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

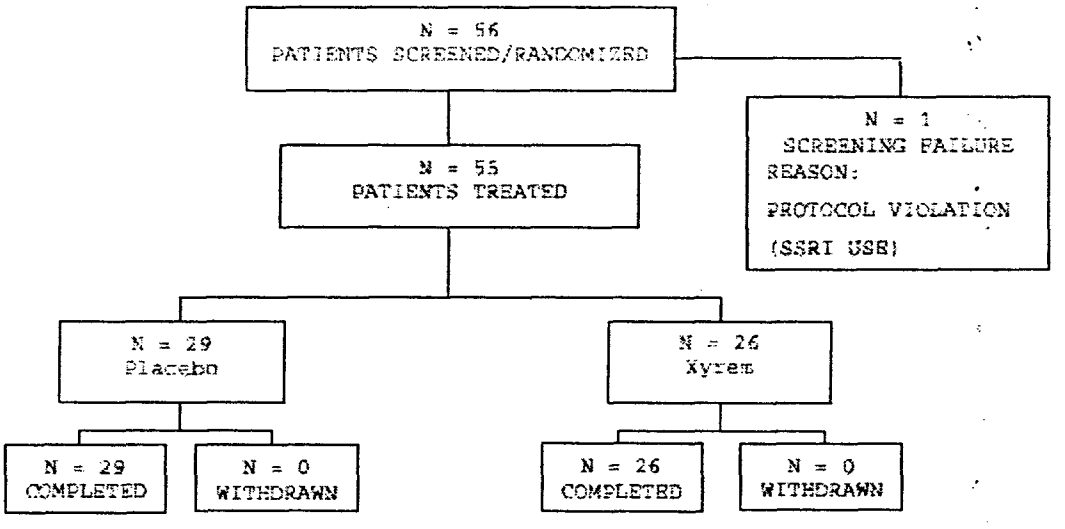
10.14 Actual Analyses Performed

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	13.9 ± 1.48	28.6 ± 2.50	14.4 ± 1.35	14.0 ± 1.50	28.4 ± 1.95
Range	12-18	11-18	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.

APPEARS THIS WAY
ON ORIGINAL

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 - 77.0	
Sex (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	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	0.718
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.

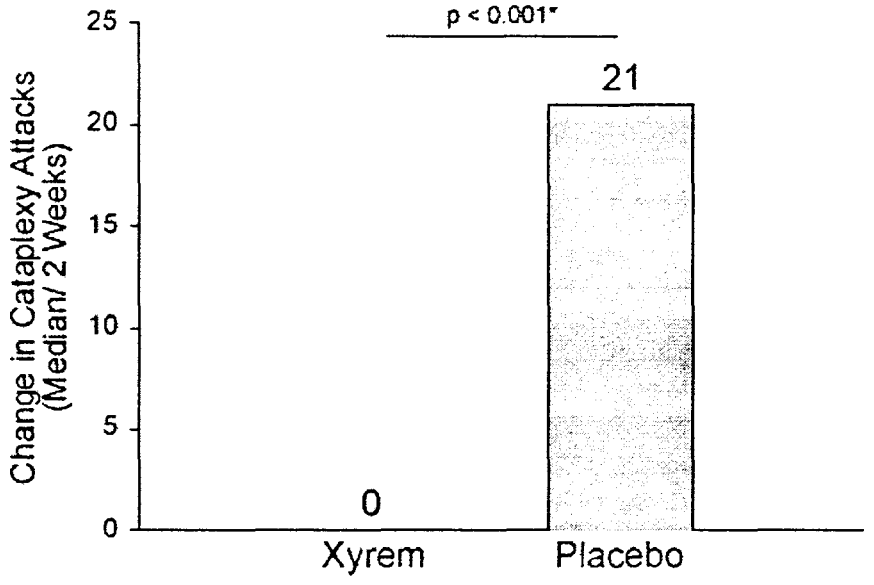
10.15.5 Primary Efficacy Analysis

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	9.0 ± 19.25	12.6 ± 30.34	3.6 ± 20.73	15.7 ± 39.88	50.4 ± 81.03	34.6 ± 59.72
Median	1.9	1.1	0.0	4.0	21.0	21.0
Minimum						
Maximum						
Rank Change						
Mean ± SD			18.1 ± 12.65			36.9 ± 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.

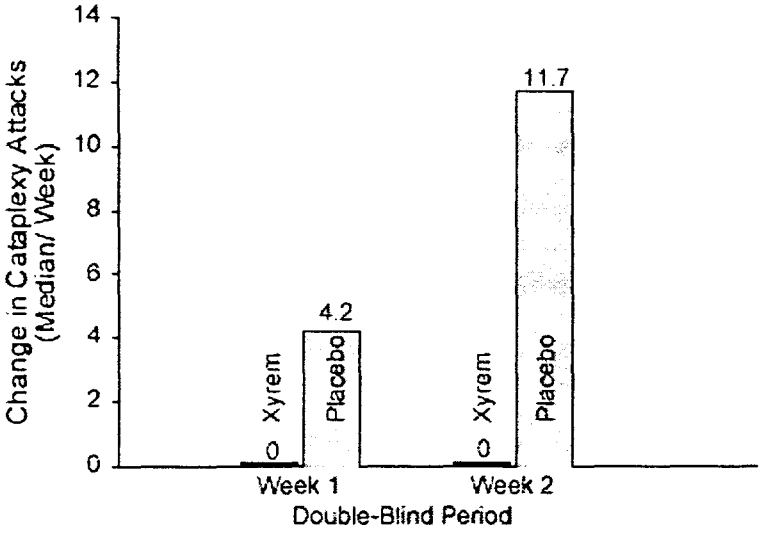


* p < 0.001, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

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 ± 11.94	0.8 ± 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	4.3
Minimum						
Maximum						
Week 2						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 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 period to 7 days.



No formal analyses were carried out to evaluate differential effects at study sites, or to evaluate drug-drug or drug-disease interactions.

10.15.6 Analysis Of Secondary Efficacy Measures

This study had no secondary efficacy measures

10.16 Safety Results

These are summarized in the NDA Safety Review.

10.17 Sponsor's Conclusions Regarding Efficacy

Xyrem® is effective as a long-term treatment for cataplexy

10.18 Reviewer's Comments

- The design and analysis plan for this study were discussed at length a priori with this Division
- The Division had agreed earlier that the randomized withdrawal paradigm used in this study would be appropriate for demonstrating the long-term efficacy of Xyrem®. Based on that agreement and the study results, I would agree with the sponsor's conclusion that this study provides evidence for the long-term efficacy of Xyrem® in the treatment of cataplexy.
- Dr Sharon Yan, Agency statistical reviewer, has informed me that she also agrees with the sponsor's conclusion that the study provides evidence for the long-term efficacy of GHB in treating cataplexy.
- An effective daily dose of Xyrem® is difficult to determine from this study since patients were not randomized to separate Xyrem® dose groups prior to withdrawal. However, it is noteworthy that although the dose of Xyrem® used in this study ranged from 3 to 9 g/day, 80% of those enrolled were receiving doses of 6-9 g/day at study entry.

  At a Peripheral and Central Nervous System Advisory Committee meeting held on 6/8/01 to discuss this NDA the sponsor did present a further analysis not included in

the formal submission. In this analysis those patients who received placebo during the randomized withdrawal phase were divided into subgroups based on the dose of Xyrem® that they were taking prior to withdrawal. Robust statistically significant differences were seen on these post-hoc comparisons between the placebo group subsets who were originally taking doses of 6 g/day, 7.5 g/day and 9 g/day, and those continuing to take Xyrem® during the randomized withdrawal phase. These results were interpreted as showing further evidence for the efficacy of doses in the 6 to 9 g/day range in the treatment of cataplexy. Note that these subgroups were not randomized.

11. Study OMC-SXB-16

The report of this study was submitted 12/16/00

This study was carried out to compare the taste of 3 different placebo formulations with that of Xyrem® oral solution.

The study was carried out on 12 healthy volunteers, all employees of Orphan Medical, Inc.

Appropriate inclusion and exclusion criteria were used.

Blind comparisons were made between sodium oxybate oral solution and the 3 different placebo formulations which contained sodium phosphate, sodium chloride and sodium citrate, respectively. The placebo solutions to be tested were presented in random order. Comparisons were made in pairs: each of the 3 placebo solutions matched with the solution of Xyrem®. Each subject was exposed to 6 different solutions

The similarity of taste for each solution pair was evaluated using the Formulation Taste Test Questionnaire. The questionnaire consisted of a visual analog scale: a line exactly 10 cm in length with the extremities labeled "identical" and "very dissimilar." Subjects were asked to complete the questionnaire, after swishing and expelling each solution of the blinded pair, by marking the visual analog scale.

The Xyrem® dose administered was 3 g.

The study concluded that the placebo formulated with sodium phosphate was the one most comparable to Xyrem® oral solution. The sodium phosphate and sodium citrate solutions were considered acceptable candidates for placebo.

No adverse events were observed during the study which was conducted in April 1999.

Note that

- For the OMC-GHB-2 efficacy study a sodium chloride placebo formulation was used
- For the OMC-SXB-21 efficacy study a sodium citrate placebo formulation was used

12. Overall Comments Regarding Efficacy

- The sponsor is seeking a claim for Xyrem® as a treatment for cataplexy and daytime sleepiness accompanying narcolepsy
- The evidence for the efficacy of GHB in treating cataplexy may be summarized as follows
  - There does appear to be evidence that GHB is effective in treating cataplexy, although there is currently no evidence that the drug is effective in treating complete cataplexy attacks, the most serious form.
  - The evidence for efficacy is mainly established by the results of Studies OMC-GHB-2 and OMC-SXB-21, and to a lesser extent by the Scrima study which has a number of deficiencies. In all 3 studies the same outcome measure, the frequency of cataplexy attacks based on patient diaries, was used. The Lammers study must be considered a "negative" one at this time.
  - The effective dose of GHB in treating cataplexy can be best defined from the OMC-GHB-2 study in which patients were randomized to specific doses of GHB and robust evidence of efficacy was seen only at a dose of 9 g/day (and not at 3 g/day and 6 g/day). In the OMC-SXB-21 and Scrima studies, there was no randomization by GHB dose: in the OMC-SXB-21 study 80% of patients had been taking GHB doses ≥ 6 g/day prior to randomized withdrawal. In the less than optimal Scrima study the protocol-specified dose was 50 mg/kg/day, and the mean daily dose estimated using body weight data was 4.5 g/day. Thus the most clearly effective dose in treating cataplexy was 9 g/day with less clear and consistent evidence of efficacy at lower doses ≥ 4.5 g/day. The evidence in favor of efficacy at the 6 g/day dose comes mainly from the OMC-GHB-2 study and is marginal and analysis-dependent. There is no evidence for efficacy at a dose of 3 g/day
- The evidence for efficacy/or the lack thereof of GHB in treating daytime sleepiness accompanying narcolepsy may be summarized as follows
  - Efficacy is supported by the sponsor's analysis of the Epworth Sleepiness Scale in the OMC-GHB-2 study (although not by the analysis performed by Dr Sharon Yan, FDA statistician on the same measure in the same study), and to a very small extent by the analysis of the frequency of daytime sleep attacks in the Lammers study which had a number of inadequacies
  - However the analysis of a number of other measures of daytime sleepiness in 3 efficacy studies could not be considered to show a statistically significant superiority of GHB over placebo. These included the following
    - The frequency of daytime sleep attacks and the duration of such attacks in the OMC-GHB-2 study
    - The Sleepiness Index (of the Multiple Sleep Latency Test), which was a primary efficacy measure, and the frequency of daytime sleep attacks, in the Scrima study
    - The severity of daytime sleep attacks in the Lammers study

- In the OMC-GHB-2 study the only seemingly effective dose in treating daytime sleepiness, based on the sponsor's analysis, was 9 g/day. In the Lammers study the mean daily dose used was 4.75 g/day
- It is unclear to what extent the analysis of the Epworth Sleepiness Scale data in OMC-GHB-2 was confounded by the concurrent use of stimulant medication (it is unclear to what extent the treatment groups were matched in this regard; see Section 6.14.3.6)
- The lack of replication of the effect of GHB on daytime sleepiness as assessed by a specific measure in more than one study is unsatisfactory, quite apart from the other deficiencies noted in the efficacy studies. As noted above, the most robust evidence in favor of
- Currently, there does NOT appear to be adequate evidence that GHB is effective in treating daytime sleepiness accompanying narcolepsy.

- Also note that this Center's Division Of Scientific Investigations carried out an inspection of the Scrima study site (see Section 15) and concluded that the data were unacceptable because most of the drug accountability records were missing. DSI recommended that data from the Scrima study not be used in support of the NDA
- In summary,
  - Evidence has been provided in this application that Xyrem® is effective in treating cataplexy. The evidence is best at a Xyrem® dose of 9 g/day, but may extend across the dose range of 6-9 g/day
  - The application does not however provide adequate evidence that Xyrem® is effective at treating daytime sleepiness accompanying narcolepsy

13. Labeling Review

Please see separate document entitled "NDA 21196 Labeling Review"

14. Overall Comments Regarding Safety Of Xyrem®

See NDA Safety Review for full details

14.1 Clinical Safety

- When GHB is used to treat narcolepsy in doses of 3-9 g/day the most common, dose-related, and seemingly drug-related, adverse events have included the following: headache, unspecified pain, nausea and dizziness. Urinary incontinence is slightly less common, but apparently dose and drug-related as well. More serious, but much less common, adverse events seen at the same dose range have included vomiting, confusion, restlessness, agitation, somnolence and generalized weakness. No deaths that could be attributed to study drug have been reported at therapeutic doses of GHB
- One healthy 39 year old woman participating in pharmacokinetic trials developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence, after a single (and initial) oral dose of 4.5 g of GHB.
- A single older narcoleptic patient who had been taking GHB for approximately 1 ½ years was hospitalized after an overdose of GHB 18 g. At the time of hospitalization he was comatose and unresponsive. He needed intubation

and artificial ventilation, and awoke 6 hours later. This incident suggests that the safety margin between therapeutic and toxic doses may not be very wide
- At therapeutic doses of GHB all adverse events appear to be reversible
- While currently there is no strong evidence that GHB in therapeutic doses is epileptogenic or that episodes of urinary and fecal incontinence due to GHB are due to seizures, there is insufficient data at present to rule out either possibility.
- "Recreational" use of GHB, generally at doses, presumed or known to be higher than the therapeutic dose has been associated with adverse events that included fatalities attributable to the depressant effects of this drug on the nervous system. However concurrent use of alcohol and of other drugs with effects on the central nervous system has been reported in many of these instances
- There is no evidence that GHB is toxic to any major organ other than the nervous system.

14.2 Withdrawal Phenomena And Abuse Potential

- There is no evidence from a small formal study with a randomized withdrawal paradigm (OMC-SXB-21) that the abrupt discontinuation of therapeutic doses of GHB used for 6 months to 3 ½ years leads to more than mild and infrequent withdrawal symptoms, except for a significantly increased frequency of cataplexy.
- There are however a number of anecdotal reports of an actual withdrawal syndrome and, possibly, addiction in illicit "recreational" users of GHB, GBL or 1-4 BD. In all these individuals, high doses of GHB or related drugs were believed to have been used at frequent intervals around-the-clock.

14.3 Additional Comments Based On Review Of Major Amendment To NDA

On March 23, 2001, the sponsor submitted a major amendment to this NDA

The purpose of the amendment was to address the following
- Deficiencies in the open-label Scharf study outlined in the safety review
- A number of questions pertaining to the safety data for clinical trials conducted by Orphan Medical
- Several related issues.

In submitting the major amendment the sponsor requested a 90-day extension to the original Prescription Drug User Fee Act deadline of April 2, 2001.

This major amendment is reviewed in a separate document. Please refer to that review for full details.

A number of comments by me about the safety of Xyrem®, based on a review of the Amendment are below. In order to understand the context of the comments further, the reader will need to refer to the review of the Amendment itself which is in a separate document.

- The manner in which data for the Scharf study have been collected, recorded, and presented in this submission cannot be said to be ideal.
- Of the 80 patients who participated in the Scharf study and did not enter the currently ongoing Orphan Medical Treatment IND study OMC-SXB-7, 64 patients might be stated to have be "accounted for" although the basis for doing so is less-than-optimal in a significant number. Further efforts need to be made by the sponsor to account fully for 11 of the remaining 16 (unsuccessful recent efforts have been made to contact 5 patients out of those 16). The 11 patients are listed below. Adverse events that were ongoing at the time of discontinuation are reasons for obtaining further follow-up in at least some of these 11 patients

01-004/
01-027/
01-054/
01-065/
01-228/
01-240/
01-262/
01-269/
01-283/
01-268/
01-256/

- None of the "adverse events" in the "unevaluable" category that occurred in the Scharf study appear to be attributable to GHB
- Urinary and fecal incontinence both appear to be unusually common adverse events in patients taking GHB and the key issues are whether such episodes are accompaniments of unrecognized convulsions, and whether GHB is capable of causing convulsions at therapeutic doses. Currently the evidence that the vast majority of episodes of incontinence in the entire NDA are related to unrecognized convulsions is weak. There does appear to be at least 1 patient in the Scharf study in whom incontinence clearly accompanied a true convulsion.
- While there are clearly a few patients (n = 2) in the entire NDA safety database who experienced, or may have experienced, convulsions while taking GHB, the presence of confounding factors (e.g., possible benzodiazepine withdrawal) makes it difficult to link the convulsions causally to GHB. Whether GHB is capable of causing other types of seizures, e.g., absence or partial complex, is even less clear
- In this NDA, and especially in the Scharf Study, the term "sleepwalking" has been used as a verbatim (investigator) term for a common adverse event. Detailed clinical descriptions of such episodes are not available for the majority of patients and their mechanism has not been delineated. A separate analysis of these episodes has not been performed by the sponsor and it is not clear how common they are in the Integrated Clinical Trials grouping, but such episodes have been associated with serious consequences (e.g., overdose, pyrogenesis, consuming toxic chemicals) in patients enrolled in the Scharf study

- The information available in this NDA does suggest that GHB is capable, at therapeutic doses, of causing a confusional state (which may be accompanied by psychotic symptoms). The incidence and seriousness of such adverse events may be slightly more pronounced at higher doses, and especially if higher doses are administered without titration. However a confusional state also appears to be capable of occurring at lower and even sub-therapeutic doses of GHB, and after maintenance treatment for several months. The presence of true confusion in patients taking GHB could lead to their taking GHB in a manner other than as prescribed. The symptoms that have been subsumed under the COSTART term "confusion" are not unusual for a sedative-hypnotic drug.
- In the majority of patients who developed "neuropsychiatric" adverse events (e.g., paranoia, hallucinations, anxiety, stupor, etc) while taking GHB in Integrated Clinical Trials it is not possible to attribute causality for the adverse event to GHB. Pre-existing psychiatric illness, and concomitant medications such as stimulants, as well as other factors, could be contributory. Even in patients in whom there was no recorded premorbid history of psychiatric illness the extent to which they were screened for such illness is not clear. However the occurrence of neuropsychiatric adverse events in patients taking GHB, even if not directly caused by the drug, could place them at risk of intentional or accidental overdose, as is suggested by the narratives in this review
- There is no firm evidence that any patients participating in the Integrated Clinical Trials had drug-induced lupus. However antinuclear antibody and antihistone antibody testing was not performed for patients participating in this study
- There is no evidence suggesting a causal link to GHB for the small number of hypoglycemic an hyperglycemic blood test readings in the NDA; several of the apparently hypoglycemic readings could in fact have represented laboratory errors. Neither is there firm evidence in AERS or in the medical literature that GHB is capable of causing hypoglycemia.
- GHB is unlikely to have been the cause of transaminase elevations seen in a few patients in the Integrated Clinical Trials.
- As noted above the manner in which the Scharf study was conducted was deficient in many ways. Of particular concern was the lack of systematic active surveillance for adverse events and missing drug accountability records. As also noted earlier in this review (see Section15) the Center's Division of Scientific Investigations is of the opinion that the Scharf Study data are unacceptable and has recommended that this study not be used in support of the application. From this reviewer's perspective the best that can be said about this study is that the vast majority of those enrolled have been "accounted" for in the sense that it is unlikely that they have suffered any catastrophic events that this Agency is unaware of. I would, therefore, recommend that this study not be used in estimates of the adequacy of exposure to Xyrem® in the safety database (see next bullet)

- The number of patients exposed to GHB in the NDA Safety Database minus the Scharf study appears sufficient to meet ICH guidelines at the 6-month and 1-year levels but not in regard to the total number of patients exposed; however allowance can be given for GHB being designated as an orphan drug and the total number exposed may therefore be acceptable.

  Note that the extent of exposure to GHB in patient-years is reduced by about 79% once the Scharf study data are eliminated. Admittedly, the ICH guidelines do not specifically address the issue of desirable exposure in patient-years.

  Further if one concludes (from the efficacy studies) that the 9 g/day dose is the only effective dose and is that to be recommended for general use the number of those exposed to Xyrem® at that dose for ≥ 6 months and ≥ 12 months does not meet ICH guidelines. On the other hand if it is concluded from the efficacy studies that the effective dose of Xyrem® ranges from 6-9 g/day, the number of those exposed at that dose range for ≥ 6 months falls somewhat short of ICH guidelines. Note that the sponsor has not supplied data for the **total** number of patients exposed for any duration (including or excluding the Scharf study) for the 6-9 g/day dose range or at the 9 g/day dose itself

  Note that ICH guideline E1A (July 1997) includes the following statements:

  "The number of patients treated for 6 months at dosage levels intended for clinical use should be adequate to characterize the pattern of adverse events over time. To achieve this objective the cohort of exposed subjects should be large enough to observe whether more frequently occurring events increase or decrease over time as well as to observe delayed events of reasonable frequency (e.g., in the general range of 0.5% to 5%). Usually 300 to 600 patients should be adequate....

  .....100 patients exposed for a minimum of 1 year is considered to be acceptable to include as part of the safety database. The data should come from prospective studies appropriately designed to provide at least one year exposure at dosage levels intended for clinical use."

14.4 Risk Management Program

The small clinical trial safety database, the narrow margin of safety and the risks of abuse and misuse all call for approval to be conditional on a risk management system that is more stringent than that proposed by the sponsor. Key additional elements of such a system should include

- Dispensing of the drug exclusively to patients with a diagnosis of cataplexy confirmed by their physicians
- Commitment by the sponsor to a detailed plan for active post-marketing surveillance for instances of diversion, abuse, misuse and adverse events of special concern
- Clear statements in the approved label, patient information sheet and patient and physician educational materials about the nature of the drug (i.e., that it contains the same active ingredient as illicitly-used GHB), the limited experience with the drug during development, the potentially serious toxicity of both therapeutic doses and overdoses

- Use of Subpart H of the Accelerated Approval regulations (21 CFR 314.500) so as to provide a means of restricting distribution of the drug and for enforcement of the risk management program. Justification for institution of these regulations is as follows
  - Xyrem® is intended to treat a serious disease (cataplexy)
  - Xyrem® provides meaningful benefit to patients over existing treatment
  - Xyrem® can be used safely only if its distribution or use is restricted

15. Study Site Inspections

15.1 Sites Inspected

The following study sites pertinent to this application were inspected by the Division of Scientific Investigations (DSI) at the request of this Division

Site	Location	Study
Orphan Medical, Inc (Sponsor)	Minnetonka, MN	OMC-GHB-2
[redacted]		OMC-GHB-2
Jonathan Schwartz, MD (Investigator)	Oklahoma City, OK	OMC-GHB-2
Lawrence Scrima, PhD (Sponsor-Investigator)	Aurora, CO	Scrima Study
Martin Scharf, PhD (Sponsor-Investigator)	Cincinnati, OH	Scharf Study

The results of these inspections are described in detail in a Clinical Inspection Summary written by Constance Lewin, MD, of the Division of Scientific Investigations, dated June 11, 2001. Please refer to that document for full details.

These inspections uncovered a number of deficiencies, the most prominent of which pertained to the Scharf open-label study.

15.2 Scharf Study Site Inspection

This inspection is described in the NDA Safety Review

15.3 Division Of Scientific Investigations Conclusions

These conclusions are summarized in the following table

Site	Study	DSI Conclusions and Recommendations
Orphan Medical, Inc (Sponsor)	OMC-GHB-2	Data acceptable
[redacted]	OMC-GHB-2	
Jonathan Schwartz, MD (Investigator)	OMC-GHB-2	
Lawrence Scrima, PhD (Sponsor-Investigator)	Scrima Study	Data unacceptable*. Recommendation: Study not be used in support of NDA
Martin Scharf, PhD (Sponsor-Investigator)	Scharf Study	Data unacceptable** Recommendation: Study not be used in support of NDA

*Drug accountability records largely missing
**Multiple deficiencies including missing drug accountability records

16. Financial Disclosure Certification

Financial disclosure certification has been submitted with this application.

16.1 Components Of Certification

This certification has 2 components

16.1.1 Certification Pertinent To Dr Lawrence Scrima

The sponsor has supplied required financial disclosure information for Dr Scrima.

Orphan Medical, Inc, entered into a financial contract with Dr Scrima on 11/10/99. The contract allowed Orphan Medical to access documentation associated with the double-blind, placebo-controlled, cross-over trial in 20 narcoleptic patients. The trial was conducted from April 5, 1986 to December 14, 1987.

The sponsor states that payments to Dr Scrima were made over 10 years after completion of the trial. While the payment was financially disclosable it did not have any impact on data collection, interpretation or analysis

16.1.2 Certification Pertinent To Other Investigators

The sponsor has supplied a list of 32 Investigators who conducted clinical trials on behalf of Orphan Medical, Inc. In regard to this list the sponsor has

- Certified that it has not entered into any financial agreement with the clinical investigators listed in the application whereby the compensation to the investigator could be affected by the outcome of the study in which the investigator was a participant, as defined by 21 CFR 54.2 (a)
- Certified that each listed clinical investigator required to disclose to the sponsor that whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2 (b) did not disclose any such arrangements
- Certified that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2 (f)

16.2 Reviewer's Comment

It appears unlikely that the financial arrangement disclosed above introduced significant bias into the results of studies carried out with Xyrem®, and submitted with this NDA.

17. Advisory Committee Meeting

A meeting of the Agency's Peripheral and Central Nervous System Drugs Advisory Committee was held in Bethesda, Maryland on June 6, 2001, to discuss this application. The overall agenda for the meeting was as follows:

"Consideration of (NDA) 21-196, Xyrem® (sodium oxybate, Orphan Medical, Inc.), proposed to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness for persons with narcolepsy. A main focus of the deliberations will be on risk management issues"

A full transcript of the meeting is to be posted at the following site about 30 days after completion of the meeting:

www.fda.gov/ohrms/dockets/ac/acmenu.htm

The following is a summary of the main outcomes of the meeting as prepared by this reviewer

17.1 Key Items Voted On

17.1.1 Question #1

The original question addressed to the sponsor was as follows:

Has the sponsor demonstrated efficacy of Xyrem® for the proposed indication to treat cataplexy and excessive daytime sleepiness in patients with narcolepsy?

If no, is there any reasonable claim for which the sponsor has presented substantial evidence of effectiveness?

The final questions voted on are below

Has the sponsor demonstrated efficacy (at 6 – 9 g/day) of Xyrem® for the proposed indication of cataplexy?

Yes = 5 No = 4

Has the sponsor demonstrated efficacy (at 6 – 9 g/day) of Xyrem® for the proposed indication of daytime sleepiness?

Yes = 0 No = 9

17.1.2 Question #2

The original question posed to the sponsor was as follows:

Has the sponsor established the safety of Xyrem® when used for the proposed indication for which substantial evidence of effectiveness has been submitted?

This question was voted on only in relation to cataplexy and to a dose range of 6-9 grams/day.

Yes = 4 No = 4 Abstain = 1

17.1.3 Question #3

Is the adoption of a risk management plan necessary for the safe use of Xyrem®?

Yes = 8 No = 1

17.2 Additional Recommendations

The following additional recommendations were made by the committee after discussion, based on questions posed by the Agency. Other questions posed by the Agency were also discussed by the sponsor but with either a lack of

consensus or with a recommendation that the particular measure not be instituted

- Labels on Xyrem® dosing cups should indicate the nature of the contents and dose
- Patients should sign an informed consent document (possibly to be combined with a completed registration document) prior to receiving the first shipment of Xyrem®
- Physicians should be required to document that they have read the educational materials supplied by the sponsor prior to the first prescription for Xyrem® being filled
- Dispensing of Xyrem® should be restricted to patients confirmed by their physicians to have cataplexy
- The patient educational materials should clearly state that the active ingredient contained in Xyrem® is gammahydroxybutyrate (GHB), that the drug has potential for being abused and that there are legal penalties for misuse and diversion of the drug

Note that the committee did NOT feel there was a need in the Risk Management Program for

- Certification of physicians prescribing Xyrem®
- A formal requirement for physicians or their staff to demonstrate the safe use of Xyrem® to patients, and for formal documentation that they had done so prior to the first prescription being filled
- A formal requirement in the risk management program for additional safeguards in the patient's home, such as a locked filing cabinet for storage of the drug

17.3 Additional Comments

Among the additional views expressed by members of the Advisory Committee and consultants was the following:

- That patients enrolled in Study #OMC-GHB-2 consisted of a sample that was enriched based on their having cataplexy; such a population may not represent the narcolepsy population at large and may not be an appropriate population in which to assess the efficacy of GHB in treating excessive daytime sleepiness
- Whether the incidence of adverse events attributable to central nervous system depression in the Xyrem® database was suppressed by the concomitant use of stimulant medication (over 67% of patients concomitantly received stimulant drugs across studies and in some clinical trials > 80% of patients did)
- That the number of patients exposed to the 6 to 9 g/day dose of Xyrem® might not be adequate to evaluate the safety of the drug: this concern appear to be the reason why the committee was evenly divided in opinion about the

19. Risk-Benefit Equation And Overall Conclusions

- **Xyrem® is effective for treating cataplexy, a chronic and lifelong disorder, which is disabling, may lead to serious injury, and for which there is currently no approved treatment; there is thus a hitherto unmet medical need for this drug.** The most clearly effective dose of Xyrem® in treating cataplexy is 9 g/day, with less robust evidence for efficacy at a range of 6 to < 9 g/day. The only evidence for efficacy at doses less than 6 g/day comes from 2 small studies that have many deficiencies.
- There is inadequate evidence at the present time for the efficacy of Xyrem® in treating excessive daytime sleepiness or other symptoms in narcolepsy
- The number of patients who have been exposed to a Xyrem® dose of 6-9 g/day in clinical trials subsumed under this NDA (and for which reliable data is available) is small, leading to a concern that the full adverse event spectrum, (including relatively frequent and potentially significant events) of this drug may not yet be evident. The drug has however been demonstrated to have efficacy for a condition which has a low prevalence (an estimated 24,000 individuals in the United States have cataplexy) and "orphan" status.
- In clinical trials, adverse events of concern that could be causally attributed to Xyrem®, and have occurred at therapeutic doses are almost entirely related to the effects of the drug on the central nervous system. These have included confusion, sleepwalking, somnolence, depressed respiration, and urinary as well as fecal incontinence. The incidence of these events has been low, and they have almost always been reversible. However, such events have had at least a potential for even more serious consequences (as evidenced in some patients with sleepwalking) . The margin of safety between doses that are clinically effective and those that have serious toxicity may be very narrow, or even non-existent, in some patients. Given the use of stimulant medications in the vast majority of patients enrolled in clinical trials included in this NDA,

there may be a possibility that the central nervous system-related adverse events of Xyrem® were made less evident by the co-administration of stimulants; this is despite the pharmacokinetic half-lives of stimulants and GHB being brief and stimulants being taken during the day and GHB at night (the pharmacodynamic effects of Xyrem® presumably extend far beyond the very brief pharmacokinetic half-life of approximately 1 hour)

- The abuse of illicitly manufactured and distributed GHB appears to be widespread in this country and increasing. Such abuse has been associated with many reports of central nervous system toxicity, including fatalities, at widely varying (estimated) doses; however, many such reports have been confounded by the co-ingestion of alcohol and of other drugs with effects on the central nervous system. There have also been reports of the development of a dependence syndrome and of addictive behavior in individuals taking high and frequent (round-the-clock) doses of GHB from the same sources, although not with Xyrem® used in clinical trials included in this NDA; however the exposure to GHB in clinical trials has not been extensive. The abuse potential of GHB has yet to be specifically evaluated in a human clinical trial, although only minimal symptoms that might be attributable to withdrawal were seen in the small randomized withdrawal efficacy study #OMC-SXB-21
- GHB has been proposed in the scientific literature as well as in lay publications as a treatment for a variety of conditions known or presumed to have a medical basis including insomnia, alcohol and opiate withdrawal, chronic fatigue syndrome, fibromyalgia, diseases causing weight loss such as AIDS as well as other entities. Based on the medical literature review submitted with this application there is virtually no evidence-based endorsement for its use for these indications. However if Xyrem® were to be approved without any limitations on off-label use it is very likely that the drug will be prescribed for these entities at least of which are known or perceived to be common. Under such circumstances it is also likely to be prescribed by physicians with much less familiarity with the drug than experts in sleep disorders

It is also to be expected that if Xyrem® is approved without any restrictions on off-label use it is likely that it will be prescribed not just for the daytime sleepiness of narcolepsy (for which there is inadequate evidence for efficacy at present), but for daytime sleepiness of other causes and even for daytime fatigue.

- There is no valid reason to presume that prescribed Xyrem® will not be subject to diversion and abuse and to the risk of accidental or deliberate overdose, as well as other adverse events. The risk of such events occurring must be expected to increase the more widely it is prescribed, and the less experienced the physicians who prescribe it. In addition, the safety of Xyrem® in patients who have conditions other than cataplexy, and in healthy individuals has not been systematically studied to any significant extent
- In summary therefore while there is evidence that Xyrem® is effective for the treatment of cataplexy and while there is a clear medical need for the drug, the small clinical trial safety database, the narrow margin of safety and the risks of abuse and misuse all call for approval to be conditional on a risk

management system that is somewhat more stringent than that proposed by the sponsor. Key additional elements of such a system should include

- Dispensing of the drug exclusively to patients with a diagnosis of cataplexy confirmed by their physicians
- Commitment by the sponsor to a detailed plan for active post-marketing surveillance for instances of diversion, abuse, misuse and adverse events of special concern
- Clear statements in the approved label, patient information sheet and patient and physician educational materials about the nature of the drug (i.e., that it contains the same active ingredient as illicitly-used GHB), the limited experience with the drug during development, the potentially serious toxicity of both therapeutic doses and overdoses
- Use of Subpart H of the Accelerated Approval regulations (21 CFR 314.500) so as to provide a means of restricting distribution of the drug and for enforcement of the risk management program. Justification for institution of these regulations is as follows
  - Xyrem® is intended to treat a serious disease (cataplexy)
  - Xyrem® provides meaningful benefit to patients over existing treatment
  - Xyrem® can be used safely only if its distribution or use is restricted

- Overall, this application can be considered to have provided sufficient evidence for the efficacy and safety of Xyrem® to justify an approvable action. For the Agency to proceed later to actual approval would, in my opinion, require the submission of additional data (see Recommendations) and agreement on an adequate risk management program as outlined above. It should be added that, in this reviewer's opinion, the benefit-versus-risk equation for Xyrem® as a treatment for cataplexy is at the present time only slightly tilted in favor of benefit and in favor of an approvable (versus a not-approvable) status.

20. Recommendations

I would recommend that this application be granted approvable status at the present time.

This recommendation is conditional upon the sponsor agreeing to the expanded risk management plan outlined by this reviewer above. Critical to this plan is that dispensing of the drug be restricted to those patients confirmed by their physicians as having cataplexy, and be carried out by a single central pharmacy.

Prior to considering final approval the following additional information should be requested from the sponsor and reviewed by this Division.

- A safety update for the ongoing Orphan studies of Xyrem®, OMC-SXB-7 and _____ should be provided (the latter study is intended to assess the efficacy of Xyrem® in treating excessive daytime sleepiness). The last safety update was submitted on 2/1/01 and had a cut-off date of 9/30/00. The status of 11 patients who were enrolled in the Scharf study and had not entered the treatment IND study #OMC-SXB-7 as of 5/31/99, needs to be accounted for

to the maximum extent possible. These patients are listed below by ID# and initials

01-004/
01-027/
01-054/
01-065/
01-228/
01-240/
01-262/
01-269/
01-283/
01-268/
01-256/

- An analysis of all patients in the entire safety database listed as having "sleepwalking", as an adverse event. Such an analysis should include detailed clinical descriptions of the episodes, whenever they can be obtained from source documents, and the following additional elements: demographics, relationship to dose, frequency, seriousness, whether leading to medication discontinuation, further evaluations (e.g., EEGs and polysomnograms) and outcome.
- The total number of patients exposed for any period of time to the following doses: 9 g/day; 6 to < 9 g/day.

Ranjit B. Mani, M.D.
Medical Reviewer

J. Feeney, M.D. _____

rbm 6/15/01
cc:
HFD-120
NDA 21196
Homonnay

EFFICACY REVIEW OF NEW DRUG APPLICATION

NDA	21196
Sponsor:	Orphan Medical, Inc.
Drug:	Xyrem
Proposed Indication:	Narcolepsy
Material Submitted:	Original New Drug Application
Correspondence Date:	9/30/00
Date Received / Agency:	10/3/00
Date Review Completed	6/15/01
Reviewer:	Ranjit B. Mani, M.D.

Table of Contents

2. Background

2.1 Indication

The sponsor wishes to pursue the following claim:

"Xyrem® (sodium oxybate) oral solution is indicated to reduce the incidence of cataplexy and to improve the symptom of daytime sleepiness in patients with narcolepsy."

Narcolepsy is a chronic neurological disorder characterized by excessive daytime sleepiness, disturbed nocturnal sleep, cataplexy, sleep paralysis and hypnagogic hallucinations. The prevalence of this condition in the United States, as per a publication cited by the sponsor, is between 0.02% and 0.07%. According to the sponsor, current treatments for this condition are limited in effectiveness and have frequent undesirable adverse events.

2.2 Important Information from pharmacologically related agents

None.

2.3 Administrative History

This drug has been developed by Orphan Medical, Inc. for the treatment of narcolepsy under IND # —— and Treatment IND # ——. Data obtained from individual sponsor-investigator INDs #s —— (M. Scharf) and —— (L. Scrima) have also been used in support of this application.

This drug product has been the subject of numerous meeting and items of correspondence involving the following: the current sponsor; this Division; the Controlled Substances Staff; the Division of Anesthetic, Critical Care and Addiction Drug Products; the Division of Orphan Drug Products; and other bodies. These contacts are too numerous to summarize in this review

2.4 Proposed Labeling

The proposed labeling for this drug is reviewed separately

2.5 Foreign Marketing

Currently, this drug product has not been marketed in any country. However, according to the sponsor

- Gamma-OH® an injectable oxybate preparation is marketed as an adjuvant anesthetic and sedative in France
- Somsanit® an injectable oxybate preparation is marketed as a sedative in Germany
- Alcover® an oxybate containing oral solution (175 mg/mL) is marketed in Italy for the treatment of alcohol withdrawal
- A powdered form of GHB is sold by —— of South Africa via the Internet, but **NOT** in the following countries: Australia, New Zealand, Norway, South Africa and the United States

For may years GHB was distributed in this country as a health food product under a variety of trade names. However, in 1990 it was removed from the market after a number of reports of adverse reactions.

2.6 Miscellaneous Background Information

In the popular media there have been many reports over the last few years of instances of overdose with illegally-manufactured GHB. A number of anecdotal single case reports/case series of a similar nature have also been published in the medical literature. There have also been similar reports linked to the use of related compounds such as gammabutyrolactone and 1,4-butanediol.

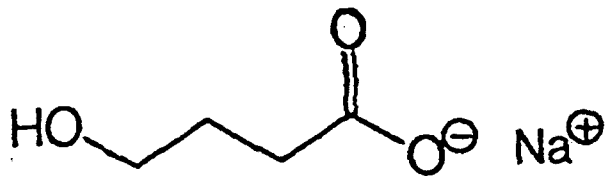
According to the sponsor, GHB users in this country derive the drug from the following sources

- Purchase from illegal vendors, including those selling the drug over the Internet
- By home manufacture: both recipes and starting materials are easily available

Public Law 106-172 (passed by the United State Congress) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements for the GHB drug product studied under an FDA-approved IND. Upon marketing approval from the FDA being received, the GHB drug product would become a Schedule III agent with Schedule I penalties for illicit use All other GHB containing products would remain Schedule I agents

3. Chemistry, Manufacturing and Controls

Gamma-hydroxybutyrate is a short chain fatty acid normally found in a variety of mammalian tissues, including the human brain, where it is a metabolite of gamma-aminobutyric acid. The chemical structure of the sodium salt of this compound is as depicted below:



The drug product is a 500 mg/mL solution. It is composed of sodium oxybate, purified water, DL-malic acid, and sodium hydroxide.

The drug product is supplied in a ——— PET amber bottle, sealed with a child-resistant camp. Additional items supplied with the bottle include

- A Press-In-Bottle Adapter (PIBA Well)
- A dispenser (Exacta-Med®)
- 2 child-resistant dosing cups

The PIBA Well will be placed into the solution by the pharmacist dispensing the drug. The drug product, PIBA Well, dispenser and dosing cups will be packaged in a carton when supplied to the patient

4. Toxicology

Salient items that I have derived from a summary provided by the sponsor are below:

- The sponsor did not conduct any acute toxicity studies but has cited literature reports of such studies instead. The sponsor has conducted repeated-dose toxicity studies in rats and dogs, reproductive toxicity studies in rats and rabbits, and mutagenicity studies. A 104-week carcinogenicity study in rats is ongoing.
- Effects of GHB in toxicology studies included reduced activity, prostration, ataxia, emesis, reduced food consumption and weight loss/weight gain. No evidence of organ toxicity was seen based on laboratory tests, and gross as well as microscopic pathological examination.
- GHB had no evidence of reproductive toxicity or mutagenicity
- In regard to carcinogenicity
  - The carcinogenicity of gammabutyrolactone (GBL), a precursor of GHB, has been studied under the National Toxicology Program. According to the sponsor "equivocal" evidence of carcinogenicity was demonstrated in male, but not female, mice based on increased adrenal medulla hyperplasia and increases in benign and malignant pheochromocytomas at a dose of 262 mg/kg/day
  - In bridging studies with GBL in the same strain of mice studied under the National Toxicology Program the sponsor has measured plasma levels of both GHB and GBL. Based on these plasma levels the sponsor has concluded that systemic exposure to GHB is similar whether GBL or GHB is administered, and that the National Toxicology Program studies are therefore valid as an appropriate evaluation of GHB. These studies were discussed with the Agency
  - A 104-week rat carcinogenicity study is currently ongoing

5. Clinical Data Sources

5.1 Sources Of All Data In Integrated Summary of Safety

5.1.1 Study Type

A total of 15 clinical trials are included in the Integrated Summary of Safety. The sponsor has grouped these studies into 4 separate pools which are outlined below. Safety data for each of these pools are described separately by the sponsor. Note that the sponsor has not included controlled clinical trials under a separate heading

5.1.1.1 Integrated Clinical Trials

A total of 402 patients participated in these trials; some of these patients participated in more than one trial. 3/402 patients received placebo only.

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks
OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	4 weeks*

*GHB and placebo were each used for 4 weeks

Further details about the above extension studies are below

Study #	Comments
OMC-GHB-3	Extension to OMC-GHB-2.
OMC-SXB-6	Treatment naïve patients (except for a single patient previously in OMC-GHB-2 and OMC-GHB-3)
OMC-SXB-7	Extension to OMC-GHB-3 (52 patients) OMC-SXB-6 (30 patients) Scharf Study (63 patients) The numbers in parentheses in this cell refer to the number of patients entering OMC-SXB-7 from each study

5.1.1.2 Lammers Trial

25 patients participated in this randomized, double-blind, placebo-controlled, cross-over trial of 4 weeks' duration (GHB and placebo were each used for 4 weeks).

5.1.1.3 Long-Term Clinical Trial (Scharf)

This long-term open-label study involved 143 patients and has lasted about 16 years

5.1.1.4 Integrated Pharmacokinetic Trials

A total of 144 subjects/patients have been enrolled in these trials which are listed in the table below. All were single dose-studies. With the exception of those enrolled in Studies OMC-GHB-4 and OMC-SXB-10 (total of 19 narcoleptic patients) all were healthy volunteers (total of 125 subjects)

Study #	Number of subjects/patients
OMC-GHB-4	6*
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13**
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

*The 6 narcoleptic patients participating in this study also enrolled in the Scharf study
**The 13 narcoleptic patients participating in this study also enrolled in OMC-SXB-6

5.1.2 Number Of Unique Narcoleptic Patients And Healthy Subjects In Integrated Summary Of Safety

I had obtained a clarification from the sponsor regarding the numbers of unique patients and healthy subjects in the Integrated Summary of Safety. The details are below

5.1.2.1 Unique Narcoleptic Patients

The number of unique narcoleptic patients participating in clinical trials of GHB is listed in the table below

Study Grouping	Number of Patients
OMC-GHB-2/OMC-GHB-3	133
OMC-SXB-6/OMC-SXB-7	183

Study Grouping	Number of Patients
Scrima	20
Lammers Trial	25
Scharf Trial	143
TOTAL	**504**

NOTE: The narcoleptic patients who participated in the pharmacokinetic trials OMC-GHB-4 (6 patients) and OMC-SXB-10 (13 patients) also participated in the Scharf and OMC-SXB-6 trials. These patients are counted in the above table under the Scharf and OMC-SXB-6 trials

5.1.2.2 Unique Healthy Subjects

The number of unique healthy subjects participating in clinical trials of GHB are in the following table. All these trials were pharmacokinetic.

Study #	Number of subjects/patients
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13
TOTAL	**125**

5.1.3 Demographics

Demographics are summarized according to the study pools used by the sponsor in this summary

5.1.3.1 Integrated Clinical Trials

Demographics for all Xyrem®-treated patients are summarized below. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	402	46.1	15.22	13.9-81.1
Weight (kg)	397	83.9	20.22	47.0-175.0
Height (cm)	396	170.3	10.33	129.0-206.0
Gender	402	Males 43% /Females 57%		

Demographics for the 3 patients treated exclusively with placebo are summarized below

Variable	Number	Mean	Standard Deviation	Range
Age (years)	3	37.5	14.43	26.1-53.7
Weight (kg)	3	90.0	15.72	76.0-107.0
Height (cm)	3	168.3	4.62	163.0-171.0
Gender	3	Females 100%		

5.1.3.2 Lammers Trial

The following table illustrates the demographics for all 25 patients in the study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	25	40	14	16-65
Weight (kg)	24	79	10	63-92
Height (cm)	24	175	7	157-187
Gender	25	Males 52% /Females 48%		

5.1.3.3 Scharf Trial

The following table illustrates the demographics for all 143 patients in this study. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range

Variable	Number	Mean	Standard Deviation	Range
Age (years)	143	45.3	14.5	13.0-75.0
Gender	143	Males 55.9% /Females 44.1%		
Race	143	Caucasian 88.8%/Afro-American 1.4%/ Unavailable 9.8%		

5.1.3.4 Integrated Pharmacokinetic Trials

The following table illustrates the demographics for all 144 subjects in these 8 studies. The table is derived from one supplied by the sponsor

Variable	Number	Mean	Standard Deviation	Range
Age (years)	144	32.3	12.24	18.0-62.0
Weight (kg)	144	73.0	11.28	50.8-114.0
Height (cm)	138	169.3	7.92	152.4-190.5
Gender	144	Males 40% /Females 60%		

5.1.4 Extent of Exposures

Total exposure and exposure by study pool (Integrated Clinical Trials, Lammers Trial, Scharf Trial and Integrated Pharmacokinetic Trials) is described below.

In all trials listed in the Integrated Summary of Safety, the number of patients and healthy subjects exposed to GHB for specified periods is illustrated in the table below

Period of Exposure to Xyrem	Number of Patients with Narcolepsy	Number of Healthy Controls
Any Exposure	504	125
≥ 6 months	354	0
≥ 1 year	179	0
≥ 2 years	127	0
≥ 5 years	79	0
≥ 10 years	46	0

Total exposure in patient-years in each of the study pools (except the pharmacokinetic trials) is listed in the next table

Pool	**Exposure to Xyrem® (Patient-Years)**
Integrated Clinical Trials	266.83
Lammers Trial	2.08
Scharf Trial	996.15
Total	**1265.06**

5.1.4.1 Integrated Clinical Trials

The cumulative duration of exposure by last dose for this group of trials is illustrated in the following table. The duration of exposure was calculated based on the 28-day month. Note that the "Any Exposure" row lists all patients who have been exposed to specific doses at any time, not just as the last dose.

Duration of Exposure	Total	Xyrem® last dose g/day				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	399	94	266	290	116	118
≥ 6 months	233	5	43	88	37	60
≥ 1 year	75	3	8	25	13	26
≥ 2 years	37	1	3	12	7	14

5.1.4.2 Lammers Trial

25 patients were exposed to a mean Xyrem® dose of 4.75 g/day (range 3.78 to 5.52 g/day) for 28 days

5.1.4.3 Scharf Trial

The cumulative duration by the Xyrem® dose administered for the longest duration is in the following table

Duration of Exposure	Total	Longest-used dose of Xyrem® (g/day)				
		3.0	4.5	6.0	7.5	9.0
Any Exposure	143	5	49	62	18	9
> 6 months	121	3	41	54	14	9
> 1 year	104	2	37	45	12	8
> 2 years	90	1	32	38	12	7
> 5 years	74	1	27	30	10	6
> 10 years	46	1	12	23	7	3

Note that 63 patients in the Scharf trial were subsequently also enrolled in OMC-SXB-7

5.1.4.4 Integrated Pharmacokinetic Trials

Exposure data for these studies was not calculated as these were all single dose studies. As noted earlier 144 patients/subjects were exposed to Xyrem® in these studies.

The dose(s) used in each these single-dose studies is indicated in the following table

Study #	GHB Total Dose	Number of subjects/patients
OMC-GHB-4	6.0 g	6*
OMC-SXB-8	4.5 g	36
OMC-SXB-9	4.5 g or 9.0 g	13
OMC-SXB-10	4.5 g	13**
OMC-SXB-11	4.5 g	36
OMC-SXB-12	3.0 g	15
OMC-SXB-14	4.5 g	12
OMC-SXB-17	4.5 g	13

*Narcoleptic patients
Note that the total dose of GHB was administered either as a true single-dose or 2 divided doses 4 hours apart

5.2 Cut-Off Date For Data In Integrated Summary Of Safety

- The only ongoing trial in the Integrated Summary Of Safety is OMC-SXB-7. The cut-off date for data in this trial is 12/31/99
- All other clinical trials in the Integrated Summary Of Safety are complete as are the safety data submitted with the NDA.

5.3 Primary Data Sources

These are studies conducted by Orphan Medical, Inc. They include the following

5.3.1 Efficacy And Long-Term Safety Studies

These are listed in the following table

Study #	Design	Number of Patients	Duration
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	136 patients	4 weeks
OMC-GHB-3	Open-label, uncontrolled, extension study	118 patients	Up to 24 months
OMC-SXB-6	Open-label uncontrolled study	185 patients	6 months
OMC-SXB-7	Open-label uncontrolled study	145 patients	Up to 24 months

5.3.2 Pharmacokinetic Studies

These are listed in the following table

Study #	Number of subjects
OMC-GHB-4	6
OMC-SXB-8	36
OMC-SXB-9	13
OMC-SXB-10	13
OMC-SXB-11	36
OMC-SXB-12	15
OMC-SXB-14	12
OMC-SXB-17	13

5.4 Secondary Data Sources

These are studies that have not been conducted by the sponsor and consist of efficacy and long-term safety studies only.

Study #	Design	Number of Patients	Duration
Scrima	Randomized, double-blind, placebo-controlled, cross-over	20 patients	4 weeks*
Lammers	Randomized, double-blind, placebo-controlled, cross-over	25 patients	4 weeks*
Scharf	Open-label extension study	143 patients	< 16 years

*GHB and placebo were each used for 4 weeks

5.5 Other Data Sources

The sponsor has also used 3 published reports of open-label studies of Xyrem® in narcolepsy to support the efficacy and safety of Xyrem®.

The outlines of these studies, including adverse event data, are summarized below. As these were open-label, uncontrolled studies, I have not summarized the efficacy data that was derived from them

Study	Scharf (1985)*	Broughton (1979)**	Broughton (1980)***
Design	Open-label, uncontrolled study	Open-label, uncontrolled study	Open-label, uncontrolled study
Maximum duration of treatment	30 weeks	20 months	7-10 days
Number of patients	30	16	14
Total nightly dose of Xyrem®	5-7 g	50 mg/kg	3.75 to 6.25 g
Adverse events	Protracted sleep paralysis (3 patients) Enuresis (1 patient) Increased sexual drive (1 patient)	"Hangover", urinary urgency, enuresis, dream-like confusional state prior to sleeping, abdominal pain, muscular weakness, left arm dysesthesia	"No serious toxic side-effects"

*Scharf MB et al. The effects and effectiveness of gamma-hydroxybutyrate in patients with narcolepsy. J Clin Psychiatry. 1985;:222-5. (Note that the patients reported in this publication are a subset of those included in the interim Scharf study report under this IND).

**Broughton R, Mamelak M. The treatment of narcolepsy-cataplexy with nocturnal gamma-hydroxybutyrate. Can J Neurol Sci. 1979;6:1-6.

***Broughton R, Mamelak M. Effects of nocturnal gamma-hydroxybutyrate on sleep/waking patterns in narcolepsy-cataplexy. Can J Neurol Sci. 1980;7:23-31.

5.6 Adequacy of Human Experience

- Xyrem® has been designated as an orphan drug product

- Based on the total number of narcoleptic patients exposed to Xyrem® in clinical trials derived from primary and secondary data sources (see Sections 5.3 and 5.4) and their duration of exposure (see Section 5.1.4)
  - The total number of unique patients exposed to this drug is below ICH guidelines
  - On the other hand the number of unique patients exposed to GHB for 6 month and 1 year periods is sufficient to meet these guidelines
- A separate review of the efficacy of Xyrem® indicates that the effective dose may range from 4.5 to 9 g/day, with the most conclusive evidence for efficacy at 9 g/day. The number of unique narcoleptic patients exposed to that dose range, and the duration for which they were exposed to that dose, is difficult to determine from the submission especially since a number of patients participated in more than one study grouping (e.g., Integrated Clinical Trials and Scharf study) and were exposed to several different doses
- The extent of human experience with this drug would not be considered adequate under ordinary circumstances, as per the ICH guidelines. However given that Xyrem® has been designated as an orphan drug, and that the narcoleptic population in this country is relatively small, a smaller safety database may be acceptable.

5.7 Data Quality and Completeness

The quality of the data available in this submission appears to be quite variable. The extent to which monitoring and data collection were systematic and accurate in the Secondary Data Source (see Section 5.4) studies is unclear.

6. Human Pharmacokinetics

The following pharmacokinetic summary is based on a summary supplied by the sponsor in this submission.

Orally administered GHB is rapidly absorbed with a t_{max} of 30 - 75 minutes and to a similar degree in narcoleptic and other patient populations; absorption characteristics are similar in males and females and are not altered by chronic dosing; t_{max} is delayed, at higher doses (suggesting a limited absorption capacity) and by the administration of food. C_{max} and AUC_{α} are reduced by the administration of the drug with food. The absolute bioavailability of the drug is < 30%.

The apparent volume of distribution divided by absolute bioavailability (V_2/F) ranges between 190 and 384 mL/kg. Inter-subject variability in the volume of distribution is high as indicated by the coefficient of variation which ranges between 16% and 84%. The drug readily crosses the placental and blood-brain barriers. Protein binding has been estimated at about 1%.

Less than 5% of an oral dose of GHB is excreted unchanged in the urine. Based on a review of the scientific literature the sponsor states that the end-product of metabolism, regardless of biotransformation pathway, is carbon dioxide. 2 main biotransformation pathways have been identified:

- A β-oxidation pathway
- A pathway involving the entry of succinic acid into the tricarboxylic acid cycle, through the initial formation of succinic semialdehyde

First-pass metabolism occurs with orally administered GHB, probably through the β-oxidation pathway, resulting in an oral bioavailability of < 30%. Intermediate compounds in the metabolic pathways for GHB do not appear to be pharmacologically active

The pharmacokinetics of GHB are non-linear. Plasma clearance is dose-dependent across the therapeutic range: following a total dose of 9 g (2 doses of 4.5 g each administered 4 hours apart) the apparent elimination half-life of GHB was 0.83 hours, which was approximately 40% longer than the mean elimination half-life following a total dose of 4.5 g (2 doses of 2.25 g each administered 4 hours apart). Chronic dosing with GHB did not alter its pharmacokinetics in a clinically significant manner: treatment with this drug for 8 weeks resulted in 13% and 16% increases in $AUC_{infinity}$ and C_{max}, respectively; these increases were not considered clinically significant.

There are no significant gender differences in the pharmacokinetics of GHB. Neither are there significant differences in pharmacokinetics between healthy subjects and narcoleptic patients, and between healthy patients and those who are alcohol-dependent. Oral clearance of GHB is altered in the presence of cirrhosis with or without ascites. Renal disease is not expected to alter the pharmacokinetics of GHB; studies in that setting have therefore not been carried out.

Formal studies indicated that GHB had no interactions with protryptiline, zolpidem and modafinil. In-vitro pooled human liver microsomal studies showed that GHB did not significantly inhibit or enhance the activities of human CYP450 isoenzymes.

7. Tabular Summary Of Key Efficacy Studies

4 studies have been used in this submission to support the efficacy of Xyrem® in the treatment of narcolepsy. These are summarized in tabular form below. For full details please refer to the NDA Efficacy Review

7.1 Study OMC-GHB-2

Study #	OMC-GHB-02 Orphan Medical			
Design	Randomized, double-blind, placebo-controlled, parallel-arm			
Duration	4 weeks			
Dosage	9 g	6 g	3 g	Placebo
Number randomized	35	33	34	34
Number completed	28	29	30	33
Main inclusion criteria	Narcolepsy for at least 6 months with both excessive daytime sleepiness and cataplexy			
Primary outcome measures	Total number of cataplexy attacks			
Main efficacy analysis (statistically significant results)	9 g dose superior to placebo, based on ANCOVA ($p = 0.0008$)			

7.2 Scrima Study

Study #	Scrima	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	50 mg/kg/day	Placebo
Number randomized	20	20
Number completed		
Main inclusion criteria	Excessive daytime sleepiness, a history of cataplexy with ≥ 10 cataplexy attacks over the 2 week baseline period and ≥ 2 REM onsets and a sleepiness index of ≥ 75 on the a multiple sleep latency test	
Primary outcome measures	Total number of cataplexy attacks per day	
Main efficacy analysis (statistically significant results)	GHB superior to placebo ($p = 0.013$)	

7.3 Lammers Study

Study #	N -1 (R 55 667 082) Lammers et al	
Design	Randomized, double-blind, placebo-controlled, cross-over	
Duration	4 weeks	
Dosage	4.75 g	Placebo

Study #	N -1 (R 55 667 082) Lammers et al	
Number randomized	25	25
Number completed	25 **	25 **
Main inclusion criteria	Excessive daytime sleepiness and at least one of the following: cataplexy, hypnagogic hallucinations, and sleep paralysis	
Primary outcome measures	Total number of cataplexy attacks Global therapeutic impression (patient) Global clinical impression (clinician)	
Main efficacy analysis (statistically significant results)	GHB superior to placebo on first two of above measures, numbered as above p = 0.002 (ANCOVA)*** p = 0.001 (McNemar's test) Not measured	

*This dose is the mean of the protocol-specified dose of 60 mg/kg/day

** The number included in the efficacy analysis was 24 for reasons which are described below in a more detailed review of the study

***This was not the protocol specified analysis. The ANCOVA was performed by the current sponsor several years after the study blind was broken and after the initial report of this study was published. The protocol-specified analysis (which was cited in the publication) was the Wilcoxon Signed Rank Test which yielded a p-value of 0.42, but which may have been an inappropriate analysis.

7.4 Study OMC-SXB-21

Study #	OMC-SXB-21 Orphan Medical	
Design	Randomized, double-blind, placebo-controlled, parallel-arm, RANDOMIZED WITHDRAWAL study after long-term open label treatment	
Duration	2 weeks (withdrawal phase)	
Study Arms	GHB	Placebo
Number receiving study drug	26	29
Number completed	26	29
Main inclusion criteria	Continuous treatment with GHB for narcolepsy for 6 months to 3.5 years	
Primary outcome measures	Total number of cataplexy attacks	
Main efficacy analysis (statistically significant results)	GHB superior to placebo, based on ANCOVA ($p < 0.001$)	

8. Integrated Review of Safety

8.1 Background and Methodology

The 15 clinical trials included in the Integrated Summary of Safety consist of the following groupings which I have already tabulated in greater detail in Section 5.1.1, but which are also listed in the table below

Study Grouping	Number of Patients/Subjects
Integrated Clinical Trials	402
Lammers Trial	25
Scharf Trial	143
Integrated Pharmacokinetic Trials	144

The patients/subjects participating in these trials comprised

- 504 unique patients with narcolepsy
- 125 unique healthy subjects

2 separate integrated analyses were performed: one for the Integrated Clinical Trials and the second for the Integrated Pharmacokinetic Trials.

Additional analyses were performed separately on the Lammers and Scharf trials for the following reasons, as stated by the sponsor

- The Scharf study was not included on account of its design and history
- The Lammers study had a "simplified method of data collection"

8.2 Deaths

8.2.1 Tabular Summary Of Deaths

11 deaths occurred, all in the Scharf study. These are tabulated below: the table was provided by the sponsor.

Pt #	Age	Sex	Cause of Death	Prior History	Time on Drug (yrs)	Last Dose of Test Drug	Date of Death
001	51	M	Colon Carcinoma	None	5.7	7/31/89	9/89
009	68	M	Cardiovascular disease and diabetes	Cardiovascular disease and diabetes	10.0	11/30/94	1/2/95
014*	49	M	Cardiac arrhythmia	Coronary atherosclerosis	8.6	10/31/95	11/26/95
017*	68	M	Cardiopulmonary arrest	Atherosclerotic heart disease	6.1	2/28/95	3/6/95
032*	74	F	Lung cancer	Persistent cold symptoms	10.2	10/19/94	10/26/94
053	57	M	Heart attack	Hypertension, left ventricular hypertrophy	10.4	7/31/94	10/10/94
200*	71	M	Metastatic carcinoma	Lung cancer	5.4	9/30/90	1990
202	56	M	Boating accident	None	1.2	3/8/86	7/10/86
232*	69	M	Bladder carcinoma	Bladder carcinoma (1981)	4.8	3/13/92	3/14/92
241	59	M	Lung cancer (small cell)	None	3.9	1/31/89	5/26/89
243	63	M	Heart Attack	Left branch block, left ventricular dysfunction	4.7	3/1/89	7/89

*Death occurred within 30 days of last dose of study drug

As the table above indicates only 5/11 deaths are listed by the sponsor as having occurred within 30 days of the last dose of study drug. In the case of one death (patient # 200) the exact date of death is not stated in the Case Report Form and presumably other source documents were used to document that the patient's death occurred within 30 days of the last dose of study drug

8.2.2 Conclusions Regarding Deaths

The listed cause of death (and a detailed review by me of patient narratives; and of Case Report Forms when needed), for all 11 patients do not suggest that their deaths could be causally related to use of GHB. Intercurrent unrelated illnesses and, in one instance, an accident appear to have been responsible

8.3 Serious Adverse Events

A total of 72 patients experienced serious adverse events. Their distribution by study grouping is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with serious adverse events
Integrated Clinical Trials	402	18 (4.5%)
Scharf Study	143	54 (37.8%)
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	0

These serious adverse events are further discussed under the 2 study groupings in which they occurred

8.3.1 Serious Adverse Events In Integrated Clinical Trials

As noted above 18 patients had serious adverse events in the Integrated Clinical Trials. These are tabulated below using investigator terms.

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Action Taken	Outcome Of Serious Adverse Event
0123 OMC-GHB-2	F 22.1	3.0	30	31	Removal of left ovarian cyst and ovary	Study drug temporarily stopped	Resolved
0181 OMC-GHB-2	F 60.1	0	-30	-29	Somniloquy	None	Resolved
0207 OMC-GHB-2	F 53.2	6.0	7	9	Acute confusional state	Study drug permanently discontinued	Resolved
0214 OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Study drug permanently discontinued	Unresolved
0231 OMC-SXB-6	M 67.9	9.0	119	119	Dizziness, confusion, nausea, vomiting, vertigo, weakness	Study drug permanently discontinued	Resolved
0238 OMC-SXB-6	M 64.3	4.5	170	171	Altered mental status, unresponsive, respiratory failure	Study drug permanently discontinued	Resolved
0801 OMC-GHB-3	M 40.6	9.0 Carry-forward dose	181	186	Myocardial infarction	None	Resolved
0814 OMC-GHB-3	M 55.7	4.5	172	255	Breast carcinoma	None	Resolved
0932 OMC-SXB-6	F 24.4	6.0	84	99	Auditory hallucinations	None	Resolved
0936 OMC-SXB-6	F 50.9	6.0	79	83	Kidney stone	None	Resolved
1030 OMC-SXB-6	F 34.8	6.0	32	None	Arthralgia	Study drug temporarily stopped	Unresolved
1032 OMC-SXB-6	F 41.7	None	-7	-6	Injury to toe	No change	Resolved
1305 OMC-GHB-3	F 73.6	9.0 Carry-forward dose	670	679	Agitation	Study drug temporarily stopped	Resolved
1433 OMC-SXB-6	F 57.0	6.0	18	18	Body aches after automobile accident	Study drug temporarily stopped	Resolved
1509 OMC-SXB-7	M 70.6	6.0	748	749	Gastroenteritis	Study drug temporarily stopped	Resolved
1630 OMC-SXB-6	M 59.7	6.0	54	57	Lower back pain	Study drug temporarily stopped	Resolved
1735 OMC-SXB-6	F 26.8	6.0	108	108	Miscarriage	Study drug permanently discontinued 6 weeks prior to adverse event	Resolved
2331 OMC-SXB-6	F 65.3	6.0	160	163	Pancreatitis Cholelithiasis	Study drug permanently discontinued	Resolved

In regard to the above list the sponsor has drawn attention to the following:

- 2 patients (#s 0181 and 1032) had serious adverse events prior to beginning GHB
- In 2 patients (#s 0181 and 0123) their "serious adverse events" were subsequently considered not to have been serious

Note that no serious adverse events occurred in placebo-treated patients in this grouping.

I have read the narratives, and where necessary the Case Report Forms, for the above patients. A further description is warranted in the following patients

8.3.1.1 Patient 0238 (Initials —)

This 65 year old man, participating in OMC-SXB-6, had been taking Xyrem® 4.5 g daily for 5 months. He had a background history of hypertension.

Immediately after his wife heard a loud noise, he was found comatose, flaccid, incontinent, bradycardic and hypoventilating. No convulsive movements had been witnessed. He required intubation and artificial ventilation. However the same day he awoke, was extubated and returned home. An EEG was normal; an echocardiogram showed ventricular hypertrophy with posterolateral wall hypokinesia, but with a satisfactory ejection fraction. A "cardiac event" was proposed as a cause for his symptoms by the hospital staff caring for him. However the Principal Investigator, after reviewing his hospital records considered the possibility that an inadvertent overdose with GHB was responsible for the episode was responsible for the episode. Study medication was permanently discontinued. Further information is not available.

8.3.1.2 Patient 0207 (Initials —)

This 53 year old woman participating in OMC-GHB-2 received Xyrem® 6 g daily. On Day 4 of treatment she developed nausea. Beginning Day 5 she became very talkative with pressured speech, and the next day was noted to be disoriented, agitated and to sleep poorly. Xyrem® was discontinued, the patient was treated with haloperidol and by the next day her confusion had resolved. An EEG was normal and a CT scan of the head showed minor temporal lobe asymmetry. The study drug was permanently discontinued.

8.3.1.3 Patient 0932 (Initials —)

This 24 year old woman who participated in OMC-SXB-6 had a history of depression dating back to 1994. Her dose of Xyrem® was increased from 4.5 g daily to 6 g daily. On Day 84 she experienced auditory hallucinations for which she was hospitalized and treated with olanzapine. Her dose of Xyrem® was then reduced to 4.5 g daily. Her hallucinations resolved and she was discharged after 14 days continuing with GHB for the remainder of the trial. Hospital discharge records indicated to her investigator that for the previous 5 years she had experienced repeated auditory hallucinations and had 2 psychiatric hospitalizations

8.3.1.4 Patient 1030 (Initials —)

This 34 year old woman participating in OMC-SXB-6 had a preceding history of lower back and knee pain for which she received acetaminophen. Her back pain was believed to be related to herniated intervertebral discs; further descriptions of her back and knee pain are unavailable. She was begun on Xyrem® in a dose of 4.5 g/day. On Day 4 of the