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*	Placebo	Xyrem Oral Solution Dosage (g/d) at Onset[b]					
			Total*	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%)	2 (2%)	6 (2%)	12 (4%)	5 (4%)	9 (7%)
Patients with SAEs	0	0	0	0	0	0	0	0
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
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

* 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

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