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 ---)

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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Patient ID	Trial	Dosage at Onset (g/d)	Trial Day*		Investigator Term	COSTART Preferred Term	Serious	Severity
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	OMC-GHB-1	6.0	7	9	Active confusional state	Confusion	Yes	Severe
0219	OMC-GHB-3	9.0	90	105	Depressed mood	Depression	No	Moderate
		9.0	91	105	Excessive tiredness	Asthenia	No	Moderate
0221	OMC-GHB-2	9.0	13	15	Dizzy	Dizziness	No	Moderate
		9.0	13	15	Increased sleepiness	Somnolence	No	Moderate
		9.0	13	15	Nauseated	Nausea	No	Moderate
		9.0	13	15	Weakness (had trouble standing)	Asthenia	No	Moderate
	OMC-GHB-3	9.0	88	106	Lethargic all day	Somnolence	No	Mild
0231	OMC-SXB-6	9.0	119	119	Dizziness	Dizziness	Yes	Severe
		9.0	119	119	Confusion	Confusion	Yes	Severe
		9.0	119	119	Nausea	Nausea	Yes	Severe
		9.0	119	119	Vomiting	Vomiting	Yes	Severe
		9.0	119	119	Vertigo	Vertigo	Yes	Severe
		9.0	119	119	Weakness	Asthenia	Yes	Severe
0236	OMC-SXB-6	4.5	170	170	Respiratory failure	Apnea	Yes	Severe
		4.5	170	170	Non-responsive	Coma	Yes	Severe
0319	OMC-GHB-3	9.0	41		Weight loss	Weight loss	No	Mild
0509	OMC-GHB-2	6.0	1	2	Restless leg syndrome increased	Hyperkinesia	No	Severe
0533	OMC-SXB-6	4.5	13		Swelling in legs	Peripheral edema	No	Severe
0615	OMC-GHB-2	9.0	9	12	Daytime sedation feeling; "drugged feeling"	Somnolence	No	Mild
		9.0	9	12	Poor concentration	Thinking abnormal	No	Mild
0637	OMC-SXB-6	7.5	93*		Restless legs	Hyperkinesia	No	Moderate
		7.5	92*		Anxiety	Anxiety	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day*		Investigator Term	COSTART Preferred Term	Serious	Severity
0701	OMC-GHB-3	6.0	32		Decreased sexual libido	Libido decreased	No	Moderate
		6.0*	32		Decreased initiative to start any activity by gradual progression	Apathy	No	Mild
0702	OMC-GHB-2	9.0	20	25	Confusion	Confusion	No	Moderate
		9.0	20	25	Forgetfulness	Amnesia	No	Moderate
		9.0	20	23	Hallucinations	Hallucinations	No	Moderate
		9.0	21	21	Nausea	Nausea	No	Mild
		9.0	22	24	Paranoia	Paranoid reaction	No	Mild
0801	OMC-GHB-3	9.0	147	179	Chest pain, patient on drug, no hospitalization, no concomitant medication	Chest pain	No	Moderate
0802	OMC-GHB-3	9.0	49	55	Nervousness	Nervousness	No	Moderate
		9.0	49	51	Metallic taste	Taste perversion	No	Mild
		9.0	49	51	Upset stomach	Dyspepsia	No	Moderate
0809	OMC-GHB-3	3.0	332	332	Inability to control body 1 h after taking medicine	Incoordination	No	Mild
0818	OMC-GHB-2	Placebo	23		Insomnia	Insomnia	No	Moderate
0821	OMC-GHB-2	6.0	39	51	Headaches	Headache	No	Moderate
		6.0	40	51	Irritable	Nervousness	No	Moderate
0824	OMC-GHB-2	9.0*	5	6	Difficulty breathing	Dyspnea	No	Severe
	OMC-GHB-3	3.0	25	29	Difficulty breathing	Dyspnea	No	Moderate
0836*	OMC-SXB-6	4.5	1		Headache	Headache	No	Moderate
0844	OMC-SXB-6	4.5	1	42	Nausea	Nausea	No	Moderate
		4.5	1	42	Vomiting	Vomiting	No	Moderate
		4.5	1	42	Headaches	Headache	No	Severe

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[1] Start	Trial Day[1] Stop	Investigator Term	COSTART Preferred Term	Serious	Severity
0911	OMC-SXB-2	3.0	2	16	Lethargy	Somnolence	No	Mild
		9.0	2	10	Nausea	Nausea	No	Moderate
		3.0	3	18	Chest pressure	Chest pain	No	Mild
1101[2]	OMC-SXB-3	4.5	156		Acute psychosis	Psychosis	No	Moderate
1134	OMC-SXB-6	4.5	3		Urinary incontinence	Urinary incontinence	No	Moderate
1142	OMC-SXB-6	7.5	31	34	Left eye exposure keratitis	Keratitis	No	Mild
1201	OMC-SXB-2	9.0	5	5	Patient lost bowel control while asleep	Incontinence, fecal	No	Moderate
1504	OMC-SXB-2	9.0	2	2	Nausea	Nausea	No	Severe
		9.0	2	2	Vertigo	Vertigo	No	Severe
		9.0	2	2	Vomiting	Vomiting	No	Severe
1631	OMC-SXB-6	6.0	23	59	Sleepwalking	Sleep disorder	No	Moderate
		4.5	44	59	Fragmented sleep	Sleep disorder	No	Severe
		4.5	44	60	Involuntary limb movements in sleep	Sleep disorder	No	Moderate
1745	OMC-SXB-6	6.0	108	109[3]	Miscarriage	Abortion	Yes	Mild
2532	OMC-SXB-4	4.5	16	43	Sleepwalking	Sleep disorder	No	Mild
		4.5	16	43	Dizziness	Dizziness	No	Mild
		4.5	39	43	Arms and legs numb	Paresthesia	No	Mild
2533[4]	OMC-SXB-6	4.5	25	81	Nausea	Nausea	No	Moderate
		6.0	74	81	Morning drowsiness	Somnolence	No	Moderate
2547[4]	OMC-SXB-6	4.5	12		Increased headaches	Headache	No	Moderate
2602	OMC-SXB-6	4.5	2	4	Increased awakenings	Sleep disorder	No	Mild
		4.5	2	4	Tongue paresthesia	Paresthesia	No	Mild
2648	OMC-SXB-6	4.5	29		"Phlegm/knot" in throat	Pharyngitis	No	Moderate
1291	OMC-SXB-6	6.0	56		Exacerbation of colitis (Crohn's disease)	Colitis	No	Moderate

(continued)

Patient ID	Trial	Dosage at Onset (g/d)	Trial Day[1] Start	Trial Day[1] Stop	Investigator Term	COSTART Preferred Term	Serious	Severity
2633	OMC-SXB-6	7.5	55	62	Nausea	Nausea	No	Moderate
		7.5	56	58	Vomiting	Vomiting	No	Moderate
3611	OMC-SXB-6	3.0	15	24	Itching and swelling of extremities	Pruritus	No	Moderate
		3.0	15	24	Itching and swelling of extremities	Edema	No	Moderate
3620	OMC-SXB-6	4.5	2	3	Sleep paralysis	Sleep disorder	No	Moderate

[1] Day relative to start of treatment.
[2] Patient 0609 was not listed as discontinued on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.
[3] Whole or partial data imputed from start of trial medication.
[4] Dosage carried forward.
[5] Patients 0936, 2632, 2633, and 2547 were listed as discontinuing due to a lack of efficacy on the end-of-trial page of the case report form, but had an AE action of "permanently discontinued" on the AE page.
[6] After subsequent analysis by the principal investigator, the AE of psychosis for patient 1101 was determined to be not related to trial medication.
[7] Patient 1745 discontinued trial medication on Day 64, due to a presumed protocol violation (pregnancy).

Of the patients listed in the table above, short narratives have already been provided under the discussion of Serious Adverse Events above for the following: #s 0207, 0231, 0238 and 1735. Brief narratives are provided for the following additional patients. Narratives for more patients do not appear to be needed based on a review of the data provided by the sponsor.

8.4.1.1 Patient 0221 (Initials —)

This 57 year old woman was enrolled in the OMC-GHB-2 trial and was begun on GHB in a dose of 9 g/day. 12 days later she complained of increased sleepiness along with dizziness, nausea and weakness (with difficulty maintaining an upright posture). GHB was discontinued and her symptoms resolved. She was next enrolled in OMC-GHB-3 during which her most common dose of GHB was 6 g/day; while taking a dose of 3 g/day, her initial dose, she reported excessive somnolence from the first day in the trial onward. After about 1.5 months of participation in OMC-GHB-3, the study drug was stopped permanently with resolution of this adverse event

8.4.1.2 Patient 3831 (Initials —)

This 31 year old woman with a previous history of eczema was enrolled in OMC-SXB-6. She took Xyrem® 4.5 g/day for 10 days followed by 3 g/day for 2 days; she then experienced itching and swelling of her extremities leading to discontinuation of GHB on Day 13. By Day 24 both itching and extremity swelling had resolved.

The 6 remaining patients who discontinued study drug permanently on account of adverse events and are not listed above are summarized in the table below. In these patients the adverse events that lead to treatment discontinuation were not considered to be drug-related

Patient ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
0123 — OMC-GHB-2	F 22.1	6.0	42	None	Unintended pregnancy	"Unresolved"
0208 — OMC-GHB-3	M 26.7	9.0	43	525	Twitching	Resolved
0504 — OMC-GHB-3	F 44.4	60	30	352	Memory loss	Resolved
0214 — OMC-SXB-7	M 42.9	9.0	877	None	Abnormal liver function tests	Unresolved
2634 — OMC-SXB-6	F 51.2	4.5	38	None	Sinusitis Generalized edema	Unresolved
3533 — OMC-SXB-6	M 52.6	9.0	86	None	Apnea (sleep apnea)	Unresolved

A narrative for Patient # 0214 has already been provided under the discussion of Serious Adverse Events. Narratives are provided below for 2 additional patients

8.4.1.3 Patient 0504 (Initials —)

This 45 year old woman participated first in OMC-GHB-2 and then in OMC-GHB-3 for a total period in these trials of 10 months. While taking Xyrem® in a dose of 6 g/day in

OMC-GHB-3 she was reported to have lapses of memory each afternoon. Xyrem® was stopped and this adverse event resolved.

8.4.1.4 Patient 3533 (Initials ,—)

This 52 year old man participating in OMC-SXB-6 had no significant past medical history. At entry into the study he was begun on GHB in a dose of 4.5 g/day. This dose was gradually increased in steps to 9 g/day. After 4 days on the last dose and after 86 days of treatment with GHB he was noted to have sleep apnea which was judged to be severe and lead to Xyrem® being stopped. The adverse event did not resolve after the study drug was stopped

8.4.2 Adverse Event Discontinuations In Scharf Trial

According to the sponsor, 19 patients withdrew from this study because of adverse events. They are listed in the following table which I have copied from the submission. Note that of the 19 patients listed, 7 patients were "withdrawn" because of death; ordinarily such patients would not be considered as having withdrawn due to adverse events. **An eighth patient (# 064; Initials —) is incorrectly listed in this table as having died**

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Pt No.:	Age[1]	Sex	Duration of Exposure (yr)[1]	Reason for patient withdrawal (as provided by the site)
001[2]	51	M	5.7	Death due to metastatic colon carcinoma
006	55	F	4.7	Increased difficulty sleeping, hospital admission to assess suspected psychiatric problem
013[2]	68	M	10.0	Died (2/95) last recorded dose gamma was 11/94. Death due to arteriosclerotic cardiovascular disease
014[2]	49	M	8.6	Death due to cardiac arrhythmia
019	43	M	2.0	Patient attempted suicide (unsuccessfully)
032[2]	74	F	10.2	Death due to lung cancer
053[2]	57	M	10.4	Died 10-10-94, heart attack
064[2]	15	F	1.8	Increased seizure activity
066	50	F	6.1	Repeated high ANA tests (antinuclear antibodies)
200[2]	71	M	5.4	Patient expired from lung cancer
232[2]	69	M	4.8	Death due to bladder cancer; CAD, and cardiac arrest
238	47	M	1.9	Decrease in short term memory
243[2]	63	M	4.7	Weight loss
244	56	F	3.9	Elevated ANA, possible Lupus Syndrome
247	34	F	0.8	Seizure
254	63	F	1.2	Interstitial infiltrate possible, pulmonary toxicity
259	41	F	0.1	Complains of feeling like zombie, stiffness in legs
271	46	M	0.5	Swelling
273	68	F	0.9	Weight loss

[1]Age and duration of exposure were based on the time of the last change in the dosage of study medication.

[2]Patients (n = 8) who died after withdrawing from the study. See Table 15 - Deaths.

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After reading through the sponsor-supplied narratives, and Case Report Forms (when needed) for the above patients further details are provided for the following patients. Patient # 019 has already been described in the discussion of Serious Adverse Events.

8.4.2.1 Patient 005 (Initials —)

This 53 year old woman was reported to have developed anger, hostility and suspiciousness, while taking dextroamphetamine and other stimulants, prior to study entry. She was begun on GHB in a dose of 5.3 g/day; concomitant medications include clomipramine as well as caffeine tablets. After taking GHB for 4.7 years that drug was discontinued when the patient had difficulty sleeping and "psychiatric problems" that were considered similar to those that occurred when she was taking stimulants. She required a psychiatric hospitalization, the outcome of which and her subsequent course are unknown.

8.4.2.2 Patient 064 (Initials —)

This 15 year old girl had a previous history of a left frontal lobe lesion, previous burr hole placement after a "concussion" and headaches. Concomitant medications at study entry included protriptyline and methylphenidate. She received treatment with GHB for 1.8 years at a mean dose of 6 g/day. While on treatment she was reported to have "increased seizure activity" (no details of the seizures are provided; it is not clearly stated that she had seizures prior to study entry), increased urinary frequency, headache, vomiting, dyslexia, an increased appetite and shortness of breath. The increased seizures reportedly led to hospitalization and to discontinuation from the study, although the last date of medication administration is listed as being unknown. No further details are provided.

8.4.2.3 Patient 066 (Initials —)

This 50 year old woman had a past medical history of hypertension, occasional chest pain, a dry skin rash, penicillin allergy, a hysterectomy and weight gain of 45 kg over 9 years. Concomitant medications at study entry included triamterene-hydrochlorthiazide, clorazepate and methylphenidate. She took GHB for a total of about 6 years, most commonly in a dose of 7.5 g/day. After a little less than 6 years of treatment she was noted to have an anti-nuclear antibody titer of 1:640 (this test was not performed earlier in the study). Over the next 3 months successive antinuclear antibody titers were 1:1280 and >1:2560, respectively. GHB was stopped; over the next 11 months follow-up antinuclear antibody titers were always > 1:160 (in a range of 1:160 to 1:1280). A diagnosis of drug-induced lupus was apparently considered. Antihistone antibody testing was not done.

The above summary is based on information obtained from the Case Report Form and sponsor narrative. However the sponsor has also supplied the following documents

- An abstract published by Dr Scharf in 1993 indicated that the same patient (whose identity was confirmed separately by Dr Scharf) developed "clinical symptoms suggestive of arthritis" after having received GHB for 68 months
- A letter to the sponsor from Dr Scharf dated 7/24/98, had been on GHB for 72 months at which time she was diagnosed to have rheumatoid arthritis was diagnosed

This diagnosis appears to have been made a few months before her first, positive antinuclear antibody test. Further clinical details are unavailable.

g/day. A further 8 days later the dose was reduced to 0.8 g/day. As her symptoms had not resolved a month later the drug was stopped. No additional information is available; it is unclear if her symptoms eventually resolved.

8.4.3 Adverse Event Discontinuations In Integrated Pharmacokinetic Trials

2 subjects discontinued study participation on account of adverse events. They are summarized in the table below:

Subject ID Initials Study #	Gender Age (years)	GHB Dose At Onset Of Adverse Event (g/day)	Study Day When Adverse Event Began	Study Day When Adverse Event Ended	Adverse Event	Outcome After Study Drug Discontinuation
ID # 012 —— OMC-SXB-9	F 30	4.5*	After initial dose	Unclear	Headache, nausea and diarrhea	Adverse events resolved
ID # 003 —— OMC-SXB-11	F 39	4.5**	After initial dose	5 hours after onset	Dizziness, nausea, vomiting, apneic episodes and fecal incontinence***	Adverse events resolved

*Administered in 2 divided doses of 2.25 g each, 4 hours apart
**Administered in a single dose of 4.5 g

***2 hours after her initial and only dose of GHB this subject began experiencing dizziness, nausea and vomiting. At the same time or shortly afterward the patient also experienced a single 2-minute period of apnea, a generally depressed depth of respiration and fecal incontinence. She was treated by rolling her over on her side, and administering oxygen by mask for several minutes on 2 occasions. All adverse events resolved over a period of about 5 hours after they first began. This summary is based on a review of the sponsor-supplied narrative and Case Report Form

In a further communication dated 2/23/01 the sponsor had, at my request, submitted further information about subject # 003 (initials —— , participating in Study # OMC-SXB-11. The information is as follows:

- This patient weighed 137 lbs (62.3 kg) and was 63 inches in height
- She received a single 4.5 g dose of GHB after a 10 hour fast
- 30 minutes after dosing she reported dizziness
- One hour after dosing and while asleep in the supine position she had labored, "decreased" respiration with inspiratory stridor. She did not improve with repositioning and was then apneic briefly before the episode resolved on stimulation and application of an oxygen mask
- After stimulation she awoke and vomited once.
- She then fell asleep again. 1 further hour later, and 2 hours after dosing her she vomited twice and then had a further episode of stridor (when lying on her side) and a brief pause in spontaneous respiration that again responded to stimulation and the use of an oxygen mask. At the same time she was fecally incontinent, but had her eyes open, could respond to verbal commands and was not observed to have any "seizure-like movements"
- 2 further hours later she was able to consume most of the offered lunch.
- Pulse and blood pressure remained normal throughout

The sponsor further stated that this food-effect pharmacokinetic study confirmed that exposure (based on C_{max} and AUC) was significantly increased, and t_{max} delayed, in the fasted state

8.5 Adverse Events Incidence Tables

8.5.1 Approach to Eliciting Adverse Events

Approaches used differed based on the clinical trial grouping, as discussed below.

8.5.1.1 Integrated Clinical Trials

In this clinical study grouping the following approach was used.

- Adverse events that occurred during the trial and up to 10 days after the last dose of study medication were recorded in detail on the appropriate page of the Case Report Form
- The frequency, severity, seriousness and relationship to study medication was recorded. A serious adverse event was defined using standard criteria. Serious adverse events were not recorded in the Scrima trial

- Medication dosage at which the adverse event began was also recorded

8.5.1.2 Lammers Trial

Only the incidence of adverse events was recorded. Serious adverse events were not recorded.

8.5.1.3 Integrated Pharmacokinetic Trials

The frequency, severity, seriousness and relationship to study medication were each recorded in a variable number of studies

8.5.1.4 Scharf Trial

The following is stated

- Adverse events were recorded retrospectively on Case Report Forms from information recorded by patients in daily diaries and from investigator-maintained medical records.
- The seriousness, severity and relationship to study medication of these adverse events was also recorded.
- A serious adverse event was defined using standard criteria

8.5.2 Adverse Events Categorization and Preferred Terms

Adverse events were initially entered in Case Report Forms using investigator terms, but were tabulated in the Integrated Summary of Safety and in the majority of study reports using

8.5.3 Key Adverse Events Tables

Key adverse event tables are grouped as follows

8.5.3.1 Controlled Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of patients in each treatment group in the following controlled clinical trials, combined: OMC-GHB-2, Lammers and Scrima.

Body System COSTART Preferred Term	Total[a]	Placebo	Sodium Oxybate
Number of patients	226 (100%)	79 (100%)	147 (100%)
Patients with ≥ 1 AE	130 (58%)	39 (49%)	101 (69%)
Body as a Whole	79 (35%)	24 (30%)	60 (41%)
Headache	39 (17%)	12 (15%)	29 (20%)
Infection	11 (5%)	1 (1%)	10 (7%)
Pain	19 (8%)	3 (4%)	17 (12%)
Cardiovascular System	11 (5%)	2 (3%)	9 (6%)
Digestive System	46 (20%)	9 (11%)	37 (25%)
Dyspepsia	14 (6%)	5 (6%)	9 (6%)
Nausea	28 (12%)	4 (5%)	24 (16%)
Vomiting	10 (4%)	1 (1%)	9 (6%)
Musculoskeletal System	9 (4%)	1 (1%)	8 (5%)
Nervous System	80 (35%)	17 (22%)	66 (45%)
Confusion	12 (5%)	1 (1%)	11 (7%)
Dizziness	36 (16%)	2 (3%)	34 (23%)
Nervousness	12 (5%)	6 (8%)	7 (5%)
Sleep disorder	15 (7%)	2 (3%)	13 (9%)
Somnolence	24 (11%)	7 (9%)	17 (12%)
Respiratory System	20 (9%)	6 (8%)	14 (10%)
Skin	15 (7%)	4 (5%)	11 (7%)
Special Senses	10 (4%)	3 (4%)	7 (5%)
Urogenital System	24 (11%)	7 (9%)	18 (12%)
Incontinence, urine	8 (4%)	0	8 (5%)

[a] Two of the trials (Scrima and Lammers) were crossover trials, with patients in both the placebo and sodium oxybate groups.

As the above table indicates

- The proportion of patients with adverse events was higher in those treated with GHB than in those treated with placebo
- The most common adverse events in those treated with GHB were headache, nausea and dizziness. All 3 were more common in those treated with GHB than in those treated with placebo; nausea and dizziness were > 3-fold more common in the GHB group

8.5.3.2 Integrated Clinical Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of patients in each treatment group in all studies in the Integrated Clinical Trials grouping. The dose listed is that at onset of the adverse event.

Body System COSTART Preferred Term	Total*	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total*	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	94 (100%)	396 (100%)	94 (100%)	266 (100%)	290 (100%)	116 (100%)	116 (100%)
Body as a Whole	200 (50%)	26 (46%)	196 (49%)	36 (41%)	76 (29%)	96 (32%)	28 (24%)	47 (40%)
Abdominal pain	29 (7%)	1 (1%)	28 (7%)	6 (6%)	5 (2%)	9 (3%)	3 (3%)	5 (4%)
Accidental injury	27 (7%)	0	27 (7%)	5 (6%)	8 (3%)	10 (3%)	3 (3%)	6 (5%)
Asthenia	31 (8%)	2 (2%)	30 (8%)	4 (4%)	6 (2%)	16 (6%)	4 (3%)	8 (7%)
Back pain	27 (7%)	3 (4%)	25 (6%)	2 (2%)	5 (2%)	10 (3%)	5 (4%)	8 (7%)
Chest pain	19 (5%)	0	19 (5%)	2 (2%)	5 (2%)	7 (2%)	3 (3%)	4 (3%)
Flu syndrome	34 (8%)	2 (2%)	32 (8%)	4 (4%)	7 (3%)	13 (4%)	7 (6%)	5 (4%)
Headache	107 (27%)	12 (22%)	103 (26%)	17 (18%)	39 (15%)	38 (13%)	11 (9%)	21 (18%)
Infection	25 (6%)	1 (2%)	24 (6%)	5 (5%)	1 (0%)	10 (3%)	3 (3%)	5 (4%)
Malaise	8 (2%)	3 (6%)	7 (2%)	1 (1%)	1 (0%)	1 (0%)	3 (3%)	2 (2%)
Pain	65 (16%)	4 (7%)	64 (16%)	11 (12%)	16 (7%)	31 (11%)	6 (5%)	14 (12%)
Viral infection	35 (9%)	0	35 (9%)	2 (2%)	6 (2%)	17 (6%)	5 (4%)	10 (8%)
Cardiovascular System	37 (9%)	2 (4%)	36 (9%)	4 (4%)	3 (1%)	17 (6%)	5 (4%)	4 (3%)
Digestive System	142 (35%)	9 (17%)	136 (34%)	23 (24%)	32 (12%)	60 (21%)	17 (15%)	20 (17%)
Diarrhea	29 (7%)	1 (2%)	28 (7%)	3 (3%)	4 (1%)	14 (5%)	6 (5%)	7 (6%)
Dyspepsia	31 (8%)	5 (9%)	26 (7%)	7 (7%)	8 (3%)	7 (2%)	2 (2%)	6 (5%)
Nausea	69 (17%)	4 (7%)	69 (17%)	9 (10%)	21 (8%)	33 (11%)	11 (9%)	27 (23%)
Vomiting	24 (6%)	1 (2%)	23 (6%)	1 (1%)	5 (2%)	10 (3%)	4 (3%)	4 (3%)
Metabolic and Nutritional System	41 (10%)	2 (4%)	40 (10%)	6 (6%)	8 (3%)	17 (6%)	10 (9%)	11 (9%)
Musculoskeletal System	83 (20%)	2 (4%)	81 (20%)	8 (9%)	16 (6%)	31 (11%)	8 (7%)	9 (8%)

(continued)

Body System COSTART Preferred Term	Total*	Placebo	Sodium Oxybate Dosage at Onset (g/d)					
			Total*	3.0	4.5	6.0	7.5	9.0
Number of patients	402 (100%)	94 (100%)	396 (100%)	94 (100%)	266 (100%)	290 (100%)	116 (100%)	116 (100%)
Nervous System	196 (49%)	17 (31%)	192 (48%)	31 (33%)	63 (24%)	90 (31%)	23 (20%)	54 (46%)
Abnormal dreams	20 (5%)	0	20 (5%)	2 (2%)	9 (3%)	7 (2%)	4 (3%)	1 (1%)
Confusion	28 (7%)	1 (2%)	28 (7%)	6 (6%)	6 (2%)	10 (3%)	6 (5%)	9 (8%)
Depression	26 (6%)	3 (2%)	26 (6%)	4 (4%)	2 (1%)	12 (4%)	3 (3%)	6 (5%)
Dizziness	74 (18%)	2 (4%)	73 (18%)	16 (17%)	12 (5%)	32 (11%)	8 (7%)	20 (17%)
Emotional lability	15 (3%)	2 (4%)	15 (3%)	2 (2%)	2 (1%)	2 (1%)	2 (2%)	3 (3%)
Nervousness	35 (9%)	6 (11%)	33 (8%)	5 (5%)	9 (3%)	13 (4%)	2 (2%)	4 (3%)
Sleep disorder	46 (11%)	2 (4%)	44 (11%)	6 (6%)	15 (6%)	22 (8%)	4 (3%)	10 (9%)
Somnolence	55 (14%)	9 (16%)	49 (12%)	11 (12%)	13 (5%)	21 (7%)	3 (3%)	12 (10%)
Respiratory System	105 (26%)	6 (11%)	102 (26%)	19 (20%)	29 (11%)	54 (19%)	13 (11%)	14 (12%)
Cough increased	24 (6%)	2 (4%)	22 (6%)	5 (5%)	6 (2%)	9 (3%)	2 (2%)	1 (1%)
Pharyngitis	42 (10%)	3 (6%)	41 (10%)	5 (5%)	7 (3%)	22 (8%)	7 (6%)	1 (1%)
Rhinitis	30 (7%)	1 (2%)	29 (7%)	4 (4%)	11 (4%)	10 (3%)	5 (4%)	2 (2%)
Sinusitis	22 (5%)	0	21 (5%)	4 (4%)	4 (2%)	11 (4%)	2 (2%)	2 (2%)
Skin	52 (13%)	6 (7%)	49 (12%)	4 (4%)	9 (3%)	22 (8%)	4 (3%)	14 (12%)
Sweating	17 (4%)	0	17 (4%)	2 (2%)	3 (1%)	6 (2%)	1 (1%)	5 (4%)
Special Senses	44 (11%)	3 (6%)	43 (11%)	4 (4%)	4 (1%)	13 (4%)	7 (6%)	7 (6%)
Urogenital System	36 (9%)	4 (11%)	36 (9%)	6 (6%)	10 (4%)	14 (5%)	6 (5%)	11 (9%)
Incontinence urine	5 (1%)	0	5 (1%)	0	0	2 (1%)	0	4 (3%)
Urinary	24 (6%)	0	24 (6%)	2 (2%)	7 (3%)	9 (3%)	5 (4%)	5 (4%)
Vaginal moniliasis								

* Patients are counted only once in each category.

The above table confirms that

- The most common adverse events in those treated with GHB were headache, pain, nausea and dizziness.
- A dose response could be seen, at least in the case of the 9 g dose, in the case of nausea.

8.5.3.3 Lammers Trial

Only a few adverse events were seen in this study as summarized by the following table taken from the Lammers study report. Note that

- Only 3 patients had adverse events while taking GHB
- Adverse events seen in this study have also been included in the Controlled Clinical Trials grouping above

Patient number	Treatment	Investigator term
8	GHB	terrible dreaming dry mouth paralysis in legs and arms anxious insecure
15	Placebo	kidney problems urination problems (stranguria)
2	GHB	severe perspiration influenza (common cold), sore throat headache frequent micturition
5	GHB	infection bladder sore throat flickering in the eyes
9	Wash out	frequent headache
17	Wash out	severe dreaming

8.5.3.4 Integrated Pharmacokinetic Trials

The following table, copied from the Integrated Summary of Safety, presents the number of adverse events that occurred in ≥ 5% of subjects in the Integrated Pharmacokinetic Trials Grouping

Body System COSTART Preferred Term	Sodium Oxybate[a]
Number of Subjects	144 (100%)
Body as Whole	21 (15%)
Headache	18 (13%)
Digestive System	44 (31%)
Nausea	37 (26%)
Vomiting	27 (19%)
Nervous System	40 (28%)
Confusion	7 (5%)
Dizziness	26 (18%)

[a] Subjects are counted only once in each category.

As the above table indicates the most common adverse events in this grouping as well are headache, nausea, vomiting and dizziness.

8.5.3.5 Scharf Trial

Given the duration of this study, adverse events were common and at least 1 adverse event was experienced by 95.1% of those participating in this trial. Adverse events that occurred in ≥ 5 % of patients in the study are in the following table

Adverse Event (COSTART)	Number of patients	% of Patients
Allergic reaction	13	9.1
Asthenia	32	22.4
Chills	19	13.3
Fever	38	26.6
Flu syndrome	55	38.5
Headache	75	52.4
Infection	16	11.2
Infection viral	81	56.6
Injury accidental	60	42.0
Malaise	33	22.1
Neoplasm	12	8.4
Pain	69	48.3
Pain abdominal	38	26.6
Pain back	29	20.3
Pain chest	33	20.1
Pain neck	15	10.5
Reaction unevaluable	33	23.1
Arrhythmia	15	10.5
Ventricular extrasystoles	10	7.0
Hypertension	21	14.7
Tachycardia	11	7.7
Vasodilatation	11	7.7
Periodontal abscess	8	5.6
Colitis	6	4.2
Constipation	8	5.6
Diarrhea	40	28.0
Dry mouth	12	8.4
Dyspepsia	36	25.2
Gastroenteritis	20	14.0
Nausea	58	40.6
Tooth disease	18	12.6
Vomiting	29	12.3
Peripheral edema	18	12.6
Arthralgia	16	11.2
Arthritis	26	18.2
Leg cramps	11	7.7
Joint disease	15	10.5
Myalgia	15	10.1
Anxiety	10	7.0
Ataxia	9	6.3
Confusion	9	6.3
Convulsion	8	5.6
Depression	19	13.3
Dizziness	39	27.3
Emotional lability	8	5.6
Hypertonia	13	9.1
Hypesthesia	12	8.4
Insomnia	10	7.0
Nervousness	20	14.0
Neuralgia	8	5.6
Paresthesia	17	11.9
Sleep disorder	45	31.5
Somnolence	15	10.5
Tremor	9	6.3
Apnea	19	13.3
Bronchitis	32	22.4
Increased cough	49	34.3
Dyspnea	27	18.9
Epistaxis	10	7.0
Lung disease	13	9.1
Pharyngitis	54	37.8
Pneumonia	9	6.3
Rhinitis	52	36.4
Sinusitis	38	26.6

Pruritus	13	9.1
Rash	13	9.1
"Sweat"?	26	18.2
Amblyopia	13	9.1
Conjunctivitis	19	13.3
Otitis media	10	7.0
Ear pain	14	9.8
Eye pain	13	9.1
Abnormal vision	9	6.3
Urinary incontinence	33	23.1

The most common adverse events in this study, at least some of which were due to intercurrent illnesses, included (in descending order of frequency) viral infection, headache, pain, accidental injury, nausea, flu syndrome, pharyngitis, rhinitis, increased cough, sleep disorder, diarrhea, dizziness, fever, abdominal pain, sinusitis and dyspepsia.

The most common adverse events considered to be drug-related by the investigator, and occurring in the first 6 months (in descending order of frequency) of GHB use were sleep walking, dizziness, nausea, pain, dyspepsia, abdominal pain, viral infection and headache. The most frequent adverse events (whether considered related to GHB or not) during that period were headache, viral infection, pain, nausea and dizziness: tables for all adverse events in this time period have been provided by the sponsor

The most common adverse events occurring after the first 6 months of treatment were viral infection, pain, headache and accidental injury. Tables for all adverse events in this time period have been provided by the sponsor.

8.5.4 Common and Drug-Related Side Effects

I have used 2 sets of studies in defining these

- Controlled clinical trials
- All clinical trials

8.5.4.1 Controlled Clinical Trials

In the controlled clinical trials group I have selected those adverse events that have been listed as occurring in ≥ 5% of Xyrem®-exposed patients and at least twice as frequently as those exposed to placebo. The following adverse events, listed using COSTART terms, fit these criteria:

Infection (5%), pain (8%), nausea (12%), vomiting (4%), confusion (5%), dizziness (16%), sleep disorder (7%) and urinary incontinence (4%)

8.5.4.2 All Clinical Trials

The 3 most common adverse events in GHB-treated patients across the 2 main clinical trial subsets (Integrated Clinical Trials, Integrated Pharmacokinetic Trials and Scharf Study) were:

Headache, nausea and dizziness.

The next table indicates their incidence in each of the clinical trial groupings

Adverse Event	Integrated Clinical Trials (%)	Integrated Pharmacokinetic Trials (%)	Scharf Trial (%)
Headache	26	13	52
Nausea	21	26	41
Dizziness	18	18	27

8.5.5 Additional Analyses and Explorations

Special analyses were performed by the sponsor for the following adverse events

- Urinary incontinence (and its relationship to seizures)
- Elevated anti-nuclear antibodies

Further analyses explored the relationship of adverse events to dose, duration of treatment, concomitant medication use, age, and gender

These items are discussed in greater detail below

8.5.5.1 Urinary Incontinence And Its Relationship To Seizures

8.5.5.1.1 BACKGROUND

Animal studies have shown a relationship between the use of high doses of GHB, and symptomatology as well as EEG changes that resemble those of absence seizures in humans. An experimental animal model for absence seizures has in fact been developed using sodium oxybate. Myoclonic jerks have also been seen in patients (outside the United States) in whom anesthesia has been induced with GHB.

In our original review of Treatment IND # ——— , this Division had noted that several GHB treated patients were noted to have nocturnal urinary incontinence There was a concern as to whether unrecognized seizures were responsible for the episodes of incontinence in these patients.

Based on the above a more detailed analysis of urinary incontinence in clinical trials of GHB, and its possible relationship to hitherto-unrecognized seizures was requested by this Division

8.5.5.1.2 METHODS

The sponsor conducted an analysis of urinary incontinence using the following methods

- Adverse events suggestive of urinary incontinence were searched for in the databases for both trials
- Adverse events that appeared to be of central nervous system origin were also looked for.
- A questionnaire was distributed to all investigators whose patients had reported urinary incontinence in Studies OMC-GHB-2 and OMC-GHB-3. The questionnaire asked investigators to list any additional nocturnal observations that would suggest the presence of seizures, ascertain the patient's urological

history prior to beginning GHB treatment and to note any new neurological symptoms

- Patients who had both central nervous system adverse events and urinary incontinence were identified as were patients who had urinary incontinence and central nervous system adverse events contemporaneously
- Overnight EEG recordings were made prospectively in 6 patients who had a prior history of incontinence during sodium oxybate treatment at a dose of 9 g/day. Note that only 4/6 patients had recordings done with what was believed to be an adequate number of scalp electrodes to reliably detect electrical seizure activity (the EEG recorded during polysomnography does not typically use enough scalp electrodes to reliably detect seizure patterns). In addition polysomnogram EEG recordings were looked at retrospectively in 2 additional patients who had urinary incontinence
- The data were reviewed by an independent expert in epilepsy, [redacted] who was asked to render an opinion as to whether the episodes of incontinence that have occurred during clinical trials of GHB could have been due to seizures.
- Other experts were also consulted by the sponsor regarding whether GHB could cause seizures.
- The medical literature was also reviewed.

8.5.5.1.3 RESULTS

8.5.5.1.3.1 Incontinence In Studies OMC-GHB-2 And OMC-GHB-3

- In OMC-GHB-2, 15 events of enuresis/urinary incontinence occurred in 8 of the 136 patients participating in that trial. 5 of these patients had at least one episode occurring at night; in the remaining 3 there is insufficient information to indicated that the incontinence occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table (note that patients were randomized equally to the placebo, 3 g/day, 6 g/day and 9 g/day doses in this study)

GHB Dose (g/day)	Number of events of incontinence
6	3
9	11
0*	1

*Not taking study drug or placebo

- In OMC-GHB-3, 51 events of enuresis/urinary incontinence occurred in 13 of the 188 patients who participated in this study. A single patient accounted for 15 events. 20/51 events were considered related to GHB by the investigator. Only a few of these events are specifically documented as having occurred at night. The distribution of these events based on the daily dose of GHB taken at the time of incontinence is in the following table

GHB Dose (g/day)	Number of events of incontinence
2.3	1
3	1
4.5	5
6	27
7.5	1
9	16

- One additional patient in each trial (OMC-GHB-2 and OMC-GHB-3) experienced fecal incontinence. The doses of GHB at the time of incontinence were 9 g/day and 6 g/day, in the OMC-GHB-2 and OMC-GHB-3 trials respectively. The patient participating in the OMC-GHB-2 trial had a single episode of fecal incontinence after which the study drug was stopped. The patient participating in the OMC-GHB-3 trial had multiple episodes of fecal incontinence, a previous history of milk allergy with diarrhea, and a negative sigmoidoscopy.
- The central nervous system adverse events that occurred in patients who had urinary incontinence included the following
  Tremor, disorientation, confusion, impaired concentration, tingling in head, tingling/numbness in face, numbness of left hand, face and leg, abnormal muscle sensations, muscle jerks/spasms, "drunkenness", and poor balance/unstable gait/poor equilibrium/impaired coordination
- 2 patients in OMC-GHB-2 and 2 patients in OMC-GHB-3 had central nervous system adverse events contemporaneously with urinary incontinence. These adverse events were disorientation, confusion and muscle jerks. Narratives have been provided for these 4 patients and do not provide any strong evidence that these patients had seizures of any kind, although one of these adverse events (muscle jerks) could conceivably have represented myoclonic jerks. Unfortunately, descriptions of the events are lacking. These 4 patients are summarized in the following table.

Study	Patient ID #	Age/Gender	GHB Dose At Time Of Incontinence	Contemporaneous Central Nervous System Adverse Event
OMC-GHB-2	0702	59/F	9 g/day	Confusion
OMC-GHB-2	0124	57/M	9 g/day	Confusion
OMC-GHB-3	0219	65/F	9 g/day	Disorientation
OMC-GHB-3	0819	57/M	3 g/day	Muscle jerks*

*This patient had a single episode of incontinence which occurred at the same time as his muscle jerks began. However the muscle jerks persisted long after his episode of incontinence ended

8.5.5.1.3.2 Incontinence In Other Clinical Trial Groupings

- In the 5 integrated clinical trials 32 of the 402 patients experienced urinary incontinence; 2 patients had fecal incontinence.
- In the 8 integrated pharmacokinetic trials 2 of 144 subjects experienced urinary incontinence and 1 subject experienced fecal incontinence. None of these individuals was observed to have seizures
- No patients in the Lammers or Scrima studies experienced incontinence.

8.5.5.1.3.3 EEG Studies

- In the prospective overnight EEG recordings in 6 patients, only one had urinary incontinence during the recording. No electrical seizure activity was apparent in any of the 6 patients. Note that the patient who had incontinence (Initials: ~~) had what was believed to be an adequate number of scalp electrodes for the recordings.
- No electrical seizure activity was seen on either of the 2 retrospectively reviewed polysomnogram EEG recordings although one recording was stated to be of poor quality.

- The sponsor believes that the EEG data described here represent a reasonable attempt to show that GHB does not cause clinically subtle seizures, and that enuresis associated with GHB is not caused by seizures.

8.5.5.1.3.4 Animal Data In Literature

The sponsor has summarized the animal data in the medical literature as follows.

- As noted above GHB is used to induce absence seizures in an experimental animal (monkey) model developed by O. Carter Snead. In that model, following an IV dose of 400mg/kg GHB, the EEG and behavioral effects in the monkey consist of an initial low-voltage slowing of brain rhythms combined with drowsiness from which the animal can be easily aroused. This state then progresses to paroxysmal rhythmic 2.5 to 3 per second high-voltage slowing, punctuated by spikes, during which the animal exhibits starring, occasional rhythmic eye movement, dilated pupils, unresponsiveness to any stimuli, and myoclonic movements. Such paroxysms are frequently precipitated by auditory stimuli. The doses and serum concentrations at which these phenomena occur depend on the age of the animal and the elapsed time between administration of the dose and drawing of the blood sample
- Higher doses can also cause generalized tonic-clonic seizures.
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 µg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 µg/ml.
- In contrast, a pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 µg/ml.

8.5.5.1.3.5 Clinical Data In Literature

These data are summarized below

- There are many anecdotal case reports and case series of intoxication with GHB reported in the medical literature, and related to illicit use of that drug
  - Many of these incidents include reports of tonic-clonic seizures. In most of these it is not clear how much GHB was ingested, and adverse reactions were often associated with concomitant alcohol consumption.
  - In one of the rare instances where the dose of GHB ingested could be estimated a 40-year-old man had a "tonic-clonic major motor seizure without a previous history of epilepsy" about 20 minutes after taking about 115 mg/kg of GHB.
  - GHB has been used in Europe as an anesthetic, and as a sedative in intensive care units, at doses of about 50 mg/kg.
  - This dose of GHB has not been associated with seizures.
  - A German study examined the effect of GHB on the EEG of 31 patients after abdominal surgery. After injection of 50 mg/kg intravenously, no seizure-like electrical activity was observed in the EEG

8.5.5.1.3.6 Expert Opinions

- According to Dr Martin Scharf, one of the experts consulted by the sponsor, no bed-partners of patients taking GHB had reported phenomena that might be considered seizure-like. Dr Scharf reportedly stated that there were about 750 patient-years of exposure to GHB (he was presumably referring to

I have summarized convulsions as recorded as an adverse effect of Xyrem® in the NDA safety database as follows.

- In the controlled clinical trials 2 (1.4% of) GHB-treated patients are listed as having convulsions whereas no placebo-treated patient had convulsions. In neither of these 2 patients was "convulsion" listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable

- In the entire integrated clinical trials grouping 10 (2.5% of) GHB-treated patients are listed as having convulsions. In none of these instances was "convulsion" listed as a serious adverse event or as a reason for treatment discontinuation. Detailed descriptions of this adverse event are unavailable

- In the Scharf study, 9 (6.3% of) GHB-treated patients are listed as having convulsions: the sponsor believes that in 5 of those instances the events coded as "convulsions" more likely represented cataplexy; of the remaining 4 patients one had seizures prior to study entry. These patients are summarized in the table below

  Of the patients in the table below: 1 patient (# 064; see description in Section 8.4.2.2) was listed as discontinuing treatment on account of seizures and in another patient (# 257; see Section 8.3.2.4) the convulsion was listed as a serious adverse event.

  For all 9 patients detailed descriptions of the events called "convulsions" are lacking. Narratives and Case Report Forms are available for 2 patients (#s 064 and 257) but do not help clarify whether the events were true convulsions, epileptic phenomena of any other kind or neither.

Patient ID	COSTART Term	Verbatim Term	No. of Events	Dose (g)[1]
043	Convulsion	Excessive cataplexy	-	6.0
048[2]	Convulsion	Convulsive-like seizure	1	8.3
049	Convulsion	Fall, sudden cataplexy	-	6.0
051	Convulsion	Fall twice, with cataplexy	-	7.5
064	Convulsion	Seizure	1	7.5
		Seizure	1	6.0
		Seizure	1	6.0
		Seizure-morning	1	6.0
		Seizure-afternoon	1	6.0
		Seizure-morning	1	6.0
		(Total events)	6	
219	Convulsion	Cataplexy, twice	-	7.5
247	Convulsion	Seizures, continuous jerking	1	6.0
255[3]	Convulsion	Grand mal seizure	1	6.0
257	Convulsion	Violent shaking and vibrations	-	5.3
		Jerking during cataplexy	-	9.0
		Severe cataplexy	-	9.0
		Cataplexy	-	12.0
		Fall due to cataplexy. Patient suffered injury, resulting in increased cataplexy.	-	11.3

[1]Dose recorded is the dose at the onset of the adverse event.
[2]This event for patient 048 was judged a serious adverse event that was related to the study medication.
[3]Patient 255 had a history of seizures of unknown etiology at enrollment.

- Based on the narratives and Case Report Forms that have been supplied for some patients with convulsions (i.e., those in whom this adverse event was listed as serious or led to study drug discontinuation) it is difficult to determine
  - If they in fact had true convulsions or any epileptic phenomenon at all (clinical descriptions of the episodes were lacking)
  - If at least some patients treated with GHB did have true convulsions, it is not clear that GHB caused their convulsions; confounding factors included the use of concomitant medications such as stimulants or tricyclic antidepressants which are themselves reputed to have epileptogenic properties
  - One patient (# 255 in the above table) was documented as having a seizure disorder even prior to receiving GHB
  - Another patient recorded as having convulsions (see Section 8.4.2.2) during a GHB study may have had convulsions even prior to the study: she also had a history of a left frontal lobe lesion and burr hole surgery
- The sponsor has stated that absence-like seizure states occur in primates at intravenous GHB doses "far exceeding the human therapeutic dose". In fact the safety margin between the highest human dose used in efficacy trials and that used in primate models to induce absence seizures, while it certainly exists, may not extremely wide as the following indicate
  - The highest human dose used in efficacy trials is 9 g/day. In a 60 kg individual this dose is equal to 150 mg/kg/day or 5550 mg/m^2/day

- Intravenous doses of 400 mg/kg in monkeys are sufficient to induce clinical absence seizures. Assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 1333 mg/kg or 26660 mg/m^2
- Intravenous doses of 200 mg/kg in monkeys are sufficient to induce epileptiform abnormalities on an EEG. Again, assuming that GHB has an oral bioavailability of 30% in monkeys this would be equivalent to an oral dose of 667 mg/kg or 13340 mg/m^2
- Epileptiform abnormalities on EEG typically appear at GHB serum levels greater than 300 µg/ml, corresponding to a dosage threshold of 200 mg/kg. Myoclonic seizures occur at levels greater than 500 µg/ml.
- A pharmacokinetic study of GHB in six patients with narcolepsy showed that after a typical 3 g oral dose the peak serum level of GHB did not exceed 125 µg/ml.
- In an additional pharmacokinetic study in 13 healthy individuals, after 2 nightly doses of GHB of 9 g each the mean C_{max} was 142 µg/mL (coefficient of variation 35%)

8.5.5.1.6 REVIEWER'S COMMENTS

- In controlled clinical trials urinary incontinence was more frequent in those treated with GHB than in those treated with placebo (5% vs 0%) suggesting that, while not very common, urinary incontinence may be caused by that drug. Furthermore, urinary incontinence in GHB-treated patients may be dose-related.
- In controlled clinical trials fecal incontinence was seen in 1 GHB-treated patient (1%) but not in any placebo-treated patient. A number of other instances of fecal incontinence were seen in the entire database, but the overall incidence of this adverse event was much lower than that of urinary incontinence
- Based on the circumstantial evidence supplied above, there is no firm evidence that urinary incontinence in any patients treated with GHB was caused by seizures, whether generalized tonic-clonic or of another kind. However only one patient appears to have had an episode of incontinence while actually undergoing EEG monitoring; in that instance the EEG did not show any evidence of epileptiform activity; this patient did appear to have an adequate number of scalp electrodes and montages.
- In the open-label Scharf study which was not included in the sponsor's formal analysis of incontinence, 33 patients (23.1%) had urinary incontinence. 1 patient (0.7%) had fecal incontinence. There has been no formal attempt by the sponsor to determine if any of these instances could have been secondary to seizures. All that the sponsor has done is to provide a summary table for those with convulsions providing further details for the patients summarized under the previous bullet. This table is above.
- Overall, the evidence that urinary incontinence associated with therapeutic use of GHB is due to unrecognized seizures, or that GHB is epileptogenic at therapeutic doses, is not strong at present. However either possibility cannot be excluded based on the available information which is very limited: studies conducted to address this matter have also been very limited in scope so far and further studies to evaluate this issue may be warranted.

8.5.5.2 Elevated Antinuclear Antibodies

This analysis has been confined entirely to the Scharf study

8.5.5.2.1 BACKGROUND

After a patient in the Scharf trial developed elevated antinuclear antibodies in 1991, this phenomenon was further investigated in that study and was also discussed with this Agency

8.5.5.2.2 METHODS

These are described only very briefly in the submission.

After the index case of elevated antinuclear antibodies was noted, the same titers were checked for all "ongoing" patients in the trial; these checks appear to have been initially done on a total of 65 patients over the 2 years after the index case was identified. After discussions with this Agency Dr Scharf continued to check antinuclear antibody titers on all patients participating in this study; data are provided for until 5/31/99, the cut-off date for the Scharf study report. A total of 87 patients had at least one antinuclear antibody titer estimated.

In a proportion of those with positive antinuclear antibodies, antihistone antibody titers were checked.

An attempt was made to correlate the antibody titers with symptoms consistent with systemic lupus erythematosus, medication-induced lupus or any other rheumatic disease using a symptom questionnaire that was supplied to the initial 65 patients who had antibody titers determined.

In each patient in whom antinuclear antibody titers were positive on more than one occasion summaries were made of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates)

The methods of sample collection, storage, analysis and interpretation were not standardized for the antinuclear antibody and antihistone antibody titer estimations: these tests were performed at a variety of laboratories. An antinuclear antibody titer of > 1:40 was considered positive.

The vast majority of patients who had the above antibody titers determined lacked baseline measurements. In the majority of instances (80%) these determinations were made after an extended period of treatment with GHB

8.5.5.2.3 RESULTS

The results of this analysis have been presented as

- Summary text
- Data listings for all patients who had antinuclear antibody and antihistone antibody testing: these listings include patient ID number, date of initial dose of GHB, date of testing, dose of GHB at time of testing and antibody titers
- A table listing all patients who had positive antinuclear antibody tests on at least a single occasion: the table included the patient number, the date treatment was started, the date of

the first antinuclear antibody, the result of the first antinuclear antibody, the total number of antinuclear antibody titer determinations, the number of positive antinuclear antibody determinations and the sequence of antinuclear antibody determinations

- Summaries of demographics, antinuclear antibody titers (with specific dates) and adverse events that developed during the course of the study (with specific dates) for all patients whose antibody titers were positive on more than one occasion

8.5.5.2.3.1 In the population of 65 patients who initially had antinuclear antibody testing done.

- 19/65 (29.2%) of patients had one or more antinuclear antibody elevations ranging from 1:40 to 1:2560
- No correlations were found between positive antinuclear antibody titers and duration of treatment, age or gender
- 15/19 patients who were antinuclear antibody-positive had antihistone antibodies done: these were negative in all but one patient who had a result that was termed "borderline positive" and who did not have symptoms characteristic of lupus
- The symptom questionnaire showed a low overall incidence of symptoms that could have been consistent with lupus with no differences between the subgroup of those with positive antinuclear antibody titers and those in whom these titers were negative

8.5.5.2.3.2 In the total population of 87 patients who had antinuclear antibody testing done

- 26/87 (29.9%) had at least one positive antinuclear antibody test. These patients are summarized in the next table which has been copied from the submission.

Table 30 Narcoleptic Patients with Positive ANA Results

PATIENT NO.	DATE RX STARTED	DATE 1ST ANA	RESULT 1ST ANA	TOTAL NO. ANA'S	NO. POSITIVE ANA'S	SEQUENCE OF ANA FINDINGS*
3	11/86	7/90	N	10	1	N-N-N-N-N-N-N-N-N-P
4	1/86	12/90	N	15	2	N-N-N-P-P-N-N-N-N-N-N-N-N-N-N
15	1/84	5/90	N	10	5	N-P-P-N-N-P-N-N-P-P
17	2/89	1/90	N	12	6	N-P-P-P-P-N-P-P-N-N-N-N
30	6/87	6/91	N	13	7	N-P-P-N-P-N-N-P-P-N-N-P-P
39	12/84	12/90	N	12	1	N-N-N-N-N-N-N-N-N-P-N-N-N
41	6/84	1/92	N	17	14	N-P-N-P-P-P-N-P-P-P-P-P-P-P-P-P-P
42	1/87	6/92	N	12	2	N-N-N-N-N-P-N-N-N-N-N-N
43	1/87	2/90	N	14	6	N-N-N-N-N-N-N-P-P-N-P-P-P-P
57	2/84	4/90	N	12	1	N-N-N-N-N-N-N-N-N-N-N-N
59	11/87	1/91	N	10	1	N-N-N-N-N-N-N-N-N-P
60	1/91	1/91	N	2	1	N-P
62	6/87	7/90	N	15	2	N-P-N-N-N-N-N-N-N-N-N-P-N
63	11/83	12/90	N	16	1	N-N-N-N-N-N-N-N-N-N-N-N-N-P-N
66	3/85	1/91	P	7	7	P-P-P-P-P-P-P
67	2/86	6/90	P	14	7	P-N-N-P-N-N-P-N-N-P-N-P-P-P
78	5/87	5/90	N	13	1	N-P-N-N-N-N-N-N-N-N-N-N-N
205	11/84	4/92	N	6	2	N-N-N-N-P-P
227	10/89	2/90	N	15	1	N-N-N-P-N-N-N-N-N-N-N-N-N-N
230	9/84	1/90	N	13	4	N-N-P-N-N-N-P-N-P-N-N-N-P
237	6/90	12/96	P	2	1	P-N
252	5/90	2/92	N	11	5	N-N-N-N-N-N-P-P-P-P-P
260	2/84	12/89	N	12	10	N-N-P-P-P-P-P-P-P-P-P-P
262	4/92	6/92	P	13	4	P-N-N-N-N-N-N-N-P-P-P-P
270	1/94	5/96	N	9	5	N-P-N-N-N-P-P-P-P
273	1/94	2/96	N	4	2	N-N-N-P

- In the above table, 9 patients had only a single positive result while the remaining 17 had multiple positive antinuclear antibody determinations
- In the above table 4 patients were positive on their first antinuclear antibody test, whereas the remaining 22 had at least one negative determination prior to a positive one

8.5.5.2.3.3 Among the 17 patients with 2 or more positive antinuclear antibody results

- There were 7 males and 10 females
- Their ages ranged from 15 to 66 years; all were Caucasian
- Daily doses of GHB ranged from 4.5 g to 11 g/day. The most frequent stable dose was 6 g/day
- When the sequence of antinuclear antibody testing was examined several different patterns of positivity/negativity were seen
- Adverse event data obtained from Case Report Forms (which I have examined) indicates the presence of very few rheumatological symptoms
- No patient was diagnosed to have either drug-induced lupus or systemic lupus erythematosus

8.5.5.2.4 SPONSOR'S CONCLUSIONS

- The incidence of positive antinuclear antibody tests in the population in this study appears to be higher than what might be expected in the general population
- Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with, or subsequently develop, symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease.
- There is no evidence that chronic treatment with GHB results in an increase in occurrence of any rheumatic or immune-mediated disease.
- In medication-induced lupus, positive antinuclear antibody titers are accompanied in most cases (90%) by antihistone antibodies.
- Use of sodium oxybate may result in elevated antinuclear antibody titers without the corresponding increase in antihistone antibodies seen in patients with drug-induced lupus
- A review of the scientific literature published since 1966 failed to uncover any study that reported the incidence of antinuclear antibodies in narcolepsy. Thus it is impossible to determine if the increased incidence of positive antinuclear antibody tests is related to GHB or narcolepsy, or is unique to this dataset
- [redacted], an expert in systemic lupus erythematosus and drug-induced lupus, whose opinion was sought by the sponsor, concurred with the sponsor's conclusions. According to her, the most that might be concluded was that sodium oxybate, like many other drugs, may be associated with low level increases in antinuclear antibody titer of no known clinical significance.

8.5.5.2.5 DISCONTINUATIONS DUE TO POSITIVE ANTINUCLEAR ANTIBODIES

2 patients discontinued from the Scharf study on account of positive antinuclear antibody tests. These patients are already described above (Sections 8.4.2.3 and 8.4.2.5)

8.5.5.2.6 REVIEWER'S COMMENTS

- There are clearly a number of readily-evident limitations to the sponsor's analysis. In addition
  - Full details of some analyses have not been supplied (e.g., the actual tables comparing the incidence of symptoms attributable to lupus in the antinuclear antibody-positive and negative groups)
  - Antinuclear antibody titers have been in only a subset of those participating in one study out of a number of studies in this NDA
- At least one patient is stated to have been diagnosed to have "rheumatoid arthritis" close to the time when she was first detected to have a positive antinuclear antibody test (1:640) and after she had received GHB for about 6 years. The test remained positive, sometimes in high titer, while she continued to receive GHB, and for 11 months thereafter. Antihistone antibodies were not checked in this patient. Unfortunately, few details are details are available regarding this patient's symptoms. However based on the information available for this patient, the following statement by the sponsor is not entirely correct
  "Sodium oxybate-treated narcoleptic patients in the Scharf trial who had positive antinuclear antibody titers did not present with or subsequently develop symptoms suggestive of systemic lupus erythematosus, drug-induced lupus or any rheumatic disease."
- There is no firm evidence that any patient treated with GHB developed drug-induced lupus.

8.5.5.3 Relationship Between Adverse Events And Dose

8.5.5.3.1 CONTROLLED CLINICAL TRIAL: OMC-GHB-2

This is the only trial in which randomized comparisons between multiple dose groups treated in parallel for the same period of time (1 month) is possible. The table below indicates that while the overall incidence of treatment-emergent adverse events were comparable across treatment groups, certain specific adverse events did show a dose-response and were most common in the 9 g/day dose group. These were: headache, pain, nausea, dizziness, sleep disorder, and incontinence of urine. Note, however, that in this trial patients were not titrated to their assigned doses

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Adverse Event (COSTART term)	Treatment Group			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Any	24 (70.6)	25 (73.5)	25 (75.8)	26 (74.3)
Headache	7 (20.6)	3 (8.8)	5 (15.2)	11 (31.4)
Infection	1 (2.9)	3 (8.8)	5 (15.2)	0
Infection Viral	1 (2.9)	1 (2.9)	3 (9.1)	0
Pain	2 (5.9)	3 (8.8)	4 (12.1)	7 (20.0)
Pain Back	2 (5.9)	0	2 (6.1)	0
Diarrhea	0	0	2 (6.1)	2 (5.7)
Dyspepsia	2 (5.9)	0	3 (9.1)	2 (5.7)
Nausea	2 (5.9)	2 (5.9)	5 (15.2)	12 (34.3)
Nausea Vomiting	0	0	2 (6.1)	2 (5.7)
Myalgia	0	2 (5.9)	0	0
Myasthenia	0	2 (5.9)	1 (3.0)	0
Amnesia	0	1 (2.9)	0	2 (5.7)
Anxiety	1 (2.9)	1 (2.9)	0	2 (5.7)
Confusion	1 (2.9)	3 (8.8)	1 (3.0)	5 (14.3)
Dizziness	2 (5.9)	8 (23.5)	10 (30.3)	12 (34.3)
Dream Abnormal	0	0	3 (9.1)	1 (2.9)
Hypertension	1 (2.9)	0	2 (6.1)	0
Hypesthesia	0	2 (5.9)	0	0
Sleep Disorder	1 (2.9)	2 (5.9)	4 (12.1)	5 (14.3)
Somnolence	4 (11.8)	5 (14.7)	4 (12.1)	5 (14.3)
Thinking Abnormal	0	1 (2.9)	0	2 (5.7)
Pharyngitis	3 (8.8)	0	3 (9.1)	1 (2.9)
Sweating	0	1 (2.9)	1 (3.0)	4 (11.4)
Amblyopia	1 (2.9)	2 (5.9)	0	0
Tinnitus	0	2 (5.9)	0	0
Dysmenorrhea	1 (2.9)	1 (2.9)	0	2 (5.7)
Incontinence of Urine	0	0	2 (6.1)	5 (14.3)

8.5.5.3.2 OTHER CLINICAL TRIAL GROUPINGS

The sponsor's analyses indicate the following

- In the Scharf trial no "strong" evidence of a dose-response relationship was seen
- In the Integrated Clinical Trials grouping, based on the dose at the time of onset of the adverse event, a higher incidence of adverse events was seen for the 9 g/day dose as compared with the other dose groups as follows
  - Those with at least one adverse event (74% for the 9 g/day dose group versus 45 to 61% for the other dose groups)
  - Discontinuations due to adverse events (12% for the 9 g/day group versus 3-5% for the other dose groups)
  - In the OMC-GHB-2 trial a dose-response effect was seen for nausea and viral infection that was statistically significant ($p < 0.05$)

Adverse events were not analyzed by dose for the Integrated Pharmacokinetic Trials.

8.5.5.4 Relationship Between Adverse Events And Duration Of Treatment

To determine this relationship the sponsor appears to have performed analyses of the OMC-GHB-3 (2-year) and Scharf trials

In the OMC-GHB-3 trial

- Almost all adverse events appeared within the first 12 months of treatment

- Only 15 additional COSTART terms were reported during the second twelve months: adverse events that occurred during the second 12 months in > 1 patient included gastrointestinal distress (3 patients), bilirubinemia (2 patients), and increased alkaline phosphatase (2 patients)

In the Scharf trial

- The profile of adverse events specifically associated with long-term use of GHB was consistent with the serious illnesses that could be expected in older adults
- The most frequent serious adverse events were related to cardiovascular disease and narcolepsy
- Factors that might contribute to this profile of adverse events included: the increasing age of patients during the trial, underlying cardiovascular abnormalities which were present in 20% of patients at baseline

Note that the only actual analyses that appear to have been performed by the sponsor consisted of separate tables of adverse events for the first 6 months of treatment versus those that appeared after the first 6 months of treatment. I have already discussed these tables in Section 8.5.3.5

8.5.5.5 Relationship Between Adverse Events And Concomitant Medications

No analyses were performed

8.5.5.6 Relationship Between Adverse Events And Age

In the 5 integrated clinical trials subset analyses based on age (< 65 years and ≥ 65 years) were performed for adverse events. The incidence of all adverse events, severe adverse events and discontinuations due to adverse events were similar between the 2 subsets. The incidence of serious adverse events was higher in the older subset, where the sample size was clearly much smaller. The results of these comparisons for GHB-treated patients are illustrated in the following table.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
All adverse events	269 (76%)	29 (67%)
Serious adverse events	12 (3%)	4 (9%)
Severe adverse events	61 (17%)	8 (19%)
Adverse event discontinuations	38 (11%)	5 (12%)

The incidence of the following specific adverse events was also similar between the 2 subsets for GHB-treated patients: nausea, dizziness, headache, vomiting and urinary incontinence.

Adverse Events	Age < 65 years N = 356	Age ≥ 65 years N = 43
Nausea	21%	23%
Headache	26%	21%
Dizziness	17%	21%
Vomiting	7%	7%
Urinary incontinence	6	7%

No similar analyses were performed for the Scharf trial or any other trial grouping.

8.5.5.7 Relationship Between Adverse Events And Gender

In the 5 integrated clinical trials subset analyses were performed based on for adverse events. The analyses for GHB-treated patients showed the following

- The incidence of the total number of adverse events was higher in women (80%) than in men (69%)
- The incidence of serious and severe adverse events, and adverse event discontinuations was similar between the 2 dose groups

These data are illustrated in the following table

Adverse Events	Male N = 171	Female N = 228
All adverse events	116 (68%)	182 (80%)
Serious adverse events	7 (4%)	9 (4%)
Severe adverse events	26 (15%)	43 (19%)
Adverse event discontinuations	15 (9%)	28 (12%)

- The incidence of several specific adverse events in the 2 subsets was as indicated in the table below. As can be seen the incidence of headache, vomiting, nausea and dizziness was higher in women than in men

Adverse event	Women %	Men %
Headache	29	22
Nausea	29	11
Dizziness	24	9
Vomiting	10	3
Urinary incontinence	2	3

8.5.5.8 Relationship Between Adverse Events And Race

No analyses of this relationship were performed

8.6 Laboratory Findings

8.6.1 Extent of Laboratory Testing During Development

The data below refer only to post-treatment laboratory testing.

8.6.1.1 Integrated Clinical Trials

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, calcium, creatinine, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, and total protein
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count
Urinalysis	pH, specific gravity, glucose, ketones and protein

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

Study #	Frequency of safety laboratory testing
OMC-GHB-2	Screening, baseline and weekly during the 4 weeks of study drug administration
OMC-GHB-3	Baseline and every 6 months
OMC-SXB-6	Screening and Month 6
OMC-SXB-7	Baseline and every 6 months thereafter

Scrima	Beginning and end of each 30-day treatment period

Criteria for determining potentially clinically significant laboratory abnormalities have been specified in the study reports

8.6.1.2 Lammers Trial

There was no provision for checking laboratory parameters during this trial

8.6.1.3 Integrated Pharmacokinetic Trials

No post-treatment laboratory parameters were checked during these trials

8.6.1.4 Scharf Trial

Laboratory parameters analyzed included those listed in the table below

Serum chemistry	Albumin, alkaline phosphatase, ALT/SGPT, AST/SGOT, BUN, bicarbonate, calcium, creatinine, cholesterol, glucose, LDH, phosphorus, potassium, sodium, total bilirubin, total protein and uric acid
Hematology	Hematocrit, hemoglobin, total and differential WBC count, RBC count, platelet count
Urinalysis	pH and specific gravity

Laboratory parameters were to be checked prior to study entry and semi-annually thereafter. Criteria for determining clinically significant laboratory results have been specified in the study report

8.6.2 Selection of Studies for Overall Drug-Control Comparisons Ana Other Analyses

3 study groupings have been selected

- Controlled clinical trial: OMC-GHB-2 (this was the only controlled trial in which safety laboratory tests were checked after study drug administration)
- Integrated Clinical Trials
- Scharf trial

8.6.3 Standard Analyses and Explorations of Laboratory Data

8.6.3.1 Controlled Clinical Trial OMC-GHB-2

8.6.3.1.1 CHANGES IN LABORATORY RESULTS OVER TIME

The sponsor has provided 2 shift tables for changes in laboratory data from baseline to Visit 6 (the end of the period of double-blind treatment)

8.6.3.1.1.1 Categorical Change In Laboratory Values From Baseline To Week 6

The sponsor's table depicts the number of patients in each treatment group who exhibited a change in specific laboratory values from baseline to Visit 6 that fell into one of the following 3 categories: "normal to abnormal", "abnormal to normal" and "no change" (i.e., no categorical change).

The following table which I have derived from the sponsor's larger table depicts the number of patients who moved from normal to abnormal in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	1	1	1	1
Alkaline phosphatase	1	1	1	0
SGPT	0	0	1	0
SGOT	0	1	0	0
LDH	0	0	2	0
Phosphorus	2	1	1	0
Total bilirubin	4	3	1	2
Total protein	0	0	0	0
Sodium	1	0	0	0
Potassium	1	0	0	1
Hemoglobin	3	0	0	0
Hematocrit	2	2	0	1
White blood cell count	2	0	0	1
Red blood cell count	2	0	0	0
Neutrophils	2	1	1	2
Lymphocytes	3	2	1	2
Monocytes	1	0	0	1
Eosinophils	0	0	0	0
Basophils	2	3	2	5
Urinary pH	0	0	0	0
Urinary specific gravity	0	0	0	0
Urinary protein	4	2	6	4
Urine glucose	0	0	0	0
Urine ketones	0	1	1	1
Urine occult blood	1	2	2	1
Urine white blood cells	1	0	2	1
Urine red blood cells	2	1	0	0
Urine squamous epithelial cells	1	0	0	0
Urine hyaline casts	1	0	0	0
Urine crystals	0	0	0	0

As the above table indicates

- Very small numbers of patients in each treatment group showed normal to abnormal changes in individual laboratory parameters
- There were no striking differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in each treatment group

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.1.2 Mean Change In Laboratory Values From Baseline To Week 6

This sponsor's table depicts the mean change (and standard deviation) from baseline to Week 6 for each laboratory parameter.

The following table which is extracted from the sponsor's table shows the mean change only for individual laboratory parameters in each treatment group

Laboratory Parameter	Treatment Group (n = number randomized)			
	Placebo (n =34)	GHB 3 g (n = 34)	GHB 6 g (n = 33)	GHB 9 g (n = 35)
Albumin	-0.10	-0.09	0.14	0.06
Alkaline phosphatase	0.07	-0.21	-4.52	-0.78
SGPT	0.62	-4.62	-4.14	-5.70
SGOT	-1.21	-3.03	-1.86	-1.15
LDH	-1.59	-10.0	4.0	-4.74
Phosphorus	0.25	-0.05	0.07	0.11
Total bilirubin	0.04	-0.07	-0.03	-0.06
Total protein	-0.02	-0.02	0.02	-0.07
Sodium	0.17	-0.07	0.24	-0.19
Potassium	-0.06	-0.09	-0.01	-0.12
Hemoglobin	-0.01	0.21	0.11	-0.15
Hematocrit	-0.42	0.50	0.79	-0.11
White blood cell count	0.20	-0.19	-0.40	-0.53
Red blood cell count	-0.04	0.04	0.05	-0.07
Neutrophils	1.19	-1.10	0.06	-3.55
Lymphocytes	-0.81	1.70	1.23	3.80
Monocytes	-0.08	-0.38	-0.36	-0.15
Eosinophils	-0.11	-0.11	-0.67	-0.11
Basophils	-0.28	-0.10	-0.32	-0.01
Urinary pH	-0.02	0.04	0.52	0.67
Urinary specific gravity	0.00	0.00	0.00	0.00
Urine white blood cells	11.36	-0.33	0.75	-0.04
Urine red blood cells	88.93	0.37	-0.75	-4.27
Urine squamous epithelial cells	0.46	0.41	0.50	0.38
Urine hyaline casts	-0.11	0.00	0.00	0.00

The above table indicates that

- Mean changes in individual treatment groups were minimal and clinically insignificant
- There were no prominent differences between the individual GHB groups and the placebo group; neither was there a tendency to a dose response in the GHB groups

Note: A maximum of 29 patients in each treatment group had records of individual laboratory parameters for both baseline and Week 6

8.6.3.1.2 LABORATORY ADVERSE EVENTS

Laboratory abnormalities that occurred in patients who eventually received study medication, and were determined by the investigator to be abnormal and clinically significant, were considered adverse events and are summarized in the following table. I have used the patient data listings in preparing this table. Note that the study drug was administered only between Visits 4 and 6

Patient ID #	Treatment Group	Laboratory Abnormality	Comments
512	Placebo	Leukocytosis in urine	Abnormality present only at Visit 5; normal at all other visits including Visit 6
1505	Placebo	Elevated alkaline phosphatase, blood glucose and total white blood cell count	Mild elevations present at all visits including screening visit
1509	Placebo	Trace occult blood in urine Mild increase in urine red cells	Trace occult blood present at Visits 2 and 5; increased urine red cells present only at Visit 5
1604	Placebo	Elevated serum potassium	Serum potassium 5.3 meq/L at Visit 5, normal by Visit 6
411	GHB 3 g	Anemia	Mild anemia (hematocrit 35.3 and 36.5 at Visits 3 and 4)
1610	GHB 3 g	Low serum potassium	Serum potassium 3.6, 3.4 , 3,3 and 3.4 meq/L at Visits 3, 4, 5 and 6, respectively
506	GHB 6 g	Proteinuria	Mild proteinuria at Visits 1 and 3; normal at other times
1204	GHB 6 g	Elevated ALT and AST	Mild elevations in ALT and AST (< 2 x upper limit of normal) at Visits 2 and 3 only
1502	GHB 6 g	Elevated uric acid and glucose	Mild elevation in blood glucose (123 - 129 mg/dl) at Visits 3 and 5. Mild elevation in uric acid (max 7.7 mg/dl) at Visits 3, 5 and 7
1302	GHB 9 g	Anemia Abnormal urinalysis	Mild anemia at Visit 1 Mild proteinuria and trace occult blood at Visits 2 and 6; hyaline casts at Visit 7

As the table indicates, in not a single instance could a laboratory abnormality in a patient who received GHB be attributed to the drug

8.6.3.2 Integrated Clinical Trials

8.6.3.2.1 CATEGORICAL CHANGES IN LABORATORY TESTS FROM BASELINE TO LAST OBSERVATION

The sponsor's table depicts the number of patients in each treatment group [placebo, and 5 Xyrem® dose groups based on last dose(3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day)] who exhibited a change in specific laboratory values from baseline to last observation that fell into one of the following 9 categories

Normal to normal	Low to normal	High to normal
Normal to high	Low to low	High to low
Normal to low	Low to high	High to high

For all laboratory parameters, the majority in each dose group (≥ 67%) was in the "normal to normal" category. The percentage with changes in all the other categories in each dose group was in the vast majority of instances very small. No dose-response was readily evident. Moreover, these comparisons are not randomized and vary in the duration of exposure to study drug; they therefore do not carry as much significance as those for a OMC-GHB-2. The significance of these comparisons is therefore small.

The only possibly noteworthy change was in serum calcium; a shift from normal to low was seen in 14/132 (10.6 %) of all patients who had this test done. The distribution of this change across dose groups is illustrated in the following table

Dose Group	Placebo	3 g/day	4.5 g/day	6 g/day	7.5 g/day	9 g/day	Total
Number With Change	0	4	2	3	0	5	14
Total number in dose group	3	16	11	45	14	43	132

None of these patients discontinued treatment on account of the change in serum calcium and there is no evidence that this change was correlated with any symptoms or clinical signs.

8.6.3.2.2 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO LAST OBSERVATION

I have reviewed the sponsor's tables which compare the mean changes in hematology, chemistry and urinalysis parameters in Xyrem®-treated patients, based on last dose (5 dose groups: 3 g/day, 4.5 g/day, 6 g/day, 7.5 g/day and 9 g/day) with the corresponding mean changes in those treated with placebo. These changes were very small, clinically insignificant and comparable across treatment groups. No clear dose-response was seen with the comparisons. Since the treatment groups are not randomized and vary in their duration of exposure to study drug; the number in the placebo group represents those treated exclusively with placebo and is exceedingly small (n=3); drug-placebo comparisons are therefore not reasonable. Since the significance of these comparisons is minimal I have not reproduced the sponsor's tables

8.6.3.2.3 POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY RESULTS

These are summarized in the next 2 tables which I have copied from the Integrated Summary of Safety. The following are noteworthy

- An increase in transaminases (SGOT and/or SGPT) in a small number of patients (all increases were < 10 x baseline). In only one of these patients (# 0214; see Section 8.3.1.6) was this increase considered a serious adverse event and/or a reason for GHB discontinuation
- None of the other potentially clinically significant laboratory changes seen below were considered serious adverse events or led to treatment discontinuation.
- There were no laboratory adverse events with a frequency of ≥ 5%

Note that there are no further details supplied or explanations offered for the potentially clinically significant laboratory abnormalities noted in the table below: these include several apparent instances of marked hypoglycemia.

Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial*			Study Day†	Result
Hematology (N = 1)					
Hemoglobin (> 3 g/dL decrease and absolute values < 12.0 g/dL)					
0814	OMC-GHB-3	4.5	10.6	391	11.5
Clinical Chemistry (N = 26)					
ALT (SGPT) (≥ 100% increase and absolute values > 75 IU/L)					
0100	OMC-SXB-7	6.0	29	948	262
0214	OMC-SXB-6	9.0	50	877	362
0507	OMC-GHB-3	7.5	39	416	109
		7.5	39	710	86
	OMC-SXB-7	7.5	39	710	86
[illegible]	OMC-GHB-3	[illegible]	27	[illegible]	149
1019	OMC-GHB-3	4.5	21	346	76
AST (SGOT) (≥ 100% increase and absolute values > 75 IU/L)					
0214	OMC-SXB-6	9.0	44	877	189
1019	OMC-GHB-3	9.0	26	398	76
Creatinine (≥ 66% increase and absolute values > 1.5 mg/dL)					
0127	OMC-GHB-3	9.0	0.8	241	1.6
0507	OMC-GHB-3	7.5	1	220	1.7
1501	OMC-GHB-3	9.0	1	720	1.9
	OMC-SXB-7	9.0	1	720	1.9
1505	OMC-GHB-3	6.0	0.6	850	1.7
	OMC-SXB-7	6.0	0.6	850	1.7
Glucose (≥ 33% decrease and absolute values < 70 mg/dL; ≥ 75% increase and absolute values > 200 mg/dL)					
0108	OMC-GHB-3	6.0	229	424	399
0115	OMC-GHB-3	9.0	104	618	217
0410	OMC-GHB-3	7.5	178	201	307
0504	OMC-GHB-3	4.5	86	279	52
05255	OMC-SXB-7	6.0	111	208	65
0550	OMC-SXB-6	6.0	88	210	56
0606	OMC-GHB-3	9.0	76	206	49

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Laboratory Parameter (clinically significant range)		Last Sodium Oxybate Dosage (g/d)	Baseline	Post-Baseline	
Patient Number	Trial*			Study Day†	Result
Clinical Chemistry (N = 26) (continued)					
Glucose (continued)					
0809	GHB-3	3.0	92	225	54
0810	GHB-3	4.5	57	219	10
0814	GHB-3	4.5	101	225	94
		4.5	103	716	66
	SXB-7	4.5	101	716	66
		4.5	101	903	65
0815	GHB-2	3.0	67	33	24
0830	GHB-2	6.0	42	17	16
	GHB-3	6.0	42	331	15
0844	SXB-6	7.0	92	57	56
1505	GHB-3	6.0	168	278	260
		6.0	166	650	403
	SXB-7	6.0	168	650	402
1708	GHB-3	6.0	144	650	49
	SXB-7	6.0	144	650	49
2124	SXB-6	6.0	107	176	68
3641	SXB-6	9.0	124	169	60
Total bilirubin (≥ 100% increase and absolute values > 1.5 mg/dL)					
0208	GHB-3	9.0	1.1	219	2.5
0504	GHB-3	4.5	0.4	338	1.6
1509	GHB-2	6.0	0.9	15	2.1

* Trial during which post-baseline value was obtained.
† Day relative to start of treatment (trial duration).

8.6.3.3 Scharf Trial

8.6.3.3.1 MEAN CHANGES IN LABORATORY VALUES FROM BASELINE TO SPECIFIC TIMEPOINTS

The sponsor has provided tables containing descriptive statistics for absolute values and changes in laboratory parameters at specific successive timepoints. These values (absolute and change) are not categorized according to last dose.

On review of these tables it is apparent that across all laboratory parameters, both the mean absolute values and the mean changes are unremarkable.

8.6.3.3.2 PROPORTION OF PATIENTS WITH ABNORMAL TESTS AT SPECIFIC TIMEPOINTS

The sponsor has provided tables specifying the number and percentage of patients with clinically significant abnormalities of laboratory tests for a number of specific timepoints, as well as listings of the patients with abnormalities.

On review of the tables and listings it appears that

- The proportion of patients having clinically significant laboratory abnormalities at each time point is generally small (0 – 16.7% with the vast majority < 5%) except in the case of abnormal serum bicarbonate. The proportion of patients with an abnormal serum bicarbonate at specific timepoints is illustrated in the following table

Time Point	Total Patients at Time Point	Number of Patients With Abnormality (%)
<= 3 months	12	3 (25.0%)
> 3 - <= 6 months	42	2 (4.8%)
> 6 - <= 12 months	42	13 (31.0%)
> 1 - <= 2 years	37	13 (35.1%)
> 2 - <= 5 years	39	17 (43.6%)
> 5 - <=10 years	38	16 (42.1%)
>10 years	22	9 (40.9%)

- The individual patient listings for abnormal laboratory results do not indicate any items of concern.
  - The abnormalities of bicarbonate were all elevations ranging from 31 to 38 mEq/L with only 9 individual readings being > 34 mEq/L; in all 9 instances the values subsequently fell to ≤ 34 mEq/L
  - Abnormalities of random blood glucose consisted of elevations in the vast majority of instances; in many of those instances serial blood glucose estimations were consistently elevated such that these individuals could have had diabetes mellitus. 4 patients had random blood glucose readings that were considered low and ranged from 38 – 48 mg/dL; at least 1 of these patients had elevated blood glucose readings subsequently.
  - There are no clinical details available for these patients and it appears unlikely that these abnormalities were attributable to GHB. Similar elevations in serum bicarbonate were not seen in the Integrated Clinical Trials

8.6.3.3.3 LABORATORY ADVERSE EVENTS

There were no laboratory adverse events that had a frequency ≥ 5%. There were no adverse event discontinuations on account of abnormal standard laboratory tests (positive antinuclear antibody tests which led to treatment discontinuation in 2 patients are discussed in Section L)

8.7 Vital Signs

8.7.1 Extent of Vital Sign Testing During Development

The data below refer only to post-treatment vital sign testing

8.7.1.1 Integrated Clinical Trials

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

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

Study #	Frequency of vital sign testing
OMC-GHB-2	Screening, end-of washout period, baseline, weekly during the 4 weeks of study drug administration and 3-5 days after completion of study drug