- She applied an ANOVA the model for which included treatment, site and the treatment-by-site interaction. The assumption of normality for this model were however violated based on the Shapiro-Wilk test (p=0.017) and she therefore carried out a log transformation of the data. On re-applying the Shapiro-Wilk test to the log-transformed data the assumptions of normality was no longer violated (p=0.7365). An ANOVA on the log-transformed data revealed a p-value for the overall comparison of 0.0034. The subsequent comparison of each GHB group with placebo revealed the following

Comparison	p-value
GHB 3 g vs placebo	0.6358
GHB 6 g vs placebo	0.0772
GHB 9 g vs placebo	0.0021

- She had earlier also performed a Wilcoxon Rank Sum test. The p-value for the overall comparison of the 4 treatment groups, using the latter non-parametric test was 0.0101. She then compared each GHB group with placebo and the p-values for each of these comparisons was as follows

Comparison	p-value
GHB 3 g vs placebo	0.4684
GHB 6 g vs placebo	0.1450
GHB 9 g vs placebo	0.0033

- Thus, according to the protocol-specified primary efficacy analysis, and the sponsor's analysis, only the 9 g/day dose showed a statistically significant superiority to placebo in reducing the total number of cataplexy attacks.
- The evidence for efficacy at the 6 g/day dose appeared marginal and analysis-dependent.
- There was no definite evidence that GHB was efficacious in treating complete cataplexy attacks, the most serious form of cataplexy. However the mean (and median) frequency of such attacks in both treatment groups was small as was the absolute change in frequency from baseline to endpoint; a trend to a treatment effect may have been seen.

6.14.2 Secondary Efficacy Measures

- In this application the sponsor has sought a claim for Xyrem® in treating daytime sleepiness accompanying narcolepsy.
- The secondary efficacy measures used to assess daytime sleepiness included the Epworth Sleepiness Scale, the frequency of sleep attacks (inadvertent naps) during the day and the duration of daytime sleep attacks (inadvertent naps)
- On the sponsor's analysis, a nominally statistically significant superiority ($p < 0.05$) of GHB over placebo was seen on the Epworth Sleepiness Scale, the frequency of daytime sleep attacks and the duration of daytime sleep attacks, as measures of excessive daytime sleepiness. However given that there were 12 secondary efficacy measures, only the analysis of the Epworth Sleepiness Scale was still statistically significant after adjustment for multiple comparisons.

- On the sponsor's analysis, the pairwise comparisons for the Epworth Sleepiness Scale indicated that only the 9 g/day dose of GHB was superior to placebo
- Dr Sharon Yan, Agency Statistical Reviewer finds the analysis of secondary efficacy measures for this study problematical for the following reasons
  - There are many secondary efficacy measures
  - The methods of analysis were not stated in detail a priori
  - In specific reference to excessive daytime sleepiness, as measured by the Epworth Scale
    - She applied the protocol-specified ANOVA model to the original scale
    - After the treatment-by-site interaction was found not to be significant, it was removed from the model after which the residuals were no longer normally distributed, even after log transformation
    - She therefore performed a Kruskall-Wallis test. The overall p-value obtained for the GHB-placebo comparison was then 0.0109. As noted earlier, the Epworth Sleepiness Scale was one of 10 secondary efficacy measures and the overall p-value for this measure did not achieve statistical significance when a Bonferroni adjustment was made.
- The results of this study, based on the sponsor's analysis, nevertheless, do provide at least some support for the efficacy of GHB in a dose of 9 g/day in treating excessive daytime sleepiness in narcolepsy.

6.14.3 Influence Of Stimulant Drugs On Efficacy

6.14.3.1 Background

At the request of the Biopharmaceutics staff at the Agency, the following request was passed on to the sponsor on April 4, 2001

"The clinical study database should be investigated further to ascertain potential pharmacodynamic interactions in narcoleptic patients with other commonly used drugs in this patient populations."

The structure of the sponsor-proposed analysis of these interactions was discussed between the Division and sponsor at a teleconference on 4/18/01. The sponsor suggested the following, which was acceptable to the Division:

- The analysis would focus on the differences in observed effects, as they related to both safety and efficacy in narcoleptic patients

  and would compare the following groups

- Patients who received sodium oxybate alone

  Patients who received a selected concomitant medication alone

  Patients who received a combination of sodium oxybate and a selected concomitant medication

The above analysis is the basis for an additional submission dated May 4, 2001 which is summarized here as well as in my NDA Safety Review.

6.14.3.2 Sponsor's Methods

6.14.3.2.1 General Observations

- Narcoleptic patients commonly use the following classes of medications to treat that disorder
  - Stimulants (e.g., methylphenidate, dextroamphetamine, methamphetamine, pemoline, modafinil) to treat excessive daytime sleepiness
  - Tricyclic antidepressants and selective serotonin re-uptake inhibitors to treat REM dissociation phenomena: cataplexy, hypnagogic hallucinations and sleep paralysis
- The entire NDA database did not include a trial specifically designed to investigate the potential pharmacodynamic interactions between Xyrem® and medications commonly used in patients with narcolepsy. Nevertheless, for analysis purposes all clinical trials in the database were examined
- However, in only the OMC-GHB-2, Lammers and Scrima trials was it possible to compare the following groups in a controlled setting
  - Patients who received sodium oxybate alone
  - Patients who received a selected concomitant medication alone
  - Patients who received a combination of sodium oxybate and a selected concomitant medication

Even in the setting of these 3 controlled trials

- Stimulants were the only medication class on which such an analysis could be performed
- Both the Scrima and Lammers trials were not suitable for the analysis on account of a small sample size and variable use of stimulants

6.14.3.2.2 Stimulant Use In OMC-GHB-2

Of the 136 patients enrolled in this trial

- 115/136 (84.6%) maintained stable doses of stimulants during the trial
- 21/136 (15.4%) did not take stimulants
- The distribution of these patients by treatment group is below

Treatment Group	Placebo	3 g/day	6 g/day	9 g/day	Total
Number treated with stimulants	28	31	26	30	115
Number not treated with stimulants	6	3	7	5	21
Total	34	34	33	35	136

Of those taking stimulant drugs

- 41 were taking amphetamines
- 55 were taking methylphenidate
- 25 were taking pemoline
- Some patients took more than 1 stimulant drug
- The distribution of these patients by treatment group is in the following table

	Treatment Group	Placebo	3 g/day	6 g/day	9 g/day	Total
Amphetamines	Number not treated with amphetamine	26	23	20	26	95
	Number treated with amphetamine	8	11	13	9	41

Methylphenidate	Number not treated with methylphenidate	17	19	24	21	81
	Number treated with methylphenidate	17	15	9	14	55
Pemoline	Number not treated with pemoline	29	28	26	28	111
	Number treated with pemoline	5	6	7	7	25

6.14.3.2.3 Analysis Of Effects Of Stimulant Drugs On Efficacy

- The 2 outcome variables chosen for the analysis were
  - The frequency of all cataplexy attacks
  - Daytime sleepiness as measured by the Epworth Sleepiness Scale
- Descriptive statistics were calculated for each of the outcome variables, for each stimulant and for patients not taking stimulants, by treatment group
- Analysis of the total number of cataplexy attacks (after log transformation) and the change in Epworth scores was accomplished using ANCOVA: the model included baseline value of the variable being analyzed (the covariate) and site and treatment as terms.
- Separate analyses were performed for each treatment group of patients, based on type of stimulant used, and any stimulant use
- Adjustments were made for multiple comparisons using the Dunnett-Hsu procedure
- An additional analysis was performed to assess the possible interaction between stimulant use and GHB treatment. This used the same ANCOVA model as above with 2 additional terms: stimulant use (yes or no) and the stimulant-by-treatment interaction. This analysis was performed for each of the stimulants above and for the stimulant group as a whole

6.14.3.3 Results: Effects Of Stimulants On Efficacy Of GHB

The differences among treatment groups were consistent between those patients taking stimulants and those not taking stimulants; this was determined using the additional ANCOVA model which included the stimulant-by-treatment-group interaction. For each stimulant and each efficacy variable this interaction was not statistically significant.

Full tables describing the analysis are in the submission. I have not reproduced them here but they appear to confirm the sponsor's conclusions

6.14.3.4 Results: Effects Of Stimulants On Safety Of GHB

These results are described in the NDA Safety Review

6.14.3.5 Sponsor's Conclusions

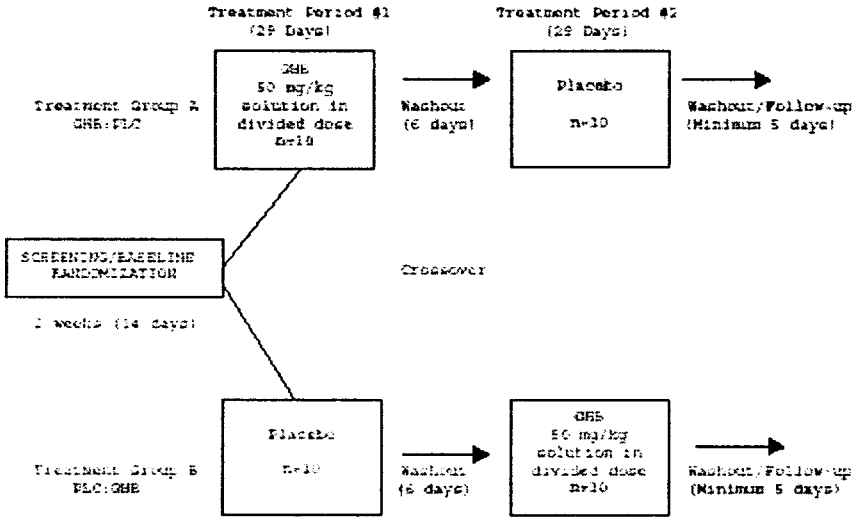
- In the analysis of cataplexy and daytime sleepiness there was no evidence of pharmacodynamic interaction between sodium oxybate treatment and concomitant stimulants
- In the analysis of adverse events there was only one body system (Digestive) in which a very weak signal of difference between those treated with GHB and methylphenidate and GHB alone was detected

- Sleep patterns identified on the polysomnogram
- Average number of REM onsets by Multiple Sleep Latency Test

7.3 Design

Randomized, double-blind, placebo-controlled, single-center, cross-over study comparing the effect of GHB 50 mg/kg total daily dose in with placebo in 20 patients with narcolepsy.

A schematic outline of the study design is presented in the figure below which I have copied from this submission.



Randomization was to be such that half of the men and half of the women participating in the study would receive GHB during the first 29-day double-blind treatment period, and placebo during the second. The remaining patients were to receive GHB first and placebo later.

7.4 Duration

4 weeks of double-blind treatment during each cross-over period

7.5 Dosage

During each period of double-blind treatment, each participating patient was to take

GHB 25 mg/kg at bedtime, and about 3 hours later (total dose: 50 mg/kg/day)
OR
Matching placebo

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