Lurasidone Meeting

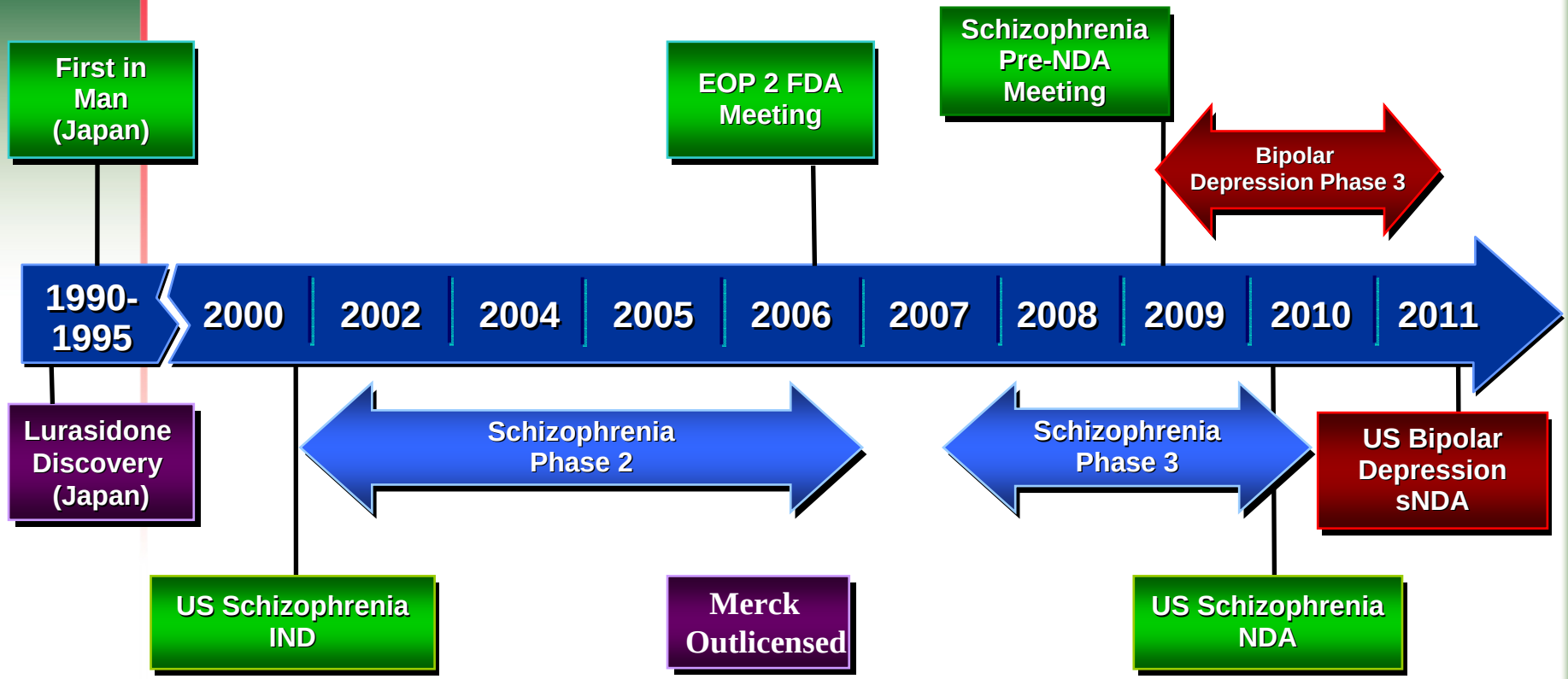
June 12, 2009

Dainippon Sumitomo Pharma Co., Ltd.

Lurasidone: Clinical Studies Summary

Antony Loebel, MD
Vice President, Clinical Development
Dainippon Sumitomo Pharma America

Lurasidone Development Timeline



Problems with Current Antipsychotic Agents

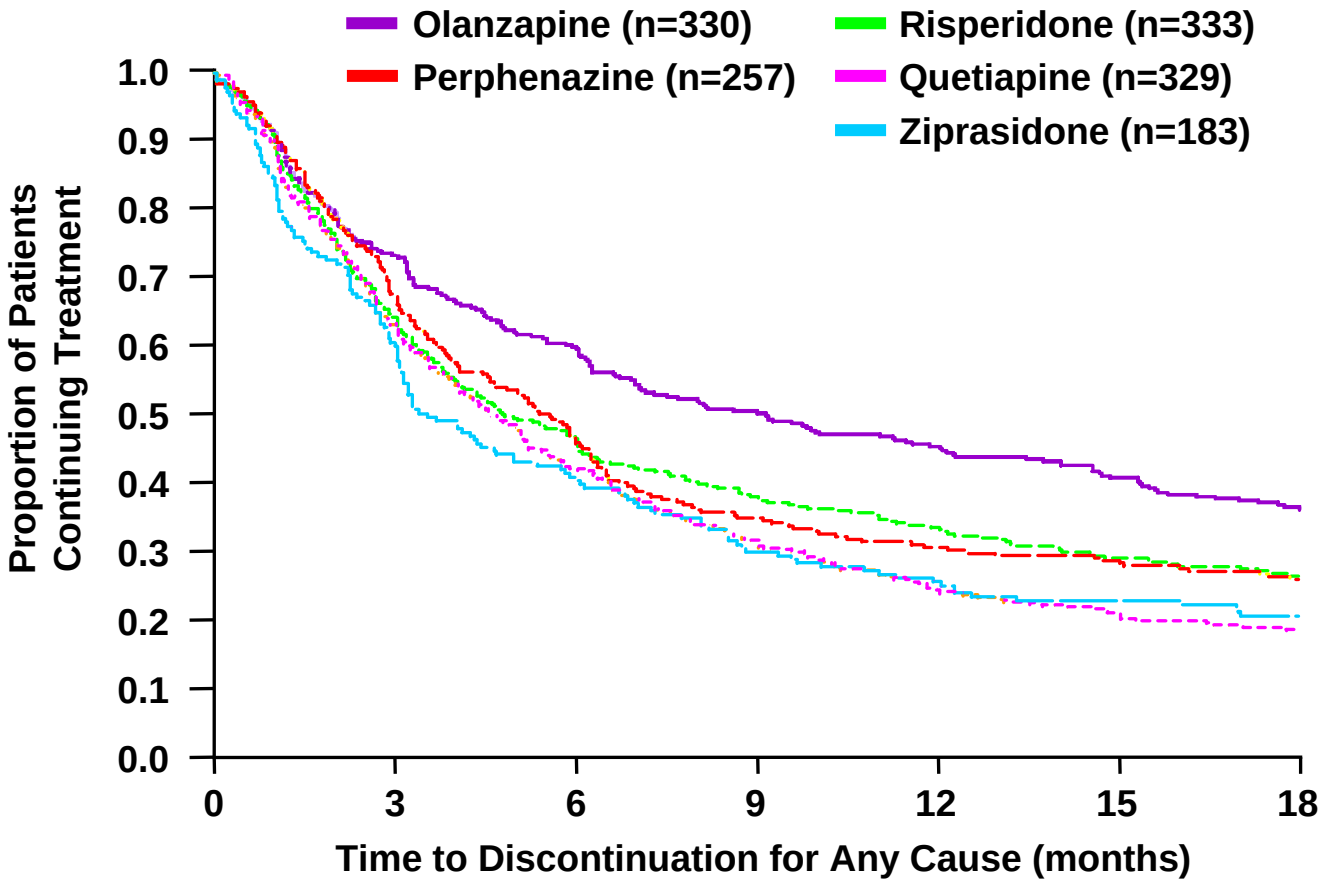
- Lack of efficacy
- EPS/akathisia
- Prolactin increase
- Metabolic syndrome
  - Weight gain
  - Lipid increase
  - Diabetes
- QTc prolongation
- Sedation
- Poor functioning
- Reduced adherence to treatment

ADA/APA Consensus Statement on Antipsychotic Drugs and Obesity and Diabetes

Drug	*Weight Gain*	*Diabetes Risk*	*Dyslipidemia*
clozapine	+ + +	+	+
olanzapine	+ + +	+	+
risperidone	+ +	D	D
quetiapine	+ +	D	D
aripiprazole*	+/-	–	–
ziprasidone*	+/-	–	–

+ = increased effect; - = no effect; D = discrepant results.
*Newer drugs with limited long-term data.
Diabetes Care/*J Clin Psych*, 2004 and others

CATIE Schizophrenia Study: Time to Discontinuation for Any Cause



Lieberman JA et al. N Engl J Med. 2005;353:1209-1223.

Psychiatrists Perceive the Greatest Unmet Needs in the Treatment of Schizophrenia and Bipolar Disorder to Involve Better/More Consistent Efficacy Balanced with Tolerable Side Effects

Unmet Needs	Schizophrenia	Bipolar Disorder
Better Efficacy	◆ Uniform effectiveness (balanced with side effect burden) ◆ Treatment of positive symptoms - violence, loss of self-control ◆ Something to enhance cognitive functioning of patients, improve intellectual capacity ◆ New alternatives – *"There are still a number of patients who are quite sick with available medications. We need new mechanisms, an increased arsenal."*	◆ More uniformly effective for depressed phase ◆ Drugs that work alone to treat all stages ◆ Control of agitation
Fewer Side Effects	◆ Better performance in terms of metabolic effects and weight gain (effects impact compliance)	◆ Fewer metabolic effects ◆ Limited side effects
Lower Cost	◆ Less expensive medications (issue for 30% of patients)	◆ Less expensive medications (issue for 10-20% of patients)
Simpler Administration	◆ Simple regimen, maybe a combination of meds patients typically take in a single capsule	◆ QD medications

DSP, data on file, 2009

Receptor Binding Profiles: Lurasidone and Other Agents

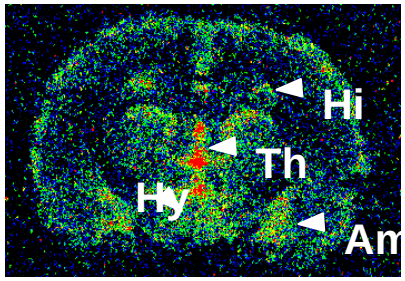
Binding Affinities (Ki; nM)	Lurasidone	Risp	Olanz	Quet	Zip	Aripip	Cloz
D_2 Antipsychotic	1.7	2.9	14	200	3	3.3	110
5-HT_{2A} Antipsychotic/ Attenuate EPS	2.0	0.2	5.8	340	0.3	34	9.2
5-HT_{1A} Mood/Cognition	6.8	260	2700	320	8.5	2.1	120
5-HT_7 Mood/Cognition	0.50	6.6	110	310	6.0	10	18
α2c Cognition	11	11	210	350	400	38	16
Histamine H1 Impair cognition, sedation, weight gain	>1000	3.5	3.8	9.0	510	67	2.0
ACh M1 Impair cognition	>1000	>1000	7.6	210	>1000	>1000	4.9
α1 Orthostatic hypotension, sedation	48	2	19	7	2	26	7

Lurasidone data on file, 2008
Bymaster,et al. Neuropsycopharmacology,1996;14:87-96 and others

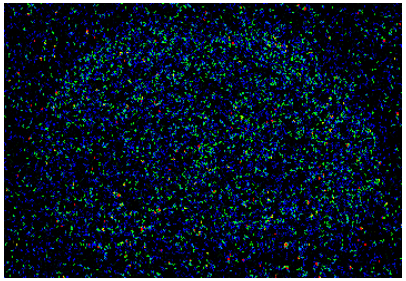
5-HT_7 Receptor Autoradiography in Rat

Lurasidone Dose-Dependently Competes with [3H]SB-269970 Binding

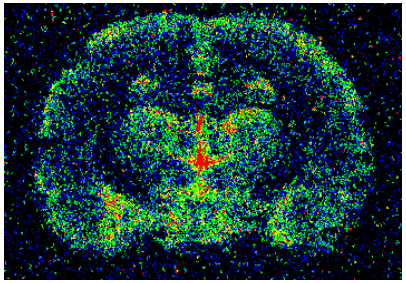
Total



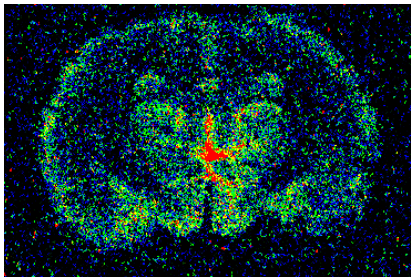
Non Specific



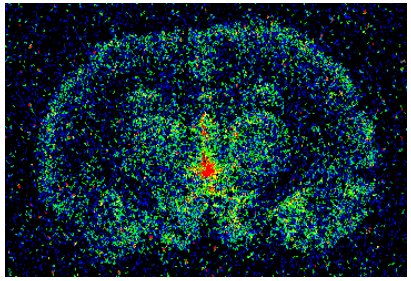
Lurasidone 1 nM



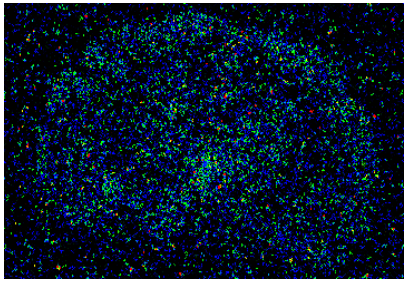
Lurasidone 10 nM



Lurasidone 100 nM



Lurasidone 1000 nM



Am-Amygdala
Hy-Hypothalamus
Th-Thalamus
Hi-Hippocampus

Available online at www.sciencedirect.com
ScienceDirect
European Journal of Pharmacology 572 (2007) 160–170
www.elsevier.com/locate/ejphar

Lurasidone (SM-13496), a novel atypical antipsychotic drug, reverses MK-801-induced impairment of learning and memory in the rat passive-avoidance test

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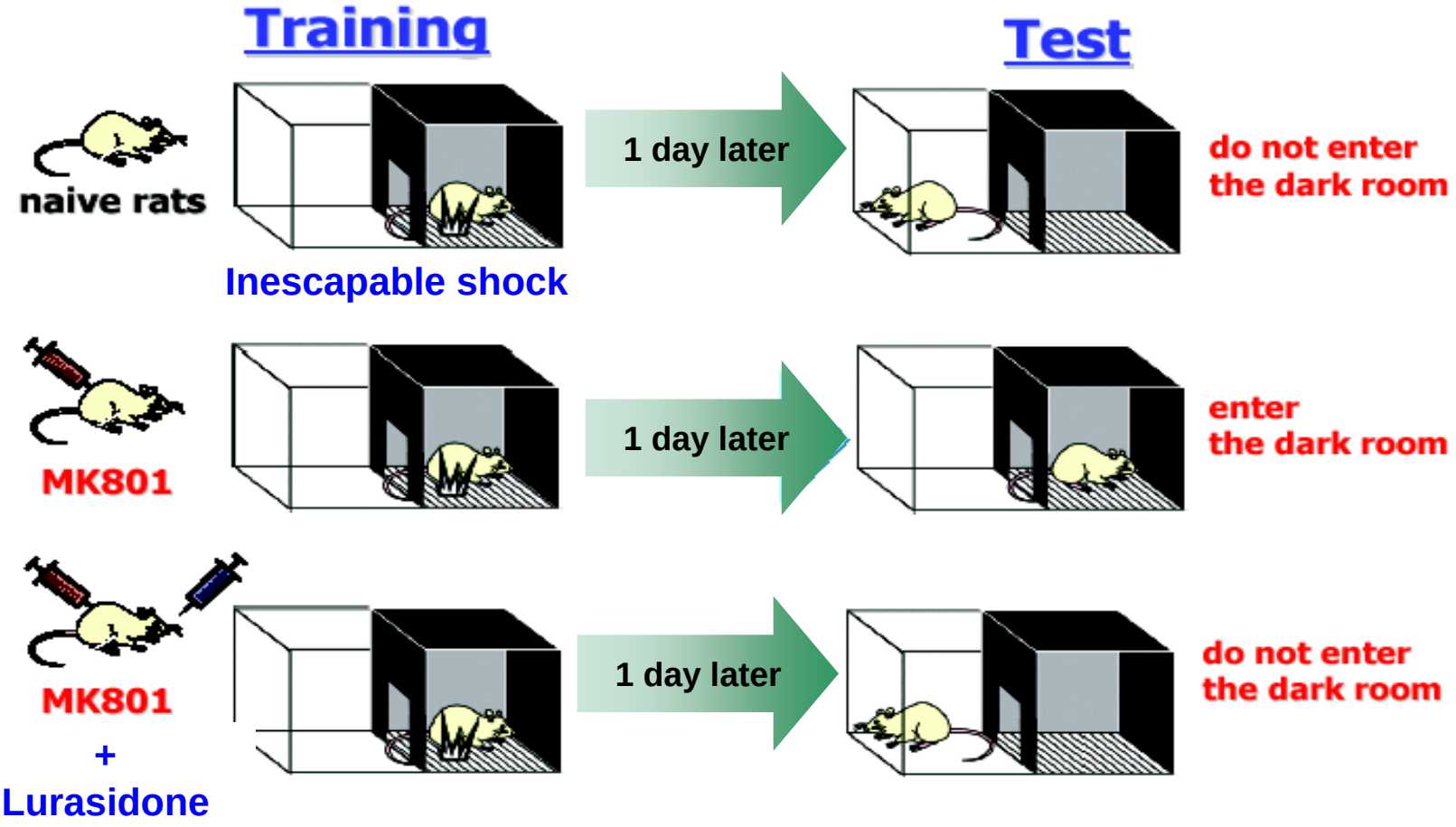
Abstract

Lurasidone (SM-13496) is a novel atypical antipsychotic with high affinities to dopamine D_2, serotonin 5-HT_7, 5-HT_{2A}, 5-HT_{1A} receptors and α_{2C} adrenoceptor. In this study, the effects of lurasidone on the rat passive-avoidance response and its impairment by the *N*-methyl-D-aspartate (NMDA) receptor antagonist MK-801 (dizocilpine) were evaluated and compared with those of other antipsychotics. The passive-avoidance response was examined by measuring the step-through latency, 1 day after the animals received foot-shock training. When given before the training session, lurasidone did not affect the passive-avoidance response at any dose tested (1–30 mg/kg, p.o.). All the other atypical antipsychotics examined (*i.e.*, risperidone, olanzapine, quetiapine, clozapine and aripiprazole), however, significantly reduced the step-through latency at relatively high doses. A pre-training administration of lurasidone significantly and dose-dependently reversed the MK-801-induced impairment of the passive-avoidance response. At doses lower than those that affected the passive-avoidance response, risperidone, quetiapine, and clozapine partially reduced the MK-801-induced impairment, whereas haloperidol, olanzapine, and aripiprazole were inactive. In addition, the post-training administration of lurasidone was as effective in countering the MK-801 effect as the pre-training administration, suggesting that lurasidone worked, at least in part, by restoring the memory consolidation process disrupted by MK-801. These results suggest that lurasidone is superior to other antipsychotics in improving the MK-801-induced memory impairment and may be clinically useful for treating cognitive impairments in schizophrenia.

Keywords: Learning; Memory; NMDA receptor antagonist; Serotonin-dopamine antagonist; Schizophrenia; Passive avoidance

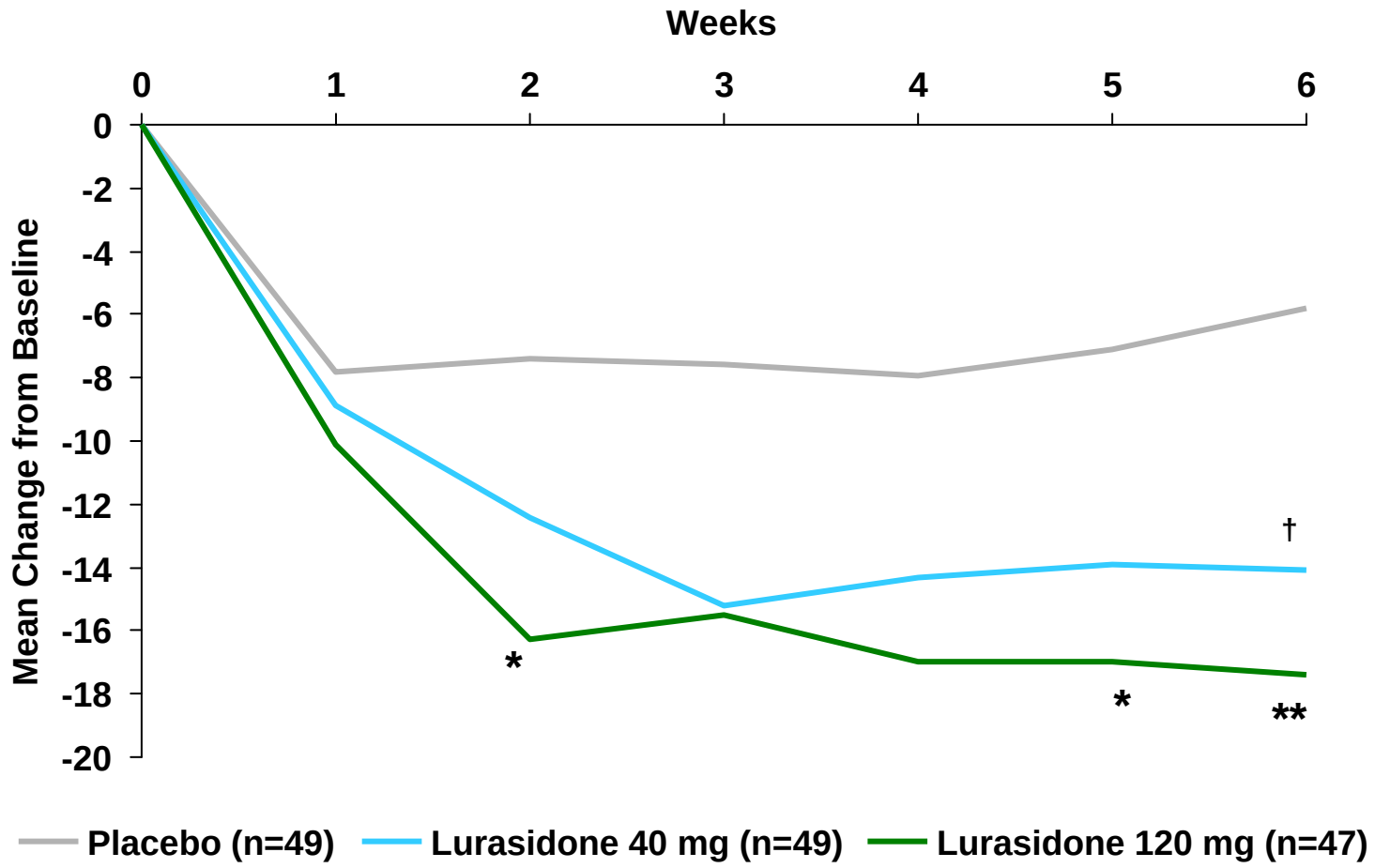
Lurasidone Reverses MK-801 Induced Learning & Memory Impairment



Lurasidone Phase 2 Studies

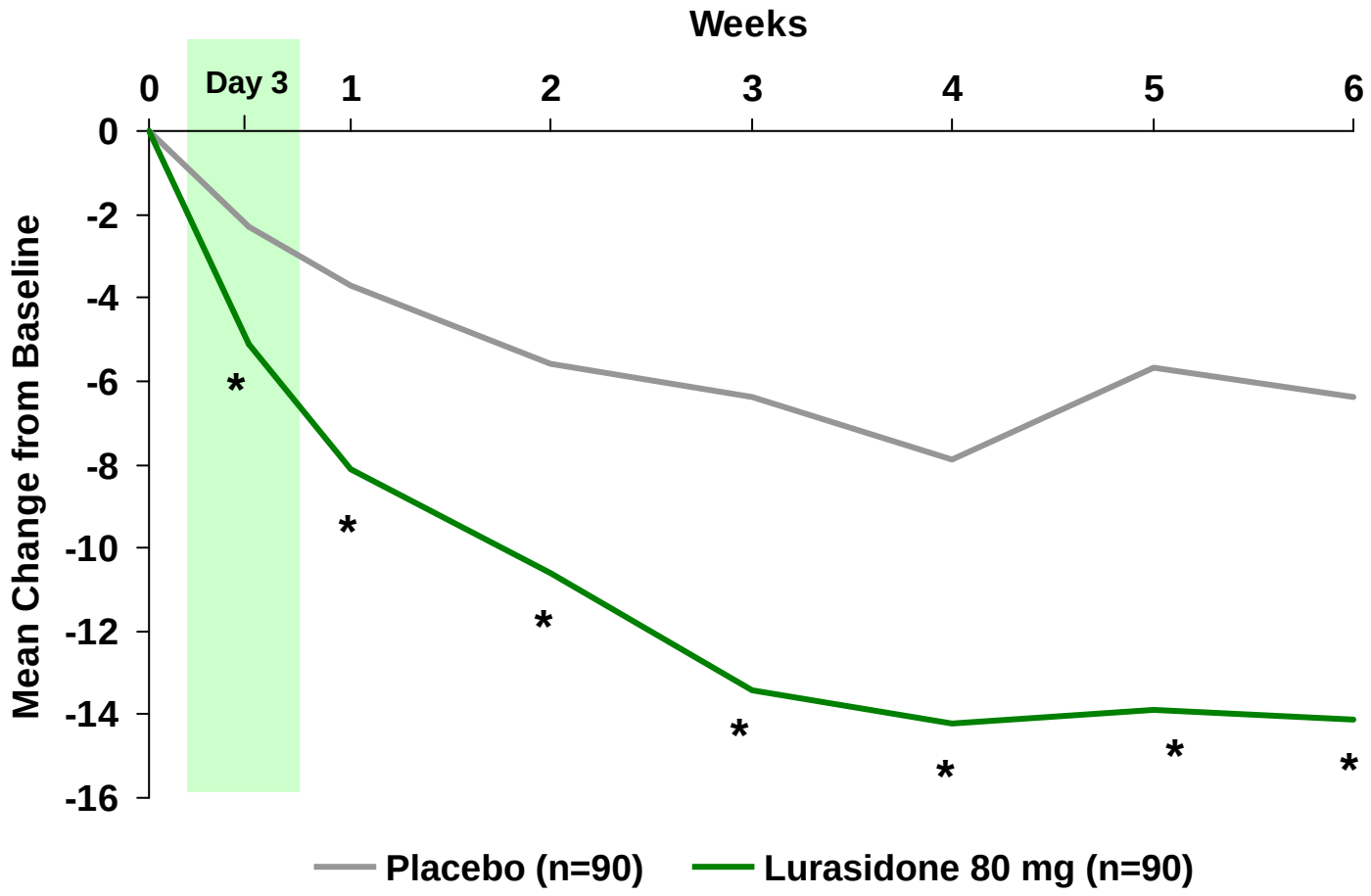
- DSM-IV schizophrenia, requiring hospitalization
- 6-week, randomized, double-blind, placebo-controlled
- All studies involved US sites only
- Primary end point: BPRS derived from PANSS (BPRSd)
- Hospitalization required for 2-4 weeks

Study 006: PANSS Total Score (ITT-LOCF)



†p=0.06
**p≤0.05; **p=0.01*
Ogasa et al. ICOSR 2003

Study 196:
PANSS Total Score (ITT-LOCF)



*p≤0.01

Nakamura M et al. J Clin Psych, 2009

DAINIPPON SUMITOMO PHARMA

Lurasidone in the Treatment of Acute Schizophrenia: A Double-Blind, Placebo-Controlled Trial

Mitsutaka Nakamura, Ph.D.; Masaaki Ogasa, M.S.; John Guarino, Ph.D.; Debra Phillips, A.S.; Joseph Severs, M.S.; Josephine Cucchiaro, Ph.D.; and Antony Loebel, M.D.

Objective: Lurasidone is a novel psychotropic agent with high affinity for D_2 and 5-HT_{2A} receptors, as well as for receptors implicated in the enhancement of cognition and mood and the reduction of negative symptoms (5-HT_7, 5-HT_{1A}, and α_{2c}). The objective of the study was to evaluate the safety and efficacy of lurasidone in patients hospitalized for an acute exacerbation of DSM-IV–defined schizophrenia.

Method: Patients were randomly assigned to 6 weeks of double-blind treatment with a fixed dose of lurasidone 80 mg (N = 90, 75.6% male, mean age = 39.7 years, mean baseline score on the Brief Psychiatric Rating Scale derived from the Positive and Negative Syndrome Scale [BPRSd] = 55.1) or placebo (N = 90, 77.8% male, mean age = 41.9 years, mean BPRSd score = 56.1). The primary efficacy measure was the BPRSd. The study was conducted from May to December 2004.

Results: At day 42, last-observation-carried-forward endpoint, treatment with lurasidone was associated with significant improvement compared to placebo on the BPRSd (least squares mean ± SE = –8.9 ± 1.3 vs. –4.2 ± 1.4; p = .012), as well as on all secondary efficacy measures, including the PANSS total score (–14.1 ± 2.1 vs. –5.5 ± 2.2; p = .004) and the PANSS positive (–4.3 ± 0.7 vs. –1.7 ± 0.7; p = .006), negative (–2.9 ± 0.5 vs. –1.3 ± 0.5; p = .025), and general psychopathology (–7.0 ± 1.1 vs. –2.7 ± 1.2; p = .0061) subscales. Significant improvement was seen as early as day 3, based on BPRSd, PANSS, and Clinical Global Impressions-Severity of Illness assessments. Treatment with lurasidone was generally well tolerated and was not associated with adverse changes in metabolic or electrocardiogram parameters. There were no clinically significant differences between lurasidone and placebo in objective measures of extrapyramidal symptoms.

Conclusions: The results of this study suggest that the novel psychotropic agent lurasidone is a safe and effective treatment for patients with an acute exacerbation of schizophrenia.

Trial Registration: clinicaltrials.gov Identifier: NCT00088634

J Clin Psychiatry

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From Dainippon Sumitomo Pharma Co, Ltd, Osaka, Japan (Dr. Nakamura); and Dainippon Sumitomo Pharma America, Inc, Fort Lee, N.J. (Messrs. Ogasa and Severs; Drs. Guarino, Cucchiaro, and Loebel; and Ms. Phillips).

Dr. Nakamura is currently employed at Setsunan University, Osaka, Japan.

This study was funded by Dainippon Sumitomo Pharma America, Inc, Fort Lee, N.J.

The data reported in the current manuscript were previously presented, in part, at the International Congress on Schizophrenia Research; March 27–28, 2007; Colorado Springs, Colo.

Acknowledgments are listed at the end of the article.

Messrs. Ogasa and Severs; Drs. Guarino, Cucchiaro, and Loebel; and Ms. Phillips are full-time employees of Dainippon Sumitomo Pharma America, Inc. Dr. Nakamura was an employee of Dainippon Sumitomo Pharma Co, Ltd, at the time the study was conducted.

Corresponding author and reprints: Masaaki Ogasa, M.S., Dainippon Sumitomo Pharma America, Inc, One Bridge Plaza, Suite 510, Fort Lee, NJ 07024 (e-mail: mogasa@dsp-a.com).

Lurasidone (SM-13496, (3a*R*,4*S*,7*R*,7a*S*)- 2-{(1*R*,2*R*)-2-[4-(1,2-benzisothiazol-3-yl) piperazin-1-ylmethyl] cyclohexylmethyl}hexahydro-4, 7-methano-2*H*-isoindole-1,3-dione hydrochloride) is a novel psychotropic agent discovered by Dainippon Sumitomo Pharma research laboratories in Japan. Lurasidone has a high affinity for dopamine D_2 and serotonin 5-HT_{2A} receptors. However, despite its potent D_2-antagonist activity, treatment with lurasidone is associated with minimal extrapyramidal side effects in animal models.[1]

Compared with other atypical antipsychotic agents, lurasidone has similar binding affinities for D_2 and 5-HT_{2A} receptor subtypes, but greater affinity for serotonin 5-HT_7, 5-HT_{1A}, and norepinephrine α_{2c} receptor subtypes.[1] Lurasidone has little affinity for norepinephrine α_1 and no affinity for histamine H_1 or cholinergic M_1 receptors.[1]

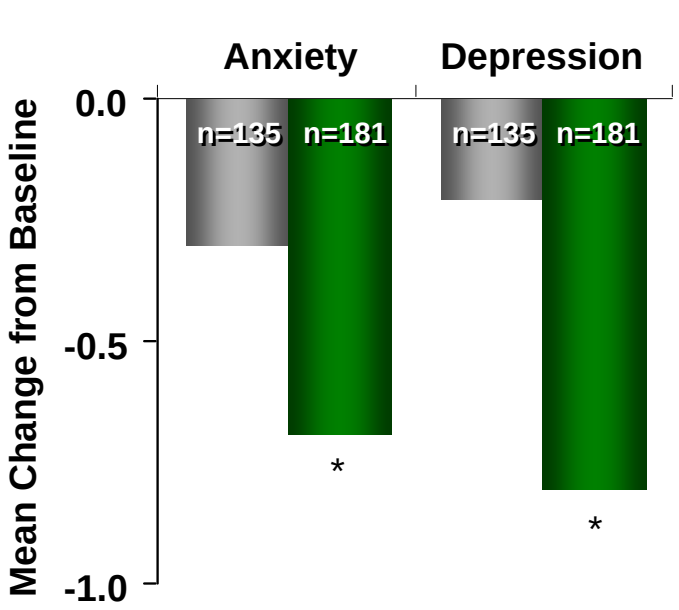
The pharmacologic and preclinical profile of lurasidone suggests that it may be an effective antipsychotic drug in humans, with a reduced potential for histamine H_1– and 5-HT_{2C}–mediated weight gain, histamine H_1– and cholinergic M_1–mediated central nervous system (CNS) depression, and α_1 adrenergic–mediated orthostatic hypotension.

The primary objective of the current study was to evaluate the efficacy of lurasidone in the treatment of patients suffering from an acute exacerbation of schizophrenia. The secondary objectives were to assess the safety and

Depressive Symptom Change: Phase 2 Data

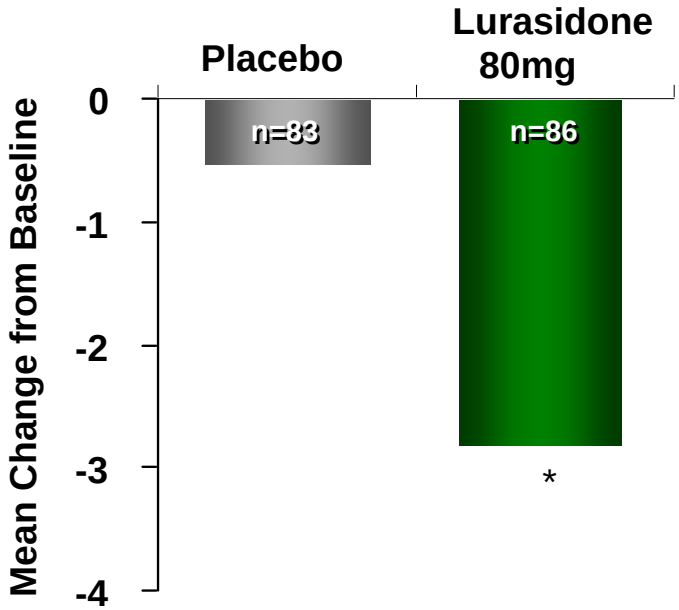
Studies 006, 196

PANSS Anxiety/Depression



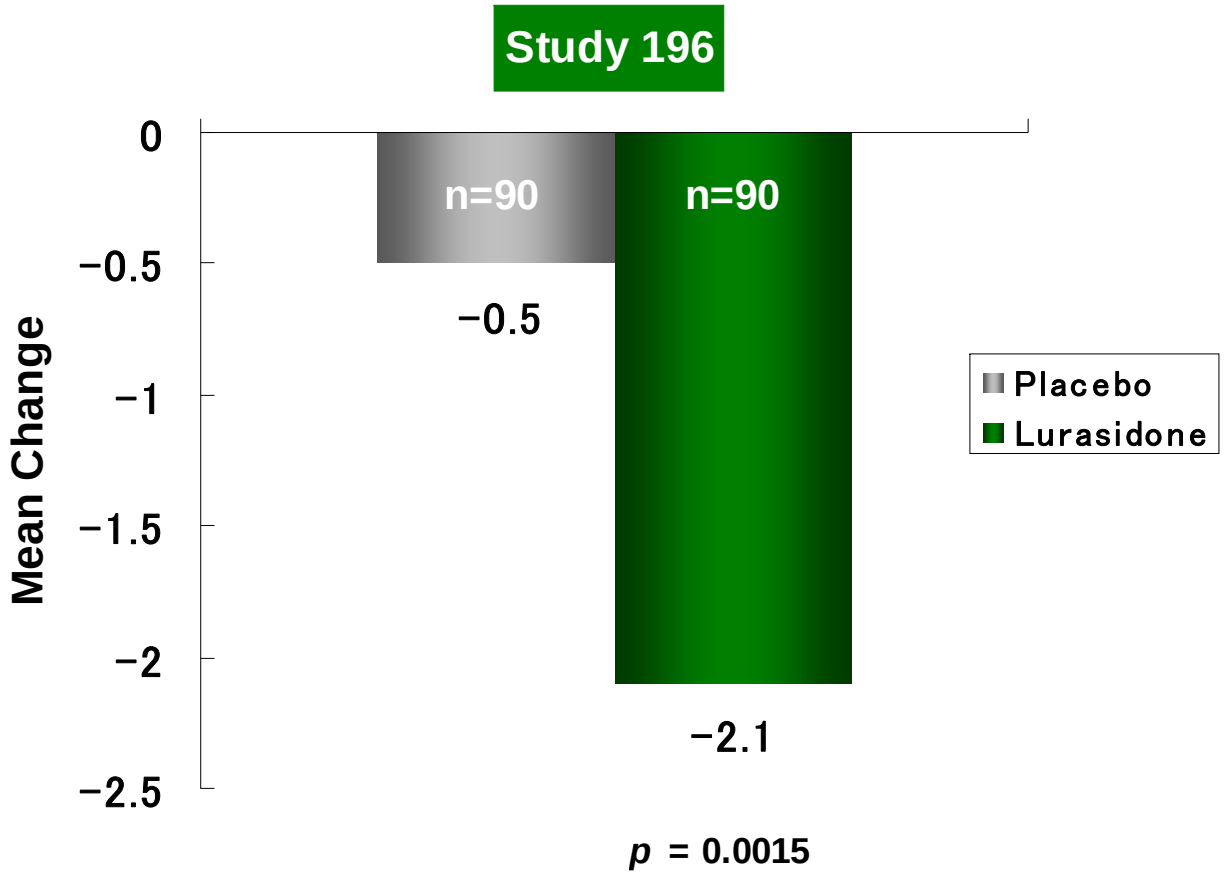
Study 196

MADRS



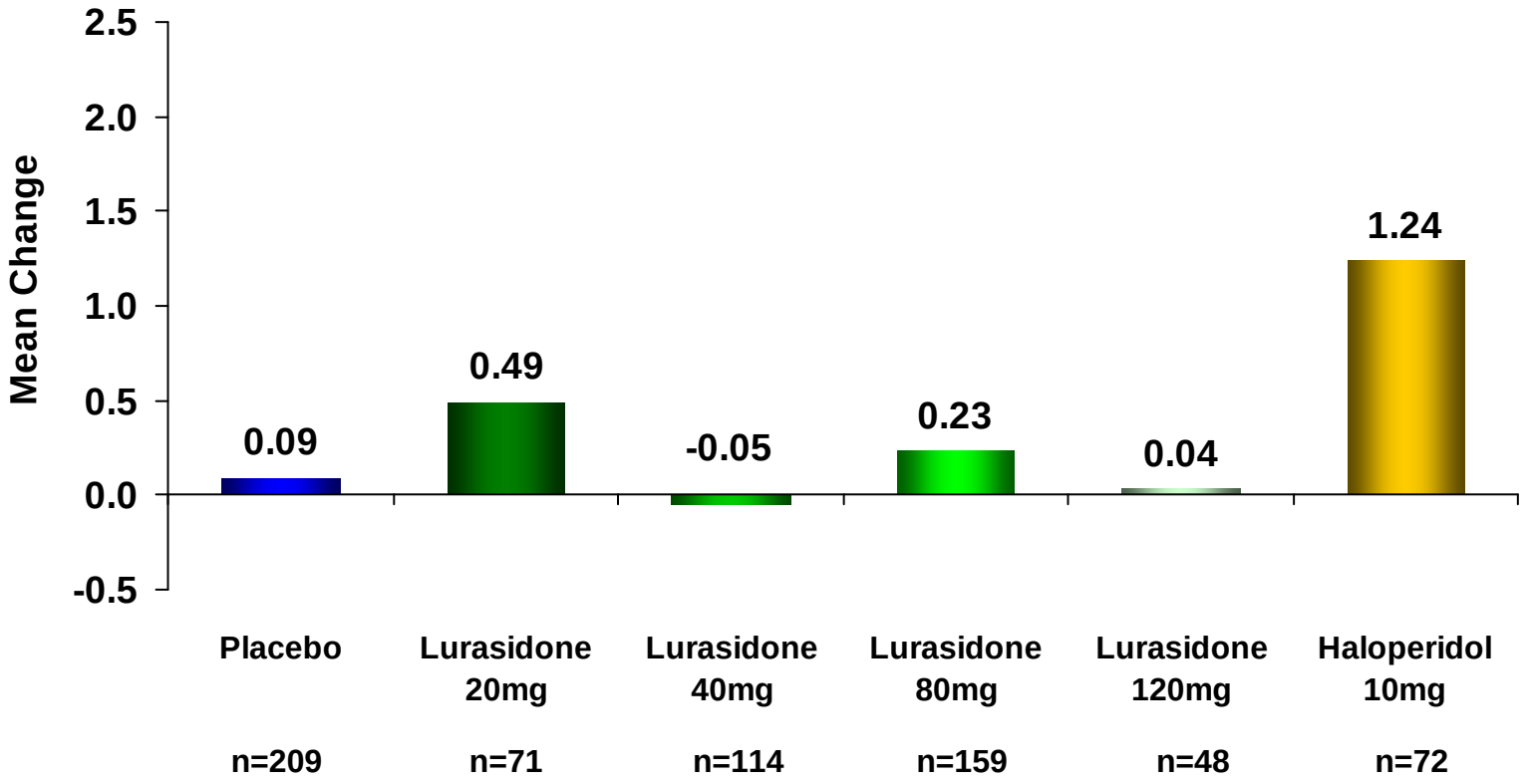
Baseline: Placebo 14.5, Lurasidone 14.2
LOCF at end point
*p<0.05 using ANCOVA

PANSS Cognitive Subscale



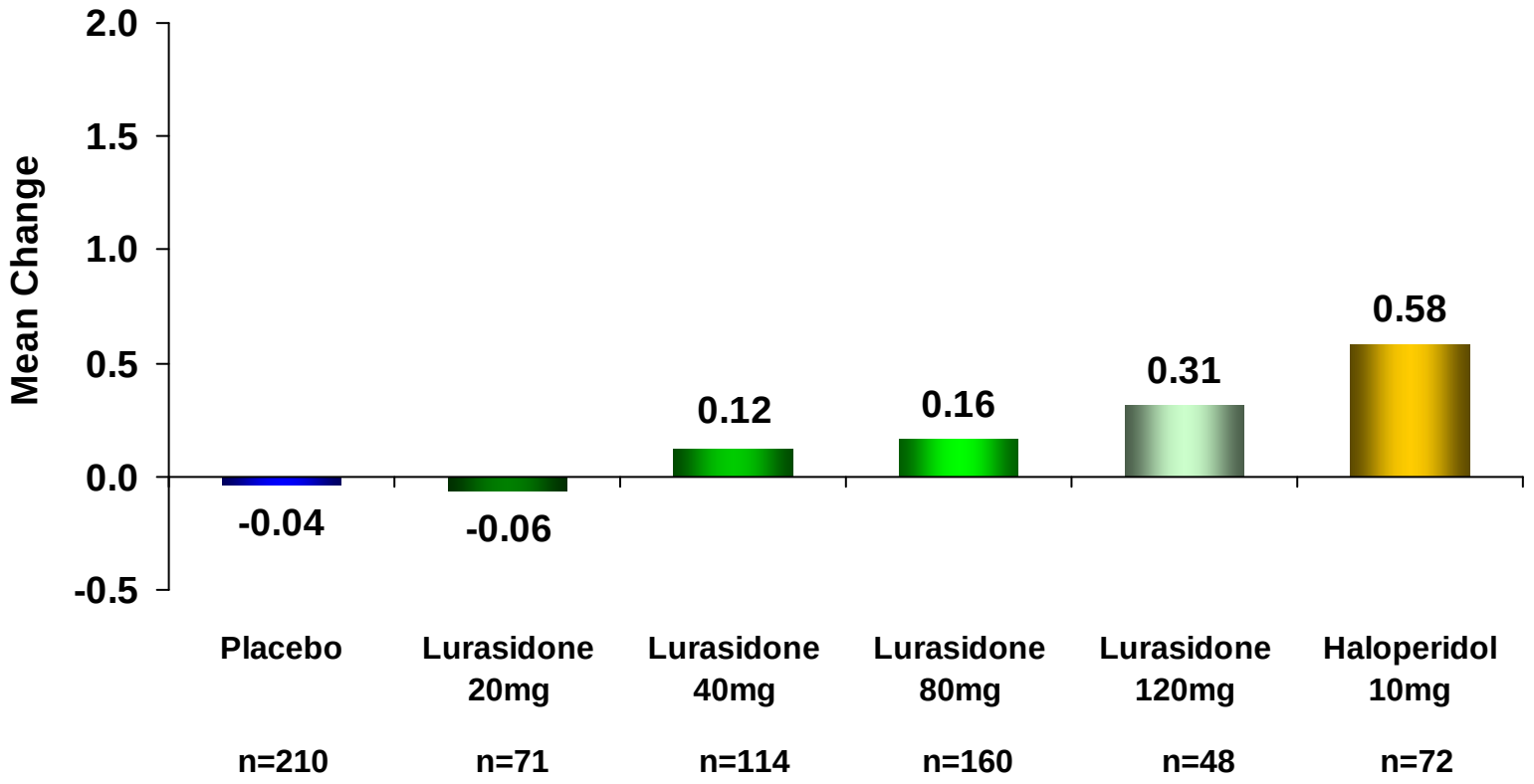
Nakamura M et al. J Clin Psych, 2009

Simpson Angus Scale (SAS): Pooled Phase 2 Studies*



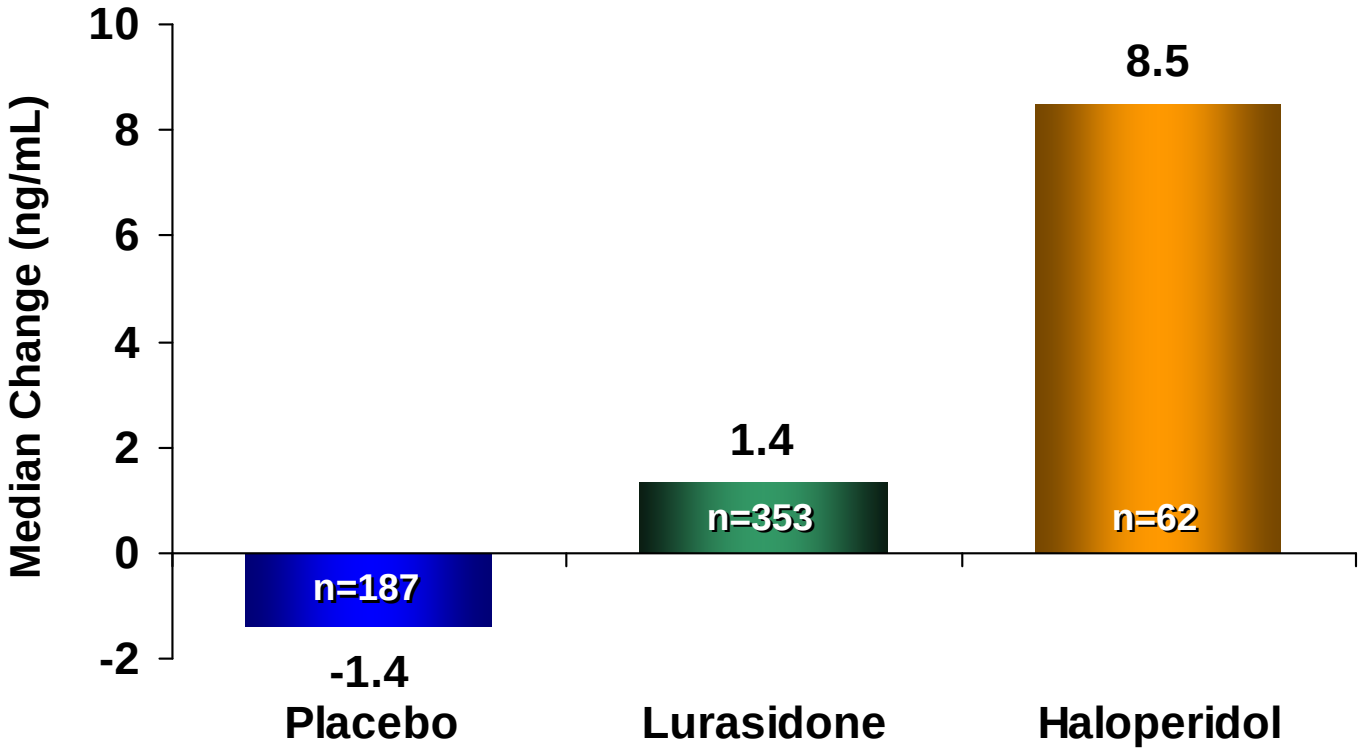
**Studies 006, 049, 196*
SAS scored 0-5 on 10 items for max possible score of 50

Barnes Akathisia Rating Scale (BARS): Pooled Phase 2 Studies*



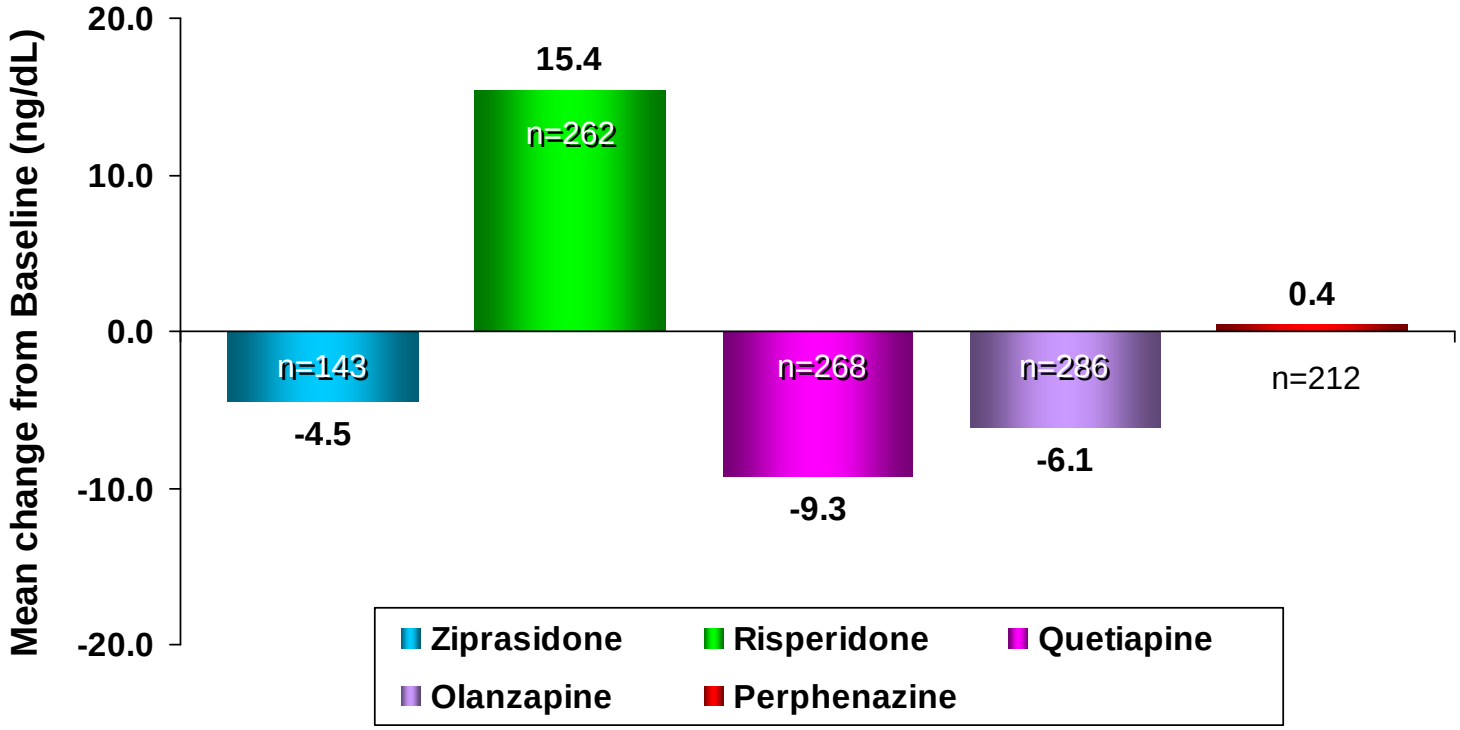
*Studies 006, 049, 196
BAS scored 0-5 on Global Clinical Assessment of akathisia; maximum score= 5

Serum Prolactin: Pooled Phase 2 Studies*



*Studies 006, 049, 196

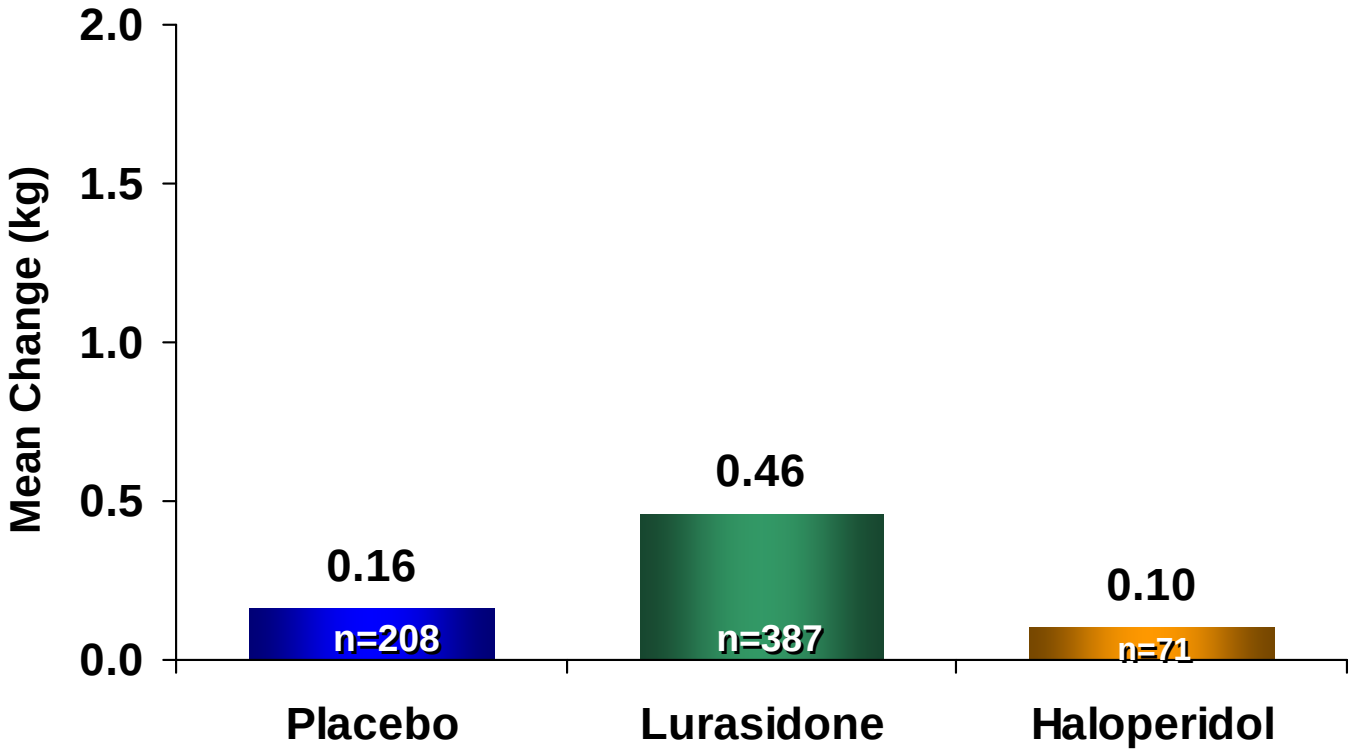
CATIE Schizophrenia Study: Prolactin



Mean Modal Dose	
Ziprasidone	112.8 mg/d
Risperidone	3.9 mg/d
Quetiapine	543.4 mg/d
Olanzapine	20.1 mg/d
Perphenazine	20.8 mg/d

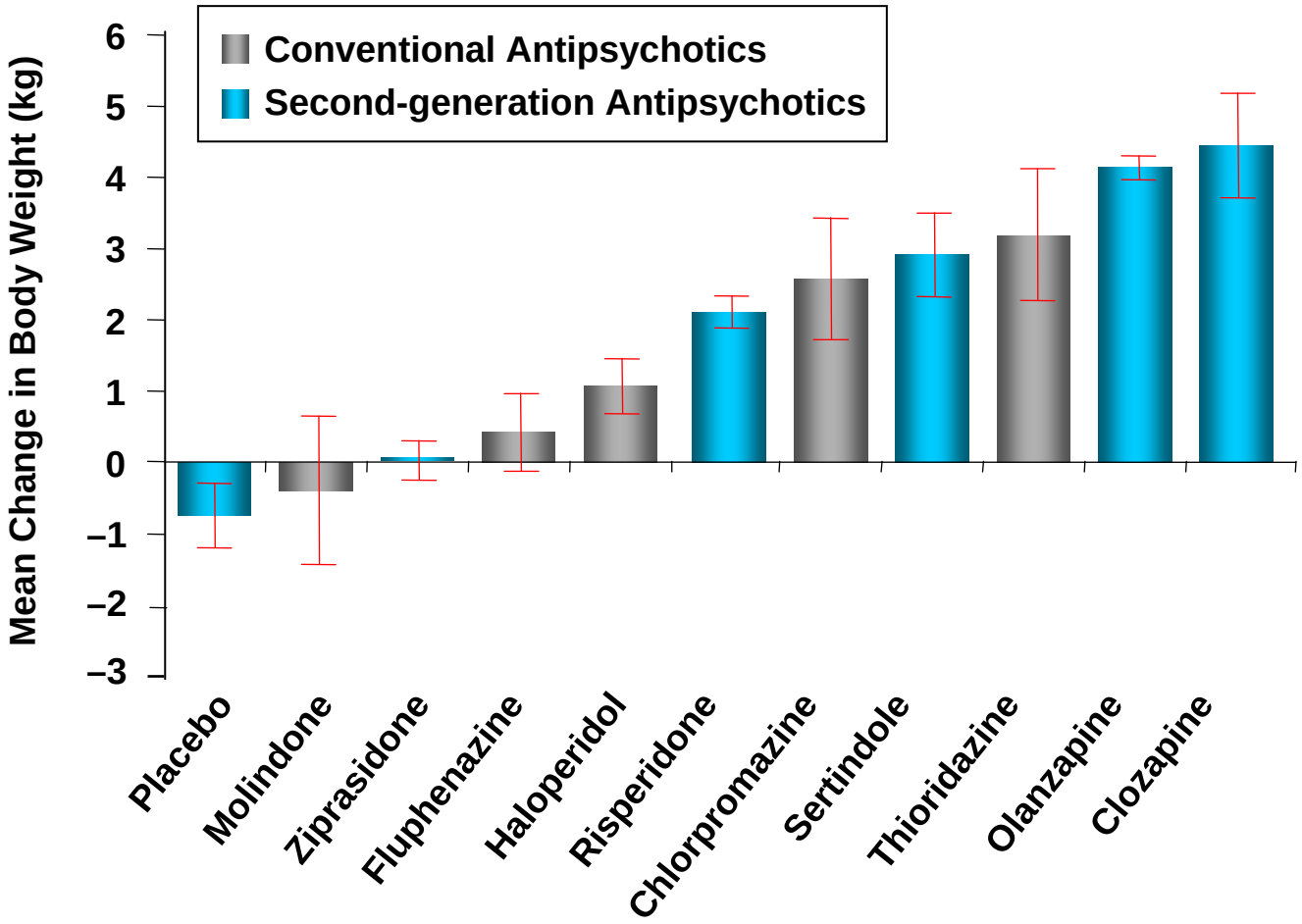
Lieberman JA et al. *N Engl J Med* 2005;353:1209-1223.

Weight Gain: Pooled Phase 2 Studies*



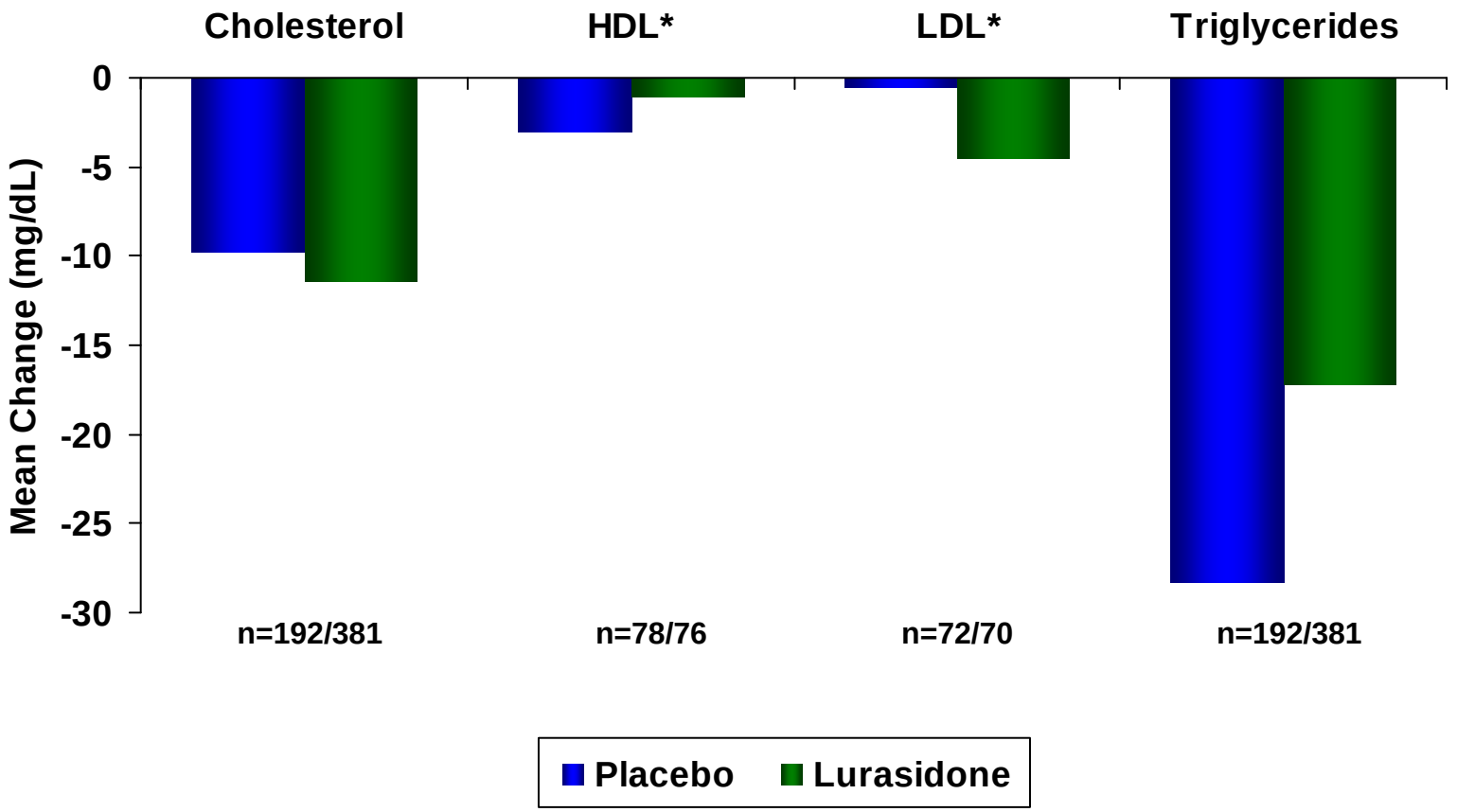
*Studies 006, 049, 196

Estimated Mean Weight Gain at 10 Weeks with Antipsychotics



Allison DB et al. *Am J Psychiatry*. 1999;156:1686-1696

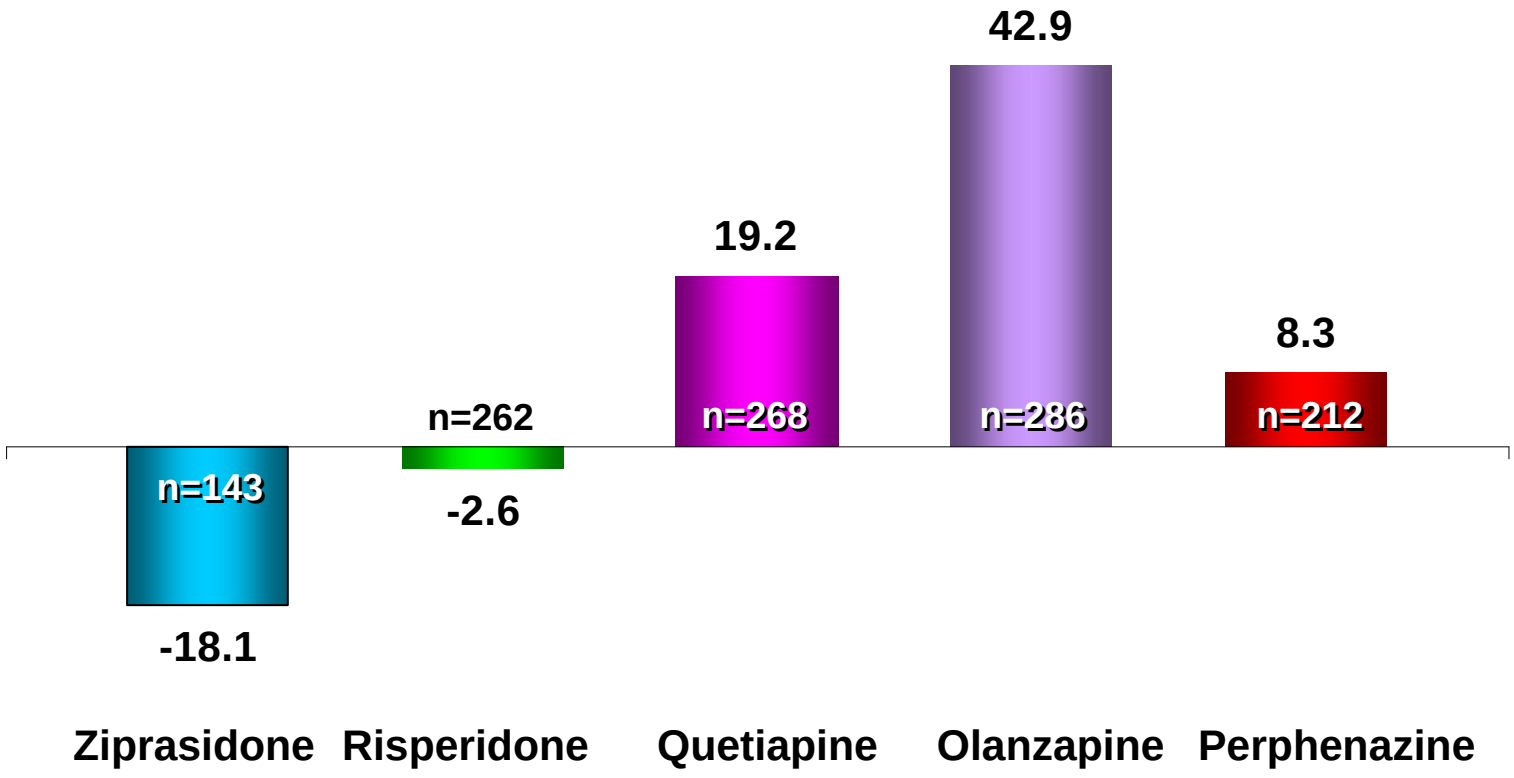
Lipid Profile: Pooled Phase 2 Studies#



#*Studies 006, 049 and 196*
**Not measured in study 049*
Fasting measures obtained per protocol

CATIE Schizophrenia Study: Triglycerides

Mean Change from Baseline (mg/dL)



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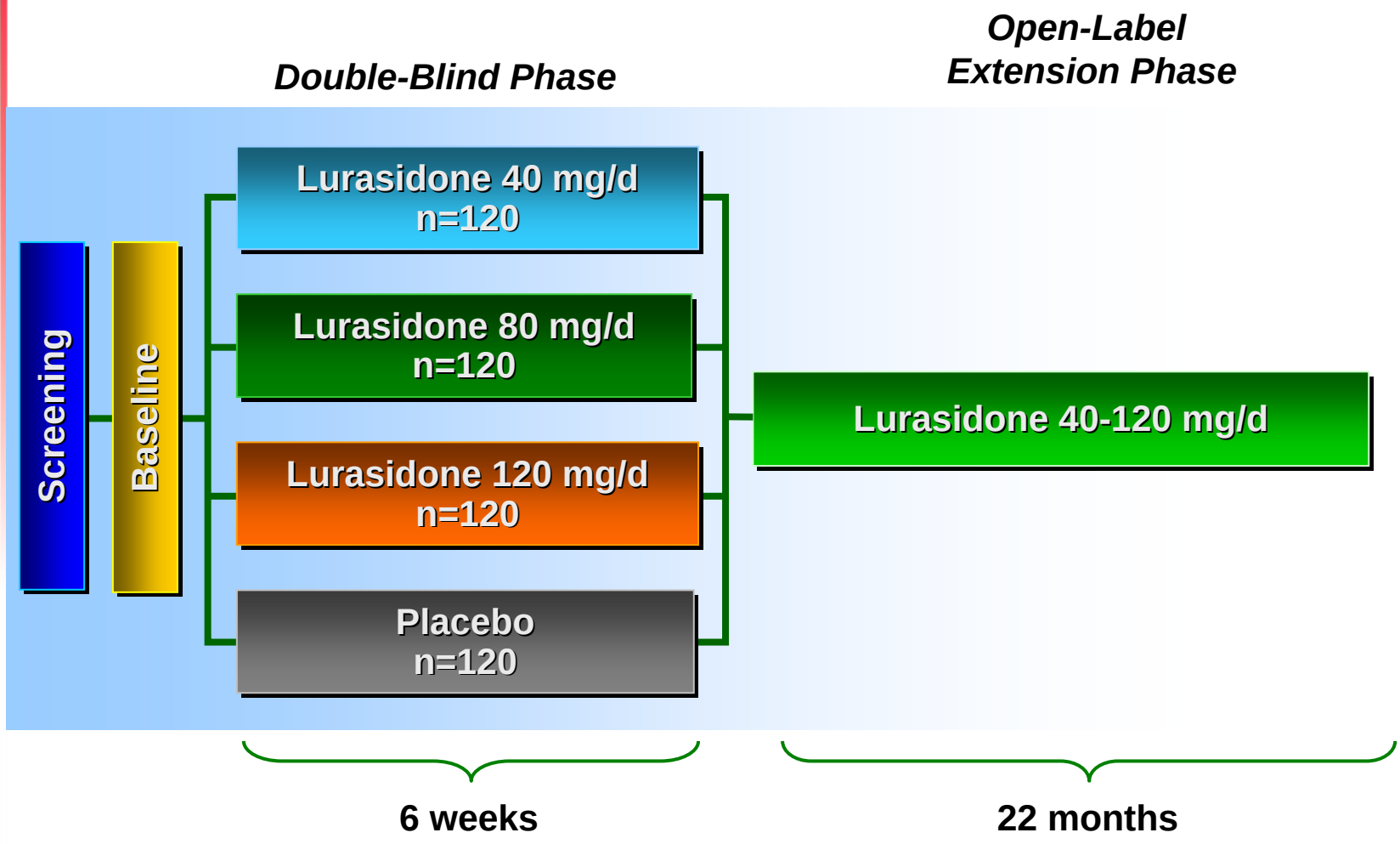
Lieberman JA et al. N Engl J Med 2005;353:1209-1223

A Randomized, Double-Blind Study Comparing 3 Fixed Doses of Lurasidone to Placebo in Patients With Acute Schizophrenia: A Phase 3 Trial

Study D1050229 (PEARL 1)

PEARL 1: Study Design



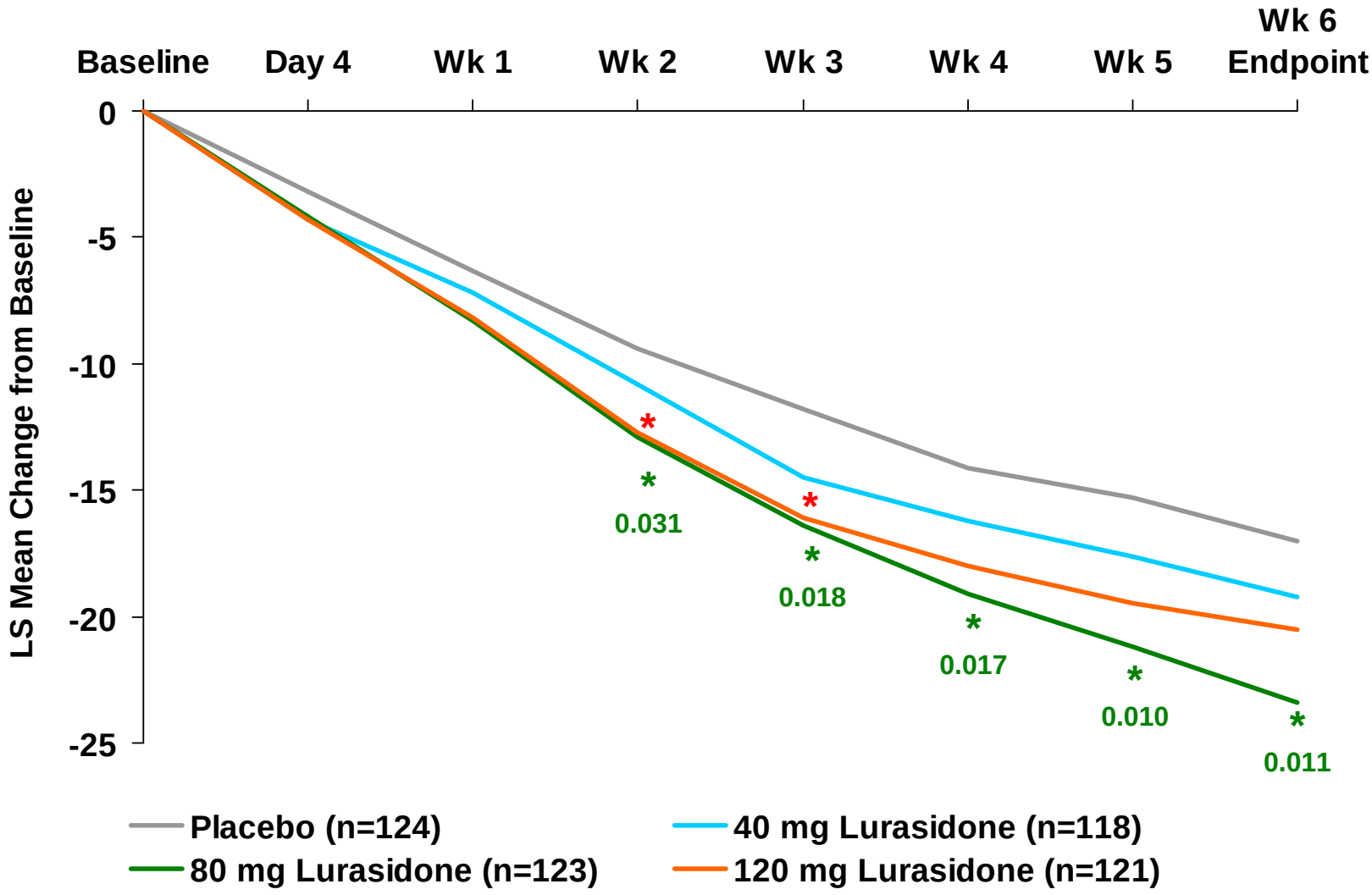
Key Entry Criteria

- DSM-IV schizophrenia
  - Acute exacerbation ≤2 months
  - ≤2 weeks hospitalization prior to screening
  - No significant improvement between screening and baseline
- Age 18-75 yrs
- Baseline Assessments
  - PANSS score ≥80; ≥4 (moderate) on at least 2 positive psychotic items
  - CGI-S ≥4
- Medically stable
- Not treatment resistant
  - Based on failure to respond to ≥2 prior antipsychotic trials

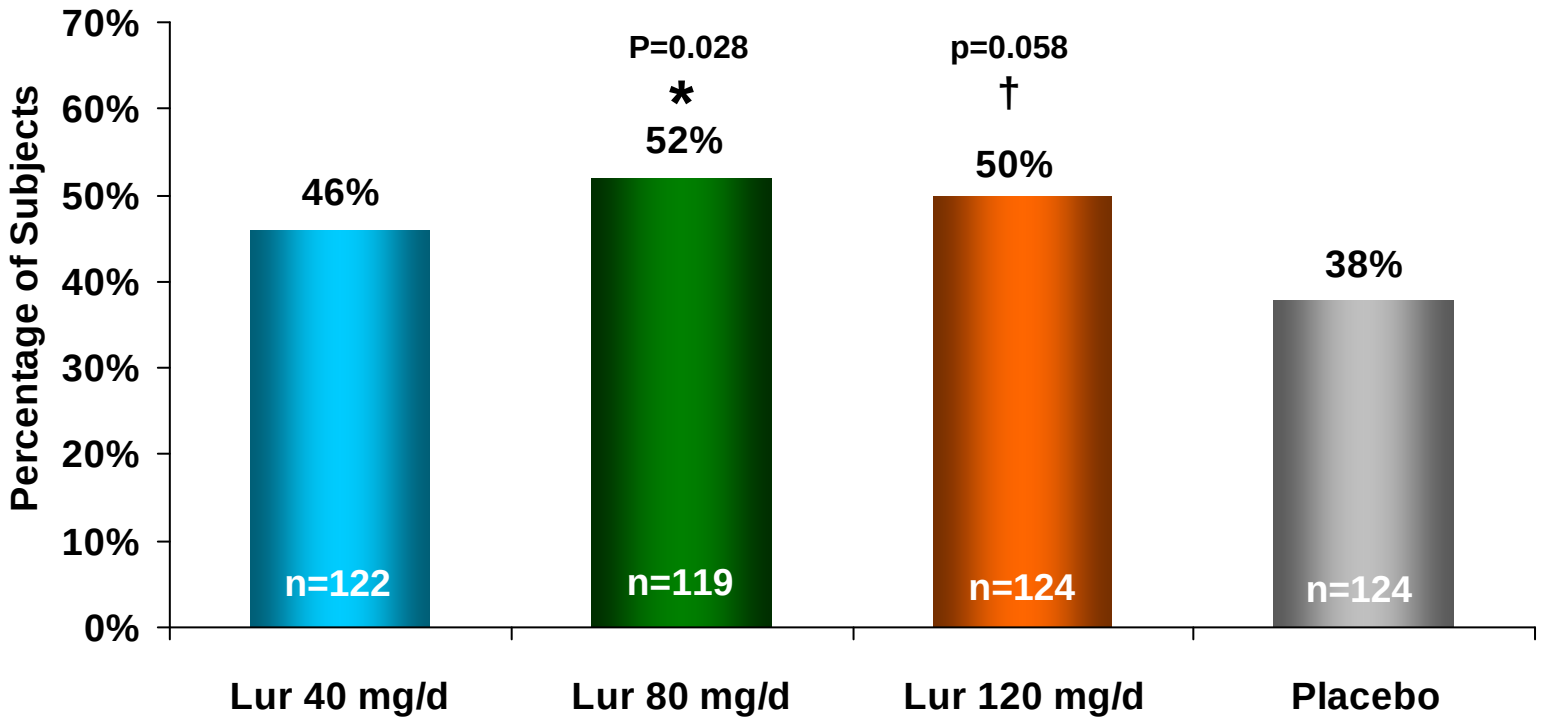
Efficacy Endpoints

- Primary endpoint
  - Baseline to 6-week/endpoint change in PANSS Total Score, using mixed model repeated measures (MMRM) analysis adjusted by Hommel procedure for multiple comparisons (dose/endpoints)
  - ANCOVA LOCF used for sensitivity analysis
- Key secondary endpoint
  - CGI-S change

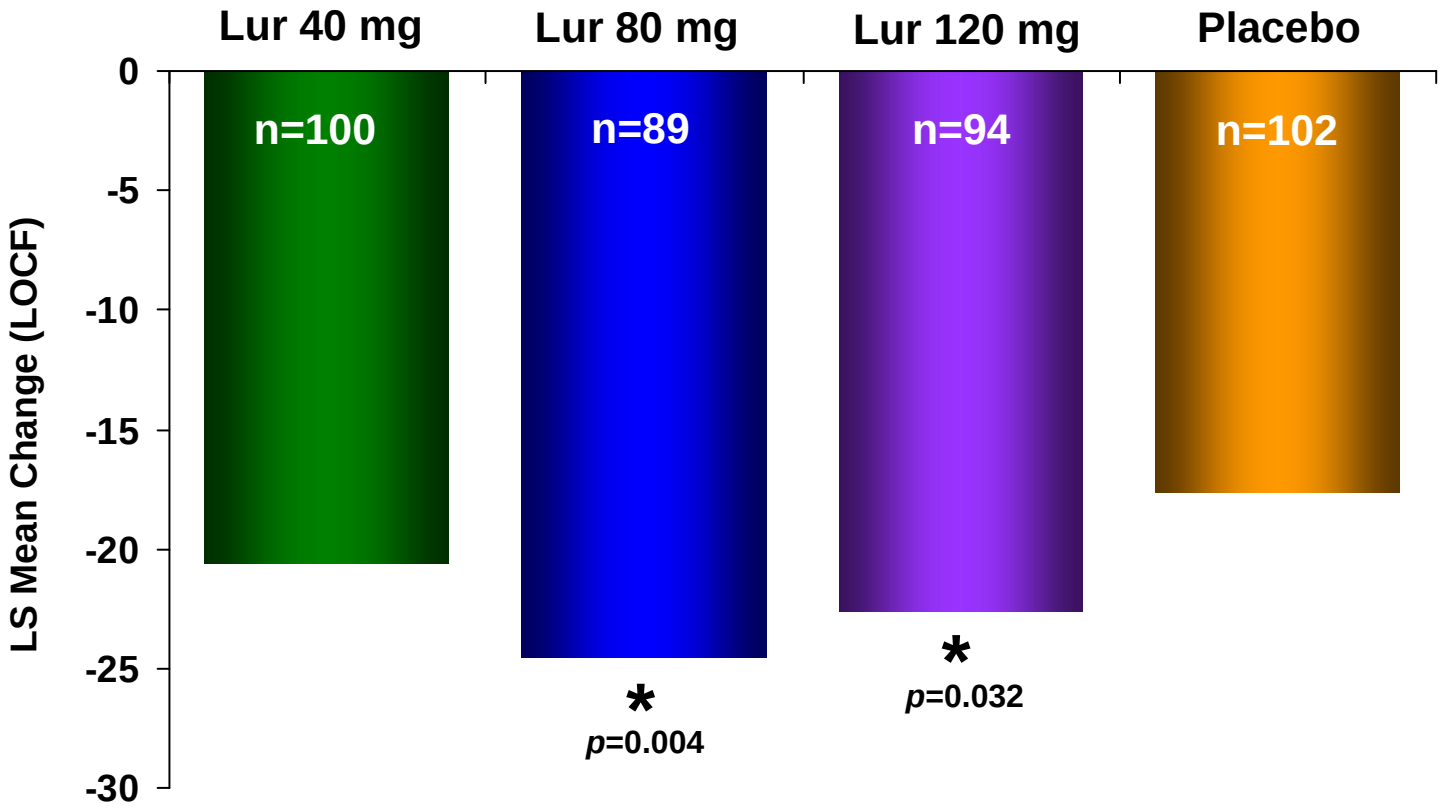
PANSS Total (MMRM)



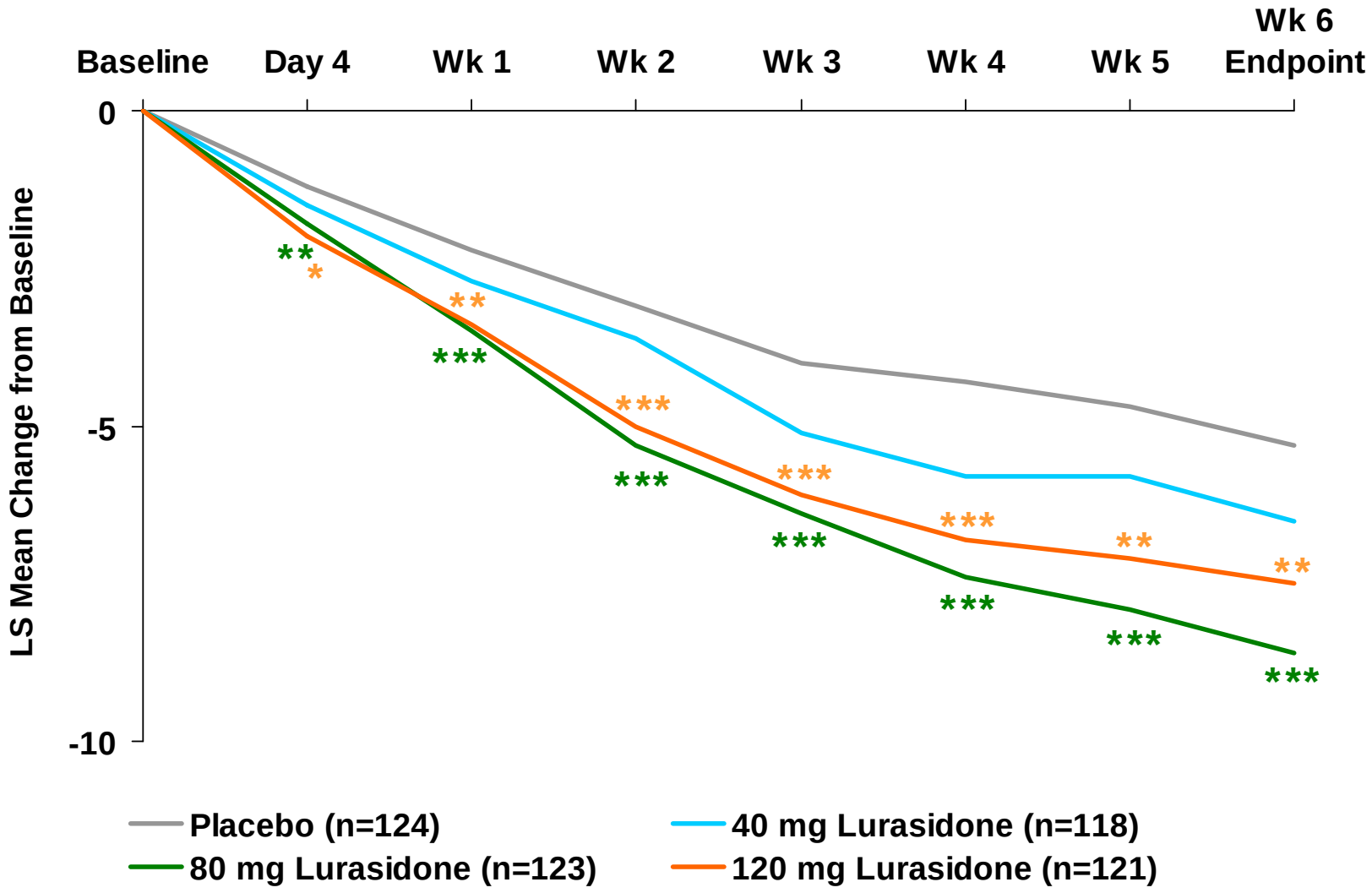
PEARL 1:
PANSS Total ≥30% Responder Analysis



PANSS Total:
Per Protocol Population

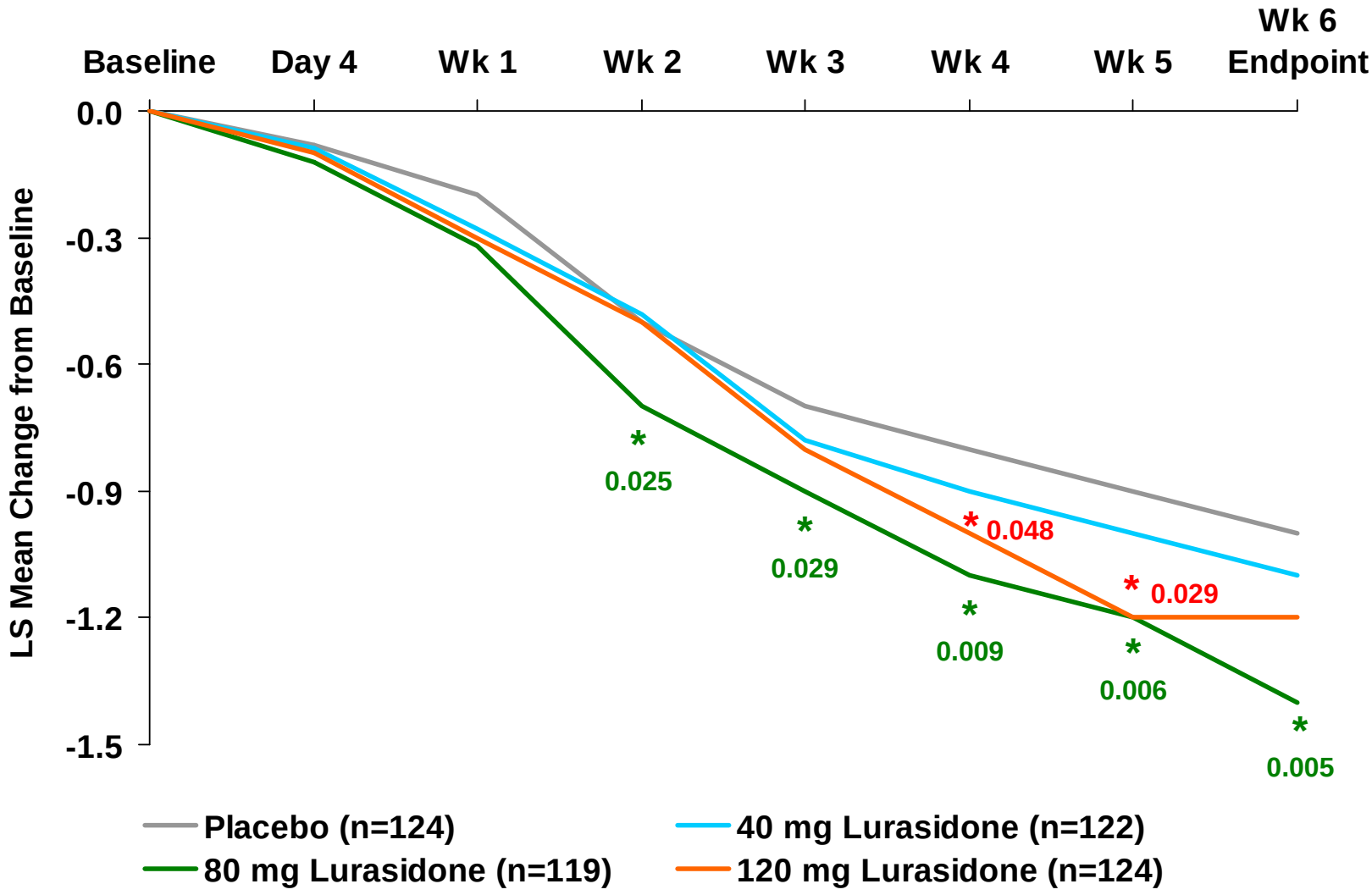


PANSS Positive Subscale (MMRM)

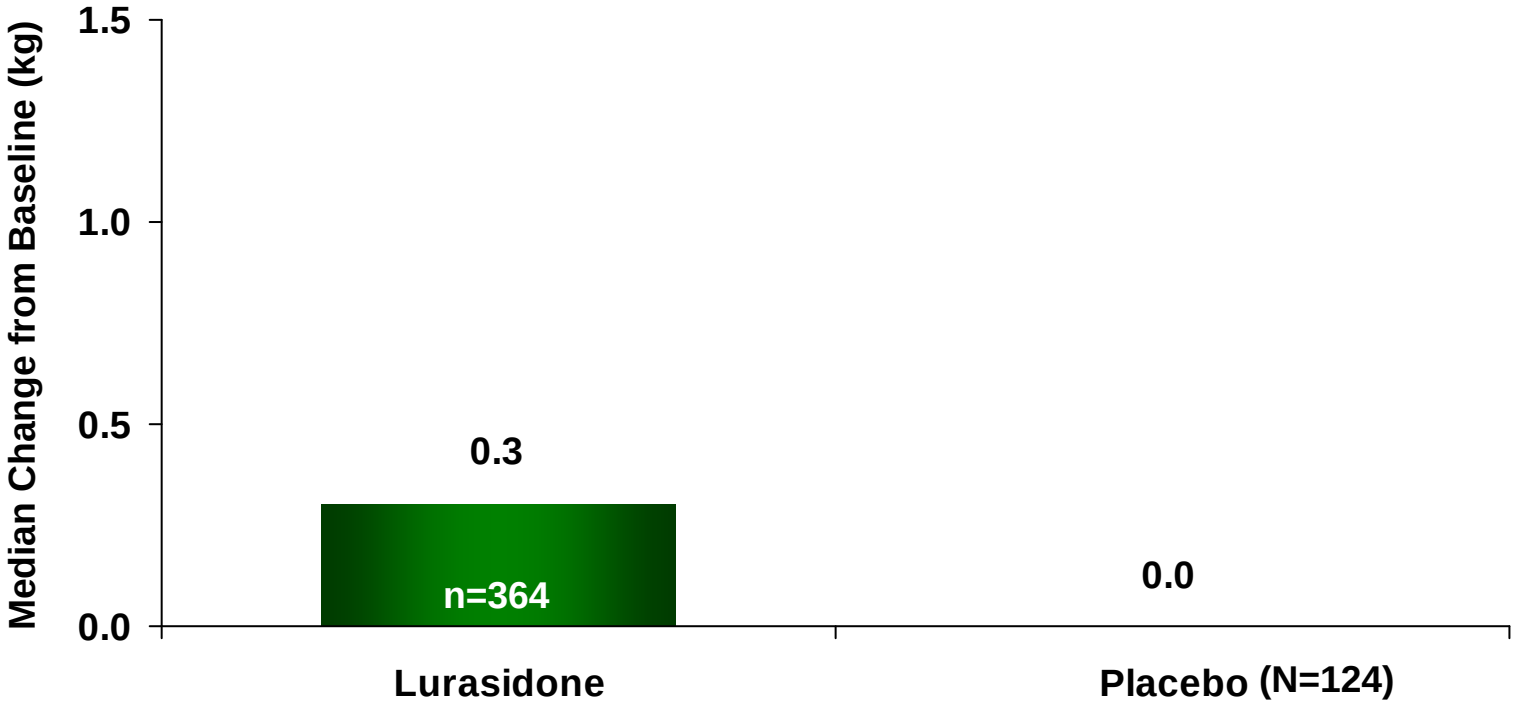


*p<0.05
**p<0.01
***p<0.001

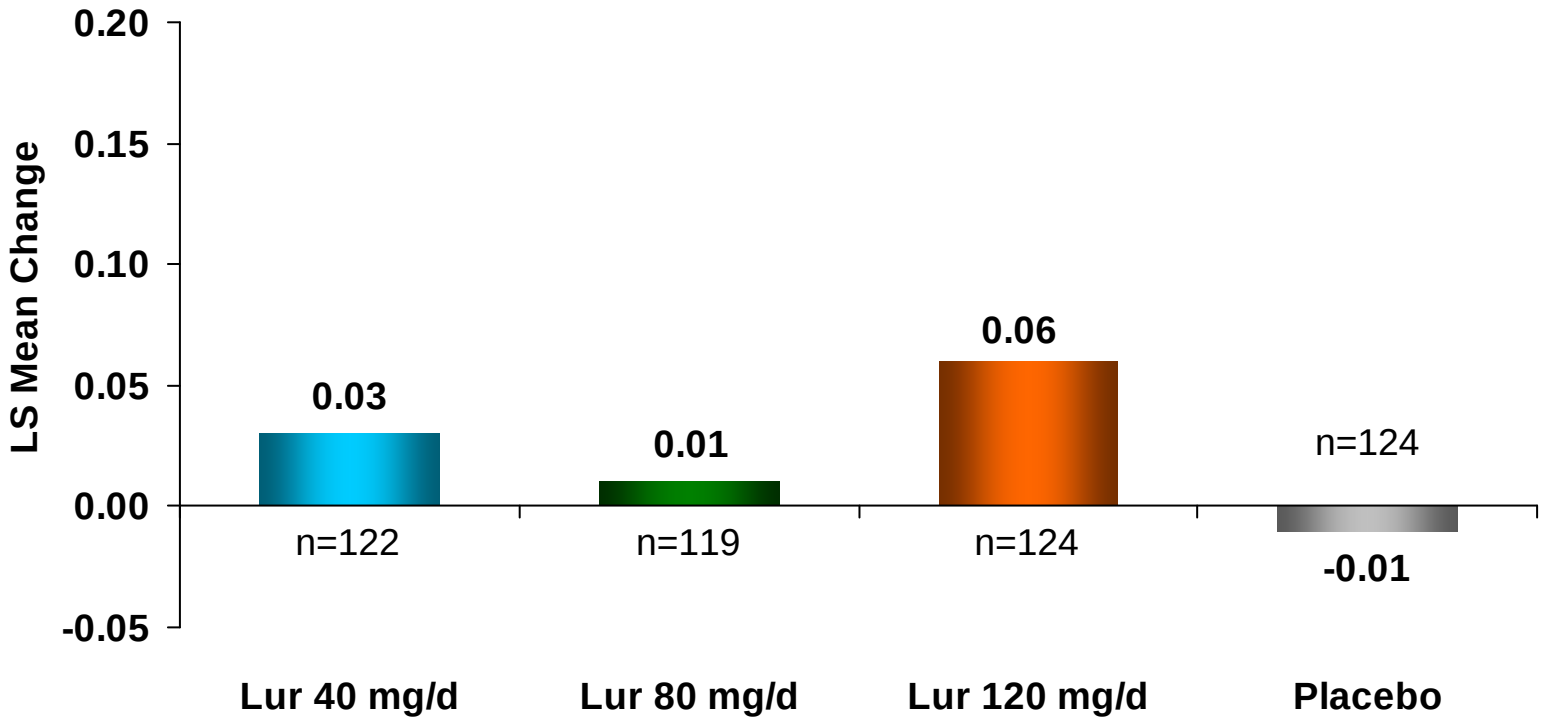
CGI-S (MMRM)


Baseline
Day 4
Wk 1
Wk 2
Wk 3
Wk 4
Wk 5
Wk 6 Endpoint
0.0
-0.3
-0.6
-0.9
-1.2
-1.5
LS Mean Change from Baseline
* 0.025
* 0.029
* 0.048
* 0.029
* 0.009
* 0.006
* 0.005
Placebo (n=124)
40 mg Lurasidone (n=122)
80 mg Lurasidone (n=119)
120 mg Lurasidone (n=124)

PEARL 1:
Weight Change (LOCF)



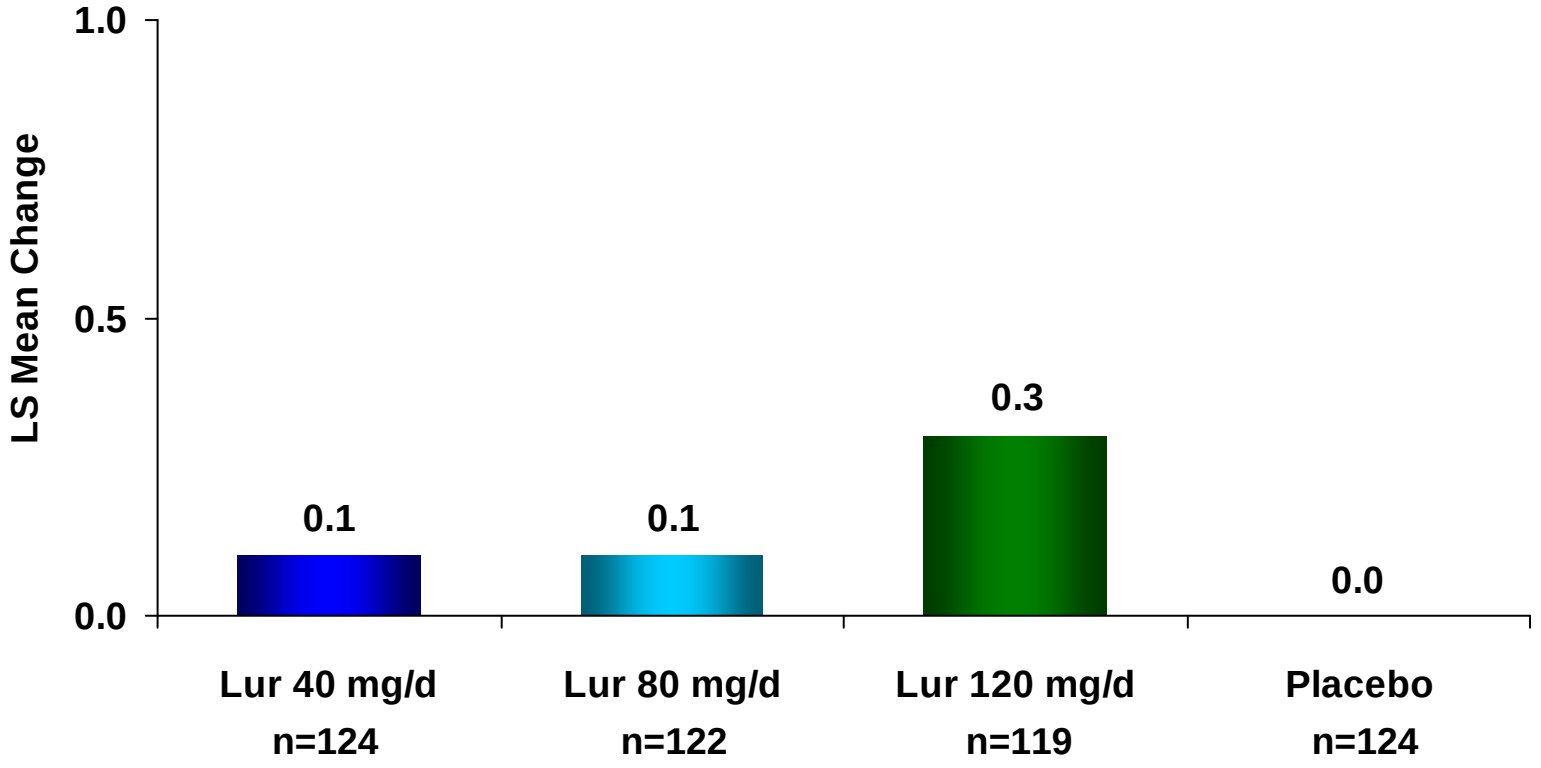
PEARL 1:
Simpson Angus Scale (SAS)



SAS scored 0-5 on 9 items for max possible score of 45

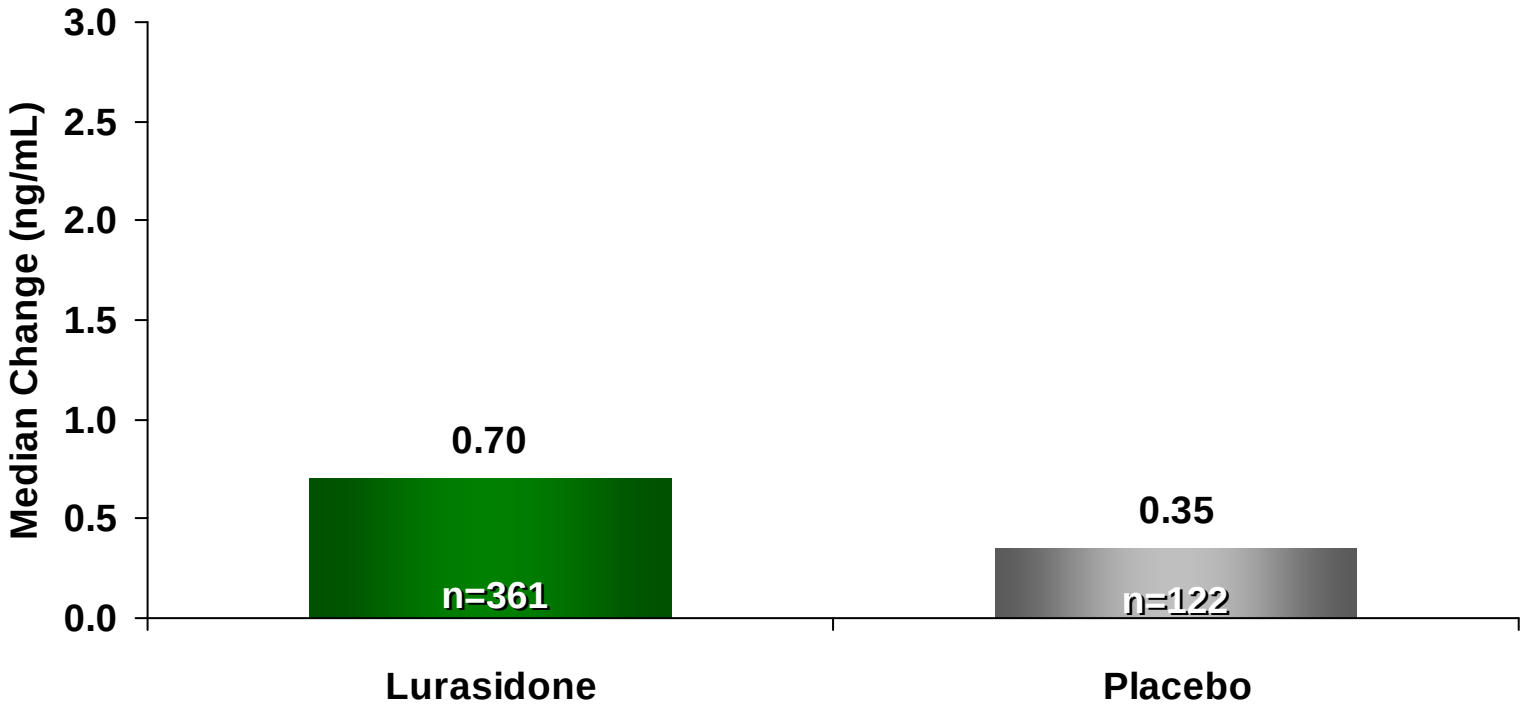
PEARL 1: Barnes Akathisia Rating Scale (BAS)

Global Clinical Assessment

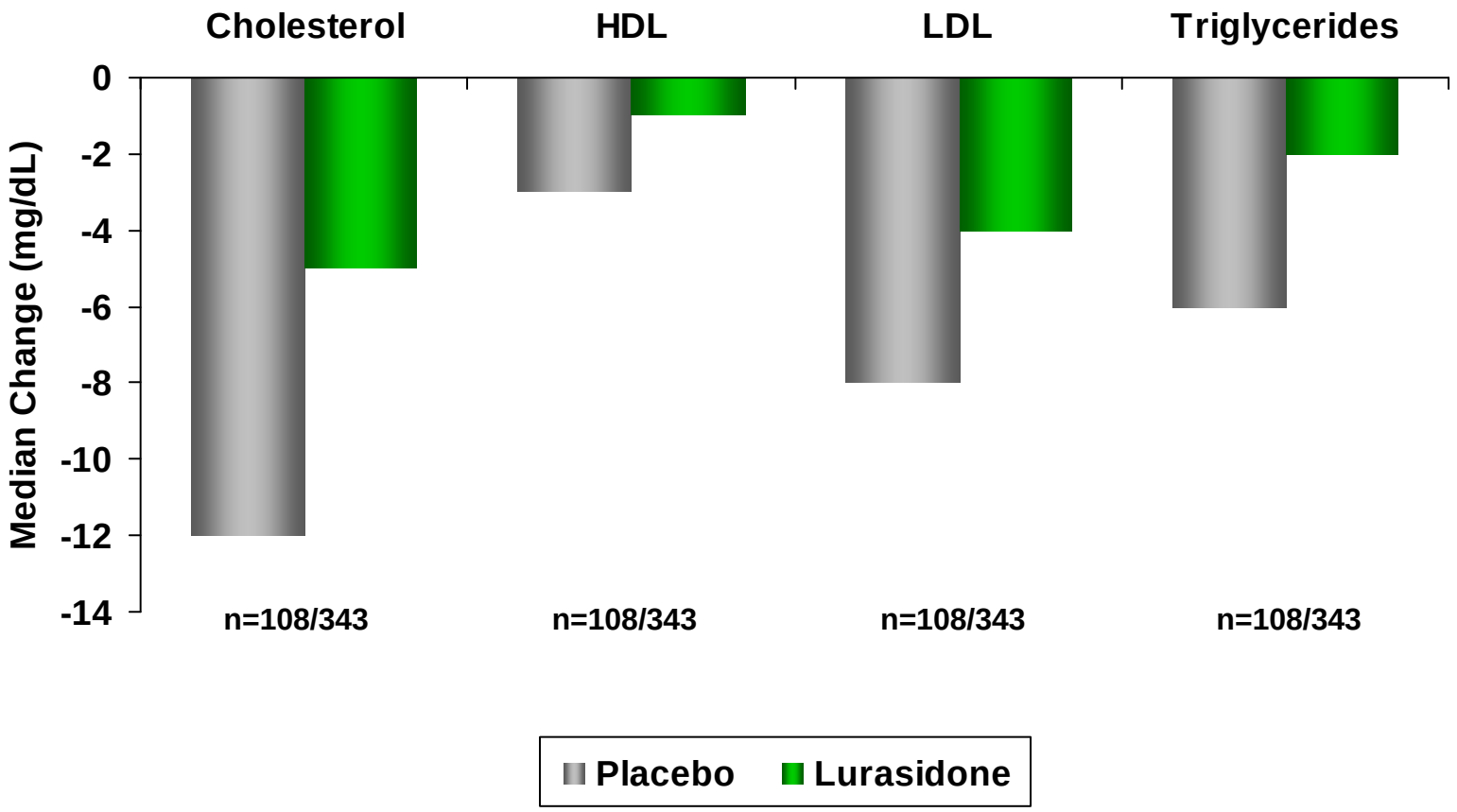


BAS scored 0-5 on Global Clinical Assessment of akathisia for a maximum possible score of 5

PEARL 1:
Serum Prolactin

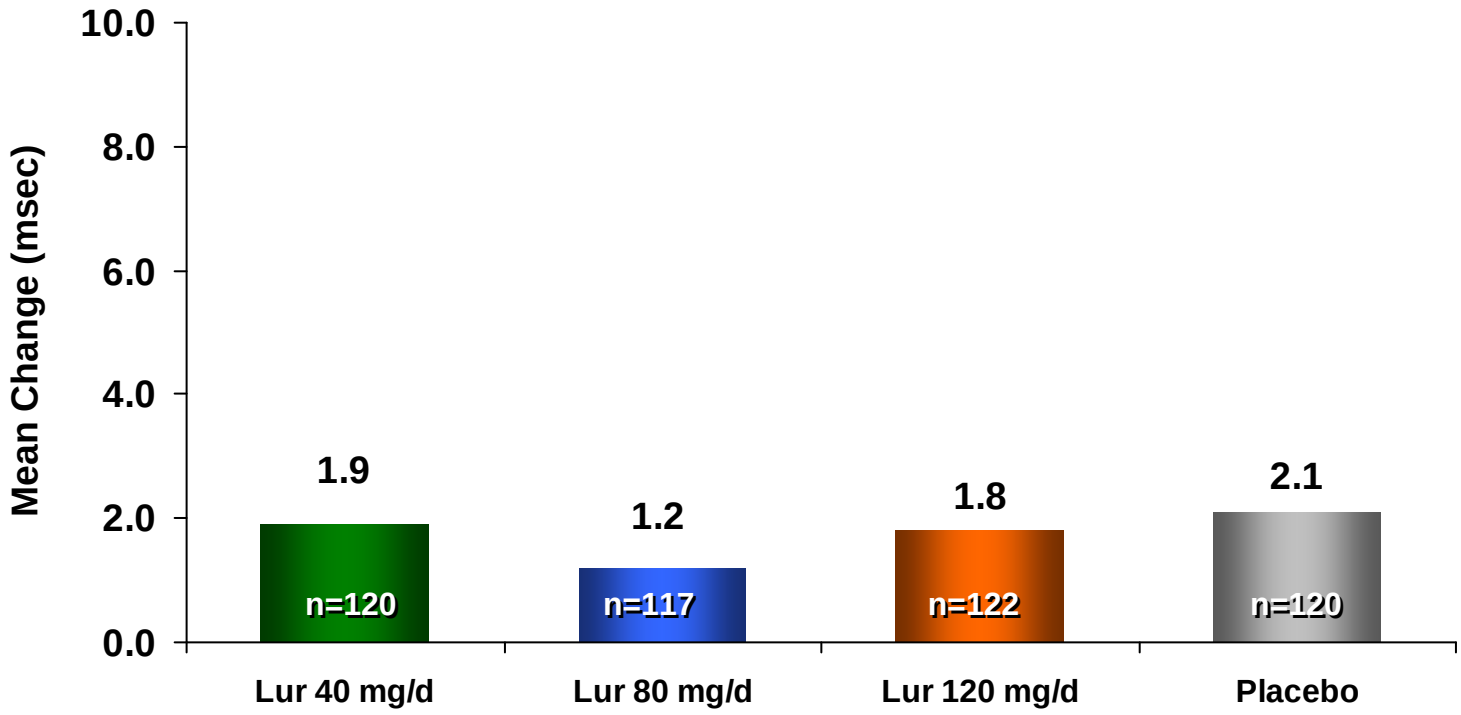


PEARL 1:
Lipid Profile



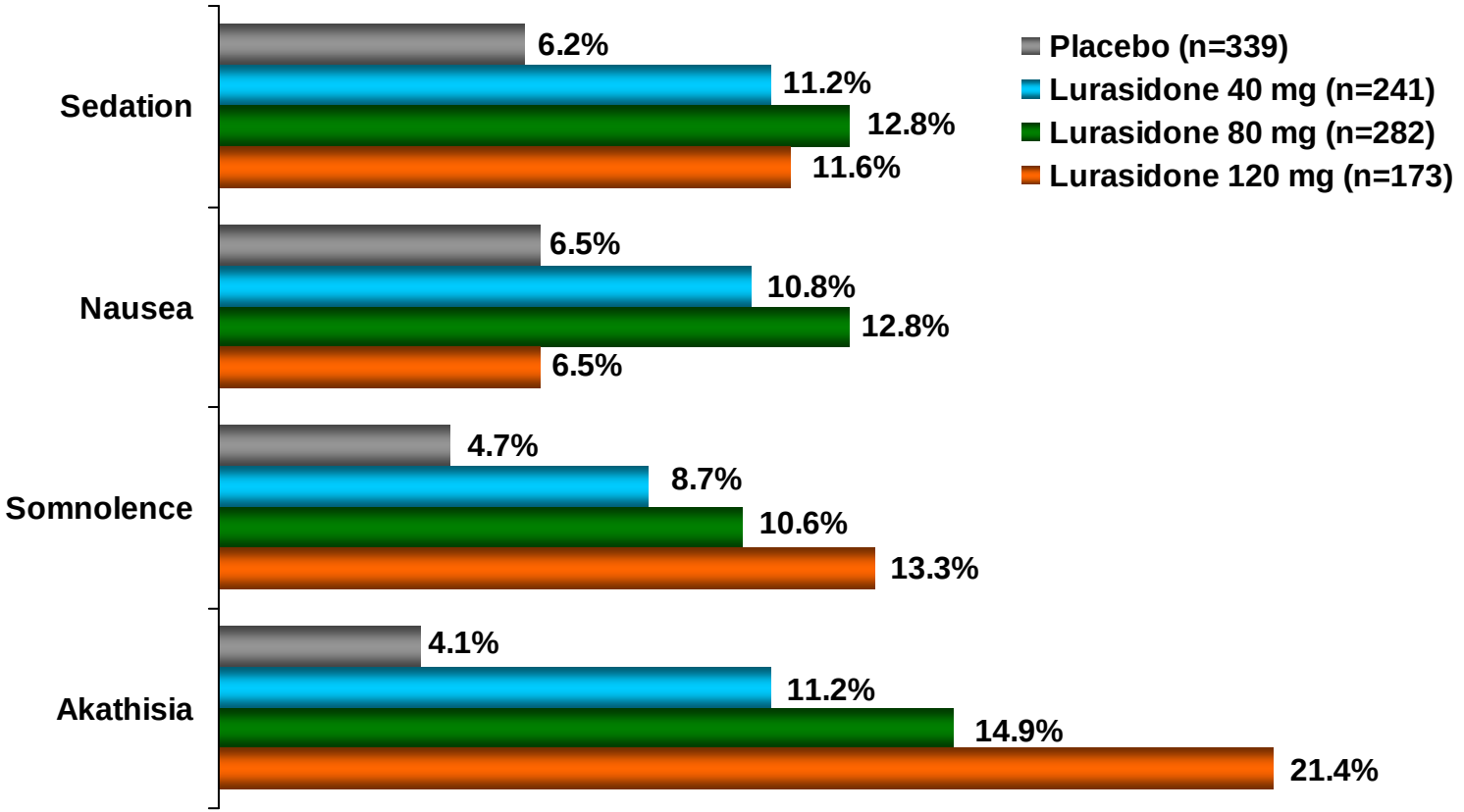
LOCF endpoint values; fasting per protocol; includes all subjects

PEARL 1:
QTcF Interval Change (LOCF)



Treatment-Emergent Adverse Event Rates (Incidence ≥10%)

Phase 2 and 3 Data
Studies 006/049/196/PEARL 1



Cucchiaro J, et al. Efficacy and Safety of Lurasidone in Phase 2/3 Acute Schizophrenia Trials. Poster. American Psychiatric Association, San Francisco, CA, May 16-21, 2009,

Lurasidone Efficacy: Summary

Consistent efficacy

- 40, 80 and 120 mg/d shown effective across 3 placebo-controlled trials
- Rapid onset (day 3 or 4) with subsequent sustained improvement noted in placebo-controlled trials
- Potential for improvement of cognitive deficits, based on preclinical and clinical data

Lurasidone Safety: Summary

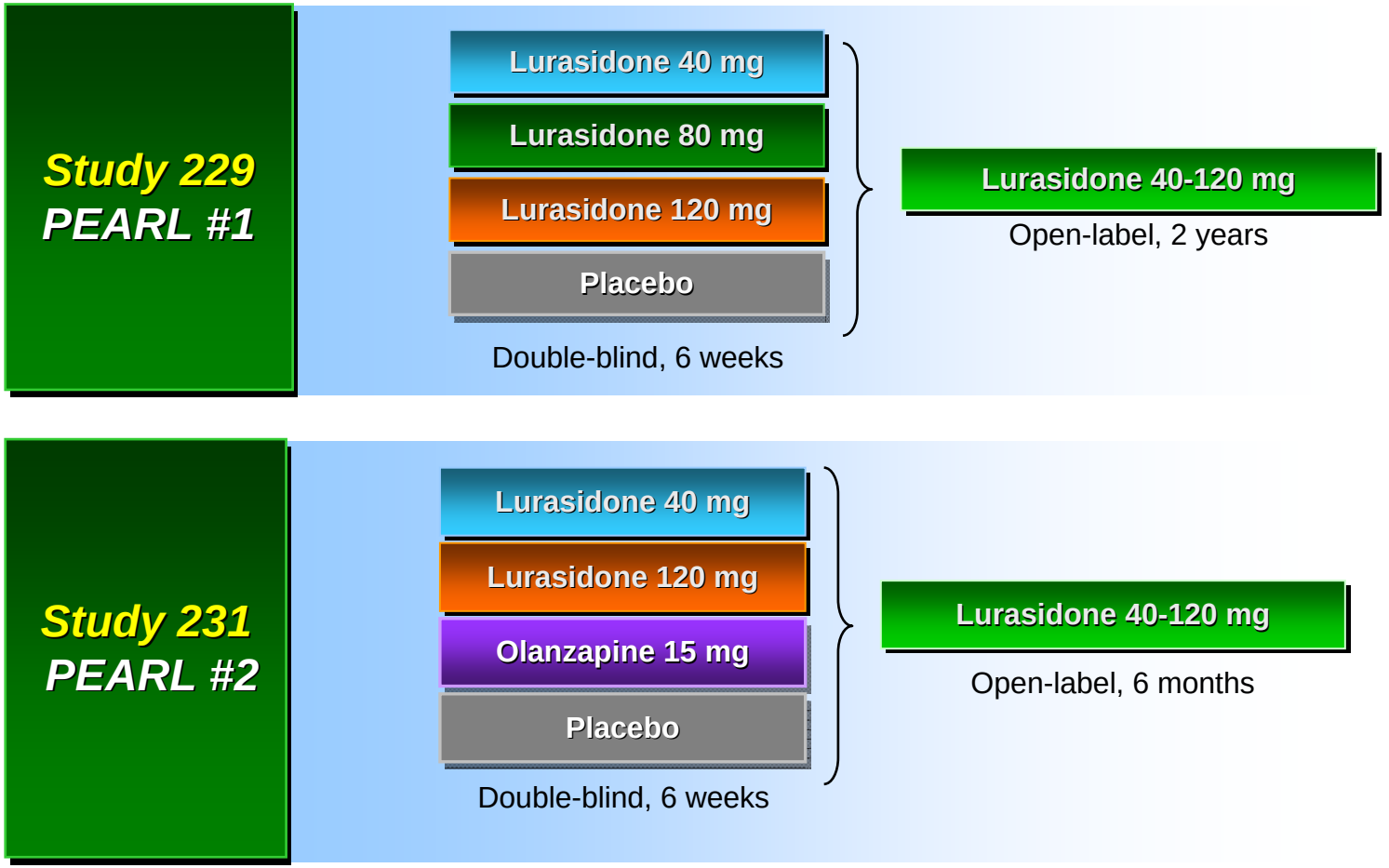
Lurasidone is well tolerated

- Low rates of EPS and akathisia
- Minimal prolactin change
- Neutral effects on weight, lipids and glucose
- Modest change in QTc interval
- Self-reported AEs are generally mild and transient

Potential for Ongoing Adherence to Treatment

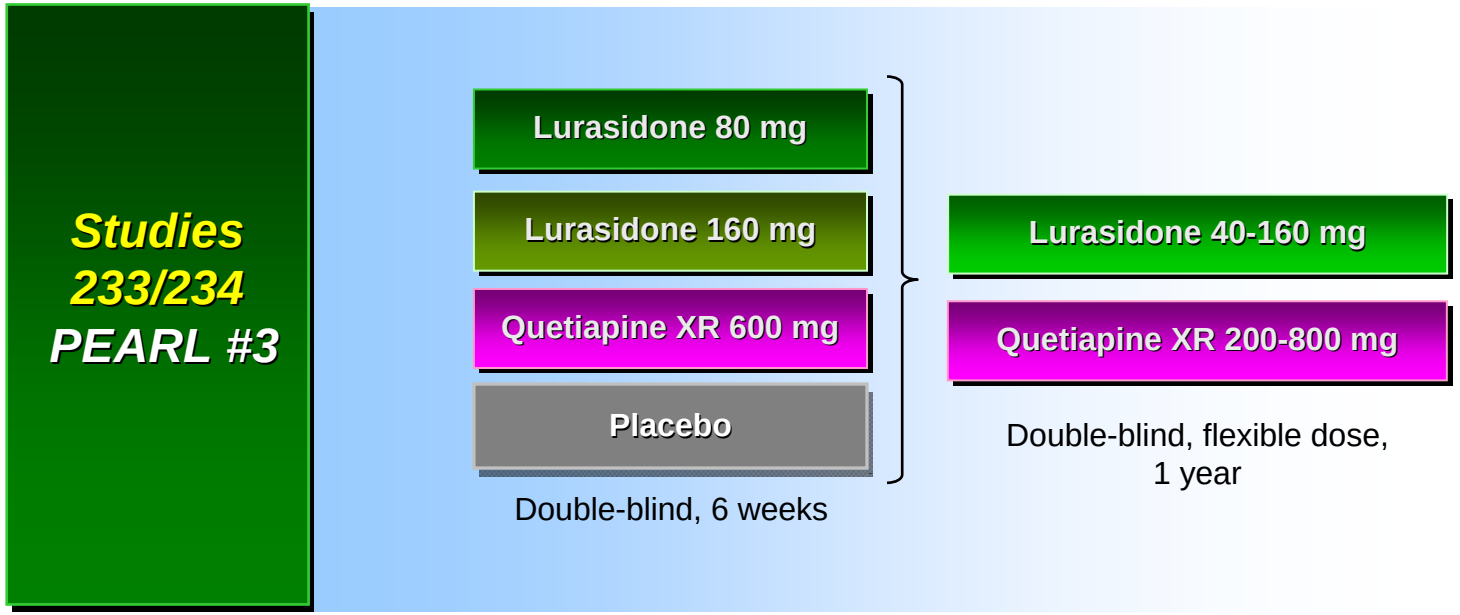
Lurasidone Development Program

PEARL 1 and 2 Trials: Lurasidone in Acute Schizophrenia



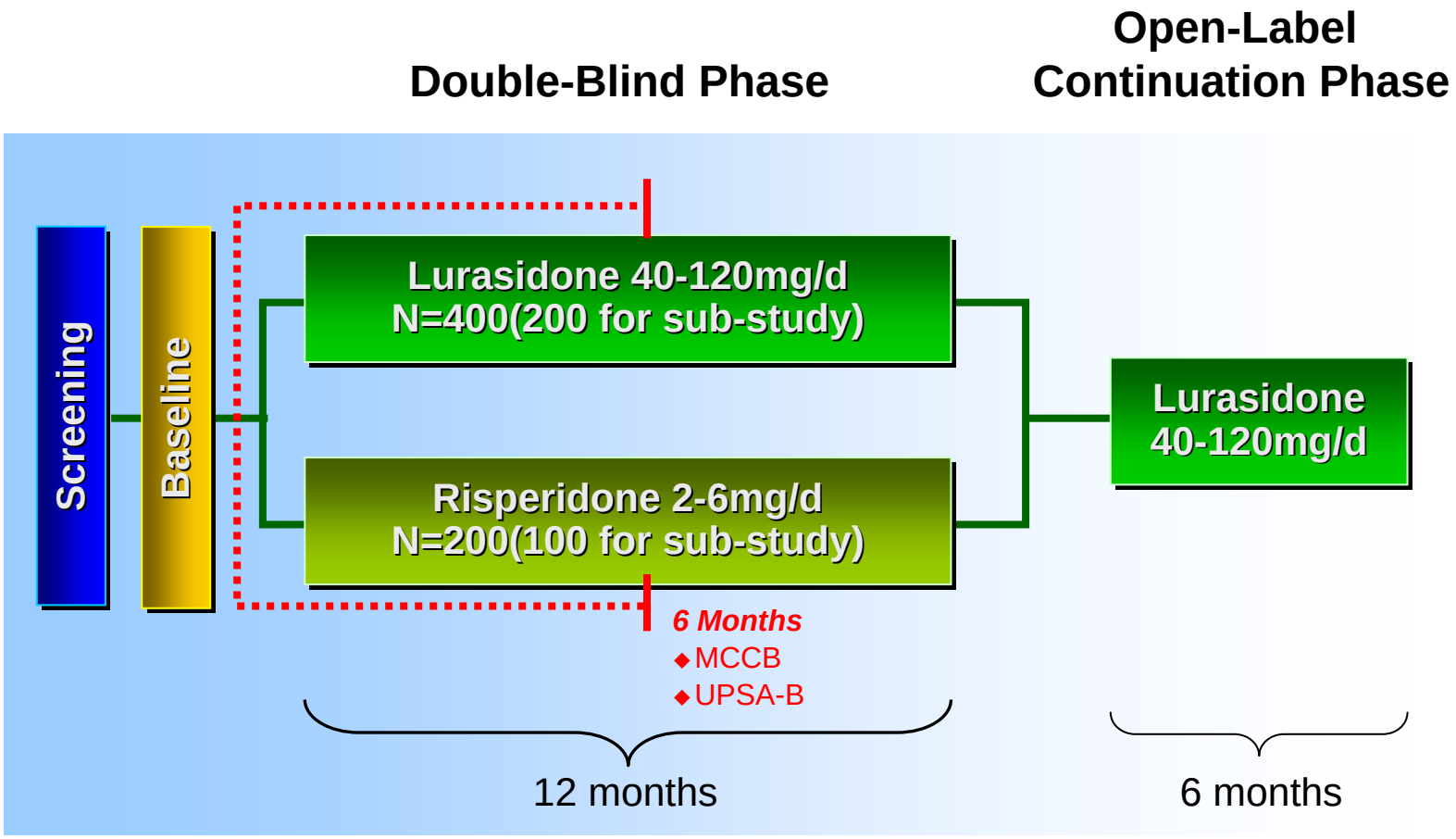
N=480/study
Lurasidone: QD dosing schedule

PEARL 3:
Lurasidone in Acute Schizophrenia



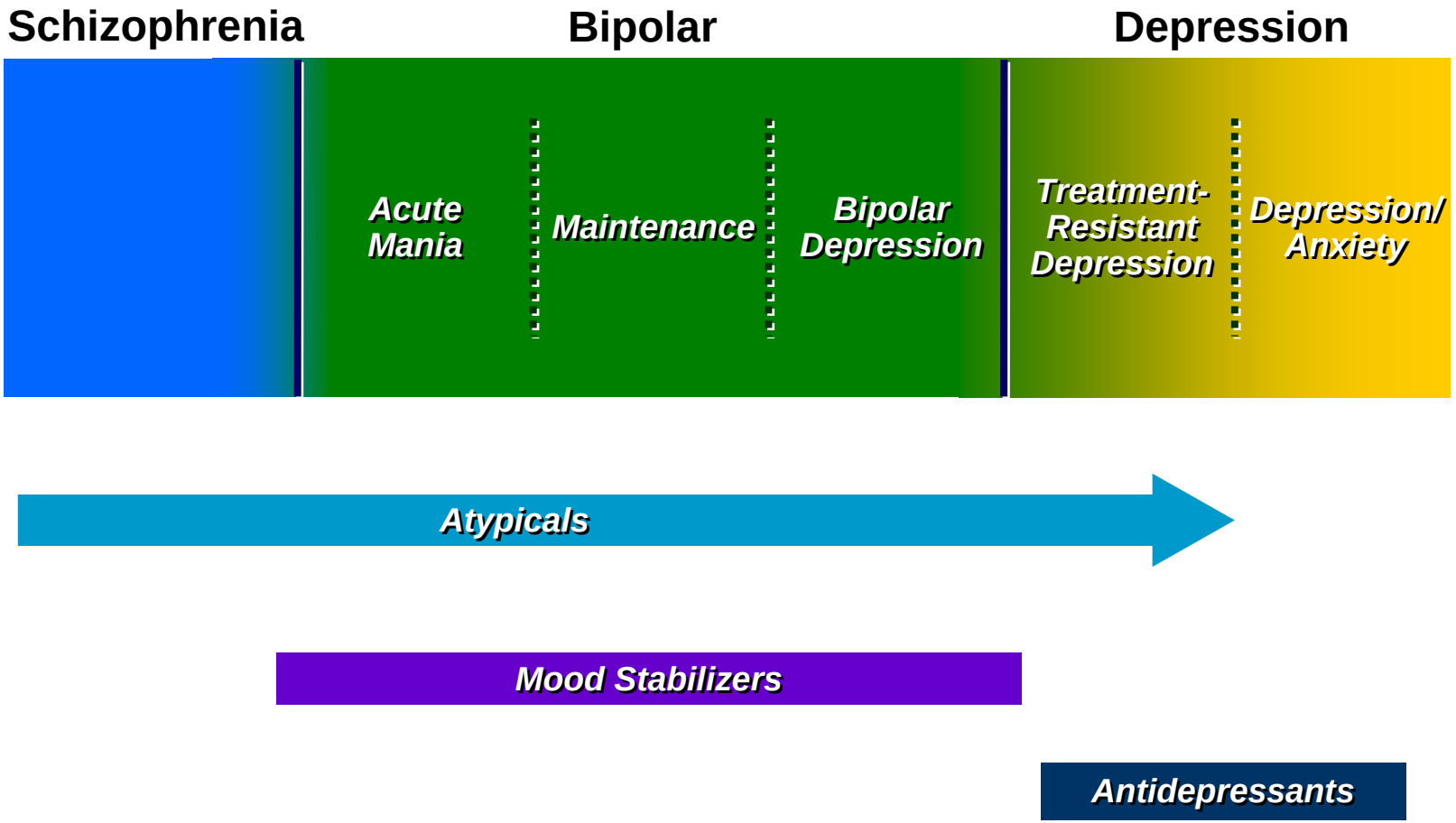
N=480/study
Lurasidone: QD dosing schedule

Long-Term Safety Study With Cognitive Sub-Study



MCCB: MATRICS Consensus Cognitive Battery
UPSA-B: UCSD Performance-Based Skills Assessment - Brief Version

Atypical Use Has and Will Continue to Expand



PREVAIL:
Lurasidone in Bipolar Depression

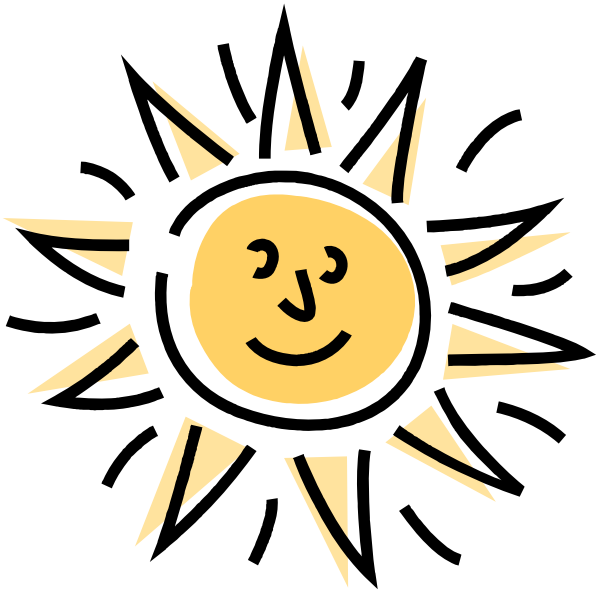
PRogram to

EValuate the

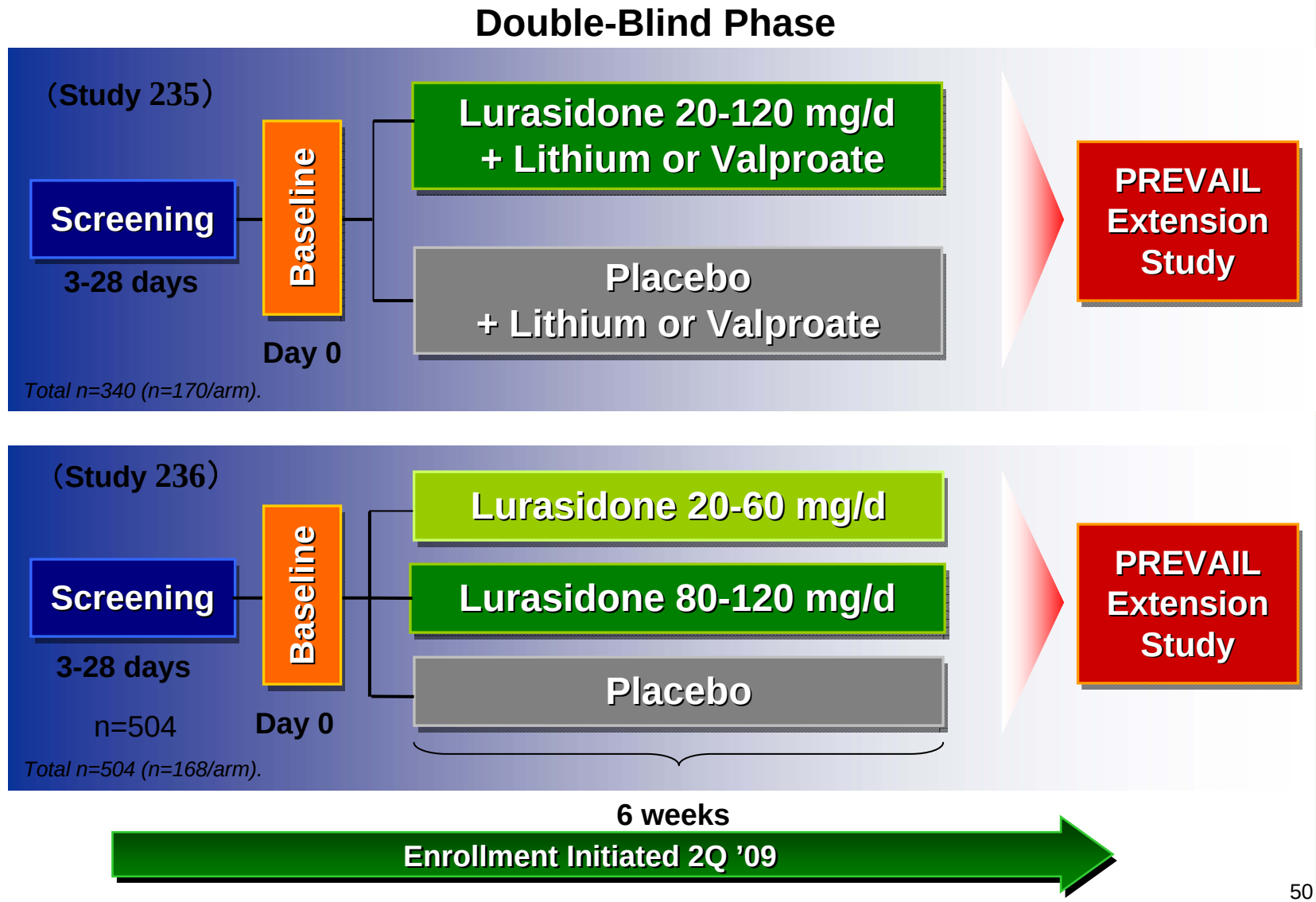
Antidepressant

Impact of

Lurasidone



PREVAIL Add-On Design (Study 235)
PREVAIL Monotherapy Design (Study 236)



Lurasidone Commercial Overview

Joseph Yen Lin
Vice President, Marketing
Dainippon Sumitomo Pharma America

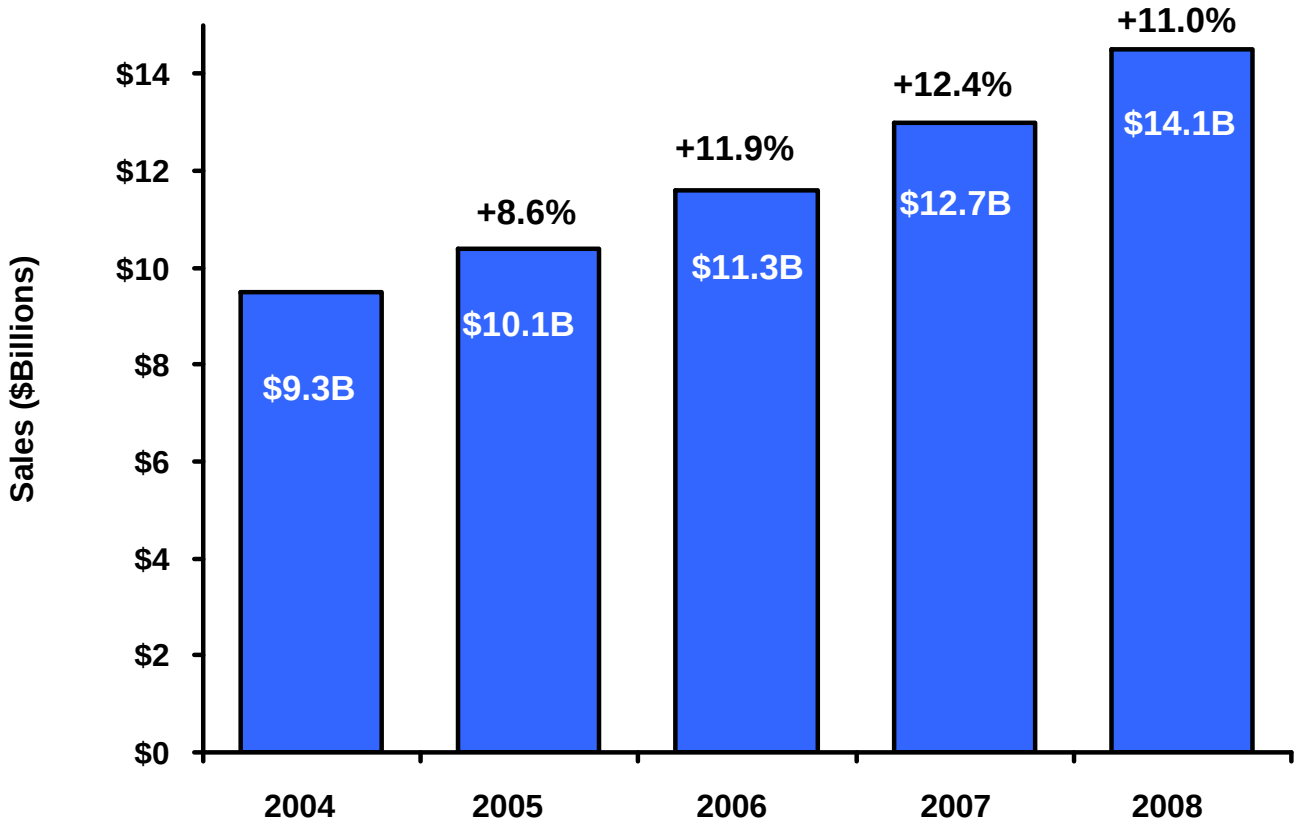
Agenda

I. Market and Disease State Overview

II. Competitive Landscape

Market Overview
Overall Growth

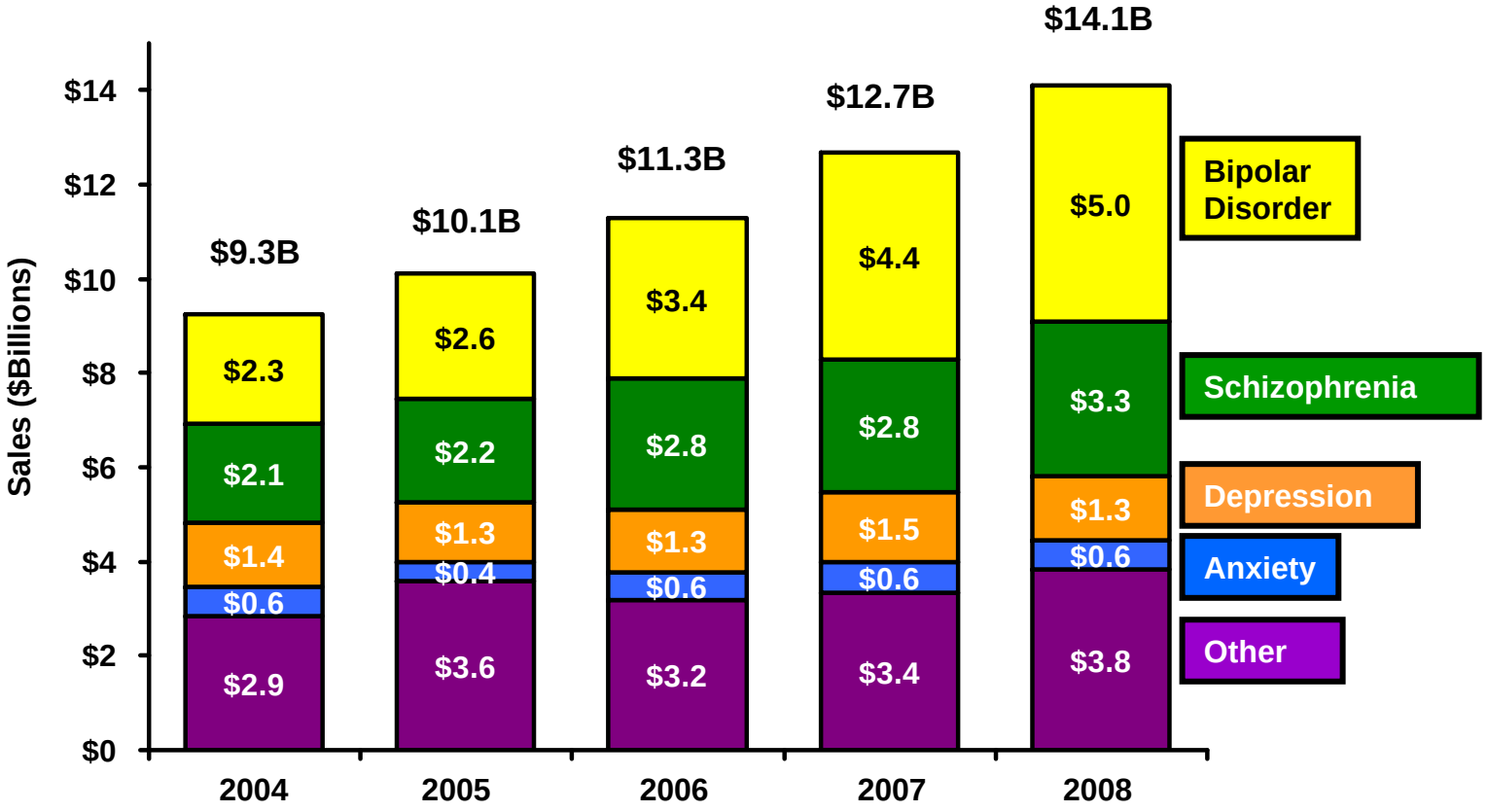
The atypical antipsychotic market is large and continues to grow at a robust rate



Source: IMS NSP Data, 2004-2008

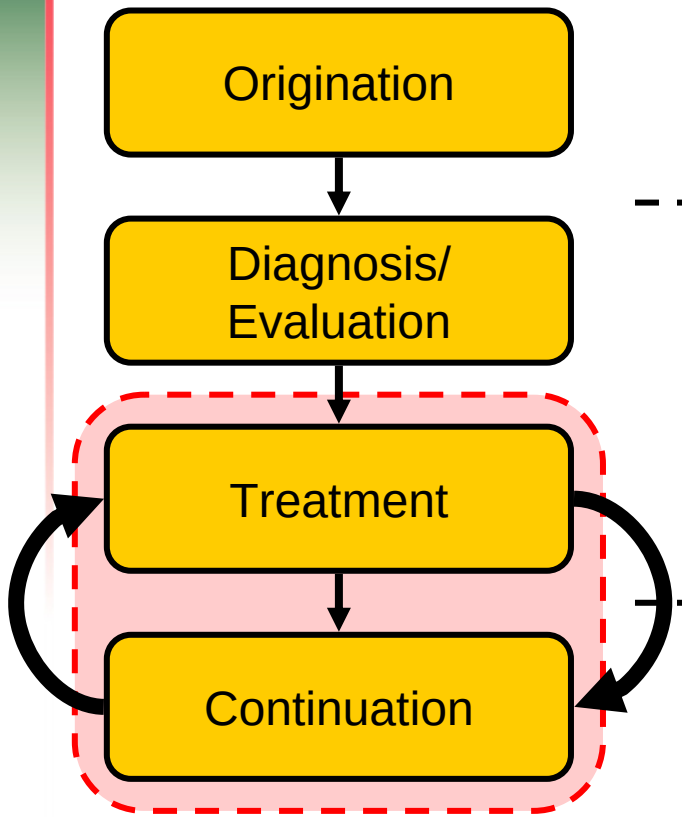
Market Overview
Growth by Diagnosis

Growth in the atypical antipsychotic category is being driven by use in bipolar disorder and schizophrenia



Source: Estimated from IMS NSP Data, 2004-2008 and NDTI 2004 to 2008

Schizophrenia Disease State Overview
Patient Flow



- U.S. lifetime prevalence of schizophrenia is 1%; approximately 2.5 million affected
- High rates of diagnosis (80%) and treatment (85%)
- Atypical antipsychotics considered the gold standard for schizophrenia
- High rates of patient discontinuation and switching
  - Lack of efficacy
  - Side effects
  - Need for new treatment options

Schizophrenia Disease State Overview
Landmark CATIE Trial

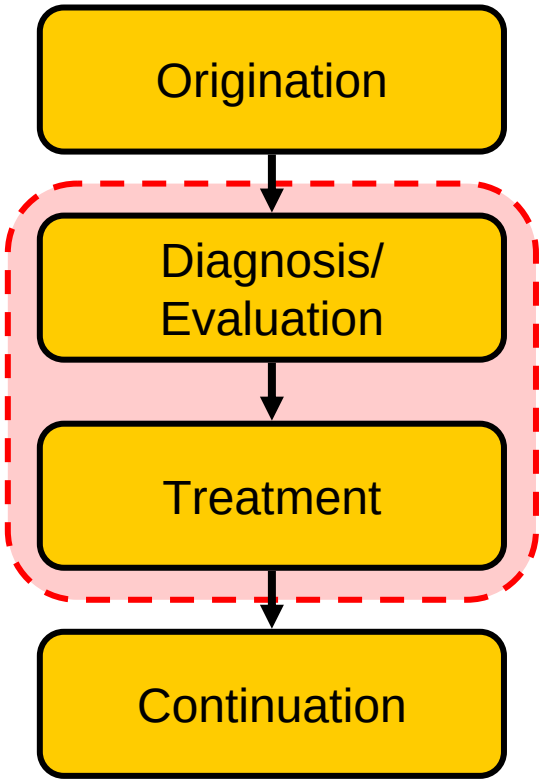
The NEW ENGLAND JOURNAL of MEDICINE

Effectiveness of Antipsychotic Drugs in Patients with Chronic Schizophrenia

Jeffrey A. Lieberman, M.D., T. Scott Stroup, M.D., M.P.H., Joseph P. McEvoy, M.D., Marvin S. Swartz, M.D., Robert A. Rosenheck, M.D., Diana O. Perkins, M.D., M.P.H., Richard S.E. Keefe, Ph.D., Sonia M. Davis, Dr.P.H., Clarence E. Davis, Ph.D., Barry D. Lebowitz, Ph.D., Joanne Severe, M.S., John K. Hsiao, M.D., for the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) Investigators

"…patients with chronic schizophrenia in this study discontinued their antipsychotic study medications at a high rate, indicating substantial limitations in the effectiveness of the drugs."

Bipolar Disease State Overview
Patient Flow



- U.S. lifetime prevalence of bipolar disorder is 2.6%; over 6 million affected

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- Relatively lower rates of diagnosis (45%) and treatment (80%) as compared to schizophrenia
- Multiple agents currently used in treatment – lithium, antiepileptic agents
- Atypicals increasingly used to treat bipolar depression
- Only 1 atypical currently approved for bipolar depression (Seroquel)

Key Takeaways

Opportunities	*Challenges*
◆*Large, growing market for atypical antipsychotics* ◆*High rate of dissatisfaction and switch; need for new treatment options* ◆*Increasing use for the treatment of bipolar disorder is a significant driver of atypical antipsychotic market growth*	

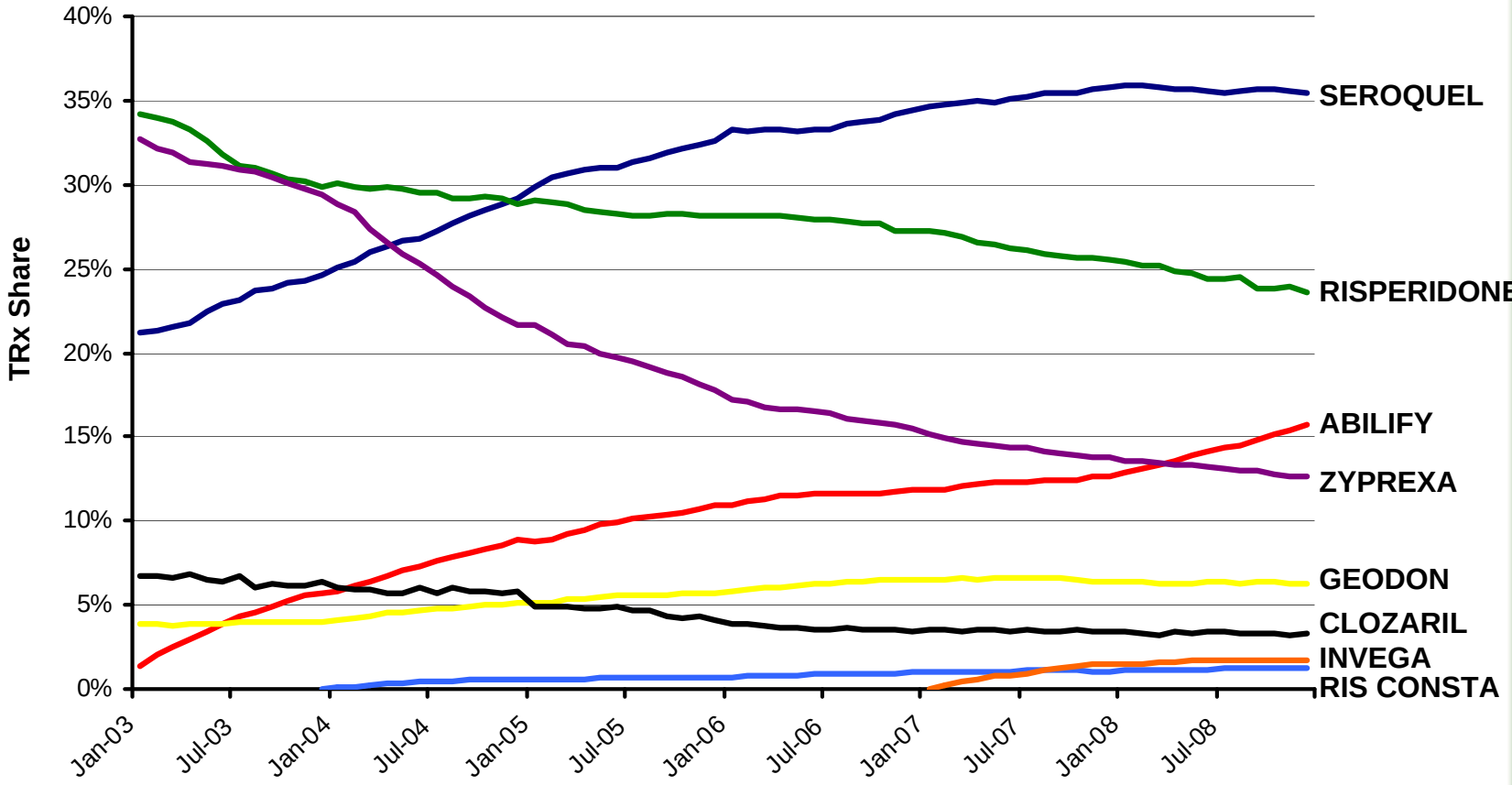
Agenda

I. Market and Disease State Overview

II. Competitive Landscape

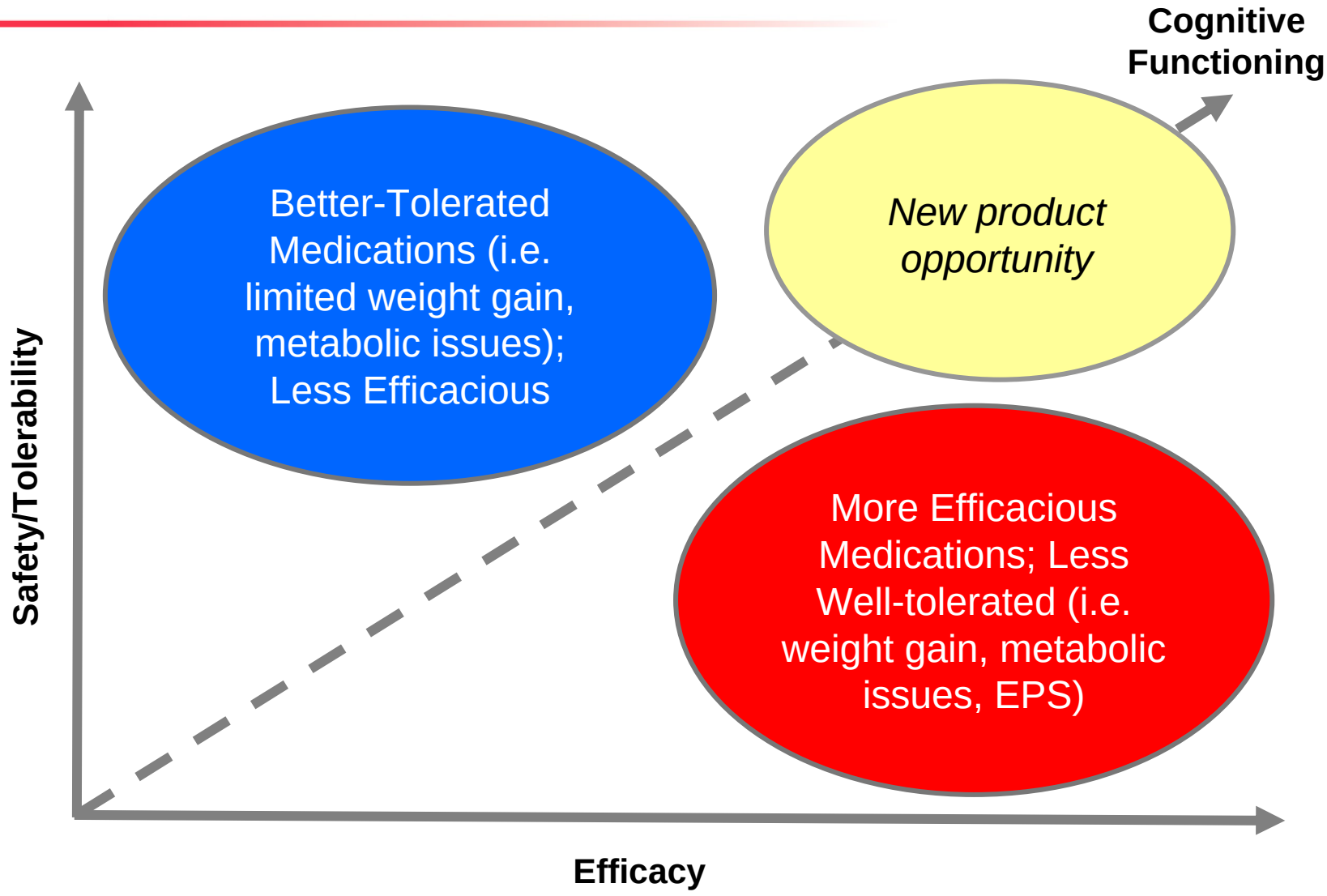
Atypical Antipsychotic Market
Current Competitive Environment

Seroquel is the clear market leader; impact of generic risperidone not yet evident

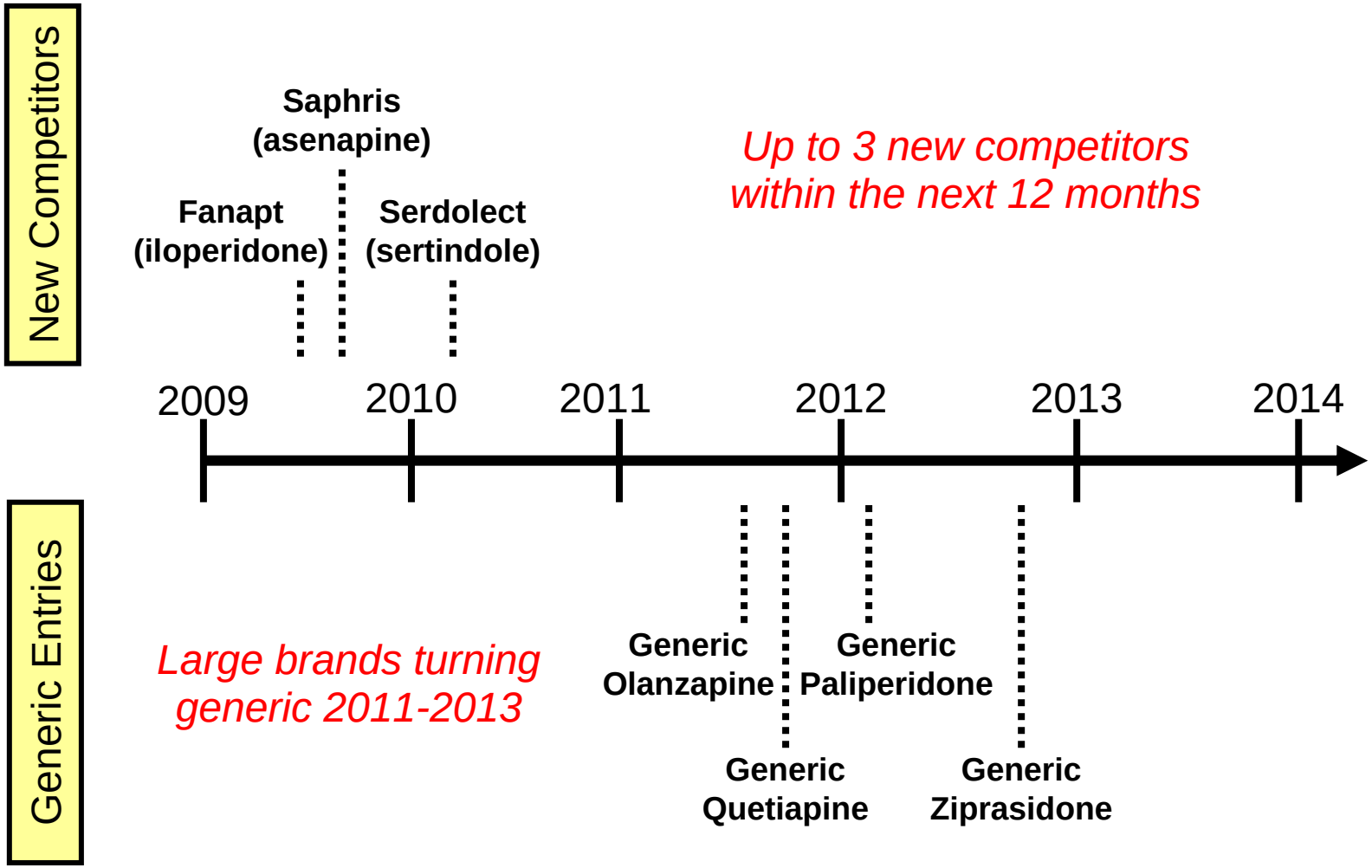


Source: IMS DataView

Atypical Antipsychotic Market
Perceptual Mapping in Schizophrenia

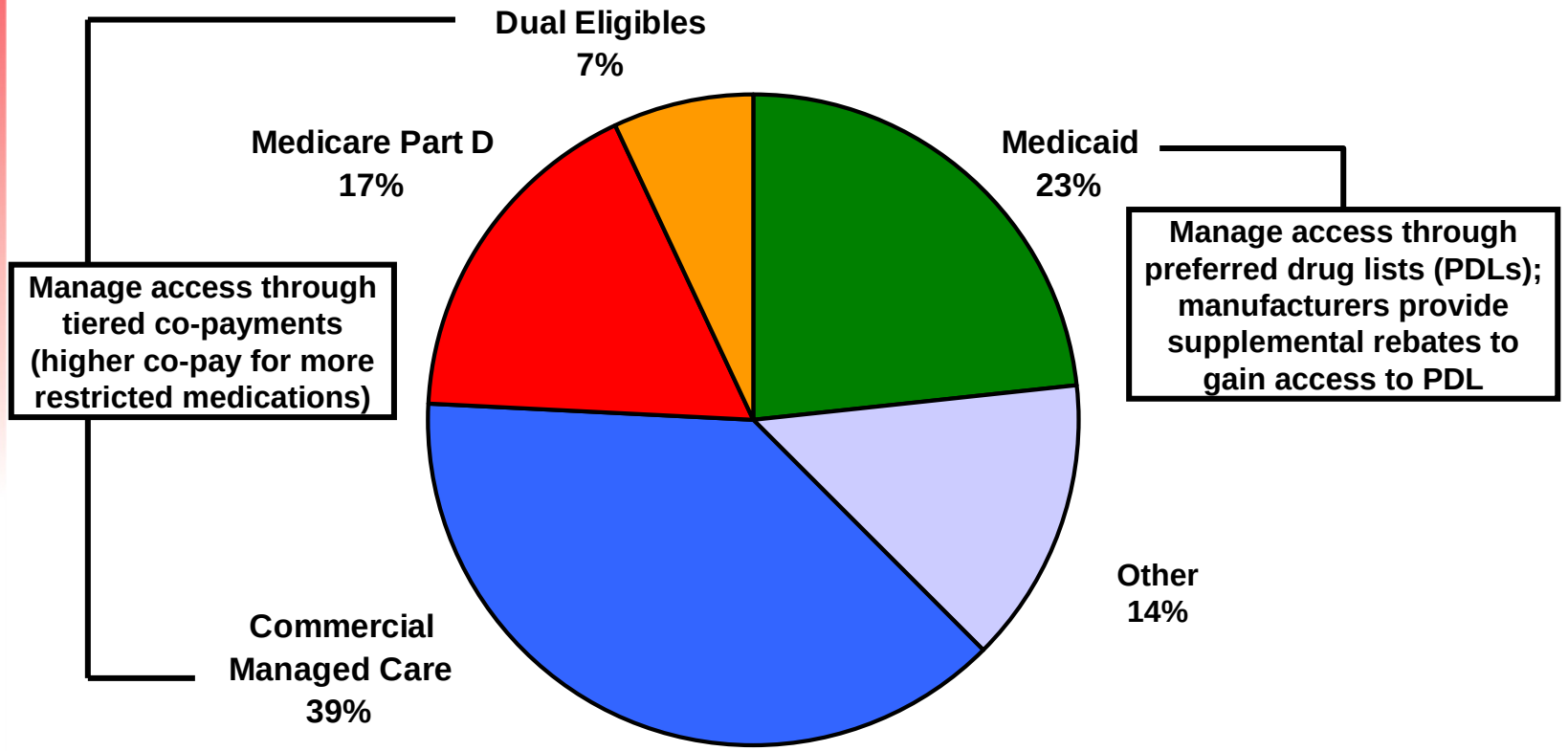


APS Market Evolution:
New Competitors, Generic Entries



Antipsychotic Payer Mix

Public and private payers likely to increase control over utilization of branded products when more generics become available



Source: IMS

Key Takeaways

Opportunities	*Challenges*
◆Large, growing market for atypical antipsychotics	◆*Highly competitive market with large brands*
◆High rate of dissatisfaction and switch; need for new treatment options	◆*New competitor launches pending*
◆Increasing use for the treatment of bipolar disorder is a significant driver of atypical antipsychotic market growth	◆*Genericization of market beginning in 2011 will change market dynamics → payers more likely to control utilization of branded products*
◆*Market opportunity for more efficacious, better tolerated medications*	

Disclaimer Regarding Forward-looking Statements

The statements made in this presentation material are forward-looking statements based on management's assumptions and beliefs in light of information available up to the day of announcement, and involve both known and unknown risks and uncertainties.

Actual financial results may differ materially from those presented in this document, being dependent on a number of factors.

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