

**Lamotrigine extended release (LTG XR):  
Conversion to Monotherapy Treatment of  
Partial Epilepsy, an Historical Control Study**

GlaxoSmithKline LLC

Peripheral and Central Nervous System  
Drugs Advisory Committee

March 10, 2011

# Agenda

## **Thomas Thompson, M.D.**

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Development Center  
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Physician Project Leader for Lamotrigine

- Overview of Epilepsy and Lamotrigine

## **John Messenheimer, M.D.**

John Messenheimer PLLC  
Epilepsy Consultant

- Brief Review of the Historical Control Studies
- LAM30055 – Design, Efficacy and Safety Results
- Comparisons between LAM30055, US 30/31 and the Historical Studies

## **Thomas Thompson, M.D.**

- Summary and Conclusions

## **Eugene M. Laska, Ph.D.**

Research Professor, Biostatistics  
NYU Medical Center

- Statistical Considerations

# Overview of Epilepsy and Lamotrigine

**Thomas R. Thompson, M.D.**

Lamotrigine Physician Project Leader

GSK Neurosciences Medicine  
Development Center

# Epilepsy is Widespread, Chronic and Serious

- Affects approximately 3 million people in U.S.
- 70% of adults with epilepsy have partial onset seizures

# Available Therapies

- Over 10 anti-epileptic drugs (AEDs) are currently utilized to treat partial onset seizures
- None of these AEDs is established as superior to any other in efficacy
- Treatment must be individualized and based on clinical response
- Typically a number of AEDs will be tried before treatment is optimized, preferably with monotherapy

# Indications for Immediate-Release Lamotrigine in Partial Seizures

- Twice-daily adjunctive therapy of partial seizures in patients  $\geq 2$  years of age
- Conversion to monotherapy in patients  $\geq 16$  years of age with partial seizures

# Reasons for Developing Extended Release Lamotrigine

- Once a day dosing
- Reduce peak-trough variability
- Reduce patient pill burden

# Steady-State Bioavailability of LTG XR Relative to LTG IR

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## Concomitant AED

**AUC** <sub>(0-24ss)</sub>  
**Ratio (90%CI)**

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Enzyme-Inducing AEDs (EIAEDs)

0.79 (0.69, 0.90)

Valproate (VPA)

0.94 (0.81, 1.08)

Neutral AEDs

1.00 (0.88, 1.14)

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N=44

## Initial Indication: extended release Lamotrigine (LTG XR) in Partial Seizures

- Once a day adjunctive therapy for partial onset seizures with or without secondary generalization in patients  $\geq 13$  years of age

# Rationale for LTG XR as Monotherapy Treatment of Partial Onset Seizures

- Allow conversion to monotherapy for patients who have benefited from adjunctive therapy with LTG XR
- Target Dose:
  - 250 or 300 mg once daily

# **Efficacy and Safety of LTG XR for Conversion to Monotherapy**

John Messenheimer, M.D.

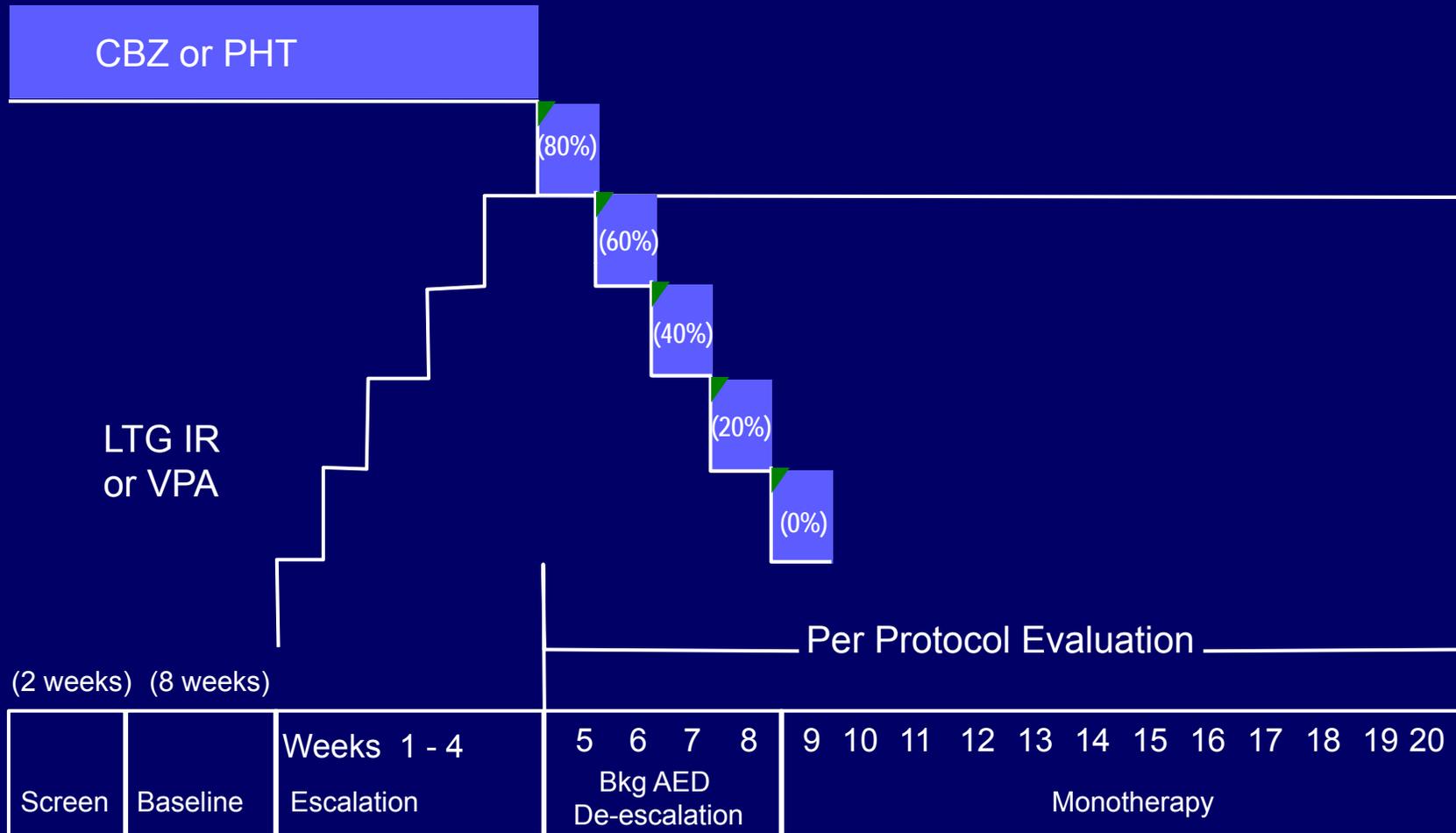
# AED Clinical Development

- AEDs initially approved for adjunctive use
  - Study drug compared to placebo
- Monotherapy indication is difficult to achieve
  - Cannot use placebo in monotherapy
  - Non-inferiority active control epilepsy trials may not be informative

# Evolution of Conversion to Monotherapy Studies

- A conversion to monotherapy trial design was introduced that:
  - Used a low dose of an AED (pseudoplacebo) as the comparator
  - Allowed subjects to exit or escape from treatment as soon as seizure frequency or severity worsened
    - Provided protection against severe seizures (status epilepticus)
    - Would be inferior to the test drug in overall seizure control

# LTG IR Conversion to Monotherapy (US 30/31)



VPA = low-dose of VPA (pseudoplacebo)

Gilliam F, et al. *Neurology*. 1998;51:1018-1025.

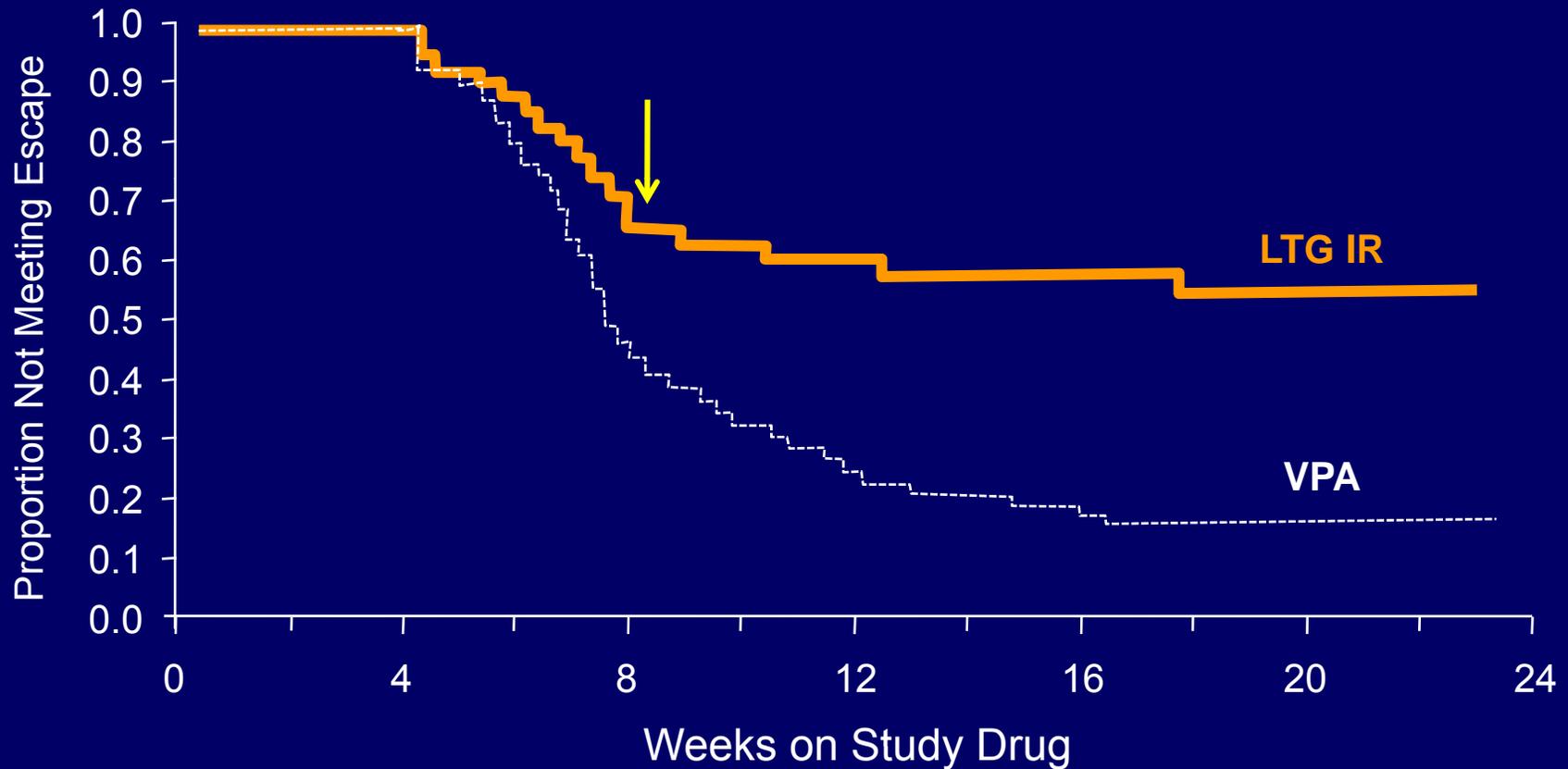
# Study US 30/31 Escape Criteria

After start of withdrawal of background AED:

- A two-fold increase from baseline in the 28-day partial seizure frequency calculated at each study visit
- A two-fold increase from baseline in the highest consecutive 2-day seizure frequency
- Emergence of a new, more severe seizure type
- Clinically significant prolongation of generalized tonic-clonic seizures

# Study US 30/31 Efficacy Results

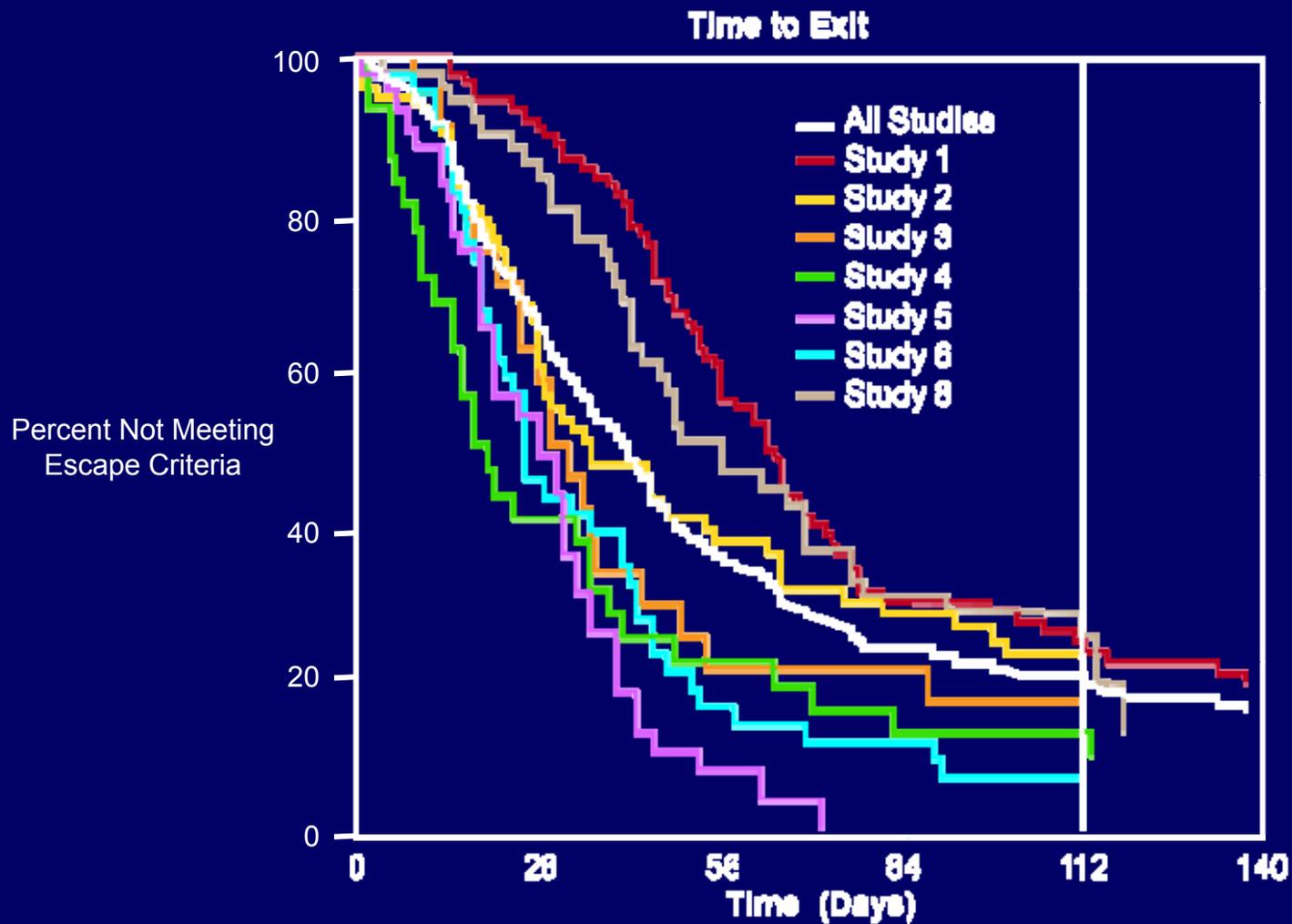
Kaplan-Meier survival curve of time to escape



# Development of Historical Control

- A total of 10 pseudoplacebo conversion to monotherapy trials were published between 1992 to 2001
- Increasing concern regarding use of an inferior treatment
- Proposal to use an historical control based on the aggregated pseudoplacebo data

# Historical Control Escape Rates for Pseudoplacebo



French et al. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia* 2010;51(10):1936-1943.

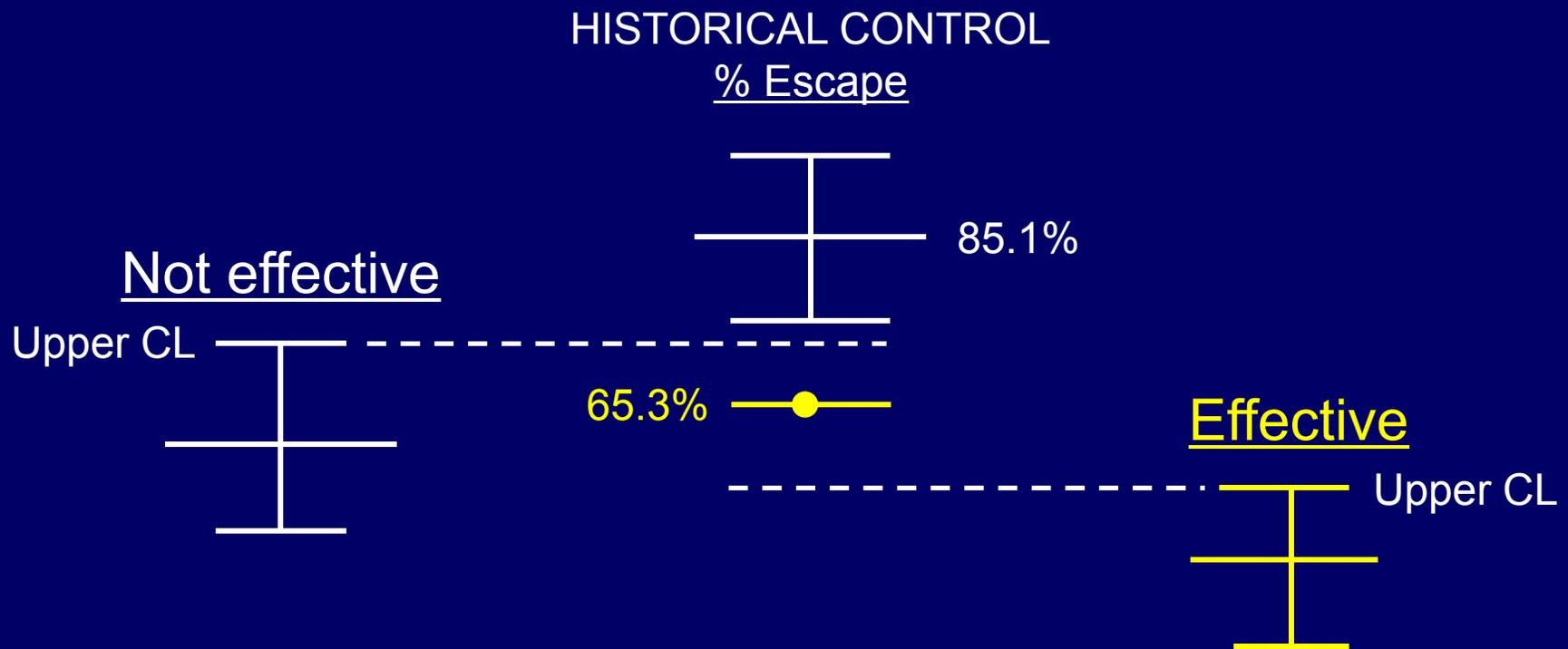
# Historical Control

## Escape Rates for Pseudoplacebo (cont.)

- Similarity of pseudoplacebo trial designs across studies is critical to allowing pooling of data for analysis
- Pseudoplacebo escape rates
  - Escape ranging from 74.9% – 95.9%
  - Estimate of combined percent escape: 85.1%
  - Lower 95% prediction limit: 65.3%

<sup>1</sup> French et al. Historical control monotherapy design in the treatment of epilepsy. *Epilepsia* 2010;51(10):1936-1943.

# Demonstrating Efficacy with Historical Control



# Study LAM30055

A Multi-center, Double-Blind, Randomized  
Conversion to Monotherapy Comparison of Two  
Doses of Lamotrigine for the Treatment of  
Partial Seizures

# LAM30055 Study Design

- Subjects inadequately controlled on AED monotherapy
- LTG XR titrated to a target dose of once-daily 250 mg or 300 mg
- Background AED gradually withdrawn
- Continue for an additional 12 weeks of monotherapy
- Seizure type and frequency monitored throughout the study through subject diary and evaluated at each study visit

# LAM30055 Key Inclusion/Exclusion Criteria

- Male or female subjects 13 years of age or older having 4 partial onset seizures per 8 weeks
- Monotherapy treatment with VPA or a neutral AED
- Subjects taking EIAEDs were excluded

# LAM30055 Efficacy Analysis

- The planned primary endpoint for LAM30055 was discontinuation for any reason (including meeting escape criteria)
- A planned secondary endpoint was the proportion of subjects meeting escape criteria
- The escape endpoint will be the focus of the evaluation

# Determination of Escape in LAM30055

- 100% source verification of seizure data was done at the end of the double-blind phase
- Due to under-reporting of escape by the investigators, the escape rates determined from the database will be presented
- Significant prolongation of generalized tonic-clonic seizures evaluated in an expanded analysis

# LAM30055 Analysis Populations

- Per Protocol Population (Primary)
  - All randomized subjects who received study drug and
    - Began withdrawal of the background AED
    - Excluding those with major protocol violations
- Intent to Treat (ITT)/Safety Population
  - All randomized subjects who received at least one dose of study drug

# Per Protocol Analysis Populations

## LAM30055 Per Protocol Definition

- All randomized subjects who took at least one dose of study drug and began withdrawal of the background AED **excluding those with major protocol violations**

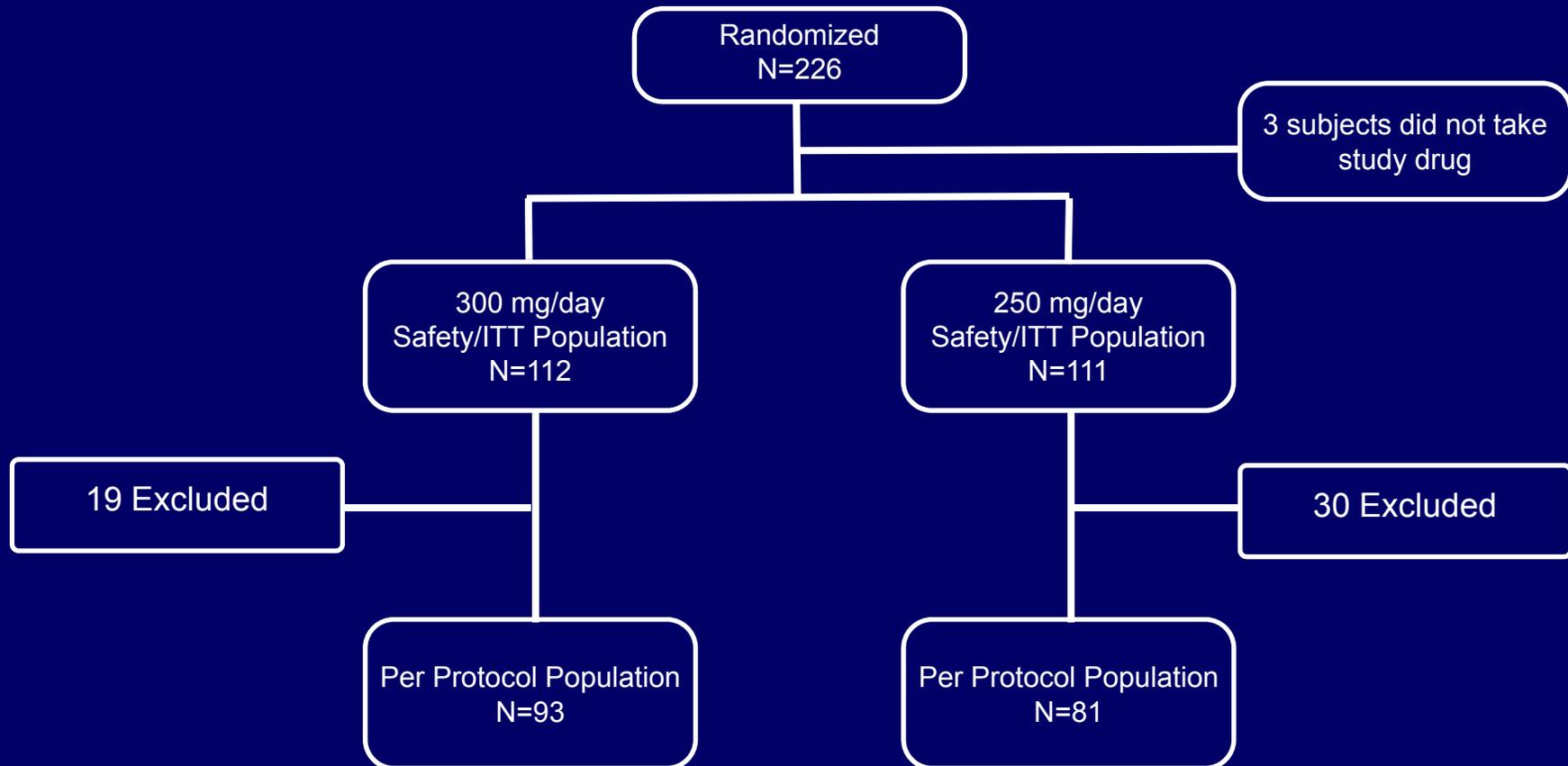
## US 30/31 Per Protocol Definition

- All randomized subjects who took at least one dose of study drug and began withdrawal of the background AED, **and who met Escape Criteria or completed 12 weeks of monotherapy**

## White Paper Per Protocol Definition

- All randomized subjects who took at least one dose of study drug and began withdrawal of the background AED

# LAM30055 Subject Populations



# LAM30055 - Per Protocol Exclusions

	No. of Subjects	
	300 mg/day	250 mg/day
ITT	112	111
PP Population	93	81
Excluded from PP Population	19	30
<b>Reasons for Exclusion from PP Population</b>		
Did not begin withdrawal of background AED	4	14
Closed study site	6	7
Entry criteria violation	3	3
Less than 11 weeks of monotherapy	2	2
Poor compliance	1	2
Received wrong treatment for >2 weeks	3	1
Exceeded allowed benzodiazepine use	0	1

# LAM30055 Subjects Randomized by Country

	LTG XR 300 mg/d	LTG XR 250 mg/d
Total Subjects randomized	113	113
Ukraine	33 (29%)	27 (24%)
United States	28 (25%)	28 (25%)
Russia	15 (13%)	20 (18%)
Argentina	14 (12%)	13 (12%)
South Korea	11 (10%)	11 (10%)
Costa Rica	7 (6%)	9 (8%)
Chile	5 (4%)	5 (4%)

# LAM30055 Efficacy Results

# LAM30055 Presentation of Efficacy Results

- Discontinuation Endpoint
- Escape Endpoint
- Expanded Escape Endpoint

# LAM30055 Proportion of Subjects Discontinuing for Any Reason

	LTG XR 300 mg/d	LTG XR 250 mg/d
Per-Protocol Population	(N=93)	(N=81)
Discontinuing (%)	26 (28%)	27 (33%)
95% CI	(18.8, 37.1)	(23.1, 43.6)
ITT Population	(N=112)	(N=111)
Discontinuing (%)	36 (32%)	49 (44%)
95% CI	(23.5, 40.8)	(34.9, 53.4)

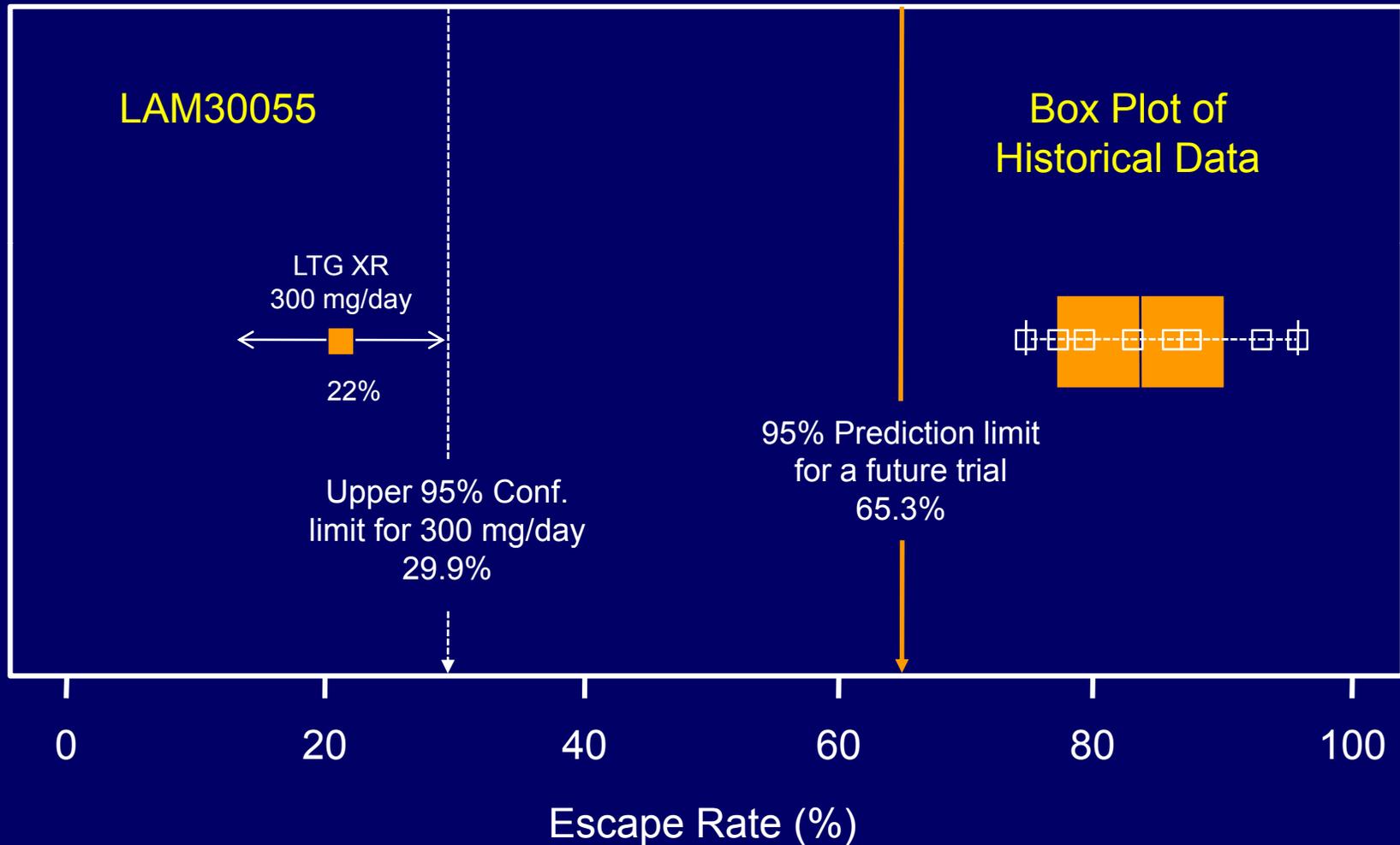
Historical Control Lower 95% Prediction Limit = 65.3%

# LAM30055 - Proportion of Subjects Meeting Escape Criteria

	LTG XR 300 mg/d	LTG XR 250 mg/d
Per-Protocol Population	(N=93)	(N=81)
Meeting Escape Criteria	20 (22%)	21 (26%)
95% CI	(13.2, 29.9)	(16.4, 35.5)
ITT Population	(N=112)	(N=111)
Meeting Escape Criteria	28 (25%)	25 (23%)
95% CI	(17.0, 33.0)	(14.8, 30.3)

Historical Control Lower 95% Prediction Limit = 65.3%

# LAM30055 Escape Rate vs Historical Control (Per Protocol Population)



## LAM30055 Expanded Definition of Escapes

- Subjects with emergence of a new, more severe seizure type
  - vs baseline only
- Subjects with significant prolongation of a generalized tonic clonic seizure
  - Subjects with adverse events possibly indicative of a severe seizure
  - Subjects using benzodiazepines for seizures

## LAM30055 – Escapes Based on AEs and Benzodiazepine Use

Outcome	AEs Possibly Related to Seizures		Use of Rescue Benzodiazepine	
	300 mg/day	250 mg/day	300 mg/day	250 mg/day
Escapes	2	2	3	4
Total Including Expanded Escapes	3	5	5	7

# LAM30055 Expanded Escape Endpoints

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	LTG XR 300 mg/d	LTG XR 250 mg/d
Per-Protocol Population	(N=93)	(N=81)
Meeting Escape Criteria	25 (27%)	24 (30%)
95% CI	(17.9, 35.9)	(19.7, 39.6)
ITT Population	(N=112)	(N=111)
Meeting Escape Criteria	33 (29%)	33 (30%)
95% CI	(21.0, 37.9)	(21.2, 38.2)

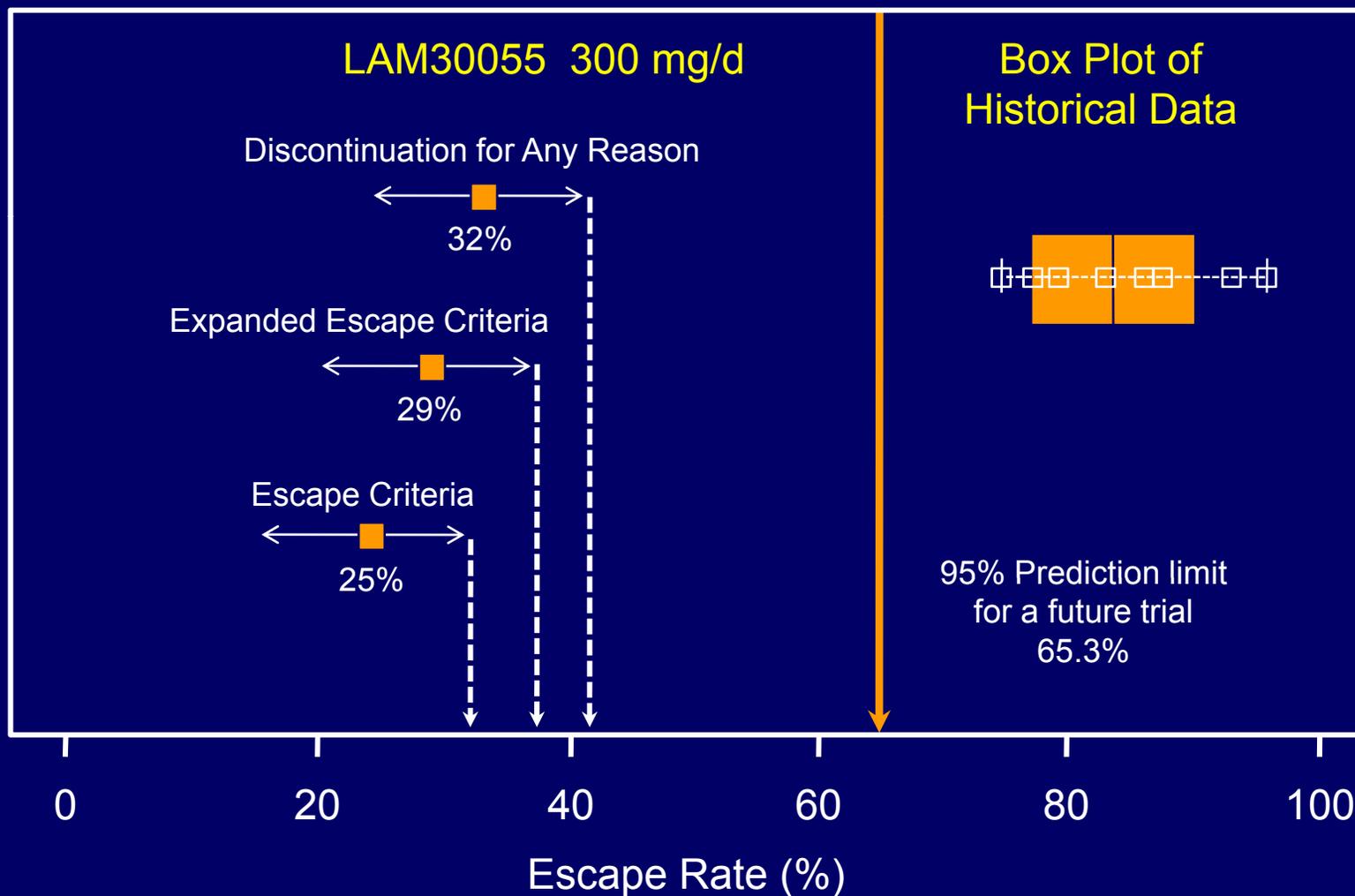
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Historical Control Lower 95% Prediction Limit = 65.3%

## Escape Rate by Criterion for LAM30055 (Expanded Escape) and US 30/31 (US 30/31 Per Protocol Population)

	LAM30055		US 30/31	
	LTG XR 300 mg/day  N=102 (%)	LTG XR 250 mg/day  N=90 (%)	LTG IR 500 mg/day  N=50 (%)	VPA 1000 mg/day  N=64 (%)
Total Escape	30	36	44	80
1 Doubling of Monthly Seizures	9	18	16	25
2 Doubling of 2-day seizures	19	20	16	31
3 New, more severe seizure type	8	8	8	25
4 Prolongation of generalized seizures	8	11	10	5

# LAM30055 Discontinuation, Escape and Expanded Escape Rates vs Historical Control (ITT Population)



# LAM30055 Safety Results

## LAM30055 Adverse Events Double-Blind Phase (Safety Population)

	LTG XR 300 mg/d N=112 (%)	LTG XR 250 mg/d N=111 (%)
Any Treatment-Emergent AE	53	61
Most Common AEs ( $\geq 5\%$ )		
– Headache	26	28
– Dizziness	11	9
– Rash	4	11
– Nasopharyngitis	6	6
– Nausea	5	5
– Somnolence	4	5
– Insomnia	0	5

## LAM30055 Serious Adverse Events (SAEs)

- 8 Subjects reported 10 SAEs
  - 2 seizure related
  - 2 trauma
  - 2 neoplasm
  - 1 each UGI hemorrhage, rash, pyrexia, respiratory failure
- There was one SAE of rash (not Stevens-Johnson syndrome)
- There were no deaths

# **Comparisons Between LAM30055, US 30/31 and the Historical Studies**

# Comparison of Demographics

Study	N	Mean Age Years	Gender (%, M/F)	Study Locations	Race (%) (White/Black/ Other)
1	94	35	54:45	US, Canada	-
2 (US 30/31)	80	36	40:60	US	69/14/18
3	24	35	38:63	-	83/4/13
4	32	-	-	-	-
5	45	35	53:47	US	87/--/13
6	46	36	41:59	US	-
7	22	38	-	US	-
8	55	35	36:64	-	85/9/5
LAM30055					
300 mg/day	112	34	50:50	US, Latin Am.,	86/4/10
250 mg/day	111	33	41:59	Ukraine, Russia, Korea	86/4/10

# Comparison of Key Baseline Characteristics

Study	N	Epilepsy Duration (yrs) Median	Seizure Frequency Median	% Taking CBZ
1	94	21	6.5	64 (average of 3 groups)
2 (US30/31)	80	20	10.0	58
3	24	21	9.5	63
4	32	-	-	-
5	45	-	5.5	100
6	46	-	6.5	46
7	22	-	-	59
8	55	-	-	-
LAM30055 300 mg/day	112	12	5.6	11 OXC
LAM30055 250 mg/day	111	13	6.0	11 OXC

# Comparison of Partial Seizure Subtypes

Historic Study	Seizure Type at Entry (%)		
	Simple Partial	Complex Partial	Secondarily Generalized
1	---	95	19
2 (US 30/31)	44	89	34
3	25	83	42
4	-	-	-
5	38	87	71
6	-	-	32
7	-	-	-
8	-	-	-
LAM30055 300 mg/day	44	63	54
LAM30055 250 mg/day	48	60	53

# Important Differences in Design

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	LAM30055	US 30/31	Historical Control
EIAEDs (CBZ or PHT)	No	Only CBZ or PHT	Yes Plus Other AEDS
VPA	Yes	No	Some Studies
Regions	US and Other	Only US	US/1 Canada

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# LAM30055 Background AEDs

## Exclusion of EIAEDs from LAM30055

- EIAEDs reduce lamotrigine concentrations by 50% vs neutral AED
- Effect persists even at low EIAED doses
- Require approximately two weeks after EIAED discontinuation to resolve

# Exclusion of EIAEDs from LAM30055

- LAM30055 excluded subjects receiving EIAEDs (CBZ and PHT)
  - Conversion to LTG monotherapy from inducers requires conversion at a dose of 500 mg/day
  - Known pharmacokinetic interactions would have required complex dosing regimen significantly different from design of historical control studies
- The White Paper analysis showed that withdrawal from CBZ did not increase the likelihood of escape vs other AEDs

# LAM30055 Escape Rates VPA vs Neutral AED (ITT Population)

	LTG XR 300 mg/day N = 112		LTG XR 250 mg/day N = 111	
	VPA	Neutral	VPA	Neutral
Escaped n/N (%)	16/73 (22)	12/39 (31)	14/70 (20)	11/41 (27)
Upper 95% CI	31.4	45.3	29.4	40.4

Historical Control Lower 95% Prediction Limit = 65.3%

## One vs Two Background AEDs at Study Entry

- Some historical control studies allowed subjects taking 2 AEDs
  - Not really on 2 AEDs
  - Required the dose of the 2<sup>nd</sup> AED
    - To be less than 50% of the minimally effective dose or
    - The concentration to be less than 50% of the minimal effective concentration

# LAM30055 US vs Non-US Efficacy

## LAM30055 Escape Rates Higher in US than Non-US Subjects (ITT Population)

	LTG XR 300 mg/day N=112		LTG XR 250 mg/day N=111	
	US	Non-US	US	Non-US
Escaped n/N (%)	10/28 (36)	18/84 (21)	8/28 (29)	17/83 (20)
Upper 95% CI	53.5	30.2	45.3	29.2

Historical Control Lower 95% Prediction Limit = 65.3%

## VPA Use in LAM30055 Higher in Non-US Subjects (ITT Population)

	LTG XR 300 mg/day		LTG XR 250 mg/day	
	VPA	Neutral	VPA	Neutral
US	18%	82%	21%	79%
Non-US	81%	19%	77%	23%

## LAM30055 Escape by Region, Dose and AED Group (ITT Population)

AED Group	Region	LTG XR 300 (n/N)	LTG XR 250 (n/N)
VPA	US	1/5	3/6
	Non-US	15/68	11/64
Neutral	US	9/23	5/22
	Non-US	3/16	6/19

**Escape Rates for Neutral AEDs Comparable in  
US and Non-US Subjects  
ITT Population  
(LTG XR 250 mg and 300 mg Groups Combined)**

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	<b>Neutral AED n/N (%)</b>
US	14/45 (31%)
Non-US	9/35 (26%)

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# **LAM30055 Efficacy vs US 30/31**

# Comparison of LAM30055 and US 30/31 Escape Rates (US 30/31 Per Protocol Population)

<b>LAM30055</b>	<b>LTG XR 300 mg/d (N=102)</b>	<b>LTG XR 250 mg/d (N=87)</b>
Meeting Escape Criteria, n (%)	26 (25%)	25 (29%)
<b>US 30/31</b>	<b>LTG IR 500 mg/d (N=50)</b>	
Meeting Escape Criteria, n (%)	22 (44%)	

## Comparison of Escape Rates Neutral AED - LAM30055 vs US 30/31 Using US 30/31 PP Definition

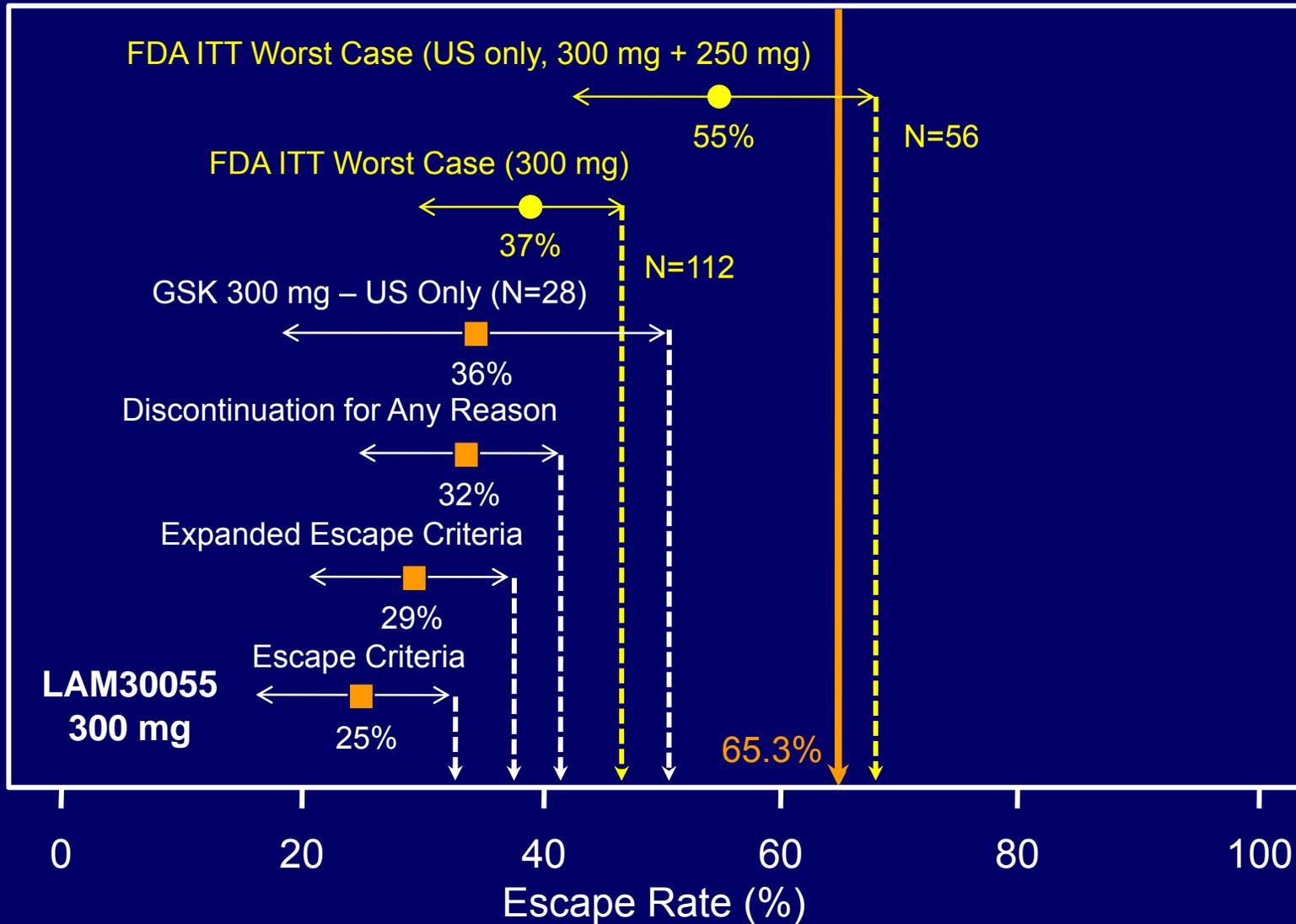
		LAM30055 (Neutral Only)	
	US 30/31	300 mg/day	250 mg/day
Met Escape Criteria n/N (%) [95%CI]	22/50 (44) [31.2, 57.7]	11/33 (33) [18.6, 51.9]	11/29 (38) [21.3, 57.6]

# Summary and Conclusions

## Rationale for LTG XR as Monotherapy Treatment of Partial Onset Seizures

- Approved as once a day adjunctive therapy for partial onset seizures
- Allow conversion to monotherapy for patients who have benefited from adjunctive therapy with LTG XR

# LAM30055 Sponsor and FDA Analyses



# Questions for Consideration

- Potential bias of active treatment Only
- Potential bias due to under-reporting of study endpoints
- Number of background AEDs
- Comparability of escape Criteria among studies
- US vs foreign data

## Potential Bias of Active Treatment Only

- Subjects in both LAM30055 and the historical control studies received one of two active treatments
- Consent forms did not identify one treatment as inferior (French 2010)
- Unlikely that physician and patient expectations explain Study 55 efficacy
  - Upper limit for escape rate for the 300 mg arm is 29.9%
  - Prediction limit is 65.3%

# Potential Bias Due to Under-Reporting of Study Endpoints

- Objective nature of seizure data allow unbiased analysis for 3 of the 4 escape criteria
  - No bias for criteria 1-3
- Expanded escape analysis addressed subjective criterion 4
- Study outcome not affected

# Number of Background AEDs

- Agency-derived prediction limit based on one background AED
  - Point estimates similar (83% vs 85.2%)
  - Wider confidence intervals
- Study LAM30055 demonstrated efficacy using:
  - White Paper prediction limit (65.3%)
  - Agency-adjusted prediction limit based on one background AED (58.6%)

# Comparability of Escape Criteria Among Studies

- Across the Historical Control Studies
  - Escape criteria covered increase in seizure frequency or severity
  - Analysis using expanded escape criteria remained below 65.3% prediction limit

# US vs Foreign Data

- Efficacy in LAM30055 was demonstrated in the US subgroup
  - 300 mg: 36% escape rate, UCL = 53.5%
  - 250 mg: 29% escape rate, UCL = 45.3%
- Neutral AED escape rates by region
  - US :  $14/45=31\%$
  - Non-US:  $9/35=26\%$

# Conclusion

- The populations, design and methodology in LAM30055 are not identical, but are sufficiently similar to the historical control studies to meet criteria for the use of a historical control
- The results of LAM30055 demonstrate that LTG XR is safe and effective at doses of 250 mg and 300 mg once daily in subjects converting to monotherapy from VPA or a neutral AED

# **Some General Considerations in Historical Control Trials**

**Characterizing the effectiveness of  
LTG XR 300 mg based on a  
meta analysis of add on therapy  
50% responder rates**

# Generic Objections to a Historically Controlled Clinical Trial (HCT)

- The HCT is essentially an open label study
- There is no randomization which is
  - the underpinning of statistical inference
  - the basis of causal inference
  - Insurance against biased treatment allocation and expected balance in prognostic factors

# **What Then is the Justification for a HCT?**

- **When a placebo controlled trial is unethical and an active controlled trial can be misleading**
- When independent data strongly suggest efficacy
- When absent treatment, the disease course predictably and consistently results in poor outcome
- When meaningful endpoints are objective
- When the effect of baseline variables on the endpoint is reasonably well understood

# Operationalizing an HCT

- Choose a relevant outcome measure and a corresponding historical data set
- Standard meta analysis assumes past trials and the HCT are **similar** in that the study parameters are drawn from a common probability distribution
- This leads to a random effects (or super population model) or a Bayesian model assuming exchangeability
- Use predictive distribution for inference in the HCT

# Major Issue

- Are the differences between the conduct and outcome of the HCT and the historical data so large that comparisons are precluded?
- What effect did absence of a placebo arm have on outcome?

# Choice of Historical Controls

## (1) Data from Monotherapy Studies

- Pseudoplacebo controlled studies (French)
  - Outcome measure: Escape rate
- *LAM30055*: Design is similar in that treatments are exchanged
- *Potential unestimable expectation bias in 055 compared to historical trials*: subjects and investigators know an ineffective treatment will not be assigned, which may induce lower escape rates

# Choice of Historical Controls

## (2) Data from Add on Studies

- Placebo controlled studies
  - Outcome measure: Responder rate (> 50% reduction in seizure rate)
- *LAM30055*: Design difference in that treatments are switched versus added on
- *Potential expectation differences in 055 compared to historical data*: background AED will not be removed vs switching to an active drug
- **Expectation in the LAM30055 arguably closer to expectations in add on trials than in pseudoplacebo monotherapy trials**

# Meta Analyses of Responder Rates in Add on Studies

- Guekht, Korczyn, Bondareva and Gusev  
Epilepsy & Behavior 17 (2010)
- Burneo, Montori and Faught  
Epilepsy & Behavior 3 (2002)
- Rheims, Cucherat, Arzimanoglou and Ryvlin  
PloS Medicine 5 (2008)
- Rheims, Perucca, Cucherat and Ryvlin  
Epilepsia 52 (2011)

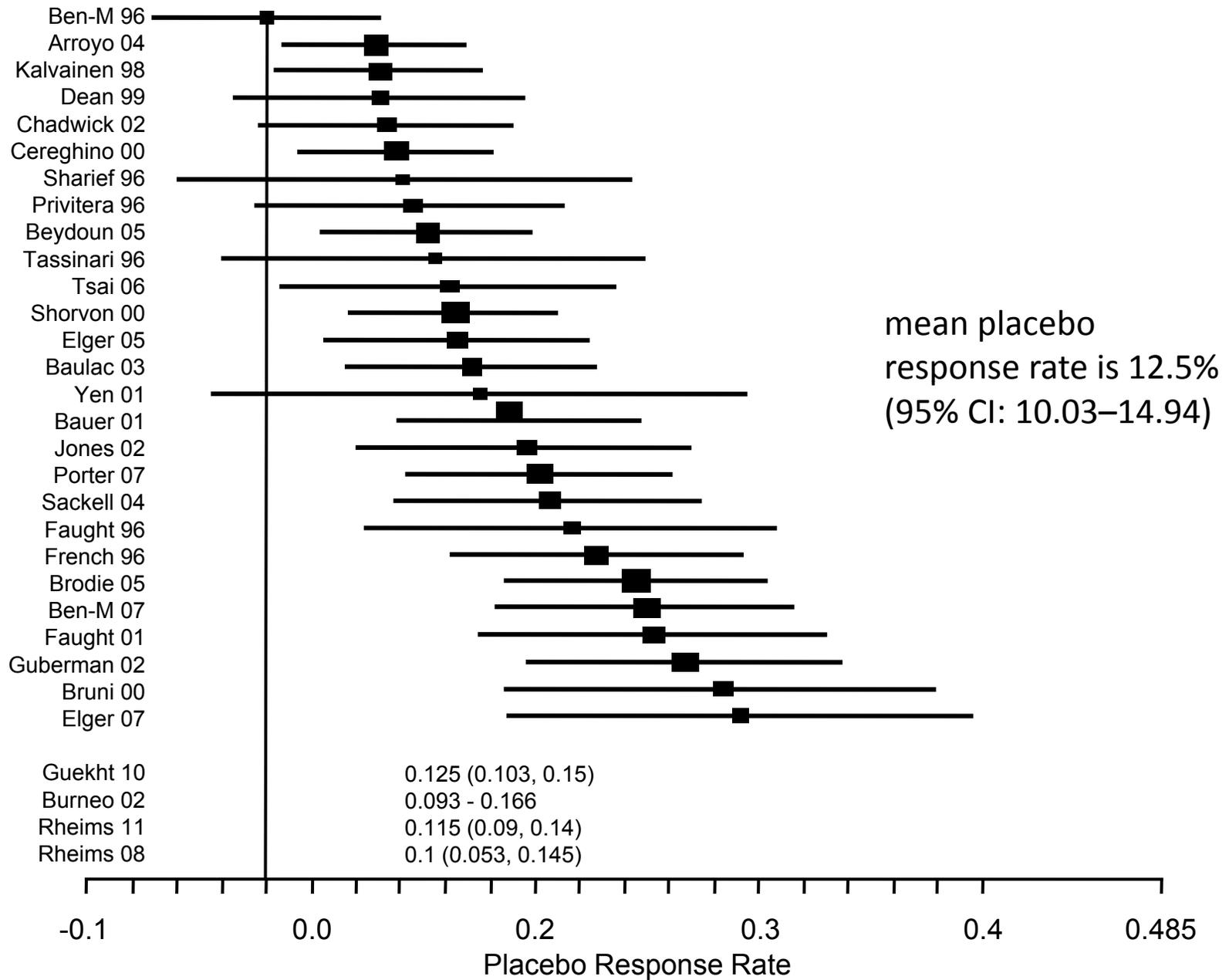
# Inclusion Criteria in the the Guekht *et al* Meta Analysis

- Outcome measure – 50% responder rate
- Subjects without major concomitant illness (including psychiatric disorders) and surgical treatment of epilepsy
- Only subjects with partial epilepsy (with or without secondary generalization)
- Parallel trials only (cross-over trials excluded)
- Number of randomized subjects >40, to ensure trials with sufficient statistical power.

# **Studies in the Guekht *et al* Meta Analysis of Add on Studies**

- 198 potentially appropriate studies identified
- 27 studies met the inclusion requirements
- 5662 randomized subjects in total
- 1887 subjects in placebo groups

# Forest Plot of Placebo Response Rate

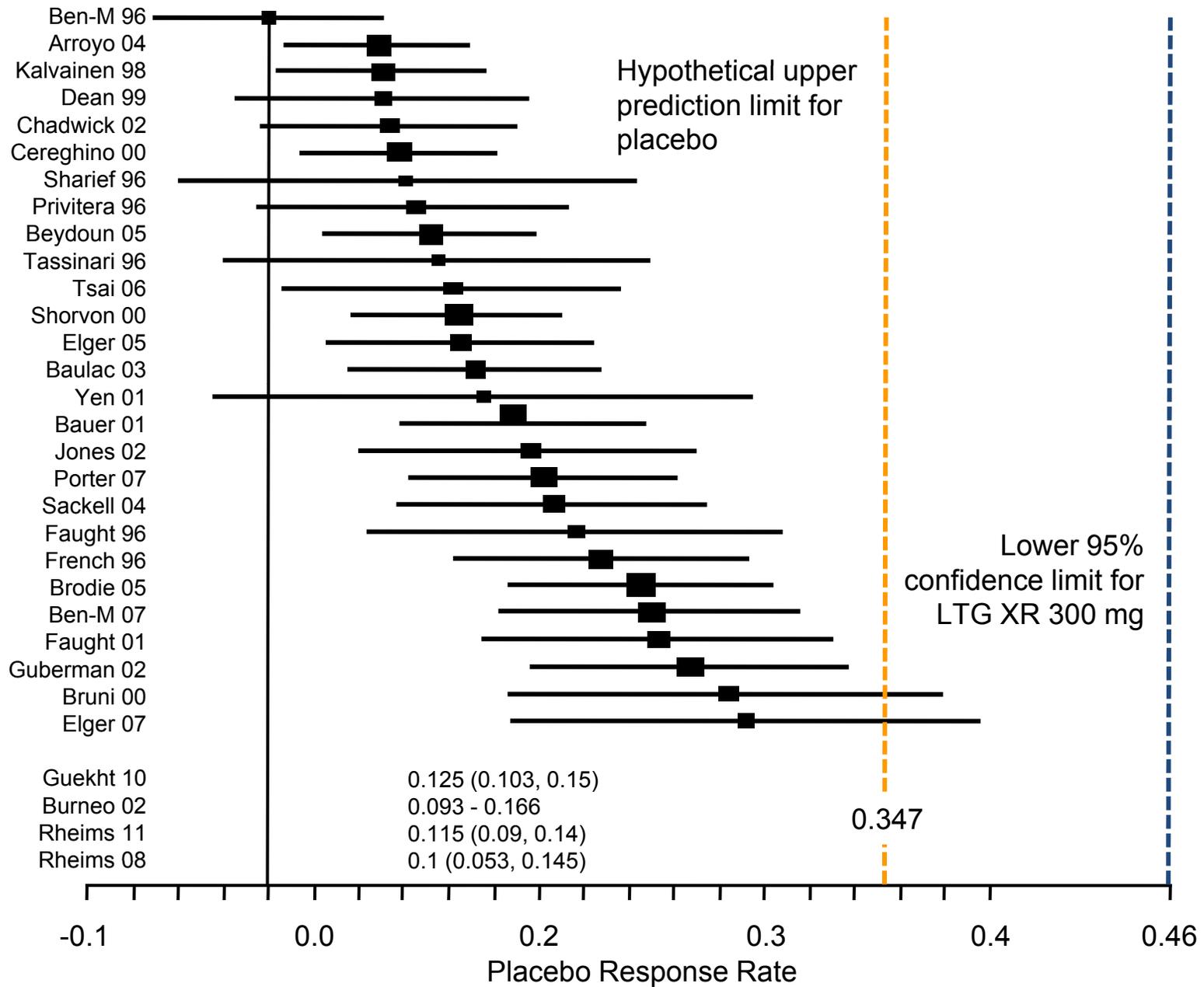


# Results: Response Rate and Upper Prediction Limit for Placebo Lower Confidence Limit for LAM30055

- The response rate calculated over the entire trial for LTG XR 300 mg was .55 (62/112)\*
- The lower bound of the 95% confidence limits is .46
- Note that responder rate (12.5) is approximately 1 – .851 the meta analysis escape rate
- The “poor man’s” upper prediction limit of the mean placebo response rate is .347 = (1-.653)
- The upper prediction limit of the mean placebo response rate is smaller than the lower 95% confidence limit for LTG XR 300

\*From the sponsor’s briefing document.

# Forest Plot of Placebo Response Rate



# Backup Slides

# LAM30055 – Number of Sites and Subjects Randomized by Country

		LTG XR 300 mg/d	LTG XR 250 mg/d
Total Subjects Randomized		113	113
	Number of Sites		
Ukraine	11	33 (29%)	27 (24%)
<b>United States</b>	<b>36</b>	<b>28 (25%)</b>	<b>28 (25%)</b>
Russia	6	15 (13%)	20 (18%)
Argentina	3	14 (12%)	13 (12%)
South Korea	6	11 (10%)	11 (10%)
Costa Rica	1	7 (6%)	9 (8%)
Chile	2	5 (4%)	5 (4%)