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.**  
Director, Neurosciences Medicine  
Development Center  
GlaxoSmithKline LLC  
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.**

**Eugene M. Laska, Ph.D.**  
Research Professor, Biostatistics  
NYU Medical Center

- Summary and Conclusions  
- 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 ≥ 2 years of age

• *Conversion to monotherapy* in patients ≥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

<table>
<thead>
<tr>
<th>Concomitant AED</th>
<th>AUC (0-24ss) Ratio (90%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enzyme-Inducing AEDs (EIAEDs)</td>
<td>0.79 (0.69, 0.90)</td>
</tr>
<tr>
<td>Valproate (VPA)</td>
<td>0.94 (0.81, 1.08)</td>
</tr>
<tr>
<td>Neutral AEDs</td>
<td>1.00 (0.88, 1.14)</td>
</tr>
</tbody>
</table>

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 ≥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)

CBZ or PHT

LTG IR or VPA

Per Protocol Evaluation

Weekly Breakdown:

- Screen
- Baseline
- Escalation
- Weeks 1-4
- Bkg AED
- De-escalation
- Weeks 5-8
- Monotherapy

VPA = low-dose of VPA (pseudoplacebo)

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

![Graph showing Kaplan-Meier survival curve with time points for LTG IR and VPA.]

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

Time to Exit

All Studies  
Study 1  
Study 2  
Study 3  
Study 4  
Study 5  
Study 6  
Study 8

Percent Not Meeting Escape Criteria

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%

Demonstrating Efficacy with Historical Control

HISTORICAL CONTROL

% Escape

85.1%

65.3%

Not effective

Effective

Upper CL
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

Randomized
N=226

300 mg/day
Safety/ITT Population
N=112

19 Excluded

Per Protocol Population
N=93

250 mg/day
Safety/ITT Population
N=111

30 Excluded

Per Protocol Population
N=81

3 subjects did not take study drug
## LAM30055 - Per Protocol Exclusions

<table>
<thead>
<tr>
<th></th>
<th>No. of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg/day</td>
</tr>
<tr>
<td>ITT</td>
<td>112</td>
</tr>
<tr>
<td>PP Population</td>
<td>93</td>
</tr>
<tr>
<td>Excluded from PP Population</td>
<td>19</td>
</tr>
</tbody>
</table>

### Reasons for Exclusion from PP Population

- Did not begin withdrawal of background AED: 4 (300 mg/day), 14 (250 mg/day)
- Closed study site: 6 (300 mg/day), 7 (250 mg/day)
- Entry criteria violation: 3 (300 mg/day), 3 (250 mg/day)
- Less than 11 weeks of monotherapy: 2 (300 mg/day), 2 (250 mg/day)
- Poor compliance: 1 (300 mg/day), 2 (250 mg/day)
- Received wrong treatment for >2 weeks: 3 (300 mg/day), 1 (250 mg/day)
- Exceeded allowed benzodiazepine use: 0 (300 mg/day), 1 (250 mg/day)
### LAM30055 Subjects Randomized by Country

<table>
<thead>
<tr>
<th>Country</th>
<th>LTG XR 300 mg/d</th>
<th>LTG XR 250 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Subjects randomized</td>
<td>113</td>
<td>113</td>
</tr>
<tr>
<td>Ukraine</td>
<td>33 (29%)</td>
<td>27 (24%)</td>
</tr>
<tr>
<td>United States</td>
<td>28 (25%)</td>
<td>28 (25%)</td>
</tr>
<tr>
<td>Russia</td>
<td>15 (13%)</td>
<td>20 (18%)</td>
</tr>
<tr>
<td>Argentina</td>
<td>14 (12%)</td>
<td>13 (12%)</td>
</tr>
<tr>
<td>South Korea</td>
<td>11 (10%)</td>
<td>11 (10%)</td>
</tr>
<tr>
<td>Costa Rica</td>
<td>7 (6%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Chile</td>
<td>5 (4%)</td>
<td>5 (4%)</td>
</tr>
</tbody>
</table>
LAM30055 Efficacy Results
LAM30055 Presentation of Efficacy Results

- Discontinuation Endpoint
- Escape Endpoint
- Expanded Escape Endpoint
## LAM30055 Proportion of Subjects Discontinuing for Any Reason

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

**Historical Control Lower 95% Prediction Limit = 65.3%**
## LAM30055 - Proportion of Subjects Meeting Escape Criteria

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

Historical Control Lower 95% Prediction Limit = 65.3%
LAM30055 Escape Rate vs Historical Control (Per Protocol Population)

- LTG XR 300 mg/day: 22%
- Upper 95% Confidence limit for 300 mg/day: 29.9%
- 95% Prediction limit for a future trial: 65.3%
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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>AEs Possibly Related to Seizures</th>
<th>Use of Rescue Benzodiazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>300 mg/day</td>
<td>250 mg/day</td>
</tr>
<tr>
<td>Escapes</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total Including Expanded Escapes</td>
<td>3</td>
<td>5</td>
</tr>
</tbody>
</table>
### LAM30055 Expanded Escape Endpoints

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

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)

<table>
<thead>
<tr>
<th></th>
<th>LAM30055</th>
<th>US 30/31</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>LTG XR 300 mg/day</td>
<td>LTG XR 250 mg/day</td>
</tr>
<tr>
<td>N=102 (%)</td>
<td>30</td>
<td>36</td>
</tr>
<tr>
<td>N=90 (%)</td>
<td>9</td>
<td>18</td>
</tr>
<tr>
<td>N=50 (%)</td>
<td>19</td>
<td>20</td>
</tr>
<tr>
<td>N=64 (%)</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

1. Doubling of Monthly Seizures
2. Doubling of 2-day seizures
3. New, more severe seizure type
4. Prolongation of generalized seizures
LAM30055 Discontinuation, Escape and Expanded Escape Rates vs Historical Control (ITT Population)

- **Discontinuation for Any Reason:** 32%
- **Expanded Escape Criteria:** 29%
- **Escape Criteria:** 25%

95% Prediction limit for a future trial: 65.3%
LAM30055 Safety Results
<table>
<thead>
<tr>
<th></th>
<th>LTG XR 300 mg/d (N=112) (%)</th>
<th>LTG XR 250 mg/d (N=111) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any Treatment-Emergent AE</td>
<td>53</td>
<td>61</td>
</tr>
<tr>
<td>Most Common AEs (≥ 5%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>26</td>
<td>28</td>
</tr>
<tr>
<td>Dizziness</td>
<td>11</td>
<td>9</td>
</tr>
<tr>
<td>Rash</td>
<td>4</td>
<td>11</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>
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

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

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

<table>
<thead>
<tr>
<th>Historic Study</th>
<th>Seizure Type at Entry (%)</th>
<th>Simple Partial</th>
<th>Complex Partial</th>
<th>Secondarily Generalized</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td>---</td>
<td>95</td>
<td>19</td>
</tr>
<tr>
<td>2 (US 30/31)</td>
<td></td>
<td>44</td>
<td>89</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>25</td>
<td>83</td>
<td>42</td>
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<td>5</td>
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<td>87</td>
<td>71</td>
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<td>-</td>
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<td>-</td>
</tr>
<tr>
<td>LAM30055</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>300 mg/day</td>
<td></td>
<td>44</td>
<td>63</td>
<td>54</td>
</tr>
<tr>
<td>LAM30055</td>
<td></td>
<td>48</td>
<td>60</td>
<td>53</td>
</tr>
<tr>
<td>250 mg/day</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
# Important Differences in Design

<table>
<thead>
<tr>
<th></th>
<th>LAM30055</th>
<th>US 30/31</th>
<th>Historical Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>EIAEDs (CBZ or PHT)</td>
<td>No</td>
<td>Only CBZ or PHT</td>
<td>Yes Plus Other AEDS</td>
</tr>
<tr>
<td>VPA</td>
<td>Yes</td>
<td>No</td>
<td>Some Studies</td>
</tr>
<tr>
<td>Regions</td>
<td>US and Other</td>
<td>Only US</td>
<td>US/1 Canada</td>
</tr>
</tbody>
</table>
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)

<table>
<thead>
<tr>
<th></th>
<th>LTG XR 300 mg/day</th>
<th>LTG XR 250 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 112</td>
<td>N = 111</td>
</tr>
<tr>
<td>Escaped n/N (%)</td>
<td>16/73 (22)</td>
<td>14/70 (20)</td>
</tr>
<tr>
<td></td>
<td>12/39 (31)</td>
<td>11/41 (27)</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>31.4</td>
<td>29.4</td>
</tr>
<tr>
<td></td>
<td>45.3</td>
<td>40.4</td>
</tr>
</tbody>
</table>

**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 2nd 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)

<table>
<thead>
<tr>
<th></th>
<th>LTG XR 300 mg/day</th>
<th></th>
<th>LTG XR 250 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=112</td>
<td>N=111</td>
<td></td>
</tr>
<tr>
<td>US</td>
<td>Non-US</td>
<td>US</td>
<td>Non-US</td>
</tr>
<tr>
<td>Escaped (n/N)</td>
<td>10/28</td>
<td>18/84</td>
<td>8/28</td>
</tr>
<tr>
<td></td>
<td>(36)</td>
<td>(21)</td>
<td>(29)</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>53.5</td>
<td>30.2</td>
<td>45.3</td>
</tr>
</tbody>
</table>

Historical Control Lower 95% Prediction Limit = 65.3%
VPA Use in LAM30055 Higher in Non-US Subjects (ITT Population)

<table>
<thead>
<tr>
<th></th>
<th>LTG XR 300 mg/day</th>
<th>LTG XR 250 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VPA</td>
<td>Neutral</td>
</tr>
<tr>
<td>US</td>
<td>18%</td>
<td>82%</td>
</tr>
<tr>
<td>Non-US</td>
<td>81%</td>
<td>19%</td>
</tr>
</tbody>
</table>
# LAM30055 Escape by Region, Dose and AED Group (ITT Population)

<table>
<thead>
<tr>
<th>AED Group</th>
<th>Region</th>
<th>LTG XR 300 (n/N)</th>
<th>LTG XR 250 (n/N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>US</td>
<td>1/5</td>
<td>3/6</td>
</tr>
<tr>
<td></td>
<td>Non-US</td>
<td>15/68</td>
<td>11/64</td>
</tr>
<tr>
<td>Neutral</td>
<td>US</td>
<td>9/23</td>
<td>5/22</td>
</tr>
<tr>
<td></td>
<td>Non-US</td>
<td>3/16</td>
<td>6/19</td>
</tr>
</tbody>
</table>
### Escape Rates for Neutral AEDs Comparable in US and Non-US Subjects

**ITT Population**
(LTG XR 250 mg and 300 mg Groups Combined)

<table>
<thead>
<tr>
<th></th>
<th>Neutral AED n/N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>14/45 (31%)</td>
</tr>
<tr>
<td>Non-US</td>
<td>9/35 (26%)</td>
</tr>
</tbody>
</table>
LAM30055 Efficacy vs US 30/31
## Comparison of LAM30055 and US 30/31 Escape Rates
(US 30/31 Per Protocol Population)

<table>
<thead>
<tr>
<th></th>
<th>LTG XR 300 mg/d</th>
<th>LTG XR 250 mg/d</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>LAM30055</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting Escape Criteria, n (%)</td>
<td>26 (25%)</td>
<td>25 (29%)</td>
</tr>
<tr>
<td></td>
<td>LTG XR 250 mg/d</td>
<td></td>
</tr>
<tr>
<td><strong>US 30/31</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meeting Escape Criteria, n (%)</td>
<td>22 (44%)</td>
<td></td>
</tr>
</tbody>
</table>
## Comparison of Escape Rates

**Neutral AED - LAM30055 vs US 30/31 Using US 30/31 PP Definition**

<table>
<thead>
<tr>
<th>Met Escape Criteria</th>
<th>US 30/31</th>
<th>300 mg/day</th>
<th>250 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>n/N (%)</td>
<td>22/50 (44)</td>
<td>11/33 (33)</td>
<td>11/29 (38)</td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[31.2, 57.7]</td>
<td>[18.6, 51.9]</td>
<td>[21.3, 57.6]</td>
</tr>
</tbody>
</table>

LAM30055 (Neutral Only)
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

- FDA ITT Worst Case (US only, 300 mg + 250 mg) 55%
  - N=56
- FDA ITT Worst Case (300 mg) 55%
  - N=112
- GSK 300 mg – US Only (N=28) 37%
- Discontinuation for Any Reason 36%
- Expanded Escape Criteria 32%
- LAM30055 300 mg Escape Criteria 29%
- LAM30055 300 mg 25%

Escape Rate (%) 0 20 40 60 80 100
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
• Rheims, Perucca, Cucherat and Ryvlin
  Epilepsia 52 (2011)
Inclusion Criteria in 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
mean placebo response rate is 12.5% (95% CI: 10.03–14.94)
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

- Hypothetical upper prediction limit for placebo
- Lower 95% confidence limit for LTG XR 300 mg

Placebo Response Rate

-0.1  0.0  0.2  0.3  0.4  0.46

Ben-M 96  0.125 (0.103, 0.15)
Arroyo 04
Kalvainen 98
Dean 99
Chadwick 02
Cereghino 00
Sharief 96
Privitera 96
Beydoun 05
Tassinari 96
Tsai 06
Shorvon 00
Elger 05
Baulac 03
Yen 01
Bauer 01
Jones 02
Porter 07
Sackell 04
Faught 96
French 96
Brodie 05
Ben-M 07
Faught 01
Guberman 02
Bruni 00
Elger 07
Guekht 10  0.115 (0.09, 0.14)
Burneo 02  0.093 - 0.166
Rheims 11
Rheims 08  0.1 (0.053, 0.145)
Backup Slides
## LAM30055 – Number of Sites and Subjects Randomized by Country

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