Lamictal® XR™ (lamotrigine) Historical-Controlled Trial

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Focus of Review

- Potential heterogeneity in the historical studies
- Comparability of the current study with the historic studies:
  - study design
  - subject population
  - evaluation criteria
  - analysis method
- Study conduct/potential bias
  - absence of randomized control; all patients on potentially effective test drug

Potential Heterogeneity in the Historical Studies

Historical Studies

Study	Year of Study	Pseudo-placebo	N	Percent Escape (%)
1	1993	600 mg gabapentin	93	76.9
2	1994	1000 mg valproate	74	77.2
3	1992	100 mg topiramate	24	83.3
4	NA	FBM 10 mic/ml	32	87.5
5	1995	300 mg oxcarbazepine	45	95.9
6	1996	300 mg oxcarbazepine	46	93.2
7	1990	15 mg/kg valproate	22	86.4
8	1989	15 mg/kg valproate	55	74.9

- A likelihood ratio test of equal probability of escape in the historical pseudoplacebo groups seems to suggest heterogeneity (p=0.018)

- Potential source of heterogeneity
  - Different pseudo-placebo
  - Differences in the definitions of the Escape Criteria
    - Available data does not permit re-evaluation of the Escape Criteria in a uniform way

Components of Escape Criteria

Study	N	Criterion #1 (%)	Criterion #2 (%)	Criterion #3 (%)	Criterion #4 (%)
1	93	26	15	12	19
2	74	27	22	22	4
3	24	25	21	25	17
5	45	18	38	22	11
6	46	33	39	13	7
7	22	27	14	9	45
8	55	35	22	18	29

Patients may meet more than one criterion

Information not available for Study 4

Study Conduct/ Potential Bias

Investigator-determined Escapes

- The number of escapes as determined by investigators is surprisingly small in Study LAM30055, compared to the internal controlled study US30/31

LAM30055		US30/31	
LTG XR 300 mg/day	LTG XR 250 mg/day	LTG IR 500 mg/day	Pseudo-Placebo
6/112 (5%)	7/111 (6%)	32/76 (42%)	55/80 (69%)

ITT Population

- Historical controlled studies are vulnerable to bias
  - Sacks et al (1982) and Miller et al (1989): a consistent tendency for historical controlled trials to yield more favorable results than randomized trials
- Epilepsy monotherapy trials using historical control may have even greater potential for bias
  - the primary endpoint captures events of worsening of seizure and involves subjective evaluation
- For Study LAM30055, escapes were under-reported
  - the sponsor re-evaluated the Escape Criteria against seizure data following completion of study, leading to reclassification of many subjects as escapes

Comparability of the Current Study with the Historic Studies

Calculation of Escapes

- **Criterion #1**: doubling of average monthly seizure frequency
  - **Sponsor**: the number of seizures 28 days prior to each visit
  - **White Paper**: methodology may have varied and some calculated 28-day frequency on a rolling basis
  - **Agency**: the highest seizure frequency for ***any consecutive*** 28 days

- **Criterion #2**: doubling of the highest consecutive 2-day seizure frequency
  - **Sponsor**: 28 days prior to each visit
  - **Agency**: ***the whole treatment phase***

- **Criterion #3**: emergence of a new, more severe seizure type
  - **Sponsor**: comparing to the seizure types in patients' lifetime history; although the criterion specified in the protocol is comparing to the baseline
  - **White Paper**: varied from study to study
  - **Per Agency request**: comparing to ***the baseline***

- **Criterion #4**: clinically-significant prolongation of generalized tonic-clonic seizures
  - **Sponsor**: no criterion #4 events reported; re-calculation not performed
  - **White Paper**: prolongation or worsening of seizure duration or frequency considered to ***require intervention***
    - Study US 30/31: 10% for LTG IR group vs 4% pseudo-placebo
    - Other White Paper studies had larger percentages (7%-45%)
  - **Per Agency request**: examined medication records and adverse event records to identify patients who qualify for escape ***based on the need for intervention***

Calculated Escapes

Criterion	300 mg/day N=108 n(%)	250 mg/day N=97 n(%)
1	12 (11)	19 (20)
2	20 (19)	18 (19)
3	8 (7)	7 (7)
4*	7 (6)	10 (10)
All	34 (31)	34 (35)

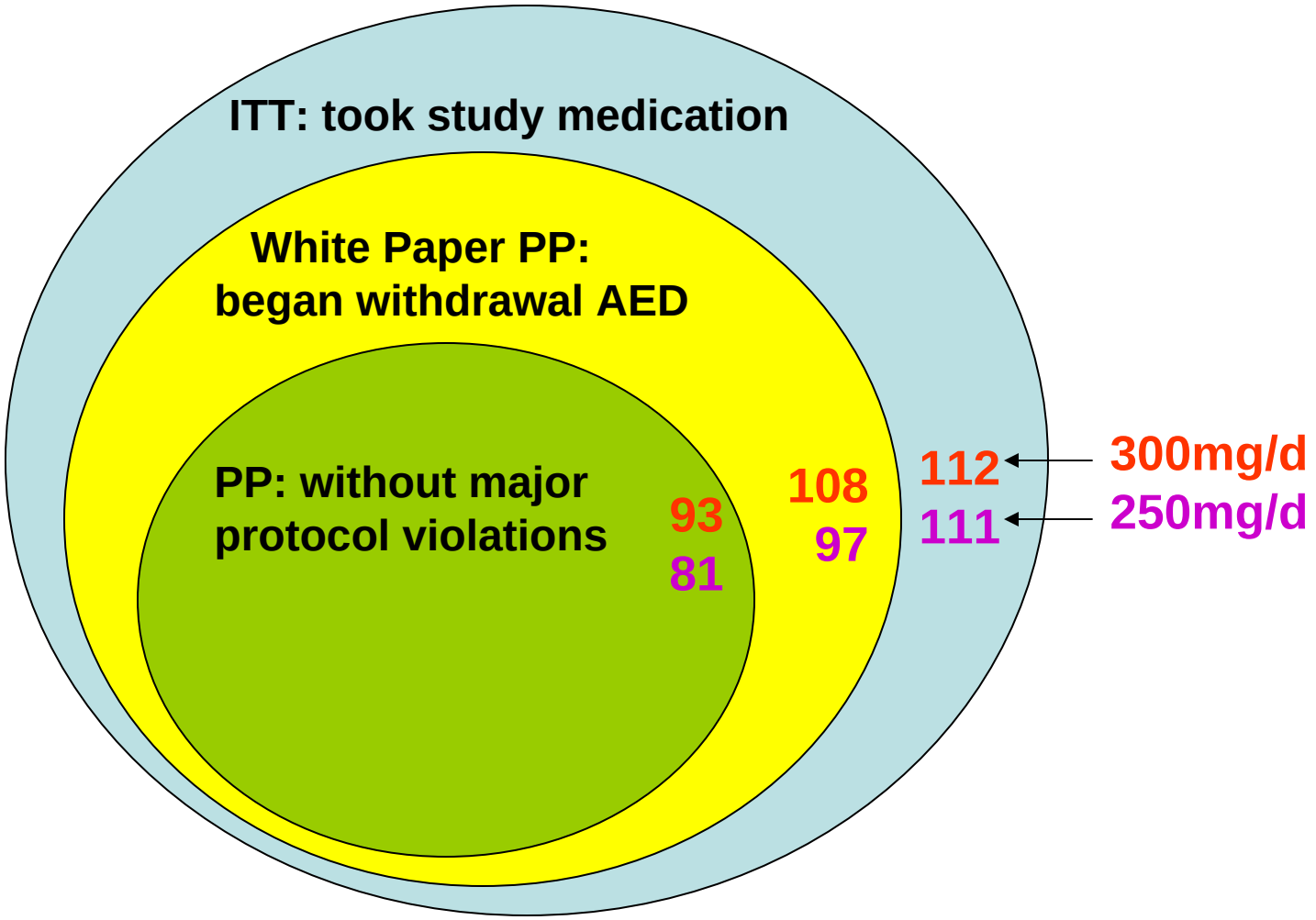
*Results updated after completion of the review

White Paper Per Protocol Population

Patients may meet more than one criterion

Escape rate of US 30/31 LTG IR ITT group was 42%

Efficacy Population



Calculation of Escapes

- Bias due to under-reporting escapes was adjusted to some extent by performing the post-hoc identification of escapes

- However, it is uncertain if the adjustment is adequate

Problem in Handling Dropouts

- ***Sponsor Analysis***: dropouts due to reasons other than meeting exit criteria were included as successes
  - 12% and 24% patients dropped out due to other reasons for 300mg/d & 250mg/d group, respectively
  - Some of the dropouts were reclassified as escapes

- ***White Paper Analysis***: Kaplan-Meier estimates in which dropouts were censored
  - 0 to 11% dropouts

- The estimated binomial proportions of escapes (sponsor method) is smaller than the KM estimates (White Paper method)
  - Historical studies: the estimated combined binomial proportion was 81.7% with a lower prediction limit of 62.7%
  - Study LAM30055: time-to-escape information was not available at the time of review

- ***Sensitivity Analysis***
  - White Paper PP population
  - Planned primary endpoint: all cause discontinuation
  - 6 patients in each group who dropped out after starting withdrawal of background AED were included as treatment failures
- ***Worst Case Analysis***
  - ITT population
  - Additional 14 patients in the 250mg group and 4 patients in the 300mg who dropped out prior to the withdrawal phase were included as treatment failures

	300 mg/day	250 mg/day
Sponsor Analysis		
n/N (%)	34/108 (31)	34/97 (35)
[95% CI]	[22.7,40.2]	[25.6,44.5]
Sensitivity Analysis		
n/N (%)	40/108 (37)	40/97 (41)
[95% CI]	[27.9,46.1]	[31.4,51.0]
Worst Case Analysis		
n/N (%)	44/112 (39)	54/111 (49)
[95% CI]	[30.2,48.3]	[39.4,57.9]

The lower 95% prediction limit is 65.3% for KM estimate, and 62.7% for binomial estimate

Population Comparability

- Regional comparisons
  - Study LAM30055 had approximately 75% non-US while historic control is all US
  - The comparability of the US and non-US subjects was not established
  - Study LAM30055: a higher proportion of subjects at US sites met Escape Criteria compared to non-US sites

	US	Non-US
Sponsor Analysis		
n/N (%)	21/50 (42)	47/155 (30)
[95% CI]	[28.3, 55.7]	[23.1, 37.6]
Sensitivity Analysis		
n/N (%)	27/50 (54)	53/155 (34)
[95% CI]	[40.2, 67.8*]	[26.7, 41.7]
Worst Case Analysis		
n/N (%)	33/56 (59)	65/167 (39)
[95% CI]	[46.0, 71.8*]	[31.5, 46.3]

*Failed to show superiority over historical control

Two dose groups are pooled

The lower 95% prediction limit is 65.3%for KM estimate, and 62.7% for binomial estimate

Escape by Region and AED Group

	Neutral AEDs	VPA
US	17/40 (43%)	4/10 (40%)
Non-US	11/31 (35%)	36/124 (29%)

White Paper Per Protocol Population
Two dose groups are pooled

Population Comparability

- Baseline seizure frequency
  - Study LAM30055: at least 2 seizures per 4 weeks
  - Historical studies: at least 2 seizures (3 studies) to at least 4 seizures per 4 weeks (4 studies)
- Baseline seizure types
  - Study LAM30055 had lower percentage of patients with complex partial seizure
- Types of background AEDs
  - Study LAM30055: non-EIAED (neutral AED or VPA)
  - Historical studies: 92% on EIAED (primarily CBZ)

- Number of background AEDs
  - Study LAM30055 allowed one background AED
  - Most historical studies allowed two AEDs
    - The percent of subjects receiving 2 background AEDs ranged between 17% and 34%
    - Patients with 1 background AED had fewer escapes than patients with 2 AEDs
  - For patients on 1 background AED, the estimated percent escape is 78.7% with a lower prediction limit of 56.0% (binomial estimate)

Summary

- The data seemed to suggest some evidence of efficacy of LTG XR as monotherapy treatment of partial seizures

- However, interpretability of these analysis results was complicated by the limitations of the historical control design
  - Comparability of subject population (25% US subjects in LAM3005 vs 100% US subjects in historical control)
  - Difference between US and non-US (higher escape rate in US than non-US)
  - Potential bias

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