



# A 6-week Randomized, Double-blind, Placebo-controlled, Comparator Referenced, Multicenter Trial of Vabicaserin in Subjects With Acute Exacerbation of Schizophrenia

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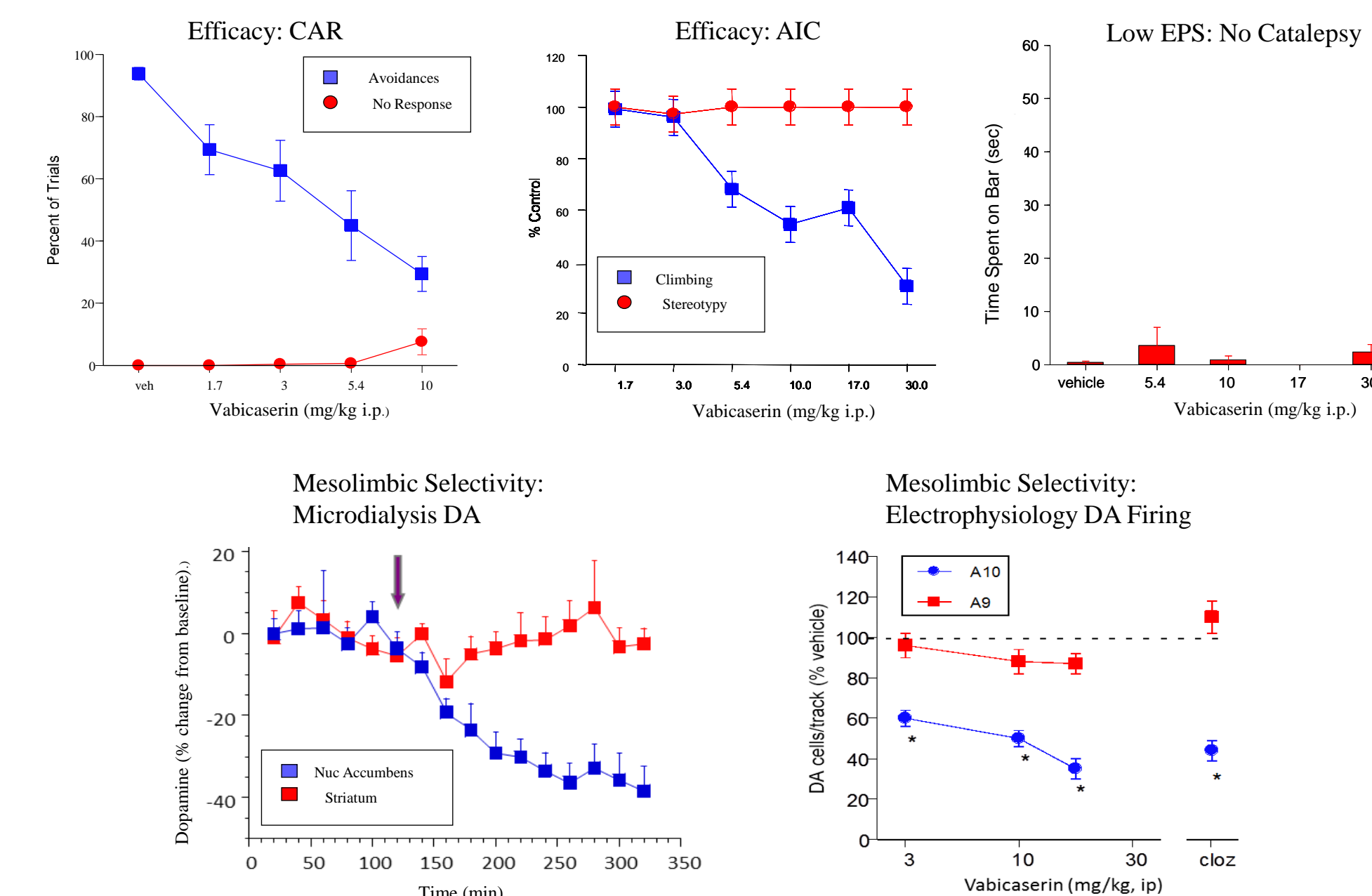
## ABSTRACT

Vabicaserin has been developed for the treatment of schizophrenia. It was evaluated in this randomized, double-blind, placebo controlled and olanzapine-referenced phase 2a study. Hospitalized subjects with exacerbation of schizophrenia were selected and randomized into one of four treatment arms: vabicaserin 200 mg/day or 400 mg/day, olanzapine 15 mg/day or placebo for a 6-week treatment. This study showed that vabicaserin was well tolerated and efficacious in the 200 mg/day dose arm, which demonstrated proof of concept in subjects with acute exacerbation of schizophrenia.

## INTRODUCTION

Vabicaserin is a potent 5-HT<sub>2C</sub> full agonist and demonstrates in vitro functional selectivity for 5-HT<sub>2C</sub> over 5-HT<sub>2A</sub> and 5-HT<sub>2B</sub> receptors. It is effective in several animal models that are predictive of antipsychotic, procognitive and antidepressant-like profiles with a rapid onset feature. It also reduces the liability on catalepsy, weight gain and sexual dysfunction. (See illustrations below.)

FIGURE 1-5. PRECLINICAL DATA (IN VIVO)



## METHODS

### Primary Objectives

To evaluate the efficacy, safety and tolerability of vabicaserin in adult subjects with acute exacerbation of schizophrenia

### Study Design

- Randomized, double-blinded, placebo-controlled, comparator referenced and multi-centered
- Dose assessed: Vabicaserin 100 mg BID (200mg/day), 200mg BID (400mg/day)
- Comparator: Olanzapine 15 mg/day
- Countries: US and India
- Central raters, independent of study sites and blinded to protocol criteria including inclusion/exclusion criteria and visit order, administered the PANSS and CGI-S in US
- Site raters administered the BPRS and CGI-I
- Primary endpoint: change in the PANSS positive score (PSS) from baseline to week 6 using central raters.

### Inclusion Criteria

- Men and women aged 18-65 years
- Hospitalization due to exacerbation of schizophrenia
- Total score on PANSS  $\geq 70$  and  $\leq 120$  by central raters
- Score of  $\geq 4$  on at least 2 of the 5 PANSS items: P1, P2, P3, P6, and G9
- PANSS PSS score of  $\geq 20$
- CGI-S  $\geq 4$

### Exclusion Criteria

- CDSS score of 3 on question 8 (suicide)
- Olanzapine use within 30 days and history of olanzapine treatment resistance
- Known resistance to antipsychotic treatment

### Efficacy Analysis

- Efficacy was analyzed using randomized subjects who have a baseline PSS and at least one post-baseline PSS and who have taken at least 1 dose of double-blind test article (mITT).
- ANCOVAs with LOCF were conducted on the primary endpoint, central rated PANSS PSS, and secondary endpoints, central rated PANSS Total and CGI-S, and site rated BPRS. CGI-I was analyzed using a CMH test.

## RESULTS

313 subjects were included in the safety analysis and 289 were in the efficacy analysis.

TABLE 1. PATIENT POPULATIONS

Number of Subjects	Placebo	Vabi 200mg	Vabi 400mg	Olanzapine
Safety Population, n=313	77	82	77	77
mITT Population, n=289	71	77	70	71

TABLE 2. PATIENT CHARACTERISTICS (SAFETY POPULATION)

Characteristics	Placebo	Vabi 200mg	Vabi 400mg	Olanzapine
Females: Males	20:57	20:62	19:58	25:52
Mean Age, years (SD)	39.77 (10.30)	39.26 (10.11)	40.79 (10.59)	39.77 (10.53)
	86.61 (22.73)	90.96 (26.48)	93.04 (25.51)	91.47 (26.91)
Mean Weight, kg (SD)				
Race, n (%)				
Asian	3 (3.90)	2 (2.44)	1 (1.30)	4 (5.19)
African American	51 (66.23)	50 (60.98)	46 (59.74)	50 (64.94)
White	20 (25.97)	29 (35.37)	28 (36.36)	22 (28.57)
Others	3 (3.90)	1 (1.22)	2 (2.60)	1 (1.30)

### Safety

- Vabicaserin was well tolerated and no major safety concerns were identified.
- The most common adverse events were GI related (Table 3) and with a slightly higher rate in female subjects.
- While olanzapine treatment resulted in weight gain (p < .001), no significant changes in weight were observed for the vabicaserin treatment groups.

TABLE 3. ADVERSE EVENTS REPORTED IN >10% SUBJECTS

System Organ Class Preferred Term	Placebo n=77	Vabi 200mg n=82	Vabi 400mg n=77	Olanzapine n=77	Total n=313
Any Adverse Event	67 (87.0)	69 (84.1)	62 (80.5)	68 (88.3)	266 (85.0)
Gastrointestinal disorders	26 (33.8)	32 (39.0)	39 (50.6)	32 (41.6)	129 (41.2)
Constipation	5 (6.5)	6 (7.3)	11 (14.3)	4 (5.2)	26 (8.3)
Dry mouth	2 (2.6)	3 (3.7)	2 (2.6)	8 (10.4)	15 (4.8)
Dyspepsia	4 (5.2)	12 (14.6)	16 (20.8)	13 (16.9)	45 (14.4)
General disorders and administration site conditions	7 (9.1)	7 (8.5)	7 (9.1)	12 (15.6)	33 (10.5)
Infections and infestations	10 (13.0)	9 (11.0)	11 (14.3)	10 (13.0)	40 (12.8)
Investigations	10 (13.0)	9 (11.0)	10 (13.0)	20 (26.0)	49 (15.7)
Weight increased	3 (3.9)	1 (1.2)	2 (2.6)	10 (13.0)	16 (5.1)
Metabolism and nutrition disorders	5 (6.5)	4 (4.9)	3 (3.9)	8 (10.4)	20 (6.4)
Musculoskeletal and connective tissue disorders	12 (15.6)	8 (9.8)	21 (27.3)	17 (22.1)	58 (18.5)
Nervous system disorders	30 (39.0)	31 (37.8)	32 (41.6)	46 (59.7)	139 (44.4)
Headache	16 (20.8)	23 (28.0)	20 (26.0)	21 (27.3)	80 (25.6)
Sedation	7 (9.1)	6 (7.3)	5 (6.5)	15 (19.5)	33 (10.5)
Somnolence	4 (5.2)	1 (1.2)	2 (2.6)	8 (10.4)	15 (4.8)
Psychiatric disorders	23 (29.9)	23 (28.0)	19 (24.7)	19 (24.7)	84 (26.8)
Agitation	8 (10.4)	7 (8.5)	6 (7.8)	3 (3.9)	24 (7.7)
Insomnia	8 (10.4)	11 (13.4)	7 (9.1)	5 (6.5)	31 (9.9)
Respiratory, thoracic and mediastinal disorders	11 (14.3)	10 (12.2)	10 (13.0)	12 (15.6)	43 (13.7)
Skin and subcutaneous tissue disorders	8 (10.4)	3 (3.7)	10 (13.0)	6 (7.8)	27 (8.6)

### Efficacy

- Olanzapine showed assay sensitivity on all the major endpoints. (Figures 6, 7, 8)
- For central rated PANSS PSS, the vabicaserin 200 mg/day group showed a significant improvement at week 6 compared to placebo (4.2 pt vs 1.9 pt, p=0.03). (Figure 6)
- The vabicaserin 200 mg/day group also separated from placebo on most of the other major endpoints:
  - PANSS total (11.3 pt improvement vs. 2.7 pt, p=0.011) (Figure 7)
  - BPRS total derived from PANSS (8.3 pt vs 4.4 pt, p=.058)
  - CGI-S (p=0.016) and CGI-I (p=0.025) (Figure 8)
- The vabicaserin 400 mg/day group did not separate from placebo on most of the endpoints:
  - Borderline separation on PANSS total (p=0.085) and CGI-I (p=0.097)
- For site rated BPRS, no significant improvement versus placebo was observed for either treatment group (200 mg/day: 5.0 pt vs 3.9 pt; 400 mg/day: 5.3 pt vs 3.9 pt).
- PK/PD: Very weak correlation between the concentration and decrease in PANSS scores.

FIGURE 6. MEAN CHANGES IN CENTRAL RATED PANSS POSITIVE SCORE

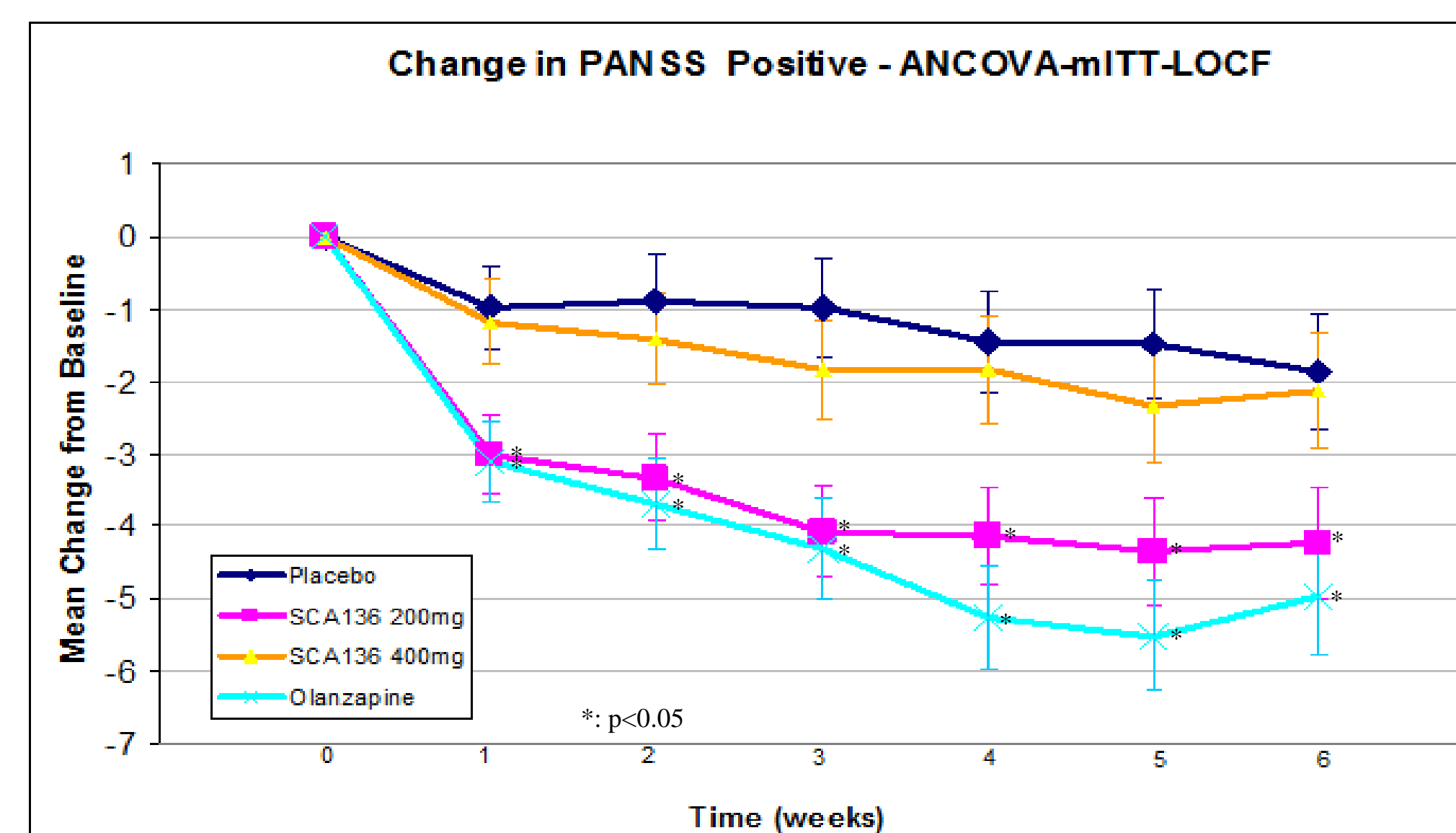


FIGURE 7. MEAN CHANGES IN CENTRAL RATED PANSS TOTAL SCORE

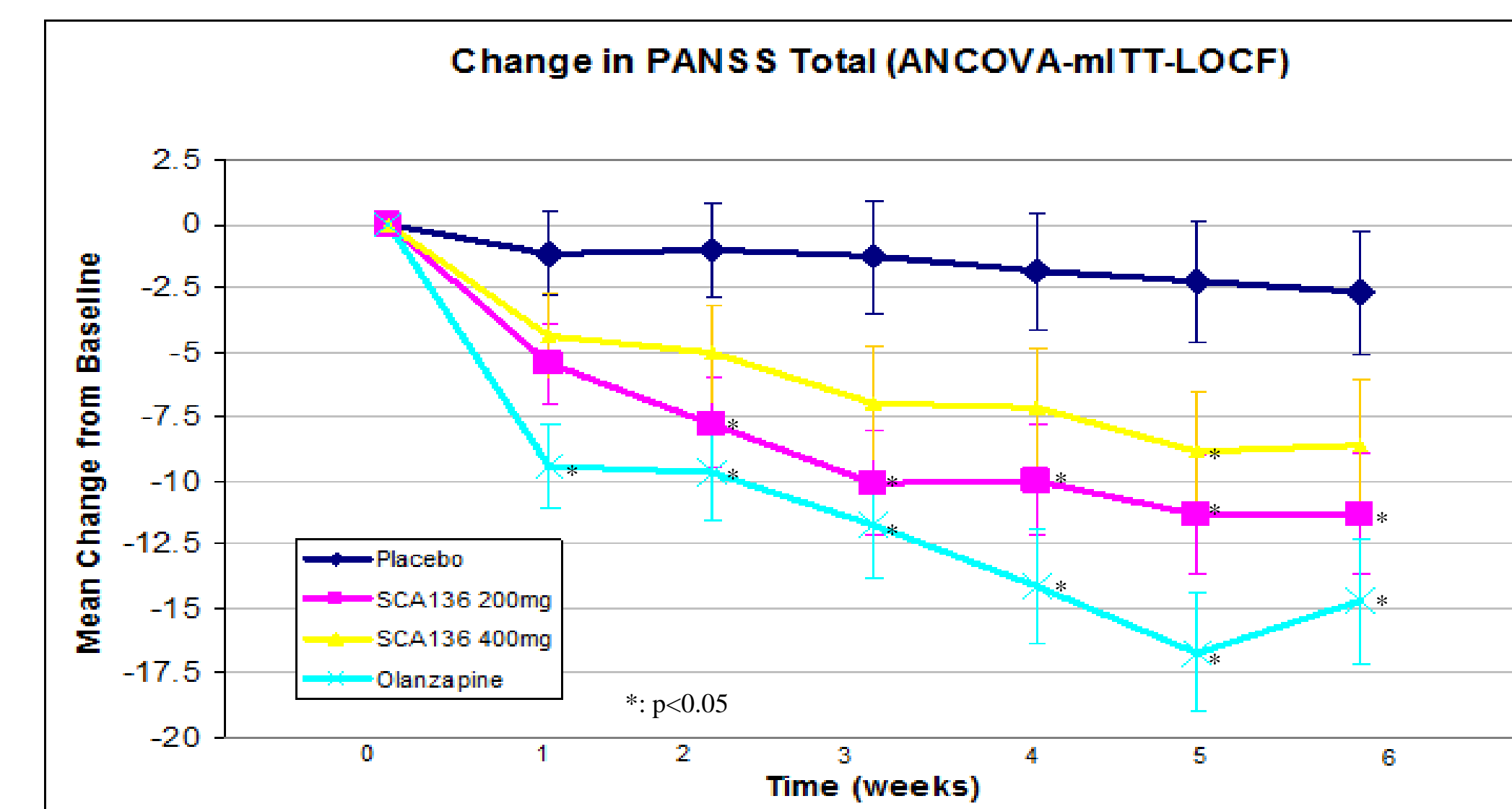


FIGURE 8. CHANGES ON SITE RATED CGI-I SCORES

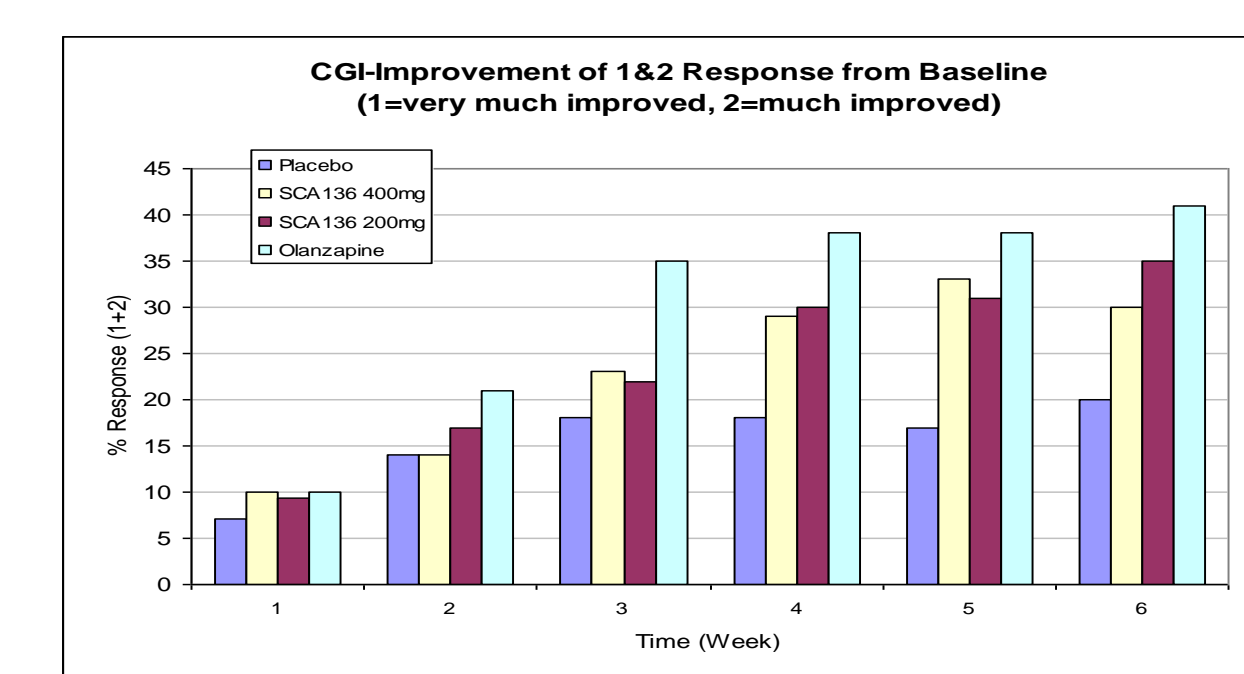
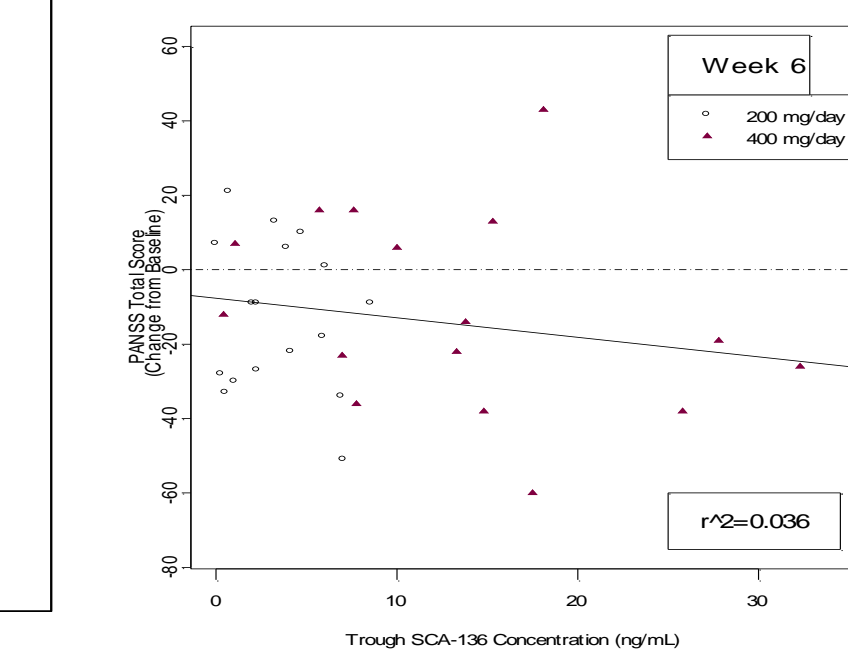


FIGURE 9. CONCENTRATION VS. RESPONSE, BY DOSE, FOR PANSS TOTAL SCORES



### Summary

In this study, both vabicaserin doses were well tolerated with no significant safety signals detected. Olanzapine treatment resulted in significant weight gain while vabicaserin treatments were weight neutral. Using central ratings, vabicaserin treatment demonstrated efficacy on the primary and all the secondary endpoints at 200 mg/day, but not at 400 mg/day, which showed a trend for efficacy. Site rated BPRS did not separate vabicaserin dose arms from placebo. Olanzapine treatment was superior to placebo as expected, these results support the safety and tolerability of vabicaserin in the target population. PK/PD relationship from population PK analysis was inconclusive though with a downward trend of improvement for PANSS total scores.

### CONCLUSIONS

The 200 mg/day vabicaserin dose group achieved proof of concept using central ratings. No major safety signals were detected in the study population. Further study is warranted to confirm the efficacy and define the efficacious dose/doses.

### REFERENCES

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