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/BLA #:	NDA 22-117
Supplement #:	SN018, SN019
Drug Name:	Saphris (asenapine)
Indication(s):	Schizophrenia (SN018) and Bipolar I Disorder (SN019)
Applicant:	Forest Laboratories, Inc.
Date(s):	Date of Document: September 12, 2014 PDUFA due date: March 12, 2015
Review Priority:	Priority
Biometrics Division:	HFD-710
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Keywords:
Interim analysis, sample size estimation

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1 EXECUTIVE SUMMARY

Asenapine is a psychopharmacologic agent for use in adults for the treatment of schizophrenia and for the acute treatment, as monotherapy or adjunctive therapy, of manic or mixed episodes associated with Bipolar I disorder.

The pediatric development program was designed to investigate efficacy and safety of asenapine in 2 different indications: schizophrenia and bipolar I disorder. The current submission consisted of one efficacy and safety trial (P05896) in adolescents between the ages of 12 and 17 years with schizophrenia, and one efficacy and safety trial (P06107) in pediatric subjects aged 10 to 17 years with Bipolar I disorder.

Bipolar I disorder Study 06107 randomized 404 subjects in a ratio 1:1:1:1 to placebo, 2.5 mg BID asenapine, 5.0 mg BID asenapine, or 10.0 mg BID asenapine. The primary endpoint was Y-MRS score at Day 21. The dropout rate was 13%. All asenapine treatment groups showed statistical significance when compared with placebo group in the primary and key secondary analyses. Various sensitivity analyses also showed consistent results.

A blinded sample size recalculation was performed based on the primary endpoint at 90% of the initially planned enrollment for both trials. Both trials showed sufficient power at the 90% interim analysis, which was likely due to lower-than-expected dropout rate. Both trials continued enrolling to the original planned sample size that met the requirement in the pediatric written request.

2 INTRODUCTION

2.1 Overview

Asenapine (MK-8274, SCH 900274, Org 5222) is a psychopharmacologic agent and was first approved in the United States on 13 AUG 2009 for use in adults for the treatment of schizophrenia and for the acute treatment, as monotherapy or adjunctive therapy, of manic or mixed episodes associated with Bipolar I disorder.

The clinical development program in the current submission consisted of one efficacy and safety trial (P05896) in adolescents between the ages of 12 and 17 years with schizophrenia, and one efficacy and safety trial (P06107) in pediatric subjects aged 10 to 17 years with Bipolar I disorder.

The pediatric development program was designed to investigate efficacy and safety of asenapine in 2 different indications:
1. Treatment of schizophrenia
2. Treatment of manic or mixed episodes associated with Bipolar I disorder.

Table 1: List of Phase 3 Studies Included in the Review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
Study 05896	Phase 3	8 weeks	30 days	102 subjects in placebo, 98 subjects in 2.5 mg BID asenapine, and 106 subjects in 5.0 mg BID asenapine	adolescents between the ages of 12 and 17 years with schizophrenia
Study 06107	Phase 3	21 days	30 days	101 subjects in placebo, 105 subjects in 2.5 mg BID asenapine, 99 subjects in 5.0 mg BID asenapine, and 99 subjects in 10.0 mg BID asenapine	pediatric subjects aged 10 to 17 years with an acute manic or mixed episode associated with bipolar I disorder.

[Source: reviewer's table]

2.2 Data Sources

The datasets for schizophrenia Study 05896 is located at

\\CDSESUB1\evsprod\NDA022117\0171\m5\datasets\p05896\analysis\legacy\datasets.

The datasets for Bipolar I Disorder Study 06107 is located at

\\CDSESUB1\evsprod\NDA022117\0171\m5\datasets\p06107\analysis\legacy\datasets.

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The reviewer was able to reproduce the results of the primary analysis and secondary analyses. The applicant submitted the tabulation datasets used to derive the primary analysis dataset and the reviewer was able to trace how the main analysis dataset for the primary and secondary efficacy analyses was derived in the two trials.

3.2 Evaluation of Efficacy

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3.2.2 Bipolar I Disorder Study 06107

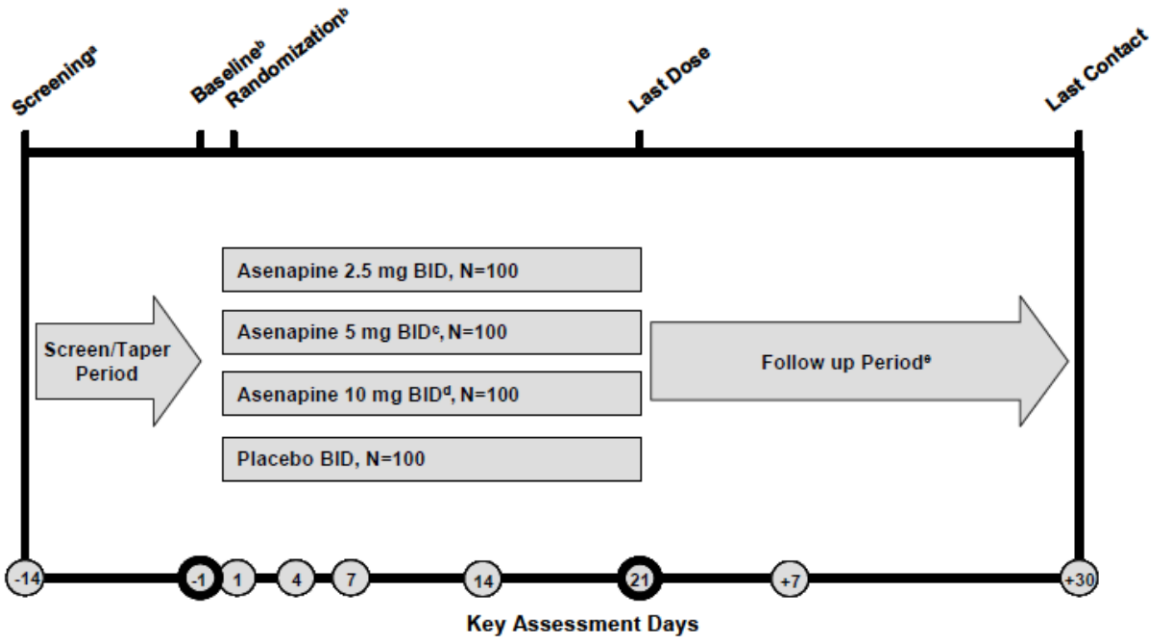
3.2.2.1 Study Design and Endpoints

This was a three week randomized, placebo-controlled, parallel-group, multi-site, double-blind trial of fixed-dose asenapine as monotherapy in pediatric subjects with an acute manic or mixed episode associated with bipolar I disorder.

The trial consisted of a screening/tapering period (2 to 14 days), a three-week treatment period, and a 30 day follow-up period. Subjects were enrolled into the trial and randomly assigned to one of the three fixed-dose treatment groups (asenapine 2.5 mg BID, asenapine 5.0 mg BID, asenapine 10.0 mg BID, or placebo) in a 1:1:1:1 ratio. Randomization was stratified by site. In this study, 404 subjects were randomly assigned to one of the four treatment groups.

In the first week of treatment, the asenapine dose was up titrated for subjects randomized to the asenapine 5.0 mg BID or 10.0 mg BID dose groups. Subjects randomly assigned to 5.0 mg BID asenapine received 2.5 mg BID until their Visit 4 (Day 4) visit. At Visit 4, the dose of asenapine was increased to 5.0 mg BID starting with the evening dose and maintained for the rest of the treatment period. Subjects randomly assigned to 10.0 mg BID asenapine received 2.5 mg BID until Visit 4 (Day 4). At that visit they began taking 5.0 mg BID until Day 7. At the Day 7 visit subjects started a 10.0 mg asenapine dose the evening of Day 7 and continued taking 10.0 mg BID asenapine for the rest of the treatment period.

Figure 4: Trial Design Diagram (Study 06107)



[Source: Sponsor's clinical study report Figure 9-1]

A blinded sample size recalculation was performed by the study statistician at 90% of the initially planned enrollment to ensure that the trial was adequately powered at a minimum of 85% at the time of the final analysis.

The Primary Efficacy Endpoint is the change in the Y-MRS total score from Baseline to Day 21. The Y-MRS is 11-item clinician-rated scale for assessing the severity of manic episodes.

The Key Secondary Efficacy Endpoint is the change in CGI-$BP_{overall}$ from Baseline to Day 21. CGI-$BP_{overall}$ 7-point scale ranging from normal, not ill (1) to very severely ill (7) and is a single value score.

Secondary efficacy endpoints include

- Y-MRS derived variables: proportion of responders, proportion of remitters, dose-response
- CGI-BP_{mania}: change from baseline
- CGI-$BP_{depression}$: change from baseline
- CDRS-R derived variables: total score, proportion of responders,
- CGAS derived variables: change from baseline, proportion
- PQ-LES-Q derived variables: total score, overall score

The Full Analysis Set (FAS) population will serve as the population for the analysis of efficacy data in this trial. The FAS population consists of all subjects randomly assigned to treatment who received at least one dose of trial medication and have both Baseline and at least one post-baseline Y-MRS assessment.

3.2.2.2 Statistical Methodologies

The primary efficacy variable was analyzed with a Mixed Model for Repeated Measures (MMRM) analysis. The model included terms for (pooled) site, treatment, visit, and treatment by visit interaction, baseline Y-MRS total score, and baseline Y-MRS total score by visit interaction as covariates with unstructured variance-covariance matrix. The model parameters were estimated using restricted maximum likelihood. In the rare event that none of the above methods yield convergence, the following structures were planned to be used in the following order: (1) Ante-Dependence, (2) Heterogeneous Autoregressive, and (3) Toeplitz. Kenward-Roger approximation was used to estimate denominator degrees of freedom. The treatment differences in terms of mean change from Baseline to Day 21 were estimated and tested from this model from the treatment by visit interaction. Several sensitivity analyses, such as LOCF, OC and multiple imputations, were performed to check the robustness of the results. In the multiple imputation sensitivity analysis, each missing data point was replaced by 10 simulated values, which were obtained by taking into account the same explanatory variables as used in the

MMRM statistical analysis model. The estimates from the 10 completed datasets were combined for the statistical inference of the estimate of treatment effect.

The key secondary endpoint CGI-$BP_{overall}$ was analyzed using the similar MMRM model for the primary efficacy variable. Only if all three primary efficacy null hypotheses (ie, three doses versus placebo on primary endpoint) are rejected, testing of the three key secondary efficacy hypotheses would be done using Hochberg's procedure using a two-sided alpha of 0.05. Similar sensitivity analyses were performed to examine the robustness of the results.

A target of 400 subjects (100 subjects per treatment arm) was planned to be randomized in the trial. Assuming a 4.7-point difference in favor of the asenapine treatment arms compared with placebo, a standard deviation of 8 increasing to 10 over a time period of 3 weeks, a correlation between subsequent visits of 0.65 and AR(1) structure between visits, an exponential drop-out rate after 3 weeks of 30% in each of the asenapine groups and 40% in the placebo group, and a two-sided significance level of 0.05 with multiplicity correction according to Hochberg's procedure multiplicity, the planned sample size would provide about 85% power for the study. The power calculation was based on 2,000 simulations that generate simulated primary efficacy variable (Y-MRS score) using the aforementioned underlying assumptions and apply the primary efficacy analysis methodology (but excluding baseline and baseline by visit interaction).

3.2.2.3 Patient Disposition, Demographic and Baseline Characteristics

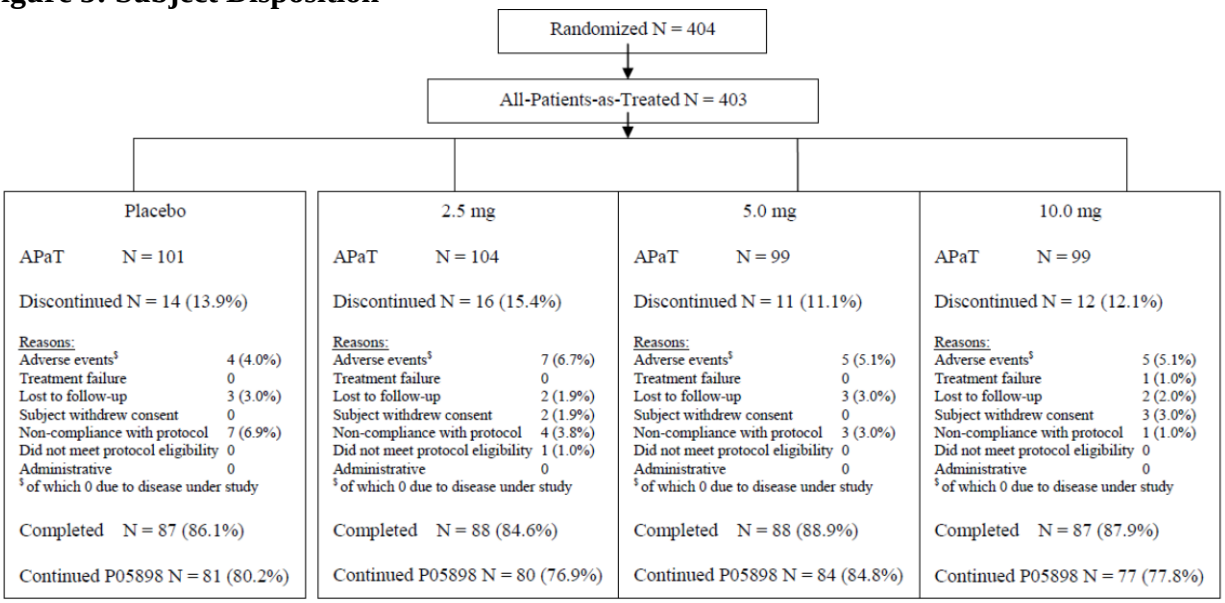
A total of 537 subjects were screened and a total of 404 subjects were randomized. The 404 randomized subjects were enrolled in the United States (n=378) and Russia (n=26).
403 randomized subjects were treated and 395 subjects were included in the Full Analysis Set. Eight subjects received at least one dose of the trial medication, but were excluded from the FAS group. Among these 8 subjects, 2 subjects (101321, 101322) didn't have baseline Y-MRS assessment, and 6 subjects (100686, 100461, 100103, 100547, 100662, 100508) didn't have any in-treatment Y-MRS assessment.

Table 7: Different Sets of Subjects in Study 06107

Subject Disposition	Placebo n (%)	2.5 mg n (%)	5.0 mg n (%)	10.0 mg n (%)	Total n (%)
Randomized	101 (100.0)	105 (100.0)	99 (100.0)	99 (100.0)	404 (100.0)
Not Treated	0 (0.0)	1 (1.0)	0 (0.0)	0 (0.0)	1 (0.2)
All-Patients-as-Treated	101 (100.0)	104 (99.0)	99 (100.0)	99 (100.0)	403 (99.8)
Full Analysis Set	98 (97.0)	101 (96.2)	98 (99.0)	98 (99.0)	395 (97.8)
Not in Full Analysis Set	3 (3.0)	4 (3.8)	1 (1.0)	1 (1.0)	9 (2.2)

[Source: Sponsor's clinical study report Table 10-2]

Figure 5: Subject Disposition



[Source: Sponsor's clinical study report Figure 10-1, verified by the reviewer]

The 87% subjects completed the treatment phase. The most common reason for discontinuation in all three asenapine treatment groups was adverse event, and the most common reason for discontinuation in the placebo treatment group was non-compliance with protocol.

The trial population consisted of an approximately equal number of male and female subjects, and the majority were white and from the US. The mean (SD) age was 13.8 (2.0) years.

Table 8: Patients' Baseline Characteristics in Study 06107

		Placebo	2.5 mg	5.0 mg	10.0 mg	Total
N		101	104	99	99	403
gender	female	63	52	56	41	212
	male	38	52	43	58	191
race	white	68	75	67	65	275
	asian	0	1	0	2	3
	black	23	21	26	27	97
	multiracial	9	7	3	5	24
	other	0	0	1	0	1
age	mean (SD)	13.7 (2.0)	13.7 (2.1)	13.8 (2.0)	13.9 (2.1)	13.8 (2.0)
	<=12	28	30	29	27	114
	>12	73	74	70	72	289
region	US	94	96	93	94	377
	non US	7	8	6	5	26

[Source: reviewer's analysis]

3.2.2.4 Results and Conclusions

The blinded sample size recalculation was performed when the 360th subject was randomly assigned to treatment on June 28, 2013. The recalculation was based on all Y-MRS total scores of 319 subjects who either completed or discontinued treatment and who satisfied the criteria for inclusion in the Full Analysis Set.

The variability at Day 21 was estimated to be 80. Assuming the study design assumptions on effect size and sample size, this would lead to a power of 99%. Based on this finding, it was decided by the Executive Oversight Committee to continue enrolling to reach the originally planned sample size of 400 subjects in total.

The primary efficacy endpoint was the change from baseline in Y-MRS total score at Day 21 using the FAS. All three asenapine doses (2.5 mg BID, 5.0 mg BID, and 10.0 mg BID) showed statistically significant improvement in change from baseline in Y-MRS total score at Day 21 compared with placebo after Hochberg's procedure for multiple treatment comparisons (Table 9). The mean Y-MRS scores of each treatment group by visit were shown in Figure 6. Various sensitivity analyses also showed consistent results (Table 10).

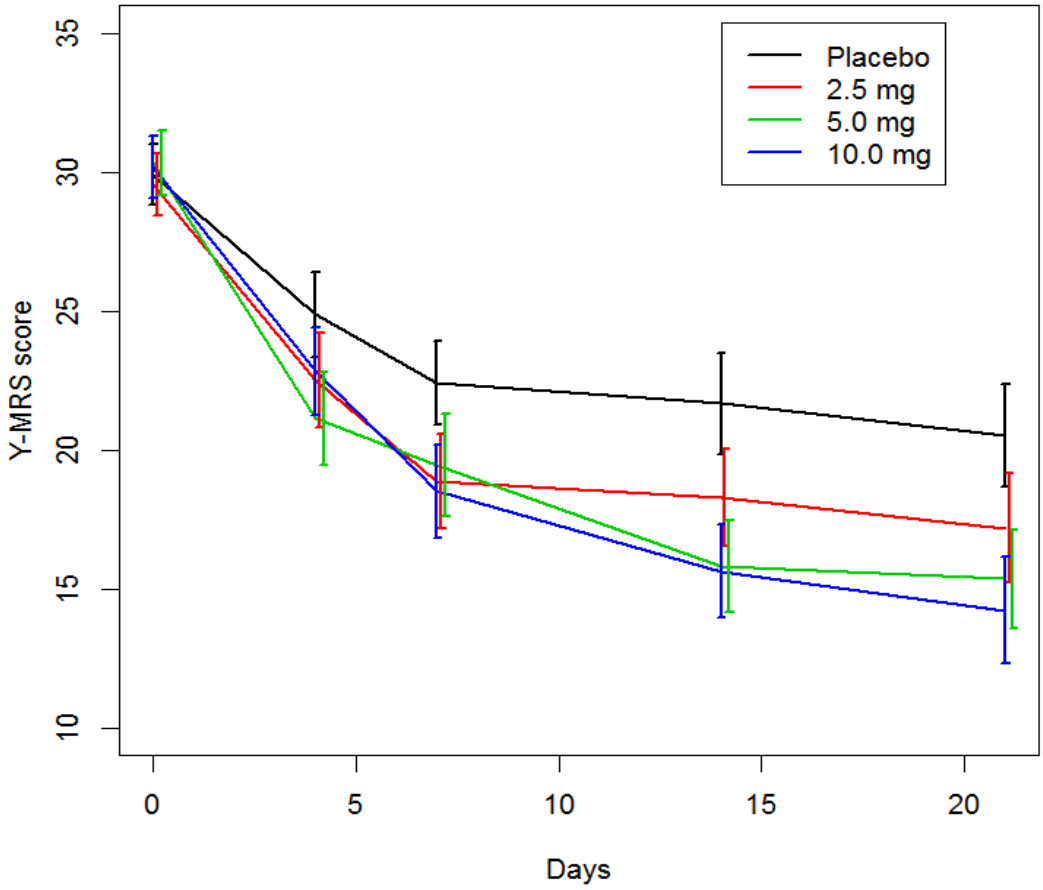
Table 9: Primary Analysis on Change from Baseline in Y-MRS Score at Day 21

		Baseline		Day 21		Change from Baseline at Day 21			
Treatment	**N**	**Mean**	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**	**LS Mean**	**(95% CI)†**
Placebo	79	30.1	(5.7)	20.5	(8.4)	-9.6	(7.8)	-9.6	(-11.3, -7.9)
2.5 mg	88	29.5	(5.7)	17.2	(9.4)	-12.3	(9.0)	-12.8	(-14.4, -11.1)
5.0 mg	87	30.4	(5.9)	15.3	(8.4)	-15.1	(9.5)	-14.9	(-16.5, -13.2)
10.0 mg	81	30.1	(5.7)	14.2	(8.8)	-15.9	(9.1)	-15.8	(-17.5, -14.1)

Pairwise Comparison	Difference in LS Means (95% CI)	p-Value	Adjusted p-Value
2.5 mg vs. Placebo	-3.2 (-5.6, -0.8)	0.008	0.008
5.0 mg vs. Placebo	-5.3 (-7.7, -2.9)	<0.001	<0.001
10.0 mg vs. Placebo	-6.2 (-8.6, -3.8)	<0.001	<0.001

[Source: Sponsor's clinical study report Table 11-1, verified by the reviewer]

Figure 6: Mean Y-MRS Score by Visit



[Source: Reviewer's figure]

Table 10: Sensitivity analyses on Change from Baseline in Y-MRS Score at Day 21

Pairwise Comparison	Sensitivity Analysis Method	Difference at Day 21		p-Value	Adjusted p-Value
		LS Means	(95% CI)		
2.5 mg vs. Placebo	MI	-3.2	(-5.6, -0.8)	0.009	0.009
	LOCF ANCOVA	-3.1	(-5.3, -0.8)	0.008	0.008
	OC ANCOVA	-3.1	(-5.5, -0.8)	0.010	0.010
5.0 mg vs. Placebo	MI	-5.2	(-7.7, -2.6)	<0.001	<0.001
	LOCF ANCOVA	-5.1	(-7.3, -2.8)	<0.001	<0.001
	OC ANCOVA	-5.3	(-7.7, -2.9)	<0.001	<0.001
10.0 mg vs. Placebo	MI	-6.1	(-8.7, -3.4)	<0.001	<0.001
	LOCF ANCOVA	-5.8	(-8.1, -3.5)	<0.001	<0.001
	OC ANCOVA	-6.4	(-8.8, -4.0)	<0.001	<0.001

[Source: Sponsor's clinical study report Table 11-2, verified by the reviewer]

The key secondary efficacy endpoint was the change from baseline in CGI-BP overall score at Day 21 using the FAS. As the primary objective was met for all the three asenapine doses, confirmative testing for the key secondary endpoint was performed. All three asenapine doses showed statistical significance in change from baseline to Day 21 in CGI-BP overall score compared with placebo (Table 11). Various sensitivity analyses on the key secondary endpoint also showed consistent results and came to the same conclusion (Table 12).

Table 11: Key Secondary Analysis on Change from Baseline in CGI-BP Score at Day 21

Treatment	N	Baseline Mean	Baseline (SD)	Day 21 Mean	Day 21 (SD)	Change from Baseline at Day 21 Mean	(SD)	LS Mean	(95% CI)[†]
Placebo	79	4.4	(0.5)	3.7	(0.9)	-0.7	(0.9)	-0.7	(-0.9, -0.5)
2.5 mg	88	4.5	(0.6)	3.2	(1.1)	-1.3	(1.1)	-1.3	(-1.5, -1.1)
5.0 mg	87	4.4	(0.6)	3.0	(1.0)	-1.4	(1.0)	-1.4	(-1.6, -1.2)
10.0 mg	81	4.4	(0.6)	3.0	(1.0)	-1.4	(1.0)	-1.4	(-1.6, -1.2)

Pairwise Comparison	Difference in LS Means (95% CI)		p-Value	Adjusted p-Value
2.5 mg vs. Placebo	-0.6	(-0.9, -0.3)	<0.001	<0.001
5.0 mg vs. Placebo	-0.7	(-0.9, -0.4)	<0.001	<0.001
10.0 mg vs. Placebo	-0.7	(-1.0, -0.4)	<0.001	<0.001

[Source: Sponsor's clinical study report Table 11-4, verified by the reviewer]

Table 12: Sensitivity Analysis on Change from Baseline in CGI-BP Score at Day 21

Pairwise Comparison	Sensitivity Analysis Method	Difference at Day 21 LS Means	(95% CI)	p-Value
2.5 mg vs. Placebo	LOCF ANCOVA	-0.6	(-0.9, -0.3)	<0.001
	OC ANCOVA	-0.6	(-0.9, -0.3)	<0.001
5.0 mg vs. Placebo	LOCF ANCOVA	-0.6	(-0.9, -0.4)	<0.001
	OC ANCOVA	-0.7	(-1.0, -0.4)	<0.001
10.0 mg vs. Placebo	LOCF ANCOVA	-0.7	(-0.9, -0.4)	<0.001
	OC ANCOVA	-0.7	(-1.0, -0.4)	<0.001

[Source: Sponsor's clinical study report Table 11-5, verified by the reviewer]

The sponsor estimated to have about 85% power to detect a 4.7-point difference in Y-MRS score between asenapine treatment groups and placebo. At the 90% interim analysis, the trial had over 99% power. This is likely due to the lower-than-expected drop out rate in the trial. The actual dropout rate was on average 13% in the trial while the expected dropout rate during initial sample size calculation was 40% for placebo and 30% for asenapine groups.

According to the sponsor, the recalculation of sample size was based on all Y-MRS total scores of 319 subjects who either completed or discontinued treatment. The reviewer selected the first 319 subjects who finished their last visit from the 360 subjects who were randomized to treatment by June 28, 2013. In this sample for interim analysis, 79 subjects were in placebo. The three asenapine treatment groups had 80, 81 and 79 subjects for 2.5 mg BID, 5.0 mg BID and 10.0 mg BID, respectively. On average, 85% subjects in this sample completed the 21-day treatment phase. Even by using only last visit information in the subjects who completed the treatment phase at the interim analysis, the power would still be 83% for a single comparison to placebo. On the other hand, the trial had over 99% power to detect a 4.7-point treatment effect in at least one dose, which means the tests can be overpowered. Even though every dose was highly statistically significant in this trial when compared with the control arm, this may not imply a clinically significant treatment effect for some doses.

Study 06107 demonstrated efficacy of asenapine over placebo in treating bipolar I disorder in pediatric subjects. All asenapine treatment groups showed statistical significance when compared with placebo group in the primary and key secondary analyses.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

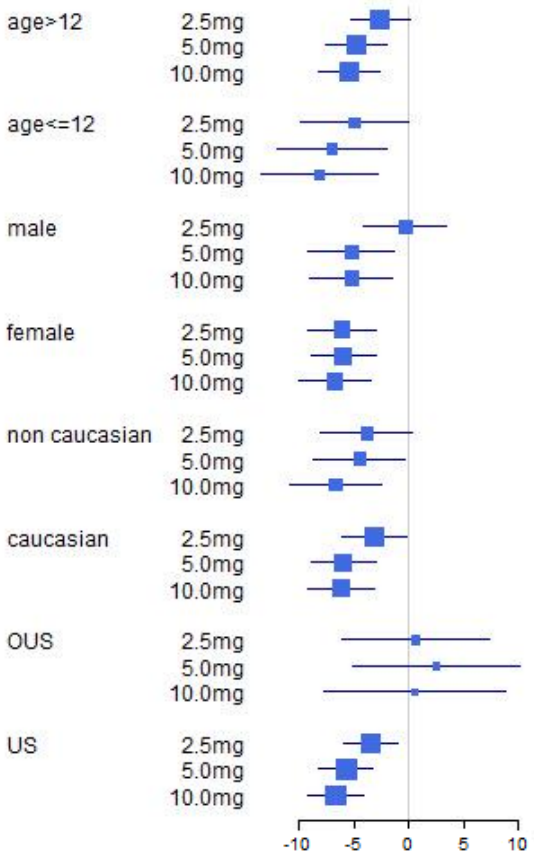
4.1 Gender, Race, Age, and Geographic Region

Subgroup analyses were performed in both Study 05896 and Study 06107 to examine the consistency of study results among various subgroups.

Figure 8 is the forest plot for bipolar Study 06107 and it summarized the change from baseline in Y-MRS Score at Day 21 by various subgroups, for example, gender, age, region and race. Other than Outside-US (OUS) subgroup, treatment effect seemed consistent across subgroups overall.

A dose-response relationship is visible in some subgroups. However, the small sample size in the subpopulations can limit interpretation and caution should be taken in interpreting the finding.

Figure 8: Subgroup Analyses in Bipolar Study 06017



[Source: Reviewer's figure]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

A blinded sample size recalculation was performed in both trials based on the primary endpoint at 90% of the initially planned enrollment. (b) (4)

(b) (4)

Study 06107 (b) (4) The actual dropout rate (13%) was much lower than expected (40% for placebo and 30% for asenapine groups) and the power calculated at 90% interim analysis was over 99%. Both trials continued enrolling to the original planned sample size.

5.2 Collective Evidence

(b) (4)

All three asenapine doses (2.5 mg BID, 5.0 mg BID, and 10.0 mg BID) in bipolar Study 06107 showed statistically significant improvement in change from baseline in Y-MRS total score at Day 21 compared with placebo after multiple comparison adjustment using Hochberg's procedure. The least square mean differences when compared to placebo group were -3.2, -5.3, and -6.2 points in Y-MRS score for 2.5 mg BID, 5.0 mg BID and 10.0 mg BID asenapine treatment group, respectively. Various sensitivity analyses also showed consistent results in the primary and key secondary endpoint.

5.3 Conclusions and Recommendations

(b) (4)

Bipolar Study 06107 had sufficient power to detect a 4.7-point difference in Y-MRS score between asenapine treatment groups and placebo and demonstrated efficacy of asenapine over placebo in treating bipolar I disorder in pediatric subjects. All asenapine treatment groups showed statistical significance when compared with the placebo group in the primary and key secondary analyses.

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/s/

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02/05/2015

PEILING YANG
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I concur with the review

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