

Efficacy and Safety of Lurasidone in Phase 2 - 3 Acute Schizophrenia Trials

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ABSTRACT

Objective

Lurasidone is a novel psychotropic agent with high affinity for D₂ and 5-HT_{2A} receptors, as well as for receptors implicated in the enhancement of cognition, mood and negative symptoms (5-HT₇, 5-HT_{1A} and α_{2c}). The objective of the studies discussed here was to assess the efficacy and safety of lurasidone in the treatment of patients hospitalized for an acute exacerbation of schizophrenia.

Method

Efficacy and safety data were obtained from 4 randomized, double-blind, placebo-controlled trials: 3 Phase II studies and 1 Phase III study in which patients meeting DSM-IV criteria for an acute exacerbation of schizophrenia were randomized to 6 weeks of double-blind treatment with a fixed daily dose of lurasidone 40 mg, 80 mg, or 120 mg. One Phase II study (Study 049) was a failed study in which haloperidol did not demonstrate significant efficacy versus placebo, and was excluded from the dose-response analysis. Cohen's d effect sizes were calculated for baseline to Week 6 change in PANSS and BPRSd total scores. The potential dose-response of lurasidone was also evaluated using a linear dose-response model.

Results

In the Phase II trials, effect sizes of BPRSd at endpoint were higher for the 120 mg dose of lurasidone (0.78) compared to the 40 mg (0.43) and 80 mg (0.42) doses. Results from the Phase III study reported here indicate that lurasidone 80 mg/day was associated with the largest treatment effect across the studied dose range. Lurasidone was well-tolerated overall, with few discontinuations due to adverse effects and minimal effects on weight, lipids and glucose.

Conclusion

The results of these placebo-controlled studies in patients with acute schizophrenic illness, suggest that lurasidone is efficacious and well-tolerated in a dose range of 40 -120 mg/day.

INTRODUCTION

Lurasidone

- Lurasidone is a novel psychotropic agent with high affinity for both dopamine D₂ and serotonin 5-HT_{2A} receptors
- The receptor binding profile of lurasidone is also characterized by:
 - High affinity for receptors implicated in enhancement of cognitive function: serotonin 5-HT₇, 5-HT_{1A}, and noradrenaline α_{2c} receptors
 - Minimal-to-no affinity for noradrenaline α₁, histamine H₁ and muscarinic M₁ receptors
- Preclinical data indicate that lurasidone reverses MK-801 induced learning and memory impairment in rodents (Ishiyama et al, 2007; Enomoto et al, 2008)
- Active comparator data from a Phase 1b study of lurasidone 120 mg/d vs. ziprasidone 160 mg/d support the potential for improved cognition and functional capacity with lurasidone treatment (Harvey et al, 2009)
- The objective of the placebo-controlled studies presented here was to assess the efficacy and safety of lurasidone in the treatment of patients hospitalized for an acute exacerbation of schizophrenia

METHODS

Table 1. Brief Summary of Designs of Phase 2 and Phase 3 studies

	Phase 2 Studies			Phase 3 Study
	Study 006	Study 049*	Study 196	PEARL 1
Study treatment, N	Lurasidone 40 mg, N=50 Lurasidone 120 mg, N=49 Placebo, N=50	Lurasidone 20 mg, N=71 Lurasidone 40 mg, N=67 Lurasidone 80 mg, N=80 Haloperidol 10 mg, N=72 Placebo, N=72	Lurasidone 80 mg, N=90 Placebo, N=90	Lurasidone 40 mg, N=125 Lurasidone 80 mg, N=123 Lurasidone 120 mg, N=124 Placebo, N=128
Study design	Randomized, DB	Randomized, DB	Randomized, DB	Randomized, DB
Duration	6 weeks	6 weeks	6 weeks	6 weeks
Diagnosis	Schiz, acute exacerbation	Schiz, acute exacerbation	Schiz, acute exacerbation	Schiz, acute exacerbation
Age range, yrs	18 - 64, inclusive	18 - 64, inclusive	18 - 64, inclusive	18 - 75, inclusive
Setting	Hospitalized for ≥1 week	Hospitalized for ≥1 week	Hospitalized for ≥4 weeks	Hospitalized for ≥3 weeks
Treatment outcomes	PANSS, BPRS, CGI-S, CGI-I	PANSS, BPRS, CGI-S	PANSS, BPRS, CGI-S, CGI-I	PANSS, BPRS, CGI-S

DB: double-blind; * Study 049 was a failed study with no significant difference in efficacy between haloperidol and placebo, or between any lurasidone dose and placebo. Therefore, study 049 was included in pooled safety assessments, but not in pooled assessment of efficacy.

- Lurasidone was administered on a once daily basis in all studies
- Fixed doses were started at study initiation without need for titration (except for the 120 mg dose which was started at 80 mg)

Assessments Included in Dose-Response Analysis

Efficacy

- PANSS total
- CGI-Severity
- Pooled efficacy analyses include Studies 006/196/PEARL 1

Safety

- Laboratory evaluations: lipid profile (non-fasting)
- Adverse events, spontaneously reported
- Pooled safety analyses include Studies 006/049/196/PEARL 1

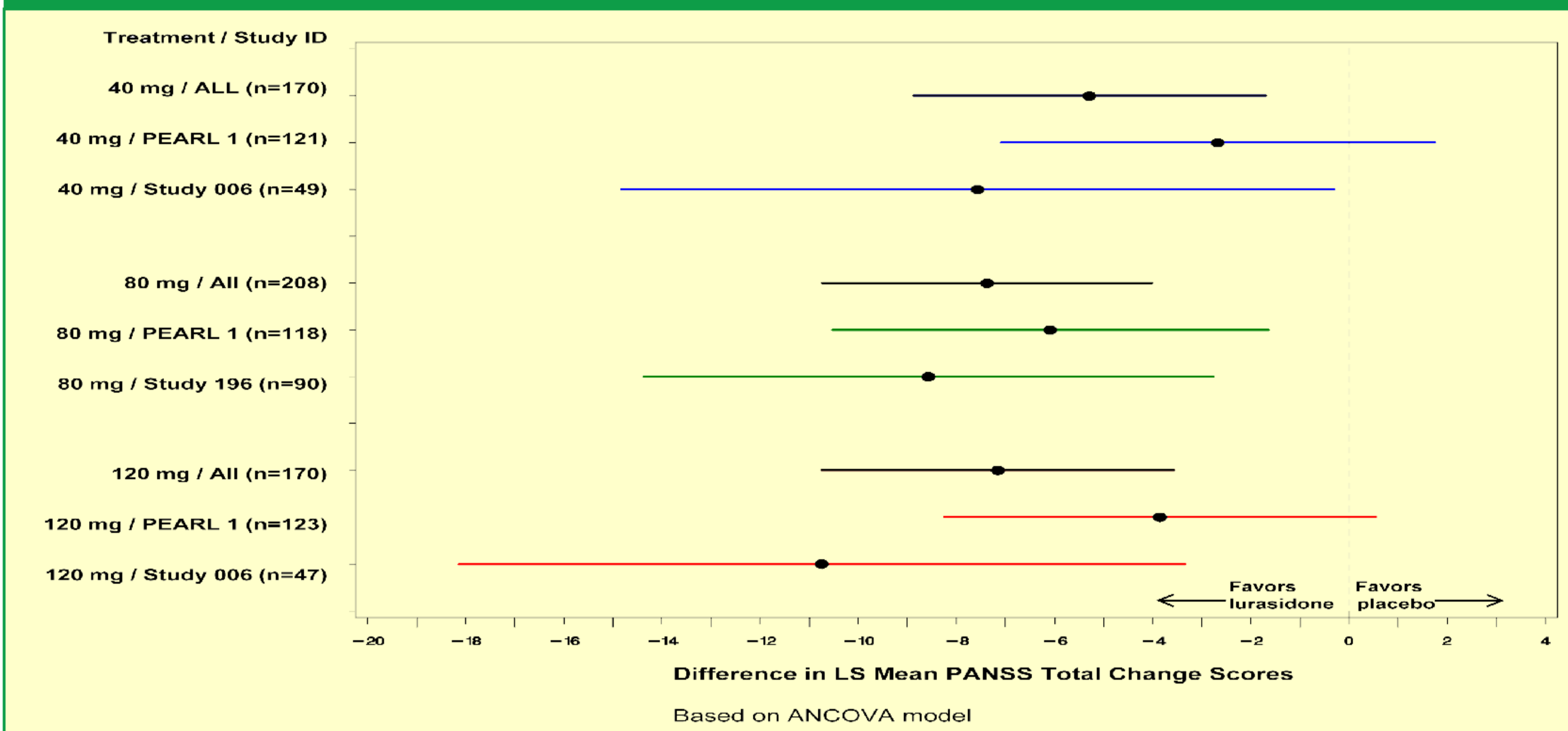
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 PHARMA AMERICA, INC.**

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Table 2. Summary of Patient Characteristics at Baseline in Phase 2/3 studies

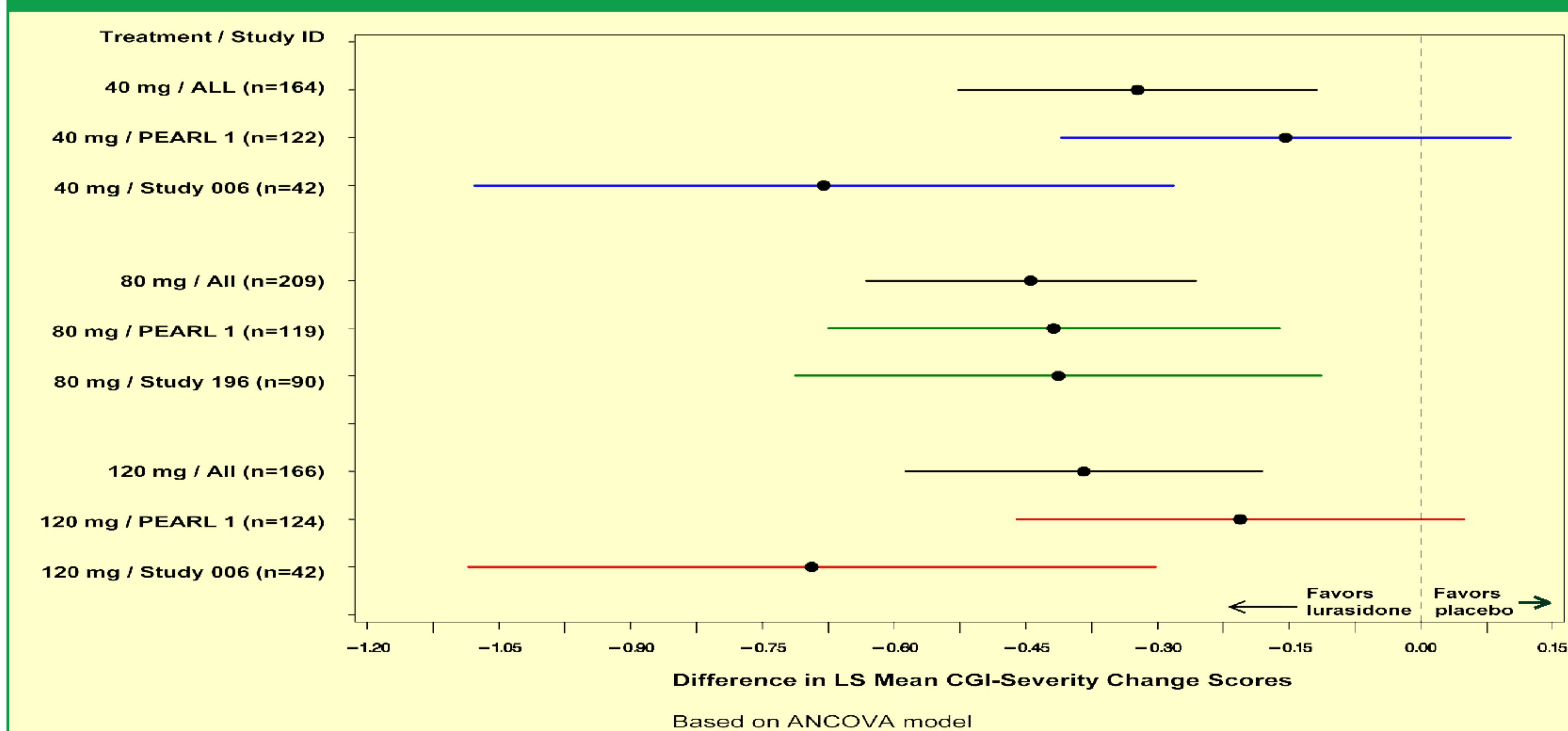
	Phase 2 Studies (006/049/196)		PEARL 1 Study	
	Lurasidone (N=327)	Placebo (N=212)	Lurasidone (N=369)	Placebo (N=127)
Male, N(%)	238 (73%)	167 (79%)	253 (69%)	93 (73%)
Age, years, mean (SD)	40.9 (9.6)	40.7 (9.8)	39.0 (10.7)	38.1 (9.8)
Race, N (%)				
White	131 (40%)	84 (40%)	178 (48%)	66 (52%)
Black	168 (51%)	109 (51%)	130 (35%)	38 (30%)
Asian	4 (1%)	3 (1%)	56 (15%)	20 (16%)
BMI, kg/m ² , mean (SD)	30.1 (7.9)	29.7 (7.1)	26.7 (5.6)	26.9 (5.7)
PANSS, mean (SD)				
Total	92.9 (13.6)	95.7 (14.0)	96.2 (10.7)	96.8 (11.1)
Positive symptoms	24.4 (4.3)	25.1 (4.5)	26.1 (3.7)	25.7 (4.3)
Negative symptoms	22.9 (5.4)	23.6 (5.5)	23.9 (4.3)	24.3 (4.5)
CGI-Severity, mean (SD)	4.8 (0.7)	4.8 (0.7)	4.9 (0.6)	4.9 (0.6)

Figure 1. PANSS total score: Difference in LS Mean [\pm 95% CI] Change From Baseline For Lurasidone vs. Placebo From Phase 2 and 3 Studies*



* Study 049 was excluded from this analysis because it was a failed study with no significant difference in efficacy between haloperidol and placebo

Figure 2. CGI-Severity: Difference in LS Mean [\pm 95% CI] Change From Baseline For Lurasidone vs. Placebo From Phase 2 and 3 Studies*



* Study 049 was excluded from this analysis because it was a failed study with no significant difference in efficacy between haloperidol and placebo

RESULTS

Figure 3. Change in PANSS Total Score: PEARL 1 Study

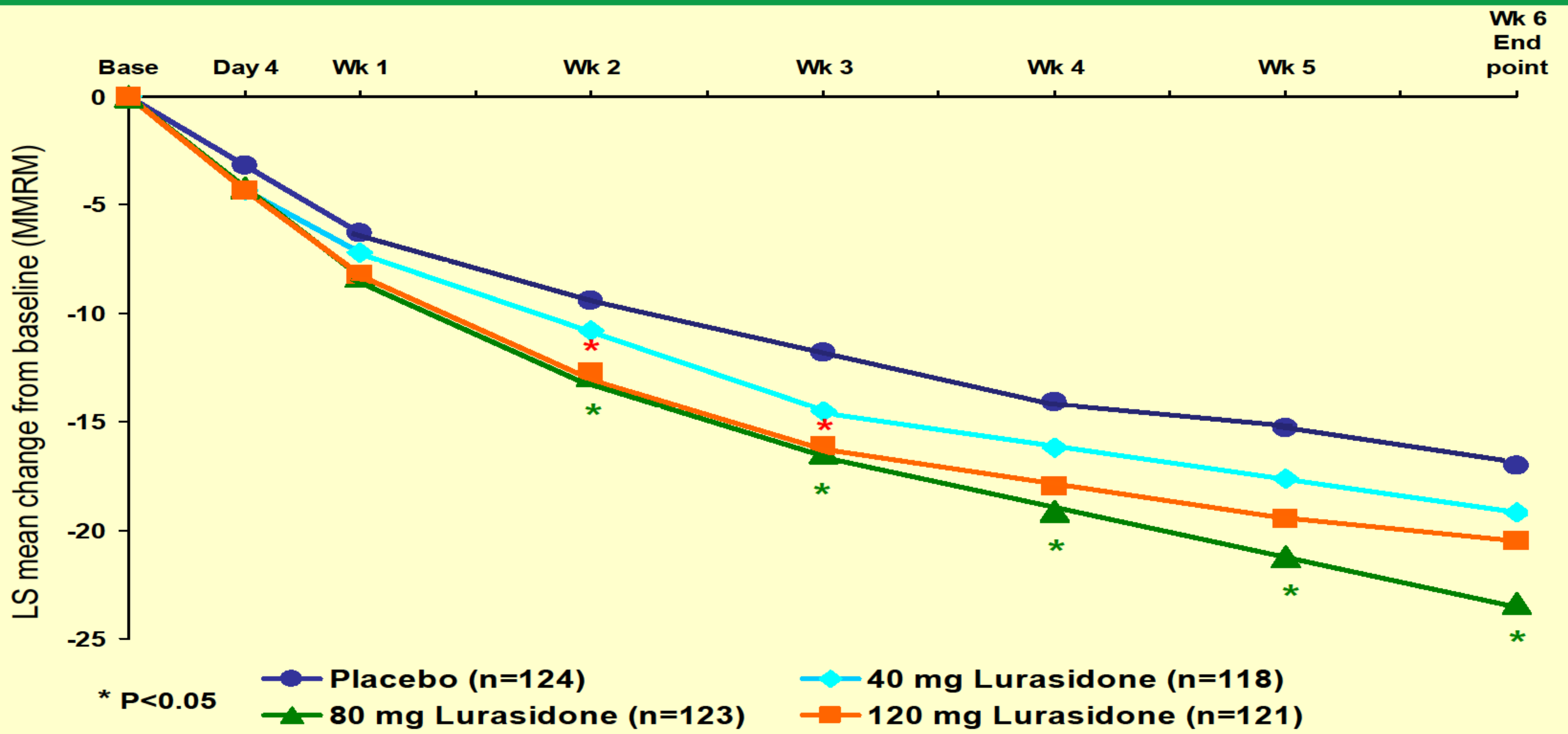
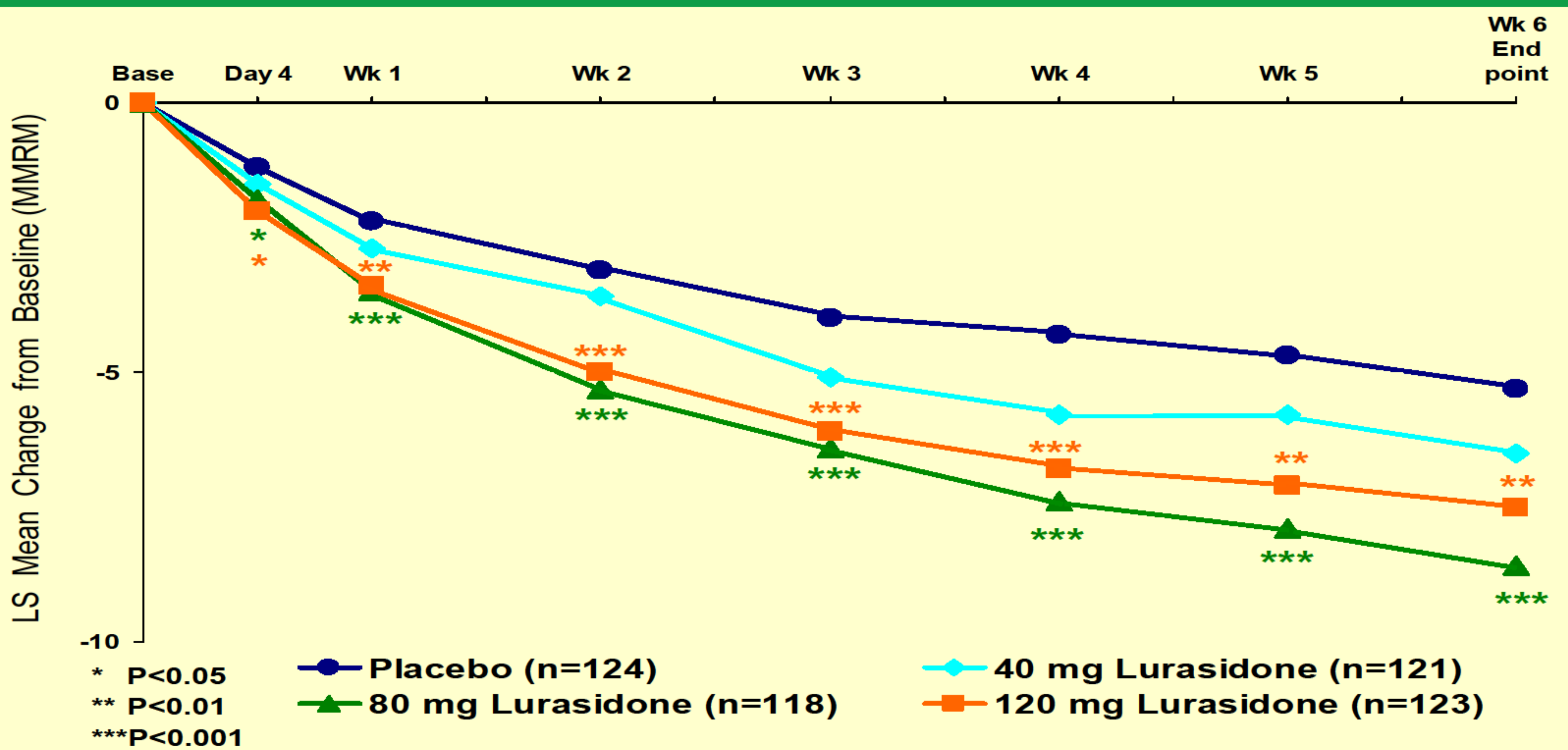
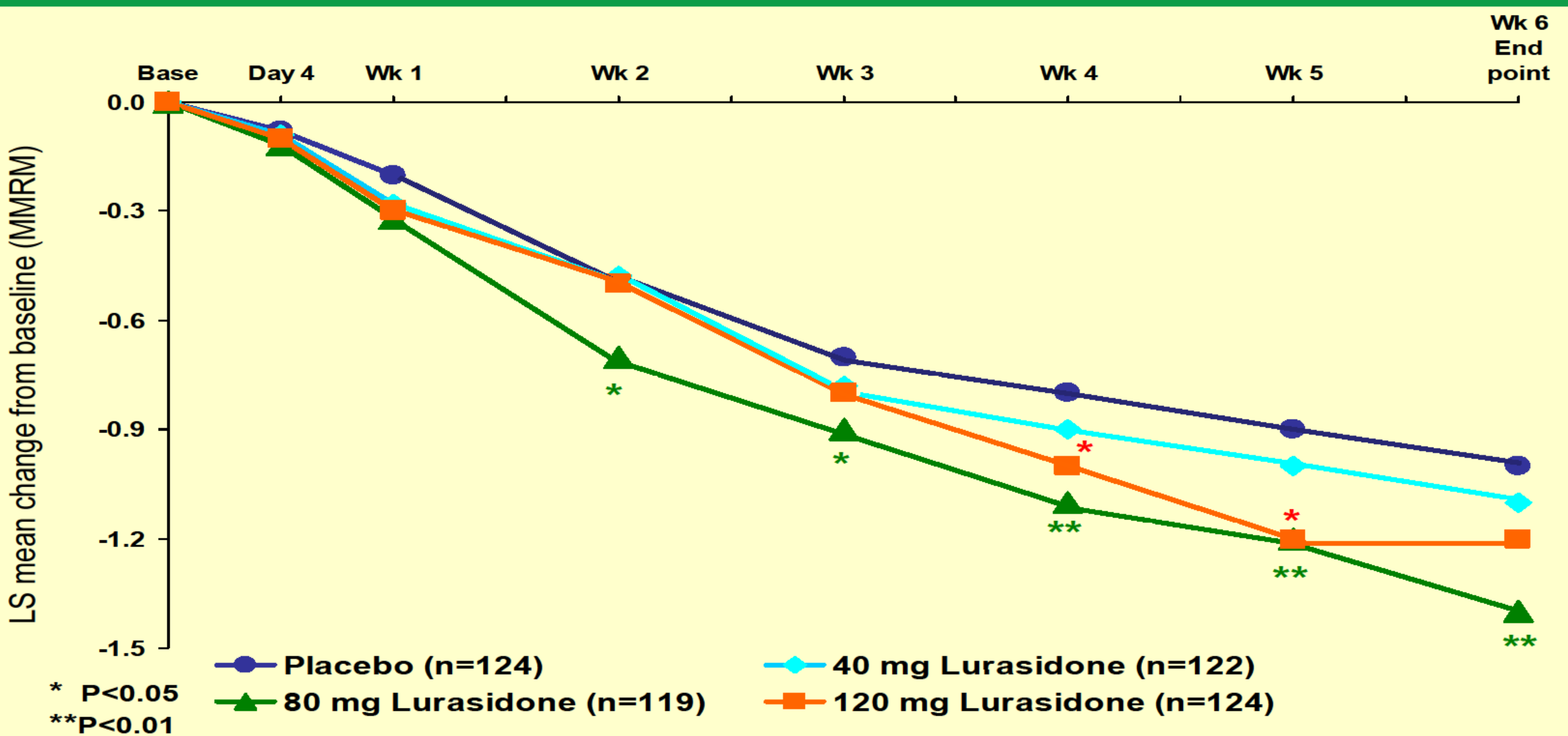


Figure 4. Change in PANSS Positive Subscale Score: PEARL 1 Study



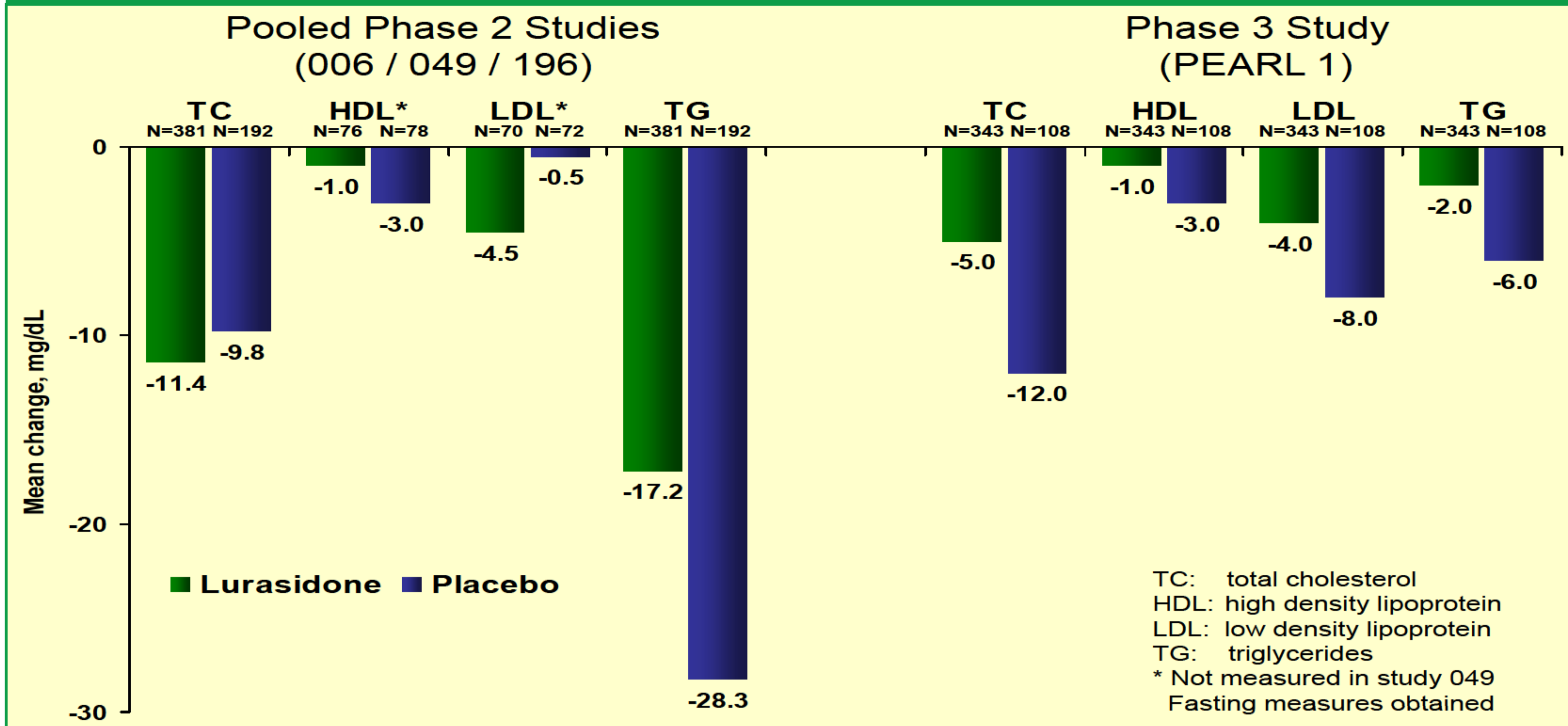
- In the PEARL 1 study, treatment with lurasidone 80 mg was associated with significant improvement on the PANSS total score from week 2 onward (Figure 3), and on the PANSS positive subscale score from day 4 onward (Figure 4)
- Treatment with the 120 mg dose of lurasidone was also significant from day 4 onward on the PANSS positive subscale, but only intermittently significant on the PANSS total score

Figure 5. Change in CGI-Severity Score: PEARL 1 Study

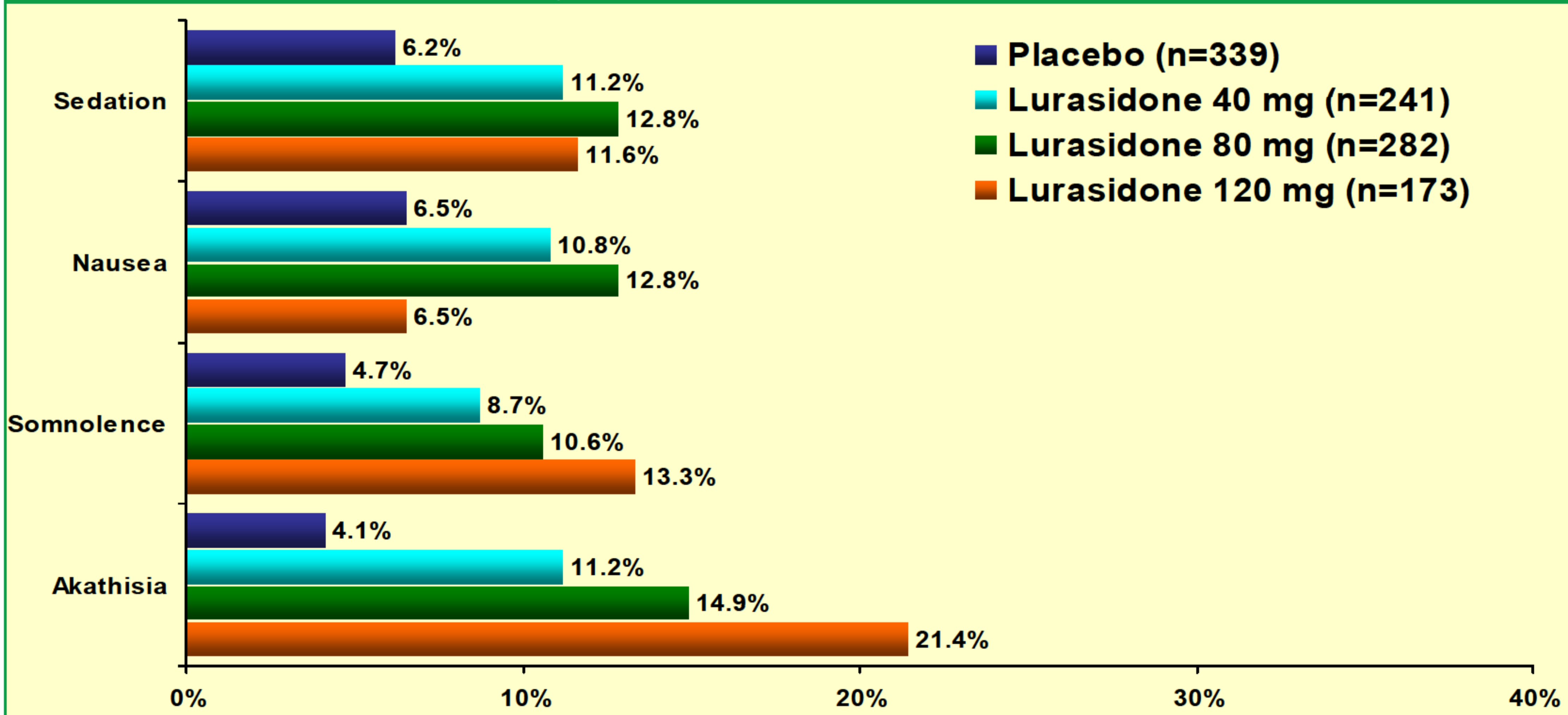


- In the PEARL 1 study, treatment with lurasidone was associated with significant improvement in the CGI-Severity score from week 2 onward on the 80 mg dose, but only intermittent significance on the 120 mg dose

Figure 6. Mean Change in Lipids: Pooled Phase 2 and Phase 3 Study Results



- Treatment with lurasidone in the 40-120 mg dosage range was not associated with a mean increase in lipids
- In the pooled Phase 2 studies the mean weight gain was 0.46 kg for lurasidone and 0.16 kg for placebo. In the Phase 3 study (PEARL 1) the mean weight gain was 0.92 kg for lurasidone and 0.30 kg for placebo
- In the pooled Phase 2 studies a similar proportion of patients reported $\geq 7\%$ weight gain for lurasidone (5.2%) and placebo (5.5%). In the PEARL 1 study, the proportion reporting $\geq 7\%$ weight gain was somewhat higher on lurasidone (8.2%) compared to placebo (3.2%)

Figure 7. Treatment-emergent Adverse Event Rates (Incidence $\geq 10\%$): Phase 2 and 3 Data (Studies 006/049/196/PEARL 1)

- In the pooled data, four adverse events occurred with an incidence of at least 10% on lurasidone (headache was not included because it occurred at a higher rate on placebo). This pooled analysis includes Studies 006/049/196/PEARL 1

CONCLUSIONS

- Lurasidone, a novel psychotropic agent for the treatment of schizophrenia, has been studied in phase 2 and 3 placebo-controlled trials
- Results of these trials demonstrate that lurasidone is efficacious and generally well-tolerated across a dose range of 40-120 mg/day
- Results of the PEARL 1 study (the first phase 3 global trial), replicated prior evidence for lurasidone's efficacy at 80 mg/day and demonstrated a generally favorable safety and tolerability profile (Nakamura et al, in press)
 - PANSS positive subscale was statistically significant at all visits from day 4 onwards for lurasidone 80 mg/day and 120 mg/day
- Lurasidone does not require dose titration and is taken once daily in tablet form with food
- Additional controlled trials are underway to fully characterize lurasidone's clinical profile and potential spectrum of efficacy in patients with schizophrenia

REFERENCES