study she complained of knee pain and on Day 31 reported generalized joint pain. At that point Xyrem® was stopped temporarily (it is uncertain for how long) but was then resumed in a dose of 6 g/day. On Day 68 on account of continued generalized joint pain, she was referred to a rheumatologist (details of this consultation are unavailable); treatment with diclofenac 100 mg/day was begun. On Day 131 the patient was stated to have patello-femoral syndrome (presumably she had knee pain at that point). Study medication was then stopped for 3 days, resumed and continued until Day 185. Her generalized arthralgia and knee pain were apparently continuing at her last visit.

8.3.1.5 Patient 1735 (Initials —)

This 26 year old woman participating in OMC-SXB-6 initially took Xyrem® 4.5 g/day for 13 days, followed by 6 g/day for 52 days. On Day 66 she was discontinued from the study on account of her becoming pregnant, a protocol violation. She had a miscarriage on Day 108.

8.3.1.6 Patient 0214 (Initials —)

This 42 year old man participating in OMC-SXB-7, was noted to have abnormal liver function tests at the Month 6 (Day 196) visit; he was taking 9 g/day of Xyrem® at that time. At that time he had a tremor and diaphoresis. His concomitant medications at that time included ascorbic acid, multivitamins, methylphenidate, acetaminophen and pseudoephedrine; earlier he had also taken a butalbital-aspirin combination, zolpidem, tramadol, alprazolam, fluoxetine and paroxetine for unknown periods of time, and modafinil for about 5 months. At that time (Day 196) his liver function studies were as follows: total protein 7.3 g/dl; albumin 4.2 g/dl; total bilirubin 0.6 mg/dl; alkaline phosphatase 135 U/L AST 189 IU/L; ALT 362 IU/L. A further 9 days later (Day 205) his liver functions were: total protein 7.0 g/dl; albumin 4.1 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 112 U/L; AST 141 IU/L; ALT 271 IU/L.

His past medical history was remarkable for migraine, hay fever, a right nephrectomy and known hepatitis C infection.

At the time of his entry into the OMC-SXB-7 study his serum liver function tests were as follows: total protein 7.2 g/dl; albumin 4.2 g/dl; total bilirubin 0.4 mg/dl; alkaline phosphatase 63 U/L AST 27 IU/L; ALT 41 IU/L (all well within normal limits)

On Study Day 205 Xyrem® was permanently discontinued. Results of follow-up liver functions, if any, are not available. It is unclear based on the Case Report Form, if his abnormal liver functions were associated with any symptoms.

8.3.1.7 Patient 0231 (Initials —)

This 67 year old man participating in Study OMC-SXB-6 took Xyrem® in a dose of 4.5 g/day for 12 days and 9 g/day for 106 days. He was reported to experience nausea, vomiting, dizziness, confusion and generalized weakness. His past medical history was remarkable for a stomach ulcer, gastroesophageal reflux disease, and a cholecystectomy. Concomitant medications included clomipramine, methylphenidate, paroxetine, imipramine and modafinil.

Xyrem® was permanently discontinued. Within 24 hours the adverse event had resolved.

8.3.1.8 Patient 1305 (Initials [redacted])

This 73 year old woman participating in Study OMC-GHB-3 became agitated, frightened and restless after taking GHB for 670 days. Her dose of Xyrem® at that time was not recorded; her last recorded dose was 9 g/day and this dose was carried forward. Xyrem® was temporarily stopped, and she was treated at an emergency room with diphenhydramine and lorazepam injections. She was discharged home having apparently recovered, and was able to complete the study (study medication was resumed but it is unclear for how long and in what dose it was administered).

8.3.2 Serious Adverse Events In Scharf Study

54 patients had serious adverse events in the Scharf study. 51 of these patients had serious adverse events that occurred after they started to receive study drug: these adverse events are tabulated below.

	Number Of Patients	Percentage of Patients Participating In Study
Total Number With Serious Adverse Events	51	35.7
Asthenia	5	3.5
Cellulitis	3	2.1
Fever	1	0.7
Headache	1	0.7
Infection	2	1.4
Accidental injury	7	4.9
Neoplasm	1	0.7
Overdose	2	1.4
Pain	6	4.2
Abdominal pain	7	4.9
Back pain	3	2.1
Chest pain	10	7.0
Substernal chest pain	1	0.7
Unevaluated reaction	11	7.7
Angina pectoris	1	0.7
Vascular anomaly	2	1.4
Arrhythmia	1	0.7
Cerebrovascular accident	1	0.7
Coronary artery disease	1	0.7
Right-sided heart failure	1	0.7
Hypertension	1	0.7
Hypotension	1	0.7
Myocardial infarction	3	2.1
Ventricular tachycardia	1	0.7
Anorexia	1	0.7
Gastrointestinal carcinoma	1	0.7
Cholecystitis	3	2.1
Cholelithiasis	2	1.4
Diarrhea	2	1.4
Gastroenteritis	1	0.7
Gastrointestinal hemorrhage	1	0.7
Rectal hemorrhage	1	0.7
Melena	1	0.7
Nausea	2	1.4
Rectal disorder	1	0.7
Duodenal ulcer	1	0.7
Vomiting	3	2.1
Diabetes mellitus	2	1.4
Anemia	1	0.7
Leukocytosis	1	0.7
Rheumatoid arthritis	1	0.7
Anxiety	1	0.7
Coma	1	0.7
Confusion	1	0.7
Convulsion	1	0.7

Depression	1	0.7
Dizziness	2	1.4
Hypesthesia	1	0.7
Stupor	2	1.4
Apnea	3	2.1
Asthma	1	0.7
Lung carcinoma	2	1.4
Dyspnea	9	6.3
Pulmonary embolism	1	0.7
Hemoptysis	1	0.7
Hypoventilation	1	0.7
Lung disease	2	1.4
Pharyngitis	3	2.1
Pneumonia	2	1.4
Respiratory diseases	2	1.4
Skin carcinoma	4	2.8
Melanoma of skin	1	0.7
Skin disease	1	0.7
Skin disorder	3	2.1
Sweating	3	2.1
Bladder calculus	1	0.7
Carcinoma bladder	1	0.7
Carcinoma breast	1	0.7
Urinary incontinence	2	1.4
Unintended pregnancy	1	0.7
Prostate disorder	1	0.7
Urinary frequency	1	0.7
Enlarged uterine fibroid	1	0.7

I have read through the narratives, and Case Report Forms where needed, for the above patients. Serious adverse events that warrant further description are listed below.

8.3.2.1 Patient 012 (Initials —)

This man was 74 years old at the time of study entry. He had a past history of cardiomyopathy, left bundle branch block and sleep apnea. About 2 years after beginning GHB and while taking a dose of 7.5 g daily he had an episode of disorientation, stupor and weakness that necessitated hospitalization and a reduction in dose of GHB to 6 g daily for one day. The episode resolved and did not recur despite the patient continuing to take 7.5 g daily.

8.3.2.2 Patient 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.

8.3.2.3 Patient 019 (Initials —)

This 41 year old man with a past history of depression and suicidal ideation was begun on treatment with GHB in a dose of 5.3 g/day. 6 months later he was hospitalized for treatment of depression at a time when he was taking GHB in a dose of 6 g/day; that medication was interrupted for a day and then resumed at 9 g/day. About 2 years after first beginning the drug he was hospitalized after a suicide attempt that consisted of taking an overdose of GHB. At that time he was dropped from the study

8.3.2.4 Patient 257 (Initials —)

This 32 year old man with a past history of a whiplash injury with numbness and paresthesia in his hands was begun on treatment with GHB 4.5 g daily while concomitantly taking protryptiline. About 3 months later he was seen at a hospital emergency room on account of complaints of chills, sweating, blurred vision, memory loss, and shaking as well as vibrating sensations. A further 6 months later shaking and vibrating sensations occurred again at which time he was also recorded as having attacks of cataplexy at least one of which resulted in a fall. 2 further years later he was hospitalized overnight after an unspecified adverse reaction that was attributed to ingesting too much GHB.

After an additional 2 years on GHB the patient fell on a long butcher knife, and perforated his colon. During the peri-operative period GHB was stopped for 10 days. About 2 months after surgery he was hospitalized on account of hypoxemia and required intubation and mechanical ventilation. Further details are unavailable. GHB was apparently not stopped at the time.

8.4 Dropouts and "Other Significant Adverse Events"

A total of 63 GHB-treated patients permanently discontinued treatment on account of adverse events. Their distribution by study grouping, according to the sponsor, is as follows.

Study Grouping	Total number of patients/subjects in grouping	Number (%) of patients/subjects with adverse events leading to discontinuation
Integrated Clinical Trials	402	44 (10.9%)
Scharf Study	143	19 (13.3%)*
Lammers Study	25	0
Integrated Pharmacokinetic Trials	144	2 (1.4%)

*Note that the sponsor has counted 7 deaths as discontinuations due to adverse events. The actual adverse event discontinuation rate is 12/143 or 8.4%.

A single placebo-treated patient (# 0818; initials ——) participating in OMC-GHB-2 discontinued treatment 1 month after study entry on account of insomnia (see Section 8.4.1)

These adverse event discontinuations are further discussed under the 3 study groupings in which they occurred.

8.4.1 Adverse Event Discontinuations In Integrated Clinical Trials

44 patients discontinued treatment on account of adverse events in this grouping

Of the 44 patients who discontinued treatment in the Integrated Clinical Trials Grouping, 10 discontinued treatment in the 3 controlled clinical trials; all 10 participated in OMC-GHB-2. The adverse events that led to treatment discontinuation in OMC-GHB-2 (n = 136) were as follows

Nausea 2.9%
Somnolence 2.2%
Confusion 1.5%
Amnesia, asthenia, chest pain, dizziness, dyspnea, hyperkinesia, fecal incontinence, insomnia, paranoid reaction, thinking abnormal, vertigo, and vomiting each 0.7%.

A listing of patients who discontinued treatment in OMC-GHB-2 is as follows; as the table indicates these adverse events were dose-related. Also note, however, that individual doses were not titrated in this study.

Patient Number	Preferred term [investigator term]
Placebo	
818	Insomnia [insomnia]
3g GHB	
901	Nausea [nausea], somnolence [lethargy], pain chest [chest pressure]
6g GHB	
207	Confusion [acute confusional state]
509	Hyperkinesia [restless leg increased], headache [headache]
9g GHB	
221	Somnolence [increased sleepiness], dizziness [dizzy], nausea [nauseated], and asthenia [weakness (had difficulty standing)]
605	Somnolence [daytime sedation feeling: "drugged feeling"], thinking abnormal [poor concentration]
702	Confusion [confusion], hallucinations [hallucinations], amnesia [forgetfulness], nausea [nausea], paranoid reaction [paranoia]
824	Dyspnea [difficulty breathing]
1201	Incontinence fecal [patient lost bowel control while asleep]
1504	Nausea [nausea], vertigo [vertigo], vomit [vomiting]

The following table, supplied by the sponsor, provides a summary for 38 out of 44 patients who discontinued treatment on account of an adverse event in the entire Integrated Clinical Trials grouping. In these 38 patients discontinuation was considered to be treatment-related by the investigator.

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