

# **Clinical Trial Methodology - Maintenance in Bipolar Disorder**

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# Clinical Trials in Bipolar Disorder- Principles:

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- **Priority** - best interest of patients
- **Goal** – Determine efficacy and safety of Rx
- **Clinical Epidemiology** – determines design
- **Phase** – determines design
- **Design** - optimize validity and feasibility
- Internal Validity **prevails** over External Validity

# Relapse Prevention Clinical Trials in Bipolar Disorder- Topics:

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- Time in remission
- Gradual vs rapid discontinuation
- Index episode
- Polarity of relapse
- Definition of relapse

# Clinical Epidemiology

# Bipolar Disorder -Clinical Epidemiology

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- Life long condition with acute episodes interspersed with periods of variable remission
  - Length of maintenance trials
  - Index episode may determine definition of remission/recovery/responder status
    - Depression - 6 months
    - Mania 2-3 months
    - Mixed - ???
    - Subsyndromal - ???

# **Clinical Trials in Bipolar Disorder- Principles:**

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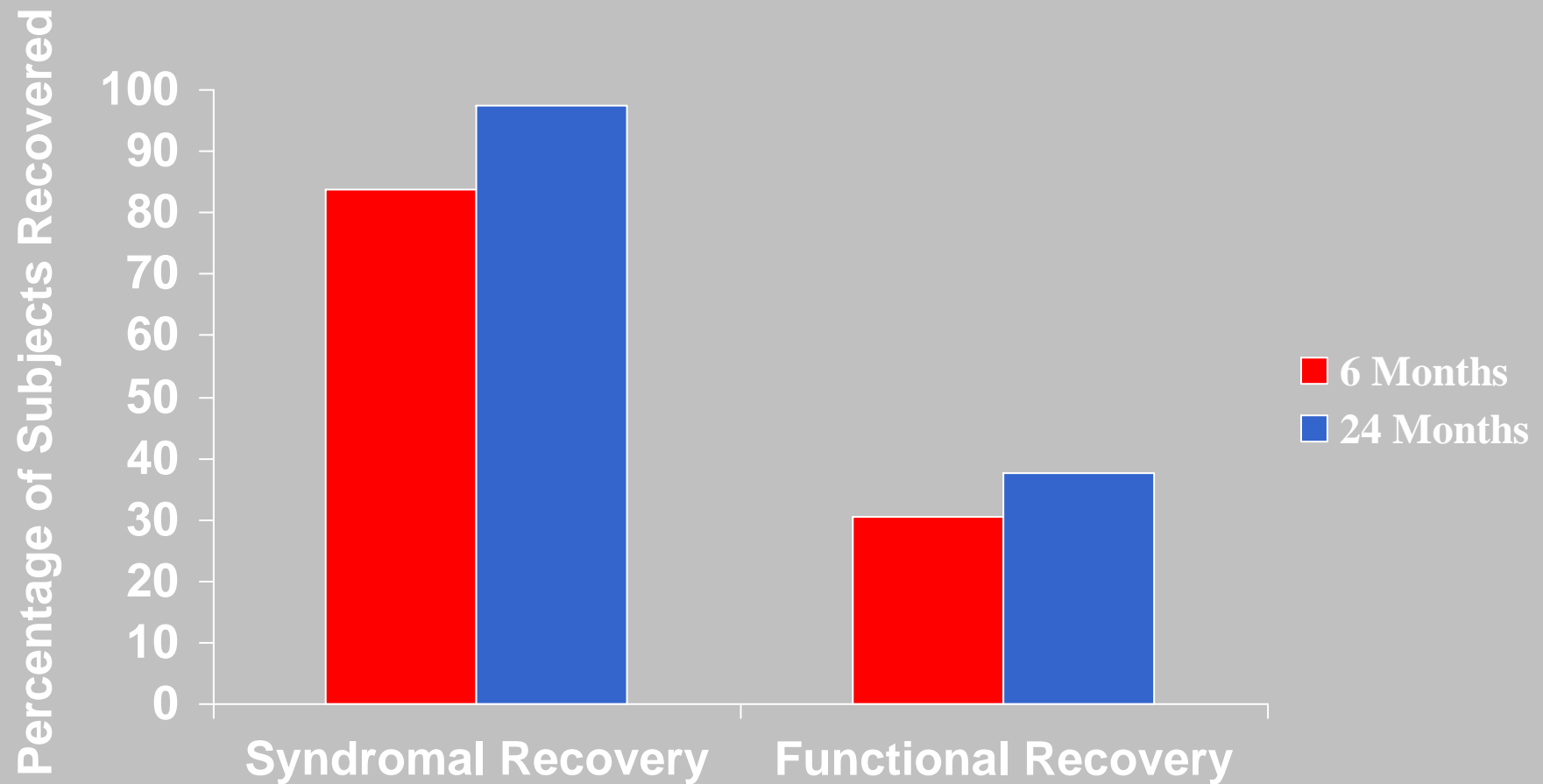
- **Clinical Epidemiology –  
determines design**

# Recovery - definition

# 2 Year Outcome: Recovery

Outcome	% of Subjects
Index episode	
Syndromally recovered	97.5
Symptomatically recovered	72.6
Functionally recovered	35.5

# Patients With First-Episode Psychotic Affective Disorders Who Reached Syndromal and Functional Recovery



**Phase determines design  
Relapse**

**Length in remission (responder Status)–**

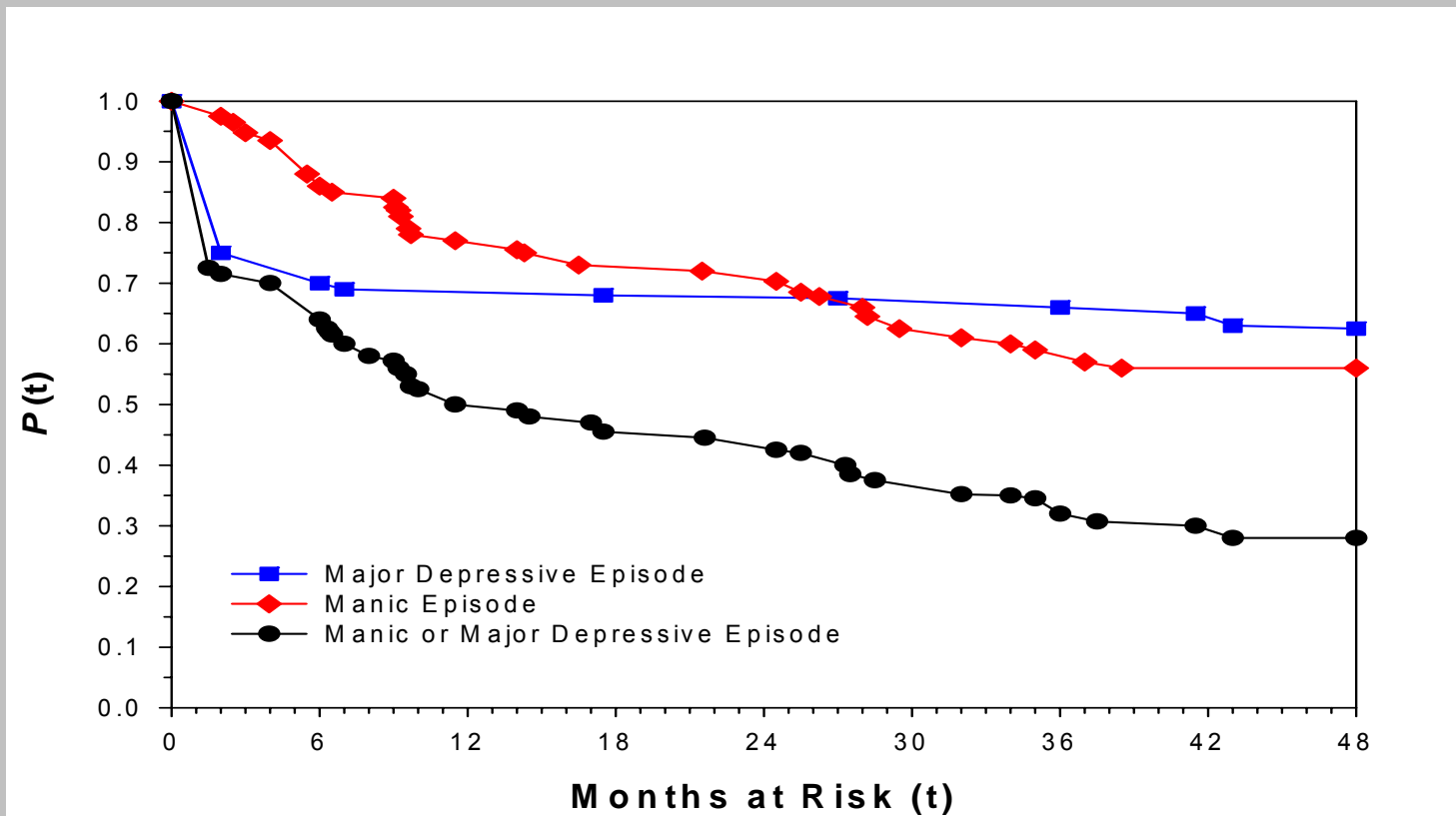
**Is length of remission associated with relapse outcome?**

# Length of Remission Period

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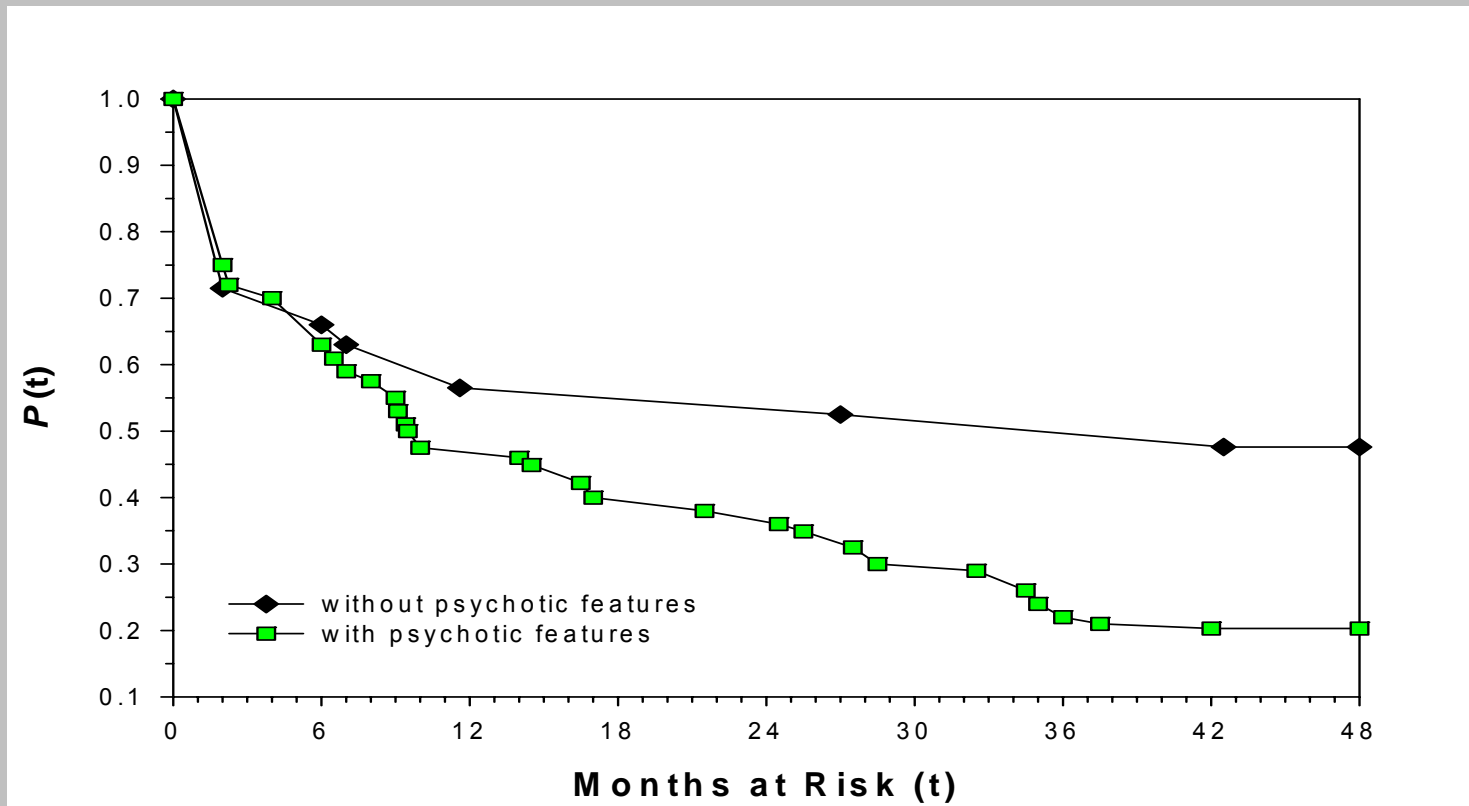
- **Does length of remission period determine risk of Relapse?**
- **length of remission period?**
  - At the time of achieving remission?
  - Weeks?
  - Months?
  - **DSM-IV - 8 weeks**
- **Design should reflect clinical epidemiology**
  - **Population enriched with atypical patients can be misleading**

# Cumulative Probability of Not Relapsing after 8 weeks in remission



No. of	75	53	52	51	51	50	47	■
Subjects	75	66	58	55	54	44	42	◆
at Risk	75	48	38	34	33	25	21	●

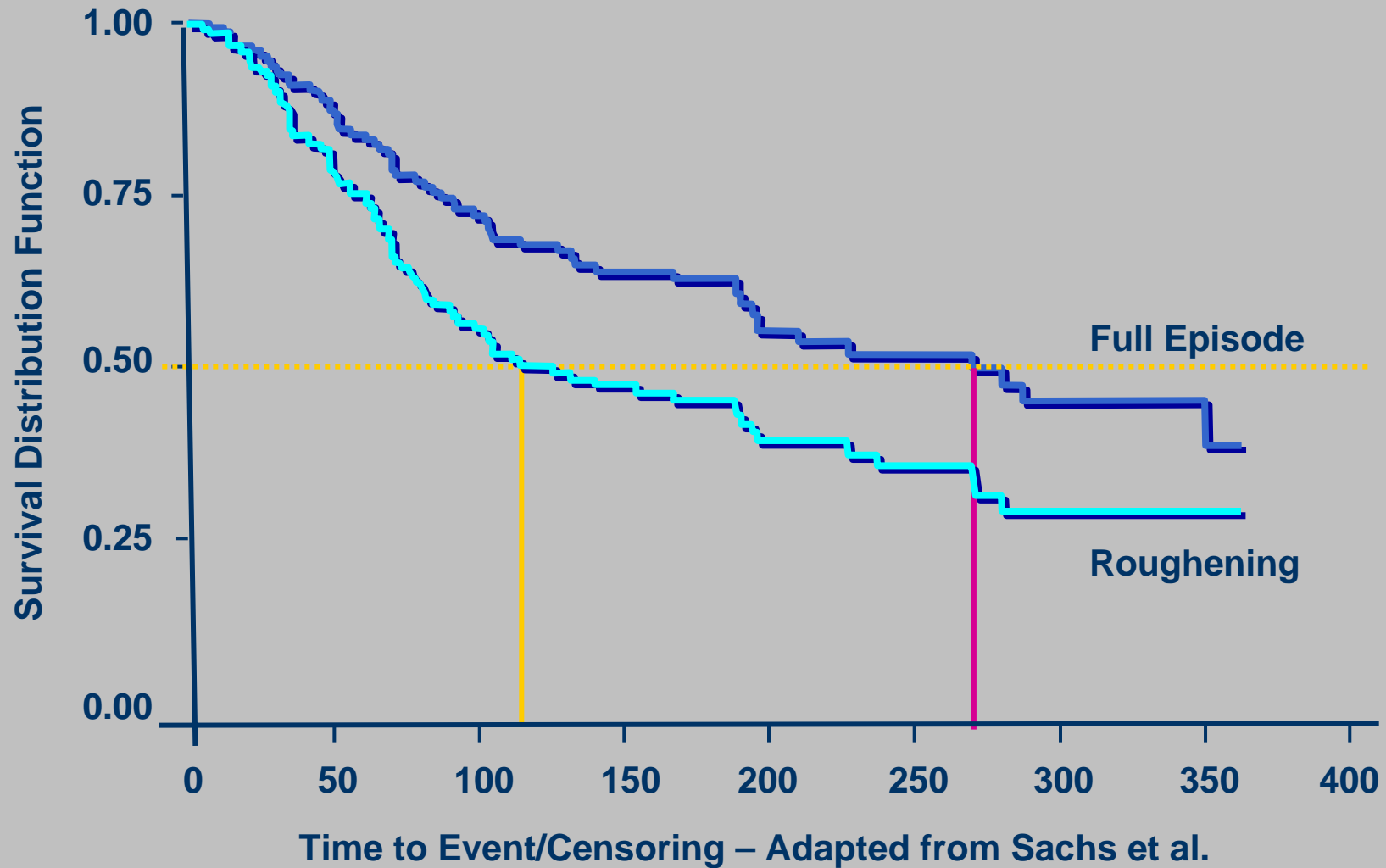
# Cumulative Probability of Not Relapsing for Patients with and without Psychotic Features after 8 week in remission



No. of	54	34	26	22	21	14	11	■
Subjects	21	14	12	12	12	11	10	◆
at Risk								

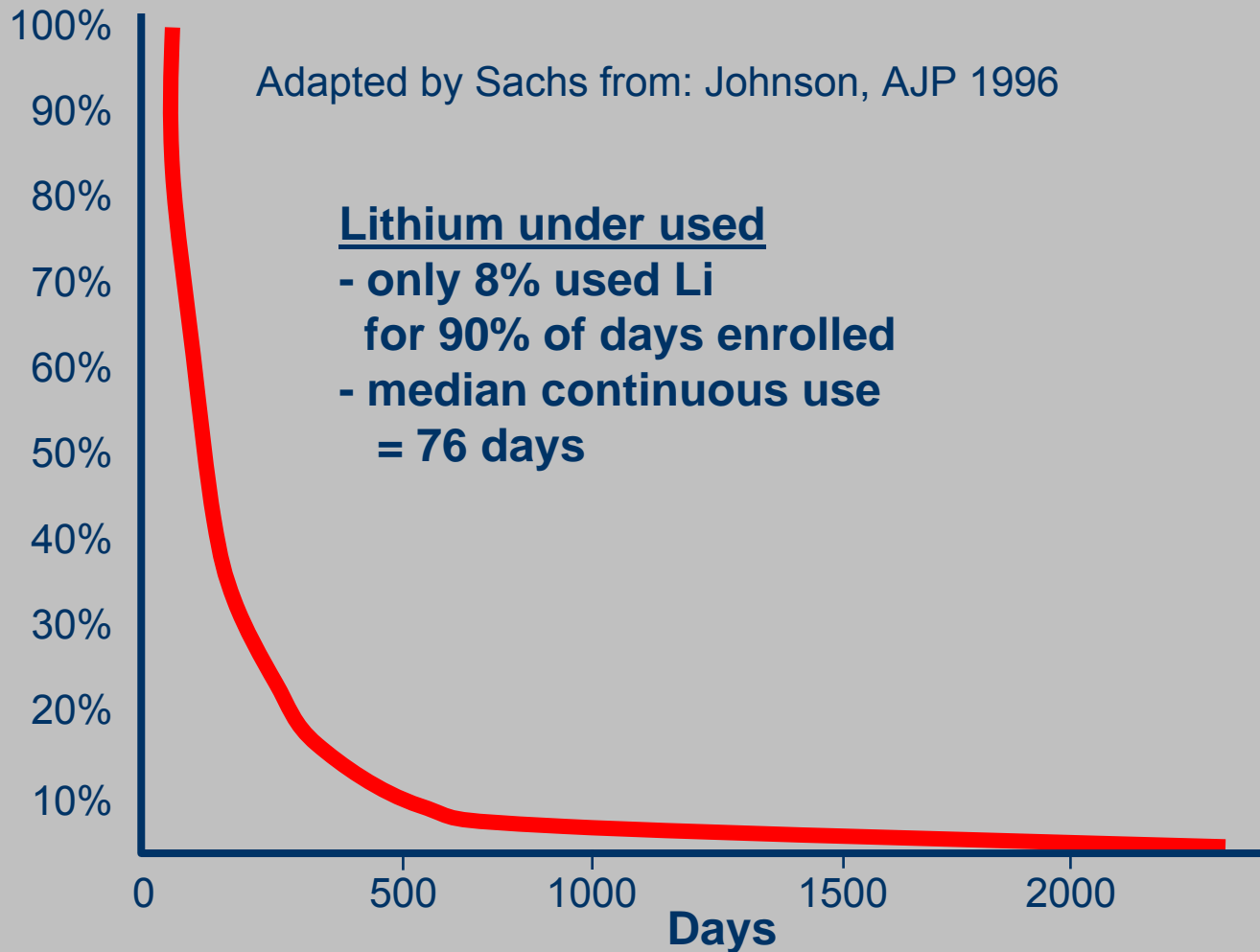


# STEP-BD Time to Relapse and Roughening after Recovery (8 weeks stable remission)



# **External Validity - generalizability**

# Lithium Use and Discontinuation in a Health Maintenance Organization



Length of first continuous period of Lithium use (n=1594)

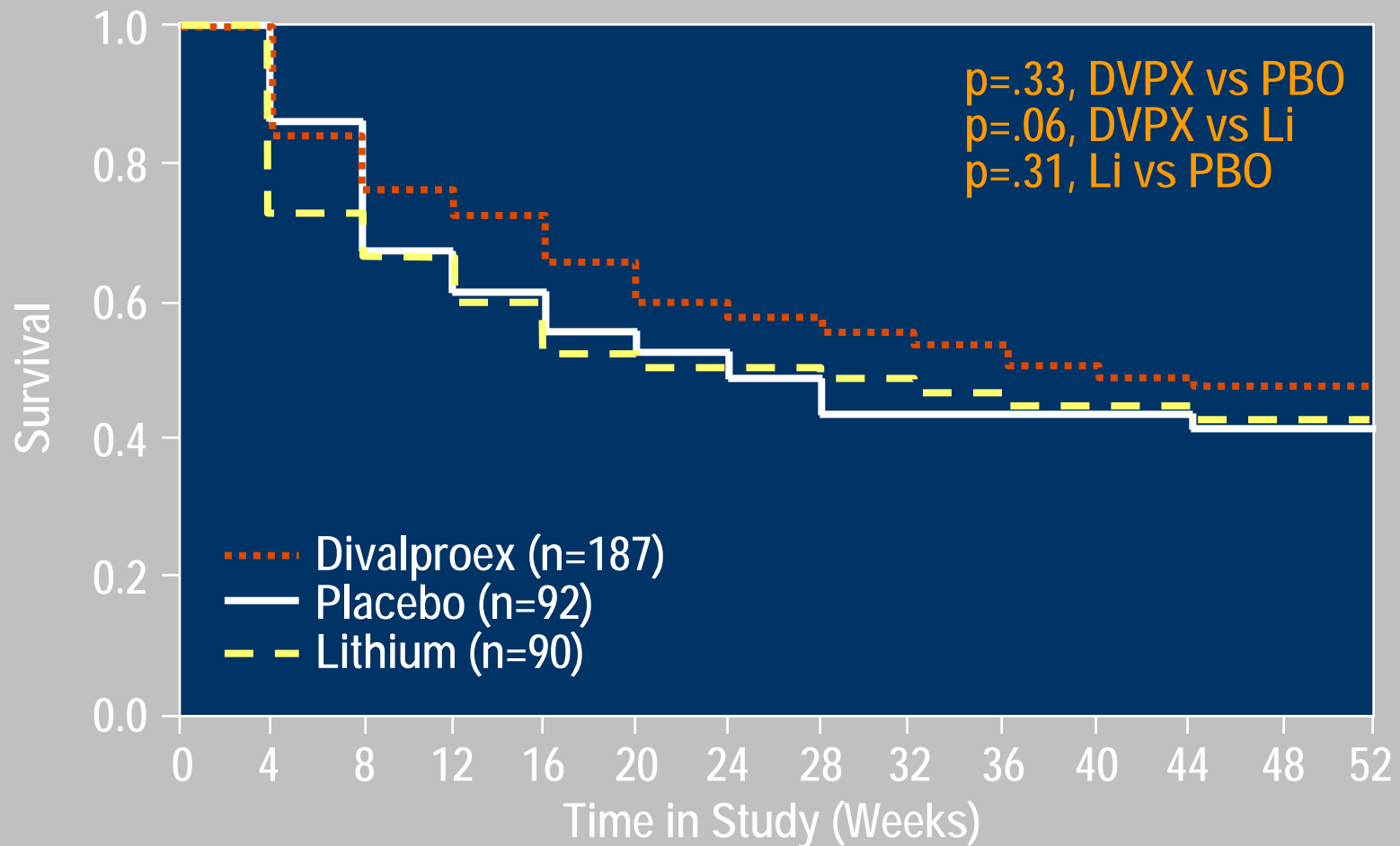
## **Definition of remission?**

- Scale score cut point
- Duration
- Treatments allowed

# **Length of Remission – clinical trials examples**

**Length of Remission –  
long**

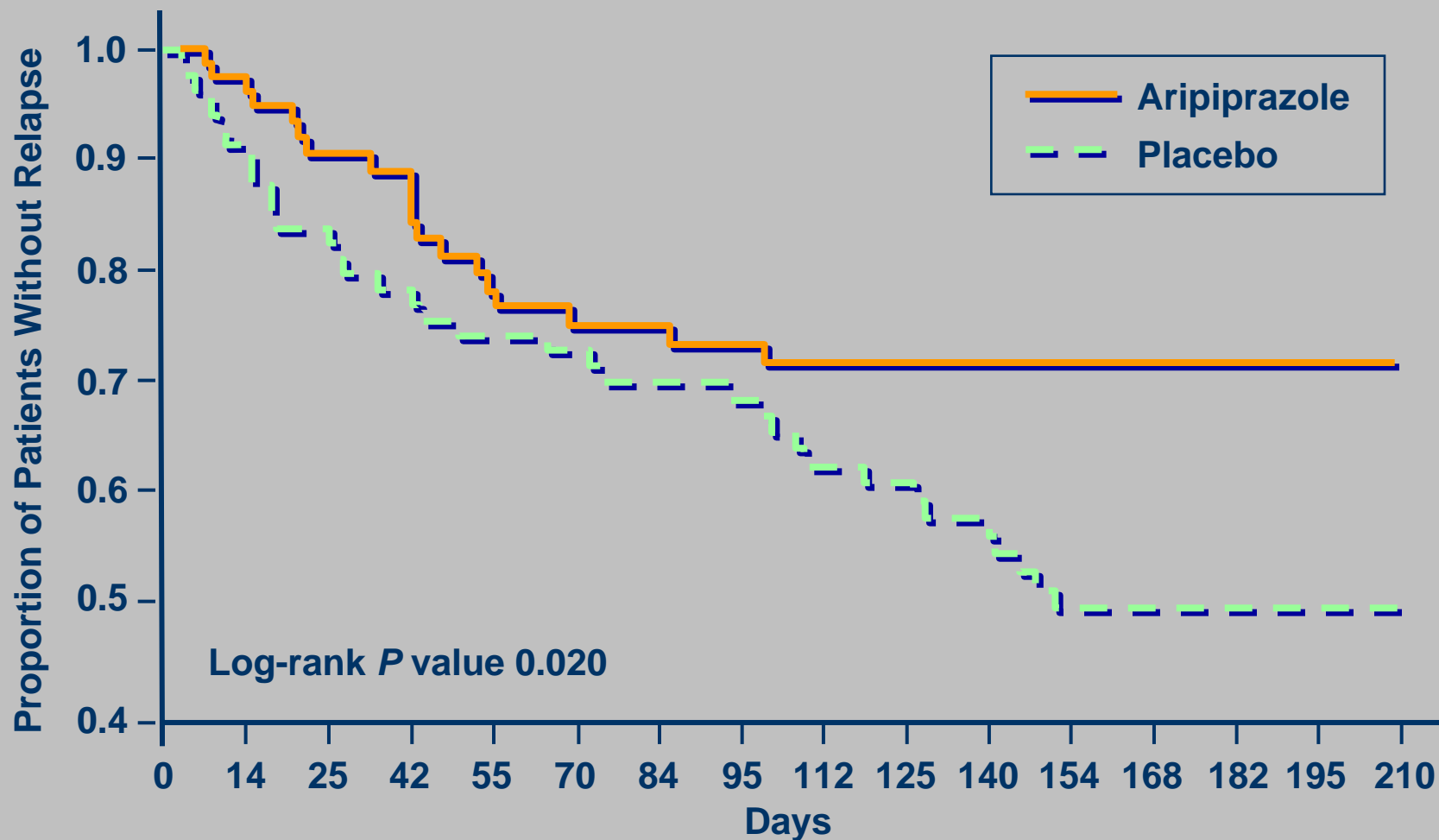
# Divalproex vs Lithium vs Placebo



Bowden CL, et al. *Arch Gen Psychiatry*. 2000;57(5):481-489.

# Aripiprazole vs placebo

Required 6 Weeks Well for Randomization

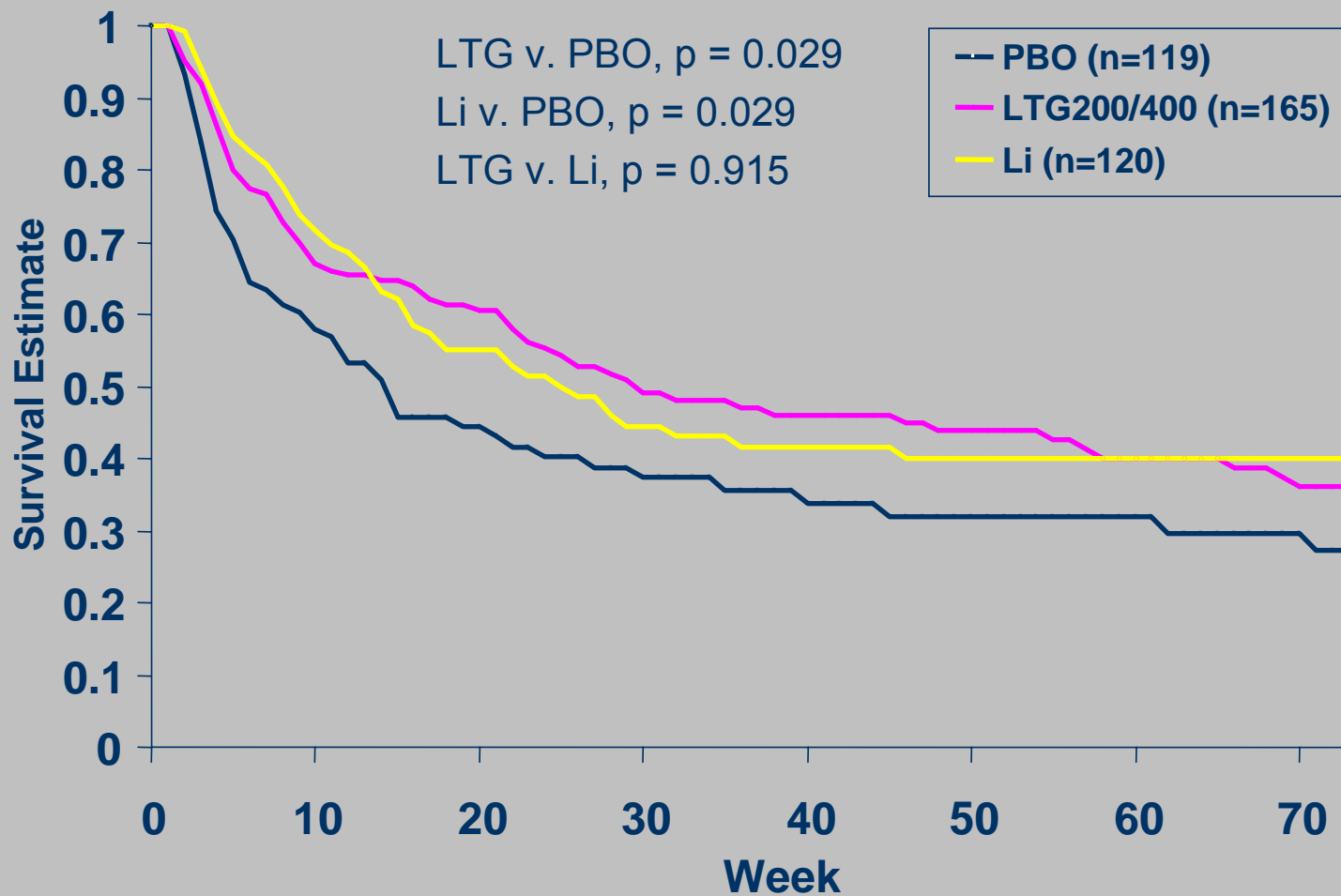


**Length of Remission –  
short**

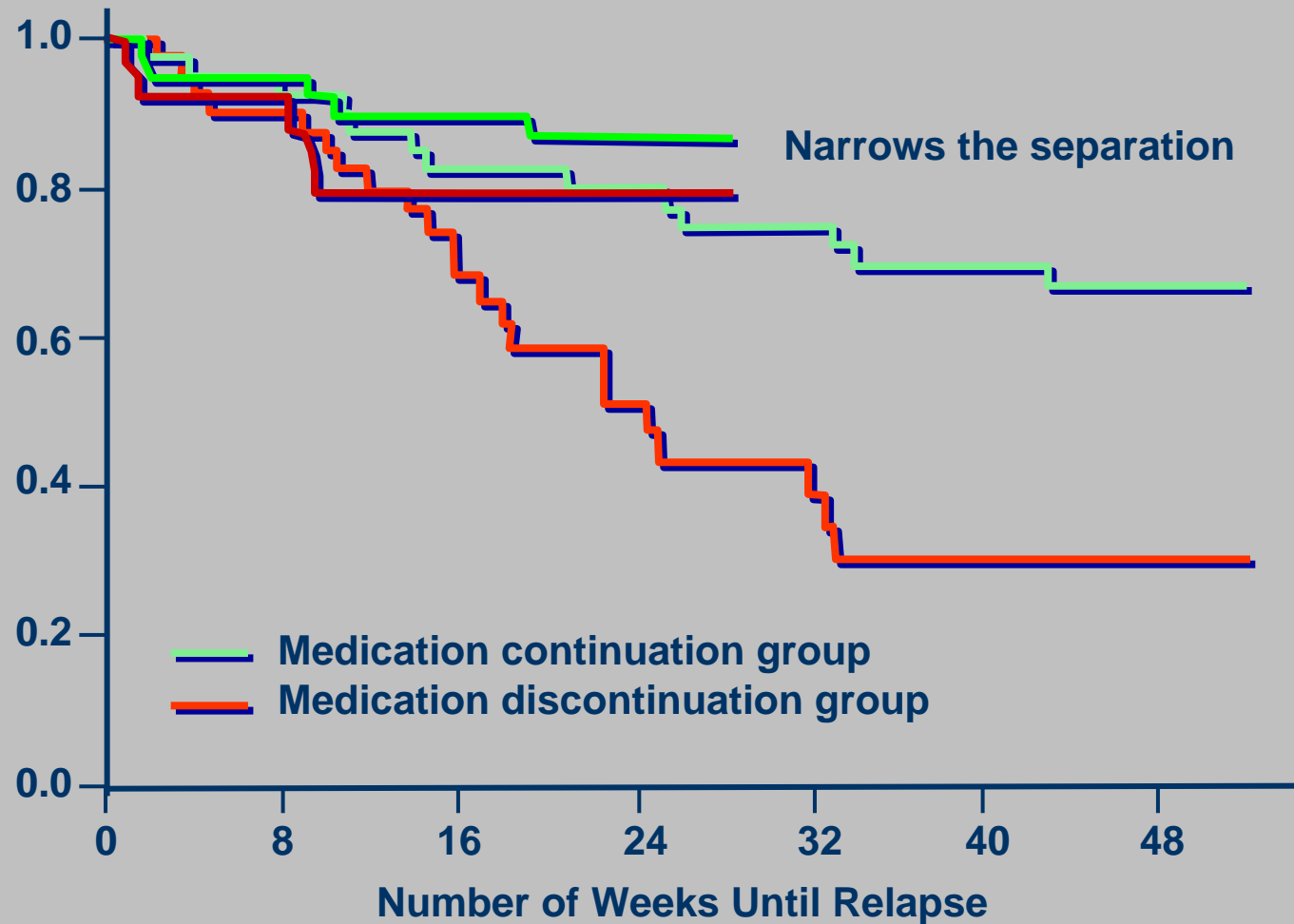
# Lamotrigine vs Li vs Pbo

Randomized after 1 week stabilization

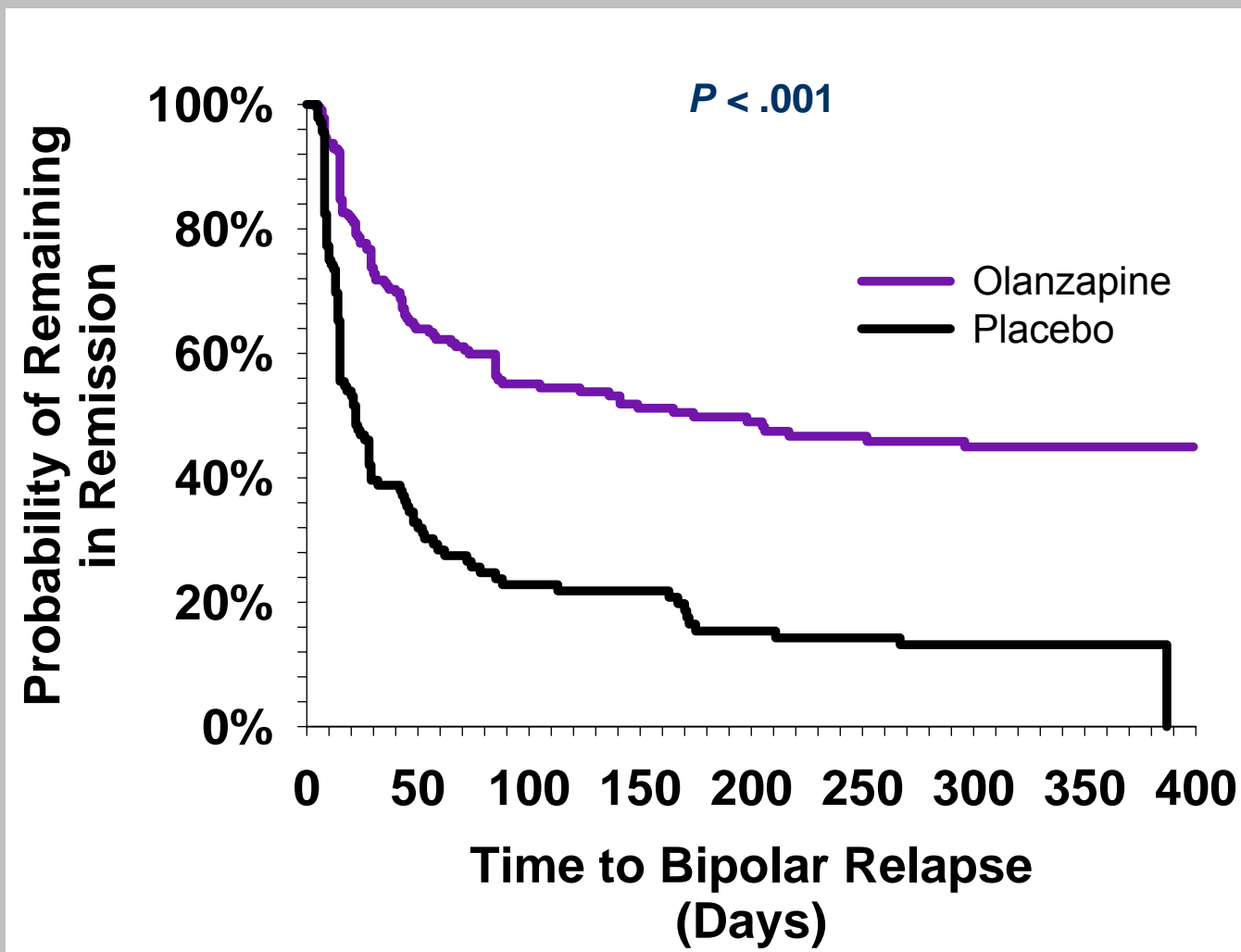
Adapted from Goodwin et al 2005



# Antidepressant Discontinuation vs. Continuation Conditional on 6 months well

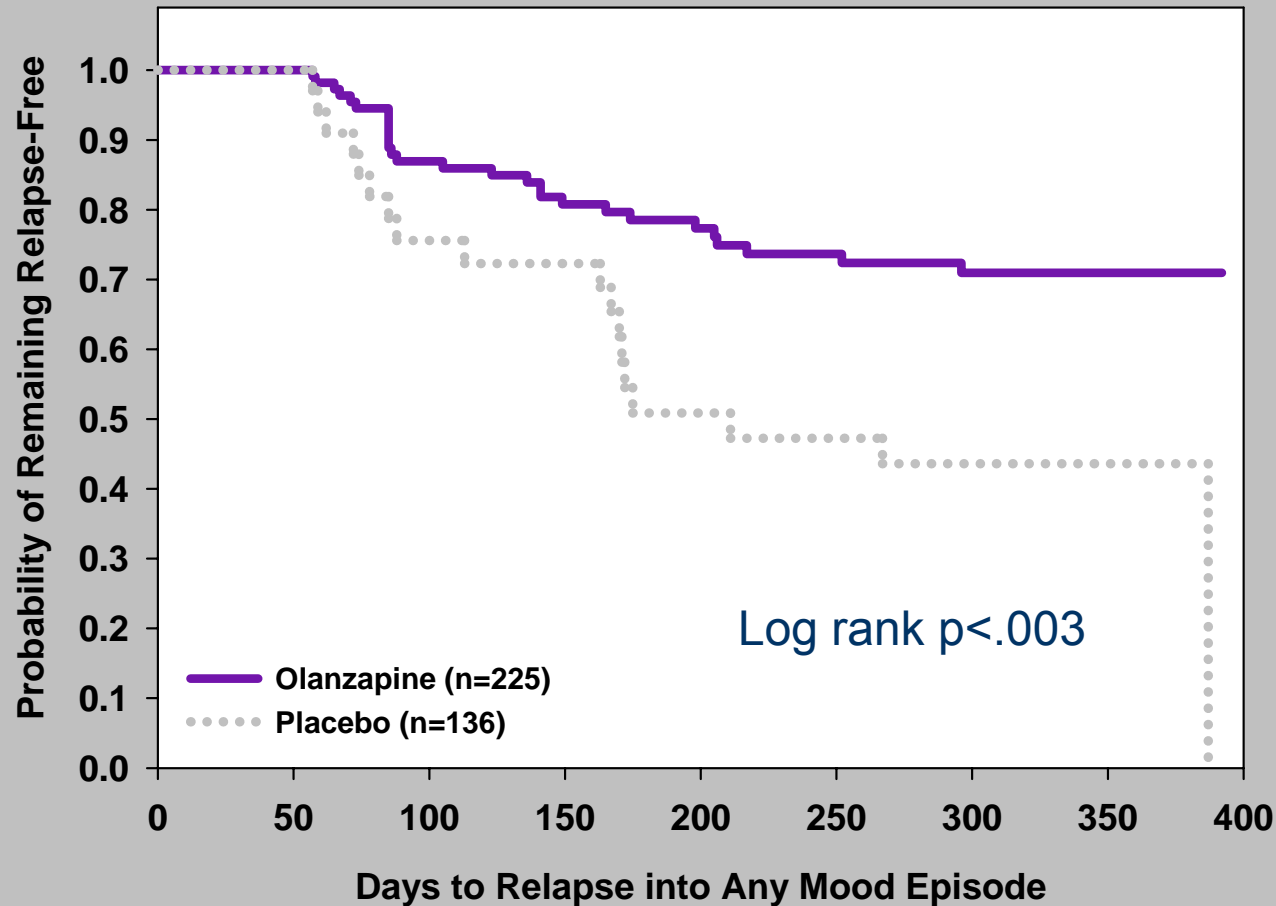


# Time to Relapse into Mania or Depression Based on Hospitalization and/or Symptomatic Rating Scale Criteria



Tohen et al. Am J Psych 2006

# Time to symptomatic relapse into any mood episode for patients remaining in remission during the initial 8 weeks of the double-blind maintenance phase of the study



Tohen et al. Am J Psych 2006

# Baseline Patient Characteristics

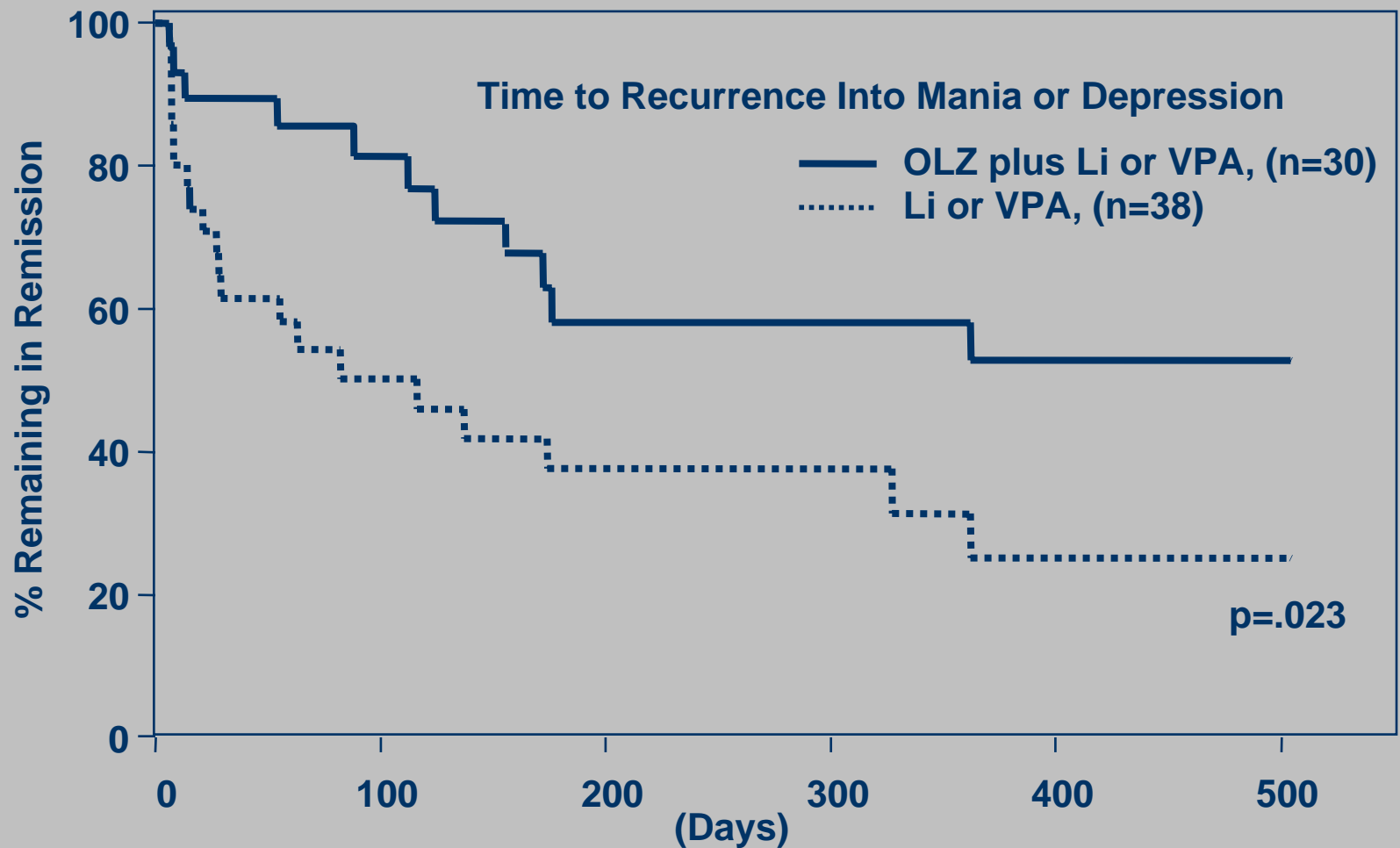
	OLZ	PBO	p-Value
Mean age (range)	41 (19-74)	40 (18-84)	.479
Females (%)	61.3	61.0	1.0
Mixed index episode (%)	33.8	33.1	.974
Psychotic features index episode (%)	16.9	20.6	.401
Rapid cycling (%)	52.9	44.1	.190
Mean YMRS score at randomization	4.3	4.0	.336
Mean HAM-D score at randomization	3.6	3.8	.073

Mean YMRS score at entry=25.1.  
Mean HAMD-21 score at entry=14.2.

Tohen, Calabrese, Sachs et al., *Am J Psychiatry*, 2006; 163(2).

# Placebo vs Olanzapine in Combination with Lithium or Valproate

Randomized after symptomatic remission of mania  
(YMRS  $\leq 12$ ) and depression Ham-D  $\leq 8$



Tohen et al. Br J Psych 2004.

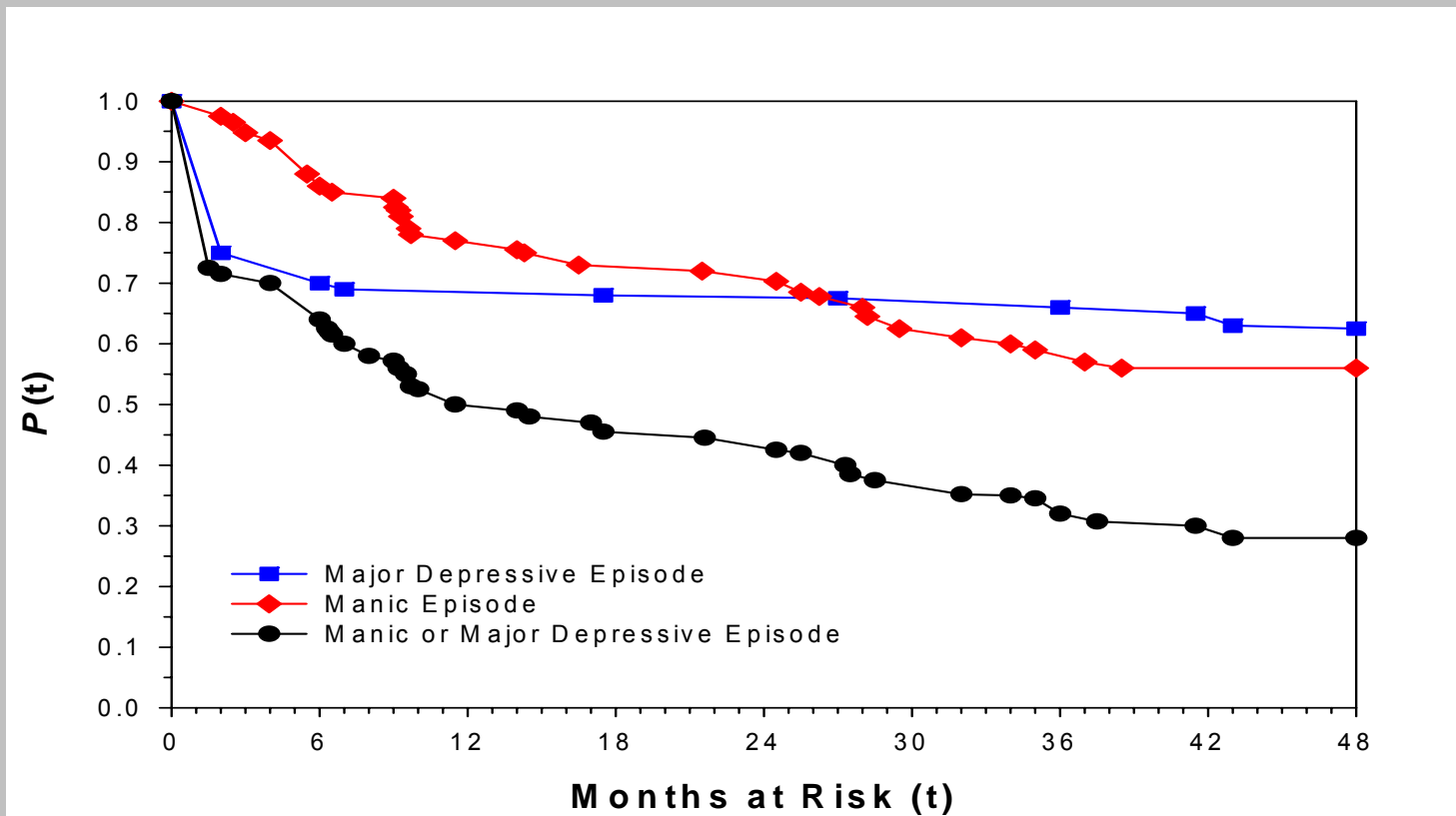
# Duration of Remission Period -ISSUES

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- Longer remission time require larger samples
  - Attrition prior to randomization rises with time
  - Event rates decrease with time (longer periods of stability predict future stability)
- Does long remission time make patients more stable **or** selects patients with a more stable course of illness?

**Does relapse polarity  
matter?**

# Cumulative Probability of Not Relapsing after 8 weeks in remission



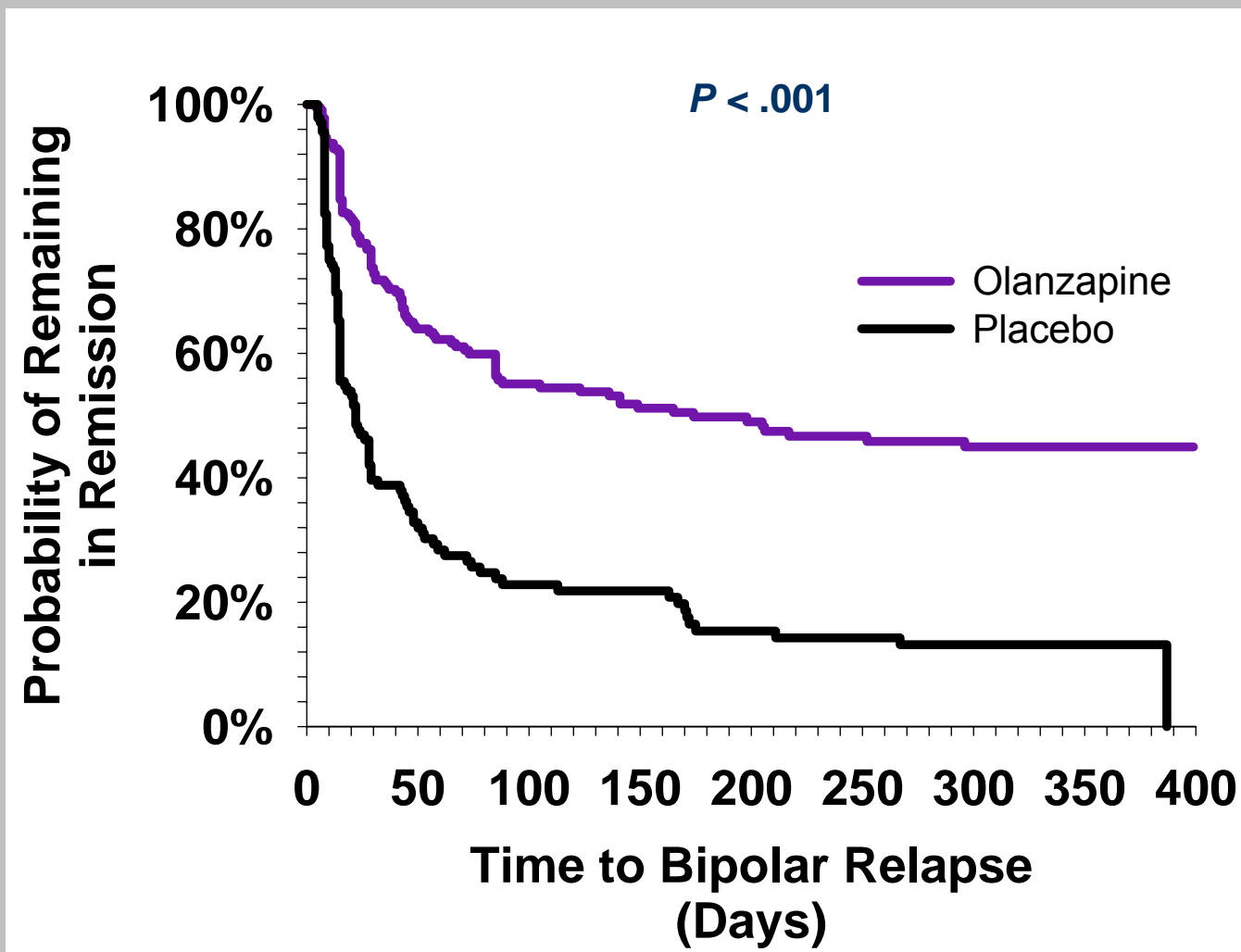
No. of	75	53	52	51	51	50	47	■
Subjects	75	66	58	55	54	44	42	◆
at Risk	75	48	38	34	33	25	21	●

# First New Episodes <2 Years of First Mania

Outcome	Proportion (%)
New episode	40.3
Relapse	1.3
Switch	4.6
Recurrence	34.4
First new episode type	
Manic (17%) or mixed (3%)	20.1
Depressive	20.1

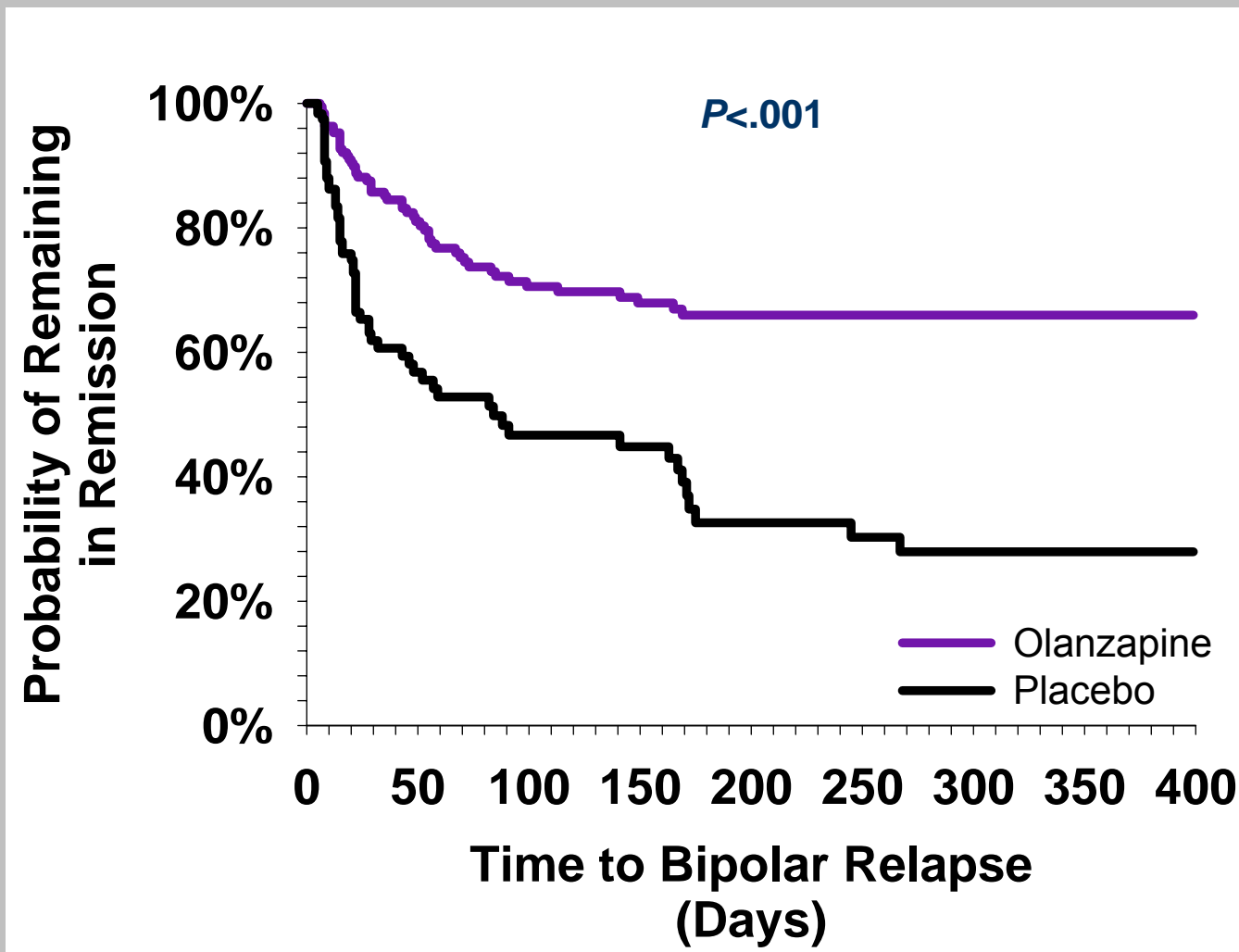
Tohen M, et al. *Am J Psychiatry*. 2003.

# Time to Relapse into Mania or Depression Based on Hospitalization and/or Symptomatic Rating Scale Criteria

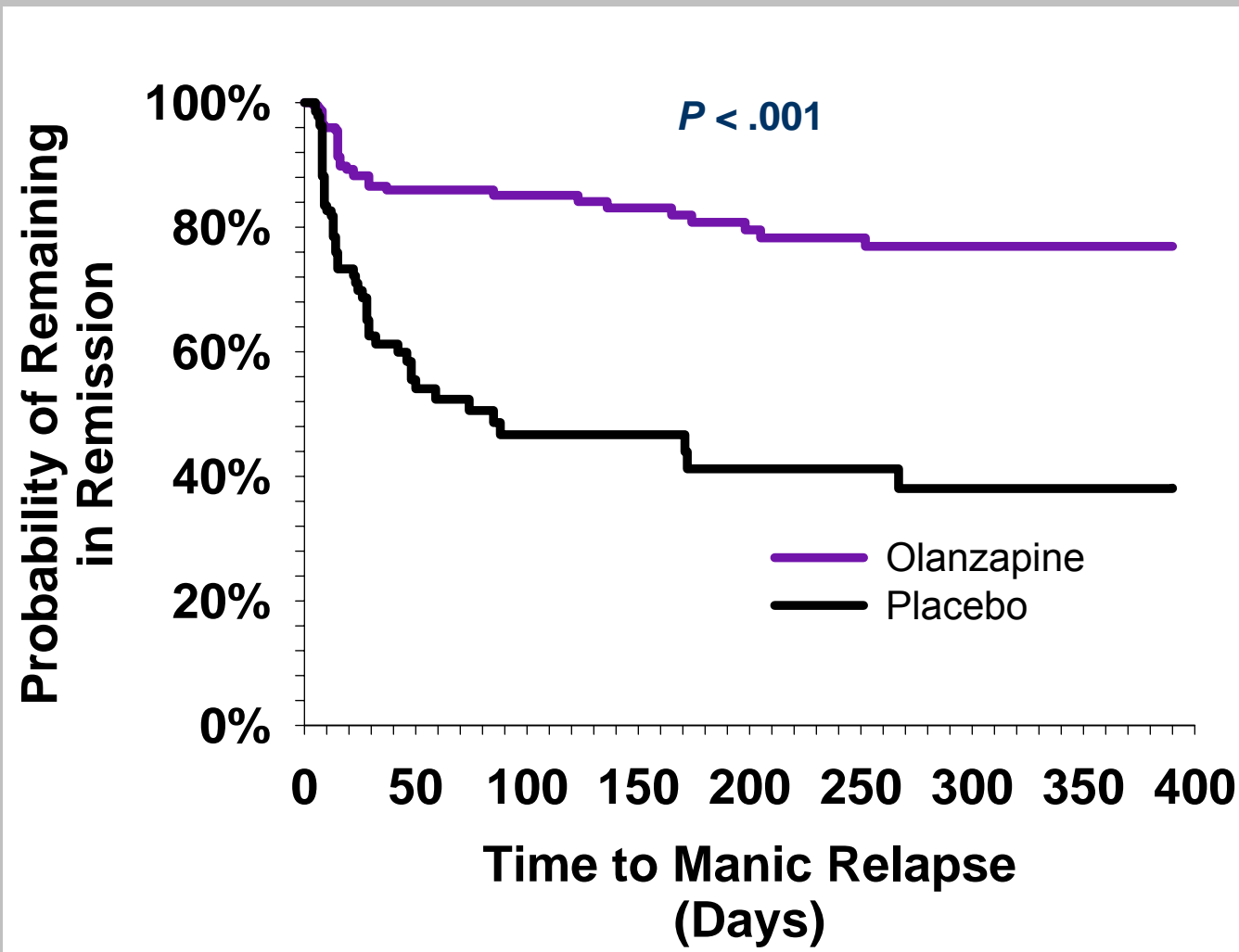


Tohen et al. Am J Psych 2006

# Time to Relapse into Mania or Depression: Based on DSM-IV Syndromic Criteria

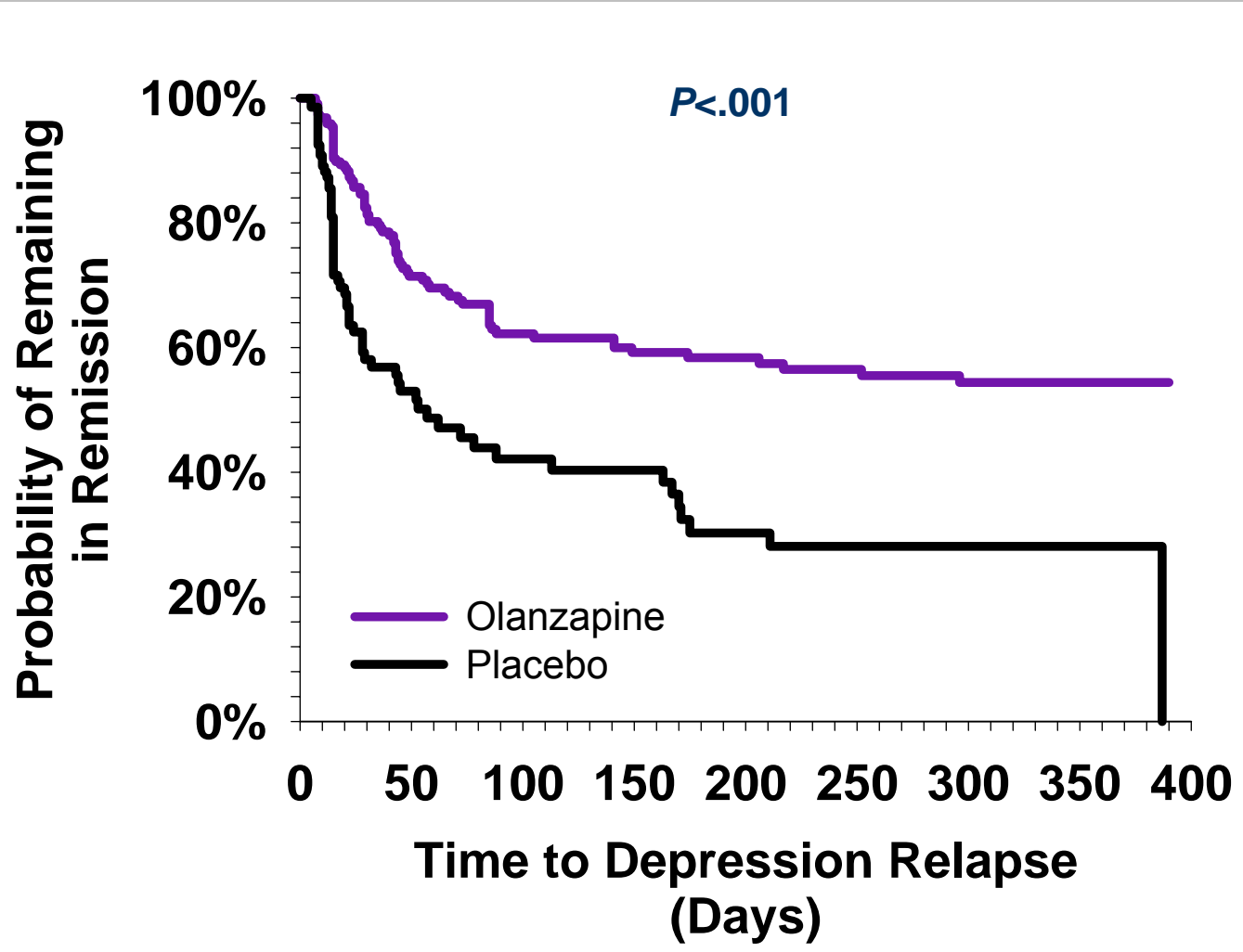


# Time to Relapse into Mania Based on Hospitalization and/or Symptomatic Rating Scale Criteria



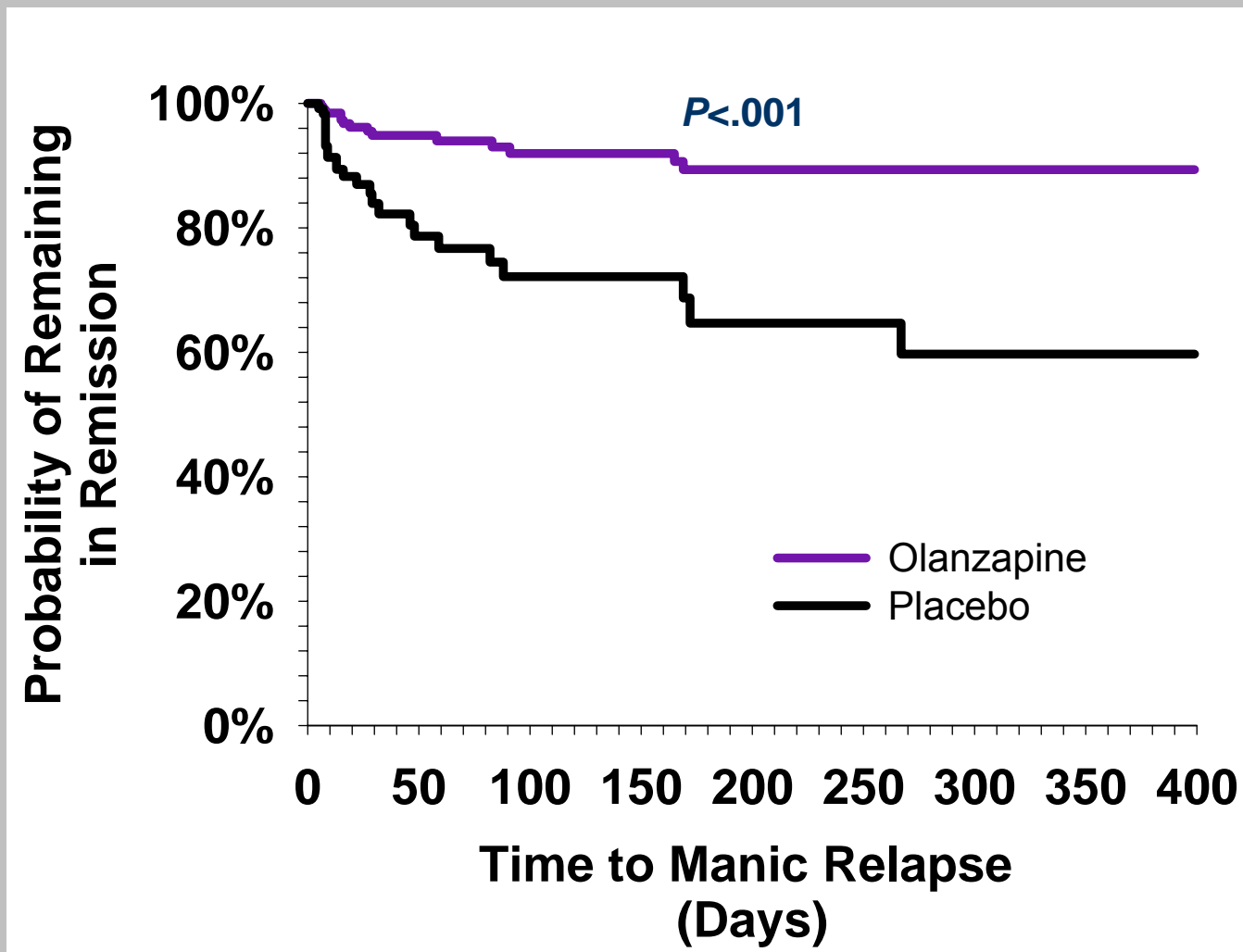
The rate of relapse at 1 year: 62%, Placebo; 23.1%, Olanzapine

# Time to Relapse into Depression Based on Hospitalization and/or Symptomatic Rating Scale Criteria

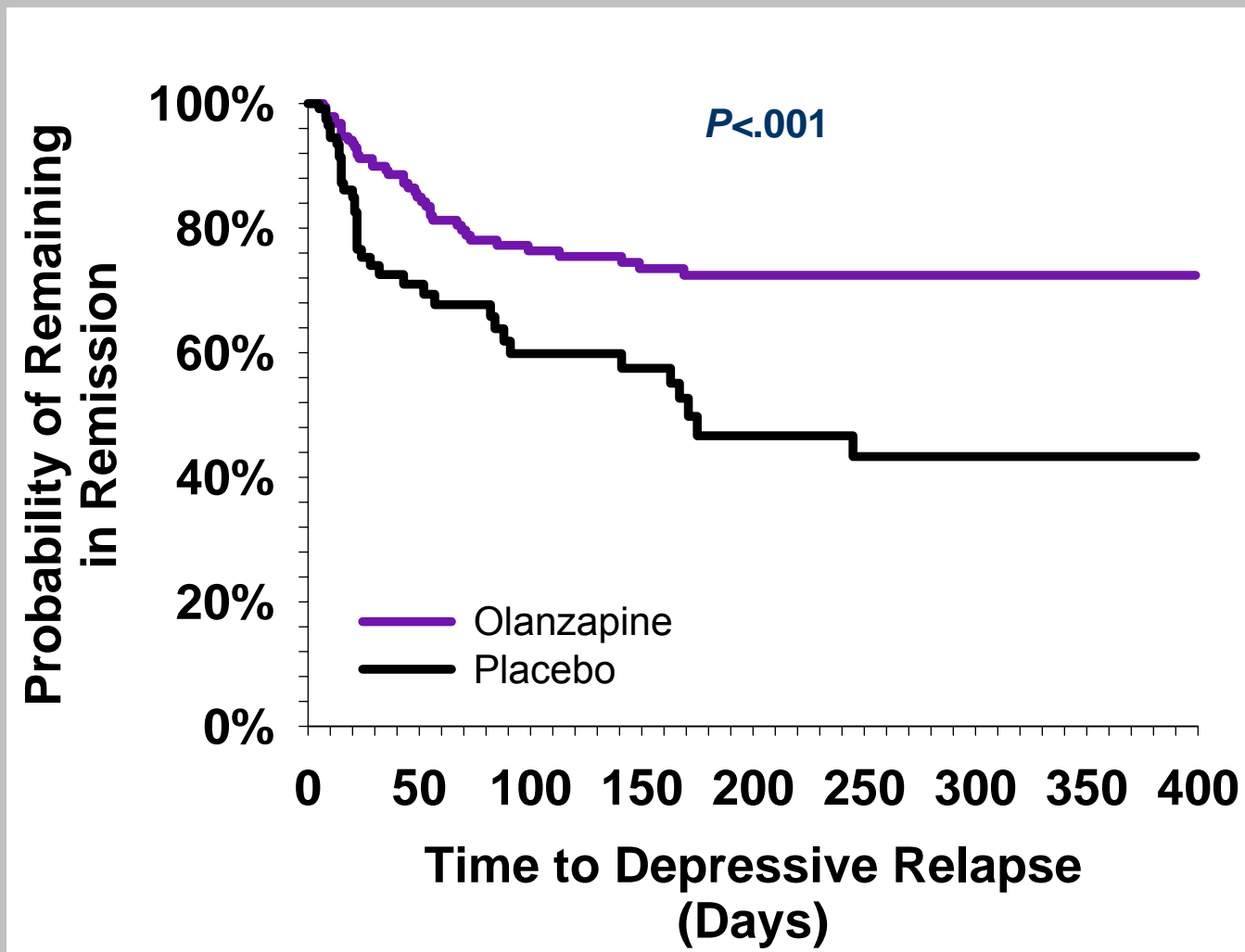


The rate of relapse at 1 year: 71.9%, Placebo; 45.6%, Olanzapine

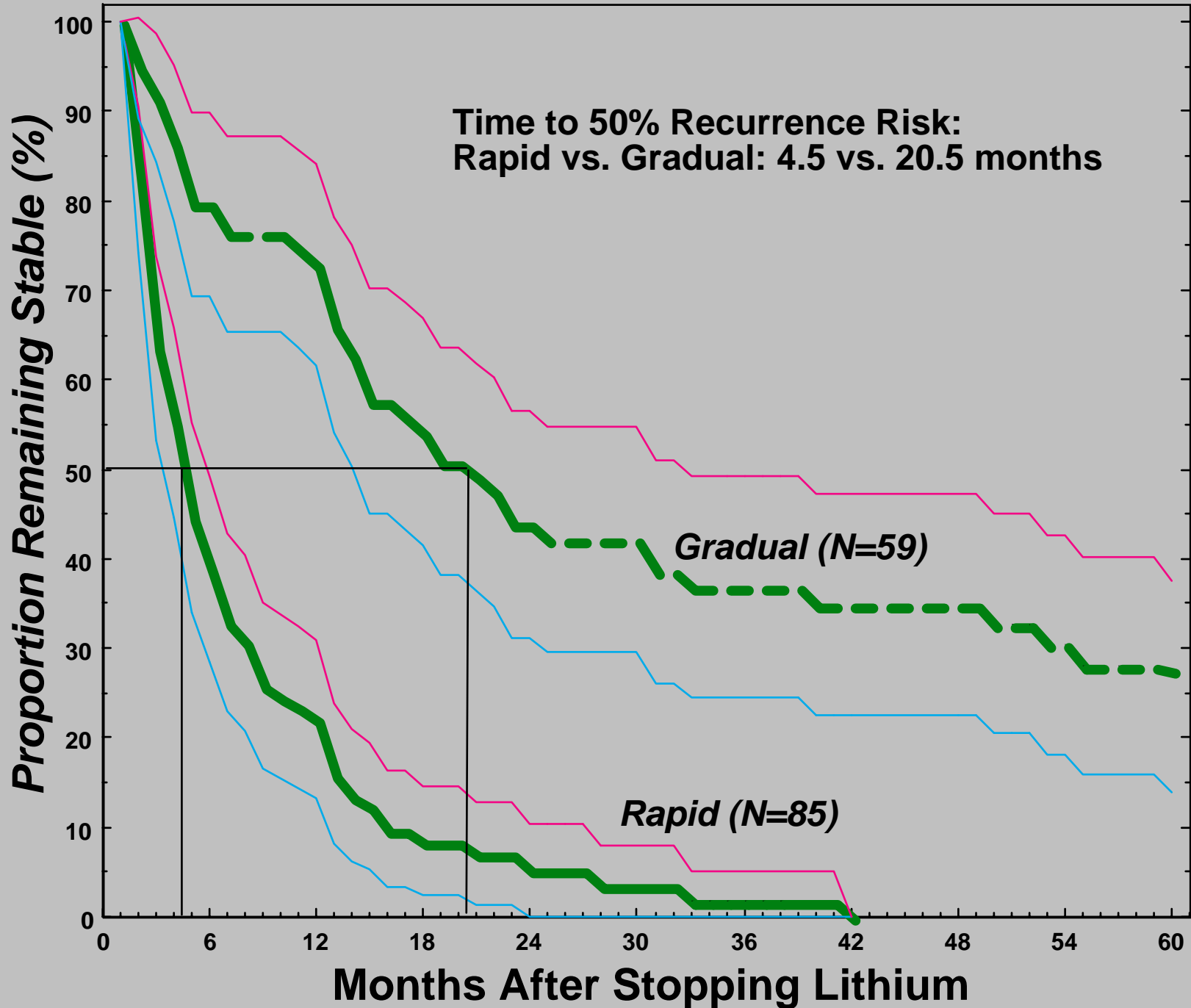
# Time to Relapse into Mania Based on DSM-IV Syndromic Criteria



# Time to Relapse into Depression: Based on DSM-IV Syndromic Criteria

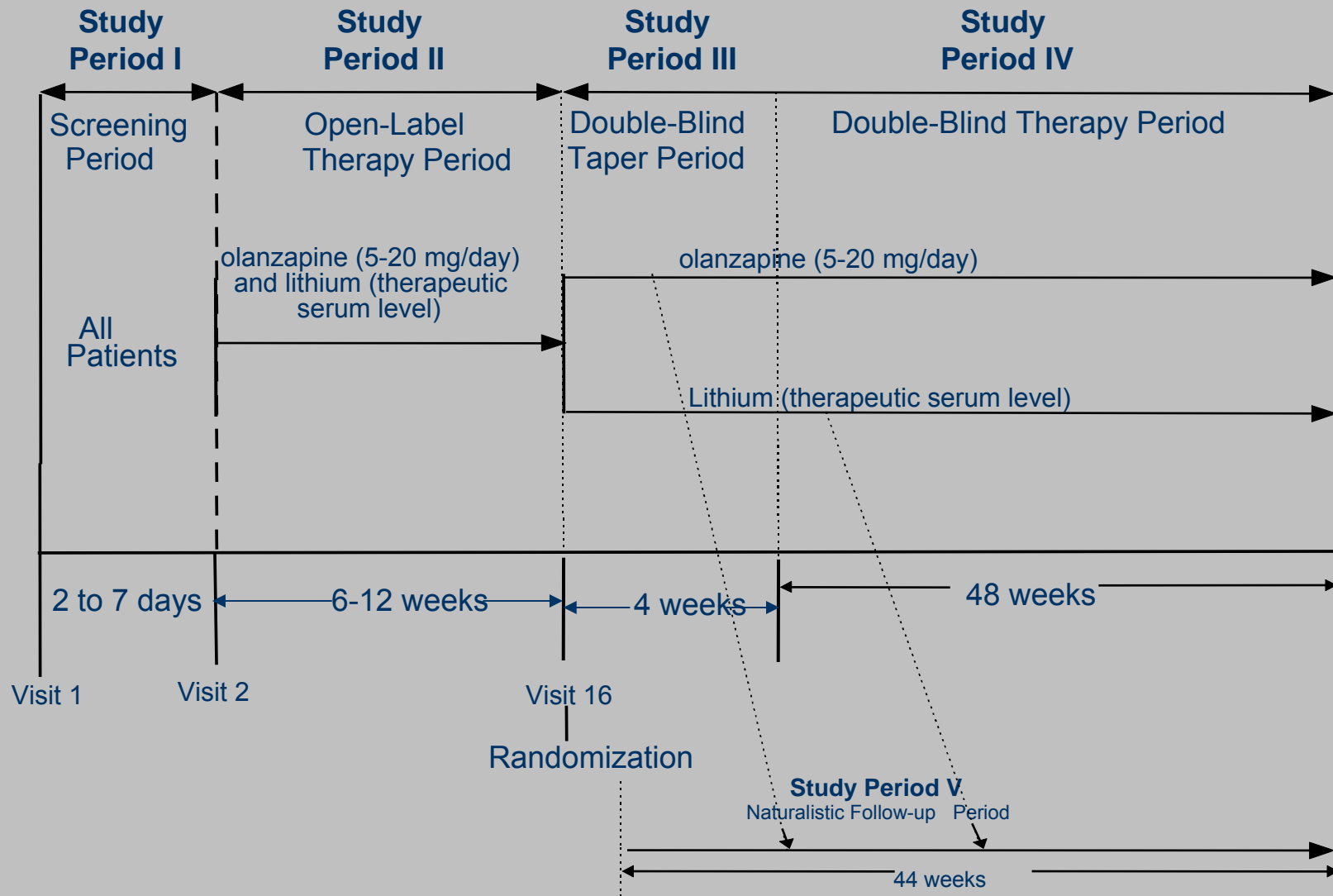


**Does gradual vs abrupt  
discontinuation  
matter?**



[From Baldessarini et al. J Clin Psychiatry 57: 441-448, 1996]

# Study Design: Olanzapine versus Lithium



# Patient Characteristics at Baseline: Randomization

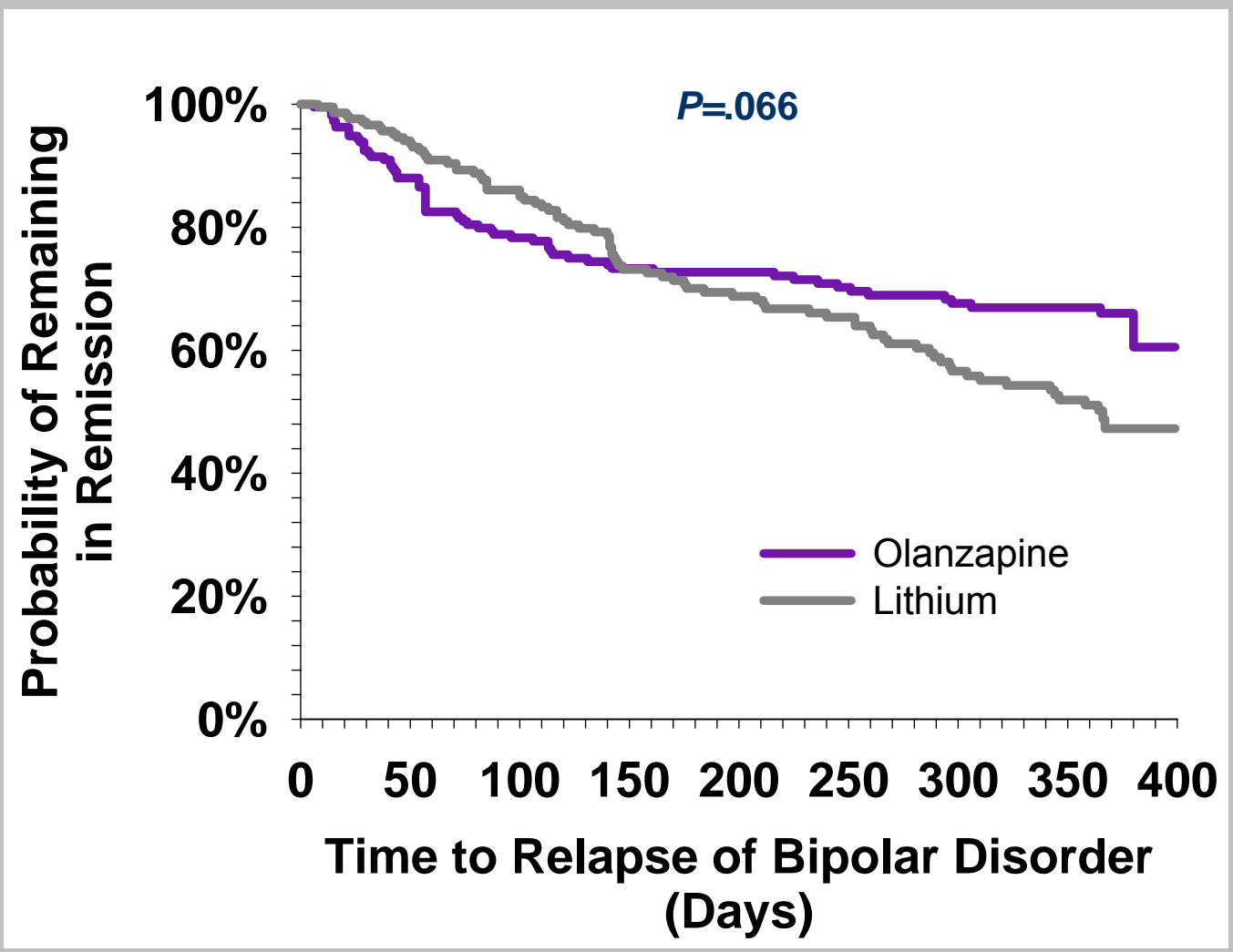
	Olanzapine	Lithium	p-Value
Mean age (range)	42.5 (20-80)	42.3 (18-77)	.645
Females (%)	52.1	53.7	.772
Mixed index episode (%)	6.9	5.6	.692
Psychotic features index episode (%)	27.2	24.8	.584
Rapid cycling (%)	2.8	3.3	.957
Mean YMRS score at randomization	3.6	3.9	.176
Mean HAMD-21 score at randomization	1.6	1.6	.309

Mean YMRS score at entry=25.8.

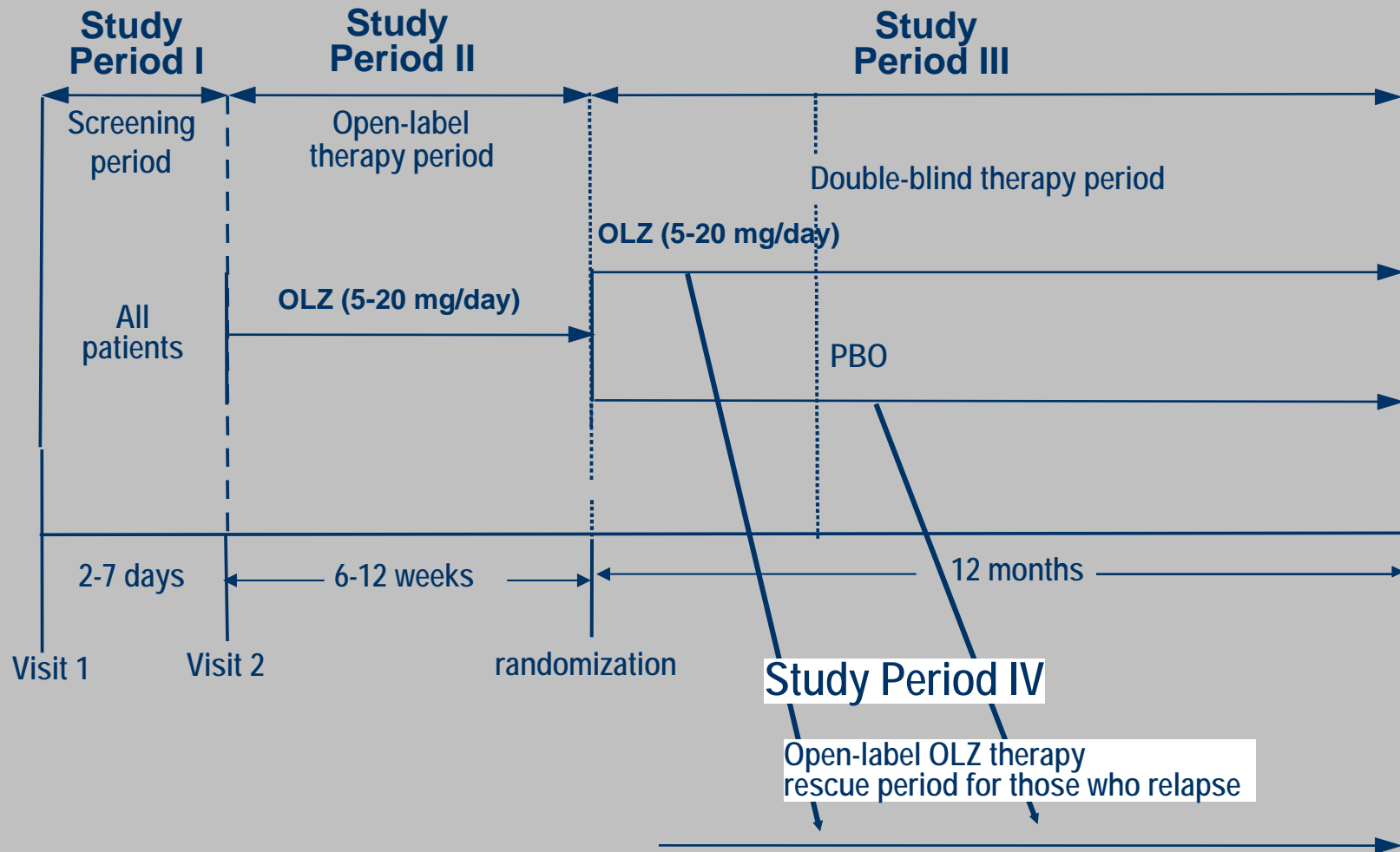
Mean HAMD-21 score at entry=5.7.

Tohen, Greil, Calabrese et al. *Am J Psychiatry* 2005; 162:1281-1290.

# Time to Relapse into Mania or Depression Based on Symptomatic Rating Scale Criteria

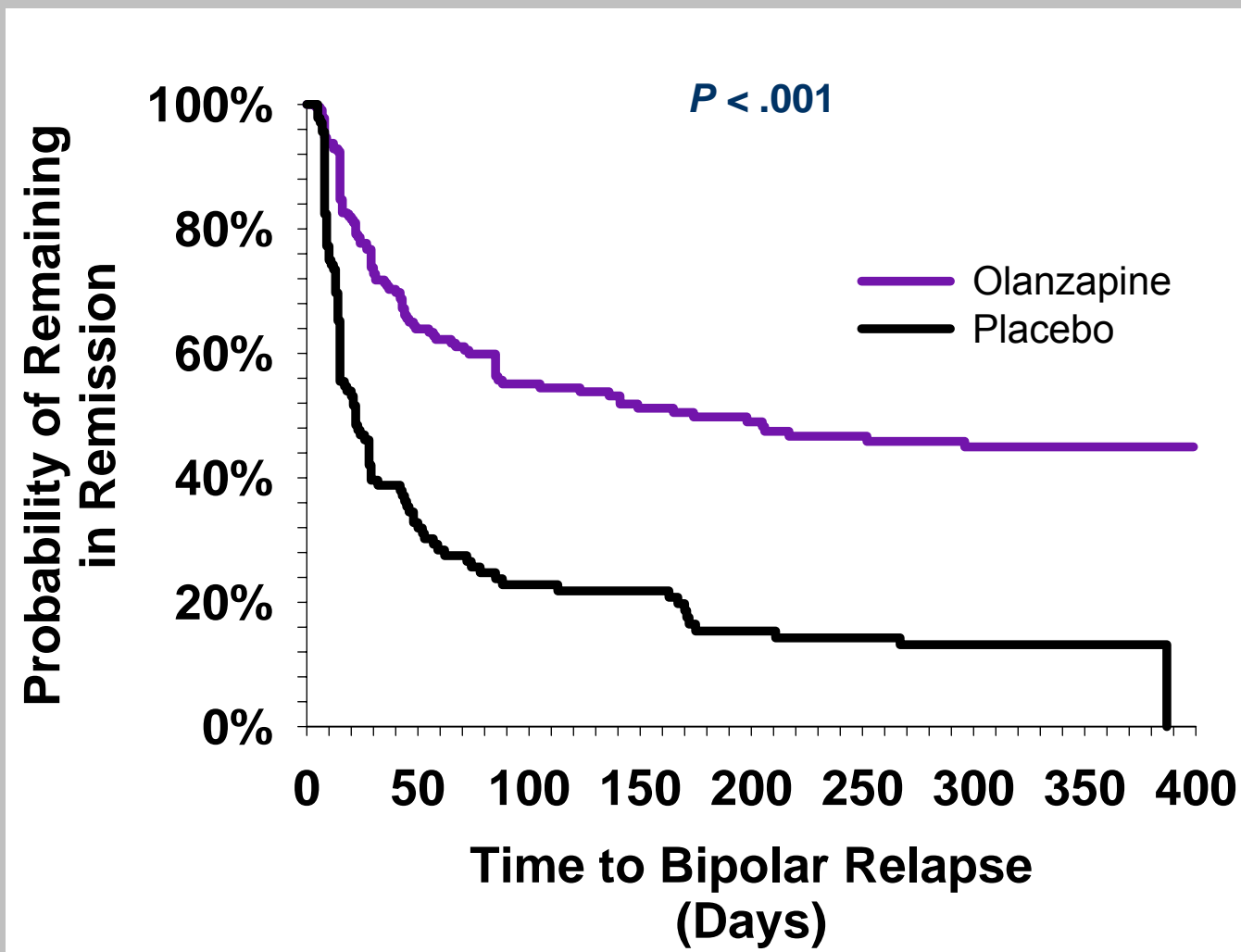


# Study Design: Olanzapine vs Placebo



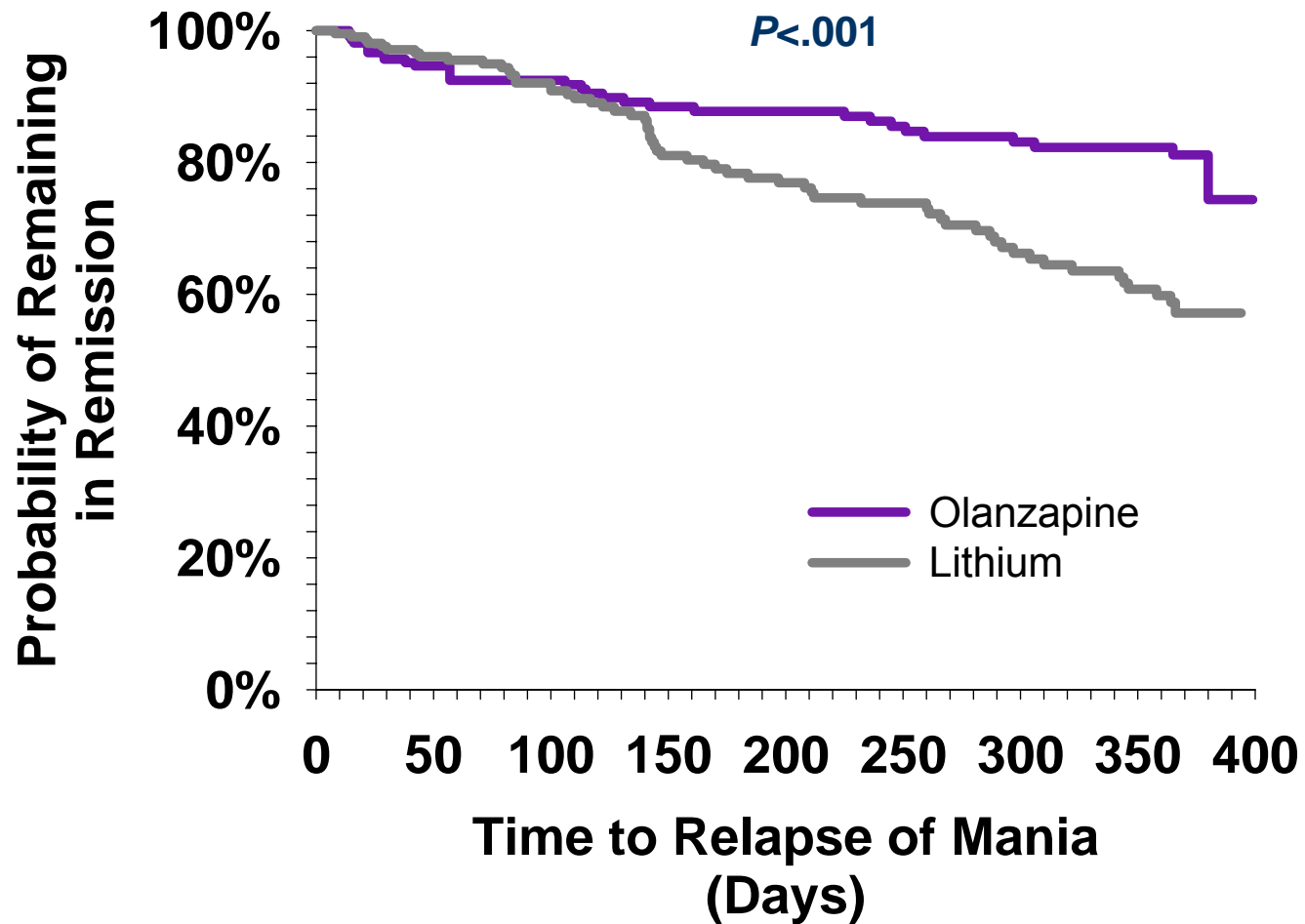
Tohen, Calabrese, Sachs et al., *Am J Psychiatry*, 2006; 163(2).

# Time to Relapse into Mania or Depression Based on Hospitalization and/or Symptomatic Rating Scale Criteria

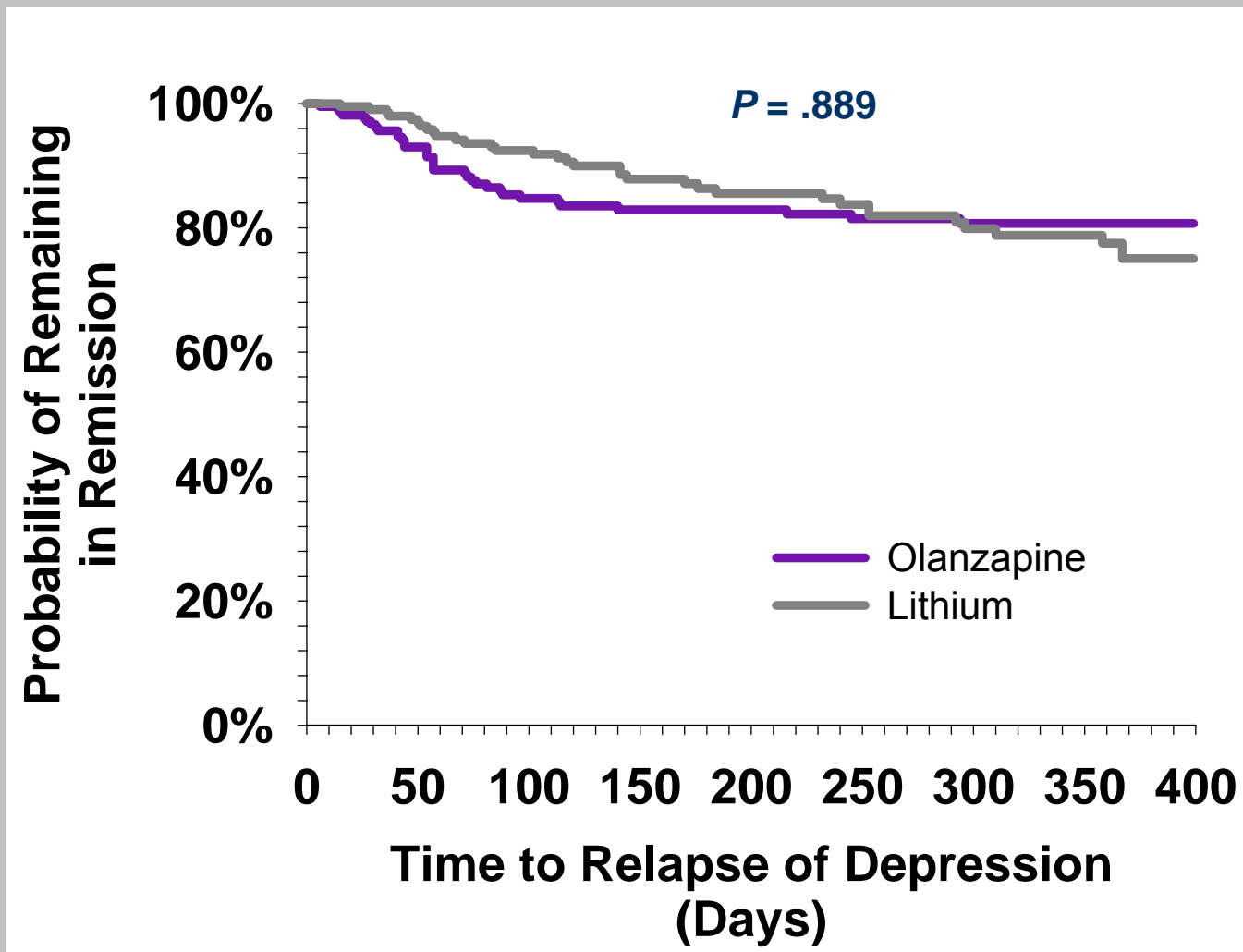


Tohen et al. Am J Psych 2006

# Time to Relapse into Mania Based on Symptomatic Rating Scale Criteria



# Time to Relapse into Depression Based on Symptomatic Rating Scale Criteria



**Does definition of  
relapse matter?**

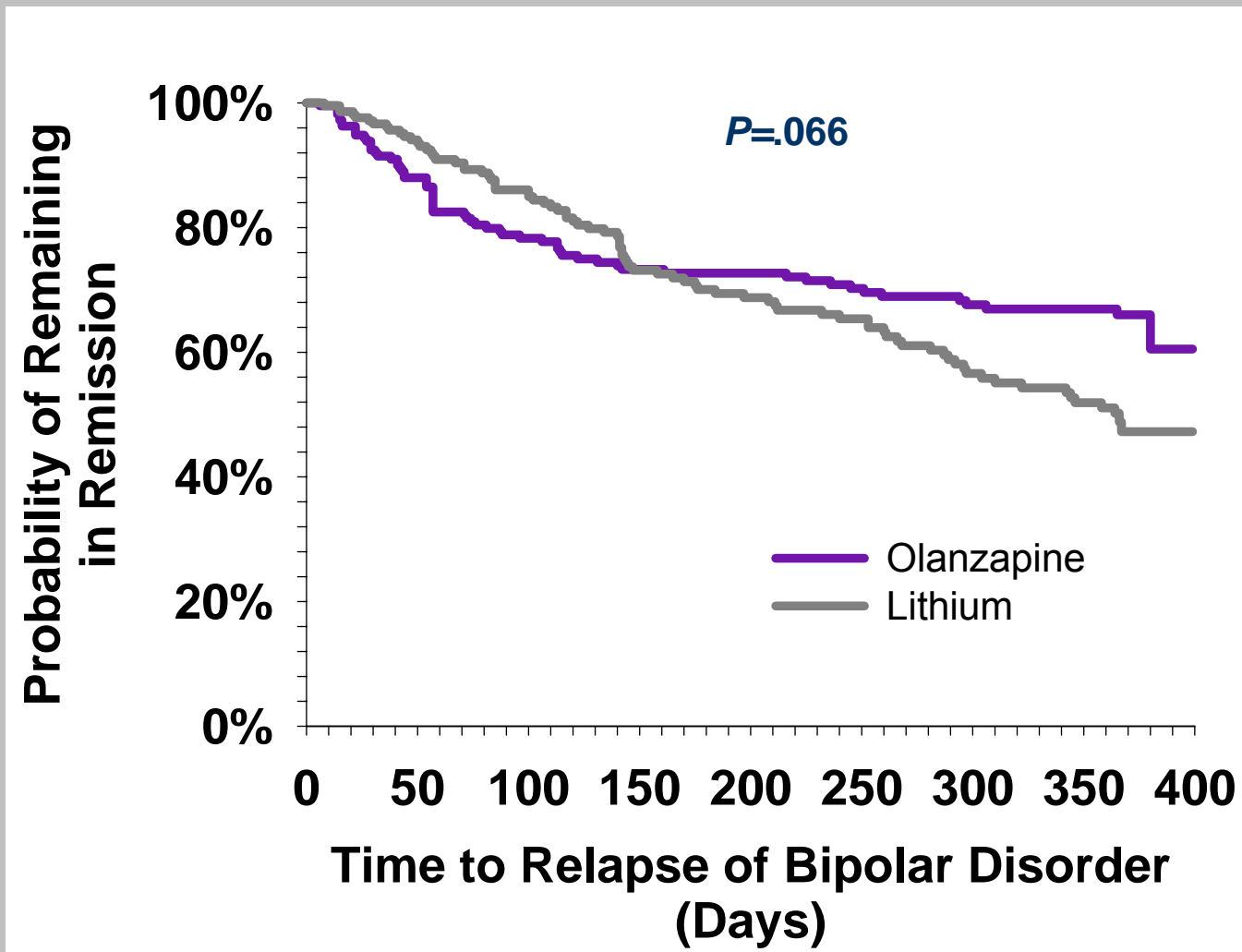
# Relapse Criteria

Date	Study Author	Study Drug	Study Duration	Criteria
2006	Tohen et al	olanzapine placebo	Maintenance phase 12 months	YMRS total score $\geq 15$ and/or HAMD total score $\geq 15$ or hospitalization for mania or depression
2005	Tohen et al	olanzapine, lithium	Maintenance phase 12 months	YMRS total score $\geq 15$ and/or HAMD total score $\geq 15$
2005	Calabrese et al	lithium, divalproex	Maintenance phase 20 months	Intervention for any mood episode (pharmacotherapy or ECT) based on clinical judgment. YMRS score $\geq 20$ for up to 8 weeks or HAMD score $\geq 20$ for 8 weeks
2004	Tohen et al	olanzapine,+ lithium or divalproex, lithium or valproate monotherapy	Maintenance phase 18 months	YMRS total score $\geq 15$ and/or HAMD total score $\geq 15$
2003	Calabrese et al	lamotrigine, lithium, placebo	Maintenance phase 18 months	Intervention for any mood episode (pharmacotherapy or ECT) based on clinical judgment

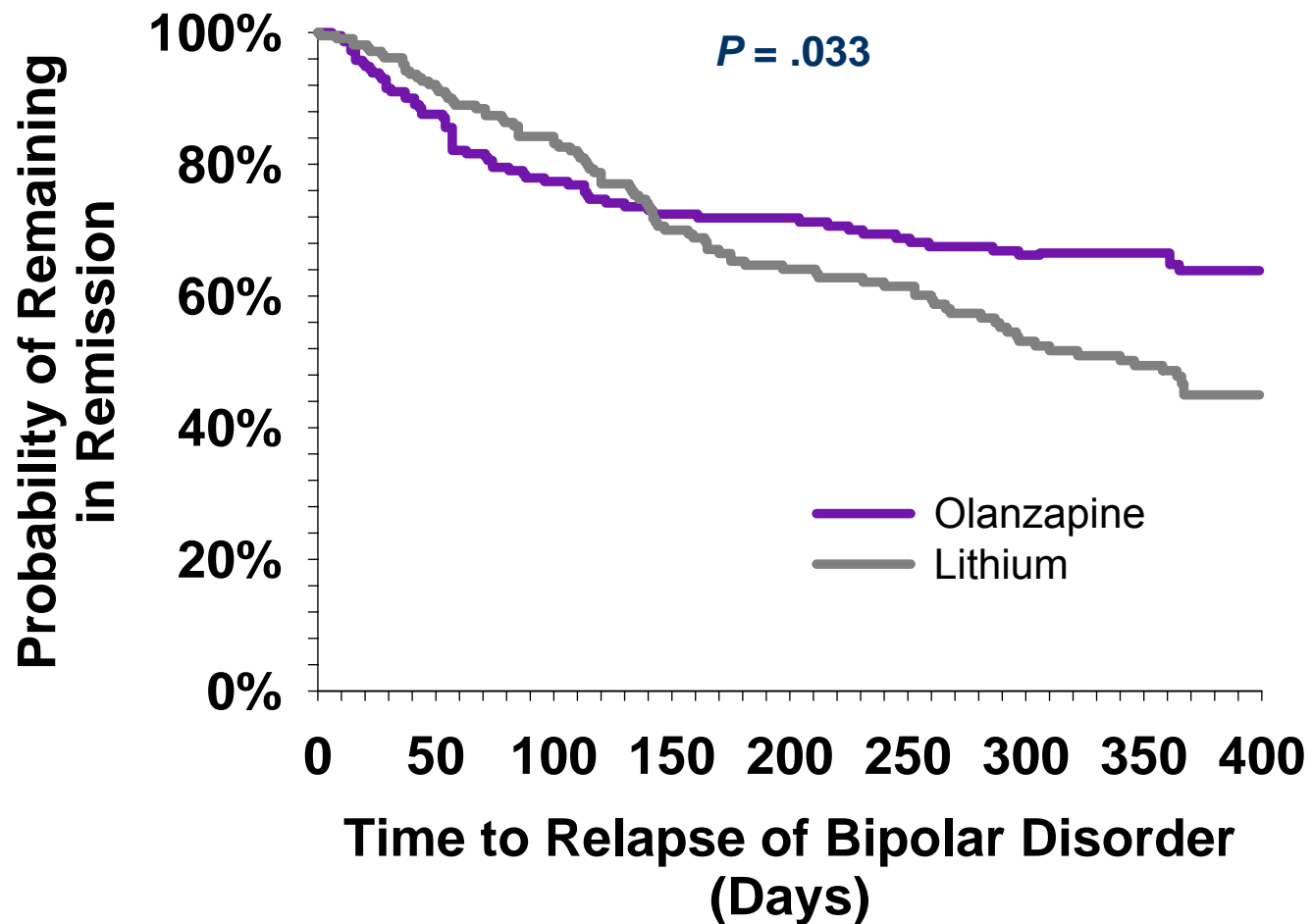
# Relapse Criteria (cont.)

<b>Date</b>	<b>Study Author</b>	<b>Study Drug</b>	<b>Study Duration</b>	<b>Criteria</b>
2003	Bowden et al	lamotrigine, lithium, placebo	Maintenance phase 18 months)	Intervention for any mood episode (pharmacotherapy or ECT) based on clinical judgment
2000	Bowden et al	valproate, lithium, placebo	Maintenance phase 12 months	Intervention for any mood episode (pharmacotherapy or ECT) based on clinical judgment

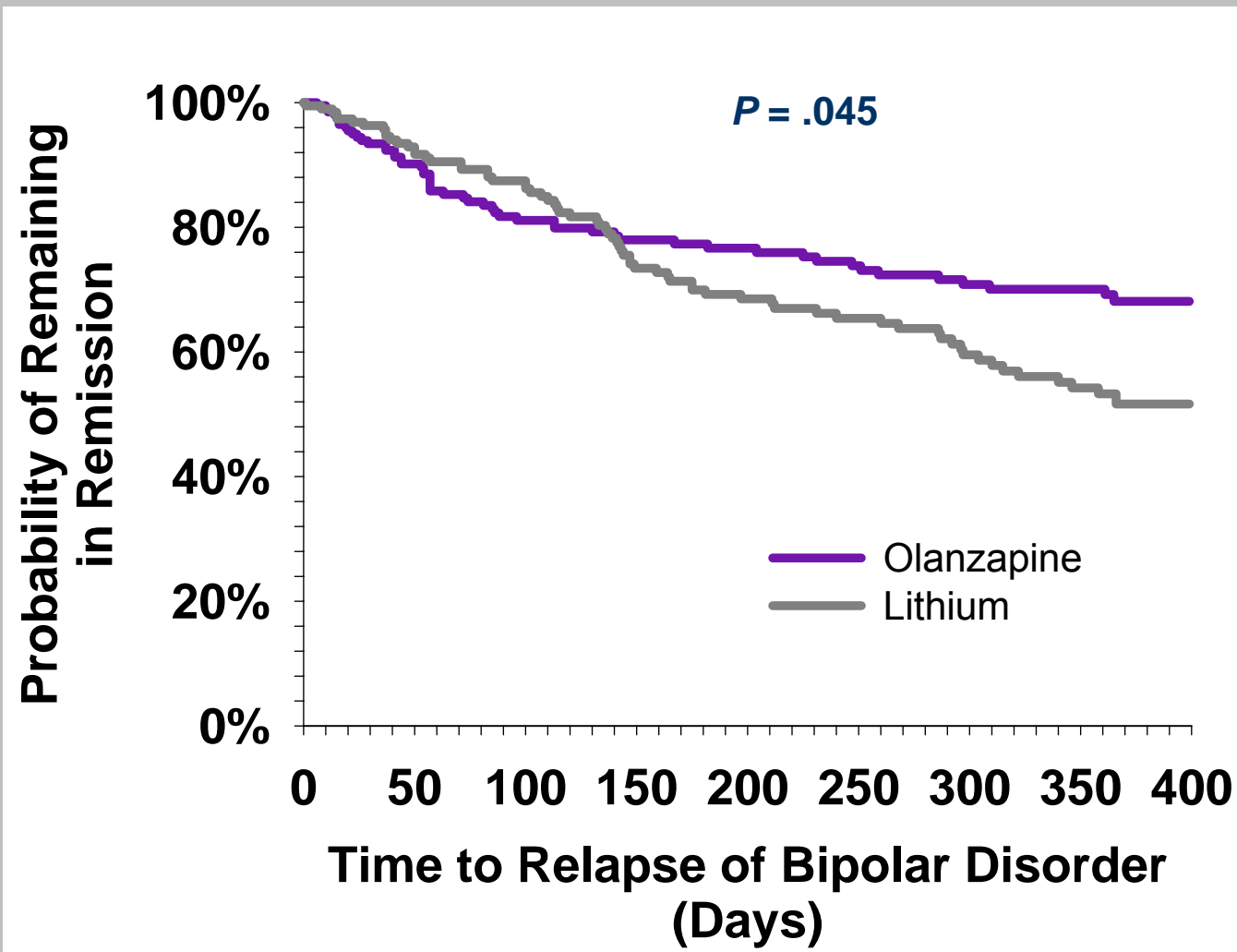
# Time to Relapse into Mania or Depression Based on Symptomatic Rating Scale Criteria



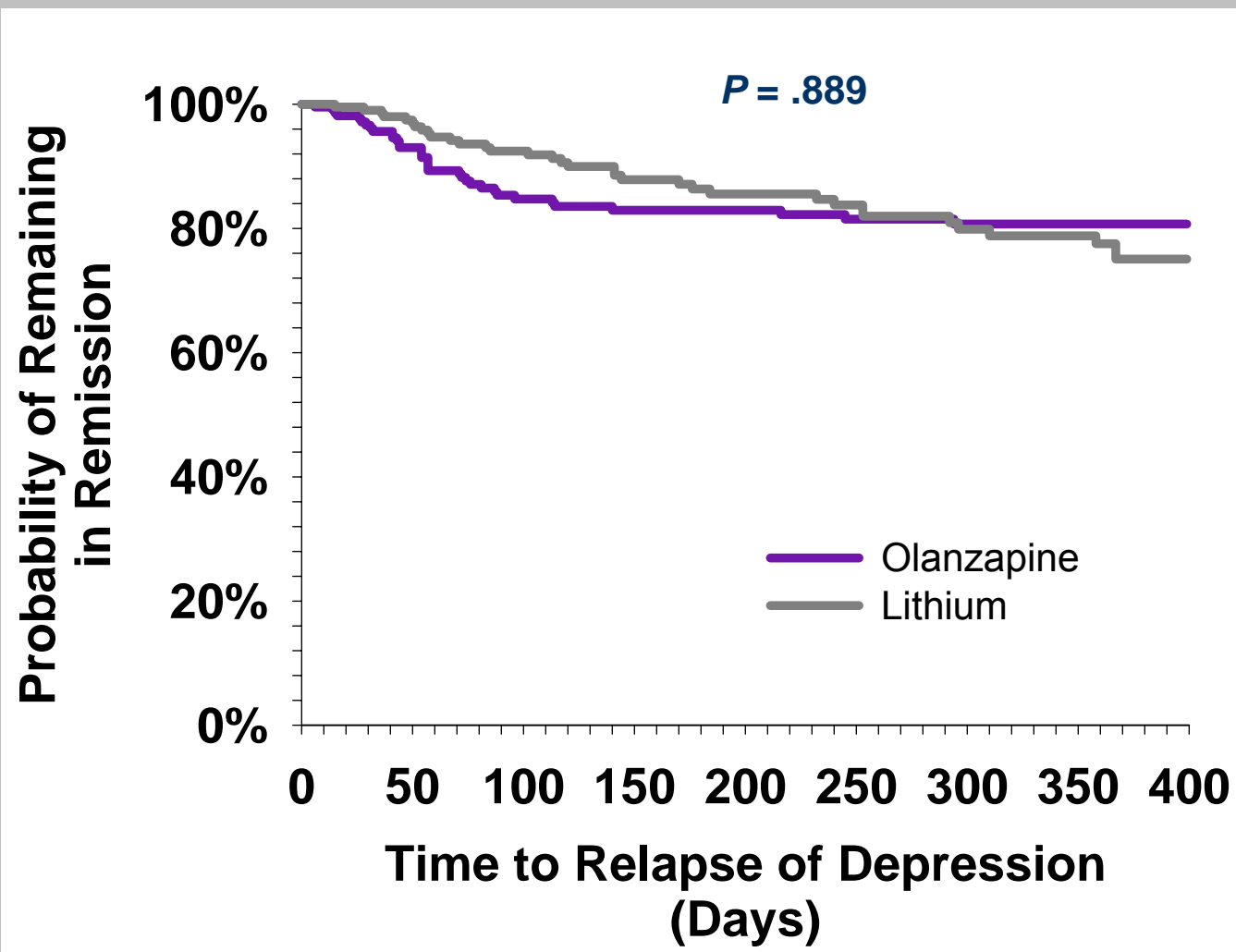
# Time to Relapse into Mania or Depression Based on Hospitalization and/or Symptomatic Rating Scale Criteria



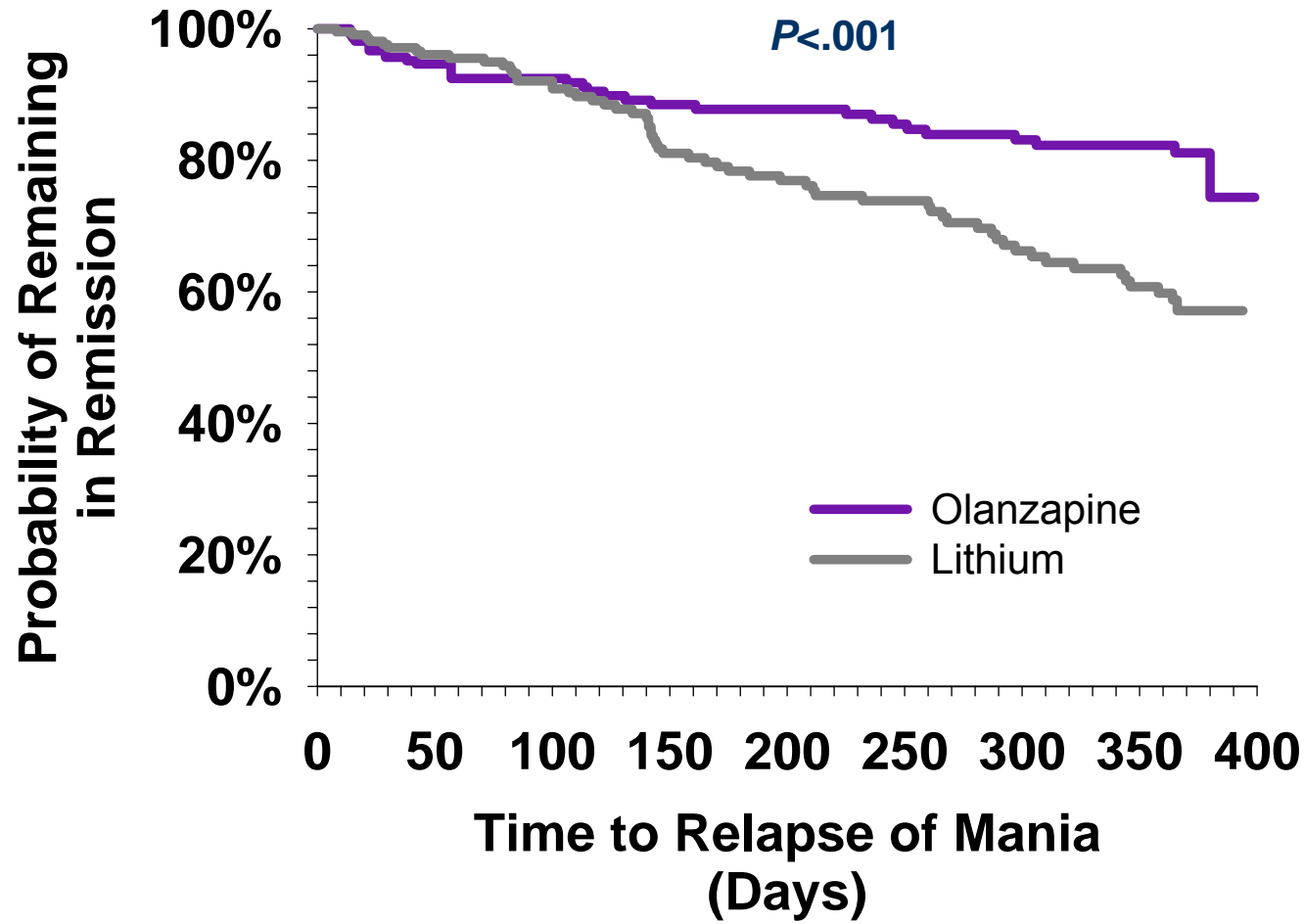
# Time to Relapse into Mania or Depression: Based on DSM-IV Syndromic Criteria



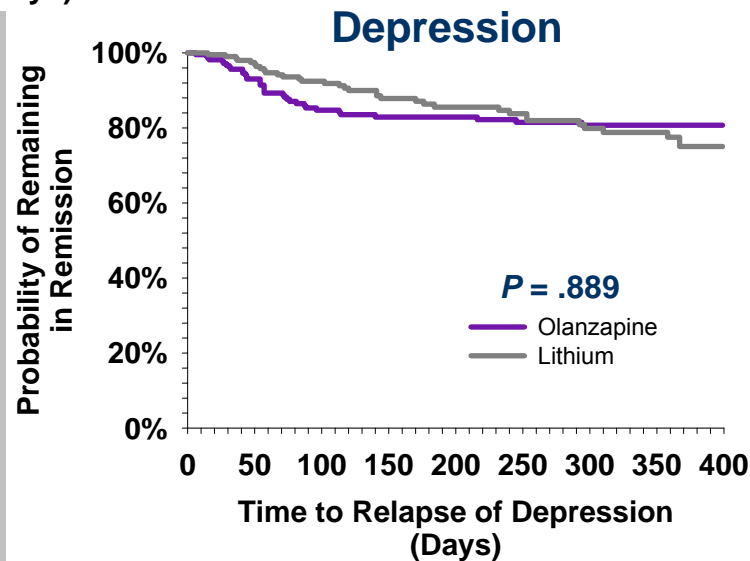
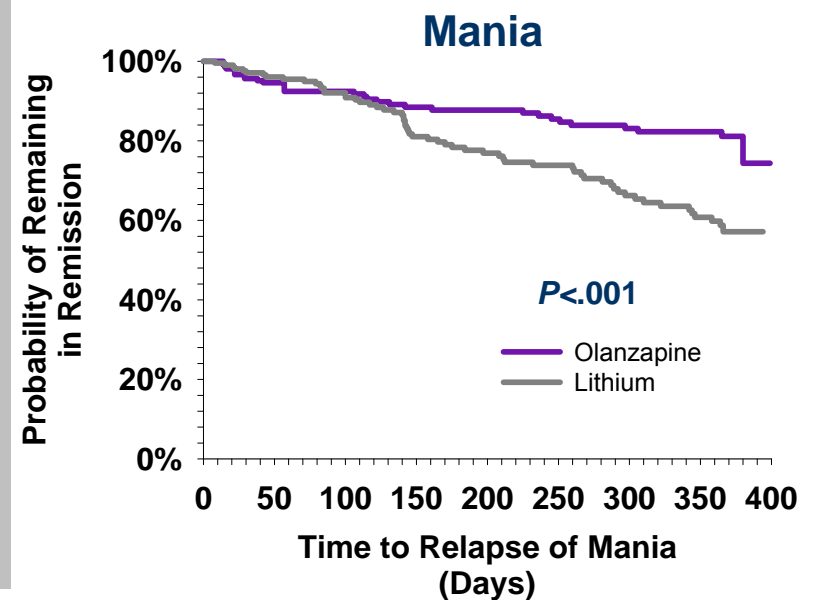
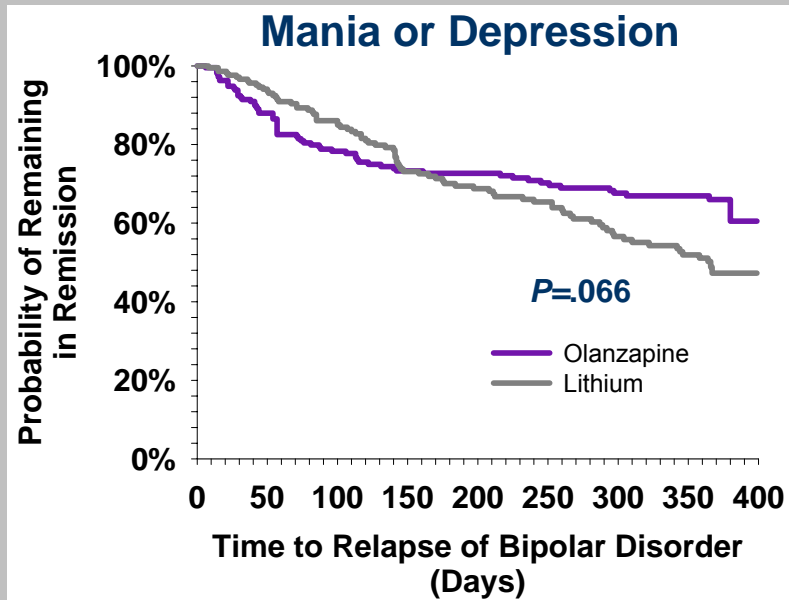
# Time to Relapse into Depression Based on Symptomatic Rating Scale Criteria



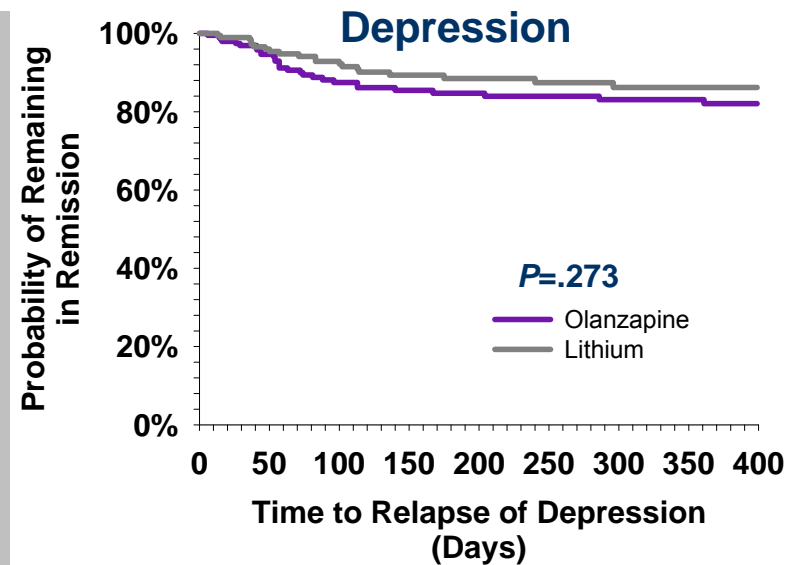
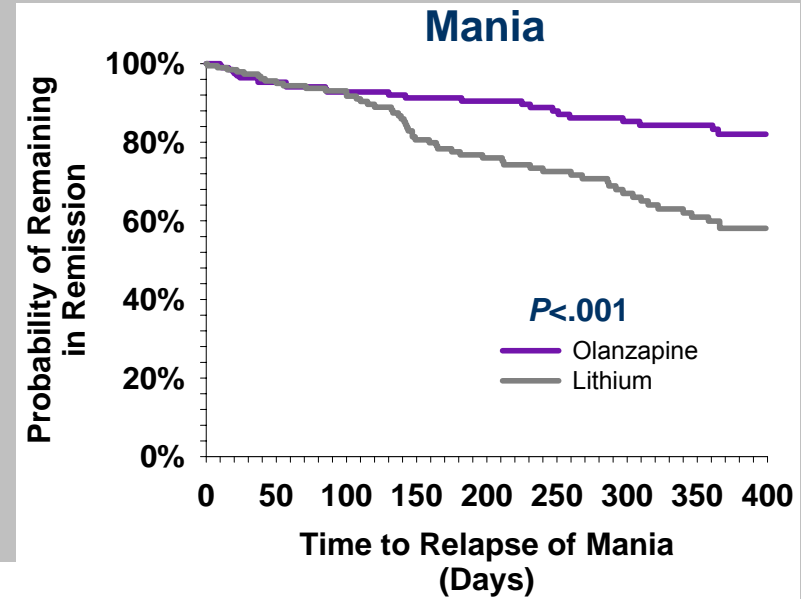
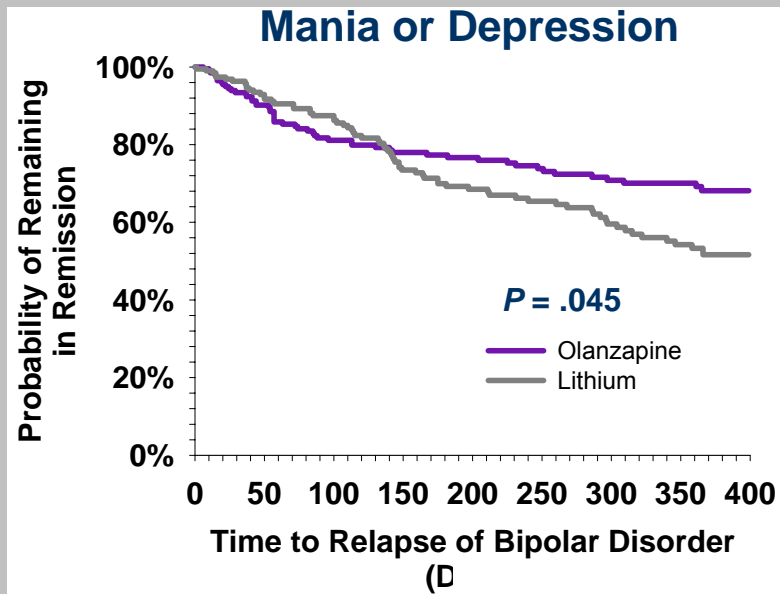
# Time to Relapse into Mania Based on Symptomatic Rating Scale Criteria



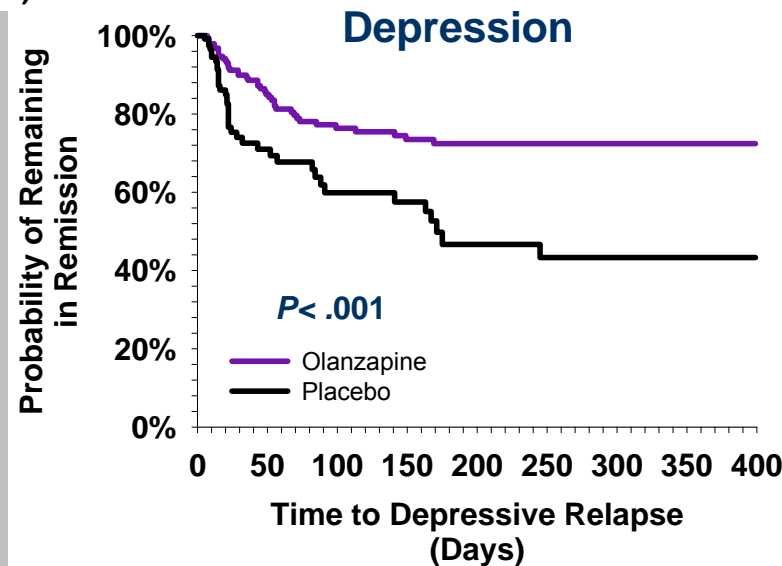
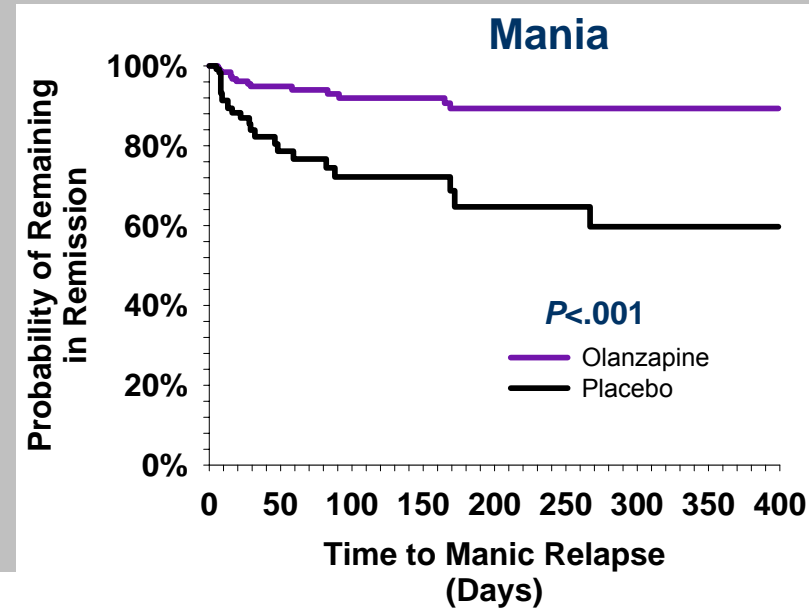
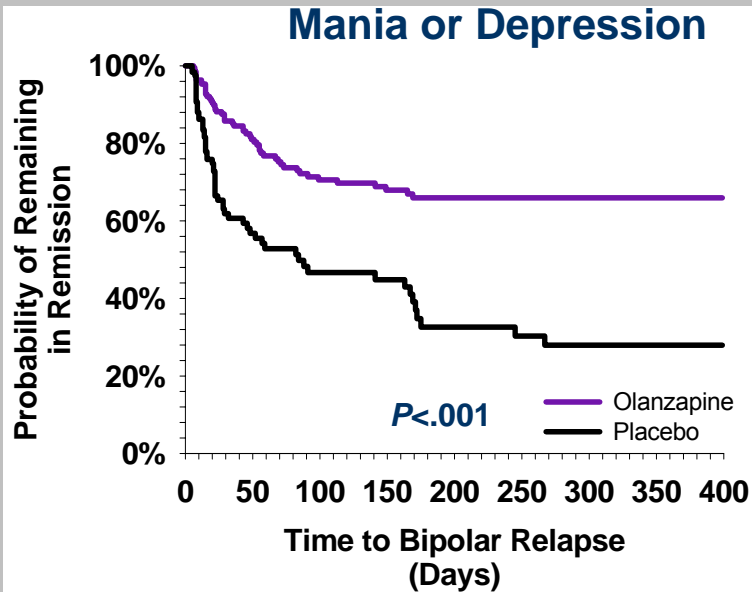
# Time to Relapse Based on Symptomatic Rating Scale Criteria



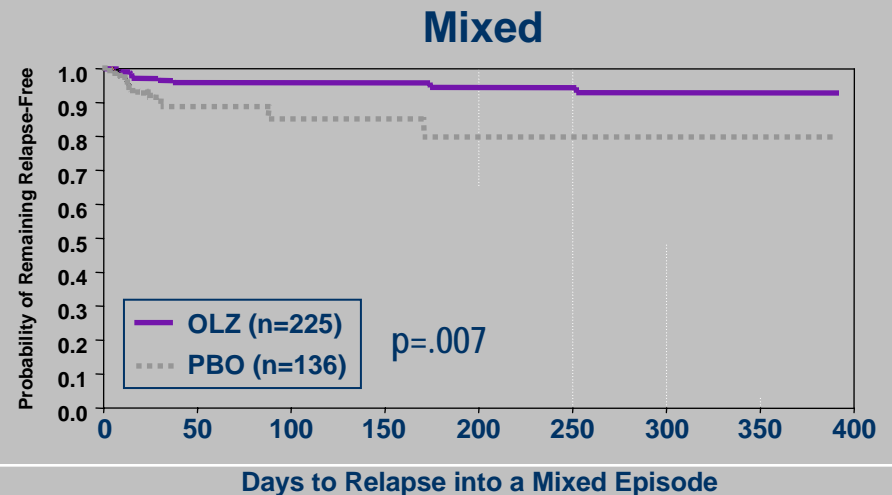
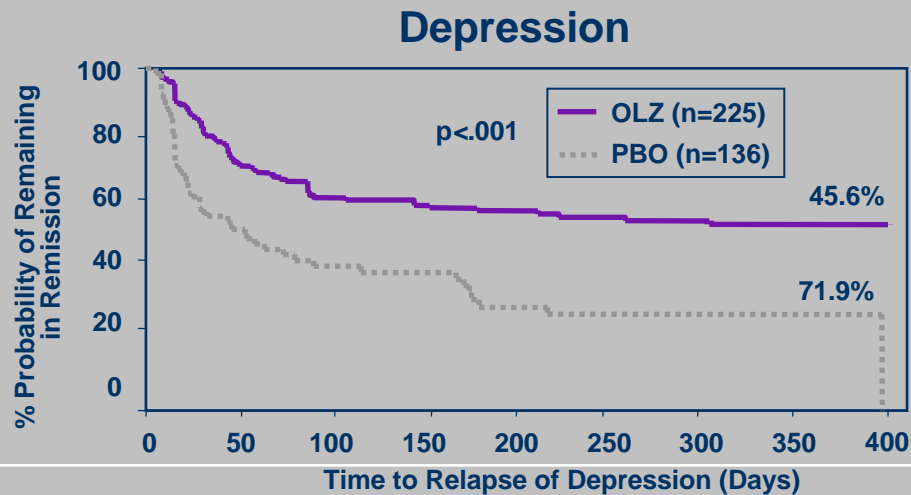
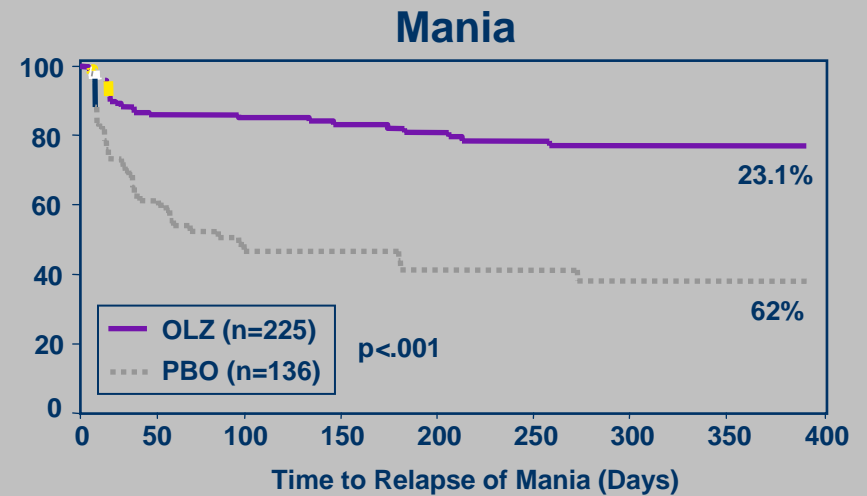
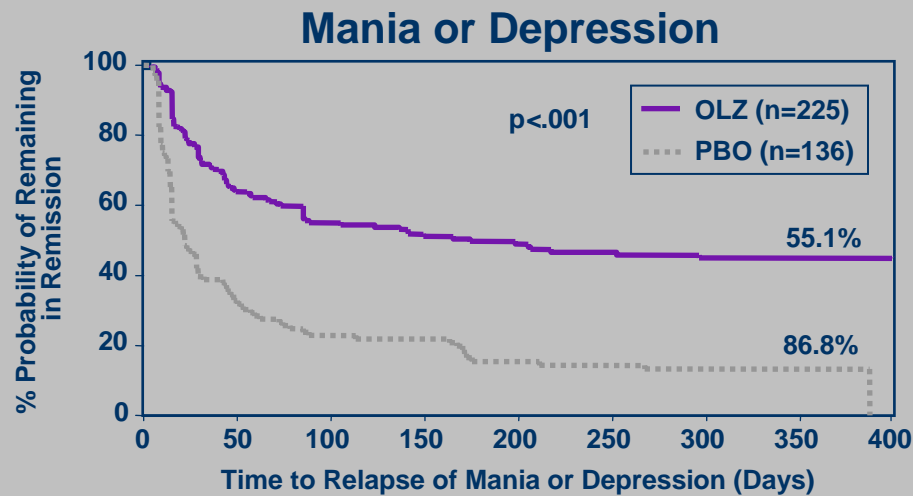
# Time to Relapse Based on DSM-IV Syndromic Criteria



# Time to Relapse Based on DSM-IV Syndromic Criteria



# Symptomatic Time to Relapse: 52-Week Placebo Comparison



# Attrition During Initial Treatment Predicted by Previous Relapse Prevention Studies at

Indication	OL Tx / Duration	Estimated Attrition at 12 weeks	Estimated attrition at 26 Weeks*
Depression	Fluox 20 mg 12 weeks	53%	73%
Panic Disorder**	Fluox 20 mg 10 weeks	56%	69%
ADHD	Atmx 1.2-1.8 mg/kg 12 weeks	31%	54%
Bipolar Disorder	Olanz 5-20 mg 12 weeks	51%	72%

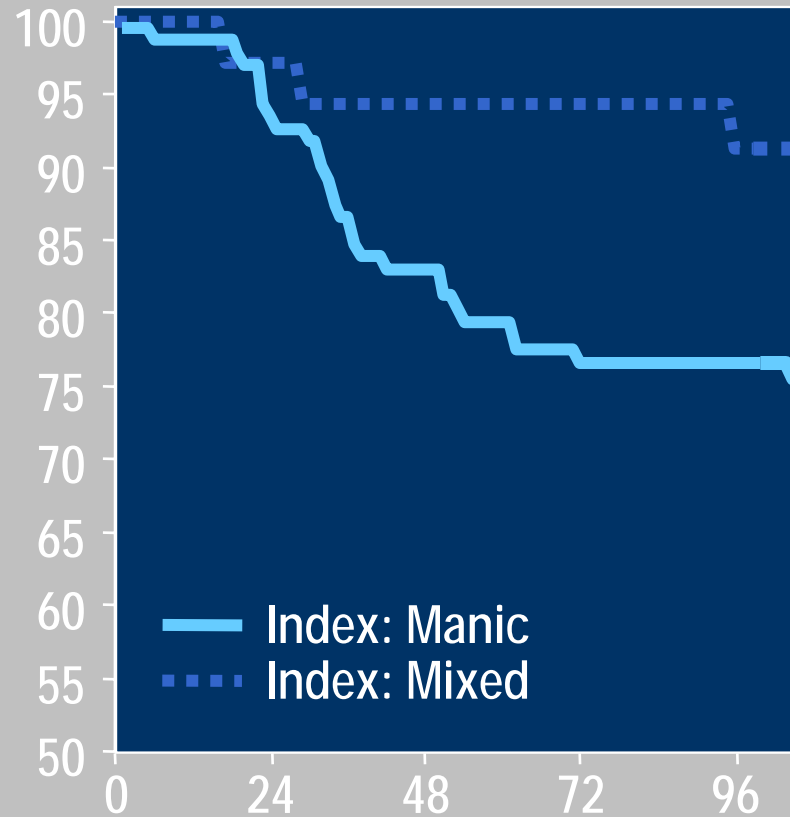
\* Attrition for 26 weeks are estimates derived by extrapolating from patient disposition or Kaplan-Meier curves during blinded treatment phase

\*\* Acute phase was double-blind rather than open label

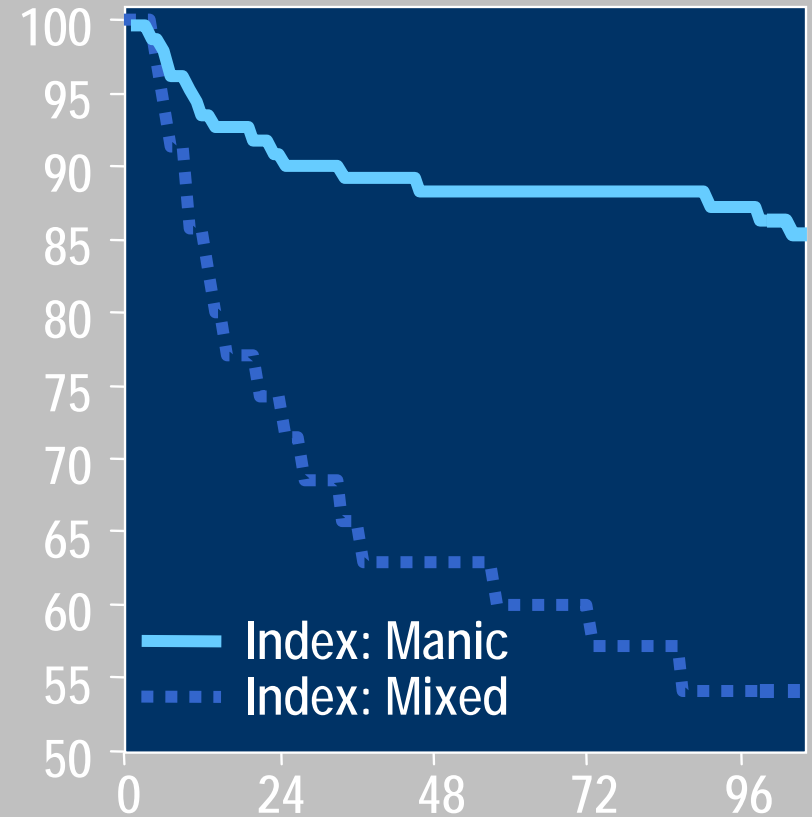
**Does index episode  
matter?**

# Does Index Episode Matter?

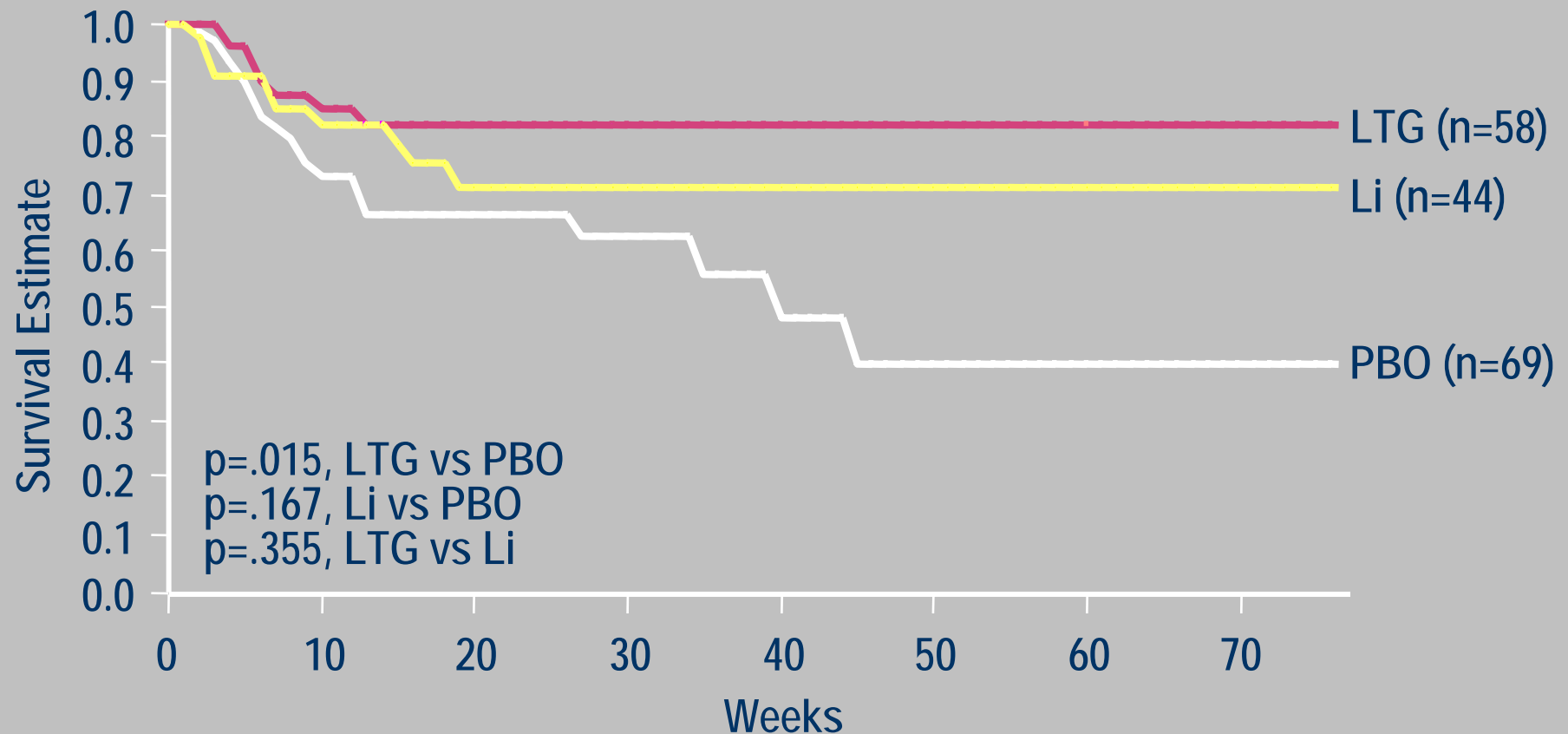
A. New Mania



B. New Depression



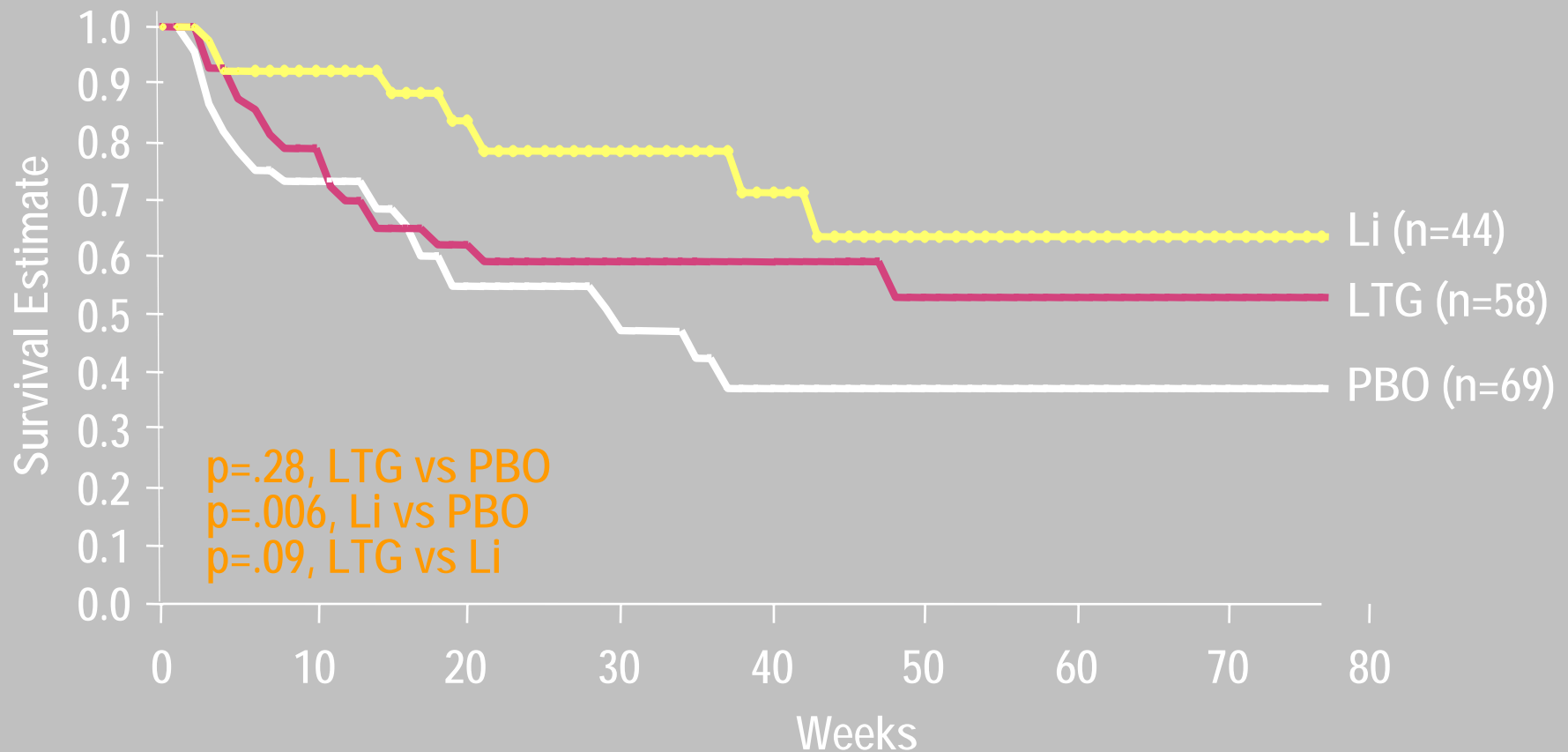
# Index Manic Episode: Time to Intervention for Depression Lamotrigine vs Lithium vs Placebo



Lamotrigine=100-400 mg/day. Lithium=0.8-1.1 mEq/L.  
Bowden CL, et al. *Arch Gen Psychiatry*. 2003;60(4):392-400.

# Index Manic Episode: Time to Intervention for Mania

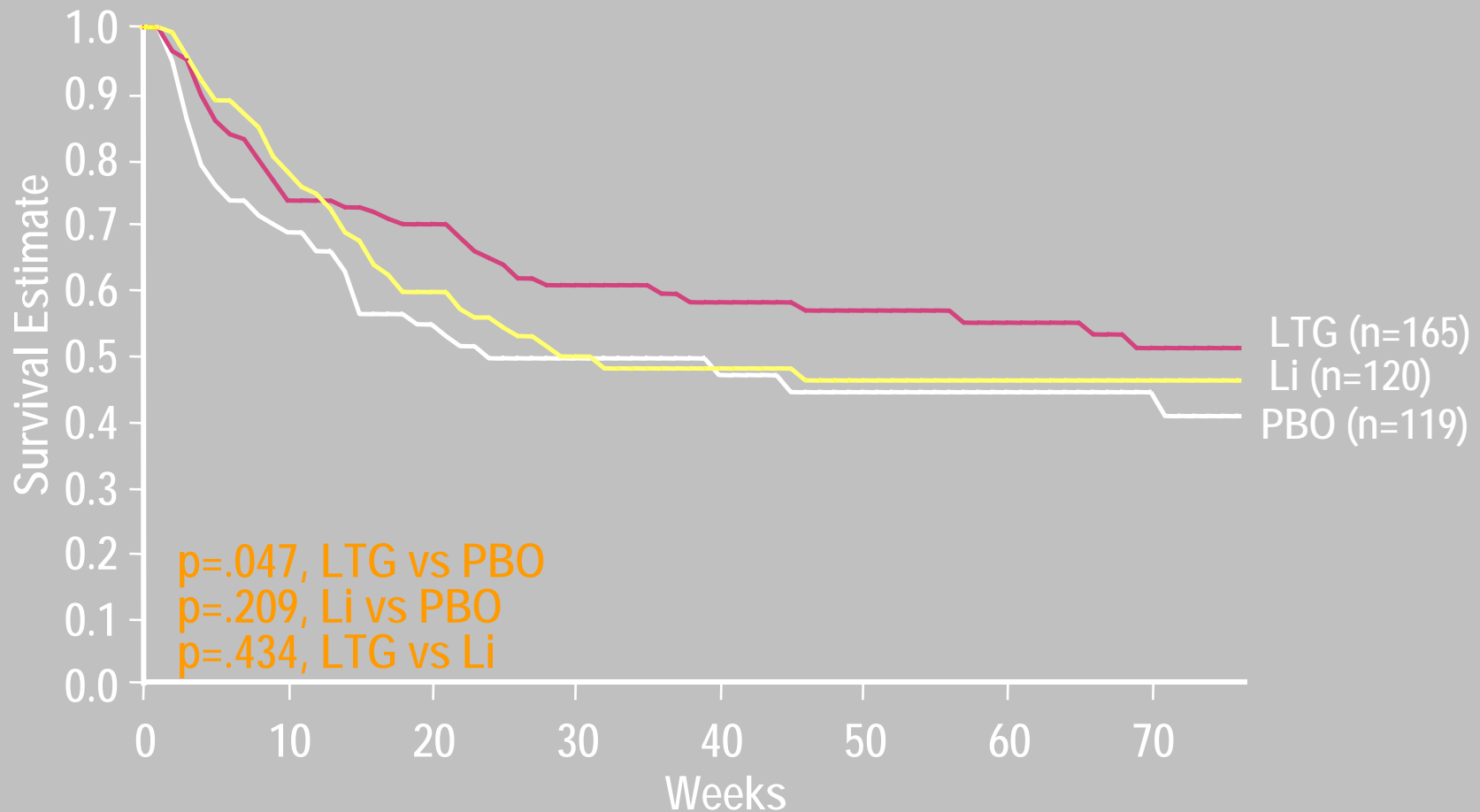
## Lamotrigine vs Lithium vs Placebo:



Lamotrigine=100-400 mg/day. Lithium=0.8-1.1 mEq/L.  
Bowden CL, et al. *Arch Gen Psychiatry*. 2003;60(4):392-400.

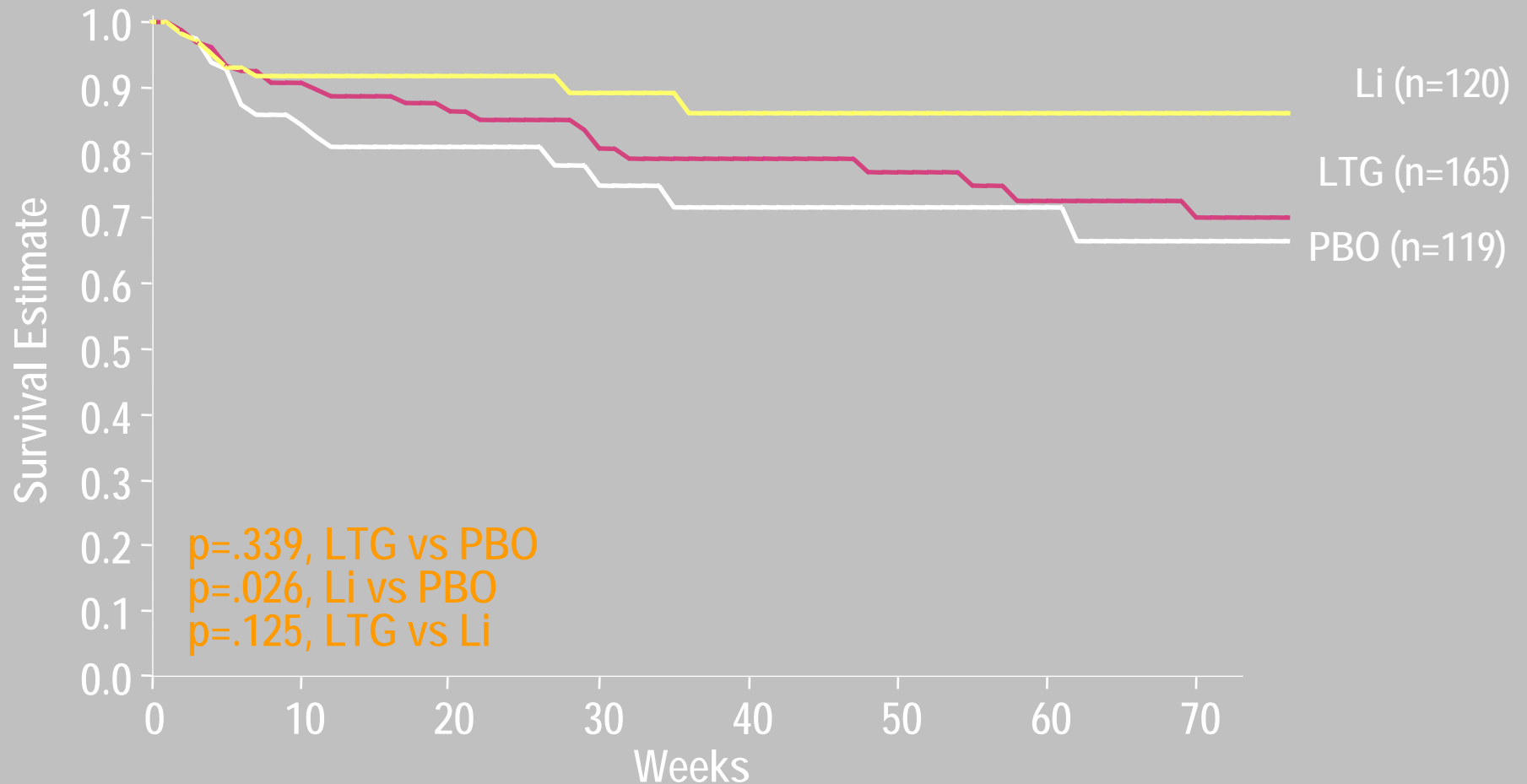
# Index Depressive Episode: Time to Intervention for Depression

## Lamotrigine vs Lithium vs Placebo

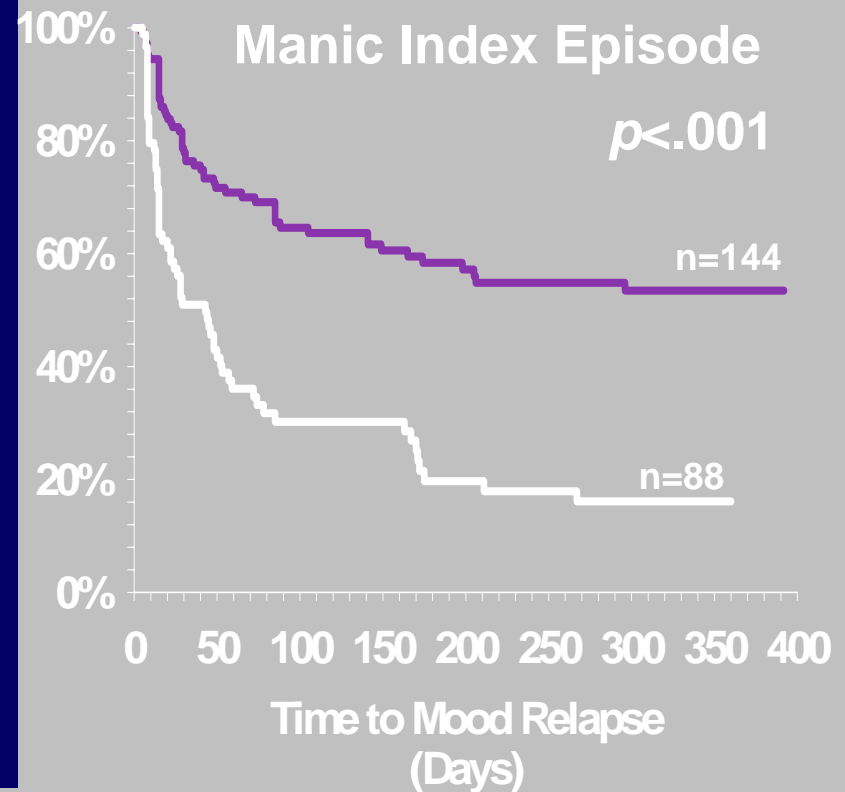
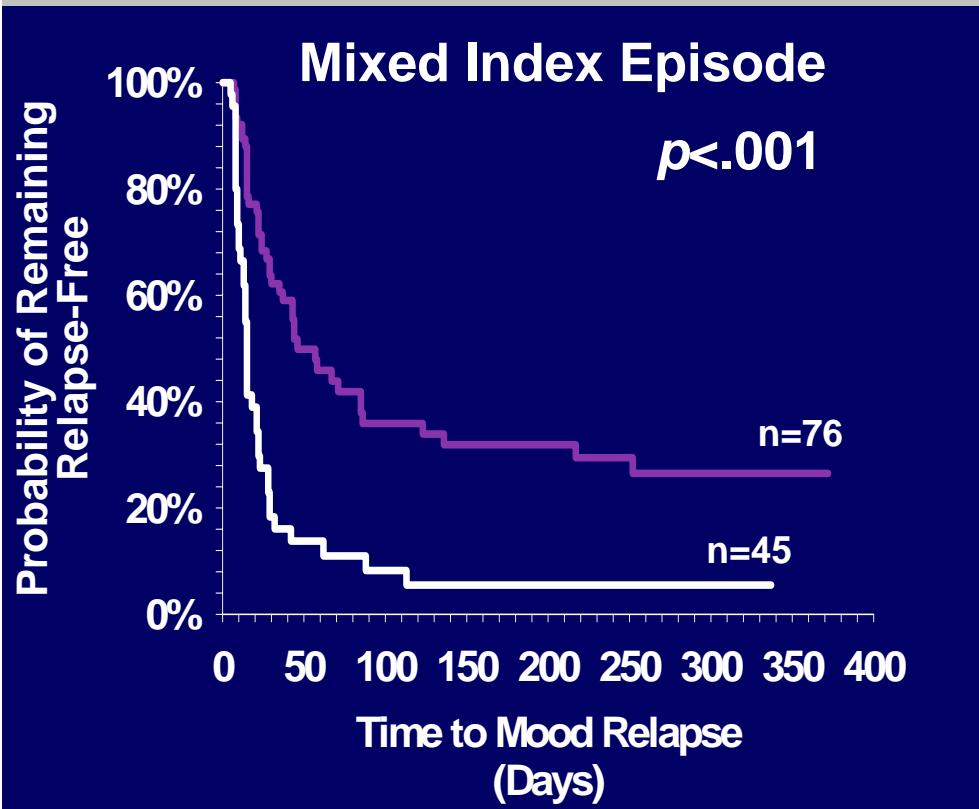


# Index Depressive Episode: Time to Intervention for Mania

## Lamotrigine vs Lithium vs Placebo



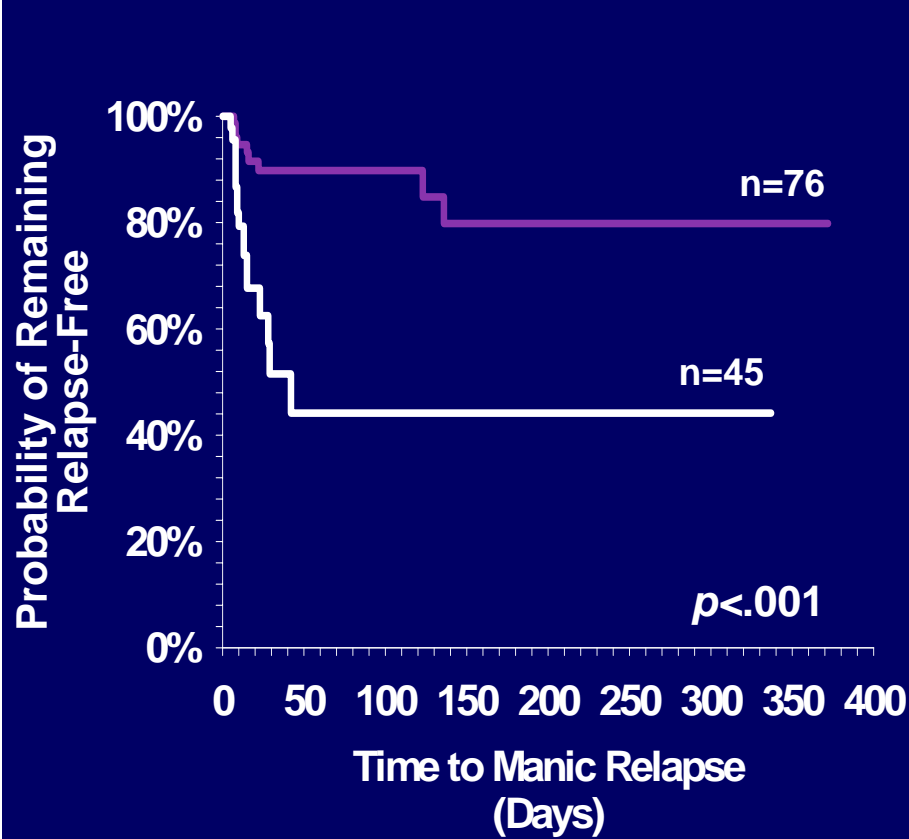
# Time to Relapse (Any Mood Episode)



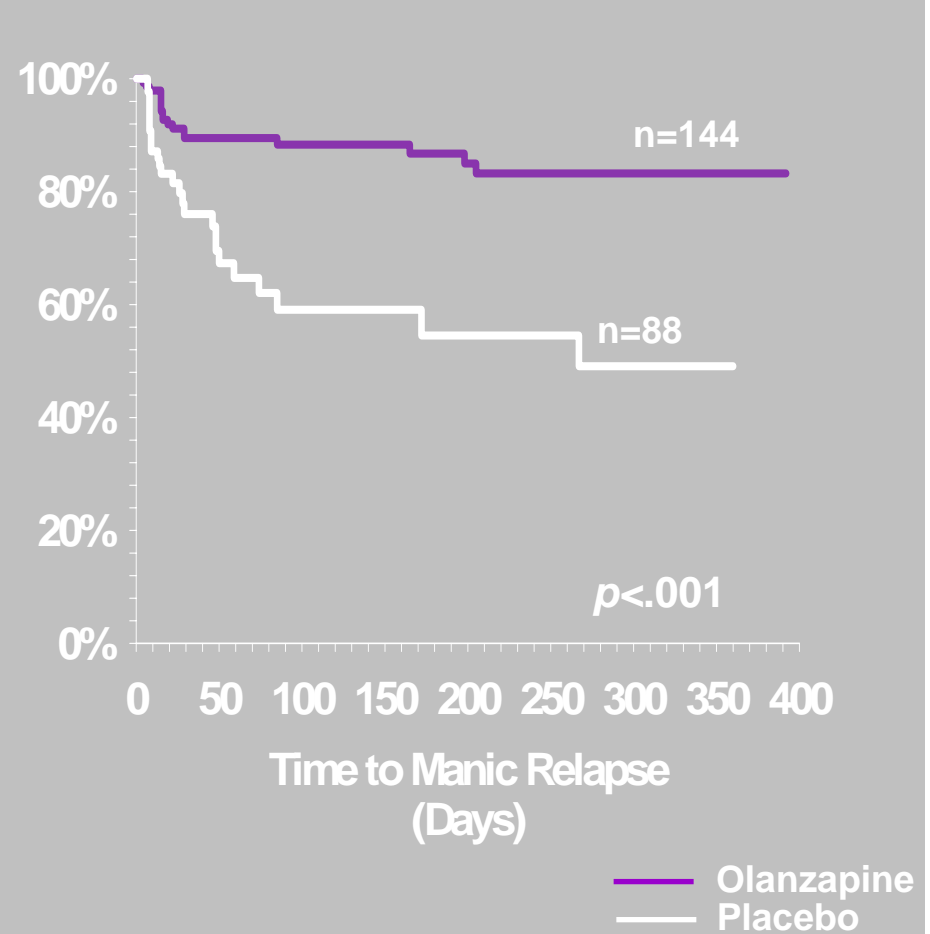
— Olanzapine  
— Placebo

# Time to Manic Relapse

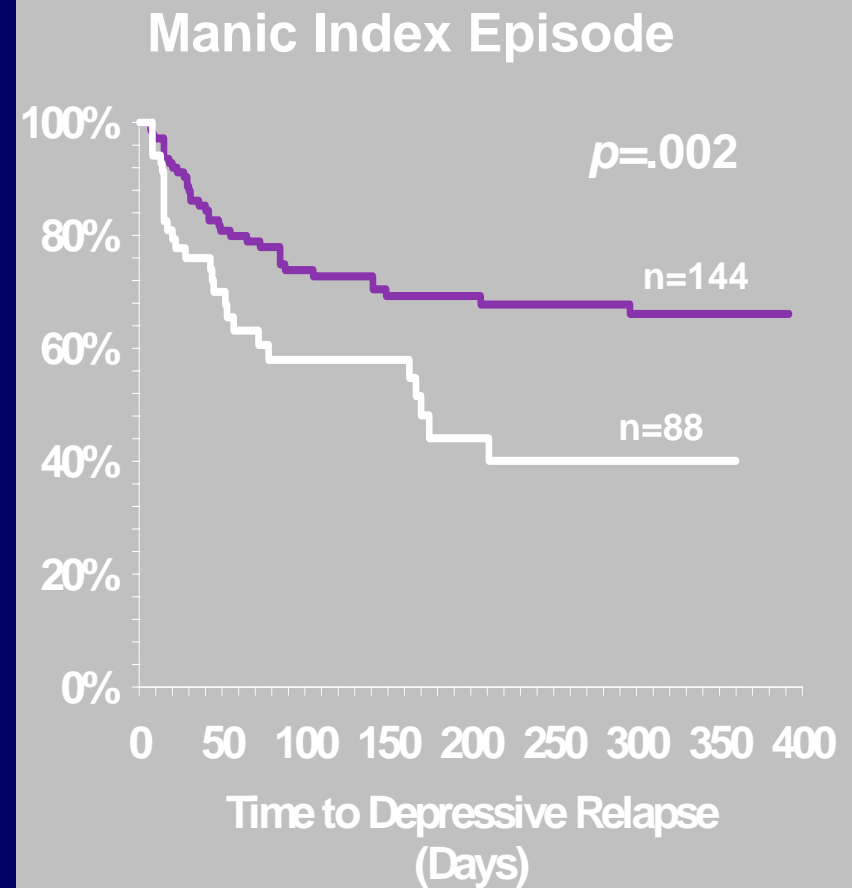
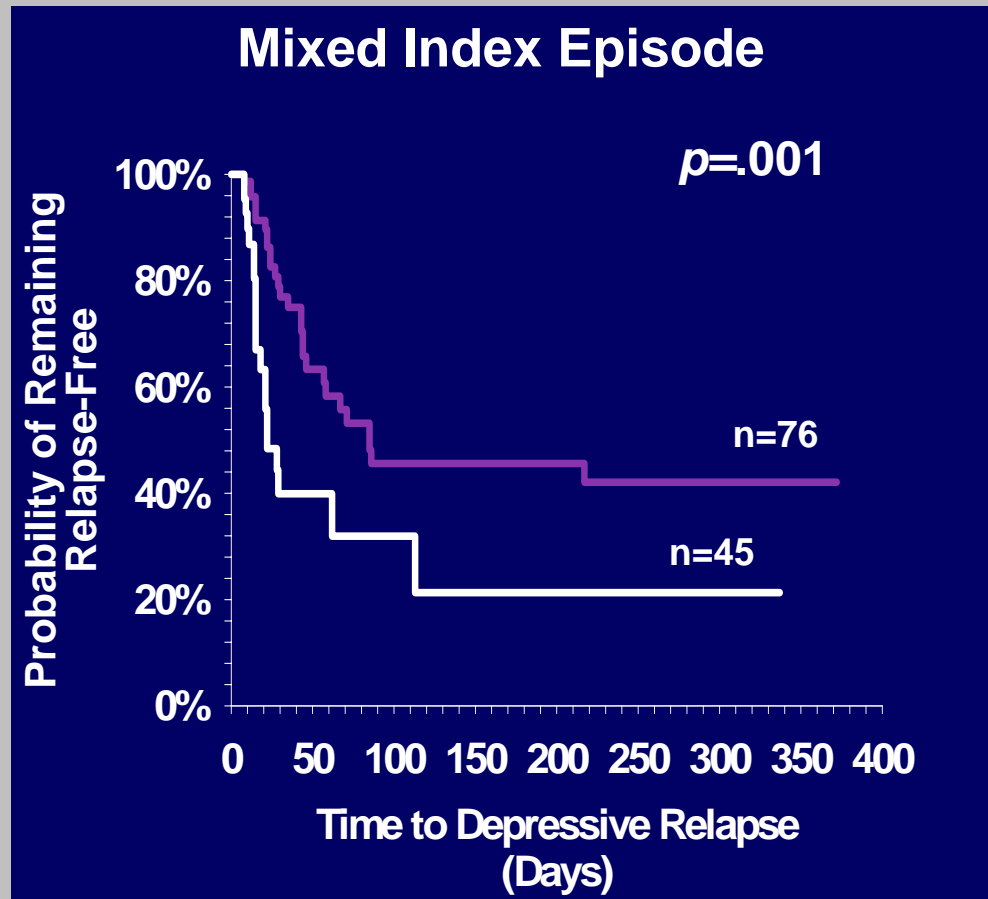
## Mixed Index Episode



## Manic Index Episode



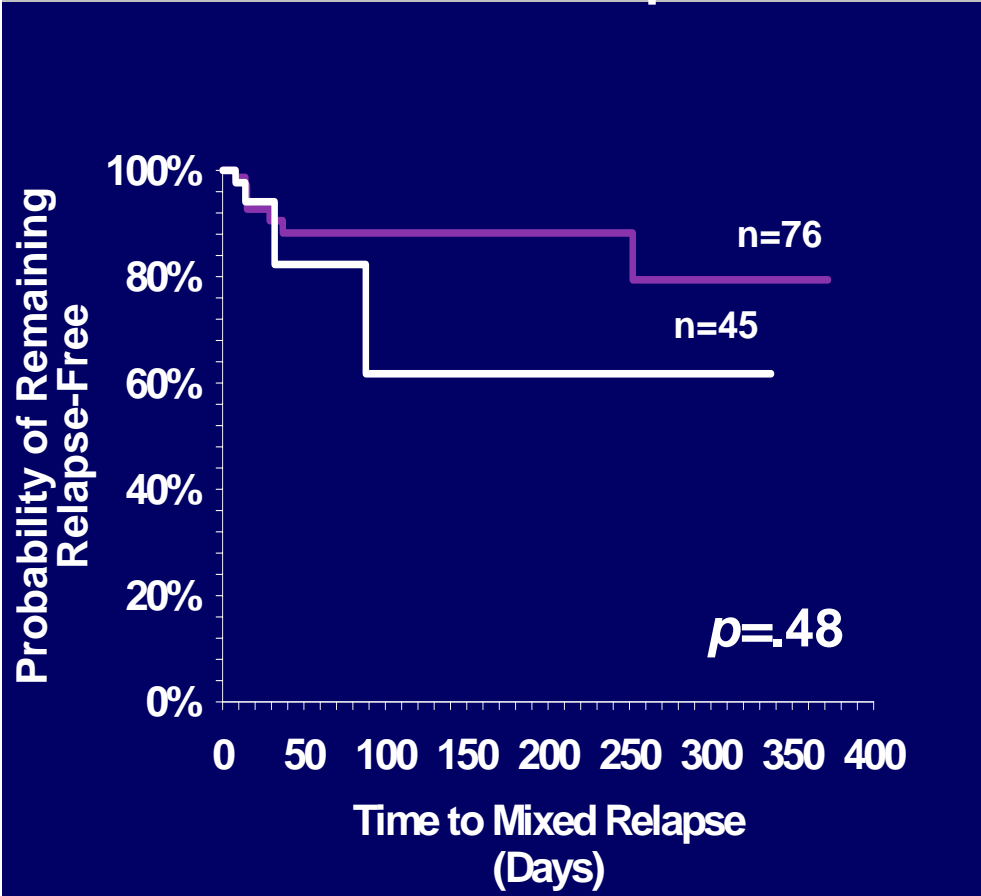
# Time to Depressive Relapse



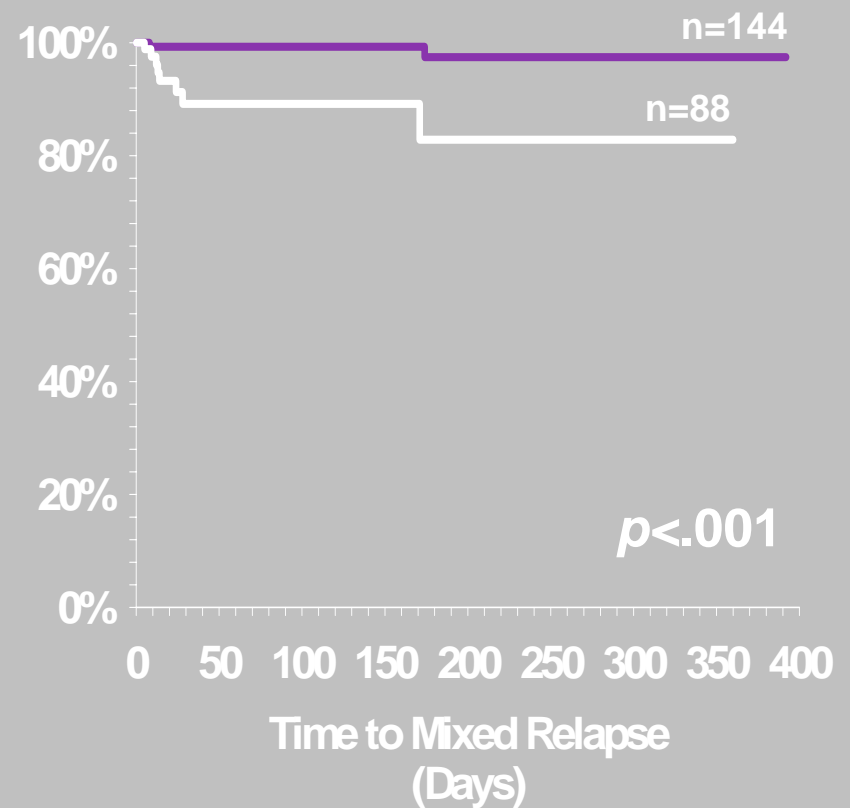
— Olanzapine  
— Placebo

# Time to Mixed Relapse

## Mixed Index Episode



## Manic Index Episode



— Olanzapine  
— Placebo

# Conclusions

# ***Relapse Prevention Clinical Trial Design in Bipolar Disorder***

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- ***Best interest of patients***

## ***Remission -***

- Period of remission appears to be needed
- Long periods of remission may produce samples unrepresentative of patients in clinical settings
- Index episode determines length of period in remission
- Need for uniformed definition

## ***Relapse -***

- Risk of abrupt discontinuation
- Definition and polarity of relapse matters
- Index episode matters
- Need for uniformed definition

***Thank you!***

# ***Clinical Trial Design***

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## **Feasibility**

- Long remission periods requires larger samples
- Larger samples increase enrollment, rater drift and sample variability