

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205122Orig1s000**

**STATISTICAL REVIEW(S)**



U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Translational Sciences  
Office of Biostatistics

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

**NDA/Serial Number:** NDA205122  
**Drug Name:** USL255 (topiramate extended-release (ER) capsules)  
**Indication(s):** Epilepsy  
**Applicant:** Upsher-Smith Laboratories (USL)  
**Date of Document:** February 11, 2013  
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## 1. EXECUTIVE SUMMARY

### 1.1. CONCLUSIONS AND RECOMMENDATIONS

USL255 as an adjunctive therapy demonstrated its efficacy for the treatment of epilepsy in the Phase III P09-004 study. The primary efficacy endpoint was the median percent change from Baseline in the weekly seizure frequency during the combined Titration + Maintenance Phase. The median percent reduction from Baseline to Titration + Maintenance Phase in weekly partial-onset seizure frequency was significantly higher in the USL255 group as compared to the placebo group. Supportive analysis of the primary efficacy endpoint provided similar results using log-transformed weekly partial-onset seizure frequency data. The efficacy of USL255 relative to placebo was also supported by other secondary efficacy outcome measures. In conclusion, Study P09-004 provides robust statistical and clinical evidence for the efficacy of USL255 in the adjunctive treatment for partial-onset seizure.

### 1.2. BRIEF OVERVIEW OF REVIEWED CLINICAL STUDY

Study P09-004 was a Phase 3, randomized, multinational, multicenter, double-blind, placebo-controlled, parallel-group study, designed to evaluate the efficacy and safety of USL255 compared with placebo as adjunctive therapy in adult subjects (18-75 years) with refractory partial-onset seizures with or without secondary generalization. The study was conducted in 16 countries, with 66 study centers. Approximately 270 men and women with partial-onset seizures with or without secondary generalization were planned so that at least 216 subjects would be randomized into the double-blind treatment phase. Based on a blinded data review, the planned sample size was adjusted to 236 subjects (118 subjects /treatment group). The duration of the study was up to 22 weeks for each subject. During an 8-week Baseline Phase (Visits 1-3), subjects must have had at least 8 partial-onset seizures and no more than 21 consecutive days without a seizure. At the end of the Baseline Period at Visit 3 (Day 1), subjects who met the study enrollment criteria were randomly assigned to receive USL255 or placebo in the double-blind Treatment Phase, which included a 3-week dose Titration Phase (Visits 3-6) and an 8-week Maintenance Phase (Visits 6-8). The Maintenance Phase was followed by a 3-week Taper Phase to discontinue the study drug.

The primary objective of the study was to assess the efficacy of USL255 compared with placebo in subjects with refractory partial-onset seizures with or without secondary generalization. The primary efficacy endpoint in the study was the percent reduction from Baseline in weekly (7-day) partial-onset seizure frequency during the Titration + Maintenance Phase. The weekly partial onset seizure (POS) frequency during the Titration + Maintenance Phase was determined by counting the POS frequency in the Titration + Maintenance Phase, dividing by number of days with seizure diary data in the phase, and multiplying by 7. Percent reduction from baseline in weekly POS frequency is then calculated as  $100 \times (B-T)/B$ , where T is the weekly POS frequency during the Titration + Maintenance Phase and B is the weekly POS frequency during the baseline phase. A secondary efficacy endpoint was the proportion of

subjects with 50% or greater reduction (responder rate) in weekly (7-day) partial-onset seizure frequency during the titration plus maintenance phase compared to baseline. Several other secondary efficacy endpoints were included. The primary and secondary endpoints were analyzed based on the intent-to-Treat (ITT) population. In the primary analysis of the primary efficacy endpoint, the treatment groups were compared using a Wilcoxon rank-sum test (WRST). Several sensitivity analyses were performed including analysis of covariance (ANCOVA). In addition, an ANCOVA analysis on the log-transformed  $[\log(y+1)]$ , where  $y$  = weekly partial onset seizure frequency over the titration plus maintenance phase] seizure frequency was performed.

#### Dealings with Dropouts / Missing Data

For the primary efficacy endpoint, the weekly partial-onset seizure frequency during the titration +maintenance phase was calculated over the number of days with non-missing seizure data in the titration +maintenance phase. No explicit imputation of missing data was made, but this approach was implicitly equivalent to using the average seizure rate during the days with non-missing seizure data to impute the seizure rate for days after study discontinuation and days with missing seizure data. As sensitivity analysis of the primary endpoint, the sponsor analyzed the percent reduction in partial-onset seizure frequency from baseline to the first 4 weeks, and last 4 weeks of the maintenance period. The findings were consistent with the findings obtained from the primary efficacy analysis.

### 1.3. STATISTICAL ISSUES AND FINDINGS

Dealing with missing data in Seizure frequency trials is a statistical challenge. The primary efficacy end point is often defined as the weekly partial-onset seizure frequency rate during the titration +maintenance phase, and the rate is calculated over the number of days with non-missing seizure data in the titration +maintenance phase. Suppose a subject is dropped out from the trial after 4 days of randomization, his/her rate of seizure frequency per week will be calculated based on the available data for the four days. This approach of dealing with missing data is the last observed average seizure frequency carried forward approach, and it is similar to the last observation carried forward (LOCF) approach. Since the seizure data are count-data and the primary endpoint is the rate of seizure per week, the Mixed Model Repeated Model (MMRM) analysis is not appropriate to analyze such data. A research on the missing data in presence rate of seizure per week is necessary to carry out.

## 2. INTRODUCTION

### 2.1 OVERVIEW

The sponsor submitted this New Drug Application (NDA) to the agency on February 11, 2013. The agency agreed with the sponsor in a Type A meeting (Oct 31, 2012) that the approval pathway of USL255 would be based on the establishment of pharmacokinetic equivalence without reliance on in vivo demonstration of clinical efficacy in adequate and well controlled, randomized clinical trials. Therefore, the sponsor did not include any controlled trial efficacy result in this NDA submission. However, during the filing meeting of this NDA, the agency thought that efficacy results of the study P09-004 might be helpful in the approval path of USL255, and hence the agency requested for the efficacy results of the study P09-004. In a response, the sponsor submitted the efficacy results of the study P09-004 along with the efficacy data on May 21, 2013.

Study P09-004 was a Phase 3, randomized, multinational, multicenter, double-blind, placebo-controlled, parallel-group study, designed to evaluate the efficacy and safety of USL255 compared with placebo as adjunctive therapy in adult subjects (18-75 years) with refractory partial-onset seizures with or without secondary generalization. The study was conducted in 16 countries, with 66 study centers. Approximately 270 men and women with partial-onset seizures with or without secondary generalization were planned so that at least 216 subjects would be randomized into the double-blind treatment phase. Based on a blinded data review, the planned sample size was adjusted to 236 subjects (118 subjects /treatment group). The duration of the study was up to 22 weeks for each subject. During an 8-week Baseline Phase (Visits 1-3), subjects must have had at least 8 partial-onset seizures and no more than 21 consecutive days without a seizure. At the end of the Baseline Period at Visit 3 (Day 1), subjects who met the study enrollment criteria were randomly assigned to receive USL255 or placebo in the double-blind Treatment Phase, which included a 3-week dose Titration Phase (Visits 3-6) and an 8-week Maintenance Phase (Visits 6-8). The Maintenance Phase was followed by a 3-week Taper Phase to discontinue the study drug. Table 1 lists the synopsis of the study. A schematic diagram of the study is also listed in Figure 1.

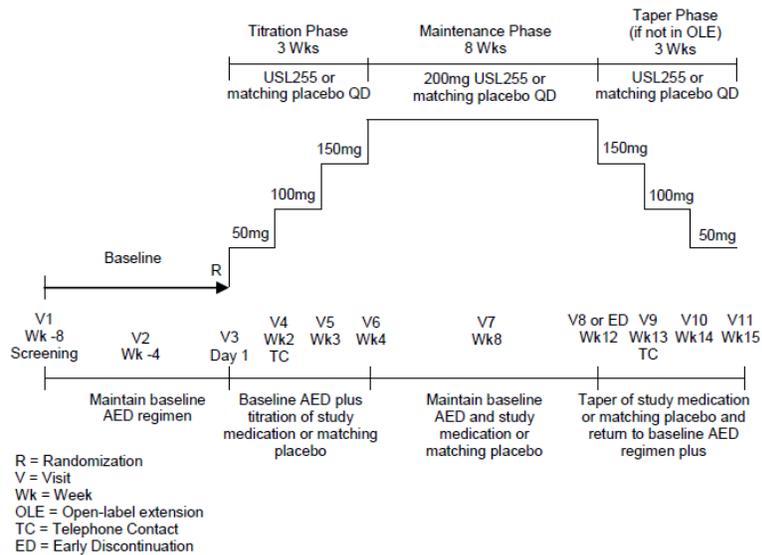
The primary objective of the study was to assess the efficacy of USL255 compared with placebo in subjects with refractory partial-onset seizures with or without secondary generalization. The primary efficacy endpoint in the study was the percent reduction from Baseline in weekly (7-day) partial-onset seizure frequency during the Titration + Maintenance Phase. A key secondary efficacy endpoint was the proportion of subjects with 50% or greater reduction (responder rate) in weekly (7-day) partial-onset seizure frequency during the titration plus maintenance phase compared to baseline. The key secondary endpoint is defined for the purpose of considering as a primary endpoint to meet country-specific regulatory requirements for approval outside the US. Several other secondary efficacy endpoints were included.

Table 1. Synopsis of Study P09-004

Study ID/ No. of Study Sites/ Location(s)	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Study Objectives	No. of Subjects Planned/ Entered/ Completed	Primary Endpoints
P09-004/66/in 16 countries (Argentina, Australia, Belgium, Canada, Chile, Germany, Greece, Hungary, India, Israel, New Zealand, Poland, Russia, South Africa, Spain, and United States)	Phase 3, randomiz ed, multicent er, double- blind, placebo- controlled , parallel- group	USL255 50-200 mg/day dosed using USL255 50 mg capsules and USL255 200 mg capsules; oral administration  Placebo 50-200 mg/day dosed using placebo 50 mg capsules and placebo 200 mg capsules; oral administration  Titration Schedule: <u>Up-titration</u> 50 mg/day USL255 or placebo daily x 7 days 100 mg/day USL255 or placebo daily x 7 days 150 mg/day USL255 or placebo daily x 7 days <u>Maintenance</u> 200 mg/day USL255 or placebo x 56 days	Assess the efficacy of USL255 compared to placebo in subjects with refractory partial- onset seizures (POS) with or without secondary generalization	216 (236 after blinded data review)/ 249/217	<i>Primary efficacy endpoint</i> Percent reduction from Baseline in weekly (7-day) POS frequency during the Titration + Maintenance Phase. <i>Key secondary efficacy endpoint</i> Proportion of subjects with 50% or greater reduction (responder rate) in weekly (7- day) POS frequency during the Titration + Maintenance Phase compared with Baseline. <i>Other secondary efficacy endpoints</i> Proportions of subjects with 50% or greater reduction (responder rate) in weekly (7-day) POS frequency during the Titration and Maintenance Phases, separately. Percent reductions from Baseline in weekly (7-day) POS frequency during the Titration and Maintenance Phases, separately. Percent reduction from Baseline in weekly (7-day) all seizure frequency during the Titration + Maintenance Phase.

Source: Study report

Figure 1. Schematic for Study P09-004



Abbreviations: AED, antiepileptic drug; QD, once a day.

(source: Study report)

The intent-to-treat (ITT) efficacy population included all subjects who were randomly assigned, received at least 1 dose of study drug, and had at least 1 post randomization seizure data point. In the primary analysis of the primary efficacy endpoint, the treatment groups were compared using a Wilcoxon rank-sum test (WRST) for the ITT efficacy population.

Several sensitivity analyses were performed including analysis of covariance (ANCOVA) comparing the treatment groups' means, with a model consisting of treatment group and geographic region<sup>1</sup> as class variables and baseline weekly partial-onset seizure frequency as a continuous covariate for the ITT efficacy population. In addition, the treatment groups' means in the log-transformed [ $\log(y+1)$ , where  $y$  = weekly partial onset seizure frequency over the titration plus maintenance phase] seizure frequency was compared using ANCOVA; the model consisted of treatment group and geographic region as class variables, and baseline log-transformed weekly partial onset seizure frequency as a continuous covariate. In an independent ANCOVA analysis, the treatment group by geographic region interaction for the ITT efficacy population was also evaluated. The empirical cumulative distribution function of the primary efficacy endpoint was displayed by treatment group to evaluate robustness of the endpoint.

Days with missing seizure diary data were removed from the denominator when computing seizure frequency. If a subject had no diary data within a particular phase (i.e., titration, maintenance, and titration plus maintenance), the weekly seizure frequency of that phase was set to missing. The subjects who have no post-baseline seizure frequency measures were excluded from the efficacy analyses.

Subgroup analyses were provided on the primary endpoint by subgroups defined by geographic region, gender, age ranges (18 to <40, 40 to <65, and  $\geq 65$ ), and race groups (Caucasian vs. non-Caucasian).

## **Disposition of Subjects**

Table 2 lists the patient disposition of the study. A total of 249 subjects were randomly assigned to treatment, including 124 in the USL255 treatment group and 125 in the placebo treatment group. The majority of randomized subjects (87.1%, both treatment groups combined) completed the study. The primary reason for early discontinuation was for an AE, with about three times as many discontinuations for an AE in the USL255 treatment group compared with the placebo treatment group. Few subjects in either treatment group discontinued because of lack of efficacy.

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<sup>1</sup> For the purpose of analysis, study centers were combined, if feasible, into the following modified geographic regions: Western Europe and similar (Belgium, Germany, Spain, Greece, South Africa, and Israel), Eastern Europe (Poland, Hungary, and Russia), South America (Argentina and Chile), North America and similar (US, Canada, Australia, and New Zealand), and India.

Table 2. Subject Disposition by Treatment Groups, All Subjects, N (%)

	USL255	Placebo	Total
Randomized	124	125	249
Completed study	103 (83.1%)	114 (91.2%)	217 (87.1%)
Discontinued early	21 (16.9%)	11 (8.8%)	32 (12.9%)
Primary reason for discontinuation			
Adverse event	12 (9.7%)	4 (3.2%)	16 (6.4%)
Lack of efficacy	2 (1.6%)	1 (0.8%)	3 (1.2%)
Voluntary withdrawal	4 (3.2%)	3 (2.4%)	7 (2.8%)
Discontinue criterion	1 (0.8%)	0	1 (0.4%)
Physician decision	1 (0.8%)	1 (0.8%)	2 (0.8%)
Other	1 (0.8%)	2 (1.6%)	3 (1.2%)

Source: study reports

## 2.2 DATA SOURCES

The study report and SAS data sets are available at <\\CDSESUB1\EVSPROD\NDA205122\0000>

## 3. STATISTICAL EVALUATION

### 3.1 DATA AND ANALYSIS QUALITY

The primary and secondary efficacy endpoints for the study P09-004 are recalculated by this reviewer from the submitted seizure frequency data sets, and the calculated numbers are consistent with the sponsor's calculated numbers. The sponsor has submitted a detail documentation of the formula used for calculating the weekly seizure frequency data of the study P09-004. The quality of efficacy data and analyses in this submission is acceptable.

### 3.2 DEMOGRAPHIC AND BASELINE DISEASE CHARACTERISTICS

Table 3 lists the demographic characteristics of the randomized subjects. The treatment groups were comparable with respect to demographics and baseline characteristics. The mean age of subjects was 37.6 years. The age distribution of subjects was similar between treatment groups. Slightly more than half (53.0%) of all subjects were males. The median baseline weekly seizure frequencies in the 2 treatment groups were similar.

Table 3: Baseline Demographic Characteristics of Subjects

Characteristics	USL255 N=124	Placebo N=125	Total N=249
Age (years)			
N	124	125	249
Mean (SD)	37.6 (10.97)	37.6 (11.11)	37.6 (11.02)
Age group (years)			
N	124	125	249
18 to <40	73 (58.9%)	77 (61.6%)	150 (60.2%)
40 to <65	50 (40.3%)	47 (37.6%)	97 (39.0%)
≥65	1 (0.8%)	1 (0.8%)	2 (0.8%)
Gender			
N	124	125	249
Male	66 (53.2%)	66 (52.8%)	132 (53.0%)
Female	58 (46.8%)	59 (47.2%)	117 (47.0%)
Race			
N	124	125	249
White	107 (86.3%)	107 (85.6%)	214 (85.9%)
Asian	9 (7.3%)	7 (5.6%)	16 (6.4%)
Black or African	1 (0.8%)	4 (3.2%)	5 (2.0%)
Pacific islander	1 (0.8%)	1 (0.8%)	2 (0.8%)
Other	6 (4.8%)	6 (4.8%)	12 (4.8%)
Duration of epilepsy (Years)			
N	124	125	249
Mean (SD)	20.9 (13.66)	20.0 (13.12)	20.4 (13.37)
Baseline weekly partial-onset seizure frequency			
N	124	125	249
Median	2.29	2.66	2.52
Mean (SD)	7.45 (27.620)	5.18 (6.212)	6.31 (19.974)
Min, Max	1.0, 297.6	0.9, 37.4	0.9, 297.6

Source: study reports

### 3.3 EFFICACY EVALUATION

#### Sponsor's reported Analyses results

Table 4 lists the primary efficacy analysis results of the percent reduction from baseline in weekly partial-onset seizure frequency during the titration plus maintenance phase in the ITT efficacy population. The median percent reduction from baseline of partial-onset seizures during the titration plus maintenance phase was significantly greater in the USL255 treatment group than in the placebo treatment group (USL255; 39.50% reduction; placebo: 21.65% reduction, P value <0.001 by the WRST).

Table 4. Percent Reduction From Baseline in Weekly Partial-Onset Seizure Frequency During Titration Plus Maintenance Phase, ITT Efficacy Population

Time Point	USL255 N = 124	Placebo N = 125	P value
<b>Baseline</b>			
N	124	125	
Median	2.29	2.66	
Mean (SD)	7.45 (27.620)	5.18 (6.212)	
Minimum, maximum	1.0, 297.6	0.9, 37.4	
<b>Titration + maintenance phase</b>			
N	124	125	
Median	1.41	2.05	
Mean (SD)	5.98 (26.604)	4.96 (8.128)	
Minimum, maximum	0.0, 287.0	0.0, 64.8	
Percent reduction from baseline to titration + maintenance phase Wilcoxon rank-sum test <sup>a</sup>			
N	124	125	
Median	39.50	21.65	<0.001 <sup>a</sup>
ANCOVA			
LSMeans (SE)	32.91 (5.092)	11.51 (5.071)	0.003
Treatment by geographic region interaction			
			0.751
<b>Log Transformed Weekly Partial-Onset Seizure Frequency During Titration + Maintenance Phase</b>			
ANCOVA			
LSMeans (SE)	1.16 (0.037)	1.33 (0.037)	0.001

Note: Weekly seizure frequency = (Total number of partial-onset seizures and partial-onset clusters during each phase / number of days with seizure diary in each phase) × 7. Percent reduction from baseline in weekly seizure frequency = [(B-T)/B] × 100, where T = weekly frequency during treatment phase and B = weekly frequency during baseline.

<sup>a</sup>Wilcoxon rank-sum test

Source: Study report

A sensitivity analysis of the primary efficacy endpoint was performed using ANCOVA to compare the treatment groups' means with a model consisting of treatment group and geographic region as class variables, and baseline weekly partial-onset seizure frequency as a continuous covariate. The ANCOVA LSMean percent reduction values for USL255 versus placebo were significantly different (32.91% vs 11.51%, respectively, P value = 0.003), and the LSMean (SE) treatment difference (USL255 minus placebo) was 21.40 (7.254) percent reduction. No significant interaction was observed for treatment by geographic region. Another sensitivity analysis-the ANCOVA LSMean log-transformed weekly partial-onset seizure frequency during titration + maintenance phase also gives a similar significant result.

Table 5 lists percent reduction from baseline in weekly partial-onset seizure frequency during titration and maintenance phase, separately. The median percent reduction in seizure frequency from baseline was significantly greater in the USL255 treatment group compared with

the placebo treatment group in both the titration phase (USL255, 33.93%; placebo, 8.57%;  $P$  value  $<0.001$ ) and in the maintenance phase (USL255, 45.70%; placebo, 22.09%;  $P$  value = 0.001) analyzed separately using the ITT efficacy Population. These findings indicate that the treatment effect started early and continued during the maintenance phase. Results from the ANCOVA performed on the LSMMeans values supported the results from the analysis performed on the median values.

Table 5. Percent Reduction From Baseline in Weekly Partial-Onset Seizure Frequency During Titration and Maintenance Phase, **Separately**, ITT Efficacy Population

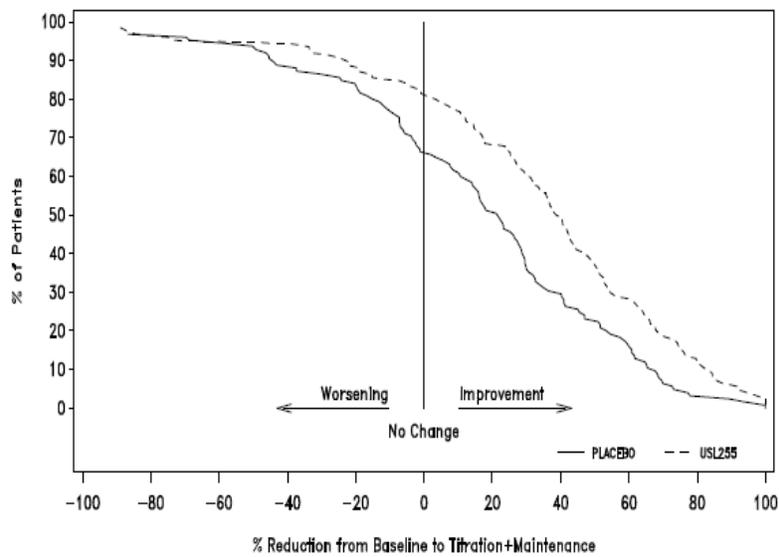
Secondary efficacy endpoint	USL255 N = 124	Placebo N = 125	$P$ value
Percent reduction from baseline in weekly partial-onset seizure frequency in <b>Titration</b> phase			
<b>N</b>	124	125	
Median	33.93	8.57	$<0.001^a$
LSMeans (SE)	27.15 (4.655)	5.77 (4.636)	$0.001^b$
Percent reduction from baseline in weekly partial-onset seizure frequency in <b>Maintenance</b> phase			
<b>N</b>	113	120	
Median	45.70	22.09	$0.001^a$
LSMeans (SE)	38.15 (6.612)	13.24 (6.413)	$0.008^b$

<sup>a</sup>  $P$  value was computed using the Wilcoxon rank-sum test. Ranks for tied data were the mean of the corresponding ranks.

<sup>b</sup>  $P$  value were computed using an analysis of covariance on change from baseline in weekly partial-onset seizure frequency, controlling for geographic region, with baseline partial onset seizure frequency as covariate.

Source: Study report

Figure 2: Partial-Onset Seizure Frequency Percent Reduction From Baseline to Titration Plus Maintenance by Patient Percentage, ITT Efficacy Population



The empirical cumulative distribution function of the primary efficacy endpoint is listed in Figure 2. The percentage of subjects achieving any specified level of reduction in seizure frequency was consistently higher in the USL255 group compared to the placebo group. For example, approximately 68% of USL255 subjects experienced a 20% or greater reduction in seizure frequency compared with approximately 50% of placebo subjects, and approximately 49% of USL255 subjects experienced a 40% or greater reduction in seizure frequency compared with approximately 30% of placebo subjects.

Table 6 lists the percentage of subjects with 50% or greater reduction (responder rate) in weekly partial-onset seizure frequency during the titration plus maintenance phase compared to baseline in the ITT efficacy population. The responder rate was significantly greater in the USL255 treatment group (37.9%) compared with the placebo treatment group (23.2%) by the planned CMH test controlling for geographic region (P value = 0.019), gender (P value = 0.012), age category (P value = 0.012), race (P value = 0.011) and also by the Fisher exact test (P value = 0.013).

Table 6: Percentage of subjects with 50% or greater reduction (responder rate) in weekly partial-onset seizure frequency during the titration plus maintenance phase

Secondary efficacy endpoint	USL255 N = 124	Placebo N = 125	P value: USL255 vs. Placebo
Responder Rate in titration + maintenance phase			
N	124	125	
N (%) of subjects with ≥ 50% reduction	47 (37.9%)	29 (23.2%)	
Fisher exact test			0.013
Cochran-Mantel-Haenszel test controlling for:			
Geographic region			0.019
Gender			0.012
Age category <sup>a</sup>			0.012
Race			0.011

<sup>a</sup>Age categories are defined as 18 to <40, 40 to <65, and ≥ 65 years of age  
Source: Study report

Table 7 lists percent reduction from baseline in weekly seizure frequency for all seizures using the ITT population. The responder rate was significantly greater in the USL255 treatment group compared with the placebo treatment group in both the titration phase (USL255, 33.9%; placebo, 17.6%; P value = 0.007) and in the maintenance phase (USL255, 44.2%; placebo, 30.8%; P value = 0.048), analyzed separately.

Table 7: Percent Reduction From Baseline In Weekly Seizure Frequency For All Seizures

	USL255 N = 124	Placebo N = 125	P value
Percent reduction from baseline in weekly seizure frequency for all seizures in titration plus maintenance			
N	124	125	
Median	39.5	21.65	<0.001 <sup>a</sup>
LSMeans (SE)	32.95 (5.092)	11.5 (5.071)	0.003 <sup>b</sup>
Responder rated in titration phase			
N	124	125	
N (%) responders	42 (33.9%)	22 (17.6%)	0.007 <sup>a</sup>
Responder rated in maintenance phase			
N			
N (%) responders	113	120	
	50 (44.2%)	37 (30.8%)	0.048 <sup>a</sup>

<sup>a</sup> P value was computed using the Wilcoxon rank-sum test.

<sup>b</sup> P value were computed using an analysis of covariance on change from baseline in weekly partial-onset seizure frequency, controlling for geographic region, with baseline partial onset seizure frequency as covariate  
Source: Study report

### Dealings with Dropouts or Missing Data

To evaluate the impact of missing data in the study, ANCOVA analyses on the primary efficacy endpoint - percent reduction in average weekly rate of drop seizures were conducted considering (i) baseline compared to (i) first 4 weeks of the Maintenance Phase, and (ii) second 4 weeks of the Maintenance Phase of ITT Population. The weekly seizure rate during the maintenance period was calculated over the number of days with non-missing seizure data in the maintenance period. The median percent reduction in weekly frequency of partial-onset seizures from Baseline was statistically significantly greater [Table 8], using the Wilcoxon rank-sum test, in the USL255 group compared with the placebo group for the first 4 weeks of the Maintenance Phase (46.94% vs. 28.51%; P = 0.002, Wilcoxon rank-sum test) and the second 4 weeks of the Maintenance Phase (48.50% vs. 26.65%; P = 0.002, Wilcoxon rank-sum test). These findings support that the missing data has no major impact on the findings based on the primary analysis in the study.

Table 8: Percent Reduction From Baseline in Weekly Partial-Onset Seizure Frequency by Modified Phases—P09-004 ITT Efficacy Population

Percent Reduction from Baseline in Weekly Partial-Onset Seizure Frequency	USL255 (N =124)	Placebo (N = 125)	P-Value
<b>To first 4 weeks of the Maintenance Phase</b>			
Median	46.94	28.51	0.002 <sup>a</sup>
LSMeans (SE)	36.62 (7.736)	13.37 (7.503)	0.034 <sup>b</sup>
<b>To second 4 weeks of the Maintenance Phase</b>			
Median	48.50	26.65	0.002 <sup>a</sup>
LSMeans (SE)	39.75 (7.197)	12.70 (6.875)	0.008 <sup>b</sup>

<sup>a</sup>Wilcoxon rank-sum test

<sup>b</sup> P value were computed using an analysis of covariance on change from baseline in weekly partial-onset seizure frequency, controlling for geographic region, with baseline partial onset seizure frequency as covariate.  
Source: Study report

### 3.4 FDA REVIEWER’S DATA ANALYSIS AND COMMENT

This reviewer re-analyzed the efficacy data of the study P09-004 according to the protocol specified statistical analysis plan and found that the statistical findings are consistent with the sponsor's reported efficacy findings. The missing data had no impact on the efficacy conclusions of the study. No qualitative interaction is present between treatment groups and geographical regions. The sensitivity analyses conducted by the sponsor also provide consistent efficacy findings as obtained from the primary analysis.

## 4. SUBGROUP ANALYSIS

Table 9 lists the median percent reduction from baseline in weekly partial-onset seizure frequency during titration plus maintenance phase for the ITT efficacy population by geographic region, gender, age ranges, and race. Within each subgroup category, the USL255 treatment group had numerically greater median percent reductions in average weekly rate of partial-onset seizures from baseline to the titration plus maintenance period compared with the placebo group. That is, subgroup analyses of the Median percent reduction in the average weekly rate of partial-onset seizures demonstrated numerically higher reduction within each subgroup category of region, gender, age ranges, and race.

Table 9: Percent Reduction From Baseline in Weekly Partial-Onset Seizure Frequency During Titration Plus Maintenance Phase by Geographic Region, Gender, Age Ranges, and Race- ITT Efficacy Population

Subgroups	USL255	Placebo
Geographic Region		
<b>Eastern Europe</b>	N = 36	N = 33
Median percent reduction in weekly partial-onset seizure rate	41.03	29.11
<b>India</b>	N = 8	N = 6
Median percent reduction in weekly partial-onset seizure rate	27.64	6.42
<b>North America and Similar</b>	N = 14	N = 30
Median percent reduction in weekly partial-onset seizure rate	31.49	4.55
<b>South America</b>	N = 34	N = 31
Median percent reduction in weekly partial-onset seizure rate	48.23	26.29
<b>Western Europe</b>	N = 32	N = 25
Median percent reduction in weekly partial-onset seizure rate	37.2	14.05
Gender		
Female	N=58	N=59
Median percent reduction in weekly partial-onset seizure rate	43.03	21.05
Male	N=66	N=66
Median percent reduction in weekly partial-onset seizure rate	37.73	23.97
Age		
18 to <40	N = 73	N = 77
Median percent reduction in weekly partial-onset seizure rate	32.0	21.65
40 to <65	N = 50	N = 47
Median percent reduction in weekly partial-onset seizure rate	48.44	17.12
≥65	N = 1	N = 1
Median percent reduction in weekly partial-onset seizure rate	76.5	100.0
Race		
Caucasian	N=107	N=107
Median percent reduction in weekly partial-onset seizure rate	40.53	21.65
Non-Caucasian	N=17	N=18
Median percent reduction in weekly partial-onset seizure rate	27.27	18.45

Source: Study report

## 5. SUMMARY AND CONCLUSIONS

USL255 as an adjunctive therapy demonstrated its efficacy for the treatment of epilepsy in Phase III P09-004 study. The study was conducted in 16 countries, with 66 study centers enrolling subjects over approximately 27 months. Subjects enrolled in this study were receiving stable doses of AED medications and had an average duration of epilepsy of 20.4 years. USL255 or placebo was added to each subject's ongoing chronic treatment regimen. The primary objective of the study was to establish the efficacy of USL255 compared with placebo

when administered once daily over 11 weeks (3 weeks of up-titration plus 8 weeks of maintenance therapy) in adult subjects with refractory partial-onset seizures with or without secondary generalization.

The primary efficacy endpoint was the median percent change from Baseline in the weekly seizure frequency during the combined Titration + Maintenance Phase. The median percent reduction from Baseline to Titration + Maintenance Phase in weekly seizure frequency was significantly different between USL255 and placebo (39.50% vs 21.65%;  $P < 0.001$ ). Supportive analysis of the primary efficacy endpoint provided similar results using log-transformed seizure data.

The efficacy of USL255 was also supported by the key secondary efficacy endpoint analysis of the responder rate (percentage of subjects with  $\geq 50\%$  reduction in seizure frequency during the Titration + Maintenance Phase). The responder rate was significantly greater ( $P = 0.013$ ) in the USL255 group (37.9%) compared with the placebo group (23.2%). The efficacy of USL255 relative to placebo was also supported by other secondary efficacy outcome measures.

The median for the percent reduction from Baseline in weekly seizure frequency for subgroups defined by geographic region, gender, race, or age category showed that the median value for each subgroup was greater in the USL255 group than in the placebo group.

In conclusion, Study P09-004 provides robust statistical and clinical evidence for the efficacy of USL255 in the adjunctive treatment for partial-onset seizure.

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/s/  
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01/24/2014

KUN JIN  
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I concur with the review.

KOOROS MAHJOOB  
01/24/2014  
I concur with the review.