10.12 Analysis Plan

10.12.1 Demographic And Baseline Variables

- The 2 double-blind period treatment groups were to be compared in regard to demographic and baseline variables
- Quantitative variables were to be analyzed using either a t-test or a Wilcoxon rank sum test as appropriate
- Qualitative variables were to be analyzed using Fisher's exact test

10.12.2 Primary Efficacy Parameter

- The primary efficacy parameter was the change in the number of cataplexy attacks per week in the 2-week period following Visit 3 (endpoint), compared with the 2-week period prior to Visit 3 (baseline). If a subject withdrew prior to Visit 4 the weekly average would be calculated based upon the data that were available
- The efficacy population was to consist of all those randomized at Visit 2 who had some post-baseline efficacy data
- The above change in the weekly number of cataplexy attacks was to be analyzed using a non-parametric ANCOVA as follows
  - The baseline number of cataplexy attacks and the change in the weekly number of cataplexy attacks were to be replaced by their corresponding ranks (mean ranks will be used when ties occur).
  - The ANCOVA would be constructed from the residuals derived from the ordinary least squares prediction of the change in the weekly number of cataplexy attacks based on a simple linear model
  - The treatment groups would then be compared with respect to these residuals using the Wilcoxon rank sum test.
  - Prior to completion of the analysis a test would be performed to compare the slopes for the 2 treatment groups.
- The significance of the mean change from baseline for each treatment group would be determined using the Wilcoxon signed rank test

10.12.3 Safety Parameters

- The safety population would consist of all those randomized to receive drug at Visit 3 who had some post-baseline safety data
- Adverse events would be summarized by treatment group and organized by preferred term and body system. Treatment groups would be compared to the incidence of each adverse event using Fisher's exact test
- Laboratory data would be summarized in tabular form as well as with the use of shift tables. Treatment groups would be compared in regard to the mean change from baseline using ANOVA. Within each treatment group the significance of the mean change from baseline will be analyzed using a paired t-test

10.12.4 Sample Size Rationale

- The sample size calculation was based on the change in weekly cataplexy attacks comparing the 2 weeks prior to randomization and the 2 weeks after randomization

- The assumptions for the sample size calculation were as follows
  - Power of 80 %
  - 2-sided α of 0.05
  - A 50 % increase in the total number of cataplexy attacks in the placebo group, and a 10 % increase in a Xyrem® group
  - A standard deviation, based on a log transformation, of about 0.30 for the change in total number of cataplexy attacks (based on a previous study)
- Based on the above, a sample size of 22 patients would be required per treatment group to detect a treatment difference.
- To allow for a minor departure from the above assumptions a total of 30 patients would be randomized to each treatment group

10.13 Protocol Amendments

These have been incorporated into the above

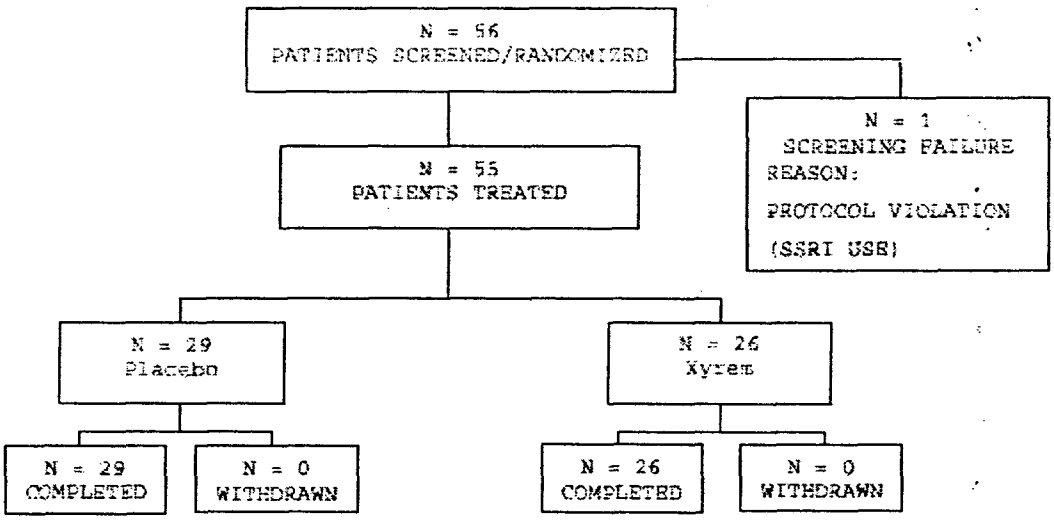
10.14 Actual Analyses Performed

10.15 Efficacy Results

The study was conducted at 14 centers. Each center enrolled between 1 and 7 patients

10.15.1 Patient Disposition

Patient disposition is summarized in the following schematic copied from the submission



Note that 1 randomized patient failed screening because of concomitant use of a selective serotonin re-uptake inhibitor (paroxetine). The blind was broken on 1 patient shortly after completion of the trial on account of a serious adverse event.

10.15.2 Protocol Deviations

- One patient was allowed into the trial despite having been treated with GHB for 3.7 years (the inclusion criteria specified that the duration of treatment should be from 0.5 to 3.5 years)
- One patient was allowed to continue in the trial despite receiving bupropion as a medication for cataplexy
- 3 patients overmedicated
- For "efficiency" 2 patients who were taking 3 g/day at study entry and continued to take that dose during the study were listed as taking 4.5 g/day
- For a number of patients Visits 1 and 2 were combined.

10.15.3 Medication Compliance

As the following table indicates medication compliance was comparable for the 2 Phase III treatment groups

Trial Medication Administration	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Total	Phase II*	Phase III	Total
Days Treated						
11	0	2		0	3	
12	1	1		0	0	
13	1	5		4	5	
14	14	13		20	13	
15	4	3		0	6	
16	1	0		0	0	
17	4	1		4	1	
18	1	1		1	1	
Duration of Treatment (Nights)						
Mean	14.7 ± 1.43	15.9 ± 1.48	28.6 ± 2.50	14.4 ± 1.35	14.0 ± 1.50	28.4 ± 1.95
Range	12-18	11-28	24-36	13-18	11-18	24-36
Compliance (%)						
Mean ± SD	105.9 ± 17.24	106.1 ± 18.80	106.0 ± 17.44	99.7 ± 6.07	102.4 ± 15.12	101.1 ± 9.28

* Placebo group patients received Xyrem during Phase II.
SD = Standard deviation.

10.15.4 Baseline And Other Demographic Characteristics

These characteristics are summarized in the next 2 tables copied from this submission. Although gender, and baseline frequency of cataplexy attacks were not entirely balanced between the treatment groups the sponsor describes the differences as not being statistically significant. Note that the daily dose of Xyrem® did appear balanced between the Phase III treatment groups.

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Characteristics	Total (N=55)	Treatment Group Xyrem (N=26)	Treatment Group Placebo (N=29)	p-Value
Age (years)				
Mean ± SD	47.7 ± 16.66	47.9 ± 17.06	47.6 ± 16.60	0.955
Range	16.3 - 82.6	19.1 - 82.6	16.3 - 73.8	
Sex (n, %)				
Male	23 (42%)	9 (35%)	15 (52%)	0.172
Female	32 (58%)	17 (65%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.5 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 - 142.0	54.0 - 142.0	55.0 - 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.735
Range	152.0 - 188.0	152.0 - 188.0	155.0 - 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.099
African-American	2 (4%)	2 (8%)	0	
Asian	0	0	0	
Hispanic	1 (2%)	1 (4%)	0	
Other	0	0	0	
Time on Xyrem (months)				
Mean ± SD	21.22 ± 12.28	23.27 ± 12.36	19.38 ± 12.13	ND
Range				

(continued)

Characteristics	Total (N=55)	Treatment Group Xyrem (N=26)	Treatment Group Placebo (N=29)	p-Value
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	31.75	19.25	39.88	
Median	3.0	1.9	4.0	
Minimum				
Maximum				
Daily Dosage of Xyrem at Screening (n, %)				
3.0 g/d	2 (4%)	1 (4%)	1 (3%)	ND
4.5 g/d	9 (16%)	4 (15%)	5 (17%)	
6.0 g/d	15 (27%)	7 (27%)	8 (28%)	
7.5 g/d	15 (27%)	7 (27%)	8 (28%)	
9.0 g/d	14 (25%)	7 (27%)	7 (24%)	

ND = Not determined. SD = Standard deviation.

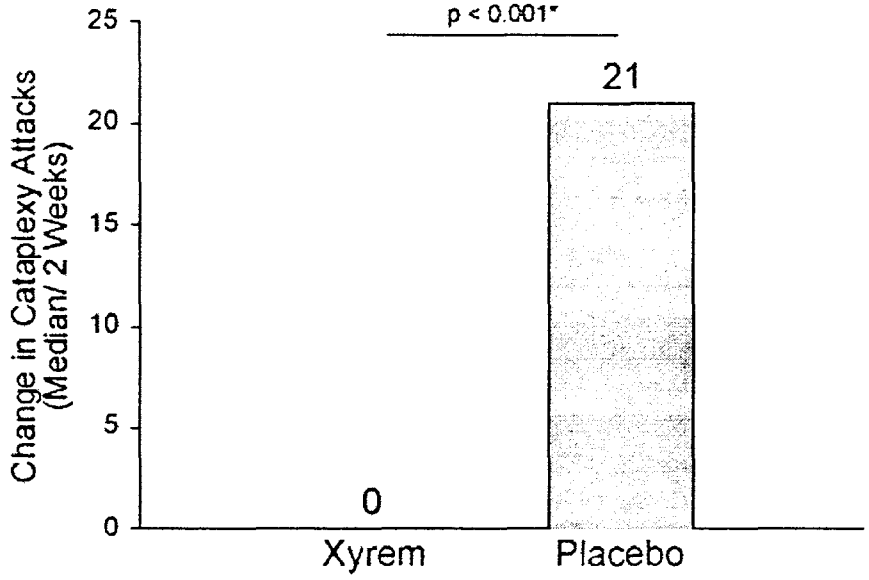
10.15.5 Primary Efficacy Analysis

An intent-to-treat analysis was performed as specified in the protocol comprising all patients who received one or more doses of trial medication during the double blind withdrawal period and had recorded baseline and post-baseline efficacy measures

The results of the primary efficacy analysis are outlined in the table and figure below. For those receiving Xyrem® during the double-blind withdrawal phase there was no median change from baseline in the number of cataplexy attacks over the 2 week period of withdrawal. For those receiving placebo during the withdrawal phase the median change in the number of cataplexy attacks during as compared with baseline showed an increase. The difference was statistically significant ($p < 0.001$). Note that the table and figure below depict median change

	Xyrem (N=26)			Placebo (N=29)		
	Phase II	Phase III	Change	Phase II*	Phase III	Change
Number of cataplexy attacks (per 2 weeks)						
Mean ± SD	9.9 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.09	34.6 ± 55.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum						
Maximum						
Rank change						
Mean ± SD			18.1 ± 12.65			35.9 ± 13.31*
Median			16.5			39.0
Minimum						
Maximum						

SD = standard deviation.
* Placebo group patients received Xyrem during Phase II.
* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.



* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

As the next table and figure indicate the median change from baseline by week in the number of cataplexy attacks mirrors that for the primary efficacy analysis above

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II*	Phase III	Change	Phase II*	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.9 ± 7.48	7.9 ± 19.94	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum						
Maximum						
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.56	3.7 ± 13.74	7.9 ± 19.94	29.7 ± 47.30	21.8 ± 35.16
Median	0.9	0.5	0.0	2.0	13.0	11.7
Minimum						
Maximum						

* Baseline (Phase II) was determined by normalizing the total number of cataplexy attacks during the 2 week study II period to 7 days.

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