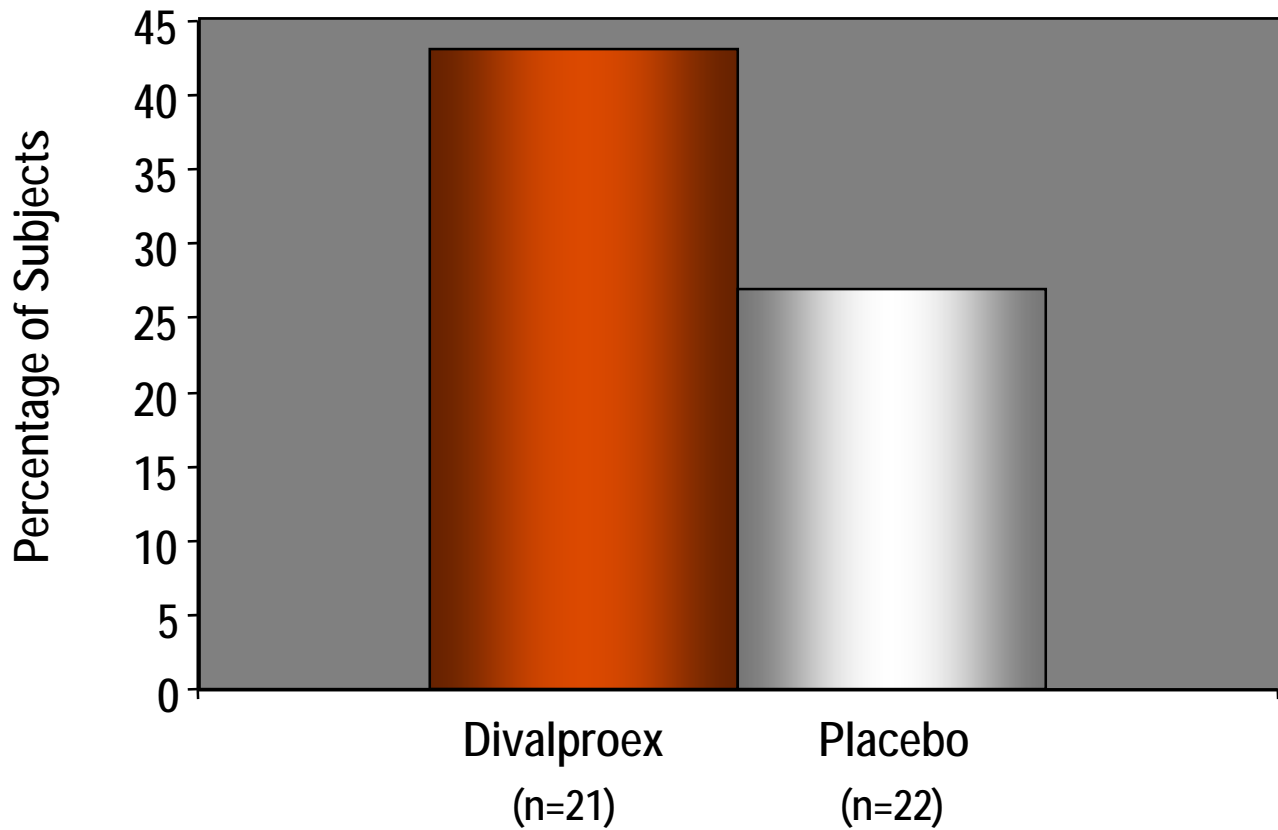


# Bipolar Depression

## Challenges in short term clinical trials

**Mauricio Tohen, MD, DrPH, MBA**  
U of Texas Health Science Center at San Antonio

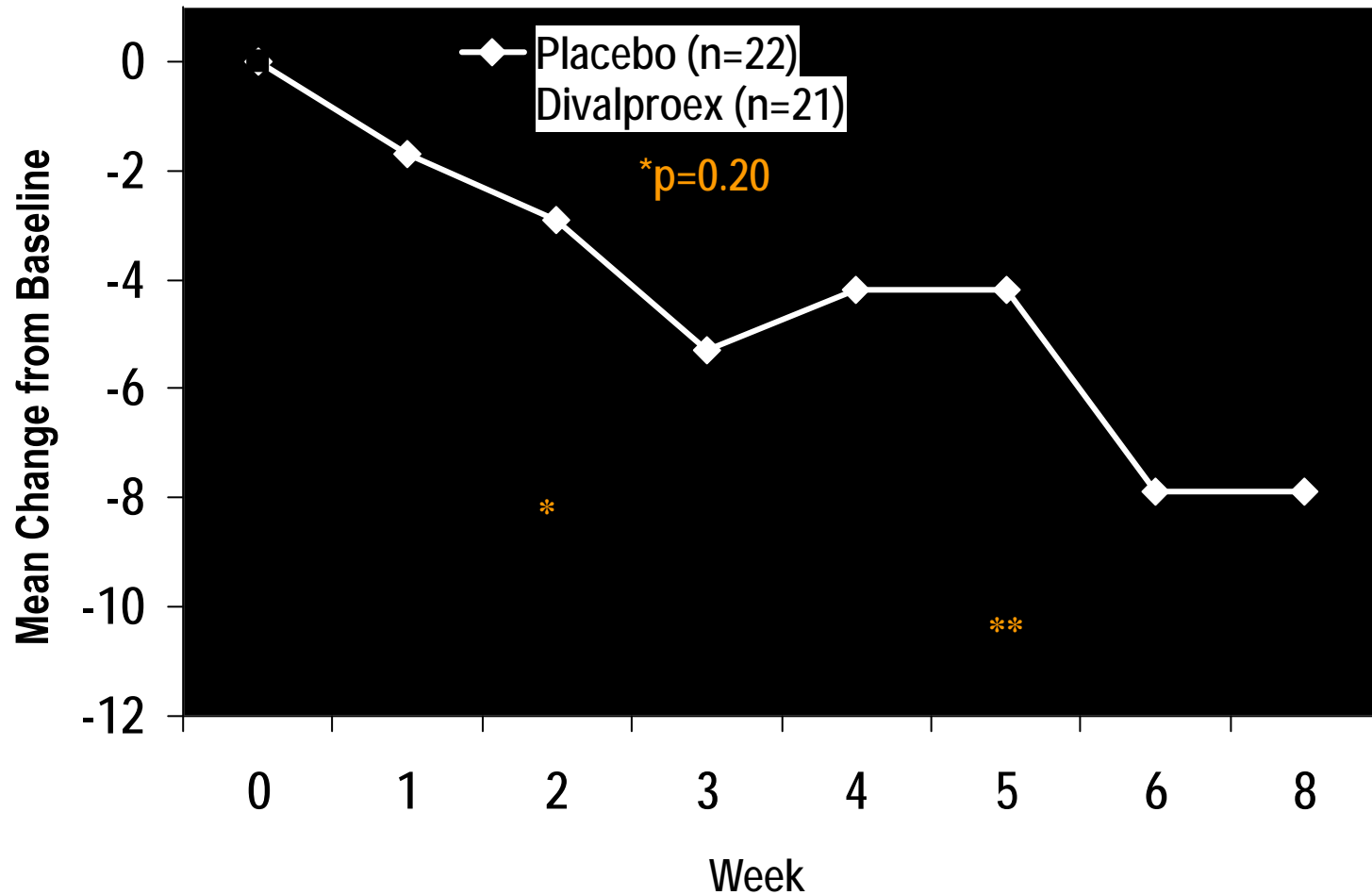
# Valproate in Bipolar Depression



p=.35 divalproex vs placebo.

Sachs GS, et al. Presented at: ACNP; Dec 9-13, 2001; Waikoloa, Hawaii.

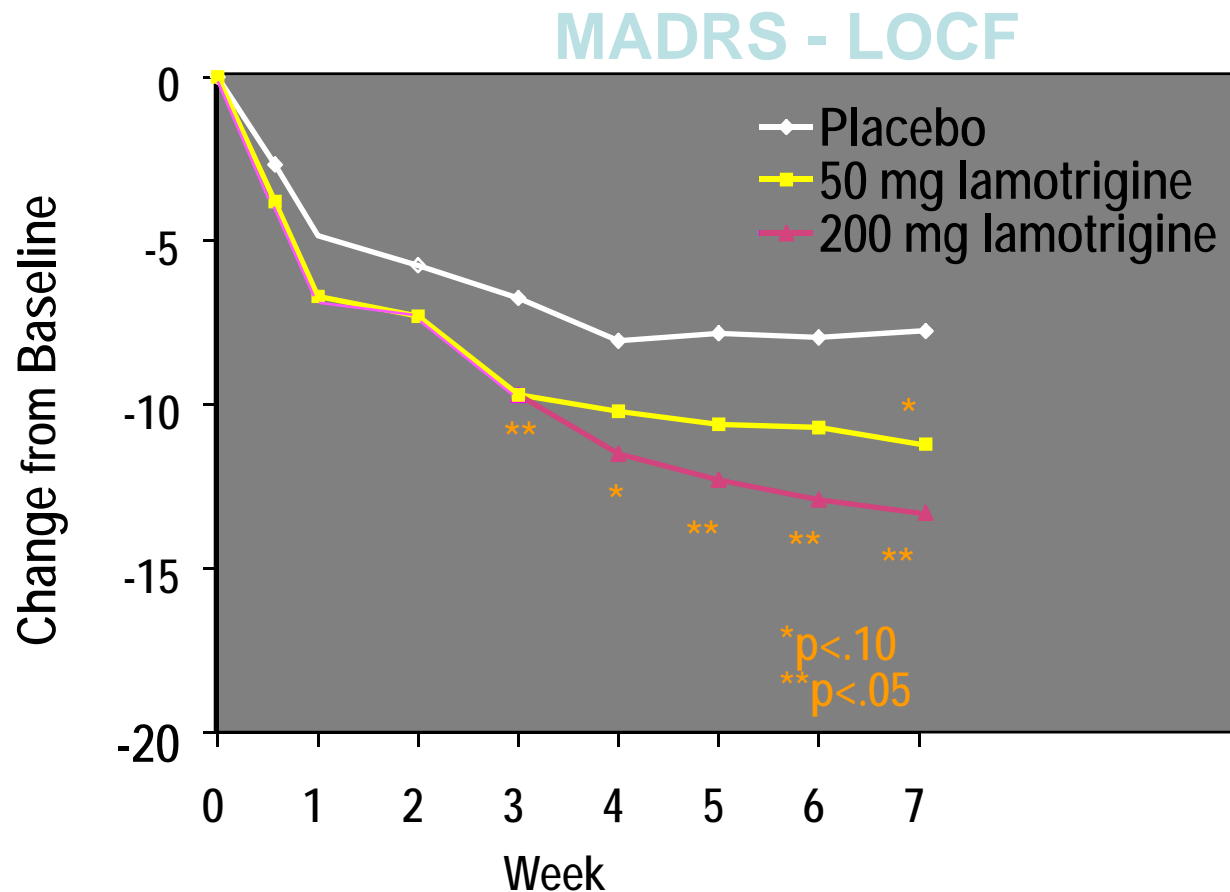
# Valproate in Bipolar Depression (cont.)



\*p=.051 vs placebo. \*\*p=.052 vs placebo. Hamilton Depression Rating Scale (HAM-D) total scores. (LOCF analysis.)  
Sachs GS, et al. Presented at: ACNP; Dec 9-13, 2001; Waikoloa, Hawaii.

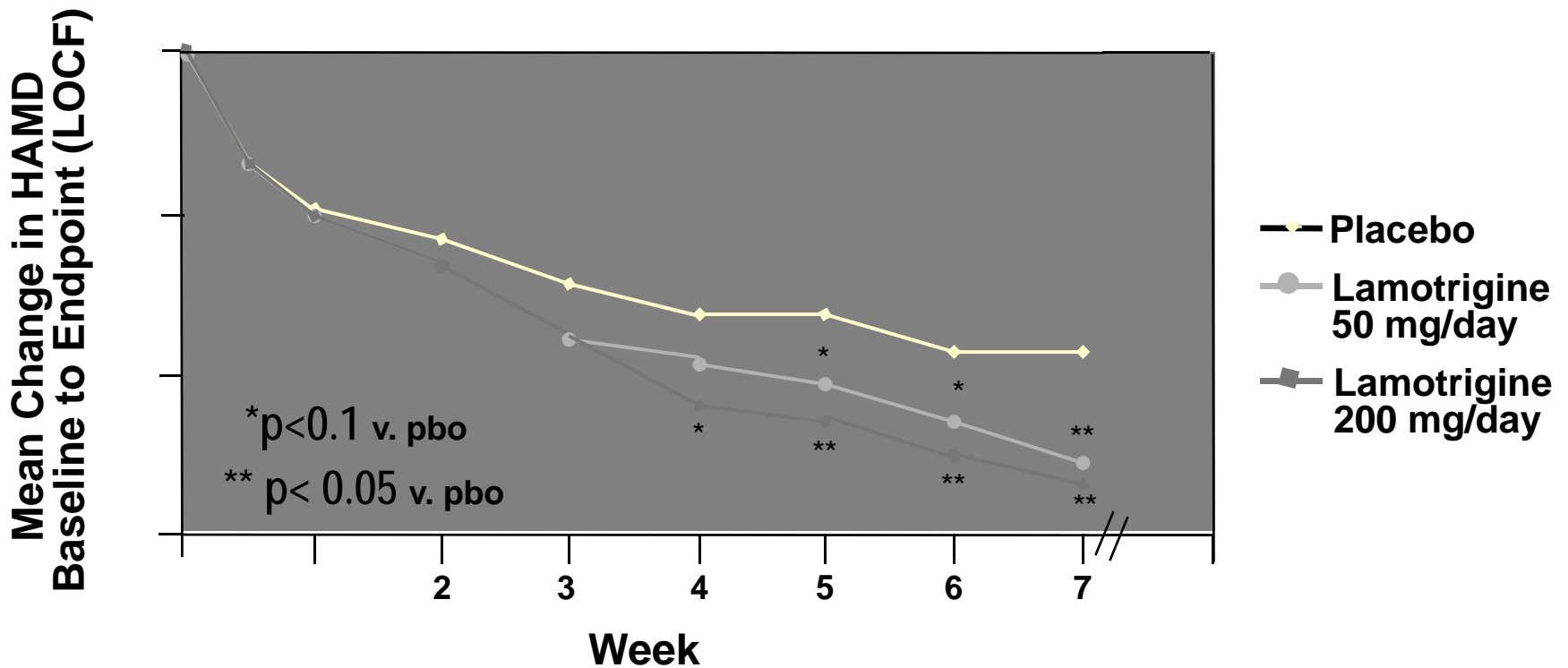
# Lamotrigine in Bipolar Depression

## MADRS change from baseline

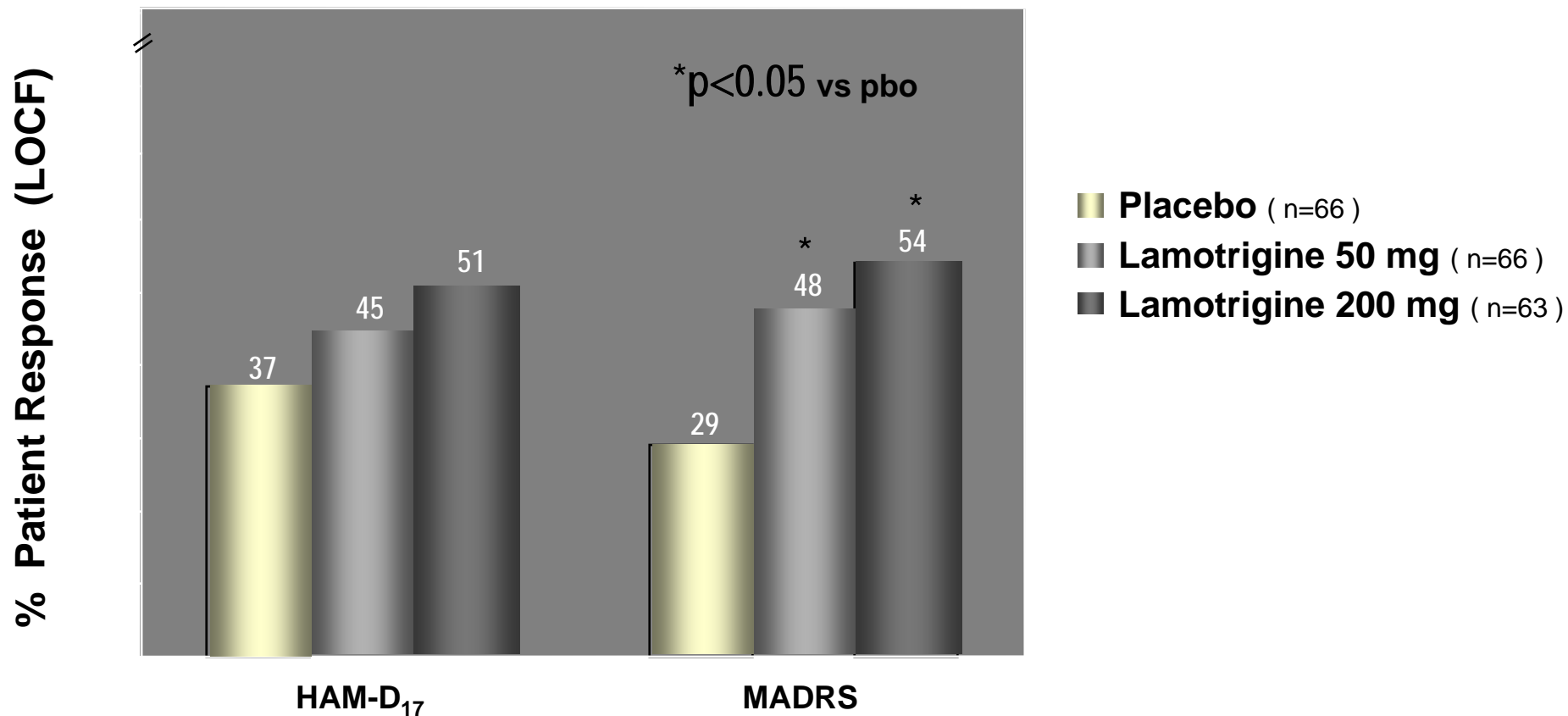


# Lamotrigine in Bipolar Depression

## HAMD change from baseline



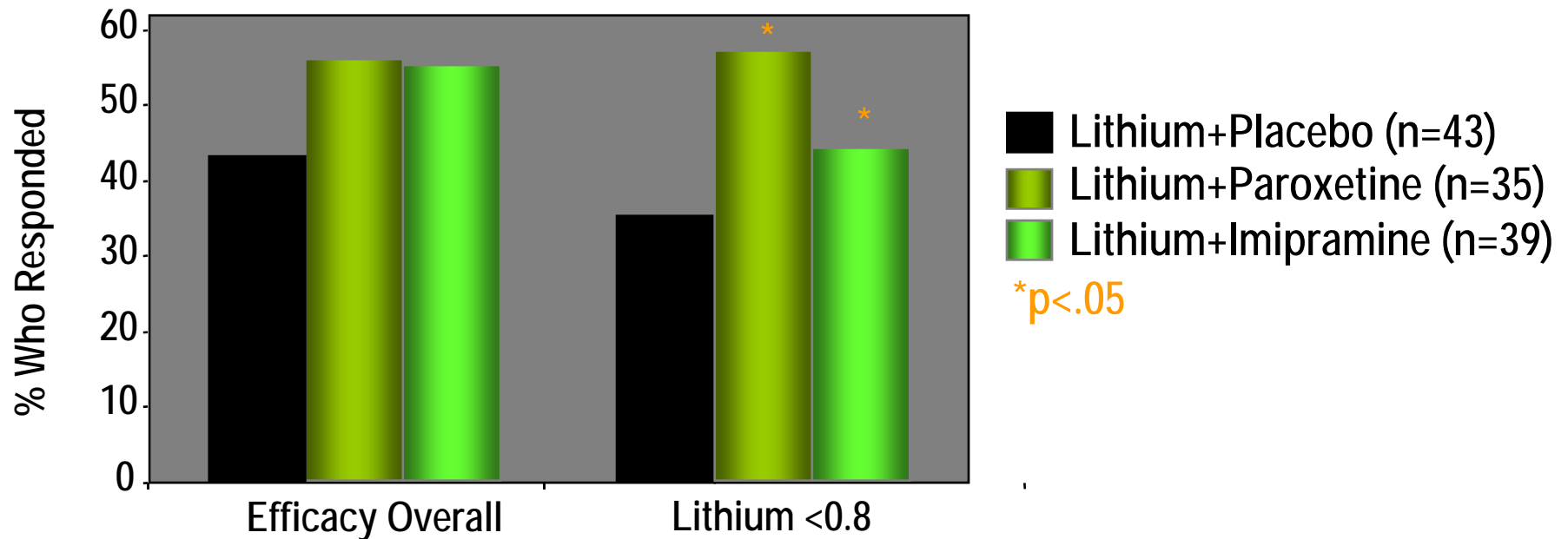
# Lamotrigine in Bipolar Depression Response



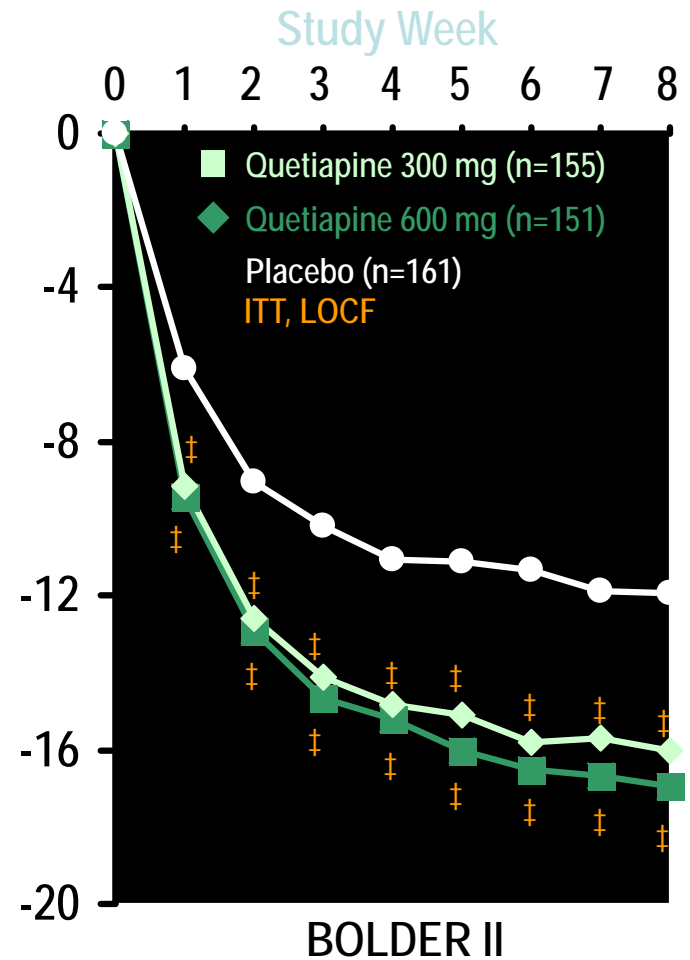
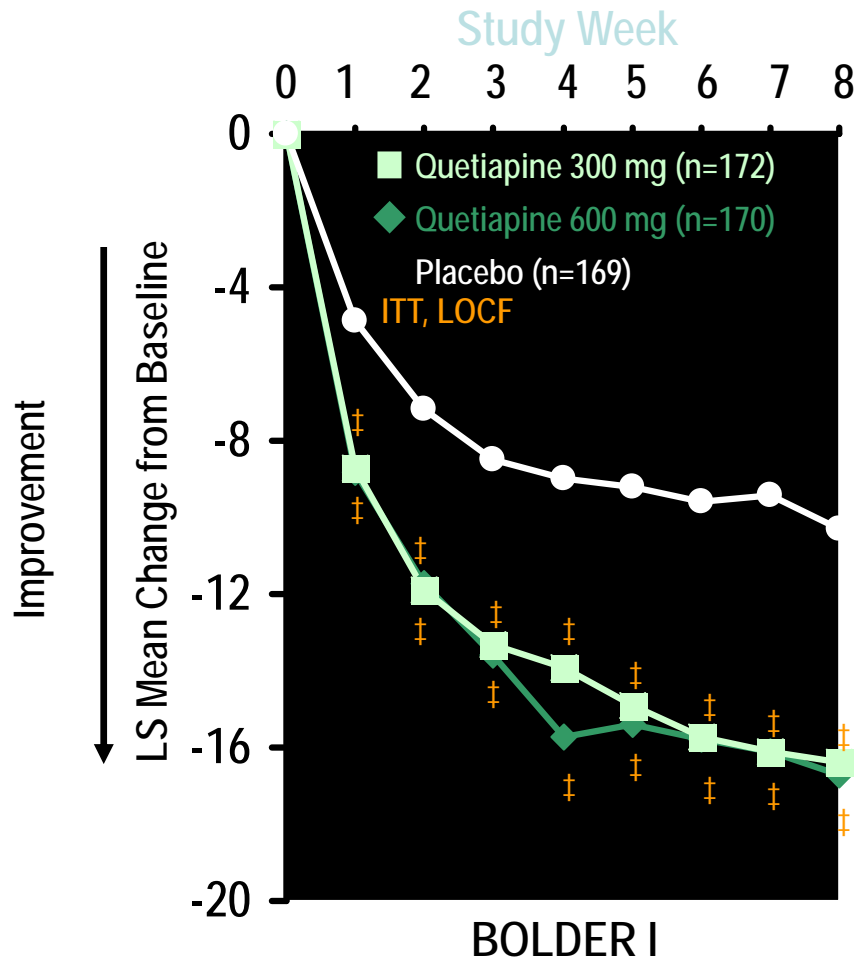
•Response defined as  $\geq 50\%$  reduction on the MADRS and HAM-D.

Calabrese JR, et al. *J Clin Psychiatry*. 1999;60(2):79-88.

# Add-On Paroxetine or Imipramine to Lithium



# MADRS Total Score: BOLDER I vs BOLDER II



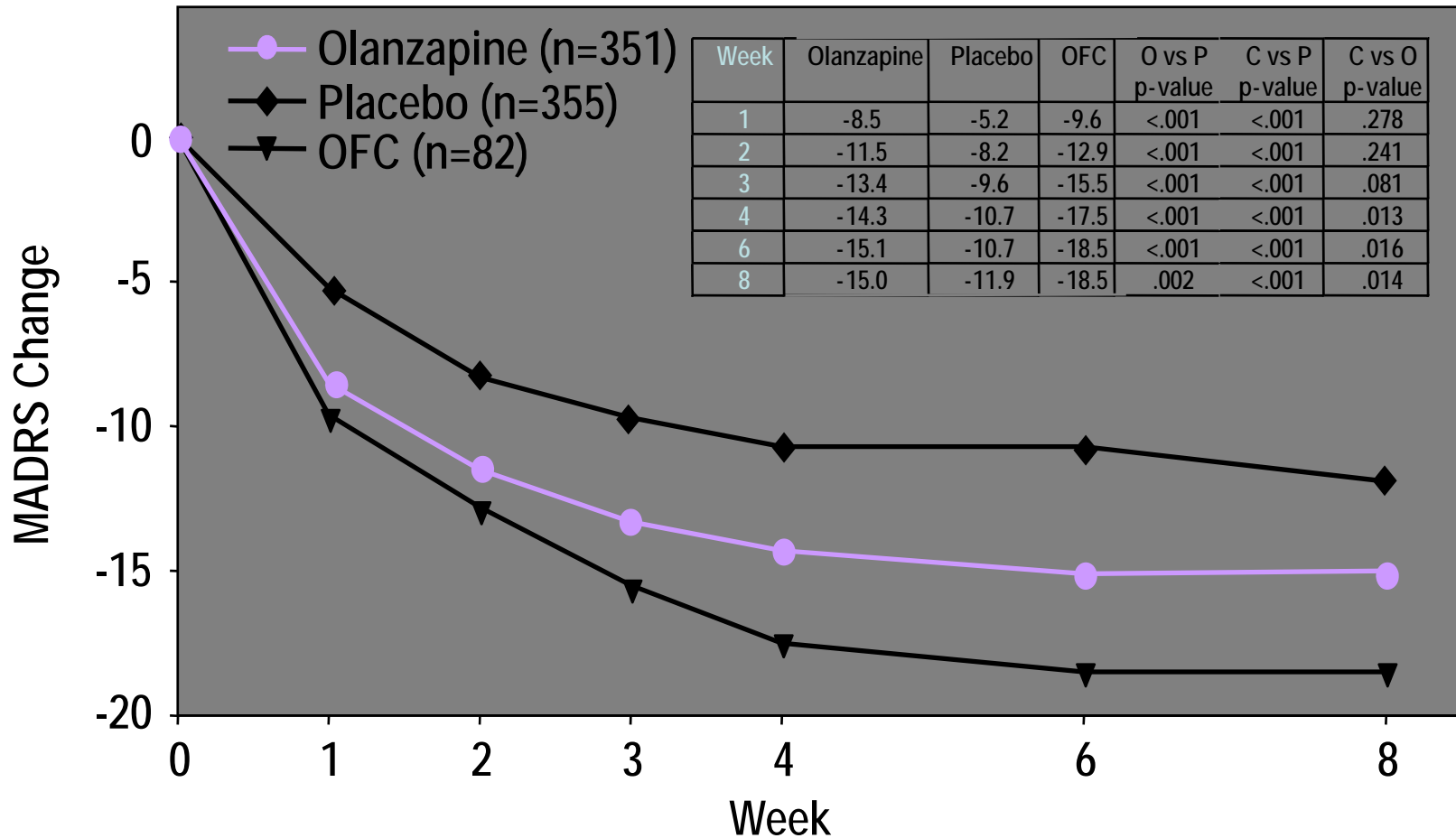
†p<.001 vs placebo.

Calabrese JR, et al. *Am J Psychiatry*. 2005;162(7):1351-1360.

# Study Design

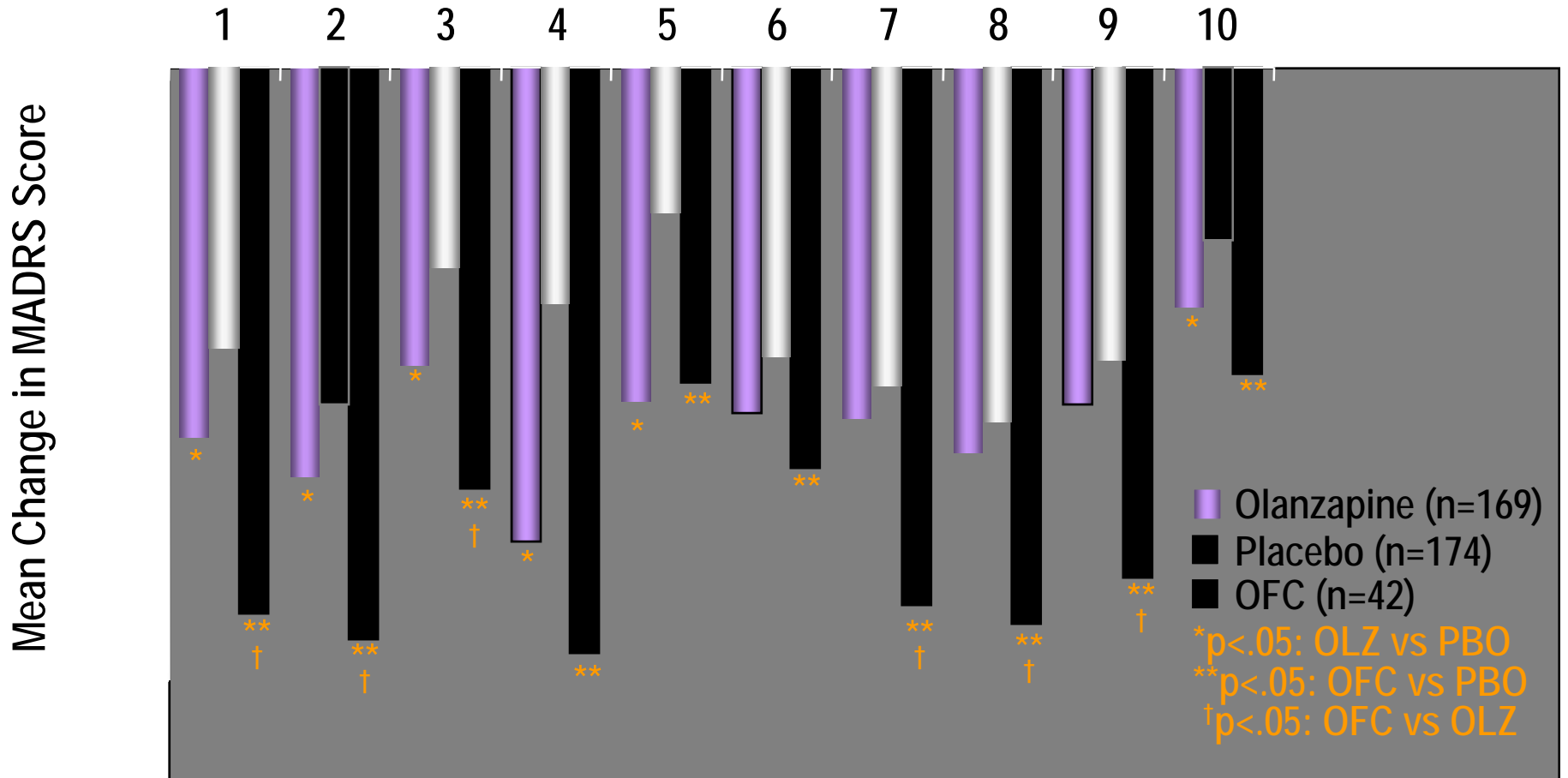
STUDY PERIOD	I. Screening	II. Acute Double Blind	III. Open Label Extension						
THERAPY	None	OLZ (5-20 mg/day) COMBO (OLZ + FLX) (6 mg/day+25 mg/day, 6 mg/day+50 mg/day, OR 12 mg/day+50 mg/day) PLACEBO	OLZ (5-20 mg/day) COMBO (OLZ + FLX) (6 mg/day+25 mg/day, 6 mg/day+50 mg/day, OR 12 mg/day+50 mg/day)						
DURATION	2-14 DAYS	8 WEEKS	6 MONTHS						
VISIT #	1	2* Weekly	6 Biweekly	8 Weekly	301 Biweekly	302 Monthly	303 Bimonthly	304 Bimonthly	306 Bimonthly

# Improvement Over 8 Weeks



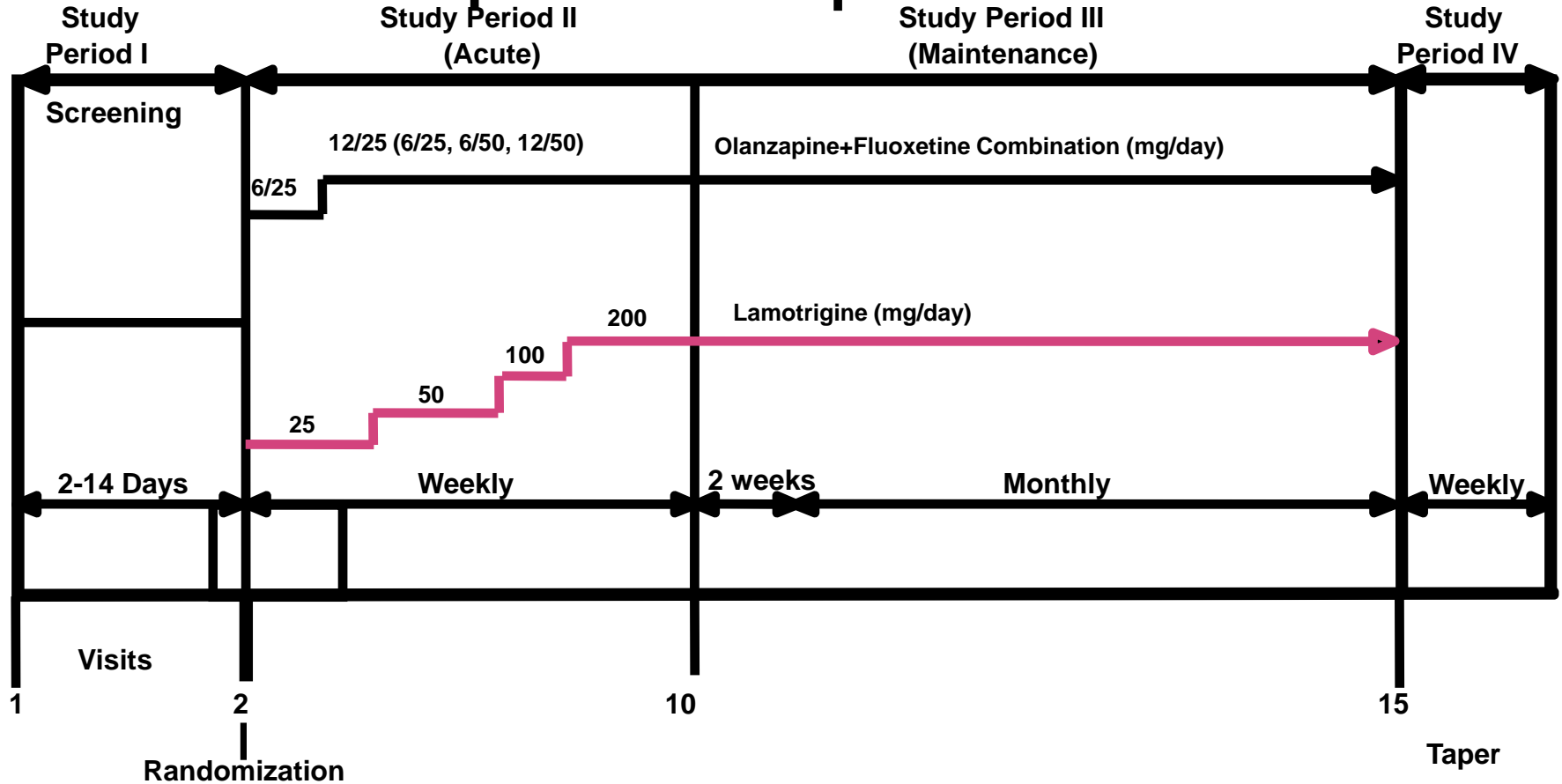
Tohen M, et al. *Arch Gen Psychiatry*. 2003;60(11):1079-1088.

# Symptom Improvement

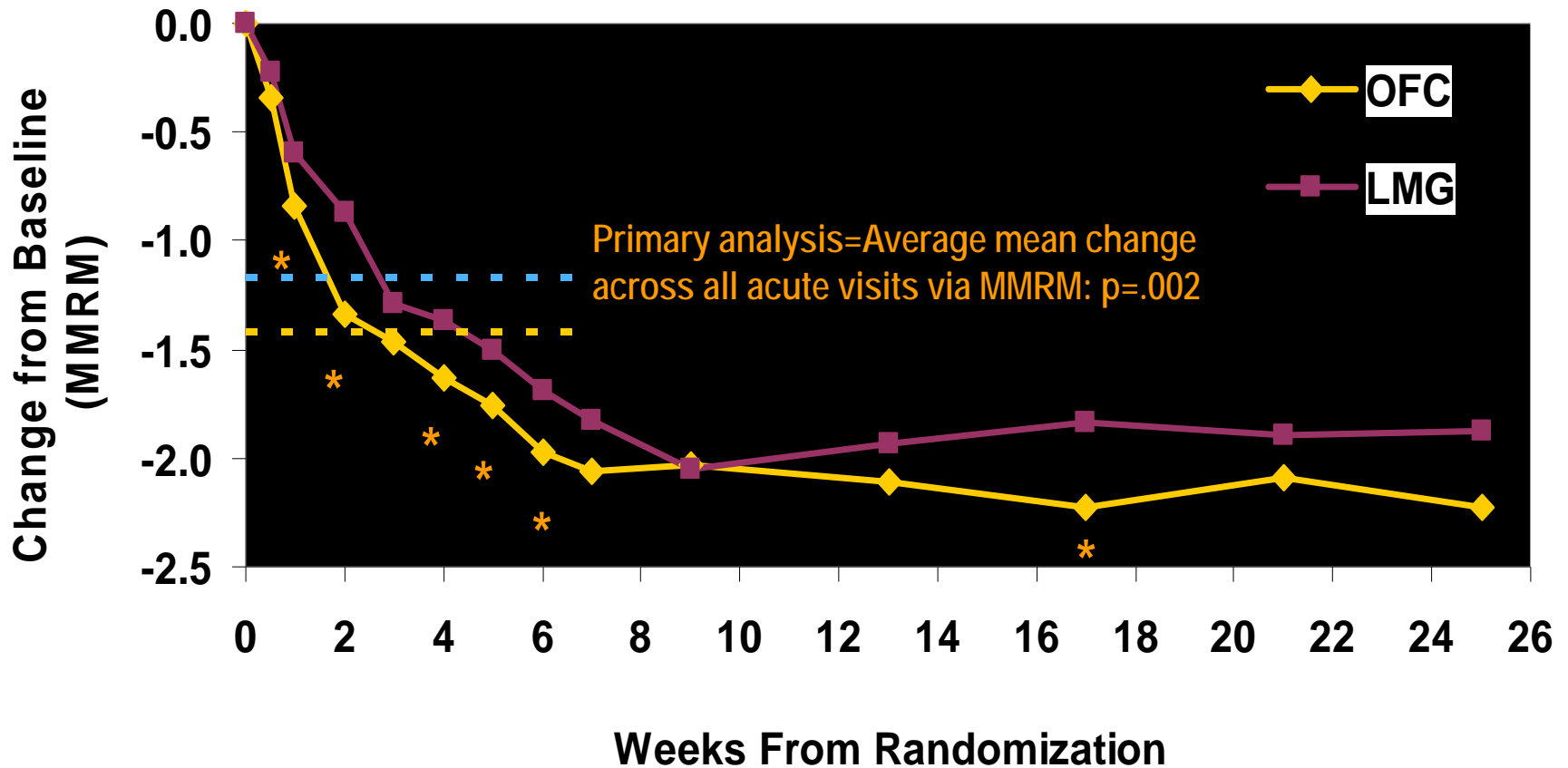


MADRS Items: 1) Apparent Sadness; 2) Reported Sadness; 3) Inner Tension;  
 4) Reduced Sleep; 5) Reduced Appetite; 6) Concentration; 7) Lassitude;  
 8) Inability to Feel; 9) Pessimistic Thoughts; 10) Suicidal Thoughts.

# Olanzapine+Fluoxetine Combination vs Lamotrigine in Bipolar Depression

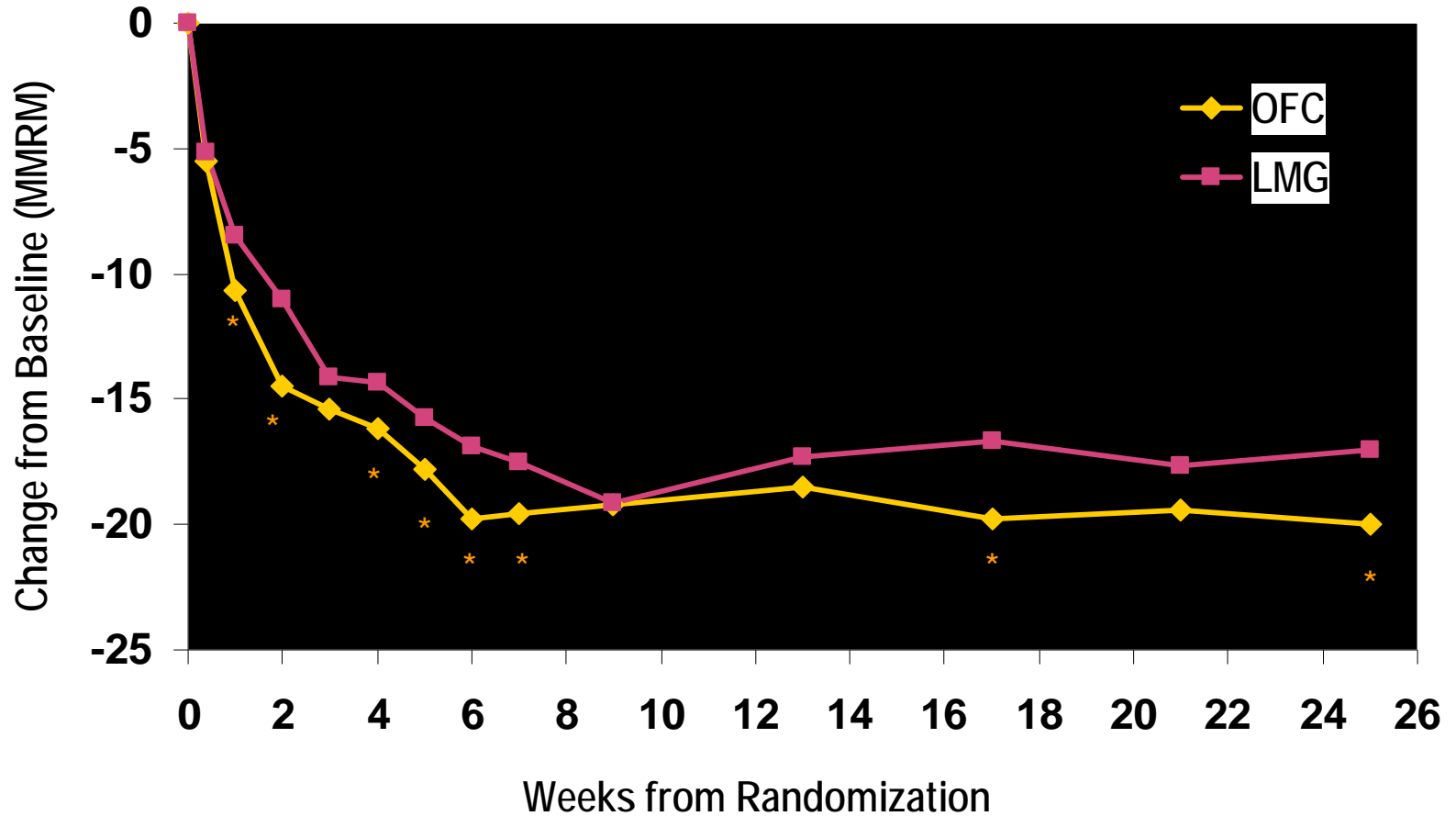


# CGI-Severity



Primary analysis (average mean change during acute phase via mixed models repeated measures [MMRM]): OFC, -1.43; LMG, -1.175;  $p=.002$ .  
CGI=Clinical Global Impressions scale. Endpoint analysis (estimates at week 25 via MMRM): OFC, -2.22; LMG, -1.88;  $p=.062$ .  
Dunner D, et al. Presented at: ACNP; Dec 11-15, 2005; Waikoloa, Hawaii.

# MADRS Total

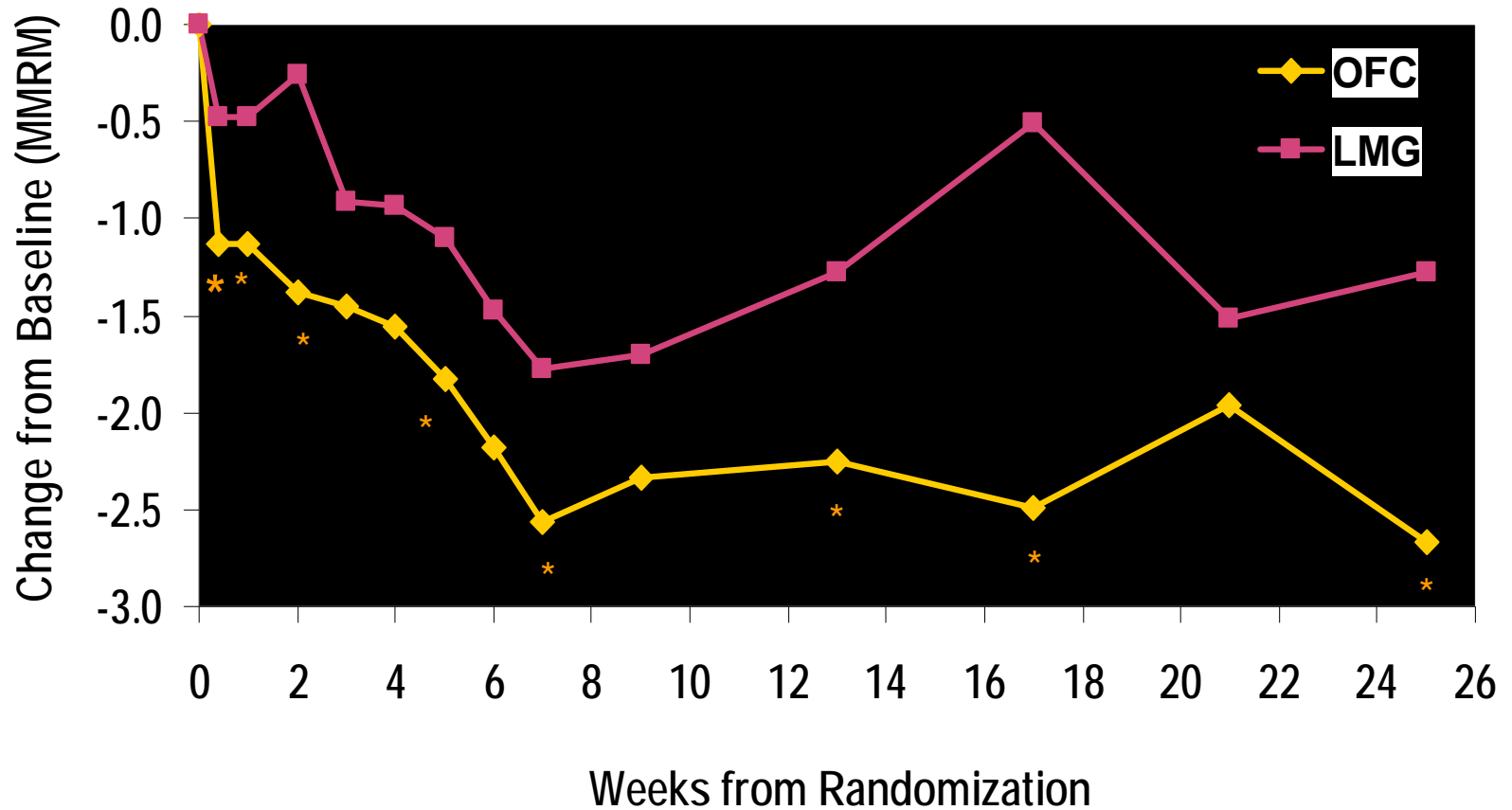


Overall: OFC -16.63; LMG -14.70;  $p=.005$ .

Endpoint results (LOCF): OFC -17.85; LMG -15.73;  $p=.029$ .

Dunner D, et al. Presented at: ACNP; Dec 11-15, 2005; Waikoloa, Hawaii.

# YMRS



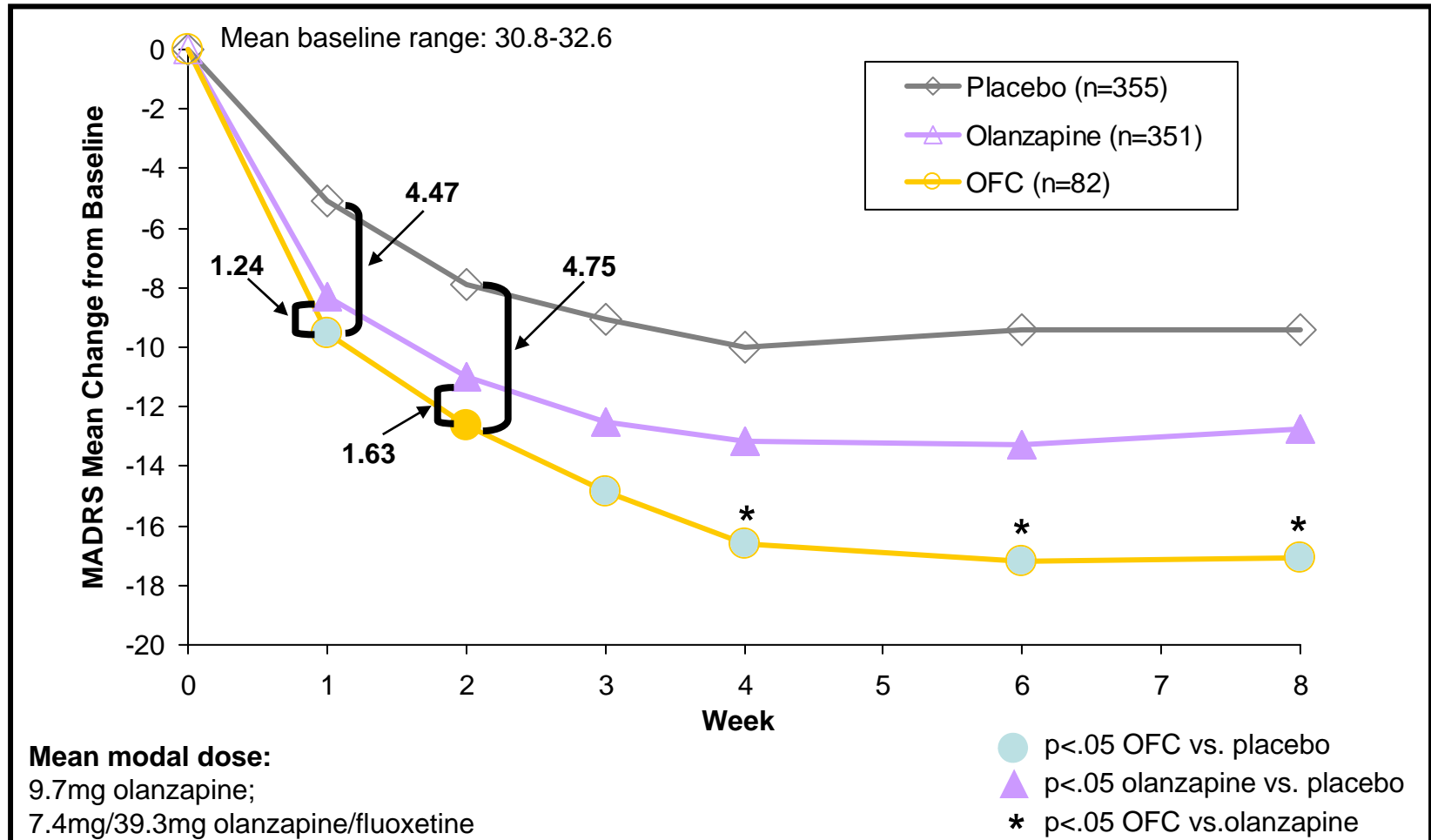
Overall: OFC -1.92; LMG -1.05;  $p < .001$ .

Endpoint results (LOCF): OFC -1.56, LMG -0.69;  $p = .008$ .

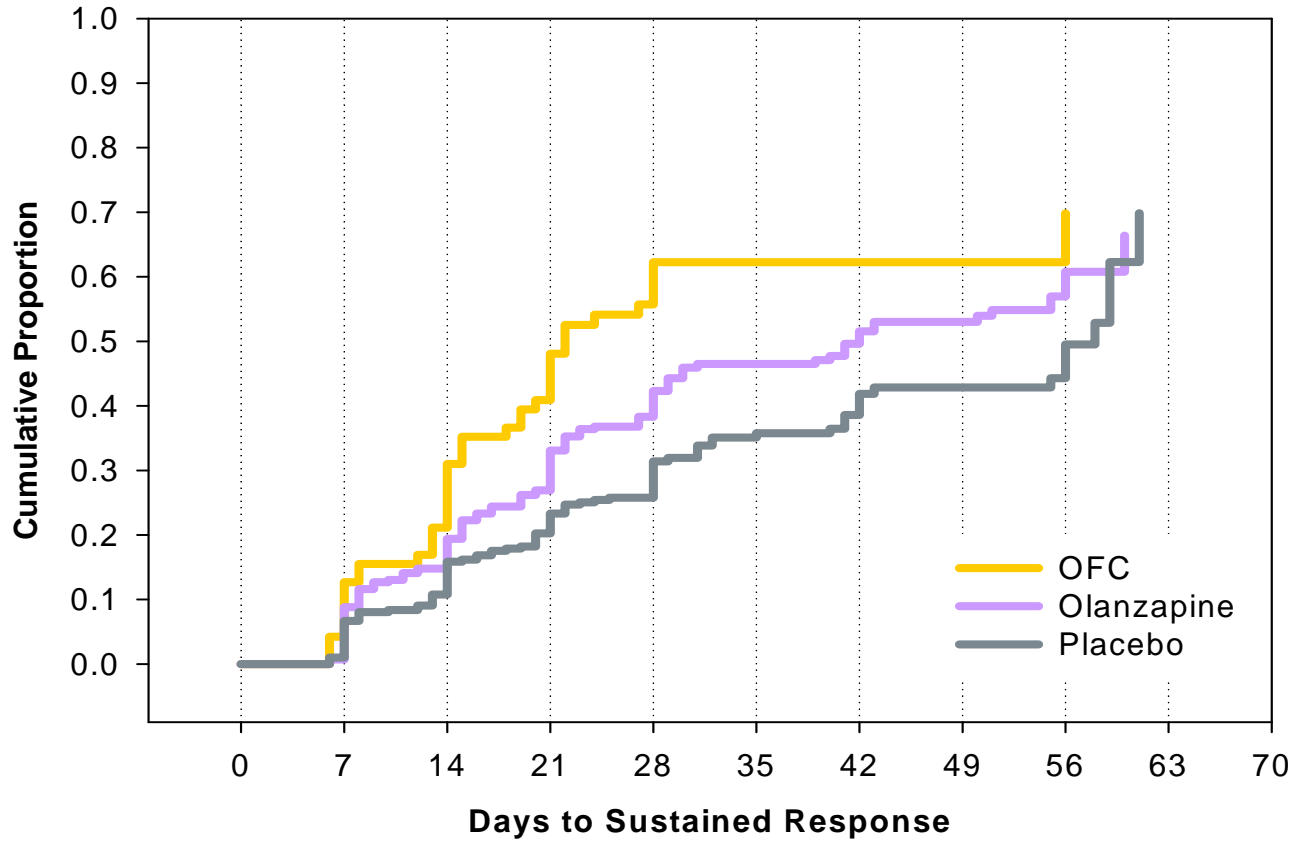
Dunner D, et al. Presented at: ACNP; Dec 11-15, 2005; Waikoloa, Hawaii.

**ONSET OF ACTION**

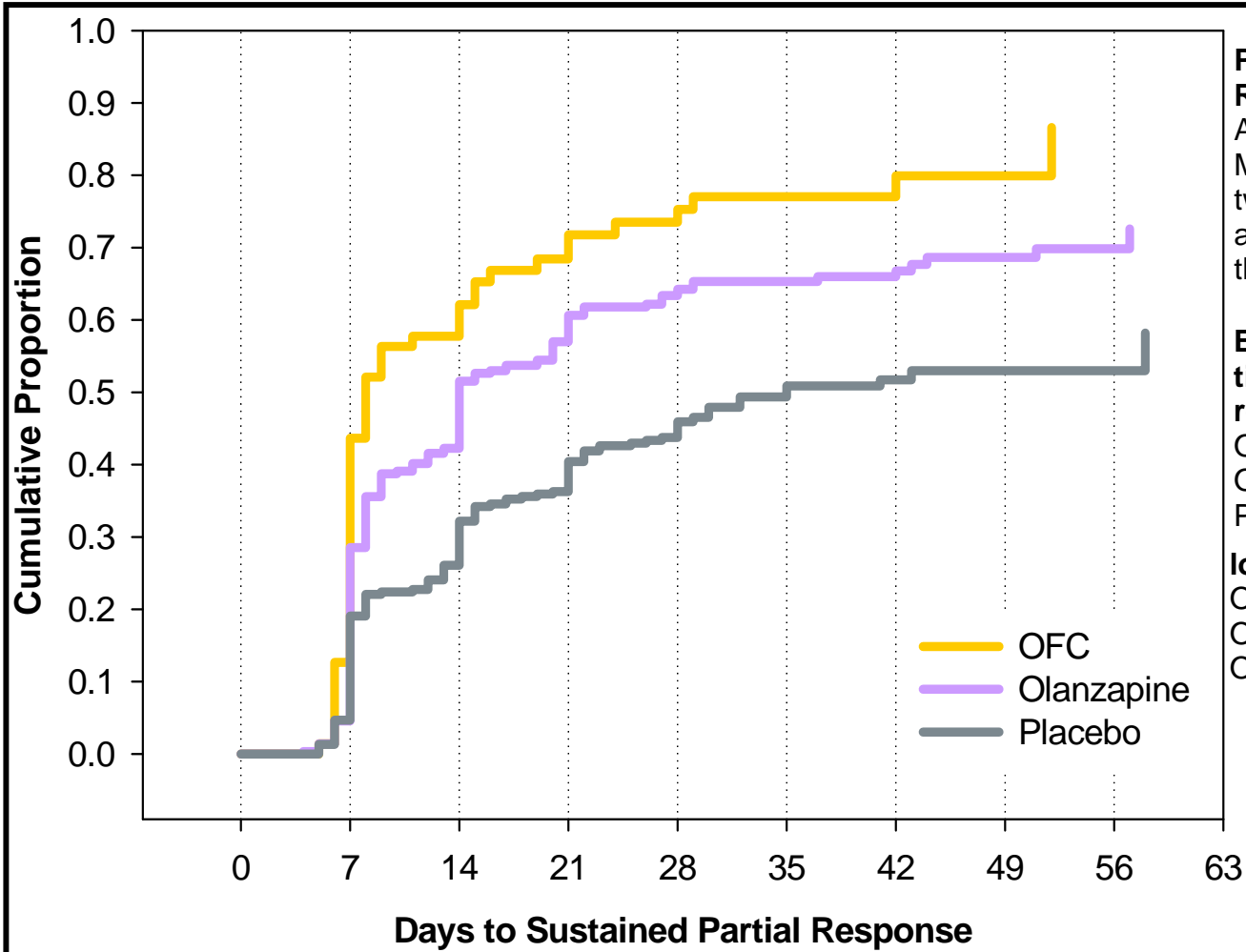
# TRADITIONAL ANALYSIS: 1 AND 2 WEEK DIFFERENCES IN MADRS TOTAL SCORES (LOCF)



# KAPLAN-MEIER SURVIVAL ANALYSIS: FULL SUSTAINED RESPONSE



**KAPLAN-MEIER SURVIVAL ANALYSIS:  
PARTIAL SUSTAINED RESPONSE**



**Partial-Sustained Response:**  
A  $\geq 20\%$  reduction in MADRS Total Score for two consecutive weeks and sustained until the end of treatment

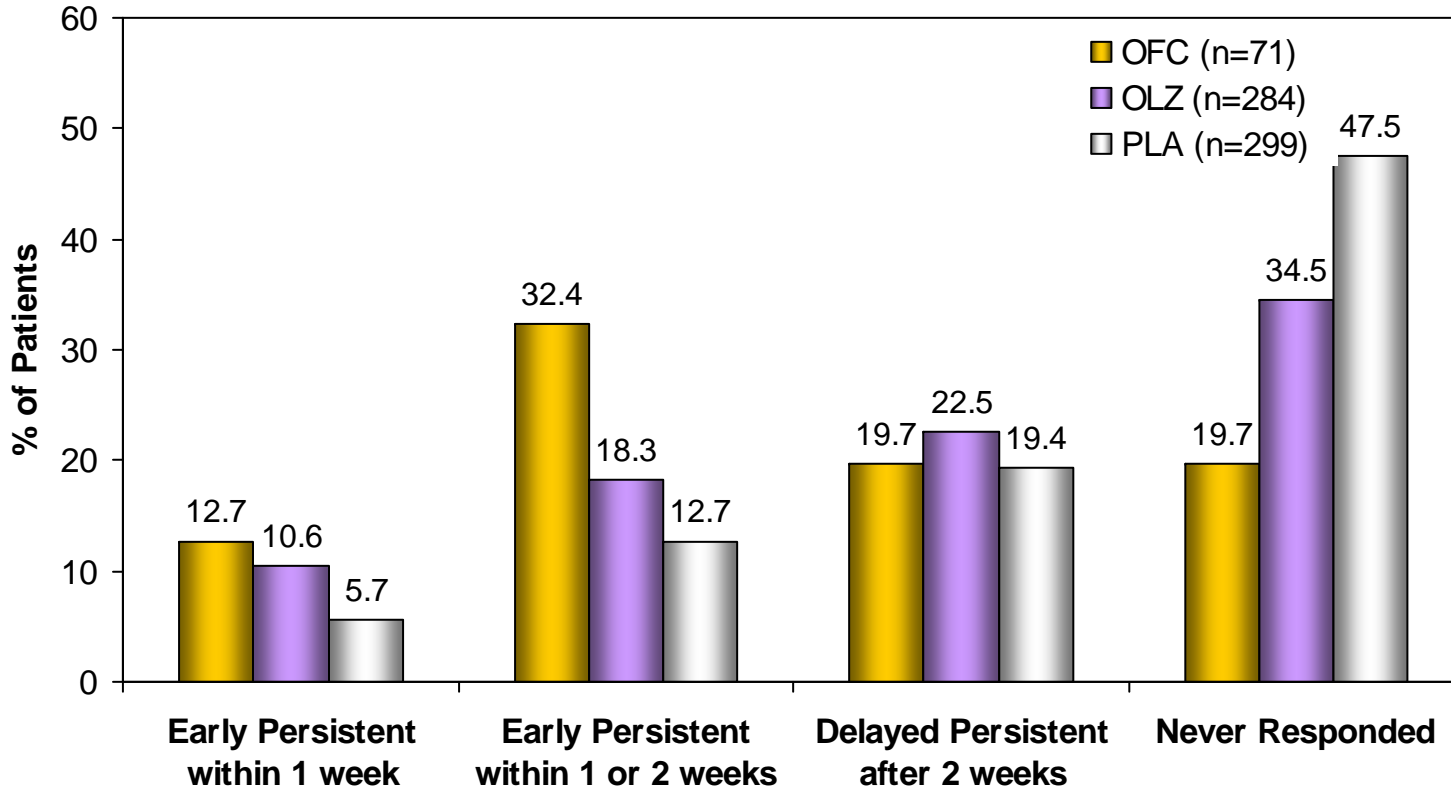
**Estimated median time to partial response:**

OFC=8 days  
OLZ=14 days  
PLA=35 days

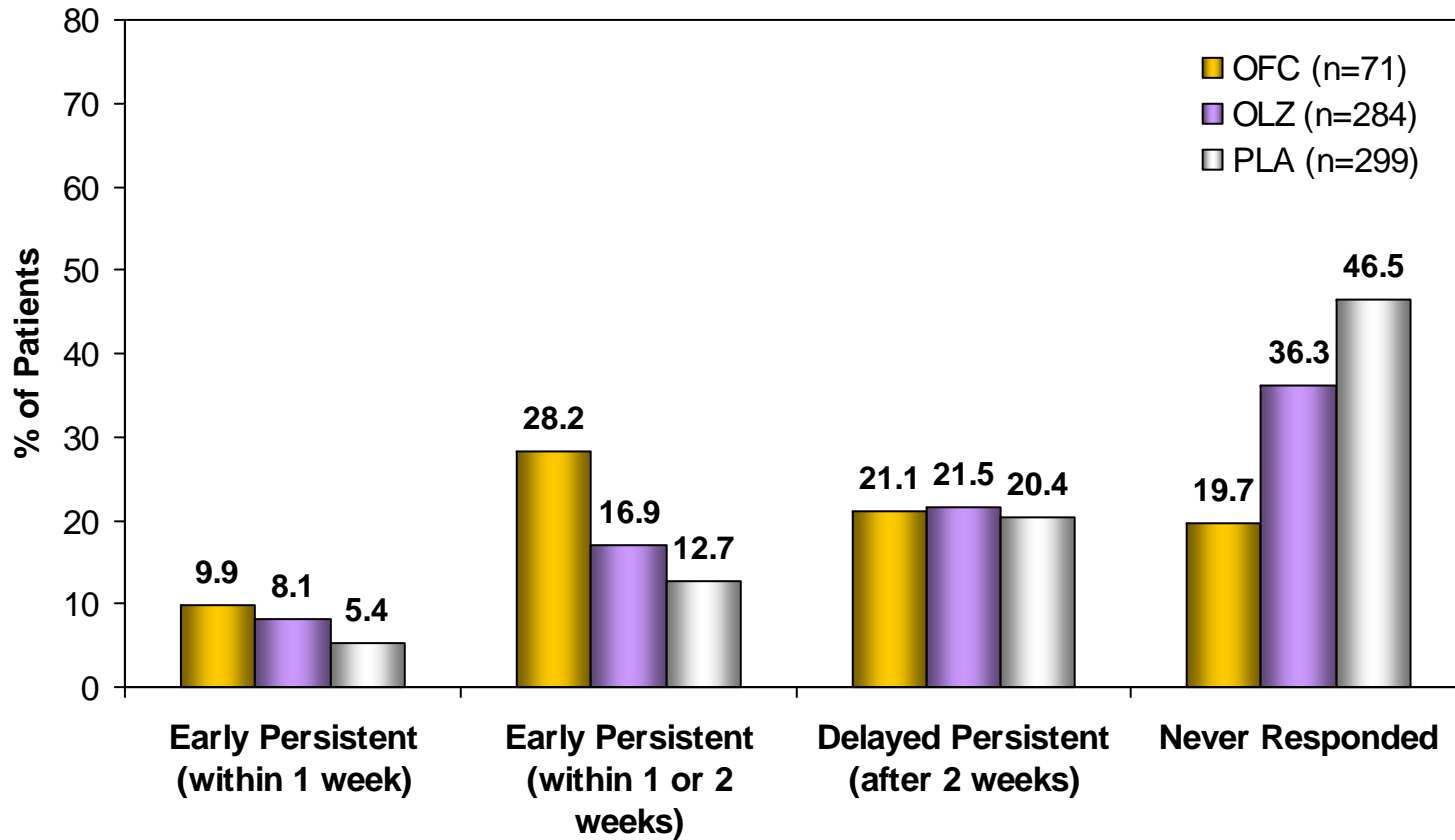
**log-rank  $X^2$  test:**

OFC vs. PLA  $p=.0001$   
OLZ vs. PLA  $p=.0001$   
OFC vs. OLZ  $p=.0085$

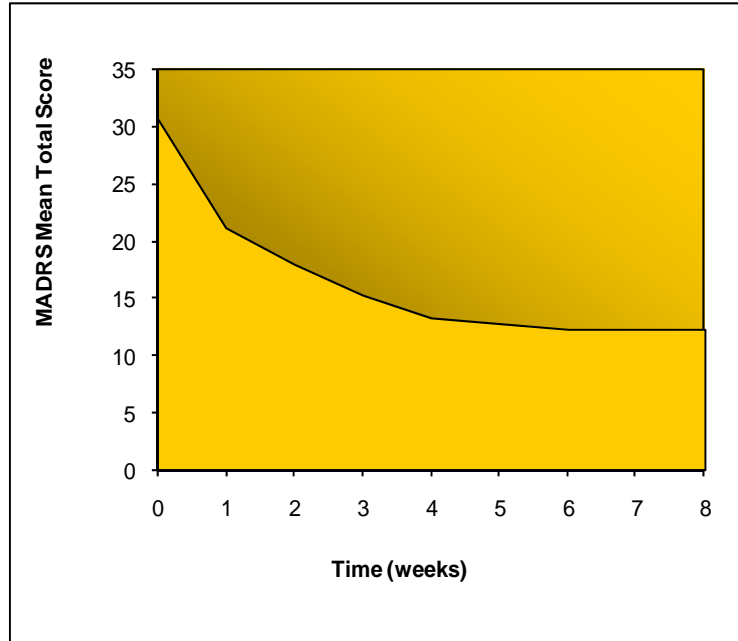
**PATTERN ANALYSIS: PERCENTAGE OF PATIENTS WHO RESPONDED WITHIN 1-2 WEEKS AND DID NOT SUBSEQUENTLY RELAPSE**



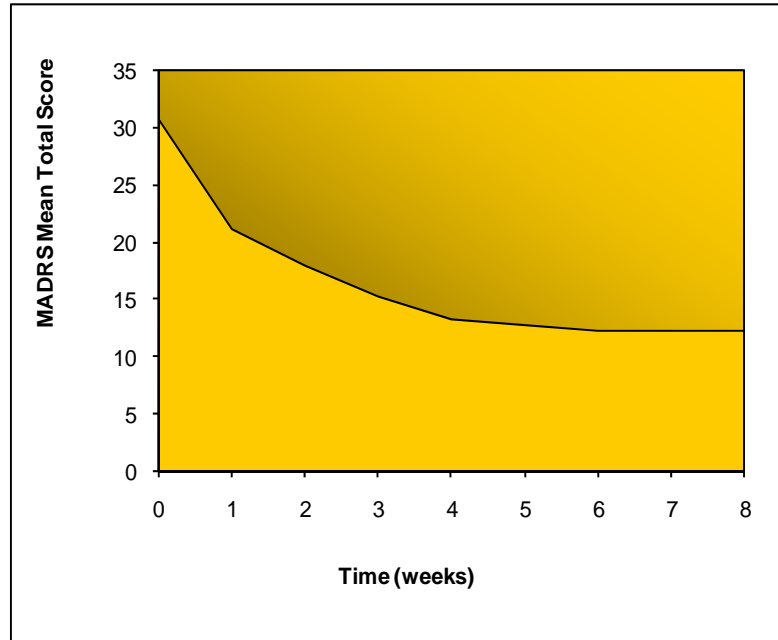
**PATTERN ANALYSIS: PERCENTAGE OF PATIENTS WHO RESPONDED WITHIN 1-2 WEEKS AND DID NOT SUBSEQUENTLY RELAPSE (MADRS SLEEP AND APETITE ITEMS EXCLUDE)**



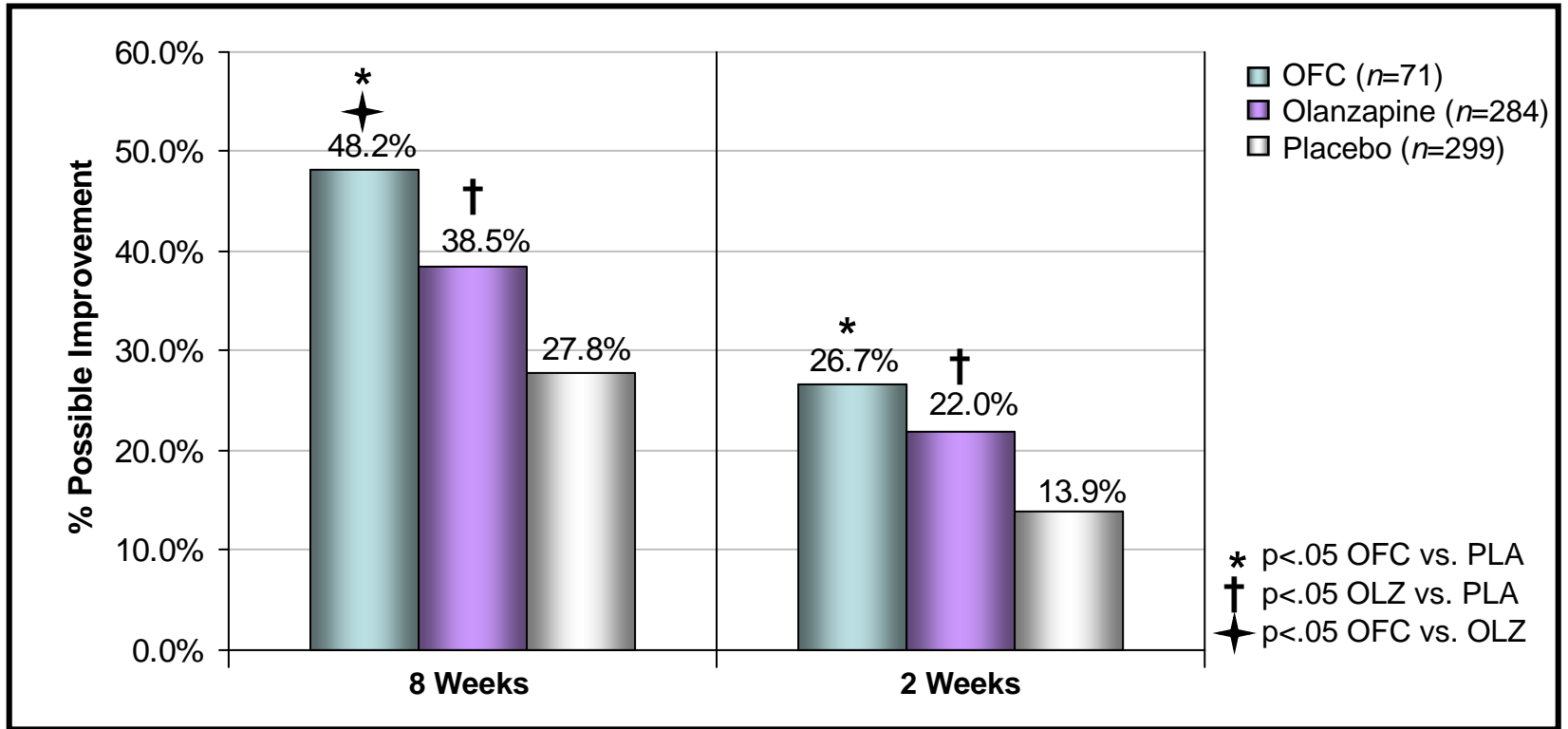
## EXAMPLES OF AREA UNDER THE CURVE (AUC) 8 WEEK AUC



## EXAMPLES OF AREA UNDER THE CURVE (AUC) 2 WEEK AUC



**AREA UNDER THE CURVE: PERCENTAGE OF TOTAL POSSIBLE IMPROVEMENT ON MADRS OVER 8 WEEKS AND OVER 2 WEEKS**



# CONCLUSIONS