebo

<sup>a</sup>The dosing for the randomized-withdrawal began the day after Visit 9.

Taper-down and Follow-up Treatment	Daily Dose				
	Visit 20 <sup>a</sup>	Visit 21	Visit 22	Visit 23	Visit 24
Kapvay <sup>®</sup>	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

<sup>a</sup>The dosing for the taper-down started the day after Visit 20.

≥30% increase (worsening) in ADHD

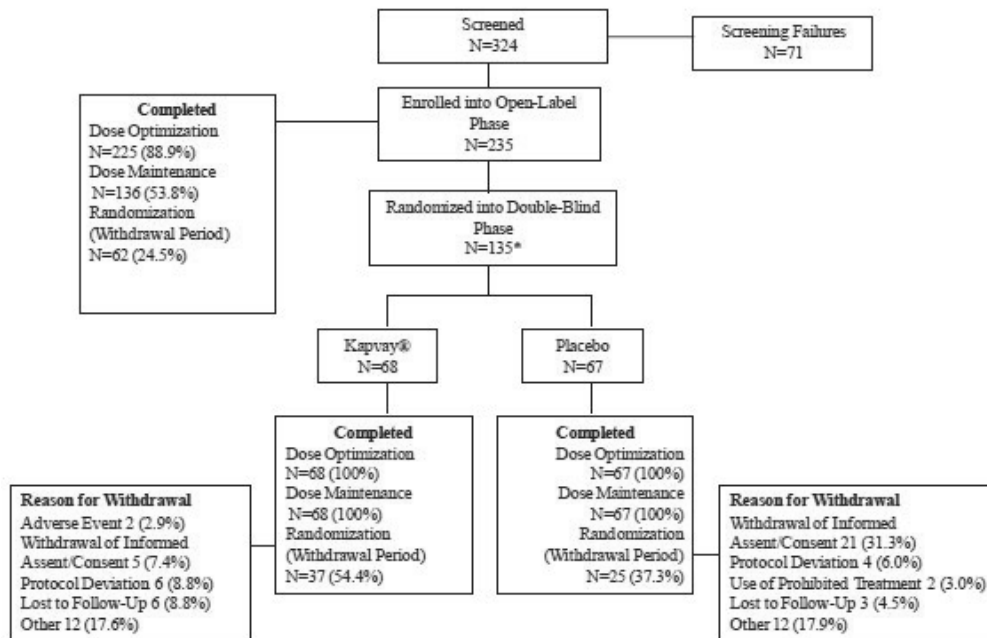
≥2 point increase (worsening) in CGI

Treatment	Scr <sup>1</sup>	Period 1				Period 2			Period 3											Period 4				
		B I <sup>2</sup>	Dose Optimization <sup>3</sup> Open-Label			Dose Maintenance <sup>3</sup> Open-Label			Randomized-Withdrawal <sup>4</sup> Double-Blind											Taper-down and Follow-up				
			Kapvay <sup>®</sup>			Kapvay <sup>®</sup>			Kapvay <sup>®</sup> or Placebo											Kapvay <sup>®</sup> or Placebo				f/u <sup>5</sup> (EIF <sup>6</sup> )
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 <sup>7</sup>	-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 <sup>14</sup>									X															
Randomization									X															
Double-Blind Study Drug Dispensed									X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Treatment Failure Calculation <sup>15</sup>										X	X	X	X	X	X	X	X	X	X	X				
Phone Contacts <sup>16</sup>																X	X	X	X					
Study Completion																								X

ADHD-RS-IV = Attention Deficit Hyperactivity Disorder-Rating Scale-4<sup>th</sup> 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

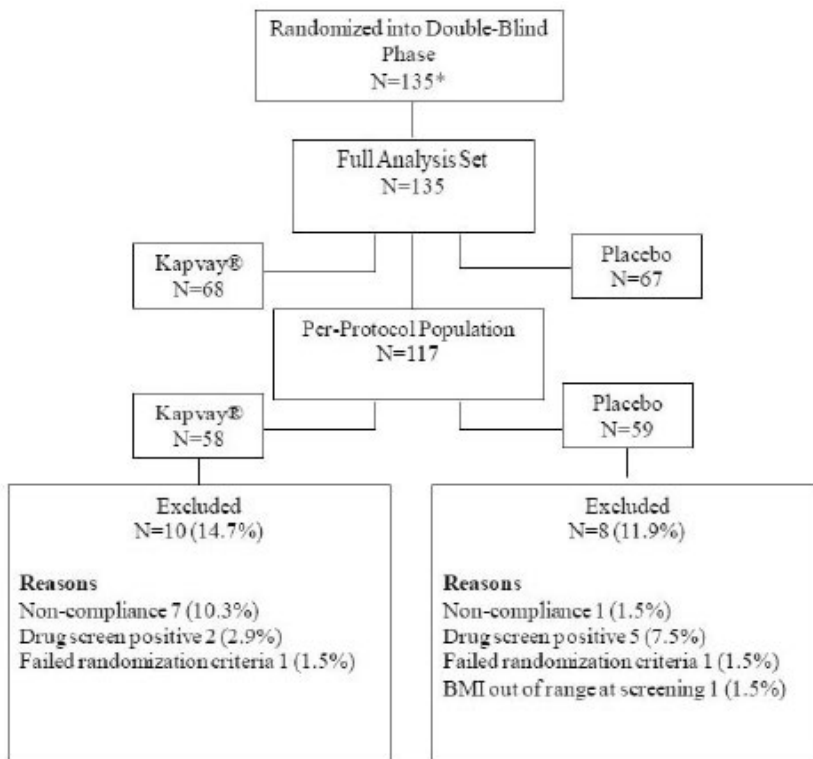

squared test at  $\alpha=0.05$ , and an equal treatment allocation

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)
<b>Age at Screening (years)</b>			
Mean (SD)	10.6 (2.93)	10.7 (2.77)	10.9 (2.98)
<b>Gender</b>			
Male	177 (70.0%)	43 (63.2%)	51 (76.1%)
Female	76 (30.0%)	25 (36.8%)	16 (23.9%)
<b>Race</b>			
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%)
<b>Ethnicity</b>			
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%)
<b>Weight (kg)</b>			
Mean (SD)	40.86 (16.162)	40.49 (15.721)	41.61 (16.978)
<b>Height (cm)</b>			
Mean (SD)	144.80 (18.012)	145.64 (17.737)	145.45 (17.928)
<b>BMI (kg/m<sup>2</sup>)</b>			
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.

(b) (4)



Reason for Withdrawal	Double-Blind Full Analysis Set		p-value from CMH test stratified by age (6-12, 13-17)
	Kapvay <sup>®</sup>	Placebo	
<b>Primary Analysis</b>			
Number of subjects	68	67	
Number of treatment failures	31 (45.6%)	42 (62.7%)	0.0454*
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	11 (16.2%)	9 (13.4%)	
Lack of efficacy <sup>c</sup>	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%)	
<b>Clinical Criteria or Lack of Efficacy</b>			
Number of subjects	49	37	
Number of treatment failures	12 (24.5%)	12 (32.4%)	0.4077
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	11 (22.4%)	9 (24.3%)	
Lack of efficacy <sup>c</sup>	1 (2.0%)	3 (8.1%)	
<b>Clinical Criteria, Lack of Efficacy, Withdrawal of Informed Assent/Consent</b>			
Number of subjects	53	57	
Number of treatment failures	16 (30.2%)	32 (56.1%)	0.0056**
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	11 (20.8%)	9 (15.8%)	
Lack of efficacy <sup>c</sup>	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-4<sup>th</sup> edition;

CGI-S = Clinical Global Impression-Severity; CMH = Cochran-Mantel Haenszel

<sup>a</sup>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.

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

<sup>c</sup>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 <sup>®</sup>	Placebo	
<b>Primary Analysis</b>			
Number of subjects	58	59	
Number of treatment failures	22 (37.9%)	35 (59.3%)	0.0216*
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	10 (17.2%)	8 (13.6%)	
Lack of efficacy <sup>c</sup>	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%)	
<b>Clinical Criteria or Lack of Efficacy</b>			
Number of subjects	47	35	
Number of treatment failures	11 (23.4%)	11 (31.4%)	0.4240
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	10 (21.3%)	8 (22.9%)	
Lack of efficacy <sup>c</sup>	1 (2.1%)	3 (8.6%)	
<b>Clinical Criteria, Lack of Efficacy, Withdrawal of Informed Assent/Consent</b>			
Number of subjects	50	54	
Number of treatment failures	14 (28.0%)	30 (55.6%)	0.0047**
<b>Basis of Treatment Failure</b>			
Clinical criteria <sup>a,b</sup>	10 (20.0%)	8 (14.8%)	
Lack of efficacy <sup>c</sup>	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-4<sup>th</sup> edition;

CGI-S = Clinical Global Impression-Severity; CMH = Cochran-Mantel Haenszel

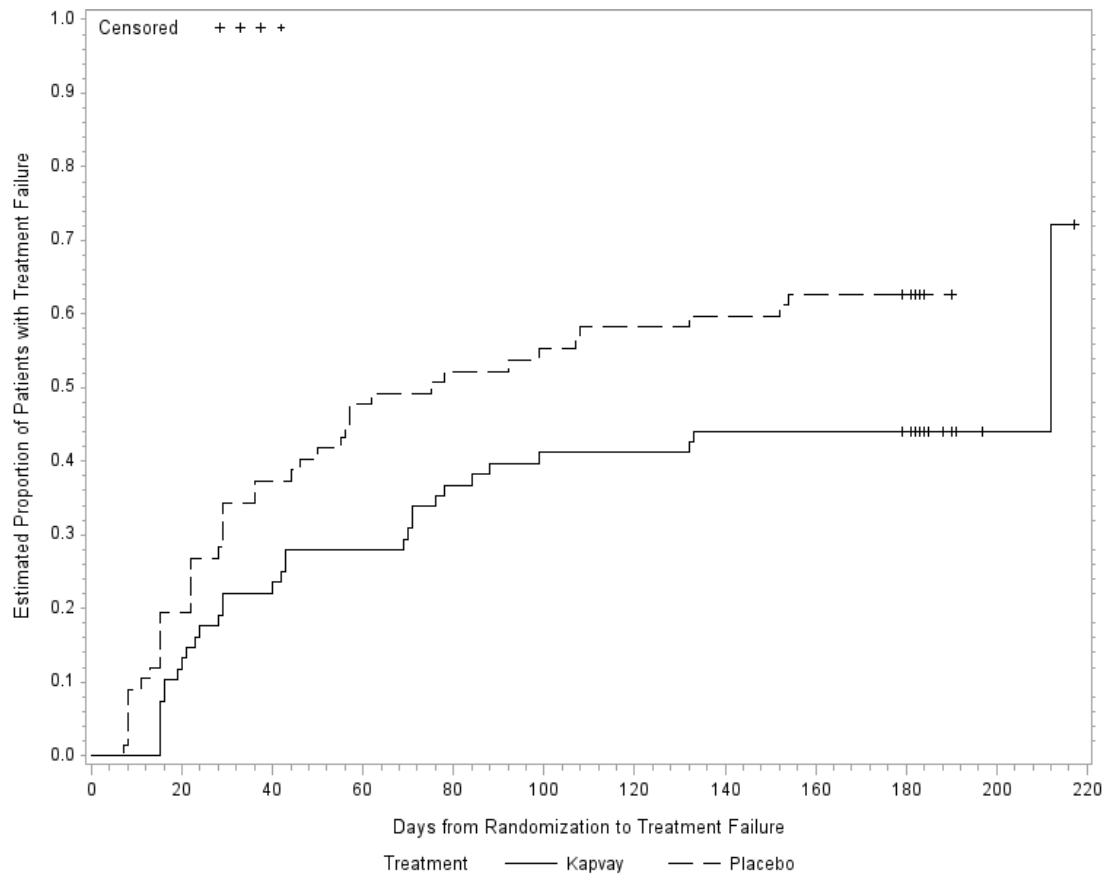
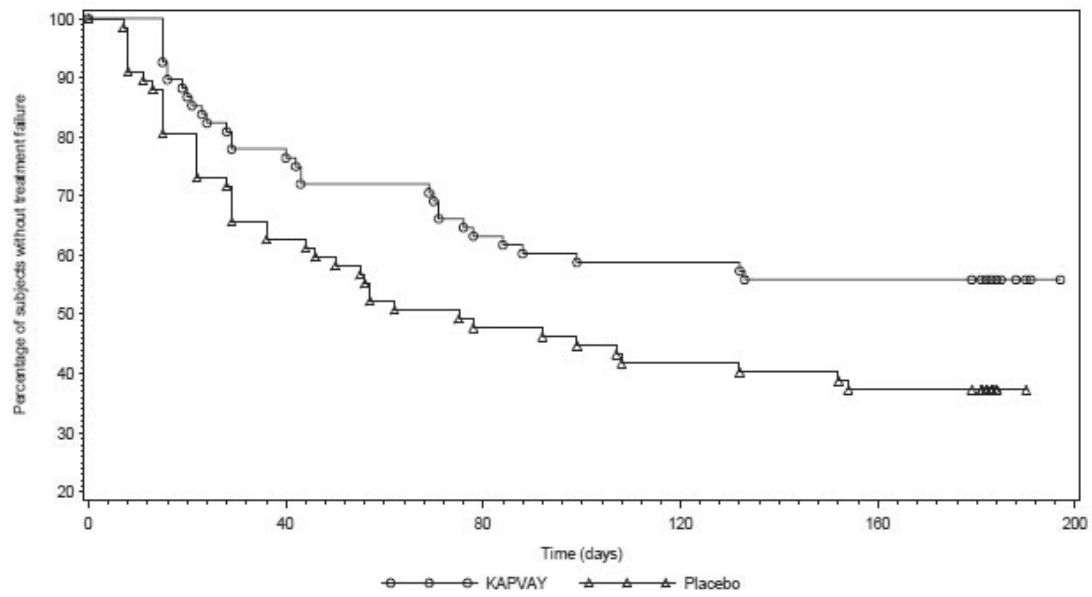
<sup>a</sup>At the same 2 consecutive visits a (1) 30% or greater reduction in ADHD-RS-IV, and a (2) 2-point or more increase in CGI-S.

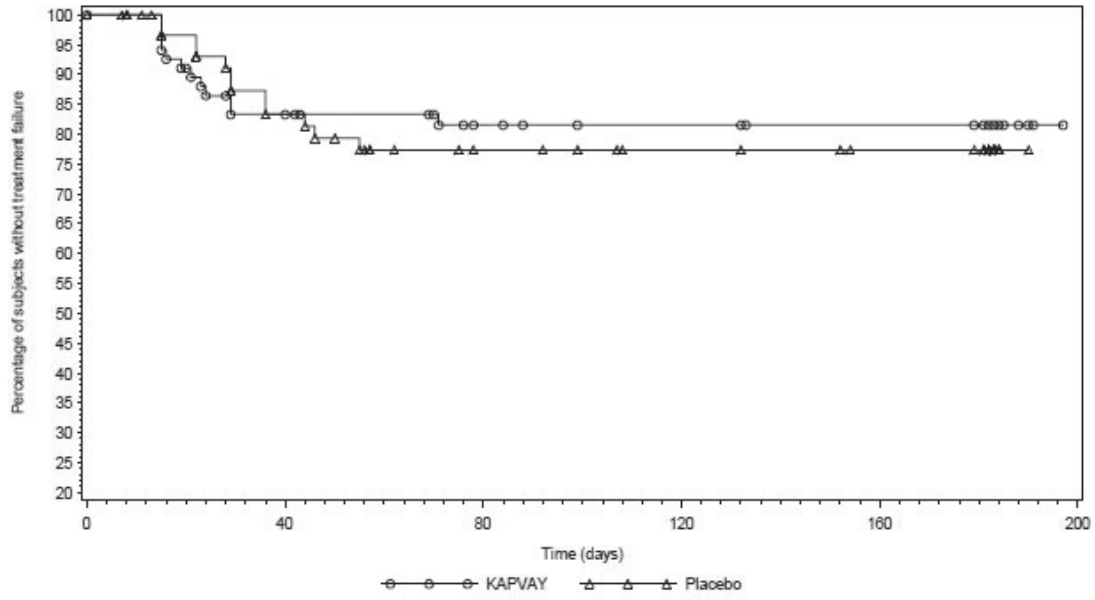
<sup>b</sup>Subject 503-002 (placebo) and Subject 538-030 (Kapvay<sup>®</sup>) withdrew consent, but met the clinical criteria for treatment failure.

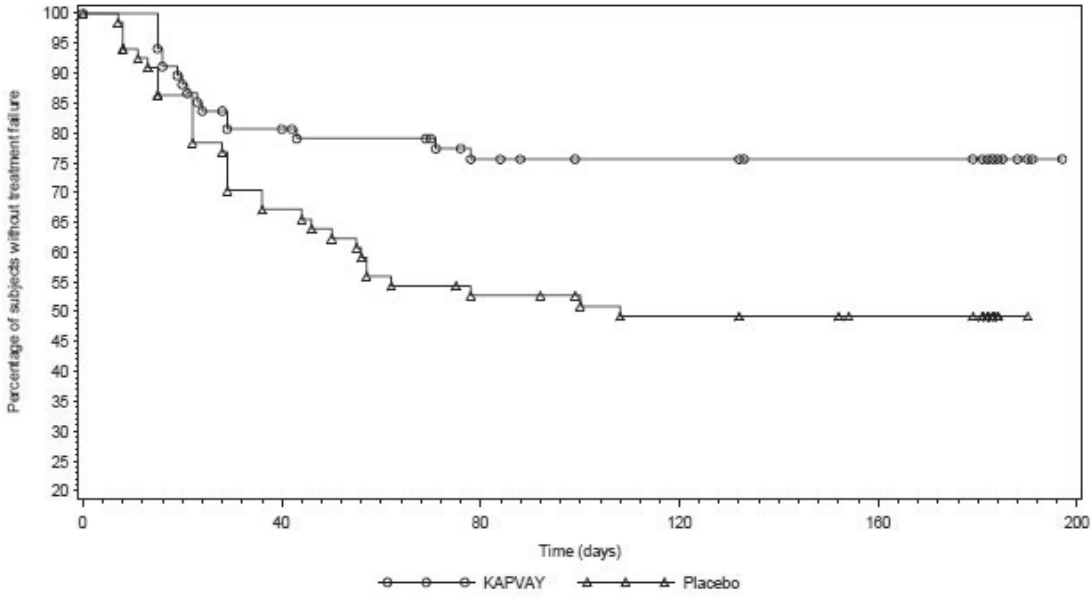
<sup>c</sup>Subjects 515-001, 518-011, and 521-001 (all placebo) discontinued the study due to treatment failure, but met only the criterion for ADHD-RS-IV.

\*Significant at the 5% level.

\*\*Significant at the 1% level.







	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	202 (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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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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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