7.3 Methods Of Analysis

The sponsor describes the methods of analysis as follows

- The analysis was performed separately on the 2 safety databases that were looked
  - Integrated Clinical Trials
  - Scharf Open-Label Study
- Each database was searched for adverse events that could indicate sleepwalking. The following were the verbatim adverse event terms looked for: "sleepwalking," "somnambulism," and "wanders in sleep."
- For each adverse event dosage at onset and start and stop trial days were calculated.
- For each of the 2 databases analyzed, summary tables were prepared grouping adverse events that could suggest sleepwalking by dosage at onset
- Tables were also prepared for each sleepwalking-related adverse event for each patient with such an event: in addition to relevant medical history and concomitant medications for each patient, the following were recorded in the table for each event: start and stop dates, dosage of GHB at onset, verbatim (investigator) term, seriousness/severity, action taken, outcome, frequency, and relationship to drug. Tables were prepared from integrated listings for the 2 databases and listings for the individual trials

The analysis performed by the sponsor also looked at concurrent adverse events, which were included in the table for individual sleepwalking adverse events. Concurrent adverse events were defined as

- Any accidental injury occurring at the time of the sleepwalking adverse event (± 1 day from trial day of onset of sleepwalking adverse event; or between the start and stop trial days for sleepwalking adverse event) with no other causal explanation
- Any other sleep disorder occurring at the time of the sleepwalking adverse event
- Any other accidental injury that may have indicated an additional sleepwalking event
- Any other adverse event that may have indicated non-compliance with the dosing regime

The results of the analysis are described separately for the Integrated Clinical Trials and Scharf Trials databases. The following description utilizes summary data, as well as the more detailed tabulations of individual events supplied by the sponsor.

7.4 Integrated Clinical Trials

7.4.1 Overall Summary

Of the 402 patients in this grouping, 28 patients (7%) had one or more episodes of sleepwalking (they had a total of 45 such adverse events) through the cut-off date of September 30, 2001. One of these 28 patients also had a separate

adverse event for which the investigator term "sleepwalking – fell" was used; the sponsor has not listed this adverse event as an instance of sleepwalking; if this event is counted as an instance of sleepwalking, the 28 patients had 46 instances of sleepwalking. Only one of these patients was receiving placebo at the time the adverse event occurred; the rest were receiving Xyrem®.

None of the instances of sleepwalking were considered serious adverse events or lead to a patient's death.

2 patients discontinued Xyrem® on account of sleepwalking.

These data are summarized along with the adverse event distribution by dose in the following table which I have copied from the submission.

Sleepwalking: All Events	Total[a]	Placebo	Xyrem Oral Solution Dosage (g/d) at Onset[b]					
			Total[a]	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	54 (100%)	399 (100%)	97 (100%)	269 (100%)	290 (100%)	133 (100%)	129 (100%)
Patients with at least 1 AE	28 (7%)	1 (2%)	27 (7%)	1 (1%)	6 (3%)	11 (4%)	5 (4%)	9 (7%)
Patients with SAEs	0	0	0	0	0	0	0	0
Patients with [illegible] AEs	1 (<1%)	1 (2%)	1 (<1%)	1 (1%)	1 (<1%)	1 (<1%)	1 (1%)	1 (1%)
Patients with severe AEs	0	0	0	0	0	0	0	0
Patient discontinuations due to an AE	2 (<1%)	0	2 (<1%)	0	1 (<1%)	1 (<1%)	0	0
Patient deaths	0	0	0	0	0	0	0	0

[a] Patients are counted only once in the total column.
[b] Some patients were exposed to more than 1 dosage during the trial(s), so the sum of patients exposed to specific dosages exceeds the total number of patients in the integrated clinical trials.

The table above does not indicate a dose-response in the incidence of this adverse event.

The actual investigator (verbatim) terms used for the 28 patients with sleepwalking were

- "Sleepwalking" or "sleepwalked" in 25 patients
- "Somnambulism" in 2 patients
- "Wanders in sleep" in 1 patient

All instances of sleepwalking were coded using the COSTART term "sleep disorder". A total of 47 patients in the Integrated Clinical Trials grouping had "sleep disorder" (COSTART). Of the 19 patients with "sleep disorder" (COSTART) who did not have sleepwalking the distribution of investigator terms was as follows

- Sleep paralysis in 10 patients
- Increased awakenings/arousals at night in 5 patients (one of whom also had sleep paralysis)
- Disruptive nocturnal sleep in 1 patient
- Micro-sleeps in 1 patient
- Somniloquy in 1 patient
- Motor activity in sleep in 1 patient
- Difficulty awakening in the morning in 1 patient

7 of the 28 patients with sleepwalking also had other conditions classified under the COSTART term "sleep disorder." The investigator terms for these patients were as follows (4 of these patients had 2 of these terms each):

- 2 patients with sleep paralysis
- 4 patients with sleep talking
- 2 patients with involuntary limb movements of sleep
- 1 patient with poor sleep maintenance
- 1 patient with fragmented sleep
- 1 patient with screaming during sleep

7.4.2 Demographics Of Patients With Sleepwalking

- 54% of patients were women (versus 57% for the entire cohort participating in the Integrated Clinical Trials)
- The mean age of the 28 patients with sleepwalking was 45.7 years (range: 15.2 to 74.2 years) versus 46.1 years for the entire cohort of 402 patients in the Integrated Clinical Trials

7.4.3 Distribution Of Sleepwalking By Clinical Trial

The 28 patients with sleepwalking were distributed as follows across the individual trials in the Integrated Clinical Trials grouping; note that some patients had episodes in more than one trial

Clinical Trial	Number of Patients
OMC-GHB-2	2
OMC-GHB-3	6
OMC-SXB-6	13
OMC-SXB-7	9
Scrima	1

7.4.4 Frequency Of Sleepwalking Adverse Events

Individual sleepwalking adverse events did not necessarily correspond to individual episodes of sleepwalking. For example, multiple sleepwalking episodes were at times subsumed under a single sleepwalking adverse event.

The numerical distribution of sleepwalking adverse events for the 28 patients with sleepwalking were as follows

Number of Sleepwalking Adverse Events	Number of Patients
1	18
2	7
3	1
5	1
7	1

7.4.5 Onset Of Sleepwalking

The onset of sleepwalking during treatment with GHB did not relate to the duration of treatment within the first 90 days of treatment as indicated by the following table. Sleepwalking episodes were however more likely to have their onset during the first 90 days rather than subsequently.

Time of Onset of Sleepwalking (Trial Days)	Number of Patients with Onset of Sleepwalking
1 through 30	7
31 though 60	6
61 through 90	7
91 through 120	2
121 through 150	1
151 through 180	2
181 through 270	4
211 through 240	1
271 through 300	1
331 through 360	1
361 through 390	1

7.4.6 Duration Of Individual Adverse Events

For 36 sleepwalking adverse events in 23 patients the duration of individual adverse events was available (i.e., start and stop dates were provided in the Case Report Forms). The duration of individual episodes of sleepwalking is not available

The distribution of the durations of individual sleepwalking adverse events is in the following table.

Duration of Sleepwalking Adverse Event	Number of Events
1 day	21
2-10 days	4
11-20 days	0
21-50 days	3
50-100 days	5
101-200 days	1
201-400 days	1
401-600 days	0
601-800 days	1

All sleepwalking adverse events ≥ 5 days (and 1 of the adverse events that lasted 1 day) in duration were listed as being intermittent.

9 sleepwalking adverse events in 8 patients had no stop date and were assumed to be unresolved. 7 of those events were listed as being intermittent; the 2 remaining events were described as being isolated

7.4.7 Falls and Injuries From Sleepwalking Adverse Events

4 of 46 sleepwalking adverse events were associated with falls, with or without injuries. that could be attributed to the sleepwalking events themselves: 3 were instances of falls during sleepwalking without any injuries being listed in the sponsor's tables; in a fourth instance the patient was described as having sustained "cut fingers/multiple bruises during sleepwalking episode/fall."

In 4 patients with sleepwalking adverse events there were 5 instances of injuries that were not clearly related to events of sleepwalking. The investigator terms used were as follows: "cut on foot;" "contusion due to head due to fall and hitting head on cabinet;" "abrasion to head resulting from fall;" bruise on forehead;" and "bruised hip." As the sponsor points out such injuries could also have resulted from attacks of cataplexy.

7.4.8 Timing Of Sleepwalking Adverse Events Relative To The Two Nighttime Doses

Such information is available for only 4 adverse events in 2 patients

- In one patient both events occurred after the first dose
- In the second patient one event occurred after the first dose and one event after the second dose

7.4.9 Factors Contributing To Episodes Of Sleepwalking

The sponsor has proposed that a number of additional factors may have contributed to the episodes of sleepwalking seen in the Integrated Clinical Trials grouping. These factors have been grouped into 3 categories by the sponsor

7.4.9.1 Relevant Medical History

Relevant (according to the sponsor) medical history predating Xyrem® exposure include the following

Medical History Predating Xyrem® Use	Number Of Patients
Sleepwalking	2
Dizziness/dysequilibrium	2
Sleep apnea	1
Insomnia	2
Nightmares	1

7.4.9.2 Concomitant Medications

Concomitant medications that the sponsor believes could have contributed to the episodes of sleepwalking are listed below

Medication	Number Of Patients
Methylphenidate, pemoline, or amphetamines	16
Modafinil or zolpidem	11
Tricyclic antidepressants, selective serotonin re-uptake inhibitors or other antidepressants	8
Antihistamines of decongestants	8
Cardiovascular medications	8
Codeine or fentanyl	3

7.4.9.3 Concurrent Adverse Events

Concurrent adverse events (other than falls) that the sponsor believes could have been contributory to the episodes of sleepwalking are listed below

Concurrent Adverse Events	Number Of Patients
Involuntary limb movements, night tremors or leg cramps	3
Sleep-talking	3
Insomnia	3
Fragmented sleep, poor sleep maintenance or prolonged sleep paralysis	3
Loss of balance or unsteady gait	2

7.4.10 Discontinuations Due To Sleepwalking In Integrated Clinical Trials

2 patients discontinued Xyrem® on account of sleepwalking. Brief narratives for these patients are provided below

7.4.10.1 Patient #1631

This 69 year old man participated in Study OMC-SXB-6. He had a history of narcolepsy with cataplexy; his concomitant medications included methylphenidate, clomipramine, atorvastatin and methamphetamine.

On Day 23 of participation in the study, and while taking a Xyrem® dose of 6 g/day he began having intermittent episodes of sleepwalking. Later he developed fragmented sleep and involuntary limb movements of sleep. On Day 59, on account of all 3 of the above adverse events continuing to occur, Xyrem® was withdrawn. All 3 adverse events resolved after Xyrem® was stopped.

7.4.10.2 Patient # 2532

This 35 year old woman participated in Study OMC-SXB-6. She has a past history of occasional dysequilibrium. She had a past history of narcolepsy; concomitant medications included modafinil and cetirizine.

On Day 16 of participation in the study whe began having intermittent episodes of sleepwalking. At the same time she began experiencing dizziness and later in the study noted numbness in her arms and legs. On account of the dizziness and sleepwalking she was withdrawn from the study on Day 43. All her adverse events resolved after Xyrem® was discontinued.

7.4.11 Sleepwalking In Controlled Clinical Trials

- The database for the Integrated Clinical Trials grouping includes both controlled and uncontrolled clinical trials
- The controlled clinical trials in the grouping are listed in the following table

Trial	Design	Duration Of Double-Blind Treatment	Number Of Patients Enrolled
OMC-GHB-2	Randomized, double-blind, placebo-controlled, parallel-arm	4 weeks	136
Scrima	Randomized, double-blind, placebo-controlled, cross-over	4 weeks	20
Lammers	Randomized, double-blind, placebo-controlled, cross-over	4 weeks	25
OMC-SXB-21	Randomized, double-blind, placebo-controlled, withdrawal	2 weeks	55

- The incidence of sleepwalking in the drug and placebo groups in each of the above trials is shown in the next table which I have copied from the submission

	Number of Patients			
	Placebo		Sodium Oxybate	
Trial	Total	Sleepwalking	Total	Sleepwalking
OMC-GHB-2	34	0	102	2
OMC-SXB-21	29	0	26	0
Scrima	20	1	20	0
Lammers	25	0	25	0
TOTAL	108	1 (0.9%)	173	2 (1.2%)

- Overall, as the above table indicates, the incidence of sleepwalking was 1.2% in GHB-treated patients and 0.9% in placebo-treated patients

7.5 Scharf Trial

7.5.1 Overall Summary

Of the 143 patients participating in the Scharf trial, 45 patients (32%) had a total of 235 adverse events of sleepwalking through the data cut-off point of May 31, 1999. The 45 patients had the verbatim term "sleepwalking" used to designate their adverse event (which was coded using the COSTART term "sleep disorder"). There were no adverse events other than sleepwalking coded under this COSTART term "sleep disorder."

None of the episodes of sleepwalking led to a patient's death or were considered serious. One patient discontinued treatment on account of episodes of sleepwalking.

These data are summarized along with the adverse event distribution by dose in the following table which I have copied from the submission.

Sleepwalking: All Events	Total	Most Commonly Taken Xyrem Oral Solution Dosage (g/d)				
		3.0	4.5	6.0	7.5	9.0
Number of patients	143 (100%)	5 (100%)	49 (100%)	62 (100%)	18 (100%)	9 (100%)
Patients with at least 1 AE	45 (31.5%)	1 (20.0%)	15 (30.6%)	21 (33.9%)	5 (27.8%)	3 (33.3%)
Patients with SAEs	0	0	0	0	0	0
Patients with related AEs	45 (31.5%)	1 (20.0%)	15 (30.6%)	21 (33.9%)	5 (27.8%)	3 (33.3%)
Patient discontinuations due to an AE	1 (<1%)	0	0	1 (1.6%)	0	0
Patient deaths	0	0	0	0	0	0

As the above table indicates the incidence of this adverse event did not appear to increase with increasing dose.

7.5.2 Demographics Of Patients With Sleepwalking

- 53% of patients were men (versus 56% for the entire cohort participating in the Scharf trial)
- The mean age of the 45 patients with sleepwalking was 46.0 years (range: 14.9 to 66.5 years) versus 45.3 years for the entire cohort of 143 patients in the Scharf Trial

7.5.3 Frequency Of Sleepwalking Adverse Events

Individual sleepwalking adverse events did not necessarily correspond to individual episodes of sleepwalking. For example, multiple sleepwalking episodes were at times subsumed under a single sleepwalking adverse event.

Recording of the frequency of adverse events was not a requirement in the Scharf trial.

However

- 11 sleepwalking adverse events in 9 patients in this trial were characterized as intermittent or ongoing.
- For the 6/11 sleepwalking adverse events with stop dates the duration was as follows: 10, 15, 49, 53, 389 and 1736 days.
- 5/11 intermittent or ongoing sleepwalking adverse events were characterized by multiple episodes as follows: 15, 16, 19, 128 and 346 episodes, respectively.

7.5.4 Onset Of Sleepwalking

The trial date of onset for the first sleepwalking adverse event experienced by patients in this trial ranged from Day 4 to Day 3520. 51.1% of patients had their first episode after 1 year on sodium oxybate.

The table below has been copied from the submission and shows the day of onset of sleepwalking adverse events in this trial

Day of Onset	All Sleepwalking AEs		First Sleepwalking AE
	No. of Patients	No. of AEs	No. of Patients
Total	45 (100%)	235 (100%)	45 (100%)
Days 1-30	5 (11.1%)	6 (2.6%)	5 (11.1%)
Days 31-60	4 (8.9%)	4 (1.7%)	2 (4.4%)
Days 61-90	0	0	0
Days 91-120	2 (4.4%)	2 (0.9%)	2 (4.4%)
Days 121-150	6 (13.3%)	7 (3.0%)	3 (6.7%)
Days 151-180	5 11.1%)	6 (2.6%)	1 (2.2%)
Days 181-210	4 (8.9%)	4 (1.7%)	1 (2.2%)
Days 211-240	4 (8.9%)	11 (4.7%)	1 (2.2%)
Days 241-270	6 (13.2%)	6 (2.6%)	3 (6.7%)
Days 271-300	3 (6.7%)	5 (2.1%)	1 (2.2%)
Days 301-330	3 (6.7%)	5 (2.1%)	2 (4.4%)
Days 331-360	3 (6.7%)	6 (2.6%)	1 (2.2%)
1 to 2 years	16 (35.6%)	32 (13.6%)	9 (20.0%)
2 to 3 years	11 (24.4%)	33 (14.0%)	2 (4.4%)
3 to 4 years	8 (17.8%)	31 (13.2%)	3 (6.7%)
4 to 5 years	13 (28.9%)	38 (16.2%)	4 (8.9%)
5 to 6 years	5 (11.1%)	14 (6.0%)	0
6 to 7 years	6 (13.3%)	9 (3.8%)	3 (6.7%)
7 to 8 years	5 (11.1%)	7 (3.0%)	0
8 to 9 years	3 (6.7%)	5 (2.1%)	1 (2.2%)
9 to 15 years	4 (8.9%)	4 (1.7%)	1 (2.2%)

7.5.5 Duration Of Individual Sleepwalking Adverse Events

Note again that individual sleepwalking adverse events did not necessarily correspond to individual episodes of sleepwalking. For example, multiple sleepwalking episodes were at times subsumed under a single sleepwalking adverse event.

The duration of individual episodes of sleepwalking is not available.

The distribution of the durations of individual sleepwalking adverse events is in the following table.

Duration of Sleepwalking Adverse Event	Number of Events
1 day*	207
2-3 days	10
5-53 days	6
> 1 year	3
"Unresolved	7

*i.e., occurred on 1 day only

7.5.6 Timing Of Sleepwalking Adverse Events Relative To The Two Nighttime Doses

This information is not available except in 1 patient who reported "sleepwalking" during the day; the sponsor suggests that may have been an episode of automatic behavior due to narcolepsy.

7.5.7 Falls, Injuries, Accidents And Overdoses From Sleepwalking Adverse Events

A total of 7 sleepwalking adverse events in 5 patients appear to have had further adverse consequences that resulted from sleepwalking.

These events are summarized in the following table

Patient #	Number Of Sleepwalking Adverse Events Associated With Additional Adverse Consequences	Nature of Additional Adverse Consequences
01-206	2	Lighted cigarettes in hand; burning nightgown
01-215	1	Drank nail polish remover
01-052	1	Fall*
01-017	2	Overdose
01-267	1	Overdose

*This 48 year old woman is reported to have had 19 individual episodes of sleepwalking between Days 148 and 536 while receiving GHB in a dose of 6.8 g/day. She is reported to have fallen during one such episodes and injured her arm and back

A further patient (#01-031) reported having a total of 136 episodes of sleepwalking in her diaries. She sustained a cut to her left index finger although it is clear if that occurred during an episode of sleepwalking.

Narratives for several patients in the above table are below. The narratives use material from earlier submissions.

7.5.7.1 Patient 01-206 (Initials ——

See Section 7.5.9.1

7.5.7.2 Patient 01-215 (Initials ——

This 46 year old woman with narcolepsy, who sustained a skull fracture 5 years prior to study entry, took GHB in a variable dose of 4.5 to 10.5 g/day in 2 or 3 divided doses despite being prescribed 7.5 g/day (this is not consistent with what has been entered in the medication logs in the Case Report Form. About 4 months after entering the study she reported symptoms of nausea, a tipsy feeling, blurred vision, and a swollen face and hands. These symptoms persisted for 14 days, no action was taken, and her doses subsequently were variable and as high as 10.5 g/day. She continued in the study for a further 4 years when she was discontinued on account of non-compliance which involved not submitting daily sleep log diaries and modifying dosing schedules without prior consultation with Dr Scharf.

A number of unexplained fits of laughter (termed "hysterical" in one instance, and "uncontrollable" at other times), and **episodes of "sleepwalking" (during one of which she tried to drink nail polish remover).** Episodes of headache, nausea, dizziness, blurred vision, enuresis, "fogginess", "stumbling around-unsure of self on feet after gamma", "drugged effect, vision blurred, unsteady on feet", "drunken stupor; rage", other similar events, and sleeplessness, were also noted during the study.

A telephone contact with the patient 12 ½ years after she discontinued from the study indicated that her neurological adverse events, with the exception of blurred vision, had resolved once GHB was discontinued.

7.5.7.3 Patient 01-017 (Initials ——)

This 63 year old man had a history of narcolepsy and sleep apnea. as well as hypertension. Initial physical examination is reported to have shown a "mild-to-moderate degree of oropharyngeal compromise."

He began taking GHB in a dose of 4.5 g daily. **About 11 months after enrolling, in an incident attributed to possible sleepwalking he ingested an additional estimated 9 g of GHB in addition to his first nightly 3 g dose of the drug. He drove himself to an emergency room, where he was administered ipecac and slept for 2 hours**

Approximately 1 ½ years after enrolling in the study he was hospitalized after an overdose of GHB 18 g, again attributed to sleepwalking. At the time of hospitalization he was comatose and unresponsive. He needed intubation and artificial ventilation, and awoke 6 hours later. He continued in the study.

Other significant items of information regarding this patient are as follows

- **He had many episodes of sleep walking and multiple episodes of urinary incontinence.**
- **In 2 instances episodes of sleep walking and urinary incontinence are listed in the Case Report Form as occurring on the same day although there is no evidence presented that they occurred at the same time.**
- **On the days when both incontinence and sleep walking are listed as having occurred, the patient's prescribed dose was 7.5 g/day**
- **As noted above this had multiple episodes of sleep walking that did not occur on the same days as his episodes of incontinence.**
- He also reported muscle jerks over the front of his trunk over a period of several years while taking GHB. These were stated to be most prominent when lying in bed in the morning as the last dose of GHB was wearing off; they could be controlled voluntarily and would disappear with ambulation, returning when at rest.
- He developed congestive heart failure during the study and died about 5 years after study entry. While participating in the study he underwent a thoracotomy for a right lung nodule that was confirmed to be a squamous cell carcinoma.

7.5.7.4 Patient 01-267 (Initials ——)

This 65 year old woman had a history of obesity, sleep apnea on treatment, and narcolepsy. She began taking GHB in a dose of 4.5 g daily.

About 4 ½ years after study entry she was reported to have taken an overdose of GHB, consuming a third nightly dose instead of merely two doses. The patient's daughter reported that the patient was shortly afterward incontinent of urine, awoke and (for unclear reasons) was covered with spaghetti sauce. She also appeared dazed and confused. Her diaries are unavailable for that period and it is therefore unclear what her regular dose of GHB was at the time. She was taken to an emergency room but had recovered by that time. She was reported to have continued GHB after that episode but ceased returning any daily diaries at all beginning about 5 ¼ years after study entry and was therefore recorded as having left the study on account of non-compliance. Repeated letters to the patient from the study center were reportedly unanswered. Further information about this patient is unavailable.

During her participation in the study she was also recorded to have multiple episodes of sleepwalking and multiple additional episodes of urinary incontinence, not apparently occurring contemporaneously. She was also seen at an emergency room for an episode of somnolence which was felt to be related to her sleep apnea. She reported swollen ankles and wrists, and pain, numbness and tingling in her feet.

(It is not clear from the above or from the Case Report Form whether the overdose occurred during an episode that would have been considered to represent "sleepwalking")

7.5.8 Factors Contributing To Episodes Of Sleepwalking

The sponsor has proposed that a number of additional factors may have contributed to the episodes of sleepwalking seen in the Scharf study. These factors have been grouped into 3 categories by the sponsor.

7.5.8.1 Relevant Medical History

Relevant (according to the sponsor) medical history predating Xyrem® exposure include the following

Relevant Medical History	Number Of Patients
Sleep apnea	13
Severe headaches or head trauma	6

7.5.8.2 Concomitant Medications

Concomitant medications that the sponsor believes could have contributed to the episodes of sleepwalking are listed below

Medication	Number Of Patients
Methylphenidate, pemoline, or amphetamines	29
Tricyclic antidepressants, selective serotonin re-uptake inhibitors or other antidepressants	26
Cardiovascular medications	10
Benzodiazepines	2
Caffeine	1

7.5.8.3 Concurrent Adverse Events

Concurrent adverse events (other than falls) that the sponsor believes could have been contributory to the episodes of sleepwalking are listed below

- Extra doses of GHB in 2 patients; none of these extra doses were taken around the time that the sleepwalking episodes occurred
- A grand mal seizure in 1 patient: this patient had intermittent sleepwalking between Days 91 and 1028 of the trial and the grand mal seizure occurred on Day 311.

7.5.9 Discontinuations Due To Sleepwalking In Scharf Trial

A single patient discontinued Xyrem® on account of sleepwalking in the Scharf trial. The following narrative is based largely on earlier submissions under this application

7.5.9.1 Patient 01-206 (Initials ——)

This 62 year old woman had a history of narcolepsy, hypertension and heavy smoking. She began taking GHB in a dose of 3 g/day. Concomitant medications included spironolactone-hydrochlorthiazide, caffeine and atenolol.

While participating in the trial she had 7 episodes of sleep walking, beginning on Day 93. 2 episodes which occurred, separated by a 2-day interval, 7 ½ months after she entered the study, led to her discontinuing GHB. During each of these episodes she was found by her husband with a burning cigar or cigarette in her hand, apparently not aware of having been smoking. On one of these occasions she was found in a room other than their bedroom asleep with a cigar in her hand. On the second occasion the cigarette was found to be burning her nightgown; her husband threatened at that point to end their marriage unless she stopped taking GHB. The patient's entries in her daily sleep log indicate that she was unaware of her actions during these episodes and had no personal recollection of them subsequently . Prior to the above 2 episodes she fell off a toilet and struck her head on the floor during another sleepwalking episode.

All her episodes of sleepwalking occurred while taking a Xyrem® dose of 6 g/day. After Xyrem® was stopped, the episodes ceased.

7.6 Sponsor's Conclusions

- A review of the 63 patients reported to have sleepwalking in the Integrated Clinical and Scharf trials revealed no dose, gender, or time-on-treatment trends for such events
- In the placebo-controlled clinical trials a slightly greater proportion (1.2%) of GHB-treated patients developed sleepwalking as compared with placebo-treated patients (0.9%)
- The first sleepwalking adverse event occurred primarily during the first 90 days in the Integrated Clinical Trials and after more than 1 year in the Scharf trial
- The explanation for the higher incidence of sleepwalking adverse events in the Scharf trial may be as follows
  - In this study patient diaries contained a specific line item for each day asking whether the patient had experienced sleep walking
  - By specifically soliciting information regarding sleepwalking the incidence may have been higher than seen in other clinical trials
- In both the Integrated Clinical and Scharf trials the majority of patients (64% in the Integrated Clinical Trials, and 88% in the Scharf trial) with sleepwalking adverse events had isolated non-recurring events. In most instances sleepwalking adverse events are of short duration and of little consequence to patients
- Sleepwalking-related injuries were uncommon in GHB-trials. The risk of injury may be reduced with preventive measures (see below)
- "Pro-active" preventive approaches are effective for sleepwalking episodes. An example is that of a male patient (#01-042) who participated in the Scharf trial began having episodes of sleepwalking after taking GHB for 6.1 years; he reported a total of 346 adverse events of sleepwalking. He lived alone in a trailer and became aware of the episodes after awaking in areas of the trailer other than the bedroom. Dr Scharf suggested that he attach a bell to the bedroom door and obtain a dog. Since then, although his sleepwalking episodes are continuing he is awakened whenever he attempts to leave his bedroom.
- The differential diagnosis of sleepwalking episodes is discussed by the sponsor (see Section 7.2). The sponsor believes that the 2 most likely explanations for such episodes in Xyrem®-treated patients are as follows

- NREM parasomnias: these are associated with slow-wave sleep and it is possible that GHB-induced slow-wave sleep may predispose susceptible patients to sleepwalking; also, the fragmented sleep and sleep deprivation seen in patients with narcolepsy may predispose patients to NREM parasomnias
- REM Behavior Disorder: this condition is common in narcoleptics, older patients and in men, and a number of patients with sleepwalking adverse events had such predisposing factors; sleepwalking-like behavior has been described in REM Behavior Disorder

7.7 Reviewer's Comments

- In most instances of sleepwalking in GHB clinical trials, a detailed description of patient behavior during that adverse event is not available; in the absence of adequate clinical descriptions, in most instances it is unclear what the investigator term "sleepwalking" represents as a clinical entity, or whether it refers to single or multiple entities. The basis of these episodes has not been further elucidated by the current analysis.
- Regardless of what the term "sleepwalking" means in the context of this NDA, it is clear that such episodes are common; almost one-third of patients participating in the long-term Scharf safety study did have one or more such occurrences, and a single patient is recorded as having as many as 346 episodes.
- The few clinical descriptions of this adverse event that are available in this NDA suggest that during at least a few such episodes patients may be confused and may act in a manner that could be seriously prejudicial to their own safety and to that of others.
- It is possible that sleepwalking as seen in the context of this application, was causally related to GHB use
  - Similar adverse events appear to be uncommon in narcoleptic patients who have not been treated with GHB.
  - Although the incidence of this adverse event was only slightly higher than that of placebo in controlled clinical trials of GHB, these were of short duration (≥ 1 month). The highest incidence was seen in the long-term Scharf study
- The sponsor has not supplied any evidence other than a single anecdote which suggests that preventive measures are of value in reducing the adverse consequences of such episodes

8. Respiratory Data In Study OMC-SXB-20

8.1 Background

This was an open-label study that was intended to evaluate the effects of 4 doses of Xyrem® on sleep architecture.

The final study report for OMC-SXB-20 was submitted on 12/16/00, i.e., after the original NDA submission, and was reviewed by me along with that submission. The effects of Xyrem® on sleep architecture as derived from this study are described in my Efficacy Review of the original NDA. Safety data from this study are described in my Safety Review of the original NDA.

Arterial oxygen saturation data from all-night recordings, and data on the frequency and severity of specific respiratory-event-related measures were collected as part of the polysomnogram recordings in this study but were not included in the original clinical trial report.

In the Approvable letter that was issued on 7/2/01 it was noted that although GHB was a central nervous system depressant and therefore capable of producing respiratory depression, no formal assessment of its effects on respiration had been performed. It was recommended that a study be performed to assess the effects of GHB on respiration. The following was stated in the Approvable letter:

"The study should examine the effects of the recommended dosing regimen (2 doses nightly, including the highest recommended dose-9 gms divided), with both doses given in the fasted state. The study should include patients who are and who are not receiving concomitant stimulant treatment, a positive control, and patients with concomitant illnesses that might increase their risk of respiratory depression (e.g., patients with COPD, sleep apnea, etc.)."

At the meeting with the sponsor held on 7/16/01 the Division agreed that the planned study listed above could be done as part of a post-marketing commitment. It was also agreed that an analysis of respiratory data from OMC-SXB-20 could be submitted as part of the Amendment currently under review.

The analysis of respiratory data from OMC-SXB-20 presented below is post-hoc and was not planned as part of the original protocol which is summarized below

8.2 Outline Of Protocol For OMC-SXB-20 Study

8.2.1 Objectives

8.2.1.1 Primary

The primary objective of this study was to characterize the polysomnographic sleep architecture in narcoleptic patients at four GHB doses: 4.5 g, 6.0 g, 7.5 g and 9.0 g daily

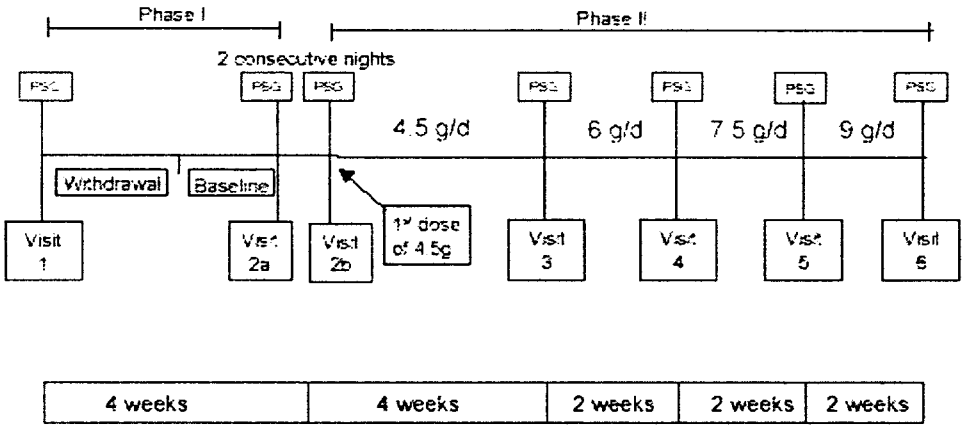
8.2.1.2 Secondary

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®

8.2.2 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. The overall design is summarized in the following diagram



8.2.2.1 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

8.2.2.2 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 then 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 were performed 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

8.2.2.3 Duration

10 weeks

8.2.3 Sample Size

20-30 planned

8.2.4 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

8.2.5 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.

8.2.6 Dosage

See Section 8.2.2

8.2.7 Outcome Measures

8.2.7.1 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

8.2.7.2 Secondary Efficacy Measures

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

8.2.7.3 Safety Measures

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

8.2.8 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

8.3 Instruments For Measuring Respiratory Event Data

Respiratory measurements were collected all night during overnight polysomnograms (7 studies in each patient) in all 21 patients constituting the intent-to-treat population. The following instruments were used to make these measurements

- Nasal thermistor or thermocouple measuring inspiratory and expiratory airflow
- Thoracic strain sensors measuring thoracic expansion as an index of central respiratory drive and pulmonary gas exchange
- Abdominal strain sensors which measure abdominal movement in order to allow determination of the patency of the upper airway (when interpreted together with nasal airflow and thoracic movement)
- Pulse oximetry: measuring adequacy of respiration to maintain oxygenation

8.4 Respiratory Effect Measures

These include respiratory event data and oxygen saturation data

8.4.1 Respiratory Event Measures

These are defined as follows (the definitions are standard ones)

8.4.1.1 Apnea-Hypopnea Index (AHI)

The apnea-hypopnea index is the incidence (events per hour) of apnea and hypopnea events associated with sleep calculated separately for NREM and REM sleep

This is calculated as follows

Number of central apneas + Number of obstructive and mixed apneas + Number of hypopneas (during REM or NREM sleep) / Number of hours of (NREM or REM) sleep

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour
Moderate	15 to 30 events per hour
Severe	> 30 events per hour

8.4.1.2 Respiratory Disturbance Index (RDI)

The respiratory disturbance index is the incidence (events per hour) of apnea and hypopnea events associated with sleep, independent of sleep stage,

represented by all sleep apnea events during the sleep period (obstructive + central + mixed) + all hypopnea events / number of hours of sleep during the study period.

It is calculated as a weighted average of AHI (NREM) and AHI (REM) with respect to the time spent in NREM and REM sleep, respectively.

The severity of sleep apnea is defined as follows based on this index

Mild	5 to 15 events per hour
Moderate	15 to 30 events per hour
Severe	> 30 events per hour

8.4.1.3 Number Of Obstructive And Mixed Apneas (OMAs)

Obstructive apnea is partial or complete upper airway obstruction during sleep. An obstructive apneic event is characterized by a transient cessation of breathing lasting > 10 seconds, in the presence of sustained respiratory effort, accompanied by oxygen desaturation of > 3% or arousal

Mixed apnea is a lack of respiratory effort during the initial apneic period followed by gradually increasing effort against an occluded upper airway. This is a variant of an obstructive apneic event during which respiratory effort is absent for several seconds after the onset of upper airway occlusion.

8.4.1.4 Number Of Central Apneas

Central apnea is defined as sleep apnea in the absence of upper airway obstruction and in the absence of inspiratory effort indicating reduced output to the muscles of inspiration from the central nervous system. A central apneic event is characterized by a cessation in airflow lasting ≥ 10 seconds, accompanied by oxygen desaturation of > 3%, or arousal, and a clear reduction in esophageal pressure swings from baseline, or absence of paradoxical respiratory effort which would indicate airway obstruction

8.4.1.5 Number of Hypopneas

Hypopnea is defined as a reduction in airflow despite ongoing inspiratory efforts. An obstructive hypopnea event is characterized by a transient reduction in breathing lasting > 10 seconds, with a clear decrease (> 50%) from baseline in the amplitude of breathing, or a decrease < 50% in the amplitude of breathing, accompanied by oxygen desaturation of > 3% or arousal.

8.4.2 Oxygen Saturation (SaO_2) Measures

These are as follows

8.4.2.1 Lowest SaO_2

8.4.2.2 Continuous SaO_2

These are data collected as mean values of 5 minutes of data during the recording period

8.4.2.3 Intermittent SaO_2

These are data collected as mean values of 1 minute of data at 8 dispersed timepoints during the recording period, including lights-out (immediately after dosing), after 30, 60, 90, 120, 150, and 180 minutes, and lights-on (about 240 minutes)

8.4.2.4 Duration Of Time That Artifact-Free Sao_2 Recordings Were < 80% And < 90% Of Saturation,

This is expressed as a percentage of the 240 minutes for the study duration and as a percentage of the total time that the SaO_2 channel was artifact-free.

8.5 Methods Of Analyzing Respiratory Data

- All measurements were digitally recorded according to standardized techniques and then transferred to a central scoring location where they were analyzed using a specified software program
- For analyzing respiratory event data
  - Each patient's record consisting of 8 hours of data for each of 7 overnight tests was subdivided into 30 second epochs
  - Validated criteria were used for scoring events to obtain the respiratory event outcome measures listed above. Scoring was done by a trained and registered polysomnogram technician who was blinded to all dosage and patient information
  - The scored respiratory events were then summarized for the first and second half of each night (i.e., in relation to the first or second dose) and for the entire night. Events were also reported for NREM and REM sleep periods and for the total (REM plus NREM).
- Oxygen saturation (SaO_2) was measured continuously and was analyzed as follows
  - Each patient record was subdivided into 5-minute intervals and each interval was examined
  - Intermittent 1-minute SaO_2 at defined timepoints was also extracted and analyzed
  - The duration of periods of SaO_2 < 80% and < 90% and the lowest SaO_2 values were also analyzed
- Changes from baseline were analyzed using 2-way ANOVA. If a statistically significant difference was found among the dosage groups, then pairwise comparisons were performed. Data were tabulated and plotted for each respiratory measure by dosage group and by patient, so as to assess group and individual effects across dosages. Two-sided p-values were reported at a level of significance of 0.05.
- For uniformity the range for all SaO_2 parameters was assigned as 50% to 110% and the range for all respiratory event parameters as 1 to 200.

8.6 Results

Only the results of the respiratory effects analysis are described below

8.6.1 Patient Disposition

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

- 21 patients completed the study. Of those who did not complete the study
  - 2 discontinued on account of adverse events and are described further in this review
  - 1 patient was lost to follow-up
  - 1 patient withdrew consent

21 patients were in the intent-to-treat population composed of all patients who received one dose of study medication and had at least one post-treatment evaluation.

8.6.2 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%

Baseline and demographic characteristics for the 21 patients in the intent-to-treat population are below

Variable	Mean	Standard Deviation
Age (years)	53.2	7.59
Weight (kg)	83.8	16.37
Height (cm)	167.6	8.66

Gender: Males 29%; Females 71%
Race: Caucasian 95%; Black 5%

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

These are summarized in the next table, copied from the original full study report.

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%)
[illegible]	[illegible]
Venlafaxine	[illegible]

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

Of the 21 intent-to-treat patients, 20 were taking tricyclic antidepressants, selective serotonin re-uptake inhibitors or hypnotics prior to entry into the study but these medications were withdrawn during the first 2 weeks of Phase I (withdrawal phase). The most frequent anticataplectic medications were venlafaxine (5 patients), zopiclone and fluoxetine (4 patients each) and clomipramine (3 patients)

8.6.4 Stimulant Medications

Patients were allowed to be a stable dose of stimulants throughout the trial

Of the 21 patients in the intent-to-treat population, 18 patients were taking stimulants. The stimulants used were dextroamphetamine (12 patients), methylphenidate (3 patients), modafinil (2 patients) and amfepramone (1 patient)

8.6.5 Medical History

All 21 intent-to-treat patients had a history of narcolepsy. Of these

- 3 patients had a history of asthma
- 1 patient had a history of recurring bronchitis and obstructive sleep apnea
- 1 additional patient had a history of obstructive sleep apnea which was not reported at the time of entry into the OMC-SXB-20 study

8.6.6 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	20
Efficacy measure	33
Safety measure	
Laboratory procedure	2
Other safety measure	2
Other	7
Total	125

8.6.7 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 Patients	4.5 25	6.0 22	7.5 22	9.0 21	Total 25
Compliance (%)					
N	25	22	22	21	25
Mean	95.9	95.5	92.7	93.3	94.9
SD	11.45	9.63	9.06	13.45	7.62
Median	100.0	98.0	95.8	93.0	96.7
Minimum					
Maximum					

8.6.8 Extent Of Exposure

The mean duration of treatment was 63.3 nights (standard deviation: 21.29) for the 25 patients who received GHB.

8.6.9 Respiratory Event Data

8.6.9.1 AHI And RDI: Change From Baseline

8.6.9.1.1 Summary Statistics

These are displayed in the following table which I have copied from the submission

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
AHI (NREM) (events per hour)								
1st half	Mean	1.5	5.1	-0.2	9.9	1.1	5.1 *	1.9
	SD	10.21	9.56	3.59	24.91	11.21	9.62	9.38
2nd half	Mean	1.7	7.1	1.1	9.0	1.4	6.5 **	1.5
	SD	14.96	12.69	6.62	21.49	8.46	12.30	11.60
Average	Mean	1.5	6.1	0.8	9.5	1.3	4.8 *	1.9
	SD	11.65	10.72	4.01	22.45	8.23	10.04	8.65
AHI (REM) (events per hour)								
1st half	Mean	1.7	7.5	1.3	6.1	3.7	-0.9	-0.4
	SD	[illegible]	11.13	10.42	[illegible]	14.11	10.20	10.32
2nd half	Mean	[illegible]	9.5	-2.3	[illegible]	[illegible]	0.2	-2.6
	SD	17.15	14.54	9.63	20.47	9.41	18.91	7.12
Average	Mean	0.7	8.5	-0.2	8.6	-0.0	-0.2	-1.6
	SD	14.93	11.92	9.97	20.41	6.69	12.49	6.90
RDI (events per hour)								
1st half	Mean	1.6	5.8	0.5	[illegible]	1.5	2.6	1.5
	SD	9.66	9.34	4.41	24.23	10.44	9.75	8.91
2nd half	Mean	0.5	8.2	0.1	9.6	-0.3	4.7 **	0.7
	SD	14.95	13.09	7.14	19.23	7.09	10.26	9.95
Average	Mean	0.8	7.0	0.3	9.8 *	0.6	3.6	1.1
	SD	11.29	10.78	3.40	20.83	7.66	6.91	7.71
		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)

Value for Visit 2a (baseline) is actual value; values for all other visits are change from baseline.
Within-treatment p values were analyzed by Wilcoxon signed rank test; between-treatment p values were analyzed by ANOVA on rank changes from baseline.
* $p \leq 0.05$ compared with baseline.
$p \leq 0.01$ compared with 4.5 g/d.
$p \leq 0.01$ compared with 6.0 g/d.
** $p \leq 0.01$ compared with baseline.
$p \leq 0.05$ compared with 4.5 g/d.
$p \leq 0.01$ compared with 6.0 g/d.

-EST POSSIBLE CC

In the text of the submission the sponsor has summarized changes that occurred from baseline and from one post-treatment visit to another, as well as those changes that were considered statistically significant ($p < 0.05$)

From this reviewer's perspective the following are noteworthy

- An increase in AHI and RDI in comparison to baseline would be consistent with a worsening in indices of sleep apnea.
- There was considerable inter-patient variability in all parameters with standard deviations consistently exceeding means
- The greatest mean increases from baseline in AHI and RDI were apparent early during the study at Visit 3, after treatment with the starting dose of GHB (4.5 g/day) for 4 weeks. The only changes that were "statistically significant" ($p < 0.05$) at that timepoint were the RDI for the first half of the night, and the RDI averaged for the entire night.
- There was no clear trend to a dose response in the mean change from baseline in these parameters, when the change was an increase

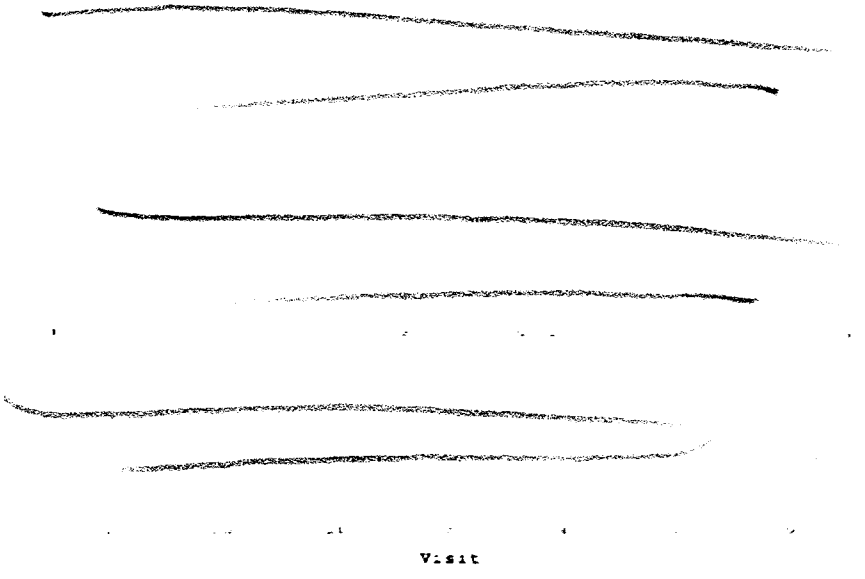
- When the Visit 5 (following 2 weeks of treatment at 7.5 g/day) parameters were compared with baseline there were "statistically significant" increases in the following
  - AHI (NREM) during both halves of the night
  - AHI (NREM) averaged for the whole night
  - RDI during the second half of the night

The sponsor's view is that the changes in AHI and RDI noted during the study lacked clinical significance.

8.6.9.1.2 By-Patient Plots

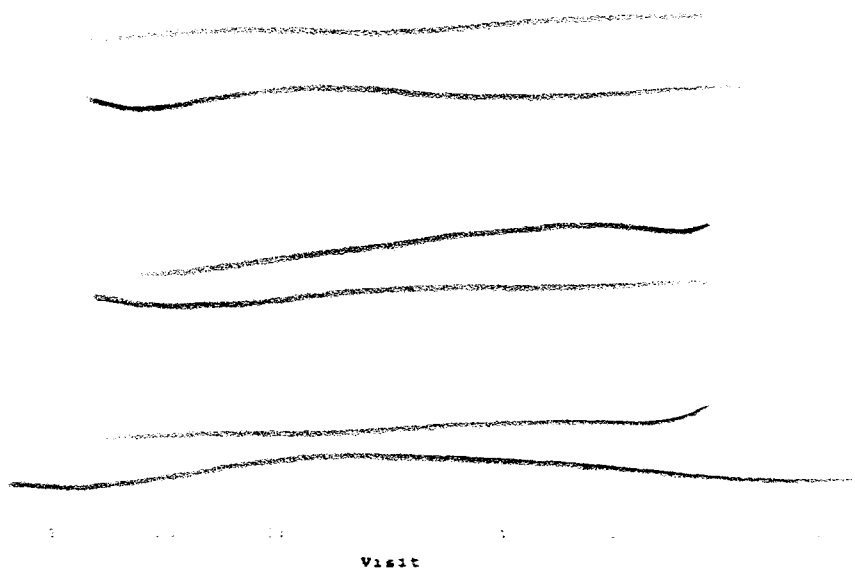
8.6.9.1.2.1 RDI

By-patient by-visit plots for the first half of the night are as follows in a figure copied from the submission



By-patient by-visit plots of the second half of the night are in the next figure, again copied from the submission.

**APPEARS THIS WAY
ON ORIGINAL**



As the above plots indicate, and as might be expected from the summary statistics tabulated in Section 8.6.9.1.1, a few patients had a prominent increase in RDI at Visit 3 (after 4 weeks of treatment at 4.5 g/day)

8.6.9.1.2.2 AHI

By-patient, by-visit plots for changes in AHI, for REM and NREM sleep, and for each half of the night generally mirrored those seen for RDI, i.e., increases were most prominent at Visit 3 (after 4 weeks of treatment at 4.5 g/day).

8.6.9.2 Sleep Apnea And Hypopnea: Change From Baseline

8.6.9.2.1 Summary Statistics

These are displayed in the following table which I have copied from the submission

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds (n = 21)	Baseline (Actual Value) (n = 21)	1st dose 4.5 g/d (n = 18)	4 weeks of 4.5 g/d (n = 20)	2 weeks of 6.0 g/d (n = 21)	2 weeks of 7.5 g/d (n = 20)	2 weeks of 9.0 g/d (n = 20)
Obstructive and mixed apneas (OA+MA)								
1st half (4 hours)	Mean	1.9	2.9	-0.3	10.5 *	3.7 *	3.8 *	4.0
	SD	6.09	7.20	2.83	20.65	10.48	9.73	13.71
2nd half (4 hours)	Mean	1.4	3.0	1.5	11.6	5.1	7.7 *	3.2
	SD	10.78	6.64	7.51	24.92	11.70	20.11	13.12
Total (Whole night)	Mean	5.5	5.9	1.0	22.1 *	8.8 *	11.5 *	7.2
	SD	15.57	13.51	5.09	50.75	21.85	33.37	26.42
Obstructive and mixed apneas (OA+MA)								
1st half (4 hours)	Mean	0.8	1.4	1.7 *	2.2	2.7	1.4	0.8
	SD	4.36	3.30	3.25	6.56	9.21	6.56	4.20
2nd half (4 hours)	Mean	-1.0	3.7	-0.1	0.6	-1.6	-1.0	-1.9
	SD	7.56	7.94	5.43	8.69	4.71	7.50	6.78
Total (Whole night)	Mean	-1.1	5.1	1.7	3.1	1.1	0.4	-1.0
	SD	9.14	10.29	7.32	13.21	6.94	9.44	9.74
Obstructive and mixed apneas (OA+MA) + REM								
1st half (4 hours)	Mean	2.0	4.3	1.4	11.7 *	4.5	5.2 *	4.8
	SD	9.64	10.29	4.24	20.51	10.31	10.11	16.59
2nd half (4 hours)	Mean	2.4	6.7	1.2	12.5 *	3.6	6.7 *	1.5
	SD	11.72	12.99	6.19	24.70	9.16	19.76	8.44
Total (Whole night)	Mean	4.4	11.0	2.7	23.2	8.0	11.8	6.2
	SD	19.51	22.94	8.59	34.49	16.62	30.24	24.20

		Visit 1 Anti-cataplexy meds (n = 21)	Visit 2a Baseline (Actual Value) (n = 21)	Visit 2b 1st dose 4.5 g/d (n = 18)	Visit 3 4 weeks of 4.5 g/d (n = 20)	Visit 4 2 weeks of 6.0 g/d (n = 21)	Visit 5 2 weeks of 7.5 g/d (n = 20)	Visit 6 2 weeks of 9.0 g/d (n = 20)
Central apneas (NREM)								
1st half (4 hours)	Mean	0.1	3.0	1.2	4.8	0.1	4.7	2.4
	SD	3.55	8.84	5.24	17.25	7.03	12.09	6.33
2nd half (4 hours)	Mean	0.0	6.9	1.7	6.7	0.3	4.7	3.8
	SD	16.21	22.51	17.13	40.11	17.99	17.99	27.27
Total (whole night)	Mean	0.1	9.9	2.9	13.5	0.5	5.3	6.1
	SD	15.36	31.11	14.55	56.61	24.45	22.09	31.55
Central apneas (REM)								
1st half (4 hours)	Mean	[illegible]	0.4	0.4	0.1	-0.0	0.3	-0.1
	SD	1.66	0.81	2.04	1.05	1.12	1.85	0.76
2nd half (4 hours)	Mean	-0.7	2.0	-0.1	[illegible]	[illegible]	-1.4	[illegible]
	SD	[illegible]	3.81	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total (whole night)	Mean	[illegible]	2.4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	[illegible]	3.94	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Central apneas (NREM + REM)								
1st half (4 hours)	Mean	[illegible]	3.4	[illegible]	[illegible]	0.1	4.5	2.4
	SD	[illegible]	8.84	[illegible]	[illegible]	6.86	13.42	7.59
2nd half (4 hours)	Mean	-0.7	8.9	1.6	9.5	-1.0	3.2	2.5
	SD	17.65	26.05	17.39	32.82	20.78	19.15	29.34
Total (whole night)	Mean	-0.6	12.3	3.2	14.8	-0.9	8.2	4.8
	SD	14.54	34.64	14.16	54.98	27.32	21.26	33.17
Hypopneas (NREM)								
1st half (4 hours)	Mean	1.4	6.8	-1.7	[illegible]	-1.1	-1.0	-0.2
	SD	18.17	14.86	[illegible]	[illegible]	[illegible]	[illegible]	16.72
2nd half (4 hours)	Mean	-1.7	5.5	-1.0	[illegible]	[illegible]	[illegible]	1.0
	SD	9.56	10.06	7.03	13.20	4.45	[illegible]	7.56
Total (whole night)	Mean	-0.2	12.2	-2.6	17.4	-1.6	6.2	0.9
	SD	25.37	22.55	11.33	30.16	16.22	26.83	22.62
Hypopneas (REM)								
1st half (4 hours)	Mean	-0.5	2.0	0.7	1.2	0.5	-1.4	-1.4 [illegible]
	SD	3.46	3.19	3.07	6.06	5.25	3.28	2.68
2nd half (4 hours)	Mean	-2.5	3.5	-2.4	-2.6 *	-2.2 *	-1.8	-1.6 *
	SD	4.65	6.36	6.52	6.44	4.34	7.60	2.21
Total (whole night)	Mean	-3.4	5.6	-1.7	-1.4	-1.8	-3.2	-3.0 *
	SD	4.66	8.11	5.15	10.36	[illegible]	8.31	3.50
Hypopneas (NREM + REM)								
1st half (4 hours)	Mean	[illegible]	8.8	-0.6	10.4	-0.7	[illegible]	-2.6
	SD	[illegible]	15.74	[illegible]	[illegible]	11.45	17.86	17.55
2nd half (4 hours)	Mean	[illegible]	9.0	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	[illegible]	15.76	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Total (whole night)	Mean	[illegible]	17.8	[illegible]	[illegible]	[illegible]	[illegible]	-2.1
	SD	[illegible]	28.08	[illegible]	41.54?	14.69?	[illegible]	24.28

Value for Visit 2a (Baseline) is actual value; values for all other visits are change from baseline.
Within-treatment p values were analyzed by Wilcoxon signed rank test; between-treatment p values were analyzed by ANOVA on rank changes from baseline.
[illegible] p ≤ 0.05 compared with baseline.
[illegible] p ≤ 0.01 compared with baseline.
[illegible] p ≤ 0.05 compared with 4.5 g/d.
[illegible] p ≤ 0.01 compared with 4.5 g/d.
[illegible] p ≤ 0.05 compared with 6.0 g/d.

From this reviewer's perspective the following are noteworthy

- There was considerable inter-patient variability in all parameters with standard deviations consistently exceeding means
- The greatest mean increases from baseline in obstructive and mixed apneas, central apneas, and hypopneas were apparent early during the study at Visit 3, after treatment with the starting dose of GHB (4.5 g/day) for 4 weeks; these changes were seen for NREM sleep and for NREM + REM sleep (combined). The only changes that were "statistically significant" ($p < 0.05$) at that timepoint were as follows.
  - Obstructive and mixed apneas (NREM) for the first half of the night and for the whole night

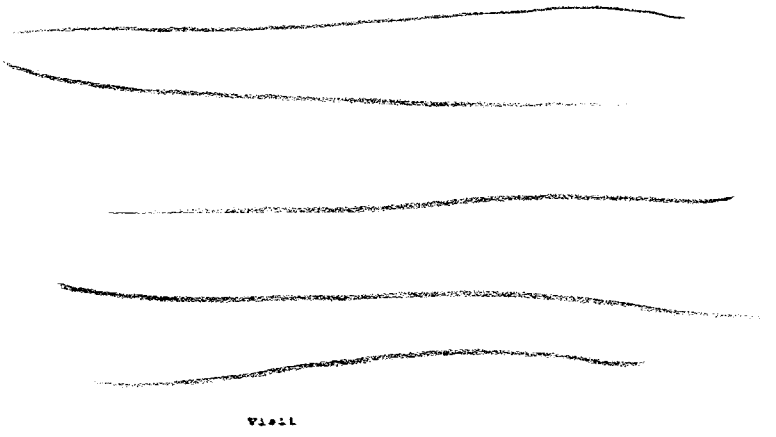
- Obstructive and mixed apneas (NREM plus REM, combined) for each half of the night and for the whole night
- There was no clear trend to a dose response in the mean change from baseline in these parameters.

8.6.9.2.2 By-Patient Plots

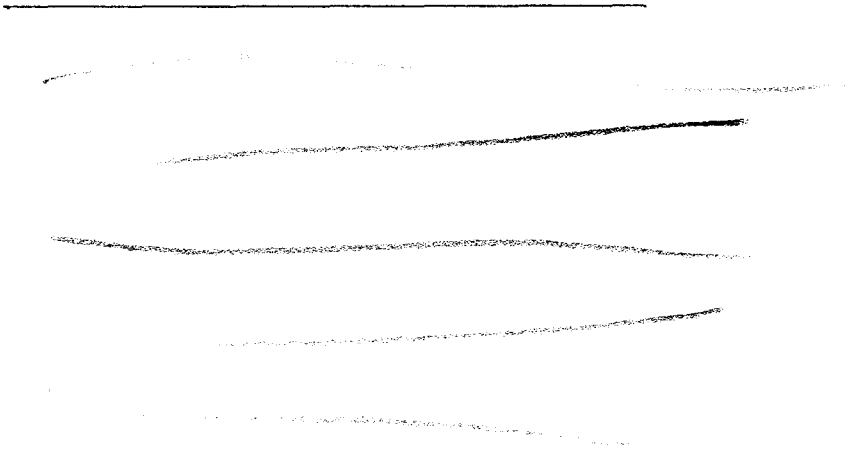
8.6.9.2.2.1 Obstructive And Mixed Apneas

A few patients had prominent increases at Visit 3 and at Visit 5 as illustrated below.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.



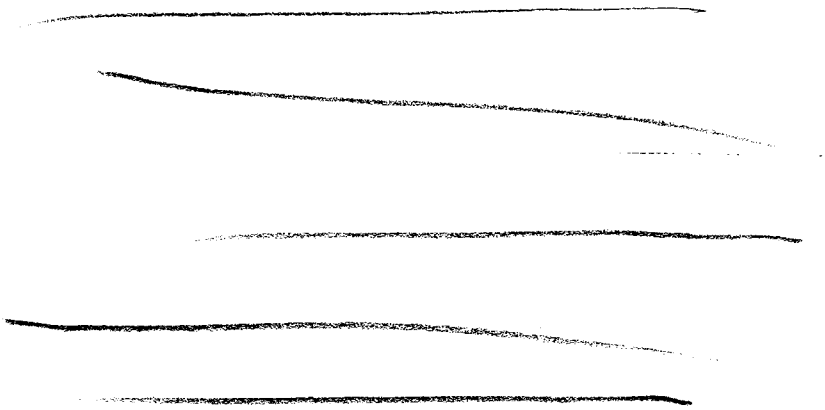
The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.



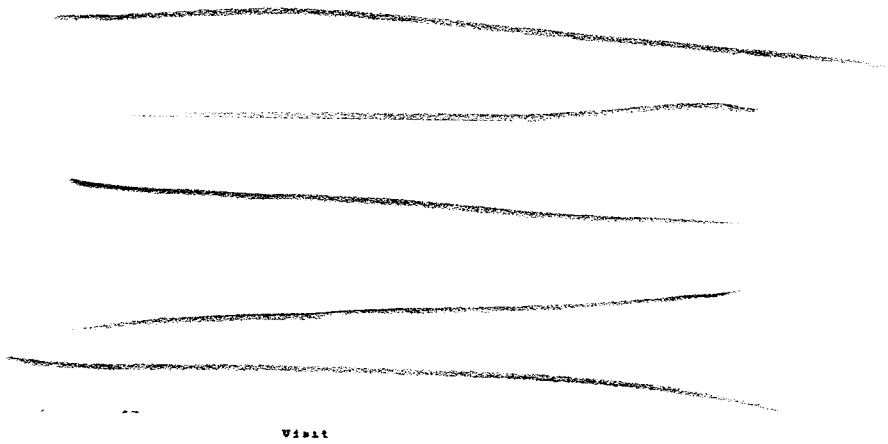
8.6.9.2.2.2 Central Apneas

The timing of prominent increases in the number of central apneas was quite variable especially for those occurring during the second half of the night, as illustrated by the following figures. However individual patients appeared to have more central apneas during the second half of the night.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.



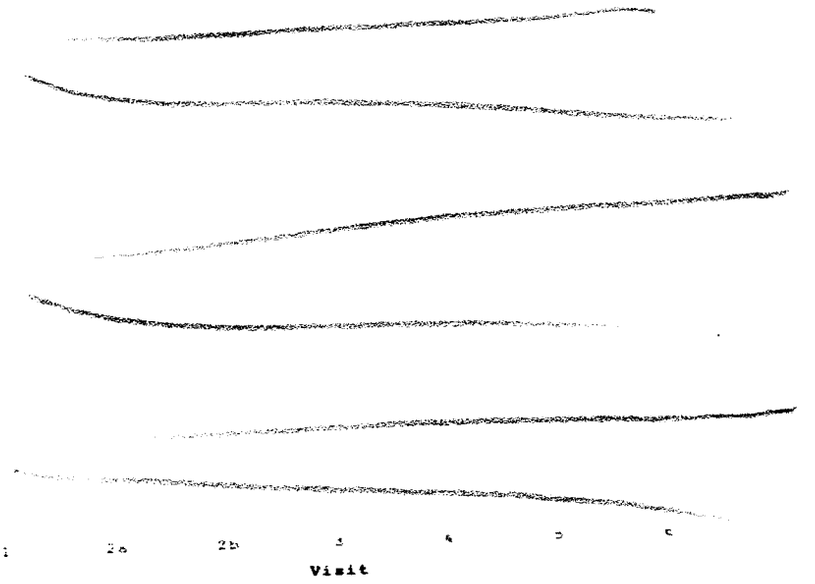
The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.



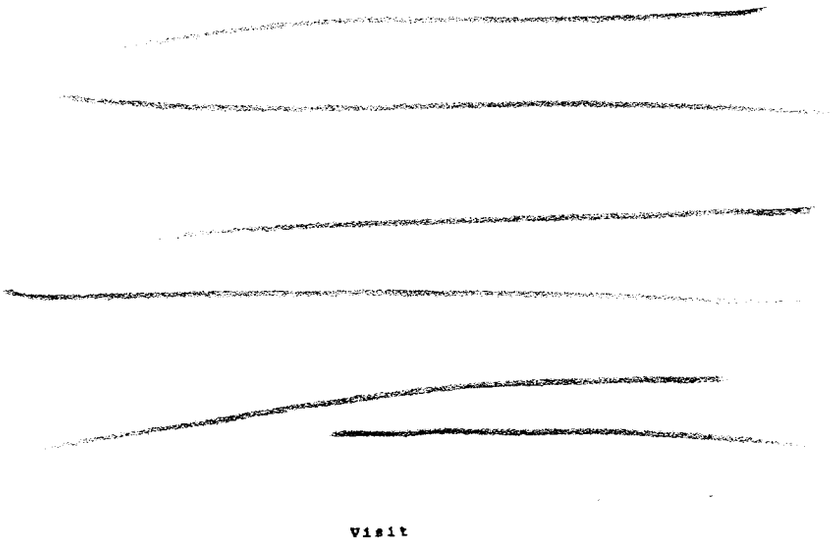
8.6.9.2.2.3 Hypopneas

The timing of prominent increases in the number of central apneas were quite variable, as illustrated by the following figures.

The first figure copied from the submission shows by-patient and by-visit plots for the first half of the night.



The next figure also copied from the submission shows by-patient and by-visit plots for the second half of the night.



8.6.9.3 Patient 017301

As noted in the by-patient plots above, this individual had a prominent increase at Visit 3, relative to baseline, in the following: obstructive and mixed apneas, hypopneas, AHI and RDI. He may have been responsible in large measure for the mean increases seen in these parameters, in the entire cohort.

This 51 year old man, had a previous history of narcolepsy, hernia, recurrent bronchitis, previous knee surgery and rosacea. He was also obese. Concomitant medications included venlafaxine, and modafinil. He was not recorded as having any adverse events during Study OMC-SXB-20 which he completed.

A polysomnogram done prior to the screening visit for this study was consistent with a diagnosis of obstructive sleep apnea syndrome.

The increase in obstructive and mixed apneas, hypopneas, AHI and RDI, seen at Visit 3 was not maintained despite further increases in dose of GHB during the remainder of the study .

This patient also had the following changes in an SaO_2 parameter, the duration of time spent with an SaO_2 less than 90%. These changes did not correlate temporally with changes in respiratory event parameters

- For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day.
- For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study.

8.6.10 Oxygen Saturation Data

8.6.10.1 Summary Statistics

The following table shows summary statistics for the following parameters: continuous SaO_2 (5-minute data), duration of oxygen desaturation (time with SaO_2 < 80% and < 90%)

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
[illegible]								
1st Half	N	19	20	19	18	20	20	20
	Mean	95.6	95.5	95.1	94.7	95.0	95.2	95.3
	SD	1.40	1.90	1.97	2.36	2.18	2.13	2.54
2nd Half	N	19	20	19	18	20	20	20
	Mean	95.4	95.5	95.3	94.7	95.0	95.1	95.3
	SD	1.69	1.88	1.96	1.97	1.96	2.31	2.61
Whole Night	N	19	20	19	18	20	20	20
	Mean	95.5	95.5	95.2	94.7	95.0	95.3	95.4
	SD	1.44	1.86	1.78	2.07	2.19	2.13	2.46
Duration of SaO2 < 80% (# of 240 minutes)								
Whole Night	N	19	20	19	18	20	20	20
	Mean	0.00	0.08	0.00	0.00	0.01	0.00	0.01
	SD	[illegible]	0.310	0.000	0.000	0.023	0.000	0.022
Duration of SaO2 < 90% (# of 240 minutes)								
Whole Night	N	19	20	19	18	20	20	20
	Mean	[illegible]	1.93	[illegible]	3.03	3.56	3.61	[illegible]
	SD	[illegible]	5.695	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti cata plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
[illegible]								
1st Half	N	19	20	17	18	21	20	20
	Mean	90.9	91.1	89.6	89.5	90.4	90.9	90.7
	SD	4.14	3.63	3.99	3.50	3.74	3.93	3.73
2nd Half	N	19	20	17	18	21	20	20
	Mean	90.9	91.1	90.6	90.2	91.3	90.5	91.9
	SD	3.42	3.64	3.38	3.77	3.29	3.65	3.21
Whole Night	N	19	20	17	19	21	20	20
	Mean	89.7	90.2	88.5	89.1	89.9	89.1	90.0
	SD	3.78	3.98	3.38	3.65	3.48	3.89	3.29
[illegible]								
1st Half	N	19	20	17	17	21	19	17
	Mean	[illegible]	90.9	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	[illegible]	4.80	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
2nd Half	N	19	20	17	18	21	20	18
	Mean	[illegible]	90.5	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	1.17	3.6	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Whole Night	N	19	20	17	19	21	20	20
	Mean	88.5	89.3	88.7	88.4	88.7	89.1	89.6
	SD	3.05	4.34	4.34	3.93	3.75	4.55	4.48

		Visit 1	Visit 2a	Visit 2b	Visit 3	Visit 4	Visit 5	Visit 6
		Anti-cata-plexy meds	Baseline	1st dose 4.5 g/d	4 weeks of 4.5 g/d	2 weeks of 6.0 g/d	2 weeks of 7.5 g/d	2 weeks of 9.0 g/d
[illegible]	[illegible]							
[illegible]	N	[illegible]	20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Mean	[illegible]	89.7	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	[illegible]	4.50	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	N	[illegible]	20	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	Mean	[illegible]	89.4	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
	SD	[illegible]	3.87	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Whole Night	N	19	20	[illegible]	19	21	20	20
	Mean	88.5	88.3	[illegible]	87.5	88.0	87.9	88.6
	SD	4.58	4.35	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

[illegible] p ≤ 0.01 compared with baseline (t test).
[illegible] p ≤ 0.05 compared with baseline (t test).

The following are noteworthy, from the viewpoint of this reviewer

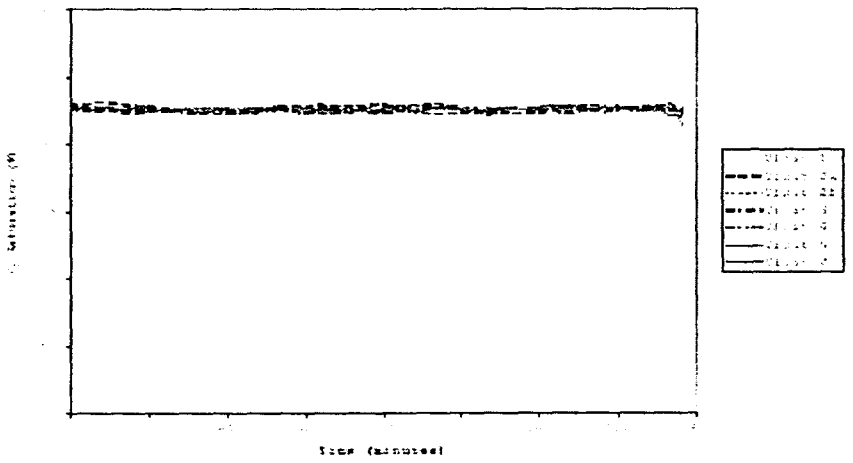
- Unlike with the respiratory event parameters, individual variability in SaO_2 was minimal
- No prominent changes were seen in any SaO_2 parameters as compared with baseline
- No dose response was apparent with any parameter
- The only "statistically significant" ($p < 0.05$), but clinically very small, change in any parameter was in continuous SaO_2 at Visit 3 for the first half of the night and for the whole night.

8.6.10.2 By-Patient Plots

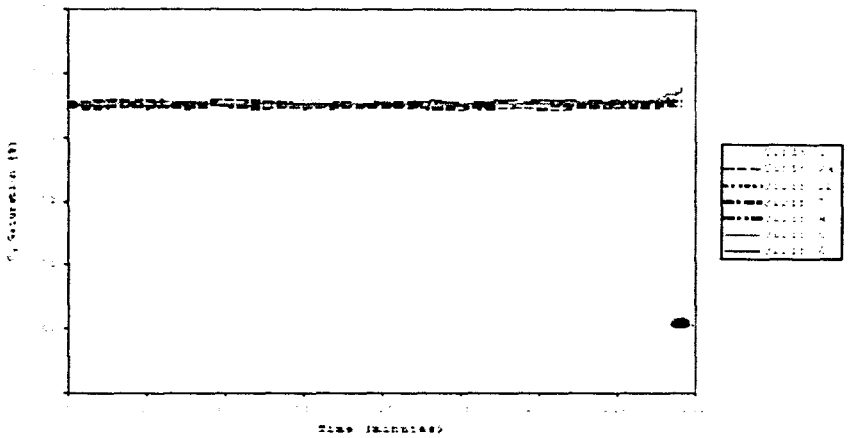
8.6.10.2.1 Continuous Oxygen Saturation

5-minute data are shown for the first half of the night and second half of night in figures copied from the submission

Mean Continuous Oxygen Saturation (5-Minute Data) vs. Time, by Visit - First Half of Night



Mean Continuous Oxygen Saturation (5-Minute Data) vs. Time, by Visit - Second Half of Night



As the above tables indicate this parameter showed no prominent changes in individual patients during the course of the study.

8.6.10.2.2 Intermittent Oxygen Saturation

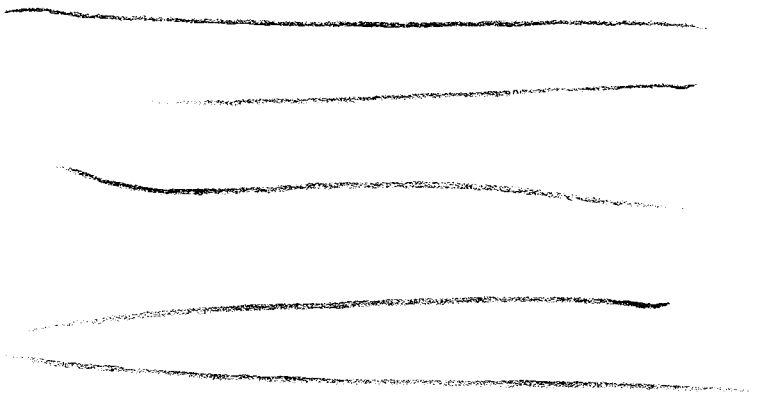
Random low SaO_2 levels were seen in a few patients without any evidence of a dose response

8.6.10.2.3 Duration Of Oxygen Desaturation Less Than 90%

This parameter was expressed a percentage of a 4-hour period.

The next figure, copied from the submission, provides a plot for this parameter for the first half of the night

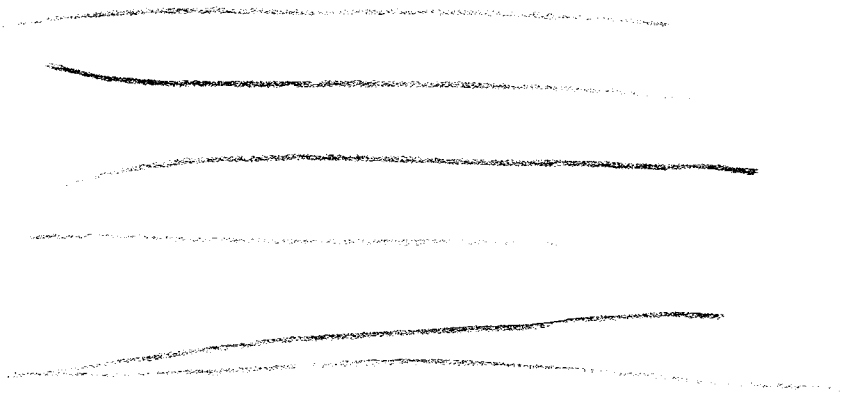
The next figure, also copied from the submission, provides a plot for this parameter for the second half of the night



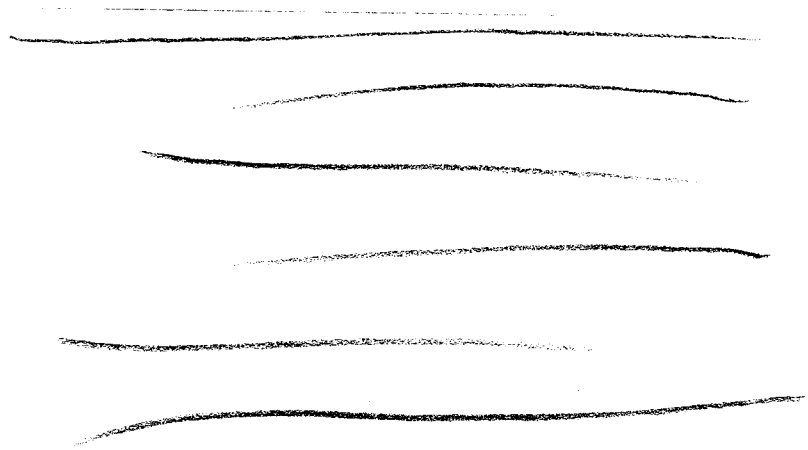
As the plots above indicate this parameter for the first half of the night increased during the course of the study for Patient 17301, and showed sharp fluctuations during the night for the same patient during the second half of the night across the course of the study.

8.6.10.2.4 Lowest SaO_2

The lowest oxygen saturation by-patient, by-visit profile for individual patients for the first half of the night is in the following figure, copied from the submission



The profile for the second half of the night is in the next figure, also copied from the submission.



The profiles for each half of the night do not show prominent changes for individual patients in this parameter.

8.6.11 Outliers For Respiratory Event And Oxygen Saturation Data

11 patients were outliers in regard to respiratory event and/or oxygen saturation data. They are summarized in the following table which I have copied from the submission.

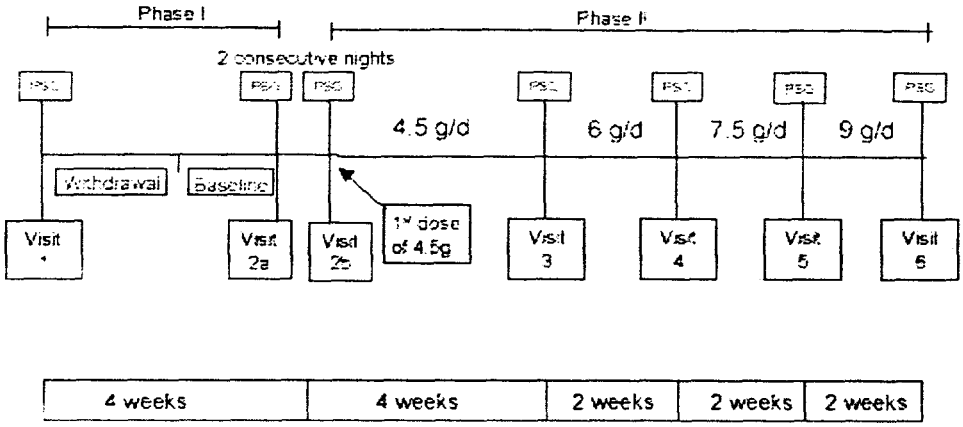
APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

Patient Number	Deviation	Visit Number(s)	
		1st Half of Night	2nd Half of Night
[illegible]	Decreased continuous SaO2 (5-minute data)	2a, 3, 4, 5, 6	2a, 5, 6
	Decreased intermittent SaO2 (5-minute data)	2a, 3, 4, 5, 6	2a, 5, 6
	Increased AHI (NREM) Increased AHI (REM)	3, 4, 5, 6 2a, 4, 5, 6	3, 4, 5, 6 2a, 3, 4, 6
	Increased OMAs	3, 4, 5, 6	3, 4, 5, 6
	Increased hypopneas	3, 4, 6	3, 4, 5, 6
	Increased RDI	3, 4	3, 4, 5, 6
	Increased time SaO2 < 90	2a, 2b, 3, 4, 5, 6	2a, 2b, 3, 4, 5, 6
[illegible]	Increased AHI (REM)	3, 4	3, 5
	Increased hypopneas	2a, 3	2a, 3
[illegible]	Increased AHI (NREM) Increased AHI (REM)	3, 4 3, 4	1, 3, 4 3, 4
	Increased OMAs	1, 2a, 3, 4	1, 2a, 3, 4
	Increased central apneas	3, 4	3, 4
	Increased hypopneas	3, 4	
	Increased RDI	3, 4	1, 2a, 3, 4
[illegible]	Increased continuous SaO2 (nadir of 77% at 150 min)		2a
	Decreased intermittent SaO2 (nadir of 75.5% at 150 min)		2a
[illegible]	Increased central apneas		5, 6
[illegible]	Increased hypopneas	5	3, 5
[illegible]	Increased AHI (REM)	3, 5, 6	
	Increased RDI	3, 5	
[illegible]	Decreased continuous SaO2	1	
	Decreased intermittent SaO2	1, 3	
[illegible]	Decreased intermittent SaO2 (nadir of 78.7% at lights on)		4
	Increased central apneas	1, 2a, 2b, 3, 4, 5, 6	1, 2a, 2b, 3, 4, 5, 6
	Increased RDI	1, 2a, 2b, 3, 4, 5, 6	1, 2a, 2b, 3, 4, 5, 6
[illegible]	Increased intermittent SaO2	1	

Patient Number	Deviation	Visit Number(s)	
		1st Half of Night	2nd Half of Night
[illegible]	Decreased intermittent SaO2 (nadir of 82.7% at lights-on)		2a
	Increased central apneas		6

So that the visit numbers can easily be correlated with the phases of the study, I have reproduced the sponsor's study design diagram below



The data in the table indicate that

- Only 2 patients (#s 017301 and 017304) had a worsening with sodium oxybate across a number of respiratory event parameters
- Only 1 patient (#017301) had a clear worsening in an SaO_2 parameter – duration of SaO_2 < 90% - after being treated with sodium oxybate. For measurements done during the first half of the night a steady increase was seen over the course of the trial beginning at a dose of 6 g/day. For measurements done during the second half of the night this parameter showed prominent fluctuations during the course of the study. The changes in SaO_2 in this patient did not however correlate temporally with the changes in respiratory event parameters.

8.6.12 Discontinuations Due To Adverse Event

A single patient discontinued treatment with Xyrem® on account of a respiratory adverse event. The narrative for this patient is below; this narrative was created from the narrative and Case Report Form provided by the sponsor.

This patient (#017304) was a 67 year old woman with a known history of narcolepsy (for 25 years), tonsillectomy, breast cancer in remission (treated with lumpectomy and radiation) and obstructive sleep apnea-hypopnea syndrome (confirmed by polysomnogram done over 1 ½ years prior to her enrollment). Concomitant medications included venlafaxine and modafinil.

At screening this patient had a false-positive urine test for benzodiazepines. After entering the OMC-SXB-20 trial she failed to attend Visit 3 (on trial date 29) and indicated a desire to discontinue medication. However she then changed her mind and attended Visit 3 on Day 36. On Day 51, a day after beginning Xyrem® in a dose of 7.5 g/day she reported being "really sensitive" and her husband noted worsening snoring, and frequent and more severe episodes of apnea. By that time she had been treated with the following doses of Xyrem®: 4.5 g/day for 35 days and 6.0 g/day for 14 days. Xyrem® was discontinued on Day 51 on account of a perceived worsening in her obstructive sleep apnea-hypopnea syndrome. The adverse event was reported to have resolved by Day 52.

Several objective parameters – AHI (NREM), OMAs and RDI – all measured during the second half of the night showed no worsening at Visits 3 and 4 as compared with Visits 1 and 2a. SaO_2 data showed no abnormalities. However the following were seen only at Visits 3 and 4

- Increased AHI (REM and NREM), central apneas, hypopneas, and RDI during the first half of the night

- Increased AHI (REM) and central apnea during the second half of the night

A further patient also discontinued treatment on account of an adverse event

This 56 year old woman (#42305) 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

8.7 Sponsor's Conclusions

- There did not appear to be a clear relationship to dose for the changes in any of the respiratory event measures, or SaO_2, in this study. Although nominally statistically significant differences between specific doses were seen for a few parameters these changes were not consistent across increasing dose, i.e., there was no clear dose-response relationship
- In earlier human pharmacokinetic studies the C_{max} and AUC had been consistently higher after the second nightly dose of Xyrem® than after the first dose. The respiratory event parameters and SaO_2 were therefore compared between the two halves of the night, on the assumption that the first and second halves of the night would correspond to the effects of the first and second doses, respectively. There was no overall difference in these parameters between the 2 halves of the night although several individual patients appeared to have more central apneas during the second half of the night

  In addition
  - The t_{max} of Xyrem® ranges from 45-60 minutes. There was no evidence of a fall in SaO_2 corresponding to the 1-2 hour period after dosing
  - Sodium oxybate shows non-linear pharmacokinetics. An increase in total dose from 4.5 g (in two divided doses 4 hours apart) to 9 g (in two divided doses 4 hours apart) results in a 3.7-fold increase in exposure, based on AUC. No increase in respiratory event data or decrease in SaO_2 was seen with an increase in dose from 4.5 g to 9 g
- Respiratory patterns are normally different between REM and NREM sleep. Respiratory event and SaO_2 data were therefore compared between REM and NREM sleep in this study. Although there were slight but variable differences between parameters at individual visits, there were no overall differences between REM and NREM sleep, and no changes with increasing dose.
- 2 patients had respiratory effects that could be considered clinically significant
  - Patient #17304 (see Section 8.6.12) discontinued treatment on account of a subjective worsening in pre-existing sleep apnea. However several objective respiratory event measures were no worse during the second half of the night than during the first
  - Patient #17301 (see Section 8.6.9.3) had a prominent increase at Visit 3 (after a Xyrem® dose of 4.5 g/day for 4 weeks), relative to baseline, in the following: obstructive and mixed apneas, hypopneas, AHI and RDI. The sponsor points out that this patient had pre-existing obstructive sleep apnea and obesity.

- The most prominent mean inter-visit changes for the whole cohort were seen between baseline and Visit 3 (after 4 weeks at 4.5 g/day) with increases in OMAs and hypopneas, and a decrease in continuous SaO_2 (5-minute data). While these changes were nominally statistically significant ($p < 0.05$) they were clinically minimal and the same trend did not continue at higher doses
- The respiratory event and SaO_2 measures were sensitive and these 2 categories correlated with each other

8.8 Reviewer's Comments

- It is difficult to draw any firm conclusions from this study regarding the effect of sodium oxybate on respiratory parameters; the reasons for such a view are as follows
  - The study was open-label and uncontrolled
  - The number of patients enrolled was small
  - There was considerable inter-patient variability in changes from baseline in all parameters with standard deviations consistently exceeding means
  - The study was intended to measure the effects of 4 different doses of GHB on sleep architecture and not to assess the effects of that drug on respiration.
  - The only true measures of respiratory function per se in this study were those related to arterial oxygen saturation. The "respiratory event parameters" used in this study were indices of sleep apnea and not of respiratory function, per se
- Among the numerous comparisons made in the sponsor's analysis, some were nominally statistically significant ($p < 0.05$). The clinical significance of the differences seen in most of these comparisons is however highly questionable.
- As the sponsor has also noted the most prominent mean inter-visit changes for the whole cohort were seen between baseline and Visit 3 (after 4 weeks at 4.5 g/day) with increases in obstructive and mixed apneas, and hypopneas, and a decrease in continuous SaO_2 (5-minute data). Again, although these changes were statistically significant they were clinically minimal and may have been driven largely by a single patient (#17301)
- There was no overall tendency in this cohort to a dose-response in regard to respiratory event parameters and SaO_2 (i.e., an increasing effect on respiratory event parameters and SaO_2 with increasing dose of GHB)
- The rather prominent increase in several parameters - obstructive and mixed apneas, hypopneas, apnea-hypopnea index and respiratory disturbance index – relative to baseline in a single patient (#17301) after 4 weeks of treatment with GHB at 4.5 g/day is at least somewhat noteworthy in itself. The same patient also showed a steady increase in the duration of time spent during the first half of the night at an SaO_2 less than 90%. However this patient did have pre-existing obstructive sleep apnea and there is no evidence that the changes in respiratory event parameters and SaO_2 were related to GHB; the respiratory event parameters in fact improved as the dose of GHB was increased through 6, 7.5 and 9 g/day, when it might have been expected that exposure to GHB was increasing.
- It is noteworthy that 18/21 patients who completed the study received stable doses of stimulant drugs throughout the trial. It is not inconceivable that such

drugs may have led to any respiratory depressant effects of GHB becoming less apparent.
- While this study clearly had limitations it cannot be said to provide any evidence that Xyrem® has, or does not have, a respiratory depressant effect.

9. Stimulant Use In Clinical Trials Of Xyrem®

9.1 Background

At the meeting between the sponsor and Division on 7/16/01, the sponsor was requested to provide an analysis of the frequency of stimulant use and overall exposure to stimulants in all 5 clinical trials considered part of the updated Integrated Clinical Trials database (see Safety Review of original NDA for details about this grouping). The clinical trials included in this grouping were as follows: OMC-GHB-2, OMC-GHB-3, Scrima, OMC-SXB-6, and OMC-SXB-7.

The request for this analysis was based on the apparently high incidence of concurrent stimulant use in clinical trials of Xyrem®, and concerns regarding the efficacy and safety of Xyrem® in the absence of stimulants

9.2 Methods

The sponsor's analysis included the overall database, each of the 5 clinical trials included in the above grouping and the 63 patients who transferred from the Scharf long-term open-label study to the OMC-SXB-7 trial

The database was searched for the following generic drug terms and related brand names: dextroamphetamine, pemoline, phentermine, amphetamine, modafinil, methylphenidate and mazindol.

The incidence of any stimulant use, and the person-time exposure to stimulants was calculated.

9.3 Incidence Of Stimulant Use

The incidence of stimulant use is summarized in the following table for the overall database, each of the 5 clinical trials included in the above grouping and the 63 patients who transferred from the Scharf long-term open-label study to the OMC-SXB-7 trial. The table is copied from the submission.

	Yes [a]	No
[illegible] (n = 437)	369 (82.1%)	78 (17.9%)
Placebo (n = 20)	16 (80.0%)	4 (20.0%)
GMT-GHB-2 (n = 136)	116 (85.3%)	20 (14.7%)
GMT-GHB-3 (n = 118)	104 (88.1%)	14 (11.9%)
GMT-GXB-6 (n = 185)	154 (83.2%)	31 (16.8%)
GMT-GXB-7 (n = 234)	172 (73.5%)	62 (26.5%)
[illegible] > GMT-GXB-7 (n = 63)	38 (60.3%)	25 (39.7%)

[a] Includes patients who had stimulant medications that were either prior medications continuing into the trial, or were concomitant medications.

As the table above indicates, overall 82.1% of patients received stimulants during clinical trials in this grouping.

9.4 Duration Of Exposure To Stimulants

The following table, copied from the submission, summarizes the person-exposure to stimulants in those who received such drugs. As the table indicates the percentage of total trial duration for which these patients took stimulants was 93.1% overall.

Patients Taking Stimulants [a]	Mean Trial Duration (days)	Mean Days on Stimulants	Percentage of Trial Duration	Duration of Exposure (Patient-Years) [b]	Mean Days off Stimulants	Percentage of Trial Duration	Duration off Stimulants (Patient-Years) [b]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
Placebo (n = 16)	98.125	16.625	100.0%	5.17	0.0000	0.0%	0
GMT-GHB-2 (n = 116)	28.482	27.620	97.7%	9.61	0.6552	2.3%	0.23
GMT-GHB-3 (n = [illegible])	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
GMT-GXB-6 (n = 154)	177.019	148.879	84.0%	62.82	28.1419	15.9%	9.89
GMT-GXB-7 (n = 174)	285.483	274.764	96.3%	142.29	10.6782	3.7%	5.53
[illegible] > GMT-GXB-7 (n = 38)	378.711	355.632	94.4%	40.22	21.0789	5.6%	2.38

[a] [illegible] patients who had stimulant medications that were either prior medications continuing into the trial, or were concomitant medications.
Mean days on stimulants x number of patients taking stimulants. 1 year = twelve 28-day months, or 336 days.

The next table, also copied from the submission, provides the duration off stimulants for those who took stimulants and those who did not. The total duration off stimulants in the entire Integrated Clinical Trials database for both categories combined was 95.27 patient-years as opposed to 361.85 patient-years for those taking stimulants

Trial	Patients Taking Stimulants [a]		Patients Who Did Not Take Stimulants		
	Number of Patients	Duration off Stimulants (Patient-Years) [b]	Number of Patients	Mean Trial Duration (days)	Duration off Stimulants (Patient-Years) [b]
Total	330	26.96	72	316.776	68.31
Prima	16	0	4	64.000	0.76
GMC-GHB-2	116	0.23	20	27.900	1.66
GMC-GHB-3	104	3.72	14	334.786	13.95	
GMC-GXP-1	194	3.68	3	154.546	14.26
GMC-GXB-7	174	5.53	63	277.403	51.19
Extract → GMC-GXB-7	38	2.38	25	370.64	27.58

[a] Includes patients who had stimulant medications that were either prior medications continuing into the trial, or were concomitant medications.

[b] Mean days on stimulants x number of patients taking stimulants. 1 year = twelve 28-day months, or 336 days.

9.5 Additional Comment By Sponsor

An earlier analysis that the sponsor presented at the meeting with the Division that was held on 7/16/01 underreported the incidence of stimulant use due to the use of fewer terms in the analysis. The current analysis supersedes the earlier one.

10. Risk Management Plan

This section contains several components

- A risk management program summary which is an edited version of that which was attached to the Approvable letter
- The Xyrem® Physician Success Program
- The Xyrem® Patient Success Program

10.1 Summary Of Risk Management Program As Currently Proposed By Sponsor

The sponsor has edited the summary version of the Risk Management Program that was attached to the Approvable letter. The submission includes an annotated and redlined version of the Approvable letter attachment.

The sponsor has also addressed specific issues concerned with the Risk Management Program in the cover letter to the submission (see Section 4.1)

The following is a verbatim version of the Risk Management Program summary as currently proposed

The components of this program are as follows:

10.1.1 Restricted Distribution Program

10.1.1.1 Manufacture

The bulk drug will be manufactured at a single site: [redacted]

The drug product will be manufactured by [redacted]

Following manufacture the drug product will be stored at a facility compliant with Schedule III regulations, where a consignment inventory will be maintained. The inventory will be owned by Orphan Medical, Inc., and the facility will be managed by [redacted] (see below) which will maintain the consignment inventory.

10.1.1.2 Distribution, Pharmacy Services And Registry

The primary and exclusive distributor of Xyrem® to patients will be [redacted] A back-up distributor, currently used for the sponsor's treatment IND # [redacted] Xyrem® will NOT be stocked in retail pharmacy outlets.

The functions of [redacted] will be to

- Dispense Xyrem® to patients
- Distribute Xyrem® Physician Success Program™ materials to patients and physicians
- Maintain inventory and distribution records
- Maintain a patient registry
- Maintain a prescribing physician registry
- Provide patient education and patient support via ongoing contact with patient and a toll-free Helpline

[redacted] will operate in the following manner

- Prescriptions will be faxed by the physician or the physician's office to [redacted]
- Upon receipt of a prescription this company will contact the prescribing physician and/or the physician's office and
  - Identify physician's name, license and DEA registration
  - Verify the prescription
  - Obtain patient insurance information
- [redacted] will then verify that the physician is eligible to prescribe Xyrem® by consulting the [redacted]. This stage of verification will include confirming that the physician has an active DEA number and will check on whether any actions are pending against the physician
- If the physician is a first-time prescriber of Xyrem® that pharmacy will then ship comprehensive printed and video materials to that physician: these materials (see Xyrem® Physician Success Program below) also contain