Study #	Frequency of vital sign testing
OMC-GHB-3	Baseline, 2 weeks and Months 1, 2, 4, 5, 6, 8, 10, 12, 14, 16, 18, 21 and 24
OMC-SXB-6	Screening, Week 2 and Months 2 and 6
OMC-SXB-7	Baseline and Months 6, 12, 18 and 24
Scrima	No provision for checking vital signs

8.7.1.2 Lammers Trial

There was no provision for recording vital signs during this trial

8.7.1.3 Integrated Pharmacokinetic Trials

Vital signs recorded and analyzed, when specified, included sitting and standing blood pressure, heart rate, respiration, body temperature and body weight.

Vital signs were to be checked in each of the single-dose pharmacokinetic trials as follows.

Study #	Frequency of Vital Sign Checks
OMC-GHB-4	Baseline and 60 hours after dosing
OMC-SXB-8	Baseline and 2, 4 and 8 hours after dosing
OMC-SXB-9	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-10	Baseline and 1, 3, and 8 hours after dosing
OMC-SXB-11	Baseline and 2, 6 and 10 hours after dosing
OMC-SXB-12	Baseline and 1, 2, 6 and 10 hours after dosing
OMC-SXB-14	Baseline and 2, 6, 10 and 24 hours after dosing
OMC-SXB-17	Baseline and 1, 2, 6 and 10 hours after dosing

8.7.1.4 Scharf Trial

There was no provision for checking vital signs in the protocol or Case Report Form.

8.7.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled Clinical trial: OMC-GHB-2 (this was the only controlled clinical trial in which vital signs were checked after administration of study drug)
- Integrated Clinical Trials
- Integrated Pharmacokinetic Trials

8.7.3 Standard Analyses and Explorations of Vital Sign Data

8.7.3.1 Controlled Clinical Trial OMC-GHB-2

The sponsor has provided a table that displays descriptive statistics for changes in vital signs across dose groups from baseline to Visit 6 (end of period of double-blind treatment). The mean changes seen were not clinically significant. The data suggested a dose-related decrease in weight and sitting diastolic blood pressure. An abbreviated form of the sponsor's main table, including only mean changes is reproduced below

Changes from baseline to Visit 6 in vital signs

Changes in vital signs	Placebo	GHB dose (g) 3	6	9
Weight (kg) - mean	0.69	-0.09	-0.34	-0.8
Sitting systolic blood pressure (mm Hg) - mean	1.41	3.56	-1.10	-0.31
Sitting diastolic blood pressure (mm Hg) - mean	2.09	0.53	0.77	-1.83
Standing systolic blood pressure (mm Hg) - mean	4.26	5.47	-1.55	0.00
Standing diastolic blood pressure (mm Hg) - mean	1.74	0.63	-0.55	-2.79
Pulse rate (bpm) - mean	-0.94	1.0	3.16	-1.76
Respiration (breaths per minute) - mean	-0.24	-0.87	-0.2	-0.19

The sponsor's main table also indicates that there were no clinically significant differences between the placebo group and the individual GHB dose groups in minimum and maximum changes for the above adverse events.

8.7.3.2 Integrated Clinical Trials

The sponsor has presented a table containing descriptive statistics for the change from baseline to last observation in vital signs. The tables indicate that mean changes for all parameters were very small and similar across all treatment groups. I have not reproduced these vital signs.

8.7.3.3 Integrated Pharmacokinetic Trials

Individual data listings have been made available for all pharmacokinetic trials except OMC-GHB-4; for the latter trial descriptive statistics have been made available for vital signs.

These data do not reveal any changes that could be considered clinically significant.

8.8 ECG

8.8.1 Extent of Electrocardiogram Testing During Development

The data below refer only to post-treatment electrocardiograms

8.8.1.1 Integrated Clinical Trials

Standard 12-lead resting electrocardiograms were performed.

The frequency at which electrocardiogram testing were intended to be checked (as per protocol) in these studies is indicated in the following table

Study #	Frequency of electrocardiogram testing
OMC-GHB-2	Screening and end of period of study drug administration
OMC-GHB-3	Baseline and Months 6, 12 and 18
OMC-SXB-6	Screening, and Month 6 (if medically indicated)
OMC-SXB-7	No provision for checking electrocardiograms
Scrima	No provision for checking electrocardiograms

8.8.1.2 Lammers Trial

There was no provision for checking electrocardiograms during this trial

8.8.1.3 Integrated Pharmacokinetic Trials

No post-treatment electrocardiograms were checked during these trials

8.8.1.4 Scharf Trial

A standard 12-lead electrocardiogram was to be checked at or prior to study entry, and annually thereafter

8.8.2 Selection of Studies for Overall Drug-Control Comparisons And Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2
- Integrated Clinical Trials
- Scharf trial

8.8.3 Standard Analyses and Explorations of Electrocardiogram Data

8.8.3.1 Controlled Clinical Trial: OMC-GHB-2

The number and percentage of patients in each treatment group whose values went from normal to abnormal in each treatment group between the baseline and Week 6 (end of double-blind period) visits is summarized in the following table

Treatment Group	Number	Patient ID #s
Placebo	2 (6 %)	512, 818
GHB 3 g	2 (6 %)	407, 1610
GHB 6 g	1 (3.5 %)	105
GHB 9 g	3 (11.5 %)	206, 217, 1309

Details of all 8 patients are summarized in the following table

Abnormal ECGs at Visit 6

Patient number	Visit 1 Interpretation	Visit 6 Comments on abnormality	Follow-up (for ECGs not labeled NCS at V6)
105	Within normal limits	Sinus bradycardia – not clinically significant	
206	Within normal limits	Consider left atrial enlargement	Not clinically significant as determined by site
217	Within normal limits	Sinus arrythmia, vertical axis	Not clinically significant as determined by site
407	Within normal limits	Normal sinus rhythm, nonspecific T wave abnormality	Not clinically significant as determined by site No Change from baseline, CRF incorrectly reported
512	Within normal limits	QRS axis range 0 to 14 horizontal axis- not clinically significant	
818	Within normal limits	Sinus tachycardia - not clinically significant	
1309	Within normal limits	OCL unifocal ventricular extra beat (VPC), RR complex V1-V2 indicate primary right bundle branch block with QRS 0.10-0.11 seconds	ECG was repeated on 12/30/97 and read by It was interpreted as Borderline ECG Within normal limits
1610	Within normal limits	Nonspecific T-wave abnormality in anterior-lateral leads when compared with ECG 08/08/97 per — — - change possibly due to hypokalemia - not clinically significant	

None of the above electrocardiogram abnormalities was felt to be clinically significant.

8.8.3.2 Integrated Clinical Trials

The sponsor has presented shift tables for the categorical change from baseline to last observation in vital signs. The shift categories were:

Abnormal to abnormal	Within normal limits to abnormal
Abnormal to within normal limits	Within normal limits to within normal limits
Abnormal to not done	Within normal limits to not done

The tables indicate that no shifts of > 10% were seen for the entire population or for the "normal to abnormal" category in any single electrocardiogram parameter.

For the within normal limits to abnormal category the distribution was as follows

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	o	0	2	3	1	3	9
Total number in dose group	3	26	88	141	61	83	402

Note that all patients in each dose group did not have electrocardiograms done both at baseline and subsequently, the last row cannot therefore be used as a denominator to calculate percentages for the second row

8.8.3.3 Scharf Trial

All electrocardiograms in the study were categorized as being normal or abnormal and a shift table generated which demonstrates categorical change by dose group from baseline. This table is reproduced below.

ECG Shift	GHB dose (g) n (%) All Patients	3	4.5	6	7.5	9
Norm to Norm	9 (6.3)	0 (0.0)	3 (6.1)	4 (6.5)	2 (11.1)	0 (0.0)
Norm to Abn[1]	36 (25.2)	1 (20.0)	11 (22.4)	16 (25.8)	4 (22.2)	4 (44.4)
Abn to Norm[2]	5 (3.5)	0 (0.0)	3 (6.1)	2 (3.2)	0 (0.0)	0 (0.0)
Abn to Abn	39 (27.3)	0 (0.0)	13 (26.5)	19 (30.6)	5 (27.8)	2 (22.2)

[1]Patients included if they had a normal baseline ECG and had an abnormal ECG anytime while receiving GHB.
[2]Patients included if they had an abnormal baseline ECG and had a normal ECG anytime while receiving GHB.

Source: Section 15-Table 8

Note that of those patients who had baseline electrocardiograms, some had a single repeat recording whether others had multiple recordings done. The interval between recordings was highly variable.

Of the 36 patients who had electrocardiograms that were normal at baseline but abnormal later

- 28 patients had abnormalities that were considered "non-specific, benign and highly unlikely to be clinically significant"
- In the remaining 8 patients the abnormalities were considered to possibly be clinically significant, but probably not related to study medication. The sponsor has provided short descriptions of the conclusions(diagnoses) drawn for the electrocardiograms for these 8 patients. The diagnoses reached in these 8 patients were distributed in the following 4 categories: except for 1 patient each who were considered to have acute pericarditis and ischemic heart disease, the remainder had multiple electrocardiograms. No additional information is available for these patients and there is no evidence that an attempt was made to correlate electrocardiogram abnormalities with symptoms, physical signs or other cardiac tests in these patients.

Left ventricular hypertrophy	1 patient
Ischemic heart disease	3 patient
Conduction system disease	3 patient
Acute pericarditis	1 patient

8.9 Withdrawal Phenomenon and Abuse Potential

An separate review of this subject is being performed by the Controlled Substances Staff of this Agency

8.9.1 Background

As indicated earlier in this review, for many years GHB was distributed in this country as a health food product under a variety of trade names; in 1990 it was removed from the market by this Agency after a number of reports of adverse reactions.

Public Law 106-172 (passed by the United State Congress on February 1E, 2000) has allowed for the designation of GHB as a Schedule I agent, with exemption from the security requirements of that schedule 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 forms and uses of GHB-containing products would remain under Schedule I, except that use under an FDA-approved IND would be exempted (as noted above).

There have been many reports in the media, 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 (GBL) and 1,4-butanediol (1,4-BD), both of which are converted to GHB in the body.

According to the sponsor, illicit GHB users in this country obtain 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

8.9.2 Purposes For Which GHB Is Misused Or Abused

These are listed by the sponsor as follows:

- As a steroid replacement in the body building community
- As a sleep aid
- As an intoxicant
- As an aphrodisiac
- As a means of enhancing the effects of alcohol and stimulants
- As a "date-rape" drug (related to its sedative and alcohol-enhancing properties)

8.9.3 Clinical Psychological And Physical Dependence In Humans

The sponsor states the following.

- Sodium oxybate does not appear to produce strong psychological or physical dependence

- No formal studies have been conducted to assess dependence with GHB
- A few case reports have suggested that chronic high-dose GHB use outside a clinical setting can, when the drug is withdrawn, lead to an abstinence syndrome comprising insomnia, anxiety, tremors and hallucinations. In the same setting dose-escalation to maintain a clinical effect has also been described. Several case reports also suggest that users outside a clinical setting may sometimes increase their dose to maintain a clinical effect.
- However
  - When GHB was discontinued after 3- and 6-month clinical trials for the treatment of alcohol withdrawal, no abstinence syndrome was seen. However during the 6-month trial an escalation of GHB consumption and craving for that drug was reported in about 10% of patients
  - In a clinical study of GHB in 48 narcoleptic patients, lasting 9 years, no tolerance to the effects of GHB was observed.
- Anecdotal reports and controlled trials suggest a potential cross-tolerance or dependence with alcohol. In alcoholics GHB may not only reduce the symptoms of alcohol withdrawal but may also decrease the consumption of and craving for alcohol
- GHB also relieves the abstinence syndrome that follows spontaneous opiate withdrawal; a similar effect on precipitated opiate withdrawal is blocked by naloxone.

8.9.4 Rebound Symptoms With GHB Withdrawal

In the randomized, double-blind, placebo-controlled, parallel-arm trial OMC-GHB-2, the incidence of adverse events suggestive of REM rebound (sleep disturbance, hallucinations, abnormal dreaming), and the incidence of cataplexy was compared between the following 2 periods

- The period of up to 5 days prior to the completion of double-blind treatment
- A period of up to 5 days between the cessation of double-blind treatment and the post-treatment follow-up visit

The difference in the incidence of adverse events was reported by the sponsor not to be statistically significant. Comparative data are not provided by the sponsor.

The sponsor has however supplied listings of adverse events which might be suggestive of REM rebound during the withdrawal period. 6 patients experienced such adverse events (each patient experienced one adverse event). These are listed in the following table

GHB dose during double-blind phase	Adverse events during withdrawal phase
3 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
6 g/day	Abnormal dreaming (1 patient) Sleep disorder (1 patient)
9 g/day	Hallucinations (1 patient) Sleep disorder (1 patient)

All adverse events were mild and, except for the instance of "sleep disorder" seen in a patient who received 3 g/day previously (in whom the adverse event

lasted 7 days), lasted 1-2 days only. It is unclear exactly what the term "sleep disorder" refers to.

The sponsor also states that there was no tendency to rebound cataplexy during the short period of withdrawal.

8.9.5 Extent Of GHB Abuse In The United States

According to the sponsor

- Sodium oxybate abuse is mentioned relatively infrequently in Drug Abuse Warning Network reports compared with other sedative/hypnotics that are abused such as benzodiazepines
- Currently sodium oxybate abuse is too rare to be listed in any database
  - In the Drug Enforcement Administration June 1998 Drug/Chemical Review it was stated that 1000 encounters with GHB had been documented over an unspecified period of time
  - Only 32 cases of GHB misuse or abuse had been reported over an 18-month period ending December 1997 in a report presented at a February 1998 American Academy of Pediatric Sciences meeting
  - The Mid-Year 1999 Preliminary Emergency Department Data from the Drug Abuse Warning Network had no mention of GHB
- Only one GHB-related death was reported to the Drug Abuse Warning Network by participating medical examiners between 1992 and 1995; in this instance the death occurred in an individual who had concurrently used alcohol and GHB.

8.9.6 Pre-Clinical Studies Of Drug Abuse Potential

The sponsor has outlined the results of a battery of animal studies that have been done with GHB. These consist of studies of drug discrimination, reinforcing effects, and tolerance and dependence.

A full review of these studies is beyond the competence of this reviewer.

Based on these studies the sponsor has made the following conclusions:

- Drug discrimination studies consistently fail to show cross-substitution with abused depressant drugs such as the benzodiazepines and barbiturates, although there is evidence for some cross-substitution with ethanol over a narrow dose range
- Self-administration studies fail to show evidence for strong reinforcing effects
- Repeated administration of sodium oxybate may result in the development of tolerance.
- Overall, "based on preclinical studies alone, there is no compelling evidence that sodium oxybate represents a significant drug abuse hazard."

8.10 Human Reproduction Data

A single patient is reported to have become pregnant while taking GHB. She is described briefly in Section 8.3.1.5

8.11 Overdose

8.11.1 Background

Descriptions of the clinical effects of GHB overdose are derived almost entirely from anecdotal reports related to illegal use of the drug

Section 8.9.2 describes the circumstances under which GHB is used or abused.

When the above anecdotal reports are reviewed, the identification of the dose of GHB used and determining the causal relationship of the clinical syndrome described to GHB are both problematic for the following reasons.

- The sources of the drug are clandestine and varied, as are the starting materials used to manufacture the drug, and the dose ingested therefore unknown in most instances; in addition an evaluation of illegally manufactured sodium oxybate liquid samples has shown a high level of inconsistency of content.
- In a number anecdotal reports, precursor chemicals, i.e., gammabutyrolactone (GBL) and 1,4-butanediol have been ingested, rather than GHB to which the adverse events have been attributed. Although these precursor chemicals are converted to GHB in the body, their pharmacokinetics are different from GHB: for example, GBL is more lipid soluble and more rapidly absorbed
- Other drugs of abuse are frequently used concurrently including alcohol, methamphetamine, and MDMA. In such instances the adverse event has been attributed to GHB based, in most instances, on the clinical history alone; blood and tissue levels of GHB have been measured only rarely. Thus in those instances it has been difficult to know to what extent GHB contributed to the patient's clinical syndrome.

Of the 5 deaths reported in the medical literature and attributed to GHB consumption, only one was clearly linked to GHB use alone.

8.11.2 Clinical Presentation

According to the sponsor the clinical presentation of GHB overdose is influenced by the dose and frequency of ingestion, and most importantly, concurrent use of other drugs.

Patients presenting in a conscious state may be agitated, combative, anxious and confused, and may exhibit hallucinations. Varying degrees of obtundation may also be seen extending to deep coma that is unresponsive even to pain; deep coma has been associated with doses ranging from 2.5 g to 30 g. With an increased depths of unconsciousness the following may also be observed: bradycardia, hypotension, depressed respiration/Cheyne-Stokes breathing and hypothermia. Obtundation may be potentiated by the concurrent use of alcohol.

Other symptoms and signs may include dizziness, nausea, vomiting, myoclonus, blurred vision, visual field abnormalities, sluggish pupillary reactions, amnesia and hypotonia.

Symptoms may appear as early as 15 minutes after ingestion and may persist for 2 to 96 hours

Note that in the NDA safety database, 2 patients took, or are presumed to have taken overdoses. These patients are further described in Sections 8.3.1.1 and 8.3.2.2.

A further instance of Xyrem® overdose has been reported in the 120-Day Safety Update (see Section 13.10.4)

8.11.3 Treatment

According to the sponsor the treatment of GHB overdose is primarily symptomatic and supportive. The measures to be instituted include

- care of the airway, with intubation and artificial ventilation as needed
- consideration of gastric aspiration and lavage with activated charcoal
- measurement of blood levels of GHB.

While flumazenil and naloxone are ineffective for the treatment of GHB intoxication, intravenous physostigmine has been reported anecdotally to produce rapid reversal of obtundation.

9. Study OMC-SXB-20

This was an open-label study that was intended to evaluate the effects of 4 doses of Xyrem® on sleep architecture. The study report was submitted on 12/16/00, i.e., after the original NDA submission. The sponsor desires that the results of this study be included in labeling.

A brief outline of the study protocol and safety data from this study are presented below.

9.1 Objectives

9.1.1 Primary

The primary objective of this study was to characterize the polysomnographic sleep architecture in narcoleptic patients at 4 GHB doses: 4.5 g, 6.0 g, 7.5 g and 9 g daily

9.1.2 Secondary

The secondary objectives of the study were to

- Assess the effect of Xyrem® on sleep as measured by the Epworth Sleepiness Scale
- Assess the effects of Xyrem® on common symptoms of narcolepsy as measured by the Narcolepsy Symptoms Assessment

- Assess EEG measures of wakefulness under soporific conditions using the Maintenance of Wakefulness Test
- Assess the safety of Xyrem®

9.2 Design/Summary of Investigational Plan

This was an open-label uncontrolled study divided into 2 phases. Stimulant medication was maintained at a constant level during the trial

9.2.1 Phase I

This phase lasted 4 weeks

- In the initial 2 weeks of this phase patients were withdrawn from tricyclic antidepressants, selective serotonin re-uptake inhibitors and hypnotics
- In the last 2 weeks of this phase patients remained free of tricyclics

An overnight polysomnogram was performed at the beginning and end of this phase. The Epworth Sleepiness Scale questionnaire was administered at about the time of each polysomnogram

9.2.2 Phase II

This phase began with the patient receiving 4.5 g of GHB nightly for the initial 4 weeks. At the end of this period the dose was increased to 6.0 g nightly and further to 7.5 g nightly and 9 g nightly at 2 week intervals. Each total nightly dose of GHB was administered in 2 equal divided doses 2.5 to 4 hours apart.

Overnight polysomnograms on the night of the first dose of Xyrem® and on the last night of each dose. The Epworth Sleepiness Scale was administered at the end of each dosing period

9.3 Duration

10 weeks

9.4 Sample Size

20-30 planned

9.5 Key Inclusion Criteria

- Informed consent
- Age ≥ 18 years
- American Sleep Disorders Association criteria for narcolepsy
- Use of stable doses of tricyclic antidepressants or selective serotonin re-uptake inhibitors for narcolepsy for at least 3 weeks. If taking stimulants must have been on a stable dose for at least 3 weeks
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential must be using effective contraception and must continue this treatment during the study
- Adequate support for duration of trial

9.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of tricyclic antidepressants or selective serotonin re-uptake inhibitors for depression or for any indication other than narcolepsy
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- History of psychiatric disorders that would preclude study participation
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1,5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of sodium oxybate within the preceding 30 days
- Use of any investigational drug within the preceding 30 days
- No clinically significant history of head trauma, seizure disorder or previous intracranial surgery
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Use of medication for narcolepsy during baseline period, other than a stable dose of stimulant medication ("stable dose" defined as one without any significant change in dose for the 5 - day period just prior to the baseline period)
- Use of hypnotics, tranquilizers, antihistamines (except for the non-sedating variety of such drugs) and clonidine at the start of the baseline period.

9.7 Dosage

See Section 9.2

9.8 Outcome Measures

9.8.1 Primary Efficacy Measures

The following objective overnight polysomnogram parameters

- Wake After Sleep Onset (WASO) in minutes following the first and second dose of Xyrem and the summation
- Total Sleep Time (TST) in minutes following the first and second dose of Xyrem and the summation
- Stage 1 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 2 sleep time in minutes following the first and second dose of Xyrem and the summation
- Stage 3 & 4 sleep time in minutes following the first and second dose of Xyrem and the summation

- Rapid Eye Movement (REM) sleep time in minutes following the first and second dose of Xyrem and the summation
- Sleep latency in minutes following the first and second dose of Xyrem
- REM sleep latency in minutes following the first and second dose of Xyrem
- Stage shifts per hour following the first and second dose of Xyrem and an average
- Total awakenings following the first and second dose of Xyrem® and the summation
- Delta power in microvolts^2/Hz following the first and second dose of Xyrem and an average

9.8.2 Secondary Efficacy Measures

- Epworth Sleepiness Scale
- Narcolepsy Symptoms Assessment
- Maintenance of Wakefulness Test

9.8.3 Safety Measures

Adverse events, safety laboratory tests, vital signs, electrocardiograms and physical examinations

9.9 Analysis Plan

- Demographic variables at baseline were summarized as follows
  - Gender and race were summarized by the number of patients in each category
  - Age, height and weight were summarized by descriptive statistics
- Efficacy variables were analyzed as follows
  - Inferential statistics were performed for descriptive purposes only as per the sponsor
  - Quantitative polysomnogram variables and the Epworth Sleepiness Scale were analyzed using 2-way ANOVA with patient and dosage as the main effects
  - If a statistically significant difference was found among dose groups using ANOVA, pairwise comparisons using the least significant difference test were performed. If the assumptions for the above ANOVA were not satisfied the rank changes from baseline were analyzed using the ANOVA model. The significance of the mean change from baseline (end of Phase I) in each dose group was determined using a paired t-test or a Wilcoxon signed rank test
  - For the above analysis the level of statistical significance was 0.05 (two-sided)
  - Variables for the narcolepsy symptom questionnaire measured as a change from the beginning of Phase I were presented by number and percentage of patients
- Safety analyses were performed as follows
  - Adverse events were summarized by body system using COSTART term and by relationship to treatment, dose and severity
  - Changes from the beginning of Phase 1 to the end of the study in laboratory parameters were summarized using descriptive statistics
  - Changes from the end of Phase I to the end of the study in vital signs were summarized using descriptive statistics
  - Changes from the beginning of Phase I to the end of the study in electrocardiogram parameters were summarized

9.10 Results

9.10.1 Patient Disposition

- 27 patients were enrolled in the study
- 25 patients were treated with GHB
- 21 patients completed the study

9.10.2 Baseline And Demographic Characteristics

Baseline and demographic characteristics for all 25 treated patients are summarized below

Variable	Mean	Standard Deviation
Age (years)	52.6	8.77
Weight (kg)	84.2	16.36
Height (cm)	166.9	8.32

Gender: Males 28%; Females 72%
Race: Caucasian 92%; Black 8%

9.10.3 Tricyclic Antidepressants, Selective Serotonin Re-Uptake Inhibitors And Hypnotics At Baseline

These are summarized in the next table, copied from the submission.

Preferred Term	Total
Number of Patients	25 (100%)
Patients Receiving Medications	22 (88%)
Clomipramine	3 (12%)
Fluoxetine	5 (20%)
Fluvoxamine	1 (4%)
Paroxetine	2 (8%)
Protriptyline	1 (4%)
Sertraline	4 (16%)
Venlafaxine	6 (24%)

TCA = Tricyclic antidepressant. SSRI = Selective serotonin reuptake inhibitors.
All medications were completed prior to the start of treatment.

9.10.4 Protocol Deviations

These are summarized in the next table copied from the submission. The table applies to all 25 treated patients

Type of Protocol Deviation	No. of Protocol Deviations
Inclusion/exclusion criteria	6
Compliance	7
Concomitant medication	28
Study visit interval	17
Error in dosing medication	23
Efficacy measure	33
Safety measure	
Laboratory procedure	2
Other safety measure	2
Other	7
Total	125

9.10.5 Treatment Compliance

Treatment compliance at each dose level is summarized in the following table copied from the submission. Mean compliance at each dose level was high.

	Dose (g)				
Number of	4.5	6.0	7.5	9.0	Total
Patients	25	22	22	21	25
Compliance (%)					
N	25	22	22	21	25
Mean	98.9	98.5	92.7	88.3	94.9
SD	11.45	9.63	9.06	13.45	7.62
Median	100.0	95.0	95.0	93.0	96.7
Minimum					
Maximum					

9.10.6 Extent Of Exposure

The mean duration of treatment was 63.3 nights (standard deviation: 21.29)

9.10.7 Efficacy Results

See summary in NDA Efficacy Review

9.10.8 Safety Results

9.10.8.1 All Adverse Events

18 out of 25 (72% of) patients participating in the study reported at least 1 adverse event.

A summary of adverse events in several broad categories, by dose at onset, is provided in the next table, copied from the submission.

	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
All Events					
Patients with At Least One Adverse Event	10 (40%)	9 (41%)	6 (27%)	10 (48%)	18 (72%)
Patients with Serious Adverse Events	0	0	0	0	0
Patients with Related Adverse Events	6 (24%)	6 (27%)	5 (23%)	7 (33%)	13 (52%)
Patients with Severe Adverse Events	0	1 (5%)	0	0	1 (4%)
Patients Discontinued Due to Adverse Event	1 (4%)	0	1 (5%)	0	2 (8%)

Note that the patient listed in the table as having a SERIOUS adverse event did not in fact have one, according to the sponsor. 4 days prior to beginning study drug the patient was diagnosed to have a yeast infection and was treated with miconazole nitrate suppositories 5 mg daily. Her white blood cell count was elevated at 11.43 K/microliter at screening. After a single dose of Xyrem® 4.5 g she withdrew her consent to participate in the study and was not available for further visits or telephone contacts. I have reviewed the Case Report Form for this patient

The next 2 tables list treatment-emergent adverse events, by dose at onset, that occurred in ≥ 5% of patients in any dose group

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total(a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Patients With Adverse Events	10(40%)	9 (41%)	6 (27%)	10(48%)	18 (72%)
Body As A Whole	3 (12%)	3 (14%)	1 (5%)	2 (10%)	9 (28%)
Accidental injury	0	1 (5%)	0	0	1 (4%)
Back pain	1 (4%)	0	1 (5%)	1 (5%)	3 (12%)
Flu syndrome	0	1 (5%)	0	0	1 (4%)
Infection	0	1 (5%)	0	1 (5%)	2 (8%)
Cardiovascular System	0	0	1 (5%)	0	1 (4%)
Migraine	0	0	1 (5%)	0	1 (4%)
Digestive System	4 (16%)	3 (14%)	0	5 (24%)	8 (32%)
Anorexia	0	0	0	3 (14%)	3 (12%)
Nausea	1 (4%)	2 (9%)	0	2 (10%)	5 (20%)
Vomiting	1 (4%)	1 (5%)	0	1 (5%)	3 (12%)
Metabolic And Nutritional System	1 (4%)	2 (9%)	1 (5%)	0	4 (16%)
Edema	1 (4%)	2 (9%)	0	0	3 (12%)
Generalized edema	0	0	1 (5%)	0	1 (4%)
Musculoskeletal System	1 (4%)	0	0	1 (5%)	2 (8%)
Myasthenia	0	0	0	1 (5%)	1 (4%)
Nervous System	3 (12%)	2 (9%)	2 (9%)	3 (14%)	8 (32%)
Anxiety	0	0	1 (5%)	0	1 (4%)
Dizziness	0	0	0	1 (5%)	1 (4%)
Emotional lability	2 (8%)	0	0	0	2 (8%)
Paresthesia	0	0	0	1 (5%)	1 (4%)
Sleep disorder	0	0	1 (5%)	1 (5%)	2 (8%)
Somnolence	0	2 (9%)	0	0	2 (8%)

COSTART Preferred Term	Xyrem Dosage at Onset (grams)				
	4.5	6.0	7.5	9.0	Total(a)
Number of Patients	25 (100%)	22 (100%)	22 (100%)	21 (100%)	25 (100%)
Respiratory System	1 (4%)	1 (5%)	1 (5%)	0	3 (12%)
Bronchitis	0	1 (5%)	0	0	1 (4%)
Respiratory disorder	0	0	1 (5%)	0	1 (4%)
Sinusitis	0	1 (5%)	0	0	1 (4%)
Skin	1 (4%)	1 (5%)	0	0	2 (8%)
Contact dermatitis	0	1 (5%)	0	0	1 (4%)
Special Senses	1 (4%)	0	1 (5%)	0	2 (8%)
Taste perversion	0	0	1 (5%)	0	1 (4%)
Urogenital System	1 (4%)	0	2 (9%)	0	2 (8%)
Breast abscess	0	0	1 (5%)	0	1 (4%)
Urinary incontinence	1 (4%)	0	1 (5%)	0	2 (8%)

(a) Patients are counted only once in each category, and only once in each body system summary.

A dose response did appear to be present for some adverse events such as anorexia, nausea and dizziness

9.10.8.2 Deaths And Serious Adverse Events

There were no deaths or serious adverse events. As noted earlier, the sole serious adverse event listed in the table in Section 9.10.8.1 was not a serious adverse event at all.

9.10.8.3 Adverse Event Discontinuations

2 patients discontinued treatment on account of adverse events. They are described further below:

9.10.8.3.1 PATIENT # 17304

This 67 year old woman had a past history of a tonsillectomy and of lumpectomy and radiation therapy for right-sided breast cancer.

In Study OMC-SXB-20 she received Xyrem® in the following consecutive dosing regimes: 4.5 g/day for 35 days; 6 g/day for 14 days; and 7.5 g/day for 1 day. On Study Day 51, after receiving her first dose of Xyrem® 7.5 g/day she experienced an "increase" in obstructive sleep apnea (it is unclear if she had obstructive sleep apnea earlier, either

preceding or during the trial) at which time Xyrem® was discontinued. Her subsequent course is unknown.

9.10.8.3.2 PATIENT # 42305

This 56 year old woman had a past history of depression with onset > 3 years prior to participating in the study. On Study Day 10 while receiving Xyrem® 4.5 g/day the patient experienced a worsening of depression; this adverse event resulted in her discontinuing Xyrem® on Day 27. Her depression reportedly resolved by Day 35

9.10.8.4 Laboratory Data

Mean changes from baseline and isolated abnormal values that were noted in the hematology and clinical chemistry data did not appear to be clinically significant. I have reviewed the individual patient data listings.

9.10.8.5 Vital Signs

Based on the descriptive statistics and individual listings provided, changes in vital signs were minimal and not clearly dose-related. I have reviewed the individual patient data listings.

9.10.8.6 Electrocardiograms

Only 1 patient had an electrocardiogram that was considered normal at baseline and abnormal at the end of the study. This abnormality was eventually determined to represent an old inferior wall myocardial infarction.

5 patients had electrocardiograms that were abnormal both at baseline and at study end. Details of the abnormalities noted are not provided.

9.11 Reviewer's Comments

The spectrum of adverse events seen in this study are broadly similar to those seen in other clinical studies of Xyrem® and do not raise any special concerns.

10. Safety Data From Study OMC-SXB-21

This study was intended to assess the long-term efficacy of Xyrem® based on a randomized withdrawal paradigm. The study is of relevance to the safety of Xyrem® in that it evaluates the potential adverse consequences of the abrupt withdrawal of therapeutic doses of the drug, including the incidence of rebound cataplexy.

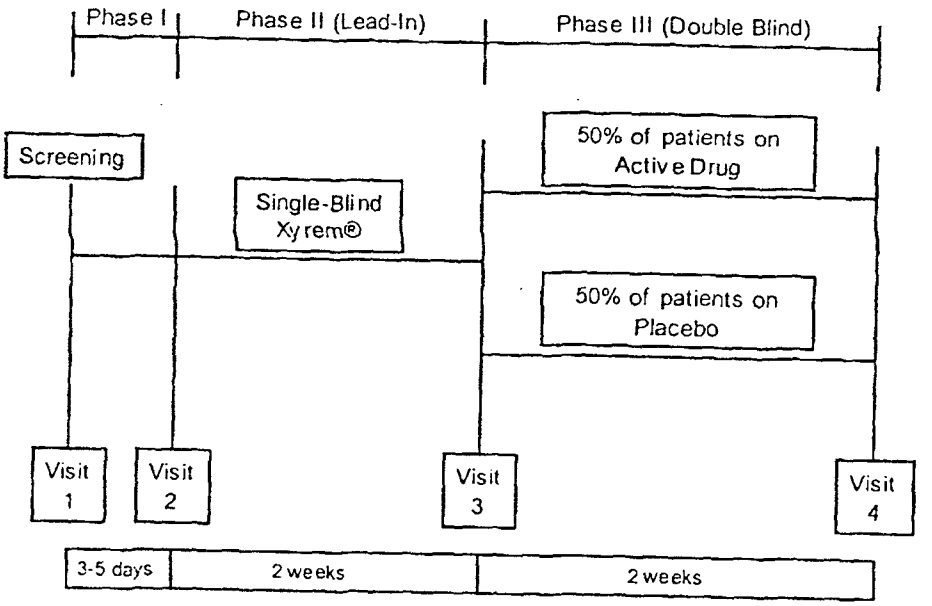
10.1 Brief Summary Of Study Protocol

10.1.1 Objective

To provide evidence for the long-term efficacy of Xyrem® based upon the return of cataplexy symptoms upon cessation of a minimum of 6 months of open-label treatment with active drug

10.1.2 Design

The design of the study is schematically summarized below



10.1.3 Duration

4 weeks (2 weeks of a double-blind withdrawal phase)

10.1.4 Sample Size

60 patients, with 30 in each treatment group in Phase 3, of the study will be included in the trial

10.1.5 Key Inclusion Criteria

- Informed consent
- Age ≥ 16 years
- Willing and able to complete the entire trial
- At least 5 cataplexy attacks per week prior to receiving any treatment (tricyclic antidepressants, selective serotonin uptake inhibitors, or Xyrem®) for cataplexy
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child bearing potential must be using a medically accepted means of birth control and must agree to continue such treatment for the duration of the study
- Treated continuously for the symptoms of narcolepsy with Xyrem® for at least 6 months, and not more than 3.5 years
- Willing to not operate a car or heavy machinery if the clinical investigator feels such a restriction is warranted
- Adequate support for the duration of the trial

10.1.6 Key Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Psychiatric disorders that would preclude participation in, or completion of, the trial
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 x upper limit of normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2nd or 3rd degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness, including sleep apnea syndrome (criteria specified)
- Occupation requiring variable shift or routine night shift work
- Use of tricyclic antidepressants, selective serotonin uptake inhibitors or medications for cataplexy other than Xyrem® in the 30 days prior to Visit 1 of the study
- Clinically significant history of head trauma; previous invasive cranial surgery; seizure disorder; use of anticonvulsant medication

10.1.7 Concomitant Medications

- The following medications were prohibited during the trial: selective serotonin uptake inhibitors and tricyclic antidepressants.
- Patients were to be cautioned regarding the use of opioid analgesics and skeletal muscle relaxants
- Alcohol was prohibited during the trial
- Over-the-counter medications needed careful review by the clinical investigator prior to use; non-sedating alternatives were to be used wherever possible
- Stable doses of stimulant medication could be used to treat excessive daytime sleepiness as clinically indicated

10.1.8 Dosage

Previously established dose of Xyrem® ranging from 3 to 9 grams daily

10.1.9 Schedule

- The visit schedule was as in the schematic above.
- The following were to be checked at Visit 1 alone: informed consent; selection criteria, medical history, cataplexy history prior to use of any medications, and "support systems".
- Physical examinations, including neurological examinations were to be performed at Visits 1 and 4
- Daily diaries were to be provided and/or checked at visits 2, 3, and 4. Diaries were to record cataplexy and adverse events.

- Concurrent medications, vital signs and adverse events were to be checked at every visit
- A pregnancy test were to be checked if applicable at Visit 1
- Routine hematology and chemistry were to be checked at Visits 1 and 4

10.1.10 Outcome Measures

10.1.10.1 Efficacy Measure

Frequency of cataplexy attacks

10.1.10.2 Safety

Adverse events, laboratory data

10.1.11 Analysis Plan

10.1.11.1 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

10.1.11.2 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

10.1.11.3 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 was to be analyzed using a paired t-test

10.1.11.4 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

10.2 Protocol Amendments

These have been incorporated into the above protocol outline.

10.3 Actual Analyses Performed

The analyses were performed according to the protocol

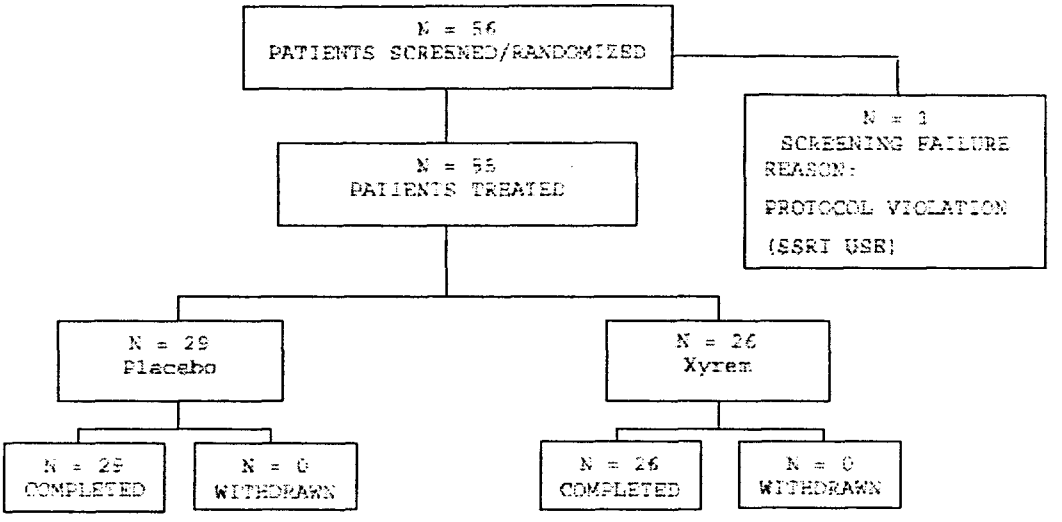
10.4 Efficacy Results

The full efficacy data are presented in this review as rebound cataplexy, which was seen in this study, is a manifestation of the abrupt withdrawal of GHB which is further described as part of this review.

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

10.4.1 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.

10.4.2 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.

10.4.3 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	0		4	4	
14	14	13		20	13	
15	4	3		4	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	23.9 ± 1.48	28.6 ± 2.50	14.4 ± 1.35	24.0 ± 1.50	28.4 ± 1.95
Range	12-18	21-28	24-36	13-28	21-28	24-36
Compliance (%)						
Mean ± SD	105.9 ± 17.24	106.1 ± 16.80	106.0 ± 17.44	99.7 ± 6.07	102.4 ± 26.12	101.1 ± 8.25
Range						

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

10.4.4 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.

Characteristics	Total (N=55)	Treatment Group Xyrem (N=26)	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	26.3 - 70.0	
Sex (n, %)				
Male	23 (42%)	8 (31%)	15 (52%)	0.172
Female	32 (58%)	18 (69%)	14 (48%)	
Weight (kg)				
Mean ± SD	80.6 ± 20.09	83.8 ± 24.31	77.6 ± 15.22	0.250
Range	54.0 - 142.0	54.0 - 142.0	58.0 - 127.0	
Height (cm)				
Mean ± SD	170.1 ± 10.25	169.6 ± 10.42	170.6 ± 10.24	0.716
Range	152.0 - 188.0	152.0 - 188.0	155.0 - 188.0	
Race (n, %)				
Caucasian	52 (95%)	23 (88%)	29 (100%)	0.035
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)	Placebo (N=29)	p-Value
Cataplexy attacks (2-week baseline)				
N	55	26	29	0.436
Mean	12.6	9.0	15.7	
SD	21.75	19.25	23.88	
Median	5.0	3.0	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.

10.4.5 Primary Efficacy Analysis

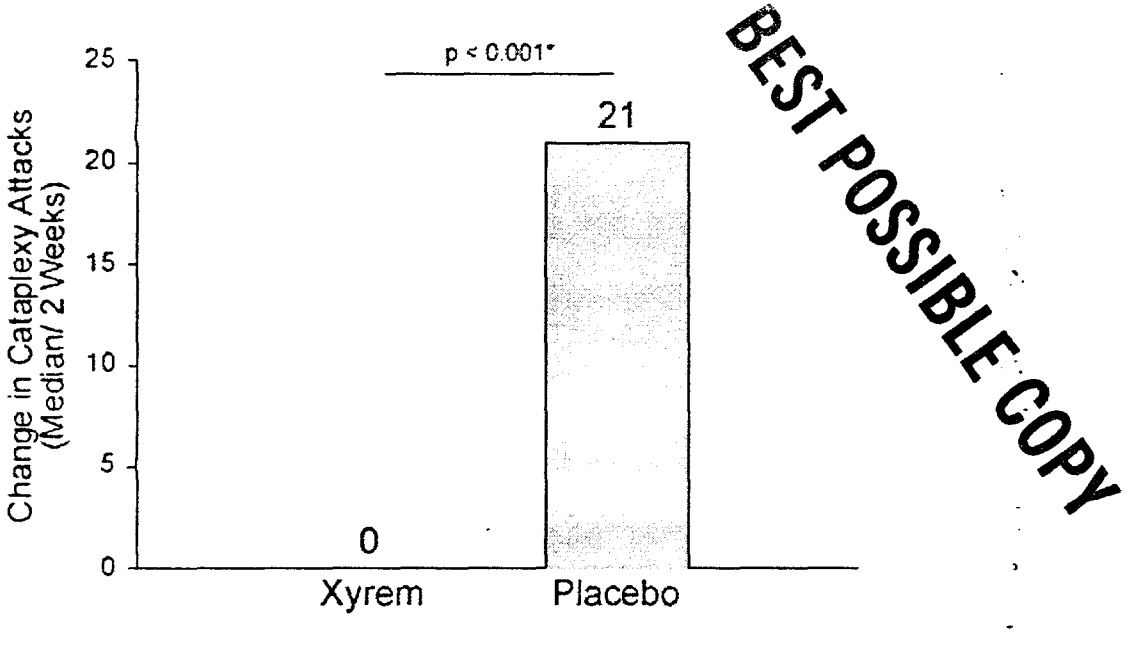
An intent-to-treat analysis was performed as specified in the protocol comprising all patients who received one or more doses of trial medication during the double blind withdrawal period and had recorded baseline and post-baseline efficacy measures

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	5.0 ± 19.25	12.6 ± 30.34	7.6 ± 20.73	15.7 ± 37.88	50.4 ± 81.03	34.6 ± 55.72
Median	0.9	2.1	0.0	4.0	21.0	21.0
Minimum						
Maximum						
Rank change**						
Mean ± SD			18.1 ± 32.65			36.9 ± 34.31*
Median			14.0			39.0
Minimum						
Maximum						

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

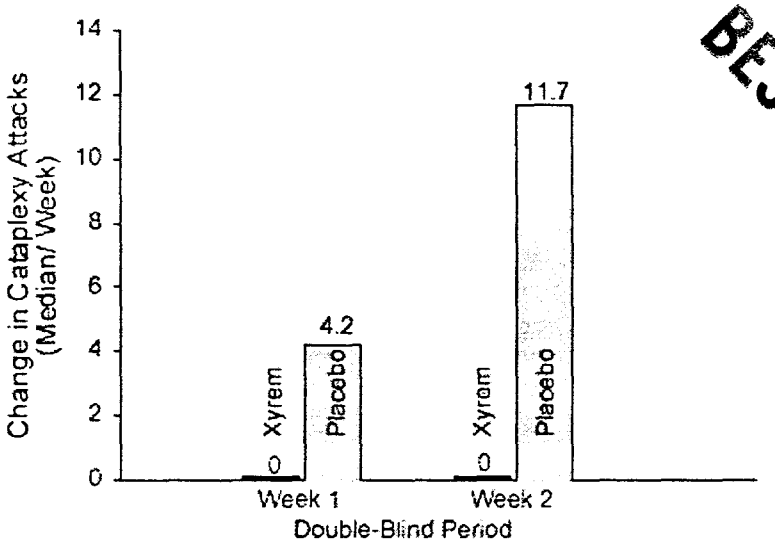


* $p < 0.001$, from ANCOVA model containing rank baseline, treatment group, and baseline-by-treatment group interaction.

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

Number of Cataplexy Attacks	Xyrem			Placebo		
	Phase II*	Phase III	Change	Phase II*	Phase III	Change
Week 1						
Number of Patients	26	26	26	29	29	29
Mean ± SD	4.5 ± 9.62	5.3 ± 11.84	0.8 ± 7.48	7.9 ± 19.64	21.1 ± 35.13	13.2 ± 22.02
Median	0.9	1.0	0.0	2.0	7.0	4.2
Minimum						
Maximum						
Week 2						
Number of Patients	29	28	26	29	29	29
Mean ± SD	4.5 ± 9.62	7.2 ± 18.66	2.7 ± 19.74	7.9 ± 19.64	29.7 ± 47.30	21.9 ± 35.16
Median	0.9	0.5	0.0	2.0	19.0	11.7
Minimum						
Maximum						

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

10.4.6 Analysis Of Secondary Efficacy Measures

This study had no secondary efficacy measures

10.5 Safety Results

10.5.1 Exposure

All 55 patients who received study medication were included in the safety analysis.

Information on the extent of medication compliance is described in the table in Section 10.4.3

Information on medication dose at study entry is further described in the table in Section 10.4.4.

26/55 (47%) of patients received their Xyrem® dose at study entry during the baseline and randomized withdrawal phases

29/55 (53%) of patients received their Xyrem® dose at study entry during the baseline phase of this study but received placebo during the randomized withdrawal phase

10.5.2 Deaths, Serious Adverse Events And Adverse Event Discontinuations

No deaths, serious adverse events or adverse event discontinuations are listed as having occurred during the study.

However a single patient (# 0232; Initials ——) developed an acute paranoid psychosis 3 days after participation in OMC-SXB-21 ended and after resuming GHB in OMC-SXB-7. A more detailed narrative for this patient is as follows:

This 44 year old woman with no previous history of psychiatric illness began taking Xyrem® on 4/1/99; from January 2000 onwards she took a stable dose of 9 g/day.

She entered OMC-SXB-21 from OMC-SXB-7. Concomitant medications at that time included modafinil, verapamil, ranitidine, aspirin and ibuprofen. She completed OMC-SXB-21 on 7/28/00 and re-entered OMC-SXB-7 taking 9 g/day again. After the blind for OMC-SXB-21 was broken it was confirmed that she had taken Xyrem® 9 g/day throughout that study as well.

On 8/1/00 she was hospitalized in an acutely paranoid state. She discharged herself from the hospital but was readmitted on 8/3/00. During her hospitalization she was treated with haloperidol, temazepam and clomipramine (clomipramine had been discontinued on 5/9/00). No GHB was administered after 7/30/00 and on 8/14/00 she told the investigator that she well. Clomipramine was apparently stopped and then resumed on 9/28/00 with a return of paranoia for a limited duration; this drug was however continued as apparently was modafinil. By 10/12/00 she had apparently returned to normal.

10.5.3 Other Adverse Events

The following tables copied from the submission display all adverse events that occurred during each phase of the study. The incidence of all adverse events during Phase III (the randomized withdrawal phase) are of particular interest; as the table indicates, the incidence of all adverse events in each treatment group was very low during this period. Of minor note is the presence of anxiety, dizziness, insomnia, "sleep disorder" and somnolence, each in 1-2 patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®, which might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be conclusive.

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group Xyrem (N=26) n (%)	 Placebo (N=29) n (%)
Phase I			
Patients with Adverse Events	**4 (7%)**	**1 (4%)**	**3 (10%)**
Body as a Whole	1 (2%)	0	1 (3%)
Accidental Injury	1 (2%)	0	1 (3%)
Metabolic & Nutritional System	2 (4%)	1 (4%)	1 (3%)
Alkaline phosphatase increased	1 (2%)	1 (4%)	0
BUN increased	1 (2%)	0	1 (3%)
Creatinine increased	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Hypertriglyc.	1 (2%)	0	1 (3%)
Nervous System	1 (2%)	0	1 (3%)
Peripheral neuritis	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Pharyngitis	1 (2%)	0	1 (3%)
Phase II			
Patients with Adverse Events	**9 (16%)**	**4 (15%)**	**5 (17%)**
Body as a Whole	3 (5%)	1 (4%)	2 (7%)
Asthenia	1 (2%)	1 (4%)	0
Headache	3 (5%)	1 (4%)	2 (7%)
Digestive System	2 (4%)	2 (8%)	0
Diarrhea	1 (2%)	1 (4%)	0
Nausea	1 (2%)	1 (4%)	0
Metabolic & Nutritional System	1 (2%)	0	1 (3%)
Hyperglycemia	1 (2%)	0	1 (3%)
Respiratory System	1 (2%)	0	1 (3%)
Rhinitis	1 (2%)	0	1 (3%)

Body System COSTART Term	Total* (N=55) n (%)	Treatment Group Xyrem (N=26) n (%)	 Placebo (N=29) n (%)
Phase II (continued)			
Skin	1 (2%)	0	1 (3%)
Fungal dermatitis	1 (2%)	0	1 (3%)
Pruritus	1 (2%)	0	1 (3%)
Skin benign neoplasm	1 (2%)	0	1 (3%)
Skin nodule	1 (2%)	0	1 (3%)
Urogenital System	1 (2%)	1 (4%)	0
Vaginitis	1 (2%)	1 (4%)	0
Phase III			
Patients with Adverse Events	**12 (22%)**	**3 (12%)**	**9 (31%)**
Body as a Whole	4 (7%)	1 (4%)	3 (10%)
Accidental injury	1 (2%)	0	1 (3%)
Chest pain	1 (2%)	1 (4%)	0
Headache	2 (4%)	0	2 (7%)
Cardiovascular System	1 (2%)	0	1 (3%)
Migraine	1 (2%)	0	1 (3%)
Heart-Lymphatic System	1 (2%)	0	1 (3%)
Lymphadenopathy	1 (2%)	0	1 (3%)
Metabolic & Nutritional System	1 (2%)	0	1 (3%)
SGOT increased	1 (2%)	0	1 (3%)
SGPT increased	1 (2%)	0	1 (3%)
Nervous System	5 (9%)	0	5 (17%)
Anxiety	2 (4%)	0	2 (7%)
Dizziness	1 (2%)	0	1 (3%)
Insomnia	1 (2%)	0	1 (3%)
Sleep disorder	1 (2%)	0	1 (3%)
Somnolence	1 (2%)	0	1 (3%)
Respiratory System	2 (4%)	1 (4%)	1 (3%)
Dyspnea	1 (2%)	1 (4%)	0
Pharyngitis	1 (2%)	0	1 (3%)
Skin	2 (4%)	1 (4%)	1 (3%)
Contact dermatitis	1 (2%)	1 (4%)	0
Rash	2 (4%)	1 (4%)	1 (3%)
Urogenital System	1 (2%)	1 (4%)	0
Urinary incontinence	1 (2%)	1 (4%)	0

* Patients are counted only once in each category.

10.5.4 Laboratory Data

The changes in hematology and clinical chemistry parameters may be summarized as follows

10.5.4.1 Mean Changes From Baseline To Last Observation

- Statistically significant changes from baseline were seen for
  - Monocytes (increase) and potassium (decrease) in the Xyrem® group
  - Total protein and albumin (decrease) and ALT (increase) in the placebo group
- Statistically significant differences between treatment groups for changes in baseline were seen for lymphocyte count and sodium
- Mean changes in each of the above categories were minor and inconsequential

10.5.4.2 Categorical Shifts From Baseline To Last Observation

All changes occurred in < 10% of patients in each treatment group and appeared to be of no consequence

10.5.4.3 Changes From Baseline In Individual Patients

No changes of clinical consequence were seen

10.5.5 Vital Signs

Descriptive statistics for changes in vital signs from baseline to last observation are summarized in the next table copied from the submission. As the table indicates these changes were inconsequential.

Parameter	Xyrem	Placebo
Number of Patients	26	25
[illegible] (bpm)		
Mean	3.8	-0.3
SD	12.57	11.64
Median	6.5	0.0
Minimum	[illegible]	
Maximum		
Respiration (breaths/min)		
Mean	0.1	0.7
SD	2.02	1.32
Median	0.0	1.0
Minimum		
Maximum		
Diastolic Blood Pressure (mm Hg)		
Mean	1.8	0.2
SD	9.42	6.92
Median	0.0	0.0
Minimum		
Maximum		
Systolic Blood Pressure (mm Hg)		
Mean	3.1	-3.2
SD	12.62	12.15
Median	5.0	0.0
Minimum		
Maximum		
Body Temperature (C)		
Mean	-0.2	-0.1
SD	0.59	0.79
Median	0.0	0.0
Minimum		
Maximum		
Body Weight (Kg)		
Mean	-0.5	1.0
SD	2.02	1.78
Median	0.0	0.0
Minimum		
Maximum		

10.6 Sponsor's Conclusions Regarding Safety

These may be summarized as follows

- The incidence and severity of adverse events was low during this trial
- Withdrawal symptoms such as anxiety occur infrequently on abrupt withdrawal of chronic therapeutic doses of GHB

10.7 Reviewer's Comments

I concur with the sponsor's conclusions

11. Key Information From Integrated Summary Of Safety And OMC-SXB-21 Safety Data

11.1 All Adverse Events

The most common adverse events that appeared to be related to GHB use (based on a higher incidence in Xyrem® treated individuals in placebo-controlled trials), and were more frequent with higher doses of that drug, included headache, "pain" (unspecified), nausea, dizziness, and urinary incontinence. These appeared to be both reversible and infrequent.

In the Integrated Clinical Trials grouping the incidence of all the above adverse events, with the exception of headache, nausea and dizziness, was relatively low. In the Scharf trial the incidence of all the above common adverse events was considerably higher, presumably reflecting the duration of the trial, at least in part.

The issue of whether urinary incontinence in patients treated with GHB could be caused by unrecognized seizures has been explored further by the sponsor to a limited degree (see Section 8.5.5.1). Currently there is no strong evidence that GHB in the doses proposed for clinical use is epileptogenic or that urinary incontinence in patients treated with GHB is caused by unrecognized seizures. However the data provided so far that attempts to address these issues is very limited and either possibility cannot be ruled out.

11.2 Deaths

None of the deaths in the Xyrem® safety database could be causally linked to the drug; all 11 deaths occurred in the long-term, open-label, Scharf study and appeared to be due to intercurrent illnesses or accidents unrelated to Xyrem®.

Death occurred in 7.7% of patients participating in the Scharf study

11.3 Serious Adverse Events

Serious adverse events that could be causally linked to GHB use, at doses in the therapeutic range, included various combinations of the following: nausea, vomiting, dizziness, confusion, restlessness, agitation, somnolence and generalized weakness. There has been no comment by the investigator as to whether the reported "generalized weakness" represented true muscle weakness or not.

In 2 patients who may have or did take a drug overdose manifestations included coma, respiratory depression, incontinence and a flaccid tone.

Note that serious adverse events were seen in 4.5% of patients who participated in the Integrated Clinical Trials and 37.8% of those who participated in the Scharf trial; the much higher incidence in the Scharf trial is probably due to the duration of that study.

11.4 Adverse Event Discontinuations

Adverse event discontinuations that could be causally linked to GHB use, at doses in the therapeutic range, included varying combinations of the following: headache, nausea, vomiting, fatigue, reduced initiative and libido, dizziness, impaired memory, confusion, restlessness, agitation, paranoia, hallucinations, urinary and fecal incontinence, somnolence and generalized weakness (including difficulty maintaining an upright posture). Adverse events in that constellation of symptoms were seen in 5/102 patients receiving GHB in the randomized controlled trial OMC-GHB-2 but were not seen in any of 34 patients who received placebo. Such adverse events do appear more common at higher doses of GHB.

Particularly noteworthy was a single healthy 39 year-old subject participating in a pharmacokinetic trial who developed dizziness, nausea, vomiting, respiratory depression and fecal incontinence after a single (and initial) oral dose of 4.5 g of GHB, administered after an overnight fast.

One patient who may have taken a drug overdose manifest with coma, respiratory depression, incontinence and a flaccid tone (this patient is also listed as having a serious adverse event).

The proportion of patients discontinuing treatment on account of adverse events in the Integrated Clinical Trials, Scharf trial and Integrated Pharmacokinetic Trials were 10.9%, 8.4%, and 1.4%, respectively.

11.5 Laboratory Data

- No clinically relevant or clinically-correlated changes in routine safety laboratory tests-hematology, clinical chemistry and urinalysis-were seen
- As described in detail earlier (see Section 8.5.5.2), elevated antinuclear antibody titers were seen in a proportion of patients participating in the Scharf study. Further details are as follows
  - This test was not protocol-specified and was performed at a variable frequency only after the detection of the index case, a patient reported to have rheumatoid arthritis. Testing was performed in a variety of laboratories
  - Antinuclear antibody testing was not performed in patients participating in any other clinical trials of GHB
  - 87 patients participating in this study had antinuclear antibody titers tested on one or more occasions. 26 of these patients (29.9%) had one or more positive titers
  - 2 patients discontinued from the Scharf study on account of positive antinuclear antibody titers.
  - The *sine qua non* of drug-induced lupus is stated to be the presence of appropriate symptoms associated with the presence of antihistone antibodies. 15 patients with positive antinuclear antibody titers had antihistone antibodies tested for: one of these patients was borderline positive, the others were negative.
  - Only one patient who had positive antinuclear antibody titers is reported to have had symptoms suggestive of a systemic rheumatic disease (the index patient who was diagnosed to have rheumatoid arthritis; see Section 8.4.2.3). This patient did not have antihistone antibody testing done

11.6 Electrocardiograms

No clinically pertinent changes in electrocardiograms were seen that could be attributed to Xyrem®.

11.7 Vital Signs

A mild dose-related reduction in weight and sitting diastolic blood pressure was seen in GHB-treated patients in the randomized, controlled trial OMC-GHB-2.

No other clinically significant changes in vital signs were seen.

11.8 Withdrawal Phenomena

- The randomized withdrawal study OMC-SXB-21 was primarily intended to assess the long-term efficacy of Xyrem®. Spontaneous and elicited adverse event indicated the presence of anxiety, dizziness, insomnia, "sleep disorder" and somnolence, each in 3-7% of patients who received placebo during that phase, whereas none occurred in those receiving Xyrem®. These data might suggest the infrequent presence of a mild withdrawal syndrome; however the total sample enrolled in this study and the number of those with these specific adverse events is too small to be anywhere near conclusive.
- In OMC-SXB-21 the frequency of cataplexy attacks was increased to a statistically significant level in those who received placebo during the withdrawal phase relative to those who received GHB during that period.
- In the randomized, controlled, parallel-arm efficacy trial OMC-GHB-2, adverse events that were noted during a 5-day period following drug withdrawal included abnormal dreaming, hallucinations and an unspecified sleep disorder (a total of 3/102 patients who received GHB during this study had these adverse events and only 1 patient, who had previously received a Xyrem® dose of 9 g/day, had hallucinations). The sponsor reports that the frequency of cataplexy was not increased during the 5-day observation period following drug withdrawal.
- Thus, in the small number of patients formally studied there is very limited evidence that narcoleptic patients receiving therapeutic doses of GHB experience more than infrequent and mild withdrawal symptoms, other than an increased frequency of cataplexy

12. Literature Review

In this NDA the sponsor has provided full publications as well as synopses for clinical studies of GHB that have been reported in the medical literature, but are not otherwise included in this application. These studies fall into 2 categories

- Studies conducted in healthy individuals
- Studies conducted for a variety of medical indications

These studies are summarized in tabular form below

12.1 Published Studies Conducted In Healthy Individuals

These are summarized in the following table

Author	Purpose Of Study	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range	Adverse Events
Yamada	Effect of GHB on EEG	10-30 mg/kg Intravenous Single dose	12	20-33	None reported
Lee	Evaluation of metabolism of GBL	1 g Oral Single dose	4	Not available	None reported
Palatini	Pharmacokinetics of GHB	12.5 to 50 mg/kg Oral Single dose	8	22-26	Nausea, dizziness, drowsiness

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; the reports by Yamada and Lee do not specifically state that no adverse events occurred.

12.2 Published Studies Conducted For Specific Medical Indications

There are also 17 additional published reports supplied by the sponsor that describe studies done for several specific medical indications:

- These indications include alcohol withdrawal, alcohol dependence, opiate withdrawal, insomnia, sleep apnea, nocturnal myoclonus, neonatal startle disease, and as an anesthetic agent.
- Only 6 of these studies were controlled
- These studies have exposed a total of 152 subjects/patients to mainly single, oral or intravenous doses of GHB.
- The maximum individual doses used were as follows
  Oral: 50 mg/kg or 4.5 g
  Intravenous:150 mg/kg
- In a single open-label study for opiate withdrawal in 2 patients the dose used was 30 or 50 mg/kg every 4 hours for 7-8 days
- Adverse events that were reported across these studies include dizziness, vertigo, nausea, headache, gastric ulceration, drowsiness, pneumonia, semi-liquid stools and muscle pain. However in a number of publications the authors did not either list adverse events or specifically state that no adverse events occurred.

These studies are summarized in the next table

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Gallimberti	Alcohol withdrawal syndrome	50 mg/kg Oral Single dose	11	28-63	Dizziness
Gallimberti	Reduction of alcohol consumption and alcohol craving	50mg/kg/day Oral 1 year	43	13-38	Vertigo, dizziness, nausea, headache and gastric ulceration
Gallimberti	Opiate withdrawal	25 mg/kg Oral Single dose	27	22-33	Dizziness
Oyama	Effects on fat and carbohydrate metabolism when used as an anesthetic	100-150 mg/kg Intravenous Single dose	10	14-48	None reported
Mamelak	Sleep induction in insomniacs	1-3 g/day Oral 3 nights	5	35-60	None reported
Mamelak	Insomnia	1-4.5 g/day Oral 3 nights	8	34-60	None reported
Van den	Anesthesia for	26.7 to 50 mg/kg	14	Not available	None reported

Author	Indication	Dose Of GHB	Number Of Subjects Exposed To GHB	Age Range (years)	Adverse Events
Bogaert	Cesarean section	Intravenous Single dose			
Mamelak	Narcolepsy and sleep apnea	60 mg/kg/day in 2 divided doses Oral 11 weeks	1	53	None reported
Strong	Reducing intracranial pressure in severe head injury	4 g Intravenous Multiple boluses	6	Not available	None reported
Hasenbos	Anesthesia for respiratory surgery	50 mg/kg Intravenous Single dose	1	64	Pneumonia
Scrima	Obstructive sleep apnea	50 mg/kg in 2 divided doses Oral 1 night	1	64	None reported
Scrima	Nocturnal myoclonus	50 mg/kg in 2 divided doses Oral 1 night	4	37-48	None reported
Bedard	Periodic leg movements in sleep in narcoleptic patients	2.25 g/day Oral 1 month	12	34-55	None reported
Ferrara	Pharmacokinetics in alcohol-dependent subjects	25 mg/kg b.i.d Oral Minimum of 7 days 50 mg/kg Oral Single-dose Day 10	10	34-56	Transient drowsiness
Series	Effects on slow-wave sleep in obstructive sleep apnea	60 mg/kg in 2 divided doses Oral 1 night	8	45 ± 2	None reported
Berthier	Neonatal startle disease	100 mg/kg (max) Intravenous Escalating doses (daily?) for 17 days	1	Newborn	None reported
Gallimberti	Opiate withdrawal syndrome	30-50 mg/kg every 4 hours for 7-8 days	2	24-30	Muscle pain; semi-liquid feces

The extent to which adverse events were systematically monitored for in these studies is unclear from the published reports ; except for the reports by Gallimberti (all), Hasenbos and Ferrara, the others do not specifically state that no adverse events occurred.

13. 120-Day Safety Update

13.1 Contents

This 120-Day Safety Update was submitted 2/1/01. It contains data from Study OMC-SXB-7 only. This was an open-label safety study conducted as part of Treatment IND # ~~~ in patients previously exposed to GHB.

The data presented in this safety update consists of adverse events reported from study initiation (3/3/99) to data cut-off (9/30/00).

An earlier interim report for this study dated 8/9/00 was submitted with the main NDA application. That report contained safety data through a cut-off date of 12/31/99.

Adverse event data from 3/3/99 through 12/31/99 are therefore contained in both the interim report of 8/9/00 (submitted with the original NDA) and in the 120-Day Safety Update.

Data from 2 additional studies, OMC-SXB-20 and OMC-SXB-21, were not in the original NDA, but were submitted on 12/16/00. OMC-SXB-20 was a small open-label study of the effects of 4 doses of Xyrem® on sleep architecture. OMC-SXB-21 was a study of the long-term efficacy of Xyrem® using the randomized withdrawal paradigm. By agreement with this Division data from these studies are not included in the 120-Day Safety Update since they have already been submitted. Safety data from both these studies have been described elsewhere in this review.

13.2 Outline Of Protocol For OMC-SXB-7

The following protocol outline was submitted with the treatment IND

13.2.1 Objectives

- To evaluate the safety of sodium oxybate when used in patients with narcolepsy for upto 24 months or until the time of marketing approval at 5 specified doses
- To evaluate changes in the primary narcolepsy symptoms during the study including cataplexy attacks, daytime sleepiness, inadvertent naps during the day, awakenings during the night, hypnagogic hallucinations, and sleep paralysis

13.2.2 Design

Open-label, uncontrolled study

13.2.3 Inclusion Criteria

- Informed consent
- Age ≥ 12 years
- Previous use of GHB for narcolepsy under an approved IND application: the trials that will feed into this study include OMC-GHB-3, OMC-SXB-6 and the Scharf trial under IND # [redacted], all of which are open-label studies: those in OMC-GHB-3 need to have completed at least 12 months of treatment; those in OMC-SXB-6 need to have completed at least 6 months of treatment; those in the Scharf trial could have received treatment for any length of time
- Willing and able to complete the entire trial
- Age ≥ 12 years
- If female must be
  - Surgically sterile OR
  - 2 years post-menopausal OR
  - If of child-bearing potential, not currently pregnant and using a medically accepted means of birth control

13.2.4 Exclusion Criteria

- Unstable diseases in any body system, other than narcolepsy, which would place the patient at risk or compromise the trial objectives
- Use of anticonvulsant medication
- History of substance abuse, as defined by DSM-IV, currently or within the past year
- Serum creatinine > 2 mg/dl; AST or ALT > 2 x upper limit of normal; serum bilirubin > 1.5 times normal; pre-trial electrocardiogram results demonstrating a clinically significant arrhythmia or 2^{nd} or 3^{rd} degree A-V block; history of myocardial infarction within the past 6 months
- Any untreated disorder other than narcolepsy that could be considered a primary cause of excessive daytime sleepiness
- Investigational therapy, other than GHB, within 30 days prior to screening visit
- History of porphyria

13.2.5 Sample Size

The study plans to enroll about 300 patients at 40 investigative centers

13.2.6 Duration

24 months or until marketing approval, whichever is sooner

13.2.7 Dosage

- The medication is to be taken twice each night, at bedtime and 2.5 - 4 hours later
- The dosage is to be titrated based on the diminution of symptoms (cataplexy, hypnagogic hallucinations, sleep paralysis and daytime sleepiness) during the day while awake, and adverse events
- The starting dose is that established in the previous trial
- If necessary, the dose may be increased upto 9.0 grams per day or decreased as far as 3.0 grams per day.
- If increments are made, it is suggested that they should consist of 0.75 grams per dose (1.5 grams per day)
- Allowing 2 to 4 weeks between dosage adjustments is recommended
- After an optimal dose of Xyrem™ is reached that dose will be maintained throughout the trial but will be altered if clinically indicated

13.2.8 Concomitant Medication

- Stable doses of other agents may be used for the treatment of narcolepsy
- Alcoholic beverages should not be misused and should not be taken for 3 hours prior to bedtime
- Patients will be cautioned regarding the use of other drugs with central nervous system depressant actions.
- All concomitant medications will be documented in the Case Report Forms

13.2.9 Schedule

- Assessments will be at the following visits: baseline, and at months 3, 6, 9, 12, 15, 18, 21 and 24 ; these are also referred to as Visits 1 through 9, respectively.
- Written informed consent, medical history and a urinary pregnancy test will be obtained at baseline only; a baseline history may not be needed depending on which trial the patient is entering this protocol from
- Safety laboratory tests (hematology, clinical chemistry and urinalysis) will be checked at baseline and at Months 6, 12, 18 and 24
- Concomitant medication and adverse events will be checked at every visit.
- Vital signs will be checked at baseline and at Months 6, 12, 18 and 24
- Narcolepsy symptoms will be assessed at baseline and every subsequent visit by using a formal Narcolepsy Symptom Assessment Questionnaire (baseline and follow-up versions)

13.2.10 Statistical Considerations

- All patients who receive a single dose or more of medication will be included in the safety evaluation
- All patients who complete more than one assessment of the Narcolepsy Symptom Assessment Questionnaire will be included in the efficacy evaluation.

13.2.11 Safety Monitoring

This will be accomplished using vital signs, adverse events, concomitant medications, safety laboratory tests and electrocardiograms as outlined above under "Schedule". A scheme for categorizing and reporting adverse events has been outlined.

13.3 Protocol Amendments

These have been incorporated into the above protocol description.

13.4 Patient Disposition

236 patients received treatment as part of this trial; they were at 26 study sites. Their disposition by last Xyrem® dose is illustrated in the following table, copied from the submission.

Patient Disposition		Last Xyrem Oral Solution Dosage (g/d)				
	Total	3.0	4.5	6.0	7.5	9.0
Treated	236 (100%)	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)
Discontinued	25 (11%)	0	3	7	5	10
Patient request	9 (4%)	0	1 (3%)	3 (4%)	2 (3%)	3 (5%)
Adverse event	10 (4%)	0	1 (3%)	2 (3%)	1 (2%)	6 (11%)
Protocol deviation	1 (<1%)	0	0	0	0	1 (2%)
Lost to follow-up	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Other	2 (<1%)	0	0	1 (1%)	1 (2%)	0
Lack of efficacy	1 (<1%)	0	1 (3%)	0	0	0

13.5 Demographics

Demographics at study entry are as follows

Mean Age 48.3 years
Mean Weight 84.4 kg

Gender Males 45% Female 55%

13.6 Dosage

Patient distribution by dose during, and at the end of the trial is summarized in the next table which I have copied from the submission

Dosage	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Last Dosage	236	5 (2%)	39 (17%)	76 (32%)	59 (25%)	57 (24%)
Patient Dosage[a]	236	7 (3%)	48 (20%)	106 (45%)	73 (31%)	59 (25%)

[a] Patient Dosage: the number of patients who took the specified dosage at any time during the trial. Patients may be counted multiple times, so the sum of patients exposed to specific dosages (y's) exceeds the total number of patients treated in the trial (236).

13.7 Patient Exposure

As noted in the inclusion criteria, patients were enrolled in this study from 3 other sources

Study	Maximum Duration Of Exposure To GHB
OMC-GHB-3	24 months
OMC-SXB-6	6 months
Scharf	16 years

The next table summarizes duration of exposure by dose received during OMC-SXB-7 only.

Drug Administration	Total	Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Exposure by Visit						
Visit 1	236 (100%)	4 (2%)	42 (18%)	98 (42%)	47 (20%)	45 (19%)
3 months (Visit 2)	223 (100%)	6 (3%)	37 (17%)	82 (37%)	56 (25%)	42 (19%)
6 months (Visit 3)	207 (100%)	6 (3%)	33 (16%)	68 (33%)	56 (27%)	44 (21%)
9 months (Visit 4)	133 (100%)	4 (3%)	18 (14%)	40 (30%)	39 (29%)	32 (24%)
12 months (Visit 5)	97 (100%)	2 (2%)	8 (8%)	29 (30%)	29 (30%)	29 (30%)
15 months (Visit 6)	48 (100%)	1 (2%)	4 (8%)	12 (25%)	16 (33%)	15 (31%)
18 months (Visit 7)	4 (100%)	0	0	1 (25%)	2 (50%)	1 (25%)
Last visit/end-of-trial	2 (100%)	0	0	2 (100%)	0	0
Duration of Treatment (days)						
N	236	7	48	106	73	59
Mean	284.0	246.9	198.7	230.0	239.2	235.8
SD	130.85	166.44	121.92	135.51	143.52	154.27
Median	272.5	292.0	187.5	187.0	188.0	207.0
Minimum						
Maximum						

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The mean duration of treatment in this updated study report was 284 days (0.78 years). Given that there were 236 patients enrolled in the study, the mean exposure to GHB for this study, based on this updated study report, was 184 patient-years.

In the earlier interim report for this study submitted with the original NDA, 145 patients had been exposed to the study drug for a mean duration of 104.4 days (0.29 years). The patient-exposure to GHB at that time was calculated as being 42.1 patient-years.

The additional exposure to GHB included in this safety update is therefore estimated at 141.5 patient-years

The 55 patients participating in the randomized withdrawal efficacy study, OMC-SXB-21, were drawn entirely from those participating in OMC-SXB-7. Patient exposure to GHB in OMC-SXB-21 is included in the above table, which takes into consideration those patients who were on placebo for 2 weeks during OMC-SXB-21.

13.8 Safety Results

13.8.1 All Adverse Events

The broad categories of adverse events and their distribution by dose are indicated in the following table, copied from the submission

As the table indicates serious adverse events, adverse event discontinuations and severe adverse events were all most common at the 9 g/day dose

		Xyrem Oral Solution Dosage (g/d) at Onset				
	Total	3.0	4.5	6.0	7.5	9.0
	236(100%)	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Patients with at least 1 adverse event	146(62%)	4(57%)	26(54%)	56(53%)	37(51%)	33(56%)
Patients with serious adverse events	16(7%)	0	3(6%)	3(3%)	3(4%)	7(12%)
Patients with severe adverse events	24(10%)	0	5(10%)	8(8%)	2(3%)	10(17%)
Patients discontinued due to an adverse event	9(4%)	0	1(2%)	1(<1%)	1(1%)	6(10%)
Patient deaths	1(<1%)	0	0	1(<1%)	0	0

13.8.2 Adverse Event Tables

The following tables outline adverse events that occurred in ≥ 5 % of patients in any treatment group. The tables are copied from the submission

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset 3.0	4.5	6.0	7.5	9.0
Number of Patients	236(100%)[b]	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Body as a Whole	72(31%)	3(43%)	11(23%)	24(23%)	23(32%)	17(31%)
Accidental Injury	12(5%)	0	1(2%)	3(3%)	3(4%)	6(10%)
Allergic reaction[c]	4(2%)	1(14%)	0	2(2%)	1(2%)	0
Asthenia[c]	5(2%)	1(14%)	1(2%)	1(<1%)	1(1%)	1(2%)
Flu Syndrome	11(5%)	2(29%)	0	2(2%)	5(7%)	2(3%)
Headache	16(7%)	2(29%)	3(6%)	5(5%)	2(3%)	4(7%)
Infection	17(7%)	0	1(2%)	8(8%)	5(7%)	3(5%)
Pain	14(6%)	1(14%)	1(2%)	3(3%)	4(5%)	5(8%)
Viral Infection	6(3%)	0	2(4%)	1(<1%)	0	3(5%)
Cardiovascular System	10(4%)	0	3(6%)	4(4%)	3(4%)	1(2%)
Digestive System	37(16%)	1(14%)	10(21%)	12(11%)	4(5%)	10(17%)
Diarrhea	12(5%)	1(14%)	3(6%)	3(3%)	2(3%)	3(5%)
Nausea	15(6%)	0	2(4%)	4(4%)	2(3%)	7(12%)
Vomiting	10(4%)	0	3(6%)	3(3%)	1(2%)	3(5%)
Hemic Lymphatic System	8(3%)	0	0	7(7%)	1(2%)	0
Metabolic and Nutritional System	20(8%)	2(29%)	1(2%)	5(5%)	6(8%)	6(10%)
Creatinine increased[c]	2(<1%)	1(14%)	0	1(<1%)	0	0
Hypercholesteremia[c]	3(1%)	1(14%)	0	2(2%)	0	0

Body System COSTART Preferred Term	Total[a]	Xyrem Oral Solution Dosage (g/d) at Onset				
		3.0	4.5	6.0	7.5	9.0
Number of Patients	236(100%)[b]	7(100%)	48(100%)	106(100%)	73(100%)	59(100%)
Musculoskeletal System	20(8%)	0	4(8%)	5(5%)	5(7%)	6(10%)
Nervous System	52(22%)	1(14%)	11(23%)	15(14%)	10(14%)	16(27%)
Depression	2(<1%)	1(14%)	0	0	1(1%)	0
Insomnia	8(3%)	0	2(4%)	2(2%)	1(1%)	3(5%)
Sleep disorder[d]	9(4%)	0	2(4%)	1(<1%)	2(3%)	4(7%)
Respiratory System	37(16%)	1(14%)	8(17%)	13(12%)	10(14%)	5(8%)
Rhinitis	8(3%)	0	2(4%)	1(<1%)	2(3%)	3(5%)
Sinusitis	13(6%)	1(14%)	3(6%)	6(6%)	2(3%)	1(2%)
Skin	14(6%)	0	1(2%)	6(6%)	2(3%)	6(10%)
Special Senses	6(3%)	0	1(2%)	1(<1%)	1(1%)	3(5%)
Urogenital System	29(12%)	3(43%)	4(8%)	11(10%)	4(5%)	7(12%)
Albuminuria[e]	3(1%)	1(14%)	0	1(1%)	0	1(2%)
Pyelonephritis[f]	2(<1%)	1(14%)	0	0	0	1(2%)
Urine abnormality[g]	3(1%)	1 (14%)	0	1(<1%)	1(1%)	0

Some patients were exposed to more than 1 dosage in the trial, so the sum of patients exposed to specific dosages (N= 293) exceeds the total number of patients in the trial (N= 236).

The spectrum of adverse events seen is not greatly different from those in the Integrated Summary of Safety in the original NDA. The most common adverse events overall in descending order of frequency were infection, headache, nausea, pain, sinusitis, accidental injury, diarrhea and flu syndrome.

The percentages of adverse events that were classified as mild, moderate or severe, were 36%, 48% and 16%, respectively.

13.9 Deaths

A single patient died during the study. The cause of death was suicide. A narrative for this patient is below:

Patient # 0531 was a 47 year old woman who had earlier participated in the OMC-SXB-6 trial and had been taking Xyrem® 6 g/day since 6/3/99. Her past medical history that the investigator was aware of at screening was remarkable for a bipolar disorder, a previous head injury with coma and a morphine allergy. Concomitant medications included thyroxine, zolpidem, an albuterol inhaler, loratadine, risperidone and temazepam. Subsequently the investigator realized that she had previously made a suicide attempt

In May 2000 she began experiencing worsening insomnia. On 6/12/00 she underwent an elective surgical procedure for metrorrhagia.

On 7/4/00 she asked friends to leave a gathering at her home as she felt unwell. After a friend was unable to contact her, emergency personnel entered her home and found her dead the following day. A post-mortem toxicology screen was positive for opiates, acetaminophen and benzodiazepines. Quantitative testing showed toxic levels of multiple drugs including hydrocodone, oxycodone, morphine, hydromorphone, nordiazepam and zolpidem. It was presumed that she had committed suicide by taking an overdose of multiple drugs. The death certificate listed multiple drug toxicity as the cause of her death with atherosclerotic cardiovascular disease also being listed as a significant factor.

Post-mortem toxicology screening for GHB was not done, but the sponsor believes that this patient did not take an overdose of that drug for the following reasons

- At her last trial visit on 5/23/00 the patient received 6 bottles of Xyrem®, each containing 200 mL of the drug (each bottle contained 500 mg/mL)
- On 7/11/00 the patient's family returned to the investigator 5 bottles (4 full and 1 empty)
- The 6th bottle containing some drug was retained by the medical examiner but the quantity of drug in that bottle is not known
- The sponsor states that the although the patient's compliance with the drug could not be precisely estimated it was calculated as being between 39 and 78%

13.10 Serious Adverse Events

16 patients, including the patient who died, are stated to have had serious adverse events. All are summarized in the tables below

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
0214	9.0	Liver function tests abnormal	Unknown	Yes
0232	9.0	Paranoid reaction	Probably related	Yes
0620	9.0	Knee replacement with postoperative paralytic ileus*	Not related	No
0508	6.0	Chest tightness/diaphoresis*	Not related	No
05257	12.0	Gastroenteritis/ dehydration	Not related	No
	12.0	Urinary tract infection	Not related	No
0531	6.0	Death (Suicide)	Not related	Yes
0545	7.5	Chest pain	Not related	No
0731	4.5	Manic depressive reaction (bipolar affective disorder)	Not related	Yes
1121	9.0	Intentional overdose	Definitely related	Yes
14644	7.5	Suicide attempt*	Possibly related	Yes
1444	4.5	Breast carcinoma (suspected)	Not related	No
1579	6.0	Gastroenteritis	Not related	No
	6.0	Back pain	Not related	Yes
1636	7.5	Chest pain	Unknown	No
2030	9.0	Psychosis	Possibly related	Yes

Patient No.	Xyrem Dosage at Onset (g/d)	COSTART Preferred Term	Relationship to Trial Drug	Led to Discontinuation
23210*	4.5	Cardiospasm	Not related	No
	4.5	Chills and fever	Not related	No
2836	9.0	Fractured ankle*	Possibly related	Yes

Further descriptions have been provided for the following patients, based on a review of all patient narratives. Events in the other patient were felt by me not to be related to the study drug.

13.10.1 Patient # 0214

This patient has already been described in Section 8.3.1.6. His liver function abnormalities were attributed to Hepatitis C infection.